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Alan C. Love *Editor*

# Conceptual Change in Biology

## Scientific and Philosophical Perspectives on Evolution and Development

Springer

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## Scientific and Philosophical Perspectives on Evolution and Development

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# Preface

I became aware of what we now call evolutionary developmental biology ("Evo-devo") in the early 1980s. Many of the contributors to this volume worked in the field earlier than this. They are (mostly) evolutionary biologists; I am a philosopher and historian of science. The three-decade history of the field that is bracketed by the 1981 Dahlem conference (Bonner 1982) and this volume comprises a uniquely exciting episode in the history and philosophy of science. My entry into the study of this field was serendipitous. It was so stimulating that I have devoted almost all of my research efforts to it since that time.

The serendipity occurred because my scholarly interests in 1980 were in the history of methodological debates within the sciences, and not particularly in biology. I was finishing up an extended study of the "cognitive revolution" in psychology of the 1950s and 1960s, in which behaviorism gave way to cognitive psychology. Many people had recognized the formal analogy between the behaviorist principle of trial-and-error learning and Darwinian natural selection. It was my expectation that evolutionary biologists all knew how natural selection worked, so I should learn from them in order to understand the nature of the psychological debate. I arranged a visit in the summer of 1983 to the Harvard Museum of Comparative Zoology (MCZ), and interviews with Ernst Mayr, Stephen Jay Gould, and Richard Lewontin. The reader of this volume can imagine what I stepped into. I had expected some unanimity about natural selection among biologists, but I found myself in the geographical epicenter of a serious, ongoing methodological controversy. Imagine my delight!

Gould invited me to the MCZ, and I spent a sabbatical year (1985–1986) in his lab, next door to Pere Alberch's office and a short distance from Lewontin and Mayr. Gould had already introduced me to the anthology that had come from the 1981 Dahlem conference (Bonner 1982), a crucial gateway to the debates. One of my first publications on the developmental approach was based on Alberch's important paper on constraint in that volume (Amundson 1994). This paper showed that developmentalists and adaptationists used divergent concepts of constraint.

It was no wonder that the debates were inconclusive when the central concept at issue was given different interpretations by the two sides.

I also refer to my acquaintance with the field as serendipitous because there was no easy way for a philosopher to identify Evo-devo as an up-and-coming field of science in the 1980s. Most philosophers of biology of that time were concentrating on topics that grew out of the population biology framework of the Evolutionary Synthesis, such as the "units of selection" problem. Notable exceptions included William Wimsatt and Richard Burian. Wimsatt introduced the notion of generative entrenchment to explain developmental constraints (Schank and Wimsatt 1986) and Burian had organized the now-famous conference on developmental constraints (Maynard Smith et al. 1985). Given my geographical isolation and heavy course load, I could bring myself up to speed only by devoting my research to the study of developmental biology and the arguments (pro and con) regarding its relevance to understanding evolution. It was a long shot. If the remarkable explosion of knowledge in developmental genetics, phylogeny, and other related fields had not happened as it did during the subsequent decades, I would have had a rather tedious and mundane academic career. Even so, my research only began to seriously pay off 10 years later.

In those days, it was pretty unclear what would count as the "success" of a developmental approach to evolution. Some advocates (now in a small minority) believed that something like Evo-devo would refute the entire Evolutionary Synthesis and replace natural selection with some other mechanism. More moderate thinkers expected a sort of "Second Synthesis" to integrate development back into mainstream evolutionary theory and create a wider or broader synthesis. My own hope was that the methodological debates would continue, at least long enough to give me a chance to eke out their dynamics. This has happened to a far greater extent than I could have hoped.

Around 1960, the Evolutionary Synthesis biologist Ernst Mayr began to broaden his interests into history and philosophy of biology, and cooperated with several non-scientists to formulate an Evolutionary Synthesis-oriented framework of concepts that set an agenda for most of history and philosophy of biology during the following decades. One outcome of my research was to critique this tradition. I characterized it as "Synthesis Historiography" and argued that it distorted history in a way that made developmental approaches to evolution seem methodologically flawed. Mayr and his associates had introduced a set of dichotomies that came to be seen as logical truths about biology and were particularly useful in arguments that concluded ontogeny was strictly irrelevant to evolution. Among these dichotomies were proximate causation versus ultimate causation and population thinking versus typological thinking, as well as certain ways of formulating the distinction between genotype and phenotype and between germline and soma. Each of these dichotomies was used during the 1980s and 1990s to argue that ontogenetic development was irrelevant to evolution. It was argued, for example, that development concerns proximate causation but evolution is about ultimate causation, and that this was why development is irrelevant to evolution. Prominent thinkers such as Mayr, John Maynard Smith, Bruce Wallace, and George C. Williams offered

these and related critiques. I have come to realize in conversation that many current biologists are skeptical that thinkers of this magnitude could have reasoned in a way that seems so simplistic today. But it is important to recognize how much our perspectives have changed since the 1990s. I have carefully documented these anti-developmentalist arguments (Amundson 2005, Chap. 11). Views that seem naïve today were in the mainstream not long ago.

The present volume offers the reader a wide range of perspectives about how an understanding of development has changed, if not transformed, our understanding of evolution. The radical anti-selectionists are absent, but a range of other views is present. No one believes, as many adaptationists did in the 1980s, that development is literally irrelevant to evolution. But there are many opinions about what exactly must happen before we can integrate our new knowledge of development into our classical knowledge of population genetics and evolutionary theory to yield an integrated perspective on evolution. I must confess that I have been swayed to some extent by the methodological arguments of adaptationists. Evo-devo practitioners who claim that their approach is perfectly consistent with population genetics are overconfident. I agree with the conclusions of Karl Niklas (Chap. 2, this volume); some major, new theoretical advance is necessary before we will have an understanding of population genetics and development that does justice to both. But Niklas's reasons are different from mine. I am more of a pluralist than he is about what counts as an "explanation" in science. The problem I see revolves around the difficulty of integrating population thinking with the mechanistic thinking of developmental biology. Some Evo-devo practitioners seem to think that merely *endorsing* natural selection is sufficient to prove a consistency between Evo-devo and adaptationist population thinking. But it takes more than this. One must understand the objections raised by Mayr and his associates, and explain just how they do not apply to current thinking. To my mind, this has not yet been done. I am delighted with current science, and smugly satisfied about how many mistakes can be seen in earlier thought, but have we shown that population genetics and Evo-devo can be melted into the same pot? I am not yet convinced.

Alan Love's Introduction offers a guide to the wide range of views in this volume regarding the changes that have been necessary to bring Evo-devo to its current, favored position. Some of the most obvious examples are the increasing respect paid to phylogenetic systematics and the explosive growth of knowledge in developmental genetics. I was slow to catch on to both of these developments. In the early days, "genetics" simply meant *transmission genetics*, with genes defined abstractly in terms of their relation to phenotypic traits. In that sense, I suspect that many of us still are skeptical about the relevance of "genetics" to development. But the term "genetics" now means something much broader—a form of conceptual change has occurred (see Love, Chap. 1, this volume). We create a false sense of continuity when we fail to distinguish between different kinds of genetics. By the time the term "genetics" became synonymous with molecular genetics, and in particular the regulation of gene expression, Evo-devo was well on its way.

Regarding systematics, I decided when I first reached the MCZ in 1985 to ignore the arguments over cladistics; the debates were too personal and the topic itself hard to comprehend. Armand de Ricqlès (Chap. 12, this volume) reports in this volume how perplexed he was that Gould, otherwise an early hero of Evo-devo, sided with Mayr in opposing phylogenetic systematics (cladistics). I can reassure him that in 1985–1986, Gould was beginning to change, and was encouraging his students to take cladism more seriously. David Hull (1988) has reported on the very personal and nasty nature of the debates during that period. Although Gould had originally opposed cladism, he was softening towards it in 1986. He convinced me to keep an open mind, but it was years before I (and many others) recognized the importance of phylogenetic systematics for the progress of Evo-devo (see Raff, Chap. 11, this volume).

I would like to draw attention to an aspect of the growth of Evo-devo that is distinct from specific methodological issues, although it does indicate an important change in perspective. The difference can be seen in popular narratives about evolution that emerge from mainstream adaptationist evolution theorists as compared to those commonly articulated from the viewpoint of Evo-devo. The mainstream narrative emphasizes adaptations and assumes a sort of autonomous individuality between species. Because true species cannot interbreed, any observed genetic or morphological similarities should be explained in terms of similar selective pressures unless lineages had recently diverged and still displayed a residual conservatism from common ancestry. One would not expect to find homologous genes in species whose phylogenetic separation occurred a long time ago. Only a few dissented from this perspective that was widely held by Synthesis theorists (e.g., de Beer 1971; cf. Raff, Chap. 11, this volume), in part because any causal mechanism that might be used to explain Unity of Type would commit the fallacy of typological thinking. Homologous genes were not only difficult to find (due to their expected rarity and for technical reasons), but even if found they had no bearing on evolution.

Today's evolutionary science is very different. Huge numbers of homologous genes have been identified, and they control some of the most abstract examples of similarities across all metazoan species (e.g., morphological axes of the body). As molecular genetics advances, we find more and more identities among genes in complex organisms and in representatives of their phylogenetically distant and morphologically simpler ancestors. This is most remarkable when those ancestral forms lack the phenotypes produced by the homologous genes in complex organisms. Choanoflagellates possess genes that are homologous to the genes for cell adhesion molecules in metazoa (King et al. 2008). But choanoflagellates are single-celled creatures! What are they doing with (what we call) "cell adhesion molecules"? Simple animals such as jellyfish have no nervous system. Yet they share the genes that are used by metazoans to build nervous systems (Arendt et al. 2008). What need did they have for these genes? Genes involved in the specification and development of the autopod (hands and feet) in terrestrial vertebrates are found in species of fish that have no autopod at all (Schneider et al. 2011).

This unmistakable trend of discovery seems to be one of the most significant developments of recent years. From a historical perspective, the importance of the

trend is its conflict with the methodological standards of the critics of Evo-devo during the 1980s and 1990s. But I see an additional complexity. These results greatly magnify the importance of the concept of exaptation (Gould and Vrba 1982), a notion that was earlier referred to as "pre-adaptation" (another form of conceptual change). It is beginning to appear that every gene that performs a biological function today performed different functions in the evolutionary past. This complexity also is manifested in the fact that today's genes perform different functions in different life stages, in different phases of development, and in other sorts of varying contexts (see Piatigorsky 2007). How are we to map population genetic analyses onto such squirming masses of genetic functions?

This observation reflects not only a fact about outside reports regarding evolutionary discoveries, but also a conceptual change in how evolutionists regard the problems facing them. My own research focuses on debates, and so I tend to emphasize conflicts between schools of thought. But even among evolutionists with broadly Evo-devo approaches, things have changed dramatically. Hanken (Chap. 4, this volume) points out how the concept of heterochrony has changed in its explanatory importance from the 1980s until today. Heterochrony and allometry were among the few developmental mechanisms available to theorists of the time, and so received a great deal of attention in earlier days. These mechanisms were applied to observable developmental events, and observations of molecular events were not yet available. Discoveries of gene homologies and re-used mechanisms of regulation changed all that. New developmental mechanisms, with clear evolutionary implications, came into play as gene expression patterns began to be mapped onto the organism and their regulation understood.

A broader change in perspective regards whether or not the observable data of certain evolutionary commonalities actually require *any explanation at all* (again see Amundson 2005, Chap. 11, for details). The mainstream view in the 1980s was that it did not. Bauplans and deep homologies were seen as mere artifacts or historical accidents; it was a typologist's mistake to try to explain them. Today it is broadly assumed that even remote correspondences are likely to reveal deep underlying causes. The very fact that the clade *Bilateria* is commonly discussed shows how radical this change is (e.g., see Freeman, Chap. 10, this volume).

One concept in particular illustrates the new conceptual breadth in perspective that evolutionists have adopted. The concept of homology is notoriously difficult to account for by means of developmental biology (de Beer 1971). Günter Wagner (Chap. 15, this volume) has taken up this challenge, and (to my modest understanding) has given a uniquely satisfying account of how homology can have the perplexing attributes that it does. The responsibility to even attempt this task shows that today's Evo-devo has duties and goals that go far beyond those of the mainstream of twentieth century evolutionary theory. It is true that Wagner and other Evo-devo thinkers had attempted this task—and failed at it—during the 1980s. But his new analysis shows how it is possible for homologous characters to possess a *sameness* that persists even while the developmental origins of those

characters are modified in different groups of descendents. What seemed like metaphysical idealism to the critics of Evo-devo has here received a mechanistic explanation. Achievements like this reveal just how far our goals and abilities have advanced.

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# Acknowledgments

This volume has developed and evolved over several years, and many people have contributed substantially to make it finally appear. The original idea surfaced in 2005 when I was transitioning to a new position at the University of California, Santa Cruz, after completing a Ph.D. in History and Philosophy of Science at the University of Pittsburgh. My dissertation had focused on explanations of evolutionary novelty and the conceptual change that occurred surrounding evolution and development from the coalescence of the Modern Synthesis to the early 2000s. I read the 1981 Dahlem conference proceedings as a young graduate student and could grasp then, even if inchoately, that something special had happened there. Given that my dissertation had (in part) tried to isolate key ways in which scientific explanations and theorizing had changed surrounding evolutionary novelty, I started contemplating applying these sorts of considerations to other conceptual elements of evolutionary developmental biology and developmental evolution. The task would be too large for one individual but having original participants from Dahlem 1981 reflect on their own research program's development and evolution could constitute an enduring platform from which others might take up the charge. There was urgency as well due to the age of some potential participants, which was unfortunately reinforced during the invitation stage. (Two weeks after I invited Brian Goodwin, we learned of his accidental death.) Things began to take shape in 2009 after funding for the project materialized and a single semester leave from teaching gave me time to prepare and organize the details. The workshop occurred in 2010 at the Max Planck Institute for the History of Science in Dahlem, Berlin. The reasons for the delay in the volume being published are like many things biological—the result of multiple, distinct (but interacting) causal factors. Some of these involve various contributors; others involve professional obligations or problems; a least one derives from personal and family issues. Rather than attempt to separate out the causal responsibility in fine detail, it is more important to celebrate the fact that the project has now come to fruition. The best and most appropriate way to do so is by thanking those who made it possible.

The research funds and release time from teaching associated with my McKnight Land Grant Professorship (2009–2011), as well as a single semester leave from the College of Liberal Arts (Spring 2009), both at the University of Minnesota, were essential to making the project happen. They provided the catalyst for taking an idea and making it a reality. I owe a special debt to Gerd Müller and the Konrad Lorenz Institute for Evolution and Cognition Research for providing ample financial support for key aspects of the workshop. This made a European location for the workshop possible. Additionally, Gerd and Günter Wagner were extremely helpful at various stages of planning the workshop, all the way back to 2005. Gerd, Rudy Raff, and David Wake played key roles on the Steering Committee for the workshop, and gave me both wise and critical input on who to invite and how. I deeply appreciate all of their assistance from start to finish.

I am very grateful to Hans Jörg-Rheinberger and the Max Planck Institute for the History of Science (MPIWG) for hosting the workshop. It was a special treat to hold a workshop reflecting on conceptual change since the 1981 Dahlem conference *in Dahlem*, making it almost a reunion event, but the MPIWG also provided an ideal meeting space with nearby accommodations, which facilitated many fruitful interactions. I would be remiss not to mention and specially thank Antje Radeck, whose administrative assistance was another essential component to having an academic workshop in Europe when its organizer was in America. She coordinated the local housing arrangements and many other details in Berlin, ensuring a functionally operational endeavor. The Minnesota Center for Philosophy of Science, and Janet McKernan in particular, provided crucial administrative support, specifically with respect to reimbursement processing.

In the preparation of the volume itself, I have had the invaluable assistance of Janet McKernan in reviewing chapter formatting and preparing the index. Additional help on the index came from Matt Spates, an able undergraduate who happily took on the task. Tom Doyle, a graduate student assistant for a portion of time after the workshop, gave me important editorial assistance with respect to all the chapters that yielded stylistic consistency, in both text and bibliography, and improved readability throughout (any remaining mistakes are due to me, not him).

I want to express my special thanks to the contributors for their patience as the volume slowly came into existence. Many of you followed through on deadlines most punctually but have been rewarded with only a wait. I am only sorry that the material could not appear sooner. But I also want to express my gratitude to all of those in attendance at the workshop in 2010 (not all of whom ended up contributing a chapter). As an assistant professor with a dream about bringing together original Dahlem participants and co-travelers alongside of historians and philosophers interested in the intersection of evolution and development, all of you made the experience greater and more stimulating than I could have imagined. It is not that everyone agreed on what was discussed but our conversations showed that the intellectual vigor was alive and well 30 years later and is, in my estimation, an important component of what makes the nexus of evolutionary developmental biology and developmental evolution so fascinating to participate in and analyze. I am confident that these explorations will be of immense value for historians,

philosophers, and scientists for years to come because they provide a key bridge between past and present conceptual inventories to display how the architecture of knowledge in biological science has been refined, revised, and transformed. This leads me to note the role that Chris DiTeresi played in audio recording the event for posterity. He flew all the way to Berlin as the "sound guy," but, of course, ended up playing a larger role and offering free (good) advice.

It is fitting that the volume is being published by Springer since they were the publisher of the 1981 Dahlem conference proceedings. I am grateful to Jürgen Renn and the rest of the editorial team of Boston Studies in the Philosophy and History of Science for discerning that this series would be a good home for these contributions. I want to thank Lucy Fleet at Springer for her steadfast and unwavering support, as well as constant prodding to make sure this volume was birthed. It is difficult to say enough good things about Lucy's role in working with me on this project. It sounds trite to remark that it would not have been possible without her, but it is true. I learned a lot about myself as an editor in preparing this volume for publication and a good chunk of it emerged from my cries of frustration to Lucy and her gentle (but firm) nudges to keep the volume on track to completion. To you I owe a special debt of gratitude. Thank you.

Finally, I am thankful for the nurture and support of my family over the past several years, and especially my wife Lolene. I am constantly reminded that I do not exist in a vacuum and am utterly dependent on those immediately around me (whether they want me around or not). I could not ask for a better environment in which to work and certainly do not deserve it. *Transit umbra, lux permanet*.

# Contents

# Chapter 1
# Conceptual Change and Evolutionary Developmental Biology

**Alan C. Love**

## 1.1 The 1981 Dahlem Conference: A Catalyst for Evolutionary Developmental Biology

The year was 1978. A very promising graduate student at UC-Berkeley, Pere Alberch, was at home in Barcelona, Spain, and wrote a letter to his advisor, David Wake, describing some of his recent intellectual interactions with biologists at a Gordon Conference on Theoretical Biology.

> So far, these days have been excellent. The Gordon Conference on Theoretical Biology was very interesting since I had the opportunity to meet a lot of people in a field that is new for me. The most important event was to meet Lewis Wolpert. He was very interested in our paper and we had a long discussion about the role of development in evolution. He also believes that "the next major breakthrough in biology will involve the integration of development in evolutionary theory", the product of this discussion is that we put him in contact to Gould to organize a small meeting, probably in Germany, where the topic will be evolution and development. We will try to bring together developmental biologists that like Wolpert are interested in general principles, with evolutionists and comparative anatomists. A small list of people that will be invited has been elaborated and it certainly includes you. Other people considered are Kauffman, Lovtrup, A.C. Wilson, etc... we have included even Pierre Grasse. George Oster is coming to Berkeley next week and he will give you more information about it (personal letter from Alberch to Wake, 8 July 1978).

In retrospect, Alberch's missive was prescient. Within 5 years there would be a veritable explosion of interest in the connections between development and evolution (e.g., Raff and Kaufman 1983; Alberch et al. 1979; Goodwin et al. 1983), following on the heels of Gould's seminal book-length treatment (Gould 1977), which included the profound discovery of homeobox gene conservation across metazoans (Scott and Weiner 1984; McGinnis et al. 1984). A fountainhead of

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that interest stemmed from the 1981 Dahlem conference that grew out of the "small list of people" referred to by Alberch. It, and the resulting edited volume (Bonner 1982), proved to be a catalyst for evolutionary developmental biology (Evo-devo) over the next three decades. Many of the participants were already well established (e.g., Eric Davidson); others were just starting out but would go on to become central figures in contemporary Evo-devo (e.g., Günter Wagner).

The goal of the original Dahlem conference on evolution and development was "*to examine how changes in the course of development can alter the course of evolution and to examine how evolutionary processes mold development*." In addition to attempts at producing answers to these "how" questions, the 1981 Dahlem conference encouraged renewed efforts to explore these research themes empirically and theoretically. The examination itself did not yield a consensus about how development evolves or how development structures the evolution of organismal traits. What it did yield was the crystallization of a growing *zeitgeist* that these questions had been ignored by population genetic conceptions of evolution undergirding the Modern Synthesis and required multidisciplinary attention, which remains an enduring aspect of Evo-devo (see Gerson, Chap. 20, this volume; Winther, Chap. 21, this volume). This multidisciplinarity was manifested at the conference and an intentional component of its structure.

> the integration of ideas from different fields is important … there is suddenly a general consensus that this is precisely what is needed at this time. There is an sentiment that a knowledge of development will give us greater insight into the mechanisms of evolution and that a knowledge of evolution will give us corresponding insight into mechanisms of development. (Bonner 1982, 4)[1]

Bonner saw the effort in terms of synthesis, "bringing the ideas of different fields together," and interpreted the Modern Synthesis as allied in spirit if lacking in substance with respect to evolution and development: "only by such integration can we obtain a perspective and fully appreciate the meaning of advances in any one specialized field." The conference participants (48 total) were drawn from a variety of disciplinary approaches (e.g., mathematical biology, paleontology, morphology, molecular biology, evolutionary genetics, developmental genetics, and experimental embryology) and taxonomic specialties (lower eukaryotes, marine invertebrates, terrestrial arthropods, and vertebrates).[2] The self-described fields of research are

[1] Some philosophers have turned their attention to "integration" as an important relation between scientific concepts, explanations, and theories that is distinct from the traditionally discussed relation of "reduction" (Brigandt and Love 2012b). For a representative sample of articles, including integrative relationships between concepts relevant to Evo-devo, see *Studies in History and Philosophy of Biological and Biomedical Sciences*, Vol. 44, December 2013 (Brigandt 2013).

[2] "We wanted to assemble as large a variety of different kinds of biologists as possible. We had molecular biologists, especially molecular geneticists, developmental geneticists, developmental biologists of different skills including neurobiology, development of invertebrates in general, of insects, and even of slime molds. We had invertebrate zoologists, including a specialist in their bioengineering, and population biologists who are concerned with the strategies of life history. We had vertebrate comparative anatomists with deep interests in evolution and development shared by a group of paleontologists, both vertebrate and invertebrate. As icing on this rather remarkable mixture we had a group of theoretical and mathematical biologists interested in these subjects at all levels" (Bonner 1982, 4–5). But not everyone was included; Bonner acknowledges that the planning committee intentionally left out botanists and behavioral biologists (14).

sometimes predictable (e.g., David Wake: "Evolutionary and developmental morphology of amphibians"), sometimes unexpected (e.g., Stuart Kauffman: "Developmental genetics—*Drosophila*"),[3] and sometimes unconventional (e.g., Günter Wagner: "Self-organization and typogenetic evolution").

The Dahlem Conference series was highly structured, if not rigid (Stearns, Chap. 6, this volume; D. Wake, Chap. 5, this volume). Each conference, whether focused on life sciences or physical and chemical sciences, followed a pre-specified outline and made very concrete demands on the attendees (Appendix 1.1). These demands were especially taxing for the rapporteurs, who often stayed awake through the night typing up the input from members of their groups (Gerhart, personal communication). With the individual papers prepared in advance and the group report completed on site, a rapid publication of the entire volume ensued (even by today's standards). The rigor of the conference did not wholly exclude extracurricular activities, including time set aside for enjoying both food and drink at the end of the day's discussions and for touring the sites of Berlin, such as Potsdam or the Natural History Museum (Fig. 1.1).

### *1.1.1 The 1982 Dahlem Volume*

The 1982 Dahlem volume consisted of an introductory chapter written by the Chairman of the Program Advisory Committee (J.T. Bonner) followed by four sections organized in terms of "levels": the Molecular Level, the Cellular Level, the Level of the Life Cycle, and the Level of Evolution (see Appendix 1.2 for lists of the group members). Bonner's introduction began with an anecdote about the fissure that had opened between evolution and embryology, but reminded readers of the many diverse and productive discussions from the twentieth century of how the two relate (Garstang 1928; de Beer 1930, 1941; Waddington 1940, 1957; Schmalhausen 1949). These four section levels did not correspond to spatial or compositional organization, but were articulated as "levels of change." This conception was not well specified and blended together with standard depictions of hierarchical levels: "from molecules to cells to organisms." Bonner then described four themes that he thought were salient, fully acknowledging that other participants might add different themes to this list:

[3] Stuart Kauffmann's self-description sounds like he was doing work similar to Antonio Garcia-Bellido or Peter Lawrence (both developmental geneticists working on *Drosophila*). But the differences are striking. For example, a special issue of *American Zoologist* from 1977 on Gene Regulation and Development in *Drosophila* contains a contribution from Kauffmann that summarizes his model for a binary epigenetic code specifying wing discs as compartments or modules (Kauffman 1977; cf. Kauffman 1973). Instead of a genetic or molecular analysis anchored in experimental methods, which characterized the other papers, Kauffmann provided a mathematical analysis of how standing chemical waves form recurrent patterns, very much in the conceptual lineage of Turing reaction-diffusion mechanisms (Turing 1952).

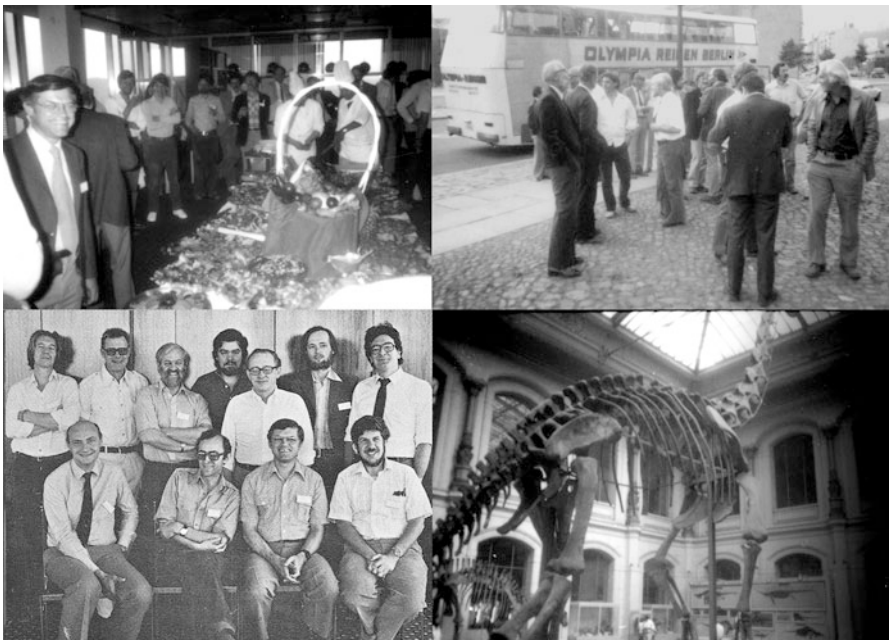

**Fig. 1.1** 1981 Dahlem conference snapshots. *Upper left*: dinner in the evening (foreground *left*, David Wake); *upper right*: conferees visiting Potsdam; *lower left*: Level of Evolution Group Photo (Standing, *left* to *right*: Brian Goodwin, Dolf Seilacher, Jim Murray, Pere Alberch, David Raup, Günter Wagner, Paul Maderson; seated, *left* to *right:* Armand de Ricqlès, Tony Hoffman, David Wake, Stephen Gould); *lower right*: *Brachiosaurus* skeleton at the Natural History Museum, which was observed on an adventurous outing to East Berlin during the conference. Picture credits: *upper left, upper right, lower right* (Armand de Ricqlès, personal photos); *lower left* (Bonner 1982, 278)

1. 'How Genes Control Development and How This Control Can Contribute to Changes During the Course of Evolution': "the question is how do genes play their part in different, complex shifts in the phenotype."
2. 'The Physical Basis of Timing Mechanisms which Play such a Key Role in Development and Evolution': "everyone agrees that the most effective way to elicit big phenotypic changes with the least genetic fuss is by heterochrony. . .but how genes control when something starts and stops in a life cycle is far less obvious. . .the wonder is. . .that we should have so little understanding of how these alterations are carried out."
3. 'The Levels of Control Above the Gene Level': "certain events seemed to be occurring in this superstructure that could not have been foreseen in the gene information alone. . .all the control signals do not emerge from the genes, although the gene instructions are the basis of all the higher levels. . .there is a hierarchy of levels of complexity."
4. 'Selection, Constraints, Random Changes, and Rigidity vs. Plasticity in Developmental Pathways': "selection is limited in what changes it can make at one

> stage of development by what has occurred at a previous stage. . .developmental constraints are related to the hierarchical levels. . .sometimes rigidity is adaptive and sometimes plasticity is adaptive."

Bonner's four themes pick out issues that arise in each of the four group reports.

The Molecular Level Group Report was entitled "Genomic Change and Morphological Evolution" (I. Dawid, rapporteur) and was supplemented with two individual papers: "Genomic Alterations in Evolution" (R.J. Britten) and "Evolutionary Change in Genomic Regulatory Organization: Speculations on the Origins of Novel Biological Structure" (E.H. Davidson). These discussions review recent findings about gene and chromosomal organization, such as gene families, introns, multigene clusters, repetitive sequences, and transposable elements, with an emphasis on "control" genes. Many of these findings were derived from work in *Drosophila*, but sea urchin studies of mRNA sequence diversity were prominent also (Davidson 1976). The global perspective was pessimistic:

> Present knowledge about genome function is not sufficient to make a large direct contribution. We do not know the mechanisms by which gene activity affects the development of an individual animal, therefore, we cannot come to useful specific conclusions regarding genomic correlates of evolutionary change at the morphological level. (Bonner 1982, 19–20)

But the group argued that what was known provided a "framework of information" relevant to understanding evolutionary change. Davidson's individual contribution encapsulated his theoretical account of hierarchical gene network control (Britten and Davidson 1969, 1971). The non-exclusive alternative was local multigene regulatory units whose organization would be reflected in chromosomal proximity rather than network interactions. Although subsequent history would favor network interactions (Davidson et al. 2002; Davidson 2006), both were offered as substantive hypotheses about how variation and novelty could originate developmentally and take on evolutionary significance.

The Cellular Level Group Report was entitled "The Cellular Basis of Morphogenetic Change" (J.C. Gerhart, rapporteur) and was supplemented by five individual papers: "A Catalogue of Processes Responsible for Metazoan Morphogenesis" (N.K. Wessells), "What does the Comparative Study of Development Tell us about Evolution?" (G.L. Freeman), "Pattern Formation and Change" (L. Wolpert), "Genes That Control High Level Developmental Switches" (T.C. Kaufman and B.T. Wakimoto), and "Ontogenetic Mechanisms: The Middle Ground of Evolution" (M.J. Katz). The group report (and individual paper by Wessells) focused on three properties of cells—shape, division, and locomotion—and three broad mechanisms of cell-cell interaction in morphogenesis—localized mitosis, localized cell death, and mechanical processes (e.g., folding or flattening)—as possible evolutionary constraints but also as contributors to evolutionary potential (see Brigandt, Chap. 14, this volume). Freeman's individual paper approached the issue of how novel features arise in evolution by examining comparative larval biology. He argued that evolutionary changes in features exhibited at larval stages accounted for major differences among animal phyla as a result of the (i) precocious, (ii) differential, (iii) combinatorial manifestation of adult anatomical elements in

larval stages of different lineages ('adultation'). Katz emphasized the importance of "ontogenetic buffering mechanisms" to accommodate these novel changes that were distinct from standard variation. Wolpert's positional information model of pattern formation (summarized in his individual paper) received much attention, but was contrasted with mechanochemical models of pattern formation (Odell et al. 1981), which have experienced increased attention recently (e.g., Chirat et al. 2013).

Another central issue for this group was the origin of cell types, such as whether multifunctional cell types have been segregated evolutionarily into more narrowly functioning cell types. This touched on the broader issue of the origin of novelty, including how new organs originate in evolution. These questions were explored via advances in understanding segmented body structure (metamerism) that derived from the genetic analysis of *Drosophila* (reviewed in the individual paper by Kaufman and Wakimoto). This was just prior to the unprecedented discovery of widespread conservation in *Hox* genes underlying the development of segments across metazoans (McGinnis et al. 1984; Scott and Weiner 1984). Other questions included: (a) whether particular developmental events (e.g., gastrulation) are necessary for the formation of particular structures, and therefore a developmental constraint on evolutionary change; (b) the presence and absence of developmental capacities in different lineages (e.g., regeneration); and (c) the cellular basis of changes in developmental timing (heterochrony) and their allometric effects (Hanken, Chap. 4, this volume; Niklas, Chap. 2, this volume). Similar to the Molecular Level Group, there was a studied ambiguity in how much could be concluded ("we could not give solid answers"). The group generally accepted that development may influence evolution ("certain basic constraints may be set on development and evolution by the properties of cells"), but was hesitant to specify how without further experimental inquiry. Suggestions for the latter encompassed investigating metamerism in arthropods or patterns in the vertebrate limb.[4]

The Level of the Life Cycle Group Report was entitled "Adaptive Aspects of Development" (H.S. Horn, rapporteur) and was supplemented by two individual papers: "The Role of Development in the Evolution of Life-Histories" (S.C. Stearns) and "Selection for Size, Shape, and Developmental Timing" (J.T. Bonner and H.S. Horn). This group made the most direct contact with functional considerations predominant in an evolutionary biology oriented around adaptation. Adaptive features exhibited in different animal ontogenies were treated comparatively on the supposition that there is no optimal way to build structures developmentally. The constraints of some particular developmental mechanism usually co-traveled with the facilitation of certain kinds of evolutionary change,

[4] A vigorous discussion of the idea of a "developmental program" occurred at the workshop, which is briefly recapitulated in the Cellular Level Group Report and was covered in a news story about the conference (Lewin 1981). The broad conclusion was that ontogeny is not described accurately as a programmatic phenomenon.

though with a range of potential and many possible combinations: "Patterns of development are in general more conservative than structures of adults. . . .However, there are many counterexamples, in which development is varied and the adult is conservative." Biomechanics (water flow, gas exchange, or muscle force) played a role in thinking about why development displays the features it does and whether evolution is constrained or facilitated as a consequence. As indicated by the title, development was treated in terms of complex life-cycles, which implied that how development constrained or facilitated evolution was related to the time in the life-cycle when particular properties were exhibited and whether the metamorphic transition from one stage to the next was more or less radical morphologically. The Group Report concluded with a yearning for more detailed, comparative empirical studies and systematic reviews of the findings: "our discussions were severely hampered at the outset by a lack of the most basic information." The reviews, in particular, should target a multidisciplinary readership.[5]

The individual paper by Stearns marks a key fault line in how ideas developed post-Dahlem (Stearns, Chap. 6, this volume). Focusing on life history evolution, which he would later write a textbook on (Stearns 1992), Stearns attempted to bridge adaptionist thinking ("what should natural selection favor?") and mechanist thinking ("how does the organism work?") in the context of life history theory. Stearns observed that the meaning of "development" differed for the life history theorist and developmental biologist; the former includes age-specific survival and reproduction patterns of less direct interest to the experimentalist investigating ontogeny. Stearns tried to build a bridge using three concepts—phenotypic plasticity, canalization, and constraint—by exploring how diverse mechanistic phenomena of these kinds can be adaptive. He attended systematically to plasticity and the entire approach was termed "developmental evolutionary ecology." For reasons that still require elucidation, the approach was largely ignored and most Evo-devo biologists were reintroduced to ecology through its physiological effects on ontogeny 20 years later (Gilbert 2001; Gilbert and Epel 2009). If a bridge had been built, no one decided to test its strength or utility; the chasm between population biology and experimental biology remained as Evo-devo, a loosely-knit research program with an emphasis on molecular developmental genetics, waxed in numbers and visibility (Amundson 2005; Love 2006b).

The Level of Evolution Group Report was entitled "The Role of Development in Macroevolutionary Change" (P.F.A. Maderson, rapporteur) and was supplemented by two individual papers: "Developmental Constraints in Evolutionary Processes" (P. Alberch) and "Change in Developmental Timing as a Mechanism of Macroevolution" (S.J. Gould). This was one of the most diverse groups present and contained paleontologists, mathematical biologists, and specialists in the

[5] "The reviews should be written in a style that is mutually intelligible to students of many academic fields. For example, developmental biology and paleontological morphology share little common language, but both must communicate their studies of shells and skeletons before one can fully understand the evolution of "novelties" that actually appear in the fossil record."

organismal and population biology of particular lineages. Their group report was the most far-reaching and conceptual of the four delivered, ranging over philosophical distinctions between universals and particulars, as well as an evaluation of the state of evolutionary theory ("neo-Darwinism"). One central theme was the possibility of predicting macroevolutionary trajectories with knowledge of the constraining features of development, especially the directionality of morphological change observed in the fossil record (e.g., punctuated equilibrium). Analyses of mammalian coat pattern formation in terms of reaction-diffusion mechanisms explained why spots, stripes, and other features are exhibited in particular species (e.g., Murray 1981). Another theme was the distinctness of macroevolutionary questions about the fate of higher taxa or the origin of phenotypic novelty from microevolutionary questions about changes in allele frequencies in populations. Heterochrony was invoked as a source for discontinuous morphological change in evolution, illustrated with multiple examples (e.g., amphibians and the tetrapod limb). Gould's influence on this conversation is palpable (Gould 1977; Gould 1980a, b), and was manifested in his individual paper, but the consensus that development is required to explain particular macroevolutionary phenomena was genuine: "[for] the origin of evolutionary novelties—developmental considerations are indispensable." Alberch's individual paper drove this point home by sharply contrasting natural selection explanations and developmental explanations for the stability of organic form and patterns of morphological variation through evolutionary time (Amundson 1994).

Contrary to the expectations of the organizers, this four-fold organization may have prevented some of the necessary and anticipated multidisciplinary interaction surrounding the relationship between evolution and development. For example, Strathmann (Chap. 3, this volume) recalls that this structuring partitioned those focused on mechanistic questions ('how' development works and might evolve, such as through gene regulation alterations) from those focused on adaptationist questions ('why' development evolved to exhibit particular features, such as complicated life histories). Subsequent trajectories for research programs were less cross-disciplinary than one might have expected given the productive dynamics of the conference (Stearns, Chap. 6, this volume). The Level of Evolution Group Report closed with a call to tackle evolution and development with the "enormous battery of techniques and thinking capacities" available. Why? "Because, apart from the evolutionary problems, even if a specific exercise fails, it forces a highly desirable interdisciplinary contact between all workers in the Life Sciences." This noble goal has certainly continued to be a hallmark of Evo-devo (Hall 1999; Raff 2000), but biologists are not so easily forced into contact with other disciplines—the desirability of multidisciplinarity is not shared by all. But the participants put their finger on something that continues to be important in present research endeavors: complex scientific problems demand multidisciplinary contributions to generate adequate explanations (Love 2008a; Brigandt and Love 2012a).

### 1.1.2 Reactions to the 1982 Dahlem Volume

Before the Dahlem volume came off the press, interest in the conference proceedings was notable. Roger Lewin wrote a news story for *Science* emphasizing one of its key themes: developmental constraints are an important factor in the dynamics of evolutionary change (Lewin 1981; see also Miller 1981). Two elements were prevalent in Lewin's recounting of the meeting: (a) natural selection was not the only relevant explanatory factor in evolution; and, (b) the contention that molecular detail is the primary locus of explanatory power. The former comprises part of a competitive narrative between the Dahlem discussion and "the almost exclusively selectionist position that has prevailed for the past several decades," and is most strongly indicated in the Level of Evolution Group. (Reviewers of the volume also detected this element of challenge [de Klerk 1982].) The latter constitutes a division over whether molecular detail was the skeleton key of explanation or whether we require "higher levels of explanation, levels above the genome, for an understanding of evolutionary change," especially the organism as an integral unit (Wagner, Chap. 15, this volume; M. Wake, Chap. 18, this volume). The interview tidbits gleaned by Lewin show just how diverse Dahlem participants were in their thinking: from Eric Davidson's confidence in the explanatory power of molecular detail and genomic organization, to George Oster's computational models of pattern formation based on physical forces; from Brian Goodwin's expectation of a periodic table of morphological forms, to Stephen Jay Gould's elevation of heterochrony to a distinct mechanism of evolutionary change. Lewin observed that many aspects of evolutionary theory were not represented at the meeting although it was held as a "rehabilitation process designed to push a neglected field of evolutionary biology closer to the center of the stage where it can join with other areas of study in shaping a fuller understanding of the origin of morphological novelties." This combining of areas of study did not occur as readily as Lewin's observation suggests (Strathmann, Chap. 3, this volume; Stearns, Chap. 6, this volume), in part because of differences in how core problems were understood across disciplines, such as explaining the origin of morphological novelties (Love 2003, 2007). But the general impression from the meeting was enthusiastic, as reflected in an interview comment by Paul Maderson: "The most important thing we have done is simply being here. The embryo has been expressly invited back into the melee of evolutionary biology" (Miller 1981).

When the Dahlem volume was published in 1982, the reviews recognized that something special was afoot. One reviewer remarked that it "suggest[ed] a lively and vibrant field of study" and prophetically noted that the resulting edited volume "is a harbinger of things to come" (Levinton 1983), a sentiment shared by additional reviewers: "*Evolution and Development* has the spark of disciplined originality" (Schopf 1982). Another saw it as an invigorating discussion of evolutionary theory: "the book is excellent and exciting. It shows that evolutionary theory itself is not in a stasis, but in a process of fascinating evolution" (de Klerk 1982). Some saw the Dahlem volume as an indicator of a broader movement: "Interest has continued to grow in this area, and enough researchers are currently involved that reviews,

symposia, and books have started to appear" (Barrowclough 1984).[6] But this broader movement was not always interpreted as the juxtaposition of evolution and development. In a joint review with another volume (Dover and Flavell 1982), Thomas Schopf discerned a different trend:

> These books represent the latest in the relentless surge of molecular biology's incorporation of evolution into its mechanistic world. They specifically focus on the continuing and growing quest for a material basis for genomic organization and genomic change, both in the development of individuals and in the origin of species. (Schopf 1982)

This was consonant with Lewin's report from the meeting, suggesting that the relationship between evolution and development was not the only thing at stake in Dahlem discussions. A growing hegemony of molecular biology's explanatory role in development (and therefore evolution) was being debated as well.

At the same time, not everyone was impressed. Levinton detected key differences between the group reports:

> The book is somewhat schizophrenic. The geneticists and cellular researchers define clearly the tremendous chasm between our knowledge of development and the way in which evolution might fit. The evolutionary biologists state with confidence that development imposes constraints that may be mapped to predict the course of evolution. Is this latter claim a bit premature? (Levinton 1983)

As noted, the fourfold group structure generated conversations within more bounded disciplinary constellations. The tenor of each group report varies. Different reviewers saw similar patterns, such as the promissory note from molecular biology ("while much has been learned about genome organization, details of the mapping between genomic structures and developmental patterns remains unknown" [Barrowclough 1984]) or that the reports were "speculative" (Schopf 1982). There also was concern about the absence of specific constituencies: "My main criticism is that the book is nevertheless too one-sided. Surprisingly, no population geneticist, no botanist, and alas no evolutionist of the synthetic theory were present at the meeting" (de Klerk 1982).[7] While it is untrue that no population geneticists were present (e.g., Günter Wagner had trained in theoretical population genetics), it is the case that botanists and those inured to neo-Darwinism were not in attendance.

But even Levinton's tentative skepticism was won over by the "evolutionary biologists" of the Level of Evolution group: "the group report by Maderson et al. and the articles by Alberch and Gould make a compelling case for the role of developmental programs in directing the course of evolution." And other reviewers concurred:

> The summary and two background papers prepared by the group studying development and macroevolution are definitely worth reading. For it has become clear that a satisfying understanding of macroevolution is going to require a detailed explication of developmental processes. This seems especially true of the origin of morphological novelties. (Barrowclough 1984)

[6] Not everyone noticed: *Nature* received the book but did not review it.

[7] Recall that John Bonner acknowledged some absences explicitly (see footnote 2).

Thus, the reception of the volume was marked by an awareness of something significant with simultaneous caution because what emerged from the meeting was an exciting prospective research agenda rather than a summary of settled empirical findings.

It is crucial to note that the conference participants did not go forth from Dahlem as standard bearers for the necessity of integrating evolution and development. Peter Lawrence, one of the Dahlem 1981 conferees, wrote a scathing review of an edited volume, *Development and Evolution* (Goodwin et al. 1983), which was released shortly after the Dahlem volume and included proceedings of the British Society for Developmental Biology with representatives from the Dahlem conference (e.g., Brian Goodwin). Lawrence pulled no punches—the title of his review was "Unpinioned opinions" (Lawrence 1984). His target was "old-fashioned" researchers whose chapters, "have a curious flavor, redolent of the past, with the gentlemanliness and lack of rigor of the good old days." The worry was that these researchers were not up-to-speed with the latest methods and results, especially molecular developmental biology, and needed to find a "balance between theory and experiment."

> To discuss usefully the interface between two subjects—like evolution and development—one depends on a deep understanding of both. Unfortunately, our knowledge of these fields is poor and the result, in the book, is a great deal of pretentious twaddle, much of it dressed up in complex terminology and appeals to defunct authorities. One . . .which, as far as I can understand it, is an attack on modern and reductionist developmental biology with particularly blunt weapons. (Lawrence 1984)

As a developmental geneticist working on *Drosophila* (Lawrence 1992), Lawrence represented those researchers whose confidence was in the growing molecular findings on the genetic control of development. This was a point of tension at the Dahlem meeting, and certainly not a consensus view. These reviews leave us with a reminder that this agitation surrounding the relevance and significance of molecular details for understanding development was just as much an issue as the necessary relationship between development and evolution. Agreement on the latter sometimes obscured disagreement on the former.

### *1.1.3 Rationale for Revisiting Dahlem*

The last 30 years has seen a plethora of empirical and theoretical results from the labor of many researchers working at the juncture of evolution and development (Haag and Lenski 2011; Love 2006b). That labor has come from many quarters and is aptly described as multidisciplinary by both practitioners (Raff 2000, 2007) and philosophers (Love 2008a, 2013a)—the label is well supported by bibliometric evidence (McCain 2010). The contributing disciplines remain heterogeneous and the need for integration is still salient (Wagner and Larsson 2003; Arthur 2004). Numerous concepts relevant to explanations in Evo-devo and other areas were canvassed at Dahlem and subsequently underwent transformations across

disciplines. Evo-devo is an ideal place to investigate philosophical questions surrounding conceptual change because the changes are occurring in real time as researchers explore unanswered evolutionary questions with a new set of experimental tools from developmental biology and elsewhere (Love and Raff 2003).

When we look back from the present day, some things have changed, such as an increased emphasis on specific topics or substantial changes in relevant biological sub-disciplines. Not all of those present at Dahlem would now describe themselves as working within Evo-devo. Probing these kinds of conceptual developments in detail offers a novel outlook on questions about how biological research is currently conceptualized and is valuable to historical and philosophical students of biology, as well as biological researchers forging and extending their research programs. These issues provided the motivation for a retrospective workshop that was interdisciplinary in a different sense. Instead of focusing on "a survey of the present state of the art of the topic at hand," a "review [of] new concepts and techniques," or even seeking consensus about these issues in contemporary research, it concentrated on the historical trajectories of diverse biological concepts from the past several decades to understand contemporary research and gain traction on the philosophical issue of conceptual change from a variety of different investigative perspectives. One shared aim remained between the original Dahlem conference and this retrospective workshop: illuminating and advancing biological inquiry ("recommend directions for future research"). Additionally, the hope was to illuminate and advance historical and philosophical inquiry. To put it in parallel with the original Dahlem workshop goals, the aim was to examine changes in how evolution and development have been conceptualized, describe alterations in the trajectories of these research programs, and better comprehend the coalescence of Evo-devo and allied investigations in such a way as to further biological and philosophical inquiry.

To fulfill these goals, the retrospective workshop was held at the Max Planck Institute for the History of Science in Berlin from July 15–18, 2010. It took the 1981 Dahlem conference as a reference point to analyze the diverse historical trajectories of biological research over the past 30 years, and generate scientific and philosophical perspectives that characterize their current status in Evo-devo (and elsewhere). At the 2010 workshop, a combination of complementary and competing perspectives on these concepts and the development of Evo-devo were offered by scientists and philosophers in order to generate a richer picture of how this and other areas of biology have advanced conceptually over several decades. Each scientific participant was asked to present on the changes and developments of conceptual aspects of their scientific research program since the mid-1980s, including connections to different aspects of Evo-devo's increasing prominence during the interim.

- *How did these concepts operate in your research in the 1980s? How do they operate now?*
- *Have these concepts waxed or waned in significance for your ongoing investigations?*

– *What empirical findings have been the most substantial?*
– *In what ways did these concepts guide your choice of methods, experimental techniques, model organisms, or collaborators?*
– *Has a concept changed its meaning in the interim, so that it is currently used differently than in earlier discussions?*
– *How do you understand your own research program in relation to what is now labeled 'Evo-devo'? Has this changed over time?*

Each philosophical participant was asked to present on similar topics but from the perspective of an outsider looking in with both historical and philosophical tools.

– *What models of conceptual change best account for the stasis and change observed for particular concepts? Do empirical findings primarily drive conceptual change or have there been critical theoretical developments that explain patterns of conceptual use?*
– *In what ways have shifts in the practices of biology transformed concepts at work in the research? Have the most important changes emerged from new experimental interventions, genomic technologies, bioinformatic tools, or something else?*
– *What concepts have disappeared from the epistemology of Evo-devo researchers? Why? What concepts that were absent or of negligible importance in the early 1980s are now significant? Why?*
– *How do these patterns of conceptual change map onto conflicts with other predominant conceptualizations in evolutionary biology (e.g., population biology and evolutionary genetics)?*

Participants revised their presented contributions in light of the discussion at the workshop prior to submitting the revised chapters represented in this volume.[8]

It is important to stress that the focus of the workshop was comparing and contrasting conceptualizations across time rather than arguing in favor of a particular theoretical vantage point today. It was not the goal of the workshop to attain consensus about these issues in contemporary research; many diverse viewpoints were represented and discussion was vigorous. Instead, the aim was to limn the contours of conceptual change in the recent history of biology in order to provoke new ways of thinking and stimulate new directions of research, both biological and philosophical. Juxtaposing these diverse contributions within a single volume augments their value across multiple disciplines simultaneously.

[8] Several participants did not contribute a chapter to the volume but their presence was critical to the stimulating discussions at the workshop: Richard Burian, Eric Davidson, Manfred Laubichler, and Gerd Müller.

## 1.2 Conceptual Change

Questions about how the theoretical ideas and categories of scientists change over time are central to understanding scientific reasoning and involve a combination of historical and philosophical inquiry. Conceptual change is heterogeneous; it includes introducing new concepts, reclassification, sub-categorization, and the reorganization of relations among concepts. For example, some ecologists have argued that the concept of "megafauna" should be expanded to include the largest ecosystem occupants: "the megafauna concept should be extended beyond an absolute animal size to be context-dependent … one ecosystem's mesofauna is another ecosystem's megafauna" (Hansen and Galetti 2009, 42). Despite ubiquitous examples such as these, much of the philosophical work on conceptual change has been done with not-so-recent history of science (Donovan et al. 1992; Brown 2007). Exploring the period from Dahlem to today and scrutinizing concepts like "developmental constraints," "evolvability," "heterochrony," "homology," "modularity," or "phenotypic plasticity" affords a unique opportunity. Not only are we examining recent conceptual changes, but the evidential basis includes reflections from those who were involved in the research where those changes occurred. Before offering a brief case study of conceptual change with respect to evolutionary novelty (Sect. 1.3) and summarizing the results found in subsequent chapters (Sect. 1.4), it is necessary to provide an overview of the philosophical problem and its different dimensions.

### *1.2.1 Conceptual Change: Varieties and Approaches*

How do scientific categories and their corresponding terminologies change over time? That this kind of change occurs is unsurprising: (1) scientific inquiry involves ongoing empirical discoveries through an accumulation of evidence via observations and experiments; (2) these discoveries have demanded and will continue to demand a variety of revisions (major and minor) to the conceptual apparatus used by scientists studying different aspects of natural phenomena; (3) therefore, conceptual change occurs and is an expected feature of scientific inquiry. But this slogan-like conclusion—conceptual change happens—can only be a beginning: "Scientific cultures develop and change. . . .in short, the ways in which we interact with our physical environment, and the ways in which we think about it, have changed and will continue to change. But how is such change to be understood?" (McGuire 1992, 132). Do individual concepts change in their structure? What is conceptual structure? How do we know we have the same concept through the purported change? Are concepts taken in isolation or with reference to a particular theory?

Philosophy of science tackles these questions by analyzing the nature of conceptual change—*how* the meaning, reference, and roles of concepts and their associated terminology change over time (Kitcher 1993; Kuhn 1962; Thagard 1992;

Arabatzis and Kindi 2013; Brown 2007; Thagard 2012). For example, how and why have biologists from different subdisciplines changed their conception of "gene" in response to advances in genetics and genomics (Brigandt 2010; Griffiths and Stotz 2013)? Other examples help to illustrate this complex phenomenon (Thagard 1992, 1999, 2013; Brown 2007):

- the introduction of a new concept ("prion")
- the rejection or replacement of a concept ("cistron" or "osculant groups")
- the failed introduction of a concept ("homogeny")
- the reclassification of things originally considered to fall under a concept ("ascidians" from "mollusk" to "chordate"), also interpretable as a change in the hierarchical relationship among concepts (from "ascidian" under "mollusk" to "ascidian" under "chordate")
- sub-categorization: the partitioning of types within a concept (varieties of locomotion: "cursorial," "saltatory," "scansorial," "fossorial," "natatorial")
- development of more abstract concepts (from "metamorphosis" to "life history characteristic")
- adding a new instance or set of entities as falling under a concept (discovery of a new species in a genus of butterflies; "poriferans" are "metazoans")
- adding or deleting relations among concepts ("planarians" express "*Otx* genes" during "brian development," as do "arthropods" and "chordates"; particular Burgess Shale species are "stem-arthropods")
- refinement or expansion of "defining" features of a concept (from "mammals" do not lay eggs, to most "mammals" do not lay eggs; from only "birds" have feathers, to "birds" and "theropod dinosaurs" have feather-type integuments)
- reorganizing relations among concepts ("population structure" is an effect of "evolutionary change"; "population structure" is a cause of "evolutionary change")

Even a casual reading of this list indicates that more could be said about each example (e.g., aren't birds just theropod dinosaurs?), but the heterogeneity of conceptual change exhibited within scientific reasoning is significant. What is labeled 'conceptual change' in different philosophical discussions can vary dramatically (Burian 1987; Buzaglo 2002; Carey 1999; Chen and Barker 2000; Ferrari and Elik 2003; Körner 1973; Nersessian 2008; Thagard 1992; Arabatzis and Kindi 2013; Brown 2007). There is widespread agreement that conceptual change is important but disagreement or at least variation in what counts as conceptual change in these discussions.

This heterogeneity calls into question whether or not there is a unified phenomenon to analyze and many philosophers of science have discussed scientific change or epistemic changes in science, emphasizing the *change* component rather than it being *conceptual* (Laudan et al. 1986; Laudan et al. 1992; Solomon 1995). *Scientific change* refers to any small or large adjustments over time in the epistemic frameworks or assumptions utilized by communities of scientists in their attempt to characterize and explain natural phenomena (Donovan et al. 1992). The slide from conceptual change to a broader sense of scientific change is encouraged by the fact

that philosophical analyses have been tied to questions about scientific theories. In some cases, understanding conceptual change is only a means to the end of understanding theory change (Soler et al. 2008). As a consequence, a conceptual "framework" or "system"—indicative of comprehensiveness or systematicity—replaces the focus on individual concepts (Gärdenfors 2000; Gärdenfors and Zenker 2013; Brown 2007).

If we remain attentive to *conceptual* change, philosophers of science have concentrated their attention on the representational dimension of concepts, as in Nersessian's model-based reasoning account (Nersessian 2002, 2003, 2008) or Thagard's account of conceptual revolutions (Thagard 1992, 1999; see also Brown 2007). Another primary concern has been how our concepts connect with the things they represent (i.e., how they refer), which arose out of work on the possibility of incommensurability between scientific communities (Feyerabend 1981; Kuhn 1962; Sankey 1994). One interpretation of incommensurability focused on the possibility of different meanings for the same terms used by competing paradigms or research traditions (*semantic* incommensurability). Philosophers exploited different accounts of reference (e.g., causal vs. descriptive) to develop perspectives on conceptual change that avoided irreconciliable semantic incommensurability, such as by viewing the reference potential of a concept as tunable via interactions with theoretical commitments and in response to empirical findings (Kitcher 1993; Kroon 1985).

The heterogeneity of conceptual change suggests that there is more to the conceptual practices of scientists than reference and not every conceptual change is the result of or dependent on changes in scientific theories. An implicit goal of the present volume is to approach conceptual change without invoking issues of reference, incommensurability, or theory change, especially the latter. Although mention of evolutionary theory is frequent, the conceptual changes discussed with respect to "developmental constraints" or "novelty" are not tightly connected to a specific biological theory. Thus, instead of working at the level of scientific change *sensu* theory change, or exploring broad sweeps of history and many different areas of science or mathematics, the contributors to this volume explore concepts at the intersection of evolution and development in a more fine-grained fashion to uncover patterns of change (see below, Sect. 1.4). Comprehending these changes requires tracking the historical trajectories of concepts in areas of research where they are used regularly (Burian 1985; Hacking 1995; Hull 1988). When these fields intersect, such as in multidisciplinary endeavors, the epistemological dynamics become more conspicuous. Researchers routinely encounter difficulties in conceiving of how 'integrated' explanations are generated when the disciplines have differences in methodology and research aims, criteria of explanatory adequacy, disciplinary structure and function, meanings for core terminology, and how central problems are defined.

In addition to philosophical interest in the epistemological development and metamorphosis of the sciences, two interrelated areas make conceptual change a salient topic. The first is the how concepts change through development in human psychology, such as how we come to have conceptions of object permanency or

causal relations (Carey 1985, 2009). The second is how concepts change through educational processes, especially with respect to complex scientific ideas.[9] Concepts from evolutionary biology demand significant departures from our everyday reasoning patterns and therefore require distinct pedagogical approaches (Kampourakis 2014). Arguably, far more attention has been given to these two areas than one finds in standard philosophical literature, although there is explicit cross-pollination between them (Vosniadou 2013).[10] This cross-pollination stems from a common inspiration in the work of Thomas Kuhn (Kuhn 1962), who emphasized revolutionary changes in theories that resulted from radical conception innovations.[11] Although many of Kuhn's claims have not held up (Thagard 1992, 2012), the phenomenon of conceptual change inspires philosophers, educational researchers, and developmental psychologists via cases that overlap these domains (Carey 2009; Chen and Barker 2000), such as when a child's naïve physical intuition corresponds with discarded physical theorizing. Many have argued explicitly that the process of conceptual change in science is directly analogous to conceptual change in developing children (Carey 2009). In both areas there is much dispute among different perspectives, such as whether educational conceptual change should be studied in individuals versus groups (e.g., classrooms) or whether children harbor "framework theories" that impart meaning to concepts. The stakes are high as results can affect educational policy directly or indirectly.

For Evo-devo, educational conceptual change is significant for understanding how individuals comprehend both development and evolution through science education. Some have argued that Evo-devo offers a more conducive route for students to understand how evolution works (Carroll 2005) or provides more perspicuous evidence for evolutionary change unavailable from other areas of biology (Gilbert 2003). But there are difficulties that students encounter when learning concepts in Evo-devo (Hiatt et al. 2013; Perez et al. 2013). Thus, the trajectories traced in this volume can contribute to rethinking how we teach Evo-devo. Even further, they might illuminate why there are continuing difficulties with integrating different disciplines at the juncture of evolution and development. For example, one of the conceptual difficulties identified in learning Evo-devo concepts is a tendency to fall back on natural selection as an explanatory strategy when there is a limited knowledge of developmental biology (Hiatt et al. 2013). This type of finding is germane to comprehending not only student learning difficulties but also why some biologists are less responsive to Evo-devo claims.

[9] "Research on conceptual change investigates how concepts change with learning and development in different subject matter areas with a focus on explaining students' difficulties in learning the more advanced and counterintuitive concepts in these areas" (Vosniadou 2013, 1).

[10] Another distinct area where conceptual change is relevant pertains to linguistic changes over time, especially scrutinizing particular semantic patterns found in scientific English through lexical and grammatical analysis (Halliday 2004).

[11] There is an additional source of inspiration for some philosophers in the work of Feyerabend (Feyerabend 1965), although much less so for educational researchers and psychologists.

### 1.2.2 What Are Concepts and How Could They Change

What is a concept and how might it change? There is widespread agreement that concepts are fundamental to human cognition, if not the fundamental units themselves, but explanations of their nature diverge quickly. A variety of distinct theoretical positions can be recognized. One survey identified *definitionism* (concepts as full descriptions of necessary and sufficient conditions for something to fall under the concept), *imagism* (concepts as based on immediate impressions of perceptual information that can be secondarily associated), *prototype theory* (concepts as lists of salient properties permitting categorization but the representation does not have to contain all of the properties of things that fall under the concept), *exemplar theory* (concepts as constituted by particulars that exemplify referents of the concept without requiring a set of shared properties), *informational atomism* (concepts lack internal structure), and the *'theory theory'* (concepts as ongoing explanatory projects or theories, subject to continual review and revision through interaction with the world) (Prinz 2002). Other distinctions can be made that yield different taxonomies (see, e.g., Murphy 2002).

Despite dramatic differences in these accounts, a key thematic strand emphasizing representation and reference can be extracted, which fits with prior philosophical work on conceptual change. Motivation for this derives in part from an interest in how perceptual concepts are combined into more complex concepts and the experimental assessment of categorization phenomena in cognitive psychology (Solomon et al. 1999). Medin and Smith distinguish the taxonomic functions of concepts (categorization and conceptual combination) and expressing relations within a taxonomy (constructing and interrogating propositional representations) (Smith and Medin 1981, Chap. 2). This latter subcomponent of expressing relations, which pertains to drawing inferences between and among concepts, has received less attention (Solomon et al. 1999). A variety of philosophers have tried to understand concepts via a methodological commitment to their use or role in reasoning processes (e.g., Block 1998; Brandom 2000; Horwich 1998; Peacocke 1992), though they have been more interested in logical concepts than scientific ones. Overall, these two orientations—representation and reference versus use and reasoning role—capture two methodologies for analyzing basic concepts, whether perceptual or logical.

This distinction between two methodological approaches to concepts is helpful because there are key differences in the procedural commitments adopted by philosophers (Brandom 2000, 2–22), one of which is pertinent here: is concept use to be understood with a prior notion of conceptual content or should a notion of content be derived from attention to the linguistic use of concepts? A methodology that concentrates on how concepts are used in scientific inquiry and explanation allows one to proceed while being noncommittal about implications for conceptual content. Because scientific concepts are linguistically articulated, analyses beginning with conceptual use or behavior may be insightful on their own without resorting to assumptions regarding a theory of content. Additionally, there is not

a requirement to first analyze basic concepts on this outlook, where issues of the nature of content are difficult enough. Instead, one can range over the complex conceptual phenomena associated with scientific reasoning.

How do concepts change? Obviously, this will depend to some degree on how the question about what concepts are is answered. Part of any adequate account of conceptual change will be a detailed understanding of the underlying neural and psychological mechanisms. For example, some authors have argued that concepts are best understood as mental models, such as analogies, visualizations, or simulations, and their manipulation in relation to new empirical information accounts for patterns of conceptual change, similar to the way representational models in the sciences are adjusted in light of new data (Nersessian 2005, 2008, 2013). Therefore, studying model use in the sciences provides a route to understanding concept use (and therefore change) in human knowers. Others, starting with a view of concepts as representational structure or "frames," stress that some kinds of conceptual change, such as reclassification, are more epistemologically significant than other kinds, such as adding instances under a concept (Thagard 1992, 1999). Another approach links conceptual use to scientific goals and tracks change in light of adjustments in these goals over time, whether in response to theorizing or new data (Brigandt 2010). The present volume does not evaluate these types of accounts of how concepts change, but they should be kept in mind as patterns of conceptual change are dissected and analyzed in Evo-devo and other related biological disciplines throughout the contributions.

## 1.3 A Brief Exemplar: Evolutionary Novelty

The methodological orientation teased out in the previous section has several elements: (a) the heterogeneity of conceptual change; (b) a deemphasis on reference and scientific theory change, and (c) a strategic preference for conceptual use rather than the nature of concepts or conceptual content. These elements are not novel and can be found in other studies: "the problem of conceptual change in science [is about] ... the nature of the practices employed by human agents in creating, communicating, and replacing scientific representations" (Nersessian 2008, 5). This orientation fits within a broader methodology attentive to scientific practice prior to an analysis of the nature of scientific knowledge. One begins by dissecting a feature of scientific practice and then moves to its characterization. Thus, we start with how scientists use concepts and their patterns of change before analyzing how the concepts represent or refer and the possible psychological mechanisms of change.

A salient feature of conceptual practice in biology is that explanations of natural phenomena involve multiple concepts, jointly deployed. Scientific concepts rarely function in isolation: "Concepts, whatever they are, seem to have the property of being tightly connected to one another as they travel along trajectories of conceptual change" (Keil and Wilson 2000, 316; see also Brown 2007; Nersessian 2008). Often the ties that bind concepts together pertain to a target of explanation. The

boundaries of conceptual context are often dependent on particular explanatory problem agendas governing areas of scientific inquiry (Love 2008a; Brigandt and Love 2012a). Participating concepts can come from diverse disciplines, which means multidisciplinary fields are ripe locations for examining conceptual change. This combinatorial conceptual behavior occurs more visibly at the junction of different disciplines. Disciplinary syntheses, such as Evo-devo, are ideal places for analyzing this relational facet of conceptual use.

At the Dahlem conference, one significant concept was "evolutionary novelty." It came up across the groups as one of the explanatory questions manifested at the intersection of evolution and development. What kinds of changes can we observe in biological reasoning about evolutionary novelty? At least three facets of conceptual change over the past 30 years can be isolated:

1. The increasing importance of debates about the meaning of homology and phylogenetic reconstruction in systematics
2. The emergence of a developmental genetic paradigm and its marginalized epigenetic discontents
3. The retreat of constraints versus selection as the main axis of debate between Evo-devo proponents and other evolutionary biologists

Although these three facets cannot be plumbed in depth here, a brief characterization in the context of the 1982 Dahlem volume and contemporaraneous literature shows how focusing attention on relationships among concepts used with one particular explanatory target in view can illuminate substantial shifts in biological reasoning about evolution and development.

The origin of novelty was at the core of Britten and Davidson's theorizing about the genetic regulation of development: "One of the most difficult issues for evolutionary theory is the appearance of new organs or of complex systems which carry out novel functions" (Britten and Davidson 1971, 126; cf. Britten and Davidson 1969). Although the idea has a ring familiarity to Evo-devo biologists today, an explanation of the origin of evolutionary novelty in terms of changes in gene regulation was a bold conceptual proposal at the time. Its prominence in the Molecular Level Group Report and individual papers should be not be overlooked. This might happen precisely because of its comfortable fit with more contemporary approaches:

> If the genomic regulatory system is organized as we have proposed, then rearrangement events may indeed have the result of constructing novel regulative systems. ... gene regulatory programs leading to the development of novel structures of great usefulness could occasionally be produced, and if of lasting significance to the organism would be selectively preserved ... It seems possible that really new functions and structures could evolve in this way. (Britten and Davidson 1971, 126, 128)

> The origin of a novelty requires the evolution of a new gene regulatory network that integrates signals into a gene expression pattern unique to that organ. ...The objective of the study of evolutionary novelties is to understand the molecular changes that produced this organ-specific gene regulatory network. (Wagner and Lynch 2010, R50)

But this comparison is misleading because the primary locus of discussion surrounding the origin of novelty was in evolutionary morphology and paleontology, where a rich literature surrounding the problem agenda existed by the time of Dahlem (Love 2006a, 2007).

An interest in explaining evolutionary novelty was especially evident in functional morphology where the concept of a "key" innovation was prominent (Bock 1965; Frazzetta 1970, 1975; Bock 1959; Liem 1973; Wake 1982). The adjective "key" indicated that the new feature had provoked an adaptive radiation, evident in the fossil record or extant speciose clades (e.g., cichlid fishes). This meant that concepts juxtaposed with novelty in trying to understand its origins from this perspective included systematic, anatomical, and ecological concepts, rather than primarily molecular concepts.[12] Paleontological studies often linked the origin of novelty with macroevolution and the origin of higher taxonomic categories (e.g., the tetrapod limb and the origin of tetrapods), invoking epigenetics and heterochrony to explain allometric patterns in the fossil record that might underlie the evolution of novel traits (Gould 1966, 1977; Løvtrup 1974). The nexus of paleontology and morphology was central to reinvigorating interest in the role of development for understanding evolution (Alberch et al. 1979), and is displayed in the Evolution Level Group Report from Dahlem: "macroevolution refers to the problems of (a) the differential origin and extinction of taxa, and (b) the origin of new phenotypic features" (Bonner 1982, 281). Though yoked with a few molecular biologists by a common interest in the problem of explaining how novelty originates evolutionarily, the paleontologists and morphologists exhibited extremely different conceptual relationships in offering possible explanations.

As seen above (Sect. 1.1.1), explaining the origin of novelty was prominent in the Cellular Level Group Report and individual papers. It was the driving concern of Freeman's individual contribution: "one has to explain the formation of new organs, the appearance of new cell types, and in some cases, a basic change in body plan" (Bonner 1982, 156). His appeal to the "adultation of larvae" is of a very different character than what is seen with gene regulation explanations, though not necessarily incompatible with them (Freeman, Chap. 10, this volume).

> By creating different topological and temporal juxtapositions of various adult organs at different stages of development in a larva, one provides the conditions in which one has the potential for initiating significant new cellular or anatomical changes by virtue of developmental interactions between these parts. (Bonner 1982, 160)

The Group Report goes further to mark out innovation (novelty) as a distinct phenomenon, as well as recognizing its occurrence at different levels of organization: "What cellular changes are true innovations as opposed to modifications of existing types? How do new organs arise in evolution?" Although the Molecular

[12] A primarily molecular perspective is observable in Eric Davidson's individual paper from the 1982 Dahlem volume: "If we understood the genomic organization underlying these specific ontogenic regulatory patterns, we might be in an excellent position to construct a useful theory of evolutionary invention at the DNA level" (Bonner 1982, 65).

Level Report did not address levels of hierarchical organization, it did share the distinction between something new and something modified. Britten's individual paper keeps them apart explicitly: "Changes in the system for regulation of genetic activity are likely to be a rich source of variation and novelty" (Bonner 1982, 41). But this distinction was not about macromutations or hopeful monsters, as is sometimes assumed. Instead, the qualitative differences were about differential capacities to produce types of variation at distinct historical points. The Life Cycle Group Report evinces this perspective: "More distant taxa provide interesting qualitative differences in developmental patterns, which by the very fact that they are not qualitatively similar, provide evidence of evolutionary innovations" (Bonner 1982, 230). What needed explanation was how the qualitative differences in developmental pattern were produced.[13] This implied that the study of development was essential to explaining the origin of evolutionary novelty.

A crucial part of this discussion was a criticism of Ernst Mayr's definition: "The problem of the emergence of evolutionary novelties then consists in having to explain how a sufficient number of small gene mutations can be accumulated until the new structure has become sufficiently large to have selective value" (Mayr 1960, 357). The Evolution Level Group Report singled out the assumptions in this definition to problematize its acceptance in evolutionary biology.

> A comprehensive explanation for the origin of "evolutionary novelties" or "neomorphs," assumed by the New Synthesis to be extrapolatable from changes in gene frequencies, is still lacking. A commonly used explanation relies on "pre- or protoadaptation," a concept which presupposes that a neomorph was never a "new" structure, merely one that was previously selectively advantageous in a different functional context. . . .the "appearance" of a neomorph can be viewed as the point in time when selection first became concerned with a "new" (i.e., preexisting, but not additional) function . . . protoadaptation has often become merely a catchall explanation for the origin of neomorphs. . . . its inherent weakness is its reliance on a posteriori rationalizations of presumed selective advantages which cannot, by definition, be experimentally verified. It seems appropriate, therefore, to ask whether or not current explanations for evolutionary novelties are sufficient and whether alternatives might be available. (Bonner 1982, 282–3)

Notice how the criticism operates at multiple levels, challenging assumptions about what properties are explanatorily relevant (e.g., gene frequencies) and what methodological standards are appropriate ("a posteriori rationalizations" that cannot be verified). A characterization of the problem of novelty that involves the necessity of explaining it with developmental considerations was not only more empirically accurate but also more methodologically sound. Although definitions of novelty remain contentious, there is relative consensus that development is required to explain its origin evolutionarily (Brigandt and Love 2012a).[14]

[13] "Novelty always represents a qualitative departure from the ancestral condition, not merely a quantitative one" (Müller and Wagner 2003, 221).

[14] "In order to achieve a modification in adult form, evolution must modify the embryological processes responsible for that form. Therefore an understanding of evolution requires an understanding of development" (Amundson 2005).

### 1.3.1 Phylogenetic Reconstruction and Homology

Although much of this discussion sounds similar to how Evo-devo biologists have argued over the past decade for the origin of novelty as a distinct explanatory agenda (Wagner 2000), there is a curious omission in the Dahlem discussion of novelty: phylogeny. Dahlem participants (and others at the time) focused on the relevance of developmental mechanisms for evolutionary change. But the only phylogenetic tree provided is a cartoon representation of the three origins of metamerism in the Cellular Group Level Report (Fig. 1.2). This lack of a specific and rigorous phylogenetic context became more noticeable as a consequence of the cladistic revolution in systematics (Hull 1988) and the increasing use of molecular data to build phylogenetic trees (Hillis 1987), which became more routine by the mid-1990s (Hillis et al. 1996) and led to dramatic reconceptualizations of the metazoan tree of life (Aguinaldo et al. 1997). It was on the radar by the time a second edition of *Embryos, Genes, and Evolution* (Raff and Kaufman 1983) came out from Indiana University Press in 1990: "if one is studying evolution of features of any specific organisms, it becomes necessary to know genealogy to be able to assign the polarity of change." Without a standardized procedure for building phylogenies, or a consensus form of representation for depicting them, it is not

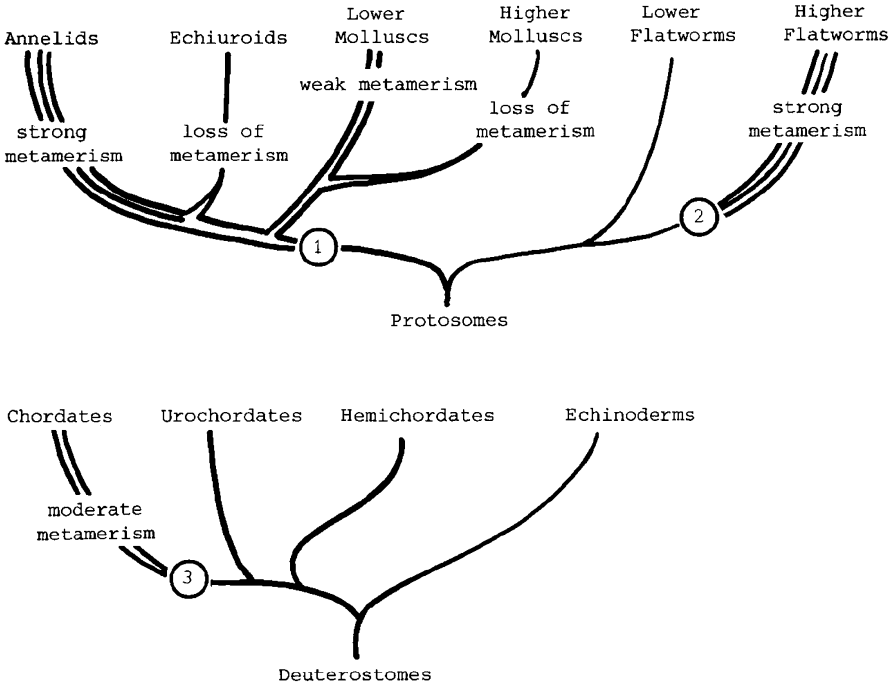


**Fig. 1.2** Three origins of metamerism (Bonner 1982, 97; Fig. 1). The only phylogenetic tree found in the 1982 Dahlem volume

surprising that Dahlem participants neglected to discuss them.[15] But it also was a consequence of the fact that the relationship between ontogeny and phylogeny was conceptualized differently in the early 1980s. Some systematists were debating the validity of the biogenetic law as a tool for reconstructing phylogeny (Fink 1982; Humphries 1988). Phylogenetic reconstruction had not yet been conceptualized as an independent methodological step in offering Evo-devo explanations of novelties and other evolutionary change.

In conjunction with developments in phylogenetic systematics and the use of molecular data, debates about the meaning of homology grew in intensity (Patterson 1988; Roth 1984, 1988; Wagner 1989; Hall 1994). Explicitly defining evolutionary novelty became more salient as definitions of homology were hotly debated. Conflicts about what counts as the same character (or character state) brought into focus what counts as a new character (or character state). Researchers achieved increasing precision in how the homology concept adopted different meanings within different explanatory projects (Brigandt 2003). At least five senses can be distinguished:

- Comparative biology: systematic and general descriptions of traits across species; comparisons that yield trait classifications
- Evolutionary Biology (transformational): describing and explaining the adaptive modification of character traits
- Phylogenetic Systematics (taxic): diagnostic feature of a taxon; homology = synapomorphy (shared, derived trait)
- Developmental (biological): describing and explaining the developmental mechanisms that produce the same character (including repeated instances within an organism—serial homology)
- Molecular Biology: sequence or domain similarity used to infer the function or effect of a new molecular entity

Within Evo-devo, it was the developmental conception that mattered: "The theoretical role of homology in [Evo-devo] is to account for the origin of similar structures within and between organisms and for structural identity in ontogeny and phylogeny" (Brigandt 2003, 14). This was in conflict with the explanatory project for homology found in traditional evolutionary biology that focused on the adaptive modification of traits. The result was a sharpening of differences in the explanatory goals of adaptationist and Evo-devo biologists (Amundson 1994).

A result of this discussion about homology was that the theoretical role of evolutionary novelty in Evo-devo became clarified: *to account for the origin of new structures within and between organisms and for structural discontinuity in ontogeny and phylogeny*. A definition was formulated in light of this clarification: "A morphological novelty is a structure that is neither homologous to any structure

[15] Dahlem participants did not miss the need for a phylogenetic framework completely: Freeman acknowledges it in his individual paper (see also, Freeman, Chap. 10, this volume) and David Wake claims that it operated implicitly as a background condition at the conference (personal communication).

in the ancestral species nor homonomous [serially homologus] to other structures of the same organism" (Müller and Wagner 1991, 243). Although not often remarked upon, the subtitle of this paper is telling: "restructuring the concept." This implied that the earlier connection to "key" innovation, which implicitly tied novelty to adaptive effects, was problematic and led to subsequent discussions of novelty in Evo-devo downplaying functional considerations.

The significance of phylogenetic reconstruction and homology for understanding conceptual change with respect to novelty cannot be underestimated. A fundamental shift was required in a related concept—homology—in order for the concept of novelty, and the explanatory project associated with it, to shift and solidify. Developmental or biological homology fit with the need for a developmental explanation of evolutionary change in characters, which meant a rejection of the transformational homology concept as appropriate for Evo-devo's explanatory agenda. This framed a restructured definition of novelty that pulled it away from functional and ecological considerations. All of this was stimulated by changes in systematics, where the cladistic revolution had transformed how phylogenetic trees were built. But a phylogenetic definition of novelty (autapomorphy), closely related to the phylogenetic definition of homology (synapomorphy) was insufficient for the task—explaining the discontinuity in ontogeny (within organisms) that governs the discontinuity in phylogeny (across organisms/species). A phylogenetic context is necessary for character polarization and establishing patterns of discontinuities in the developmental capacities available to produce variation, but insufficient for mechanistically explaining their origin and transformation in lineages (Calcott 2009). The conceptual change was incorporated as a methodological stricture—"reliable phylogenies are crucial" (Raff 1996); "the sequence transitions we hypothesize should be mapped onto independently constructed phylogenies" (Gerhart and Kirschner 1997; see also, Wagner et al. 2000).

### *1.3.2 Developmental Genetics and Epigenetic Discontent*

Another substantial conceptual transformation was the emergence of a developmental genetic paradigm for explaining novelty. In addition to standard bearers like Eric Davidson and his collaborators (Cameron et al. 1998; Peterson and Davidson 2000; Davidson and Erwin 2006), many researchers carved out a distinctive research program that accounted for the origin of novel structures in terms of regulatory changes in gene expression (Carroll 1995, 2001, 2005; Carroll et al. 2001; Gompel et al. 2005).

> The evolution of new morphological features is due predominantly to modifications of spatial patterns of gene expression. Changes in the expression of a particular gene can result from alterations either in its *cis*-regulatory sequences or in the deployment and function of the *trans*-acting transcription factors that control it, or both. Understanding the evolution of new morphological traits thus requires both the identification of genes that control trait formation and the elucidation of the *cis*- and *trans*-modifications that account for gene expression differences. (Gompel et al. 2005, 481)

This explanatory paradigm is an empirically justified successor (with modifications) to Eric Davidson's earlier theoretical views summarized at the 1981 Dahlem conference. The empirical justification arose from the discovery and elucidation of *Hox* genes in establishing segment identity, as well as similar phenomena for other regulatory gene families (Gerhart, Chap. 8, this volume), and fine-grained analyses of *cis*-regulation and transcription factor binding (e.g., Yuh and Davidson 1996; Yuh et al. 2001) that yielded complete networks for some early developmental events (Davidson et al. 2002). The deep evolutionary conservation of these regulatory gene families encouraged looking at them in connection with novelties in different lineages (Lee et al. 2003; Panganiban et al. 1997) and nurtured (at least for a time) a narrative of *master* control genes (Gehring 1998). The concept of a genetic toolkit coalesced to classify these conserved regulatory genes and account for why some lineages exhibited more evolvability than others (Kirschner and Gerhart 1998). This cashed in on a promissory note from Katz's individual paper in the 1982 Dahlem volume about how evolutionary change could be accommodated within developing systems by ontogenetic buffering mechanisms.[16] Members of the genetic toolkit (modules) could be reused, rewired, and recycled to produce a variety of evolutionary change and account for the origin of evolutionary novelty without disruption of the functional integrity of the organism (Kirschner and Gerhart 2005).

In more than one way, the developmental genetic paradigm for evolutionary novelty exhibited the "relentless surge of molecular biology's incorporation of evolution into its mechanistic world" (Schopf 1982). At the Dahlem conference, especially in the Cellular, Life-Cycle, and Evolution Group Discussions, the different levels of hierarchical organization found in organisms and populations, as well as how these interact via epigenetic processes, were paramount for cell biologists, mathematical modelers, paleontologists, and morphologists. Whether it was tissue interactions, self-organization, or physical rules, the molecular level was not adequate to account for the developmental properties that influenced the course of evolution, including the origin of new features. Subsequent to Dahlem, these currents of thought remained but became increasingly marginalized. The work of Stuart Kauffman on self-organization garnered tremendous attention but then faded from view (Kauffman 1993). Mathematical modelers who emphasized the significance of physical rules to understand the origin and evolution of traits like the tetrapod limb (e.g., Oster et al. 1988) gradually moved on from Evo-devo (Wang and Oster 1998), passed away tragically (Wake 1998), or were converted to the developmental genetic paradigm (Shubin et al. 1997). Other perspectives became more radicalized and, as a consequence, were ignored (e.g., Webster and Goodwin 1996). Although a few individuals have championed an approach that is

[16] "Were a single mutation to increase the size of a limb, the excess motor neurons already present in the spinal cord could immediately form larger functional neuromuscular populations. Such a limb mutation need not wait for other fortuitous concordant mutations in the nervous system. . . . Those particular mutations that can be absorbed into a well-integrated phenotype are the evolutionarily favorable mutations, and thus evolution will tend to be channelled in their direction" (Bonner 1982, 210).

based on the explanatory power of physical principles and epigenetic interactions continuously for several decades (Newman 1994; Newman and Müller 2000; Newman et al. 2006; Newman 2012), the approach has struggled to gain wide traction among Evo-devo biologists who do not share its pessimism about the explanatory power of the developmental genetic paradigm.[17]

The relational conceptual change flowing from the emergence of a developmental genetic paradigm involved a deemphasis or separation of "novelty" from concepts such as "epigenetic interaction," "self-organization," and "hierarchical levels." It also involved a foregrounding of relationships with concepts linked to gene regulation networks and associated molecular mechanisms (Gerhart, Chap. 8, this volume). These were major departures from the way that the origin of novelty was conceptualized as an explanatory project at the Dahlem conference. Although there was agreement that development is required to understand the origin of evolutionary novelty, the conceptualization of development as resulting primarily from developmental genetic interactions, without explicit attention to epigenetics and hierarchical levels within the organism, shows that the resolution of an internal debate at Dahlem (documented above, Sect. 1.1.2) produced significant alterations in relationships among concepts related to explaining the origin of novelty in evolution (but see Wagner, Chap. 15, this volume).

### *1.3.3 Constraints vs. Selection*

The central bone of contention in discussions at the Dahlem conference was the relationship between constraints and natural selection in explaining evolutionary change. Reactions to the conference and the 1982 Dahlem volume show this message came through loud and clear (Sect. 1.1.2). From the mid-1980s to the late 1990s, developmental constraints and natural selection, especially whether one was more or less important than the other, were the primary axis of debate and discussion for evolution and development. These discussions reached a high-water mark in the collaboratively authored paper on developmental constraints that came out of a subsequent conference focused on similar issues and included several Dahlem conferees (Maynard Smith et al. 1985). Debate raged on the topic (Moran 1994). Adaptationists argued that natural selection could overcome all manner of constraints given enough time and genetic variation (Reeve and Sherman 1993). Evo-devo biologists defended the explanatory significance of constraints in understanding the pattern and process of evolution (Gould 1989; Hall 1996; Raff 1987; Wake 1991).

[17] "The failure of the current theory of evolution to deal with the problem of origination is the major obstacle to a scientific understanding of organismal form . . .a synthetic, causal understanding of both the development and the evolution of morphology can be achieved only by relinquishing a gene-centered view of these processes" (Müller and Newman 2003).

One of the earliest philosophical analyses of Evo-devo seized on this controversy and used Alberch's individual paper from the Evolution Level Group as a key source (Amundson 1994). Evolutionary biologists understood constraint as 'constraint on adaptation,' whereas developmental researchers understood it as 'constraint on form.' Constraints on adaptation required assessments of optimality (non-optimal phenotypes are constrained); constraints on form focused on impossible morphologies due to development (independent of adaptive value). This divergence of meaning signified a deep difference in the explanatory endeavors of standard evolutionary biology and Evo-devo, similar to what we observed for homology (Sect. 1.3.1). It marked a fault line between: (a) functionally oriented biologists, who explained the process of evolutionary change from one adult phenotype to another via population processes, such as natural selection, which sorts genotypes, alters allele frequencies, and yields adaptive outcomes; and, (b) structurally oriented biologists, who explained the process of evolutionary change from one ontogeny to another via developmental processes, such as morphogenesis, which can be altered in different ways to generate novel morphologies (Amundson 2005).

The vigorous debate over constraints and selection of the 1980s and 1990s faded from view in the 2000s. What happened? One reason the debate faded was that the developmental genetic paradigm had crystallized and did not need to fight a battle with adaptationists to justify its explanatory project. Second, attempts were made to find a characterization of constraint that could include selection processes, thereby mitigating the supposed conflict between them.

> we can define constraint as a mechanism or process that limits or biases the evolutionary response of a character to external selection acting during the focal life stage. . . .This definition reconciles constraint and selection because its relativism accommodates the dichotomous view by suggesting that constraints are manifested in their effects of selection while allowing selection itself to serve as a constraint. (Schwenk and Wagner 2003, 58–9)

This type of account intentionally diffused the tension by dissolving the dichotomy. Third, Evo-devo biologists increasingly shifted their attention away from developmental constraints, with its negative valence on what is prevented from happening, to how development facilitates evolutionary change—evolvability (Brigandt, Chap. 14, this volume; Kirschner, Chap. 9, this volume). Although these are two sides of a coin, and both were visible in original Dahlem discussions, the investigations into properties of evolvability did not appear opposed to natural selection explanations and thus permitted a parting of the ways. Evo-devo biologists could work on their problems of interest, such as the origin of evolutionary novelty, in isolation from adaptationist evolutionary biologists. This situation remains with us today.

The fading of debates about constraints versus selection permitted the origin of evolutionary novelty to be pursued in relation to different concepts. Instead of being the result of "breaking" or "overcoming" constraints, evolutionary novelty could be explained by reference to concepts that picked out properties conferring evolvability, such as modularity or exploratory behavior. Once set in a developmental genetic paradigm independent of standard evolutionary biology, the agenda

of explaining evolutionary novelty operated in a different context from what was observed in the 1982 Dahlem volume. Conceptual change with respect to concepts in the vicinity of "evolutionary novelty" signal important theoretical and methodological transformations that have occurred in the past 30 years. The problem of explaining the origin of novelty was reconfigured post-Dahlem such that even those who disagreed about the developmental genetic paradigm were in agreement that natural selection was not a candidate explanation.

> The origination of morphological structures, body plans, and forms should be regarded as a problem distinct from that of the variation and diversification of such entities (Müller and Newman 2003, preface).
>
> The notions of evolutionary innovation and particularly of evolutionary novelty make sense only if they support a distinct research program (Müller and Wagner 2003, 226).
>
> What this means at root is that traditional microevolutionary theory is not useable for treatment of the molecular mechanisms by which evolution of the animal body plan has occurred (Davidson 2006, 192).

When combined with developments in phylogenetic systematics and associated discussions about homology, conceptual change with respect to evolutionary novelty reorganized an entire area of biological investigation, though not with respect to an overarching scientific theory. This reorganization involved major shifts in how multiple concepts from diverse life science disciplines are brought together to explain natural phenomena and helps account for how Evo-devo carved out a distinct disciplinary identity by the early 2000s (Raff 2000). These types of changing relations among concepts are not unique to Evo-devo and can be found in many other sciences. Instead of reference and incommensurability in relation to competing scientific theories, the core issue is divergent explanatory goals of researchers attentive to different problem agendas and their ability to extract different meanings for the same concept (e.g., homology). The consequences for ongoing biological research are correspondingly different. They foreground the need to distinguish scientific problems in order to circumvent interpretations of explanations as competing rather than complementary. Philosophical work that assists in clarifying and explicating these problem agendas achieves this goal and helps delineate the roles played by different disciplinary contributions in multidisciplinary research endeavors (Love 2008b).

## 1.4 Patterns of Conceptual Change: Emerging Themes and Generalizations

Some of the patterns identified in the previous section are reinforced and elaborated in the contributions to this volume. For example, it is clear that explicit phylogenetic thinking was not present at the 1981 Dahlem conference in the way that became distinctive in subsequent Evo-devo (Amundson, Preface, this volume;

Winther, Chap. 21, this volume). Additionally, the rhetorical edge of Evo-devo challenging all of evolutionary biology has dulled (Amundson, Preface, this volume), though it has not disappeared (Kirschner, Chap. 9, this volume). Some patterns of exclusion evident at the original Dahlem conference persist: there continues to be a marginalization of botany and plant evolution (Niklas, Chap. 2, this volume). This section is intended only to highlight emerging themes and generalizations from the individual chapters where the evidence and argumentation for them is found.

### *1.4.1 Adaptation, Allometry, Heterochrony, and Homoplasy*

One of the striking conceptual changes to have occurred since the 1981 Dahlem conference is the downgrading of heterochrony as a preferred explanation for developmental changes relevant to evolution (Hanken, Chap. 4, this volume). This was expressly called for in the 1990s (Raff 1996, Chap. 10), but took effect by the 2000s. Hanken reminds us that heterochrony has a long and venerable history before Gould's 1977 touchstone treatment (e.g., de Beer 1930, 1941), and that it continues to be critical in studies at the intersection of evolution and development, both paleontological and neontological. But heterochrony is not enough. The developmental genetic paradigm has elevated the significance of changes in the spatial location of gene expression (heterotopy), as well as changes in the level of expression (Arthur, Chap. 16, this volume). Expanding the repertoire for modes of developmental change that can influence evolutionary paths increases our capacity to explain diverse patterns in the history of life and test these possibilities experimentally.

Closely associated with heterochrony were allometric analyses that attempted to connect shifts in the timing of different developmental events with correlated shape changes exhibited in the morphology of different lineages. Notably, Niklas (Chap. 2, this volume) makes considerable headway in reviewing the current status of allometric analyses by concentrating on plants rather than animals. This is a good example of how the bias in representation of researchers at Dahlem, and subsequently in Evo-devo, has somewhat retarded progress on this front. Niklas demonstrates how advances in the modeling of allometric relationships between metabolic rate and body mass have yielded descriptive tools that many Dahlem participants desired (although theoretical explanations are still up for grabs), despite the fact that many current Evo-devo proponents are not as interested in using them. The case is different for network theory because of the centrality of gene network regulation in the developmental genetic paradigm (Davidson et al. 2002).

As noted (Sect. 1.3.2), physical approaches that were predominant at Dahlem have had a marginal status in understanding the origin of evolutionary novelty and other phenomena of interest to Evo-devo researchers (see Newman, Chap. 19, this volume). Another reason why physical considerations are relevant is because of performance requirements on embryos and larvae (Strathmann, Chap. 3, this

volume). The distancing from functional considerations observed in the case of how evolutionary novelty is defined (Sect. 1.3.1) was only one instance of how a structural viewpoint came to dominate the discourse of Evo-devo (Amundson 2005). What Strathmann highlights though is that function is not the same as adaptation; attending to performance requirements is not equivalent to measuring selection coefficients or building optimality models. Developing embryos, and especially larvae, have performance requirements that were recognized in pre-Dahlem studies of the ecology of marine invertebrates, though in a way orthogonal to the evolutionary biology associated with the Modern Synthesis. Part of the reason for this was institutional; those trained in approaches asking "why" embryos and larvae exhibit specific properties came from marine labs (e.g., Friday Harbor or Woods Hole), rather than university labs where questions of "how" predominated. These approaches were not well represented at Dahlem but have subsequently grown, both under the influence of new molecular genetic methods and novel paleontological tools. The questions of interest are different from many standard Evo-devo problems, such as the origin of evolutionary novelty, and include: why are there embryos at all? How are cell cycle duration, asynchronous cleavage, and cell fate determination related to risk during development (embryonic or larval)? How are marine invertebrate larval forms related to physical constraints, such as fluid flow? In all these questions, there is a worry about getting lost in the particularities of individual lineages. But the scope of generalizations must be determined by the empirical details and evolution doesn't necessarily favor universal explanatory principles—funding might. Strathmann ends on a cautionary note about the fact that certain kinds of research may be favored for financial support because they seemingly conform to expectations about what we should discover in nature.

Another major conceptual change that flows from the cladistic revolution is the increased salience of similarity in evolution—homoplasy (D. Wake, Chap. 5, this volume). Instead of the basic contrast between homology due to common descent and analogy due to convergent evolution, patterns of similarity were discovered to result from shared developmental resources or processes ("parallelism"), most famously exemplified in the evolution of eyes (Arendt 2003). David Wake's multi-decade research program on lungless salamanders has made the diverse origins of homoplasy a key target of explanation (Wake 2009). How does similarity (morphological or otherwise) evolve again and again? This problem is intimately related to determinations of sameness due to common descent in evolution—homology. Just as developments in phylogenetics provoked discussion and reformulations of homology, they also provoked discussion and reformulations of homoplasy (Hall 2003; Sanderson and Hufford 1996). An increased appreciation for shared patterns of development underlying homoplasy in salamander lineages encouraged Wake to challenge its common attribution to the action of natural selection (Wake 1991). This reinforced one horn of the Dahlem debate about the asymmetric importance of molecular level explanations. The diversity of homoplasy encountered empirically by Wake and his colleagues meant that a hierarchical perspective on organisms was essential to dissecting their evolution (M. Wake,

Chap. 18, this volume). This helps account for why David Wake is favorable to but not enthralled with the developmental genetic paradigm. A pivotal conceptual change since Dahlem is the divergence among researchers in whether or not a hierarchical perspective is essential for evolutionary theory, inclusive of Evo-devo research. For those who think it is, the integration of approaches that deal with these different spatiotemporal scales is a methodological prerequisite: "New, robust phylogenetic hypotheses and molecular, genomic, and developmental techniques enable integrated exploration of the mechanisms by which similarity arises" (Wake et al. 2011, 1032; see also, Griesemer, Chap. 13, this volume).

### *1.4.2 Phenotypic Plasticity, Developmental Variation, and Experimental Biology*

Phenotypic plasticity is at the core of the individual paper by Stephen Stearns in the 1982 Dahlem volume. His revisiting of the concept to explore changes that have happened since exposes a growing gap between life history theory and Evo-devo (Stearns, Chap. 6, this volume). Through a lively narrative of his Dahlem-propelled research in the 1980s, Stearns reminds us of the theoretical insight that reaction norms tend toward one of two optima for size and age at maturity depending on the growth environment: mature large and young for rapid growth, mature small and old for slow growth. These and cognate developments in life history theory yielded powerful generalizations about what evolution would do in different circumstances. But these generalizations were independent of how development occurred (e.g., determinate versus indeterminate growth). This accounts for why those invested in a developmental genetic paradigm for explaining the origin of novelty and other evolutionary changes would have seen life history theory as increasingly irrelevant. Stearns discerns this disconnect explicitly in the fact that macroevolutionary questions about lineage specific effects of history and ontogeny remain poorly integrated with these generalizations from life history theory. In this instance, conceptual change involved a growing apart of approaches that were put into contact during Dahlem but never found appropriate bridges to link their endeavors despite both being at the intersection of evolution and development. Some of this can be attributed to life history theory focusing on plastic, continuous traits, such as growth, and Evo-devo concentrating on modular traits that are distinguishable as homologous or novel, but a possibility of rapprochement exists in growing attention to the mechanistic basis of the tradeoffs that life history theory has analyzed for the past several decades.

Plasticity also has been an experimental target for those interested in its developmental-physiological aspects (Nijhout, Chap. 7, this volume). This strand of research is not only distinct from abstract evolutionary theorizing but also from the developmental genetic paradigm, as Nijhout makes explicit: "I do not work at the level of the gene . . . because, from my perspective, most of the really interesting

problems in biology actually play out at higher levels." This physiological perspective was not as visible at Dahlem and did not play a role in the deliberation of its participants. Larval forms were in view but the timing of onset for metamorphosis or seasonal polyphenisms were not. The predominant use of model organisms within the developmental genetic paradigm (e.g., *Drosophila*) tends to downplay the existence of phenotypic plasticity due to variation in environmental physiological variables (Love 2010a). The control of polyphenisms (e.g., ant castes) due to developmental timing and amount of signals like juvenile hormone has been dissected causally, whereas the control of body size and associated allometric effects have remained more elusive although they involve similar hormone-mediated mechanisms. Nijhout's perspective shows how changes in the conceptual relationships around phenotypic plasticity in a developmental-physiological research program differ from those around phenotypic plasticity in a life history theory framework. Instead of tradeoffs, maturity, and mortality, robustness and its underlying mechanisms become salient. The resulting conceptualization of how development has an impact on evolution also differs. Hypotheses such as genetic accommodation postulate that changes in environmental variables can lead to the expression of a novel trait due to phenotypic plasticity, which is subsequently locked in genetically apart from the original environmental trigger (West-Eberhard 2003). Although these hypotheses have historical antecedents (e.g., the Baldwin effect), they were not in view at Dahlem and only later became the subject of Evo-devo research (Kirschner, Chap. 9, this volume).

It is sometimes difficult to conceive how much we have learned since the 1981 Dahlem conference about mechanisms that underlie the developmental production of variation. One of the original rapporteurs from the Cellular Level Group summarizes many of these discoveries and the substantial adjustments in biological thinking with which they are associated (Gerhart, Chap. 8, this volume). Here we see a potential counterexample to some approaches to conceptual change that minimize the addition of instances to a concept (e.g., Thagard 1992). Gerhart's detailing of the Bmp and Wnt signaling pathways demonstrates how these particular instances are responsible for shifts in our thinking that are not necessarily true of all signaling pathways. This is because these particular pathways are involved in establishing multiple foundational features during development in all multicellular animals, such as the dorsal-ventral orientation of the body (de Robertis and Sasai 1996). These results are of a piece with the already noted discoveries of *Hox* gene conservation in processes of segmentation identity across phylogenetically divergent clades. The entire conceptual orientation of developmental biology has been transformed: "For some researchers, development can now be reduced to the interplay of cell-cell signaling and transcriptional regulation; almost everything about this interplay has been learned since 1981" (Gerhart, Chap. 8, this volume). One can quickly get lost in the molecular details of any one of these pathways, but it is this level of detail and the surgical experimental interventions from which it was derived—in conjunction with phylogenetic conservation—that constitute their explanatory power. Changes in the values of variables for the components and interactions in these signaling pathways can account for evolutionary changes in

various lineages. Instead of an abstract conception of signaling pathway, conceptual change is occurring at a more concrete level, such as Bmp-mediated dorsal-ventral patterning. This specificity is relevant to longstanding evolutionary questions, including why vertebrates are dorsoventrally inverted in comparison with bilaterian invertebrates (Gerhart 2000).

The cornucopia of molecular genetic findings with respect to development has spurred conceptual origination. John Gerhart and Marc Kirschner introduced the concept of "facilitated variation" as a way to capture how these molecular mechanisms make a distinctive evolutionary contribution (Gerhart and Kirschner 2007; Kirschner, Chap. 9, this volume). The basic idea is that conserved molecular processes facilitate viable variation for organisms during development. Facilitated variation appears to contradict the tenet of "random variation," which is a core part of standard population genetics and evolutionary theory. Instead of phenotypic variation being "random" in the sense of unrelated to fitness benefit, developmental mechanisms tilt the balance towards phenotypic variation that is viable. Additionally, phenotypic variation is not isotropic in the sense of being equally likely to occur in any direction (where direction is about dimensions of phenotype space, not fitness benefit). The contradiction is only apparent because genetic variation can be random with respect to fitness benefit while phenotypic variation is facilitated by conserved mechanisms of development to yield viable organisms. Fitness differences relevant to the operation of natural selection exist within a population containing these viable organisms. But, in the spirit of Dahlem, ontogenetic processes influence the direction and character of evolutionary change because the phenotypic variation available for selection to act upon is biased by development. The path from genotype to phenotype has privileged trajectories. Yet the arrival of this concept coincided with constraints moving into the background and evolvability moving into the foreground (Brigandt, Chap. 14, this volume). Kirschner documents the numerous conceptual influences that led to "facilitated variation" and we are again reminded of how concepts travel in groups, from "evolvability" and "plasticity" to "weak linkage" and "exploratory behavior." A major result of this analysis is that the conceptual clustering found in Evo-devo research is distinct from the conceptual clustering found in many areas of evolutionary investigation. The reason why is that the architecture of problems in evolutionary biology is more diverse and variegated than implied by common appeals to "evolutionary theory" and these problems govern the patterns of conceptual covariation exhibited in attempting to explain different evolutionary phenomena (Love 2010b, 2013b).

### *1.4.3 Models, Larvae, Phyla, and Paleontology*

Anyone who has read within Evo-devo literature will have encountered the concept of a "body plan" (e.g., Hall 1996). Its relationship to traditional taxonomic categories, such as phylum, is complicated because an implicit notion of body plan was

often used to define phyla and frame evolutionary problems (e.g., the origins of phyla). Freeman (Chap. 10, this volume) wades into this nexus of concepts as an original Dahlem conference participant. Prior to Dahlem, embryos of different stages (and fossils) were used to reconstruct phylogenetic relationships and the possible changes leading to the origin of body plans in different metazoan lineages. The reconstructive efforts were dependent on assumptions about the stability of these different embryonic stages through evolutionary time. Variability exhibited by embryos put pressure on this methodology, but also led researchers to identify places where the stability seemed especially poignant. The concept introduced to label these stable developmental stages in English by Klaus Sander (also a 1981 Dahlem conferee) was the "phylotypic stage." Sander was building on the work of Seidel, a German zoologist (Freeman, Chap. 10, this volume), but something was lost when subsequent researchers concentrated on understanding why the phylotypic stage manifested: they neglected that Seidel was attempting to show how changes in early development are relevant to evolutionary change. Freeman documents changing conceptions of phyla, phylogeny, and body plans over the past 30 years and makes important connections between these ideas and the developmental genetic paradigm that coalesced in the interim, which resonates with Seidel's original motivation for looking at variability in early development. Freeman reinforces the significance of phylogenetic reconstruction being an independent methodological step (Sect. 1.3.1), and he shows how concepts central to Evo-devo were taken up in ways that differed from their original deployment (e.g., focusing on explaining the stability of the phylotypic stage). This is ironic given that their original deployment was to the end of understanding how changes in early development underlie evolutionary innovations in animal lineages.

The role of larval biology was evident in Freeman's individual paper and the Life Cycle Level Group discussions. A member of that group, Rudy Raff, recounts how his own research increasingly focused on the developmental mechanisms underlying the evolution of larval forms. Raff was aware firsthand of the dramatic molecular genetic discoveries in developmental biology because they occurred in the laboratory of his colleague and co-author Thom Kaufman (Kaufman and Wakimoto, individual paper; Scott and Weiner 1984; Raff and Kaufman 1983), and he was intimately involved in bringing molecular data to the phylogenetic reconstruction of metazoans (Field et al. 1988; Aguinaldo et al. 1997). *The Shape of Life* (Raff 1996) synthesized disparate Evo-devo research and provided a conceptual framework that included deemphasizing heterochrony and emphasizing modularity. The bulk of his experimental work in Evo-devo has focused on two closely related species of sea urchins from the genus *Heliocidaris* that exhibit different modes of development and larval forms. Indirect developing sea urchins with a pluteus larva were closely studied in the developmental genetic paradigm by Eric's Davidson's lab (with the purple urchin, *Strongylocentrotus purpuratus*). Using this research for leverage (e.g., selecting features to scrutinize, such as cell lineages, or gene expression patterns to compare), Raff and colleagues spent several decades investigating evolutionary changes in development and the way development affects evolutionary change through a comparison of *H. tuberculata*

(an indirect developer) and *H. erythrogramma* (a direct developer). In contrast to expectations, they uncovered radical and rapid evolutionary changes early in ontogeny with respect to canonical events such as axis specification. The details of these developmental changes and the directionality they imparted to evolutionary trajectories had broader implications for the origin and evolution of larval forms (Raff 2008). Conceptual change is evident in the multidisciplinary research program that characterized this work. Population genetics, descriptive embryology, experimental embryology (including hybridization studies), developmental genetics, comparative biology (especially the concept of homology), systematics, and paleontology all played a role as an integrated package in both deemphasizing heterochrony (while still using it) and making modularity salient, as well as yielding novel conceptualizations of old evolutionary problems like the origin of larval forms prior to the Cambrian period.

Paleontology has long been in the middle of the intersection between evolution and development (Love 2007). But since Dahlem this presence has taken on new dimensions (de Ricqlès, this volume). de Ricqlès demonstrates how international context is relevant for conceptual change. Although clearly aware of the Modern Synthesis and its associated population genetic framework, their supposed stranglehold on evolutionary thinking was not present in the French context like it was in many Anglophone environs. This meant a rapid assimilation of cladistics (which de Ricqlès debated with Gould at Dahlem) and a methodological pluralism when studying evolutionary phenomena. The outcome was a novel combination of developmental histology and vertebrate paleontology that garnered insights into the evolution of bone structure from both biomechanics and genetics alongside the effects of adaptation and phylogenetic history. Intriguingly, de Ricqlès interprets a shift in his own thinking subsequent to Dahlem, as this multidisciplinary research program matured, from a deterministic to a probabilistic outlook on the evolutionary process. This conceptual change occurred at the broad level of philosophical assumptions about the nature of evolution.

Philosopher James Griesemer (Chap. 13, this volume) offers a penetrating interpretation of David Wake's multidisciplinary investigative project devoted to understanding the development and evolution of homoplasy as "model taxon" research. Instead of using a single species as a model (as is common in much developmental biology), Wake and colleagues exploited an entire clade of salamanders. What this provided was a platform for the integration of different methodologies, whether phylogeny, functional morphology, development, or ecology, at different hierarchical levels of organization (molecular, anatomical, organismal, populational; see M. Wake, Chap. 18, this volume). This platform served as the point of departure for the sustained study of evolutionary problems like homoplasy and the developmental details necessary to understand it. Grisemer clarifies how this came together progressively in different periods of Wake's career, sometimes as a function of new lab personnel, sometimes as a function of new techniques becoming available. The model taxon acts as an anvil on which conceptual change is forged out of the applications of diverse tools to a package of problems and phenomena. The results can be selectively exported to illuminate different packages

in other lineages without presuming to generalize all of the findings within the model taxon platform to other species. It is precisely the multidisciplinary nature of investigation which this platform structure nurtures that underlies the productive conceptual changes that resulted, including but not limited to a more precise distinction between parallelism and convergence (D. Wake, Chap. 5, this volume).

### *1.4.4 Constraint and Evolvability*

If there was a watchword from Dahlem it was constraint. But the fading of discussion and debate about constraints was not the disappearance of a core concern but rather its transformation into an active research program about evolvability (Brigandt 2007, Chap. 14, this volume; see also, Sect. 1.3.3). This transformation occurred because of changes in the role the concept "constraint" played in biological discourse. As observers made clear at the time of Dahlem, a key part of the debate revolved around the adequacy of selection-based explanatory approaches in evolutionary biology. Both advocates of constraints and defenders of the standard evolutionary framework saw the concept in this light. Constraint also played a role as a target of developmental explanation in biological research (Amundson 1994). What accounts for the bounded patterns of morphology or the lack of particular characters or character states in the history of life (Alberch, individual paper)? Is it functional integration of suites of traits, or physical rules of morphogenesis, threshold mechanisms, or side effects (spandrels)? In this role, the opposition to natural selection was muted since these answers did not directly compete with selection-based explanations. Their aim is different, such as accounting for how novelties originated at particular phylogenetic junctures due to developmental thresholds. Brigandt (Chap. 14, this volume) argues that the rhetorical shift from "constraint" to "evolvability" is related to how evolvability directs attention to the investigation of properties that contribute to its manifestation. This detaches the research from opposition to selection-based accounts. The goal is to detail the properties that confer evolvability on lineages (of which different forms of constraint are a part). Conceptual change in the role of the constraint concept accounts for why it faded from view with the ascendancy of evolvability and co-travels with a reduction in rancorous debate about the adequacy of selection explanations.

Günter Wagner—present at the 1981 Dahlem conference—is one of the architects of this transition from constraint to evolvability, as well contributing to the restructuring of concepts ("novelty") and reinterpretation of others ("homology"). As remarked in the preface (Amundson, Preface, this volume), Wagner's recent work on homology shows the fruits of sustained conceptual change in relation to these various concepts (e.g., Wagner 2007, Chap. 15, this volume). The crucible of this change is the recognition that the organism is a "fact of nature." In order to understand how development has an impact on evolutionary change, one has to understand how development has an impact on characters that can vary. This implies that understanding the capacity of a lineage to evolve with respect to

particular characters will only be possible when the nature of organismal characters and their generation during ontogeny is better understood. As a consequence, the concept of the "genotype-phenotype map" has played a central role in the work of Wagner and colleagues (e.g., Wagner and Zhang 2011). Theoretical explorations (still ongoing) have probed what kinds of mapping relations encourage or prevent changes from happening, and thereby have an impact on evolvability. But what is it for a character to exhibit evolvability? This question requires understanding what undergirds the identity of a unit that can be stable and yet evolve in different lineages (i.e., what underlies homology). The new concept emerging from the nexus of conceptual change in homology, novelty, and molecular developmental genetics is the "character identity network." A key finding in many areas of Evo-devo research is the ability of homologous characters to vary in composition and developmental production (True and Haag 2001; Wray 1999). Sameness or character identity is explained with reference to "core" gene regulatory networks that permit substantive variation, as well as reiteration in other areas of the organism (hence, serial homology). Again, we see conceptual adjustments resulting from the juxtaposition of different research strategies, especially when not confined to only one level of organization. Interacting across the fourfold structure of the original Dahlem discussion groups is a recipe for fruitful conceptual change.

Wallace Arthur displays a similar cross-level productivity of conceptual change with his focus on the integrative role of "developmental repatterning" (Arthur, Chap. 16, this volume). Arthur walks us through major steps in the development of his own thinking to arrive at this point. The first was a conceptual innovation via analogy and the fusion of existing concepts. Using the idea of "cell lineage" in combination with a tree representation to capture causal links during development, Arthur formulated the notion of a "morphogenetic tree," which was a canvas upon which to conceptualize different effects that changes in development could have on evolution. Exploring these possibilities brought additional conceptual layers in terms of developmental "bias" and "drive" through a shift in thinking about "selective constraints" (biases in the survival probability of variants) to "developmental constraints" (biases in the ontogenetic production of variants). This percolated out of studies on centipede segment development and evolution. The third phase of his conceptual development involved formulating more abstract categories to frame Evo-devo research. This required some failed attempts at wordsmithing but found a point of equilibrium in developmental repatterning to capture the diversity of evolutionary phenomena depicted by other concepts (e.g., novelty, evolvability), while maintaining a link to the developmental phenomenon of patterning. Developmental repatterning encompassed changes in time, space, amount, or type (heterochrony, heterotopy, heterometry, heterotypy). This shows how an abstract concept can help to solidify more concrete subcategories that compose it. As envisaged expectantly at Dahlem, the result of this conceptual craftsmanship is to further biological inquiry and Arthur closes by showing how this is accomplished with respect to questions about the scale, size, and direction of evolutionary changes due to developmental repatterning.

In a related move of increased abstraction, Wimsatt (Chap. 17, this volume) delineates how the concept of "generative entrenchment," which encompasses constraint, can operate as a theoretical tool in ongoing inquiry. The degree of generative entrenchment is a measure on how many elements are causally downstream of a particular element in a developmental pathway. More causal dependencies will mean a stronger pressure to conserve that element in the pathway. An element is conserved (entrenched) because it is crucial for the production of subsequent outcomes (generative). The origins of this abstract concept are intertwined with various Dahlem participants (e.g., Kauffman and Gould), as well as contributors to this volume (e.g., Arthur and Newman), so there is good reason for it to resonate with Dahlem discussions about "constraints" and allied concepts (e.g., the "phylotypic stage"). But three influences show how relations between concepts make a difference in how conceptual change occurs. First, the concept of "pleiotropy" from genetics influenced the meaning of generative entrenchment because it exemplified the right kind of causal dependencies. Second, the concept of "burden" from the work of Rupert Riedl illustrated generative entrenchment in anatomical terms (Riedl 1978). Third, and most important, Wimsatt was influenced by Herbert Simon's hierarchical model for the evolution of complex systems (Simon 1969). All of these pushed Wimsatt toward an abstraction that could capture the shared, underlying causal structure with which they were associated. Different assumptions about generative entrenchment were probed with simulations in population genetic models to explore ranges of interesting parameters, the robustness of specific patterns, and identify unanticipated outcomes. And this abstraction has facilitated the application of these ideas far beyond the confines of Evo-devo into the domains of cultural evolution and human cognition (Caporael et al. 2013). Conceptual change and development is demonstrably a function of the conceptual context in which ideas are nurtured and mature.

### *1.4.5 Hierarchies and Interdisciplinarity*

The themes of hierarchy and interdisciplinarity have been prevalent in many, if not most, of the contributions and echo the attitudes of those present at Dahlem in 1981. Marvalee Wake (Chap. 18, this volume) takes up the theme of hierarchies and integration directly, arguing that Evo-devo is constituted by these in its pursuit of explaining the development and evolution of organismal complexity. This is both possible and a problem because Evo-devo is interdisciplinary. For example, Evo-devo is not antithetical to reductionist approaches, such as are seen in a developmental genetic paradigm, but it must find ways to weave these results together with those from approaches at other levels of organization in order to get at the many dimensions of biological complexity. Importantly, hierarchies must be conceived in many dimensions, including both structural and functional relations as well as developmental and evolutionary time scales (cf. Love 2006a). The integration of these diverse hierarchies investigated by different disciplines comes from the concept of "organism." This is the template that guides the diverse disciplinary

contributions into an explanatory alignment that is accurately described as *integrative*. But "integrative biology" is often used hastily to label endeavors that are simply interdisciplinary: "synthesis talk is cheap; really accomplishing integration between different research traditions. . .is not easy" (Laubichler 2009, 19). Genuine integration is difficult but one acid test is securing new insights into the complexity of development and evolution. And this has occurred in Evo-devo because it has been able "to unify diverse approaches at several hierarchical levels to examine the nature of evolutionary change" (M. Wake, Chap. 18, this volume).

Sets of diverse approaches that have resisted unification in biology revolve around physical principles (Newman, Chap. 19, this volume). Many Dahlem participants were intrigued by the explanatory potential of physical principles for morphogenesis and pattern formation, but these were relegated to the background with the ascendancy of a developmental genetic paradigm (Sect. 1.3.2). Newman isolates the resistance in theoretical commitments of the Modern Synthesis that are derived from nineteenth century physical science perspectives (e.g., Newtonianism). This resistance has encountered severe obstacles in light of new findings in condensed matter physics. Newman recounts conceptual developments in physical science related to ontogeny, such as Turing reaction-diffusion mechanisms, which are applicable to non-living chemical systems as well. Newman's own work has been instrumental in formulating blends of physical concepts with those from genetics to explain core problems in Evo-devo, such as the origin of body plans (Newman et al. 2006). One of the most significant is the idea of "dynamic patterning modules," which combines the notion of modularity with genetic and physical components (Newman and Bhat 2008). For example, cell-cell adhesion is a dynamic patterning module that can be deployed within an organism modularly by expressing genes for cell-cell adhesion proteins at particular locations or times upon which physical principles operate to yield distinctive shapes and structures. The building blocks of development that foster evolutionary change are physico-genetic hybrids. Conceptual change at the intersection of physics and Evo-devo displays the fecundity of ongoing adjustments in the relationships among concepts, even if the physical approach to Evo-devo remains a minority position (Sect. 1.3.2).

That Evo-devo is interdisciplinary is undisputed. How Evo-devo is interdisciplinary is a harder to specify. Marvalee Wake (Chap. 18, this volume) tackled it epistemologically by arguing that interdisciplinarity is a necessary condition for integrating across hierarchical levels. Gerson (Chap. 20, this volume) casts new light on this interdisciplinarity using the outlook of sociology. He offers the notion of a "juncture" to capture the overlapping intersections among diverse specialities that comprise Evo-devo. Two intersections were critical for Evo-devo: (1) the intersection of paleontology, systematics, and morphology that led to a reorientation around the need for developmental considerations to address macroevolution; and, (2) the intersection of molecular genetics and cell biology that revolutionized developmental biology. To understand how these overlapping intersections generated the Evo-devo juncture, Gerson details the organization of research work in terms of "research systems" that have a focus, mode and style of research, and preferred problem structure and strategy (among other features). A juncture does not

automatically beget integration as differences in these features of research systems exist within Evo-devo and account for ongoing difficulties in bringing different conceptual resources to bear on evolutionary problems. Additionally, there are institutional constraints that prevent integration because aspects of research style have become bureaucratically sclerotized in conjunction with the rationalization of scientific work in specialties. Thus, alliances represented in constellations of concepts discussed throughout the other contributions may be temporary and unstable for reasons beyond epistemological criteria of adequacy. Evo-devo exhibits a diversity of partial integrations, many of which are illuminating, but some of the divergence in conceptual development already identified may be due in part to sociological factors of the organization of biology's intellectual work.

Winther (Chap. 21, this volume) concentrates on three styles and three paradigms that overlap with varying success in Evo-devo. The styles—mathematical modeling, mechanism, and history—each exhibit distinctive prerequisites and procedures for how to do research. Mathematical modeling involves five sequential activities of building, manipulating, explaining, objectifying, and probing the assumptions and inputs to a model. Mechanism involves decomposition, physicochemical description, experimental manipulation, and the stable export of results to new contexts. History involves the narrative placement of parts or objects in a justified causal structure such as a phylogeny. The paradigms—adaptationism, structuralism, and cladism—establish broad interpretive constraints on research by having standardized exemplars, a general framework, and sociological community. Adaptationism emphasizes the fit between organism and environment; structuralism is oriented to the development and organization of part-types; cladism stresses the need for phylogenies to reflect the evolutionary process. All three styles are found in all three paradigms and the location of overlap among them is described as a "trading zone" where certain exigencies encourage communication and lubricate productive interactions across diverse cultures that instantiate different clusters of styles and paradigms. This "richly overlapping domain" is in some ways an epistemological analogue to Gerson's sociological juncture, though in both cases there are elements of each in the mix. Winther acutely demonstrates how some locations in Evo-devo's trading zone have become more integrated than others (e.g., structuralism and cladism). Trading zones exhibit both competition and collaboration in complex relational arrays, which is exactly what the different contributions in this volume have demonstrated. Exploring these trading zone dynamics advances biological investigation and our philosophical comprehension of how the science of Evo-devo operates in its many disciplinary dimensions.

## 1.5 Evo-devo Evolving

A recent paper in *Nature* begins with a claim that was nothing short of controversial at the time of Dahlem: "Evolution involves interplay between natural selection and developmental constraints" (de Bakker et al. 2013, 445). A citation from the paper

is to work from the early 1980s done by one of Dahlem's prominent participants, Pere Alberch (Alberch and Gale 1983). We can take this as a signal that Evo-devo has arrived and the "rehabilitation process designed to push a neglected field of evolutionary biology closer to the center of the stage where it can join with other areas of study in shaping a fuller understanding of the origin of morphological novelties" (Lewin 1981) has been effected. Studies showing the asymmetric filling of phenotypic space, such as those by David Raup (a Dahlem participant in the Evolution Level Group), which served as an inspiration for discussions about constraints (e.g., Raup 1966), now appear in unexpected places. A study of plumage color space in birds showing how little of it is occupied appeared in *Behavioral Ecology* (Stoddard and Prum 2011), not a morphological, paleontological, or developmental journal. But the sentiment seems lifted directly from Dahlem: "In Aves, some plumage colors may be difficult or impossible to make: the gamut is constrained by physical, developmental, or physiological constraints on signal diversity" (1042). A strictly oppositional relationship no longer characterizes adaptation and development even though the Evo-devo research aim is the same: "we explore how a realistic approximation of this genotype-phenotype map provides a richer and more quantitative understanding of the limitations that development may impose on adaptation" (Salazar-Ciudad and Marin-Riera 2013, 361).

The gap between microevolution and macroevolution has closed on some fronts, such as in studies of closely related Drosophilids where regulatory evolution has been tracked on a very fine scale (Haag and Lenski 2011). For example, researchers were able to show that the evolution of trichrome morphogenesis was due to single-nucleotide substitutions in an enhancer region leading to changes in the timing and level of gene expression of a particular transcription factor (Frankel et al. 2011). But paleontological contributors are still prominent in Evo-devo, as is the mechanism of heterochrony, displayed recently in a study arguing that bird skulls are paedomorphic (i.e., descendants morphologically resembling juvenile ancestors). The requisite integration called for by Bonner and colleagues three decades earlier is explicitly pursued: "we use a geometric morphometric approach integrating developmental, neontological, and palaeontological data ... and have provided a powerful new example of how heterochronic changes, paedomorphic and peramorphic, were crucial in the origin and evolution of birds" (Bhullar et al. 2012, 223, 226). An increased phylogenetic resolution of metazoan relationships (Dunn et al. 2008) in combination with the latest genome sequencing technologies has facilitated the discovery of unexpected evolutionary patterns, such as the independent evolution of muscles in cnidarians and bilaterians (Steinmetz et al. 2012). The long term study of model taxa (Griesemer, Chap. 13, this volume) has generated robust results across speciose clades, demonstrating that developmental changes can be both adaptive and non-adaptive due to correlations among traits. This makes it crucial to always have a comparative framework of developmental information when putting forward evolutionary explanations for specific traits: "without understanding the developmental mechanisms underlying character evolution it will remain difficult to infer process from pattern" (Jaekel and Wake 2007, 20441).

The "discipline" of Evo-devo is heterogeneous so it is not surprising that conceptual change since Dahlem has been heterogeneous. Evo-devo is composed of many different research programs, such as comparative embryology, epigenetics and experimental embryology, evolutionary developmental genetics, and theoretical biology. It harbors a diverse set of research questions that are not new but were often neglected by twentieth century evolutionary biology: how did development originate? How are established processes of development modified evolutionarily? What is the contribution of development to the origin of phenotypic novelty? (Müller 2008). Although the impact of Evo-devo on evolutionary theory remains a subject of intense debate (Pigliucci and Müller 2010), the conceptual change documented in this volume testifies to the manifold ways in which biological reasoning has been transformed at the intersection of development and evolution. This complicated history is now surfacing in a variety of different formats (e.g., Raff 2012). Among other things, the future of Evo-devo will involve the incorporation of new methods from synthetic biology (Wagner 2012) and an increased attention to the development and evolution of unicellular organisms (Haag and Lenski 2011; Love and Travisano 2013), though it is difficult to predict exactly how the research will unfold. Prognosticators after Dahlem guessed some things correctly, whereas others were impossible to discern. These future pathways will no doubt bring new conceptual changes to the Evo-devo juncture. As a consequence, it will remain a rich source of epistemological activity for historians and philosophers to gain a better understanding of how different disciplines focused on problems at the intersection of evolution and development progressively succeed or fail to explain how changes in the course of development can alter the course of evolution and how evolutionary processes mold development.

**Acknowledgments** I am grateful to the participants at the 2010 Dahlem workshop "Conceptual Change in Biological Science: Evolutionary Developmental Biology, 1981–2011," held at the Max Planck Institute for the History of Science in Berlin, the contributors to this volume, and especially the members of the workshop Steering Committee (Gerd Müller, Rudolf Raff and David Wake). All of you made it possible to better see and understand significant patterns of conceptual change over the past three and half decades. I owe a special thanks to David Wake for sharing the personal letter from Pere Alberch that opens this chapter.

## Appendix 1.1

Stipulations of the Dahlem Conferences (taken from Bonner 1982, but present in all research reports associated with a Dahlem Conference)

### *The Dahlem Konferenzen*

*Director*: Silke Bernhard, M.D.

*Foundation*: Dahlem Konferenzen was founded in 1974 and is supported by the Stifterverband für die Deutsche Wissenschaft,[18] in cooperation with the Deutsche Forschungsgemeinschaft[19] and the Senat of the City of Berlin.

*Objectives*: The task of the Dahlem Konferenzen is:

- To promote the interdisciplinary exchange of scientific information and ideas
- To stimulate international cooperation in research, and
- To develop and test different models conducive to more effective scientific meetings.

*Aim*: Each Dahlem Workshop is designed to provide a survey of the present state of the art of the topic at hand as seen by the various disciplines concerned, to review new concepts and techniques, and to recommend directions for future research.

*Topics*: The workshop topics (in the Life Sciences and the field of Physicochemistry) should be:

- Of contemporary international interest,
- Timely,
- Interdisciplinary in nature, and
- Problem-oriented.

*Procedure*: Dahlem Konferenzen approaches internationally recognized scientists to suggest topics fulfilling these criteria and to propose members for a Program Advisory Committee, which is responsible for the workshop's scientific program. Once a year, the topic suggestions are submitted to a scientific board for approval.

*Participants*: The number of participants is limited to 48 for each workshop. They are selected exclusively by a Program Advisory Committee. Selection is based on international scientific reputation alone and is independent of national considerations, although a balance between Europeans and Americans is desirable. Exception is made for younger German scientists for whom 10 % of the places are reserved.

*The Dahlem Workshop Model*: A special workshop model has been developed by Dahlem Konferenzen, the *Dahlem Workshop Model*. The main work of the workshop is done in four small, interdisciplinary discussion groups, each with 12 members. Lectures are not given.

Some participants are asked to write background papers providing a review of the field rather than report on individual work. These are circulated to all participants 4 weeks before the meeting with the request that the paper be read and questions on them formulated *before* the workshop, thus providing the basis for discussions.

During the workshop, each group prepares a report reflecting the essential points of its discussions, including suggestions for future research needs. These reports are distributed to all participants at the end of the workshop and are discussed in plenum.

[18] The Donors Association for the Promotion of Sciences and Humanities.

[19] German Science Foundation.

*Publication*: The Dahlem Workshop Reports contain:

– The Chairperson's introduction,
– The Background Papers, and
– The Group Reports.

The Dahlem Workshop Reports are available in two series:

1. Life Sciences Research Reports (LS)
2. Physical and Chemical Sciences Research Reports (PC)

## Appendix 1.2

Group membership for the four sections of the 1981 Dahlem conference

### *The Molecular Level*

I. Dawid, Rapporteur
R.J. Britten, E.H. Davidson, G.A. Dover, D.F. Gallwitz, A. Garcia-Bellido, F.C. Kafatos, S.A. Kauffman, K. Moritz, S. Ohno, J. Schmidtke, G. Schütz

### *The Cellular Level*

J.C. Gerhart, Rapporteur
S. Berking, J. Cooke, G.L. Freeman, A. Hildebrandt, H. Jokush, P.A. Lawrence, C. Nüsslein-Volhard, G.F. Oster, K. Sander, H.W. Sauer, G.S. Stent, N.K. Wessells, L. Wolpert

### *The Level of the Life Cycle*

H.S. Horn, Rapporteur
J.T. Bonner, W. Dohle, M.J. Katz, M.A.R. Koehl, H. Meinhardt, R.A. Raff, W.-E. Reif, S.C. Stearns, R. Strathmann

### *The Level of Evolution*

P.F.A. Maderson, Rapporteur
P. Alberch, B.C. Goodwin, S.J. Gould, A. Hoffman, J.D. Murray, D.M. Raup, A de Ricqlès, A. Seilacher, G.P. Wagner, D.B. Wake

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# Part I
# Adaptation, Allometry, Heterochrony, and Homoplasy

# Chapter 2
# Adaptive Aspects of Development: A 30-Year Perspective on the Relevance of Biomechanical and Allometric Analyses

**Karl J. Niklas**

> *Any discussion of adaptation is in danger of going around in circles unless the inherently comparative nature of adaptation is fully recognized at the outset*
>
> — Horn et al. (1982)

## 2.1 Introduction

The biologists contributing to the 1982 group report on the *Adaptive Aspects of Development* described themselves as so "dazzled by the variety of developmental patterns displayed by . . . animals and plants" that their "discussions were severely hampered at the outset by a lack of the most basic information" and called for "more critically comparative reviews about the constraints on development and possible adaptive patterns of development" (Horn et al. 1982, p. 217, pp. 230–1). They ended their report with a wish list of research goals, each ultimately requiring an understanding of the limits of developmental variation and a careful assessment of whether this variation results from natural selection, the operation of physical forces, historical accident, or some combination of all three (Horn et al. 1982). To achieve these goals, the participants repeatedly alluded to how biophysical and allometric analyses could help biologists understand the interactions among (and the constraints imposed by) size, shape, and development—a sentiment that resurfaces in many of the other conference group reports and papers (e.g., Bonner and Horn 1982; Gould 1982).

The conviction that biophysics and allometry could provide insights into adaptive evolution by natural selection (or any other evolutionary phenomenon) is understandable. Biophysical analyses quantify the extent to which physical laws and processes set specific kinds of limits on growth, development, and the final appearance of organic structures. They offer one way to understand the functional

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relationship between organic form and the abiotic environments in which it operates. In turn, the effects of physical laws are size-dependent and allometric analyses offer an important tool with which to evaluate size-dependent effects. In addition, biophysical and allometric analyses can be applied to extinct as well as extant organisms. They therefore provide a comparative approach that is fully capable of spanning all of evolutionary history.

The goal of this paper is to review the status of biophysical (*sensu* biomechanical) and allometric analyses in 1981 and to see if these disciplines have matured in ways that can achieve the aims of the 1981 Dahlem conference. The topic of network theory in the context of developmental biology is also treated. However, my disciplinary focus is more on allometric than biomechanical analyses. In part this is because biomechanics *sensu stricto* is grounded in physics and engineering, which by their nature have not fundamentally changed in ways that would alter our perception of evolution or adaptation. But, more importantly, I focus on allometric analyses because of recent (and controversial) attempts to formulate explanations for allometric trends, which have a direct bearing on whether evolutionary history largely reflects the operation of natural selection, physical forces, historical accidents, or some combination of all three (e.g., West et al. 1997, 1999; Savage et al. 2004).

The organismic focus of my review is primarily on plants for four reasons. First, the scope of biodiversity is so vast that no *experimentum crucis* exists. Because every lineage has a unique history, even if debates about evolutionary patterns are resolved for one lineage, their resolution remains problematic for other lineages in the absence of detailed study. Second, plants (here defined broadly as eukaryotic photoautotrophs) comprise over 90 % of all visible living matter. Therefore, if generalizations about evolution are based on the relative frequency of phenomena, plants provide an opportunity to formulate broad statements about evolutionary phenomena. Third, plant development and structure are simple compared to those of animals. It is easier therefore to analyze them. Fourth, I am a botanist.

Regardless of this phytocentric bias, my thesis is that the participants of the 1981 Dahlem conference knew that neither biomechanics nor allometry *sensu stricto* could provide mechanistic explanations for the phenomena that occupied their attention because these disciplines lacked mathematical formulations that could make their observational consequences explicit. The 1981 Dahlem attendees however did know that both disciplines were indispensable tools for formulating quantitatively rigorous hypotheses about how physical laws and processes affect development and evolution. Thus, even in the complete absence of an explanatory foundation, biomechanical analyses can be used to quantify how well a specific structure or organism performs a particular function or set of functions, even though it cannot explain why that structure evolved and survived natural selection. In this manner, biomechanics can help to explain why some combinations of structures occur rarely or not at all, while other combinations are more commonplace, especially when biophysical analyses are wedded to theoretically constructed morphospaces (e.g., Raup 1962; Niklas 1997; McGhee 1999). By the same token, allometric analyses can identify size-dependent or size-covariant trends during an organism's ontogeny, or across a spectrum of different species differing in size, without recourse to any underlying theory (Niklas 1994).

Another issue is whether allometric or biophysical analyses have evolved sufficiently to address some of the major questions raised by the 1981 Dahlem conference. It is true that both approaches have become more sophisticated technologically. It is also true that attempts have been made to formulate comprehensive theories about size-dependent trends (e.g., West et al. 1997, 1999; Savage et al. 2004). However, technological sophistication does not translate automatically into explanatory insight, nor can a theory be said to exist until its principal assumptions are tested and confirmed experimentally. Seen in this light and based on the available evidence, I believe that little has actually changed conceptually since 1981 and that mechanistic explanations for the phenomena discussed in the Dahlem proceedings continue to be elusive. Attempts to answer these questions must rely on additional disciplines, such as genomics and molecular developmental biology, although these also present their own set of conceptual challenges.

## 2.2 Biomechanics and Allometry in 1981

The state of biomechanical research around the time of the 1981 Dahlem conference is effectively summarized in the seminal book entitled *Mechanical Design in Organisms* (Wainwright et al. 1976). This book was cited in three separate contributions to the 1982 published proceedings. It therefore undoubtedly served as the then current model for what biomechanics could bring to a discipline that was to become known as evolutionary developmental biology (evo-devo).

*Mechanical Design in Organisms* reviews the fundamental principals of engineering theory clearly, perhaps even brilliantly. It also shaped the course of subsequent research in the areas of animal biomechanics and biomimetics. However, compared to more recent treatments, its scope was limited in a number of ways that must have caused the 1981 Dahlem participants some consternation. First, although it treats the mechanical properties of bones and other parts of the mammalian body plan, it deals largely with the physical properties of invertebrates; plants are mentioned four times but only in terms of the material properties of tissues and materials, such as wood and cellulose, neither of which are sufficient to cover even the basic aspects of plant biomechanics (see Niklas 1992). It therefore lacked the broad comparative phyletic scope the 1981 participants called for. Second, *Mechanical Design in Organisms* touches on the ecological aspects of animal biomechanics only briefly and on evolution (adaptive or otherwise) not at all.[1] Third, even though allometry is an integral part of biomechanical analyses, the effect of size is considered only in the context of defining stress, flexural stiffness, and other engineering size-dependent properties. Fourth, it provides only a cursory treatment of fluid mechanics—a topic treated at length (but removed from virtually any consideration of solid mechanics) by Steven Vogel in his

[1] These topics were treated later by Wainwright and Reilly (1994).

extremely influential and important 1981 book *Life in Moving Fluids*. The lack of a more extensive treatment of fluid mechanics in *Mechanical Design in Organisms* is curious for at least two reasons: many of the co-authors of *Mechanical Design in Organisms* are well known for their research on marine invertebrates and most of the organisms used as mechanical examples are aquatic.

Biomechanics came of age post-1981 Dahlem. However, seen from the perspective of 1981, the discipline as summarized by *Mechanical Design in Organisms* and *Life in Moving Fluids* must have appeared quite fragmented with an almost idiosyncratic fixation on the mechanical properties of the hard parts of marine invertebrates. Perhaps for this reason, the word "biomechanics" never actually appears in the 1982 published Dahlem proceedings. Arguably, this state of affairs very likely contributed to the participants' desire for more data drawn from a broader ecological and phyletic spectrum of organisms.

The esteem in which allometry was held at the time can be gleaned from reading Stephen J. Gould (1977) who, as a participant of the 1981 conference, opined that "Although allometric cases could be catalogued by the hundreds, it is not clear that they qualify ... as a 'mechanism of macroevolution.' They arise as a result of change in developmental timing, but they produce a small quantitative output for a small quantitative input" (Gould 1982, pp. 336–7). Nevertheless, Gould added "... allometric variants, although small and graded as their inputs, might still have relevance to macroevolution ... if they constrain available variation and impart a preferred direction to evolutionary change not based upon natural selection (but upon systems of covariation in development)" (Gould 1982, p. 337).

Even though he used allometry as an adaptationist early on in his career (Gould 1966), Gould's subsequent distaste for adaptationist explanations (or unquantifiable speculations about adaptation) is clearly outlined in his later publications. However, there are three additional reasons why he may have underplayed the usefulness or relevance of allometry other than the absence of evidence for the covariance of developmental phenomena. First, no credible explanation for size-dependent phenomena existed at the time. Even J.S. Huxley (the co-inventor of the word "allometry") failed to identify a rational and objective explanation for his now famous formula (i.e., $Y = bX^a$) in his 1932 book *Problems of Relative Growth*. Second, statisticians and biologists even now vigorously disagree as to which among competing regression protocols are the most appropriate for size-dependent analyses (e.g., Smith 1980; Harvey 1982; Seim 1983; Ratner 1985; Prothero 1986; McArdle 1988; Jolicoeur 1990; Riska 1990). And, third, the very need for these protocols in allometric analyses had been called into question by no less a personage than D'Arcy Thompson—to whom Huxley dedicated *Problems of Relative Growth* (Thompson 1942).

Given this state of affairs, it is reasonable to ask why the 1981 Dahlem participants gave biomechanical (or more accurately "biophysical") and allometric analyses as much attention as they did. There are at least two plausible reasons. First, any effort to determine whether physical laws and processes influence evolutionary history, development, or biological form-function relationships has to allude at the very least to a biophysical approach—no organism, plant or animal,

can obviate the laws of physics or chemistry. Second, the focus of many of the participants (particularly Gould) on heterochrony necessitated a discussion of allometry as a descriptive tool at the very least. Indeed, a careful reading of the 1982 conference proceedings suggests that the participants were interested in biomechanics or allometry only to the extent that these disciplines could be applied to resolving the relative importance of adaptive evolution by means of natural selection versus physical constraints and to assess the effects of size and developmental timing on organic shape.

## 2.3 Progress Since 1981?

Ironically perhaps, the faint hopes raised by the 1981 Dahlem participants that biophysical and allometric approaches could answer some of their questions stimulated other researchers, such as myself, to adopt a biophysical/mathematical approach to understanding development and evolution. Although my undergraduate degree was in mathematics, my Ph.D. thesis dealt with the morphology and chemistry of early Paleozoic, taxonomically problematic plant fossils. In 1982, I was using organic geochemistry to help resolve the phylogenetic affinities of these and other enigmatic plant fossils. However, after reading the 1982 Dahlem publication, I was inspired to return to my love of mathematics and physics and use these tools to quantify form-function relationships for both extinct and extant plants. Indeed, part of my frustration as a trained paleobotanist was my inability to actually experiment on the plants that I was studying. After reading the conference proceedings, *The Mechanical Design of Organisms*, and *Life in Moving Fluids*, I learned how to do the experiments I had only dreamed of before. This necessitated familiarizing myself with basic engineering, delving more deeply into statistics, and learning how to build wind tunnels. But a wonderful door had opened in my life. And I happily walked through it.

Biomechanical and allometric practice and theory have seen considerable progress since 1982. In biomechanics, new technologies have expanded the experimental repertoire of testing organic materials and structures even at the cellular and subcellular levels (for a review, see Niklas 1992). Nonlinear viscoelastic theory has advanced to a level where we can predict the behavior of fluid-like, organic materials. Indeed, the conceptual and practical problems that once separated the study of fluid mechanics from solid mechanics in books like *The Mechanical Design of Organisms* and *Life in Moving Fluids* (Vogel 1981) have been nearly eliminated. Genetically modified organisms have also been developed to test theories about the mechanical roles of particular materials, e.g., tobacco plant mutants lacking the ability to synthesize lignin have been used to determine whether lignin strengthens stems and leaves. In the field of allometric analyses and statistics, large data sets spanning thousands of species have been assembled for detailed analyses, and consensus has been reached (more or less) on the statistical protocols and computer software required for these analyses, e.g., reduced major

axis (RMA—otherwise known as standardized major axis) regression analysis has emerged as the "standard" protocol (Niklas 1994, 2004).

The real issue however is not whether progress has been made in the *general* advance of studying biomechanical and allometric phenomena, but rather whether progress has been made in providing mechanism-based explanations for phenomena that intrigued the 1981 Dahlem conference participants. Put differently, have these disciplines advanced beyond merely quantifying phenomenology? This question is addressed in the following section in the context of allometry.

## 2.4 Theories Versus Phenomenological Descriptions

J.S. Huxley was not the first to notice that much of the organic variation attending ontogenetic changes in size can be described by a simple formula. However, much like Charles Darwin, Huxley was the first to demonstrate convincingly that a very large body of data collected from diverse organisms could be described under the rubric of an intellectual construct and to publish this finding in the form of a book. Largely through Huxley's efforts and the publication of his *Problems of Relative Growth* (Huxley 1932), the allometric formula $Y = bX^a$ gradually became an accepted analytical tool.

Nevertheless, the absence of an explanation for this formula was painfully noticeable from its inception. In his otherwise very favorable review of *Problems of Relative Growth*, the polymath C.F.A. Pantin wrote that Huxley's

> formula is necessarily empirical. Of the causes of differential growth we have little knowledge; their investigation is the problem at issue. A variety of possible relations might, in fact, reduce approximately to this formula. But it is not the object of the formula to establish the correctness of a particular hypothesis as to the cause of differential growth; it merely expresses the observed facts with considerable accuracy in a simple way, so that many very significant features emerge which would not otherwise do so. (Pantin 1932, p. 7760)

Like many others since his time, Pantin drew a distinction between a description of a phenomenon and an explanation for the phenomenon. Indeed, he was certainly aware that, from a purely mathematical perspective, no theory can ever emerge from a formula like $Y = bX^a$ because it sets no boundary conditions on the numerical values of $a$ or $b$ and because it makes no statement regarding the nature of $Y$ and $X$. Indeed, the fractal relationship between the length of a coastline and the length of a stick used to measure it conforms to this equation. Logically, therefore, if there is nothing to predict, there can exist no theory to explain it. The allometric formula is nothing more than a mathematical statement about virtually any fractal relationship.

What is meant by a "theory" to explain size-dependent trends in biology is an explanation of the numerical values of the fractal-like *scaling exponents* that reappear when organisms differing in size are compared to one another using the formula $Y = bX^a$. Perhaps the most famous of these exponents is the ¾ scaling

exponent that describes the proportional relationship between basal metabolic rate $B$ and total body mass $M_T$ of vastly different animal and plant species (i.e., $B \propto M_T^{3/4}$). This proportional relationship is known as Kleiber's "rule" (Kleiber 1947). It has inspired many theoretical explanations (e.g., McMahon 1973; Blum 1977; Gray 1981). However, none is as far-reaching or as controversial as the theory proposed by G. West, J. Brown, and B. Enquist (West et al. 1997, 1999; see also Savage et al. 2004). West, Brown, and Enquist (henceforth WBE) argue that all biological scaling relationships are governed by ¼ (or multiples of ¼) power laws because all organisms, even unicellular ones, have internal fractal-like energy/mass delivery networks that have evolved by natural selection to minimize the energy and time required to absorb, distribute, and deliver resources internally. Although criticized on empirical and theoretical grounds, and challenged by alternative conceptual approaches (e.g., Banavar et al. 1999; Dodds et al. 2001; Darveau et al. 2002; Weibel 2002; Solow 2005; Kolokotrones et al. 2010), the WBE theory currently remains the most comprehensive allometric "theory," so much so that in the context of macroecology it can be called "the theory for everything."

Unfortunately, the basic assumptions upon which the WBE theory rests have not been tested directly. Support for this theory has thus far come exclusively from the concordance between the predicted and observed numerical values of scaling exponents and from computer simulations showing that an idealized WBE plant, i.e., a hypothetical plant that manifests all predicted ¼ (or multiple ¼) scaling relationships rapidly outcompetes all other simulated plants, even those that deviate in only one scaling exponent (Hammond and Niklas 2012).[2] However, any theory that stipulates ¼ (or multiples of ¼) power rules will necessarily agree with empirical observations, regardless of whether the basic assumptions of the theory are correct or false (Niklas 1994, 2004). The only real test of a theory is whether its fundamental postulates are shown to be correct. To date, no such test has been devised or implemented for the WBE theory.

## 2.5 Can Allometry Answer Size-Shape-Development Questions?

In the absence of a *bona fide* allometric theory, can allometric analyses still be useful in answering some of the questions raised during the 1981 Dahlem conference? I believe that they can. Here, I set up an experimental design with three components to illustrate how allometric analyses can be used to assess the prevalence of adaptive versus contingent evolution.

[2] A core assumption of the WBE theory is that ¼ scaling exponents result from natural selection operating to maximize the supply of nutrients and minimize the time of delivery. If true, an idealized WBE plant ought to outcompete all 'non-optimal' plants.

The first component of this demonstration is a data set for the dry biomass of the leaves, stems, and roots of seed plants (angiosperms and conifers) that either lack or posses very little secondary growth (data from Niklas and Enquist 2001, 2002; Niklas 1994, 2004, 2005).[3] Across a broad spectrum of these species, the scaling exponents governing the size-dependent relationship among the dry mass of leaves, stems, and roots (denoted by $M_L$, $M_S$, and $M_R$, respectively) are statistically indistinguishable from one (i.e., $M_L \propto M_S \propto M_R$). It therefore follows that the mass of all above ground body parts (i.e., $M_A = M_L + M_S$) scales one-to-one (isometrically), or nearly so, with respect to below ground biomass (i.e., $M_A \propto M_B = M_R$) (Niklas 2004, 2005). Inserting the requisite allometric constants (with successive numerical subscripts) into these proportionalities gives

$$M_L = b_0 M_S = b_1 M_R \tag{2.1}$$

$$M_A = M_L + M_S = (1 + 1/b_0) b_1 M_{B=R} \tag{2.2}$$

The second component of this demonstration is a data set for the dry mass of the structural analogues of leaves, stems, and roots among non-seed plants including green and brown algae, mosses, and representatives of every extant seedless vascular plant lineage (Table 2.1). The juxtaposition of these data with those from seed plants provides an opportunity to determine whether a single partitioning pattern for biomass holds true across all plant lineages.

The third component of my demonstration is the argument that, if a single "canonical" biomass partitioning pattern exists across all polyphyletic plant lineages, it provides evidence for adaptive (functional) equivalence and detracts from the hypothesis that developmental constraints are responsible (Harvey and Pagel 1991; Niklas 1994). The "developmental constraint" hypothesis posits that natural selection acts on different body parts in opposing directions (gauged by biomass or some linear dimension), and that developmental covariance among these parts limits the extent to which a body plan can change evolutionarily. The "functional equivalence" hypothesis argues that particular body parts must change in size with respect to changes in the size of other body parts to maintain comparable functional levels of performance dictated by biophysical or physiological (invariant) "rules."

These two hypotheses are not mutually exclusive in all respects. Natural selection operating on how organs perform certain biological tasks can act indirectly on the developmental patterns that give rise to organ structure, shape, size, etc. Put differently, if function-function covariants are the objects of selection, the developmental variations that give rise to them will also be the objects of selection. Certainly, organisms can neither obviate the laws of physics and chemistry nor the principles of engineering and mathematics. Thus, constraints on development have existed since the dawn of life.

[3] Dry biomass is used rather than fresh mass because the water content of plant tissues can change diurnally dramatically and because water content tells us little about the actual biomass or metabolic "investment" involved in the construction of a plant.

**Table 2.1** Species-groupings used to evaluate biomass partitioning patterns. For taxonomic relationships among these taxa, see Bold (1967), Bierhorst (1971), Bremer et al. (1987), Lewis and McCourt (2004)

| | |
|---|---|
| Algae (polyphyletic) | |
| *Brown algae (Laminariales)* | |
| | *Alaria* sp. |
| | *Costaria costata* |
| | *Laminaria agardhii* |
| | *Nereocystis luetkeana* |
| | *Postelsia palmaeformis* |
| | *Pterygophora californica* |
| | *Saccorhiza dermatodea* |
| Sihonous (unicellular) chlorophycean algae | |
| | *Culerpa prolifera* |
| Charophcean algae (sister group to the land plants) | |
| | *Chara contraria* |
| | *Nitella flexilis* |
| Land plants (monophyletic embryophytes) | |
| Non-vascular plants (mosses) | |
| | *Dawsonia superba* |
| | *Funaria hygrometrica* |
| | *F. flavicans* |
| | *Polytrichum commune* |
| Vascular, seedless plants (pteridophytes) | |
| "Microphyllous" | |
| | *Equisetum arvense* (a horsetail) |
| | *Hupertizia lucidium* (a lycopod) |
| | *Selaginella krausianna* (a lycopod) |
| "Megaphyllous" | |
| | *Botrychium virginianum* |
| | *Marsilea quadrifolia* |
| | *Polystrichum acrosticoides* |
| | *Psilotum nudum* |
| | *Regnellidium diphyllum* |
| | *Salvina natans* |

However, the concepts of "developmental constraints" *sensu stricto* and "constraints on development" are different; the first posits that developmental repertoires are "internally" regulated and limited genomically, whereas the second argues that the external environment limits which among possible developmental patterns persist in evolutionary time (Amundson 1994). Therefore, the "developmental constraint" hypothesis *sensu stricto* can be rejected if the biomass partitioning patterns observed for phyletically unrelated lineages are statistically and allometrically concordant, because it is known that the plants in my two data sets have vastly different developmental choreographies. Indeed, the brown algae (here limited to members of the Laminariales) and the chlorophycean algae provide critical tests. All of the evidence indicates that the ontogeny of brown algae is

radically different from that of vascular plants, and that the chlorophycean algae represent a clade distinct from the green algal lineage most closely related to the land plants, i.e., the charophycean algae (see Bremer et al. 1987; Gifford and Foster 1988; Graham and Wilcox 2000).

Therefore, the allometric trends of the seed plants can be used as a null hypothesis and the allometric trends of the brown and the chlorophycean algae serve as the phyletic "out-groups" to test whether "developmental constraint" or "functional (adaptive) equivalence" is predominant. The tactic is to (1) quantify the biomass partitioning pattern for all paired variables of interest across ecologically diverse seed plants, (2) superimpose the same kinds of data obtained from the other plant lineages, and (3) determine which (if any) taxa emerge as statistical outliers with respect to the allometry of seed plants (i.e., data that fall outside the 95 % confidence intervals for the RMA regression estimates of seed plant allometry). Three paired (and biologically interdependent) variables of interest are identified by the null hypothesis. These are $M_L$ vs. $M_S$, $M_L$ vs. $M_R$, and $M_S$ vs. $M_R$ (Niklas 2000).

My statistical test is intentionally conservative for three reasons: (1) the 95 % confidence intervals of regression curves tend to contract as both the sample size and correlation coefficient increase across different data sets; (2) the seed plant data set is especially robust in both respects; and, (3) the 95 % confidence intervals are thus comparatively easily trespassed by other plant life-forms, i.e., "outliers," are not only readily apparent, they are "encouraged."

## 2.6 Analyses of the Data Sets

Across all possible comparisons, the biomass partitioning patterns of the different plant lineages are isometric and statistically indistinguishable as gauged by their scaling exponents (Table 2.2). Likewise, bivariate plots of all of the paired variables of interest reveal few if any brown algal outliers, and, those that do occur are outnumbered by seed plant outliers (Fig. 2.1). For example, five outliers are observed for the scaling of $M_L$ with respect to $M_S$. However, three are a fern (*Botrychium virginianum*), a lycopod (*Hupertzia lucidulum*) and a horsetail (*Equisetum arvense*) and only two are brown algae (Fig. 2.1). Like all extant horsetails and the majority of lycopods, *E. arvense* and *H. lucidulum* have small "microphyllous" leaves; those of *E. arvense* are vestigial and non-photosynthetic. Thus, a single, interspecific partitioning pattern for biomass appears to exist and lends support for convergent (adaptive) evolution among the various plant lineages.

The existence of natural functional organ-categories resonates reasonably well with the functional obligations that have been traditionally ascribed to each of the analogous body parts assigned to one of the three functional organ-categories. The foliose structures of marine green, red, or brown algal macrophytes intercept sunlight and exchange gasses with the fluid that surrounds them in physical and chemical ways that are not fundamentally dissimilar from those influencing the exchange of mass and energy between the air and the foliage leaves of

**Table 2.2** Summary statistics of reduced major axis (RMA) regression of $\log_{10}$-transformed data for seed plant leaf, stem and root dry mass (original units in kg; denoted by $M_L$, $M_S$, $M_R$, respectively), above- and below-ground body parts (denoted by $M_A$ and $M_B = M_R$, respectively), and data for analogous body parts of seedless vascular plants and charophycean algae and brown algae (see Table 2.1 for species listing; for analyses, see Niklas 2000)

| | *a* (95 % CIs) | log *b* (95 % CIs) | $r^2$ | *n* |
|---|---|---|---|---|
| Seed plants | | | | |
| log $M_L$ vs log $M_S$ | 0.90 (0.88, 0.92) | −0.19 (−0.25, −0.13) | 0.91 | 862 |
| log $M_L$ vs log $M_R$ | 0.93 (0.91, 0.96) | −0.03 (−0.11, −0.06) | 0.87 | 668 |
| log $M_S$ vs log $M_R$ | 1.01 (0.98, 1.04) | 0.10 (−0.01, 0.20) | 0.87 | 673 |
| log $M_A$ vs log $M_B$ | 1.04 (1.02, 1.06) | 0.38 (0.31, 0.45) | 0.88 | 1,223 |
| Seedless vascular plants and charophycean algae | | | | |
| log $M_L$ vs log $M_S$ | 0.91 (0.70, 1.13) | −0.05 (−0.83, 0.73) | 0.86 | 16 |
| log $M_L$ vs log $M_R$ | 0.78 (0.51, 1.06) | −0.66 (−1.58, 0.25) | 0.84 | 16 |
| log $M_S$ vs log $M_R$ | 0.96 (0.68, 1.24) | −0.26 (−1.22, 0.70) | 0.89 | 16 |
| log $M_A$ vs log $M_B$ | 0.85 (0.64, 1.07) | −0.31 (−1.05, 0.43) | 0.91 | 20 |
| Brown algae (laminariales) | | | | |
| log $M_L$ vs log $M_S$ | 0.83 (0.47, 1.20) | 0.20 (−0.65, 1.06) | 0.92 | 8 |
| log $M_L$ vs log $M_R$ | 0.87 (0.58, 1.16) | 0.52 (−0.22, 1.26) | 0.95 | 8 |
| log $M_S$ vs log $M_R$ | 1.04 (0.57, 1.51) | 0.38 (−0.83, 1.58) | 0.91 | 8 |
| log $M_A$ vs log $M_B$ | 0.89 (0.80, 1.03) | 0.59 (0.32, 0.86) | 0.99 | 8 |

tracheophytes. Likewise, just as roots and holdfasts provide anchorage to a substrate, the mechanical functionality of the aerial stems of vascular plants, the stem-like axes of mosses, and the stipes of many brown algae is nearly identical from an engineering perspective, despite differences in the hydraulic (and thus anatomical) obligations of these otherwise very different structures.

That the size-dependent (scaling) requirements of developmentally different structures (which appear to share the same or very similar functional obligations) are not truly "invariant" is evident from the inspection of the absolute rather than the proportional biomass relationships among leaves, stems, root, and their corresponding analogs. Note that the scaling exponent describes the proportional relationship between two variables, whereas the allometric constant defines the absolute values of the variable of interest. Table 2.2 shows that these constants can have numerically broad 95 % confidence intervals, which indicates that some species groupings occupy a wide range of body part sizes.

No theory yet explains how or why allometric constants vary across species or lineages. However, the numerical "latitude" of these "constants" indicates *a posteriori* the "permissible variation" in the range of biomass occupied by each functional organ-category, which is otherwise confined by the operation of physical and chemical laws or processes. Metaphorically speaking, the data-scatter observed for all of the biomass scaling relationships reflect the size corridors though which plants have evolved as their size range expanded or contracted over evolutionary history. That these corridors have well defined limits attests to the operation

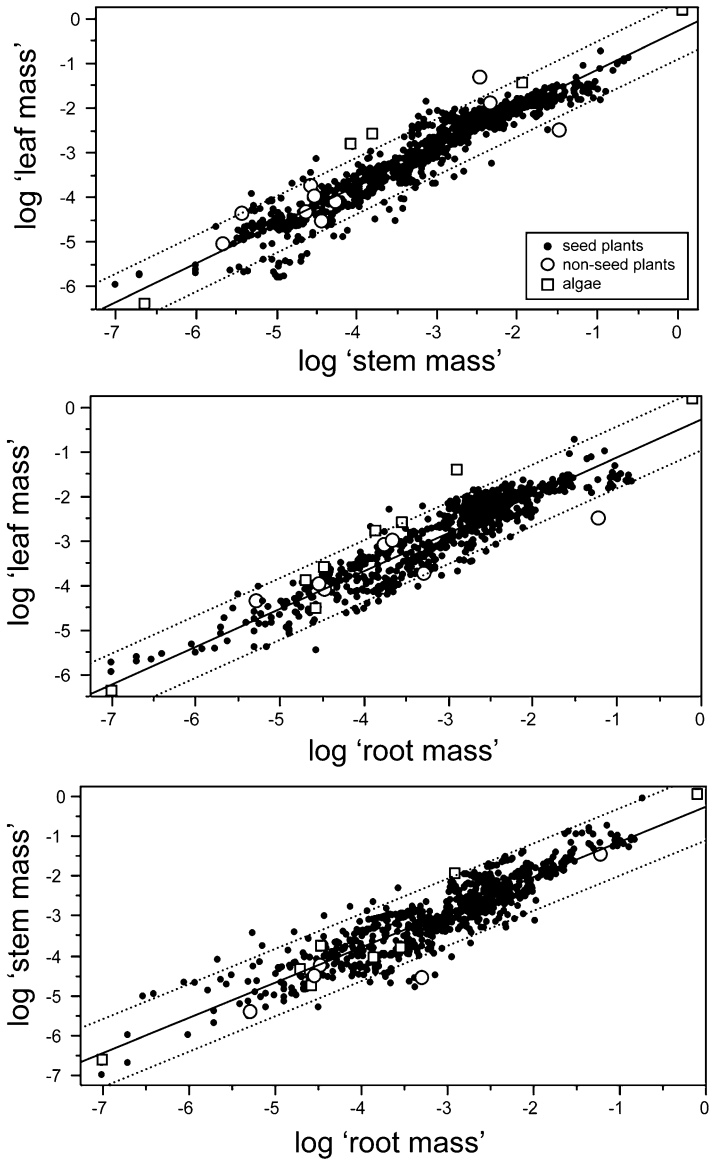


**Fig. 2.1** Bivariate plots of $\log_{10}$-transformed data for the dry mass of the leaves, stems, and roots of seed plants and the dry mass of the structural equivalents of these organ types in other species-groupings (see Table 2.1). *Solid* and *dashed* lines are the respective reduced major axis regression curve and its 95 % CIs for the seed plant data

of physico-chemical laws and processes, the objects of biophysical enquiry. However, it is also clear that some taxa "pushed these limits" (and are thus statistical outliers), which illustrates life's remarkable ability to generate innovative solutions to biotic and abiotic challenges.

## 2.7 Developmental Networks

The 1981 Dahlem conference participants discussed developmental constraints at great length and how molecular biology could unravel the relationship between development and evolution. This optimism permeates much of the current literature, the majority of which is devoted to identifying the genes and gene networks underlying targeted aspects of morphogenesis and development. Although this approach is technologically very sophisticated, it currently has little or no explanatory power (other than that gene networks exist). I want to explore this aspect further by showing that our understanding of genetic networks is always incomplete unless the entire gene-network is mapped as an integrated system.

A synoptic treatment of Boolean logic circuits is beyond my scope (for classic references, see Halmos 1963; Harrison 1965; in terms of plant development, see Stein 1998). However, there are only two basic kinds: combinatorial circuits, in which the output signal depends exclusively on the near instantaneous value of the input signal, and sequential circuits, in which the output signal also depends on the history of previous inputs. Both types depict a signaling pathway as an electrical circuit containing one or more switches. The "logic" of a circuit is the algorithm that describes the conditions (logical propositions) dictating whether a signal passes through a circuit. Parallel and serial circuits exist. The former provides multiple responses to the same signal depending on instantaneous conditions, because parallel circuits allow an initial input signal to flow through two or more pathways, permitting two or more output signals at each terminus. Generally, the number of responses is given by $2^N$, where $N$ is the number of switches. Responses coordinated by parallel logic circuits can achieve seemingly continuous variation in response to the passage of a single input signal if they contain even a modest number of switches (e.g., $2^{N=10} = 1{,}024$), if some switches activate or suppress other switches in the circuit, if the circuit has two or more input signals, or if the output signals interact combinatorially. Also, if switches respond to more than one signal, the number of possible output signals is $S = 2^{2^N}$, where $S$ is the number of input signals to which switches respond. Note that when $N = 5$, $S = 4.29 \times 10^9$.

Although a complex logic circuit can be simplified mathematically, four caveats are evident when biological systems are approached in this way (Niklas 2003): (1) there is no *a priori* method to determine which among logically equivalent circuits is biologically real, i.e., oversimplification can produce false circuit diagrams; (2) incomplete signaling pathways may appear to 'work' when diagrammed, i.e., missing components are not invariably obvious; (3) parallel logic circuits may obtain invariant output signals that give the appearance that input signals pass through serial switches, i.e., a bifurcating signal transduction pathway is more readily misdiagnosed than a serial pathway; and, (4) nothing in a logic circuit per se indicates when and how long a switch is turned on or off or how long a genomic or metabolic product lasts, i.e., the temporal components of signaling can be lost.

To be useful, logic circuits must be wedded to the subsystems they supervise. There are a variety of signal-activated subsystem configurations. The simplest is

error-activated, i.e., the output signal is used to modulate the input signal. This configuration has four essential components (see Harrison 1965; Hill and Peterson 1968): (1) a comparator to measure the difference (error) between the actual and the desired output of the subsystem; (2) an actuator/suppressor to convert the error-signal into an internal signal; (3) the actual machinery or assemblage that is controlled (the subsystem assembly); and, (4) a feedback element to direct the immediate output signal of the assemblage back to the comparator (Fig. 2.2a).

Feedback is defined as the property of a closed-loop system that permits the comparison of the output signal (or some other variable controlled by the subsystem) to the input of the subsystem (or an input to some other internal component) so that the control action is some function of the input-to-output ratio. In many ways, the feedback element is the most important of the four components because it confers four characteristics: (1) an increased range of input signals over which the subsystem responds satisfactorily; (2) reduced sensitivity to variations in the output to input signal ratio; (3) reduced effects of nonlinear distortions; and, (4) a tendency toward initial oscillatory behavior. Negative and positive feedback loops exist and a single loop can serve in both capacities, especially in the case of a subsystem hot-wired by a sequential (history-dependent) logic circuit (for an interesting example, see Bhalla et al. 2002).

By definition, subsystems are networked to other subsystems by shared circuits. This feature reduces the erratic behavior of the system as a whole. The linkage of two or more subsystems results in two important properties: (1) the ability to achieve global stability; and, (2) the feedback signaling of numerous components (a phenomenon called "recursive combinatorial regulation"). Global behavior confers homeostasis, whereas recursive combinatorial regulation permits a network to repeatedly cycle through a programmed series of transformations.

## 2.8 The Incompleteness Theorem

No single actuator/suppressor switch exists in isolation because each subsystem circuit requires an activation or suppression signal. One subsystem must receive a signal and temporarily function as an epistatic actuator. When switched on or off, this subsystem sparks the operation of the entire network, suppressing or activating one or more of the networked subsystems. However, once the entire system is set into operation, no "master" switch exists. If a developmental master switch ever existed, it was turned on when the first living cell evolved during the Precambrian.

This feature governs the working of *any* networked system and instantiates what I called the biological "incompleteness theorem," i.e., the operation of *any* biological subsystem cannot be fully diagnosed in isolation of the operations of the other subsystems to which it is networked (Niklas 2003). This theorem, which is an analog to Kurt Gödel's (1931) incompleteness theorems, can be proved mathematically, but it is easily illustrated by a hypothetical example consisting of two nuclear genes (*G1, G2*), their enhancer-promoters (EP1, EP2), a cell membrane docking

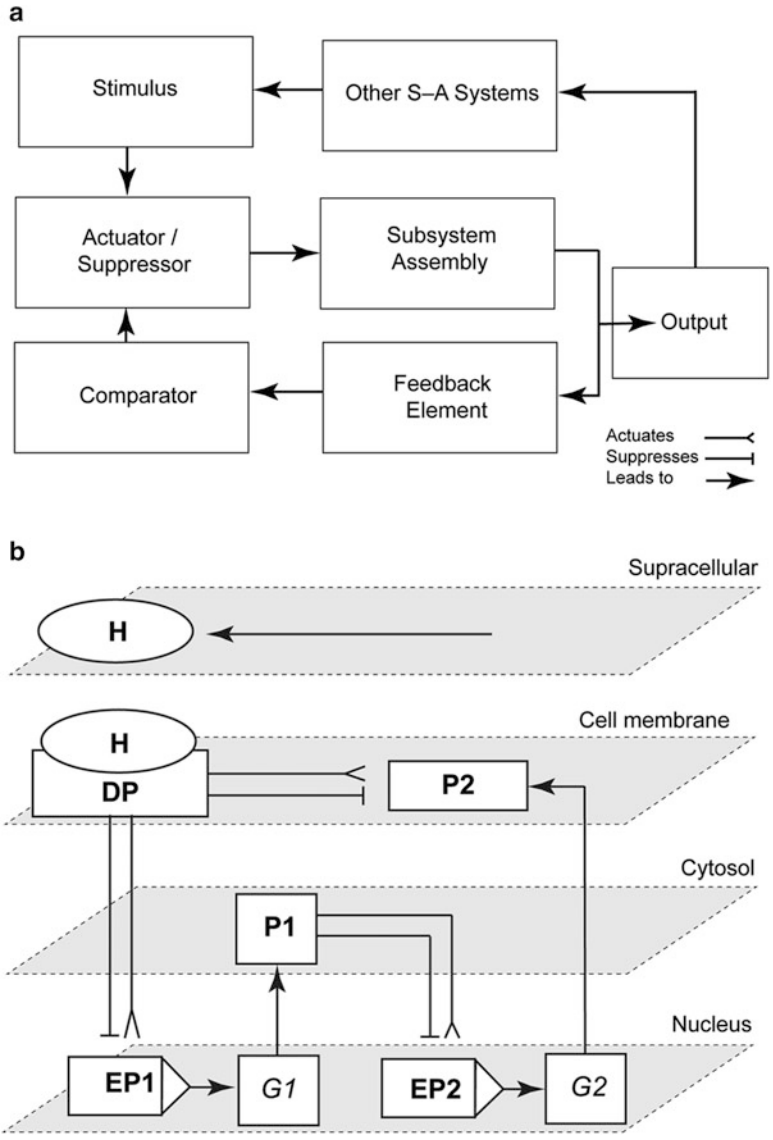


**Fig. 2.2** Schematics of a simple, signal-activated subsystem and the "incompleteness theorem" (Adapted from Niklas 2003). (**a**) A signal-activated (S-A) subsystem with an actuator/suppressor, a subsystem assembly, a feedback element, and a comparator. The output signal (response to an input stimulus) feeds into other signal-activated (S-A) systems. (**b**) Schematic of the "Incompleteness theorem" for a circuit/subsystem consisting of a docking protein *DP* activated by a hormone *H* that mediates signalling to a cell membrane-bound protein *P2*, a cytoplasmic protein *P1*, and the enhancers/promoters (EP) of two genes *G1–2*. The network is structurally self-contained, but its operation depends on the delivery of the external signal (*H*)

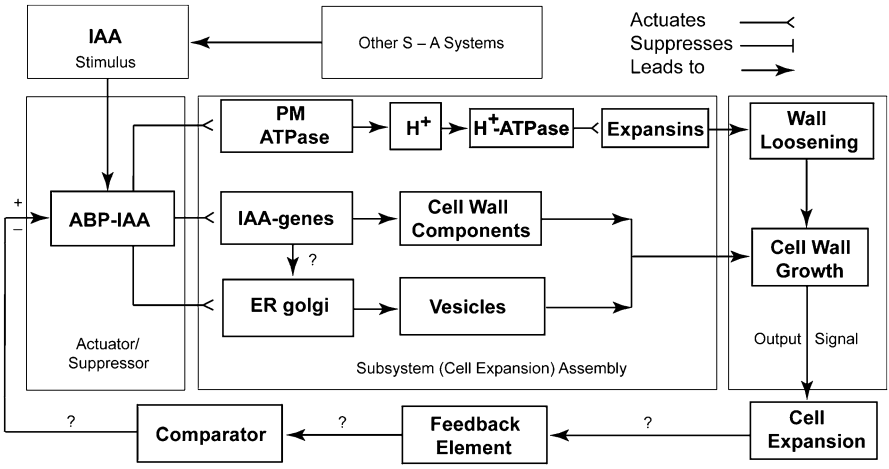


**Fig. 2.3** Circuit/subsystem diagram for cell expansion mediated by *IAA* and the *IAA* binding protein ABP1. *PM* plasma membrane, *ER* endoplasmic reticulum, *CWC* cell wall components. See text for additional details

protein (DP) activated or suppressed by a hormone (H), and two regulatory proteins (P1, P2) (Fig. 2.2b). At the *structural* level, this network is a self-contained system regardless of the presence of H. However, in terms of its *operation*, this network is suppressed or activated by H, which is delivered from an *external* source that is regulated by one or more other network systems.

Consider now the logic circuit for the regulation of cell wall loosening as mediated by indole-3-acetic acid (IAA), wherein the plasmalemma-bound auxin binding protein 1–IAA conjugate (ABP1-IAA) is diagrammed as the actuator/suppressor switch for ATPases (Fig. 2.3). Once activated, the cell wall is acidified, cell wall bonds are broken (expansin proteins have been implicated in this process), and turgor pressure drives cell expansion (not shown). The ABP1-IAA switch also triggers delayed cytoplasmic and genomic responses involving the synthesis and delivery of cell wall components. This logic circuit diagram shows that sustained osmoregulation and cell wall loosening are required for continued cell expansion. The diagram also shows that the feedback loop and comparator for the output signal of the cell expansion machinery are unknown and must be sought experimentally. The IAA degradation, the down-regulation of solute concentrations, the synthesis of new cell-wall-binding polymers, the reorientation of cellulose microfibrils, the deposition of secondary wall layers, and the degradation of wall-loosening enzymes are among the many viable candidates for these missing network components. However, it is clear that cell wall loosening involves numerous other suppressor/actuator subsystems, many of which remain poorly understood, and largely ignored despite claims that this developmental system is fully diagnosed (e.g., Liepman et al. 2010).

The logic circuit for the regulation of cell wall loosening reveals the extent to which our understanding of an important and intensively studied developmental

subsystem is limited. It also illustrates the extent to which this developmental "subroutine" must be integrated with numerous other developmental subsystems (such as those regulating polar auxin transport and osmoregulation) before its role in plant development is completely comprehended. No subsystem functions in isolation. Each is integrated with the operation of all other developmental systems. Consequently, regardless of how well a subsystem is dissected and manipulated experimentally, its role will always be incompletely understood if isolated from an organism's entire spatiotemporal developmental repertoire. This 'incompleteness theorem' presents a daunting intellectual challenge, given the extraordinary complexity of the developmental biology of even so seemingly simple things as unicellular plants, animals, and fungi. Nevertheless, it provides a perspective that resonates with many of the participants of the 1981 Dahlem conference.

## 2.9 Plato's Cave and the 1981 Dahlem Conference

The 1981 Dahlem conference participants pondered the usefulness of network theory as well as biophysical and allometric tools to identify constraints on development. In general, they felt the available data were inadequate to resolve this question and called for a broader, more comprehensive *Weltanschauung*, a quest that is still justified. I have tried to illustrate how tools such as allometric analyses, biomechanics, and network theory can be brought into service to answer some of the important questions raised during the 1981 conference. I have also tried to expose some of the intrinsic limitations of these tools. In the context of allometric analyses, the numerical values of the scaling exponents used to describe any allometric trend depend on the phylogenetic composition of the data and these values will progressively differ numerically among data sets as the sample sizes of these data sets decrease (see Table 2.2). In the context of network theory, the piecemeal dissection of any system, even one as comparatively simple as the expansion of the plant cell wall, can lead to completely erroneous interpretations of experimental results (see Fig. 2.3).

These and other concerns draw attention to one interpretation of Plato's allegory of the cave, i.e., we acquire concepts by our perceptual experiences of physical objects, but we are deluded if we believe that these concepts are truly on the same level of reality as the things we perceive. This allegory is particularly important when biology is reduced to molecular biology, physics, mathematics, or statistical inference. For example, even if we assume that a one-to-one pattern of biomass partitioning is not a statistical artifact, can we really evaluate whether it is biologically important? Mathematically, isometry is trivial in the sense that a one-to-one proportionality maintained across any series of objects differing in size requires no special biophysical "rules" (or metabolic "effort"). Yet, the state of being a "trivial condition" in light of solid mechanics or physiology does not preclude the possibility that a phenomenon is biologically non-trivial. Indeed, "simple" often translates into "elegant."

Likewise, can we say that a developmental system is "understood" once the genes that drive it are identified even when their gene products remain unknown? Indole-2-acetic acid (IAA) is known to alter gene expression in very rapid and selective ways. This explains why IAA signaling is linked to a large number of physiological and developmental responses, including gravitropism, cell wall extension, embryo axis polarity, and vascular tissue differentiation. But not one of the products of these genes has been identified and even a very general description of their downstream effects on plant development remains frustratingly elusive.

In many ways, we are at the same stage as classical genetics was before the Modern Synthesis when it was difficult to reconcile Mendelian quantitative genetics with the Darwinian supposition that evolution involves gradual phenotypic changes. The rapidly expanding information gained from biophysics, allometry, and genomics has not been integrated with the knowledge from more traditional physiological, developmental, or evolutionary disciplines. This situation will change, but only when we collectively consider all levels of biological organization simultaneously, from the molecular to the phenotype, as well as their evolutionary history. This challenge requires a new mindset. It will also require exploring taxa from deeper nodes in phylogenetic trees. The task is intimidating, but if left unaccomplished we run a risk described in T.S. Eliot's *Four Quartets*:

*It seems, as one becomes older,*
*That the past has another pattern, and ceases to be a mere sequence–*
*Or even development: the latter a partial fallacy*
*Encouraged by superficial notions of evolution,*
*Which becomes, in the popular mind, a means of disowning the past.*

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# Chapter 3
# Do Functional Requirements for Embryos and Larvae Have a Place in Evo-devo?

**Richard R. Strathmann**

## 3.1 Introduction

Has conceptual change occurred in studies of the evolution of development since the 1981 Dahlem conference (Bonner 1982)? My answer to this question focuses on explaining traits of embryos and larvae in terms of functional requirements, with examples drawn from my area of research. Although studies of performance and function preceded Darwin, he added natural selection as a criterion for performance. Selectionist thinking on performance and function can explain many features of organisms without information about genes and their role in developmental processes. Performance can be related to survival and reproduction, aspects of fitness, without measuring natural selection. Requirements for performance during development were implicitly accepted but mostly ignored in the Modern Synthesis. A similar neglect occurs in Evo-devo as well. For example, although the journal *Evolution & Development* includes papers on the functional biology of marine larvae when there are evolutionary implications, there has been little integration of studies of the evolution of developmental processes with analyses of how traits of developing organisms affect their performance in the wild. Nevertheless, explanations of the evolution of development are incomplete without tests of hypotheses about function. Development occurs in particular environments. Embryos and larvae are subject to natural selection. Measuring selection on embryos and larvae in natural populations is usually difficult, but the consequences of traits for performance in particular environments can be ascertained.

The separation of studies of developmental processes from the functional biology of developing organisms has a long history, but the 1981 Dahlem conference was broadly inclusive. Bonner's (1982, 4–5) comment on the strategy of the

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workshop was that "We wanted to assemble as large a variety of different kinds of biologists as possible." His list included "invertebrate zoologists" and "population biologists who are concerned with the strategies of life history." That was broad enough to include people like Mimi Koehl (biomechanics), Steve Stearns (life history ecology), and me (marine larval biology). At the workshop, Stearns (1982, 237–8) contrasted two ways of understanding organisms: "Two major approaches to biological understanding are the adaptationist and the mechanist. The first attempts to answer the question: What should natural selection favor? The second attempts to answer the question: How does the organism work?"

I shall discuss functional requirements for development within three time periods. (1) The first is the varied kinds of studies of marine embryos and larvae *prior to the 1981 Dahlem conference*. Many of these studies emphasized performance in the marine environment and do not fit the usual history of Evo-devo. (2) The second is the prominent interest in developmental constraints and the limited integration of mechanist and adaptationist approaches to evolution *at the 1981 Dahlem conference*. (3) The third is connections between adaptationist and mechanist studies of development *since the 1981 Dahlem conference*. These connections are illustrated with examples of adaptationist studies of the traits of embryos and larvae. These are examples of how adaptationist approaches explain developmental traits and how adaptationist questions about trade-offs and limits remain unanswered in the absence of information about developmental processes.

## 3.2 Approaches to Studying Marine Embryos and Larvae in the First Part of the Twentieth Century

The histories of Evo-devo that I have read do not fit my experience as a marine biologist. I have been little concerned about deficiencies in the Modern Synthesis (or neo-Darwinism), and have not been focused on developmental processes that link genotype to phenotype. Until the 1970s, few molecular genetic methods were available for population or developmental studies of marine organisms, and most marine organisms are inconvenient for breeding through generations. Marine organisms did, however, offer evidence of ancient evolutionary divergences in development, which motivated extensive comparative studies in the nineteenth century and later. Also, planktonic development, in which solitary embryos and larvae develop with little protection, focused attention on risks. Variation in fished populations added to an interest in how embryos and larvae cope with environmental challenges. In the twentieth century, interest increased in (a) functional requirements for marine development, (b) ecological consequences of developmental traits, and (c) the characteristics of more recent evolutionary divergences. Finally, developmental studies exploited the ease with which marine embryos could be manipulated, and these manipulative experiments included comparisons among clades. Aspects of development in the sea have led to a different set of interests

and hypotheses on the evolution of development. During the first half of the twentieth century, studies of development in marine animals continued on topics extant from the nineteenth century, but an interest in the adaptations of embryos and larvae as a part of their life histories increased. Here are some examples.

(i) Hjort's (1914) critical period hypothesis suggested that variation in larval survival explained variation in recruitment to fisheries. This hypothesis brought attention to the transition from an embryo dependent on materials in the egg to a larva dependent on food in the plankton. Hjort's hypothesis emphasized the influence of a varying and often challenging environment on embryos and larvae.

(ii) Giard (1905) coined the term poecilogony for varying developmental paths, within a species, to the same adult phenotype. Giard's examples, even when not truly intraspecific, contradicted the expectation of greater stasis in traits at earlier rather than later developmental stages. Garstang (1928) proposed that the torsion exhibited by gastropods evolved as a protection for veliger larvae against predators. Other hypotheses from Garstang also emphasized larval adaptations as a source of evolutionary innovations. Early in the twentieth century Giard, Garstang, and others were describing examples of development that contradicted von Baer's and Haeckel's ontogenetic rules and attempted to explain them in functional terms—as adaptations of embryos and larvae to a challenging environment.

(iii) Wilson's (1932, 1952) studies of annelid larvae included adaptive plasticity in the timing of metamorphosis, innovations in rudiments of postlarval structures, and requirements for speed in metamorphosis, all of which were explained in terms of change of habitat.

(iv) Thorson's (1936) studies of arctic marine invertebrates expanded investigations of biogeographic trends in modes of larval development and parental protection of embryos by encapsulation or brooding.

(v) Studies of the functional morphology of larvae were scattered among numerous investigators. Werner's (1955) examination of how a veliger larva uses prototroch and other cilia to concentrate, transport, and ingest food particles is just one example. Werner recognized more clearly than previous authors what a larva needs to do to feed on scarce phytoplankton.

(vi) Experimental studies of how cell fates and body axes are established relied on the manipulation of embryos. Investigations of cytoplasmic localization and cell interactions, as in Hörstadius's experiments with sea urchin embryos, were pursued in disparate embryos, which provided comparisons for evolutionary inferences. Manipulative experiments also demonstrated the extraordinary resilience of embryos to recover from perturbations. Hypotheses on developmental processes that were derived from these manipulations have been further elaborated and tested by molecular genetic observations.

(vii) Scenarios for the origin and early diversification of animals also remained popular, as in Jägersten's *Evolution of the Metazoan Life Cycle* (1972). This book is still cited frequently, despite methodological flaws, because of its

discussions of functional morphology and heterochrony (= "adultation" for Jägersten). Of the various marine studies, those of the sort exemplified by Hörstadius and Jägersten most resemble the interests found in Evo-devo today.

From the early to mid twentieth century, adaptationist and comparative approaches to understanding the development of marine organisms posed diverse kinds of questions, included kinds of development that were distinctively marine, and were little influenced by population genetics and the Modern Synthesis (although selection was a concept used in inferences about adaptation). These questions and the approaches used to answer them are mostly omitted in the histories of Evo-devo that I've read or heard at conferences.

Another influence on marine studies of evolution and development was institutional: small sets of researchers with diverse questions were often in contact at marine laboratories, which facilitated concepts and methods crossing disciplines. As an example, Robert L. Fernald initiated a graduate course at the Friday Harbor Laboratories entitled "Comparative embryology of marine invertebrates." The influence of Fernald and this course is easily overlooked because he never published on the topics treated in it and many of the participating students were from other institutions. The course emphasized comparative embryology more than experimental embryology but participants included developmental biologists, invertebrate zoologists, ecologists, and (later) paleobiologists. They arrived with different questions about embryos and larvae, but left with new hypotheses for their research, in part because of their interactions with one another. After auditing the course, Richard Vance, an ecologist, devised a life history model linking feeding versus non-feeding larval development to trade-offs between fecundity and parental investment per embryo (Vance 1973). His model stimulated much research because his equations were simple and easily understood; because its assumptions and predictions were widely recognized as oversimplifications, numerous studies attempted improvements. More personally, my own graduate studies had been in biological oceanography and marine ecology. Fernald's course initiated my interest in why embryos and larvae developed their forms. At the time, the answers to those "why" questions lay more directly in requirements for performance in marine environments than in developmental processes.

## 3.3 Adaptation in Development at the 1981 Dahlem Conference

The 1981 Dahlem conference addressed performance but did little to integrate adaptationist and mechanist questions. This omission left the nature and significance of limitations on adaptation unclear. One barrier to integration was the separation of discussion sections by "level" (Molecular, Cellular, Life Cycle). These categories tended to separate mechanist and adaptationist approaches.

The conference also included little on requirements for performance in the marine environment, where metazoans originated and diversified into the major clades. Recognition of early twentieth century interests in adaptations for development in the sea appeared in the citations of influential studies, such as Bonner's reference to Walter Garstang (Bonner 1982, 2). But most of the representative authors noted above (Sect. 3.2) were not mentioned, except by Freeman (1982), who was discussing features of ancient metazoan life cycles and thus marine larvae.[1] Hjort, Giard, Wilson, Thorson, and (unsurprisingly) Werner went uncited in the 1981 workshop reports.

How and whether studies of the performance of developmental stages enters Evo-devo depends on the questions being asked. An adaptationist approach is necessary (though insufficient) to answer questions about why organisms' development evolved one way rather than another, or how developmental constraints affect the performance or fitness of organisms. But the study of fitness or performance was not necessary to meet several other goals at the 1981 Dahlem conference. Some were dissatisfied with the neo-Darwinian emphasis on changes in gene frequencies and wanted to open the black box between genotype and phenotype; a model where genes produced traits through a black box, with no known mechanisms for pleiotropy, was insufficient. Others concentrated on demonstrating a constraint on form without considering fitness or performance (Alberch 1982).

Developmental constraints exist, and studies since the 1981 Dahlem conference have increased our understanding of these constraints, especially via analyses of the molecular genetics underlying pleiotropies. But the interest in constraint has waned as knowledge of flexibility in development has increased. Developmental processes are remarkably permissive of evolutionary change. Stabilizing selection appears to play a large role in evolutionary stasis (Wray and Strathmann 2002).

Measuring stabilizing or directional selection is often impractical, and often the events of interest are in the remote past. One can, however, identify functional requirements that must be met by organisms as they develop. The analysis of the functional requirements for developing animals has not been a conspicuous part of the Evo-devo literature. There has been more emphasis on *how* development has changed (or not) than on *why* development has changed (or not).

## 3.4 After Dahlem 1981: Examples of Functional Constraints on Embryos and Larvae

In the three decades from 1980 to 2010, studies of evolution and development have been transformed by molecular genetic methods; they have profoundly changed how marine biologists study gametes, embryos, and larvae. Starting in the 1970s,

[1] There are two citations of Garstang (pp. 157, 166), two of Hörstadius (pp. 158, 163), and three of Jägersten (pp. 158, 160, 163).

and especially from the 1980s onward, molecular methods opened up new possibilities for exploring evolutionary population genetics (Hart and Marko 2010), molecular genetic aspects of development, and the phylogeny of marine organisms (Telford and Littlewood 2009). Also, paleontology has provided indications of larval evolution, including body fossils of Cambrian arthropod larvae (Zhang et al. 2007), inferences from shell apices of different timing for the origins of feeding larvae in molluscs (Nützel et al. 2006) and brachiopods (Freeman and Lundelius 2005), and inferences from skeletal calcite crystal axes and gonopores about the timing of losses of a feeding pluteus stage (Emlet 1985; Jeffery 1997). The discoveries from molecular genetics and paleontology have vastly increased our understanding of the evolution of development.

These studies are often separated from the functional biology of embryos and larvae, in part because different questions are asked. Most questions in Evo-devo concern the history of changes in developmental processes, but some questions that might be asked in Evo-devo cannot be answered without investigating the functional requirements imposed by the environment of embryos and larvae. Below are several examples of adaptationist studies that illustrate how information about performance and developmental processes can be combined to yield a better understanding of the evolution of development.

Examining the functional consequences of traits of organisms is far from new, but some of the approaches reviewed here use methods not applied to development before 1981. The examples illustrate kinds of explanation that seldom arise in developmental biology. The examples span development from egg to metamorphosis. I have drawn examples from my areas of research, but similar examples of performance requirements during development can be found in studies of other organisms and habitats.

### *3.4.1 Why There Are Embryos: The Unicellular Bottleneck in Life Histories*

Embryos exist because of a unicellular bottleneck in the life histories of multicellular organisms. The inferred reason is the functional advantages of genetic uniformity, or rather near uniformity (Kondrashov 1994; Grosberg and Strathmann 1998). Most of the proposed advantages of sex cannot be obtained without a unicellular stage. Without reduction of the individual to a single cell, both syngamy and meiosis would produce chimaeric individuals with genetically heterogeneous cells. Instead of partitioning genetic variation among offspring, all offspring would be compromised by numerous genotypes. That much seems obvious, but asexual organisms also accumulate genetic heterogeneity unless there is a unicellular bottleneck. Mutation is one source of intercellular genetic variation within an organism. Invasion by foreign cells is another source of genetically distinct replicators within an organism. (Genetically distinct replicators include parasites

and mutualists.) The unicellular bottleneck does not, by itself, resolve all problems from conflicts among separate replicators, but it can reduce genetic heterogeneity of mitochondria, chloroplasts, or other vertically transmitted symbionts. The potential advantages of a unicellular bottleneck are numerous, but a cost is vulnerability due to reduced size and capabilities. Diverse modes of development have evolved as means of surviving while restoring the capabilities of a multicellular organism. The extent to which risks from somatic mutation and symbionts favor a unicellular bottleneck has stimulated theoretical discussion with little connection to empirical studies that employ molecular genetic methods.

Several biologists have suggested all or part of the preceding hypothesis, in most cases as a new insight without any citation of other authors. These biologists did not, to my knowledge, include developmental biologists, except for Wolpert (Wolpert and Szathmary 2002). It is curious that people who study embryos are unlikely to ask why there are embryos.

### *3.4.2 Risk and the Evolution of Embryonic Cell Cycle Durations*

For embryos and larvae in the sea, estimated mortality rates are high for planktonic embryos and small planktonic larvae. Estimated instantaneous mortality rates of $> 0.1\ d^{-1}$ are usual (Strathmann 1985; Rumrill 1990; Lamare and Barker 1999; Ohman et al. 2008). In contrast, embryos that are protected in broods or egg masses appear to be safer, with estimated mortality rates of $< 0.1\ d^{-1}$ being common (Strathmann 1985; Rumrill 1990). Intraspecific comparisons for a wrasse also demonstrated the importance of parental protection for reducing mortality rates of embryos (Warner et al. 1995).

In comparisons among species within four clades (asteroids, gastropods, brachiopods, and phoronids) development was slower for species with more protected embryos. Planktonic embryos that develop singly developed faster than embryos protected in broods or egg masses, with time from first to second cleavage as the measure (Strathmann et al. 2002b). A similar correlation between embryonic protection and cell cycle duration occurs in other habitats. In many cases, larger unprotected embryos have shorter early cell cycles than smaller protected embryos. For example, the early cell cycles in the clawed frog *Xenopus laevis* are shorter than in the mouse *Mus musculus*, despite the smaller egg and higher temperature for the mouse.

The contrast suggests either selection for slower development of embryos at low risk or genetic drift when there is little or no selection for fast development. The hypothesis of selection is plausible because of the constraints that short cell cycles impose on embryos. Hypothesized benefits of longer cell cycles include less maternal investment in rate-limiting materials, correction of errors, and more or different early transcription (Strathmann et al. 2002b).

### 3.4.3 *Risk, Scope for Asynchronous Cleavages, and Evolution of Cell Fates*

Slow development of protected embryos could connect parental protection of embryos and the evolution of earlier differentiation of cell fates, which could confer functional advantages. Although the longer early cell cycles of protected embryos can allow more early transcription, it is not known how often that difference in transcription evolves following a change in risk or whether it is common for differences in gene expression among cell lineages to appear earlier in more protected embryos. There are some suggestive comparisons. Mice have more early transcription and longer early cell cycles than *Xenopus*. Cytological evidence suggests more early transcription in the embryos of marsupial frogs than in frogs with less protection and faster development (del Pino and Loor-Vela 1990). To my knowledge, the generality of associated evolutionary divergences in development rates, early transcription, and early differentiation of cell lineages has not been explored. An examination of molecular level trade-offs for durations of early cell cycles could be an illuminating combination of mechanist and adaptationist approaches.

Does slower development with protection permit innovations in early development? Here is a speculative hypothesis for the evolutionary possibilities associated with the asynchrony permitted by protection. In gastropods, protection of embryos is associated with a smaller number of cells when the mesentoblast is formed. There is an evolutionary trend toward greater asynchrony among cell lineages, with relatively slower cleavages in the micromeres (van den Biggelaar and Haszprunar 1996). In patelloidean limpets, trochoideans, abalones, and other gastropods that are predominantly free-spawners, early cleavages are rapid and nearly synchronous. In these gastropods, there are more cells (from more divisions of the micromeres) when the mesentoblast is formed. The association of longer early cell cycles with protection suggests that slower development in gastropod lineages with more protected embryos has permitted the evolution of greater asynchrony among cell lineages. The relatively slower cleavages in the micromeres of protected embryos may provide an opportunity for induction of bilaterally distributed fates in micromeres at an earlier stage of micromere divisions and differentiation. In some gastropods the micromeres that ancestrally formed part of a radial arrangement of prototrochal cells (Damen and Dictus 1994) form other structures of the head, possibly because micromeres can develop bilaterally distributed fates at earlier cleavage stages (van den Biggelaar 1971).

Adaptationist and mechanist approaches could be productively integrated to explain patterns in the evolution of developmental processes that result from differences in protection. The adaptationist approach can relate cell cycle durations to risk but needs the mechanistic data to explain possible trade-offs. The mechanist approach can use functional constraints to explain the evolution of developmental processes, but only if there are data indicating performance criteria that the environment imposes on development. Both approaches benefit from improved phylogenetic inferences that establish independent contrasts.

### 3.4.4 Limits on the Protection of Embryos

Parental protection affects the evolution of embryos and has evolved many times. Alternatives to parental protection and its physical constraints differ in air and water, and between freshwater and the sea. Water differs from air in being denser, more viscous, and (of course) wetter. The sea differs from freshwater in permanence and degree of multidirectional transport. Features of the sea permit planktonic development as an alternative to protection (Strathmann 1990).

Although free spawning and planktonic development are adequate in the sea, they are not necessarily the safest way to develop. That leads one to ask why there is so little parental protection of embryos in many marine animals. There is not yet a general answer to the question, but oxygen supply appears to limit protection on or in the body of aquatic animals with high fecundity and also restricts the construction of non-brooded egg masses. Oxygen is not highly soluble in water; diffusion into a mass of embryos is slow, and the viscosity of water limits flows through interstices between embryos (Strathmann and Strathmann 1982, 1995). In many clades of marine animals, embryos are brooded in species with small adults, and not in species with large adults. Fecundity tends to increase with body weight or body volume. The space necessary to deploy embryos in a thin layer increases approximately with body area. The tendency for smaller adults to provide greater parental care (on or in their bodies) does not seem to be found among terrestrial animals. It is a feature with consequences for the evolution of embryos that is peculiarly aquatic.[2]

Constraints on oxygen supply to embryos are one of several constraints on the evolution of protection. Risk constrains embryonic cell cycle durations, and short embryonic cell cycles constrain features like transcription and the asynchrony of cleavages.

### 3.4.5 Constraints on Performance that Constrain Traits of Blastulae

Embryos that develop singly in the plankton develop motility at a younger age and earlier stage than more protected embryos (Staver and Strathmann 2002). Many animals develop cilia early so that blastulae and gastrulae can swim. There are indications that swimming could reduce risk by keeping embryos away from predators on the seafloor, but the evidence is slim. Whatever the advantages of early upward swimming, comparisons of the speeds of sinking and swimming of echinoid blastulae and early trochophores suggest performance standards that

[2] The constraint is not universal. A few large marine animals, like crabs, can ventilate large broods. These have evolved ways of increasing the porosity of a mass of embryos, and of pumping water in and out of the brood. There is, however, an energetic cost, despite decapod crustaceans' elegant solution to the size problem (Fernández et al. 2000; Baeza and Fernández 2002).

restrict combinations of traits: swimming speed declines with increasing size, sinking speed is unrelated to size, and excess density scales (approximately) as the inverse of length squared (McDonald and Grünbaum 2010). These results suggest that selection on performance in swimming constrains overall density of blastulae and thus their construction. Swimming speeds adjusted to neutral weight were unrelated to size for trochozoans but declined with increasing size for the sample of echinoids, suggesting clade-specific differences in the scaling of swimming with size that could result in clade-specific differences in selection on egg size.

The sizes and distribution of cells of blastulae also affects their passive stability for upward swimming. Passive stability plus their overall width also affects the stability of blastulae in shear from turbulence (McDonald 2012). Blastulae and gastrulae have evolved to cope with particular environments. Explaining their traits requires analyses of performance relevant to those environments.

### *3.4.6 Physical Constraints on Performance that Constrain Forms of Plutei*

Developmental processes are insufficient to explain the form of the pluteus larvae of echinoids and ophiuroids. The functional requirements of feeding and swimming for the larval form establish what the developmental processes must produce. Food for planktonic larvae is scarce, and growth of echinoderm larvae is at least somewhat food limited, which indicates that the maximum rate for clearing a volume of water of food particles is a relevant measure of larval performance (Fenaux et al. 1994). Maximum clearance rate is proportional to the length of the pluteus' ciliary band (Hart 1996). In echinoids and ophiuroids, the ciliated band is extended on arms supported by skeletal rods. The pluteus form appears to be effective for feeding. Plutei of echinoids and an ophiuroid had a greater clearance rate per cell of the ciliated band than did the bipinnariae of asteroids and an auricularia larva of a holothuroid (Hart 1996). However, compromises between performance in feeding and performance in swimming constrain pluteus structure.

One compromise is for passive stability in upward swimming. The center of gravity must be posterior to the center of buoyancy. This requirement accounts for the posterior body skeleton, which is not needed for body support but provides gravitational stability. The body skeleton compensates for the anterior arm skeleton, though it adds weight that increases excess density and the sinking rate (Pennington and Strathmann 1990).

Form also affects stability in shear. Shear results from turbulence and occurs on the scale of body dimensions of plutei. The arrangement of arms affects tilting of the larval body in the shear. Plutei tilted by vertical shear move into downwelling water (Grünbaum and Strathmann 2003). Grünbaum's numerical model of flow generated by ciliated bands of pluteus larvae indicates effects of the number,

lengths, and angles of larval arms on their stability in shear. In the model plutei had 2–12 arms (with total length of arms constant), a center of gravity, and a center of buoyancy. Speed and capacity to carry weight were low with high arm elevations, but high arm elevations increased stability in shear (Grünbaum and Strathmann 2003). Most plutei have high arm elevations, suggesting that stability in shear is important for them. Observations of eight-armed plutei swimming in vertical shear confirmed the model's prediction: an upward swimming gravitationally stable pluteus was tilted by vertical shear, swam across flow lines, and thereby moved into downwelling water (Strathmann and Grünbaum 2006). The forms of diverse plutei are consistent with the model's predicted compromises between stability in shear and capacity to carry weight. Being weighted for passive orientation to accomplish upward swimming can result in swimming from upwelling toward downwelling water. Clay and Grünbaum (2010) found differences in stability in shear for four-, six-, and eight-armed plutei, and inferred from additional modeling (by approximating the observed arm lengths) that departures from a narrow range of morphologies in the developmental sequence would impair performance in swimming.[3]

The methods for investigating functional constraints on pluteus forms include numerical modeling of flow from ciliated bands and observations of swimming in shear. The model plutei constitute a morphospace, with parameters that include centers of gravity and buoyancy, arm lengths, arm numbers, angles between arms, and angles of elevation of arms. The occupation of this pluteus morphospace is limited by functional constraints. Adding performance criteria to a morphospace indicates developmental sequences that will be favored by selection.

Investigations of the constraints on swimming blastulae and on pluteus forms are still in progress, but the moral to be drawn from these examples is clear. Developmental processes evolve to produce a form but do not explain why that form must be produced by development. One cannot understand the disparate forms of embryos and larvae without studies of what is required for adequate performance—and ultimately for survival—in their usual habitats. Gene regulatory networks and other features of development explain *how* forms are produced but cannot explain *why* those forms are produced. If a goal of Evo-devo is to explain the diversity in development, it must include functional constraints on each stage in the life history.

### *3.4.7 Performance Compromises and Evolutionary Transitions*

The long looping ciliary bands of echinoderm larvae achieve high clearance rates but are poorly positioned for swimming. The high arm elevations of plutei result

[3] In ongoing research, K.Y. Chan is seeking to increase the realism of these simulations further with model plutei based on images from confocal microscopy.

in a lateral rather than posterior direction for a large component of the ciliary current. The bands of auricularia and bipinnaria are tilted so that there is a posterior component to the current along most parts of the loop of ciliary band. Cilia beating directly in the posterior direction are more effective in swimming, as with the transverse rings in the non-feeding doliolaria stage or the field of cilia of many non-feeding echinoderm larvae (Emlet 1994; Strathmann and Grünbaum 2006). When a lineage of echinoderms evolves nutrient rich eggs and loses the requirement for larval feeding, the form of the ciliary band is usually lost and the larvae become spheroidal. Once these changes with non-feeding are far advanced, there is little on which selection could operate were larval feeding to again become advantageous (Strathmann 1974; Raff and Byrne 2006).

In contrast, the prototrochal ciliary band of trochozoans is well situated for both swimming and feeding (Emlet 1991). The prototroch is common to both feeding and non-feeding larvae, and feeding and non-feeding larvae are often similar in form. Evolutionary loss of larval feeding usually has a small effect on this larval form, as long as motility is still required (Strathmann and Grünbaum 2006).

### *3.4.8 Juvenile Rudiments as Modules*

Modularity can enhance evolvability, but selection could favor modularity in development for a variety of functional reasons. One functional advantage is enhanced plasticity in response to environmental challenges. Modularity permits plasticity in the size of structures and the timing of their development. The evolution of juvenile rudiments as modules separate from ephemeral larval bodies provides opportunities for such adaptive plasticity, and the advantages of the plasticity may enhance selection for the modularity of rudiments.

Rudiments of juvenile structures evolve for a variety of reasons. They are sequestered where larval function is unimpaired but can be deployed rapidly at metamorphosis (Hadfield et al. 2001; Page 2000), and, relieved of functional demands, the rudiments can grow while cells are less differentiated (Ricklefs et al. 1994). The evolution of juvenile rudiments as separate modules also allows adaptive heterochrony during development in response to abundant and scarce food. When food is scarce, echinoid larvae allocate growth to the development of longer larval arms (the ephemeral larval body) and delay the development and growth of the juvenile rudiment. The plasticity appears to be functionally advantageous. The longer ciliary band on the longer arms increases the capacity to catch food (Hart and Strathmann 1994). When food is abundant, the juvenile rudiment grows earlier, allowing earlier development toward metamorphic competence. Rudiments of juvenile structures can also serve as a nutrient reserve during hard times, being resorbed when food is scarce and regrown when food becomes abundant, as in the cyphonautes larva of bryozoans (Strathmann et al. 2008).

As West-Eberhard (2003) has discussed, selection can maintain modularity because of the current advantages of plasticity but with long-term consequences for evolutionary change. In the case of echinoids, the modularity that allows heterochronic developmental plasticity in the feeding larvae may facilitate the evolution of a shift to the earlier development of the juvenile rudiment in non-feeding larvae (Bertram et al. 2009; Raff and Byrne 2006).

### *3.4.9 Casual Assumptions About Dispersal as a Function*

Functional explanations of features in development are often mentioned as if they were obvious, but hypotheses of function that seem plausible may be incorrect. Tests of hypotheses on function can require diverse kinds of information. As an example, many sessile or sedentary marine animals have planktonic feeding larvae that are among the best dispersers on earth—some cross oceans (Scheltema 1988). If a trait allows an organism to do something spectacularly well, it is tempting to conclude that the trait evolved to perform that function. However, diverse kinds of evidence indicate that extended development as a planktonic swimming larva is not an adaptation for dispersal (Strathmann 2007).

1. Observed dispersal is often less than what larvae could achieve by passive drifting in ocean currents (Strathmann et al. 2002a; Shanks 2009).
2. There are no structures or behaviors of feeding larvae that are unambiguously for long distance dispersal.
3. Planktonic feeding larvae are often an obligate part of reproduction, not a response to deteriorating local conditions.
4. With obligate dispersal on large scales (>10 km), net export from good to poor habitat is expected to increase with increasingly large-scale dispersal.
5. Spreading offspring in space can enhance rate of increase over generations by reducing variation in increase among generations ("bet hedging"), but gains are expected to diminish with increasing scale of spread.
6. Obligate dispersal on large scales is an obstacle to colonization, and the founding of persisting populations at remote habitat patches occurs without long larval durations.
7. Some entirely pelagic animals have planktonic larvae like those of benthic animals.

In contrast, the *behavior* of larvae that are released near metamorphic competence appears to function for dispersal. These larvae commonly swim upward initially, toward the light or against gravity, and then down after a short time. Larvae that feed in the plankton for long periods disperse the most but appear to be trying to disperse less. Larvae that are in the plankton briefly try to disperse. Doing something spectacularly well need not imply selection for doing it.

### *3.4.10 Stasis and Change in Body Plans*

An appreciation of the distinction between phylum (as applied to a clade) and body plan (as designating ways bodies are organized) has increased since the 1981 Dahlem conference. The confounding of phyla with body plans has resulted in misconceptions about the early origins and subsequent stasis of animal body plans. If one defines body plans using the kinds of structural features that distinguish phyla, rather than by membership in a phylum, then one sees that the early appearance of phyla does not imply a subsequent stasis in body plans.

A review of changes in body plans throughout the Paleozoic or subsequent to the divergence of classes within phyla indicates that changes in functional demands have played a key role in numerous changes of animal body plans, many of which are associated with changes in nutrition, locomotion, or body size (Wray and Strathmann 2002): bilaterians can lack a gut; ecdysozoans can form colonies with modules connected by stolons; annelids can lack setae or coelom; gastropods can be bivalved; and ascidians can lose a notochord, with some *Molgula* species unchordating while not changing their genus.

Changes in a body plan trait that result from the loss of a functional requirement suggest that the trait has been maintained by stabilizing selection rather than a developmental constraint. But requirements for developmental processes, as well as other functions, can impose a burden that restricts evolutionary change (Riedl 1978). The notochord of tailless ascidians may provide an example of a developmental burden that persists after the removal of other functional burdens (Takada et al. 2002; Gyoja et al. 2007). Two tailless *Molgula* species retain precursors of notochord cells that express *Brachyury* but do not divide or express *Brachyury* to the extent that occurs in tailed molgulids. Actin genes for larval muscle have become pseudo-genes. Initial stages of notochord development may be retained for some developmental functions even though the notochord and tail have been lost.

## 3.5 Generalizations and Particulars

In the preceding examples, some studies of performance resulted in broad generalizations about development; others applied to a narrow range of animal embryos and larvae. Performance involves particular ways of surviving and reproducing in particular habitats. Similarly, despite the generality of some roles of genes in animal development, evolutionary changes in the roles of genes in developmental processes also involve a long list of particular cases. Evo-devo can suffer from the same particularity as functional morphology.

Is that disappointing? Not if one is trying to explain the diversity of organisms and their development. But this diversity—the many particulars that make up the living world—is not a fashionable topic for funding. Academics value generality,

but the diversity of life on earth involves the peculiarities of disparate organisms and environments. Broad generalizations about evolution do not account for the particular and diverse kinds of organisms that we encounter. If we limit our studies to those that lead to the broadest generalizations, we may be more successful as academics and less successful in understanding life on earth.

## 3.6 Reflections on Research Interests, Evo-devo, and Evolutionary Theory

Studies of developmental processes, phylogeny, and the paleontological record are insufficient for understanding why organismal development has evolved as it has. A complete understanding of how mutation, selection, and drift produced past and present organisms is unattainable, but performance requirements greatly narrow the possibilities. Studies of performance and its consequences go a long way in explaining *why* change and stasis have occurred. That is clearly an advance beyond a description of *how* they have occurred.

A common and fair complaint by Evo-devo enthusiasts at the 1981 Dahlem conference was that the Modern Synthesis did not adequately include development. One could also complain that Evo-devo has not adequately considered functional demands on organisms during their development. But it is hardly surprising that biologists' interests vary. As a graduate student I paid more attention to Waddington, de Beer, and Garstang than to Dobzhansky, Simpson, and Mayr, but I paid the most attention to the *functional biology* of marine organisms. I came to my interest in embryos and larvae from my studies at a field station that provided opportunities to observe development live and in great variety. Marine embryos and larvae are objects of beauty, and my goal has been to explain why they look the ways they do. That is not the usual justification for research and not the one I put in grant proposals or publications, but it holds my interest. Watching eggs—little spheroids—turn into swimming, feeding, reacting animals is fun. Changes in morphology are a key part of that fun. The conceptual tools for developing and testing explanatory hypotheses for those forms and their changes come from diverse sources; certainly not just the Modern Synthesis and certainly not just the most common approaches in Evo-devo. What I wanted to know about the form and behavior of embryos and larvae was answered mostly but not entirely by studies of what performance requirements they must meet and how they meet them. I continued to feel that way after the 1981 Dahlem conference. I appreciate that developmental processes affect evolutionary processes, but my working assumption continues to be that selection has shaped embryos and larvae. Selection occurs within limits set by ancestral equipment, but Evo-devo hasn't yet (to my knowledge) revealed much about why embryos and larvae have evolved the forms and behaviors that they have.

Why should one care if the Modern Synthesis attained great prestige and other approaches to evolutionary biology perhaps less? In a competitive research

environment, it is common for biologists to promote their questions and hypotheses at the expense of others' interests and questions. Researchers can gain prestige and resources by promoting their area of study as central to explaining a phenomenon of broad interest.[4] One source of these differences in interests and hence, perhaps, of philosophical differences, is our mating system. If we all belonged to the same clone, the jostling for possession of the high ground would not occur. There would be more mutual appreciation; however diverse our studies, when appreciating others we would be appreciating ourselves.

One reason to care about research agendas and theoretical stances is that knowledge is limited by the distribution of resources for research. Has the enthusiasm for particular kinds of questions affected hiring or funding for those interested in the evolution of development? The program for Developmental Biology at NSF took a very narrow view of developmental biology, with an emphasis on proximate mechanisms and a few model systems. That frustrated developmental biologists interested in evolution because the program's criteria excluded comparative methods for testing hypotheses and most aspects of the evolution of development. In turn, practitioners of Evo-devo have largely excluded life history theory, functional morphology, and behavior as they apply to developing animals, but these studies continue under the names of other disciplines with funding from a variety of sources that are not specifically concerned with development and often not explicitly concerned with evolution. I would never be hired as either a developmental or evolutionary biologist but I did get a job as a marine biologist. (By lucky chance, Biological Oceanography at NSF acquired a program director with broad interests, and my research has been funded mostly from that source.)[5]

A difficulty for many kinds of research is a criterion for funding: the question in a proposal should be of general interest. But if no one else has asked the question, it is not yet of general interest. For pursuit of funding, hypotheses in a proposal should be original but not too original. Advances in Evo-devo will be aided by unexpected results from proposed research and small deceptions in grant proposals.

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[4] One also sees the device of "my hypothesis is the null hypothesis; your hypothesis is the alternative hypothesis."

[5] This highlights another obstacle to studies of marine organisms: many biologists regard terrestrial phenomena as general and marine phenomena as special cases. One editor of *American Naturalist* commented that marine invertebrates are not of general interest. The sea is the largest habitat on earth, a habitat in which organisms originated and diverged into the major clades. It is not, however, the habitat of the editor.

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# Chapter 4
# Is Heterochrony Still an Effective Paradigm for Contemporary Studies of Evo-devo?

**James Hanken**

## 4.1 Introduction

If there is one topic that can be most closely associated with the tremendous resurgence of interest in the relation between evolution and development that characterized biology in the late 1970s and 1980s, then surely it is *heterochrony*. The role of change in the relative timing of developmental events has been emphasized again and again since before the term heterochrony was coined by Ernst Haeckel in the mid-nineteenth century. But this interest virtually exploded when Evo-devo was reborn in the late twentieth century following the publication of several seminal books and papers (e.g., Gould 1977; Raff and Kaufman 1983), the convening of timely workshops and symposia (Bonner 1982; Goodwin et al. 1983; Raff and Raff 1987), and the founding of new journals. These events reflected the growing recognition that a greater appreciation and consideration of the role of developmental patterns and their underlying mechanisms was needed to achieve a more comprehensive understanding of the evolution of organismal form and phyletic diversification than was offered by the prevailing Modern Synthesis (Hamburger 1980; Roth and Wake 1985). Thus, the 1981 Dahlem conference (Bonner 1982) straddled a key period in the history of evolutionary biology and provides a convenient and valuable vantage point from which to observe the history of these and related ideas.

The heterochrony literature is enormous, and it is not my goal here to present a comprehensive assessment of this exciting and much-debated topic. Readers interested in such compilations are encouraged to consult any of several lengthy reviews (Hall 1990; McKinney 1988; McKinney and McNamara 1991; Raff 1996). Rather, I present a more personal assessment of how views of heterochrony and its

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importance have changed over the last 30–40 years, from the standpoint of one who came of age in the late 1970s and early 1980s (academically speaking) and who has continued to work in Evo-devo, in one capacity or another, ever since. My treatment emphasizes the shorter interval that bracketed the 1981 Dahlem conference, but also benefits from the important perspective that has emerged over the last few years as a result of the tremendous increase in knowledge and understanding of the molecular-genetic mechanisms of development and of how these mechanisms are perturbed in the evolution of morphological diversity.

## 4.2 History of Heterochrony up to 1981 Dahlem

The recognition that changes in developmental timing may underlie evolutionary changes in juvenile and adult morphology has a long and complicated history. Ernst Haeckel, the sensational nineteenth century German naturalist, embryologist, evolutionist and philosopher, both popularized the concept—he literally coined the term "heterochrony"—and embedded it within an explicitly phylogenetic paradigm (Haeckel 1866). But Haeckel was far from the first scientist to call attention to the fact that embryos differ in the relative timing of developmental events or that such changes are related to differences in form that are manifest later in ontogeny (Gould 1977). Haeckel's views, however, and especially his "biogenetic law"—ontogeny recapitulates phylogeny—embraced the recapitulation doctrine, which by the early twentieth century was untenable to many leading embryologists. In 1930, Gavin de Beer presented a classification of evolutionary patterns that included several different types of heterochronic phenomena. This classification, which abandoned most of the claims and assumptions of recapitulation and rejected the causal connection between ontogeny and phylogeny that is implied in the biogenetic law, was published again a decade later and illustrated then for the first time (de Beer 1940; Fig. 4.1). de Beer's ideas had lasting impact. Indeed, they "formed the basis for most discussion, in the English literature at least" for much of the remainder of the twentieth century (Gould 1982, 334). At nearly the same time, in 1932, Julian Huxley's *Problems of Relative Growth* explored the implications of changes in developmental timing in an evolutionary context. Huxley implicated "rate-genes" as possible regulators of differential growth and, hence, morphological diversification (Fig. 4.2), a theme that he would later elaborate (Huxley 1942), along with Richard Goldschmidt (1940). Interestingly, while largely coincident in time, the ideas of Huxley and de Beer differed in important ways, reflecting these two Oxford-trained scientists' contrasting views regarding the appropriateness of seeing causal connections between ontogeny and phylogeny (Churchill 1980).

Gould (1977) provided a lengthy historical review of heterochrony as a concept and how its definition in and application to evolutionary theory changed from the mid-1800s through the first three quarters of the twentieth century. Disappointed that previous definitions, applications, and graphical depictions of heterochrony lacked sufficient clarity to offer meaningful insights into underlying developmental

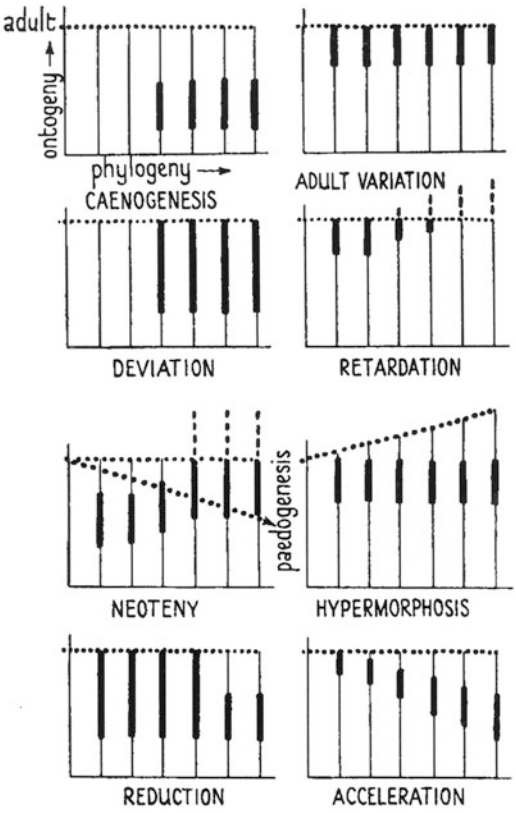


**Fig. 4.1** de Beer's eight categories of heterochrony (1940, Fig. 2). Each graph depicts an ancestor-descendant sequence (from *left* to *right*) and an individual ontogeny (from *bottom* to *top*). The *thick black lines* denote "evolutionary novelty." The distinct pattern of evolutionary change depicted in each graph is regarded as a separate category, and each receives its own name (e.g., caenogenesis, retardation). As noted by Gould (1977), only some of de Beer's categories are actually modes of heterochrony (neoteny/paedogenesis, retardation and acceleration), and these "reduce to" discrete manifestations of two underlying processes, acceleration and retardation

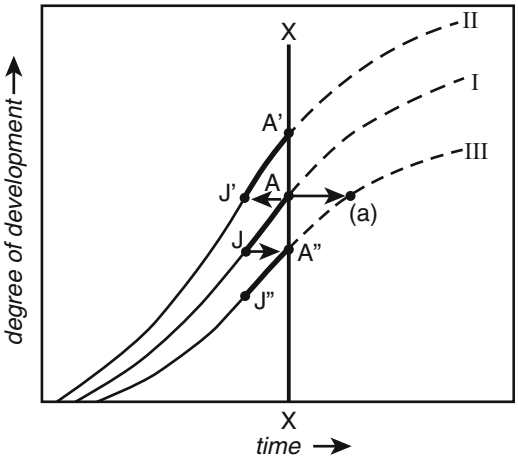


**Fig. 4.2** Huxley's depiction of the possible alternative effects of mutations in "rate-factors" (or "rate-genes") on the developmental rate of a given character (1932, Fig. 104). Rate acceleration allows a derived ontogeny (line II) to exceed the degree of development attained in the ancestor (I). With rate deceleration (III), the derived ontogeny terminates before it reaches the degree of development attained by the ancestor. These two contrasting outcomes correspond to two of de Beer's (1930, 1940) eight categories of heterochrony, *acceleration* and *retardation*, respectively. Vertical line (X—X) denotes the time during ontogeny when differentiation ends

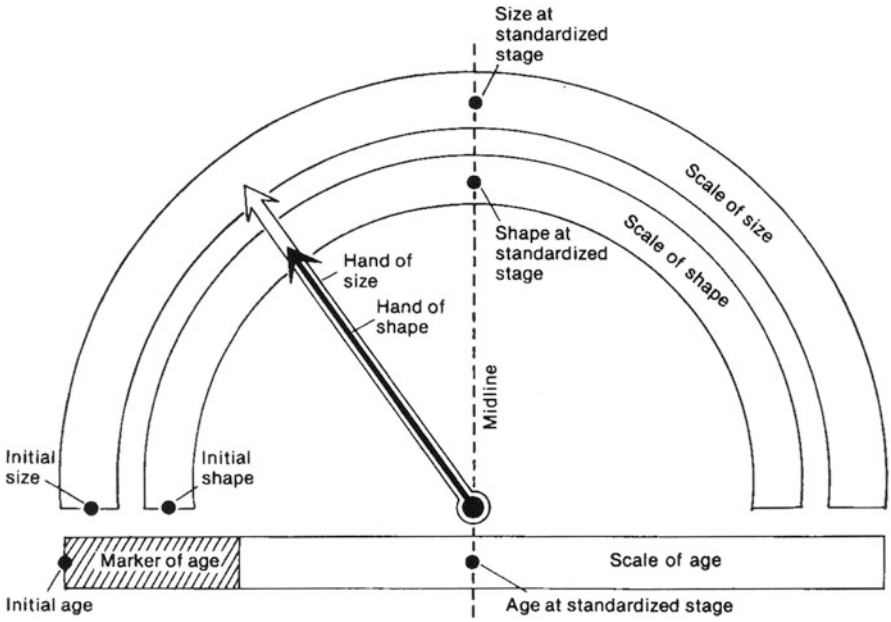


**Fig. 4.3** Gould's "clock model" was offered as a means of graphically depicting correlations among organismal size, shape, and age during ontogeny, as well as dissociations among these three parameters that might occur during evolution (1977, Fig. 33)

mechanisms, Gould proposed a "clock model" to explicitly represent—independently and in combination—the effects of change in age, shape, and size (Fig. 4.3). In doing so, he hoped to achieve a synthesis of "the two great literatures on size and shape: the quantitative measurement of allometry ... and the study of heterochrony, a subject that has doggedly maintained a purely quantitative and descriptive approach" (246).

Gould's (1977) book spurred widespread interest in the relation between evolution and development in general, and in heterochrony in particular. Arguably the most significant response was a paper published only 2 years later by Alberch et al. (1979), with Gould as one of the four co-authors. Building on the intention to more explicitly identify underlying developmental processes and mechanisms that led Gould (1977) to devise the clock model, this paper offered a more quantitative method for describing how heterochronic changes in ontogeny might mediate morphological evolution and explain phyletic trends. It defined a finite number of "heterochronic processes" (e.g., progenesis) and the corresponding "controlling parameters" (e.g., timing of the offset of development), as well as the morphological and phylogenetic results obtained when those parameters change during evolution (Fig. 4.4). Gould himself would later concede that his clock model "was incomplete and insufficiently quantified to rank as an adequate formalism for heterochrony [but that] Alberch et al. ... have devised a complete and operational system" (Gould 1982, 334).

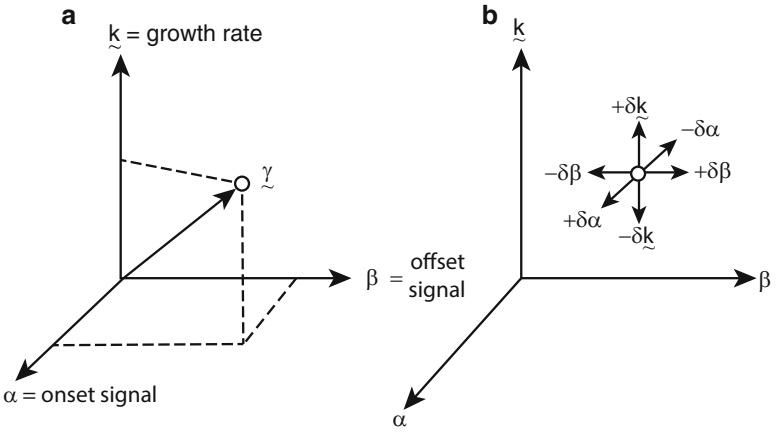


**Fig. 4.4** As an improvement on Gould's (1977) two-dimensional clock model, Alberch et al. (1979, Fig. 14) conceptualized ontogeny as occupying a three-dimensional "age-size-shape" space. (**a**) Heterochronic changes within that space comprise positive and negative perturbations in any of four growth parameters: onset age (or signal), offset signal (age or organ size), growth rate (size or shape), and initial size at the commencement of growth. (**b**) Possible perturbations to three of the four growth parameters (changes in initial size are not included in either panel)

It is hard to overestimate the combined impact of Gould (1977) and Alberch et al. (1979) on comparative biology for the following decade. The combination of a more explicit and operational terminology for use in describing heterochronic phenomena, a simple yet effective way to graphically depict differences between ancestral and descendant ontogenies, and the general acceptance that heterochrony might underlie and at least in part explain many of the most important morphological and phyletic trends in evolution, motivated the undertaking of large numbers of empirical analyses of heterochrony in groups as disparate as flowering plants, Mexican salamanders, and primates, including humans (Guerrant 1982; Hanken 1984; Shea 1983). This surge of interest in heterochrony is conveniently and simply illustrated by an analysis of the annual number of scientific publications that include "heterochrony" in their title or abstract, as tracked by several of the largest bibliographic databases (Fig. 4.5). Even though the word was first coined by Haeckel in the latter half of the nineteenth century, its use increases beginning in the late 1970s and early 1980s and has remained high to this day.

This is the environment and general attitude regarding heterochrony that prevailed among many comparative biologists at the time of the 1981 Dahlem conference. Gould's concurrent assessment of most prior work on heterochrony is stark and merciless: "the previous lack of a rigorous framework has spawned 200 years of squabble and incomprehension and has led to the common impression among evolutionists that this subject is both arcane and unprofitable" (1982, 334). Yet, he continues, "the subject of change in developmental timing still exerts its major fascination through the claim that small inputs might lead to large and

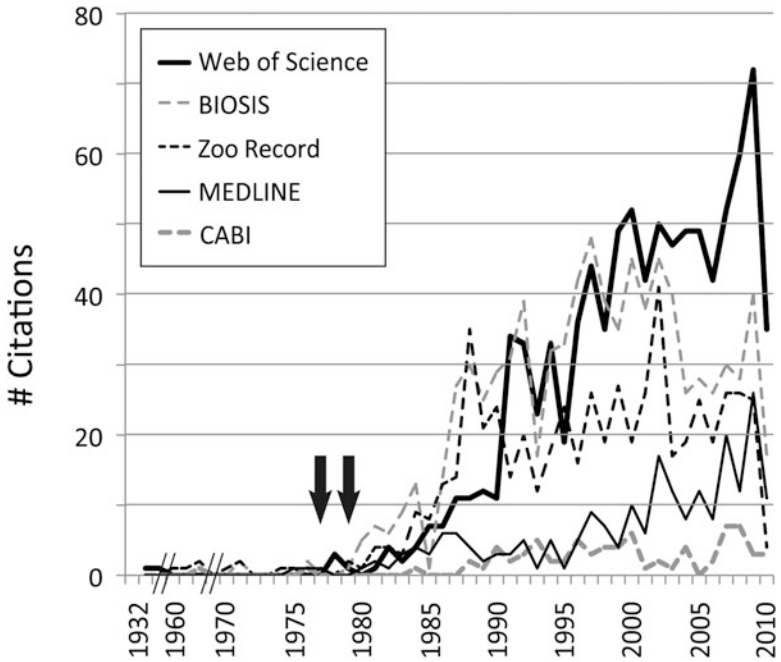


**Fig. 4.5** Number of times per year that a scientific paper was published that has the word heterochrony in its title or abstract, as indexed in five bibliographic databases: Science Citation Index Expanded [=Web of Science®], *BIOSIS* Previews and Zoological Record (Thomson Reuters, Philadelphia, PA); MEDLINE (National Library of Medicine, Bethesda MD); and CAB Abstracts (CABI, Wallingford, England). "Heterochrony" first appears in 1932 and continues to be used rarely until the mid-1970s, when its use increases dramatically. That increase continues, in at least two databases, to the present day. The two *black arrows* indicate the years of publication of Gould (1977) and Alberch et al. (1979). Each database tracks a different set of journals, although several of them track many of the same titles. Zoological Record, Science Citation Index Expanded, and CAB Abstracts track citations beginning in 1864, 1899 and 1910, respectively. Citations in MEDLINE and *BIOSIS* Previews begin much later, in 1966 and 1970, respectively. Results depicted here were obtained in July 2010

surprising outputs" (Gould 1982, 338). Subsequent analyses would continue to emphasize and explore the role of heterochrony in mediating morphological evolution and accounting for phyletic trends, such as the origin of complex novelty, homoplasy, and developmental constraint (e.g., Alberch 1983; Bininda-Emonds et al. 2003; Richardson 1999; Wake and Larson 1987).

## 4.3 Heterochrony After 1981 Dahlem

Interest in heterochrony continued to swell in the years following the 1981 Dahlem conference. Viewed from today's perspective, nearly 35 years on, these studies can be seen to represent two divergent intellectual paths. One direction comprises a

large number of mostly empirical studies of morphological variation in particular taxonomic groups, which demonstrate the valuable insights into evolutionary pattern and process offered by formal heterochronic analysis. A second path, however, is defined by researchers who highlight the limitations of heterochronic analysis. These researchers assert that other developmental processes, distinct from heterochrony, must be considered to effectively and adequately represent the evolutionary patterns involved in morphological diversification, let alone the underlying developmental mechanisms. Examples of the two contrasting approaches, and their basic conclusions, are described here.

### *4.3.1 Heterochronic Analysis is Indispensable*

Most analyses of heterochrony in the years following the 1981 Dahlem conference comprise empirical studies that analyze ontogenetic and phylogenetic data in particular clades. For the most part, these studies attempted to resolve observed trends in terms of the heterochronic processes and possible outcomes that were defined as part of Gould's (1977) original clock model, but especially as represented in the subsequent formalism provided by Alberch et al. (1979). Several authors, however, sought further modification of the formal representation and nomenclature of heterochrony. These modifications were intended to correct perceived deficiencies or limitations in the model of Alberch et al. (1979), which ranged from incorrect or confusing terminology (McNamara 1986) to a principal if not exclusive focus on interspecific comparisons (Reilly et al. 1997). Shea (1983), for example, proclaimed the need to distinguish between time- and rate-dependent processes that may yield identical morphological patterns. Thus, in place of Alberch et al.'s *paedomorphosis* and *peramorphosis*, Shea offered four new terms, *time hypo-* and *hypermorphosis* and *rate hypo-* and *hypermorphosis*. McKinney and McNamara (1991) added new terminology and further extended the heterochrony paradigm to the developmental and cellular processes that underlie patterns of morphological variation, particular those that mediate cell-cell interactions and resulting histodifferentiation early in ontogeny. McKinney and McNamara distinguished these *differentiative heterochronies* from *growth heterochronies* of late ontogeny, and argued that the latter were the focus of most prior studies of heterochrony. Differentiative heterochronies were identified as comprising two categories of phenomena, *global* and *local,* and the local differentiative category was further subdivided into two distinct types, *size differentiative* and *novel differentiative*. Befitting a discussion among systematic biologists who are frequently called upon to formally describe, differentiate, and name species, one author even offered a "key to heterochronic processes," which provided "diagnostic characters of each process" (McNamara 1986, 11).

Perhaps the most comprehensive criticism and revision of the model of Alberch et al. (1979) was offered by Reilly et al. (1997). They conceded that the model had come to be "accepted by nearly all workers in the field" (120), but identified a series

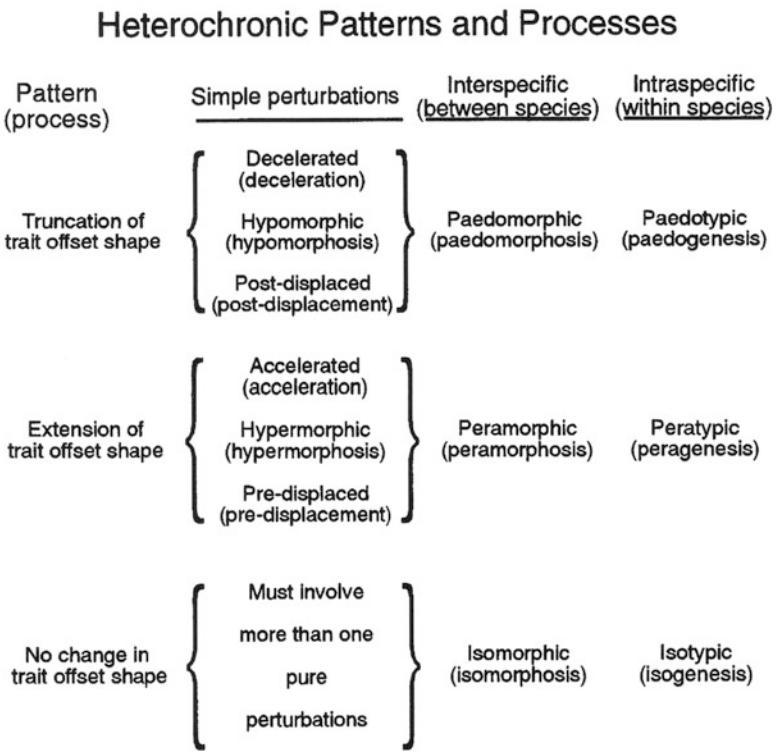


**Fig. 4.6** Revised classification of heterochronic patterns and processes. Reilly et al. (1997, Fig. 7) offered this "integrated terminology to describe intra- and interspecific heterochronic phenomena" to correct perceived errors in the model of Alberch et al. (1979), including its restriction to phylogenetic patterns (interspecific variation). The terminology recommended here is more extensive than that offered by Alberch et al.; for example, nearly all terms in the rightmost column are new, as is its explicit application to intraspecific phenomena. Parentheses denote "process names," each associated with a corresponding "pattern name"

of minor problems with the recommended terminology for describing heterochrony and one fundamental objection to the model: whereas it was intended to be used to evaluate phylogenetic patterns (i.e., interspecific comparisons), it was frequently applied to intraspecific comparisons. They found the model to be "confusing and incomplete," and that this had "led to varying degrees of misunderstanding about heterochrony among evolutionary biologists" (120). To address these problems, Reilly et al. (1997) revised the terminology of Alberch et al. (1979) as it pertains to interspecific heterochrony, but they also provided new, additional nomenclature for heterochrony that specifically applies to intraspecific phenomena (Fig. 4.6).

In evaluating the above studies of heterochrony, it is important to remember that those who were critical of the terminology, scope, and other aspects of specific models (e.g., Alberch et al. 1979) also, for the most part, accepted the basic premise that heterochronic analysis is indispensible to a meaningful understanding and

explanation of morphological diversification. Reilly et al. (1997) prominently asserted that "heterochrony may underlie all morphological variation and possibly is *the* developmental phenomenon producing all morphological change" (120).

### 4.3.2 Heterochronic Analysis is not Enough

At the same time that numerous empirical studies of morphological variation in particular taxonomic groups were demonstrating the valuable insights into evolutionary pattern and process that could be achieved by formal heterochronic analysis, a second path was beginning to be laid down by other researchers who highlighted the limitations of just such an approach. These authors argued that other developmental phenomena, distinct from heterochrony, must be considered to effectively and adequately discover many of the developmental mechanisms that underlie observed patterns of morphological diversification, or even to appropriately represent the patterns themselves. Although these authors do not deny an important role for heterochrony at some level, or that heterochronic analysis can provide valuable insights, they do assert that heterochrony does not tell the whole story. Indeed, in some instances heterochrony may not even tell the most significant part of the story.

Parichy (2001), for example, compared pigment pattern evolution and development among closely related species of salamanders (Fig. 4.7). He sought to test

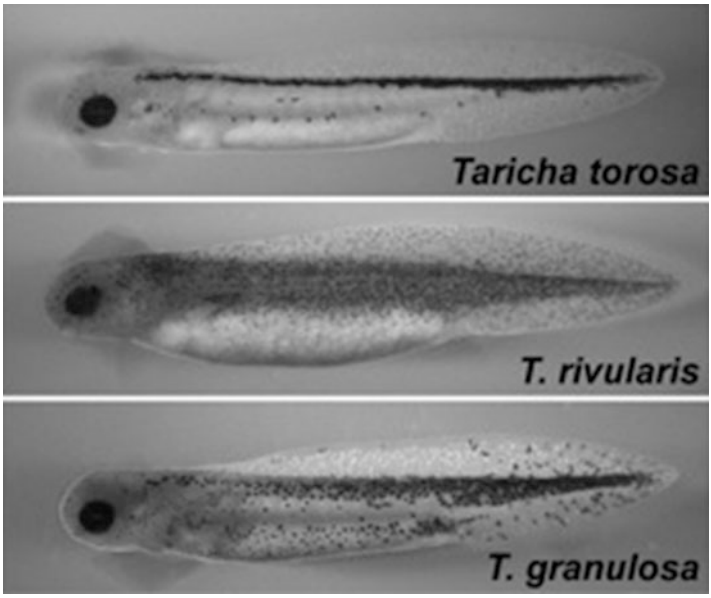


**Fig. 4.7** Larval pigment patterns vary among species in the salamander genus *Taricha*, principally in the degree to which dark pigment cells (melanophores) form a discrete longitudinal stripe on each side of the body (Parichy 2001, Fig. 7.9)

whether "interspecific diversity is causally related to heterochronies at the cellular level," or if, instead, differences among species "result from nonheterochronic changes in developmental mechanisms" (230). His conclusion was unequivocal. While conceding that "a heterochronic framework can be a useful heuristic device as it ensures consideration of various possibilities for rate and timing changes that otherwise might be overlooked," he concluded that "it is unlikely that broad patterns of heterochrony will be identified as causally related to pigment pattern evolution" (258). Moreover, "a heterochronic framework is not essential for understand [*sic*] evolutionary changes in developmental mechanisms. In some instances, it can be positively misleading. . . .investigations directed solely toward testing for heterochronies may provide relatively little insight on their own" (259).

Comparable objections or qualifications regarding heterochrony as an explanatory tool are reflected in other studies that emphasize the importance of developmental processes that mediate *spatial* patterning instead of changes in developmental timing. Zelditch and Fink (1996), for example, championed *heterotopy*, evolutionary change in the spatial patterning of development, as having at least a complementary and in some cases a prominent role in morphological evolution, particularly in the origin of morphological novelty. Interestingly, the term heterotopy was also coined by Haeckel (1866) as a complement to heterochrony, but for various reasons it never achieved anything close to the amount of attention that has been showered on heterochrony (Hall 2001). Hall (1990, 1999) and Raff and Wray (1989) offer additional discussions of the limitations of heterochrony as a conceptual and explanatory tool.

De-emphasis on heterochrony as the primary if not exclusive determinant of morphological variation, or even as a satisfactory explanation, may be seen, at least in part, as a consequence of the ongoing explosion of knowledge regarding the molecular-genetic mechanisms that mediate the genesis of organic form and how these mechanisms may be perturbed to generate phenotypic diversity (Carroll et al. 2005; Gerhart and Kirschner 1997; Wilkins 2002). The ability to implicate the action of specific genes in the generation of novel morphologies in the context of increasingly well understood models of spatial pattern formation—even when the associated genetic changes are associated with changes in the timing of gene expression—provides to many investigators a fuller and more detailed understanding of the mechanisms of evolutionary diversification than does a purely phenomenological description of a heterochronic pattern. One excellent example is the recent comparative analysis of beak morphology in Galapagos finches by Abzhanov et al. (2004, 2006). Interspecific variation in beak size and shape, which can be explained at one level simply in terms of differences in temporal aspects of growth and other heterochronic parameters (Campàs et al. 2010), is revealed to reflect the action of a small number of specific genes, each of which mediates craniofacial patterning in particular ways, combined with differences in the intensity and location of gene expression among species (Fig. 4.8).

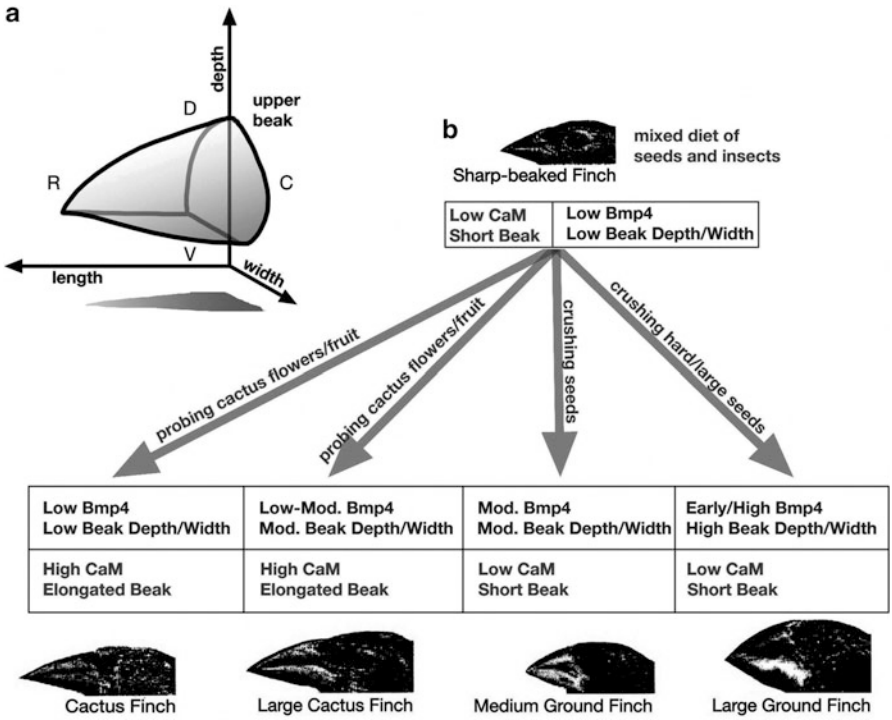


**Fig. 4.8** Levels of bone morphogenetic protein (Bmp) and calmodulin (CaM) expressed during embryonic development mediate beak growth along different axes, facilitating the evolution of distinct beak morphologies among species of Darwin's finches (Abzhanov et al. 2006, Fig. 4). The sharp-beaked finch displays a basal beak morphology from which elongated and deep/wide beaks evolved in the more derived species. Abbreviations: *C* caudal, *D* dorsal, *R* rostral, *V* ventral

## 4.4 Heterochrony in the Future: Is It an Effective Paradigm?

Evolutionists borrowed "an old word in a new context" when, beginning with de Beer (1930) and continuing for much of the twentieth century, they embraced heterochrony as "the general phenomenon of change in the timing of development" (Gould 1982, 334). In the extreme, heterochrony was represented as an all-encompassing phenomenon that is central to understanding virtually any and all aspects of phenotypic diversification. Even when underlying processes were considered, there was a conviction that these phenomena too are most effectively characterized or described in the language of heterochrony.

Increasingly, however, there has been a recognition, particularly among developmental biologists but also among comparative biologists (e.g., Thomson 1988), that the underlying molecular and developmental mechanisms may be

more effectively understood in terms of processes other than heterochrony. Although heterochrony is an effective descriptor of many patterns of morphological variation among related taxa and provides valuable insights into changes in development that effect morphological transitions during evolution, including in some instances the origin of morphological novelty, an exclusive focus on heterochrony is unwarranted except in isolated cases (Ambros and Horvitz 1984; Raff et al. 1984) This more nuanced view of heterochrony—as an important paradigm, but not the sole paradigm—provides a more comprehensive depiction and understanding of the developmental basis of evolutionary change.

At least superficially, this more nuanced paradigm is faithful to earlier theories. Haeckel required two distinct categories of ontogenetic change—heterochrony and heterotopy—to explain the evolutionary patterns he saw, and the duality of ontogenetic processes and their underlying mechanisms has been recognized again and again in the study of evolutionary morphology (Brylski and Hall 1988a, b; Radinsky 1983; Zelditch et al. 2000). Heterochrony still has an important role to play in contemporary studies of Evo-devo, but it is not an all-encompassing and exclusive role. Rather, heterochrony is one of several analytical tools needed to achieve a complete understanding of the developmental basis of evolutionary change.

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# Chapter 5
# Homoplasy, a Moving Target

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## 5.1 Background

My doctoral dissertation dealt with evolutionary diversification of a lineage of salamanders, the Lungless Salamanders (family Plethodontidae), the largest salamander clade, then with 173 species and now with ~443 species (AmphibiaWeb 2014; Wake 1966). Aquatic larvae are characteristic of salamanders, including many plethodontids, but most plethodontids have direct development—an encapsulated embryo passes through a gilled phase but hatches as a miniature of the adult. Some plethodontids spend their entire lives as gilled aquatic forms, in essence larvae that ultimately mature sexually while remaining larvamorphs. I was struck by the extent of homoplasy in the clade. For example, gilled forms had achieved sexual maturity in several different clades. While homoplasy of life history might be expected in salamanders, other kinds of homoplasy should not have been more common than in other taxa. Many features had evolved homoplastically: projectile tongues, autotomy planes in tails, interdigital webbing, increases in numbers of vertebrae accompanied by body and tail elongation, and fifth toe loss (as well as other traits). Larval reproduction, termed neoteny in salamanders, was well known in other salamander families (e.g., axolotls, mudpuppies, olms, and sirens). I came to understand that neoteny, a particular kind of paedomorphosis—the appearance of embryonic or youthful traits of ancestors in later, adult stages of descendants—took many forms in this lineage. I envisioned metamorphosis as being something more than simply the transformation of a larva into an adult. It was a span of time during which development was accelerated for many features, with diverse outcomes. When direct development evolves, metamorphosis (in the sense of an identifiable transformation from a gilled aquatic organism to a fully terrestrial one) is

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abandoned and selection is relaxed; some traits develop as in metamorphosing species, others develop more slowly or more rapidly. Some traits never appear. Thus, loss of metamorphosis is in effect an enabling event that leads to new opportunities through a kind of mixing and matching, which can produce innovation, but may also promote homoplasy. This relaxed or differential metamorphosis led to heterochrony and heterotopy, changing both the relative timing of different developmental events and the spatial relationships of morphological traits during development.[1] I saw such phenomena as opportunities for evolutionary experimentation.

Skip forward a decade. My research on homoplasy had progressed. I focused special attention on the convergent evolution of projectile tongues in salamanders, and showed that the most extreme kinds had evolved independently three times in plethodontids alone (e.g., Lombard and Wake 1977). Differential metamorphosis had played an important role. For example, loss of a functional larval stage had enabled the extreme specialization of very long tongues because intervening developmental stages did not have to function as parts of suction-generating mechanisms in larvae. Then Steve Gould's book *Ontogeny and Phylogeny* appeared (Gould 1977). A neotenic salamander, the famous Mexican Axolotl, was on the cover and its story was an important part of the book. Axolotls were mysterious organisms when first studied by scientists in the nineteenth century. They resembled giant salamanders but had gills as adults and their classification was uncertain. Then the French biologist Duméril raised some in the laboratory. Whereas the parents remained larval throughout life, the offspring metamorphosed into salamanders. Axolotls were seen as an example of evolutionary reversal, a violation of Dollo's Law (see below) and one of the three modes of homoplastic evolution (the other two are convergence and parallelism).

The mid-1970s was a time of intellectual ferment from which Evo-devo emerged. At Berkeley we enjoyed the presence of François Jacob, who was appointed a Hitchcock Professor, one of our most distinguished visiting professorships. Jacob delivered a memorable lecture on what he termed "tinkering" (derived from the French term, *bricolage*), which struck a chord with faculty and students, and led to much discussion (Jacob 1977). Jacob emphasized the contingent nature of evolution and argued that exact convergence was unlikely (e.g., eyes of squids and mammals are remarkably similar in some respects but very different in others).[2] It was just at this time that I was asked to write a review of Gould's 1977 book, and I distributed a draft to some graduate students and faculty members for their feedback (Wake 1978). As a result, I decided to offer a graduate seminar course, together with my colleague George Oster (a mathematical biologist with a background in physics), using *Ontogeny and Phylogeny* supplemented by articles such as Jacob's

[1] I used the term "differential metamorphosis" for this mode of evolution. Although the term did not "take," I use it here to refer to the phenomenon.

[2] Gould, too, argued in favor of contingency, as in his famous metaphor about how replaying the tape of life would have a very different outcome (Gould 1989).

(whose views continue to resonate; cf. Bock and Goode 2007). That course enrolled several graduate students who went on to publish important research in Evo-devo, including Pere Alberch, Jacques Gauthier, Ed Guerrant, and Jim Hanken (see Hanken, Chap. 4, this volume). We quickly focused on what we considered to be the central issue in Gould's book, his clock-face model of heterochrony. We found the presentation to be metaphorical and imprecise, but also inspirational. When the seminar finished several of us wrote up our thoughts in a more formal style than Gould had used. We sent a draft to Gould and invited him to join us as a co-author. He liked what we had done and did not take it as criticism (which was not our intent—his "model" had stimulated us to go further), but instead responded positively and offered numerous suggestions for clarification and examples to illustrate our points. Pere Alberch, then a mid-career graduate student, took the lead in developing the paper and he was the first author, with Gould, Oster, and me appearing in alphabetical order. The manuscript was published in *Paleobiology* (Alberch et al. 1979) and it became one of my most cited papers. Our intent was to produce a quantitative method for describing how heterochronic changes in ontogeny translate into patterns in phylogeny. We were more concerned with structuralist dynamics than historical contingencies at this point. We envisioned integrating development with evolutionary ecology to examine morphological evolution. "Tinkering" was inherent in the method, made explicit in control parameters that modified "ontogenetic trajectories," a concept we introduced.

## 5.2 Origins of the Dahlem Conference

Pere Alberch conducted his thesis research in the framework of the burgeoning field of evolutionary developmental biology (e.g., Alberch 1980; Alberch and Alberch 1981) and in the spring of 1978 Oster took him to a Gordon Conference, where he met Lewis Wolpert. Pere, a native of Barcelona, went directly from New England to his home, and from there he wrote me a letter (July 8, 1978).

> The Gordon Conference was very interesting since I had the opportunity to meet a lot of people in a field [Theoretical Biology] that was new for me. The most important event was to meet Lewis Wolpert. He was very interested in our paper and we had a long discussion about the role of development in evolution. He also believes that 'the next major breakthrough in biology will involve the integration of development in evolutionary theory' and the product of this discussion is that we put him in contact to Gould to organize a small meeting, probably in Germany, where the topic will be evolution and development. We will try to bring together the developmental biologists that like Wolpert are interested in general principles, with evolutionists and comparative anatomists. A small list of people who will be invited has been elaborated. . .

This is the kernel that eventually became the Dahlem conference of 1981. Alberch later recorded his own impressions of these discussions (Alberch 1995, reprinted in Rasskin-Gutman and De Renzi 2009).

While I do not remember the details of what took place next, I know that Lewis Wolpert approached Silke Bernhard, the long-time organizer of Dahlem conferences in Berlin. I was invited to an organizational meeting chaired by John Bonner at Princeton, I believe in the fall of 1980. I do not remember everyone who participated but I think all who constituted the Program Advisory Committee were present: John Bonner, Eric Davidson, Gary Freeman (see Freeman, Chap. 10, this volume), Steve Gould, Henry Horn, George Oster, Helmut Sauer, David Wake, and Lewis Wolpert. It was a positive experience for me, and out of this meeting came the basic invitation list for the subsequent conference. Later some "younger German scientists" were invited to participate in the conference, including Günter Wagner (see Wagner, Chap. 15, this volume), who, although an Austrian, was doing a post-doc in Germany, and Christiane Nüsslein-Volhard, who was an active participant in the conference discussions.

## 5.3 The Dahlem Conference on Evolution and Development

The original conference took place in May 1981 at the Europa Center located in West Berlin. I remember it as stimulating and rewarding. Dahlem conferences were well organized, or, more to the point, *rigidly* organized. Participants were arranged in four groups, and most discussions took place within the group and intergroup meetings. A couple of journalists were present. Manuscripts (subsequently published in the book) were distributed ahead of time and were intended to be foci of discussion, but the group meetings tended to more or less ignore these and develop their own "personalities." Interaction was less widespread than I had anticipated, but adequate; the more molecularly oriented group (Group I) treated the occasion as an opportunity for detailed research discussions. I felt that the other three groups reacted more in the spirit of what the organizers hoped would happen. I agree with the assessment of Alberch (1995) that dialogue between developmental, cellular, and molecular biologists, on the one hand, and ecologists, systematists, and population geneticists, on the other, was premature; little common ground was found.

It is important to remember the intellectual context in which the conference took place. I have already mentioned Gould's book, Jacob's talk and publication, and my own work with Alberch, Gould, and Oster. Other important background ideas came from Susumu Ohno's stimulating book *Evolution by Gene Duplication* (1970) and King and Wilson's (1975) postulation that changes in gene regulation were more important than genetic mutations for major steps in evolution, including human evolution. It was an exciting period of discovery in genetics as it related to development, and one had the impression that we were on the brink of something big. Nüsslein-Volhard and Wieschaus (1980) had completed their massive mutation screen in *Drosophila* and that work was enthusiastically discussed. Walter Gehring had been invited although he was unable to attend, but Klaus Sander, Antonio

García-Bellido, and Peter Lawrence ensured that homeotic genes and genetic compartments were much discussed. *Hox* clusters were as yet known only in *Drosophila*. Discovery of the homeobox and the idea of a genetic toolbox were still a few years off (McGinnis et al. 1984; Scott and Weiner 1984; reviewed in Lawrence 1992). There was a sense that we were on the verge of major research breakthroughs that would establish a field of study—what later became Evo-devo.

The conference made a lasting impression on me. While I cannot say that it changed my personal research direction in any profound way, it reinforced the trajectory of my research and left me far better informed than before and put me in touch with central workers in the area of research combining evolution and development.

## 5.4 Pere Alberch—An Early Force in Evo-devo Research

Pere Alberch was a strong presence at the meeting. He had moved from my lab directly to an assistant professorship at Harvard, without a post-doc, on the strength of his promise and some noteworthy papers (Alberch et al. 1979; Alberch 1980). Pere was one of the early figures in Evo-devo research and his lab was an exciting place for graduate students and post-docs (such as Neil Shubin, John Reiss, Annie Burke, Chris Rose and Gerd Müller). He wrote important papers on limb and tongue evolution, topics close to my own research interests, and in retrospect his creative work is seen as seminal and prescient; he has been credited as a central figure in the origin of Evo-devo (Reiss et al. 2009; Rasskin-Gutman and De Renzi 2009). His star burned brightly, but he and his research were difficult to categorize—not sufficiently molecular, not sufficiently herpetological, not mainline development—and he was denied tenure at Harvard. He returned to his native Spain where he assumed a professorial position and directorship of the Museo Nacional de Ciencias Naturales in Madrid, a position he held with distinction for about 10 years. He was about to move to Valencia, Spain, to assume a professorship and head a new program in Evo-devo in 1998 when he died of heart failure in his sleep at the age of 43 (Wake 1998).

## 5.5 Homoplasy—A Key Concept in Evo-devo Research

A primary motivation for my interest in the relation between development and evolution was my struggle with homoplasy, the evolution of similarity (morphological, in the case of my research) in independent lineages. Historically homoplasy had been variously termed convergence, parallel evolution, and evolutionary reversal. Convergence is straightforward and readily detectable if one uses an appropriate definition (e.g., false resemblance resulting from different developmental pathways in different phylogenetic lineages). Parallelism, in contrast, has always

caused problems ("a sort of intermediate case between "true" and "false" resemblance" (Eldredge and Cracraft 1980; see also Hall 2008; Arendt and Reznick 2007; Abouheif 2008). Generally, parallel evolution is considered to be that kind of homoplasy in which similar developmental genetic mechanisms are deployed to produce similar morphological outcomes. Reversal is even more difficult. There have been many reported refutations of Dollo's famous "law"—that organs lost in the course of evolution cannot be regained (see discussion below).

I mentioned that my doctoral dissertation dealt with comparative morphological evolution in a large family of salamanders, the Plethodontidae or Lungless Salamanders (about two-thirds of the living species of salamanders are included in this taxon), in which homoplasy of many sorts seemed rampant (Wake 1966). In the intervening years it has only become more evident that homoplasy is ubiquitous. I saw the developing field of Evo-devo, combined with new methods and approaches in phylogenetic systematics (e.g., Fink 1982), as the way to study the causes of homoplasy. What immediately became evident is that studying homoplasy is not easy because one must first confront the question of homology, a topic that has been under nearly continual discussion among evolutionary biologists for more than a century and a half. The problems of exactly what constitutes homology conceptually and how to define it practically have been so extensively studied that it may seem like folly to attempt to say anything new.

I taught a course in evolutionary biology at Berkeley for 30 years. The students were advanced undergraduates and first-year graduate students who already had been exposed, or even inculcated, in population genetic approaches to the subject. Therefore, I focused more on conceptual issues, including species, homology, phylogeny, individuation, integration, and the like; I also considered the evolution of morphology, which got us into Evo-devo, species formation, and related topics. I have long felt that evolutionists spend too much time worrying about old words.[3] The terms often predated Darwin, or were formulated without even a loose notion of evolution. (Species is a case in point.) I agree with Dobzhansky's famous aphorism: "Nothing in biology makes sense except in the light of evolution." The vast majority of biologists accept that species are the outcome of evolutionary processes. But most biologists, even many evolutionary biologists, treat species as if they are essentially biblical species! They are seen as "real" entities that have arisen in some manner akin to "birth" ("speciation"!), even though for most taxa, especially vertebrates, species are usually outcomes of the subdivision or fragmentation of pre-existing species, and achieve "reality" through the extinction of intermediates and the passage of time. As a consequence, the phylogenetic reconstruction of species relationships is fraught with peril. Homology is even more problematic. Its roots are ancient (Panchen 1999, economically summarizes the history of the idea; see also Laubichler 2000); the key to any modern understanding of the term is the idea that all life is connected—that the trait of interest is inherited,

[3] Admittedly, I have contributed to these discussions, having devoted some effort in sorting out terms related to heterochrony (Alberch et al. 1979).

and often transformed—and that in the course of phylogenesis a homologue is the *same thing* in different species, even in all of its evolutionary manifestations. In contrast, what we today call homoplasy is the *appearance of sameness* in traits found in different species that are not homologues. How can we know the difference?

Aristotle and Belon used different kinds of logic to conclude that whales were mammals and fish, respectively (Panchen 1999). Today we consider a robust "natural" phylogeny to be a necessity prior to any homology assessment. Increasingly, homology assessment is but a technical detail (although a critically important one) in cladistic procedure. But I fear that with regard to the concept of homology, we evolutionary biologists have made a mountain out of a molehill. The homology debate is a distraction from the larger questions of how morphology evolves, why it stays the same, why it gives the appearance of having re-evolved in different species, and how we arrive at an integrated science of form that incorporates phylogeny with the genetics of development and morphogenesis in a truly evolutionary framework (Wake 1999). There has been one history of life (in particular at the level of multicellular organisms, in which lateral gene transfer is so rare that we can ignore it), and it is a genealogical necessity that a trait is "the same thing" as it is transmitted from parent to offspring. Thus, by hierarchical translation it also becomes a phylogenetic necessity. The sole reason for the existence of homology is evolution and phylogeny. Some think homology is profoundly important, but I fear it is simply a trivial outcome of history. What is not trivial is how the morphology that is the same in different species is generated and how "the same thing" evolves into diverse manifestations during phylogenesis; this is the domain of Evo-devo. In particular I find it promising, even fascinating, to employ homoplasy heuristically. One can postulate that similar structures ought to have similar developmental genetic and morphogenetic foundations, whether they are homologues or homoplasies. This opens up abundant avenues of research (Wake et al. 2011).

But, is it easy to determine what is homoplastic and what is homologous? This question is in the realm of phylogenetics, which is given too little attention in Evo-devo research. Gould (1977) and Alberch et al. (1979) clarified the distinctions between the different kinds of heterochrony in terms of developmental and evolutionary processes, but it was Fink (1982) who made it clear that phylogenetic discipline was a necessary component in such studies. Heterochrony is involved in homoplastic evolution—a vivid example being the repeated appearance of reproductively mature larvamorph taxa in different salamander lineages. Alberch et al. assumed that relevant analysis would be done in a phylogenetic context, while Fink reformulated their approach in terms of phylogenetics and showed how to detect heterochronic ontogenetic processes in nature. Fink appropriately insisted on the necessity of the prior existence of phylogenies "to which process analysis can be applied." He went on to observe that while convergence can often be detected with a minimal phylogeny (eyes of cephalopods and vertebrates, and fins of whales and fish, come to mind), parallel evolution can be detected, "if at all," only with the sophisticated analysis of large datasets. His observation is even more relevant for the most troublesome of the three forms of homoplasy—evolutionary reversals.

Dollo's Law on the irreversibility of evolution is viewed by some as a simple statement about the low probability of the recurrence of a trait based on its being the result of the integration of a large number of parts. While "laws" in biology have little credence, what might be called Dollo's *maxim* or *generalization* has been difficult to overturn despite much effort, especially with respect to organs. The recent debate concerning claims of evolutionary reversal is instructive. Goldberg and Igic (2008) issued a general refutation of claims of evolutionary reversal, arguing that the accompanying phylogenetic analysis was usually insufficiently rigorous. A case in point was the re-evolution of digits in a South American lizard *Bachia*, an attenuated snake-like lizard with greatly reduced limbs. The claim was that some species derived from ancestors that had lost particular digits had regained them (Kohlsdorf and Wagner 2006). Goldberg and Igic found the phylogenetic argument unconvincing. In response, the original authors recruited a phylogenetic analyst and reasserted their position (Kohlsdorf et al. 2010). I remain unconvinced, in part because of the still somewhat equivocal phylogenetic analysis. More importantly, I do not find the argument for reversal convincing because no member of *Bachia* loses *all* of its digits, and digits are reiterated serial elements; as long as the developmental genetic mechanisms underlying digital production in general are retained, I do not consider this a case of reversal in Dollo's sense. Rather, it falls into the zone called mesoevolution (Abouheif 2008), studies between microevolution and macroevolution that explicitly focus on issues such as deep homology and its relation to the evolution of development.

Homoplasy was a problem for me in 1966. While I think I made some progress after the Dahlem conference (Wake 1991), homoplasy remains a challenge today. But substantial progress has occurred in a couple of areas. Our understanding of the genetic foundations of development and morphogenesis were in their infancy at the time of the Dahlem conference. Baguñà (2009) has nicely summarized major steps in these areas from the time of the Dahlem conference to the present, starting with the discovery of the homeobox, the recognition that regulatory systems are widely conserved across taxa, the discovery of the important role of gene duplication in vertebrate phylogeny, the findings that *cis*-regulatory modules evolve by mutation, co-option and reshuffling, the understanding that there is a kind of molecular toolbox for development, the formulation of the concept of gene regulatory networks, sequencing of whole genomes, and the dawn of the age of genomics, and subsequently phylogenomics. We now live in an age of experimental Evo-devo.

But progress was made in another area as well—phylogenetics (nicely summarized by Felsenstein 2004), where there have been high levels of research activity up to the present. For morphologists the key development was the emergence of the field of cladistics, which democratized systematic procedures and took the field out of the hands of specialists (taxonomic "authorities"). Soon it became clear that we morphologists needed help, partly because homoplasy proved to be even more common than many of us had thought possible. Starting in the late 1960s, the stirrings of a new field of molecular phylogenetics began to emerge. By the time of the Dahlem conference, use of allozymes in systematics was common, but one could not readily develop phylogenies from such data. Various indirect methods of

estimating differences in DNA were employed (immunological approaches, DNA hybridization), and those of us working in this area awaited the discovery of methods of direct sequencing of DNA, which became available by the late 1980s. There has been a veritable explosion of approaches to combine DNA sequence data and other data (principally morphological) to generate increasingly robust phylogenetic hypotheses. A renewed focus on homoplasy has been one major result. When such approaches are extended from living to fossil taxa, the impact of homoplasy becomes ever clearer. Wiens et al. (2010) studied squamate reptiles and showed how molecular data change interpretations of fossils, concluding that "parallel adaptations to a burrowing habitat in multiple lineages seem to erase the historical signal" and lead the most sophisticated analyses of morphological data from fossil and living taxa to give the wrong answer. While phylogenies are essential for homology and homoplasy assessment, phylogenetic methods may fail when the data are inadequate or when the analysis is at a scale where genealogy has not yet translated into phylogeny, such as detecting parallel evolution in loss of armor in different sublineages within a single stickleback species where geneology is so young (and intraspecific) that it has not yet translated into phylogeny (Goldberg and Igic 2008). Especially troubling are instances where several different phylogenetic methods give statistically significant results, which are determined to be incorrect when new data are added (Wiens et al. 2010).

## 5.6 Hierarchical Issues and Levels in the Assessment of Homoplasy

If one accepts the definition of morphological parallelism as deriving from the same developmental genetic framework, then it is but a short step to the argument that the trait in question is a homologue at a deeper hierarchical level (Hall 2008). However, I insist that what determines homoplasy is phylogeny *at the focal level of analysis*. The *Mc1r* gene in vertebrates is associated with pelage color in mammals and skin color in lizards. The same mutation appears to be responsible for pale fur in some desert rodents and pale skin in two only distantly related lizards that live in the White Sands of New Mexico (Manceau et al. 2010; Rosenblum et al. 2009). Certainly this is a case of homoplasy, qualifying as parallelism at the level of the apparently bleached hair and skin of the taxa involved (by the definition above). But at the level of the gene it may be the same thing, a homologue. The mutations in these homologous genes are likely independent, but more research is needed to trace the gene through its convoluted evolutionary history over more than 150 Ma! The gene might be the "same" in many molecular traits, but it will be very difficult to reject the hypothesis that it is an independent invention in lizards and mice, and maybe even in the two lizards. Rigorous testing would require an enormous amount of work and is probably impossible (from a phylogenetic perspective) because of the extinction of relevant taxa. We may have to take it at face value from molecular

biology that this gene is indeed the same thing, and for the purposes of making progress in Evo-devo research we might as well accept its homology because we have no reason (at present) not to do so.

What has been called "deep homology" is the recognition that structures such as eyes of vertebrates and cephalopods (Piatagorsky 2008) and appendages of arthropods and vertebrates (Shubin et al. 2009) share some developmental genetic systems in common, which are derived from common ancestors and deployed in different organismal and evolutionary contexts. In this sense, the clearly homoplastic organs (because ancestors of both groups lacked fully formed eyes, as well as multipart appendages) share some remotely similar features due to their extremely ancient common ancestry. These examples simply reinforce my point (Wake 1999) that homology is really nothing but the outcome of common ancestry expressed in many different ways, and to lose any sleep over "the homology problem" is to take it too seriously.

## 5.7 Homoplasy Since Dahlem

Pere Alberch conducted his doctoral research on the largest clade of salamanders, the genus *Bolitoglossa* of Middle and South America. In several papers (Alberch 1981; Alberch and Alberch 1981) he developed a theme that I had introduced earlier (Wake 1966; Wake and Brame 1969): that the fully webbed hands and feet of members of this genus were paedomorphic and that they represented embryonic stages of ancestors transformed into adult stages of descendants. Embryonic salamanders have tiny pads out of which digits emerge as development proceeds. Pere showed that there were two very different kinds of webbing. Some species were indeed paedomorphic, with poorly developed digits that were reduced to tiny dots of bone terminally; these were generally miniaturized species and can be considered to have retained embryonic pads, although of larger size, into adulthood. There was no evidence that these tiny pads (which superficially appear to be webbed) served any special adaptive function. In contrast, the webbing spreading between the elongating digits in generally larger species, which had grown out of the basal pad phalanges, were well developed. Pere showed (1981) that species with large webbed hands and feet were capable of producing suction, and reasoned that in such species these structures were adaptations for arboreal locomotion. Researchers had noted that upland species generally had individuated digits with relatively little webbing and often were terrestrial, whereas species in the lowlands, whether large or small, were fully padded or webbed and were arboreal (Wake and Lynch 1976). *Bolitoglossa* is widespread and it seemed that ancestral unwebbed species had given rise, repeatedly, in different parts of the vast range of the clade, to species that had invaded the lowlands by developing pads or webs, or both, and becoming arboreal (because terrestrial lowland habitats in the tropics seem saturated with other forms of life, some quite hostile to salamanders).

Jaekel and Wake (2007) re-evaluated this problem and showed that all species of *Bolitoglossa*, whether webbed or not, follow a similar developmental trajectory shared only by one other species, a large-footed, webbed member of a cave-dwelling species of the distantly related genus *Chiropterotriton*. They concluded that webbing was functionally ineffective (except in *Chiropterotriton*) because the area of the pad or webbed appendage was insufficient to make a difference in the ability of an organism to locomote or even cling to an above ground surface. There are seven clades within *Bolitoglossa*, based on molecular phylogenetic analysis (Parra-Olea et al. 2004). Padded species, nearly fully webbed species, or both (with intermediates) occur in all seven clades, but species with well-individuated digits are found in only three clades. The implications of these diverse findings are that the ancestral *Bolitoglossa* likely was a small, paedomorphic form with padded hands and feet,[4] and the free-digited species of the uplands have been derived independently in different upland areas from southern Mexico into Colombia. This kind of homoplasy—reversal to a digited condition found in out-group taxa—was not previously considered likely. The reversal is not "perfect" in that the free digits develop differently than those of out-group taxa. I do not consider this example to constitute a rejection of Dollo's Law because even fully padded miniature species of *Bolitoglossa* have rudiments of digits; but it is a vivid example of homoplasy. At the level of the organ and organism, this example may not constitute a reversal. At the level of population biology and ecology it is one, because free digits are functional and hence likely to prove adaptive (relative to the postulated padded hands and feet of ancestors) for terrestrial, and some kinds of scansorial salamanders.

Following the 1981 Dahlem conference I focused intently on homoplasy, which at the time was generally thought to be evidence of natural selection. I felt this was too narrow a focus and developed the argument that another realm of explanation, one focused on phenotype generation, offered an alternative perspective (Wake 1991). I contrasted functionalist (externalist, adaptationist) with structuralist (internalist, generative) "ways of seeing" (e.g., Wake and Larson 1987), trying to avoid conflating explanations for the generative evolution of the form and explanations for the adaptive evolution of form, attempting to achieve an integration of both through phylogenetic analysis. My focus remained plethodontid salamanders, whose phylogenetic history and patterns of life history evolution I thought I understood thoroughly. The desmognathine plethodontids evidently had the most generalized larvae, adapted to life in rapidly flowing streams. Two different lineages of miniaturized desmognathines evolved terrestriality with encapsulated embryos that hatch as miniatures of the terrestrial adults (Wake 1966). Desmognathines constituted one of two major clades. The second included three major clades, one of which had aquatic larvae that were mainly but not exclusively stream-adapted, whereas the other two had evolved direct terrestrial development,

[4] E.g., all species of *Bolitoglossa* have incompletely developed tarsal elements (Alberch and Alberch 1981; Wake 1991).

either from a common ancestor with the trait or perhaps independently. However, new molecular evidence in the last decade turned this picture upside down (Mueller et al. 2004; Chippindale et al. 2004; Vieites et al. 2007). Desmognathines now are recognized as being deeply nested within an otherwise direct-developing clade, so an evolutionary reversal has occurred. While this reversal has profound ecological implications, it is doubtful that Dollo would regard it as a refutation of his "law" because encapsulated embryos differ relatively little from free-living larvae during early development (Kerney et al. 2011) so no "organ" was lost and regained. These examples highlight only some of the problems associated with attempted refutations of Dollo's Law, which in my eyes has as much validity as it did 30 years ago.

Another Evo-devo issue in my research at the time of the Dahlem conference was the homoplastic evolution of highly projectile tongues in plethodontid salamanders (Lombard and Wake 1977, 1986). According to the 1966 phylogenetic hypothesis, there was extensive homoplasy, with freely projectile tongues evolving three times and somewhat less extensively projectile tongues evolving three additional times. The key factor was loss of lungs, which meant that prior functional constraints were relaxed and extreme specialization possible. The three most specialized instances followed different biomechanical pathways in developmentally different lineages, using one of two options. The first of these was associated with direct-developing species, where the tongues developed directly with no need to function in larvae. The second option, less biomechanically efficient, was the result of a kind of "compromise" necessitated by the constraint that the larval tongue act to wave the gills and produce suction for feeding in the aquatic medium. New insights were obtained from extensive developmental neurobiological studies in the late 1980s and 1990s (summarized in Roth and Wake 2001). The question was revisited when the new phylogenies were obtained and the homoplasy was discovered to be even more extreme than previously believed. The two clades with the most extreme tongue projection capabilities, formerly considered to be fairly close relatives, now were determined to be only distantly related; hence the convergence was even more impressive (Mueller et al. 2004; Wake et al. 2014).

Following the Dahlem conference I undertook studies of brain evolution in salamanders with my long-time collaborator Gerhard Roth of Bremen, Germany. It had long been recognized that salamanders has simple brains, organized poorly and seemingly primitive. However, by integrating across hierarchical levels and using modern phylogenetic analysis, we recognized that the brains of salamanders were secondarily simplified, giving a false impression of simplicity and showing what might be considered as a return to what can be inferred for ancestral patterns of tetrapod brain organization. We showed that this secondary simplification is the outcome of a cascade of events: (1) genome size increase; (2) consequent cell size increase; (3) consequent increase in cell cycle time (particularly important in these ectotherms); and, (4) inhibition of cell migration because of large cell sizes and metabolic issues (reviewed by Roth and Wake 2001). The end result of this cascade is apparent embryonic or juvenile anatomy that is not simple in function but paedomorphic in appearance. Such homoplastic evolution occurred independently in the three orders of living amphibians, as well as in the distantly related lungfishes (Roth et al. 1993).

Perhaps the clearest example of the difference between convergence and parallelism in my own work relates to body form evolution in plethodontid salamanders. A common homoplasy in salamanders, as also in lizards, is the elongation and attenuation of the body in fossorial and semifossorial species. The simplest developmental solution to the problem of how to accomplish body and tail elongation is an increase in the number of vertebrae, accomplished early in development by delaying the offset signal for segment formation. Often individual species display local and geographic variation in the numbers of trunk vertebrae, sometimes varying by three or more vertebrae within a single population. Many of these species show patterns of geographic variation in vertebral numbers. This phenomenon was studied by one of my former students, who showed that both environmental and genetic factors affected adult vertebral numbers (Jockusch 1997). The radiation of a bolitoglossine clade of plethodontid salamanders in the tropics offers a sharp contrast. One nested clade, *Oedipina*, displays variation in trunk vertebral number, with from 18 to 23 being found among its 38 species, most showing some intraspecific variation; the remaining 252 species of tropical bolitoglossines have a fixed number of trunk vertebrae (14), with extremely rare variation. One small clade, *Lineatriton* (three species, recently synonymized with the genus *Pseudoeurycea*) is unique among caudate amphibians in being slender and attenuate, superficially resembling species of *Oedipina*. It has accomplished this in an entirely different manner—its 14 trunk vertebrae are each elongated, with shortened ribs (Wake 1991). The common homoplasy is a classic example of parallel evolution enabled by inherent variation in vertebral number and is subject to selection as part of a process of adaptation. I long thought the convergent situation in *Lineatriton* was unique, but molecular analysis revealed that the three species constituted another instance of parallel evolution; two species were close relatives of one clade within the large genus *Pseudoeurycea* (50 species), but one was closely related to a separate clade within that genus (Parra-Olea and Wake 2001). This complicated example of homoplasy thus involves two distinct developmental modes producing a common morphotype and ecotype, each deployed repeatedly.

A final example of extreme homoplasy in salamanders takes us back to Steve Gould's (1977) book, with an axolotl on the cover and an extended discussion of paedomorphosis in salamanders inside. When nineteenth century biologists attempted to classify sexually mature, aquatic, gilled amphibians (such as the axolotl), they were initially stumped and tried a number of options. When captive-bred axolotls suddenly metamorphosed it became apparent that they were salamanders and the term neoteny became linked with axolotls. As group after group was studied it was recognized that different salamander taxa displayed an array of paedomorphic states that had evolved homoplastically. These paedomorphic species became nearly impossible to classify and many arguments ensued over the years. Wiens et al. (2005) explicitly dealt with this problem by producing phylogenetic hypotheses based on treating all salamanders equally, regardless of the developmental stage of adults. They conducted analyses using molecular characters alone, and molecular plus morphological characters, concluding that the inclusion of traits related to paedomorphosis consistently gave the wrong

answer. Pervasive, organism-wide paedomorphosis can produce many homoplasies all at once. Only with the advent of molecular data have comparative biologists gained tools to examine the extent and implications of homoplasy. Studies of other taxa have reached similar conclusions: "convergent evolution acting on groups of characters in concert—can lead to highly supported but erroneous phylogenies" (Holland et al. 2010, 433).

## 5.8 The Future of Homoplasy in an Evo-devo Context

Homoplasy offers exceptional opportunities to students of Evo-devo (Wake et al. 2011). Why does evolution tend to "run in grooves" within clades, following avenues of least resistance to reach the same endpoint again and again? What determines the limitations on form? Why don't forms evolve to fill the potential morphospace, instead giving rise to similar forms repeatedly? How does integration across several hierarchical levels occur, for example from increased genome sizes within cells to repeated patterns of evolution at the level of whole organisms? For many years, functionalist (selectionist, adaptationist) approaches to such problems have been emphasized. Is it not time to rationalize or integrate structuralist perspectives in a more positive and definitive manner?

**Acknowledgments** I thank Alan Love for his successful efforts to organize and find funding for our conference, and for the participants for their stimulating presentations and discussion. Marvalee Wake has discussed many of the issues addressed in this paper with me over the years, and she has given me valuable feedback on the manuscript. I thank Rasmus Winther for constructive comments on the manuscript. George Oster refreshed my memories concerning the origins of the 1981 Dahlem conference. My research has been funded by the National Science Foundation throughout my career. I have benefited enormously from my interactions with gifted graduate and postdoctoral students, and with colleagues, first at the University of Chicago, and since 1969, at the University of California at Berkeley.

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# Part II
# Phenotypic Plasticity, Developmental Variation, and Experimental Biology

# Chapter 6
# The Concept of Phenotypic Plasticity and the Evolution of Phenotypic Plasticity in Life History Traits

**Stephen C. Stearns**

## 6.1 The Evolution of Plasticity in Life History Traits

Life history theory seeks to understand how organisms are designed by natural selection to achieve reproductive success in the face of external challenges posed by the environment and under the constraints of internal tradeoffs among traits. It has achieved considerable success in answering questions such as: Why are organisms large or small? Why do they mature early or late? Why do they have a few or many offspring? Why do they have a short or a long life? And why must they grow old and die? Life history theory asks how to optimize a fitness measure—reproductive success—under the constraints of finite inputs, competing allocations, and risks that differ among the traits to which allocations are being made.

I knew the issue of phenotypic plasticity in life history traits was important when I was a Miller Fellow at Berkeley (1975–1978), for I had seen it in the experiments I did as a PhD student at British Columbia (1972–1975). In those experiments it was clear that age and size at maturity and fecundity were all strongly influenced by population density, nutrition, and temperature. If one wanted to study genetic differences among populations, those environmental influences had to be controlled. While one also could have asked why some populations were more sensitive to given environmental factors than were others, at Berkeley I could not yet see a way to connect phenotypic plasticity to life history theory. I was advised by Dave Wake to stick to my ideas and be patient. In fact, it took 5 years and the motivation of the Dahlem Conference, among other things, to achieve a substantial new insight. In this section I describe the general impact of the Dahlem Conference on my research and how I returned from the conference to confront an unexpected experimental result that stimulated a model that resolved part of the issue of

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plasticity. I then sketch the subsequent history of those insights and conclude this section with a surprising confirmation from an unexpected source.

### 6.1.1 The Impact of the Dahlem Conference

Life history evolution was included as a theme in the 1981 conference because J.T. Bonner, who took the lead in organizing the conference, had had a long-standing interest in the evolution of life cycles. I was invited because of my expertise in life history evolution, and I added to the conference my interest in phenotypic plasticity. There was little discussion of either life history evolution or phenotypic plasticity at the conference because it was dominated by people primarily interested in development and morphology. They had (and still have) a different definition of what is to be explained, and how to go about explaining it, than those primarily interested in life history evolution. Nor did the conference provide me with much specific feedback that would help to advance my research, for most of the people at the conference were not well enough informed in my own field to give such feedback. What it did provide was motivation and self-confidence. As a young scientist, leaders in the field treated me as a full colleague for a week, and I had a chance to hear of many cases in which those leaders had taken intellectual risks, defended unpopular positions, and gone out on a limb in pursuit of a new idea. Their examples encouraged me to behave similarly.

### 6.1.2 An Experimental Result Stimulates a Model

I returned to Reed College to confront an unexpected experimental result. I was just completing the rearing of two populations of mosquito fish through two generations in a common garden experiment. The populations stemmed from an ancestral population in 1905; since then they had evolved independently. My common garden experiment was giving me a snapshot of their condition 75 years, or about 150 generations, later. The conditions under which the fish were raised in the first generation differed from those encountered by the second generation. The first generation was raised in sibling groups until ten days old and then in isolation until they matured; in the second generation individuals were raised in isolation from the day they were born until they matured. That difference in the environment in the first ten days of life caused a considerable difference in growth rate and in age and size at maturation, a difference that could be clearly ascribed to phenotypic plasticity. The critical observation was that the reactions to the difference in environment were different in the two populations; the reaction norms for age and size at maturity had evolved just as rapidly as the traits themselves (Fig. 6.1). That observation suggested that it might be productive to model the evolution of norms of reaction using life history theory.

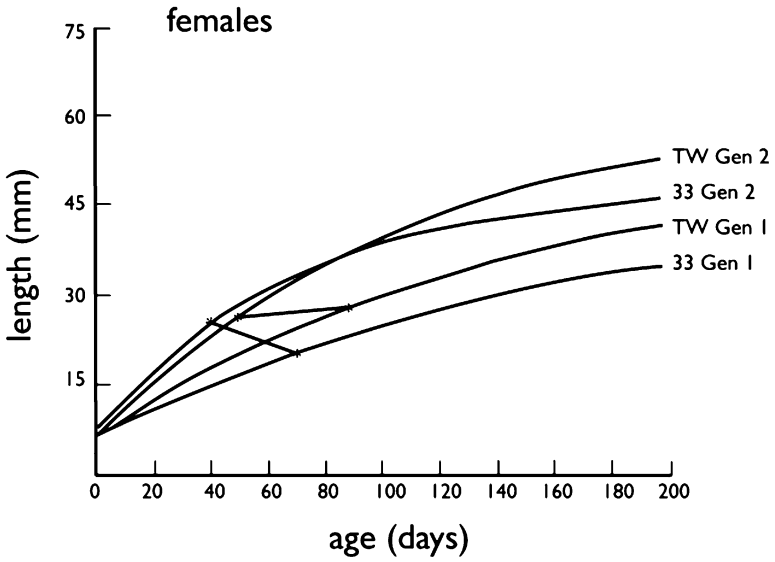


**Fig. 6.1** Growth curves and reaction norms for age and size at maturity for two populations of fish (TW and 33) raised either with their sibs for the first 10 days of life (Gen 1) or in isolation from birth (Gen 2). Note that not only the mean ages and sizes at maturity have evolved; so has the plastic response to the difference in rearing environment (Redrawn from Stearns and Crandall 1984)

I walked across the hall to the office of my colleague in the Physics Department, Richard Crandall, who had already collaborated with me on a theory to predict the evolution of age and size at maturity. I told him about the result and sketched on the blackboard a picture of what I thought we could predict—not just the evolution of the traits in a constant environment but the evolution of the entire reaction norm for a range of environments defined by different growth rates. Richard said, "Go faster." We soon had predictions for the evolution of reaction norms for age and size at maturity. I presented our results at a meeting of the Fisheries Society of the British Isles held at Plymouth in July 1982, and they appeared as a chapter in the book that resulted from the meeting (Stearns and Crandall 1984). Despite appearing as a chapter in a book, it has had a broad impact, having been cited more than 260 times.

I moved to Basel, Switzerland in October 1983. That fall a Swiss student with good training in mathematics and engineering, Jacob Koella, asked if he could be my graduate student. I said I would accept him if he could complete the pre-requisites in zoology and pass the Vordiplom exam, and I suggested that while he did that we could work together on further exploring the model that Crandall and I had developed. The result was a paper in *Evolution* (Stearns and Koella 1986) that significantly extended the earlier results and reached a much larger audience (it has been cited 848 times). It helped to launch a larger research project that has involved many scientists unconnected to Crandall, Koella, or myself.

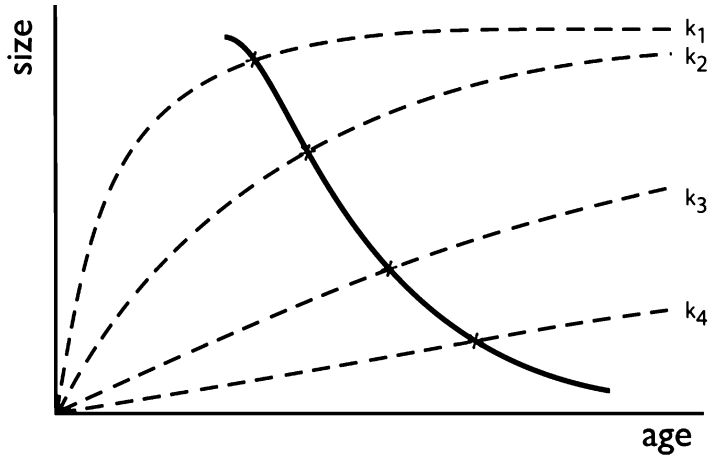


**Fig. 6.2** Growth curves (*dashed lines*) and the optimal reaction norm for age and size at maturity (*solid line*) as predicted from life history theory (Redrawn from Stearns and Koella 1986)

The key result in the 1986 paper is depicted in Fig. 6.2. Evolution should shape a reaction norm that makes age and size at maturity contingent upon the growth environment: if growing fast, mature large and young; if growing slow, mature old and small. The position and shape of the reaction norm are seen as genetically determined and shaped by a history of selection. The particular point along the reaction norm at which an individual matures depends on the environment in which that individual has been raised. Each point on the reaction norm yields maximum fitness for that growth rate. The reaction norm plot thus neatly demonstrates how nature and nurture—genes and environment—can interact to determine the actual age and size at which an individual matures, an event that is determined by both the history of selection that the population has encountered over many generations and that particular individual's history of developmental interaction with the environment in a single generation.[1]

### *6.1.3 Mode of Growth Makes a Difference*

Most of the cases explored by Stearns and Koella in their 1986 paper dealt with organisms for which the assumption of indeterminate growth was reasonable. However, many organisms, including birds, mammals, and holometabolous insects, have determinate growth, i.e. growth that ceases with maturation. David Berrigan

[1] The paper also noted that other shapes of reaction norms would be predicted if growth rates are correlated with adult or juvenile mortality rates or if growth is determinate or indeterminate, but it did not explore those cases in detail.

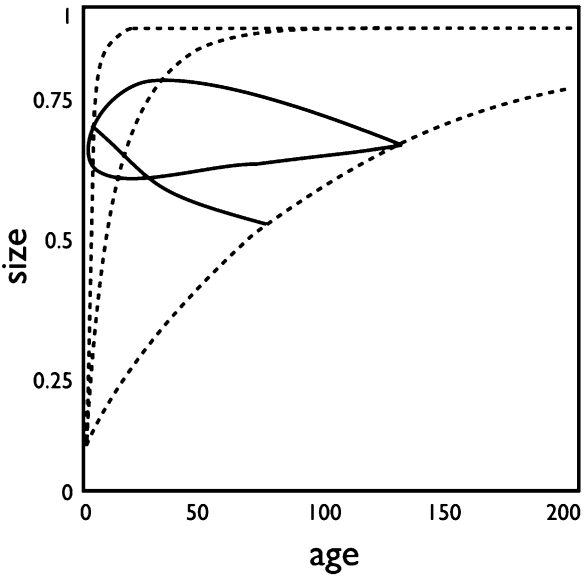


**Fig. 6.3** Growth curves (*dashed lines*) and optimal reaction norms for age and size at maturity (*solid lines*) under three different sets of assumptions (Redrawn from Berrigan and Koella 1994)

and Jacob Koella (Berrigan and Koella 1994) explored the consequences of determinate vs. indeterminate growth and of mortality coupled to growth rate. They made the same key assumption that Stearns and Koella did: that genes encounter all growth environments equally frequently.

Figure 6.3 summarizes their results. Changing the mode of growth makes no qualitative difference to the predictions, but changing the coupling of mortality to growth makes a big difference. If mortality increases with growth rate, dome-shaped reaction norms for age and size at maturity are predicted. If mortality decreases with growth rate, the reaction norms are predicted to be C- or L-shaped. If mortality is not strongly coupled to growth rate, then the reaction norm is predicted to be L-shaped. An L-shaped reaction norm depicts one form of the growth environment contingency rule found earlier: if growing fast, mature large and young; if growing slow, mature old and small.

### *6.1.4 Spatial Population Structure Makes a Difference*

One key assumption of the 1984 chapter and 1986 paper was that evolution optimizes age and size at maturity independently at each point on the reaction norm. This is equivalent to assuming that genes encounter all growth environments with equal frequency; the population is thoroughly and repeatedly mixed across any spatial heterogeneity, and there is no spatial structure associated with growth and movement (i.e., no source-sink structure in the environment). The consequences of relaxing that assumption were independently explored by Alasdair Houston and

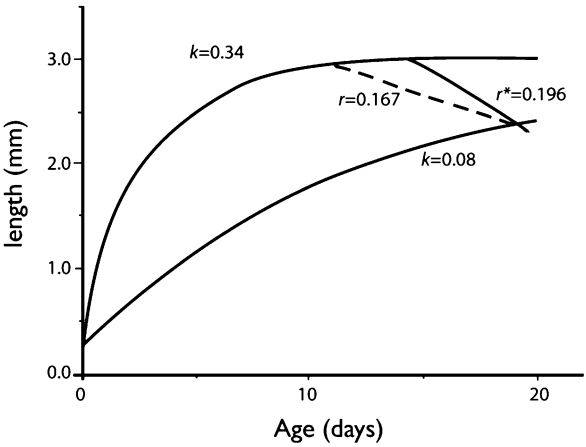


**Fig. 6.4** Growth curves (*solid lines* curving upward to the right) and two optimal reaction norms for age and size at maturity. The *dashed line* trending downward to the right is the prediction from the scenario used by Stearns and Koella (Stearns and Koella 1986). The *solid line* trending downward to the right is the improvement suggested by Kawecki (Kawecki and Stearns 1993)

John McNamara (Houston and McNamara 1992) and by my student Tad Kawecki (Kawecki and Stearns 1993). Here I give just the Kawecki version.

Kawecki saw phenotypic plasticity evolving in response to spatial rather than temporal heterogeneity. In a spatially heterogeneous environment there is a net flow of individuals from sources to sinks, and those movements imply that fitness should be calculated across the full range of habitats rather than separately in each habitat. Thus the optimal phenotype in a given habitat, while certainly influenced by conditions there, is also linked to the performance of individuals in other habitats. Kawecki generalized the Euler-Lotka equation to deal with fitness in an environment in which individuals disperse among habitats when newly born and then stay in an environment for life. In that case, maximizing the rate of increase over all habitats is equivalent to maximizing the reproductive value of newborns in each habitat. He used the new equation to find optimal reaction norms for age and size at maturity and for fecundity. Figure 6.4 illustrates the magnitude of the effect by comparing the new prediction for the reaction norm to the one predicted using the Stearns and Koella model. Maturation is predicted to occur at a later age and slightly larger size when growth is rapid, but the rule of thumb remains the same: when growing rapidly, mature young and large; when growing slowly, mature old and small. The new model was an important conceptual advance, for it defined a measure of fitness that took proper account of spatial variation and movements of individuals among environmental sources and sinks, but it did not result in differences in predictions that would be easy to distinguish empirically from the older models (at least not in cases like the one depicted in Fig. 6.4).

### *6.1.5 Adaptive Dynamics Matters*

During the 1990s a new school of evolutionary modeling arose that called itself *adaptive dynamics*. It aimed to make the predictions of evolutionary models more ecologically realistic by requiring that they be consistent with population dynamics,

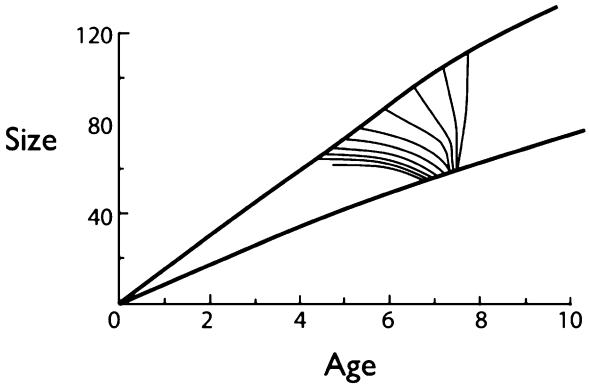


**Fig. 6.5** A family of optimal reaction norms for age and size at maturity, each corresponding to a different degree of fishing pressure and all experiencing a particular type of density-dependence. Note that the majority of them embody a rule seen in Figs. 6.1, 6.2, 6.3, and 6.4: when growing fast, mature large and young; when growing slow, mature old and small (Redrawn from Ernande et al. 2004)

frequency dependence, and density dependence. The general idea was that ecology would shape the evolution of performance traits, including life history traits, and that those evolutionary changes in performance traits would then change ecological dynamics and thus selection pressures. This would then feed back into further evolutionary change, and so forth, in a continuing causal cycle. Using such approaches, Bruno Ernande, Mikko Heino, and Ulf Dieckmann (Ernande et al. 2004) predicted optimal reaction norms for age and size at maturity in fish populations that were experiencing various kinds of density-dependence and different degrees of fishing pressure. Their results (Fig. 6.5) confirm that the most frequently predicted norm of reaction is one that embodies what by then was coming to be seen as the standard contingency rule: when growing rapidly, mature young and large; when growing slowly, mature old and small. Since then Heino, Dieckmann, and others have amplified their models to bring them into closer contact with the kinds of data that can actually be gathered, particularly in fisheries biology. In so doing they have developed the concepts of probabilistic reaction norms and eco-genetic modeling, among others (Dieckmann and Heino 2007; Heino and Dieckmann 2008; Dunlop et al. 2009).

For present purposes, however, Figs. 6.2, 6.3, 6.4, and 6.5 are sufficient to convey the general message that I am trying to communicate. After the 1984 and 1986 publications of the ideas that reaction norms evolve and that their evolution can be predicted, a standard scientific process ensued. The assumptions of the original model were examined, and the robustness of the predictions to the relaxation of the assumptions was tested. Some significant changes in qualitative predictions were found, in particular when mortality and growth rates are coupled, but the most frequent prediction remained qualitatively the same: when growing rapidly, mature young and large; when growing slowly, mature old and small.

In that process the conceptual basis of the models was broadened and deepened, incorporating considerable ecological complexity. The fact that the most frequently predicted qualitative pattern did not change suggests either that the original predictions were robust to the relaxation of the assumptions, or that the original predictions were a case of getting the right answer for the wrong reasons. Our tests of these models are not yet sufficiently advanced to decide between those two alternatives. One way to adjudicate the issue would be to use experimental evolution to contrast reaction norm evolution in spatially vs. temporally variable environments. This might be feasible using fruit flies in experiments lasting 5–10 years, which would take a full-time staff of 3–4 people to run. They would be time consuming and expensive and have not yet been done. In the meantime, the predictions are proving to be a good descriptor of observed variation in many systems, both in fish populations and, as we will see in the next example, human females.

### 6.1.6 *A Surprising Confirmation from an Unexpected Source*

One of the cases explored in the 1986 paper was that of maturation in human females (Fig. 6.6). It was inspired by the work of Rose Frisch, who had compiled extensive data on maturation patterns in nineteenth and twentieth century women in England and the United States (Frisch 1978). Frisch had documented a decrease in age at maturity of about 4–5 years from the nineteenth to the twentieth century, attributing it to better nutrition and less stress. The Stearns and Koella model

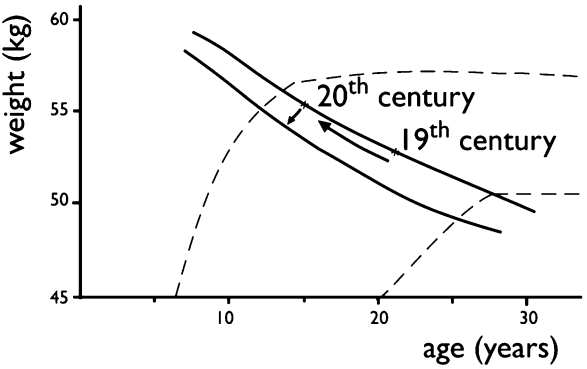


**Fig. 6.6** Optimal reaction norms for age and size at maturity in human females (*solid lines*) evoked by different growth rates (*dashed lines*). The upper reaction norm depicts the plastic shift from the nineteenth to the twentieth century, when better nutrition and growth caused women to mature larger and younger. The low reaction norm depicts the predicted shift of the entire curve down and to the left in response to the reduction in infant and child mortality caused by better hygiene, widespread use of antibiotics, and vaccination campaigns (Redrawn from Stearns and Koella 1986)

predicted a shift similar in size and direction (Fig. 6.6, upper solid line). We then asked, what would happen if juvenile mortality rates continued to be held at the low levels that they achieved early in the twentieth century with advances in medicine and hygiene? The answer, given in Fig. 6.6, is that the entire reaction norm for age and size at maturity should shift down and to the left. It is predicted to do so because the model contains the assumption that earlier reproduction is costly since it increases infant and juvenile mortality. If juvenile mortality is decreased by modern medicine and hygiene, that reduces the cost of earlier reproduction, thus shifting the cost-benefit balance and making earlier reproduction, up to a point, the better option.

In 2009 I began a research project that aimed to measure the strength of natural selection in contemporary human populations. We have been using data from the Framingham Heart Study, which contains about 14,500 individuals in three generations of roughly 5,000 individuals each. Many traits have been repeatedly measured on those individuals. Most of them are traits thought to be related to heart disease, but the database also contains (for many individuals) the information an evolutionary biologist needs to measure selection: lifetime reproductive success, or completed family size. We analyzed the partial regressions between a number of traits and lifetime reproductive success to estimate the strength of selection on each of the traits (Byars et al. 2010). Among the traits analyzed were age at first birth and adult height. We found significant selection acting on both traits and projected the expected evolutionary change over the next ten generations as a decrease in height of 2.1 cm and a decrease in age at first birth of 5.3 months. That is precisely the direction of the shift predicted 24 years earlier (Fig. 6.6).

We also estimated the rates at which the evolution of these two traits was projected to occur: 0.032 haldanes for height and 0.010 haldanes for age at first birth. (One haldane is one standard deviation per generation.) Those projected rates place humans at the lower end of the range of rates that have been estimated for natural populations of plants and animals (Hendry and Kinnison 1999). In other words, contemporary human populations are expected to evolve at rates similar to those observed in other species. This is one of a string of cases that both illustrates the utility of the idea of predicting the evolution of reaction norms for life history traits and adds incrementally to its credibility.

I now turn to the influence of the Dahlem Conference on my conceptualization of the role of development in life history evolution.

## 6.2 Conceptualizing the Role of Development in Life History Evolution

In 1985 I began a book on life history evolution, writing more than 200 pages before throwing them away because I was not satisfied with the explanatory framework. My dissatisfaction came for reasons that resulted from both the Dahlem Conference

and from the exposure to Evo-devo that I got at Berkeley. In 1987 I began anew and came up with a framework with four elements that I saw as necessary and sufficient to explain trait evolution in general, not just life history traits in particular. Here is that explanatory framework as it eventually appeared in the book (Stearns 1992):

1. Demography relates life history traits to fitness and determines selection intensities.
2. *Quantitative genetics and reaction norms determine how rapidly a trait will change in multi-trait evolution and how traits are expressed in heterogeneous* determine *environments*.
3. Trade-offs between the fitness costs and benefits of changes in traits are mediated by connections to other traits.
4. *Lineage-specific effects capture the impact of history and development*.

I have put the influence of the Dahlem Conference and my Berkeley experience in *italics*. Note that items 1–3 concern microevolution, while item 4 concerns macroevolution. The first three remain poorly connected to the fourth.

Scientists working on Evo-devo have often complained about the hegemony of genetics in evolutionary explanation and the neglect of development. For anyone who might be thinking about repeating that complaint, I would like to call attention to item 2 in which development—in the form of reaction norms—was planted squarely in the middle of the explanation of evolutionary quantitative genetics. That placement removes the stimulus for any complaint from the portion of Evo-devo that deals with the role of reaction norms in evolution, but it does not remove that stimulus for the much larger part of Evo-devo that is concerned with other features of the genotype-phenotype map and with the historical assemblage of the developmental system. Thus whether one feels that the complaint remains justified is to some extent a diagnosis of the side of the conceptual fault-line within Evo-devo on which one sits. On one side sit the micro-evolutionists concerned with reaction norms; on the other sit the macro-evolutionists concerned with morphology.

## 6.3 Teaching About the Role of Development in Evolution in General

The history of science tends to concentrate on key research articles and to neglect the impact of teaching on the conceptual development of the next generation of scientists. If teaching is effective, it serves not only to conserve the best insights of the past and pass them on in compact form; it also can serve as an agent of change. Conceptual change can be measured by tracking the tables of contents of widely used textbooks (Love 2010).

When I wrote my introductory textbook on evolutionary biology with Rolf Hoekstra (Stearns and Hoekstra 2005), we built development into the explanatory framework as one of the mechanisms that generate trait variation in microevolution.

Evo-devo entered as contributing to the macroevolutionary framework that constrains the expression of variation. And reaction norms entered as explaining how genes and environment interact to cause phenotypic variation.

The book, which was aimed at evolution courses taught somewhat earlier in the curriculum than has been standard in the United States, was widely adopted in North America, Europe, and elsewhere. (At one point it had about 25 % of the world market for evolution texts.) The lectures I give in the Yale introductory biology course are based on that book; they are now available for free on the web through Open Yale Courses, iTunes, and YouTube. They have also been translated into Chinese, giving this view of evolution one of the largest university audiences on the planet. It is a view that allocates roughly one-third of the evolutionary process to development: selection works on phenotypes; genomes record and transmit the intergenerational response to selection; and development determines the phenotypes presented to selection. The Dahlem Conference and my experience at Berkeley shaped the design of that textbook and changed the organization of both introductory biology and evolution courses at more than one university.

## 6.4 Dahlem Conferences as a Model for Teaching[2]

Dahlem Conferences do not have the usual format in which speakers present their work and others listen. Instead, twenty authors are invited to write background papers that present relevant topics in a stimulating and provocative fashion. These papers are circulated well in advance to the roughly 60 participants (including the authors), who are asked to prepare by reading them. This step is designed to get everyone on the same page before they arrive. The conference lasts a week. The participants form four discussion groups, each of which is charged on Monday with writing a report that summarizes the state of the field by Friday. The combination of advance preparation, concrete task, brilliant minds, and looming deadline elevates discussion to a high level and results in an experience that for many is exhilarating. The point was to have a good discussion; the problem was how to create a structure that would elicit it naturally; the solution was effective.

Having taken part in two Dahlem Conferences, in one of which I was on the organizing committee, and having used the format for another conference (Stearns 1999), I wanted my graduate students to have similar experiences.[3] It would not be possible to include the preliminary step of having papers written and circulated, for tasks of that magnitude do not fit readily or fairly into graduate programs, but it was

[2] Parts of this section are taken from an unpublished essay, Designs for learning, available at www.eeb.yale.edu/stearns/designs.htm

[3] I was so impressed by the conference design that Silke Bernhard invented that I arranged for the University of Basel to give her an honorary degree.

possible to create a structure that used some of the same elements to accomplish a similar goal. In the process we discovered some unforeseen advantages.

I decided to call the structure a workshop in population biology. It would last a week and take place at a remote location where we could work and have the potential to interact all day every day. I picked Guarda, a town in the lower Engadine (Switzerland). Like many towns in the Swiss Alps, there are apartments for rent; we usually rented apartments that would hold about 40 people, six of whom were faculty and their partners. Guarda is a lovely village—it won an annual award as most beautiful village in Europe—and the alpine meadows around it are in spectacular bloom in late June and early July. The location did not hurt.

After some experience, we settled on the following design. We arrived on Saturday afternoon. On Sunday morning, we met in plenary, the program for the week was explained, and each of the participants wrote down in headline format three topics they were interested in discussing. We sorted the participants by interest into groups of four or five and gave them the task of writing a research grant by Friday. They met regularly 2 h each morning and 2 h each afternoon, and they were told that the faculty would be dropping into their discussions to observe and to help.

A key feature of the design was that some of the professors were world-famous scientists whom all the participants knew immediately by reputation. They were instructed not to give the students ideas; they could only improve ideas that the students had already come up with. We soon discovered that when some famous person was dropping in to hear what one had to say, the participants worked incredibly hard and made rapid progress. They rarely limited themselves to the two 2 h sessions per day, often working long into the night.

Another design element was social contact. Between working sessions participants went for walks in the Alps with the famous visitors. Participants were regularly invited to the faculty apartment for drinks before dinner, and we asked each student apartment to invite each faculty couple to dinner once during the week. We also had after-dinner talks in which the visitors chatted informally about their latest ideas. And on Friday evening there was a farewell party to which everyone contributed food and drink. The impact of all this socializing on the students was enormous. They were mixing freely and chatting informally with heroes. Getting comfortable with heroes is a very good way to learn to be a colleague.

A third design element was the mix of participants. We started in the first year with master's and PhD students from Basel. After success had bred confidence and visiting faculty had enjoyed the experience (and spread the word), we advertised the workshop and invited graduate students and postdocs from all over Europe. They applied in increasing numbers, some even coming from North America. Having a mix of master's students, PhD students, and postdocs gave different levels of experience in each of the discussion groups. The more experienced helped the less experienced, and those with better English helped those whose English was not yet fluent.

More than 600 participants have attended the Guarda workshops. They continue to be organized by Dieter Ebert and Sebastian Bonhoeffer (http://www.evolution.unibas.ch/teaching/guarda/), and they have spawned similar workshops that

continue each year in Vancouver, Paris, and Lausanne. For many participants it has been a transformative experience. Its key element is social contact with intellectual heroes in the context of a clearly defined task that is carried out in a supportive local community. The heroes are, by their presence and attention, valuing one's own ideas by contributing to their development and refinement. I got that key element from Silke's design of the Dahlem Conferences.

## 6.5 How Do I Now Understand My Research in Relation to Evo-devo?

I have answered above the question of how the Dahlem Conference influenced my teaching about development and evolution. Here I turn to how it influenced my research.

In 1981 Evo-devo had not yet congealed into a research enterprise, drawn its boundaries, founded its journals, and written its textbooks. Life history evolution was included in the 1981 conference but did not later become part of Evo-devo. Why did that happen? I think there were two main reasons.

First, life history theory has been dominated by selectionist thinking from the start, whereas Evo-devo has been dominated by tree-thinking and mechanistic approaches to development. Life history evolution concentrates on microevolution while giving a nod to macroevolution. Evo-devo concentrates on macroevolution while giving a nod to microevolution. Thus the first reason is a difference in explanatory paradigms.

This difference in paradigms was amplified by strong currents in the intellectual environment—the growth of Evo-devo did not occur in a vacuum. It was strongly influenced by the controversy over adaptation and constraint that was set off by Steve Gould and Dick Lewontin's paper on the Spandrels of San Marco (Gould and Lewontin 1979). Their argument was forceful, and their reputations were weighty. The result was interest in, and deference to, explanations that were focused on constraint rather than adaptation, particularly within Evo-devo, a field that Gould had helped to resurrect with his 1977 book (Gould 1977). Given the tenor of the times, it was not surprising that phenotypic plasticity and reaction norms, particularly optimal reaction norms, were not on center stage in Evo-devo conversations. For about a decade, adaptationism became somewhat politically incorrect. In the 1990s the pendulum swung back, and by the turn of the millennium balance was largely restored (Stearns 2002).

Second, although both fields seek to explain the evolution of the phenotype, they concentrate on different kinds of traits. Life history evolution concentrates on plastic, continuous traits such as growth, reproduction, and survival, asking how they interact to yield reproductive success. Evo-devo concentrates on canalized, modular traits and on the evolution of morphological form and novelties. Thus the second reason is a qualitative difference in the sets of traits to be explained. That

qualitative difference in what is to be explained naturally elicits significant differences in the styles of explanation.

Here again developments in Evo-devo were not occurring in a vacuum. In this case, the critical element in the intellectual environment was the rise to prominence in the 1990s of phylogenetic explanations and tree-thinking. The traits used in phylogenetic systematics are those readily coded as binary characters, to which the discrete, canalized modules found in morphology are much better suited than the continuous, plastic traits that are the focus of life history evolution.

The impact of the controversy over adaptationism is well known and has already stimulated a literature in both the history and philosophy of science. The impact of the rise of tree-thinking on the intellectual focus of cognate fields has not, to my knowledge, received similar treatment. It deserves it.

In contrast to life history evolution, which restricts its attention to the direct components of fitness, phenotypic plasticity is a concept that applies broadly to many traits involved in evolutionary processes, some of which are only very loosely connected, if at all, to life history evolution. There it plays an important role in ideas about genetic assimilation and the evolution of novelty (West-Eberhard 2003).

## 6.6 A Major Change in Life History Evolution Since 1981

In 1981 life history evolution was a field with a theoretical branch dominated by demography and quantitative genetics and an empirical branch dominated by evolutionary experiments on whole organisms and comparative analyses of phylogenetic patterns. While both activities continue, a new research program has developed that seeks to uncover the mechanistic basis of tradeoffs. Those efforts are summarized in a book edited by Flatt and Heyland (2011). Some of its main messages make clear that this part of life history evolution is moving closer to the explanatory style of Evo-devo:

1. Tradeoffs can be mediated by conflicts in signaling as well as by zero-sum resource allocation. In some cases lifespan can be extended by manipulating a signal without decreasing reproductive output.
2. One such signal is found in an ancient, broadly shared pathway that mediates tradeoffs in many species: the Insulin/Insulin Like Signaling Pathway.
3. The connection between genetic tradeoffs, as expressed in genetic covariances or correlated responses to selection, and physiological tradeoffs, as expressed in signaling conflicts or resource allocations, is not yet clear. This remains a black box in the genotype-phenotype map.

Thus, one important element of life history evolution, tradeoffs among key traits, may well be mediated by an ancient, broadly shared mechanism—a paradigmatic element of Evo-devo explanations. That discovery, and others that should follow, could move the explanatory styles of the two fields closer together. In turn, that could stimulate collaborative research that might take more substantive steps

towards connecting at least some elements of the two fields. For example, modern genetic tools could be used to manipulate elements of the Insulin/Insulin Like Signaling pathway in flies, worms, or mice, and the consequences could be tracked in the transcriptome, metabolome, and phenome for a series of contrasting environments. The result would be not only a much more complete picture of the integrated plastic response as it is distributed throughout the organism, but an operational definition of the modules into which the integrated organism can be naturally partitioned. The overall procedure could be generalized to morphological analyses where central signaling pathways could be similarly manipulated.

## 6.7 An Intellectual Rift?

The conceptual unification of science is an ideal honored in rhetoric and neglected in practice because it is opposed by strong forces that promote specialization. In reading through the history of recent ideas on tradeoffs, I was struck by the very different intellectual styles and research strategies of two types of scientists: those who do theory and synthesis, and those who do experiments to discover mechanisms. Some of us do both, but many of us do either one or the other, and few of us balance both approaches because we are not equally good at them. For considerable periods, the two camps can operate almost entirely independently. One result is that theoretical predictions can remain untested for decades while information on mechanisms that is only loosely connected to theory accumulates to great depth. That has been the case with tradeoffs in life history evolution.

## 6.8 Summary

The 1981 Dahlem Conference was a great motivator. In my case, it helped to trigger ideas on how to predict the evolution of reaction norms for life history traits; it changed the way that life history evolution and evolution in general are taught, at least in some places; and it provided a model for a new kind of graduate course. Between 1981 and 2010 there has been an important shift in emphasis in life history evolution research towards the investigation of the mechanistic basis of tradeoffs. I do not think this was much influenced by the 1981 Dahlem Conference, but it did yield discoveries that have brought the explanatory paradigms of life history evolution and Evo-devo closer together. If in the future life history evolution does get better connected to Evo-devo, I think it will probably be through research on mechanisms that uncovers patterns similar to those found in Evo-devo, not through theory. Were that to happen, it would contribute to a conceptual unification much to be desired: the connection of micro- to macro-evolution.

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# Chapter 7
# A Developmental-Physiological Perspective on the Development and Evolution of Phenotypic Plasticity

**H. Frederik Nijhout**

## 7.1 Introduction

### *7.1.1 My Path to Plasticity*

I came to phenotypic plasticity via developmental physiology. I am interested in higher-level control mechanisms that operate in development. That is, I do not work at the level of the gene, mostly because many people are there already and because, from my perspective, most of the really interesting problems in biology actually play out at higher levels of organization. At the time of the 1981 Dahlem conference, I was primarily interested in working out the developmental physiology of insect metamorphosis, and in particular how the timing of, and body size at, metamorphosis were regulated. I knew about phenotypic plasticity and the fast-growing field focused on exploring relations between evolution and development, but never thought I would have much to contribute to those enterprises. Although my interest in phenotypic plasticity and its role in development and evolution have grown and matured over the years, I am still a developmental physiologist at heart, and this review will bear much of that hallmark insofar as it will focus on organismal and physiological aspects of phenotypic plasticity and its evolution.[1]

Much of my early work focused on the mechanisms that control metamorphosis in insects. Metamorphosis is arguably the single most interesting phenomenon in all of developmental biology. A maggot and a fly, or a caterpillar and a butterfly, are

[1] It is worth highlighting that this is in contrast to others who have focused on phenotypic plasticity (Stearns, Chap. 6, this volume). My primary concern has been uncovering the developmental and physiological mechanisms of phenotypic plasticity, rather than articulating an abstract theory of phenotypic plasticity (e.g., life history theory).

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utterly different creatures with few characters in common. Yet, in a matter of a few days, one transforms into the other. This is not like the progressive increase in complexity we see in embryonic development, but a profound transformation of one complex organism, with adaptations to a particular environment and mode of life, into a totally different complex organism adapted to a completely different mode of life.

The control of metamorphosis, likewise, is not by progressive patterns of gene expression in which one set of genes activates the next, as we see in embryonic development. Embryos are small, and the entire organism is within reach of diffusing regulatory factors that spread from cell to cell. In post-embryonic development, by contrast, the animal is large and there is a need to coordinate developmental processes over much greater distances than can be accomplished by diffusion. This requires long-range signaling via nervous and endocrine systems.

One of the key problems related to the control of metamorphosis is the timing of its onset. Because adult insects do not grow after metamorphosis, the timing of metamorphosis has to be carefully regulated so it occurs at the species-specific body size. At the time it was clear that insects do not "count instars" and that metamorphosis could be delayed, or completely prevented, by simply underfeeding or starving a larva. But by starving larvae at progressively higher weights we found that at a certain point, when they had reached about half of their normal maximal weight, they metamorphosed normally, and at exactly the same time as larvae that were allowed to continue feeding. We called this the "critical weight." We found that the critical weight can be measured with considerable accuracy and we learned to use it to predict exactly when any individual caterpillar will stop growing and start metamorphosis.

We also investigated what happens at the critical weight and found that when larvae achieve it the level of juvenile hormone (hereafter, JH) in the blood drops rapidly and that the level of JH–esterase, the enzyme that catabolizes JH, rises abruptly (Browder et al. 2001; Jesudason et al. 1990; Nijhout and Williams 1974a). JH actively inhibits the secretion of the prothoracicotropic hormone (PTTH) and of ecdysone, the molting hormone; the period of time between the critical weight and the secretion of ecdysone, which causes the larva to stop feeding and initiates the metamorphic process, is the time required to eliminate JH. Injection of JH during this period extends the feeding phase of the larva and causes it to continue growing to enormous size. By manipulating food and hormones, we were able to induce about a three-fold variation in body size. This demonstrated that body size is a plastic trait, even though body size appears to be genetically fixed and normally tends to vary little (about 10 % around the mean).

We knew all these things about growth, body size, and metamorphosis around the time of the 1981 Dahlem conference, but thought of them purely in terms of mechanistic developmental physiology. Upon reading the edited volume resulting from the 1981 Dahlem conference (Bonner 1982), and Steve Gould's *Ontogeny and Phylogeny* (Gould 1977), I became increasingly interested in the evolutionary causes and consequences of growth and metamorphosis in insects. Metamorphosis is a form of phenotypic plasticity. I think of it as a "sequential polyphenism"

because in sequential parts of its life cycle an insect is highly specialized and adapted to dramatically different environments and modes of living (much like the seasonal adaptations of plumage in birds). Larvae are adapted for feeding and growth, often on specialized food resources, whereas adults are specialized for dispersal and reproduction.

Metamorphosis is not just a progression of increasing complexity as seen in embryonic development. Instead, it consists of development to a stable, highly adapted morphology (the larval stage; e.g., a caterpillar) that persists for a long period of time, followed by a transformation into a very different—also highly adapted—morphology (e.g., the adult butterfly), which likewise persists stably for some time. The evolution of the larval stage in insects has become uncoupled from the evolution of the adult stage, and each has evolved unique and quite unrelated specializations (Gillott 1995). Therefore, one can think of metamorphosis as an example of phenotypic plasticity, where the environment—via nutrition—determines at what time the critical weight is achieved and thus the timing of the switch from the larval to the adult form.

There is one feature of insect metamorphosis that makes it even more interesting and compelling as an example of phenotypic plasticity: many insects have the ability to metamorphose into one of two (or sometimes three) very different-looking adults, depending entirely on the environment they experienced as larvae. Probably the best-known example of this, and the first one we worked on (started by Diana Wheeler in my lab), is the system of castes in ants. In many ants there are three female castes: workers, soldiers, and queens (there are no male castes). A female larva can metamorphose into any one of these three castes, depending on the nutrition and pheromones it received. These social castes differ greatly in body size, allometric proportions of head, legs and other body parts, behavior, longevity, and reproductive capacity (only the queen reproduces).

In researching the control of caste determination in the harvester ant (*Pheidole bicarinata*), we found that JH controlled the caste switch between workers and soldiers. Any larva, no matter its size or nutritive history, can be made to develop into a soldier by a topical application of JH during a brief critical period at about the middle of the last larval instar (Wheeler and Nijhout 1981). We found that JH prolongs the feeding phase (thus resulting in a larger body size at metamorphosis), and also alters the growth trajectory of imaginal disks of the head. Both effects produce soldiers that are larger than workers, with disproportionally large heads (Wheeler and Nijhout 1981, 1983, 1984). We subsequently worked on the mechanisms that control the expression of alternative phenotypes in several other polyphenisms, notably the horn polyphenisms of scarab beetles (with Doug Emlen and Armin Moczek), and the seasonal color pattern polyphenism of butterflies (with Bernd Koch and Debbie Rountree). The polyphenisms of butterflies are particularly striking in that the alternative forms can be so vastly different that in the past some have been described as different species. It is an interesting problem in both development and evolution how it is possible to develop two phenotypes that are as different as different species, when there is not a single genetic difference

between them (i.e., any larva can develop into either phenotype depending entirely on the temperature or photoperiod under which it grows up). This compelling question has guided a good portion of my research over the years.

## 7.2 The Status of Phenotypic Plasticity Circa 1981

The status of our understanding of phenotypic plasticity and its role in evolution at the time of the 1981 Dahlem conference was described in a major chapter by Stephen Stearns entitled "The Role of Development in Life History Evolution" (Stearns 1982). Its primary focus was on how phenotypic plasticity enables tradeoffs between growth, differentiation, reproduction, and longevity. In this chapter Stearns emphasized the important role played by ecology in life history evolution, and suggested that the time was ripe for a field loosely called "developmental evolutionary ecology." This prescient call has been realized only recently in an effort spearheaded by Scott Gilbert (Gilbert 2003, 2005), and culminating in a book-length review and synthesis (Gilbert and Epel 2009).

Elsewhere in the 1982 Dahlem volume, the role of development in plasticity appears in a few speculative paragraphs of the Group Report by John Gerhart about the developmental mechanism of allometry in vertebrate limbs (Gerhart 1982). Allometry refers to changes in the relative sizes of body parts with respect to variation in overall body size within a species (Huxley 1932). It had long been recognized as a feature of animal morphology that required explanation, and several reports in the 1982 Dahlem volume outlined how biologists have described allometry and interpreted its role in evolution (Bonner and Horn 1982; Gould 1982; Maderson 1982). Although allometries had been described for more than half a century, very little was known about their developmental basis, or about how those developmental processes can or did evolve. Several authors, among which notably Gould (1982), speculated about how allometry could constrain the evolution of morphology as well as the evolution of body size (Gould 1977, 1982). Gerhart (1982) pointed out that the proportional sizes of bones in the fully developed limb depend on three developmental factors: the size of the initial allocation of cells, the rate of growth, and the timing of the cessation of growth. If each of these factors is independently controlled for each bone, then the evolution of different proportions for the size of limb bones in different species could be due to evolutionary changes in any or all of them. Allometry—as opposed to isometry—would arise if the three processes scale equally with plastic variation in body size.

The development of some phenotypically plastic traits, such as the seasonal features of vertebrates (e.g., antlers in deer [Goss 1968; Suttie et al. 1984] and plumage in birds [Ralph 1969; Witschi 1935]), were understood to be controlled by hormones like testosterone and prolactin. In insects, the control of metamorphosis by JH and ecdysone was also becoming well understood (Doane 1973; Schneiderman and Gilbert 1964). But these features were studied primarily in the

context of endocrinology or developmental physiology; little thought was given to their genetics or evolution.

In evolutionary biology, the effect of the environment on the development of the phenotype was well recognized and embodied in the concept of the *reaction norm* (Schmalhausen 1949; Woltereck 1909). This describes the way that a phenotype associated with a particular genotype changes along an environmental gradient (Schlichting and Pigliucci 1998). In evolutionary genetics, the environment was primarily seen as an agent of natural selection. The fact that environments could alter the phenotype without affecting the genotype was mostly taken as a cautionary tale: the environment should be controlled carefully in selection experiments, and its effects on the phenotype should be assessed and statistically eliminated (if possible). The latter—elimination—was the approach taken by quantitative genetics.

It was understood in quantitative genetics that the variation of the phenotype could be attributed to different causes. Fisher (1930) assumed that the genes that affect a phenotype operated additively, which allowed him to develop a simple statistical approach to predicting how selection would alter the phenotype. This approach laid the foundation for quantitative (or statistical) genetics (Falconer and Mackay 1996; Lynch and Walsh 1998). Phenotypic variance is seen as the sum of additive genetic variance (which is responsible for the resemblance between parents and offspring), dominance variance (due to the nonlinear effects of alleles), and environmental variance, due to the fact that different individuals experience different environments that affect the expression of their phenotypes. The effects of dominance and environment are typically referred to as "deviations" because they are responsible for the imperfect match between genotype and phenotype: if it were not for the environment and the nonlinear/non-additive effects of genes, the additive effect of genes would accurately predict how the phenotype would change under selection. But since the effects of these deviations can be measured by breeding experiments, they can be statistically eliminated. Quantitative genetics measures the breeding properties of a population and uses this information to predict how the mean phenotype of a population will change after selection. The predictions are accurate for only a few generations of selection because the breeding properties of a population change as the phenotype and genetic background change. This requires that the quantitative genetic parameters be measured all over again to accurately predict the outcome of the next round of selection.

Phenotypic plasticity is handled in two ways within a quantitative genetics framework. One way is by measuring the contribution of environmental variation, by analysis of variance, and using that to explain away some of the non-genetic variance in the trait. Another way is by treating the phenotype as a threshold character with two values, and assuming that this is produced by a threshold in a continuous, normally-distributed, underlying *liability*. Neither approach is satisfactory from a developmental viewpoint because they do not get at the underlying mechanisms.

## 7.3 The Developmental Biology of Phenotypic Plasticity (Post-Dahlem 1981)

During the three decades since the 1981 Dahlem conference, developmental biologists have been concerned primarily with elucidating the molecular mechanisms of gene regulation during early development in model systems (see Gerhart, Chap. 8, this volume). Model systems have been enormously useful and are an indispensable tool for developing a deep understanding of the key role of regulatory genes in embryonic development (Carroll et al. 2004). Perhaps the most important discovery to emerge from this work is the extraordinary conservation in the genes that regulate early development in animals across metazoan phyla. Embryos from insects to nematodes, to sea urchins and humans, use a highly conserved "tool box" of regulatory genes to specify the primary body axes, regions of the body, and appendage compartments. And highly conserved intracellular signaling pathways and intercellular paracrine signaling mechanisms have been shown to regulate growth (Baker et al. 1993; Grimberg and Cohen 2000) and cell differentiation (Artavanis-Tsakonas et al. 1999; Carroll et al. 2004; Martin and Hall 2005).

The tools and experimental approaches used to study development in model systems have, so far, been poorly suited to elucidating the developmental mechanisms that underlie phenotypic plasticity (Love 2010). In most studies with model organisms, both the physical environment and the genetic background are held constant, even to the extent of using highly inbred strains as the preferred experimental systems. This is completely reasonable because variation in the environment and the variation of non-target genes are seen as undesirable "noise" that interferes with the elucidation of the genetic mechanisms under study. The need for a high level of control also implies that phenotypic plasticity is seen as troublesome and irrelevant. As a consequence, most of the work that has attempted to uncover the developmental basis of phenotypic plasticity has been done with non-model organisms. The developmental basis of phenotypic plasticity has been studied primarily in the context of polyphenisms, body size regulation, and allometry.

### *7.3.1 Polyphenisms*

The work in my laboratory (outlined above), and an ever-increasing body of experimental work by others, has led to several important insights about general principles of the developmental control of polyphenic development. First, all of the polyphenisms studied thus far (both in vertebrates and invertebrates) are controlled by hormones (Bento et al. 2010; Nijhout 1994, 2003b; Oda et al. 2011; Pfennig 1992; Wheeler and Nijhout 2003). The environment does not have a direct effect on developmental processes but is perceived by the central nervous system, stored and integrated, and eventually leads to the secretion of neurohormones that indirectly control alternative patterns of gene expression, which results in the development of

alternative phenotypes. Second, these hormones act as developmental switches between discrete alternative phenotypic outcomes (Nijhout 1999, 2003b). Third, tissues and organs have well-defined sensitive periods during which they are susceptible to hormonally controlled switching. Presumably, these critical sensitive periods are due to the tissue-specific temporal patterns of expression of either the receptors for the hormone or of aspects of signaling cascades activated by the hormone (Jindra et al. 1996; Kremen and Nijhout 1998; Riddiford et al. 2000; Talbot et al. 1993; Truman et al. 1994). Thus, postembryonic development is compartmentalized into semi-independent modules, just like embryonic development, but differs in that the overall control and coordination is accomplished by hormones, produced and controlled by the central nervous system. In effect, the CNS is in control of postembryonic development.

A general scheme for the control of polyphenic development in insects has emerged over the past few decades (Fig. 7.1). At some point during development there is an environment-sensitive period during which information is gathered and integrated. This information can be about photoperiod, temperature, nutrition or pheromones; the general idea is that these are signals that act as predictors of a future environmental change. The environment-sensitive period is typically many days long, which presumably promotes the unambiguous detection of the signal, and occurs several days to several weeks before the development of the alternative phenotype. Thus, the environmental signal is integrated and stored, and later, at some point during metamorphosis, results in a hormone-mediated switch in developmental pathways. The endocrine switch occurs by one of four mechanisms, depending on the species:

(i) Change in hormone level to above (or below) a particular threshold (as occurs in soldier induction by JH in ants; Wheeler and Nijhout 1981, 1983);
(ii) A tissue-specific change in the threshold of sensitivity to a hormone (as occurs in response to the soldier-inhibiting pheromone in ants; Wheeler and Nijhout 1981, 1984);
(iii) A shift in hormone secretion so it either falls within or outside a window of hormone sensitivity (as occurs in the seasonal color polyphenism in butterflies; Koch and Bückmann 1987; Rountree and Nijhout 1995);
(iv) A shift in the hormone sensitive period (as occurs during polyphenic horn development in beetles; Emlen and Nijhout 2001; Moczek and Nijhout 2002);

In insects the primary hormones involved in the control of polyphenism are ecdysone and JH (Nijhout 1999, 2003b), and there is evidence that neurohormones also play a role in switching between forms in some species (Hardie 1987; Tanaka 2000, 2004; Zera 2003). Ecdysone acts via a nuclear receptor so it directly controls gene transcription, and tissue-specific isoforms of the ecdysone receptor control alternative patterns of gene expression (Cherbas et al. 2003; Jindra et al. 1996; Riddiford et al. 2000; Schubiger et al. 2003; Talbot et al. 1993). A hormone sensitive period in these cases corresponds to a period during which a particular tissue expresses the receptor. JH does not appear to act via a traditional receptor, but binds to many different proteins in a cell and possibly retargets intracellular

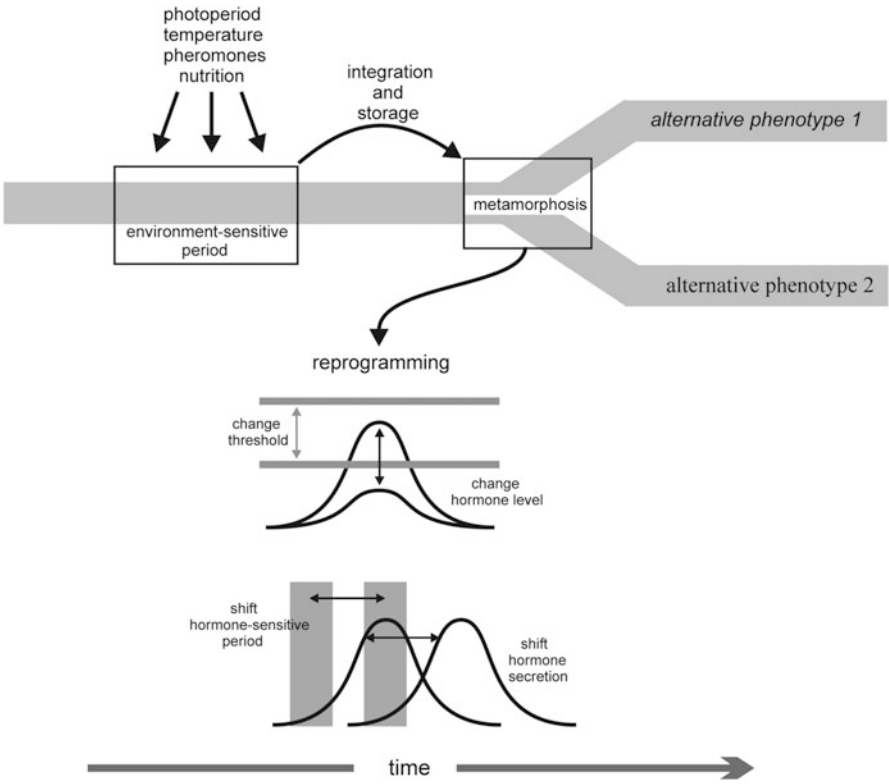


**Fig. 7.1** General mechanism for a polyphenic developmental switch in insects. During larval life there is an environment-sensitive period when cues from the environment are received, integrated, and stored. At a later time, usually during metamorphosis, this stored information results in the reprogramming of development, resulting in the development of one of two alternative phenotypes. Reprogramming involves a change in the pattern of gene expression controlled by a change in hormone signaling. This can involve a shift in hormone concentration above or below a threshold, or a shift in the threshold, which causes an alternative pattern of gene expression. Alternatively, the switch can be controlled by a shift in the timing of the hormone so it falls within or outside a hormone-sensitive period; or the sensitive period can shift so that it either coincides or fails to coincide with an above-threshold level of the hormone. In each case, the hormone induces, directly or indirectly, a different pattern of gene expression that results in the development of the alternative phenotype

signaling cascades (Hodin 2009; Wheeler and Nijhout 2003). In many cases, the JH-sensitive period is determined by the timing of ecdysone secretion and the action of ecdysone appears to be required for the morphogenetic effects of JH to become manifest (Nijhout 1994).

The way hormones alter developmental pathways is still rather poorly understood. The gene expression patterns downstream of ecdysone signaling have not been studied sufficiently, and the molecular effects of JH are likewise little understood, even after many decades of study. Changes in the genetic network underlying

wing polyphenism in ants has been elucidated (Abouheif and Wray 2002). The wing-patterning network in the winged castes of ants is similar to that of *Drosophila*. In the wingless castes, this network is interrupted at a few species-specific locations by a failure to express genes for critical transcription factors (Abouheif 2003; Abouheif and Wray 2002; Nahmad et al. 2008). So, in this case, a relatively simple change in gene expression accounts for a major morphological polyphenic shift (alate vs. apterous). At a more global level, several authors have investigated the overall patterns of change in gene expression that follow a polyphenic switch. In honey bee larvae there is a massive change in gene expression in both presumptive worker and presumptive queen larvae shortly after the JH-sensitive period for caste induction (Evans and Wheeler 1999, 2001). There also is a massive change in gene expression associated with caste development differences in termites (Scharf et al. 2003). Other studies of gene expression have shown that several hundred to several thousand genes differ in expression in different environments (Snell-Rood et al. 2010), and that the differences in gene expression in alternative environments are as great as those between the sexes (Snell-Rood et al. 2010). Whether these differences in gene expression are causes (high in the control hierarchy of a developmental switch), effects (low in the chain of events that leads to the alternative phenotypes), or just spurious correlations is difficult to tell.

Evidence is accumulating that the development of some alternative phenotypes, particularly in social insects, is associated with large changes in DNA methylation (Angers et al. 2010; Elango et al. 2009; Kronforst et al. 2008; Moczek and Snell-Rood 2008). Methylation of promoter regions of DNA controls gene expression by restricting which genes are available for transcription (Siegfried and Simon 2010). Therefore, it is possible that some of the effects of hormones in the development of alternative phenotypes are mediated through epigenetics.

Polyphenisms often come about by a discrete developmental switch (Fig. 7.1), although it is usually possible to produce animals with a range of intermediate traits between the two canonical forms in the laboratory (Nijhout 2003b). These intermediate forms are rarely found in nature. This raises the question of whether the discrete alternative forms in a polyphenism might be due to the fact that animals experience discretely different environments in different generations: predators or pheromones are either present or absent; day length is either long or short; food quality is either good or bad; temperature or population density is either high or low. Little is known about the mechanisms that sense and integrate relevant environmental cues, but it is possible that they involve a threshold response. For instance, the seasonal polyphenism in *Araschina levana* is associated with diapause, so that the orange-and-brown spring form emerges from a diapausing pupa and the black-and-white summer form emerges from a direct-developing pupa (Koch and Bückmann 1987). In diapause induction, insects accumulate photoperiod information during a critical period (Denlinger 2002); it is unambiguous because diapause lasts several months. But in the laboratory it is possible to initiate development during diapause with an injection of ecdysone at any time. If ecdysone is injected during the sensitive period for seasonal form induction (the first nine days of diapause), it is possible to produce a series of smooth intermediates between

the two canonical forms (Nijhout 2003b). Such intermediates are never seen in nature, but our ability to induce them artificially shows that the developmental program that switches between the two forms does not involve a threshold response.

The polyphenic thresholds we see in animals that have not been artificially manipulated are probably due to a higher-level regulatory mechanism. For example, the threshold resides in the mechanism that controls hormone secretion in polyphenisms that are associated with diapause, rather than in the direct effects of hormones themselves (Nijhout 2009; Oostra et al. 2010). Another locus of control resides in the mechanism that controls the hormone-sensitive period. In the horn polyphenism of dung beetles, the threshold is set by a shift in the hormone sensitive period for JH (Emlen and Nijhout 2001; Moczek and Nijhout 2002). In large horned males this sensitive period occurs about a day later than in small hornless males, and by that time JH has declined below the level at which it inhibits horn development. The position of this hormone-sensitive period with respect to body size can evolve rapidly (Moczek 2003; Moczek et al. 2002; Moczek and Nijhout 2002; 2003), and variation in its timing may account for the evolution of divergent scaling relationships between populations and species (Moczek 2003; Moczek et al. 2002).

### *7.3.2 Body Size and Allometry*

Body size is a plastic trait. Although under ideal and constant conditions there is relatively little variation in final (adult) body size in species with determinate growth, variation in temperature and nutrition can have profound effects on final body size. In poikilotherms there is an inverse relationship between rearing temperature and body size, called the temperature-size-rule (Atkinson 1994; Walters and Hassall 2006), and insufficient nutrition can reduce body size, sometimes to as little as half of normal (Nijhout et al. 2006a).

Although much has been learned about how cell division and growth are controlled, surprisingly little is known about the developmental mechanisms that control body size or the sizes of body parts. Many authors have noted that the size of an organ, or a body part, is a product of the size and number of the component cells (Azevedo et al. 2002; De Moed et al. 1997; Partridge et al. 1994; Robertson 1959). The view that size is a function of the product of cell size and cell number would seem to reduce the problem of size regulation to two distinct problems: the control of cell size and the control of cell number (or cell division). The idea that the control of body and organ size may be a simple function of the control of cell size and cell number emerged from the studies of Alpatov (1930) and Robertson (1955, 1959), who showed that genetic differences in *Drosophila* wing size were due to differences in cell number, with cell size remaining constant. By contrast, when body size variation was due to the environment (temperature), this variation was due to variation in cell size, not cell number. Thus, depending on circumstances, size variation can be accomplished by variation in either cell division or cytoplasmic growth, or (presumably) both.

Much of the work on size regulation in *Drosophila* has focused on the role of inter- and intracellular signaling pathways (Shingleton 2010; Shingleton et al. 2009). This work has revealed much about the control of cell division and patterned growth, particularly in the wing imaginal disk (Baena-López et al. 2005; Resino et al. 2002; Shingleton 2010). But exactly how body size and the precise relative sizes of organs and appendages are controlled is still unclear (but see Nijhout and Grunert 2010).

The problem of size regulation of a body part, or of the body as a whole, is primarily a problem of when to stop growing. In a revealing experiment, Neufeld et al. (1998) manipulated clonal cell proliferation in the *Drosophila* developing wing disk and showed that changes in cell division rates were offset by changes in cell size, resulting in an overall conservation of size. Thus there appears to be a mechanism that regulates the size of the wing that is independent of cell size or cell number. There are several theories about what this mechanism might be: decapentaplegic and Wnt signaling (Affolter and Basler 2007; Day and Lawrence 2000; Kopp and Duncan 2002; Martin-Castellanos and Edgar 2002; Neumann and Cohen 1997); autocrine insulin signaling (Nijhout 2003a); and, the sensation of physical stress produced by different growth rates in different parts of the structure (Shingleton 2010). The actual mechanism still remains to be elucidated.

The mechanisms for the control of body size are understood in a few species of insects. In several species of blood-sucking and herbivorous Hemiptera there are abdominal stretch receptors that monitor distention of the abdomen as the larva feeds and grows. When a critical degree of stretch is reached, a message is sent to the brain to secrete PTTH, which stimulates the secretion of ecdysone, thereby causing the animal to stop feeding and initiate the metamorphic molt. Artificial distention of the abdomen likewise triggers the molt, and cutting the ventral nerve cord, which prevents the stretch message from being sent to the brain, also prevents molting (Chiang and Davey 1988; Nijhout 1979, 1984). So far, stretch receptors have only been found in the Hemiptera. Moreover, it is not clear how such a mechanism could lead to plasticity in body size.

A different and probably more general mechanism has been elucidated in *Manduca sexta*, whose body size is determined by the critical weight (Davidowitz et al. 2003; Nijhout and Williams 1974b). The critical weight is the size at which the caterpillar begins preparation for metamorphosis. It involves shutting off the glands that produce JH and increasing the activity of JH-esterase, an enzyme that breaks down JH (Browder et al. 2001; Jesudason et al. 1990). JH serves to maintain gene expression that is characteristic of a larva, and inhibits metamorphosis (Nijhout 1994). During the last larval instar, JH actively inhibits secretion of PTTH and ecdysone (Nijhout 1975; Nijhout and Williams 1974a; Rountree and Bollenbacher 1984). When JH is fully eliminated, this inhibition is relieved and the larva secretes ecdysone, which terminates the feeding phase and growth. The critical weight occurs when the larva is about half-grown; it takes several days for JH to be eliminated, during which the larva grows to its final full size. Although we do not yet know how the critical weight is assessed physiologically, it is an exact multiple

of the initial weight of the instar (Nijhout et al. 2006a), which suggests that it is measured relative to a trait that is established at the molt.

In *Manduca*, plasticity of adult body size comes about in two ways. First, variation in early larval growth due to variation in nutrient or temperature affects the size at which a larva molts to the last instar, and thus its critical weight. Second, *after* the critical weight is reached, an invariant and nutrition-independent amount of time passes before ecdysone is secreted, and feeding and growth stop; variation in nutrition and growth during this phase can have a profound effect on final body size (Nijhout et al. 2006a; Nijhout and Grunert 2010).

If all organs and tissues grow at the same rate and for the same period of time, along with the body, then they will remain in the same proportion to the body as body size varies. The result will be isometry, meaning that body shape and the proportions of body parts do not change as body size changes. Holometabolous insects (i.e., insects with compete metamorphosis) have an interesting pattern of growth that affects the scaling relationships among their body parts. The body grows during larval life, but many adult body parts (such as wings, eyes, antennae, legs, genitalia) remain undifferentiated as imaginal disks and grow little during this period. For example, when *Manduca* larvae stop growing, the wing imaginal disks have achieved $<5$ % of their final size. Most of the growth of wings (and other imaginal disks) occurs in the prepupal and pupal stages. Thus the growth of imaginal disk-derived structures takes place in a closed system—their growth proceeds at the expense of the rest of the body. As the imaginal disk-derived structures grow, the remainder necessarily becomes smaller by comparison.

The resulting scaling and allometric relationships among body parts, and among appendages and the body as a whole, do not lend themselves to a simple mechanistic interpretation. Huxley (1932) had assumed that the two structures to be compared grow simultaneously and for the same period of time. Because growth occurs in a closed system, there is a possibility that growing structures compete for the same set of resources (e.g., nutrients or growth factors), and this can lead to the nonlinear allometries so often found in insects (Emlen and Allen 2003; Feener et al. 1988; Nijhout and Wheeler 1996). Moreover, and perhaps more interestingly, if one of those resources is in short supply (or cannot be provided fast enough), and one body part is better at garnering that resource, this would lead to a developmental tradeoff in the relative sizes of body parts that could constrain their independent evolution. Such tradeoffs have been experimentally demonstrated between the wings of butterflies and between horns and eyes in dung beetles (Nijhout and Emlen 1998), and between horns and the genital apparatus in dung beetles (Moczek and Nijhout 2004; Parzer and Moczek 2008). The body parts most liable to such tradeoffs are those that grow rapidly to a large size (and thus consume more resources), and parts that grow simultaneously. In insects, growth of body and appendages depends on endocrine signaling and is controlled primarily by ecdysone and insulin-like growth factors. Ecdysone is known to act as a mitogen in insect epidermal cells (Kato and Riddiford 1987), and both ecdysone and insulin are

required for the normal growth of imaginal disks (Nijhout and Grunert 2002; Nijhout et al. 2007). Variation in the timing and level of these factors, as well as variation in the expression of their receptors, have an impact on appendage growth (Bohni et al. 1999; Brogiolo et al. 2001; Nijhout and Grunert 2002, 2010; Nijhout et al. 2007; Oldham et al. 2000, 2002; Rulifson et al. 2002; Shingleton 2010; Stern and Emlen 1999; Tobler and Nijhout 2010). These hormones and growth regulators circulate at very low concentrations, and it is possible that they can be sequestered by rapidly growing tissues, leaving an insufficient concentration to support the normal growth of other tissues.

Developmental tradeoffs result in negative correlations between the sizes of the interacting body parts. In some scarab beetles that have large thoracic horns there is a negative correlation between wing size and horn size (Kawano 1995), and in leaf-cutting ants and army ants there is a negative correlation between head size and leg length (Feener et al. 1988). Such negative correlations have been interpreted as evolutionary adaptations to plastic variation in body size. For instance, horns are proportional to body size and large-horned beetles are better at defending territories; smaller short horned beetles then evolved larger wings that facilitate dispersal (Emlen and Allen 2003; Emlen and Nijhout 2000; Kawano 1995). Likewise large ants evolved large heads and are better at defending a colony, and small ants evolved longer legs that facilitate foraging and carrying food (Feener et al. 1988). In both these cases there is a negative correlation between the relative sizes of parts as body size varies plastically. These correlations appear to be genetically-determined and the underlying mechanism that causes these negative correlations could be a developmental tradeoff (but see the cautionary note in West-Eberhard (2003) about interpreting negative correlations when the underlying mechanism is not known).

A nice example of the control of body size and allometry as plastic traits, which also involves feedback regulation, is found in soldier determination of the ant *Pheidiole bicarinata*. As in other species of ants, any larva can develop into either a soldier or a worker, depending entirely on the environment encountered during its larval phase. In *Pheidole*, JH controls the development of soldier traits. The level of JH during larval life depends on the quality of nutrition (Wheeler 1991). An elevated level of JH during a brief sensitive time window late in larval life alters the critical size of the larva. The result is a larger body size before metamorphosis, and an altered rate of growth in the head imaginal disks, yielding large bodied soldiers with disproportionally large heads (Wheeler 1991; Wheeler and Nijhout 1983). But not all well-fed larvae develop into soldiers. Adult soldiers produce a soldier-inhibiting pheromone that raises the threshold of sensitivity to JH in larvae during the sensitive window and this prevents the production of an excessive number of soldiers (Wheeler and Nijhout 1984). An interaction between nutrition, which elevates JH, and the inhibiting pheromone, which reduces the sensitivity to JH, controls the percentage of soldiers in a colony within fairly narrow limits.

## 7.4 Developmental Reflections on Phenotypic Plasticity and Evolution

### *7.4.1 Phenotypic Plasticity vs. Robustness*

Schlichting and Pigliucci (1998) have argued that there are two types of mechanisms responsible for phenotypic plasticity: (1) *Allelic Sensitivity*, in which the expression of a gene or activity of gene product is directly sensitive to an environmental variable; and, (2) *Regulatory Control*, in which the environment controls gene expression indirectly by acting on a regulatory switch and resulting in a threshold response. These gene-centered distinctions do not capture the entire diversity of mechanisms that give rise to plasticity and we can relax their strict definition to include a broader set of regulatory processes. The environment can affect the *rate* of many developmental, physiological, and biochemical processes directly and this can lead to altered phenotypes without necessarily involving a change in gene expression. Likewise, regulatory control does not have to be exercised directly at the level of the gene. Polyphenisms are examples of regulatory control where hormones affect the course of development. Some hormones, such as steroids like ecdysone and testosterone, do directly control gene expression. But many other hormones, such as insulin and JH, affect intracellular signaling pathways that alter cell and tissue development without requiring altered gene expression.

Allelic sensitivity, in the broad sense, is likely to be the ancestral or primitive form of phenotypic plasticity (Nijhout 2003b; Nijhout and Davidowitz 2003). This is because the biological processes that give rise to the trait must obey the laws of physics and biochemistry, and that means that they will be sensitive to variation in physical and chemical factors such as temperature, osmotic pressure, and ionic composition, micronutrients such as vitamins and minerals that act as cofactors of enzymes, as well as reactive oxygen species and other toxins that are byproducts of metabolism or that are taken in from the environment. The plastic phenotypic variation that arises from such natural factors is unlikely to be beneficial. Indeed it is likely to be detrimental in much the same way that most random mutations that affect the phenotype are detrimental.

Animals have evolved a broad diversity of mechanisms to minimize or eliminate this native plasticity. The terms robustness, canalization, and homeostasis all refer to the observation that the phenotype is relatively insensitive to genetic and environmental variation. The difference between the terms is largely semantic and different traditions within biology have adopted and defined one or another of these terms for their own particular purpose. With the exception of physiological homeostasis, the actual mechanisms that give rise to phenotypic stability remain largely unknown and unexplored, except at the theoretical level where there is an abundant literature (Polak 2003; Snell-Rood et al. 2010; Wagner 2005). Robustness and canalization of the wild type is inferred when an environmental shift has no effect on the phenotype, when a mutation has low penetrance, or, in quantitative

genetics, when GxE interaction is small or absent (Falconer and Mackay 1996; Lynch and Walsh 1998). Robustness is actually quite difficult to detect if one does not know the mechanism. This is because a mutation in a gene that is not involved in generating the phenotype in question is not expected to affect that phenotype, yet the phenotype could mistakenly be called robust to that mutation. Likewise, if a trait is not affected by a shift in an environmental parameter that is irrelevant to the mechanism that generates that particular trait, then it could be mistakenly interpreted as environmental robustness. It is difficult to know how many examples of supposed mutational or environmental robustness are in fact due to the irrelevance of the measured variable to the particular trait. Only if the variable is unambiguously known to be causally related to the trait can one be certain that measured robustness is real. For this one needs to know the mechanism by which the gene in question affects the target phenotype.

The best understood robustness mechanisms are related to physiological homeostasis, which stabilize the internal milieu in the face of environmental challenge and variation. Mammalian body temperature regulation is often presented as the archetypal stabilizing feedback mechanism (Schmidt-Nielsen 1997), and has inspired thinking about how other mechanisms that stabilize phenotypic features may work. But other physiological homeostatic mechanisms can be much more complex. For instance, the simultaneous regulation of the osmotic balance, ionic composition, and volume of the blood depends on the dynamic interaction of the specific and complex internal anatomy of the kidney (proximal and distal convoluted tubules, the Loop of Henle, collecting duct, and an osmotic gradient) with hormones (diuretic hormone, angiotensin, aldosterone) produced in different parts of the body (Guyton 1981; Schmidt-Nielsen 1997). Less studied are the mechanisms that lead to salt-hunger, fat-hunger, and sugar-hunger, which presumably are adapted to maintain a proper balance of the various compounds required for metabolic and maintenance functions. These and other physiological mechanisms regulate amazingly stable internal environments in multicellular organisms.

Several robustness mechanisms operate at the cellular and molecular level. Chaperone proteins, such as the heat-shock proteins, protect the folding pattern of other proteins. HSP70 is expressed under environmental stress and protects proteins from inactivation and denaturation (Roberts and Feder 2000; Santoro 2000; Williams et al. 2009); HSP90 stabilizes the folding of a subset of proteins involved in signal transduction, hormonal response, and gene transcription (Rutherford and Lindquist 1998; Young et al. 2001). Under stress, the function of these chaperones is overwhelmed and they allow for the misfolding of proteins. Some of these misfolded proteins exhibit novel functions that affect the phenotype, but protection by chaperones normally prevents the expression of this novel function. By stabilizing a particular folding pattern, chaperones are believed to allow the accumulation of cryptic genetic variation in those proteins, which may be released as phenotypic variation upon exposure to an environmental stressor. The accumulation of genetic variants can provide the basis for rapid evolutionary change (Jarosz and Lindquist 2010; Mitchell-Olds and Knight 2002; Wagner et al. 1999). Robustness mechanisms in biochemical networks have been extensively explored and

documented (Blank et al. 2005; Deutscher et al. 2006; Edwards and Palsson 2000), and range from buffering by parallel pathways or simple product and substrate inhibition (Brandman and Meyer 2008; Nijhout et al. 2008; Reed et al. 2010; Wagner 2005), to more complex mechanisms involving long range allosteric activation and the inhibition of enzymes by metabolites in distant regions of the network (Nijhout et al. 2006b, 2008).

The mechanisms of homeostasis and robustness in development are, by comparison, poorly understood. The best model that explains the robust character of development is the gradient-threshold mechanism, where a diffusible morphogen (typically a transcriptional regulator) becomes distributed in a graded fashion between source and sink regions, and where different levels of the morphogen induce spatially different gene expression. Some of these downstream gene products are also diffusible morphogens, and this results in cascades of ever more finely detailed and locally differentiated patterns of gene expression. This general model for patterning gene expression seems to apply to the specification of antero-posterior and dorso-ventral axes in embryos, to regional specification along the antero-posterior axis, and to progressively finer regional specification in the developing appendages of both vertebrates and invertebrates (Carroll et al. 2004).

One advantage of using a gradient-threshold mechanism is that it is independent of the absolute size of the field (assuming the gradient is linear between source and sink), and easily "repaired" by intercalation should the developing structure be damaged. This gives a gradient-threshold mechanism an inherent robustness to plastic variation in overall size. If the size of a body part changes due to an environmental perturbation, the gradient can re-establish all the intermediate values and all the "normal" processes can unfold in the new developmental field. Not only can such a mechanism ensure that the spatial pattern of gene expression and resultant morphological features scale appropriately as overall size varies, but it also can be used to regulate growth and the overall size of a structure. A morphogen is held at different constant values at different locations in a body part, and cells can detect the local gradient and respond by cell division and intercalary growth to expand the field and reduce the steepness of the gradient until the right size is achieved (García-Bellido et al. 1994; Milan et al. 1996). Robustness mechanisms in development thus appear pre-adapted to regulate morphogenesis to plastic variation in size.

### *7.4.2 Phenotypic Plasticity and Robustness in Evolution*

Plasticity and robustness uncouple genetic variation from phenotypic variation (Schlichting and Pigliucci 1998; Stearns et al. 1991; Stearns 1982; Wagner 2005). Plasticity produces phenotypic variation without genetic variation; robustness does the opposite, resulting in the absence of phenotypic variation in the presence of genetic variation. Insofar as selection acts on the phenotype and the evolution of a heritable trait requires a change in the genotype, mechanisms that reduce or

eliminate the correlation between genotype and phenotype have been thought to pose constraints on evolution.

Generally, plasticity and robustness have been treated as opposite and mutually exclusive phenomena: a particular trait is either plastic or robust. But if plasticity is treated as a phenotype, then adaptive plasticity itself must be robust because it produces reliable alternative phenotypes in different environments. The alternative forms seen in polyphenisms are as stable and reliable as any monophenic morphology.

The molecular, genetic and physiological homeostatic mechanisms, which have evolved to stabilize the phenotype against non-adaptive plastic variation, clearly do not produce an invariant phenotype. A trivial reason for this is that homeostatic mechanisms are not perfect. A more interesting reason is the evolution of adaptive phenotypic plasticity. Schlichting and Pigliucci (1998) have discussed in detail how an already-existing plastic response can evolve adaptively. But in order to evolve an adaptive plastic response *de novo*, from a pre-existing robust phenotype, it is necessary to somehow disrupt that homeostatic mechanism.

### *7.4.3 Evolution of a Conditional Trait*

How does a conditional trait evolve? This can be studied by considering the evolution of polyphenism. How does a polyphenism arise in an initially monophenic species? Can it arise as a single event, or is it possible to evolve a conditional developmental response gradually? A gradualist scenario would require two sequential steps: first, the evolution of a linear reaction norm that produces the two alternative phenotypes plus continuous intermediates across an environmental gradient; and, second, the evolution of that reaction norm so it becomes progressively more nonlinear and step-like. A different possibility is the *de novo* origin of a polyphenism from a true monophenic ancestor. West-Eberhard (2003) has proposed that plastic phenotypes, including polyphenisms, arise by the same evolutionary mechanism that give rise to other novel traits.

The received view is that new traits arise by mutation. Mutations are random with respect to environmental conditions and most are assumed to be deleterious; an advantageous mutation is a rare event. Only dominant advantageous mutations will be expressed phenotypically often enough to become subject to selection (Haldane 1924). Selection gradually increases the frequency of this new mutation until it becomes fixed in a population. A vast literature in evolutionary biology and evolutionary genetics has been devoted to the exploration of this particular scenario. Presumably the novel advantageous trait produced by the mutation is further refined by additional (equally rare) mutations (Orr 1998).

An alternative and more plausible scenario for the origin of novelty derives from the findings of Baldwin (Baldwin 1896) and Waddington (Waddington 1953, 1956), and has been elaborated by West-Eberhard (2003) as follows. A new trait can arise by either a mutation or an environmental stressor that evokes a novel

phenotype by disturbing a homeostatic mechanism that normally stabilizes the phenotype. Phenotypic homeostatic (or robustness) mechanisms suppress the effects of mutations and allow the gradual accumulation of a large number of mutations of small effect. Because of the buffering due to the homeostatic mechanism, these mutations have little or no effect on the phenotype and are effectively neutral with respect to selection. They are generally referred to as cryptic genetic variation (Gibson and Dworkin 2004). An environmental stress (or a mutation) that disrupts a homeostatic mechanism allows the effects of the accumulated mutations to become expressed as a broad range of novel phenotypic variation upon which natural selection can act. If the environmental stressor recurs regularly, and if one of the expressed phenotypes is suited to the novel environment, then—in that environment—selection will gradually fix combinations of alleles that stabilize the novel phenotype.

This mechanism does not require a rare and fortuitously advantageous mutation, but relies on the presence of relentlessly accumulating mutations, most of which are of small effect (since the large-effect mutations will not be buffered by the homeostatic mechanism and thus will be eliminated). West-Eberhard (2003) discussed several reasons why the induction of novel phenotypes by this mechanism, and particularly by environmental induction, is more likely to account for the origin of novel traits. First, environmental induction immediately induces the widespread occurrence of the new trait, whereas in mutation it would be restricted to a single individual. Second, the new trait is induced in a broad range of genetic backgrounds and therefore more likely to occur in a favorable genetic background, whereas a mutation would occur only in a single genetic background. Third, environmentally-induced traits are less likely to be eliminated by natural selection because recurring environments will induce recurrence of the trait.

But inducing a novel and advantageous trait is just the beginning of its evolution. It is unlikely that the novel trait will be optimally integrated into the rest of the phenotype immediately, and it is likely that the environment that induced the trait also induced disadvantageous traits. Thus, continued selection will refine and optimize the trait, integrate it better into the rest of the phenotype, and eliminate disadvantageous traits. This further evolution is called *genetic accommodation* and is believed to occur without the need for new mutations because selection operates on the large number of small-effect alleles that have accumulated as cryptic genetic variation. The concept of genetic accommodation has caused some confusion in the literature because various authors have misunderstood its different aspects and have comingled genetic accommodation with *genetic assimilation* or the *Baldwin effect*. Clarification can be achieved by contrasting genetic accommodation with other well-established concepts for the origin of novel traits (Table 7.1). Genetic accommodation, in contrast with other models of evolution, emphasizes that many different processes operate in the origin, establishment, and refinement of a trait. Most previous models of evolution, and in particular the dominant mutation-selection model, have tended to assume (explicitly or implicitly) that changes in the frequency of one gene (or at most a few) are all that needs to be considered when explaining the origin and fixation of a novel phenotype.

**Table 7.1** Different mechanisms for the origin and evolution of novel traits

| | Mutation-selection | Genetic assimilation | Baldwin effect | Genetic accommodation |
|---|---|---|---|---|
| Initiated by mutation | X | – | – | X |
| Initiated by environmental shift | – | X | X | X |
| Modifies standing genetic variation | – | X | X | X |
| Improves form/function of trait | – | – | – | X |
| Increases genetic regulation of trait | – | X | X | X |
| Improves integration of a trait | – | – | – | X |
| Removes harmful pleiotropic effects | – | – | – | X |
| Eliminates disadvantageous traits | X | – | – | X |
| Alters frequency of expression | X | X | X | X |
| Refines conditions of expression | – | – | – | X |
| Leads to fixation of novel trait | X | X | – | X |
| Leads to improved plasticity of trait | – | – | X | X |

This view that novel traits arise first by environmental induction, followed by genetic accommodation that changes gene frequencies in the genetic background, stands in stark contrast to the mutation-first view that has dominated thinking about evolution for the past century. A great amount of theoretical work has been done in support of the latter view, though there appears to be no firm evidence that a complex trait has ever arisen by a pure mutation-first mechanism.

There is no *a priori* reason to assume that the evolution of polyphenism is different from the evolution of any other novel trait. Thus it could start with an environmental shift that releases cryptic genetic variation, followed by selection that favors the conditional expression of genes in different environments. Indeed, Suzuki and Nijhout (2006) have shown that artificial selection on an environmentally-induced trait can produce a larval color polyphenism in *Manduca sexta*. Some Lepidoptera larvae have a color polyphenism in which the later larval instars can be either green or black-brown, depending on temperature. The brown form is typically expressed only in the autumn and presumably is an adaptation that camouflages the larva against brown backgrounds exposed by dead and dying foliage. The larvae of *Manduca* are green throughout their entire life, and we found that temperature shifts and shocks have no effect on this phenotype. However, there is a mutation in *Manduca* that causes larvae to develop a black melanin

pigmentation. This mutant causes a decline in the level of JH, and the green phenotype can be rescued by injection or topical application of JH. When larvae of this black mutant strain are temperature shocked during a well-defined critical period, they develop a broad range of color phenotypes, ranging from almost pure black to almost normal green. Selection experiments in such shocked larvae succeeded in establishing two genetic strains, one in which the larval black color was fixed and insensitive to temperature, and another in which the larvae were polyphenic: black when reared at temperatures below 24 °C and green at temperatures above 24 °C. The key to the successful evolution of this polyphenism was the black mutation, which disturbed the carefully regulated levels of JH and enabled temperature shocks to induce JH-dependent phenotypes that were normally suppressed by the mechanism that stabilizes JH. The black mutation was thus an enabling mutation that allowed cryptic genetic variation to be revealed. The mutation did not produce a polyphenism, but created the circumstances in which a polyphenism could evolve by selection. It is a nice example of how the disturbance of a homeostatic mechanism (for JH) can lead to the evolution of a conditional phenotype (body color).

## 7.5 Concluding Remarks

Phenotypic plasticity can be studied at many levels. Much work has been done at the descriptive level to define and measure plasticity, at the statistical level to analyze it, and at the theoretical level to attempt to explain its origin and persistence. We also have learned much about the developmental mechanisms that allow plastic and conditional phenotypes to emerge from a single genotype. The center of gravity of developmental biology in the last twenty years has been on the elucidation of genetic regulatory hierarchies in embryonic development and this has given the impression that "control" of development resides at the level of the gene: genes are said to control almost every aspect of development, from cell division and growth to the differentiation of tissues, organs, and appendages. Most studies of regulatory mechanisms in development stop at the gene, without considering that genes do not turn themselves on. Neither do other genes turn them on in an infinite causal regression. Although gene transcription does require the products of other genes (such as transcriptional regulators), if we are to take the concept of "control" seriously then we need to consider not only the hierarchy of transcriptional regulators but also the factors that actually make the difference in whether a genetic pathway is turned on or not. These factors are almost always non-genetic (i.e., not a gene or a gene product). The reason for this is that if it were a gene, there would always be yet another gene above it in the regulatory hierarchy. But the causal hierarchy of a developmental switch always begins with a signal that depends on a non-genetic mechanism. In embryonic development, the initiation often begins with the penetration of sperm. When embryos are small, the localized initiation of new developmental events depends on the physical process of diffusion, such as

the initiation of limb growth. Without diffusion there could be no signaling over distance, so one may ask whether novel gene expression in a new location is controlled by the activator of that gene or by the physical process that put that activator in the right location. In this review I have dealt with processes that occur much later, in postembryonic development, when the organism is large and diffusion is not an effective way of carrying developmental signals. Instead, new developmental events and alternative pathways are initiated by physical factors such as environmental signals (temperature and photoperiod), nutrition, stretch receptors, and hormones. These signals not only control the onset of new developmental processes but also serve as the initiators of alternative developmental pathways whose outcome we recognize as phenotypic plasticity. The regulation of postembryonic development has not been well studied, perhaps because our obsession with gene regulation somehow makes these higher-level control processes seem less interesting or accessible. These higher-level processes, however, are also the ones that account for homeostatic or robust properties of the phenotype and how they function is of compelling interest to those who wish to develop a mechanistic understanding of the role of development in constraining evolution and the evolution of developmental mechanisms.

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# Chapter 8
# Cellular Basis of Morphogenetic Change: Looking Back after 30 Years of Progress on Developmental Signaling Pathways

**John Gerhart**

## 8.1 Pre-dawn

I was rapporteur for Group II of the 1981 Dahlem conference, whose members convened to discuss "The Cellular Basis of Morphogenetic Change."[1] Now, 30 years later, I continue as rapporteur to summarize cell–cell signaling in development, a topic implied by our discussions but only realized through the experimental breakthroughs of the subsequent decades. Group II included mostly experimental developmental biologists, many of whom had taken up new questions and approaches aligned with the then-recent advances in genetics and cell biology. Several members thereafter contributed greatly to the breakthroughs of the next decades in molecular-genetic-developmental biology. Concluding the 1981 report, we couldn't say much about evolutionary changes in morphogenetic mechanisms because most mechanisms had only been understood at a descriptive level. Morphogenesis was a complex concept that included all processes by which developing embryos generate their adult form, but it was beginning to resolve into two areas of emphasis. One concerned the actual mechanisms by which embryos change shape, such as cell shape change, adhesion, migration, and proliferation; the other concerned mechanisms of pattern formation by which a field of embryonic cells generates cell differences, even though those differences may not entail overt changes of cell shape, movement, and number. (They might, for example, involve changes of gene expression.) This second emphasis came closer than the first to the venerable embryological conjecture that position determines fate in the embryo.

[1] Gary Freeman (Chap. 10, this volume) was also a member of Group II.

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It was more about placement than about size and shape. Pattern formation was an ascending subject in 1981.

Group II had an important role in the Dahlem conference program because embryonic development was still synonymous with the generation of morphology for many biologists, and morphological comparisons were still the basis for classifying organisms and building phylogenies. Some participants shared a background in comparative vertebrate embryology and knew well the correlations of anatomical differences and developmental differences among the vertebrate classes. It was *descriptive* Evo-devo. Increasingly though, developmental biologists were coming not from zoology or even biology, but from physical sciences, biochemistry, and genetics. They were informed by insights surrounding DNA and inheritance, gene expression according to the Central Dogma, and gene regulation by DNA-binding repressor proteins (mostly illuminated by studies of bacteria). The topic of pattern formation connected the newcomers to the anatomical developmental biologists.

While the 1981 report reflects the "the late pre-molecular state" of developmental biology, it and the entire Symposium volume contain glimmerings of the new molecular genetic era. Pattern formation was a bridging subject to the new era. "Inspiring concepts" of developmental mechanisms were available for patterning, morphogenesis, and cell differentiation. There was a conviction among researchers that animals as different as insects and vertebrates had commonalities of development, if only we could see deeply enough. I will note a few key insights and inspiring concepts of the time and then indicate accomplishments of the decades thereafter that have deepened the understanding of the cellular basis of morphogenetic change and have contributed to the new Evolution of Development (Evo-devo).

### *8.1.1 Pattern Formation by Positional Information and Cell Interpretation*

Lewis Wolpert, a Group II member, had introduced the concepts of "positional information" and "cell interpretation" (Wolpert 1969). Positional information, as the phrase implies, concerns the information a cell obtains about its position within a field of identical cells. The proposed mechanism for establishing position involved "signals" or so-called morphogens that become distributed in a graded manner across the field, such that each cell receives a unique quantity of the signal related to its distance from the boundary of the field. Interpretation concerns the cell's response to the quantity of signal, especially its transcriptional response. Different cells of the field match the different quantities of signal to different gene expression outputs to create a pattern of differences. Wolpert deserves great credit, in my opinion, for providing a simple explicit model connecting extracellular signals to intracellular gene expression as a basis for pattern formation. As he summarized, "the genome and developmental history of the cell present the choices; position is the chooser."

His emphasis on the patterning of gene expression in space (also called "region-specific" gene expression or the spatial regulation of genes) differed from the emphasis of others who focused on cellular differentiation per se. For example, Monod and Jacob (1961) and Britten and Davidson (1969) proposed several kinds of genetic regulatory circuits that would stabilize different cells in different gene expression profiles though their genomes were the same. While the authors discussed the capacity of inducer-like signals to drive cells into one or another state, they didn't specify means for distributing signals in multicellular space. The Wolpert model for development as a whole involved repeated rounds of extracellular signaling and intracellular transcriptional responses, and this interplay is still central to current models of development involving the regulation of the time, place, and amount of gene expression, where "place" depends on pattern formation.

However, little was known then of developmental signals, their reception by cells, or their effects on transcription. They were called morphogens or inducers, and a plausible mechanism for generating their distribution across cells involved a source (cells producing the signal) and a *sink* (nearby cells inactivating the signal). Crick had published a source-sink model for distributing a small molecule signal such as cAMP (Crick 1970), which was well known to promote the aggregation of *Dictyostelium* amoebae into a multicellular mound and slug (as discovered by John Bonner, an organizer of the 1981 Dahlem conference), and which was known to bind to the regulatory subunit of an inactive protein kinase in vertebrates, releasing the active catalytic subunit to phosphorylate several enzymes of glycogen metabolism, thereby activating or inhibiting them (Cohen 2002). However, no effect of cAMP on transcription was yet known. Besides sources and sinks, Hans Meinhardt (Group III), in collaboration with A. Gierer, had devised and explored a self-organizing reaction-diffusion model involving fast diffusing activators and slow diffusing inhibitors for generating signal distributions across fields of identical cells (Meinhardt 2001). The models had the interesting system property of restoring pattern after parts of the field were rearranged or removed. Jonathan Cooke, also in Group II, had studied the patterning process of somitogenesis in amphibian embryos (*Xenopus*) of normal and half size, and in collaboration with the mathematician Christopher Zeeman devised a "clock-wavefront" model for the serial blocking-off of somites from the axial mesoderm (Cooke and Zeeman 1976), the same number despite the embryos' size differences. This model enjoyed a substantial revival in the 1990s with the discovery of various genes expressed in waves during these events (Pourquié 2003), a process now known to require Notch and FGF signals. Thus, the subject of signaling and pattern formation was well represented in terms of inspiring ideas and early observations. Most proved useful for the emerging developmental biology.

### *8.1.2 Compartments in Development*

Developmental compartments had been recently defined by García-Bellido (Group I) and Lawrence (Group II) as fields of contiguous, non-clonal cells in the embryo

("polyclones"), all cell members of which express one or more selector genes that encode products controlling the cell's immediate developmental options. Other compartments expressed other selector genes controlling other options. The best known compartments in 1981 were those of the anterior and posterior halves of the *Drosophila* wing imaginal discs and wings themselves; the posterior compartment differed from the anterior in the cells' expression of the *engrailed* gene. A thought-provoking finding, going back to Curt Stern in the 1960s, was that when a small clone of *engrailed*-deficient mutant cells was created in the midst of the posterior compartment, it developed as a patch of anterior wing tissue with a bristle-hair pattern like that of tissue situated at a mirror image position in the anterior compartment, reflected across a boundary at the wing's longest midline. The *engrailed* selector gene, which was later recognized as encoding a transcription factor, controlled the cells' future developmental responses to signals that were distributed symmetrically in both the anterior and posterior parts.

Though Tom Kaufman couldn't attend in 1981, he provided a chapter for the Dahlem conference volume laying out the likely role of *Hox* genes as selector genes controlling developmental differences in the segments (a series of compartments) of the posterior head, thorax, and abdomen of the *Drosophila* body. This work, building on decades of study by Ed Lewis on homeotic mutants, soon led to the discovery of the homeobox as a sequence motif of the eight gene members of the *Hox* complex, a key advance soon used for comparisons of body axes across bilateria in the newly emerging Evo-devo (Scott and Weiner 1984; McGinnis et al. 1984). Segments were discussed by several members of the group (e.g., Gunther Stent), as examples of repeated units, perhaps developing by similar processes in animals of different phyla. These were the early ideas about genes controlling developmental responses of cells to intercellular signals. Compartments were not yet recognized as the constituents of an organism-wide map of expression domains of genes encoding transcription factors and signaling proteins.

### *8.1.3 Developmental Mutants*

Christiane Nüsslein-Volhard summarized for Group II her recent work with Eric Wieschaus on the *Drosophila* mutants they had generated, isolated, and beautifully classified as ones blocked in anterior, posterior, dorsal, or ventral development, or altered in segment number (pair rule) or segment polarity. These distinctions already implied different developmental pathways (Nüsslein-Volhard and Wieschaus 1980). This work was seen as very promising, but some of us—including myself—thought it would be immensely difficult to identify the genes. And even if the genes were successfully identified, it probably would not be informative about development because, for example, a large number of genes of small effect might be involved. However, within the next 3 years, she and members of her laboratory completed the saturation mutagenesis and screens, refined their analysis of epistasis to deduce developmental pathways, and isolated and characterized the affected

genes by applying newly available molecular genetic methods such as transgenesis and mRNA injection (Rubin and Spradling 1982). Many of these genes encoded transcription factors, and the associated transcriptional cascades underlying axial patterning were soon described. Some genes encoded signaling components (e.g., Anderson and Nüsslein-Volhard 1984). The new developmental biology broke forth in the mid-1980s, first with *Drosophila*, and soon thereafter with vertebrates such as *Xenopus*, mouse, chick, and zebrafish. For these great advances that ushered in the new molecular-genetic-developmental biology, Nusslein-Volhard, Wieschaus, and Lewis received the 1995 Nobel Prize in Physiology or Medicine. But in 1981, few of us (I think) foresaw the speed and extent of the transformation of our field, or anticipated the major role of a rather small number of transcription factors and signaling proteins in early development.

### *8.1.4 Morphogenesis per se*

Morphogenetic activities of cells in gastrulation and neurulation were discussed at the Dahlem conference (see the chapter therein by Norman Wessells), but they were not integrated with other issues about development. Following previous analyses by Holtfreter of amphibian gastrulation, George Oster and Lewis Wolpert, both of Group II, had been actively seeking to resolve the complex rearrangements of embryos into a finite set of discrete cellular behaviors (an engineering perspective). These might serve different organisms in different times, places, and amounts for their differing morphogenesis. Only later were certain kinds of morphogenesis discovered to involve cell intercalation, boundary reactions, and planar polarity signaling (Keller 2002). Although early insights into cytoskeletal functions and modes of cell motility were appreciated, the cell biology of morphogenesis was a task for the future.

### *8.1.5 Early Perceptions of Conserved Components and Toolkits*

The notion of a "toolkit" wasn't used in the early 1980s, but there was widespread acceptance that various functional components of animals are similar across great phylogenetic distance and act in the generation of phenotype. Protein functions had been well defined and compared in biochemistry, especially metabolism and macromolecule synthesis, physiology, and molecular genetics. The Central Dogma canonized the deep commonality of information flow in all organisms. Researchers of bacterial self-reproduction really believed that "What's true for *E. coli* is true for elephants" (a statement attributed, with modification, to Jacques Monod). Many of us regularly argued for conservation as we wrote the health-relevance section of our

grant applications for research on "model organisms." But an evolutionary biologist colleague said to me at the time: "We don't need to know about the things that don't change." The test case seemed to be development. Since different modes of development were presumed to be responsible for the different morphologies of organisms, would conservation run through development as well? Our Dahlem group discussions implied that it did, at least in some aspects. Different bilateral animals were seen to possess many of the same (conserved) cell types but arranged differently; and, as noted above, morphogenetic processes were seen as resolvable into a set of basic cell behaviors used in different organisms. Klaus Sander in Group II presented the case for the conserved phylotypic stage of insects, which is the product of their early development; furthermore, the conserved phylotypic stage for vertebrates, sometimes called the "pharyngula", had been taken seriously as far back as Haeckel. Then, Alberch et al. (1979) had recently proposed that conserved modules of developmental processes could be used to generate different morphologies in different animals provided that evolutionary (regulatory?) changes caused them to start earlier or later, or to proceed faster or slower. However, despite these appreciations, the contrast was not yet asserted in 1981 between evolutionarily changing gene regulation and the conservation of the coding sequences and gene products under regulation, nor was morphological novelty attributed to changes of the time, place, and level of usage of conserved components. The vastness and antiquity of the metazoan toolkit of conserved proteins and RNAs only became undeniable with the sequencing of genomes, now of nearly 100 metazoans. Though the recognition of the crucial role of regulatory change in evolution is sometimes attributed to King and Wilson (1975), I think the idea only swept the molecular-genetic-developmental community in the mid to late 1980s as the *cis*-regulation of eukaryotic genes was clarified, for example, with the analysis of *even-skipped stripe 2* expression in *Drosophila* (Goto et al. 1989; Harding et al. 1989).

### *8.1.6 Toward the Present*

For some researchers, development can now be reduced to the interplay of cell–cell signaling and transcriptional regulation; almost everything about this interplay has been learned since 1981. Insights built up in the mid to late 1980s about transcription factors as enhancer binding proteins and about *cis*-regulatory regions, as did the first evidence of signaling proteins. When Hafen et al. (1987) reported that the homeotic *sevenless* mutant of *Drosophila*, one in which rhabdomere 7 of each ommatidium of the eye is missing, is defective in a gene encoding a transmembrane receptor tyrosine kinase related in sequence to a recently analyzed oncogene, they spoke of it as ". . .a receptor for positional information." Development, it seemed, had become comprehensible. As exemplified below, signaling between developing cells is indeed now well understood, and it does usually operate through transcriptional regulation to effect pattern formation, though the patterning process is more complicated than initially imagined. Many young developmental biologists now

accept that *cis*-regulatory differences cause different metazoans to express different members of their large toolkit of conserved components at different times, places, and amounts in development, generating different morphologies and physiologies.[2]

## 8.2 Signaling in Development, 1985–2010

Developmental signaling pathways were discovered as researchers analyzed developmental mutants (e.g., *Drosophila wingless*, *toll*, *hedgehog*, and *dpp*), or isolated serum "growth factors" needed for the in vitro culturing of normal and transformed cells. Currently 15–20 pathways are distinguished, depending on the exact definition of "pathway," and 5–10 of these participate over and over in various patterning events of early development. In these developmental pathways, the external signal leads to the internal activation or inhibition of a pathway-specific transcription factor or cofactor. They include the TGF-beta pathway, particularly the versions involving Bmp and Nodal signals; the Wnt pathway, with its three branches (canonical, planar polarity, and calcium mediated); the Hedgehog pathway; the Notch-Delta pathway; the receptor tyrosine kinase pathway involving small G-proteins, MAP kinases, Phospholipase C, and PI3kinase; the nuclear hormone receptor pathway, and the JAK-STAT pathway. Each operates with its own highly conserved set of protein components that include signaling ligands, receptors, intracellular transduction components, and transcription factor targets. Each is used repeatedly in development, at many times, places, and amounts, which differ in different animals. Most pathway components have been found even in sponges (Srivastava et al. 2010), but not in unicellular eukaryotes (except for receptor tyrosine kinases in choanoflagellates), indicating that these pathways date back to the earliest episodes of metazoan multicellularity. A few other pathways contribute to special aspects of development, such as the receptor phosphatase pathway, the nitric oxide/guanylyl cyclase pathway, and the apoptosis pathway. Some of the 15–20 have roles mostly in physiology, such as the large G-protein-coupled 7-pass transmembrane receptor pathway (e.g., for neuropeptides and hormones), and the ligand gated ion channels. The Bmp pathway (belonging to the TGF-beta group) and the Wnt pathway illustrate well the importance of signaling in development and evolution, and will now be described.

The Bmp pathway participates in at least 40 aspects of vertebrate development, including dorsoventral axis formation, the induction of the nervous system and somites, the dorsoventral patterning of neural cell types in the spinal cord, the development and patterning of fins and limbs, and the development of bones, teeth,

[2] As this *cis*-regulatory view of evolution was emerging, Marc Kirschner and I felt it was important to look more closely at the components of the toolkit and the targets of regulation for special properties that might facilitate the generation of phenotypic variation (see Kirschner, Chap. 9, this volume).

jaws, beaks, hair follicles, retinal patterning, heart, and blood. A list nearly as long could be made for *Drosophila* development, though for different organs and cell arrangements. The Wnt pathway functions in vertebrate development in anterior-posterior axis formation, organizer formation, posteriorization of the neural plate, fin and limb bud development, planar polarity patterning (e.g., orienting hair cells of the ear), and morphogenesis by convergent extension cell intercalation. (The *Drosophila* list is also long.) Since both pathways are involved in early steps of axis formation in vertebrates, I will discuss their roles in those aspects of development. Indeed, both pathways are targets of the inducers released by the well-known Spemann's organizer of the vertebrate embryo, and detailing these pathways will illuminate the organizer's function and the action of inducers. Then I will summarize the use of these pathways in axis formation in other organisms, as gained from comparative work, since these advances have contributed significantly to Evo-devo. Indeed, the studies of signaling pathways have directly addressed the cellular basis of morphogenetic change in development and evolution, exactly the subjects we would like to have discussed in 1981.

### *8.2.1 Bmp and the Organizer*

In amniotes, Spemann's organizer—also called the embryonic organizer or Hensen's node—is a complex signaling and morphogenetic center of the gastrula and neurula embryo. Development by means of an organizer is a shared trait of vertebrates. Spemann and Mangold (1924) discovered its capacity to organize the body axis when they transplanted it from the dorsal lip of the blastopore of a newt early gastrula, where it constitutes a mere 5 % of the embryo, into the ventral side of a second newt gastrula. At the site of the transplant, the graft healed and, during subsequent development, it organized an entire second body axis around itself, opposite the primary body axis developing around the resident organizer of the second newt. The secondary axis contained differentiated anteroposterior and dorsoventral body dimensions with components of all three germ layers, including a neural tube from the ectoderm, somites and heart from the mesoderm, and anterior gut structures from the endoderm. These derived from surrounding tissue that, without the graft, would have developed into ventral posterior parts (epidermis, posterior somites, lateral plate, and posterior gut). The dorsal lip was the only fragment with this axis-organizing capacity. It seemed to release inducers onto the surrounding tissues that controlled their developmental fates. Two main subregions of the organizer have been distinguished. One is the so-called trunk-tail organizer, the cells of which release various signals (e.g., Bmp antagonists), engage in cell-intercalation morphogenesis ("convergent-extension"), and develop into the notochord of the trunk and tail. The other is the head organizer, which releases not only Bmp antagonists but also Wnt antagonists, engages in a spreading migration kind of morphogenesis, and differentiates into prechordal plate mesoderm of the head. The subregions also differ in their gene expression profiles.

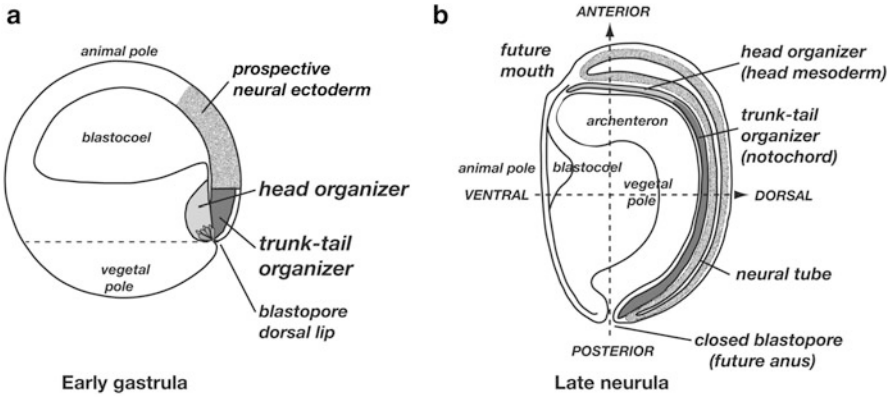


**Fig. 8.1** The vertebrate organizer before (panel a) and after (panel b) gastrulation and neurulation. A *Xenopus* embryo is shown. The organizer is initially a cube of endomesoderm cells in the dorsal lip of the blastopore of the gastrula. After neurulation it is a narrow elongated array of cells stretching the length of the embryo on the dorsal side from the anus to the anterior tip and back ventrally to the mouth. The organizer has at least two parts, the head organizer coming to lie under the anterior nervous system (forebrain/midbrain), and differentiating as head mesoderm, and the trunk-tail organizer coming to lie under the posterior nervous system (hindbrain/spinal cord), and differentiating as the notochord. These two parts differ in the signals they secrete and in their morphogenetic activities. The organizer functions as a signaling source as it moves, contributing to anteroposterior and dorsoventral patterning of the body axis

The signaling and morphogenetic roles of the organizer in development have been best analyzed in the amphibian *Xenopus laevis*. As gastrulation begins, its 500 cells are arranged in a cube in the dorsal lip (Fig. 8.1a); by the end of neurulation, its cells have rearranged into a rod, one cell wide, stretching the length of the embryo (Fig. 8.1b). It is a moving signal source, and its own morphogenesis contributes to signal distribution. The signals have major developmental effects, such as inducing the neural plate and the somites. No wonder early embryologists were convinced that inducers exert precise and detailed instructive effects on surrounding cells. The discovery of actual inducer proteins has been a major advance of the past 15 years, and current insights into their actions have come from several laboratories (reviewed in Harland and Gerhart 1997; De Robertis and Kuroda 2004; De Robertis 2009; Niehrs 2010). These inductive events orchestrated by the organizer are part of the larger process of dorsoventral patterning of the body axis during gastrulation and neurulation. For this patterning, the entire organizer secretes Bmp antagonists (Chordin, Noggin, and Follistatin), as well as a Bmp-like ligand ADMP (a surprise explained later). As these antagonist molecules interact with the Bmp that is produced by surrounding cells of the embryo, a graded distribution of Bmp and ADMP is set up across the embryo—low near the organizer and high far from it, according to which the overt dorsoventral axis is patterned (De Robertis 2009). The organizer also contributes to the anterior-posterior patterning of the body axis during gastrulation: the head organizer secretes the Wnt antagonists Dkk, Frzb (Sfrp3/4-related) and Crescent (Sfrp1/5-related), which

antagonize Wnt ligands produced by cells of the ventral and lateral parts of the embryo, to set up a graded distribution of Wnt ligands—low anteriorly near the head organizer and high posteriorly. According to this distribution, forebrain/midbrain development occurs anteriorly, while hindbrain/spinal cord development occurs posteriorly (reviewed by Niehrs 2010).

### 8.2.2 *Molecular Details of Bmp Signaling in Dorsoventral Patterning*

The Bmp signal transduction pathway was discovered in *Drosophila* during the analysis of mutants for leg development and separately discovered in assays of blood components that provoked dermal bone formation when they were injected subcutaneously into mice (hence the name "bone morphogenetic protein" or Bmp). The steps are now well understood (Shi and Massague 2003; see Fig. 8.2). After being secreted by cells of the embryo, the Bmp signaling protein binds to transmembrane receptor proteins on the same or other cells (making Bmp both an autocrine and paracrine factor). Bmp is a dimeric ligand protein; during binding it crosslinks the extracellular parts of two receptor molecules, bringing together their intracellular tails, which possess protein kinase activity. One tail adds phosphate from ATP to the other tail, activating it to add phosphate from ATP to an inactive transcription factor protein, Smad1, residing in the cell's cytoplasm. Phosphate addition to Smad 1 (designated "Smad1p") activates it to bind several cofactor proteins, and the complex enters the nucleus. There it activates or represses the transcription of specific genes that have *cis*-regulatory DNA sequences suited to bind it. Thus, the external Bmp signal sets off a series of intracellular reactions leading to a specific gene response determined by the cell's position and developmental history (contained in its genetic regulatory circuitry). None of these steps was known in 1981. Questions naturally arise about how much information, energy, and materials are needed for the signal input, the "cause", to generate the "effect" of transcriptional output. The "weak linkage" of each transduction step to the next one means that very little energy and information is needed to activate the next; each protein intermediate is built as a sensitive switch with two states (inactive and active) that interconvert easily—the addition or removal of phosphate suffices to throw a switch, which throws the next switch, and the signal doesn't attenuate during transduction. Weak linkage is a characteristic of other signaling pathways as well.

While these are the pathway's basic signal transduction mechanics, the dorsoventral patterning process also requires the generation of a particular distribution of Bmp signal over the entire dorsoventral dimension of the embryo. Several cell behaviors are involved. First, those cells producing Bmp have an autoactivation circuitry that maintains their Bmp production and secretion. They respond to their own signal via their own receptors, and they continue to activate internal Smad1p, which then activates expression of the Bmp encoding gene, leading to more Bmp protein

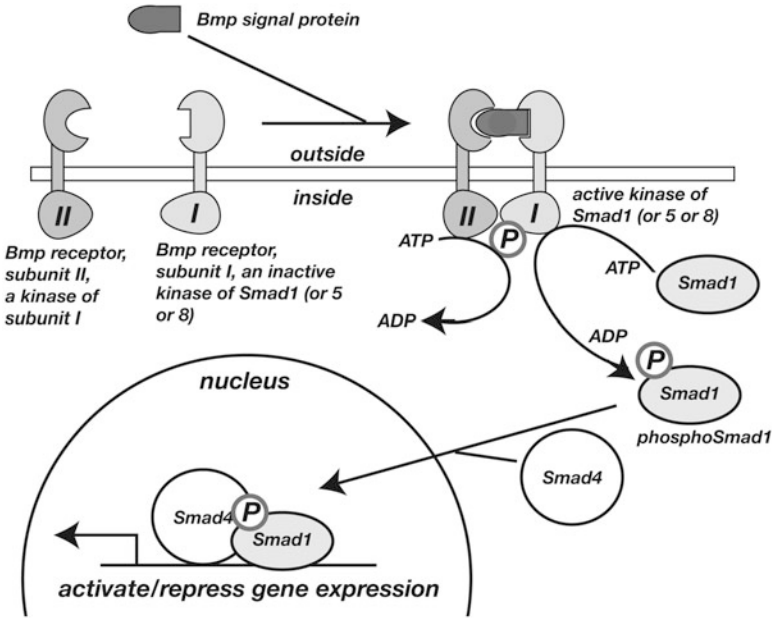


**Fig. 8.2** The Bmp signaling pathway, a member of the TGF-beta family of pathways. This pathway participates in dorsoventral patterning of the body axis of diverse bilateral animals, such as vertebrates and insects. Notice the series of intracellular signal transduction steps following the binding of Bmp (the signal ligand) to the external face of the receptor. Steps include: (1) the pairing and cross activation of two receptors' cytoplasmic tails by phosphate addition; (2) the active tail's addition of phosphate to an inactive Smad1 protein to form Smad1p, thereby activating its transcription factor functionality; and, (3) the formation of a complex between Smad1p and other cytoplasmic proteins. The transcription factor complex then enters the nucleus and activates the transcription of some genes and represses others that have *cis*-regulatory DNA regions suitable to bind the complex

production and secretion. At the same time, Smad1p activates four other genes involved in Bmp distribution: *BAMBI*, which encodes a truncated receptor protein thought to limit the cell's responsiveness to its own signal; *CV-2* and *Twg*, which encode proteins that bind to Bmp extracellularly and modify its activity; and *Xolloid*, which encodes a special protease degrading Chordin, one of the Bmp antagonists (see below). The entire set, including *Bmp*, is called the Bmp synexpression group. If Bmp protein spreads to non-producing neighboring cells that have Bmp receptors and inactive Smad1 protein, it binds and triggers them to begin the Bmp autoactivation cycle and production of all synexpression members. Thus, Bmp production spreads in a field of embryonic cells unless it is counteracted.

As gastrulation starts, most cells of the embryo are producing Bmp and engaging in autoactivation. The exception is the organizer (500 cells of the 10,000 cell gastrula), which has different behavior. Its cells do not produce Bmp because they have been prevented from doing so as part of their previous development as an organizer. Instead, they produce the Bmp antagonists Chordin, Noggin, and

Follistatin, which are all secreted proteins capable of binding tightly to Bmp and to ADMP, the Bmp-like protein also secreted by the organizer. None of the genes encoding these proteins belong to the Bmp synexpression group. Their expression in organizer cells would be repressed by Bmp or ADMP, which could bind to cell receptors and activate Smad1. However, Bmp and ADMP mostly fail to do so in the region of the organizer because its cells produce antagonists in such large excess that all ADMP and Bmp are tied up and denied receptor binding. However, if Bmp or ADMP does locally exceed the antagonist levels (a condition that can be effected by experimental manipulations), then indeed organizer cells cease producing antagonists and ADMP, and switch to Bmp production; the organizer shuts down. This kind of cell behavior is also critical for the patterning process.

Generation of the Bmp distribution across the body axis then involves the interaction of these two cell populations, the small organizer population secreting antagonists and ADMP and the large non-organizer population consisting of prospective ectoderm, mesoderm, and endoderm, all secreting Bmp. Antagonists, free or in complex with ADMP, spread from organizer cells into the surroundings rich in Bmp, CV-2, Twg, and the Xolloid protease. They preferentially bind to Bmp from neighboring cells and prevent it from binding to Bmp receptors, thereby interfering with the cellular autoactivation circuits. These cells soon cease production of Bmp and other synexpression group members. This antagonism results in a new region low in unbound Bmp and ADMP, situated close to the organizer. Farther away though, and with time, antagonists are less and less a quantitative match for Bmp. Also, the accumulated Xolloid protease steadily degrades Chordin, one of the antagonists, that is in a complex with Bmp or ADMP (a "sink" effect), releasing them for binding to receptors and for autoactivation of local cells. Chordin and Xolloid are especially important players in generating the graded distribution of Bmp and ADMP across the embryo, lowest near the organizer and highest farthest away. As Chordin spreads away from its highest concentration in the organizer, it carries ADMP and Bmp with it, dumping them as it is destroyed. This shuttling effect elevates the Bmp-ADMP levels far from the organizer (Reversade and De Robertis 2005; Ben-Zvi et al. 2008). None of these subtle interactions could be anticipated in 1981.

As gastrulation proceeds, spreading antagonists disrupt production of Bmp and other synexpression group members in approximately half the ectoderm and mesoderm bilateral to the organizer, generating large dorsal regions depleted for Bmp and ADMP. Farther from the organizer (i.e., more ventrally) other large regions of cells retain high Bmp and ADMP, with the autoactivation circuitry yet intact. This signal distribution constitutes a "Bmp-Chordin axis" that precedes the development of the overt dorsoventral axis by cells as they respond to the different Bmp levels and make their distinct transcriptional responses.

Two major events ensue from this signal distribution: (a) the development of the neural plate or epidermis in different regions of ectoderm, and (b) the development of somites or lateral plate in different regions of mesoderm. The neural plate forms dorsally near the organizer, whereas the epidermis develops ventrally, away from it. The organizer's Bmp antagonists (Chordin, Noggin, and Follistatin) are the long-sought neural inducers, though acting rather differently from what was expected by

early embryologists. In ectodermal cells of the gastrula, Bmp—by way of Smad1p—activates genes of epidermal development and represses those of neural development, concomitant with Bmp autoactivation (Fig. 8.3). This gene expression option (epidermal versus neural) and the susceptibility of the option to Smad1p

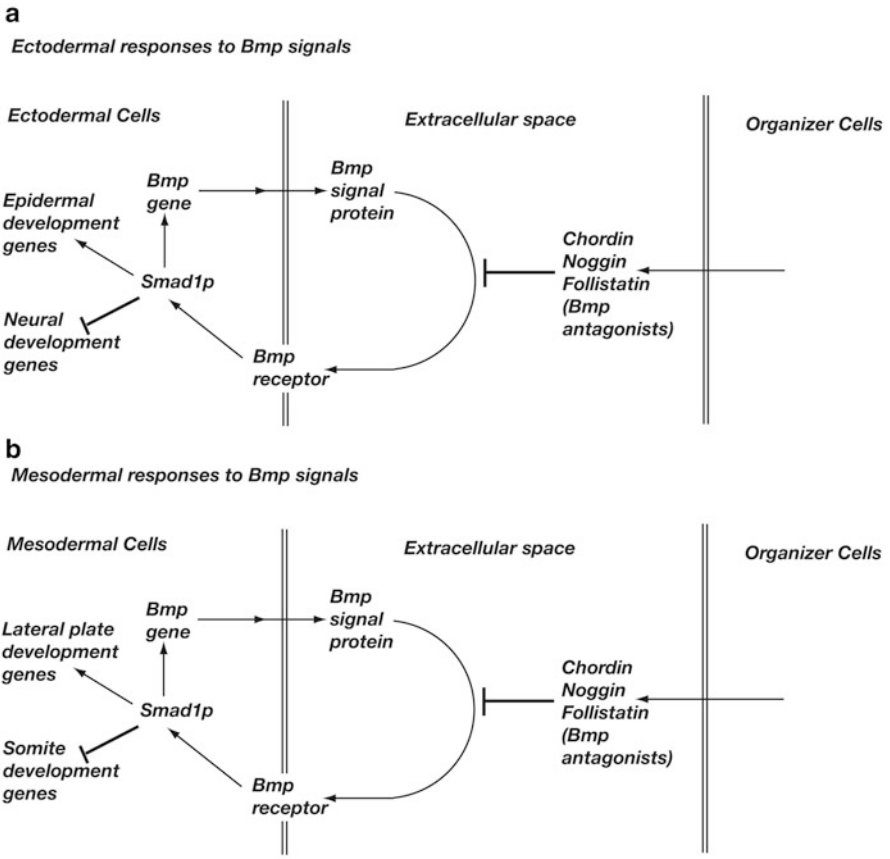


**Fig. 8.3** Signaling and transcriptional circuitry for the induction of neural tissue (panel a) and somites (panel b). *Arrows* signify activating effects; *blunt headed lines* indicate inhibitory or repressive effects. Panel a: On the left are shown ectodermal cells; their competence includes the options of development to neural tissue or epidermis. They produce and receive Bmp signaling protein, and Smad1p is maintained as an active transcription factor in an auto-activation circuit. Via Smad1p, Bmp activates the epidermal development option and represses the neural option. On the right are shown organizer cells; they produce Bmp antagonists, the proteins Chordin, Noggin, and Follistatin. In the center is the extracellular space in which spreading antagonists meet Bmp and bind it tightly; it can no longer bind to receptors on the ectodermal cells, and without continued Bmp stimulation, the cells fail to maintain Bmp production, activation of the epidermal option, and repression of the neural option. In regions of ectoderm near the organizer, the neural option is derepressed, and neural development begins. Panel b: On the left are shown mesodermal cells; their competence includes the options of development to somites or lateral plate, different from the ectodermal options. The remainder of the Panel is the same as in a. Somite development is derepressed near the organizer where Bmp has been bound by antagonists. Lateral plate develops in distant regions with high Bmp

regulation, is only available in ectoderm at this time (and not later); it represents the ectoderm's competence to respond to inducers. In ventral ectoderm experiencing high Bmp, cells subsequently develop as epidermis; the neural option is never derepressed. However, in dorsal ectoderm near the organizer, Bmp levels are too low to activate Smad1p and epidermis development, due to antagonists, and too low to repress neural development. Without repression, this ectoderm begins to neuralize and form the neural plate. The circuitry is well described by the default model based on double negative regulation (Weinstein and Hemmati-Brivanlou 1999). All ectoderm cells have the intrinsic capacity to develop as either epidermal or neural tissue, but the neural option is initially self-repressed in ectoderm by its own Bmp. Then, antagonists from the organizer inhibit Bmp from binding and repressing the neural option in ectoderm close to the organizer, thereby releasing them. Neural development is the default option, derepressed when Bmp repression is itself repressed. When Bmp is entirely removed from the embryo under various experimental conditions, the entire ectoderm develops as neural tissue. Similar double negative circuitry occurs in many instances of embryonic patterning.

Simultaneously, the organizer induces somites in the mesoderm, an event with many similarities to neural induction. In dorsal mesoderm close to the organizer (which is at the same time extending as the notochord), the Bmp level is low due to excess antagonists, whereas in the ventral mesoderm Bmp remains high. The mesoderm's competence to respond to the Bmp, and hence Smad1p distribution includes the options to develop as somites or as lateral plate, markedly different from the ectoderm's competence. In line with the default model, the mesoderm's option for somite development is repressed by Bmp via Smad1p, whereas lateral plate development is activated. Hence, lateral plate development is activated ventrally, and somite development is derepressed dorsally. Although endoderm, the third germ layer, is less studied, it may also undergo default patterning, with anterior gut development favored in low Bmp regions and posterior gut favored in high Bmp regions. The three germ layers have different competences, that is, different either-or options for development. But all three choose an option based on Bmp activation and derepression. These insights about competence and induction have only been gained in the past 15 years.

Numerous experimental results support this narrative of dorsoventral patterning. When antagonists are overproduced by experimental intervention, or when Bmp and ADMP production are disrupted (by morpholino antisense oligonucleotides or by mutation), the ectoderm develops mostly as neural plate. Reciprocally, when antagonists are experimentally depleted, or when Bmps are overproduced, the ectoderm develops mostly as epidermis. Similar results are obtained for the mesoderm, but with somites or lateral plate as the outcomes.

Embryologists had previously considered it likely that inducers are instructive molecules that bind to ectoderm and mesoderm cells and introduce substantial information about the next developmental steps. As it turns out, the inducer-like antagonists produced by the organizer don't even bind to surrounding cells, and thus have no capacity to instruct them. Instead they bind to extracellular Bmp, preventing its binding to cells, and thereby release the cells to develop as neural

tissue or somites, which they do according to the genetic regulatory circuitry of their internal competence (or as Wolpert called it, their "interpretation"). Derepression used to be called "permissive induction" in older terminology. The entire dorsoventral patterning process exemplifies weak linkage. Within the multi-step cause-effect chain between inducers and particular developmental responses, the response options are already built into the cells and only need to be derepressed by blocking a repressor. Very little information, energy, and materials are introduced by the inducer to bring about its effect. Elsewhere we have argued that this kind of linkage facilitates the evolutionary change of developmental processes (see Kirschner, Chap. 9, this volume).

The dorsoventral patterning process, as a whole, has properties that confer robustness on the Bmp distribution across the embryonic body. Researchers have wondered why the organizer produces ADMP, a Bmp-like molecule, when surrounding tissues themselves produce Bmp, and why the organizer and surrounding regions possess complex repression and autoactivation circuitries. From recent analyses and modeling (Reversade and De Robertis 2005; Ben-Zvi et al. 2008; Plouhinek and De Robertis 2009), it appears that these components, interactions, and circuits confer size regulation on the distribution mechanism, at least in chordates and hemichordates. Embryos that are halved or doubled in size at the start of gastrulation can still establish a normally patterned dorsoventral axis in which the neural plate and somites are scaled to the altered size. When the ventral half of an early gastrula is removed, Bmp levels drop in the remaining tissues near the organizer, and this diminution derepresses ADMP and antagonist production in the organizer. The additional ADMP is shuttled by Chordin to the Bmp side, increasing the combined Bmp-ADMP level high enough to impose epidermis development there. Still, Bmp-Admp levels grade off dorsally with sufficient steepness that the neural plate develops in only half the remaining ectoderm, as is also the case in a full sized embryo. Even if Bmp production is eliminated by antisense morpholino oligonucleotides, shuttled ADMP from the derepressed organizer can make up the difference and support a rather normal dorsoventral axis (Reversade et al. 2005). Thus, size regulation appears to be an important behavior serving embryos of different sizes of the same species (e.g., from different sized eggs), or embryos of different species with greatly expanded anterior or posterior parts of the body axis, as seen in D'Arcy Thompson's famous examples (see Niehrs 2010).

### *8.2.3 Evo-devo of Bmp-mediated Dorsoventral Patterning*

A major insight of the past 20 years has been the recognition that most—if not all—extant bilateral animals use a Bmp-based dorsoventral patterning process in their development, implying that the process is as ancient as the bilaterian common ancestor. Other vertebrates resemble *Xenopus* in their dorsoventral patterning (using Bmp, ADMP, Chordin), as does the non-vertebrate chordate, amphioxus (a cephalochordate). But ascidians (urochordates) are an exception; they use Bmp and Chordin elsewhere in their rapid determinative development, but not in neural

and somite inductions. Since cephalochordates probably split from the line to vertebrates prior to the urochordate split, the chordate ancestor likely used the Bmp-antagonist patterning process. Stepping outside the chordate clade, my colleagues and I have investigated the hemichordate *Saccoglossus kowalevskii* to see if this vermiform, gill slit-bearing deuterostome (phylum: Hemichordata) also uses the process; the answer is definitely yes (Lowe et al. 2006). Genes encoding Bmp, Xolloid, CV-2, Twg, and BAMBI are expressed strongly on the dorsal midline of the ectoderm, whereas those of Chordin and ADMP (but not Noggin and Follistatin) are expressed on the ventral midline of the ectoderm. All aspects of dorsovental patterning in the three germ layers depend on the high-to-low Bmp distribution between midlines. When early embryos are exposed to high levels of Bmp protein, they develop as radially symmetric dorsalized forms with a thick neck connecting the proboscis and collar, and no mouth, while anteroposterior divisions of the body remain normal. In these forms, genes that are normally expressed in dorsal ectoderm (e.g., *neuralin, tbx2/3, dlx*) become expressed around the entire body, whereas genes normally expressed ventrally become fully repressed; all germ layers are affected. For example, within endoderm, a gill slit marker gene (*pax1/9*) becomes expressed around the entire circumference of the pharyngeal endoderm of the body. Inversely, when embryos are treated with antisense siRNAs to Bmp mRNA, thereby depleting Bmp protein, they develop as radially symmetric ventralized forms with a circumferential mouth and such a thin neck that the proboscis breaks off from the body. Still the anteroposterior divisions of the body are normal. In these ventralized embryos, genes that are normally expressed in ventral ectoderm (e.g., *chordin, admp, netrin*) become expressed around the entire body, and genes normally expressed dorsally become fully repressed. Again, all germ layers are affected. From these outcomes, we conclude that all aspects of the hemichordate dorsoventral axis depend on the Chordin-mediated Bmp distribution, implying that the deuterostome ancestor had this process. In contrast, the anteroposterior axis must be patterned by Bmp-independent processes. The vertebrate organizer, it seems, co-opted Bmp-antagonist production from ectoderm into its morphogenetically active mesoderm; vertebrates didn't alter the basic deuterostome patterning process, just the means to distribute antagonists.

Bilateral animals of the protostome supertaxon also use a Bmp distribution mechanism in their dorsoventral development, though with differences in detail from deuterostomes. In *Drosophila*, Chordin (without Noggin and Follistatin) is produced in ventral ectoderm (not mesoderm) and Bmp in dorsal ectoderm, whereas ADMP is not used. Mutants affected in Bmp or Chordin production are greatly altered in their allocation of neural and epidermal ectoderm, as well as axial muscle and lateral mesoderm (Ferguson and Anderson 1991). Likewise, the leech *Helobdella* produces Bmp dorsally in its embryonic bandlets, and the Bmp-antagonist Gremlin ventrally, an antagonist unrelated to Chordin, Noggin, or Follistatin (Kuo and Weisblat 2011). Planaria produce Bmp in a dorsal stripe of ectoderm, and the antagonist is unknown (Reddien et al. 2007). From these cases, it seems that a Bmp distribution mechanism involving the Chordin antagonist was present in the bilaterian common ancestor. Subsequently, antagonists and the

Bmp-distribution mechanisms may have diversified in different clades. Bmp and several antagonists are present even in the cnidarian *Nematostella*, a purported radial diploblast, and several genes are expressed bilaterally near the antagonist source (Matus et al. 2006). Thus, some level of bilaterality may have preceded the "bilateral" common ancestor of protostomes and deutrostomes; bilaterians may have just enhanced and exploited an older Bmp-antagonist patterning mechanism.

These comparisons raise evolutionary questions about body inversion and left-right asymmetry. Chordates are the only known group producing Bmp ventrally and antagonists dorsally. Hemichordates produce Bmp on the dorsal side, as does *Drosophila*, and both produce antagonists ventrally, the inverse orientation to chordates. These discoveries have revived interest in the 1822 proposal of Geoffroy St. Hilaire that bilateral invertebrates resemble vertebrates in anatomical crosssection except that one is the dorsoventral inverse of the other (Arendt and Nubler-Jung 1994; Holley et al. 1995; De Robertis and Sasai 1996). From the hemichordate evidence, inversion of the body probably occurred within the early chordate lineage, while hemichordates and other bilateria remained uninverted. Consistent with inversion, sea urchin and hemichordate embryos turn out to express certain "left-right" genes on the right side of the body that are expressed on the left side of chordates (*lefty, nodal, and pitx*) (Duboc et al. 2005; Wlizla and Lowe, personal communication). The most dramatic anatomical modification in chordates, aside from behavioral changes orienting the body upside down, appears to be the relocation of the mouth to the Bmp side of the body, whereas in hemichordates and *Drosophila* it occupies the Chordin side.

### *8.2.4 The Wnt Pathway and Anteroposterior Patterning*

The vertebrate organizer also plays a role in anteroposterior patterning via the Wnt signaling pathway. We can, as with Bmp, inquire about the generality of this pathway's usage for axis formation among metazoans. Just as the organizer releases Bmp antagonists, it also releases Wnt antagonists (but only from its head organizer portion), and these are necessary for the patterning of the anterior end of the embryo, especially the forebrain and midbrain portions of the nervous system.

Like the Bmp pathway, the Wnt pathway involves a series of signal transduction steps (Logan and Nusse 2004; see Fig. 8.4). The extracellular ligand binds to a transmembrane receptor; the receptor sets off a chain of intracellular activations and inactivations; these lead to transcription factor activation and new gene expression. But the molecular details of the steps differ greatly from those of the Bmp pathway (Fig. 8.3). Without Wnt signals, embryonic cells internally produce the beta-catenin protein by translation of an mRNA, but the protein level remains very low in the cytoplasm because a special "marking complex," composed of Axin, Apc, and Disheveled proteins, as well as a protein kinase (glycogen synthase kinase3 beta), binds beta-catenin protein and attaches a phosphate to it from ATP. The marked protein is recognized by the proteosome complex, which

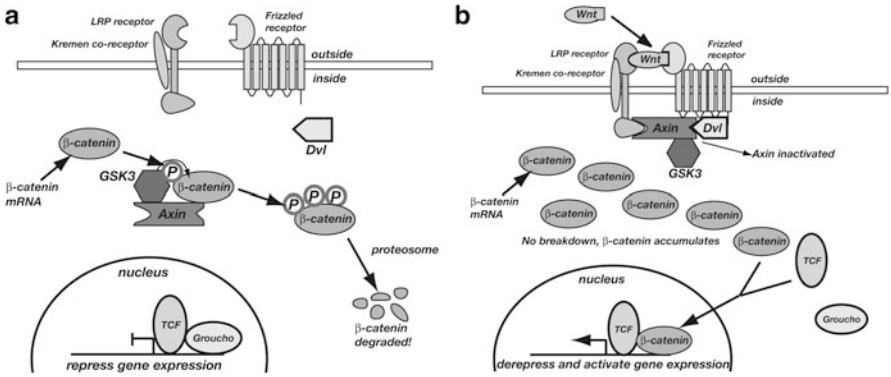


**Fig. 8.4** The Wnt signaling pathway participates in anteroposterior patterning of the body axis in diverse animals such as vertebrates and insects. Panel a: The breakdown of beta-catenin protein in the absence of Wnt signals. Panel b. The accumulation of beta-catenin in the presence of Wnt signals. Notice that the series of signal transduction steps is completely different from that of the Bmp pathway. When the Wnt signal binds to the receptor, the receptor removes from usage several proteins that otherwise mediate breakdown of the beta-catenin protein. This accumulated protein then forms a complex with the TCF transcription factor, activating it to initiate transcription of some genes and preventing it from binding the Groucho protein and repressing other genes

degrades it into inactive peptide fragments. Thus, beta-catenin protein is continuously made and destroyed in the absence of Wnt signals, a seemingly futile cycle. However, this futility is critical for Wnt signaling. When the signal arrives and binds to the extracellular portion of a Wnt receptor, the receptor's cytoplasmic tail is activated to bind the Axin and Dishevelled proteins, thereby removing them from the marking complex. Beta-catenin protein cannot be marked by phosphate addition and thus not destroyed. It accumulates to sufficiently high levels in the cytoplasm to complex with the TCF transcription factor and displace TCF from the Groucho repressor protein. The beta-catenin-TCF complex enters the nucleus, enhancing transcription of some genes, and TCF no longer represses transcription of others. In this way, external Wnt proteins alter transcription internally.

The organizer is a Wnt-free territory of cells, just as it is a Bmp-free territory, whereas the surrounding regions of ectoderm, mesoderm, and endoderm produce various Wnt signaling ligands (as they also produce Bmp proteins). As dorsal axial mesoderm of the trunk develops into somites, it produces the Wnt8 signaling protein and secretes it onto regions of the neural plate that are forming in the directly overlying ectoderm. Wnt8 is a "posteriorizing" neural inducer. Neuralized ectoderm responds to it by developing toward posterior rather than anterior neural fates (e.g., hindbrain and spinal cord), and posterior neural development involves the expression of the entire Hox cluster of genes. However, posteriorization does not occur in the anterior part of the neuralized ectoderm because the head organizer has migrated there, spread out underneath it as prechordal mesoderm, and secretes powerful Wnt antagonists that block Wnt posteriorizing effects, namely, the antagonists Frzb, Crescent, and Dkk. Frzb acts by resembling an extracellular piece of a

Wnt receptor, but it lacks the transmembrane portion and cytoplasmic tail. It binds Wnt8, keeping it from binding to the cell's functional Wnt receptor. Dkk ("Dickkopf") acts differently, by binding part of the Wnt receptor and preventing reception of Wnt ligand. Protected from the posteriorizing Wnt ligands by these antagonists, the anterior neural plate develops into anterior neural tissue, such as forebrain and midbrain. Additionally, Wnt levels are probably graded in the mid-neural plate region lying over the boundary of the head organizer and trunk-tail organizer, leading to the patterning of intermediate neural parts such as posterior midbrain and anterior hindbrain (Kieker and Niehrs 2001). Other molecules, such as retinoic acid and FGF, are also important for full posterior neural patterning and for posterior mesoderm patterning.

Dramatic results from laboratory investigations support these insights. When Wnt antagonists are experimentally overproduced throughout the embryo or when Wnt signals are eliminated (by morpholino antisense oligonucleotides, siRNAs, or mutation), thus creating a low Wnt environment everywhere, the neuralized ectoderm develops entirely as anterior neural tissue. Reciprocally, when antagonists are experimentally depleted or when Wnt signals are overproduced, neuralized ectoderm develops entirely as posterior neural tissue. As evidence that both Wnt antagonists and Bmp antagonists are needed for head development (e.g., anterior neural tissue), Glinka et al. (1997) introduced a mixture of mRNAs encoding the Bmp antagonist Noggin and the Wnt antagonist Dkk into the ventral equatorial region of *Xenopus* cleavage stage embryos and found that the post-neurula embryos developed a well formed secondary head on the ventral side. The result gave credence to the paired hypotheses that anterior neural tissue is only formed when, first, neuralization of ectoderm is derepressed by Bmp removal and, second, neuralized ectoderm develops to anterior fates when protected from Wnt posteriorization.

### *8.2.5 Evo-devo of Wnt-mediated Anteroposterior Patterning*

The Wnt antagonists of vertebrate embryos are produced by morphogenetically active mesoderm cells of the head organizer, cells that originate in the dorsal lip of the blastopore and migrate actively to their site of effect under the anterior ectoderm. In the non-vertebrate chordate, amphioxus, the antagonist source is not the dorsal lip but the central region of vegetal plate endomesoderm, which is displaced to a broad anterior location by archenteron formation (Yu et al. 2007). In hemichordates, Wnt antagonists are produced not by mesoderm or endomesoderm but by ectoderm, and in bands encircling the anterior body surface rather than just on the dorsal side. Still, the antagonists are used at the same final location and to the same patterning ends as in vertebrates; they are just delivered to the anterior site of action by different tissues and means. The Wnt-mediated anteroposterior patterning process probably dates back at least to the deuterostome common ancestor. As in dorsoventral patterning, organizer mesoderm of vertebrates seems to have co-opted

Wnt antagonist production from the ectoderm, but vertebrates have not changed the usage of antagonists in the ancient anteroposterior patterning process. Outside deuterostomes, the Wnt pathway is also used for aspects of anteroposterior patterning, not only in the protostomes where it is used in segment formation and in the posterior growth zone of certain arthropods (McGregor et al. 2008; Martin and Kimelman 2009), but also in the patterning of the body column of radial (partially bilateral) diploblastic animals such as *Nematostella* and *Hydra* (Cnidaria) (Lee et al. 2007). Wnt antagonists such as Dkk are probably involved in *Nematostella* patterning, though perhaps not in some protostomes that may have evolved other means to limit the range of Wnt effects. Thus, the Wnt-mediated patterning of the anteroposterior axis may date back to the bilateral common ancestor, and perhaps before, with evolutionary diversifications of the antagonists and distribution mechanisms in the various lineages.

## 8.3 Summary of Signaling and Pattern Formation

If we had known them in 1981, we would have included the above insights about signaling and patterning in our Dahlem discussions of the cellular basis of morphogenetic change in development and evolution. The progress of the past 30 years supports the assertion that signaling and transcriptional regulation—together—explain much of the development and evolution of pattern formation.

1. Signaling pathways of 15–20 kinds are highly conserved across metazoans, most dating back to the earliest multicellular forms but not to single celled eukaryotes. They mediate a wide variety of cell interactions that are basic to multicellularity, including pattern formation in development. Of these, 5–10 are used to connect cell position and cell fate in the embryo.
2. In general, pathways transduce an extracellular signal into an intracellular effect, most often a change of gene expression in the case of developing embryos. To do this, the signal binds to a transmembrane receptor that sets off a chain of activations of protein intermediates, directly leading to the activation or repression of transcription factors, and hence to altered gene expression that is important for development. Some pathways can also directly alter cytoskeletal, secretory, and other signaling functions.
3. The cause-effect behavior of pathways on transcription is based on the weak linkage of components in the transduction chain, which are mostly sensitive, pre-loaded, switch-like proteins. Little energy, information, or material is needed to release the pre-set response of the next step. Small protein modifications suffice, like phosphate addition or removal. Signal attenuation is reduced. Weak linkage connections have many evolutionary advantages (Kirschner, Chap. 9, this volume).
4. Many of these pathways operate within multi-component (~20–30 components) signal distribution processes that are important for pattern formation in

development. In addition to the signal transduction chain itself, the processes involve extracellular and intracellular agents that control the distribution, effectiveness, and persistence of the signal, and the responses to it. The vertebrate organizer provides a well-analyzed example. Through its interactions with surrounding cells of ectoderm, mesoderm, and endoderm, a Bmp distribution is set up across the embryo that patterns the dorsoventral axis, and a Wnt distribution is set up that patterns at least part of the anteroposterior axis.

5. Patterning processes can have "system properties," such as robustness, adaptability, size regulation, reaction-diffusion dominance, lateral inhibition, and boundary formation. Remarkably, many of the components, interactions, and system properties are widely shared by metazoans and probably date back to the bilaterian common ancestor (or before).
6. Each of the conserved signaling pathways is used over and over at different times (heterochrony) and places (heterotopy), and in different amounts (heterometry), in different patterning processes of the animal's development. The profiles of developmental usage vary among different animals. Furthermore, pathways are used in different combinations in different developmental episodes. Much of the evolution of body plans, morphology, and pattern involves the reallocation of pathways and signal modifiers in development.
7. Since the pathways directly affect transcription, they can be easily included in genetic regulatory circuits. From the signaling perspective, the pathways act in patterning and are themselves patterned.
8. Researchers are still elucidating the means of signal transport or translocation through groups of cells and the means by which embryonic cells accurately measure signal strength (Kerszberg and Wolpert 2007).

The early hypotheses of positional information, interpretation, and signal distribution, as well as of compartments and selector genes, as set out at the 1981 Dahlem meeting, served as valuable contexts and bridges for the breakthroughs that emerged over the next three decades.

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# Chapter 9
# The Road to Facilitated Variation

**Marc W. Kirschner**

## 9.1 Introduction

The charge for this meeting was historical and to some degree philosophical: to trace the development of branches of evolutionary thought that emerged out of the 1981 Dahlem conference. At the time there was a sense of expectation that new paradigms in biology were emerging, particularly in molecular, cellular, and developmental biology. Though these did not necessarily concern evolutionary biology, it was hard to imagine they would be forever irrelevant. Did these new paradigms solidify? Were they relevant to important problems in evolution? Did molecular, cellular, and developmental biology change the way we think about evolution and, if so, how? By 1981, the Modern Synthesis, with its effective union of genetics and natural selection, had hardened into a program of broad explanatory reach. However, as biological knowledge exploded, explanations derived from the Modern Synthesis occupied smaller and smaller portions of the landscape of biology. By contrast, molecular, cellular, and developmental biology expanded, drawing much of its inspiration from chemistry, rather than natural history or genetics.

In 1981 it was still the early days of molecular biology, but the Dahlem conferees tried to imagine the impact of this new field. Looking back on their efforts, we might be tempted to judge them unsuccessful. After all, the next 30 years of biology could not have been more unexpected, and unforeseen. Yet even though they failed to foresee most of the specific developments (such as cell signaling, genome sequencing, the cytoskeleton, epigenetics, and microRNAs), and even though they failed to fully appreciate the generality of some of the concepts they discussed (such as selector genes and the phylotypic stage), the Dahlem conferees grasped the most important idea: that knowledge of how the phenotype is constructed would be

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crucial to explain the pace and direction of evolutionary change. A more timid assembly of scientists might have reached a different conclusion, for solid explanations of how the phenotype was constructed were not yet at hand. Their recommendation to the post-Dahlem generation might have been very different: focus on discovering more evidence to support what was already believed about evolution. Science, after all, proceeds very conservatively even as it celebrates its previous revolutions. Disappointed by that aspect of science, the historian Henry Adams, in 1867, though fascinated by evolution, walked away from making a career in it. As stated in his autobiography, Adams felt that the biology of his time "labored only to heap up the evidences of evolution; to cumulate them till the mass became irresistible" (Adams 1918, 231). The conferees in 1981 saw their task differently; they sensed that tectonic changes in how we view evolution were about to emerge. And they were right; evolution would be forever changed by the molecular understandings of cell and developmental biology.

## 9.2 Historical Perspective

In the mid-1990s, John Gerhart and I looked at the impact of biochemistry, cell biology, and developmental biology on evolution and began to formulate some general ideas about the origin of phenotypic variation. These ideas evolved through several books and articles into a theory called *facilitated variation* (Gerhart and Kirschner 1997, 2007; Kirschner and Gerhart 1998, 2005). Efforts of others complemented and paralleled these ideas. A few scientists who looked from natural history and evolution toward molecular biology, or who looked from molecular biology toward natural history and evolution, raised similar questions about the creation of the phenotypic landscape on which selection acts. I will not try to fully develop the history of these ideas, as that would be a book in itself, but here I describe some of their roots and significance.

Before the rediscovery of Mendel's laws and Weismann's separation of germline and soma, the distinction between genotypic variation and phenotypic variation was unclear. The phenotype was what was observed, and what Darwin thought selection acted upon. Aspects of the phenotype could be measured—height, weight, color, shape. However, most aspects could not easily be assigned a quantitative value. It is now straightforward to express the genotypic composition of an organism as a string of letters, each of which can take on four values (A, T, G, or C). What remains unclear is the relationship of the genotype to the phenotype, and, in particular, the means by which the genotype is converted to the phenotype. This conversion is exceedingly complex even for the simplest organisms.

The advent of Mendelian genetics did not change the notion that the phenotype was the target of selection; it just added a heritable basis for phenotypic change (i.e., change in the genotype). The comingling of the concepts of phenotypic and genotypic variation was a source of confusion in the early years of the twentieth century as geneticists tried to distinguish the two. A strict separation of the

genotype from the phenotype mirrors the strict separation of the germ cells and soma. It is generally true that germ cells contribute little to the phenotype, and that somatic cells contribute nothing to the genotype. More precisely, the DNA sequence is not an agent of function; it is an inert and protected source of information. By contrast, proteins, RNAs, and their products are not usually sources of heritable information, but agents of function. There is a possibility that the genotype could be influenced by the environment via epigenetic inheritance (Jablonka and Lamb 2005), but it is still an open question whether epigenetic processes are major contributors to inheritance.

In the early twentieth century, various ideas were proposed about how phenotypic variation could be both constrained and responsive to the environment, and how the environment could directly influence heritable variation. Richard Goldschmidt's *hopeful monsters* and Osborn's *orthogenesis* were enunciated at roughly the same time that Darwin's seminal work fell into disfavor. However, claims that evolution was driven by direct effects of the environment on phenotypic variation failed to explain anything; subsequent molecular studies made them untenable. Nevertheless, these types of approaches represented an effort to breach the phenotype–genotype divide.[1] It is easy to see why one of the tasks of the Modern Synthesis was to suppress these heretical ideas. However, along with that justified suppression came a general unwillingness to consider the nature of phenotypic variation as an important problem. Developmental biology was increasingly divorced from genetics and evolution. Even though great discoveries were being made in embryology (e.g., Hans Spemann on embryonic induction and Curt Stern on developmental genetics), they had little influence on population genetic theory. Embryology and evolution remained quite separate, with only a few exceptions.

Against the backdrop of this increasing divergence of embryology and evolution through the twentieth century, the last 30 years in biology displays a dramatic rapprochement with its advances and accomplishments surrounding how the phenotype is created from information encoded in the genotype. There is no question that biology also accumulated many more "evidences" for evolution in experimental population genetics and paleontology. However, the contributions from molecular biology to our understanding of evolution were different; they focused not on variation but common descent. By 1981, the commonality of protein sequences, enzymatic pathways, and cellular mechanisms across vast phylogenetic space offered independent support for common descent, strengthening the inferences already drawn from the fossil record and comparative anatomy. But all of this said more about conservation and less about how phenotypic variation arises. Without the latter, not much could be inferred about the path of evolutionary change and its tempo.

[1] "The change from species to species is not a change involving more and more additional atomistic changes, but a complete change of the primary pattern or reaction system into a new one, which afterwards may again produce intraspecific variation by micromutation" (Goldschmidt 1940, 205).

The inability to quantify phenotypic variation in the same simple way that genotypic variation can be quantified undermines more conventional population genetic approaches that attempt to achieve a full understanding of the pace and direction of evolutionary change. We know that the only important phenotypic variation is non-lethal (or else it cannot be inherited), but is it true that non-lethal variation is always limited, as Darwin thought, and if so, why? Without an understanding of the processes generating phenotypic variation, people had different intuitions about the extent of non-lethal variation. Some who reject Darwinian evolution altogether have said that there is not enough time for random variation to produce the extremely refined phenotypes that we celebrate. How could a brain, wing, hand, or placenta arise in a lineage that did not have these? Others have argued that time is so vast and variation so plentiful (and populations so large) that virtually any kind of innovation can occur by small incremental changes. On this latter view there is so much variation that selection can be all-powerful in shaping evolution. Can we now say something empirically about whether phenotypic variation is plentiful, both in quality and quantity? Can we understand how variation produces apparent novelties of extreme complexity on the timescale of the geological record?

## 9.3 An Explanatory Challenge to the Modern Synthesis

Some evolutionary biologists would acknowledge what we have learned from cell and developmental biology but still assert that it does not help us understand the pace or path of evolution. "Until we have a predictive theory of developmental genetics, our understanding of the molecular basis of development—however fascinating and important in revealing the hidden history of what has happened in evolution—sheds little light on what variation is potentially available for the use of selection" (Charlesworth 2005, 1619–20) Such statements discourage us from using molecular and cell biology to think about phenotypic variation and selection.

The sufficiency of population genetics to explain all of evolution is often stated in the most absolute terms:

> First, evolution is a population-genetic process governed by four fundamental forces. Darwin articulated one of those forces, the process of natural selection, for which an elaborate theory in terms of genotype frequencies now exists. The remaining three evolutionary forces are non-adaptive in the sense that they are not a function of the fitness properties of individuals: mutation is the ultimate source of variation on which natural selection acts, recombination assorts variation within and among chromosomes, and genetic drift ensures that gene frequencies will deviate a bit from generation to generation independent of other forces. Given the century of work devoted to the study of evolution, it is reasonable to conclude that these four broad classes encompass all of the fundamental forces of evolution. (Lynch 2007, 8597)

On the other hand, as early as 1931, Sewall Wright pointed in the direction of the cell to understand evolutionary change: "The older writers on evolution were often

staggered by the seeming necessity of accounting for the evolution of fine details . . . for example . . . of all the bones. Structure is never inherited as such, but merely the types of adaptive cell behavior, which lead to . . . types of structure under particular conditions" (Wright 1931, 147). In the early 1990s, John Gerhart and I began to think more about these "adaptive cell behaviors," especially ones that were adaptive in a developmental context, with the hope that our understanding of cells would help us appreciate the nature and extent of phenotypic variation.

When we began writing our book, more and more connections were being made between evolution and molecular and cell biology. First, there was the remarkable conservation among diverse forms of life, including DNA, metabolism, cell structure, and *Hox* genes. I remember when the extent of this conservation finally hit me. Gans and Northcutt (1983) had argued persuasively that the vertebrate brain and insect brain must have separate origins. Approximately 10 years later, Boncinelli and his colleagues found early expression of the same selector genes in the head of insects and vertebrates (Finkelstein and Boncinelli 1994). A series of fragile but plausible anatomical speculations fell quickly to unambiguous molecular findings.

Theodosius Dobzhansky was famous for his challenging dictum that, "Nothing in biology, makes sense except in the light of evolution." He meant that everything about an organism could be explained as an adaptation to selective conditions. Was this an aspirational statement or did Dobzhansky really believe that it was true? In 1974, molecular and cell biology was certainly in a ferment of advance on almost every front but nothing major in these broad areas of biology came from the study of evolution. (Much more came from the study of chemistry.) John and I began to wonder whether the opposite was true: nothing in evolution makes sense except in the light of cell, molecular, and developmental biology. Today it is clear that each of these ways of looking at biology is necessary; it is the properties of the cellular processes as much as the selection and segregation-modification of DNA that explain the nature of the organism.

Darwin's theory of evolution can be understood as comprised of three sub-theories: a theory of selection, a theory of heredity, and a theory of the nature of phenotypic variation. The last theory is essential if we are going to understand evolution since it is the phenotype that is under selection. Perhaps because evolutionary biologists of the mid-twentieth century knew so little about how the phenotype was constructed, they contrived ways to minimize its importance. Gould documents this sleight of hand in the carefully constructed argument that phenotypic variation is so abundant as not to be limiting. Under these conditions, Gould argued selection could be all-powerful and embryology—like cosmology and thermodynamics—can be acknowledged as interesting and dismissed as uninformative for evolution (Gould 2002). But what if the majority of evolutionary biologists were wrong and phenotypic variation turned out to be limited and channeled? If so, then phenotypic variation, rather than selection, would have a greater influence on evolution. This idea was heretical to proponents of the Modern Synthesis. Yet they had no basis whatsoever for their assumptions about the amount of phenotypic variation available in evolution. To discount the importance of

phenotypic variation, the followers of the Modern Synthesis assumed that phenotypic variation exhibited three properties: "copious in extent, small in range of departure from the mean, and isotropic" (Gould 2002, 60). This meant that selection would be the most important force in shaping the phenotype. But it is unlikely that *any* of these assumptions is actually true. Our task in thinking about the phenotype from the cell and molecular perspective was not only to evaluate whether phenotypic variation exhibited these properties, but also to say something constructive about them.

Though evolutionary biologists generally ignored phenotypic variation, they held strong views on the subject, some of which turned out to be wildly incorrect.

> Many of the higher categories are unnatural groupings of unrelated animals that have become very similar owing to convergence. There was much search for homologous genes that would account for such similarities. Much that has been learned about gene physiology makes it evident that the search for homologous genes is quite futile except in very close relatives. (Mayr 1963, 609)

The notion of *gradualism*, with echoes back to Charles Lyell, assumed that everything would change in an organism in proportion to its distance from a common ancestor. However, modern biochemistry, cell biology, and molecular biology have demonstrated that this is simply not the case. In many processes and genes there is deep conservation going back to early life, including several conserved processes that have changed little since the origin of eukaryotes, metazoans, chordates, vertebrates, and mammals. This conservation—seen at the level of process, developmental strategy, and protein sequence and function—is surrounded by many examples of rapidly diverging genes and functions. Perhaps even 30 years ago at the 1981 Dahlem conference, there was a sense that these assumptions would soon be replaced by validated information and that views, such as those of Mayr, would prove to be naïve.

Of the three assumptions held by evolutionary biologists about the nature of phenotypic variation, the least plausible is isotropy. For the genotype, if any base could be replaced by any other with equal likelihood, then it is easy to see how variation might be isotropic. Divergence in sequence would then be random. Even if this were not strictly true, rough isotropy might arise if changes in any genes were equally likely no matter which base was modified. However, the phenotype is not the genotype. It is hard to imagine what random phenotypic variation would look like. What does it mean to say the eye can change equally in all dimensions of the phenotype? If we are considering only heritable (i.e., non-lethal) mutations, then surely not all heritable changes in a given phenotype are equally possible. Indeed, the conservation of protein sequence does not arise from resistance to genetic change but the elimination of almost all changes that have lethal effects. Phenotypic variation is built on the history of developmentally forming that phenotype. It can change in some ways more easily than others. Thinking about phenotypic *anisotropy* was a key foundation of facilitated variation.

The next assumption, that variation is "copious in extent," must be evaluated in terms of the population size and the underlying mechanisms undergoing change. No

one doubts that phenotypic variation must be copious enough to accomplish evolutionary change. But the recognition that small populations of animals with long generation times undergo major transitions at times of great radiations suggests that major changes came quickly (e.g., the evolution of whales in the early Eocene or body plans in the Cambrian explosion).

Finally, the assertion that variation must be "small in range of departure from the mean" is also problematic. The word "small" is slippery here. An expectation of small departures from the ancestral phenotype ensures that selection governs the exact path of evolution (given randomness in genotypic variation). It is assumed that adaptations must accommodate the changed phenotype in order to render it non-lethal (phenotypic accommodation). But organisms already have ways to render variation compatible with function. The successful breeding of dogs with different snout structures and sizes suggests that normal development can accommodate very different morphologies in just one generation. Furthermore, "small departure from the mean" implies a smaller selective advantage and therefore a smaller rate of evolutionary change.

Thus, it appeared to us that the problem with current evolutionary theory was not that it was wrong or inconsistent, but that it was woefully *incomplete*. Just after Darwin, many biologists thought that the problem of phenotypic variation was the most important problem to understand. For example, in William Bateson's massive *Materials for the Study of Variation* (1894), he searched the world for examples of the discontinuous nature of what he called homeotic transformations, which became the basis for his much-reviled view of discontinuous evolution (Bateson 1894). The question of discontinuity is still unresolved. Darwin wanted selection to be continuous; he was obsessed with infinitesimal change in the process of evolution, even though he had observed many examples of abrupt changes when breeding flowers and pigeons (Howard 2009). According to Howard, Darwin's belief in continuous variation was his great blind spot in not coming up with a Mendelian model for genetics. Despite the data staring him in the face, Darwin concluded:

> If selection consisted merely in separating some very distinct variety, and breeding from it, the principle would be so obvious as hardly to be worth notice; but its importance consists in the great effect produced by the accumulation in one direction, during successive generations, of differences absolutely inappreciable to the uneducated eye—differences which I for one have vainly attempted to appreciate. (Darwin 1860, 32)

Genetics, according to Mendel, was anything but continuous, and it took a special effort to argue how quantitative variation could emerge from multigenic traits. The relationship between discontinuous genetic change and phenotypic change could be anything from continuous to abrupt. To resolve these issues of "small deviations from the mean," we cannot rely on genetics or selection alone. We need to understand the relationship of genotype to phenotype.

The task of relating genotype to phenotype has been the principal task of modern biology. Watson and Crick's model for the structure of DNA gave an immediate mechanism for genetic transmission, but it was not merely a model for genetics—it was the beginning of understanding how the phenotype was created. The central

dogma made tangible the earlier contributions of Sewall Wright and Beadle and Tatum on how proteins, the creative agents of the phenotype, were encoded in DNA and inherited as a string of informational signals acted upon by a nonselective transcriptional and translational apparatus. The search for the genotype–phenotype map is reflected in many of the accomplishments of the past 50 years, from Jacob and Monod's discoveries regarding gene regulation to Wieschaus and Nüsslein-Volhard's dissection of early fly development. Although many groups have used genetic methods, their goals and accomplishments had more to do with how the phenotype was created and not how genetic information is segregated and mutated. For the past 40 years the vast majority of geneticists have been at work on the relationship between genotype and phenotype, and not problems associated with the organization and nature of the genotype itself.

## 9.4 Traversing the Path from Genotype to Phenotype

In our professional careers, John Gerhart and I have been involved in the great effort to understand how the genotype and phenotype are connected. We were skeptical of the now generally discarded view that there was a "genetic program" for development, which had some currency before the cellular and molecular advances in developmental biology over the last 25 years. Furthermore, we were keenly aware of many programs running in cells that were not instructed directly by signals from the genome, such as cell motility, metabolism, and nerve transmission. All of these depended on the encoding of protein sequences in the genome, but, once expressed, ran rather independently. The genotype–phenotype map would have to take their properties into account and they would play a role in the nature of phenotypic variation, its isotropy, its abundance, and its deviation from the mean. We began where Monod left off, trying to describe in detail how enzymes regulate metabolism by using their ability to alternate between states ("allostery"). Soon allostery would assert itself in many cellular mechanisms, particularly ones for regulating gene activity and mediating signaling from one cell to another. We also had worked together (and separately) on other complex cellular processes, including the cell cycle, morphogenesis, and the early stages of embryonic development in vertebrates. We investigated and reflected upon the complex phenotypic mechanisms in eukaryotic cells, especially those found in metazoans. We, like many other scientists, began to understand how variation could look continuous or discontinuous when filtered through mechanisms peculiar to multicellular organisms.

In the late 1980s, we were actively engaged in early molecular and cellular investigations of how the vertebrate egg achieves its provisional patterning and the molecular mechanisms involved in classic problems like embryonic induction. We also were aware of the major advances in understanding how the body plan of insects is established, the importance of *Hox* genes and other selector genes, and the common developmental pathways being discovered in vertebrates, insects, and nematodes. Additionally, we were inundated with new sequence data showing the

conservation of genes and processes. The materials for addressing the problem of phenotypic variation were now at hand. We were unsure how germane these discoveries would be to the large questions of evolutionary biology, and whether insights could be gleaned about the path and tempo of evolution, but we knew that no one had previously been able to consider the origin of phenotypic variation from this perspective. We decided to write a book about evolution and development, focused on these new understandings.

I had the opportunity to put forward a few of our nascent ideas at a symposium in honor of John Bonner in 1990, which was subsequently published (Grant and Horn 1992). The most memorable event for me at that symposium was meeting Mary Jane West-Eberhard, who had been thinking a great deal about phenotypic variation—particularly phenotypic plasticity—and its possible role in evolution. Her support for our ideas greatly encouraged John and me to complete our task (and the book was finished in 1996). More importantly, she made us aware of the sophisticated thinking about phenotypic variation and evolution that had been developing among a few evolutionary biologists, whose knowledge of evolution was much deeper than our own. Our book had grown from a short treatise to a detailed review of biochemical, cell biological, and developmental biology from the perspective of evolution. We did our best within the limits of what was known to find examples from disparate places in the animal world and compile mechanisms that had not yet received much attention. We surprised ourselves by formulating some new general ideas about why phenotypic variation is so non-lethal and why developmental processes can generate new forms so easily.

## 9.5 Facilitated Variation

Ten years later, we published a second book, *The Plausibility of Life* (2005), which focused on a theory of generating new phenotypes, which we called *facilitated variation*. In the two decades during which we developed this theory, we became more aware of older cognate efforts to understand the pace of evolutionary change and the phenotypes that would arise, as well as others who had contributed to these subjects since our first book was published. It is not possible here to provide a history of these contributions, but generally they can be divided into ideas about evolution derived from looking at phenotypes and ideas about evolution that came from the study of molecular mechanisms. We carefully studied the Baldwin effect and its curious lack of impact on mainstream evolutionary thought. Baldwin, Osborn, and Morgan explicitly made connections between physiological adaptability and evolutionary adaptability. Although Baldwin's examples were behavioral, others generalized them to morphology and physiology (Baldwin 1896; Osborn 1896; Morgan 1896). Baldwin's idea was simple: the ability of an organism to alter its phenotype (behavior, physiology, or structure) in response to perturbation would help to generate a derived subset of the population that stably expressed the adaptation. If true, this was important because physiological adaptability is a vital

part of the phenotype and plausibly under selection. It would mean that there could be a corresponding selection for processes that facilitate the production of phenotypic variation more likely to have selective advantage at least under some circumstances. This selection could be a by-product of selection for a current benefit, such as physiological adaptability.

George Gaylord Simpson's analysis of the Baldwin Effect fascinated us (Simpson 1953). Simpson concluded that the Baldwin effect did not violate the tenets of evolutionary theory or Mendelian genetics. Nevertheless, he dismissed it as unlikely to play an important role in evolution, and this seems to be where the field of evolutionary biology left the problem. In practice, it provided another reason to not consider the increasingly complex mechanisms that were being described around physiological adaptation.

Another important effort to connect flexibility in development with selection was I.I. Schmalhausen's thoughtful book—*Factors in Evolution*—first published in Russian in 1946. It considered in much broader terms how evolutionary changes arise by altering the mix of endogenous traits and how selection for features that suppress lethality would lead to increased genetic variability and increased rates of evolution (Schmalhausen 1986).

Finally, Conrad Waddington's well known experiments with *Drosophila*, where he rapidly selected a four-winged fly in response to ether exposure, the loss of a wing vein in response to heat, or a modified anal plate in response to increased salinity, were vivid representations of "genetic assimilation" (Waddington 1953). The explanation for these experiments paralleled Schmalhausen's independently derived ideas. Both argued that in the right selective environment physiological adaptation facilitated evolutionary change.

These historical inputs were catalyzed by Mary Jane West-Eberhard's arguments about how phenotypic plasticity facilitated evolutionary change (West-Eberhard 1989). Phenotypic plasticity—the range of options the organism has in producing different phenotypes from an existing genotype—is a form of physiological adaptability that is clearly under selection. In some cases it is reversible, like increased muscle mass in response to exercise, and in some cases it is not, such as the various castes of social insects. Stabilizing existing variation by mutation and remixing modular aspects of the phenotype could be a potent means of reducing the creativity needed from mutation to alter the phenotype. In her classic volume on phenotypic plasticity, West-Eberhard reached well beyond insect castes and physiological adaptations to include molecular details (West-Eberhard 2003).

Two other names bear mentioning: Karl Liem and Richard Dawkins. Karel Liem's work focused on key innovations that allowed the rapid evolution of different jaw morphologies in cichlid fish (Liem 1973). Liem considered how developmental processes and anatomy have the capacity to facilitate evolutionary change. It was unusual in evolutionary studies to see the phenotype as having properties that affected not only its own fitness but also its capacity for evolutionary change. Richard Dawkins was significant for clearly enunciating the concept that different phenotypes had different capacities to evolve. He was one of the first people to cite evolvability as a property of the phenotype and raised the question of

whether "some kinds of embryology might be especially good not just at surviving but at *evolving*" (Dawkins 1986, 352).

When we began to reflect 20 years ago on what we knew about molecular mechanisms in cell and developmental biology, we had strong indications that the new experimental studies held keys to answering the kinds of questions that Waddington and Schmalhausen had asked 40 years before. We also sensed that the most important insights would come from cell and developmental biology, but since these were in the throes of conceptual disruption, it seemed unlikely that the new understandings would have been properly incorporated into evolutionary theory at that time. For starters, we knew there was far greater conservation in biological mechanisms than anyone would have expected but that this conservation was surrounded by tremendous diversity. Conservation also suggested that there might be common mechanisms in cell function and embryonic development.

There has long been a strong desire to find general laws for the conserved mechanisms in biochemistry and molecular biology. For example, general models of transcriptional regulation were extrapolated from bacteria to complex organisms (e.g., Jacob and Monod, Britten and Davidson). We were wary of such extrapolations, often epitomized by Monod's epigram, "What is true for *Escherichia coli* is true of an elephant."[2] There was a risk in assuming that mechanisms are essentially unchanged based on superficial similarities. Michel Morange correctly notes that, "Monod always remained reluctant to admit the blurring action of natural selection. He did not accept the plurality of mechanisms to explain the behavior of regulatory enzymes" (Morange 2010, 80). Though specific mechanisms might be convergent, we sought deeper structural and functional generalities. Aware of the limits to our knowledge, and the limits to any generalities that might emerge, we concentrated on a subset of life, eukaryotes and primarily metazoans. We also confined ourselves to organisms that were well characterized molecularly. But even in 1990, there was a fair amount of biochemical information for many vertebrate species, and some invertebrates, and a great deal of comparative embryology for very diverse species going back to the late nineteenth century.

Evidence for deeper and more general mechanisms to explain both diversity and conservation emerged gradually as we wrote *Cells, Embryos, and Evolution*. As a result, the very long book was rewritten several times with major modifications before we submitted it to the publisher in 1996. We thought hard about how forcefully we should state our most general conclusions. If we began with broad conceptual frameworks, it would make the arguments and examples easier to understand. But we felt more confident in the examples than we did in the conclusions. We opted to give prominence to the examples and second place to the conclusions. Only in the last chapter, after nearly 600 pages of comparative biochemistry, cell biology, and embryology, did we reveal the scaffold of an interpretation.

[2] This seems to have been a misquotation of Monod's comment in 1954: "Anything that is true of *E. coli* must be true for elephants, except more so" (Morange 2010).

Seven years later, after presentations, discussions, new developments, and the comments of others, we had a clearer view of what to say about the nature of physiological variation and its explanation on the molecular level. This led to a better understanding of evolvability, in part through helpful comments from Walter Fontana, who urged us to distinguish clearly the variation component from the selection component. The selection component was the fortuitous coincidence between a property of an organism and a new condition external to the organism, such as might happen when a foreign organism is introduced to an environment that has no predator. It may radiate quickly, not due to its special capacity to vary, but due to its fortuitous immunity from predation. But the variation component of evolvability was our main quarry. We defined it as the capacity of an organism to generate non-lethal phenotypic variation in response to genotypic variation, especially phenotypic variation that would have a likelihood of increasing fitness. This component of evolvability was related to fundamental, conserved processes of the cell. As a consequence, evolvability might be conserved. Properties of these cellular processes would be expected to confer a special capacity of the organism to vary its phenotype and to do so with a small input of genetic change. A more explicit argument for the variation component of evolvability was incorporated into the theory of facilitated variation (Gerhart and Kirschner 2007; Kirschner and Gerhart 2005). We chose examples that were accessible to a broad range of biologists and avoided the complicated mechanistic descriptions presented in *Cells, Embryos, and Evolution*.

Others converged on similar ideas about the importance of understanding the basis of phenotypic variation. Sean Carroll's *Endless Forms Most Beautiful* emphasized the facility with which gene expression changes can occur due to the modular nature of the transcriptional regulatory machinery in metazoans and the accumulating evidence that such processes were the basis of important evolutionary changes (Carroll 2005). Rudolf Raff's book, *The Shape of Life*, had emphasized—as we did—conservation in developmental mechanisms, focusing more on constraint than evolvability (Raff 1996). Assembling evidence for constraint was an important step in refuting the view of many evolutionary biologists that all phenotypic variation was equally probable.

Our formulation of facilitated variation was grounded in the nature of conservation and variation at the cellular and molecular level. At the level of fundamental cellular and developmental mechanisms there is a great deal of conservation. Innovation did not accumulate in biological systems uniformly, simply reflecting divergence from a common ancestor. This was most evident in a set of mechanisms that we called *core processes*. These processes arose early in lineages and then were stabilized. Although the origins of core processes are sometimes discernable, once they became stabilized they only distantly resembled their antecedents. Since the passage of time could not explain their comparatively fast diversification and subsequent stabilization, we were forced to consider that the core processes remained under the same type of selection despite the continued or even accelerated evolution of clades. Thus, as representatives of the earliest forms of life, bacteria had invented metabolism, cell membranes, DNA based heredity, and ribosome based protein synthesis. These changed some in the evolutionary diversification

of eubacteria, archaea, and eukaryotes, but the modifications were small compared to what had been accomplished. Eukaryotes invented mitochondria, the nucleus, mitosis, many signal transduction pathways, and a diverse cytoskeleton with little change thereafter. We can detect antecedents for some of these, but the large suite of activities was stabilized for perhaps two billion years. Similar explosions and stasis occurred around metazoan multicellularity, body plans of bilateral organisms, vertebrate limbs and arthropod appendages, the invention of the tetrapod foot, and the mammalian placenta with its unique trophoblast. This was a kind of punctuated equilibrium at the level of cellular and developmental mechanisms. Though obvious, it had not been previously enunciated and documented.

## 9.6 Evolvability

The radiation and stasis in core processes raised the question of whether constraint had limited further variation in these processes or whether they persisted under continued selection for the variation they supported, such as changes in the time, place, and amount of use of these processes due to regulatory changes. That constraint in core processes could be evidence for deconstraint was a relatively new idea, although it was clearly implicit in Dawkins' ideas about evolvability. It also can be observed in more familiar contexts. Human society is filled with constrained core elements that deconstrain change elsewhere: the common gauge of railroads, the common frequency and voltage in our electrical systems, receptacles for electrical plugs, screws, keyboards, USB ports, and diameters of pipes. All of these enable the varied use of different materials to produce diverse outcomes. Deconstraint for many human devices depends on constraint.

The core processes themselves construct the phenotype, informed by regulatory events that define timing, location, cell type, and contingency, which in turn were determined by signals from the environment or from other cells. We labeled this ease of responsiveness to changes in regulation the property of "weak linkage," a term first coined by Michael Conrad for a more specific form of facile connectivity (Conrad 1990). Weak linkage helps to explain a degree of modularity in biology, but it is not a formal description. Instead it refers to the biochemical features of many systems, particularly those found in transcription, intracellular and extracellular signal transduction, regulated secretion, and cytoskeletal changes in cells. Weak linkage is the most important biochemical and cellular strategy used in biology and the most unique to it. Systems—some as small as single allosteric molecules—exist in on-off states. Binding, inhibition, modification, or stabilization, drive these two state systems from one to the other state. Mechanistically, these regulatory interactions do not establish the alternative states but simply stabilize states that the system can already reach. Biology is replete with such systems, often regulated by allosteric proteins. A classic example is the lac repressor of Jacob and Monod, and there are many examples of eukaryotic transcription factors that shift from one state to another. Of particular interest are proteins driven

by enzymatic reactions (not mass action), such as GTP binding proteins like heterotrimeric G proteins or small G-proteins (e.g., Ras or Rac). Some systems are two-state by virtue of dissipative chemical reactions that can be inhibited or activated. The flux of glycogenolysis versus glycogen synthesis is driven by the posttranslational modification of a chimeric enzyme containing a kinase and a phosphatase. Various flipping of states is encoded in two-state pathways governing differentiation, signal transduction, sex determination, cell division, etc. Whole developmental pathways or inductions are regulated by inhibition or release from inhibition in large fields of cells, each provided with alternative states. Weak linkage is special because so little genotypic change is needed to change the phenotype. Core processes are easily made contingent on new signals of low specificity and therefore the barrier for generating novel phenotypic variation is reduced.

A very special form of weak linkage is found in exploratory processes, which shift spontaneously among a large number of states. New phenotypes are not created but simply stabilized by new interactions. Among the major mechanisms that we have introduced, exploratory processes strike people as the most surprising and novel. They are prevalent in biology at many levels, but they often hide in plain sight and are the explanation of last resort. The most prominent example of an exploratory process is evolution itself, which involves variation and selection, although assessing the range of phenotypic variation available is very difficult. A better-known exploratory process at the molecular level is adaptive immunity in vertebrates, which was initially counterintuitive. A specific immunological response to an antigen seemed to require a direct response to the insult in the form of a specifically designed protein. But instead millions of cells are generated, each with a randomly mutated antibody molecule, waiting for the specific antigen to stimulate proliferation of that cell. In a person's life, only the tiniest fraction of cells find any use and elaborate circuits must be established to suppress the activity of unwanted cellular responses. Yet this exploratory process avoids the need to pre-establish a narrow range of responses or to design a general mechanism that creates new proteins for every novel challenge.

Of more significance for morphological evolution is the exploratory behavior of microtubules that polymerize in random directions from their point of nucleation at the centrosome and are stabilized by distal factors. This behavior allows stabilizing agents to be anywhere in the cell. New configurations of microtubules that generate new cell morphologies can be produced without any modification to the microtubule system. Such exploratory processes like microtubules are robust to random noise in development but also have the capacity to produce new configurations and hence new stabilizations during evolution. In addition to cellular systems, there are exploratory processes among groups of cells in the formation of the vasculature, in the wiring of neural circuits, in the establishment of domains in the embryo by secreted signaling molecules, and in the behavior of foraging ants.

Modularity in developmental systems is sometimes invoked as providing a form of evolvability. The compartmentation of the embryo at early multicellular stages, first appreciated in seminal developmental genetic studies of *Drosophila*, is of a very

specific type incorporating many examples of weak linkage. Embryos of a clade have similar compartments, indicated by the expression domains of unique collections of transcription factors and signaling molecules. The Hox code is conserved among bilaterians but there is modification as well. Early controversial claims about the overall similarity of vertebrate embryos are now supported molecularly in the form of highly conserved sets of selector genes (e.g., *Hox* genes). These compartments are much more conserved than the adult anatomy that is built upon them. Why such a degree of conservation at this stage of development? The answer hearkens back to a more primitive anatomy of the common bilaterian ancestor. Given that the conserved compartment or domain structure is not immutable to change, and may have been extensively modified in phyla other than chordates and arthropods, it suggests that the domain map is continually under selection. Yet the domains are only indirectly related to final phenotypes, which are under selection. Thus, their stasis would have to be related to some function they provide to the *many* variable anatomies that are built upon them. We have argued that the domain map can still be used to generate diverse features even though these subdivisions no longer correspond to existing anatomical features. The domain maps allow for the independent regulation of different regions of the embryo and put few restrictions on the phenotype. Further, they are readily emplaced by diverse patterning mechanisms in the egg, which have undergone extensive modification. A process that is tolerant of change in the egg and supportive of diverse anatomical forms in the adult, while at the same time organizing separate domains of development and reducing the pleiotropy of mutation by limiting its effect to specific regions, is a remarkable mechanism. And the transcriptional and signaling networks are all weakly linked and easily modified. This highly conserved mechanism that generates unique "places" in the embryo is under continued selection for the deconstraint it provides to phenotypic variation in the egg and adult.

The last of the major mechanisms that facilitate phenotypic variation and provide for increased evolvability (in its variation component) is stabilization of the range of physiological variation. Schmalhausen argued that the envelope of possible physiological variations, stabilized in different states, could produce major variation in the embryo. Mary Jane West-Eberhard's arguments that phenotypic plasticity is a ready source of evolutionary change echo a similar theme. However, particularly in the ideas of Schmalhausen, Waddington, and Baldwin, the focus was on physiological responses to *external* conditions, such as temperature, salinity, and stress. We have argued that the most significant use of physiological variation in phenotypic variation is in the wide range of options that *cells* have during embryonic development. Cells have a range of capacities: to proliferate, to change the products they secrete, to change shape, to respond to signals, and to signal other cells. These capacities constitute a reaction norm in many dimensions and features of weak linkage conveyed by transcriptional, cytoskeletal, and signaling systems can vary the cell phenotype along those norms. The envelope of possibilities integrated in all dimensions that a cell encompasses is quite large and, due to weak linkage, quite accessible. This large range of accessible possibilities challenges the expectations that phenotypic variation be small in deviation from the mean or isotropic, and helps to explain why it may be copious in extent.

## 9.7 A Different View of Evolution

The empirical findings and theoretical consequences from cell and developmental biology delineated above require a major revision in the understanding of the nature of phenotypic variation espoused by the Modern Synthesis. Sewall Wright's concept of "adaptive cell behaviors" now seems prescient. Although Wright had no idea in 1931 about transcription, the cytoskeleton, and signal transduction, and could not have formulated general properties like weak linkage or exploratory systems, he did urge us to shift our attention away from the shapes of bones to cells. Our changed perspective also illuminates George Gaylord Simpson's dismissal of the Baldwin effect. As a paleontologist in the pre-molecular era, Simpson had his focus on the shapes of bones and not cells. Given that the properties of the core cellular processes were not yet elucidated, it would have been difficult to conceptualize organisms as having the capacity to produce a copious extent of novel variation that could be used to make new anatomical structures.

We now view anatomical innovation in a different light. The extensive radiation of the vertebrate head owes much to the invention of neural crest cells, whose nearly unlimited proliferative potential can generate massive but localized bone growth in any region. For example, they are essentially unconstrained in their growth in the small regions that will form the antlers in adult male deer but compartmentation limits the location of this growth. Whether it is jaws, dinosaur head shields, antlers, or elephant trunks, neural crest cells choose among the wide envelope of possibilities for gene expression, cell migration, cell signaling, secretion, and responsiveness to the environment. The evolution of the vertebrate head instantiates diverse exploratory processes that depend on the local map generated by compartmentation of selector genes for instructions on migration and differentiation, which in turn depend on weak linkage to tie new behaviors together. The general responsiveness of the cells is a stabilization—by heritable genetic change—of one phenotype among many plastic opportunities.

One type of physiological stabilization deserves special mention. Both Schmalhausen and Waddington considered a class of physiological stabilizations, which Schmalhausen called morphoses and Waddington called genetic assimilation, where selection and variation are unrelated. (Waddington's selection experiments on *Drosophila* under non-specific stressed conditions are the best-known; see above, Sect. 9.5.) Schmalhausen argued that a fortuitous superposition of a stress that revealed morphological variation with an unrelated selection pressure could facilitate change. More recently, Lindquist and colleagues have referred to a similar process as "evolutionary capacitance." In all three cases, the goal was to explain how unusual novelties arise readily in populations.

Today, our best understanding of this phenomenon derives from experiments showing that heat shock can cause unusual phenotypic variation in *Drosophila* due to the depletion of a chaperone protein, Hsp90 (Rutherford and Lindquist 1998). Hsp90, in addition to blunting and suppressing the deleterious effects of heat and other stresses, also plays a role in the normal folding and assembly of important

transcriptional and signaling components. Thus, it is not surprising that stress, specific inhibitors of Hsp90, or mutations of *hsp90* cause dysmorphology in development. Because developmental systems are themselves adaptive, these dysmorphologies are rarely exhibited as undifferentiated masses of cells, like tumors, but instead are modifications of normal structures, which can maintain some functionality or create new functionality. For example, reduction in the activity of *hsp90* could cause larger eyes. There is no sense in which eye size is an adaptive response to heat, but it produces a phenotype that can be selected upon by something related to eye function, such as low light conditions.

This extends West-Eberhard's view of phenotypic plasticity to phenotypes not normally encountered but which lie just beyond the standard reaction norm. The transformation of vestigial wing structures ("halteres") in flies into wings under the influence of ether was selected for not by resistance to ether but by Waddington himself. These "hopeful monsters" depend initially on the environmental perturbant (although this could also be a genetic factor). However, if there is a fortuitous selection for that phenotype while the organism is under stress, the new phenotype could be selected. West-Eberhard points out that the response to environmental or genetic perturbation can lead to a later genetic accommodation, which under selection can produce evolutionary change. This process could facilitate a very rare phenotype (West-Eberhard 2008). Our work has focused on the molecular processes that allow such accommodation to take place.

It is hard to estimate the impact of these ideas on the scientific community. To some degree, facilitated variation is not a compact theory and leaves open the possibility of discovering mechanisms other than weak linkage, exploratory behavior, compartmentation, and stabilization of physiological variation that would contribute to the variation component of evolvability. But it does establish some principles relevant to the ease of generating phenotypic novelty. Special conserved processes facilitate variation by rendering it both more extensive and less lethal for a given amount of random genetic variation. Regulation is easily achieved on the transcriptional level by weak linkage, employing the flexibility of transcription factor binding, the distant effects of chromatin modification, and the many ways of controlling the amount, location, timing, and contingency of expression on other events. Regulation also exists on the posttranscriptional level where simple changes create sites for phosphorylation, ubiquitylation, and other modifications. The major anatomical and physiological innovations achieve new states with small changes, which also entails minimal lethality. Finally, many of the core processes are supportive of novelty. For example, limb morphogenesis can proceed in large steps due to the adaptive nature of the musculature, nerves, and vascular system. More and more examples can now be produced to support these general views and the validity of the mechanisms themselves is not in doubt. The field of evolution and development, Evo–devo, is growing in terms of the breadth of organisms studied, the ability to use genomic analyses on organisms that do not possess accessible genetic systems, and the use of computational models to capture some of the properties of these systems.

Despite these accomplishments, the evolutionary literature rarely refers to insights derived from cell and developmental biology, and there is surprisingly little discussion of phenotypic variation or evolvability. Many professional scientists working in evolution appear to have a strong interest in maintaining the narrative of the Modern Synthesis. Evolutionary biology often drifts into oversimplification, dogmatism, and hero worship. To be sure, Darwin was a transcendent figure who tackled perhaps the greatest problem in biology with impressive logic and detailed observation. Yet no area in science is so committed to the story of its founder as the field of evolution. A kind of orthodoxy is promulgated in textbooks and popular books with Darwin as the starting point. Arguments in the field are polemical and often bitter, which contrasts with the nature of discussions in other areas of the natural sciences, which today are much more measured and sober. Too much effort in evolutionary biology is seemingly directed to fulfilling Darwin's most fundamental ideas and expressing them as mathematical theorems—"heaping up evidences" and "culminating them," as Henry Adams remarked nearly 150 years ago. Attempts to broaden the scientific argument are often frowned upon and treated as forms of heresy. Yet efforts to extend Darwin's ideas, and those of his disciples, pose no obvious challenge to his basic accomplishments. Further, there is no reason to believe that Darwin would have thought that understanding the variation component of biological change is less important to evolution or less exciting than natural selection or the mechanisms of inheritance. Darwin's voracious appetite for scientific discoveries in other fields suggests just the opposite.

Darwin emphasized that the goal of biological systems is to vary and adapt. We cannot understand variation and adaptation unless we understand the cellular details through which this variation and adaptation is expressed. Phenotypic variation may seem messy and non-mathematical, but the most general truths in science (including evolution) emerged in these qualitative ways. Messy fields full of details, like chemistry, geology, and medicine, have managed to derive powerful theoretical understandings of complex phenomena, such as shown here for cellular and developmental biology. In some cases, this was followed by mathematical codification and in other cases not. Facilitated variation might be an enduring theory of great explanatory power or simply a provisional theory challenging a new generation to understand phenotypic variation in terms of cellular and developmental mechanisms. In either case we can now view the 1981 Dahlem conference in a favorable light, as having pointed the way towards considering *phenotypic variation* as the great unsolved but not unsolvable problem, essential to any comprehensive theory of evolutionary change.

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# Part III
# Models, Larvae, Phyla, and Paleontology

# Chapter 10
# Phyla, Phylogeny, and Embryonic Body Plans

**Gary Freeman**

## 10.1 1859–1980

Haeckel coined the words "phylum" and "phylogeny" in *Generelle Morphologie der Organismen* (1866). Phylum has a two-part definition: (a) a higher order community of descent, and (b) the extant and fossil species that share the same body plan. Phylogeny is the record of the evolution of a community of descent through time. The ideas expressed by these terms predate their coinage. They are an elaboration on points that Darwin made in 1859 in his chapter on classification in *On the Origin of Species*. Darwin argued that if the Linnaean classification system, with its hierarchical organization, was based on the use of homologous characters (rather than morphological similarity), then it was consistent with and best explained the evolutionary origin of different groups of animals.

Homologous characters are features in separate taxa that have evolved from a common ancestor. At the time when Darwin wrote, there were three main criteria for identifying homologous characters in a set of related animals: (1) a character should have the same relative position along the body; (2) the parts that make up a character should have the same form and composition (tissues); and, (3) a character should have the same origin, as defined by germ layer composition during embryogenesis. Structural rather than functional considerations were of primary importance for the purpose of identifying homologues.

One problem with this approach involved making judgments about whether a given character was homologous within or across body plans. Analogous characters reflecting functional adaptations that have evolved independently in different lineages can be mistaken for homologous characters. Darwin argued that homologous characters could be identified more easily in embryos because they were not fully functional and therefore natural selection could not act on them (Table 10.1). Darwin

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**Table 10.1** Darwin on the utility of the body plan for identifying homologous characters

| Adults | | Embryos | |
|---|---|---|---|
| Single functional characters | + | Single characters | ++ |
| Body plans | ++ | Larval stages (functional embryos) | +++ |
| Vestigial organs | +++ | Embryonic body plan | ++++ |

The number of + signs after a given class of characters provides a qualitative estimate that a given type of character is homologous

called larvae functional embryos because, even though they had a functional larval action system, in most cases they lacked a functional adult action system. Overall similarity based on homologous characters was used to assign a taxon to a given place in a phylum; this was essentially a phenetic approach to classification.

Embryos were used in a different way to generate phylogenies. Darwin argued that by following the process of embryogenesis in a species one could get clues about how morphological change took place during the course of evolution in a lineage and the order in which innovations occurred.

> The adult differs from its embryo owing to variations supervening at later stages and being inherited at a corresponding age. This process, whilst it leaves the embryo almost unaltered, continually adds—in the course of successive generations—more and more differences to the adult. Thus the embryo is a sort of picture, preserved by nature, of the ancient and less modified condition of each animal (Darwin 1859, 338).

Haeckel expanded on these arguments about the role of embryological studies in classification and phylogenetic reconstruction, and Darwin acknowledged his contributions.

> Professor Häckel has recently brought his great knowledge and abilities to bear on what he calls phylogeny, or the lines of descent of all organic beings. In drawing up the several series he trusts chiefly to embryological characters, but receives aid from homologous and rudimentary organs, as well as from the successive periods at which the various forms of life are believed to have appeared in our geological formations. He has thus made a great beginning, and shows us how classification will in the future be treated (Darwin 1872, 333).

The Darwin/Haeckel formulation for classifying animals and constructing phylogenetic trees linked these operations to the study of body plan development. The only developmental stages they initially considered were post-gastrula stages. Table 10.2 provides a chronology for the appearance of some of the important papers on methodological approaches and the use of embryonic body plans in the construction of phylogenies during the period between 1859 and 1980.

### *10.1.1 The Fossil Record*

Paleontological studies during this period made three important points about the origins of phyla.

**Table 10.2** 1859–1980: thinking about phyla and body plans

| Date | Phylogeny | Embryonic body plans | |
|---|---|---|---|
| | | Post-gastrula | Pre-gastrula (promorphology) |
| 1859 | Darwin, *On the Origin of Species* | X | |
| 1864 | X | Müller, larvae as platform for evolution | |
| 1866 | Haeckel, phyla and phylogenetics | X | |
| 1873 | X | X | Lankester, diploblast→triploblast, radial→bilaterian |
| 1874 | X | X | Haeckel, gastrea |
| 1878 | | X | Whitman, cell lineage |
| 1908 | X | Grobben, superphyla | |
| 1925 | | | Wilson, integration of cell and developmental biology |
| 1950 | Hennig, cladistics | | |
| 1960 | | X | Seidel, phylotypic stage |
| 1980 | | | Nüsslein-Volhard/Wieschaus, genetic dissection of early development |

Chronologies with publication dates of bench mark papers in the area of phylogenetic reconstruction and the contribution of post- and pre-gastrula embryos to phylogenetic reconstruction and/or evolutionary developmental biology. The column that a paper is in indicates the category it belongs to; sometimes a paper belongs to more than one category and in these cases an X is placed under the other category(s)

1. Extant animal phyla appeared relatively abruptly during the Cambrian period of the early Paleozoic era. At the time they appeared, representatives of these phyla had a global marine distribution. During the Ediacaran period that immediately preceded the Cambrian, there were metazoan animals that also had a global marine distribution (Glaessner 1984). However, it was difficult to relate these fossils to those that first appeared during the Cambrian; some of these fossils were sessile colonial organisms, whereas others were bilaterians capable of locomotion.
2. Studies on the origin of classes within extant phyla with a high fossilization potential showed that in most cases new classes appeared more or less simultaneously during the early Paleozoic era. For example, in the Brachiopoda all nine classes that make up the phylum appeared during the Cambrian (Cohen and Weydmann 2005; Williams et al. 1996). The major exceptions to early morphological disparity have involved the generation of new classes via adaptation to new ecological settings, such as the colonization of land and parasitism.
3. Members of many extant animal phyla frequently have complex life cycles with small larvae adapted to life in the plankton; following a period of growth they metamorphose into benthic organisms that feed using different mechanisms, in part because of their increased size. It was not clear when this type of complex life cycle first originated. By the 1870s studies on changes in the morphology of

growth stages of Cambrian trilobites demonstrated that most of these species had a planktotrophic protaspis larva (Chatterton and Speyer 1997), which suggested an early evolutionary origin of larval forms.

### *10.1.2 Phylogeny*

Hennig (1950) introduced a new method for inferring phylogenies based on homologous characters. Even though the Darwin/Haeckel rationale was still the basis for classifying animals, by 1940 there was a substantial literature on the limitations of using the sequence in which characters develop in embryos for the purpose of inferring phylogenies (de Beer 1940). Although many systematists postulated phylogenies on the basis of the classifications they constructed, they lacked an objective basis for testing them. Hennig constructed phylogenies primarily using adult characters from extant organisms; developmental studies were only used for the purpose of helping to determine whether or not a given character was a homolog.

Hennig's system is based on the assumption that closely related groups are more likely to share recently evolved traits than groups that are not as closely related. Characters common to all members of a group are not used for phylogenetic reconstruction. Phylogenetic divergence is represented as a sequence of dichotomous branches that generate sister groups (a cladogram). A given sister group is defined by a difference in one or more character states. The node that separates two sister groups represents an unnamed hypothetical ancestor. Many of the character states of a node can be specified and it can correspond to a named species in a sister group at a lower point in a hierarchical cladogram. Character states (which define a species) are organized as a hierarchy of sets within sets. Hennig's ideas on phylogenetic systematics had an immediate effect on systematic practices in continental Europe, however it took over 30 years (and a number of modifications) before it became the dominant morphologically based system for doing phylogenetic reconstruction in the English-speaking world.

### *10.1.3 Pregastrula Embryos*

Pregastrula embryos were first used to make phylogenetic arguments in the 1870s. Haeckel advanced the generalization that all multicellular animals gastrulated (the 'gastrea theory'), which indicated common descent. Lankester distinguished two grades of animals: diploblasts and triploblasts. Diploblasts had two germ layers—ectoderm and endoderm—and were radially symmetrical with an oral-aboral (O/A) axis. Triploblasts had three germ layers—ectoderm, mesoderm, and endoderm—and were bilaterians with a dorsal ventral (D/V) plane superimposed on an anterior-posterior (A/P) axis. Both Haeckel (1874) and Lankester (1873) argued that

members of the diploblastic grade functioned as ancestors to members of the triploblastic grade. During this same period Whitman (1878) showed using a cell lineage analysis during early cleavages in a leech that one could predict the locations of the A/P and D/V axes and the site of mesodermal germ layer origin, well before gastrulation. Subsequently, comparative cell lineage studies were used to argue for early embryonic homologies across phyla involving patterns of cleavage, embryonic symmetry properties, and the origin of germ layers and cell types (Wilson 1899). Embryological criteria were also used to divide groups of phyla into families referred to as superphyla. Two of these superphyla were the Protostomia and Deuterostomia (Table 10.2, Grobben). Among bilaterians, the blastopore that forms during gastrulation becomes the mouth in Protostomia; in Deuterostomia the mouth is a new formation.

In the mid-1890s, a research program based on the experimental manipulation of embryos was initiated that aimed to get at the causal basis of development (Table 10.2, Wilson 1925). It attempted to integrate genetic and developmental thinking by examining these phenomena at a cellular level. Work on a variety of bilaterian species in different phyla showed that during the course of early development the A/P axis was always established prior to the D/V axis and that the establishment of the D/V axis depended in part on the A/P axis. At the same time, parts of embryos with a known presumptive fate were raised in isolation or grafted to ectopic sites and monitored for further development. In this way the time when a particular region of an embryo was specified and the conditions of its specification could be ascertained (Slack 1992). This work showed that some parts of early embryos were specified by inherited cytoplasmic components, while other parts depended on signals from neighboring regions. There was a mix of ways in which parts of embryos were specified depending on the phylum or class. Work involving hybridization experiments on related species with different embryonic phenotypes showed that maternal factors synthesized during oogenesis could have a major effect on development. Studies on the cytoplasmic organization of oocytes and different stages of development, such as fertilization and early cleavage stages, showed that there could be marked changes that played a role in biasing the way in which cells that inherited these cytoplasmic domains differentiated and affected the differentiation potential of neighboring cells. During the period just before the 1981 Dahlem conference, work in the area of developmental genetics (Nusslein-Volhard and Wieschaus 1980) led to a dissection of the pathways that were responsible for early regional specification in *Drosophila*.

### *10.1.4 Evolvability of Embryos: Post-gastrula*

In the first part of the twentieth century a discussion began on what constitutes an embryonic body plan (Woodger 1929). One outcome of this discussion was the attempt to highlight developmental stages that appeared to have the greatest potential for evolutionary change. For both Darwin and Haeckel this was the period after gastrulation, exemplified in many cases by the larval stage; however, at the time they

were writing not much was known about embryogenesis prior to gastrulation. Shortly after the publication of *On the Origin of Species,* Müller (1864) wrote *Für Darwin*. There he used developmental studies on Crustacea to provide evidence that the nauplius larva served as a developmental platform for the evolution of different orders of crustaceans. As this type of larva went through progressive molts in different lineages the characteristics of the different orders appeared. This viewpoint implied that in many cases larvae were not later intercalations into an ontogenetic pathway, but played an early and integral part in the evolution of a given clade. For example, Hyman (1940) showed a phylogenetic tree with a dipleurula larva at the base of the deuterostome branch and a trochophore larva part way up the protosotome branch, implying that these larvae played a role in generating a number of phyla.

### *10.1.5 Evolvability of Embryos: Pre-gastrula*

Subsequent thinking about embryonic body plans occurred after studies on the role of pregastrula stages in phylogenetic reconstruction and the advent of experimental studies on early development. Seidel wrote a paper on the relationship between ontogeny and phylogeny for a symposium at a meeting of the German Zoological Society celebrating the 100th anniversary of the publication of *On the Origin of Species* (Seidel 1960). In a series of diagrams he provided examples from cnidarians, annelids, molluscs, echinoderms, and vertebrates of different morphological pathways used during pregastrula and early gastrula stages within a phylum. These examples showed that there could be a potential developmental basis for evolutionary change operating at early stages of development. At the end of each diagram Seidel used the term "körpergrundgestalt"(KGG) for the stage the different developmental pathways converged on. In taxa with a biphasic life cycle there were KGG stages for both larvae and adults. Alfred Kühn, Seidel's major professor, first developed the notion that there could be different early developmental pathways that converged on the same end point in a clade. In a study on the different developmental pathways that led to the polyp stage in hydrozoans, Kühn (1914) first used KGG, the term that was later translated into English as "phylotypic stage" by Sander (1983). All of these biologists defined KGG in the same way: the stage of maximum similarity between different orders that make up a class or different classes that make up a phylum. The stage was defined in concrete morphological terms; it could be achieved at different times relative to other developmental events, such as gastrulation, or the formation of a functional larval stage in the different subtaxa that made up a larger taxon.

The last part of Seidel's paper reviewed experiments on a variety of early embryos by different investigators that dealt with the developmental basis for evolutionary change. These experiments included work from his lab and the lab of his former graduate student Krause on the comparative morphology and experimental embryology of insects. Cladistic studies had mapped out the evolutionary relationship in this group. Their work and the work of their students used a variety of species that ranged from the basal order Odonata to the derived order Diptera. Three of the clade-wide comparisons discussed by Seidel can be summarized here.

1. There are two types of oogenesis in insects: panoistic and meroistic. Panoistic oogenesis occurs in basal orders with larger eggs and slower development, whereas meroistic oogenesis occurs in derived orders with smaller eggs and rapid development.
2. During early embryogenesis in insects, nuclei divide in the central part of the egg. Subsequently, they migrate to the periphery and form a cellular blastoderm. This process takes place at a slower rate and in an asynchronous manner in basal orders and is controlled by a cleavage center, whereas it occurs at a faster rate and in an almost synchronous manner in embryos of derived orders under conditions where a cleavage center does not appear to be operating.
3. In basal insect orders there is an activation center in the egg that acts on a differentiation center to specify the head-forming region, while the thoracic and abdominal regions are specified by a region behind the head (after gastrulation has already begun). In derived insect orders the entire body axis—head, thorax, and abdomen—are specified prior to gastrulation as a consequence of the interactions of factors at the anterior and posterior ends of eggs.

Sander (1976) provides a more detailed description of these studies. This combination of observations and experimental studies across a phylogenetically well-defined taxon provided some of the best evidence for evolutionary change being mediated by changes in early development. Initially, Seidel's 1960 paper had almost no impact outside of continental Europe. When Seidel's work was cited in the 1990s, biologists concentrated on the phylotypic stage and ignored the importance of events that led up to it, which was Seidel's main point.

### *10.1.6 1859–1980: Conclusions*

Haeckel described six phyla of multicellular animals in 1866; by 1980 there were about 30 phyla. During the later part of this interval, the procedures used for inferring phylogenies based on embryos were largely replaced by cladistic methods. However, embryos were still used to make inferences about homologies for the purpose of classifying animals, and homologies were extended to early developmental stages. At the same time a number of limitations of the Linnaean system for classifying organisms became apparent. The boundaries of a given hierarchical level, especially at higher taxonomic levels such as phyla, were frequently in flux (e.g., Anderson 1973). Because the hierarchical terms used to describe the relationships between the members of given phylum are relative, a given term such as class cannot be used for the purpose of making comparisons within and between phyla; more information is always needed. As a rank free method for classifying organisms and determining phylogenetic relationships, cladistics subverted the use of the Linnaean system, even though this system is still the vernacular used among biologists for convenience in communicating large-scale phylogenetic generalizations.

At the 1981 Dahlem conference (Bonner 1982) there was almost no mention of the terms phyla and phylogeny. The point was made that better phylogenies were necessary in order to investigate the developmental basis for evolutionary change. And there was a substantial discussion of embryonic body plans and how they are generated, but largely without the aid of a phylogenetic context. During the 30-year period following the conference there has been a marked increase in the amount of scientific work done in the area of Evo-devo that pertains to phyla, phylogeny, and body plans.

## 10.2 1981–2010

### *10.2.1 The Fossil Record*

During this period a number of relevant paleontological developments emerged.

1. Prior to 1981, dates of a given Paleozoic period varied widely. Improvements in dating based on measurements of uranium/lead isotopic ratios in zircons generated during volcanic activity made these period dates much more reliable. For example, the base of the Cambrian was dated at 570 Ma but is now dated at 543 Ma (Bowring et al. 1993). Dates for Ediacaran animals showed that most of the sites where fossils had been discovered predated the Cambrian by less than 20 Ma. These Ediacaran fossils are preserved as casts. Work on material from the Doushantuo Formation in China uncovered fossils where cells and tissues could be recognized. These fossils included members of the extant phyla Porifera (Li et al. 1998) and Cnidaria (Chen et al. 2002), as well as a bilaterian (Chen et al. 2004). This material predated the Cambrian by 40–50 Ma and provides a much larger window in time during which the precursors of the extant bilaterian phyla could evolve.
2. After 1981 quantitative estimates of morphological disparity for a given clade were based on measurements of average pair-wise differences for multiple characters in different species at different points during the clade's history. The majority of these studies showed that morphological diversification occurred more rapidly than taxonomic diversification during the early history of a phylum (Erwin 2007). A related approach has compared the frequency and extent of morphological variation within older basal species to younger and more derived species that belonged to the same clade. A much higher proportion of polymorphic characters was found in species that lived during the Cambrian than in the post-Cambrian (Webster 2007). The high morphological disparity between species, and the high within-species morphological variation during the Cambrian, may reflect the fact that developmental systems were less well canalized at this time. The higher within-species variation could be responsible for the morphologies that selection acted on, making large morphological changes possible during speciation in the Cambrian.

3. Paleontological studies increased the number of extant and extinct phyla that had feeding larvae during the Cambrian (e.g. Freeman and Lundelius 2008; Müller and Walossek 1986). These cases show that the biphasic life cycle had a very early origin, at least among the protostomes. Some members of all extant phyla with feeding larvae during the Cambrian have feeding larvae today. There are different views on the origin of the biphasic life cycle and its evolutionary significance. Nielsen (2009) argues that benthic adult stages were added onto ontogenies that contained a pelagic feeding larva; Raff (2008) argues that the larval stage has been intercalated into a life cycle that initially involved direct development to an adult. The presence of larvae in a number of phyla during the early Cambrian puts constraints on Raff's arguments.

### *10.2.2 Phylogeny*

Table 10.3 summarizes some of the major ways in which ideas about phyla, phylogeny, and body plans have changed since 1981. The advent of molecular methods has had an enormous impact on phylogenetic reconstruction. Body plans provide an indirect assessment of genetic relationships between species while

**Table 10.3** 1980–2010: thinking about phyla and body plans

| | | Embryonic body plans | |
|---|---|---|---|
| Date | Phylogeny | Post-gastrula | Pre-gastrula (promorphology) |
| 1988 | Field et al., molecular phylogeny | | |
| 1993 | X | Slack et al., *Hox* genes and phylotypic stage | |
| 1994 | Phillippe et al., monophyly of metazoans | | |
| 1996 | | Raff, module integration | |
| 1997 | Aguinaldo et al., superphyla | | Gerhart/Kirschner, cell biology of Evo-devo |
| 2001 | | Galis/Metz, testing phylotypic stage | Davidson, genomic regulatory systems (echinoderms) |
| 2006 | | | Davidson/Erwin, GRNs and body plan evolution; Imai et al., GRNs (tunicates) |
| 2008 | Dunn et al., sequence sampling from multiple genes and taxa | | |

Chronologies with publication dates of bench mark papers in the area of phylogenetic reconstruction and the contribution of post- and pre-gastrula embryos to phylogenetic reconstruction and/or evolutionary developmental biology. The column that a paper is in indicates the category it belongs to; sometimes a paper belongs to more than one category and in this case an X is placed under the other category

molecular genetic methods have the potential to offer a more direct assessment by enumerating base differences in homologous regions of orthologous genes for species pairs. Field et al. (1988) published the paper that jump-started this field. Many of their conclusions about animal phylogeny have not stood the test of time, largely because of the small number of species used and the fact that many of the procedures adopted for analyzing their data did not address all of the relevant variables or had not been fully worked out.

Subsequent work by Phillippe et al. (1994) confirmed the argument of Haeckel and Lankester that metazoan animals are a monophyletic group with diploblasts functioning as the sister group of the bilaterians. They also confirmed Grobben's (1908) assertion that there are two superphyla within the bilaterians: protostomes and deuterostomes. Aguinaldo et al. (1997) further divided the protostomes into two sub-superphyla: ecdysozoans and lophotrochozoans. At lower hierarchical levels, the phylum Annelida absorbed the phyla Echiura, Sipunculida, and Pogonophora, the phylum Brachiopoda absorbed the phylum Phoronida, and the phylum Arthropoda absorbed the phylum Pentastomida. Many sister groups relationships within phyla changed.

The initial work in the field of molecular phylogeny utilized the DNA that codes for the 18s subunit of ribosomal RNA and was sometimes supplemented by sequences from one or a few genes. Recently Dunn et al. (2008) used protein-coding sequences from the orthologues of multiple housekeeping genes that are common to all cells in conjunction with broad phylogenetic sampling to improve the resolution of phylogenetic trees. Molecular phylogenetic methods, which do not rely on body plans, appear to produce more convincing trees than cladistic methods using body plan characters when the two methods are compared within the same clade (e.g. Cohen and Weydmann 2005).

### *10.2.3 Post-gastrula Embryos*

One body of work on post-gastrula body plans after the 1981 Dahlem conference focused on the phylotypic stage. The primary issue became one of explaining the evolutionary stability of this stage along with two ancillary issues: (a) is there a phylotypic stage? and, (b) how does one get at the basis for the developmental stability of the phylotypic stage? The role of post-gastrula embryos in evolutionary change demonstrated by Müller (1864) has been largely ignored. Richardson et al. (1997) argued that vertebrate embryos do not have a phylotypic stage because the different clades in this group show body plan variations due to allometry and heterochrony at the tail bud stage of development. If they had read Seidel or Sander on the phylotypic stage and the comparative evolutionary developmental biology of insects (which they do not cite), then they would have known that this stage is defined independently of allometric and heterochronic considerations.

A number of studies have tried to demonstrate the existence of the phylotypic stage by examining gene expression patterns before, during, and after the

phylotypic stage. One recent study used new genes that have evolved over the last 40 Ma in six *Drosophila* species to demonstrate that they are expressed primarily prior to and after the phylotypic stage, suggesting that gene expression patterns tend to be conserved during the phylotypic stage (Kalinka et al. 2010).

Slack et al. (1993) proposed that this stage exists and is stable because at or just prior to this stage there is a suite of gene activity that sets up a pattern of positional information along the body axes of the embryo that will be used in the placement of various parts of the body plan. The authors argue that the *Hox* gene cluster and other position specific genes play this role. A mutation in one of these genes that disrupts the body pattern will lead to lethality. While *Hox* genes may play this role in some groups of embryos at the phylotypic stage, they do not do so in all phyla (e.g., see Kenyon et al. 1997 for the nematode *Caenorhabditis*).

Raff (1996) has argued that the number of modules and their connectivity at the phylotypic stage explains its stability. A module is a discrete population of cells that initially exhibit a pattern of gene activity that is reinforced by local signals sent by the cells in the module to each other. The pattern of gene activity in a given module can also be modified by signals from other modules. According to Raff's scenario, the early embryo only has a small number of simple modules that primarily establish axial properties without much connectivity between them. By the phylotypic stage there has been an increase in the number of modules and their connectivity. Because of the connectivity between modules at this stage, a deleterious mutation that affects a given module has a high probability of having a negative pleiotropic effect on development mediated by other modules. Thus stabilizing selection will preserve the phylotypic stage. After the phylotypic stage the number of modules is maintained and cell-cell communication persists in these modules, but connectivity decreases between modules lowering the probability that a mutation in a given module will have pleiotropic effects.

The only evidence for this scenario is indirect. It is based on a meta-analysis that purports to show that a variety of teratogens that act in different ways are more effective in causing prenatal mortality and multiple defects in embryos when administered at the phylotypic stage in mammals (Galis and Metz 2001). Because of the research aims motivating this work, teratogenic effects on pre-gastrula and early gastrula stage embryos were probably underestimated because most embryos that died could not be counted. Although gene circuits that define some modules have been described (e.g., Olsen 2006), there is little quantitative data on how many modules there are and the amount of connectivity between modules at different stages of development in well-studied organisms.

### *10.2.4 Pre-gastrula Embryos*

Seidel examined the early embryology of insects in a phylogenetic context. Insects are a subgroup in the class Hexopoda that originated from the class Crustacea about 100 Ma after the Cambrian. The only comparable study that has been done for a

group that originated during the Cambrian involves the Brachiopoda (Freeman 2007). The Cambrian fossil record shows that multiple classes with disparate morphologies were generated during a relatively short period of geological time. Representatives of four of the classes have extant descendants today with larvae and the different regions of the larvae in the four classes can be homologized. Fate maps were prepared for representatives of these four classes. These maps describe the regions of the egg and cleavage stage embryo from which regions of the larvae are derived, the morphogenetic movements associated with gastrulation, and the origins of the germ layers. Experiments were done to determine when and how the A/P and D/V axes of these larvae were set up and to establish when and how the different regions of these larvae were specified. All three types of studies showed that the process of regional specification is quite different in these four classes. In the class Lingulata there are two extant species belonging to different families that, on the basis of the fossil record, diverged during the Cambrian. In the class Rhynchonellata there are extant species from two different orders that had diverged by the Silurian-Devonian boundary. In both cases each species pair showed essentially identical fate maps, patterns of regional specification, and the axial systems were set up at the same time and in the same way. This strongly suggests that the differences in regional specification in the different classes originated at the time the classes formed.

A number of discoveries in the 1980s in the fields of cell and molecular biology had a large impact on the field of developmental biology with implications for the evolvability of species. These studies included the dynamic role of the cytoskeleton in moving and tethering maternal messenger RNAs at different spatial positions in eggs and embryos, the basis for communication between cells via ligands, their receptors, and second messenger systems. This work provided a concrete basis for the ontogeny of axial systems in embryos. Work on cell adhesion and the cytoskeleton provided a basis for explaining morphogenetic movements. Work on the *cis*-regulation of gene activity provided a basis for directing all of these activities, including the processes of regional specification and cell differentiation (Gerhart and Kirschner 1997).

Initially, the evidence for homologies during early embryogenesis was based on patterns of expression for a specific gene; sometimes this was complemented by data on the morphological response to a knockout of that gene. Now evidence is increasingly drawn from gene regulatory networks (GRNs) that function as a developmental module. Davidson's book, *Genomic Regulatory Systems* (2001) is an introduction to this approach. It is a classic example of proselytizing for a new scientific idea, and in this sense it resembles Haeckel's *Generelle Morphologie der Organismen*. Abouheif (1999) has outlined some of the properties of GRNs and the criteria for recognizing when a given GRN would be regarded as homologous in different species. A GRN resides in a discrete population of cells in an early embryo even though its influences can extend beyond these boundaries. The component genes in the network have to be identified and their regulatory interactions defined. A given gene can function by activating or repressing another gene in the network. The criteria for establishing homology among GRNs in different species are: (1) the

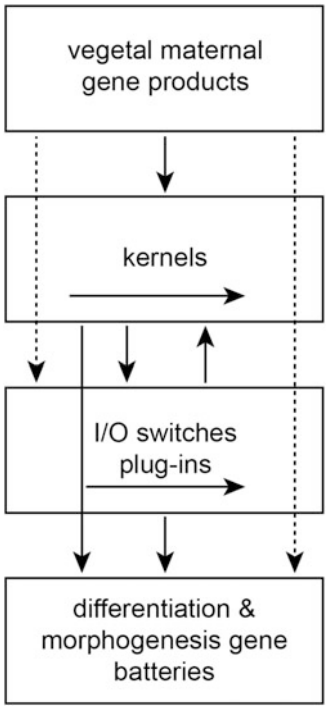


**Fig. 10.1** Levels of gene regulatory control within the endomesodermal specification and differentiation module. Regulatory interactions within and between levels are indicated by the *arrows*. The *arrow* from maternal RNAs to the I/O switches and plug-ins, in addition to the differentiation and morphogenesis gene batteries, is *dashed* because it has not been demonstrated but is a possibility (Adapted from Davidson et al. 2002 and Davidson and Erwin 2006)

boundaries of the networks must be similar; (2) the genes being compared must be orthologs; (3) the genes must interact in a similar way; and, (4) the phylogenetic relationships between the species being compared must be well-defined and established using a different set of criteria.

Davidson et al. (2002, and subsequent publications) have documented a GRN for the specification of endomesoderm in echinoid larvae. This network is located in the vegetal region of the embryo. The network has a hierarchical structure (Fig. 10.1). Davidson and Erwin (2006) have characterized the properties of the different levels that make up the hierarchy. At the top there are uncharacterized vegetal maternal gene products, laid down during oogenesis, which activate genes in the hierarchy referred to as kernels in the cells that inherit the vegetal determinants. Each of the kernel genes codes for transcription factors that interact with each other via recursive networks to keep all of the genes activated; knocking down one kernel gene will shut off the others, preventing endomesoderm formation. The kernel genes regulate I/O switches and plug-in genes that interact among themselves, feedback on the kernel genes, and act directly on differentiation and morphogenesis gene batteries. I/O switches and plug-in genes play a major role in subdividing the vegetal region of the embryo into mesodermal and endodermal regions, and then further subdividing each of these. For example, the mesodermal region will be further subdivided into primary mesenchyme cells that will form the larval skeleton, muscle, coelomic mesoderm cells, and pigment cells. The middle

layer of the GRN hierarchy also regulates ligands and receptors that play a role in both short and long range cell signaling, such as the Wnt pathway. At the same time, this middle layer turns on the cells in the differentiation and morphogenesis gene batteries at the bottom of the hierarchy in the cell domains that have been specified. While only a small number of genes operate at the top of the hierarchy, this number increases by an order of magnitude as one moves downward to each of the two lower levels. This module is far larger than anything Raff (1996) appears to have envisaged prior to the phylotypic stage.

Davidson and Erwin assume that the main structural features of the endomesodermal GRN in echinoids can be generalized to explain early development in all animals. They predict that all members of a phylum or superphylum will have homologous kernels, that there will be alterations in plug-ins and I/O switches associated with class, order or family level evolutionary events, and that alterations of cell differentiation and morphogenesis will characterize speciation events. They argue that the frequency and impact of genomic changes during the course of evolution that occur in GRNs depend upon the position of the genes in the network. Because changes in a kernel gene can lead to lethality, these genes will be maintained by stabilizing selection. Therefore the kernel circuits will persist, giving a phylum identity and stability through time; the kernel genes will also tend to stabilize the gene circuits that play a role in early regional specification.

The fossil record indicates that the phylum Echinodermata originated during the Cambrian; at least eight classes originated during this period. The five extant classes originated during the Ordovician, with the possible exception of the Crinoidea. Extant echinoderms are divided into two subphyla: Pelmatozoa and Eleutherozoa. Each of these subphyla probably had a separate origin during the Cambrian (Fig. 10.2a). The phylogeny shows that the holothurian-echinoid branch evolved from an asteroid-like ancestor.

For the purpose of comparing changes in the endomesodermal GRN during evolution, Davidson and Hinman decided to compare echinoids and asteroids (Hinman et al. 2003, Hinman and Davidson 2007). Echinoids typically have a pluteus larva with arms that are supported by a calcite skeleton, while asteroids typically have a bipinnaria larva that lacks arms and a skeleton. Hinman and Davidson (2007) showed that the kernel genes and their circuits were largely conserved between the two classes, however at lower levels in the hierarchy there were a number of changes in gene circuits. One important set of changes involved the import of the skeletogenic GRN from the adult to early developmental stages in order to build the larval skeleton in echinoids (Ettensohn 2009). Even at the level of I/O switches and plug-ins there was conservation of subcircuits that were recursively wired (McCauley et al. 2010).

Given the claim by Davidson and Erwin (2006) that the kernel genes and circuits that make up the endomesodermal module are a phylum or superphylum specific trait, it is important to examine this part of the module in crinoids because this class of echinoderms is phylogenetically most removed from the echinoids. The Echinodermata are a member of the deuterostome superphylum (Fig. 10.2b). All of these phyla and the subphyla within the Chordata originated during the Cambrian.

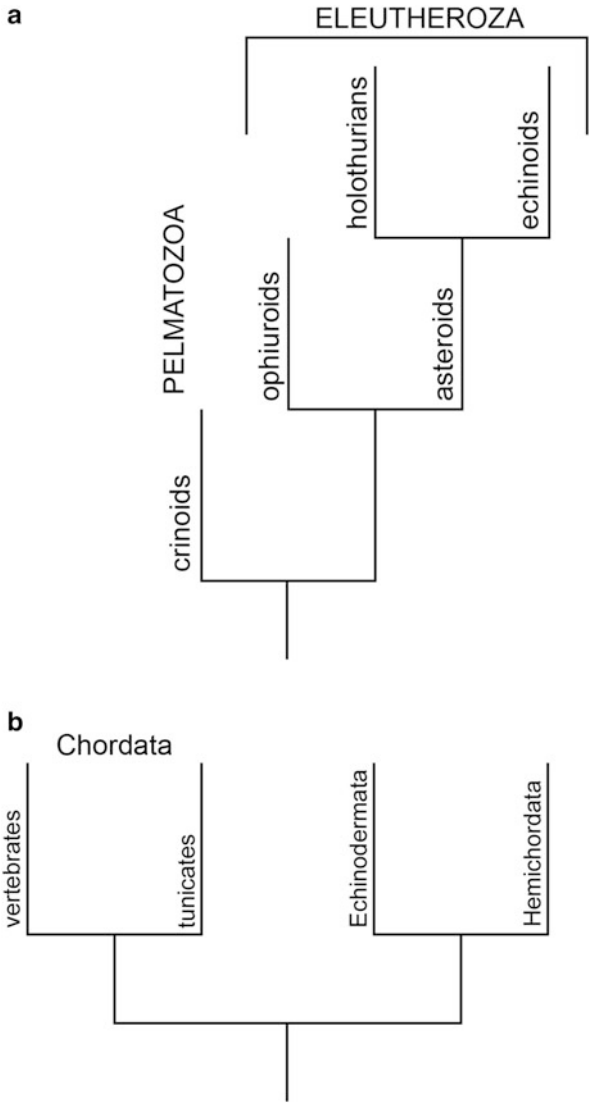


**Fig. 10.2** (**a**) Phylogeny for extant echinoderm classes. This phylogeny is based on 18s rDNA (Wada and Satoh 1994). (**b**) Phylogeny for major extant deuterostome phyla and subphyla based on expressed sequence tags from multiple housekeeping genes (Dunn et al. 2008)

Within the chordates the tunicates are a sister group to the vertebrates. The genome of the ascidian *Ciona* has been sequenced and the GRN responsible for the specification of most of the cells that make up the embryo between the 16 cell and gastrula stage, including the endomesodermal region, has been determined (Imai et al. 2006). The echinoid endomesodermal kernel is not present in tunicates and the organization of the GRN is quite different; there is a very low level of gene network connectivity in the different regions of the tunicate embryo (Lemaire 2006). There is no credible comparative evidence that supports the hypothesis that the

developmental stability of phyla results from the conservation of recursive connectivity at high hierarchical levels in their gene regulatory circuits.

Will the comparative study of GRNs be the most informative way to organize information and advance hypotheses about the developmental basis for evolutionary change? While comparative GRN catalogs may make it possible to say something about the genetic basis for evolutionary change, a great deal of additional information about early development is necessary in order to interpret them. The evolutionary roots of bilaterians are found in their pre-bilaterian ancestors with one major axis of symmetry and two germ layers. One has to consider this platform when thinking about early development in bilaterians (Martindale and Hejnol 2009). One of the first events occurring in the embryos of most species is the establishment of its A/P axis. This frequently depends on localized maternal mRNAs. One must know what these mRNAs code for, the circumstances under which they are translated, the nature of the cytoskeletal systems that are responsible for their localization, and the time when localization events occur. The actual establishment of an axis depends on the sources of signaling molecules, the distribution of their receptors, and second messenger systems throughout the whole embryo. Ligands can function as morphogens that provide concentration dependent positional information, or they can be part of a simple switching system. Effector proteins can be coded for by maternal messengers or via zygotic gene transcription. If one organizes GRNs around discrete universal developmental events, such as the formation of the primary or secondary axis, or regional specification events (e.g., the subdivision of endomesoderm to form endoderm and mesoderm, or the specification of different kinds of mesoderm), then the developmental homologies that operate in lineages will be better grounded empirically. This will provide a comparative developmental basis for studying evolutionary change.

If GRNs are organized around basic developmental events, then one has to consider what additional gene expression information will be needed. The endomesodermal GRN for echinoid embryos is located in the vegetal region of the embryo; however, signaling molecules that have their origin and act in this area also have a major impact in other regions some distance from the vegetal pole where other GRNs play a role in specifying the O/A axis (Yaguchi et al. 2008) and the neurogenic center at the animal pole of the embryo (Wei et al. 2009). If Wnt signaling, which plays a role in the establishment of the A/P axis, is inhibited the O/A axis will not form, and the size of the neurogenic region will expand dramatically. There are vegetally localized maternal factors that have not been characterized at the top of the echinoid endomesodermal GRN. At the fourth cleavage in echinoids, maternal effects cause each macromere at the vegetal pole to divide, yielding a small vegetal micromere that gives rise primarily to the larval skeleton and a macromere. If this division is equalized, then early skeletogenesis does not occur (Ettensohn 2009). Although GRNs have been described at a global level in ascidians (Imai et al. 2006), the role of vegetal and posterior-vegetal maternal (PEM) mRNAs, which play a major role in patterning the embryo's A/P axis and in specifying cell types in the embryo, was excluded. These maternal RNAs have been characterized in some detail (Prodon et al. 2007). There is also a centrosome

attracting body associated with these mRNAs that is responsible for unequal cleavages in the posterior cells that inherit it. If the region that contains these factors is removed from the egg prior to cleavage, then the posterior region of the embryo will transform into a mirror image of the anterior half (Nishida 1994). These maternal mRNAs play a major role in increasing the connectivity between different regions of the ascidian embryo (Kumano and Nishida 2009). At a functional level, the PEM of ascidians is similar to the vegetal endomesodermal region of echinoids; it may be partially homologous.

## 10.3 General Conclusions

Each time period examined in this essay began with a review of the fossil record during the late Neoproterozoic when diploblastic phyla and stem group bilaterians originated and the early Paleozoic when extant bilaterian phyla originated. One take-home lesson from the paleontological literature is that the origin of extant phyla was accompanied by the generation of early morphological disparity within a phylum followed by relative stasis. These studies also provide data on the life cycles of the major animal phyla during the period when they originated, and constrain the length of time during which major macroevolutionary events occur.

Both Darwin and Haeckel tied the study of post-gastrula embryonic body plans to the classification of animals because these body plans could be used to establish character homologies. They also used developmental sequences in post-gastrula embryos to establish phylogenies. Prior to the 1950s, the role of post-gastrula developmental histories in the construction of phylogenies was discredited. The adoption of cladistic methods, with their emphasis on adult morphology, decreased the relevance of developmental studies. The advent of molecular phylogenetic studies based on DNA has largely supplanted morphology-based inferences in extant animals because it provides a more direct basis for inferring genetic similarities. This advance has allowed biologists to use phylogenies that are generated independently of morphological data to test hypotheses about the basis for evolutionary change, thereby removing an element of circular reasoning (Raff 1996).

Comparative developmental studies that began during the late nineteenth century highlighted the important role that processes occurring in early embryos had on subsequent developmental events and their potential for explaining evolutionary change. This was accompanied by the rise of causal analyses of development, which aimed to replace the morphology-based view of post-gastrula embryology with a promorphological view, where a set of processes and interactions in early embryos generated an organism. One outcome of both comparative and causal analyses of early development was the realization that there could be a great deal of variability across different phyla and classes within phyla.

By the 1960s two research traditions in evolution and development had begun to emerge. One primarily utilized post-gastrula developmental stages and focused on developmental pathways that underlie phenotypic features in organisms that

function as adaptations in the ecological context of the organism. It has a microevolutionary emphasis. The other research tradition primarily utilizes pre-gastrula stage embryos and is based on the comparative analysis of mechanisms that mediate development. It seeks to reconstruct (at least in outline) the developmental features that led to the origin and early evolution of major groups of organisms. This research program was first articulated in its modern form by Seidel (1960). It has a macroevolutionary emphasis.

One general question of interest to Evo-devo biologists is the identification of ontogenetic platforms that support evolvability. Raff's (1996) hypothesis that the phylotypic stage is refractory to evolutionary change because it is composed of multiple modules exhibiting high connectivity is one possible answer. This refractory period could provide the basis for the phylum level morphological stability indicated by the fossil record. Raff argues that evolutionary change should be possible at earlier and later stages of development because there is much less connectivity. The data on developmental connectivity in early embryos of echinoderms and ascidians shows that it is substantial and that disruption of these pathways leads to gross developmental abnormalities and lethality, falsifying one of Raff's predictions. Unfortunately, there is not comparable data for the phylotypic and post-phylotypic stages of development for these groups. The GRN studies of Davidson and Erwin (2006) on early development may provide a basis for explaining phyletic stability; they do a much better job of providing a framework for explaining innovations at higher taxonomic levels within an evolutionary context.

If one is going to study evolvability, the GRN approach has the greatest potential of generating meaningful results. But the reification of GRNs will not turn these networks into early embryos. In this essay I have outlined some of the additional pieces of information that are needed, and ways of organizing this data (e.g., in terms of their contribution to basic developmental events, such as axis formation and early regional specification processes) that are needed to allow one to look at GRNs in a larger context so that it can be compared using phylogenetic methods. While embryos have lost their initial role in making phylogenetic inferences as envisaged by Darwin and Haeckel, they have taken on a new role in providing a causal explanation of how development shapes evolutionary change.

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# Chapter 11
# Evo-devo and the Evolution of Marine Larvae: From the Modern World to the Dawn of the Metazoa

**Rudolf A. Raff**

## 11.1 A New Science Foreseen

Evolutionary developmental biology (Evo-devo) is the study of how developmental processes evolve and influence the evolution of form. Evo-devo is now a well-defined discipline with well-integrated problems, conceptual and technical approaches, and organizational infrastructure. Not so long ago, this wasn't the case. In 1981, when interest in the relationship between evolution and development was growing again, John Bonner presciently organized a conference representing diverse disciplinary viewpoints to thrash out what such a science should be about. This became the famous 1981 Dahlem conference held in what was then West Berlin (Bonner 1982). A major hope was that the newly revived discipline of developmental biology might offer an explanatory mechanism for macroevolution that was as powerful as natural selection is for microevolution.

At the time, our options for finding a novel developmental mechanism were limited. The concept of "developmental constraint" offered the best possibility (see Brigandt, Chap. 14, this volume). This hypothesis suggested that developmental processes would have evolved over time into tightly integrated complexes that could not be changed readily by selective pressure because most changes would cause developmental failures. In an apparent paradox, profound morphological evolution does occur, so the hypothesis also suggested that a number of important changes not only could be tolerated, but must have occurred. A constraint in the number of important changes meant that the outcomes would be biased to a limited range of possible directions. The narrow range of permissible outcomes would determine what courses of macroevolution would be possible. This hypothesis was

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developed by Pere Alberch (1982), and promoted by Steve Gould, who represented constraint by the metaphor of a polygon. A die can only fall on a side. If bias limits changes, the outcome may not be predictable, but it must fall into a restricted number of possibilities.

Alberch and Gale (1983) performed important experiments with salamanders and frogs showing that experimental colchicine induction of digit loss mimicked evolutionary patterns of reduction. Their results supported the idea that the pattern of digit loss in tetrapod evolution was constrained. But a key problem was that it proved difficult to find these limiting constraints in development. Beyond this empirical difficulty, the centrality of older ideas about Evo-devo, including heterochrony and developmental constraints, were soon displaced by new discoveries in the years following the 1981 Dahlem conference. Major progress in Evo-devo would come throughout the 1980s with the arrival and maturation of two new disciplines: molecular systematics and developmental genetics.

## 11.2 Body Plans and Regulatory Genes

One of the revolutionary events in Evo-devo that took place within a few years of the 1981 Dahlem conference was the discovery that animal phyla with distinct body plans shared developmental regulatory genes. The original thought was that phyla had diverged so long ago that they were unlikely to share such genes (Mayr 1963). By the late 1980s, this viewpoint had to be abandoned with the discovery that developmental regulatory genes were shared by a broad spectrum of animal phyla. The shift occurred when the labs of Thomas Kaufman and Walter Gehring discovered the homeodomains, which quickly resolved into realizing that *Hox* genes were found everywhere among eumetazoan animals. Other regulatory genes were later found to expand that generalization. It seems like a historical surprise that all of us accepted common descent, but did not realize that descent with modification itself strongly implied that regulatory genes should be shared among distinct body plans (see Freeman, Chap. 10, this volume). Once it was shown experimentally—essentially by accident—then it not only made sense but also was difficult to envision why shared developmental regulatory genes hadn't been the starting assumption. *Hox* genes were quickly seen as providing a unifying basis for axis development in animal body plans (Slack et al. 1993).

Although developmental genetics was well represented at the 1981 Dahlem conference, phylogeny was mentioned only peripherally. However, during the 1980s, phylogenetics would become indispensable to Evo-devo. We began to realize the need for a rigorous phylogenetic framework in which to place the discoveries from molecular and developmental studies. Evo-devo depends on phylogeny because we cannot understand the evolution of a structure if we don't know the pattern of its evolutionary history. A phylogeny of the organisms bearing a feature allows the determination of what precursor a feature evolved from, and whether similar structures evolved independently in more than one lineage—convergence. The question of

*how* convergent features evolve can only be answered *if* convergence can be recognized. That can only be done through phylogenetic analysis.

The ideas about animal phylogeny that were available around 1980 had been set out primarily in the 1940s and 1950s. By the time of the Evo-devo revival in the mid 1970s, these ideas had frozen into dogma and were codified in prominent invertebrate zoology textbooks. Evolutionary biologists began to realize the critical significance of applying rigorous approaches to tracing lineages of organisms and the features they carry. That meant using new cladistic methods and new kinds of data for inferring phylogenies. Systematics got an enormous boost in the 1980s with the growing ability to use DNA rather than morphology to infer deep phylogenies (Field et al. 1988; Raff et al. 1989). Emil Zuckerkandl and Linus Pauling (1965) had laid the foundations for the study of molecular evolution in a seminal paper, pointing out that genes could evolve as "molecular clocks," and that protein sequences could be used to construct the phylogenetic relationships of organisms. When the technology was developed to rapidly sequence nucleic acids, gene sequences took over this role, and made possible molecular-based phylogenies for animals and plants. Evo-devo papers now abound with thickets and forests of phylogenetic trees.

By a decade after the 1981 Dahlem conference, a more inclusive paradigm of work had arisen in which paleontology, molecular systematics, and developmental genetics could be applied in non-model clades of evolutionary interest. The dominance of developmental genetics, most of which was "borrowed" from the study of model organisms such as *Drosophila*, set much of the experimental program in the following years. Candidate genes that were first identified in model systems were then isolated from non-model organisms in a wide swath of Evo-devo studies. These methods were adapted to allow for the manipulation of the expression of specific genes in a variety of species. That is still largely what is done, although genomic approaches are now allowing searches for non-candidate genes in a wider range of organisms (e.g., Choi et al. 2010).

## 11.3 Framing the New Science of Evo-devo

In 1975, I started to organize my thinking about Evo-devo by creating a course for graduate students.[1] I also began writing a book to explore and synthesize the components of a discipline, envisioning that it could help steer the formation of a modern Evo-devo. I asked my geneticist colleague Thomas Kaufman to join me. Thom was engaged in the study of the homoeotic genes that control the layout of body development, and he would assume a major role in the revolution of our understanding of the genes that regulate development in the animal kingdom. We

[1] The term we first used was Devo-evo. By consensus it was eventually changed to Evo-devo, which was deemed less awkward and more meaningful (Hall 2000).

taught the 1977 class together as a way of developing the content of the book, and drafted an outline. *Embryos, Genes, and Evolution* was published in 1983.

*Embryos, Genes, and Evolution* was the first attempt to link evolution with the new developmental genetics, and it was the first book to map the direction that Evo-devo would take. We integrated the older traditions that focused on the study of the evolution of development with new experimental approaches being created in developmental biology. We had to borrow most of the experimental examples we cited at the time from work done for reasons other than Evo-devo, but we aimed to stimulate the growth of a new field that would create its own research questions and experimental systems. We suggested several future directions, although our examples now seem primitive because the field has made so much progress. I would follow up on promoting Evo-devo through writing *The Shape of Life* (1996) to explore new ideas and the development of the discipline. I joined with Wallace Arthur, Greg Wray, Sean Carroll, and Michael Coates in 1998 to launch a journal dedicated to Evo-devo: *Evolution & Development*.

### *11.3.1 The Shape of Life*

The themes I addressed in *The Shape of Life* were broadly similar to those of *Embryos, Genes, and Evolution*, but they were informed by the revolution in developmental genetics and I discussed studies explicitly targeted at Evo-devo that had taken place in the intervening years. I also considered the effects of current Evo-devo studies on the roles of the classical concepts of heterochrony and constraint, including how to interpret the developmental hourglass. Further, I formulated a version of the concept of modularity in development at the same time that Günter Wagner (1996) was forging other aspects of the concept. In *The Shape of Life*, I suggested that modules are the units in which developmental genetics forms elements of a developing animal, and that modules can undergo evolution. Modules are semi-autonomous domains that progressively form in a developing animal. They can range from structures like eyes, to embryonic territories, to domains of the brain. Modules possess discrete gene networks, each resulting in a particular, localized and temporally distinctive, pattern of gene expression.

Modules are important because they can be both the units of evolutionary change and of constraint. Existing modules evolve, and new modules get added as new structures evolve. New modules become integrated into systems of cell-cell communication, adding structural and genetic complexity, but do not require the invention of new regulatory genes. In the course of evolution, as modules become more deeply integrated into highly interactive developmental systems, they may become less likely to evolve than modules with fewer connections. Some body plan features are stable because they underlie entrenched integrative roles, and a module may become so well integrated that the probability of reorganizing a deeply integrated feature becomes extremely unlikely, although not impossible. The body plans of animal phyla established in the Cambrian are examples. Despite

extensive evolution of novel features in some phyla, the basic ground plans of each phylum have remained recognizable for more than 500 million years, and no new phyla have arisen since the Cambrian.

This observation leads to the hypothesis that some modules should be sources of developmental constraints that act as a brake to slow down evolution. In other aspects, modules—as genetically defined units—can be "plugged in" somewhere else in the developing organism. The co-option of a module allows novel times or locations of expression of a set of genes. The result is the evolutionary integration of an existing module into a new role, location, or time in development. Changes in regulation of timing (heterochronies), changes in strength of interactions, or becoming subject to new upstream control elements all make modules important entities that are available for natural selection to operate on. Co-options of modules have been crucial in the evolution of development. For example, newly incorporated modules would not yet be vital to the development of the core defining elements of a body plan. Therefore, new modules could give rise to important new features that, because they are still developmentally peripheral to the core of the animal's body plan development, could evolve rapidly.

The appendages of vertebrates provide a good example of evolutionary developmental integration. Vertebrates originally lacked appendages, but acquired fins by the incorporation of existing regulatory genes into the evolution of a new modular structure (the developing fin bud). This was added to and integrated into the basic vertebrate body plan. Regulatory networks were co-opted in the evolution of a novel module that added an entirely new feature (Tabin 1992).

At this time I was led to think about the apparent extreme conservation displayed at a common point of ontogeny in animals. For vertebrates, this is referred to as the phylotypic stage, midway through development (see Freeman, Chap. 10, this volume). Animals that exhibit a related body plan most closely resemble each other at this stage, although earlier and later stages of development diverge. In *The Shape of Life*, I depicted development as an hourglass, with evolutionarily divergent embryos at the top and divergent adults at the bottom. The phylotypic stage lay in the narrow waist of the hourglass. I suggested that phylotypic stage conservation came from a delimited phase of maximum linkage among developmental modules involved in building the body plan. Denis Duboule (1994) presented a similar hourglass diagram, which he proposed arose from the role of Hox gene organization and their conserved role in laying out the body axis.

Recent studies confirm that there is something special about the developmental genes transcribed during the phylotypic stage. Kalinka et al. (2010) and Domazet-Loso and Tautz (2010) observed a genomic hourglass that corresponds to the developmental hourglass. In two phyla, represented by zebrafish and species of *Drosophila*, they showed that the expression of suites of genes are conserved in key developmental processes involved in laying out the body plan. Irie and Kuratani (2011) reported a similar result. An important correlation exists between the expression of genes that evolved during the origins of animal body plans in the Cambrian radiation and their expression in the phylotypic stage of living animals. This result provides a foundation for considering how deep developmental-genetic constraints influence evolution.

Still, a need for caution remains; just because something is conserved over long periods in evolution does not mean that it can't change in the face of strong selection. For example, *Hox* gene order is highly conserved, but it has changed dramatically in sea urchins (Cameron et al. 2006). Many aspects of genome order have changed in the vertebrate relative *Oikopleura* (Denoeud et al. 2010). These lessons have been manifested in my own investigations of the sea urchin pluteus, a mode of larval development that has been conserved for at least 200 million years, but also dispensed with rapidly by several lineages (Raff and Byrne 2006).

## 11.4 My Steps to Experimental Evo-devo

In 1985, I began working with Beth Raff, Norm Pace, Kate Field, Gary Olsen, and other colleagues on building a phylogeny of metazoan phyla by rRNA sequencing. This was the first large-scale effort using rRNA sequences to infer a phylum-level phylogeny of the animal kingdom (Field et al. 1988), and was followed by an ever more sophisticated set of molecular phylogenies from several laboratories over the next two decades. A better comprehension of the relatedness of phyla and a high degree of resolution has been obtained with larger databases and more advanced methods (e.g., Aguinaldo et al. 1997; Hejnol et al. 2009).

At that time, I also started a quest for an experimental system that could be developed to explore Evo-devo questions. I reasoned that because animal development arose in the sea, marine species should reveal key features of the Evo-devo of early animals, such as the origins of larval forms. The general direction in Cambrian evolution was from direct development to indirect-developing larvae in a number of phyla (Nützel et al. 2006; Raff 2008, 2009). But, in some phyla, there have been evolutionary shifts back to modes of direct development—many quite recent and rapid, driven by life history demands. Could we find marine species with divergent development that are closely related to species with the conserved developmental mode for a particular clade? These had to be readily obtained and the study of their development had to be experimentally tractable.

The ontogeny of indirect-developing sea urchins has been well studied, and provided a solid foundation for the study of larval evolution. Thus, I sought a sea urchin Evo-devo system where three crucial kinds of information would be abundantly available for comparisons of basal features to derived ones: ancestral developmental states, experimental tools, and derived developmental states. A species where there have been substantial changes in development in the span of a short phylogenetic branch should supply this information. With that aim, I started work in 1985 on the sea urchin *Heliocidaris erythrogramma* as a model for embryo and larval evolution. This is a common Australian intertidal sea urchin that has evolved a derived, direct-developing larva from the ancestral pluteus retained by its sister species *H. tuberculata*. *H. tuberculata* has a characteristic pluteus larva, and yet the two species diverged only four million years ago (Zigler et al. 2003). Finally, *H. erythrogramma* embryos are experimentally accessible for culturing, microinjection, micromanipulation, in situ

hybridization, and other methods generally used to study indirect-developing sea urchins, allowing comparable data to be collected.

Our first major studies of *H. erythrogramma* focused on its embryonic cell lineages and the reorganization of embryonic development. Greg Wray determined cell lineages by the injection of fluorescent dyes into cleavage stage embryos (Wray and Raff 1989, 1990). Surprisingly, its cell lineages were highly modified from the lineages reported for *Strongylocentrotus purpuratus*, which develops via a pluteus (Cameron et al. 1987). Jon Henry showed that there had been major changes in determination, with the left-right axis being determined in the egg rather than during embryogenesis (Henry and Raff 1990; Henry et al. 1990; Raff and Smith 2009). These studies began to paint a striking picture—deeply entrenched features of early development could evolve radically and rapidly—and set the stage for a suite of investigations into the role of gene expression in the evolution of embryonic development. We also garnered insights into how the evolution of development was entwined with ecology and population structure. In collaboration with Steve Palumbi, we demonstrated that unlike sea urchins whose plutei could disperse long distances, an examination of population structure using mitochondrial genotypes revealed that *H. erythrogramma* larvae and genes did not travel far from their maternal home (McMillan et al. 1993). Therefore, developmental mode could have a powerful impact on population-level evolution.

## 11.5 Cross Species Hybrids and Parallel Evolution

In the late 1990s I joined with Beth Raff to study the extent of developmental genetic divergence between *H. erythrogramma* and *H. tuberculata* (Raff et al. 1999, 2003). We took the approach of making hybrids between the two species. Beth worked out a technique that allowed cross-species fertilization. We expected that if hybrids resulting from fertilization of *H. erythrogramma* eggs with *H. tuberculata* sperm (*H.e. X H.t.*) produced a larval form then we might see some hybrid features. We hardly expected what we actually saw—the hybrids were viable, and developed through metamorphosis into a juvenile sea urchin. Hybrids exhibited a novel phenotype that was dependent on the *H. erythrogramma* maternal program, although both genomes were expressed and features of the pluteus appeared as development proceeded. Notably, *H. erythrogramma* lacks a larval mouth or pluteus arms. These features were restored in the hybrid. A significant observation was that hybrids in which *H. tuberculata* eggs were used (*H.t. X H.e.*) failed to develop larval axes and died as gastrulae. This asymmetric result indicated that aspects of dorsal-ventral and left-right body axis specification had shifted to maternal control in *H. erythrogramma*, whereas they are controlled zygotically during early development in the ancestral pluteus.

By means of a second hybrid study (Raff et al. 2003), we tested the idea that most of the evolutionary change occurred in the *H. erythrogramma* branch subsequent to the divergence from *H. tuberculata*. We knew that crosses between indirect-

developing species that had diverged long ago but both developed via a pluteus often developed into a hybrid pluteus, indicating conservation. So we fertilized *H. erythrogramma* eggs with sperm from a pluteus-making species (*Pseudoboletia maculata*), which is about forty million years distant. The *H.e. X P.m.* hybrids looked very similar to those of *H.e. X H.t.*, which supports the hypothesis that plutei retain more conserved gene regulation networks than do direct developers like *H. erythrogramma*. Indeed, hybridization of the two indirect-developing species, *H. tuberculata* and *P. maculata* give rise to hybrids that show larval features derived from both parents, and make an overall well organized pluteus.

## 11.6 Axis Formation, Signaling, and Heterochronies

Because axis formation is crucial to embryonic development, and because our cell lineage and cross-species hybrid studies showed that axis formation was profoundly modified in *H. erythrogramma*, unraveling the evolutionary changes in axis formation became crucial. We began by studying the Wnt signaling cascade involved in establishing the Animal-Vegetal (A-V) axis in indirect-developing sea urchins (Kauffman and Raff 2003). We predicted that the formation of the A-V axis (the primary axis), which arises from the operation of a system set up during oogenesis in both *H. erythrogramma* and indirect developing sea urchins, should have a similar mechanism. The molecular execution of the A-V axis mechanism in indirect-developing sea urchins takes place in early ontogeny, and had been well defined (Angerer and Angerer 2000). That information gave us the starting point for studying the molecular basis of evolutionary changes in axis formation in the highly modified *H. erythrogramma*, but we also had to devise methods for experimentally investigating its large eggs—100 times the volume of the average indirect-developing egg. We found that the same *Wnt8* gene expression system underlies execution of the A-V axis in *H. erythrogramma* as in indirect-developing species but there were a few differences in timing. The similarity is important in anchoring other aspects of axis formation. These studies facilitated the development and validation of methods for generating and understanding developmental phenotypes produced by gene over-expression or knockdown in *H. erythrogramma*.

We followed up by examining other genes involved in the formation of the two other larval axes: Dorsal-Ventral (D-V) and Left-Right (L-R). Wilson et al. (2005a, b) showed that expression of the gene *Otx* was important in the reduction of the oral (ventral) side in *H. erythrogramma* development, including the loss of the larval mouth. In the case of the L-R axis, we discovered two major evolutionary changes. The first—noted above—was that determination of the L-R axis had shifted to being maternally controlled in *H. erythrogramma*. The second was that operation of the gene *Nodal* was crucial to the execution of both D-V and L-R axes, as in indirect development, but there were striking alterations in developmental timing that point to a role for heterochronies, as well as a downshift in levels of gene activity (e.g., *Otx*), in the radical evolutionary changes to development exhibited by *H. erythrogramma* (Smith et al. 2008; Raff and Smith 2009).

## 11.7 Intermediate Stages in the Evolution of Direct Development

Few things in the study of evolution are more satisfying than discovering an intermediate, transitional state. These prize discoveries are usually transitional fossils. In the case of embryos and larvae, this is a pretty rare possibility. However, there is a large diversity of living larval forms, even within a clade that is largely conservative in development, such as sea urchins. The majority of species that have been studied exhibit a feeding pluteus larva. A smaller proportion of species (~20 %) have modes of development in which the pluteus has evolved into a non-feeding larva, as in *H. erythrogramma*. A miniscule number have larval forms that appear intermediate in egg size and developmental mode between the two extremes.

We chose to examine one of these rare intermediates to glimpse the nature of the first steps in evolving a non-feeding direct-developing larva from a pluteus. The sea biscuit *Clypeaster rosaceus*, collected in Panama with our colleagues Haris Lessios and Kirk Zigler, is distinguished by having a large egg and develops to metamorphosis via a pluteus larva in an unusual fashion (Emlet 1986). The pluteus of *C. rosaceus* does not need to feed in order to undergo metamorphosis, which it does rapidly (in about seven days, instead of four weeks). We saw this unusual developmental pattern as a possible analog for the missing evolutionary intermediate between the pluteus and the *H. erythrogramma* larval form. The plutei of *C. rosaceus* are opaque and, when sectioned, we observed that the formation of the left coelom was highly accelerated, a feature of direct development associated with an early onset of the formation of adult features (Smith et al. 2007). This finding suggested that the features selected upon in the evolution of direct development might be both rate of development of a key feature of adult development and independence from feeding in the plankton. Direct development is supported by the nutrients stored maternally in the large egg, and *C. rosaceus* is almost as great in egg volume as *H. erythrogramma*. Loss of pluteus features and gains of other novel features follow these initial steps (Byrne et al. 1999; Love and Raff 2006).

## 11.8 Evolution of Larval Forms in the Metazoan Radiation

I've been discussing the origin of one direct-developing form, *H. erythrogramma*, which evolved recently from an indirect-developing ancestor with a feeding pluteus larva. But that's not the full story. Paleontological and phylogenetic data suggest that early metazoans were direct developers, and that indirect development with distinct larval forms arose in some lineages during the Cambrian (Raff 2009). Ecdysozoans and chordates are primitively direct developers, whereas lophotrochozoans and the clade containing echinoderms and hemichordates independently evolved indirect development. This means that all clades within the phylum had evolved feeding, indirect-developing larvae before the origins of crown group

echinoderms. We put forward a possible mechanism by which gene co-option from the adult might have allowed for the rapid evolution of the first indirect-developing embryos (Sly et al. 2003).

As crown group echinoderms, sea urchins are indirect developers primitively. The pluteus larva was present in the Jurassic, but we don't know if this larval form was characteristic of Paleozoic echinoid clades or if other indirect-developing feeding larvae were present. The modern structure of the adult sea urchin test only appears in the Triassic after the Permian extinction. Direct-developing larvae like that of *H. erythrogramma* do not represent a return to the direct-developing larva of the echinoderm plus hemichordate ancestor. However, one characteristic of both modern and ancient direct developers is a large, food rich egg (Nützel et al. 2006; Raff 2008, 2009). The fossil record of the Precambrian and Cambrian is consistent with the prediction of large egg sizes for the Cambrian (Steiner et al. 2004), with smaller egg sizes (correlated with indirect-developing larvae) appearing later in the Cambrian, in at least some lineages (Nützel et al. 2006).

## 11.9 Embryos, Evolution, and Homology

One of the most significant points illustrated by our studies of *H. erythrogramma* is the flexibility of modular evolution. Some gene expression territories of *H. erythrogramma* (modules) are arguably homologous to those characterized for indirect-developers, although gene expression and morphological features may be shifted heterochronically or heterotopically. The ectoderm of *H. erythrogramma* represents a different kind of modular evolution. Overall, the larval ectoderm of *H. erythrogramma* is homologous to that of the pluteus, but there is no unambiguous correspondence to the aboral and oral ectoderm territories of the pluteus. The two obvious ectoderm modules in *H. erythrogramma* are the ectoderm lining the vestibule and its appendages ('vestibular'), and the ectoderm that covers the rest of the larva ('extravestibular'). Vestibular ectoderm arises shortly after gastrulation, and contains a quarter of the cells produced in the cleavage of the embryo. In indirect-developers, the vestibular ectoderm arises late in larval development from a small region within the oral ectoderm territory.

Raff and Sly (2000) showed that skeletogenic, coelomic, and vegetal plate gene expression territories are conserved in *H. erythrogramma*, although they arise from cell lineages distinct from those of the pluteus. The ectoderm, as in indirect developers, is divided into modular territories. However, an oral ectoderm territory characteristic of the pluteus is absent in *H. erythrogramma*. The oral ectoderm is restored in hybrids of *H. erythrogramma* eggs fertilized by *H. tuberculata* sperm (Sect. 11.5). Thus, the embryonic modules could evolve by changes in the expression of dominant regulatory genes within territories and entire modules could be eliminated in evolution. Love and Raff (2006) built on the results of Raff and Sly (2000) using two concepts of homology to understand the transformation seen in *H. erythrogramma*. We exploited Müller's (2003) concept of "organizational

homology," which provides a basis for the separation of historical continuity from evolutionary changes in underlying generative mechanisms. Although the larval ectoderms of *H. erythrogramma* are derived from pluteus ectoderms, they no longer correspond to the pluteus oral and aboral ectoderm territories.

In the pluteus, the ciliary band separates the ectoderm territories. *H. erythrogramma* has a ciliary band as well, but it does not separate ectoderm territories. It lies instead *within one* of the *H. erythrogramma* ectoderm territories (the extravestibular), not *between two*. Furthermore, there is no clear way to establish homology on the grounds of molecular markers between the pluteus aboral ectoderm and the extravestibular ectoderm of *H. erythrogramma*, nor between the pluteus oral ectoderm and the vestibular ectoderm *H. erythrogramma*. These results suggest a sort of "blending" of downstream markers and therefore the *H. erythrogramma* ectoderm territories appear to be novel ectoderm modules. In terms of Wagner's (1996) ideas about the role of parcellation and integration in the evolution of new homologs, the extravestibular ectoderm of *H. erythrogramma* is an integration of two previously separate territory elements or modules of the pluteus (oral plus aboral ectoderms); they have been incorporated to produce a single novel territory.

We only have a preliminary hypothesis about how this might have occurred. Smith et al. (2008) (see also Raff and Smith 2009) found that although determination of L-R and D-V axes is maternal, their execution is similar to that of the pluteus via the roles of *Nodal* expression defined by Duboc et al. (2004, 2005). Thus major upstream gene regulation that sets apart vestibular and extravestibular ectoderms resembles that of oral and aboral ectoderms, but downstream gene expression patterns have been modified, with a mixing of formerly discrete patterns of downstream gene regulation. The loss of a role for *Otx* in left side differentiation in *H. erythrogramma* (Wilson et al. 2005a, b) hints at regulatory changes, but we are as yet unable to connect the gene regulation dots that underlie the integration pathway that has fused old modular homologs into a new unit.

It is notable that although *Nodal* expression functions in the same way in *H. erythrogramma* and pluteus development, there are dramatic heterochronies in the onset of its morphogenetic consequences. The mechanism behind these heterochronies is not known, but *H.e. X H.t.* hybrids exhibit heterochronic changes distinct from both of the parental species. This suggests that heterochronies may arise from changes in gene regulatory network interactions.

## 11.10 Soft-Bodied Fossils and Fossil Embryos

Fossils can provide an important source of information for Evo-devo. Although fossils of adult soft-bodied early animals provide startlingly vivid and detailed views of creatures not preservable in the usual way (e.g., as bones, teeth, and shells), they aren't the only remnant of the metazoan radiation preserved in the soft-bodied fossil record. Fossilized developing embryos and larvae can inform our ideas of the evolution of development. In 2005, Phil Donoghue, a paleontologist at

the University of Bristol, challenged Beth and me with a simple sounding question: "Could a marine embryo be fossilized?" The background to this was the long-debated case of Late Precambrian fossil embryos from Doushantuo, China. These fossils look like cleaving embryos, comparable in size to *H. erythrogramma* (Xiao et al. 1998; Hagadorn et al. 2006).

We quickly found that the fastest destructive agent of a newly killed embryo was autolysis of cell components by its own enzymes. This problem could be blocked easily by the inactivation of proteins, which we first did using beta mercaptoethanol (Raff et al. 2006). We later discovered that holding the embryos in anaerobic seawater accomplished the same result, and via a more geochemically feasible process (Raff et al. 2008). The answer was thus, yes—marine embryos can be fossilized. But the results had greater implications for understanding a more general problem: unraveling the mechanisms that made possible the entire range of soft-bodied preservation observed in Cambrian animal faunas, as well as those from other geological eras.

We went on to show that bacteria, which would seem to be inexorably destructive agents, exhibit remarkable suites of interactions with killed embryos. Some marine bacterial strains indeed destroy cellular structure and consume dead embryos within a few days. Others invade the tissue and rapidly consume it, but form is preserved in an extraordinary way. These strains produce a stable biofilm that replaces—with fidelity of form—the structure of the embryo. We labeled these biofilms "pseudomorphs" (Raff et al. 2006). In subsequent experiments, we have found that embryos replaced with bacterial biofilms (pseudomorphed) can, in the appropriate conditions, allow or facilitate the deposition of minerals, including calcium phosphate and iron sulfides (Raff et al. 2008; unpublished studies).

This last twist of research with *H. erythrogramma* may seem like a peculiar divergence away from Evo-devo, but it's really a part of a deep connection between paleontology and Evo-devo (Raff 2007). Fossils reveal ancient extinct body plans; they directly inform Evo-devo by giving it a past. Information on character states from fossils can inform phylogenetic trees by revealing the direction of the evolution of developmental features. Fossils also provide an evolutionary clock. The fossil record, along with radioisotope decay dating, is the source of the primary data that we use to date past events. Divergence time estimates and estimates of the rates of "molecular clocks," which provide rates of developmental evolution, also come from the geological record. Thus, fossils can set boundaries for evolutionary hypotheses that are generated from living developmental systems, and for predictions of ancestral development and morphologies.

Finally, although fossils rarely yield data on developmental processes, the extraordinary preservation of soft-bodied animals and of embryos has the potential to tell us a great deal about a small sample. The taphonomic studies we are prosecuting using *H. erythrogramma* embryos are a novel way to understand how that fossil record was made and what information it is capable of carrying.

## 11.11 Dahlem: One More Thing

What did I learn from the 1981 Dahlem conference? Was it a revolutionary moment? Like many events in our personal histories, the answer is not entirely clear. I don't think the conference was revolutionary, but it had the abrupt effect of starting to sort out how the discipline might proceed. I had already developed a view of the complex of components that should compose Evo-devo, and Thom Kaufman and I had completed much of the work on *Embryos, Genes, and Evolution*. I met a number of people involved in the pioneering efforts occurring on multiple fronts at that time, and formed acquaintanceships with investigators whose ideas and work have contributed enormously to Evo-devo over the years.

Additionally, I gained several key insights from early approaches to Evo-devo. First, some approaches, such as those focused on rules of pattern formation, could be quite removed from biological mechanisms, especially from genetic mechanisms. Second, we had to move beyond traditional concepts like heterochrony. Third, the most direct strategy for understanding the evolution of development would likely come from applying molecular biology and genetic methods to investigate how development was regulated. Finally, I realized that I needed an informative experimental organism and more knowledge about life history evolution. Fortunately, my first exposure to the latter came from working in the panel that considered life history at the 1981 Dahlem conference, which John Bonner invited me to take part in. Within a few years, the experimental organism came in the form of *H. erythrogramma* (Sect. 11.4). The rest is history.

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# Chapter 12
# Dahlem 1981: Before and Beyond

**Armand J. de Ricqlès**

## 12.1 Introduction: An "Orthodox" Training

Scientists are usually not trained to analyze the intellectual pathways they more or less unconsciously follow during their careers. They may be somewhat aware of the various pitfalls induced by personal remembrances and of the unconscious "reconstructions" or rationalizations linked to autobiographies, not to speak of the *pro domo* pleading. But it may be profitable in trying to understand patterns of conceptual change. Therefore I will begin with a review of my intellectual background and situation during the years immediately preceding the 1981 Dahlem conference, and how this might explain why I was selected to participate.

I started as an assistant in comparative anatomy at the Science Faculty of Paris University in 1961, after a standard curriculum in biology and geology. Contrary to a long tradition among English (and French) speaking historians of biology who, by and large, convey the simplistic idea that French biologists remained Lamarckian up to the 1960s–70s (e.g., Mayr and Provine 1980), the intellectual situation among evolutionary biologists was much more subtle and interesting in France during the immediate post-war years (Grimoult 2000), the period of my undergraduate education (late 1950s/early 1960s). As well recorded in Grimoult's extensive and uncompromising survey (2000), every well-known university professor in the various domains of natural history and biology—paleontology, genetics, marine biology, entomology or embryology—were committed evolutionists. But for them this meant a belief in Darwinian "*descent with modification*" or in the *theory of the reality of evolution* (Løvtrup 1982), rather than in the all encompassing, almighty explanatory power of the Darwinian mechanism of *natural selection* (Gayon 1988). This created a very peculiar intellectual situation for students. On the one hand, the

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data emerging from every quarter of natural history in favor of evolution was conveyed enthusiastically; on the other hand, the underlying mechanisms proposed were viewed with much caution. A pluralistic approach to evolutionary mechanisms was often advocated, with the idea that natural selection was obviously a part of the package but was not working alone; much remained to be discovered about the mechanisms of evolution. To name only one individual of that era, the much-maligned Professor Pierre-Paul Grassé, editor of the great *Traité de Zoologie*, was an enthusiastic and energetic evolutionist (in the sense just defined), who effectively promoted evolution to the general public through the media. Although he is described as a despiser of genetics, it is critical to underline that Grassé organized in his own laboratory the full practical teaching curriculum about Mendelian genetics in the fruit fly and other models, and this material was mandatory for all biology students in Paris.

It is true that Lamarckism, or more precisely neo-Lamarckism, had been an almost official theory of evolution in the University of the Third Republic, roughly from the 1870s to the 1930s (de Ricqlès 2008, 2010; Loison 2010). But in spite of the supposed influence and power of the "hyper tardive Lamarckians" (as Grimoult depicts them), the practical situation had changed considerably by the late 1950s. First, Mendelian genetics was taught at school on a generalized scale to all pupils. Second, the turmoil caused in France by the "Lysenko affair" and the Communist party enforcing belief in the "heredity of acquired characters" from 1948 to 1953 (cf., de Ricqlès 2006) ultimately had devastating effects on neo-Lamarckism. Third, it is generally not recognized abroad that the synthetic theory of evolution was rather well known in France at the time. It was formally introduced to France by a Rockefeller Foundation sponsored meeting organized by the CNRS as early as 1947 (de Ricqlès 2008). At the meeting, the American paleontologist George Gaylord Simpson explained the synthetic theory to his French colleagues, which acted as a revelation to a new generation of young French scientists in the aftermath of the second world war. They quickly became like apostles of the Modern Synthesis. Among them were paleontologists such as Henry Tintant and Louis Thaler, geneticists like Claudine Petit, and comparative anatomists and developmental biologists like Charles Devillers (Devillers 1991). This generation, in turn, became the mentors of my own generation of students, who thus became intimately familiar with the synthetic theory of evolution; it was taught to us almost as an orthodoxy. This situation was enforced by the translation into French of major books, like Simpson's *Tempo and Mode* as early as 1950 (Simpson 1950, 1951); by the publication of the seminal 1947 Meeting (Piveteau 1950); and, by various analyses of the Modern Synthesis, most notably in the masterful historical review of evolutionary theories by Paul Ostoya, the uncle of Louis Thaler, and editor of the respected monthly *La Nature* (Ostoya 1951).

To cut a long story short, my generation learned biology within the framework of the Modern Synthesis and Mendelian genetics but—at least for some of us—the intellectual environment did not allow us to easily accept the Modern Synthesis as a fully developed and completely satisfactory answer to the issue of biological evolution. There was an acknowledgement that the synthetic theory was the current

"least bad" intellectual package available to account for actual evolutionary mechanisms (e.g., de Ricqlès 1979a), But there was also a reluctance to fully embrace the theory in all of its details for several reasons:

(i) *The propensity of the theory toward triumphalism*. The Modern Synthesis (potentially) explained all biological evolution; there was nothing outside of the theory worth exploring in order to understand the history of life and its current state.

(ii) *The propensity of the theory toward sclerification*. The Modern Synthesis too often turned into dogma. The "right" mutations selected by the "right" pressures from the environment will always account for the observed adaptive results, given ad hoc explanatory scenarios, generally impossible to test (Devillers and Ricqlès 1982). Hence the organism was easily pulverized into various traits, each of them receiving its proper adaptive/selectionist explanation. Nothing could limit the effects of natural selection to exquisitely shape organisms and refine their functions: its explanatory power seemed implausibly boundless.

(iii) *The organism was neglected and forgotten*. Comparative and evolutionary biology before and after Darwin (including Darwin himself) had put great emphasis on the morphologies and functions of individual organisms, shown in the sciences of systematics, comparative anatomy, and physiology. With the advance of population thinking, there was a shift away from the organism. The focus became studying the quantitative fate of genes within populations, thus "jumping over" the organism level. This was resented bitterly by some of us, especially those more interested in comparative morphology and systematics, "the soul of natural history" (as Darwin put it). There was also a palpable tension or paradox because, after all, the individual organism remained the main unit of selection within Darwinian orthodoxy, as well as the end result of the interactions among genes and the environment during ontogeny.

(iv) *The lack of developmental biology, morphogenesis, and embryology within the Modern Synthesis*. In spite of the efforts of some scientists, such as Sir Gavin de Beer, Conrad Waddington, and Richard Goldschmidt, the issue of ontogenesis—the development of the organism—was treated as a "blackbox" of little interest and relevance for the study of animal evolution. In so doing, the Modern Synthesis departed from centuries of intellectual tradition, which had always tried to link and decipher (even through odd and spurious ways) the significance of individual ontogenesis by reference to some larger order "developments" (Mengal 1993). Such ideas took various shapes in pre-Darwinian times, from idealistic metamorphosis, to the speculations of *Naturphilosophie*. In the framework of evolution, the wider term of comparison for ontogeny finally took the form of *phylogeny*, the story of species lineages. Thus the idea reached its mature form during Darwin's life under Haeckel's "fundamental biogenetic law" that ontogenesis is a brief recapitulation of phylogenesis (1866).

Even before the emergence of the Modern Synthesis, the Law of Recapitulation, in spite of its popularity and some heuristic value, experienced devastating criticisms that stemmed from both the advances in Mendelian genetics and discoveries surrounding paedomorphosis and neoteny. For instance, Garstang (1922) rephrased Haeckel's dictum as, "Ontogeny does not recapitulate phylogeny, it creates it." For all that, the situation of developmental biology relative to the Modern Synthesis from 1940s to 1970s could be best summarized as a form of apartheid, at least in the vertebrate realm (de Ricqlès 2004). Many evolutionary researchers with a deep interest in developmental biology chafed under this situation and sought to integrate development into a wider evolutionary synthesis. This was especially the case with one of my mentors, Professor Charles Devillers (1914–2000), who lamented the lack of developmental biology within the orthodoxy of the Modern Synthesis, and was an advocate for the birth of a new developmental genetics that he was fortunate enough to see dawn well before his life's end.

(v) *The lack of a distinction between evolutionary patterns and evolutionary processes within the Modern Synthesis, including independent methodologies to study them*. Because the only level where actual evolutionary process could take place were populations, specific groupings were favored and supra-specific taxa were viewed as practical artifacts destined to express biodiversity through formal Linnean categories. Accordingly, the Modern Synthesis emphasized the construction of scenarios to explain evolutionary processes only at the infra- or peri-specific levels (de Ricqlès 1997). Conversely, macroevolution merely described the end-result of microevolutionary processes accumulated over geological time. And since macroevolution only described *patterns,* no distinct evolutionary processes could exist at such supra-specific levels. Nevertheless, generalizations such as "mammals evolved from reptiles" were a part of the common phraseology within the vulgate of the Synthesis. The philosophy of phylogenetic systematics (cladistics) provided a basis to question these premises and the practices of the Modern Synthesis (the so called "new systematics") as soon as the work of Willy Hennig (1965, 1966) became known outside of the German-speaking realm (mid-1960s).

During the 1960s and 1970s, my own technical expertise became histology, comparative anatomy, and vertebrate paleontology. Because I was especially interested in "lower" tetrapods, I first focused my histological knowledge on the morphogenesis of the skeleton in extant amphibians (de Ricqlès 1964–65). Later, I developed methods in paleohistology to study developmental features of paleozoic and mesozoic tetrapods. This was accomplished within a broad comparative framework, taking into account the Synapsids (mammalian lineage) and, subsequently, reptilian lineages including crocodiles, dinosaurs, and birds (e.g., de Ricqlès 1975, 1976, 1980).

## 12.2 Conceptual Perspectives on Evolution and Development Circa 1981

Many of the grounds for dissatisfaction with the Modern Synthesis described above, and the themes of research interest shared by those of us discontented with it, were central elements of the 1981 Dahlem conference. For example, I met Stephen Jay Gould in 1977, having exchanged correspondence with him earlier, and his involvement in the Dahlem conference mirrored my own dissatisfaction with the synthesis and interest for research subjects outside of it. Among the subjects of common interest to us was—first and foremost—the importance of heterochronies in evolution (a subject interest also shared with Dave and Marvalee Wake). The use of urodele amphibians as an extant model to analyze heterochronies as possible evolutionary processes among fossil stegocephalians and amniotes has remained an important subject of study ever since (e.g., de Ricqlès 1975, 1979b, 1989). The possibility of pursuing informative analyses of late development among fossil vertebrates followed thanks to skeletal histology and paleohistology. Some examples of this work are the skeletal heterochronies in the secondary adaptation of tetrapods to aquatic habitats (e.g., de Ricqlès and Buffrenil 2001; Houssaye et al. 2008) and growth patterns among archosaurs (e.g., Horner et al. 2001; de Ricqlès et al. 2001; Main et al. 2005).

Much more generally, the relevance of heterochronies for the study of relationships between developmental and evolutionary biology, and the integration of development into evolutionary thinking, has blossomed as a most important consequence of Dahlem 1981 (e.g., Ricqlès 2004; see also Hanken, Ch. 4, this volume). Important monographs, popular textbooks, and hundreds of specialized research papers have followed on the heels of this inspiration, bringing an important input of the morphological sciences into the current Evo-devo synthesis.

Some Dahlem 1981 participants (including myself) also shared views on very general, even philosophical, aspects of evolutionary biology. These included the repudiation of simple, linear deterministic causation as a relevant explanation of evolution. Historical contingencies and the chance convergence of multiple causal factors were viewed as essential aspects of evolutionary history, following views already clearly expressed by Cournot (1872). Accordingly, even if retrospective explanations can be formulated, predictions of evolutionary trajectories are hardly possible (other than the trivial-mechanistic). This conclusion was linked to the contrast between nomological (law-seeking) and palaetiological (historical) sciences, and the need for evolutionary analysis to integrate both of them. An intrinsic unpredictability stemmed from the historical component of evolution, and a similar unpredictability (but one that could ultimately be reduced to causal explanations) was reflected in the emergence of new properties along the succession of ascending levels of biological organization.

There was also a conviction that not all biological structures could be understood merely as actual (or past) adaptations resulting from the operation of natural selection, which paved the way for the concept of *exaptation* (Gould and

Vrba 1982). Other substantial issues underplayed by the Modern Synthesis were (a) the significance of *structural* conditions and properties of biological materials (e.g., architectural, topological, geometrical, and dimensional), as previously expressed by Seilacher (1970), and, (b) the actual *historical* (phylogenetic) situations that acted as pre-established "constraints" from which (and within which) natural selection had to operate. Finally, there was discomfort with the way proponents of the Modern Synthesis contrasted microevolution and macroevolution. Here there were a variety of opinions, including some that restricted macroevolution to patterns only, and others who regarded the span of microevolution to macroevolution as a *hierarchy of processes* rather than a doctrinal opposition or dichotomy.

Gould (and others) had already published on important aspects of these approaches and views by the time of Dahlem 1981 (Alberch et al. 1979; Gould 1977, 1980a, b). Over the next three decades Gould elaborated on these themes (e.g., de Ricqlès 2002, 2010), culminating in his *magnum opus* (Gould 2002). But Dahlem 1981 was far from simply a meeting for expressing a consensus of dissent. For example, I disagreed with Gould about the appropriate theoretical perspective for an evolutionary approach to systematics. Gould accepted a version of "Mayrian" evolutionary systematics, whereas I was an advocate in favor of cladistics. I never understood why Gould did not readily embrace cladistics, which seemed to me a necessary part of his hierarchical view of evolution. If macroevolutionary processes above the species levels exist, then they require (in my view) treating historical/genealogical/genetical entities (clades) as realities in (or of) nature. As a consequence, material processes, such as clade selection, could apply to them. If supra-specific groupings are only convenient "Linnean pigeon holes" or formal categories for taxa (e.g., poly- or paraphyletic), then they do not convey a material, genetic kinship and hence cannot behave as entities that are subject to unique (macro) evolutionary processes.

## 12.3 Conceptual Stasis and Change Since Dahlem 1981

As noted above, many aspects of these evolutionary subjects and the issues they raised were discussed at the time of the 1981 Dahlem conference. They have remained an inspiration for many of us during the intervening decades. But the constraints of careers have extensively modulated what each of us has done and how much we have published in the various fields considered. I concentrated on the comparative histology of bone and developed paleohistology as a method to introduce the study of late ontogenetic development and natural history traits into the realm of tetrapod paleobiology (e.g., de Ricqlès 1992; de Ricqlès et al. 2004). Rather than elaborate on these scientific developments in more detail (cf. Stockstad 2004; Erickson 2005), it is more useful to focus here on the contextual background in which they occurred over the decades following Dahlem 1981. To be frank, it has

been a constant strain and struggle for me to keep the natural history oriented parts of biology (e.g., systematics, morphology, paleontology, organismal biology, and ecology) alive and evolving within the university ecosystem. This persistent effort was required because of the overwhelming pressure from cell physiology, molecular biology, pharmacology, and other allied approaches that strove to seemingly swallow everything within the framework of a biomedical and applied vision of biology. Seen in retrospect, the necessary nurture and care of our particular "intellectual" problems (e.g., phylogenetics, phenotypic plasticity, gene regulation, and evolvability) was downplayed in light of the preeminent sociological problem of disciplinary survival and renewal. In these science wars, where the niches in a Darwinian academic ecosystem were limited, internecine battles in evolutionary theorizing were not the most pressing concern.

The 1970s were dominated by the hard-fought campaign to introduce modern phylogenetics (cladistics) into the curriculum. Simultaneously, it became more and more obvious that the western pattern of economic development, viewed so far as an unquestionable fact of progress in all its aspects (even by the Soviet Union, which tried to compete with it under a different political system), would sooner or later bring the world ecosystem to a dead end. It was thus time to introduce new curricula integrating ecology, inventory systematics, and conservation biology alongside of the more traditional subjects. This has blossomed along a variety of pathways (and not always satisfactorily), but at last evolutionary ecology appears to be well integrated with other aspects of evolutionary science.

During the early 1980s, and following the inspiration of Dahlem 1981, those of us in the Paris university context introduced a new evolutionary biology cursus (from Masters Degree to PhD) based on a multidisciplinary integration of many relevant disciplines (from paleontology to population genetics). This involved several universities in Paris, as well as the Paris Museum of Natural History. Through extensive meanderings and a not quite predictable evolution, this cursus still frames the education of students in evolutionary biology at the Museum and Paris 6 University (and elsewhere). The 1990s were dominated by the mutual rediscovery of molecules and morphology because the new phylogenetics at last made possible a dialogue between, and even some integration of, molecular and morphological sciences. This was later expanded as the molecular genetics of development opened up new relationships with organismal morphology. In turn, this was further extended with the flood of empirical findings about the molecular evolution of developmental genes, which brought along with it astounding connections between molecules, morphology and systematics. It generated a completely renewed comparative developmental biology. These developments have extensively modified the "classical" Modern Synthesis, which in part metamorphosed into the new "Evo-devo" paradigm, where the organism and its morphology find again, at last, their well-deserved place (de Ricqlès and Padian 2009; de Ricqlès 2010). Perhaps unsurprisingly, the seeds for much of this conceptual development in evolutionary theorizing can be found in Dahlem 1981.

## 12.4 The Conceptual Landscape of Evolution and Development Today: The Case of Bone Tissue

Many of the conceptual themes that were present in the context of Dahlem 1981 are manifested in current research by myself and colleagues on bone tissue, including the analysis of complex causality in biology through the integration of historical, functional and structural factors. Bone—as a tissue—is an extraordinarily complex biological system; it exists within highly varied structural patterns, connected to numerous functional processes and physiological demands. Histovariability describes how bone tissue exhibits changes within the individual body depending on the age, sex, specific bone, specific location within a given bone, or given site within a section. Histodiversity describes bone tissue changes that obtain between conspecific individuals within a species, between closely related taxa, between higher-level, supraspecific groups, including within and among higher vertebrate clades.

Traditionally, bone histovariability and histodiversity have been explained within the framework of a single point of view; either historical, or functional, or structural factors are given preeminence. For example, paleontologists readily interpret data by reference to the systematic–phylogenetic situation of the organisms observed. Other biologists interpret data with reference to functional features, such as the ontogenetic circumstances of bone development or the biomechanical functions of mature bone. Nevertheless, a robust comparative histological analysis demonstrates that bone results from a complex set of factors that require biologists to integrate the phylogenetic, structural, and functional inputs (de Ricqlès 1975–78). For some time there were no tools available to pass beyond this qualitative analysis but now the situation has changed. Recently developed statistical methods have been used (Desdevise et al. 2003) to partition the variation so that it becomes possible to assign the outputs and interactions among historical, functional and structural factors of bone tissue variability (Cubo et al. 2008; de Ricqlès and Cubo 2010). This gives a material example of "Seilacher's triangle" (Gould 2002), which had been more of a heuristic than an operational tool, and provides new ways to elucidate the complex web of causality that is the signature of historical sciences. Evolution is simultaneously a historical (palaetiological) and a non-historical (nomological) science.

## 12.5 Concluding Remarks

Thirty years later, the pivotal importance of Dahlem 1981 is more and more apparent. Indeed, there has been a "before" and an "after" for many of the original participants. During the conference they discovered that they were not alone in their reluctance with some (or many) aspects of the Modern Synthesis, even though everyone attending accepted it as the necessary starting point from which more satisfactory intellectual extensions and explorations could take place. Accordingly,

subsequent to Dahlem 1981, there was a new spirit of intellectual freedom relative to the orthodoxy of the Modern Synthesis, which has proved fruitful over the intervening decades. This has led to the modification and revision of theoretical outlooks in many research fields. The edited volume deriving from the conference (Bonner 1982) has also proved immensely influential on a whole generation of evolutionary and developmental biologists. It has operated as a catalyst for the emergence of what was to become the "super Evo-devo synthesis" (de Ricqlès and Padian 2009).

From my own philosophical vantage point, Dahlem 1981 initiated a major shift, later immensely developed by molecular genetics, towards a probabilistic rather than deterministic vision of evolutionary mechanisms. This does not underplay the importance of natural selection as a causal mechanism of evolutionary change. Instead, it both relativizes the role of natural selection, by taking into account more fully the historical and structural constraints within which selection can act, and extends it, by taking into account the multiple levels of biological organization where selection operates. This probabilistic view, which emerges from an integrative approach to structural, functional, and historical factors in evolution from both nomological and palaetiological perspectives, is observable in the final views of Stephen Jay Gould (Gould 2002) who, for people like myself, has been and remains the very soul of Dahlem 1981, before and beyond.

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# Chapter 13
# What Salamander Biologists Have Taught Us About Evo-devo

**James R. Griesemer**

*Isolated cases lack the impact that arises when one must confront the often conflicting lines of evidence that arise from a long-term focus on the evolution of a diverse monophyletic taxon (Wake 1991, 544).*

*Taxon-based research in evolution permits. . .a multidimensional approach. . .with lessons learned from research on salamanders. The clade is widespread and diverse, yet sufficiently small that one can keep all of the species in mind. This facilitates research from diverse perspectives. . . (Wake 2009, 333).*

## 13.1 Introduction: Evolutionary Morphology, Model Taxa, and the Evo-devo "Juncture"

The 30th anniversary of the 1981 Dahlem conference on Evolution and Development (Bonner 1982) presents an opportunity to assess the role of various kinds of approaches to problems, practices, and principles of interdisciplinary research as they contributed to patterns of conceptual change in different biological specialties over the second half of the twentieth century. Specifically, the integration (Hall 2000), extended synthesis (Pigliucci and Müller 2010), or "juncture" (Gerson 2007, Gerson, Chap. 20, this volume) of evolutionary and developmental biology—"Evo-devo," "Devo-evo," or "evolutionary developmental biology"—had roots in several specialties, including: molecular approaches to developmental biology, genetics, and systematics; functional, developmental and evolutionary morphology; paleontology; and, population and quantitative genetics approaches to the evolutionary synthesis.

Many biological specialties in the post-war period were transformed by "molecularization"—the advent, introduction, use, and spread of molecular data, results, and methods in the first half of the twentieth century (Kay 1993) into other, previously non-molecular specialties in the second half of the twentieth century

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(e.g., Dietrich 1998). The interdisciplinary or intersectional practice of Evo-devo drew substantial impetus from the rise of molecular developmental biology following the working out of the structure of DNA and the genetic code in the 1950s and 1960s, and empirical and theoretical inroads made on the molecular biology of gene expression in the 1970s and 1980s. Moreover, the molecularization of many biological specialties in this period also saw a broad shift toward reliance on "model organisms" (Ankeny 2001, 2007, 2010; Ankeny and Leonelli 2011; Bolker 1995; Burian 1993; Clause 1993; Hanken 1993; Hedges 2003; Kellogg and Shaffer 1993; Leonelli 2007; NIH 2011; Rader 2004). These became the primary material basis of the laboratory systems involved in much, but not all, of the research contributing to Evo-devo by the end of the century.

These milestones in molecular biology suggested progress toward a broad conception of the nature and function of "developmental genes" and gene regulatory networks and their significance for evolutionary and developmental biology (e.g. Davidson 1982, 2001; Gerhart and Kirschner 1997). An equally important resource, however, for the broad array of specialties pertinent to Evo-devo was the molecularization and standardization of phylogenetic systematics (Hull 1988; Haber 2005) and the molecularization of evolutionary and population genetics through the introduction of theories and methods for studying evolution at the molecular level (Dietrich 1998). The use of molecular characters in phylogeny reconstruction was pivotal for the investigation of morphological problems of Evo-devo since it provided a means for constructing phylogenies independent of the morphological characters under investigation. Theories and methods of molecular evolution were likewise important for reshaping investigation of evolutionary processes, especially for priming consideration of non-adaptive explanations of molecular and morphological character evolution, which was crucial to loosening the restrictive presuppositions of pan-adaptationist thinking.

In this essay, I discuss the "taxon-based" research program of David Wake, an evolutionary morphologist involved in the emergence of Evo-devo and co-organizer of the 1981 Dahlem conference. I show that historical and philosophical studies of Wake's 50-year investigation of the salamanders (Order Caudata) reveal a sustained effort to demonstrate the continuing value of taxon-centered research as opposed to or distinct from model organism research, which also was able to take advantage of progress due to molecularization. Although Wake focused on the "organismal" level, he was an early adopter of molecular data for phylogenetic analysis of the evolution of evolutionary novelties, homoplasy and speciation (see also Sunderland 2012, in preparation). Thus, the move to molecular levels of analysis is not exclusive to the broad concentration of biological research in the twentieth century on model organisms. Wake developed a distinctive practice of generalizing or extrapolating "lessons" as well as results from his taxon-focused research on salamanders. I will characterize some of Wake's contributions to the emergence and conceptual development of Evo-devo in terms of lessons learned from his use of the salamanders as a "model taxon." Model taxa are intended to be monophyletic clades in which the whole clade constitutes the model, in contrast to model or experimental organisms, which are species used as models. Wake's primary model taxon is the monophyletic family of lungless salamanders, the Plethodontidae, and a monophyletic genus within the plethodontids, *Bolitoglossa*.

A key contribution to Evo-devo from Wake's research program was stimulating conceptual change in the status of the phenomenon and concept of homoplasy—similarity due to convergent, parallel or reverse evolution rather than due to descent from common ancestors (Wake 1991; see Wake, Chap. 5, this volume). Wake's work helped transform homoplasy from a "problem" (difficulty) for phylogenetic analysis to an "interesting question" (Wake et al. 2011, 1032; cf. Wake 1996; Wray 1996) for integrative research in Evo-devo and evolutionary biology, to a conceptual tool for comparative evolutionary studies (Wake 2009; Griesemer 2013).[1] Wake champions integrative research in Evo-devo using molecular and morphological studies of mechanisms through which organism phenotypes develop and function. Such studies are used to inform *comparative* work on the evolution of form through the study of patterns of similarity across species of a clade, as well as investigation of causal mechanisms underlying form. Comparative work requires more than one species and, for Wake, clades are important units of investigation. Clades, like particular species, can serve as models when empirical results or methodological lessons about inference procedures gained from their study can be, and are intended to be, generalized or exported.

Evolutionary research requires the study of variation. Unlike population biology, which mainly studies variation within species or co-variation between populations and their environments, evolutionary morphology follows Darwin's comparative methods, using variation among species as a means to inferring processes that might have led to the evolution of varying forms within and among lineages.[2] Research on the evolution of form requires study of forms (how parts articulate to constitute an organization), functions (how organized parts work), and development (how parts are made and put together to create functional organization).

A core contribution of developmental genetics to Evo-devo is the mechanistic details of how a genomic "toolkit" for the development of form, widely shared across species, can be deployed ("expressed") in varying circumstances (species and environments) to make "endless forms" (e.g., Carroll 2005). In contrast, evolutionary morphology works out mechanistic details of how varying kinds of organizations of phenotypic parts can serve similar functions in diverse contexts or diverse functions by similar means. Examples from Wake's research include direct vs. larval development; feeding with a projectile vs. protusible tongue; terrestrial or arboreal locomotion with various morphologies of hands and feet (webbing,

[1] There is a terminological obstacle to discussing conceptual change in scientific "problems." A problem can be something that poses a methodological or inferential *difficulty* or roadblock to the conduct of research. But a problem is also routinely described as a research or pedagogical *question* to be answered. Much of the philosophical and historical literature on scientific practice uses the term 'problem' to mean the latter—a research problem to be solved (e.g., Kuhn 1970; Laudan 1977). Wake et al. (2011) talk about "problems" in the former sense of methodological or inferential difficulty and use "question" to mean the latter sense. Here, I will use the term 'difficulty' to mean a "problem" of the former sort and use 'problem' to mean a research question.

[2] Comparative morphology extends back as far as the ancient Greeks, but comparative methods and problems prior to the mid-nineteenth century are far beyond the scope of this essay.

mesopodial structures), and reproduction in adult vs. larval form (achieved by paedomorphic development) (see also Griesemer 2013).

Developmental genetics works "outward" from a basis in the mechanistic study of a select few experimental or "model organisms" by generalization and application to a wider variety of taxa. Evolutionary morphology works "inward" from a basis in the comparative study of a wide variety of taxa to a select few morphological, developmental, or functional principles and patterns, discovered by comparative, mechanical, functional, and experimental analysis (Wake 1982, 605). Together, the contributions of these and other specialties to the Evo-devo juncture show that an adequate picture of the joint operation of development and evolution requires a nuanced understanding of mechanisms at many articulated hierarchical levels of similarity and difference, and historically contingent processes of evolution also operating at a hierarchy of levels.

The concept of a model taxon introduced here expands discussion of model systems beyond model or experimental organisms (see Ankeny and Leonelli 2011) in the conduct of modern biological research. I argue that model taxa, as well as model organisms and other kinds of experimental systems, played their part in the historical emergence of Evo-devo as a "juncture" of biological research specialties. A juncture is characterized by a "joint (and competitive) attack on a common problem" (Gerson 2007, 451; Chap. 20, this volume), not necessarily involving either a shared approach or synthetic theory. Evo-devo is aptly characterized as such a juncture: several specialties contribute to attacking common problems jointly, but a greater measure of autonomy of approach, goals, and methods (and, somewhat less institutional entrenchment), is evident than would be the case in the successful emergence of a new "discipline." Wake et al. (1991) identified key elements of this juncture in "the possibilities for new synergisms, of the heuristic value of interdisciplinary interaction, and of the opportunities of an expanded evolutionary and developmental synthesis that excite the imagination" (583). They noted that discussants at their workshop reached no consensus on whether "the reciprocity between disciplines that interests both evolutionists and developmentalists," which "raises the possibility of new kinds of interaction that might substantively benefit both fields" (1991, 582), would lead to a new discipline or only to an exchange across the borders of their specialties. The authors of the report (led by Wake) sensed more than a temporary intersection of interests, noting that "This new discipline is emerging at the confluence of three traditional areas of study: development, evolution, and phylogenetics." They concluded that, "without doubt, a new field has arisen. This new area of investigation is synthetic, incorporative and integrative" (1991, 583).

The conceptual expansion of the category of model systems to include model *taxa* reinforces the finding that the historical emergence of Evo-devo involved something more like juncture formation than consensus around a revolutionary or synthetic theory or consolidation of practices. Evo-devo is more than a specialized offshoot of molecular developmental biology with its discoveries of "developmental genes" widely distributed among animal species. It was significantly shaped and influenced by evolutionary morphologists such as Wake and his students (Love

2003, 2006, 2008; Love and Raff 2003; Olsson et al. 2006; Raff and Love 2004), and involves a number of other specialties, notably phylogenetic systematics (as claimed in Wake et al. 1991).

The clade composed of salamanders has properties that suit it as a "platform" for research on a wide variety of research problems and not just as material that displays some one phenomenon of interest to an exemplary degree or as a proxy for some other target of interest, such as a human disease. Wake touts the virtues of salamanders as a research subject in terms analogous to those used to describe virtues of model organisms.

> The clade is widespread and diverse, yet sufficiently small that one can keep all of the species in mind. This facilitates research from diverse perspectives: systematics and phylogenetics, morphology, development, ecology, neurobiology, behavior, and physiology. (Wake 2009, 333)

On the other hand, instead of ease of breeding and husbandry of live animals in the lab, we have as virtues extensive collections and effective curation of many dead specimens in different museums with institutions for loaning, sharing, and communicating about specimens (Sunderland 2012, 2013). Instead of a small number of cells or chromosomes to manage the combinatorial complexity of phenomena under investigation, a small number of species is the important virtue. Instead of fast generation time, a relatively long evolutionary history (for vertebrates), affording much species-level diversity, is virtuous.[3] The potential of salamanders to serve as a platform comparable to contemporary model organisms is limited, however, because it is tied to collections of preserved specimens (Sunderland 2012), and therefore less portable/repeatable/sharable than highly mobile and easily distributed standardized strains of fast-breeding model organisms supported by a national or global infrastructure of stock centers, husbandry protocols, and biological supply companies. Salamanders do display an interesting suite of cellular traits that contrast with those of typical model organisms, making them interesting models for a variety of morphological, developmental and evolutionary purposes (see below).

Historical change in the conceptual status of homoplasy from a difficulty (for phylogenetics) to a research problem and conceptual tool (for evolutionary biology and Evo-devo) reveals distinctive features of Wake's use of the salamanders (Order Caudata) generally, but particularly some of its subgroups (family Plethodontidae and super-genus *Bolitoglossa*) as model taxa. Homoplasy is a phenomenon manifested in *relations* of similarity among species; i.e., it is a property of clades, not individual species. Model organisms (i.e., species) *per se* cannot display homoplasy, nor can model-organism research focused on individual species and lacking specified comparative contexts investigate the phenomenon. The problem and concept of homoplasy, like homology, is *inherently* comparative.

[3] In the case of salamanders, however, the diversity is ecological-functional despite a rather broadly "generalized" vertebrate morphology. Indeed, there are few morphological characters to distinguish subclades due to rampant homoplasy (Wake 1993).

Over the course of Wake's career working with salamanders as a model platform for a wide variety of research questions in comparative anatomy, functional and evolutionary morphology, systematics, ecology, evolution, Evo-devo, and conservation biology, it became clear that in salamanders, and especially plethodontid salamanders, the phenomenon of homoplasy is "rampant" (Wake 2009, 335). As a consequence, the clade could serve as a model in the traditional sense of displaying a property or phenomenon of interest to an exemplary degree. The extent to which Wake argued for *integrative* approaches to such phenomena, drawing on multiple specialties, suggests that the salamanders could also be used to address a wide variety of research problems, and thus serve as a platform, albeit subject to limitations atypical for familiar model organisms.

The development of a variety of new tools, methods, practices, and infrastructure in several disciplines in the second half of the twentieth century facilitated the conceptual development and articulation of the "lessons" Wake exported, particularly to Evo-devo.[4] Although the lessons explored here concern "inference rules" learned from evolutionary morphology studies of salamanders, their potential to block routine inferences in other specialties, and applied as well to multidisciplinary, integrative work in evolutionary biology and Evo-devo, new tools and methods from other specialties were also integral to the lessons learned about salamanders. New phylogenetic practices, such as *computer-based* cladistic inference using parsimony or other inference methods on molecular as well as morphological data, were critical to Wake's generalizations and played a significant role in the rise of Evo-devo more broadly. Phylogenetics has been as important to Evo-devo as developmental genetics in framing concepts and inference rules, if not in supplying the data, at work in the juncture. New methods of sequencing genes and informatics representations of genetic information in databases, along with their application to studies of gene regulation in development, provided new tools, concepts and methods that served Wake's integrative approach to the problem of homoplasy enriching it as a contribution to the conceptual development of Evo-devo.

Interpreting Wake's "taxon-focused" research program (Wake 2009) in terms of the conceptual development and use of salamanders as a model taxon helps display the remarkable consistency with which Wake has shown that salamanders can serve as a platform for a wealth of research problems as diverse as for any model organism. Moreover, salamanders have methodological, strategic, and inferential lessons to teach evolutionary and Evo-devo biologists in addition to contributing empirical results from a "generalized vertebrate" group to our understanding of a clade (vertebrates) to which both salamanders and humans belong. The fact that the salamander platform has not *spread* as widely as have some other models is explicable, but not pertinent to its status *as* a platform for a model system, either as exemplary of a phenomenon or as a platform for a research system.

[4] See Gerson (2007) on the role of developments in research technology in the emergence of Evo-devo.

## 13.2 Wake's Taxon-Focused Research Program in Evolutionary Morphology

David B. Wake earned his MS (1960) and PhD (1964) from the University of Southern California. He was an instructor and assistant professor of Anatomy at the University of Chicago (1964–1969), thereafter moving to the University of California, Berkeley in 1969 as an associate professor of Zoology and Associate Curator in the Museum of Vertebrate Zoology. He became Director of the Museum in 1971 and Professor of Zoology in 1973, serving in those capacities until his retirement in 1998. He has been very active in research since retirement, continuing to add to a list of more than 385 publications as of 2012 (Wake n.d.).

Wake was trained as a comparative morphologist and systematist, but one who relied on evidence from development to understand the evolution of form (Wake 2002). Thus, he was prepared to combine approaches at the earliest stages of his career. He also was primed to notice the revolution in methods of studying genetic variation promoted by colleagues at Chicago (Hubby, Lewontin, Throckmorton) in the use of protein electrophoresis in the mid-1960s, and again at Berkeley when evolutionary reasoning about molecules (using microcomplement fixation and electrophoresis) and morphology by colleagues Maxson, Wilson and Sarich was emerging (see, e.g., Wake et al. 1978; Maxson et al. 1979; Larson et al. 1981; Maxson and Wake 1981). Wake's evolution course at Berkeley in the mid-1970s scrutinized arguments in Lewontin's 1974 book, *The Genetic Basis of Evolutionary Change*, on the role of electrophoresis evidence of genetic variation, as well as the cladistic revolution in systematics following the publication of Hennig's work in English (1965, 1966).[5]

Like many morphologists, Wake had an uneasy relationship to the Modern Synthesis (see Ghiselin 1980, 2006; Raff and Love 2004; Wake 2002). Morphology and development were sidelined from some evolutionary discussions as population genetics took hold of (or "hardened") the synthetic theory; molecular evolution challenged the synthetic theory's emphasis on selection over drift and traditional "evolutionary" systematics as championed by Mayr and Simpson. But Wake was not a hostile critic of either the synthesis or molecular approaches. Instead, he sought an integration of methods and concepts from the evolutionary synthesis (chiefly the study of genetic variation relevant to development and speciation, the analysis of form, and adaptive radiation), as well as from developmental biology

[5] I was an undergraduate student in genetics at Berkeley (1973–1977). I took Wake's evolution course in 1975 or 1976 and an independent study course with Wake on Gould's *Ontogeny and Phylogeny* in 1977 to fulfill a requirement in biological diversity. Wake's student, James Hanken, was my TA. Lewontin's book was required reading, Alan Wilson (my biochemistry teacher) was making a splash with his innovative studies of rates of evolution, and Pere Alberch, my classmate in embryology, was becoming an innovator in thinking about evolution and development. I arrived at Chicago as a graduate student after Lewontin had left (I got his office on the 4th floor in the Zoology building), but the electrophoresis and phylogenetics revolutions were still fresh in Lynn Throckmorton's teaching.

and the new molecular and phylogenetic systematics. He was open to the value of molecules both for phylogeny and as causal components of developmental mechanisms. The role of molecules in phylogenetics was especially salient to the investigation of homoplasy.

In the twentieth century, new problem-based and tool-based specialties arose (e.g., genetics; computer science, statistics) as the broad subject-based disciplines (e.g., biology, geology, chemistry) continued to fragment.[6] As they did, audiences for scientific work segregated and recombined, leading to new alliances that could attack research problems and serve as audiences in place of the disciplines that had formed around broad categories of research *subjects* (physics, chemistry, biology, psychology). These alliances and junctures provided new and different sorts of contexts than either the specialties or disciplines had previously provided for presenting, interpreting, and evaluating the significance of empirical findings and development of concepts, methods, and theoretical models. Increasingly through the century, intersections and alliances of researchers organized around platforms for research systems that could be used to pursue many different research problems, allowing those not sharing problems to still share subject matter in the restricted sense of working with the same model system, share resources in an expanded sense (including national computing and database infrastructure, federal funding agencies, and society journals), and even to collaborate.

I have suggested that Wake held a remarkably constant commitment to integrative approaches to understanding the evolution of animal form throughout his career, from the 1960s to the present (Griesemer 2013). His audiences, however, changed with the growth and development of the fields that were shaped, segregated, and recombined over the past half-century, as did the tools, methods, and concepts he used. Some of Wake's research interests (e.g., morphological homoplasy) extend back to the beginnings of his career, but their value, salience, and significance shifted with the changing array of specialties and junctures. Homoplasy was a concept recognized by nineteenth century biologists who were interested in the causes of similarity among different species and how similarities were organized into patterns. Wake (1996, 2003) traces the concept of homoplasy back to the nineteenth century and Richard Owen, who interpreted homology in terms of archetypes or essential forms and homoplasy in terms of analogies due to shared function, and the term to E. Ray Lankester. Its significance was transformed by Darwin, who read homology as similarity produced by the process of descent from a common ancestor and homoplasy as convergence. Natural selection, the main cause of descent with modification, could produce homoplasy by causing organisms in different lineages to converge on a common character serving similar adaptive functions in similar environments. This view left open whether the developmental mechanisms producing similar characters were themselves similar or disparate.

[6] In biology, these were taxon-based disciplines (zoology, botany) with taxon-based specialties (mammalogy, malacology, protozoology, phytology, or pteridology); see Gerson (1998). One scientist's problem is another scientist's tool, so the distinction cannot be all that sharp.

We can "periodize" Wake's career in terms of conceptual (and methodological) developments in the specialties that he sought to integrate, as these changed through the decades, particularly systematics and developmental biology.[7] These changes are relevant to Wake's continued advocacy of integrative biology in that the idiom most suitable for expressing such a view changed with the times. Systematics witnessed a cladistic "revolution" near the beginning of Wake's career that had wide repercussions for the practice of evolutionary morphology and systematics, not least because it shed new light on concepts of homology and homoplasy and the relation between natural selection and various structural constraints (genetic, developmental) in the evolutionary process. Developmental biology was transformed by molecular studies of gene expression and discoveries leading to the concept of a widely shared "developmental toolkit" of pattern-forming genes in the 1980s–1990s.

In the 1960s, Wake drew on "evolutionary" taxonomy (see Hull 1988) to classify salamander species, genera, and families, though with special attention to osteological and embryological features. Wake's self-identified specialty in this period was "evolutionary morphology" (e.g., Wake 1966, 1; cf. Wake 1982). His material was exclusively morphological (i.e., not molecular). In the mid-1960s, "cladistics" emerged as a new concept and methodology in systematics that was vigorously debated and then established as a new specialty within systematics in the 1970s (see Hull 1988). Numerical methods in systematics had been explored from a variety of perspectives in the 1960s and spread alongside increasing access to mainframe computing, which supported work with large data sets and complex evolutionary relationships (see Felsenstein 2001, 2004). Phylogenetic systematics, as cladistic methods applied to phylogenetic inference became known, offered new tools and also a new audience for Wake. Cladistic inference using parsimony relied on derived traits that are shared due to common ancestry (synapomorphies) to reconstruct phylogenies. Homoplasious traits are shared and derived traits that are *not* due to common ancestry. These were interpreted in the 1980s as noise in the data, complicating phylogenetic analysis and inference (Wake 1996; Sanderson and Hufford 1996; Eldredge and Cracraft 1980; Felsenstein 2004). Key concepts and methods (such as congruence, concordance, and consistency) were constructed to be mindful of the need to minimize the amount of homoplasy, or "*ad hoc* assumptions," one had to assume for a given phylogenetic tree hypothesis. Additional algorithms for phylogenetic inference (e.g., maximum likelihood, bootstrap, and Bayesian methods) did not support the treatment of homoplasy as a mere difficulty in such categorical terms: homoplasious characters are "noisier" than synapomorphies, but have phylogenetic significance (Sober 1988; Felsenstein 2004). As alternative methods became available through the development and distribution of computer software packages for phylogenetic inference (e.g., Hennig-86, PAUP, MacClade, PHYLIP), cladistics emerged from the "Dark Ages" of the 1980s and

[7] "Periodization" is a way of describing how embryologists model developmental processes by dividing them into stages in order to express a narrative structure in terms of hypotheses of developmental fate susceptible to empirical testing (Griesemer 1996). Here, I apply similar reasoning in discussing conceptual development of the histories of biological specialties.

the schism between cladists and statistical phylogeneticists began to heal in the 1990s (Felsenstein 2001). As a result, the character of the problem of homoplasy also began to shift.

Treatment of homoplasy as a difficulty for phylogenetic inference arose in molecular evolutionary studies as well during the 1970s and 1980s. In the 1970s, molecules were sometimes pitted against morphology as a "better" or "more reliable" approach to phylogeny reconstruction. However, homoplasy is even more rampant in DNA sequence evolution because there are only four bases (A, T, C, G), hence only three possible character state changes for any given nucleotide position. Therefore, at the nucleotide level, mutation will cause many convergences, parallelisms, and reversals.

Wake urged a "synthetic" or "integrative" approach to the morphological problem: use molecules to build phylogenies robust to the pitfalls of inference about morphological evolution, such as rampant homoplasy, but also integrate evidence from an increasingly molecular baseline for mechanistic inference about development. Wake's calls for integrative approaches were expressed variously across the decades, in terms of different concepts to be integrated, depending on newly forming alliances and junctures across the discipline-based specialties as these shifted, segmented, and recombined.

In the 1970s, Wake used a combination of dynamical models and biomechanical experiments to examine the hyoid skeletal architectures and their functional consequences for extending the tongue to catch prey—"feeding mechanisms"—in lungless Plethodontid salamanders (Lombard and Wake 1976, 1977; discussed in Griesemer 2013). He also presented a lesson for functional morphologists on the virtues of having a theoretical model as a basis for empirical hypothesis testing in biomechanical performance experiments. In the 1980s, he argued for combining comparative and experimental approaches, to integrate functional and evolutionary morphology, while rejecting doctrinaire cladists' "neutrality" on the evolutionary significance of morphological characters (Wake 1982). Despite his critique of cladistic *philosophy*, Wake used cladistic *methods* to extend his work with Lombard and others on the evolution of feeding mechanisms in the Plethodontids (Lombard and Wake 1986).

In the late 1980s and early 1990s, Wake argued that new perspectives from structuralism were more effective than neo-Darwinism in treating problems of organismal form and self-organization, and therefore should be "used concurrently" with neo-Darwinism, which focuses on historically contingent population processes (Wake and Larson 1987; Wake 1991). Later in the 1990s, with Neil Shubin, Wake argued that, "Patterns of variation, when integrated with developmental biology, inform about the relationships between morphological integration and homology" (Shubin and Wake 1996, 51).[8] In 2002, Wake argued for a combination of mechanistic and historical biology for studies of "behavior, physiology, and development"

[8] Shubin was a Miller post-doc at Berkeley and worked closely there with Wake. Shubin had been a graduate student at Harvard, where he worked closely with Pere Alberch, one of Wake's students.

to illuminate the limitations of adaptationist inferences in behavioral ecology and evolutionary genetics (Autumn et al. 2002). Finally, another expression of Wake's message favoring integrative approaches emerged in a 2007 paper on the evolution of webbed feet in *Bolitoglossa*. Wake argued that repeated evolution of morphological characters cannot properly be given an adaptive explanation unless the inference is considered in a wider context of morphological character evolution and particularly with an understanding of developmental mechanisms (Jaekel and Wake 2007).

In each of these cases, the audience for the integration lesson is different. In the 1970s, it was functional morphologists who were urged to consider evolutionary perspectives. In the 1980s, it was a lesson to both functional and evolutionary morphologists and also to phylogenetic systematists on the importance of considering the evolution of form and function alongside phylogenetic inference using characters as "data." In the 1980s and 1990s, the targets were emergent philosophical perspectives such as structuralism and the need to combine them with neo-Darwinism rather than oppose it. Through the 1990s and into the 2000s, the lesson also was that evolutionary explanations, particularly adaptive ones, must be combined with accounts of the developmental mechanisms capable of producing the phenotypes subject to natural selection.

To Wake, homoplasy was a widespread *phenomenon*, not just a "difficulty" but also a research problem whose causal explanation in terms of underlying biomechanical and developmental mechanisms was of central interest (see Wake 1996). At about the same time Wake was writing papers explicitly arguing for (morphological) homoplasy as a research problem (e.g., Wake 1991, 1996), the phylogenetics community was beginning to view it as a research problem, as well as a difficulty. For example, the language and treatment of homoplasy in Eldredge and Cracraft 1980 (or any other cladistics text from about 1975–1985), where homoplasy is discussed as a complication and its use in phylogenetic inference as potentially "ad hoc," differs from that of Wiley et al. (1991), where homoplasy is a feature of data discovered through phylogenetic analysis. In Sanderson and Hufford (1996)—the first book devoted to homoplasy—it is treated as a phenomenon in its own right with implications for mechanistic and dynamical explanations of phylogenetic data. This marks a key turning point in the relation between phylogenetics, evolutionary morphology, and developmental biology. Homoplasy arises as a "symptom" in phylogeny reconstruction to be explained as a comparative pattern resulting from the operation of developmental and/or evolutionary processes.

In the 1970s and 1980s, the role of molecular characters in phylogenetic inference was debated as new tools in molecular biology became available to a wider range of researchers than chemists and biochemists. Protein electrophoresis technology allowed non-chemists to study molecular properties of proteins sampled from biological populations, and evolutionists in particular to study molecular variation within and among populations. DNA sequencing methods were developed in the 1970s alongside the internet and internet-accessible databases.[9] The

[9] As benchmark, note that the TCIP/IP internet protocol and GenBank both launched in 1982.

automation and scaling-up of sequencing in the 1980s by means of various technical innovations (e.g., PCR, fluorescent dye methods), and application to the human (and other genome) projects starting in 1990, allowed evolutionists to study variation at the lowest levels (nucleotides).

These technical changes proved valuable to systematics, facilitating phylogenetic reconstruction with molecular characters independent of the morphological characters of evolutionary interest.[10] The choice of molecular characters (e.g., nuclear vs. mitochondrial genes) could be made depending on the spans of evolutionary time of interest. These developments in molecular biology also shed new light on homoplasy, both because DNA exhibits abundant homoplasy (as explained above) and because it clarified how problems and concepts of homoplasy and homology depend on the hierarchical level(s) of description and mechanism. For example, morphological traits of species with recent common ancestors could have homoplasious DNA sequences expressed in trait development. Homoplasious traits (such as in vertebrate and invertebrate visual systems) could involve developmental mechanisms using shared sequences in the toolkit, exhibiting developmental "homologies of process" but homoplasious or divergent morphologies and phenotypes (Gilbert et al. 1996; Gilbert and Bolker 2001). As in phylogenetics, homoplasy became a phenomenon of interest rather than only a difficulty to be overcome. It was a problem that had to be addressed on multiple hierarchical levels, which meant that it represented a rich phenomenon of complex systems of potential interest to just the sorts of specialties that were beginning to form the Evo-devo juncture in the 1980s. Evolutionary biologists were becoming interested in developmental processes and mechanisms as potential alternative causes to adaptation and the role of development as an obstacle to adaptationist thinking. Molecular geneticists and developmental biologists were becoming interested in generalizing results from studies of gene expression to developmental and phenotypic patterns of wider representational scope. Phylogenetic systematists were becoming interested in bringing molecules and morphology together in cladistic inference. And, finally, population biologists were becoming interested in the *interplay* of selective mechanisms with developmental and genetic constraints (see Maynard Smith et al. 1985).

Dividing Wake's work into periods in this way is somewhat artificial. In his own estimation, he has worked continually on central themes of his research program from the beginning (Wake, pers. comm., June 7, 2012).

> Since I began biological research I have been fascinated with morphological homoplasies, especially the biological basis for their independent generation. Perhaps this fascination developed because I chose to pursue evolutionary morphological and systematic studies of a difficult group, relatively featureless salamanders. The most featureless were the most difficult—clades that contained miniaturized species, clades that displayed general uniformity despite being speciose and in which the few derived traits were distributed in

[10] Not that molecular evolution *per se* was uninteresting, but it is not especially germane to Wake's story or to the role of evolutionary morphology in Evo-devo other than by adding yet another contrast between selection and alternative evolutionary mechanisms (drift).

> bewildering arrays, and clades that contained species displaying varying degrees of paedomorphosis. It was my studies of salamanders that first made clear to me that the study of the causes of homoplasy requires a hierarchical approach. (Wake 1996, xxi)

Since many of Wake's lessons were learned through work in the nascent Evo-devo juncture before the 1980s and extend to the present, they contribute to integrating developmental research results, concepts, and reasoning into evolutionary research as well as informing research strategies in the expanding, distinctive Evo-devo juncture itself.[11]

## 13.3 Model Organisms and Model Taxa: Exporting Lessons Learned

Wake's contributions to the emergence and conceptual development of Evo-devo include lessons learned from his use of the Plethodontidae as a "model taxon" about the concept of homoplasy and how to reason using integrative rather than research-specialty-specific inference rules. To see this explicitly, we need to understand the concept of a model taxon and how it differs from related notions of model organism and experimental organism (Ankeny and Leonelli 2011).

### *13.3.1 Model Organisms*

A distinctive feature of the history of biology in the twentieth century is the expansion and eventual dominance of research based on model organisms rather than a wide variety of taxa (Churchill 1997). This dominance did not mean that other taxa were correspondingly neglected, although biological education and research did trend toward teaching and learning about fewer and fewer species and more and more about problems, principles, techniques, and applications (Gerson 1998). It became concomitantly harder to gain funding for work on "non-model" organisms in some specialties (Gilbert 2009). An increasing number of taxa were used as experimental systems for research purposes during the twentieth century, but only a few functioned as "model organisms" (Ankeny and Leonelli 2011). Importantly, the problem agenda, tools and methods, infrastructure, and institutions (conventional practices) of biological research became increasingly

[11] It is important to emphasize that while I focus on David Wake, many colleagues, collaborators, post-docs, and students have been involved, including: Jessica Bolker (New Hampshire and Shoals Marine Laboratory), Allan Larson (Washington University), Neil Shubin (University of Chicago), Stephen Stearns (Yale), Gerhard Roth (Bremen), and Marvalee Wake (Emerita Professor of Integrative Biology, Berkeley), among others. Space does not permit a wider report on the spread of Wake's "salamander platform" to other investigators or research organizations.

organized around experimental research systems, driven substantially by those working on standardized model organisms as "platforms" for research.

Research problems in the twentieth century were increasingly identified by their position in an analytical problem space (e.g., problems of form, physiology, heredity, development, disease etiology, environment, evolution), rather than a taxonomic problem space (what are frogs, fish, rodents, or primates; how do they develop, function, evolve?). The modern "rationalization" of research fit into broader patterns of change in the organization of twentieth century industrial and office work, especially in the US (see Gerson 1998, 2007).

Some model organisms, such as rat and mouse among biomedical researchers or worm and frog among animal developmental biologists, became organizing platforms for vast research systems involving many laboratories in organizations worldwide. From 1974 to 2003, more than 3,000 research organizations sponsored work on model organisms (see Evans 2007); over 6,000 laboratories use the plant model *Arabidopsis thaliana* (Leonelli 2007). During this history, research problems were slowly adjusted to fit the models as much as the models were chosen to fit the problems (Burian 1993), a sign that models are functioning as platforms in a system of research rather than merely as exemplars. Some models (e.g., *Caenorhabditis elegans*, *A. thaliana*, and *Danio rerio*), were developed *explicitly* as platforms for a wide variety of research problems from several disciplines using tools and methods that were becoming widely shared, in part through the construction of community "infrastructure" (e.g., genome sequencing and information dissemination and sharing through online databases), rather than being developed as experimental organisms for their suitability to a particular problem or phenomenon (Ankeny and Leonelli 2011). Research on diverse taxa, such as in evolutionary and systematic biology (and more recently ecology), came to depend on the problems, tools, and infrastructure built for the model systems. For example, one had to use genes sequenced in model organisms as reagents, tools, or information applicable across the phylogenetic spectrum for genetic, developmental, evolutionary, or biomedical research. Very recently, the range and distribution of model organisms has allowed yet another shift of procedure: choosing the "right" *model* organism for the job (problem, phenomenon of interest to study) rather than developing or repurposing a model organism as an experimental system from scratch (Metscher and Ahlberg 1999; see also Burian 1993).

The successful expansion of research systems built on model organism platforms has fostered a tendency, however, to adopt a narrow sense of what counts as a model organism, which constrains and confines historical and philosophical understanding of "modern" biology in general and the origins of inter-disciplinary "junctures" such as Evo-devo in particular. This narrow perspective leaves little conceptual room for the contributions of fields such as evolutionary morphology, which have not generally focused on model organisms as research subjects, except recently as sources of molecular data or "results" imported for comparative purposes (see Love 2003, 2006; Love and Raff 2003).

In fact, "model organism" has a much wider variety of meanings than the 13 model organisms listed on the NIH web page, "Model Organisms for Biomedical

Research" (National Institute of Health n.d.). The NIH 13 include: two mammalian models (mouse, rat), ten "non-mammalian models" (two yeast, one fungus, one amoeba, one round worm, one flea, one fruit fly, one fish, one frog, and one chicken), and one "other" (the plant, *Arabidopsis thaliana*). The current trend of "model organism" research has led to bandwagon effects (Fujimura 1996), driving a shift toward a wider meaning of "model organism" as any use of an experimental organism that is exemplary of a phenomenon of interest and studied using tools and results *derived from* the NIH 13, regardless of how widespread the phenomenon is or how relevant to biomedicine or other application.

### *13.3.2 Representational Scope and Target, Payoffs, and Exports*

Ankeny and Leonelli (2011) have instructively framed discussion of the character, status, and history of model-organism based biological research, in contrast to the wider class of experimental-organism based research, in terms of the representational scope and representational target of a model, together with considerations of the goals of researchers.[12] They characterize experimental organisms as chosen largely to pursue the investigation of a particular phenomenon (the target) with the expectation that results may have varying scope. Results may not generalize widely and be quite specific to the experimental organism or species from which it was established. They may generalize to a somewhat wider taxonomic group, such as the family, class, order, or kingdom to which the species belongs. Or, researchers may only be interested in generalizing to a particular other species such as *Homo sapiens*, as in much biomedical research using experimental "proxies" or surrogates for humans, human organs, or human diseases. In contrast, model organisms target the "organism as a whole," to achieve "complete knowledge of the fundamental processes at work in these organisms, including the molecular, cellular, and developmental processes" (Ankeny and Leonelli 2011, 317). The wide generalizability of results obtained in work on model organisms, according to Ankeny and Leonelli, is due to their basis in "genetic conservation" (2011, 316); i.e., in the genetic properties or mechanisms expected or assumed to be universal or widespread. Results from model organisms are therefore intended or expected to generalize to many or all species.

We should resolve two different senses of generality and generalization implicit in the idea of representational scope. Non-evolutionary biologists sometimes take generalization to all taxa, all life on Earth, or all life to be more or less synonymous with "universal." Monod's famous dictum—"Anything that is true of *E. coli* must be true for elephants"—was not taken as a claim of precise phylogenetic scope about either the paraphyletic group consisting of bacteria plus Elephantidae or

[12] See also Bolker (2009) for a distinction between exemplars and surrogates.

about the monophyletic clade that spans both, but rather about what Monod believed would turn out to be "universal" features, discovered in bacteria and generalizable to any *arbitrarily* chosen other species, such as "the elephant." Species and (monophyletic) clades are historical individuals (Ghiselin 1997) over which the distribution of molecular properties and phenomena Monod discussed is *contingent*. Generalizations over contingent distributions—even wide ones—are not "law-like" *in virtue of* wide representational scope (see Waters 1998). Arguably, Monod's quip was meant and taken in quite a different way, as an expression of underlying "law-like" discoveries regarding the operation of *fundamental* mechanisms, even if its instantiations happen to be (currently) limited to a contingent distribution of life on Earth.[13] Therefore, generalizing "results" from research using a model organism to a wider representational "scope" should consider explicitly whether the generalization concerns a contingent distribution over taxa or potentially fundamental or universal distribution over processes, functions, or mechanisms.[14]

Ankeny and Leonelli (2011) draw a further contrast between experimental and model organisms in terms of the goals of research. They claim that in seeking integrative models of the "whole organism," communities of model organism researchers hold a shared epistemic goal to use "a variety of disciplinary approaches, with the long-term hope of contributing to large-scale comparative work across *these* organisms" (316, italics added). Experimental organism work *per se* seems generally or typically not to aspire to disciplinary integration of this kind, although that is surely specialty and practice specific. Ankeny and Leonelli argue that the current trend toward a broadly expanded use of the term 'model organism,' to mean more or less any experimental use of an organism as a model system with which to study a particular phenomenon, should be resisted as muddying our understanding of what is distinctive about model-organism based research and why it has proved successful.

They also recognize that for only a few model organisms developed *after* usage of the term had spread throughout the biological community, such as *C. elegans*, *A. thaliana*, and *D. rerio*, does there seem to be an explicit effort to "gather resources and build infrastructure" *for the sake of* integrating a range of disciplinary approaches. In many more cases, such as mouse, rat, fruit fly, sea urchin, and leopard frog, an organism of convenience, or one thought exemplary for a particular phenomenon or problem, was chosen as the right (or at least as a suitable) *experimental* organism for a particular research job (problem or phenomenon of interest).

[13] Contingent distributions over all life on Earth would turn out to be fundamental if those patterns would appear again if "life's tape" were rewound and replayed (see Gould 1989).

[14] This distinction is similar to the one made by Gerson (2007) between part-whole and instance-kind relations. Gerson argues that there was a general shift in twentieth century biology from the former to the latter, and that this helps explain why certain specialties were excluded from the evolutionary synthesis, which emerged as an instance-kind sort of field, and why specialties that formed the Evo-devo juncture were all or mostly part-whole specialties. See also Winther (2006) on "compositional" biology.

A select few experimental organisms, notably mouse and fruitfly, were then developed into research "platforms" for inter- or multidisciplinary research through standardization of strains, protocols, practices, and infrastructure.

A *model taxon* is a collection of species, intended to be a monophyletic clade, whose uses also can be described in terms of representational scope and representational targets. Model taxa contrast with both experimental and model organisms as salient models in the ways characterized by Ankeny and Leonelli, and in other ways as well. Consider a third dimension—additional to scope and target—that I will call *payoff* and a third sense of generalization beyond "taxa" and "universal properties, principles, or propositions" that I will call *export*.

### 13.3.3 Export—A Third Notion of Generalization

Some generalizations are better characterized as "exports"—applications or claims of applicability, on the basis of local success with a particular system studied, to some other particular, local system (or instantiation). Exportable "results" are more "general" than non-exportable ones. Monod's quip, read literally, exports results from one species (*E. coli*) to another vaguely identified historical individual (the family Elephantidae or some one of its few living species). The contrast of representational "exports" to taxonomically general "representational scope" is not sharp due to continuing ontological confusion and controversy regarding the nature of species, clades, and named taxonomic groups (see Ghiselin 1997), but my sense is that molecular biologists often generalize over taxa as though these were more or less over instances to kinds. The procedure looks more or less like generalization in physics for the sake of finding law-like or fundamental relationships, or at least for discovery of mechanisms of wide applicability. I use "export" to signal application of a result from one historical individual research subject to another (or a lesson from one research specialty to another) without necessarily supposing that generalization takes some *class* of individuals as its representational scope. The point of introducing the concept of "export" is to characterize how a methodological lesson learned studying a model used in one specialty and applied to studies of another model by a different specialty can work to shape and effect conceptual change in junctures involving both specialties, such as Wake's contributions to Evo-devo, exporting lessons learned from salamanders to inference rules applied in studies of, say, fruit flies, mice, or fish.

### 13.3.4 Lessons Learned Can Become Exportable Payoffs

Moreover, there is a third representational *dimension*—"payoff"—that is as salient to the uses of model systems as representational scope and target. This third dimension is what I have been considering under the label of representational or

exemplary "lessons." Lessons, like results, are payoffs of the labor of research, but even harder won than any empirical result. In many cases, it is the lesson rather than the particular empirical result that is of interest beyond a narrow circle of specialists. Ankeny and Leonelli, and many of the scientists committed to model organisms, talk of the generalization of "results," whereas I consider procedural or inference-rule "lessons" as different *sorts* of "payoffs" to be exported or generalized. An exportable, procedural or inference lesson (payoff "moral") might be something like, 'plot developmental characters to be studied on a robust phylogeny *before* choosing a model organism that is "right" for the job of explaining their development' (cf. Metscher and Ahlberg 1999), or simply "phylogeny matters" as much to developmental explanation as it does to evolutionary explanation (Wake 2009).

Lessons can be exported to or imported from research specialties in a variety of patterns, but here I focus on a few examples that concern specialties contributing to the Evo-devo juncture. Lessons can be exported into or out of the juncture or among specialties contributing to it. Wake et al. (1991) discussed contributions of developmental biology to evolutionary biology and conversely, as well as integrative contributions to the juncture (which they interpreted as an emergent discipline). These modes of export and import are not sharp or easily discernable in practice, since it is difficult to partition scientific research into well-defined specialties distinct from scientific practices "within" junctures like Evo-devo.

One kind of inference-rule in junctures like Evo-devo pertains to lessons one contributing specialty seeks to impose on work within the juncture. For example, a lesson contributed from developmental genetics about Evo-devo inference might be that evolution is more likely to be driven by *cis*-regulatory network change than by structural gene mutations (Davidson 2001). These lessons often function as obstacles to inference another specialty took as valid according to their own disciplinary practice. Davidson's rule blocks evolutionary explanations appealing only to sequence changes because these are claimed to be relatively rare drivers of evolution (or developmental evolution). Another example of a rule that works as a roadblock to inference is Hall's evolutionary rule that "loss of adult organs does not imply loss of the developmental potential to form those organs" (Hall 2000, 177).

Sometimes, a lesson about procedure or inference rules can be *imported* from work in a juncture by researchers drawing a lesson for their own (or a third) specialty, such as an inference rule about adaptation drawn from studies of development in the Evo-devo juncture. Wake draws such an inference about adaptive explanations of trait change as a result of his work on the evolution of digit number in amphibians in the Evo-devo juncture (e.g., Autumn et al. 2002), which he applies to challenge adaptive inference by behavioral ecologists and evolutionary geneticists. The roadblock is that evolutionary convergence on a derived character state, such as a reduced number of digits in frog or salamander species not sharing recent common ancestors, cannot *automatically* be taken as evidence for adaptive evolution unless a history plus developmental mechanism hypothesis is ruled out first. The rule that developmental constraints together with homoplasy (e.g., independent evolutionary loss of ancestral adult characters) can simulate adaptive convergence

appears to be a *universal* roadblock to direct inferences from pan-adaptationist premises or genetic arguments that have been adopted within some specialties in evolutionary biology.

### *13.3.5 Packages of Problems and Phenomena*

A key role for model taxa is to apply lessons learned about methodology and reasoning regarding a particular class of "results" for which model-taxon based research is especially suited: comparative studies, across many species, of variant modes of integration, of multiple mechanisms, to jointly "solve" a package of problems.[15] Each species in the model taxon integrates a set of (evolved, developmentally constrained, inherited) mechanisms from the full range of phenomena characteristic of the clades to which it belongs. "Organisms are integrated systems showing complicated couplings that limit and bias the kinds and directions of trait evolution" (Roth and Wake 1989, quoted in Wake 1996).

Research *problems* of interest to scientists *can* be viewed independently of one another. Thus, research involves picking and choosing among those species which can serve as suitable experimental organisms or else choosing among those model organisms that best suit the problem. Additionally, scientists can view their research problems as "packaged" in varying ways by each species of a clade because "each species is 'an experiment in nature'" (see M. Wake, Chap. 18, this volume). If their research strategy is integrative, scientists are likely to be interested not only in how a variety of particular phenomena are distributed across taxa, but also how the phenomena are packaged into articulated collections and how the *packages* are distributed. Species of a clade may vary in the mechanisms through which its member organisms develop form, and thus *package* the mechanisms that underpin how each solves its package of problems. Model taxa are chosen, designed, and constructed to support the comparative study of species, as representations of particular integrative solutions to packages of problems, across *variation* in packages of phenomena. Comparative research on integration of phenomena and mechanisms is likely to reveal limitations of work with single model organisms because the former project inherently concerns *variation* in the phenomena and mechanisms studied by the latter.

Ankeny and Leonelli contrast the pursuit of single phenomena using an experimental organism (which might be a model organism) with pursuit of whole

[15] Here I am using "problem" in yet a third way (cf. footnote 1). 'Problem' here refers to some environmental "challenge" "solved" by organisms. This is the sense of the term 'problem' that Lewontin (1978) and Gould and Lewontin (1979) found fault with in their critique of adaptationism. Organisms or species do not "solve" "problems" "posed" by "the environment," according to their critique. It would take me too far afield to address this criticism by constructing a fully adequate set of terms to talk about "problems." So, I commit their adaptationist fallacy on this occasion for the sake of convenience.

organisms integrating, as it were, all their phenomena. When Thomas Hunt Morgan chose to "adopt" *Drosophila melanogaster* (literally, off the window sill) as an experimental organism of convenience to teach about and study hereditary transmission, he was developing the fly into an experimental (and teaching) organism (see Allen 1975). But "the fruit fly" transitioned from an experimental to a model organism to a platform for a model system as the Morgan lab (and others) formed a community around the exchange of flies and standardization of both flies and protocols for working with them, developed specific strains to use as materials for investigating a growing range of phenomena, and established a communication network through the Drosophila Information Service (Kohler 1994).

The contrast of single-phenomenon targets (represented by experimental organisms) with full-array phenomena targets (represented by whole, integrated model organisms) specifies the ends of a continuum in the "packaging" of phenomena. Packaging is partly a matter of concern to the organisms of each particular species chosen as a research subject because they must (or tend to) *function* as integrated wholes if they are to survive and reproduce. Packaging is *also* partly a matter of the interests in co-variation of phenomena by the researchers who study them. When Mendel studied seven segregating factors in the development of pea hybrids, he was not *studying* the whole integrated genetic (let alone biological) system of *Pisum sativum*, but rather picking out a "package" of traits and factors of interest for his purposes. The peas had much more inclusive packages to manage in their reproduction, development, and survival.

While making the full array of phenomena of an experimental organism *available* for study by turning it into a model organism that can serve as a platform for research, scientists cannot typically keep the *full* package of phenomena of a "whole organism" in mind when pursuing research problems of interest to them. That would be akin to making and using a totally accurate map, which would have to be as large and unwieldy as the terrain mapped. Practical mapmakers must focus attention on representing a few features of interest in a map intended to be used for a small range of purposes. It is no less important for scientists to restrict their empirical research interests to at most small packages of a few phenomena and problems at a time. Hence the intention to *use* a model organism to *represent* the whole organism package amounts to the hubris of total representational accuracy, or of the intention that the model organism should serve as a platform for *open-ended and as yet unspecified* research by many investigators, with many different interests. Packages of phenomena and research problems in model systems fill the continuum from the single-minded pursuit of a particular phenomenon as representational target (e.g., non-disjunction of chromosomes in *Drosophila melanogaster*) up to the (pipe dream of) total representation of fully integrated whole organisms as a Peircean ideal.

Use of the term "model organism" as the sole element of the contrast class to "experimental organism" with regard to the range of representational targets, underemphasizes the crucial distinction between the use of an experimental organism as a material basis for empirical investigation in a particular laboratory setting (see Griesemer and Wade 1988; Griesemer and Yamashita 2005) and its use as a

*platform* for a research system worked on by a community (Gerson pers. comm.; cf. Evans et al. 2006 for a different context). "Platform" is a useful term, getting at the material, system, and infrastructural aspects of research more than at the problem- or phenomenon-specific choice and use of an experimental organism as the "right organism or tool for the job" (Clarke and Fujimura 1992; Burian 1993).

To sum up, we have several senses of generalization appropriate for characterizing representational scope: taxonomic scope, universals or kinds (property, process, or proposition), and applicability or exportability directly to other *local* situations. We also have two senses of representational target: phenomena or problems, which come in packages ranging from single phenomena up to "whole organisms," but most typically workable packages that can be managed by researchers and their laboratories limited by time, money, skill, sentiment, and background knowledge (Gerson 1976). Finally, we have a distinction between (non-exclusive) *roles* of a model system as exemplary of phenomena or as a platform for research. With these distinctions in mind, I turn to Wake's use of salamander clades as model taxa in addition to model organisms and other kinds of experimental systems to show how model taxa have played their part in the historical emergence of Evo-devo as a "juncture" (Gerson 2007; Chap. 20, this volume) of biological research specialties.

## 13.4 Lessons Learned: Integrating Evolution, Development, and Phylogeny to Understand Packages of Phenomena Across Species of Salamander Model Taxa

Above, I periodized Wake's research according to some conceptual developments in other specialties with which Wake's own specialty of evolutionary morphology intersected in the course of his development of the salamander "system." Here I consider Wake's integrative research projects more specifically and periodize them according to the research problems and phenomenon packages salient to the emergence of Evo-devo in the 1980s. My focus is on three types of publication: (1) empirical work that establishes a baseline for the use of salamanders as a platform for a variety of research problems; (2) empirical results on specific suites of research problems derived from studying patterns of variation in packages of phenomena across multiple species, using approaches that integrate concepts and combine methods from several specialties; and, (3) benchmark reviews that summarize collections of empirical results and afford comparative interpretations that support "lessons" suitable for export to other specialties or junctures.[16]

[16] Wake's publication list up to 2012 has been extremely useful as an aid to building my narrative (Wake n.d.). Given the immensity of Wake's *oeuvre*, I can only sample a few representative works and must ignore his work on a variety of interrelated topics, such as global biodiversity.

In the 1960s, Wake's research was centered on the integration of comparative anatomy and systematics into evolutionary morphology. His 1966 dissertation established a baseline of osteological information for the family Plethodontidae—comparable to working out linkage maps for *Drosophila melanogaster* chromosomes in its empirical, technical, and conceptual significance for the use of salamanders as a platform for a variety of research projects. To a lesser extent, Wake also pursued questions of functional morphology in this early period.

In the late 1960s and early 1970s, Wake began joint work with his student, Eric Lombard, exploring protrusible vs. projectile tongue projection methods (Wake and Lombard 1971; Lombard and Wake 1976, 1977; cf. Griesemer 2013), and with his student John Lynch on the distribution of salamanders in the new world tropics. Wake and Lynch (1976) established baseline information on the distribution and ecology of the tropical plethodontids. Wake also began collaborations with students (e.g., Julie Feder and Allan Larson) and colleagues (Linda Maxson, Richard Heighton) on genetic variation in salamanders, partly with an eye toward investigating the role of microevolutionary processes in producing morphological patterns of macroevolutionary change (Larson et al. 1981).

In 1978, Wake reviewed Gould's 1977 book, *Ontogeny and Phylogeny*, which he read with student Pere Alberch and colleague George Oster (Wake 1978, 1998). Their joint paper with Gould (Alberch et al. 1979) formalized Gould's "clock model" of heterochrony. This, together with prior work in Wake's laboratory and the Museum of Vertebrate Zoology, set Alberch on the path to a series of papers "integrating ontogeny and adaptation" through a combination of comparative, experimental, and mathematical modeling methods (Alberch 1981, 84; cf. Alberch 1980, 1982, 1989; Alberch and Alberch 1981; Alberch and Gale 1983, 1985; Alberch and Blanco 1996). Alberch also urged Lewis Wolpert and Gould to organize a meeting on development and evolution, which eventuated in the Dahlem conference of 1981, organized by John Bonner, Wolpert, Oster, and Silke Bernhard (Alberch to Wake, letter, July 8, 1978; see Wake, Chap. 5, this volume).

In all this work prior to the 1981 Dahlem conference, Wake established baseline morphological information on the Plethodontids, including the large neo-tropical genus *Bolitoglossa*, and on many other salamander species and clades for research on problems of the evolution of form. An example of the latter is the North American tribe Plethodontini, with two true terrestrial genera lacking larval stages (*Ensatina* and *Plethodon*) and one genus, *Aneides*, which includes morphologically adapted arboreal species (Larson et al. 1981). Wake also established baseline natural history, ecology, and geographic distribution information on the tropical salamanders pertinent to questions of the role of natural selection and developmental processes causing the key innovations involved in the tropical radiation into arboreal habitats in this mostly temperate, terrestrial group. Finally, Wake began work on genetic (protein) variation in an attempt to understand how to integrate studies of micro- and macroevolution, about which controversy raged around 1980.

Together with his students and colleagues, Wake identified two packages of phenomena in the 1970s and early 1980s that became significant units of study in

the salamander system for research problems in the Evo-devo juncture that are comparable to the linkage groups and chromosomes of *Drosophila melanogaster*. For convenience, I will label these using the names of important collaborators: (i) "Alberch's package" of autopod (hand and foot) phenomena—variation in the bones of the mesopodium (wrist and ankle), digits, and inter-digital webbing, and body size; and, (ii) "Lombard's package" of tongue and hyoid skeletal bones together with variations in biomechanical function. In a similar but more extended timeframe, a third package emerged: (iii) "Sessions-Larson-Hanken-Roth's package": salamanders tend to have large genomes, large cells, few cells, long cell cycle times, long cell migration times in development, and many have miniature body size and simplified brain structure. (Sessions and Larson worked on genome size and developmental rate, e.g., Sessions and Larson 1987; Hanken worked on miniaturization, especially in *Thorius*, e.g., Hanken 1982, 1983; Hanken and Wake 1993, 1998; Roth worked on cell and brain size, e.g., Roth and Wake 1983, 1985; Roth et al. 1984, 1994, and papers up through about 2001.)[17] Work on these packages yielded not only empirical results that could be held up as exemplary for phenomena of morphological and molecular evolution across the vertebrates; many of the papers cited already offer such generalizations. They also supported lessons learned from integrative approaches to the salamander model taxon (and its sub-models, such as the Plethodontini, Plethodontidae, and *Bolitoglossa*). These lessons were typically presented in review papers that serve as yet a third set of benchmarks by which to periodize the history of Wake's research program.

A representative sampling of key review papers needed to track Wake's contributions to Evo-devo includes the following. Wake (1982), in *Perspectives on Biology and Medicine*, reviewed the state of functional and evolutionary morphology and applauded its re-emergence as a significant and vibrant area after several decades of subservience to medical school training in comparative anatomy. Maderson et al. (1982) is the group report from the 1981 Dahlem conference entitled "The Role of Development in Macroevolutionary Change." One of its themes is to rebalance the role of law-like, mechanistic, or structuralist thinking through the study of development in evolutionary biology after a period of emphasis on contingent, historical factors following the Modern Synthesis of the 1940s–1970s. Wake and Larson (1987) reviewed empirical results from the investigation of several packages of phenomena or units of study from the salamander system, including: paedomorphic evolution of the premaxilla bones in Plethodontids, the Alberch package, the Larson package, and some aspects of the relation of micro- to macroevolution that derived from work on genetic variation in relation to morphological change among salamander species (see, e.g., Parra-Olea et al. 2004).

Wake (1991), in *American Naturalist*, is perhaps the most illustrative review essay with regard to exportable lessons learned about homoplasy from the salamander system. The general lesson is that "Homoplasy complicates phylogenetic

[17] This is not intended as a complete list of significant packages of phenomena developed in the Wake Lab, but only a description of some that were particularly relevant to Evo-devo work.

analysis enormously, but at the same time it enriches our appreciation for the diversity of evolutionary processes" (564). The argument flows from a consideration of the packages mentioned above, with special attention to how developmental constraints temper adaptive explanation. The essay begins with Wake's methodological lesson (repeated from Wake and Larson 1987) that: "an understanding of the evolution of biological form—morphology—was unlikely unless one combined two distinct and independent approaches: neo-Darwinian functionalism and biological structuralism, in the context of rigorous phylogenetic analysis" (1987, 543). The argument is that convergence and other "non-divergent" modes of evolution cannot by themselves constitute evidence of the operation of natural selection; "alternatives must always be considered."

Autumn et al. (2002), in *The Quarterly Review of Biology*, single out the example of amphibian digit loss, comparing salamanders (which tend to lose toe number 5 as they evolve to smaller size) and frogs (which tend to lose toe number 1). Although reduction in digits can be adaptive (e.g., in the evolution of bird wings), it is mainly due to correlated effects of miniaturization in these amphibians. The lesson aimed at adaptationist explanation is stated clearly (and even with a sense of exasperation). In Wake's example and those discussed by co-authors:

> there was a synergy between mechanistic and historical biology that led to discoveries that would have been impossible without this approach. We believe that this integrative approach will advance the field of evolutionary biology more rapidly than an approach targeted solely at fitness and local adaptation because more information is used to reach conclusions, and because conclusions will be easily testable. Biologists should not be threatened by the opportunity to use new tools (e.g., new phylogenetic comparative methods...) to answer mechanistic questions, while at the same time increasing the strength of their evolutionary conclusions. The most interesting questions are generally the ones that involve complex systems. Such systems, however, do not lend themselves to easy answers based on thought experiments. Conclusions made without knowledge of the causal linkage among the parts of a complex integrated system are untestable and are likely to be false. Even if researchers are mechanistically oriented so that evolutionary questions do not interest them, phylogenetic methods may be necessary to make valid comparisons among species. Even if researchers are interested in adaptation and not in mechanism, understanding of mechanism may be necessary to reach a robust and rigorous answer. (2002, 405)

Finally, a key review paper, Wake (2009), in *Annual Review of Ecology and Systematics*, formulated an extensive list of lessons from the full range of Wake's research: "General evolutionary messages from studies of salamanders" (2009, 336). The essay's title sums up the sense that the point of developing the salamanders as a taxon focus or model taxon, beyond understanding these creatures, has been to present a series of lessons both empirical and conceptual/methodological: "What Salamanders Have Taught Us About Evolution." The general lesson of the integrative approaches needed to understand the variety, evolution, and development of complex packages of morphological phenomena is that: "An integrated, hierarchically organized, multidimensional program of research on a taxon illuminates many general principles and processes" (2009, 333).

## 13.5 Conclusion: Lessons Learned

Understanding Wake's views on any Evo-devo topic like the significance of homoplasy requires that we examine his combinations of approaches to the salamander model platform and system. Wake's research often combined heterochrony (evolutionary shifts in the timing of developmental events and processes), homoplasy, homology, phylogenetic inference, developmental constraints on the evolution of form, genetic variation, key innovations, and adaptive radiation into new niches, not to mention speciation, adaptation, and geographic distribution. Wake argued throughout his career, including in general discussions of Evo-devo (e.g., Wake et al. 1991), that these phenomena are deeply entwined, so research problems regarding them are best addressed jointly. I have focused on homoplasy only because it illustrates the role of salamanders, especially the Plethodontidae, and *Bolitoglossa* as model taxa. Without the combination of a taxon focus and desire for integrative approaches, Wake likely would not have made such substantial contributions to Evo-devo in terms of lessons, concepts, empirical results, and students able to replicate, extend, and vary implementations of the salamander system of research.

It would take us far beyond the scope of this broadly historical and philosophical essay on the integrative character of Wake's research program to report and analyze the details of empirical methods and studies through which Wake reached particular results informing these lessons for Evo-devo (but see Griesemer 2013 on the projectile tongue studies). Key recent examples include his analysis of the derived, homoplastic trait of highly webbed feet in the species of the genus *Bolitoglossa* (Jaekel and Wake 2007). In only one species in one outgroup from the seven genera and four families studied was there evidence that webbing is adaptive (as shown from a mathematical model of allometry). For all the others, constraints on size resulting from paedomorphic development cause juvenile webbing to be retained in the adults. It is remarkable how productive the "Alberch package"—identified around 1978—has been, not only to continue extracting important empirical results but also in exporting inference lessons about phenomena of fundamental importance to Evo-devo.

> The repeated evolution of a morphological character in particular has been used to infer adaptive processes. Our results show that this inference may not be robust for individual traits but needs to be considered in a wider context of morphological characters. We conclude that without understanding the developmental mechanisms underlying character evolution it will remain difficult to infer process from pattern. (2007, 20441)

Now, in a sense, drawing lessons from empirical work is neither surprising, nor new, nor exclusive to work with model taxa. It is what anyone does in trying to argue that one's work carries significance beyond the scope of the study at hand. In Wake's case, however, the lessons are directed not only at empirical generalization by displaying salience across wide representational scope, nor only at empirical relevance beyond the immediate representational target phenomenon to other phenomena. Wake has consistently argued that, for understanding the evolution

of complex forms, the approach must be integrative across specialties or else specialists working in isolation are unlikely to succeed due to failures of inference. The salamander biologist's lessons for Evo-devo show how to prevent inference failures by sharpening up the rules of inference that work in the juncture between evolution, development, and phylogeny, *provided* those working in the Evo-devo juncture also view their work as integrative, pioneering an as yet uncharted, emergent, inter-disciplinary space, rather than as separate contributions from a variety of specialties answering only to the logic of their own disciplines.

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# Part IV
# Constraint and Evolvability

# Chapter 14
# From Developmental Constraint to Evolvability: How Concepts Figure in Explanation and Disciplinary Identity

**Ingo Brigandt**

This essay investigates historical and philosophical questions about the concepts of "developmental constraint" and "evolvability". The concept of constraint was central for developmental approaches to evolution in the 1980s but faded into the background throughout the 1990s, seemingly replaced by more important notions, such as evolvability (Sect. 14.1). The historical part of my discussion presents two diverging accounts as to why the concept of developmental constraint moved into the background while the concept of evolvability became more salient. On the first account, the concept of constraint was used to criticize adaptationism but did not underwrite evolutionary explanations, and thus was replaced by the concept of evolvability, which in contrast provides a positive explanatory project (Sect. 14.2). On the second historical account, the concept of constraint has always been part of a positive explanatory project in evolutionary research and thus is continuous with the notion of evolvability (Sect. 14.3). There is some truth to both of these perspectives, yet the second one turns out to be historically more adequate and intellectually more revealing than the first. The two accounts offer different portrayals of how the concept of constraint was understood and employed, so that my historical discussion sheds light on the roles and meaning of the concept of developmental constraint.

Section 14.4 turns to philosophical questions about the concepts of constraint and evolvability. Here the epistemological project is to understand the different intellectual purposes for which scientific concepts are used. Of course the concept of evolvability nowadays figures in scientific explanations, but I argue that other biological concepts (e.g., modularity) are more crucial for explaining evolvability. Rather than providing explanations, the concept of evolvability more effectively fulfills a second, distinct intellectual purpose—setting an explanatory agenda so as

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to provide intellectual identity to a scientific discipline. One of the central aims of evolutionary developmental biology (Evo-devo) is to account for evolvability, and thus the concept of evolvability contributes to its disciplinary identity. In a similar fashion, the concept of developmental constraint provided intellectual coherence to developmental approaches to evolution in the 1980s. In contrast to prevailing assumptions, the agenda-setting function of a certain concept can be as or more salient than the explanatory capacity of this concept, which suggests that more philosophical attention should be devoted to the diverse functions of scientific concepts. I conclude my discussion with remarks about the relationship between evolvability and natural selection (Sect. 14.5).

## 14.1 Historical Background

During the nineteenth century, evolution and development were generally conceived of as closely related phenomena (Bowler 1988). Haeckel's biogenetic law viewed ontogeny and phylogeny as parallel patterns, and postulated a mechanistic link between the two processes. Even those who were less convinced of recapitulationism studied development to understand evolutionary change (Hall 2000). However, this was to change substantially. With the advent of Mendelian genetics, genetics and embryology became separate fields, severing the previously related notions of heredity and development. While genetics and evolutionary theory formed the basis of the Modern Synthesis, embryology and developmental biology were largely irrelevant to evolutionary biology throughout most of the twentieth century (Amundson 2005). Apart from a few isolated instances, such as the notion of heterochrony (de Beer 1930; Gould 1977; Brigandt 2006), only in the last three decades has the possibility of a new (or renewed) link between evolution and development come into view (Bonner 1982). Evo-devo is typically construed as an (emerging) synthesis that actualizes this possibility.

In the 1980s, one focal point for demonstrating how developmental biology mattered to evolutionary biology was the concept of developmental constraint (Seilacher 1974; Gould and Lewontin 1979; Gould 1980a, b, 1989; Alberch 1980, 1982, 1983; Oster and Alberch 1982; Alberch and Gale 1985; Maynard Smith et al. 1985). This was clearly on display in the discussions at the 1981 Dahlem Conference 'Evolution and Development' (Bonner 1982). The question as to how cellular, developmental, and morphological properties restrict possible evolutionary trajectories was addressed directly by three different discussion groups: 'The cellular basis of morphogenetic change' (Gerhart 1982), 'Adaptive aspects of development' (Horn 1982), and 'The role of development in macroevolutionary change' (Maderson 1982). Additionally, it served as the central theme in the individual essay 'Developmental constraints in evolutionary processes' (Alberch 1982).

Despite its historical centrality, the concept of constraint increasingly moved to the background of Evo-devo's discourse throughout the 1990s. Although it remains

relevant for contemporary biologists (Wagner et al. 2000; Schwenk and Wagner 2003), constraint appears secondary to other concepts now prominent at the intersection of evolution and development, such as evolutionary novelty (Müller and Wagner 1991, 2003; Müller and Newman 2005) and evolvability (Kirschner and Gerhart 1998; Gerhart and Kirschner 2003; Hendrikse et al. 2007). How did this transition occur, and why?

## 14.2 "Constraint" as a Critique of a Selection-Centered Approach

One reason for the centrality of the concept of constraint to developmental approaches to evolution in the 1980s is as part of a critique of a neo-Darwinian explanatory framework based on natural selection; constraint is thereby construed in opposition to selection. Even though this concept was introduced, endorsed, and actively used by paleontologists, morphologists, and developmentally oriented biologists investigating evolution, the term "developmental constraint" became widely known within evolutionary biology largely due to Stephen J. Gould and Richard Lewontin's (1979) vehement critique of what they called the "adaptationist program". While offering several different criticisms of adaptationism, the existence of developmental constraints was their central argument.[1] "Spandrels" are non-adaptive outcomes of morphological evolution arising not from selection but from architectural-developmental constraints (Gould 1980a, b, 1989). In addition to the occurrence of non-adaptive traits, other authors in this period addressed the fact that constraints make the production of certain phenotypes impossible (Raup 1967; Alberch 1980, 1983; Alberch and Gale 1985). Natural selection is irrelevant if a variant cannot be generated due to developmental constraints, even if it would have been strongly favored by selection had it arisen. If there are large ranges of developmentally impossible phenotypes in morphological space, then the distribution of form observed across taxa is not so much to be explained by selection but the action of constraints (Alberch 1982).

In addition to grounding a critique of a selection-centered approach, the concept of developmental constraint yielded an indirect critique of the neo-Darwinian framework by way of its commitment to a phyletic gradualism. It primarily was Gould who advertised punctuated equilibrium as an "alternative paradigm" (Eldredge and Gould 1972), while the punctuated equilibrium model was originally introduced by Niles Eldredge (1971) in a form largely compatible with neo-Darwinism (using allopatric speciation as the explanation for rapid change).

[1] "Ever since Gould and Lewontin (1979) raised the specter of nonadaptive architectural constraints in evolution, the invocation of developmental constraints for explaining why certain phenotypes occur has been popular among those skeptical of purely adaptationist approaches" (Reeve and Sherman 1993, 20; see also Schwenk and Wagner 2003).

Still, the punctuated equilibrium model was generally construed as contrary to neo-Darwinian phyletic gradualism, and this model was discussed approvingly by proponents of developmental approaches to evolution, including the Dahlem 1981 conference participants (Maderson 1982). Punctuated equilibrium was one of several macroevolutionary phenomena taken to be significant and related to the concept of constraint because the main explanation for the absence of net morphological change during periods of stasis was attributed to developmental constraints (Maderson 1982). Thus, in addition to the concept of constraint being opposed to adaptationism, it supported the theory of punctuated equilibrium by accounting for phyletic stasis, resulting in a further (but indirect) critique of neo-Darwinism (Gould 1980b).

Developmental constraints frequently have been conceived in opposition to selection (Burd 2006; Pagel 2002; Schwenk 2002). In particular neo-Darwinists saw the idea of constraint as a direct challenge to their evolutionary framework, and reacted to the perceived opposition (Charlesworth et al. 1982; Reeve and Sherman 1993; Amundson 1994). A variety of counterarguments were given, some of which were quite dubious or even disingenuous. Charlesworth, Lande, and Slatkin (1982) claimed that "the concept of organism, including constraints of history, development and architecture, which Gould (1980b) seeks to restore to evolutionary biology, has always been an integral part of the neo-Darwinian theory" (480), but this is in tension with their critique of macroevolutionary approaches based on developmental constraints and their stated defense of neo-Darwinism—a theory in which "selection is regarded as the main guiding force of phenotypic evolution" (474). Despite maintaining that constraints were integral to neo-Darwinism, none of the population-genetic models used by Charlesworth et al. (1982) took the influence of developmental constraints into account effectively. Overall, the main reaction to the threat posed by the idea of developmental constraints was to acknowledge the existence of constraints but claim that their influence on the course of evolution was comparatively small and usually did not override the effects of selection. Developmental constraint and natural selection were viewed as two forces acting in opposite directions, with neo-Darwinists considering the latter as the stronger and more effective force.[2]

Although the concept of developmental constraint can be used to argue against adaptationism (and against any explanatory framework centered on natural selection), this is a limited epistemic role for the concept to play. Merely criticizing an approach and its putative explanations falls short of providing an alternative that explains evolutionary phenomena—and putting forward explanations is the main criterion of adequacy for any scientific approach. This can be illustrated vividly by intelligent design creationism. All that intelligent design proponents have to offer

[2] "[This empirical case] casts considerable doubt on the idea that developmental constraints restrict the power of selection to accumulate small changes in the phenotype" (Charlesworth et al. 1982, 477).

are arguments against evolutionary theory. These arguments may be vacuous and recycled versions of repeatedly debunked traditional creationist arguments, but the most blatant defect of intelligent design is that it does not offer any alternative theory that would explain biological phenomena (such as the structural commonalities and differences across species or their geographical distribution). An analogous point can be made about the concept of developmental constraint. No matter how good it is at exposing the problems of neo-Darwinian theory, only arguing against an explanatory framework does not yield a positive account that actually explains evolutionary phenomena.

On my first historical account, this limitation is one possible reason why the concept of constraint has largely faded in contrast to other concepts, such as evolvability, which embody a positive explanatory project germane to evolutionary change. Evolvability is the ability of organisms to generate heritable and viable phenotypic variation, which forms the mechanistic basis of morphological change. Thus, an explanation of evolvability addresses an evolutionary phenomenon. While considerations about development are essential to an account of evolvability, unlike developmental constraint (as portrayed above), evolvability is not set in opposition to selection, but, in fact, operates on a *different dimension* than selection. In every generation, heritable phenotypic variation is first generated—the manifestation of evolvability—and then natural selection acts on the available variation. Selection presupposes the availability of phenotypic variation, and therefore evolvability, which means that an account of evolvability need not be in conflict with an evolutionary theory centered on natural selection; instead, a theory of evolvability *completes* evolutionary theory. Marc Kirschner and John Gerhart (2005) frame the issue in this fashion: "The Three Pillars of Darwin's Theory of Evolution [are] a theory of natural selection, a theory of heredity, and a theory about the generation of variation in the organism" (10). Darwin had an adequate account of how natural selection works. His theory of heredity (pangenesis, endorsing the inheritance of acquired characters) turned out to be false, but classical genetics filled this gap by offering an adequate account of heredity. Kirschner and Gerhart emphasize that the third 'pillar' is still missing—we are in need of a theory of how phenotypic variation is generated, i.e., an account of evolvability that completes evolutionary theory based on natural selection.

This first historical portrayal stresses how the concept of developmental constraint was construed as being in opposition to selection. The concept was primarily used to criticize adaptationism but it could not deliver evolutionary explanations. A primarily negative depiction of constraint goes some way toward illuminating why biologists came to shift away from "developmental constraint" and focus on "evolvability", setting aside a concept whose only function was critical for one that could be part of a positive explanatory agenda in evolutionary biology (and is not in conflict with the idea of selection). But there is more to the history of the concept of developmental constraint.

## 14.3 "Constraint" as an Explanatory Project in Evolution

In his justly famous analysis entitled "Two concepts of constraint," Ron Amundson (1994) demonstrated that constraints are not just limits on adaptation, which opens up the possibility that "constraint" need not be in conflict with an evolutionary theory centered on selection. Amundson agreed that there is one construal of constraint, used especially by neo-Darwinists, which conceives of them as constraints on adaptation (constraint$_A$). If one's agenda is to explain *adaptation*, then a natural strategy to use is an optimality model. If a predicted optimal character state does not match the observed state, then the modeling assumptions may be wrong or the selectively optimal state cannot be reached due to constraints. Thus, constraint is conceived as restricting adaptation and resulting in suboptimal traits. This is the portrayal of constraint laid out in the previous section, which portrays constraint and selection as antagonistic forces.

Amundson pointed to a curious implication of this notion of constraint. The only way to infer constraints$_A$ is from the presence of suboptimal traits, which presupposes an optimality model. If the only reason for postulating constraints is a prior adaptation hypothesis, then there is no room for a concept of constraint outside of a selectionist framework. However, Amundson emphasized that developmental approaches to evolution introduced a concept of developmental constraint that was independent of a selectionist framework. This distinct conception was constraint on form (constraint$_F$), which focused on the how the generation of morphological form is shaped by developmental processes. Thus far my historical discussion has dealt primarily with critiques of adaptationism and thus with constraint$_A$, but constraint$_F$ is the construal of constraint frequently used by those who introduced the concept of developmental constraint. This complicates the story about why biologists adopting a developmental approach to evolution shifted their focus away from "constraint" toward other notions such as "evolvability". Most importantly, Amundson (1994) argued that whereas from the constraint$_A$ perspective developmental constraints were not operative for optimally adapted traits (so that no developmental considerations are of explanatory relevance), "Developmentalists would claim that their contributions are a proper part of the full explanation of even the most wonderfully adapted trait" (585). This points to a possible *positive explanatory role* for the concept of developmental constraint in the 1980s. If constraint$_F$ plays a role in the explanation of any trait ("even the most wonderfully adapted trait"), then developmental constraint might be the flipside of evolvability.

In my view, defended in more detail elsewhere (Brigandt 2007), evolvability and developmental constraint are identical phenomena, or at least two aspects of one phenomenon. Evolvability is the ability to generate viable and heritable phenotypic variation. This variation has a certain structure, where some variants are more likely to occur than others and changes in some characters tend to be correlated. An account of evolvability is meant to explain why in a given taxon (or for given characters) a certain probability distribution and covariation structure obtains with respect to phenotypic variation (Hendrikse et al. 2007). But developmental

constraint—as already construed in the 1980s—is not only the impossibility of certain variants being produced, but any "bias on the production of variant phenotypes … caused by the structure, character, composition, or dynamics of the developmental system" (Maynard Smith et al. 1985, 266). Therefore, evolvability and constraints both pertain to the way in which heritable phenotypic variation is structured. The concept of evolvability may focus on positive biases (generation of viable phenotypes), whereas the concept of constraint often focuses on negative biases (restrictions on the regular production of some phenotypes), but they refer to different aspects of the same phenomenon.

In Sect. 14.2 I emphasized that evolvability is fully compatible with selection, as it operates on a different dimension: first phenotypic variation is generated due to evolvability, and then, second, selection acts on some of the available variation. The historical portrayal of "constraint" in this previous section assumed that constraint was viewed as a force on the same dimension as but operating in opposition to selection. Although this is the case for the notion of constraint$_A$, it does not hold for a construal that conceptualizes constraint as the flipside of evolvability, such as constraint$_F$. Constraint$_F$ was in fact the understanding used by George Oster and Pere Alberch (1982, Fig. 11): first random genetic change leads to non-random change among available phenotypes due to developmental properties including constraints, and subsequently natural selection acts and results in the eventually realized phenotypes. From this perspective, constraint is not in opposition to selection but rather an orthogonal mechanism.

Apart from making the concept of developmental constraint compatible with evolutionary explanations involving selection, a construal that views constraint and evolvability as two aspects of one phenomenon has the major advantage that it assigns a positive explanatory agenda to the concept of developmental constraint. Accounting for constraint is at the same time accounting for evolvability, so that any study of constraint sheds light on the possibilities for generating phenotypic variation and novelty. To be sure, this is a way one *can* understand the notion of developmental constraint, but for the purposes of my historical discussion the crucial question is whether this *was* the case in the 1980s, i.e., whether in this period constraint was seen as tied to what nowadays goes by the name of evolvability.

Did research on constraint of the 1980s have the generation of morphological variation and novelty in view? We have already seen one reason in support: Amundson's (1994) characterization of constraint$_F$ shows that development was understood to be part of the explanation of the evolution of any trait. A closer look at the primary literature of this period bolsters this interpretation. Even though the term "evolvability" was not common in the 1980s, the published reports of the 1981 Dahlem conference contain the following notions that were seen as tied to developmental constraint: evolutionary "adaptability" (Bonner 1982, 308), "facilitating" evolutionary change (302, 308), evolutionary "opportunity" (90, 101, 103, 217, 221, 329), and (macro-)evolutionary "potential" (108, 109). These terms are closely related to what nowadays is dubbed "evolvability" (and the possibility of novelty). The developmental properties of organisms were seen as generating this

capacity for morphological change: "the opportunities a particular developmental mechanism might hold for future evolutionary change" (107), "developmental mechanisms facilitating macroevolutionary change" (302). Even though there is an impression that developmental approaches to evolution in the 1980s were all about how development restricts evolutionary change and makes the generation of some phenotypes impossible, morphological transformation and macroevolutionary change were of major concern at the Dahlem 1981 workshop—including the issue of evolutionary "novelty" (33, 35, 41, 79, 80, 219, 220, 232, 282, 283, 294, 301, 308, 309, 318). Most importantly for our purposes, evolvability (to use the current term) was seen as the flipside of constraint:

> Developmental factors not only provide constraints but may also be a prerequisite for explaining adaptations of higher organisms. . . . Development specifically deals with the origin and limits of morphological novelty and phenotypic transformation. (Bonner 1982, 307, 329)[3]

Occasionally constraint was equated directly with evolvability: "constraints as such and as evolutionary opportunities" (218, 220); "constraint (what novelties are possible and also—the positive side—what novelties are facilitated)" (308).

Let us take a closer look at how developmental constraint was construed in this period. Five basic effects of constraints were acknowledged:

(a) Constraints make the generation of certain phenotypes impossible (Alberch 1982).
(b) Constraints can result in spandrels, i.e., the adaptive evolution of one trait entailing another trait as a developmental by-product (Gould and Lewontin 1979). Although this pertains to the generation of traits (a more constructive role for constraint), it was used by Gould to emphasize non-adaptive aspects of evolution (Gould 1980a, b, 1989).
(c) Constraints can lead to discontinuous morphological evolution due to thresholds in morphogenetic mechanisms (Alberch 1982). As a result, constraints explain how morphological change can be non-gradual.
(d) Constraints lead to specific sets of available developmental trajectories, such as the bifurcation of developmental pathways (Oster and Alberch 1982). They determine what routes of morphological evolution are possible (and not merely what evolutionary outcomes are impossible). This sense of constraint plays a clear-cut role in explaining morphological evolution: "[development's] contribution will be to provide an understanding of the possible morphological transformations" (Alberch 1982, 327).

[3] Further language of this kind is found throughout the volume: "each mechanism [to build organisms] implies a specific set of opportunities and a specific set of constraints" (Bonner 1982, 242); "innumerable constraints and opportunities based upon inheritance and architecture" (343); "evolutionary potentials and constraints" (229); "Constraints and Opportunities in Tetrapod Limb Evolution" (300). See also Sander (1983): ontogenetic networks yield "(a) network-dependent opportunities for evolutionary innovation and (b) network-dependent restraints effecting evolutionary conservation" (139).

(e) Constraints can lead to such coordination among traits that they vary in an integrated and functional manner (Wagner 1986), shaping the potential for the future evolutionary change and the evolution of complex characters.

In addition to these five basic effects attributed to constraints, developmental approaches to evolution in the 1980s had three distinct but compatible ways of using the concept of constraint as part of a positive explanatory agenda, which often were jointly employed by researchers. *First*, morphological evolution was explained as being due to the influence of both constraints and natural selection (Maderson 1982). For example, David Wake (1991) argued that homoplasy can be due not only to convergent evolution based on selection but also arise from developmental constraints. Instead of replacing selection-based explanations with accounts in terms of constraint, Wake's endeavor was to analyze in what ways selective forces and developmental constraint had influenced the evolution of a certain phylogenetic lineage. A combination of external (selective) and internal (developmental) factors explains morphological trends.

*Second*, the reduction or loss of a developmental constraint opens up the possibility for subsequent morphological change and innovation: "These departures from the ancestral growth patterns involve a release from developmental constraints, permitting the introduction of new growth programs" (Maderson 1982, 303). In the context of the punctuated equilibrium model, constraints are not only the cause of morphological stasis (Sect. 14.2), but the disappearance of constraint was seen as leading to periods of rapid, punctuated morphological change. The origin of novelties can stem from the breaking up of developmental constraints that prevailed in ancestral lineages and therefore the concept of constraint was germane to explaining morphological evolution: "certain basic constraints may be set on development and evolution by the properties of cells themselves, and ... evolutionary 'escapes' from these constraints may mark macroevolutionary change" (Gerhart 1982, 107).

*Third*, developmental constraints provide the possibility of morphological variation and novelty. This is the most interesting explanatory use of the concept, as developmental constraints are not just viewed as preventing novelty (to be broken for novelty to arise), but as evolutionary opportunities (Wake et al. 1991). To use a modern term, some developmental constraints undergird evolvability. One context in which this explanatory role of the concept of constraint was visible was complex and coordinated phenotypic change. Viable and functional evolutionary modification of a complex character requires that changes in many individual traits are coordinated. Günter Wagner argued that developmental constraints can play the role of ensuring coordinated structural variation and integrated morphological evolution:

> [the] evolution of functionally coupled characters is highly dependent on an appropriate allocation of variance and thus depends on an appropriate pattern of developmental constraints. (Wagner 1986, 150; see also Wagner 1988; Müller 1989)

This explanatory task was already in view at the Dahlem conference discussions: "the crucial role that such ontogenetic buffers play in the evolution of novel

structure and function; a novelty is of no use unless it can be functionally integrated with what is already there" (Horn 1982, 220).

Another example from the Dahlem conference of constraints conceptualized as opportunities is the dependence of metazoan cell division and migration on a cell's contact and interaction with other cells. This feature of cells permits the evolution of complex metazoan cellular organization in the first place:

> This dependence would seem to constrain cell behavior, but at the same time it provides the wherewithal, the 'opportunity,' for multicellularity, for the integrated activity of cells in tissues. (Gerhart 1982, 90–91)

These ideas are manifested currently in the viewpoint that structures and processes may be conserved because they are governed by certain constraints, which at the same time allow for modularity and thus evolvability at higher levels of organization (Kirschner and Gerhart 2005; Gerhart and Kirschner 2007). At the 1981 Dahlem conference, structures above the cellular and histological level were seen as entailing constraints as well as creating the ability for morphological change and innovation in the case of adaptive radiations.

> The evolutionary 'choice' of a particular developmental pattern early in the evolution of the body plan of a group of organisms limits the range of future adaptations in a lineage. Yet it may provide unique opportunities for adaptations that are not open to other groups with other body plans. A particularly instructive example, where much is known about both evolution and development, is the five-part radial symmetry of starfish and their relatives, which imposes severe limitations on development and on body form, yet allows extensive adaptive radiation. (Horn 1982, 221)

Developmental constraint and evolutionary opportunity were intimately related in this period:

> Every time that someone mentioned a 'constraint,' someone else reinterpreted it as an 'evolutionary opportunity' for a switch to a new mode of life, and a third person would bring up the subject of the complementary 'flexibility.' (Horn 1982, 217)

This close connection to (what is now called) evolvability also obtained for theories using notions closely tied to the concept of developmental constraint, such as Rupert Riedl's concept of "burden" (Riedl 1978; Wagner and Laubichler 2004) and William Wimsatt's concept of "generative entrenchment" (Wimsatt and Schank 1988; see Wimsatt, Chap. 17, this volume).

In the first historical portrayal (Sect. 14.2), the concept of developmental constraint was *exclusively* (or at least primarily) used to object to a selection-centered explanatory agenda in evolution. On this interpretation, it could only criticize explanations—not yield an alternative explanatory framework—and steadily came to be replaced by concepts supporting a positive explanatory agenda, such as evolvability. But this is not the whole story. Although neo-Darwinians construed constraint as a force antagonistic to selection (in line with the first historical account), the forerunners of Evo-devo often saw constraint and selection as orthogonal issues: developmental mechanisms account for how heritable phenotypic variation is biased or limited, and a subsequent, independent question is how natural selection operates on the available variation. Constraint was tied to what is

now called evolvability in that development was conceived as the basis for the biasing as well as the generating of phenotypic variation. Most importantly, the concept of developmental constraint was part of an explanatory project in evolutionary research of the 1980s; developmental approaches to evolution aimed to account for the possibility of morphological transformation in terms of constraints and other developmental features of organisms. Thus, rather than a concept that did not support an explanatory agenda being replaced with a concept that does, the second and more adequate historical story reveals much more continuity in the shift from "constraint" toward "evolvability". It is largely a rhetorical move, from the limiting aspects towards the enabling aspects that development has for morphological evolution.[4]

To be sure, such a rhetorical shift may matter substantially for the general perception of Evo-devo, and deemphasizing "constraint" while emphasizing "evolvability" may well help this approach be accepted by evolutionary biologists beyond the Evo-devo community. Why does developmental constraint primarily retain negative associations? In the late nineteenth and early twentieth centuries, natural selection was often seen as only negative—exclusively eliminating variants. Many were skeptical about selection being able to produce novel and functional phenotypes. Nowadays it is generally acknowledged that the negative and positive impacts of selection go together; selection reduces the prevalence of maladapted characters and increases the presence of well-adapted characters. Why is it so hard for many evolutionary biologists to view the positive flipside of constraint (i.e., evolvability), instead of identifying it only with restricting the possibility of phenotypic variants? We need not answer this question to recognize the continuity between the concepts of constraint and evolvability, which I emphasize here to highlight neglected facts about the historical understanding and use of the concept of developmental constraint in the 1980s. But it may be that the acceptance of Evo-devo's explanatory contribution will remain decidedly mixed until these negative connotations are transcended. And, despite this perspective of "constraint"-based research from the 1980s being in continuity with current "evolvability"-centered Evo-devo, the latter is not generally accepted as being compatible with traditional neo-Darwinian evolutionary theory even though evolvability and selection operate on different dimensions. Not every evolutionary biologist is happy to embrace the relevance of evolvability (and constraint) for the study of adaptive morphological evolution.[5]

[4] In agreement with several other contemporary Evo-devo biologists, Wallace Arthur views constraint and evolvability as related but deplores the traditional focus on the label "constraint": "It is important, in relation to this question, to acknowledge that such a role for developmental bias is potentially both positive and negative. This is particularly so because in much previous literature the overuse of 'constraint' has painted too negative a picture of the evolutionary role of developmental processes" (Arthur 2006, 1; see also Arthur 2000).

[5] Likewise, even current Evo-devo biologists focusing on the "evolvability" label (and pursuing Evo-devo questions rather than being preoccupied with criticizing adaptationism) point to false assumptions embedded within the traditional neo-Darwinian model, such as the tenets that phenotypic variation is largely unbiased and only gradual morphological change is possible.

## 14.4 How Concepts Figure in Explanation and Disciplinary Identity

A philosophical issue contained in this discussion of the concepts of developmental constraint and evolvability is the different scientific purposes for which concepts are used. This raises epistemological questions about the use of mental representations in scientific practice. Concepts are mental representations, which represent features of the external world. Psychologists construe concepts as cognitive structures, as they contain knowledge (or at least assumptions) about the phenomena they represent. Words or terms are used to verbally express a concept. Concepts—both scientific and ordinary—figure in cognition and reasoning, and can serve multiple, different intellectual functions. Many concepts are used for the purposes of classification. Often concepts are used in combination to draw various kinds of inferences; for instance, assessing how likely the occurrence of an event is (prediction), determining whether some objects have a property given that other objects are known to have it (category induction, analogical reasoning), or assessing how likely a claim is given background knowledge (hypothesis confirmation). Apart from classifying objects and predicting events, some scientific concepts are used for the purpose of explaining events and other phenomena. Concepts as mental representations support explanations if these representations include causally relevant features, e.g., causal processes, mechanisms, or causal laws.

Given that explanation is one of the prime functions of scientific concepts, how does the concept of evolvability fare on this count?[6] To answer this I have to start with some remarks on dispositions, since evolvability is a disposition (Love 2003). For every disposition (propensity), there is also the disposition's characteristic manifestation, and the physical basis of the disposition. Consider the disposition of solubility in water. Salt has this disposition, which manifests itself by the salt dissolving when put in water. A sample of salt has this disposition even if it never dissolves (e.g., because it never comes into contact with water). Thus, dispositions are present even if never manifested. The reason why a disposition obtains is the disposition's physical basis. Salt is water-soluble because of its ionic crystal structure. While the disposition obtains only when its physical basis is present, one can know the disposition without knowing the physical basis: one can ascertain that salt is water-soluble without knowing why. Now consider evolvability, an organism's disposition to generate viable and heritable variation. The manifestation of this disposition is the actual occurrence of some phenotypic variation in future generations. (In the long run, evolvability also manifests itself in phylogenetic patterns of character change, though this pattern is due both to a taxon's particular evolvability and the effects of natural selection.) The physical basis of this disposition is the developmental basis of evolvability—whatever internal and developmental features of organisms make them and their characters evolvable. An account

[6] Equivalent considerations apply to the concept of developmental constraint, given that constraint and evolvability are two aspects of the same phenomenon, as discussed in Sect. 14.3.

of evolvability is meant to shed light on the developmental basis of evolvability, where this developmental basis may differ across taxa.

Does the concept of evolvability support explanations? The disposition of evolvability is the cause of its manifestation (actual variation generated), so that the concept "evolvability" refers to a cause of phenotypic variation. However, this concept offers a rather shallow or superficial explanation—just like the dormative virtue in Molière's *Le Malade imaginaire*. In this play the doctor 'explains' why opium makes people fall asleep with reference to the substance's dormative virtue (its ability to make people sleepy). But an appeal to a 'dormative virtue' seems to be nothing more than a redescription of the phenomenon to be explained. To be sure, the doctor identifies a genuine cause (opium) rather than pointing to a causally irrelevant factor. But a complete explanation only comes from laying out the physical basis of opium's ability to make people fall asleep, i.e., how physical aspects of the substance trigger certain physiological reactions. In the same fashion, the concept of evolvability refers to a causal disposition, and technically speaking explains the disposition's manifestation—albeit in a shallow fashion. A deep explanation of a taxon's evolvability (including the relative likelihood of different variants) only comes from an account of the *developmental basis* of evolvability. Such an account of evolvability is not given by invoking the mere term or concept "evolvability"; instead, other biological concepts that describe this developmental basis do the explaining. For those who are convinced that evolvability is largely explained by gene regulatory architecture (Erwin and Davidson 2009), the concepts of gene regulatory network (GRN), GRN kernel, GRN plug-in, GRN I/O-switch, and gene differentiation battery will be major explanatory ingredients. In Gerhart and Kirschner's theory of facilitated variation, the concepts of weak regulatory linkage, state selection, and exploratory behavior (which are not exclusively manifested at the genetic level, but apply to features on different levels of organization) are central notions used to account for evolvability (Kirschner and Gerhart 2005; Gerhart and Kirschner 2007). Another relevant concept is modularity (Bolker 2000; Schlosser and Wagner 2004). Sorting out the significance of these different concepts for successfully explaining evolvability is an empirical question, to be settled by ongoing research. Some set of these concepts (jointly employed) will play the primary role in explanations concerning evolvability and the generation of phenotypic variation because they causally account for the developmental basis of the disposition of evolvability.

Given that the concept of evolvability can support only shallow explanations on its own, it suggests that we ought to search for another epistemic function of this concept. Consider the question of what kind of discipline Evo-devo is and how it is related to other biological fields. One possible reply is that Evo-devo is an autonomous discipline, with its own methods, concepts, and explanatory models; it determines its major problems and acceptable answers on its own. While the idea of Evo-devo as an autonomous discipline suggests a significant distance from other disciplines, an alternative is to emphasize the integrative nature of Evo-devo and its close connection to other disciplines. Indeed, a much more common position is to characterize Evo-devo as an emerging synthesis of at least evolutionary biology and

developmental biology, if not also paleontology, phylogeny, and morphology (Gilbert et al. 1996; Pigliucci 2009; Wagner and Laubichler 2004; Wake 1996). Although these connections to various biological disciplines are real, a vision of several biological fields merging into a unified whole—even forming one discipline—may well be too optimistic and at odds with the partial disciplinary specialization of contemporary science (Brigandt 2010; Bechtel 1986). A more cautious third view is that Evo-devo is an intersection of different approaches, or a coordination within and among different disciplines.

The characterization of Evo-devo, both in terms of composition and boundaries, is a controversial question (Brigandt and Love 2010, 2012). Evo-devo's identity is still in flux, and it does not yet have all the institutional characteristics of a genuine discipline (Gerson, Chap. 20, this volume). But we do not have to settle on any specific answer about the disciplinary identity and institutional nature of Evo-devo in order to observe that the problem of evolvability provides a significant amount of intellectual coherence. Hendrikse et al. (2007) argue that evolvability is (or ought to be) the central problem of Evo-devo, noting that not all research currently carried out under the label "Evo-devo" speaks to this core concern. If we acknowledge that there might be several main problems on the Evo-devo agenda, then the explanation of the origin of evolutionary novelty is another obvious candidate. Indeed, Alan Love (2005, 2006, 2008) has already emphasized that novelty is what he calls a problem agenda (i.e., a set of interrelated questions). His insight is that problem agendas come with criteria of explanatory adequacy that set standards for what would count as a satisfactory explanation. In the case of evolutionary novelty, the criteria of adequacy entail that the intellectual resources of and ideas from several biological disciplines have to be used (developmental biology, paleontology, phylogeny, etc). The problem agenda's interrelated component questions and criteria of explanatory adequacy give some idea of how the different intellectual components have to be integrated; a problem agenda coordinates interdisciplinary research (see also Brigandt 2010). In a similar vein, I view the *concept* of evolvability as setting a problem agenda, and thereby providing intellectual identity to Evo-devo (even though there are other problems that bear on Evo-devo's identity). The problem of evolvability implies which approaches and disciplines contribute to an explanation of evolvability, guiding interactions among researchers and the efforts devoted to solving this problem. My point is that the concept of evolvability provides a significant amount of intellectual identity to Evo-devo *without* having to answer what kind of discipline Evo-devo is or what its institutional boundaries are. The systematic pursuit of the problem agenda of evolvability will result in an explanatory framework, but we do not have to decide whether this explanatory framework will correspond to exactly one discipline (e.g., by a theory of evolvability being the theoretical core of the discipline of Evo-devo).

I interpret the concept of developmental constraint as having played an analogous scientific-epistemic role in the 1980s. Developmental approaches to evolution at this time clearly did not constitute a discipline, but the concept of constraint did set a problem agenda that provided intellectual coherence to these approaches (even if this fell short of a disciplinary identity). Moreover, the concept of developmental

constraint led to research coordination. Although not as systematic and influential as current Evo-devo efforts, this coordination did guide interaction among researchers from different disciplines—some were paleontologists, some were primarily developmental biologists, and others were morphologists.

One of the primary epistemic functions (intellectual purposes) of scientific concepts is to explain natural phenomena. Some concepts have a higher explanatory impact than others. The concepts of evolvability and developmental constraint support explanations in a weak fashion only (because evolvability and constraint are explained primarily by other biological concepts), but this does not belittle the scientific importance of these concepts. On the contrary, my discussion points to another important role that scientific concepts can have—to set a problem agenda. And in the case of the concept of evolvability, the problem agenda provides some of the disciplinary identity for Evo-devo. As a result, the concept of evolvability fulfills a major epistemic function—it is more important in setting an explanatory agenda than in explaining phenomena. This is analogous to how the concept of evolutionary novelty may be more valuable in setting an explanatory agenda than in categorizing biological traits (Brigandt and Love 2010, 2012). The definition of "novelty" is contested, the issue being how to distinguish novel from non-novel structures, with some arguing that a clear line between a quantitative variant and a qualitative morphological difference cannot be drawn. Some scientific concepts must draw clear boundaries in order to serve the epistemic function of classification. If this was the primary function of the concept of novelty, then its prospects would be dim given the debates about what counts as novel. However, another—and in my view more important—function of the concept of novelty is to set an explanatory agenda. Even if a trait is counted by some definitions as novel but by others as non-novel, a mechanistic explanation of its evolutionary origin is an intellectual achievement. By setting a problem agenda the concept of novelty can play an important scientific role even if its definition remains contested.[7]

## 14.5 Conclusion: How to Distinguish Evolvability and Selection?

My discussion has focused on the historical shift away from the concept of developmental constraint toward the concept of evolvability. One possible historical account is that the concept of constraint—as used prominently in the 1980s—was *exclusively* employed in a critique of selection-centered neo-Darwinian

[7] Setting an explanatory agenda is an epistemic function that is of a very different kind than most other functions of concepts (Brigandt 2012). Scientific concepts typically have the function of representing the natural world by classifying natural phenomena, predicting natural phenomena, or explaining natural phenomena. A problem agenda is not a representation of the natural world, but a goal for scientific practice.

explanations. This would be a major limitation of this concept, since merely criticizing an explanatory framework does not yield an alternative explanation. The modern concept of evolvability undoubtedly figures in an explanatory project about the mechanisms underlying evolutionary change. On this historical interpretation the transition from "constraint" to "evolvability" is the replacement of a concept that cannot support an explanatory project by a concept that can. However, a closer look at the history shows that even though the concept of developmental constraint was used to criticize adaptationism, it was also used by its proponents as part of an explanatory project that attempted to understand how the developmental properties of organisms make integrated morphological change and the generation of novel forms possible—very much akin to how an account of evolvability is understood nowadays. Thus, there is a large amount of historical continuity because the transition from "constraint" to "evolvability" was not a substantial intellectual shift but more of a rhetorical change. I have also addressed different epistemic purposes for which concepts can be used. An obvious intellectual function of a scientific concept is to give explanations. The concept of evolvability does support explanations, but to a small degree only in that the phenomenon of evolvability is actually explained by other biological concepts (e.g., modularity), which lay out what the ability to generate morphological variation consists in. Still, the concept of evolvability fulfills a vital epistemic function by setting out a problem agenda. Accounting for evolvability is one (though not the only) item on the Evo-devo agenda, so that the concept of evolvability contributes to defining the intellectual and disciplinary identity of evolutionary developmental biology. I have argued that the same applied for the concept of developmental constraint in the 1980s, where it generated intellectual coherence and coordinated research even though developmental approaches to evolution did not form a genuine discipline.

I conclude with a puzzle about the relation of evolvability and selection. The manifestation of evolvability is heritable phenotypic variation, and phenotypic change across generations is due to both evolvability and natural selection. It may be hard to distinguish the influence of each empirically in concrete cases, but the question I want to raise instead is what distinguishes them *in principle*. One possibility is that evolvability and selection are two ontologically distinct processes. In each generation, first phenotypic variation is created due to evolvability, and then on a second, separate level selection operates on the existing variation. An advantage of this two-level scheme is that it offers some clarification to different terminologies surrounding constraint. Biologists may speak of developmental constraints, morphological constraints, ecological constraints, and selective constraints (among others), which some have taken as an indication that the notion of constraint is hopelessly muddled (Antonovics and van Tienderen 1991). On a two-level scheme, developmental and morphological constraints belong to the first level (i.e., the generation, biasing, and restriction of phenotypic variation). So-called ecological and selective 'constraints' are not constraints on the generation of variation at all, but they reflect the influence of natural selection and thus belong to the second level.

While it is attractive to construe evolvability and selection as operating on ontologically distinct levels, this neat separation may not be possible given biological reality. The two levels cannot be understood as temporal stages. It is not the case that in each generation there is first a period of time where phenotypic variation is created followed by a period where the variation is selected. On the contrary, evolvability can lead to phenotypic variation at any point of an organism's life cycle, and likewise selection can favor traits at any point of a life cycle. Selection having any actual impact logically presupposes that relevant variants are present, but the variation in a specific character at a particular life-stage need not *temporally* precede the presence of natural selection (favoring or disfavoring some states of this character at this life-stage).

A more promising strategy is to suggest that evolvability is determined by factors internal to organisms, whereas natural selection (selection pressure) is determined by factors external to organisms. However, there are extended phenotypes in the case of behavioral characters, niche construction, and symbioses, so that such heritable phenotypic characters (manifestations of evolvability) are not solely determined by the internal constitution of an organism. Due to phenotypic plasticity, even characters that are within organisms are influenced by external factors. Evolvability is context-dependent—putting organisms in a different environment may change their evolvability (Love 2003). Thus, evolvability cannot be exclusively determined by internal factors. Likewise, what characters are favored by natural selection is not solely determined by factors external to organisms. Organisms from different species can occupy the same environment, but they face quite different adaptive problems and selective pressures—due to the internal differences among organisms from different species.

My diagnosis of this issue is that evolvability, being about generating viable heritable variation, necessarily has to include considerations about the viability of organismal features and the reproductive ability of organisms. Such considerations about viability and reproductive ability are also the core of natural selection, which means evolvability and selection are entwined. Evolvability and selection pertain to the functioning of organismal systems (developmental processes and an organism's interaction with other organisms and its abiotic environment), but I have argued that partitioning the various causally interrelated factors bearing on functioning into internal versus external does not yield an acceptable distinction between evolvability and selection.[8] Changing the internal constitution of a taxon's organisms (e.g., their genome) changes the taxon's evolvability, but may also impact the selection regime. Since some material factors impact *both* evolvability and

[8] Although the two-level model could assign developmental constraints, morphological constraints, ecological constraints, and selective constraints to one or the other level (suggesting that the levels can be distinguished), it is less clear what to make of so-called "functional constraints". Given that functional constraints concern an organism's developmental dynamics/internal mechanics, as well as the effects on survival and reproductive ability, they seem to touch on both evolvability and selection.

selection, it is not possible to separate material features into those constituting evolvability and those constituting selection pressure.

This question is broadly analogous to recent philosophical debates about how to interpret selection and drift, and how to construe their relation (Beatty 1984; Brandon 2006; Matthen and Ariew 2002; Millstein 2002; Stephens 2010; Walsh et al. 2002). While some maintain that selection and drift are distinct forces, others argue that selection and drift are not causes but features of a statistical theory. Some even suggest that selection and drift cannot be separated in principle. As opposed to the above strategy of attempting to argue that evolvability and selection are *ontologically* distinct processes, another possibility is that it is only a *conceptual* distinction made by us. Our mathematical models (e.g., as found in quantitative genetics) simply assume that heritable variation and natural selection are distinct entities without an account of how material factors (features of organisms and their environment) ontologically determine the generation of variation and action of selection as separate processes. From this vantage point, evolvability and selection may be seen as two different *epistemological* perspectives. One explanatory project is to account for evolvability. Here selection is taken as a background condition (whatever features precisely determine selection pressure), and the task is to lay out the factors that result in the generation of heritable morphological variants in a taxon or that bias the generation of some morphological traits over others. Another explanatory project is to account for adaptation. Here the generation of heritable morphological variation is taken for granted (whatever its cause evolvability involves), and the task is to explain why certain traits have been favored in ancestral environments, resulting in adaptive evolutionary change. To some it may seem unsatisfactory to say that evolvability and selection are not distinct in nature but only a conceptual separation that we make in our minds. I acknowledge this reaction but leave the issue for future reflection and scholarly debate.

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# Chapter 15
# Reinventing the Organism: Evolvability and Homology in Post-Dahlem Evolutionary Biology

**Günter P. Wagner**

## 15.1 Introduction

The 1981 Dahlem conference was the first meeting at which a vision of an evolutionary biology integrated with developmental biology was articulated and discussed by a substantive body of distinguished evolutionary and developmental biologists. While it is clear that the ideas associated with the Dahlem conference did not originate there, it juxtaposed them in a transformative way for many participants, including myself. It was the first time that I perceived that a broader transformation of evolutionary biology was afoot, one in which the conceptual scope of evolutionary biological research would expand far beyond what was sanctioned in (mostly) population genetic conceptions of evolutionary theory at the time. The event was enormously stimulating and inspiring for my generation of (then young) evolutionary biologists, and for that reason it is still appropriate to use the periodization explicit in my title. There is a difference between the scope of the evolutionary biology before and after the 1981 Dahlem meeting. But what exactly was different and in what way does it matter?

I will argue that pre-Dahlem evolutionary biology had a tendency to neglect the *organism* as a fact of nature. Part of the motivation that led to the 1981 Dahlem conference was the perception among some evolutionary biologists that the intense focus on population genetics represented a serious shortcoming in the structure of evolutionary theory. Two main views existed about how this situation could be rectified. On the one hand, there was an emphasis on macroevolution pioneered by Stephen J. Gould and Niles Eldredge (Eldredge and Gould 1972). On the other,

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there was the view that an integration of developmental biology into evolutionary theory would allow a broader, organismal understanding of evolution (Gould 1977; Riedl 1977, 1978; Gould and Lewontin 1979; Alberch et al. 1979; Wake and Larson 1987). These two views were not unrelated since a potential link existed between them, namely that the integration of developmental biology into evolutionary theory might be necessary to explain macroevoutionary trends and patterns. That was, for instance, the vision expressed by Rupert Riedl in his 1975 book on "*Order in Living Systems*" (English edition 1978).[1] Similarly, the resurrection of heterochrony by Stephen Gould, Pere Alberch, and David Wake, and the groundswell of interest in developmental constraints belong in this intersection between macroevolution and developmental evolution (Gould 1977; Alberch et al. 1979; Hall 1984; Raff and Wray 1989).

## 15.2 The Ontology of Pre-Dahlem Evolutionary Biology

Whether scientists want to acknowledge it or not, most branches of science are based on a well-defined ontology: a set of concepts with an associated theory of what they refer to (i.e., what things are "real") and how they are valued (e.g., what is relevant and deserves attention). A scientific ontology also excludes concepts that are seen as mere inventions and thus potentially a distraction. The clearest ontology of any science I know is that of classical chemistry, with a relatively short list of basic types of entities acknowledged: the main parts of atoms, electrons and nuclei, atoms themselves, and configurations of atoms, either in the form of molecules or less rigid things like complexes. There also are special subcategories of things, like charged atoms, which are called ions, or "unhappy" but uncharged molecules, i.e. radicals, but essentially that is the world of classical chemistry.

Population genetic theory also has a similarly well-defined ontology. It starts with the gene or its material basis (DNA), and its variants, alleles, and haplotypes. Then the ontology jumps to populations that are statistical aggregates of alleles and haplotypes, and from there to species (if one is so inclined to recognize species as real entities). Beyond that there is little to be said. Yes, there are things in the world called organisms, but they are relegated to second-class citizenship, if at all, either as vehicles for the transmission of genes, or as epiphenomena that do not have theoretical significance within this presentation of evolutionary thinking. One consequence of this ontology is a very restricted view of evolution, culminating with the "definition" of evolution as any change in gene frequency.

$$\text{Evolution} = \Delta p \neq 0$$

[1] In today's language, Riedl's term "order" refers to law-like patterns of phenotypic disparity.

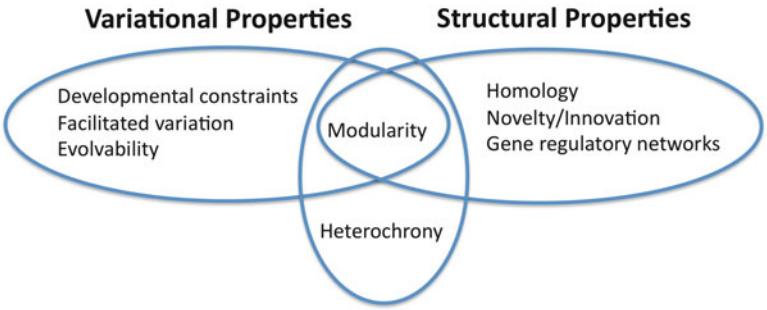


**Fig. 15.1** Topics and concepts of post-Dahlem evolutionary biology. The two larger clusters of concepts refer to variational and structural aspects of organismal design. The overlap between them is modularity, which has both variational and structural aspects. Somewhat orthogonal to these two themes is heterochrony, which played an important role in early investigations into the evolution of development. Heterochrony also relates to modularity, as it assumes dissociability of developmental processes (see, for instance, Gould 1977)

Dissatisfaction with this one-sided view of evolution was a major motivating factor that led to the articulation of an alternative vision, which was built on the idea that development needs to be part of the evolutionary narrative. Several single-author and edited books from the pre-homeodomain era of developmental biology testify to this effect (Gould 1977; Riedl 1978; Raff and Kaufman 1983). My argument is that the 1981 Dahlem conference signified an organismal turn in the history of evolutionary thinking that added three items to the ontological list of evolutionary theory: character/homolog, development, and organism. There are a number of subsidiary concepts around these core ideas: developmental constraint, gene regulatory network, genetic toolkit, canalization/robustness, modularity, evolvability, facilitated variation, homology/novelty, phylotypic stage, deep homology, and the *cis*-regulatory model of developmental evolution. These ideas can be organized into three partially overlapping concept clusters (Fig. 15.1). One cluster contains heterochrony and modularity, the latter a pre-requisite of the former (see Hanken, Chap. 4, this volume). Another cluster can be classified as referring to variational properties of organisms, such as variational modularity, developmental constraints, facilitated variation and evolvability. And finally there is a cluster describing more structural aspects of organismal phenotypes: homology, modularity, novelties, and gene regulatory networks. In the following two sections I briefly discuss what has been learned since the 1981 conference about two key concepts, one variational (evolvability) and one structural (homology/character identity).

## 15.3 Evolvability

Evolvability, simply put, is the ability to evolve (Wagner and Altenberg 1996). As such, it is an unremarkable concept, since it seems to state the obvious; since evolution has happened, organisms have to be evolvable. The concept derives its

theoretical bite, however, from a number of observations showing that evolvability is not inevitable.

The basic neo-Darwinian model of evolution is as simple as it is powerful. Heritable phenotypic variation arises spontaneously through mutations at the DNA level. If one or a combination of these mutations endows the organisms with a fitness advantage, then these mutations and their associated phenotypes will spread in the population. There is no doubt about the basic correctness of this schema. But things become interesting when one asks what is the chance that a random mutation at the gene level leads to an advantageous phenotypic change. The answer is: it depends on the way genetic variation maps onto phenotypic variation (also called "the genotype-phenotype map"). This mapping is best understood for artificial systems and mathematical models, but there have been recent advances which suggest answers for proteins and RNA, as well as for the biology of the cell (Gerhart and Kirschner 1997).

The basic observation is that *not every* system which can be conceptualized as having a genotype and phenotype is evolvable by random mutation and selection (Wagner and Altenberg 1996). Consider a conventional computer code as a metaphor for a genotype and the executed program output as the phenotype. As early as the 1960s, people tried to evolve computer programs in accord with the Darwinian model and miserably failed when using conventional programming languages of the time, such as FORTRAN. This does not mean that there are no programming languages that can evolve new programs by mutation and selection; many can be found in evolutionary programming, an active field of computer science. The key difference between conventional programming languages and evolvable ones (e.g., AVIDA) is how allowable "mutations" affect the syntax of the program. For instance, older programming languages directed a "jump" from one statement to another by line number in the code. A consequence of this is that any "mutation" that leads to a deletion or duplication of a line of code will misdirect the Jump instruction when the "indel" (insertion and/or deletion) happens between the Jump command and its target line. In contrast, evolvable programming languages organize the Jump command by tags, meaning that a tag at the target line defines the target of the Jump. A tag is recognized therefore regardless of where in the program the line is located. Hence, indels of lines of code will not affect the execution of Jump commands unless the deletion or duplication affects the tagged line itself. This example illustrates that the organization of a more or less complex system determines the probability that random changes can lead to functional and sometimes even advantageous changes.

Theories of evolvability arose independently in mathematical population genetics (Fisher 1930; Fisher's geometric model [FGM]), evolutionary computer science (Holland 1992; genetic algorithms, genetic programming), and engineering (Rechenberg 1973). Here I will briefly introduce FGM since it motivates much of recent research into issues like the "cost of complexity" (Orr 2000) and the structure of the genotype-phenotype map. It represents a significant advance in understanding why complex organisms are as evolvable as they are.

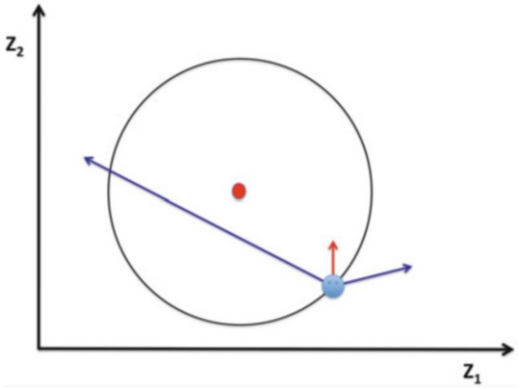


**Fig. 15.2** Fisher's geometric model of adaptive evolution. Each point of the (here two-dimensional) plane represents a phenotype; characters $Z_1$ and $Z_2$ are the dimensions of the phenotype space. The adaptive optimum is indicated by a *solid small dot*, and the circle around it represents phenotypes with the same fitness. The *solid dot* on the large circle represents a phenotype and the *arrows* pointing away from that phenotype represent phenotypic displacements caused by different mutations. The *vertical arrow* represents an adaptive mutation, i.e., the derived phenotype is closer to the optimum. The other *arrows* are deleterious mutations that decrease the fitness of the phenotype

FGM assumes that the phenotype of an organism can be represented as a vector of real numbers, each of which is the state of some quantitative character (e.g., limb length). The model further assumes that each mutation acts by changing this vector in some random direction by a finite amount (Fig. 15.2). Finally, the model assumes that fitness is maximal at some point in this *n*-dimensional "phenotype space" and decreases monotonically with the distance from the optimum. Fisher then used this model to calculate the probability of an increase in fitness given the geometrical constraints of the model. One conclusion he drew was that the rate of adaptation decreases dramatically with the number of dimensions, i.e. with the complexity of the phenotype. His other conclusion was that the probability of improvement approaches an upper limit of 50 %, irrespective of complexity, as the size of the mutational change in phenotype space becomes small with respect to the distance to the optimum. From these two results, Fisher concluded that evolvability is guaranteed even for very complex organisms (i.e., organisms with a highly dimensional phenotype space). This is the basis for the emphasis on small mutations in classical neo-Darwinian evolutionary theory.

The flaw of the conclusion drawn from FGM is that small phenotype changes also carry with them correspondingly small fitness effects. Thus, even small mutation effects do not guarantee evolvability since natural selection still needs to select these mutations (Kimura and Crow 1978; Orr 2000). A number of papers have been published over the past 20 years that generalized the original model and tested the robustness of the results from FGM (for a summary, see Wagner and Zhang 2011). One conclusion from FGM is known as the "cost of complexity" argument, which predicts that an increase in complexity leads to a more than

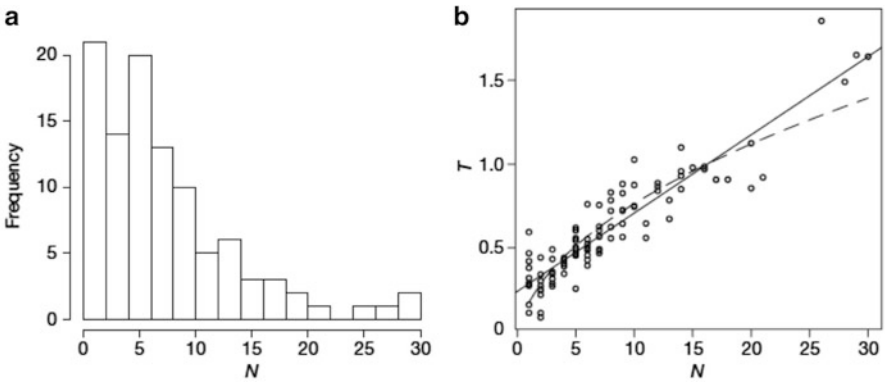


**Fig. 15.3** Distribution of genetic effects on 70 skeletal characters in an experimental mouse cross. (**a**) Frequency of genes with *N* pleiotropic effects. Note that the majority of genes affect far fewer traits than the 70 measured characters. (**b**) Increase of the total effect *T* of mutations with the number of traits affected. This increase in total effect size contradicts the assumptions of the model by Orr (2000) that underlie the cost of complexity argument (Data from Wagner et al. 2008)

logarithmic decrease in evolvability (Orr 2000). This implies that a decrease in evolvability seems to be an inevitable consequence of increasing complexity. However, there are novel experimental results that challenge this conclusion.

One key assumption of the model supporting the cost of complexity argument is that each mutation potentially affects all phenotypic traits of the organism. This assumption seems reasonable given the pleiotropy of many major effect mutations (Wright 1968), and is enshrined in the principle of "universal pleiotropy."[2] The structure of FGM assumes universal pleiotropy in the sense that each mutation can potentially affect each character and has been used this way in evolutionary biology. However, until recently, this assumption had not been tested rigorously on large data sets. In one study the Cheverud lab produced QTL maps of genes affecting 70 skeletal traits in the mouse (Kenney-Hunt and Cheverud 2009). The surprising result was that the vast majority of QTL affected only a small number of measured traits—less than 10 % (Wagner et al. 2008) (Fig. 15.3). The generality of this conclusion was then confirmed on a number of large data sets from yeast, nematode, and mouse, showing the same pattern of low pleiotropic effects (Wang et al. 2010). There are a number of other studies that point in this direction and lead to the conclusion that pleiotropy is quite restricted or modular and not even close to universal (Wagner and Zhang 2011).

Large scale data from QTL, mutation, and knockdown effects demonstrate that a key assumption of FGM and the cost of complexity argument is not fulfilled,

[2] Most evolutionary biologists interpret universal pleiotropy to mean that mutations potentially affect all characters (universal *across phenotypes*). However, a close reading of the historical sources for the term (Fisher and Wright) clearly show that universal pleiotropy was understood as universal *across mutations*, i.e. the principle that all mutations have pleiotropic effects, not that all mutations affect all traits.

thereby explaining the evolvability of complex organisms (Wagner and Zhang 2011). Does this mean that the cost of complexity argument is useless? The obvious answer is no, and goes to the heart of the reason why evolvability is an important concept in any theory of organismal evolution. It shows that in order to be evolvable, complex organisms must be organized in such a way as to avoid the "curse of dimensionality" that is intrinsic in the variation of complex systems. The curse of dimensionality is a mathematical fact and has to be true given certain assumptions. Hence organisms and the nature of genotype-phenotype maps are an important part of any population genetic theory of evolution since only organisms with an appropriately structured genotype-phenotype map can escape from the curse of dimensionality. This explains how complex organisms avoid the cost of complexity and exhibit high degrees of evolvability (in the sense of being responsive to natural selection). Therefore, the organism and its variational properties are an essential part of any conceptual framework for evolutionary biology, and thus the variational properties of organisms have theoretical significance—they are more than a vehicle for genes or an epiphenomenon of gene frequency changes.

At this time, an important open question is how organisms acquire a genotype-phenotype map that endows them with evolvability sufficient to answer environmental challenges. It could be coincidental to how gene regulatory networks evolve or an actively selected property (Kashtan and Alon 2005; Crombach and Hogeweg 2008; Draghi and Wagner 2008; Pavlicev et al. 2011). The jury is still out on this issue (Pigliucci 2008).

The question of how evolvability is maintained in spite of the immense material and functional complexity of organisms is central for understanding how an immense array of complex organisms have arisen and can maintain their ability to adapt to changing environmental conditions. Organismal structure, i.e. the statistical structure of the genotype-phenotype map, determines evolvability and therefore plays a central role in the explanation of adaptive evolution. Evolvability is one of the biological attributes in which organismic structure plays a critical explanatory role and thus the organism has theoretical and conceptual relevance, if not centrality.

## 15.4 Homology and Novelty

A decidedly unpopular topic for most of the twentieth century was homology. Widely recognized as the basis for all of comparative biology, but frustratingly difficult to nail down, it was largely abandoned by evolutionary biologists (Amundson 2005). During dinner at the meeting of the Society for the Study of Evolution in 1988, immediately before my first talk on homology at the President's symposium, a prominent population geneticist said: "whenever someone starts talking about homology, I walk out of the room."[3] Since then, however, the topic

[3] In fact he did walk out the room as soon as I started my talk. To be fair, however, he had a meeting and told me beforehand that he had to leave.

of homology has come to the fore with the rise of evolutionary developmental biology, as witnessed by the number of papers and books published since then on this topic. Once biology returned to questions about the evolution of development, homology was an unavoidable topic; it is one of the legacies of the organismal turn in evolutionary biology.

The basic issue of homology is the fact that multicellular organisms are composed of, for the most part, recognizable building blocks, such as different cell types, tissues, and organs, as well as other more inclusive body parts, like limbs and brains. What is interesting is that these building blocks often have a high level of historical continuity—many of them characterize major metazoan or plant clades. As characteristic apomorphies of major clades, these building blocks have to be as old as these clades (hundreds of millions of years). They also have to retain their recognizable identity over this time during which these body parts evolve. Furthermore, building blocks originate at fairly well defined times in phylogeny and thus have circumscribed lifetimes. When they originate they are recognized as novelties, and this is the reason why the problem of homology is closely tied to question about evolutionary novelties (Müller and Wagner 1991; Wagner 2014).

Homologues are thus units of phenotype organization for higher organisms with a high tendency to retain identity for long periods of time (Brigant 2003). The question is how to explain their nature and origin in light of the progress achieved in research on the molecular biology of development over the past three decades. I think we are now poised to answer this question, i.e., to make a productive connection between the abstract notion of homology and the specifics of mechanistically developmental biology. In particular, this connection is achieved between character identity (homology) and gene regulatory networks (developmental mechanisms). The gist of this connection can be seen in a simple, rhetorical syllogism, borrowed from Eric Davidson:

(a) It is broadly agreed that different body parts are different because each is able to express a distinct gene regulatory program (i.e., character identity is rooted in differential gene expression).
(b) By implication, character identity must be related, somehow, to the gene regulatory networks that enable differential gene expression.

This syllogism emphasizes a kind of consensus about the linkage between anatomical features and the empirical details of developmental mechanisms. The argument for this connection can be framed more philosophically: the gene regulatory network perspective on homology leads to a concrete interpretation of the otherwise hard-to-pin-down, abstract notions of homology and character identity. As a consequence, it fleshes out the meaning of organismal complexity: a complex organism is composed of differentiated, historically continuous building blocks, which are underlain by distinct gene regulatory networks, and have been recognized by comparative anatomists for more than 200 years as homologues.

Before the significance of this concrete interpretation can be recognized, it is necessary to overcome a difficulty that has plagued homology for more than a century. It has been clear since the first comparative studies on embryonic induction

**Table 15.1** Comparison of concepts relating to gene identity and character identity

| Genes | Morphological characters |
|---|---|
| Locus | Character identity/homology |
| Allele | Character state |
| Ortholog | (Special) homology |
| Paralog | Serial homology |
| Gene duplication | Innovation (or novelty?) |

by Mangold and Spemann that homologs (i.e., corresponding body parts) can develop from different mechanisms (Spemann 1915). This fact was a curiosity in early developmental biology but became unavoidable with the advent of comparative molecular genetics and has been documented in great detail (Hall 1994, 2003; Wilkins 2002). This leads to a puzzle: if different genes can, in different species, regulate the development of the same body part, then how can character identity be tied to gene regulatory networks? This seems to contradict the concrete interpretation that connects homology and developmental mechanisms. To solve this puzzle we need to reflect on what homology really means.

Recall Richard Owen's original definition of homology: "the same organ in different animals under every variety of form and function." The difficulty is to explain what is meant by "the same organ." It is clear that Owen does not mean a very high level of similarity because he is speaking about sameness "under any variety of form and function." This difficulty can be addressed if we make a distinction between character *identity* and character *states*. To biologists trained more in genetics than in comparative anatomy, the distinction is perhaps best explained by analogy to the distinction between gene *loci* and *allele*: character identity is to character state what a gene locus is to an allele (Table 15.1; for discussion, see Wagner 2007). A gene locus is a historical entity that forms a line of descent, while the different forms of a gene are called alleles. In the same sense, a character derives its identity from the fact that it is passed down the generations and forms a lineage (like genes form lineages of descent), but characters can be instantiated by different shapes, forms, and functions, i.e. in different character states.

In other words, the identity of a gene is also not defined explicitly, but sometimes is recognizable from similarities in nucleotide sequence. Gene identity is a highly theoretical concept, which assumes that genes are transmitted in a regular fashion from generation to generation. It is this genealogical context that defines the identity of the gene. Homology can be understood in a parallel fashion: parts of the body are inherited from generation to generation and thus form a lineage tree. During the process of descent, modifications occur that affect the similarity of the different manifestations of the character in different species.

The fact that character identity is conceptually decoupled from phenotypic similarity makes it clear that differences in the genetic mechanisms realizing the character are to be expected for the "same" character in different "forms and functions." A different question, however, is whether all parts of the genetic makeup of a morphological character are equally variable and only reflect different

character states. In fact, the variability of the gene regulatory network underlying characters is highly structured: some aspects are variable and others conserved. For instance, the signaling pathways used to induce the differentiation of specific body parts are, surprisingly, highly variable. The conceptual tension discovered by Mangold and Spemann between early developmental biology and homology was about the variability of inductive signals. At the same time, other parts of the gene regulatory network are highly conserved, such as those that communicate the signals from outside the cell to the genes that actually build the phenotype of the cell or character. These networks have been called "core networks" or "character or cell identity networks" (Wagner 2007).

In spite of the variability of character development due to evolutionary changes in character state, each generation has to have a molecular genetic "device" to allow a subset of the cells in the embryo to express a different set of genes than others. This is well understood in the case of cell type identity, where a number of these core gene regulatory networks have been identified (see Fig. 15.4a). Hence, as long

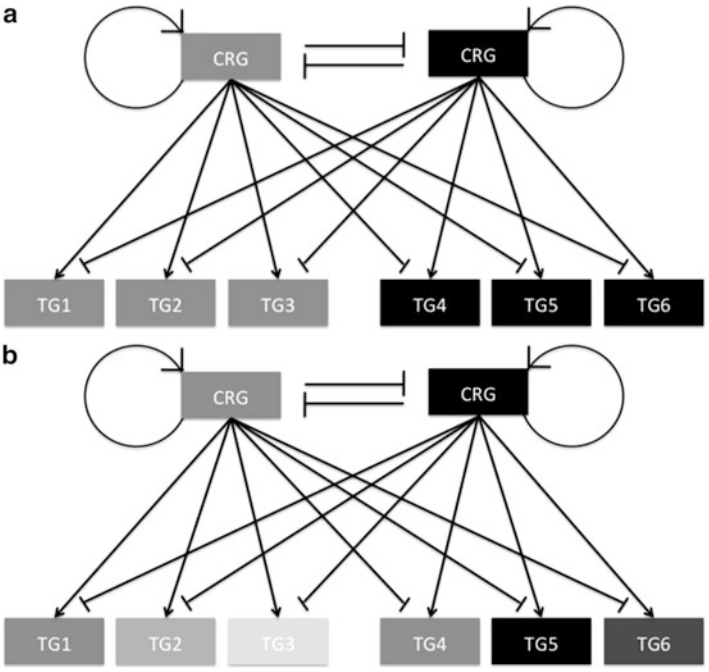


**Fig. 15.4** Cartoon model of the gene regulatory network structure underlying cell type identity according to Graf and Enver (2009). (**a**) This cartoon represents two cell fates: "*green*" and "*red*" cell type identities. Each identity is controlled by a set of core regulatory genes (CRG), which form an auto-activating network that inhibits the CRG for alternative cell identities. Each CRG network activates the target genes (TG) of its own cell type and inhibits the expression of TG for the alternative cell identity. (**b**) This cartoon illustrates that the same CRG network can regulate the expression of different sets of target genes (indicated by different colors). This means that the character state, here the phenotype of the cell, is an independent property from the cell type identity

as the phenotypic character exists, there has to be some kind of core or character identity network causing the differential expression of genes. The existence of a distinct character identity is linked to the continuing existence of a corresponding character identity network, and it is these networks that are the most conserved parts of the gene regulatory network underlying the development of a character or cell type. *Homology,* i.e.*, historically transmitted character identity, is explained concretely by the existence of core gene regulatory networks.*

This idea can be summarized in a three layered cartoon model of the genetic control of development (see Fig. 15.5). The gene regulatory network is presented from the perspective of a cell that receives signals from other cells (or the environment) and directs the activity of downstream target genes that realize the actual phenotype of the differentiated cell, such as enzymes or extracellular matrix proteins. The first layer of the model contains *positional information signals* that tell a cell where it is located in the embryo and thus what cell fate it has to assume. These are mostly extracellular signaling molecules like cytokines and hormones. To the surprise of many, this upstream level of gene regulation is also highly variable between species and thus not rigidly tied to character identity. The next level is a gene regulatory network that takes the input from the positional signals and translates it into a distinct gene regulatory network state. These are the genes that have been called core networks for cell types (Graf and Enver 2009; Fig. 15.4a) or, more generally, character identity networks (Wagner 2007; Fig. 15.5), or "kernels" sensu (Erwin and Davidson 2009) for body regions. These gene regulatory networks are highly conserved and quasi-rigidly linked to character identity and homology. Downstream of the character identity network are the genes that realize the

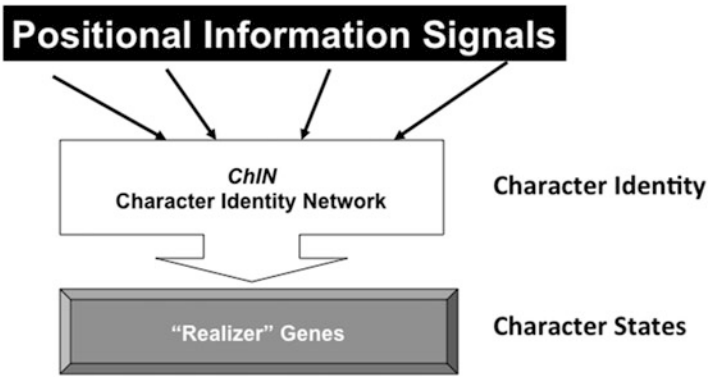


**Fig. 15.5** Three tier model of developmental regulation. At the *top* is the layer of positional information signaling that gives a cell information about where in the embryo it is located and what fate it is to assume. This level of regulation turns out to be highly variable between species. These signals are integrated by the core regulatory network or character identity network, which transforms the positional information signals into the activity of target genes. The lowest level contains the target genes regulated by the ChIN. These genes determine the phenotype of the cell or the character. Comparative developmental biology reveals that the ChINs are highly conserved among species and thus are a candidate for the material basis of character identity

phenotype of the character. This latter layer of genes is responsible for the character state and thus has to be as variable as the character state itself. Overall, this model suggests that the material (concrete) basis of homology is found in the character identity network enabling the expression of the character state specific genes.

This model also illuminates the abstractness of the homology concept, i.e., that character identity is not tied to any particular phenotype of the body part, as Owen insisted long ago ("the same organ under every variety of form and function"). The character identity network is "abstract" in the same sense because it does not rigidly determine the phenotype of the corresponding organ. This was perhaps first shown by the role of the *Ubx* gene in determining hindwing identity in insects, which provides another good example of the difference between character identity and character state, as well as the nature of character identity genes and networks. Ancestrally, pterygote insects have two pairs of wings on their second and third thoracic segments, the forewing and the hindwing. Most extant insects have both structures, but not all of them have wings in the traditional sense, i.e., body appendages dedicated to flying. For example, bees and wasps have four wings in the functional sense, but flies have only two, which are homologous to the forewings of the other insects. The third thoracic segment, however, does have a dorsal appendage that is homologous to the hindwing of other insects, but it is not a wing in the functional sense. This dorsal appendage is a haltere, a club-shaped appendage that acts as a sense organ. Hence, we have two character identities, forewing and hindwing, and two character states, a wing blade and a haltere. The haltere is the character state of the dipteran hindwing. From genetic studies of *Drosophila* (a dipteran) it became clear that the expression of *Ubx* is critical for the development of the haltere. The famous mutation that compromises *Ubx* function leads to the duplication of the forewing on the third thoracic segment. But it was not clear whether *Ubx* is necessary for the haltere phenotype or for hindwing identity. The answer came with two studies. The first showed that *Ubx* is also expressed in the blade shaped hindwing of four winged insects like butterflies and the second showed that a knockdown of *Ubx* in the flour beetle *Tribolium* leads to the development of two sets of elytra (Tomoyasu et al. 2005).

One way beetles and their relatives differ from other insects is that their flying wing is the hindwing and their forewing structure evolved into a protective cover, called elytra. Thus, elytrum is a character state of the forewing of beetles. Although some have interpreted the phenotype of the Drosophila *Ubx* mutation as an atavism in which the ancestral blade character of the hindwing has been restored, the *Ubx* knockdown phenotype of *Tribolium* cannot be interpreted this way. There is no insect in which the hindwings were ever shaped as elytra, and it would also not make much sense functionally. Hence, it is clear that removing the function of *Ubx* leads to a change in character identity, namely a switch from hindwing to forewing identity (Deutsch 2005). In addition, these results shown that *Ubx* determines hindwing identity regardless of character state; the function of *Ubx* in determining hind wing identity is "abstract," i.e., divorced from the character state.

The features of character identity networks are best explored in the so-called core networks of mammalian cell types. The salient structural aspects have been

summarized by Graf and Enver (2009) (Fig. 15.4a). The Graf-Enver model has two layers of gene regulation: core regulatory genes and target genes. Core regulatory genes have four basic functions: (1) positively regulating each other's expression to provide stability to the gene regulatory network state defining a cell type ("autoactivation"); (2) suppressing the activity of gene regulatory networks that represent alternative cell types; (3) activating the target genes that realize the phenotype of the respective cell type (i.e. "realizer genes"); and, (4) actively repressing the realizer genes of alternative cell types. The Graf-Enver model helps to explain the abstract nature of cell and character identity. Cell identity is tied to the activation of alternative core gene regulatory networks that regulate the target genes responsible for the phenotype of the cell. The connection between regulatory genes and target genes, however, is not rigid, since it can be altered easily by changes in the *cis*-regulatory elements of the target genes. Hence, the phenotype produced by the target genes can change without any corresponding changes in the core regulatory genes tied to cell identity (Fig. 15.4b).

A mechanistic feature not captured by the Graf-Enver model but that is important in determining alternative gene regulatory network states (and thus cell fates) is the cooperativity of the transcription factors coded for by the genes of the core regulatory network (Fig. 15.6). By "cooperativity" I mean the fact that transcription

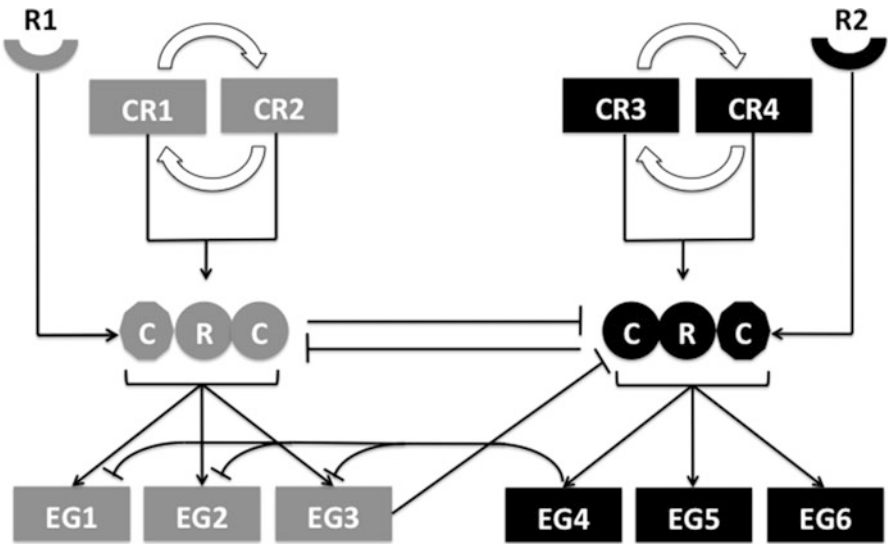


**Fig. 15.6** Extended Graf-Enver model of cell type identity. Here it is shown that core regulators (CR) produce transcription factor proteins that form a physical complex, and that the formation of the complex can be influenced by signaling through the cell surface of nuclear receptors (R). This complex can be called a core regulatory complex (CRC) and is the protein species that cooperatively regulates the target genes. The antagonism between alternative cell fates can be realized in a variety of ways, as indicated by the regulatory links between the "*green*" and the "*red*" network. For instance, the formation of the CRC for the alternative cell types can be inhibited by the CRC of the focal cell type, or a target gene of one cell type inhibits the formation of the alternative CRC. It is also possible that one of the target genes of the *red* cell type is inhibiting the expression of the target genes of the *green* cell type

factor proteins form physical complexes. These physical complexes are the actual regulatory entity acting on target genes. Transcription factor cooperativity has been documented in many systems and also contributes to the crisp distinction between alternative cell types, rather than a gradual blending of one type into the other. It also may be a factor in the evolutionary stability of core regulatory networks. Cooperativity requires that the interacting transcription factor proteins be co-adapted to each other. Once such a co-adaptation has evolved, however, the transcription factor protein becomes non-equivalent relative to other members of its transcription factor family (e.g., *Hox* or *Pax*). As a result, the co-adapted transcription factor protein is not easily replaceable by orthologous transcription factors. Through protein–protein interaction among the transcription factor of the core network, the members of the network are bound together as an integrated gene regulatory network in evolution. That might explain why core networks tend to persist like homologies, i.e. as historical identities.

In this section I have argued that the old and abstract notion of homology can become integrated with our increasingly sophisticated understanding of development and gene regulation. I hasten to add that my viewpoint is far from mainstream, and it will take time to determine whether this model is robustly exemplified. There are sufficient empirical findings to initially support this view (Wagner 2007, 2014), but it is too early to say how general these findings are. Nevertheless, this view of homology serves as an illustration of how an organismal perspective—informed by developmental genetics—can lead to a more comprehensive view of organismal evolution.

The recent, post-Dahlem research on homology, originally spurred by discoveries in comparative developmental genetics, puts questions about the structure of the organism at the center of evolutionary biology. Homologues are building blocks of organisms and their evolutionary history is the history of body plan structure. Therefore homology and character individuality are central for capturing what organisms are and how their traits evolve.

## 15.5 Coda: The Role of Concepts in the Sciences

The 1981 Dahlem Conference on Evolution and Development signified a conceptual turn in evolutionary biology, a turn from a population genetic view to a view that includes an organismic perspective. I offered two examples of advances that are predicated on this organismic perspective: evolvability and homology or character identity. Since neither of these ideas are wholly new, one might ask: how is current evolutionary biology different from pre-Dahlem evolutionary biology? The answer is not in the presence of these concepts but rather the roles that they now play. *In my view, a concept is only as good as the research program it inspires*. Thus, whether an idea is "good" depends on the skill of its proponents to turn that idea into a productive research program; concepts should play the role of inspiring and guiding progressive empirical and theoretical investigation. One way how

this occurs is through giving an abstract idea a more concrete interpretation, as illustrated in the case of homology and character identity networks. Importantly, technical limitations and opportunities influence the degree to which a concept can play this kind of role at any point in time. Hence, whether any of the ideas explained above will be useful in the near future depends on what research related to them is possible now. Since many of these ideas have a holistic bent—evolvability is not the attribute of a single gene but of a whole system of interacting genes, cells, and tissues (and even individuals) that make the organism—the kind of data relevant to addressing these questions requires a certain scale that was unattainable for much of the twentieth century. Only with global tools, such as genome sequencing, functional genomic techniques (e.g., RNA-Seq; see Wang et al. 2009), and systems biology in general, are data relevant to these questions accessible. To cite just one example, the definitive paper on the question of the extent of mutational pleiotropy (Wang et al. 2010) used several very large datasets to test for the phenotypic scope of genetic variation. Datasets of that size have never before been available to molecular biology. This suggests that the crucible for the ideas discussed and inspired at the 1981 Dahlem conference is *now*. The true value of these ideas will only be revealed if the organismal branch of evolutionary biology is able to seize the opportunities that have accumulated over the past 30 years and elucidate a more comprehensive understanding of evolution.

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# Chapter 16
# Internal Factors in Evolution: The Morphogenetic Tree, Developmental Bias, and Some Thoughts on the Conceptual Structure of Evo-devo

**Wallace Arthur**

## 16.1 Introduction

Those of us who have become practitioners of Evo-devo arrived via many different routes, starting at various disciplinary bases, from molecular genetics to paleontology. My own starting point was population biology—and in particular a mixture of population genetics and evolutionary ecology. My PhD (written in 1977) was based on changes at the population level; the individual organism (and its development) did not feature prominently. I became interested in Evo-devo in 1980 (before the label existed) in a sort of Eureka moment, which resulted from reading a paper on developmental genetics that I happened upon accidentally (Garcia-Bellido et al. 1979).

That paper described the discovery of developmental compartments in the "model animal" *Drosophila melanogaster*. I had been entirely ignorant, prior to reading it, of the major advances that had been made in *Drosophila* developmental genetics, including the discovery of externally-invisible compartments in which different genes were expressed to create and maintain various kinds of "positional information" (Wolpert 1969), such as whether a particular region (compartment) was at the anterior or posterior end of a segment. The authors of that paper were justly proud of this and other discoveries in terms of the development of a particular type of animal, but, not being evolutionary biologists, were content to describe these in a single-species (i.e., a non-comparative) context. The effect on me as a reader interested primarily in evolution was to raise the fascinating question of how the expression of developmental genes changed in the long term, as one insect evolved into another. And of course there was no reason to stop there: as a

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monophyletic group that arose from a unicellular ancestor, the whole animal kingdom was a broader backcloth against which comparisons could be made.

For the next 2 years after discovering that wonderful paper, I read avidly in the area of developmental biology—an area that my BSc course had given only minor attention to and my PhD program had avoided almost entirely. All the time I was thinking about possible connections between development and evolution. I published my first paper on such connections in 1982 and my first book in this interdisciplinary area 2 years later (Arthur 1984). Although I did not know it at the time, this was the start of 'Phase I' of my career as a student of Evo-devo.

## 16.2 Phase I: The Morphogenetic Tree

Many scientists, myself included, are guided by a sort of gut feeling about the importance of something. Our studies are strongly influenced by a desire to elucidate the importance of the thing concerned. The 'thing' that I became most interested in during my early days as a student of Evo-devo was the causal structure of development, and how it might change during evolution.

In one sense, the causal structure of development is cyclical. This is encapsulated by the old (unanswerable) question: "which came first, the chicken or the egg?" Development of the egg produces an embryo, further development of which produces a chicken, which matures into a hen, which then lays another egg. However, while entire life-histories are cyclical (and indeed are often referred to as life-cycles), embryonic (and post-embryonic) development is not. So, what is development's causal structure?

Reading my way into developmental biology in the early 1980s, I quickly came to the conclusion that animal development has a strong hierarchical (or tree-like) component to its causal structure. This idea requires some explanation.

First, I need to introduce the idea of a *causal link*. This is the link between a cause and its effect. In vertebrate development, an example is the signal in skin tissue, from the underlying dermis to the externally-visible epidermis, to make certain structures (e.g., hairs in mammals, feathers in birds). At its most abstract, you could simply write this link as D → E. Another example, this time at the genetic level, is the signal from extracellular molecules of the protein Hedgehog to the trans-membrane receptor protein Patched, which results in a chain reaction within the cell that leads to certain genes in the nucleus being expressed (i.e., switched on). Again, this causal link can be written in an abstract form: H → P.

Note, however, that we are already straying into more complex ground, because the genes that are ultimately expressed in the nucleus are several causal links downstream of the initiating protein (i.e., Hedgehog). So now we have not just a single link but rather a causal *pathway*. And indeed this term has become firmly embedded in the literature: developmental biologists talk of the "Hedgehog signalling pathway," and many other signalling pathways too. Another term is *cascade*. For example, the series of groups of genes and their products that interact to

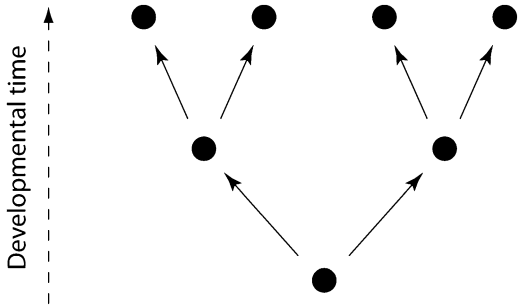


**Fig. 16.1** The morphogenetic tree, shown in its simplest form, as a hierarchy of causal links (*arrows*) between developmental 'entities' (*circles*; see text for an example). In reality, the hierarchy must be far more complex, with trifurcations (etc.) rather than just bifurcations, as well as non-hierarchical elements such as cross-links and feedback loops (i.e., reticulation) (Redrawn from Arthur 1988)

produce segments in *Drosophila* (and arthropods in general) is often referred to as the segmentation gene cascade. The usage of these two terms is not consistent enough when different authors refer to pathways/cascades in different creatures to state either that they are synonymous or that they are not. However, it is often the case that "cascade" is used for a larger series of interactions than "pathway."

Now for the next complication: pathways and cascades are essentially linear, or at least sound as if they should be. But development does not occur via a series of linear pathways running in parallel and not interacting with each other. So a more complex and appropriate metaphor would be preferable. The one that I came up with was a *tree* (Fig. 16.1). I called it a "morphogenetic tree" because it was intended as an abstract representation of branching patterns of causal links, which seemed to capture far more of the essence of the causal structure of *morphogenesis* (literally, the generation of form) than a linear pathway. As we will see, even the more complex tree picture has its deficiencies, but for now let us examine its positive side.

A mammal, during its development, can be thought of as a branching pattern (or tree) of cell lineages. That is, "parental cells" at any one stage in development divide and produce "daughter cells" at a later stage. The latter will always be more numerous than the former, as long as the rate of cell proliferation exceeds the rate of cell death, which it usually does, as evidenced by the fact that a mammal starts life as a single cell and ends life (if it reaches adulthood) as an entity consisting of trillions of cells. The fact that we have a cell-lineage tree does not mean that there is *necessarily* also a tree of causal links, but it does give us a pointer in that direction.

Many developmental processes work through mobile agents called morphogens. These are made in some cells and then secreted out to travel some distance though the extracellular matrix and attach to receptors on the surfaces of other cells, whose developmental fate they help to determine. The Hedgehog protein in *Drosophila* mentioned above is one such morphogen, as is the related protein called Sonic hedgehog in vertebrates.

Morphogens, however, are limited in their degree of spread. They are able to traverse distances of tens or hundreds of cells, but not millions. So, as the embryo grows, the control of what is happening in its different parts must be different. In some cases, this control takes the form of activation of similar pathways or trees of causal links in different places (e.g., the left- and right-hand sides of a bilaterally symmetrical animal). However, in most cases different causal systems must be at work because the developmental outcomes are different (e.g., the developing heart versus the developing brain).

As development proceeds from its earliest phases, such as cleavage and gastrulation, to its later ones, such as "organogenesis" in which the heart, brain, and other organs begin to be made, the number of causal links must increase. And, at a genetic level, the number of developmental genes expressed must also increase (as a part of the overall process), because many genes are switched on only in one particular tissue or organ (e.g., *tinman* in heart development).

Since the most abstract version of the morphogenetic tree (Fig. 16.1) can be interpreted as picturing *any* kind of causal link, it could be used for the links between developmental genes and/or their products. However, it is possible to sketch a more specifically gene-based view by adding an extra dimension—the magnitude of a developmental gene's effect (Fig. 16.2). It seems reasonable to expect that, *on average*, such effects decrease as development progresses. This is because the earliest developmental decisions, such as which end of the embryo is to become anterior, are very major and affect the whole developing organism.

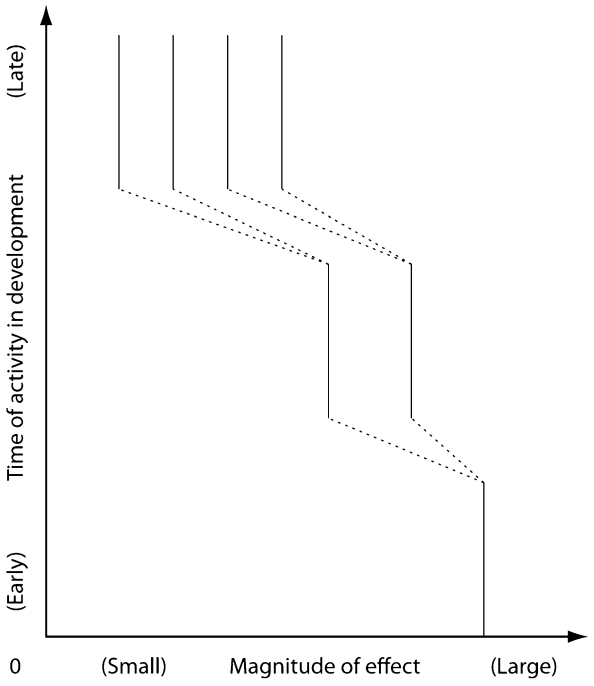


**Fig. 16.2** Gene-based version of the morphogenetic tree. The main idea is that the phenotypic effect of a developmental gene decreases with the "lateness" in development of its main expression period (Redrawn from Arthur 1988)

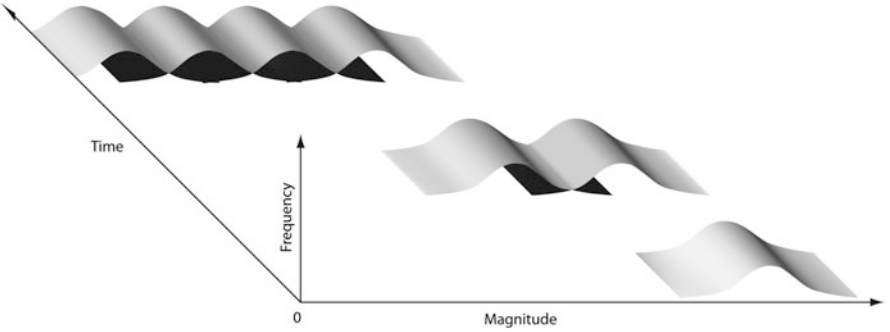


**Fig. 16.3** Mutation-based version of the morphogenetic tree. The added feature compared with Fig. 16.2 is that each gene is characterized by a distribution of possible magnitudes of effect on development because each is subject to mutations of varying severity, rather than having a single, fixed, magnitude of effect (Redrawn from Arthur 1988)

However, later decisions may only affect one organ, and those later-still may be described as fine-tuning—such as determining the relative final sizes of the digits of a tetrapod limb.

This gene-based view of the morphogenetic tree suffers from two major problems, one developmental, the other evolutionary. In terms of the development of one particular organism, a developmental gene may be switched on at an early stage of development, then switched off, and later switched on again. There are many known cases of this. In terms of connecting the gene-based morphogenetic tree with evolution, the main problem is the potentially variable range of sizes of mutational effect on the phenotype for any developmental gene. So for evolutionary purposes—thinking about how morphogenetic trees may evolve—associating each gene with a single magnitude of effect is too simplistic. Rather, we should construct a mutation-based view of the tree (Fig. 16.3).

Let's think about how evolution would work if this mutation-based morphogenetic tree is a reasonable (albeit simplified) view of the causal structure of development. The most important piece of evolutionary theory to introduce here is called "the Fisher principle," after the British population geneticist Ronald Fisher, who articulated it in his book *The Genetical Theory of Natural Selection* (Fisher 1930). The basic premise is that the larger the phenotypic effect of a mutation the lower will be its probability of being selectively advantageous (Fig. 16.4). Specifically, tiny-effect mutations will have a probability of nearly 0.5 of being advantageous, while massive-effect ones will have a probability of zero.

There are several problems with the Fisher principle. First, it assumes a single fitness optimum, whereas in practice there may be two or more. Second, it lacks a developmental component—but we can remedy this by connecting it with the morphogenetic tree. Third, and perhaps most seriously, there is no way to connect Fisher's abstract "magnitude of effect" with actual mutational changes in real organisms. Indeed, since different mutations often cause different *types* of change,

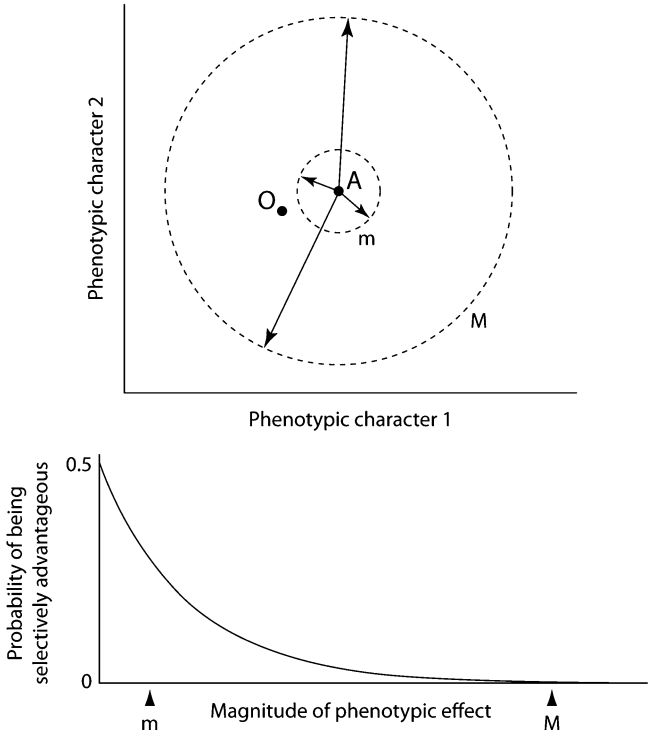


**Fig. 16.4** The Fisher principle. *Top*: from any actual starting point (A), small-effect mutations (m) have a reasonable probability of shifting the phenotype to a point nearer the optimum (O), while large-effect mutations (M) have a zero probability. *Bottom*: generalization of this two-point comparison to all possible magnitudes of effect. Note that the probability of a mutation producing a fitness increase falls gradually from 0.5 to 0 as its magnitude of developmental effect rises (Source: Arthur 2011)

rather than simply different magnitudes of the same type of change, the idea of having a single *x*-axis (as in Fig. 16.4) is a serious over-simplification. Nevertheless, we can accept the principle for now, and consider how evolution will work assuming both the morphogenetic tree and the Fisher principle are valid.

The main conclusion to emerge from these considerations is that later developmental stages will evolve more often than earlier ones, though most of the evolutionary changes in those later stages will be small. The earliest stages will evolve very infrequently, but when an evolutionary change does occur in an early stage it will be comparatively large in terms of its effect on the developing organism. This theoretical conclusion matches some of the available information that we have on the evolution of development in real animals. It provides a possible explanation of von Baer's 'law' (a *pattern* rather than a law) of embryonic divergence, even if it does not explain the variant that is referred to as the egg-timer or hourglass pattern (Fig. 16.5), in which the point of maximum similarity in cross-taxon comparisons is near, but not at, the start of the developmental trajectories.

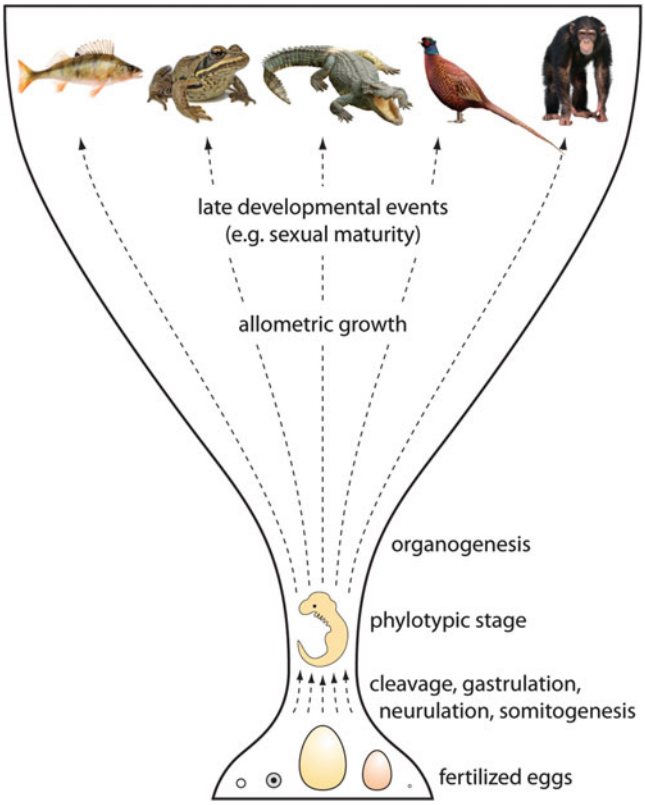


**Fig. 16.5** The developmental egg-timer or hourglass. This shows that the point of maximum similarity in cross-taxon comparisons of developmental trajectories is not at the very start of development. However, it is quite close to the beginning (at a point called the phylotypic stage: see text for details). Hence, the implied symmetry of an hourglass is misleading (Source: Arthur 2011)

What has come into focus gradually here is a relatively greater constraint on the evolution of early (but perhaps not the very earliest) developmental stages compared with later ones. But this is not *developmental* constraint, in which the production of new variants is constrained (Maynard Smith et al. 1985); rather, it is *selective* constraint, in which the availability and spread of fitter variants is constrained. This selective constraint on early developmental stages was also implicit in the concepts of "developmental/internal selection" (Whyte 1965), "burden" (Riedl 1978), and "generative entrenchment" (Schank and Wimsatt 1986; Wimsatt 1986). Effectively, this was a case of four authors—Lancelot Law Whyte, Rupert Riedl, Bill Wimsatt and me—reaching the same general conclusion in different ways (and using different terms). At the core of all our thinking was that in addition to directional selection for adaptation to particular environments, there would always be stabilizing selection for internal integration, and that the weight of this would fall disproportionately on early developmental stages.

However, there is also a problem. How do early stages, like the "phylotypic stage" (Sander 1983) that is implicit in the egg-timer pattern, evolve at all? Might it be that even the smallest-effect mutations of the developmental genes acting at those stages (such as the vertebrate pharyngula and the insect germ band) have sufficiently large phenotypic effects that they have a negligible probability of being advantageous? Clearly not, since those stages *have* evolved (e.g., the pharyngula and the germ band both show considerable variation; also, they are very different from each other). But, nevertheless, when the fitness consequences of large-effect mutations in early development have been studied, they have in almost all cases been found to result in major fitness decreases. This is true, for example, of the homeotic mutations studied in *Drosophila*, and it is one of the main reasons for the rejection of Goldschmidt's saltational theory of evolution (Goldschmidt 1940, 1952).

There are two possible ways out of this problem. First, "negligible" is not zero, so some major changes in early development may have spread by classical Darwinian selection. Second, there is another form of selection that is less "severe" than the Darwinian kind—I called this *n*-selection (Arthur 1984). The *n* comes from the "net reproductive rate" of a population, and the criterion for success in *n*-selection is simply that, at low and middling population densities, *n* is positive—i.e., the population (of a new type) will grow. The reason that this selective test is less severe than that of standard Darwinian selection is that the new type (arising from mutation) does not have to survive in competition with the original type.

But how might such a situation arise in nature? How might a new variant be spared the usual competition with the type from which it arose? Here is a possible scenario involving the evolution of maternal-effect genes, and specifically the gene for chirality (direction of coiling) in snails. Whether a snail shell coils to the left (sinistral) or to the right (dextral) is determined by a maternal-effect gene (Sturtevant 1923) acting during the earliest phase of development, cleavage (Fig. 16.6). Most genera, and indeed most families of snails, are homogeneous with respect to chirality—all the individuals coil in the same direction—and this affects many aspects of the body as well as the shell. But how, then, does a sinistral family originate within a clade that is otherwise dextral, especially given that having reversed coiling appears to engender mating difficulties (Johnson et al. 1993) and thus confers a fitness decrease?

One possibility is that a mother snail carrying a dominant sinistral mutation becomes separated spatially from the rest of the (dextral) species. All her offspring will be sinistral. Although some dextrals will appear in the $F_2$ generation and thereafter, they will be in the minority and so, given their comparative lack of mating success, may be eliminated by selection. If so, we have a rapid shift from one character state to the other, which may or may not be sustained in the longer term, depending on the length of time the spatial isolation lasts.

Of course, this is all very improbable—especially the temporal coincidence of the mutation and spatial separation. But since the phylogenetic distribution of sinistrality and dextrality shows that switches in chirality have been very rare in gastropod evolution, an improbable mechanism is just what is needed to explain them. The problem is not so much for the snails but for us—hypotheses based on

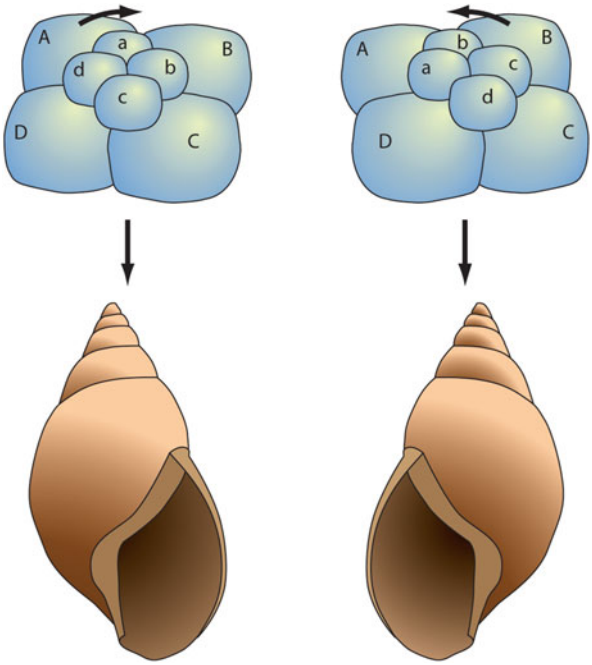


**Fig. 16.6** The chirality of a snail is determined at the earliest stage of development—cleavage. Clockwise shifting of the micromeres (*a–d*) relative to their macromere progenitors (*A–D*) gives a dextral snail (LHS); anticlockwise shifting gives a sinistral one (RHS) (Source: Arthur 2011)

improbable mechanisms that will occur only once or twice in a long period of evolutionary time are very difficult to test.

Unfortunately, this is not a good example to generalize from because a symmetry reversal is a very specific *type* of change in body layout. In the origins of novelties (like the chelonian shell) and body plans (like the vertebrate skeleton), other, very different types of change must have been involved. These are harder to envisage, though some progress has been made recently in relation to the chelonian shell (Nagashima et al. 2009). The problem is that the relevant variants are usually no longer available for study in the way that chirality variants are in the few extant polymorphic gastropod species (*Lymnaea peregra, Partula suturalis*, and a handful of others). But somehow we need to be able to get at this issue of *types* of effect caused ultimately by mutation, rather than reducing the problem to an oversimplified unidimensional "magnitude" of effect.

## 16.3 Phase II: Developmental Bias, Constraint, and Drive

Progress on thinking about a scientific issue is like the process of embryogenesis—it flows in a quasi-continuous way. Nevertheless, just as it is useful to recognize developmental stages (while keeping in mind the limitations of this notion), it is also useful to recognize *phases* in the progress of scientific thinking, either of an

individual or of the entire community of scientists belonging to a particular discipline.

Looking back at my own thinking about the evolution of development over the last 30 years, I tend to see it as falling into three main phases, albeit with significant overlap. In this chapter, I am referring to each according to what I regard as my main focus of interest in the phase concerned. Phase I (Sect. 16.2) was centered on thinking about the hierarchical element of the causal structure of development, and its evolutionary implications, such as selective constraint on some early developmental stages due to the adverse effects of mutational changes in those stages on overall organismic integration. My first book in which this was the central theme was *Mechanisms of Morphological Evolution* (Arthur 1984); my last was *The Origin of Animal Body Plans* (Arthur 1997).

In Phase II my emphasis shifted from selective constraint to developmental constraint. In other words, I began to focus more on biases in the production of variants rather than on the biases in their survival probabilities that we refer to as selection. The reason for this shift is still not entirely clear to me. It was partly due to dissatisfaction relating to the difficulties in testing the evolutionary ideas associated with the morphogenetic tree—though, as we will see, testability issues are far from absent in relation to developmental constraint. It was also partly due to a shift in my practical research. I became interested in a natural pattern of character states—centipede segment numbers—that seemed to cry out for an explanation in terms of what could and could not be produced by development rather than in terms of fitness differences. The pattern is the universality of odd numbers of leg-bearing segments (LBS) throughout the class Chilopoda, with its 3,000+ species of centipedes (Fig. 16.7). This pattern had been revealed a long time ago and was brought to the attention of the evolutionary biology community in the late 1980s (Minelli and Bortoletto 1988).

I first emphasized, from a theoretical perspective, the likelihood of this pattern being a result of developmental rather than selective constraint (Arthur and Farrow 1999). Subsequently, I shifted the focus of my lab to include a major study on the developmental genetics of segment formation in what has become a sort of "model centipede," the coastal geophilomorph species *Strigamia maritima*. Initial studies of the expression of *engrailed* (a segment-polarity gene) showed that segments essentially formed one at a time in anteroposterior order (Kettle et al. 2003). These early studies thus gave no clue about the basis of the all-odd pattern. However, subsequent studies on two genes upstream of *engrailed* (carried out by Ariel Chipman in the lab of my collaborator Michael Akam in Cambridge) revealed a different pattern of expression (Fig. 16.8) that potentially solves the all-odd pattern of segment number observed in nature (Chipman et al. 2004). The two genes upstream of *engrailed* were *odd-skipped-related-1* (*odr1*) and *caudal* (*cad*). The most interesting thing is that there is a change in *cad* expression from an initial double-segment periodicity (*cad* being co-expressed with *odr1*) to a single-segment periodicity (*cad* being coexpressed with *engrailed*). This change is due to the intercalation of secondary stripes of *cad* expression between the primary ones.

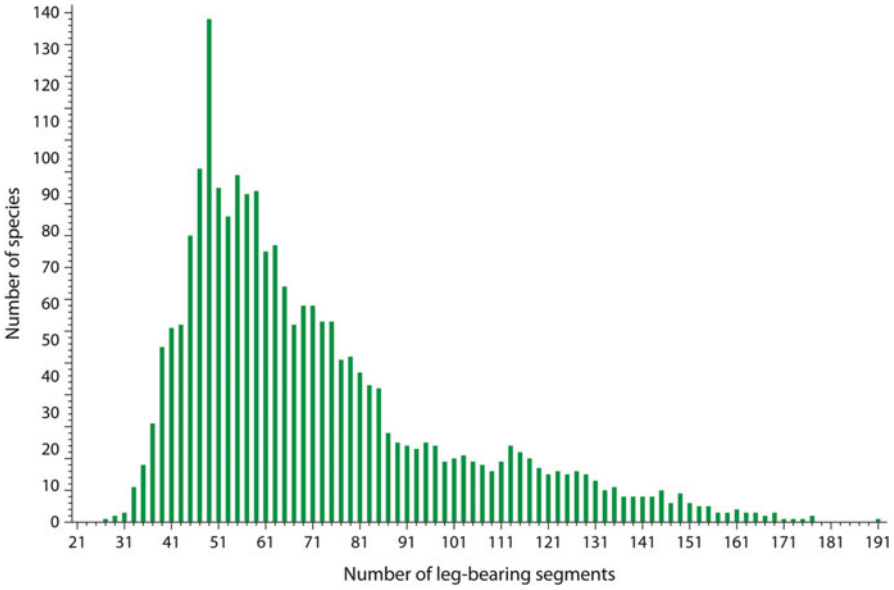


**Fig. 16.7** The distribution of leg-bearing segment (LBS) numbers in the centipede order Geophilomorpha. Note that almost all odd numbers are represented between the lowest and highest ones (27 and 191), while no even numbers are represented (Source: Arthur 2011; modified from Minelli and Bortoletto 1988)

There are two ways to interpret this fascinating finding. The first is to note that intercalation of secondary stripes between any number of primary ones will give an odd number: two primaries become three after the insertion of a secondary one in between them, but three primaries become five stripes when intercalations have happened between P2 and P3, as well as between P1 and P2. So an odd total number of stripes results regardless of whether the number of primary stripes is odd or even. However, an alternative interpretation is to think of this system as creating double-segment units that are later split into single-segment ones. Although this would produce an always-even rather than always-odd result, this may be appropriate given that the centipede poison-claw segment, which is conventionally excluded in counts of LBS number, is almost certainly a modified LBS (Hughes and Kaufman 2002). In that case, the total number of such segments is always even. Whichever is correct, a developmental interpretation is clearly preferable to a selective one. A selective hypothesis involving a major depression of fitness for all even LBS numbers (or all odd ones if we include the poison-claw segment) seems most implausible.

This case-study has a major strength but also a major weakness. Its strength lies in the fact that it provides an unusually clear connection between the developmental-genetic production of a character and the distribution of its states in nature. However, its weakness lies in its uniqueness; it provides a bad starting point from which to generalize, just as was true of the snail chirality case-study.

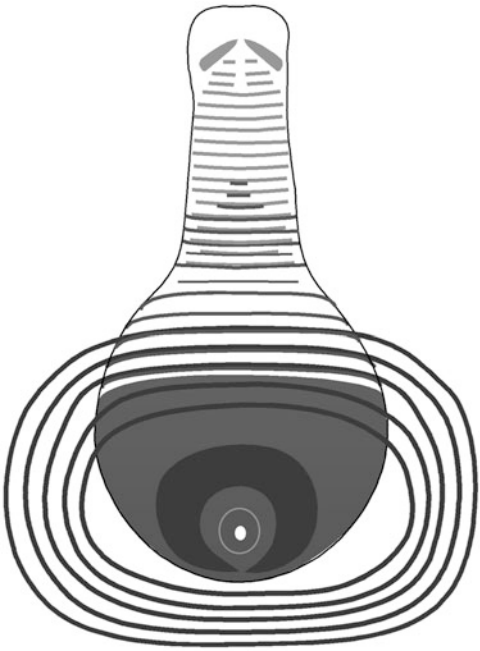

**Fig. 16.8** Early development of the geophilomorph centipede *Strigamia maritima*. This cartoon diagram shows the expression patterns of three genes: *odd-skipped-related* (*dark grey*), *caudal* (*medium grey*), and *engrailed* (*light grey*). The key feature to note is the intercalation of secondary stripes of *caudal*, changing its periodicity from a double-segment to a single-segment pattern (Source: Arthur 2011; original in Chipman et al. 2004)

I can think of no other case in the animal kingdom where the pattern of variation observed in a meristic character takes the form of a long series of odd numbers and a complete absence of even ones.

It was while involved with the early stages of this case-study that I became dissatisfied with the term "developmental constraint" because of its negative connotations. Steve Gould had recognized this problem and tried to solve it by pointing out that the term had been used in previous centuries in both positive and negative ways. In particular, he drew attention to the ancient turn of phrase 'I feel constrained to speak,' which means the same as our current phrase 'I feel compelled to speak' (Gould 1989). But asking for the resuscitation of a long-gone usage is a lost cause. A much better solution to the problem of the perceived negativity of constraint is to accept that this is now the standard usage and come up with a new, positive term that is complementary in meaning.

The more positive term I came up with was "developmental drive" (Arthur 2001). So we can either say that centipede LBS number is 'constrained from' even-numbered character states or that it is 'driven into' odd-numbered ones. This makes clear that the overall pattern can be looked at in both positive and negative ways. Also, drive and constraint can then be seen as two logical sub-categories of the broader category of *developmental bias*.

To develop this argument further, and to illustrate it in a general way, we need to depart from the case-study on centipede segment numbers, both because of its unique nature and because it represents an unusual case of absolute bias, whereas most developmental bias is relative. A better starting point from which to generalize

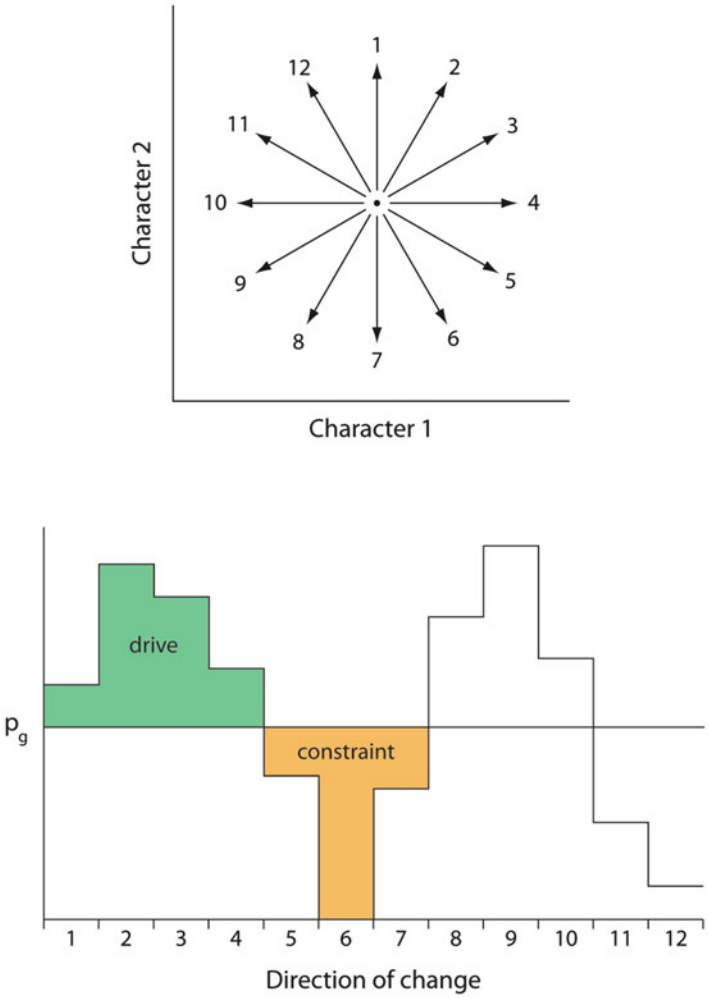


**Fig. 16.9** Developmental bias illustrated in an abstract way by looking at 12 possible combined amounts of change in two morphological characters (e.g., the lengths of tetrapod forelimbs and hind limbs). The 12 combined directions are shown at the *top*: all but the horizontal and vertical ones involve some degree of positive or negative covariation of the characters. The *bottom* graph shows two ways in which the probability of generating each of the 12 combined directions of change ( $p_g$) might behave. Note that there is only one line of equiprobability (the *horizontal line* in the graph), whereas there are a potentially infinite number of patterns of varying probability (represented in the graph by just a single one: the 'flight of steps' pattern). This means that developmental bias must be the rule rather than the exception in nature (Source: Arthur 2011)

is the pattern of covariation of fore- and hind-limb lengths in tetrapods; or, more generally, the pattern of combined change in two continuously-varying morphological characters. Possible patterns are shown in Fig. 16.9 (top). The 12 patterns shown (an arbitrary number; it could equally well be 100) include positive

covariation (e.g., 2, 9), negative covariation (e.g., 6, 12), and independent variation (e.g., 1, 4). One interesting question to ask in relation to these various patterns is: what is their likely relative frequency of being generated by mutations affecting limb development?

This question is answered (to a degree) in Fig. 16.9 (bottom). Here we see that equiprobability of generation (horizontal line) represents only one out of an almost infinite number of patterns ("flights of steps"; just one of these is shown). Thus from an *a priori* point of view we expect developmental bias to be the rule rather than the exception in nature. Furthermore, studies on the covariation of real characters in particular species confirm this expectation, both for the example mentioned above (tetrapod fore- and hind-limb lengths) and for others, such as covariation in the sizes and pigmentation patterns of two different eyespots on the wings of butterflies of the species *Bicyclus anynana*. Experimental attempts to "break" these patterns of covariation (and the underlying developmental bias) through artificial selection were successful in relation to eyespot size (Beldade et al. 2002) but not in relation to pigmentation (Allen et al. 2008; see Fig. 16.10). This is a fascinating result because it indicates that in some cases developmental bias and natural selection will determine the direction of evolution *together*, while in other cases selection will "overcome" developmental bias.

I have begun to equate developmental bias with character covariation. This requires some explanation because it concerns the connection between Evo-devo and quantitative genetics. Often quantitative geneticists deal with patterns in the covariation of two characters in adults. They have established techniques for

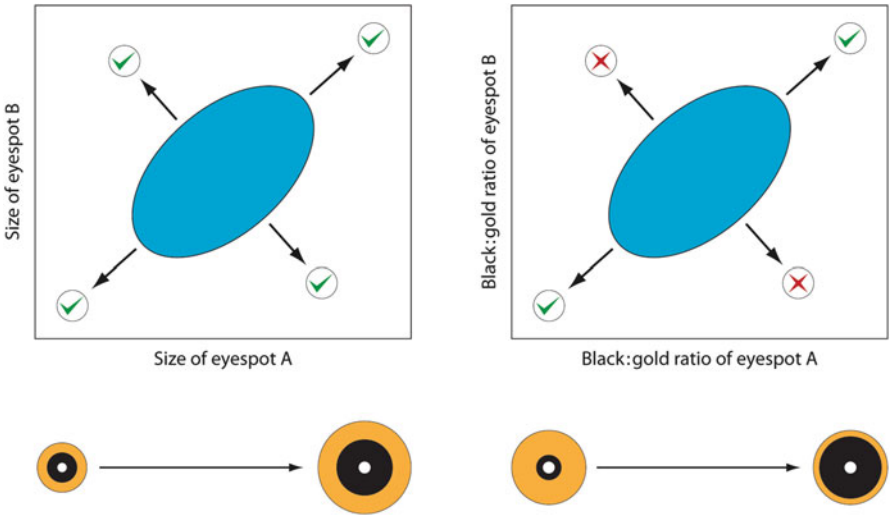


**Fig. 16.10** Diagrammatic summary of the results of artificial selection experiments designed, effectively, to "break" developmental bias in the pattern of variation in butterfly wing eyespots. This was successful for eyespot sizes but not for eyespot pigmentation (Source: Arthur 2011; based on data in Beldade et al. 2002 and Allen et al. 2008)

quantifying these patterns and for estimating the relative magnitudes of genetic and environmental contributions to the observed phenotypic covariation. However, they usually do not delve into the developmental basis of the observed patterns. In contrast, students of Evo-devo focus on the developmental origins of such covariation, and refer to it as developmental bias (or constraint).

These two approaches are complementary, but have not always been perceived as such. In the famous debate over adaptationism and the significance of "spandrels" (Gould and Lewontin 1979), the use of different languages by different camps made their different approaches seem conflicting rather than complementary. Gould and Lewontin criticized the "adaptationist program" without acknowledging the insights of early population geneticists, notably J.B.S. Haldane: "the actual steps by which individuals come to differ from their parents are due to causes other than selection, and in consequence evolution can only follow certain paths" (Haldane 1932, 77 in the 1990 Princeton reprint edition). Equally, one quantitative geneticist responded to Gould and Lewontin by saying that, "the genetic variance-covariance matrix of quantitative genetic theory measures developmental constraints" (Cheverud 1984, 155). In an important sense, Cheverud missed the point—the variance-covariance matrix of quantitative genetics measures the *outcomes* of developmental constraints (or more generally biases), but says nothing of their developmental causation.

Luckily, the situation is improving. This is largely because some individuals now cross the divide between Evo-devo and quantitative genetics more effectively than did their predecessors. A good example is the work of Chris Klingenberg and colleagues on the evolution of structures like the mouse mandible and the *Drosophila* wing. Although taking a primarily quantitative, population-based approach rather than a developmental-genetic one, Klingenberg concludes from his studies that, "the developmental system 'channels' the phenotypic expression of variation" (Klingenberg 2002, 3).

I tried to summarize my views on developmental bias and related issues in *Biased Embryos and Evolution* (Arthur 2004), which still reflects, despite its age, the importance with which I view this concept. But, by 2004, I had transitioned into Phase III of my study of Evo-devo.

## 16.4 Phase III: Developmental Repatterning and the Conceptual Structure of Evo-devo

Many foci of Evo-devo research involve concepts that are hard to define. These include developmental bias and constraint, evolutionary novelties (Mayr 1960; Müller and Wagner 1991), body plans (Arthur 1997), modularity (Raff 1996), evolvability (Kirschner and Gerhart 1998), and the phylotypic stage (Sander 1983; Richardson et al. 1997). As well as being hard to define, most of these concepts are controversial, both within Evo-devo itself and also between many

advocates of an Evo-devo approach and some advocates of the longer-established neo-Darwinian approach (the narrower-minded ones; perhaps just a small minority).

It struck me as I entered Phase III that, if possible, it would be better to have an overall conceptual framework for Evo-devo that was broadly agreed upon as reasonable before leaping into heated debates about one or other of the many individual concepts that compose it. Not only would that be preferable because we could start with some "light" and generate the "heat" later, but it might solve another problem too—the relationships of the various Evo-devo concepts with each other. Often, individual practitioners of Evo-devo concentrate on their concept of choice without making very clear any connections it might have with others. Although this is not always the case, here are two notable examples: (i) Is evolvability the opposite of developmental constraint, selective constraint, or both? (ii) Is the origin of body plans a subset of the origin of evolutionary novelties more generally, or not? Venn diagrams might be useful given their simplicity and clarity, but they have rarely been used for classifying Evo-devo concepts.

My first attempt at producing a controversy-free conceptual structure for Evo-devo (Arthur 2000, 2002) was doomed to failure because of the choice of a troublesome phrase: *developmental reprogramming*. Despite this, the underlying rationale was justified. At the level of the gene, we have an umbrella-term which, when used in its broadest sense, can cover all possible changes: *mutation*. Individual mutations range in size from point mutations affecting a single DNA base to chromosomal aberrations involving potentially thousands of genes. They also range widely in type: mutations can be in regulatory or coding regions; they can be germline or somatic; dominant or recessive, and so on. At the population level too, we have an umbrella-term for all *systematic* changes in gene-frequency: *selection*. Again, this can take many forms: directional, stabilizing, or disruptive; density-dependent and/or frequency-dependent, or independent; caused by biotic or abiotic agents; etc. Admittedly, if *all* changes in gene frequency are to be included (stochastic *and* systematic) then we need two cover-terms rather than one—selection and *genetic drift* (in its various guises, including the founder effect and population bottlenecks).

Before 2000, there was no umbrella-term for all changes at the level of the individual, as opposed to the level of the gene or the population. Some people might have thought that there was, but they were wrong. For example, the book title *Heterochrony: The Evolution of Ontogeny* (McKinney and McNamara 1991) seems to imply that heterochrony is the overall word that we need; it is not. After all, heterochrony is simply evolutionary change in developmental timing, and this is but one of many ways in which development can change during evolution. I attempted to deal with this lack of an umbrella-term by introducing developmental reprogramming. But this term suffered from two problems, one of which should have been foreseen, whereas the other could not have been. The foreseeable problem was that to some schools of Evo-devo the term "reprogramming" smacked of genetic imperialism, implying that everything to do with development was programmed into the genome. Although I had not intended that inference to be

drawn (I was well aware of developmental plasticity), I should have considered that it might have been. The less predictable problem was that in the mid and late 2000s "reprogramming" became used in a much narrower way—in the sense of reprogramming individual cell fates (Park et al. 2008). Studies using the term in this way proliferated rapidly.

It thus became necessary to make a different choice of umbrella-term for all evolutionary changes in development. One possibility that is simple but does not work is *developmental change*. This fails because development in any one organism is a process of change and thus it makes no sense to use "developmental change" in an evolutionary sense as well; the phrase would be inherently ambiguous. The embryonic process of cleavage represents developmental change. It really would not help if, say, the evolutionary switch from spiral to radial cleavage was also described as "developmental change".

In the end, the choice was simple and obvious, and not very far from my starting point: *developmental repatterning* (Arthur 2011). For development itself, we often use "pattern" and "patterning" at various levels of organization. The phrase "gene expression pattern" is now familiar to all. And, at a higher level, "pattern formation" is often used to distinguish a certain type of developmental process from cell differentiation. For example, going from stem cell to striated muscle cell in a human is cell differentiation, but producing a spindle-shaped muscle (like the biceps) versus flattish ones (such as those stretching over our skull) is pattern formation. It thus seems an obvious step to go from the *patterning* of development in an individual to the *repatterning* of development in evolution.

In fact, I had already toyed with this possibility back in 2000. However, I was put off it because "ontogenetic repatterning" had been used (Roth and Wake 1985) in a less inclusive way, to refer to all forms of evolutionary change in development *except* those that produced recapitulation. But since that usage did not catch on, it no longer seems a problem.

So, we have our umbrella term and can now use it as the basis for classifying all manner of Evo-devo concepts, not just the "internal" ones (Fig. 16.11). The four primary kinds of repatterning can now be seen as changes in time, space, amount, or type (heterochrony, heterotopy, heterometry, or heterotypy, respectively). In comparing the outcome of repatterning in two divergent lineages, we can see that recapitulation is one (but only one) possibility. The causes of repatterning can be both genetic and environmental (thus, no risk of genetic imperialism), but an environmentally-induced repatterning must ultimately have some heritable element if it is to contribute to evolution. Finally, it can be seen that developmental repatterning occurs at all evolutionary scales—micro, macro, and mega—albeit the question of whether it differs between these scales, either in an absolute way, or (more likely) in a statistical way, remains an open and interesting question (see below).

Some may write off the use of developmental repatterning as an umbrella-term and the linking of various Evo-devo concepts to it (Fig. 16.11) as a mere filing system. However, I strongly believe that until a new discipline can agree on a conceptual framework, including the definitions and interrelations of its main

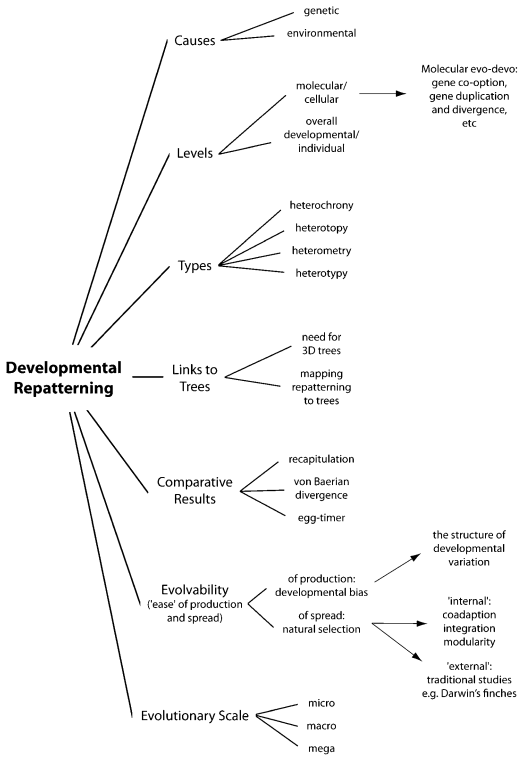


**Fig. 16.11** A proposed scheme of Evo-devo concepts with the overall idea of developmental repatterning occupying a central position. See text for further explanation (Source: Arthur 2011)

concepts, it has not come of age. But I believe that Evo-devo now *has* come of age through the efforts of many people (including, but not limited to, the participants of the Dahlem meeting). The advantage of this "coming of age" is that we can distinguish between genuine scientific questions in Evo-devo and semantic questions that stemmed from people using terms in different ways. We can now undertake the task of addressing those real questions.

## 16.5 And So, into the Future

What are the most important questions that we should now be asking in Evo-devo? In my view, there are three important problems, each central to a particular domain of inquiry:

1. *What are the mechanisms at work in repatterning development in small-scale, routine evolution?* At the population level we believe, as Darwin did, that the main mechanism is natural selection. But further questions arise from this answer. First, what is the balance between "internal" selection for organismic integration and "external" selection for adaptation to particular environments? Second, is this a real dichotomy or rather a continuum as I have argued

elsewhere using the concept of *trans-environment fitness profiles* (Arthur 1997)? Third, what individual-level mechanisms are involved in developmental repatterning? We need to go beyond broad descriptions like heterotopy to actual developmental processes. An example of such a process is the one leading to altered patterns of cell-cell induction that take place in the heterotopic repatterning found in the evolution of the nematode vulva (Sommer and Sternberg 1994).

2. *Are the same mechanisms, at both individual and population levels, responsible for the larger-scale repatterning that we see in the origins of novelties and body plans?* This relates to the question of whether evolution is scale-dependent or independent (Erwin 2000; Leroi 2000). We now know enough to go beyond arguments based on some imaginary unidimensional variable, such as the magnitude of phenotypic effect of a mutation. Those arguments (e.g., between Fisherian and Goldschmidtian views) can be superseded by arguments based on *types* of repatterning. But there is much that we still need to learn about how to describe and classify types before we can ask meaningful questions, such as whether the origins of novelties and body plans involve (at least in a statistical sense) different types of variants than their microevolutionary counterparts.
3. *What is the relative importance of developmental bias and natural selection in determining the direction of evolution?* This long-standing question remains, as does the question of how the two processes interact. But we can now approach these questions with studies on real examples, as well as with general concepts that have been more clearly defined. So past arguments about words can be replaced by arguments about processes in the future.

Those are just three key problems, each representing an important domain of inquiry with many associated questions, for the Evo-devo of 2013 and beyond. Other authors may (and no doubt will, in this volume and elsewhere) come up with others. Having exciting questions to ask is great. And being able to begin answering some of them, as we have in the last three decades, is great too. Although some biologists have argued that Evo-devo is a transient meeting of minds that will soon pass (Duboule 2010), I have a much more positive outlook. I believe that Evo-devo will endure, progress in its own right, and become more thoroughly integrated with general evolutionary theory than in the past. In time this will produce a "post-modern synthesis" that includes the developmental repatterning that the Modern Synthesis of the mid-twentieth century excluded. If this optimistic view turns out to be correct, then we will finally have arrived at a synthetic view of evolution that truly merits the use of the term. We're not there yet, but we're getting close.

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# Chapter 17
# Entrenchment as a Theoretical Tool in Evolutionary Developmental Biology

**William C. Wimsatt**

## 17.1 The Origin of an Idea

Stuart Newman and I began as post-docs at Chicago together in the fall of 1969, when Stuart Kauffman also joined the faculty. We were in different departments (I was in Richard Lewontin's lab), but met early because of common interests in "theoretical biology," their "new" department at Chicago.[1] I had been interested in developmental biology, its history, and its relevance to evolution since graduate school.[2] The germ of

[1] This was a remolding of the old committee on mathematical biology under the influence of Richard Lewontin and leadership (as newly recruited chair) of Jack Cowan. Under Rashevsky's leadership that committee has had a far if sometimes eccentric reach in the university and the world. Such diverse figures as linguist Eric Hamp and sociologist-cognitive-computer-scientist-organization-theorist-economist Herbert Simon took or sat in on courses there. The new department was both more focused and more biologically based (though still with a broad reach), and development was one of the key elements of that focus.

[2] Indeed, even earlier: as an undergraduate at Cornell, I took Frank Rosenblatt's course (1962) in "Brain Models and Mechanisms." Rosenblatt (1962) created the first well-developed connectionist theories of brain organization. His was both a populational and developmental theory in which he aimed to model systems that would, with experiential feedback, learn to recognize patterns. Rosenblatt argued that there wasn't sufficient genetic information to specify neural connections completely, so rather than seeking to model adult abilities with networks specified in detail, he sought to model *classes* of randomly connected networks (specified only at a molar level, characterized by probability distributions for connections in a multi-level framework) that could *develop* the relevant capacities through reinforcement learning. In this he anticipated Kauffman's approach to looking for *generic* properties of classes of randomly organized gene-control networks, but I was thus also primed for the evolutionary relevance of development. In graduate school at the University of Pittsburgh (Pitt) I took a historical and modern course on developmental

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my contributions to this volume goes back to 1972 when I sought (initially for a class!) to adapt an argument from Herb Simon's classic paper (1962) to construct a model of causal dependency in development that would apply to the evolution of developmental structure and generate fitness values for different variations that could be used in population genetic models. I presented an early version of this "developmental lock" model at a conference in April 1974, along with a model of organizational reliability in hierarchical series-parallel networks (another attempt to model phenotypic organization in a way that could be utilized in population genetics). In the papers circulated in advance for that conference, Steve Gould (to my great relief!) taught me the difference between the views of von Baer and Haeckel.[3]

My basic idea was that elements of a developmental trajectory—traits, entities, behaviors, or processes—could be classified by how many other elements were causally downstream of them in development. The more dependent elements they had downstream, the more conservative they should be in evolution because changes in them should have a bigger chance of more deleterious consequences (i.e., in both frequency and size). I called this idea "generative entrenchment." These elements played a larger role in *generating* the phenotype as an adaptive structure, and so were *entrenched* and conserved through that role (Wimsatt 1986). But entrenched elements were not limited to internal features. This distinguished generative entrenchment from genetically based approaches like pleiotropy. Evolution utilizes not only stable elements of gene action, but also presupposes stable features of the environment in constructing the phenotype, as well as their relationship. (Fitness—as Lewontin often emphasized—is a relation between organism and environment. Thus, I reasoned: if evolution optimizes fitness, the structural and dynamical aspects of this *relationship* are the appropriate targets of investigation). If either the environment or the genome in its milieu become more stable than usual (or are simply *assumed* to be fixed), it becomes easier to ignore them, and to focus on the dynamics involving the changeable element, and models often do this. Thus fitness may be treated as a contribution of individual genes (ignoring the rest of the genome) or of the genome (ignoring the embodied phenome in its environment) as a heuristic in modeling or in experimental designs, but it is only that.[4]

biology taught by Stanley Shostak in 1967. I first met and established ongoing contact with Steve Gould in the summer of 1968 at the wedding of his undergrad roommate, Carl Putz, who was my roommate at Pitt. Before the 1981 Dahlem conference, I had also interacted with John Bonner, and benefitted from Dave Raup as a colleague. Rudy Raff, Günter Wagner, Gerd Müller, and Steve Stearns have all influenced my perspectives in different ways since.

[3] I feared earlier that I had "explained" a rather crude recapitulation with the "developmental lock"—a problem that to my mind made it unpublishable, and was delighted to realize that instead I had explained von Baer's laws. Gould's paper for this 1974 conference at the American Academy of Arts and Sciences (convened by sociologist Talcott Parsons) was an early sketch of the view developed later in *Ontogeny and Phylogeny* (1977). My series-parallel reliability model anticipated that of Oster and Wilson (1977) for ant colonies. Wilson, Lewontin, and Mayr were also there. Unfortunately, the conference papers were not published.

[4] I first delineated such "reductionistic" heuristics and argued for their biasing effects in the units of selection controversy (Wimsatt 1980), but they are common to reductionistic approaches everywhere (Wimsatt 2007, see both text and appendices).

But rather than taking what is fixed as given, one may ask *why* it is fixed. In this early model, I first glimpsed an alternative account of the elements regarded as innate in behavior that are not necessarily rooted in genes. This new account integrated naturally with a more ecological and interactionist view of development, and related to genetics only indirectly. Though it applies to gene action, and presumes genetic activity where relevant, it also involved naturally selected elements of the interaction with structurally stable elements in the environment. I soon realized that this property—*degree of generative entrenchment*—had broader implications and uses in relating development and evolution. As I looked more, I also discovered that others had come to similar conclusions.[5]

Assessments of relative evolutionary fixity (or taxonomic breadth) are now widely used to untangle developmental architectures in diverse areas of evolutionary developmental biology (Evo-devo). The causal impact of changes in different places in developmental architectures are assumed to be major factors in explaining these evolutionary fixities and differential rates of change, as well as the occurrence of evolutionary innovations (and far more frequent developmental monstrosities).[6] Where did this hypothesis (now more properly a methodology) come from, and why is it important? I distinguish several intellectual or conceptual lineages by which this methodology has emerged, one of which corresponds to my own path and, therefore, is elaborated in more detail.

## 17.2 Four Paths to Generative Entrenchment

### *17.2.1 Pleiotropy*

The use and awareness of generative entrenchment as a product of pleiotropy is a central theme—one approached by both top-down and bottom-up methods in modern Evo-devo. It was a long time coming, and it is interesting to know why. The path to pleiotropy as an evolutionary force might be resolved into different strands, which spanned different disciplinary foci and phyla, and were not strictly sequential. I begin with Haeckel already in place, although many of the themes could have been traced to multiple nineteenth century sources, including Darwin, Mendel, von Baer, and early Bateson.

[5] Aside from the work delineated below on entrenchment, this more interactionist idea emerged simultaneously with but independently from "developmental systems theory" [DST] (Oyama 1985), with which it shares many assumptions. But DST needs an engine to drive it: DST urges that we take the whole developmental system into account, without privileging genes, but includes no mechanisms capable of driving evolutionary processes (Wimsatt 2001). Self-organization (widely cited in this literature) and generative entrenchment can both do this, and should ultimately serve complementary roles in doing so (as argued in Wimsatt 1986, 2001).

[6] This is extensively documented in Frietson Galis's work, discussed at length below.

The first of these strands might be called the classical period (between ~1915–1975) because of the hegemony of classical genetics that gave us a full-blooded concept of the gene and the concept of pleiotropy or multiple effects of gene activity (even though any account of gene activity was absent from classical transmission genetics). This period was dominated by a move away from Haeckel and recapitulation and the rise of classical transmission genetics. Everyone was in such a hurry to deny recapitulation that they were not interested in studying anything close to it. And transmission genetics not only lacked a significant and convincing connection to macroevolution, but also was largely disconnected from development as well. Because of widespread dissatisfaction with its lack of an account for the generation of characters paralleling the powerfully predictive accounts of transmission, there were numerous failed attempts to connect the two. Two important ones were the (embryological) reduplication hypothesis of Bateson and Punnett (1911, and defended until 1922) that was an attempt to explain linkage, and Goldschmidt's "peapod" version of the chromosome (1917), attempting to give a stereospecific account allowing for the release and activity of factors in the cytoplasm and their re-localization in the chromosome. Both were shown to deliver multiple predictions about patterns of linkage that failed miserably, and both were demonstrated to require profoundly unrealistic additional assumptions (reviewed in Carlson 1967; Wimsatt 1987, 1992). Developmental genetics proved largely intractable and lacked any generalizable organizing machinery comparable to that provided by linkage mapping. Because of this, embryologists had gone their own way. Theodore Boveri, crucial to both traditions from 1890 up until his early death in 1915, was the last in this period to do so. He left a substantial impact on cytology, but was largely forgotten for his broader aims. Similarly, Bateson's (1894) interest in homeotic and other large mutations that turned out to be so crucial later succumbed with his capitulation to the rise of chromosomal mechanics in 1922. Although pleiotropy was well known and widely documented from the beginning among geneticists (Morgan 1916; Morgan et al. 1925), it was not pursued for potential connections with development or evolution.[7] Most mutations studied by classical geneticists in this period were large (they had to be readily visible and classifiable with low-power dissecting microscopes), and would have been (usually very) maladaptive in nature; if pleiotropic (which many of them were), they would have been worse.[8] Perhaps most centrally, the emphasis in this period was on

[7] One might say that it was almost an embarrassment to population genetics, since pleiotropy, like epistasis would have seemed to reduce the likelihood of additive (and thus heritable) gene effects. Wright (1968) was unusual in noting pleiotropy's probable role in the severity of deleterious mutations involving polydactyly in his guinea pigs.

[8] Morgan et al. (1925) review the properties and expression of over 500 mutations. See Kohler (1994) for a broader discussion of their methodology. Dobzhansky's immensely influential (1941), in which he used different patterning of giant salivary gland chromosomes indicating inversions and translocations to distinguish *Drosophila* species in nature, together with the fact that hybridization between species differing by inversions was usually severely deleterious, reinforced hostility to views like those of Goldschmidt who sought the (very occasional) hopeful monster as a product of major mutational changes.

finding rare useful mutations for evolution (and artificial selection). Stasis was not of interest, and differential stasis was not even considered. Among macroevolutionists discussing Dollo's law and why it held, no one appeared to go further than to see irreversibility as a product of the improbability of a multi-mutational reversal.[9] A reopening of broadly Haeckelian themes was marked in the United States by Gould (1977), in which he clearly distinguished von Baer's views from Haeckel's, and affirmed the former.[10] But Gould's work was dominated by his interests in changes in developmental timing, and so mostly led elsewhere. In the US, Haeckelian themes didn't re-enter until Raff and Kauffman (1983), but were soon to be transformed again, in the third period.

A second strand tracks researchers who tried to articulate genetics and embryology again starting in the mid-to-late 1930s up through the late 1970s. Hadorn and Waddington who employed both empirical and theoretical approaches are exemplars here. They individually had the necessary pieces, but never quite put them together. Riedl (1975, 1978), who cites both Hadorn and Kühn (1965) for inspiration capped the close of this period with an extremely full treatment of the relation between "burden" (i.e., generative entrenchment) and evolutionary conservatism. It was broad, deep and general, dealt with different rates of change and successive entrenchment in evolutionary time, and was as rich in morphological detail and organizational principles as it was sketchy about genetics. It deserved widespread acceptance. I link it with this period because of his sources of influence, rather than with the following, because his subsequent impact was surprisingly small, for reasons I elaborate elsewhere (Wimsatt 2006) and will sketch again below.

In this strand there was an awareness of multiple possible causes of evolutionary stasis, but stasis and changeability were treated as opposites, rather than as a continuum of different rates of evolutionary change. This may owe something to the concurrent separation of macroevolution and embryology (with typological thinking in that period) from microevolution, where evolutionary rates and concerns with variation were a natural concern. Thus Hadorn (1945, 1955, 1961) had an encyclopedic discussion of know lethal mutations in diverse phyla, and specific examples indicating how highly pleiotropic and interactive such mutations could be.[11] He also discussed deleterious but non-lethal mutations but did not explore

[9] Curiously, no one appeared to juxtapose Darwin's abhorrence of macromutations with the simultaneous effects of multiple mutational changes to get a pleiotropy or entrenchment based account of Dollo's law.

[10] Although Gould (1977) drew a strong contrast between von Baer and Haeckel, Raff and Kauffman (1983) lumped them together. Richards' detailed biography of Richards (2008) argues that his views on recapitulation were far more nuanced than usually presented by his critics.

[11] Hadorn introduced the distinction between highly interactive and pleiotropic, which became important in distinguishing the impact of mutations acting at the phylotypic stage (Sander 1983) with others that were just very pleiotropic. The distinction (as developed, for example, by Galis) is between a mutation which has multiple but characteristic specific effects, each with relatively high penetrance, and one which may have a multiplicity of substantial effects of diverse kinds with substantial variation in specific effects from case to case.

different evolutionary rates involving degrees of pleiotropy, perhaps because all of them were quite severe.[12] Also relevant here is the developmentalist focus on categorical effects versus the population geneticist's awareness that the fitness effects of a mutation might be strongly dependent on environment, and possibly even survivable or positive under altered conditions.

Another near miss is the second edition of Balinsky's classic embryology text (1965), where he added a page closing a new section on gene expression to argue the inevitability of differential magnitudes of effect of gene expression at different stages in development (p. 537). Earlier changes ("those which are not lethal") have later effects, whereas later changes could not have earlier effects. He uses this asymmetry to argue for a relative conservatism of earlier features and to explain von Baer's laws. But there is no use of developmental cascades of different sizes (which he could have drawn from Hadorn!) and the point is not developed further. I find no citations to Balinsky in subsequent applications within developmental genetics or Evo-devo.

Two other individuals are of special interest in this period, and in transition to the third period, which I mark with the publication of Sander's widely cited 1983 paper introducing the idea of the "phylotypic stage." The first is C.H. Waddington, whose attempts to link evolution and development was essentially unparalleled. He ranged through biochemistry, development, genetics, and evolution, and his 1939 *Introduction to Genetics* was noted for its much greater breadth in search of applications (including to development) than other influential texts of the period (e.g., Sturtevant and Beadle's classic 1939 text of the same title, which focused on linkage and chromosomal mechanics). Waddington's 1956 magisterial review, *Principles of Embryology*, brought an enormous range of developmental data in diverse phyla to bear in search of more general mechanisms. His 1957 *Strategy of the Genes* was a theoretical exploration of the articulated roles of development and genetics in evolution, but focusing on plasticity and genetic assimilation as adaptive creative forces, and developmental canalization as the main stabilizing force. An appendix by geneticist Henrik Kacser was rich in schematic, hypothetical, biochemically-mediated, potential, genetic control circuits to accomplish various control functions (5 years before Jacob and Monod) and still looks remarkably modern (not unlike Eric Davidson's circuits, in spirit). Waddington's influence continued through four conferences he organized that became the four volumes of *Towards a Theoretical Biology* (1968–1972), whose diverse essays still pivoted around evolution and development. Yet I think it likely that Waddington's focus on canalization and its developmental elaboration solved for him both the ideas of evolutionary stasis and of genetically or environmentally induced innovation. Thus, he used Hadorn but never explored the possible impact of differential pleiotropy on fitness and evolutionary conservatism.

[12] Williams' very influential (1966) uses the severity of fitness reduction of *bithorax* mutants to scoff at Waddington's experiments with genetic assimilation of *bithorax* as indicating a possible mechanism to explain the evolutionary incorporation of larger innovations.

In 1983 (in the same volume on *Development and Evolution* as Sander's article) John Maynard Smith's short article considers the possibility that things later in a tree-like developmental cascade might be more evolutionarily variable than earlier ones because of the differential magnitude of their effects. But it is only one of several topics on the relation of evolution to development and not his major focus. By then, Wallace Arthur (1982) had taken up this mantle from population genetics and was moving more heavily into developmental biology (1984, 1988, 1997), elaborating his cell-lineage inspired "morphogenetic trees" as a full-blown account of differential entrenchment. The similarities of Arthur's morphogenetic trees to Weismann's diagram in 1892 of the germ track in *Rabditis nigravenosa* shows a missed opportunity for a developmental theory of differential rates of evolution, demonstrating that it could have been done with cell lineages even before the rise of classical genetics.

In his epochal 1983 paper focusing on insect development, Sander first describes what Raff and Raff (1987), Elinson (1987), and Raff (1996) would call the "hourglass" pattern, with larger variability in different species in the same phylum early in development, greatly reduced variability at what Sander baptized as the "phylotypic" stage, and then increasing variability thereafter through adulthood.[13] The focus on the phylotypic stage, its nature and consequences is what I would call the third strand, which leads naturally to the modern state of the discipline, in which the fourth strand broadens to become a stage. Many later researchers trace their involvement with the association between pleiotropy and evolutionary conservation to this paper, but almost no one did so immediately.[14] The phylotypic stage became a major focus along with and a little later than the *Hox* genes, plausibly because both provided patterns of similarity that applied across many diverse groups and thus were likely targets for forming a general theory.

Much of the subsequent work using pleiotropy as an explicit tool was judging the temporal occurrence of the expression of genes resulting in morphological variants relative to the phylotypic stage. This was especially characteristic of Frietson Galis's work, a paradigmatic exemplar of a "top-down" approach relating conservation or variability to degree of pleiotropy in more macroscopically characterized traits. ("Bottom up" work looked at the detailed characteristics of gene control networks.) Galis utilized morphological and selectionist arguments together with cross-phylogenetic and (later) genetic information to ultimately draw conclusions

[13] The idea of a phylotypic stage as being a "neck" in an "hourglass" with greater variation both earlier and later in development dates back to Seidel (1960), but did not become a matter of focus until Sander (1983) and Raff (1996). This is somewhat of a puzzle. Both are frequently cited, Sander is cited more than three times as frequently as Seidel. This could be due to the greater visibility of Sander's paper: in English, rather than German, and in a very visible conference volume when interest in the relation between evolution and development was blossoming.

[14] The phylotypic stage attracted attention first, but then the "hourglass pattern" itself became a topic of dispute with those who expected a more cone-like pattern, as well as those who saw neither (e.g., Richardson et al. 1997). Increasing evidence for the "hourglass" has emerged over the past 15 years (see Raff 1996; Galis and Metz 2001; Kalinka et al. 2010; Kalinka and Tomancek 2012).

about the genetic organization of the phylotypic stage and the factors affecting conservation and variation in the vertebral column and digits. Before tracing her trajectory, it is necessary to establish its context.

#### 17.2.1.1 Top-Down Approaches to Pleiotropy

Much attention was directed toward determining the nature of the phylotypic stage and why it was so strongly conserved in different members of the same phylum. This continues today (see, e.g., Kalinka et al. 2010; Kalinka and Tomancek 2012; Irie and Kuratani 2011; Sect. 17.2.4, below). One hypothesis on the conservation of the phylotypic stage involved its robustness, first advanced and tested in simulations of the segment polarity network (von Dassow et al. 2000). This hypothesis could explain how earlier variation in the hourglass could be tolerated rather than fixed by still deeper entrenchment than the phylotypic stage. A second hypothesis (Sander 1983; Raff 1996) was that the neck of the phylotypic stage represented a maximum of tolerable interactive complexity as the embryo grew in size and global gene interactions. This increased until the advent of organogenesis in the transition out of the phylotypic stage, when the interactive consequences of any gene expression became more local and modular.[15] At this point, the regularities of von Baer's law with increasing divergence at later developmental stages could be expected—albeit with exceptions for canalization, robustness, redundancy, or modularity downstream, which reduce entrenchment (Wimsatt and Schank 2004). A third hypothesis for lower variability during the phylotypic stage was the critical development of some specific and important architectural feature during that period, such as the neural crest.

Frietson Galis's work addressed these and many other hypotheses. She trained as a behavioral ecologist but became interested in the functional consequences and evolutionary significance of different cichlid jaw morphologies. When publications in that area led to invitations to write a book on the evolutionary significance of functional morphology, she decided to learn more about the vertebral column, both for its rich adaptive variability in different phyla and its central place in vertebrate architecture. It soon puzzled her that in spite of the wide variation in number of cervical vertebrae in reptiles, birds, and amphibian, their number in mammals (seven) was highly conserved.

This conservation was not a consequence of limited variation. Frequent morphological variations occur in human embryos (for which there is much embryological data), but particularly in the seventh cervical vertebra. These variations

[15] This is more complicated because to understand the earliest divergence of the "hourglass" one needs to look at the variability of the niche of the zygote, or to the egg, a (possibly much more divergent) property of the reproductive adult, in response to different ecological situations, or to a more fully protective maternal effect stabilizing and facilitating a supportive environment as in placental mammals. Furthermore, unless some canalization of the phylotypic stage occurs, either the apparent similarities at that stage among diverse phyla are illusory (Richardson et al. 1997), or there must be some other cause for the convergence (e.g., Newman 2013).

characteristically showed a projection like that of the ribs of the thoracic vertebra, suggesting a *Hox* mediated homeotic segment transformation. Indeed, it later emerged (Varela-Lasheras et al. 2011) that various mutations with an effect on *Hox* genes had this effect. Such variations were usually associated with other severe anomalies in various organ systems, especially the nervous system. The human medical literature (relatively rarely used by workers in Evo-devo) also revealed that these abnormalities were strongly associated with diverse embryonic cancers and with stillbirths. This suggested strong stabilizing selection against these variations and cancers as the reason for the evolutionary conservation of the number of cervical vertebra in mammals (Galis 1999). Reptiles and amphibians had low rates of cancer, explained by their low metabolic rates. But birds had high metabolic rates, and also high variability in number of cervical vertebrae (as high as 25 in swans). Galis hypothesized that birds must have low cancer rates, and was delighted to discover that they did (Galis and Metz 2007). Further investigations (e.g., Galis and Metz 2003) broadened support for anti-cancer selection in humans as a source of developmental and evolutionary constraints.

The teratological literature surveyed by Galis and Metz (2001) showed that there was higher mortality with disturbances that occurred at this stage, thereby both confirming and explaining the existence of a phylotypic stage in mammals. Moreover, the diversity of abnormalities rather than the presence of a single major syndrome suggested widespread interaction, rather than disturbance of a single important process as the cause, thus confirming the hypotheses of Sander and Raff against the third hypothesis (at least for humans). The robustness hypothesis for the phylotypic stage also attracted her attention, and she changed phyla to examine whether the robustness of the segment polarity network (expressed during the germ band stage) explained its conservation (Von Dassow and Munro 2000; Von Dassow et al. 2000). Galis et al. (2002) reviewed extensive data to argue that the broader patterns of expression of segment polarity genes in the extended segmented germband stage in insects was highly conserved because of its pleiotropic cascades. But Galis and colleagues argued that the two results were consistent, but that the adaptive local robustness of the network studied by Von Dassow and Munro (2000) was accompanied by major effects arising from changes in inputs to the network with major downstream consequences, and the more molar observed conservation patterns were due to pleiotropic entrenchment, not to the robustness of the network itself. This was a revealing articulation of two apparently contradictory results, and suggested the likely complexity of other interactions of robustness and entrenchment as alternative and complementary causes of developmental and evolutionary stability (Wimsatt 2007b).

There were other puzzles. How could the number of cervical vertebra be so variable, and cancer rates so low in birds? How could they vary in particular mammals, such as manatees and sloths (Galis and Metz 2007; Varela-Lasheras et al. 2011)? What about phyletic differences in the possibility of limb regeneration (Galis and Metz 2003) or variation more distally in the vertebral column (Varela-Lasheras et al. 2011)? Puzzling over the descent of birds from theropod dinosaurs (Galis 2001) led to more general accounts of digit formation and evolutionary

constraints on digit number (Galis et al. 2001). This generated diverse hypotheses concerning differences in developmental time (later in the phylotypic stage, and thus less constrained for digits and still less for phalanges, and for cervical vertebra in birds), modularity and meristic traits (Galis et al. 2010), and interaction with biomechanical constraints and ecological niche in explaining the patterns of variation in the thoracic-lumbar vertebral boundary (Ten Broek et al. 2012).

Thus, with ingenuity and exploitation of diverse experimental, medical non-experimental, and cross-phylogenetic morphogenetic and genetic sources, the seventh cervical vertebra in humans became a touchstone for rich explorations of the causal networks in and around the phylotypic stage, and the interaction of functional and developmental constraints in analyzing the characteristics and variations of the vertebral column.

#### 17.2.1.2 Bottom-Up Approaches to Pleiotropy

Among those using pleiotropy in arguments for conservation, one might characterize the difference between top-down methods (e.g., Galis, Raff, or D. Wake), and bottom-up methods (e.g., Gerhart, Kirchner, Davidson, or Newman) by whether they utilized the interactions and properties of specific genes or gene circuits, or whether they began with morphological traits or general characterizations of the actions of mutations connected with them (e.g., the arguments of Galis or Raff concerning the character of interactions at the vertebrate phylotypic or germ band stage). This would classify the work of Von Dassow and Munro (2000) and Von Dassow et al. (2000) as bottom-up, although Galis et al. (2002) engaged directly with them. They do so however by talking about the number of pleiotropic cascades emanating from the segment polarity network rather than the particular characteristics of any one of them. Thus, top-down and bottom-up methods can and should converge and articulate, which is happening increasingly elsewhere in Evo-devo.

If we look to the beginnings of bottom-up work with pleiotropy, Britten and Davidson (1969) pose a general architecture for gene action in eukaryotes designed for and assuming pleiotropy. In Britten and Davidson (1971) they close their discussion of the roles of repetitive and non-repetitive DNA in their model with a hypothetical discussion of the evolution of regulatory complexity in metazoans, and its consequences for novel mutations of different sizes. In this they supposed an evolutionary sequence of new *cis*-regulatory structures also acting sequentially in development such that the acquisition of successive layers in evolution made adaptive variations in deeper ones less likely, thus locking in deeper architectures. This schematic evolutionary story is the direct ancestor of the GRNs and cassettes of Davidson (2006), Davidson and Erwin (2006), and Erwin and Davidson (2009). Curiously, this implication is not drawn out or even repeated in Davidson's contributions to the 1981 Dahlem conference—perhaps because their hypothetical scenario of 1971 had no further data to elaborate it in 1981.

Readily available data from comparative genomics (the taxonomic distribution of different DNA sequences of different degrees of similarity) and their inferred

relative fixity led to different proposed architectures of pleiotropy for *cis* and *trans* regulatory modes (e.g., Gerhart and Kirschner 1997; Kirschner and Gerhart 2005). This approach has matured in several directions with the explosion of cross-genomic information. A massive review of 7,180 genes in *Drosophila* species found widespread association between pleiotropy and conservatism (Artiere et al. 2009). Another result of cross-phyletic comparison is the extraction of more abstractly characterized kinds of genomic architecture, indicating, for example, a kernel underlying specification in the heart progenitor field (Davidson 2006, Fig. 17.1). By comparing the circuitry in *Drosophila* and vertebrates, one can extract elements they have in common—presumably ancestral to both.[16]

But this figure reflects an emerging common theme: the level of organization that is conserved is commonly functional rather than structural. This conserved kernel must be characterized at a high level of abstraction—not in terms of sequence, or even genes (because these structural characterizations vary across lineages this diverse). This characterization is in terms of functional roles, demonstrating that the preserved structure is at a far higher level of abstraction than gene sequences. (It is a move in the direction of generative entrenchment with respect to functional roles rather than genetic sequences.)

Gerhart's focus on developmental signaling pathways (Gerhart, Chap. 8, this volume) and Newman and Bhat (2009, Chap. 19, this volume) discussion of dynamic programming modules fit here as bottom-up cognate lines of elaboration of a search for a basic algebra of deeply entrenched metazoan architectures. They differ however in that Gerhart's approach sees signaling pathways as specialized articulations of genetic architectures with broader constructive consequences for organizing the action patterns of the genome, whereas Newman sees the DPMs as evolutionarily later genetic stabilizations of natural tendencies of cellular bodies to interact collectively in response to basic physical forces like surface tension, viscosity, adhesion, diffusion, and lateral inhibition. These perspectives seem complementary in the same way that top-down and bottom-up perspectives are for entrenchment more generally. This is an area in which we can hope for further articulation of viewpoints.

#### 17.2.1.3 Sub-functionalization in Proteins: Pleiotropy In-Between

Top-down and bottom-up approaches to pleiotropy have concentrated on control genes, but work on the evolutionary analysis of proteins, undertaken before much of anything was known about control gene architecture in eukaryotes, was also influential. This constituted an "in-between" approach, but one well suited to the emerging knowledge of protein primary structure. Allostery in proteins with multiple sites or regions provides a case of pleiotropy (involving different regions) within the functioning of the protein molecule. As might be expected, those regions

[16] Rasmussen (1987) had perhaps the earliest example of a developmental circuit diagram, presented below as Fig. 17.5.

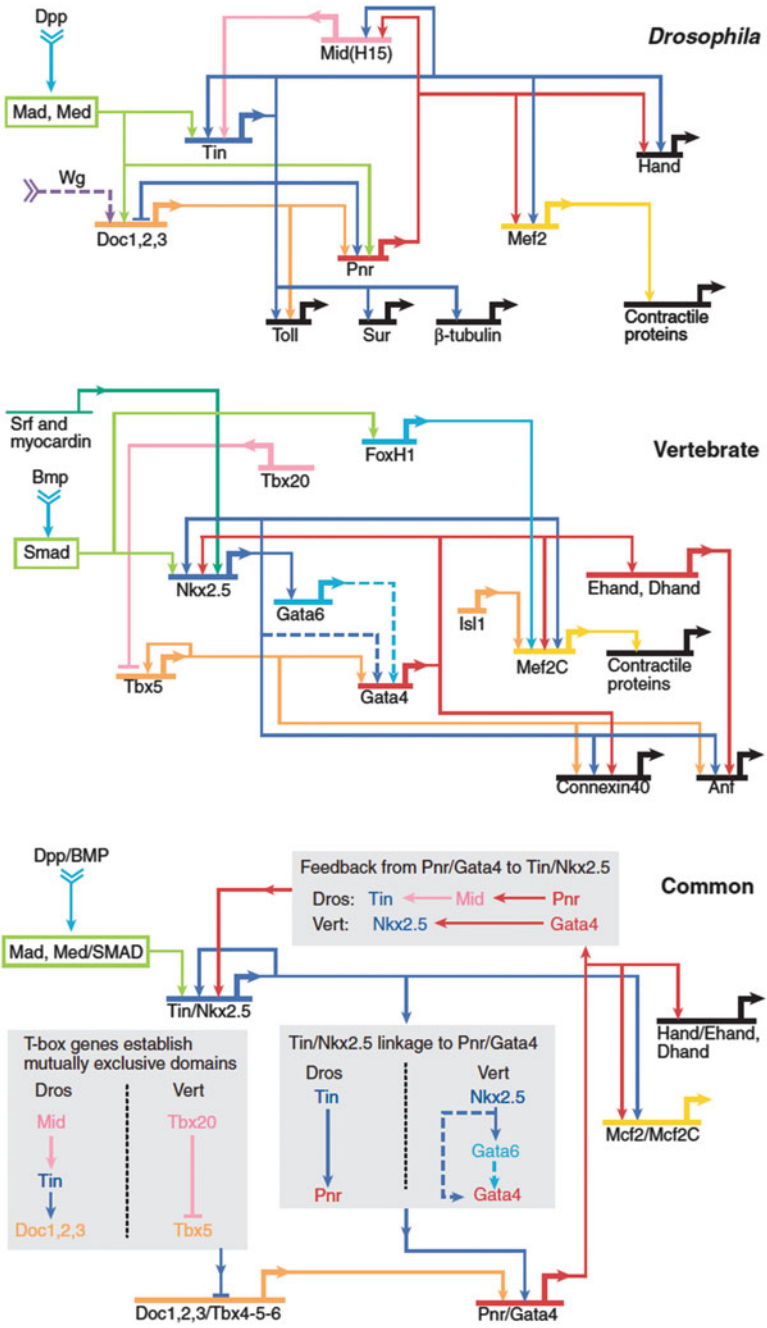


**Fig. 17.1** The hypothesized kernel for heart specification, as shown in *Drosophila*, vertebrates, and the common presumed precursor that is conserved in both (Davidson and Erwin 2006, 799). The level of abstraction pertains to functional roles in the circuit, not gene sequences or genes

are more highly conserved than others not so involved. In 1972, R.E. Dickerson used a cross-phylogenetic study of the soluble electron-transporting molecule Cytochrome c from 38 different organisms to compare the variability at different amino-acid sites, ranging from strict conservation to as many as nine different amino acids). When allowing for the hydrophobic or hydrophilic character of the side chains (which affect folding), in conjunction with x-ray diffraction studies of the stereospecific configuration of the molecule in oxidized and reduced sites, Dickerson was able to determine: the region of conserved amino acids internal to the folded molecule that bound the heme, the changing configurations of the molecule in its oxidation and reduction phases, the active regions on opposite sides of the molecule where it forms a complex with the oxidase and reductase, a negatively charged region, and an otherwise anomalous hydrophobic site involved in closing the molecule around the heme. Comparison of the rates of mutation accumulation per amino acid in the histones, Cytochrome c, hemoglobins, and fibrinopeptides showed successively higher rates of substitution in proteins with less constrained functions. These inferences involved the basic logic of differential entrenchment and evolutionary conservatism.[17]

### *17.2.2 Burden*

An alternative to investigating genetic pleiotropy is to draw connections between the size or breadth of effect of a phenotypic variation and its evolutionary conservatism. This traces back to Darwin's arguments *against* the role of macromutations or sports in evolution on the grounds that they would likely be deleterious by disturbing the "correlation of growth." This approach is significantly developed in Riedl's (1975, 1978) systematic elaboration of "burden." A morphologist specializing in marine species, Riedl's examples are primarily morphological. Nonetheless, it was an approach in which it was possible to see macroscopic developmental dependencies, such as in limb development, that subsequently have been pursued by many others (e.g., Alberch, Müller, and Newman). Genetics is acting in the background, but the argument was not made in genetic terms, since little genetic information was available in 1975.[18]

Riedl (1975, 1978) starts with an account of systems theoretic and informational concepts applied to gene action to argue that burden could in principle act at the genetic level, but then he turns to macroscopic order in morphology. He proposes four perspectives on order, adapted to talking about macroscopic morphological

[17] I read this article when it came out in April of 1972, and used it in my biology course for the next 5 years. I think it influenced my developing ideas of generative entrenchment, and particularly the idea—not emphasized by Wallace Arthur at first—that entrenchment applied "all the way down."

[18] This holds for the last two variants, elaborated by Arthur and Wimsatt (see below, Sects. 17.2.3 and 17.2.4), and also Budd (2006). I contextualize and discuss Riedl's account at length elsewhere (Wimsatt 2007a), so it is only sketched here.

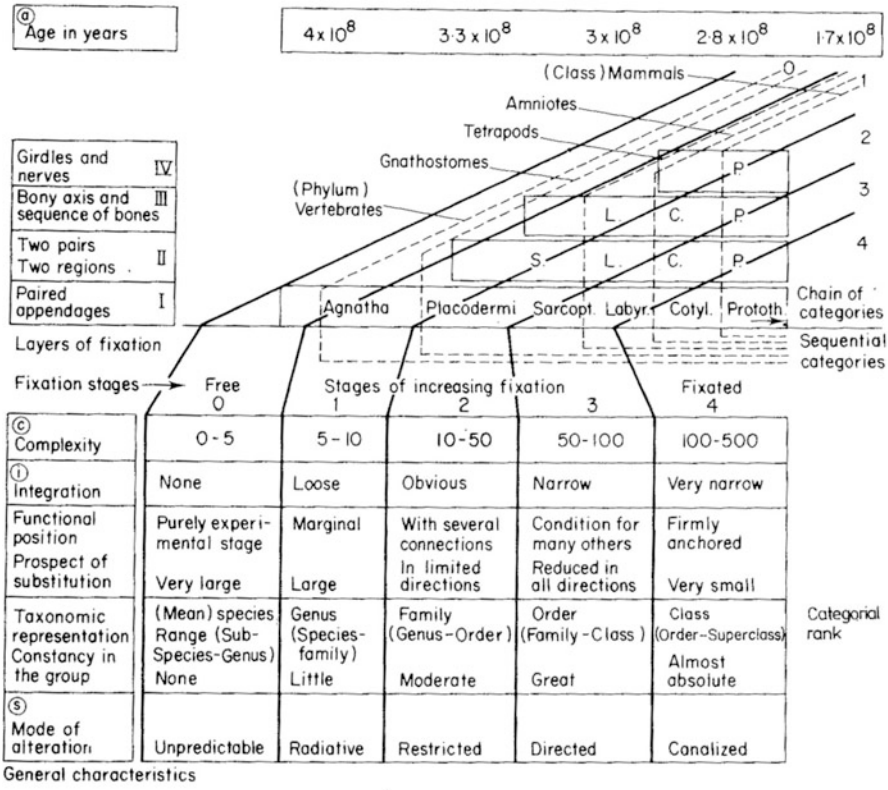


**Fig. 17.2** Fixation path of a group of features as illustrated by the mammalian limb (Riedl 1978, 157). The table illustrates the step-by-step accumulation of different layers of fixation (I–IV) and their associated stages (0–4) in limb evolution

dependency in development: (1) standardization and the use of multiple, standardized parts (such as vertebrae or body segments); (2) hierarchical order, in multiple realizations, from part-whole relations to hierarchy in taxonomy; (3) an elaboration of different ideas of interdependence; and (4) "traditive" or temporal order, indicating how developmental constraints would prevent, for example, mutations that transform one body plan into another. Throughout, he considers factors that increase developmental dependency on an element, and argues that this dependency accounts for the evolutionary conservation of the element. As an element acquires a longer evolutionary history, it should tend to become more evolutionarily conserved, showing less variation (Fig. 17.2). This list of factors does not indicate the reticulate complexity of Riedl's examples, many of which are sensible and convincing, such as the serial dependency of changes in digits.

Riedl's work did not get the attention it deserved for several reasons. It appeared during the rising hegemony of population genetics, whose adherents tended to dismiss developmental biology as irrelevant or unnecessary to evolutionary theory

(e.g., Williams 1966; Wallace 1986). Second, it appealed to cybernetics and to "general system theory,"[19] which had seemed promising in the 1950s but—in the absence of significant empirical knowledge of gene action—had lost their attractiveness by the 1970s. Third, some errors engendered confusions. For example, Riedl equated "burden" (which generated conservatism through *inter*-generational stabilizing selection) with "canalization" (which to Waddington signified *intra*-generational physiological or ontogenetic regulation of state or trajectory). Because Waddington's notion of canalization (e.g., 1956, 1957) was widely established among developmental biologists and population geneticists interested in development, many likely misunderstood Riedl's concept of "burden." Finally, in a disastrously formulated paper (Riedl 1977), he espoused loose connections with a broader systemic, hierarchical picture of the universe and other philosophical views while failing to illustrate his theory of burden with even a single biological example (of which he had many). This was a fatal expository choice to an empirically oriented English-speaking community of biologists, effectively convincing many possible readers not to bother with the English translation of his 1975 book (Riedl 1978). And since he drew no connections with von Baer's embryological ideas, there was little if any traction for his views among developmental biologists.

### *17.2.3 Morphogenetic Trees*

In June of 1985, I went to the International Congress of Systematic and Evolutionary Biology meetings in Sussex to give my first paper solely dedicated to the developmental lock model. I was astounded to discover that someone else gave a paper that day on the same topic; I sought out and met Wallace Arthur the next day. Thus began a long (if sporadic) and friendly interaction. Our approaches had points of convergence as well as key differences (see Arthur, Chap. 16, this volume).[20] But we shared one thing: we both came to development from a primary focus in population genetics. As a result, we both sought to connect processes at two very different time scales that others often treated as incommensurate (e.g., noted by Raff 1996). Our initial models were also grounded in a common attention to hierarchy: tree structure. Arthur's derived from his attention to gene action in branching cell lineages, a natural organizational feature in metazoans that robustly generates tree structure, and he elaborated this matrix to include various modulating factors (Fig. 17.3). My "developmental lock" model (Fig. 17.4) had tree structure because it spanned a branching tree of developmental possibilities (in a way more like Waddington's alternative pathways in epigenetic landscapes), in which earlier

[19] "General systems theory" should not be confused with systems biology. Ironically, the rise of systems biology has reinvigorated "systems" talk, as well as cybernetic language and intuitions.

[20] I had outlined my approach earlier (Wimsatt 1981). Arthur had published a paper containing his ideas in 1982, followed by their development in his first book (Arthur 1984).

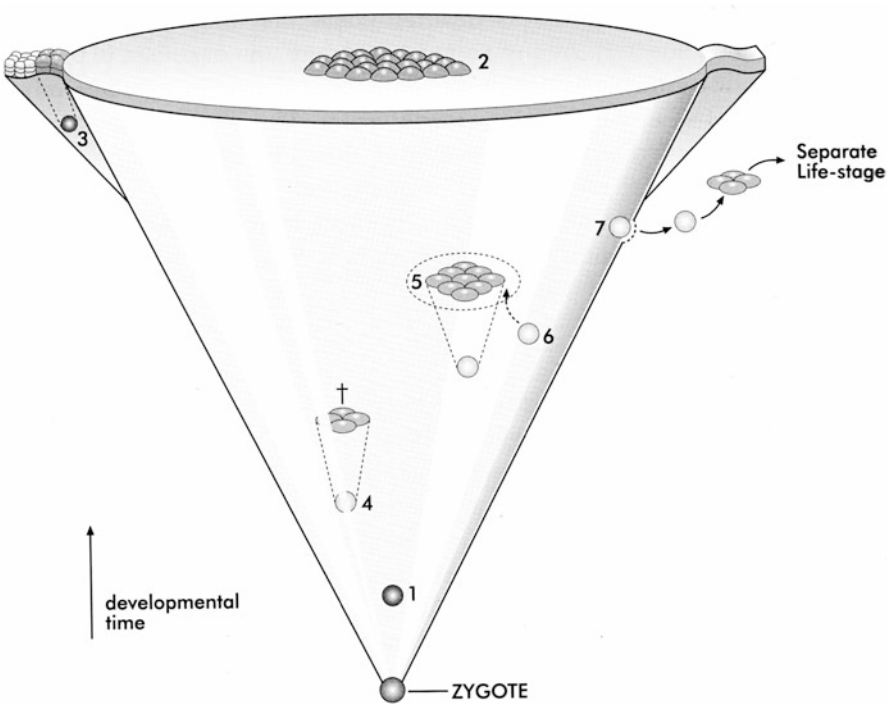


**Fig. 17.3** A more complex view of the 'developing organism as inverted cone' model (Arthur 1997, 196). (*1*) Cell in which gene A is turned on; (*2*) descendants of cell in (*1*); (*3*) cell in which expression of gene A marks proximal end of appendage; (*4*) cell in which gene B is active but, due to slow proliferation and/or cell death in descendants, there is little to no effect on the adult disc (despite early activity of gene B); (*5*) gene C, a diffusible morphogen, is active in a clone of cells and has a region of effect greater than its region of expression; (*6*) cell that is affected by gene C by migrating into the vicinity of its influence; (*7*) cell that begets a new life stage (e.g., the larval stage of a complex life cycle)

choices affected later possibilities (Wimsatt 1986). I was influenced by the literature on the heuristic search of large decision trees, such as the representation of chess games in extensive form.

Both of us noted and exploited the fact that our models could explain von Baer's laws, and Arthur went on to consider the role of developmental constraints as a possible explanation for the Cambrian explosion with lowered subsequent variability in body plan (Arthur 1984, 1988, 1997). To render his model consilient with microevolutionary accounts, he also proposed a form of selection, "***n***-selection," in which a variant at least replacing itself could get established in a small isolated population even if it were lower in fitness than the population norm. This variant could expand and succeed by something like Sewall Wright's "shifting balance" process with finer tuning of the deeper modifications that increased their fitness. A corroborating result came from simulations by Lenski et al. (2003), demonstrating how many ultimately successful variants had gone through a stage of lowered

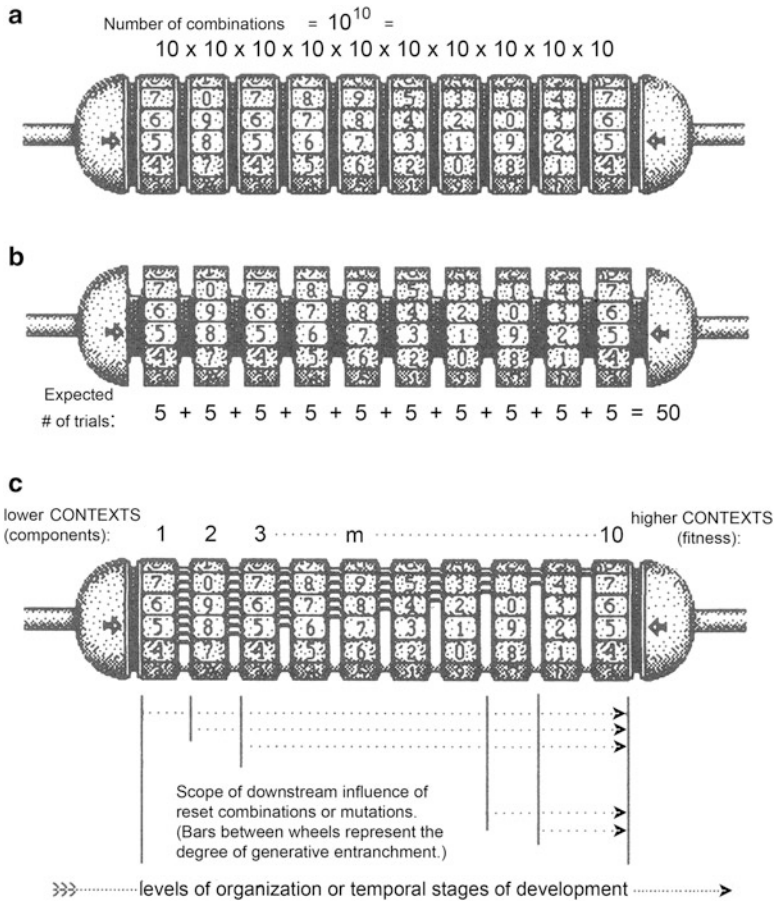


**Fig. 17.4** The developmental lock (Wimsatt 1986, 193). (**a**) Simon's complex lock—10 wheels with 10 positions per wheel. In the "complex" lock, the correct combination is only discoverable as a complete solution. (No clues are given for partial solutions.) Expected number of trials = $10^{10}/2 = 5 \times 10^9$. (**b**) Simon's "simple" lock—as in (**a**), but a faint click is heard when each wheel is turned to its correct position, allowing independent solutions to parts of the combination. (The advantage of near-decomposability in problem solutions is the ratio of the expected number of trials for the two locks = $5 \times 10^9/50 = 10^8$. (**c**) The developmental lock. This lock is a hybrid of Simon's two locks. Suppose a "click" is heard when each wheel is set to its (conditionally) correct position, but what position is correct is a function of the actual positions (whether correct or not) of any wheels to the *left* of it. Therefore, a change in the position of any wheel randomly resets the combinations of all wheels to the *right* of it. (Simple if worked from *left* to *right*, since the partial solutions to the *left* are not disturbed by work on wheels to the *right*, but complex if worked from *right* to *left* (in the sense that partial solutions are not preserved)

fitness, which was a necessary component in their success.[21] Schank and I explored similar moves in two papers from that period by analyzing generative entrenchment in Monte Carlo simulations of large multi-locus population genetic models in the context of the genetic load problem, as posed by Kauffman (1985). The neo-Darwinian paradigm dictated that microevolution was driven by incremental mutations of small effect (i.e., no macro-mutations). But this is not absolute, though commonly treated as such in classical population genetic models. Arthur and I both emphasized that larger positive mutations were exponentially less likely, but not impossible, so we both explored the realm of meso-evolution, between micro- and macroevolution. Our simulations (Wimsatt and Schank 2004) coincidentally confirmed the workability of Arthur's ***n***-selection mechanism.

Arthur and I both saw that entrenchment is but one process among several that interact to form an adaptive, evolved system. Entrenchment also illuminates and explains the phylogenetic evolutionary tracks of these systems. But there are (often complementary) differences in our approaches:

1. I have attempted to give a more general characterization of generative entrenchment to argue that differential entrenchment (different degrees of entrenchment for the different elements in a system) is a *generic* trait. It is almost impossible to build or imagine a differentiated system of any kind—for artifacts as well as living organisms—that does not have differential entrenchment. (Our simulations had shown that differential entrenchment is more important than entrenchment per se.) Furthermore, I argued that if you start with a symmetric and equal set of entrenchments, any deviation from this—driven either by mutation (e.g., adding a downstream modifier that would increase the entrenchment of a specific gene) or by environmental change—would tend to be amplified; i.e., the process is symmetry breaking (Wimsatt 2001). *So differential entrenchment is doubly generic or robust. It is an unavoidable property of all complex adaptive structures, and would tend to be amplified from a relatively homogeneous state by selection.*
2. This generality means that generative entrenchment is applicable beyond biology to evolutionary processes that are cognitive, cultural, social, or technological. Entrenchment applies to artifacts as much as to organisms. Indeed, in these areas, where genes have no significant purchase, it should be even more important than within Evo-devo. Entrenchment structures take up some of the organizational load in accounting for evolutionary change that is normally borne by genetics.

[21] It appears that population geneticists tended to treat a relatively improbable event as impossible—the same kind of mistake that emerges in ruling out (rare, positive) larger mutations. The surprising feature of their simulations was how many trajectories ending in positive solutions (~40 %) had gone through local minima of fitness (a possibility normally ignored by population geneticists), and many of the optimal solutions embodied suboptimal elements as necessary components.

3. If correct, theories in each of these other areas need to look for developmental dependencies among life-cycle components, or in cyclical processes in maintained structures (Wimsatt in press; 2013) as well as evolutionary patterns in changes in their domains. Few of them do.
4. Arthur and I have responded differently to counterexamples or limitations to a general von Baerian pattern. Arthur's approach has been to delimit and restrict the von Baerian model (Arthur 1997, 264–277). I have tried to preserve the intuition that bigger changes are much harder to make, and look for mechanisms whereby apparent or expected greater entrenchment can be avoided. Violations of a von Baerian pattern may not be counterexamples to the greater conservatism of more entrenched features. Most striking here is the hourglass pattern of variation with a minimum of variation at the phylotypic stage and greater variation both earlier and later (Raff 1996; Kalinka et al. 2010).[22] The mechanisms involved have analogues in non-biological cases; we have found six mechanisms facilitating escape from entrenchment in biology and many more for culture (Wimsatt and Griesemer 2007). In a striking analogue to entrenched signaling proteins, the required preservation of the communication protocol, TCP/IP has been claimed to generate an hourglass of variation between lower- and higher-level hardware and software, although apparently for different reasons (Akhshabi and Dovrolis 2011).
5. A crucial general feature of "escape mechanisms" by which deep modifications can be made is for changes to preserve rough functional equivalence for the entrenched feature. Three different and important examples in biology—tandem duplication, functional redundancy, and robustness—each provide ways to make allowable substitutions through preservation of the relevant functional role (Wagner 2005; Wimsatt in press). Because these changes to another structure preserve functional roles in relevant respects, it may facilitate exaptive evolution in other dimensions.

### *17.2.4 Generative Entrenchment*

To further explain similarities and differences between my approach and Arthur's, I must return to my starting point. The differences serve to explain some of the directions our research has taken.[23] I had initially been inspired by Herbert

[22] I first learned of Raff's direct-developing echinoderms that apparently deleted the larval stage with relative impunity in his talk at the Field Museum in the spring of 1989. His richly characterized and analyzed counter-example to von Baer's laws fascinated me, and helped to convince me that I should look to a systematic investigation of organizational features that could reduce entrenchment, or otherwise facilitate change of deeply entrenched features.

[23] Although written in the first person (appropriate from 1972 to 1984), this research in the 1980s and later involved close collaboration with two graduate students, Nick Rasmussen and especially Jeff Schank, who each made important contributions to how it developed, and later with Jim Griesemer (in the late 1980s and again after 2003).

Simon's 1962 article, "The Architecture of Complexity," in which he proposed a hierarchical model for the evolution of complex systems. Simon demonstrated that a complex system of a given size could evolve exponentially more rapidly if it aggregates in stages, forming stable sub-assemblies that then aggregate as larger complexes, rather than aggregating all at once. He employed this against a thermodynamic argument that evolution did not have time to assemble complex biomolecules (Jacobson 1955). In a discussion of Haeckel's biogenetic law, Simon suggested that evolution utilizes prior complexity and builds on or modifies it: "to make a gastrula, take a blastula and modify it" (Simon 1962, 480). But the latter is not an instance of his mechanism (so he proposed it without explaining it). Simon's models for complexity increase through aggregation, such as might explain evolution through parasitism or symbiosis (the evolution of eukaryotes), but did not account for the architecture of developing systems other than to suggest that what evolves is a "developmental program" (Wimsatt 1974). But he had other resources that I was able to incorporate into a new model.

One of Simon's models—an account of how a safecracker solves a combination lock by listening to the tumblers fall into place one at a time—was used to illustrate the advantages of near-decomposability in problem solving. Near-decomposability is the ability to break a complex problem into components that can be solved independently and then combined to produce a compound solution. (It is closely related to the advantages of modularity in development and evolution.) I visualized Simon's model as a multi-wheel bicycle lock (Fig. 17.4). If Simon's lock was modified so that the earlier wheels (to the left) each set combinations for all later wheels (to the right), then the lock could be solved in near decomposable fashion from earlier to later (left to right), but not in the other direction. This cumulative asymmetry constituted a simple model for developmental dependency that had interesting properties. For example, one would expect an exponentially declining probability for earlier mutations to be adaptive because they had to meet exponentially increasing numbers of constraints downstream.

This was a simple model—far too simple—and I needed to figure out how to extend it, to allow for the interaction of entrenchment with other factors, and generalize it, so that it could apply to more complex and varied developmental architectures. I played with it for close to a decade before first discussing it in print (Wimsatt 1981, 1986). The subsequent work of Rasmussen (1987) and Schank (Schank and Wimsatt 1988, 2000; Wimsatt and Schank 1988, 2004) made significant progress in these directions. But another factor was a part of my original motivation. I had been studying accounts of animal and human behavior by those who advocated the importance of innate factors, such as European ethologist Konrad Lorenz (1965). These had inspired linguist Noam Chomsky (1972), whose linguistic theory made widespread use of innate factors and generative systems. But their accounts (e.g., talk of "genetic blueprinting") were at odds with what was known or plausible about the operation of developmental factors. I employed the "developmental lock" model to correct this—to give an alternative

account of "innate" factors, in which innateness could be explained in terms of differential developmental dependency. The simple model was suited for making these conceptual points and generative entrenchment explained the criteria used for innateness in a natural and unitary way better than any of the extant approaches (Wimsatt 1986, 2003). Although I conceived of generative entrenchment as acting more generally in development (Wimsatt 1981; Glassmann and Wimsatt 1984), accounts of innateness were my first target. Innateness was assumed to indicate something that was genetic and necessarily internal, both of which I thought to be mistaken. I argued that evolution selected for increased fitness, a relation between organism and environment, not anything that was genetic or internal directly. I outlined conditions under which organism–environment relationships or something external to the organism could be entrenched, and thus treated as innate in this modified sense. This suggested the possibility of extended stable (and thus heritable) structures in the environment utilized by the organism (Wimsatt 1986), and thus anticipated the general approach of niche construction theory (Odling-Smee 1988; Odling-Smee et al. 2003).

Early on I appreciated the potential generality of generative entrenchment. Not only were there natural intuitions of dependency-induced conservatism in biological evolution, there were similar intuitions implicating it in scientific, technological, and cultural change. I wrote and circulated exploratory papers investigating the application of generative entrenchment in these domains.[24] As just one example, Mark Turner (1991) used these materials to argue that the transformation from figurative to literal meaning through extended use (a fixation of meaning in language in which initially loosely connected associations became essential) could be explained by generative entrenchment.

Closer to home, Nick Rasmussen used generative entrenchment to articulate the structure of the developmental program in *Drosophila*, using relations among 22 developmental mutants to construct a complex series–parallel network of developmental locks. On a visit to Caltech in spring of 1986, I showed it to Ed Lewis, who was very encouraging, and it was published shortly thereafter (Rasmussen 1987, with the developmental lock on the journal cover). Rasmussen's "circuit diagram" (Fig. 17.5) represents (to my knowledge) the first attempt to diagram the molar causal architecture of development in any metazoan organism. It remains basically correct even though it does not represent features like the organized action of the *Hox* genes.

[24] This was sketched in Griesemer and Wimsatt (1989), and in my contributions to Callebaut (1993). Later it was developed in substantial detail (Wimsatt and Griesemer 2007; Wimsatt 2007b, 2010, 2013).

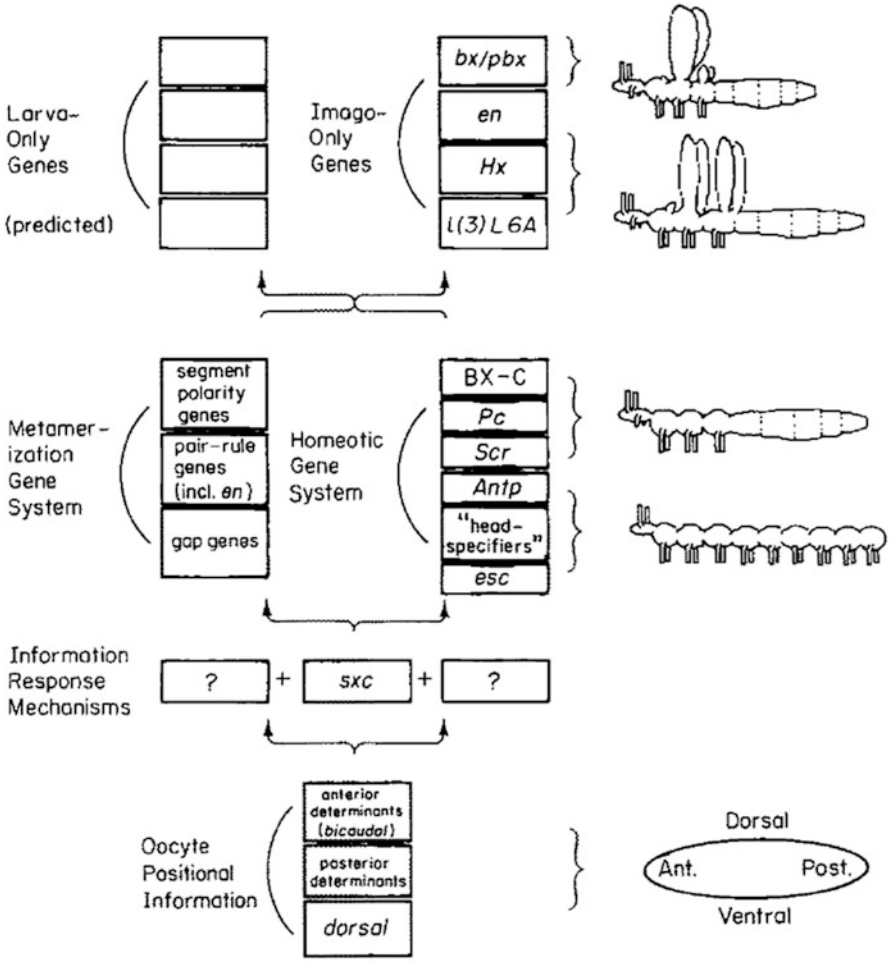


**Fig. 17.5** A new model of developmental constraints summarizing the generative entrenchment relation genes and gene functions in the *Drosophila* development system (Rasmussen 1987, 293). Greater entrenchment is toward the *bottom* of the figure. To the *left* of each group of genes is the name of the major subsystem to which they belong. *Arrowheads* indicate direction of information flow in the "program." To the *right* are representations of the form generated by the indicated gene functions. These approximate the sequence of fly evolution. For the sake of simplicity, only five abdominal segments are depicted

## 17.3 Population Genetic Models of Generative Entrenchment

In spring of 1985, Stuart Kauffman described his simulations with the evolution of small model gene control networks at the Spring Systematics Symposium at the Field Museum in Chicago. His results appeared to show that selection could not

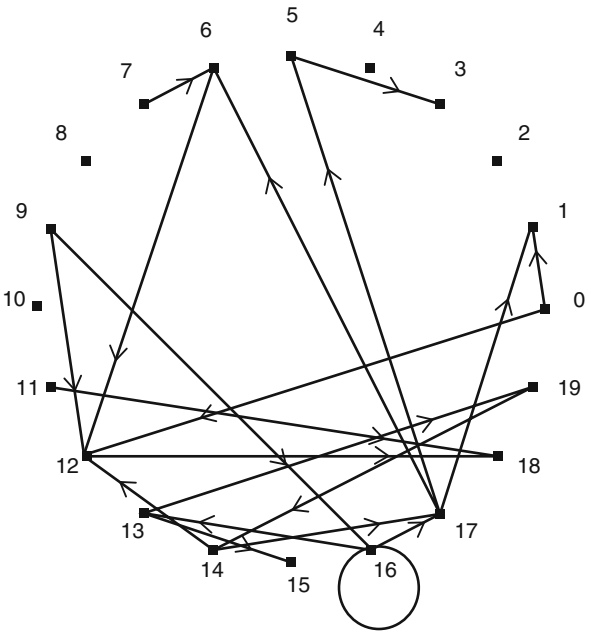


**Fig. 17.6** A Kauffman-style, randomly connected digraph showing causal dependencies in a gene-control network with 20 genes and 20 connections. This network shows naturally occurring differential entrenchment

maintain complex circuit structures for even simple networks. In random networks with 20 genes and 20 connections, a high mutation rate (0.005 per connection end per generation), and reasonably intense selection (0.05 per connection), only about half of the connections survived in a population of 100 organisms after 1,000 generations.[25] Larger circuit structures would be broken down quickly with this loss rate. Kauffman (1985, 1993) used this to argue that most aspects of biological organization must be maintained because they were highly probable generic states, and that natural selection played only a small role.

Jeffrey Schank, then a graduate student with me, set out to replicate Kauffman's simulations, and also to test my theory of generative entrenchment. Kauffman's circuits displayed differential entrenchment (Fig. 17.6), but his simulations did not use it. Although he counted the loss of any circuit connection equally, some connections would have many others downstream, while other connections had few or none. Changes to the more entrenched connections would be expected to

[25] Kauffman picked a high mutation rate so that he could get results in a reasonable amount of time with population sizes of 100 for the smaller circuits. He supposed that the inversely proportional relationship between circuit size increase and mutation rate decrease would preserve the qualitative conclusions. But the result was deeply paradoxical because then current estimates had suggested genome sizes of 100,000 genes, and data on amounts of heterozygosity in populations suggested that ~95 % of these should be preserved over time spans much longer than 1,000 generations. This was much larger than Kauffman's results would suggest unless the vast majority were selectively neutral. But then how could they maintain adaptive organization against drift?

cause much larger disruptions in circuit behavior. Modeling the dependency structure of a causal network with a directed graph was more general and adaptable than limiting it to developmental locks (or series-parallel networks of them). If the fitness assigned to the whole circuit in a Kauffman-style model was redistributed to reflect the differential entrenchment of nodes, then entrenchment was reflected in contributions to fitness. With circuits analyzed in this manner, Schank's simulations yielded strikingly different conclusions. Although the circuits still lost about the same overall proportion of connections due to mutation, *all of the losses occurred among the less entrenched nodes*; the more entrenched ones were preserved (including those that were only as strongly selected as in Kauffman's circuits). This meant—contra Kauffman—that reasonably complex structures could be preserved among the more entrenched nodes.

Furthermore, population genetic models normally specify the genetics, and then subsequently assign fitnesses using externally determined criteria (e.g., empirically determined or arbitrary values used to ascertain the possibilities of the model). By contrast, models like ours that assign fitnesses based on the entrenchment of the components are using features of the internal organization of the phenotype to give an *intrinsic* assignment of fitness. This important move—an advantage more readily exploited with developmentally based models—has been explored more fully by others since. Thus Aldana et al. (2007) employ such models to analyze robustness and evolvability in circuits like those found in *E. coli*.

Another problematic assumption of Kauffman's simulations was that the "fit" solution was always a unique circuit configuration, any deviation from which lowered fitness. There was no robustness—no fitness invariance over a range of (neighboring) states. Any mutation would have negative consequences, and large genomes would have impossibly large genetic loads. But increased robustness has a significant role to play in selectively maintaining adaptive structures, by making many of the likely mutations functionally equivalent and selectively neutral (Aldana et al. 2007; Wagner 2005). Like Andreas Wagner, we (Schank and Wimsatt 1988) argued for "degrees of genericity"—like an entropy measure, for different adaptations—showing that the most plausible cases would involve selection for states of modest genericity or robustness—i.e., that would show at most small variations in fitness over a range of neighboring states. This kind of robustness is likely selected for, and should be driven particularly by sexual recombination (Wimsatt 1987, 1994). Azevedo et al. (2006) and Livnat et al. (2008) show the plausibility of a "mixability theory of sex" via analytic and simulation means, utilizing this as a mechanism to select for robustness. This reformulation of the problem respects Kauffman's intuition about selection in complex structures. But unlike his proposed solution, these approaches allow the genericity to be distributed as localized robustness or canalization among diverse adaptive macrostates that are maintained (in neutral or nearly neutral zones, rather than as specific states) by selection, thereby rejecting the false dichotomy between generic and

selectively maintained states.[26] So generative entrenchment apparently plays a major symbiotic role with robustness.[27]

We had observed the effects of entrenchment (Schank and Wimsatt 1988), but did not know how they scaled up. The presence of differential entrenchment appeared not only to preserve the more entrenched nodes, but also to preserve a larger proportion of nodes than in circuits with otherwise equally weighted connections. Was this true? If so, what was the explanation? To explore this, we needed more versatile, detailed, and larger models. Over the next 3 years, with new software and more powerful computers, we scaled up the simulations to substantially larger sizes, while at the same time changing the assumptions to make them more adaptable and realistic.[28]

1. Aside from ignoring the effects of entrenchment, and the absence of robustness for selected states, Kauffman's most unrealistic assumption was that all of the mutational losses in his circuits would sum to 1. That is, a genome of 20 genes would still have a fitness of 0.05 if 19 of its alleles were rendered non-functional, and only reach zero fitness when all genes were knocked out. (Reproductive impotence required total destruction—"road kill"!) But no real organisms would be viable if even a small fraction of their genomes were mutated to non-functional states, and mutations in many genes would be unconditional or conditional lethals. *This implies that selection in any complex system is always a truncation selection process. This is an extremely important fact, and a very robust one*. Thus, we need a truncation selection model with different size contributions of genes and a total possible sum of individual mutational losses much greater than 1. (Standard truncation selection models, like Kauffman's model, had characteristically assumed equal fitness loss for all genes.) This unrealistic assumption suppresses an important phenomenon, discussed below (Wimsatt and Schank 1988, 2004). Starting with a fitness of 1, as mutations occur they should be subtracted from that number until the resulting fitness is zero or negative. At that point the organism does not reproduce, even though it may still have many genes functioning correctly. Changing to a truncation selection model with heterogeneous selection coefficients for different connections increases significantly the number of genes that can be maintained by selection, for reasons that will emerge. We define the ***exposure***, ***k***, as the sum of

[26] Wimsatt and Schank (2004) show that near neutrality can lead to an importantly different evolutionary dynamic than strict neutrality, but, given the work of Lenski et al. (2003), near neutrality could do this as well as strict neutrality.

[27] We are not yet in a position to say generally how often entrenchment is built on top of robustly determined features, or whether deep entrenchment acts to stimulate selection for increased robustness. Specific analyses to determine whether "deep" architectural features of circuits are maintained by robustness or entrenchment favor entrenchment (see, e.g., Galis et al. 2006), but these don't answer the question in general.

[28] See Wimsatt and Schank (2004) for a more complete list of changes.

possible mutational losses of each gene occurring individually.[29] This will in general be significantly larger than 1. We set it equal to 4 in most of our simulations though it is presumably significantly larger than this for real organisms.

2. We allowed for circuit sizes up to 260 connections (13 times as large as Kauffman's, and approaching a realistic range for the number of simultaneously segregating alleles). With population sizes of 100, this allowed for runs of up to 4,000 generations, sufficient for the mutation-selection balancing processes to come to equilibrium.[30]
3. We allowed for five multiple fitness classes of connections of specifiable sizes so that we could investigate the effects of different fitness distributions, reflecting different developmental architectures. Where the fitness contribution of a connection falls in the distribution of fitnesses is far more significant that its absolute magnitude (Wimsatt and Schank 2004), again reinforcing the importance of differential entrenchment. After investigating the effects of tree-like structures with different rates of branching, we did most of our work with a branching rate of 2 (which affected number of connections in neighboring fitness classes) and a fitness ratio of ½. The choice of these two parameters gave five fitness classes that make equivalent contributions to fitness. In the circuit most investigated, there were fitness increments of .1, 0.05, 0.025, 0.0125, and 0.00625, in classes with 8, 16, 32, 64, and 128 connections, and an exposure contribution of 0.8 for each connection class, for a total of 248 connections with 496 mutable sites. Each genome had a total exposure of 4, and each connection had a mutation rate of 0.0025 per connection end, for a total of 0.005 per connection.[31] The fitness values assumed bracketed the fitness value of 0.05 used by Kauffman.

[29] This allows an important move towards realism, but still embodies a problematic simplification because the additional loss due to a gene will depend on what other losses occur. The idea of having fitness classes of different sizes was to allow for different numbers of downstream consequences, but with building this into the initially assigned fitnesses, the changed topology of the circuit after a mutation is no longer taken into account because we are no longer working directly from that topology to compute fitness contributions. Tracking the changing topologies was in principle possible, but immensely more demanding in computational and memory capacity and beyond what we could do in 1987–1989. Aldana et al. (2007), with far greater computational power, utilized the changing topologies.

[30] In 1987–1989, our simulations were limited to a maximum total data of 32 K bytes. So increasing the number of loci required that we avoid large populations.

[31] Mutations were always to connections with another gene in the genome. This definition made "back mutation" possible, with calculable rates. Connections on a predefined list were "good," and all others were "bad." One gets credit for a good connection, but additional identical good connections didn't count. The crosshatched connections in the three cases have the same relative fitnesses (Fig. 17.8).

Our simulations that adopted these more adaptable and realistic assumptions yielded the following results:

1. We found large increases in the numbers of genes that could be simultaneously maintained by selection (on the order of 95 alleles—Kauffman had 10 or 11), including all of the alleles in the more strongly selected classes. This substantially weakened or at least redirects Kauffman's claims. If, in addition, robustness enters the picture (with neutrality or near neutrality of many allelic substitutions), then far larger and more complex entrenched structures become maintainable by selection.[32] This removes an important obstacle and generates a more plausible picture of the evolution of complex organisms. (The real number of maintainable connections would be much larger than in our simulations, since we assumed an unrealistically high mutation rate in order to get discernible effects in simulations with smaller genomes.)
2. We were able to discover the details of what and how connections were maintained. Population genetic simulations with parameters motivated by developmental concerns have taught us new things about selection forces in such models. First, all of the more strongly selected (or more entrenched) connections were preserved. Thus, in our model (Fig. 17.7, bottom), essentially all of the connections in the top three classes (0.1, 0.05 and 0.025) were preserved, and 67 % of the connections in the fourth class (0.0125). Most of the losses were in the bottom class. In Kauffman's simulations only half of the connections with fitness contributions of 0.05 were preserved. So differential entrenchment is more important than absolute selection intensity, and is capable of preserving even modestly entrenched connections.
3. The course of selection is counterintuitive: the top three classes initially *decline* in frequency as mutations accumulate, and then reverse to fixation. (The fourth class stabilizes, while the fifth—constituting the connections with the smallest fitness increments—continues to decline, approaching equilibrium at a low value by 4,000 generations.) This points to an overlooked mechanism of interaction that is an analytical consequence of such models but could not have been seen if all of the connections were equal in value. To understand why there are these trajectory reversals, consider Fig. 17.8, which is a schematic representation of the circuit in Fig. 17.7, with ⅛ as many connections (31 instead of 248)—one in the top class, two in the second, four in the third, etc. It is diagrammed as a "floating iceberg," with sea level being the truncation threshold. We see from a comparison of the three "icebergs" that when the Darwinian fitness of the population declines (height of the top of the iceberg above sea level), the *relative* fitness contributions of connections *increase*. Thus, with a mean Darwinian fitness declining from 1 to 0.5 to 0.25, mutations with effect 0.1, 0.05 and

[32] Wagner and Zhang (2011) review evidence that pleiotropy, though widespread, is rarely massive, suggesting a usable degree of variational modularity for evolution.

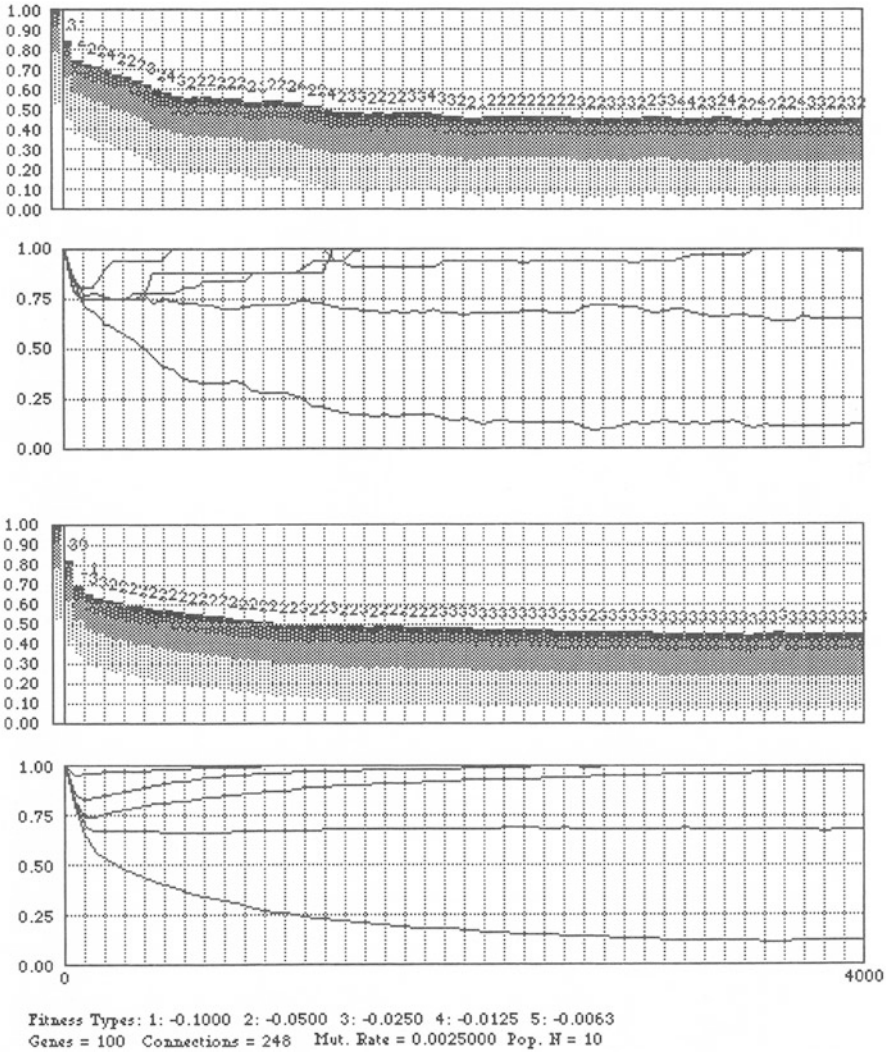


**Fig. 17.7** (*Top*) A simulation of the evolution of frequencies in five fitness classes in a population of 248 locus gene-control networks (run #50 depicted). (*Bottom*) Average is from 50 runs

0.025 have the same relative fitness contributions.[33] Figure 17.7 shows that the different classes come to equilibrium at different rates, with the most strongly selected alleles getting to equilibrium first. The bottom class keeps "leaking out" after the others have arrived at their equilibria, lowering the mean Darwinian

[33] This argument supposes that the absolute fitness contributions of the alleles are constant. This is not necessarily the case, but is presumably true for a subclass of alleles.

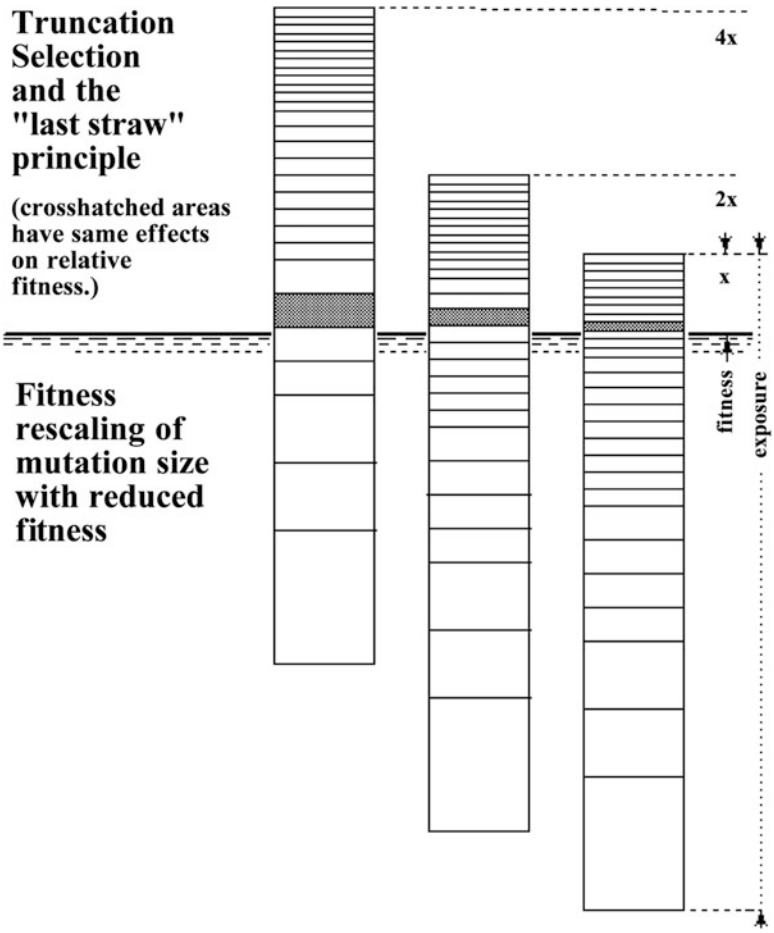


**Fig. 17.8** Schematic "iceberg" model of truncation selection in circuits like those simulated in Fig. 17.7, which shows that relative fitness amplification occurs with reduced mean Darwinian fitnesses

fitness, and (as in Fig. 17.8) generating relative fitness increases that reverse and drive up frequencies in the three top classes, which yields a population of genomes that are "near the edge" of truncation selection.

4. Individual runs of the simulation deviate through stochastic fluctuations from the average equilibrating trajectories, and constitute natural perturbation experiments. Figure 17.7 (top) is a particular run in which two out of eight alleles in the top class are lost early but then back mutate. This causes a rapid response in the other classes, showing counteracting deviations that lead to an averaging across all of the classes (see Wimsatt and Schank 2004 for further discussion). From the simulation trajectories in this case, we see that larger positive mutations, larger positive changes in the environment, or new, larger back mutations

to positive alleles generate a rapid response, with positive mutational changes rapidly going to fixation (faster than the lower fitness classes can respond) and raising the mean Darwinian fitness. The result is a fitness margin that relaxes selection by scaling down the relative fitnesses across the board, and allows an explosion of new, smaller variants that are now no longer conditional lethals. *This phenomenon of an explosion of variation following a major mutational change or in a relaxed environment is supposed in many evolutionary scenarios.* (I take this prediction to be a positive feature of the model though I know of no hard data bearing on it, or any other models that have succeeded in predicting it.)

5. It also confirms the workability of Arthur's "***n***-selection" model and demonstrates a kind of diffuse epistasis that compromises "selfish gene" approaches because it shows that, even without any local epistasis, you cannot define selection coefficients independent of the state of the rest of the genome.[34] This is a fundamentally new criticism of the "selfish gene" paradigm.
6. For organisms in nature, we would assume that there is a continuous distribution of mutational effects of different sizes. But in these models there were only alleles with non-zero fitness contributions and the size of fitness contributions in the smallest positive class is crucial for their behavior. If smaller, it allows a closer approach to the "edge" and a greater inflation of relative fitnesses in the larger classes (as seen in the comparison of two simulations with minimum fitness classes of 0.02 and 0.0625, respectively; Wimsatt and Schank 2004). There is an important, unintuitive discontinuity in analytical models: because of genetic load and truncation selection, "nearly neutral" mutations have different effects than "neutral" mutations, and are likely crucial to the dynamics of selection in complex systems. This also applies in the evolution of robustness (Wagner 2005).
7. One consequence is that *the equilibrium frequency of a connection is strongly dependent on its position in the distribution of fitness contributions—more so than on its absolute selection intensity*. Therefore, again, it is *differential* generative entrenchment that matters. In simulations with circuits with the same total exposure, a connection with a fitness contribution of 0.025 was at a frequency of 0.25 if in the bottom fitness class, but of 0.93 if in the top class.[35]

These models have revealed unanticipated features of population genetic models and generated realistic phenomena simply from the internal dynamics of a more realistic truncation selection process (e.g., the release of variation with relaxed

[34] The metaphor analogizing genic selection to switching rowers in a shell (Dawkins 1976) to pick out the fittest in effect ignores the fact that the rowers must use a common shell. Analogously, genes are always embedded in an interactive genome, and must bear the consequences of their collective activity, so Dawkins' metaphor is crucially flawed. He never considers the role of the boat in making good times when he switches the rowers!

[35] This was made possible by looking at circuits with 33, 65, 130, and 260 connections, with proportional distributions scaled to produce analogous results, so that only the *relative* position in the distribution of a connection class with given fitnesses has changed.

selection). Far more sophisticated and larger simulations than these exist now (these were done in 1985–1989), but they show that looking at population genetics using models constructed with parameter values designed to capture developmental phenomena can help to resolve questions in evolutionary theory (e.g., whether genetic load problems force acceptance of a primarily neutralist theory), and bridge the gap between population genetics and developmental biology, or between microevolution and macroevolution by drawing attention to phenomena in the range of meso-evolution. No one had constructed models with many loci that were both truncation selection models and had multiple fitness classes, so no one discovered the phenomena that emerge.

## 17.4 Future Directions?

I expect more insights into the relations between macroevolution and microevolution to emerge from attempts to connect population genetic and developmental concerns. I also expect that the intermediary of "meso-evolution" will provide a bridge, in the same way that Brownian motion provided a bridge between the Newtonian microphysical, many–many body problem and macroscopic thermodynamics. At the edge of their overlap, the idealizations of the macro- and micro-approaches break down; new theory and data located in this region should be of pivotal importance. But since entrenchment has feet in both camps, it should be an important part of the picture. The work of Günter Wagner and Wallace Arthur fits here, bridging both domains, as does the growing presence of biologically motivated physicists who seek to generate more realistic models of the developmental architectures of simple organisms (e.g., Aldana et al. 2007; Torres-Sosa et al. 2012; Newman, Chap. 19, this volume). Analyses of the general architectural features of such models is crucial, such as work on robustness, evolvability, and evolutionary innovation (Wagner 2005; Wagner and Zhang 2011), because it motivates population genetic models with characteristics that have not been tried before (e.g., Livnat et al. 2008). And we cannot forget that all of our biological processes are built on and with physical processes, and must be responsive to them at all stages in the evolution of more complex systems. The early co-evolution of physical forces and genetic systems should be of particular interest, and the kinds of research that Carl Woese pursued in the last half century on the emergence of informational systems deserves our attention and should be articulated with the co-evolution of metabolic systems.

Additionally, I expect (and hope to see) extensions of a developmental perspective (and generative entrenchment) into other areas. In culture, science, and technology, we have broadly adaptive change without an underlying genetics. This is a curious (unnoted) inversion in problem structure from that of evolutionary biology. Classically, for biological evolution, transmission genetics was easy and developmental genetics much harder. Transmission was readily observable in whole organisms and their descendants, and untangling biological development has required far

more in resources and tools to reveal its causal skein. For culture and technology, analysis of transmission is difficult and complex—there are multiple parents with varying degrees of credit for most ideas and technologies, with different patterns of inheritance likely in successive generations, and no general analogue to the systematic inheritance structures of genetics (Wimsatt 1999, 2010). Thus, we have the equivalent of frequent cross-phylogenetic viral transmission, and transmission that can skip multiple generations (e.g., with inspiration from ancient artifacts or texts). Species are not well distinguished, in part for this reason.[36] In this situation, case studies are more revealing than general models, and the search for case studies that count as "the right organism for the job" and as good "model organisms" for answering other questions are even more important. There are interacting cultural reproduction processes operating on multiple time scales, and multiple information channels. Moreover, ideas, technologies, and the social supports scaffolding their development and transmission are inextricably intermeshed with processes of transmission and selection. Separating out the hereditary component from these is difficult or impossible (Wimsatt 1999; Wimsatt and Griesemer 2007), and we cannot treat heredity, selection, and development as complementary but near-decomposable problems, as we usually do in population biology.

But for all of this confusion, there is a complementary advantage: developmental dependencies are much more obvious, accessible, and easily manipulated than for the study of biological organisms. Since we construct our culture and our technology, and since culture must be learnable, the developmental dependencies should often be relatively obvious to us, since that is how we acquire the information and skills. Culture, science, and technology provide multifarious modes of external scaffolding to extend our reach and capabilities (Caporael et al. 2013). Though easily overlooked, it is out there and mostly accessible for analysis. Thus, even when we cannot distinguish cultural species, we should be able to evaluate dependencies, redundancies, modularities, robustness, and canalization. We should be able to assess the relative changeability of many cultural elements in terms of their net entrenchments, and do so without having to find "cultural genes." Analysis of this scaffolding, and of our interactions with it, should be capable of giving us a theory of evolutionary change without having a straightforward analogue to genetics (Wimsatt in press).

One crucially important feature for culture that we recognize in biology is the emergence of "combinatorial alphabets" (or perhaps, with a syntax, combinatorial algebras). We are already aware of the genetic and protein codes, but Gerhart and Kirschner's focus on developmental signaling pathways (Gerhart, Chap. 8, this volume; Kirschner, Chap. 9, this volume) and Newman's discussions of dynamic

[36] Culture is in some ways like an ecosystem in which reproduction for most species is so dependent on rich, articulated structures in the environment that the notion of independent species breaks down. I came to appreciate this through economist Kenneth Boulding's striking remark that, "A car is just an organism with an exceedingly complicated sex-life."

programming modules (Newman, Chap. 19, this volume) give us "morphological alphabets" that affect cell aggregation and differentiation. Similar explosions for culture and technology emerged with words in spoken languages, and the transition from iconic to alphabetic scripts in written languages. The emergence of machine tools and standardized mechanical parts permitted a combinatorial explosion of machines constructed with standardized parts. These types of explosions were later repeated for electronic parts, and, with the advent of computer languages, programming instructions and syntax led to programs adapted to accomplish an enormous variety of tasks. All of these are immensely productive and rapidly generate strong entrenchment relations, demonstrated by the persistence of both English and metric thread standards and the continued use and architecture of COBOL and FORTRAN programs. These and similar cases give us powerful handles by which to analyze culture and technology.

The 1981 Dahlem conference was a milestone, and one that should be emulated. Shortly before the 2010 workshop reflecting on this milestone and motivating the present volume, we had a different conference to highlight the growing interest in developmental processes in cultural evolution (Caporael et al. 2013). There, the key concept was scaffolding—the constructed and heritable external aids that we with our culture have built to reproduce and cumulate our developmentally acquired, expanding capabilities. Our scaffolding is both a product of and structures our individual and social hereditary processes, and facilitates the production of new adaptive variants. The participants at this other conference were appropriately diverse, ranging across culture, psychology, technology, sociology, and economics; many have derived significant inspiration from the 1981 Dahlem conference. We hope that our attempts to incorporate developmental considerations to the evolution of culture, technology, and science may be as successful in the next 30 years as the Dahlem conference has been in the last.

**Acknowledgments** In addition to the formative influence of many of the people in this, or in the original 1981 Dahlem volume, I would like to acknowledge the help and influence of Alan Love for extended and penetrating editorial commentary, and the pleasures of co-teaching Evo-devo and working together. Günter Wagner pointed me to the work of Frietson Galis when I was in a quandary as to how to trace the growing influence of pleiotropy in assessments of evolutionary conservatism in the last 15 years. Thanks to Frietson herself for many illuminating articles and conversations. Scott Gilbert confirmed and amplified my intuitions on C.H. Waddington. The remarkably constructive and open atmosphere of the "Dahlem revisited" conference in Berlin in July 2010 owes a great deal to the participants, to the charge of its organizers to us, and to the hospitality of the Max Planck Institute for History of Science, and the support of the Minnesota Center for Philosophy of Science and the Konrad Lorenz Institute for the Study of Evolution, Development and Cognition. Finally, the Minnesota Center for Philosophy of Science and the support of my Winton Professorship in the College of Liberal Arts at the University of Minnesota during this period have been invaluable, and the environment as challenging and stimulating as anyone could wish.

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# Part V
# Hierarchies and Interdisciplinarity

# Chapter 18
# Hierarchies and Integration in Evolution and Development

**Marvalee H. Wake**

## 18.1 Introduction

Evolutionary developmental biology (Evo-devo) is, by its nature and even its label, "integrative." The components of evolution and development are often, but not often enough, treated with reference to bridging (at least) two levels of biological organization. Concomitantly, hierarchical and integrative research approaches and methods are implied. But has the relatively recent adoption of hierarchical and integrative approaches been a consequence of the emergence of Evo-devo over the past several decades and its leading a trend toward more synthetic scientific research, or has it, rather, been a product of the deployment of the new tools, techniques, and ideas in biological science (more broadly) that facilitate a more integrative methodology? How do hierarchical and integrative approaches relate to understanding the interrelationships of development and evolution, and what do they offer? Have such approaches been adopted consciously by researchers?

One of the primary factors that has promoted attention to the utility of hierarchical approaches and the need for integration across levels of organization is the urgency of conceptualizing the complexity of biological phenomena and their connections with various physical and social parameters—what might be labeled "twenty-first century biology." At least two decades ago, scientists began to seek ways to break "complexity" into its constituent parts, and concomitantly to ascertain the range of scientific expertise that should be brought to bear on major questions and problems. At last a consciousness that biology must deal with questions of complexity is developing. The integration of multiple levels of investigation is essential to understand what we recognize as complexity. Diverse techniques and theory, as well as the incorporation of a broader scientific base

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(biological sub-disciplines, physical and social sciences, etc.) are necessarily involved, with the particular mix depending on the nature of the questions being asked (Barbault et al. 2003).

This essay is an examination of the development of Evo-devo, particularly as it has (or has not) involved hierarchical thinking and integrative research, both of which are often recognized as having given life and direction to the concepts and practices of Evo-devo. The perspective offered here emerges out of my own research that emphasizes both evolution and development, but which has attempted to take a broadly hierarchical and integrative approach to evolutionary biology *sensu lato*. Additionally, I have a strong interest in assessing how such hierarchical and integrative approaches have contributed to the development of Evo-devo. I am an evolutionary morphologist who, like a number of biologists, was "integrative" before the term gained cachet, having studied development, functional morphology, and reproductive biology in evolutionary/phylogenetic frameworks for many years. My work in Evo-devo spans levels from chromosomes and sperm to lineages, and examines courtship and fertilization, embryonic-fetal development, ontogeny, fetal-parental associations, and the evolution of life history modes. My integrative approach incorporates perspectives on lineage diversification at all hierarchical levels of organization. I will reflect on areas of Evo-devo that I believe have received deserved attention, as well as less noticed areas of research that should garner more attention. Given my theme of the relationship of hierarchical and integrative approaches to the development of Evo-devo, I focus on their roles and impact throughout. Although I provide a broad overview, use several examples, and cite a considerable body of literature, this is by no means an exhaustive treatment. The aim is to stimulate interest and further discussion.

Research in Evo-devo uses a diversity of approaches—evolution of development, development of evolutionary change via new processes versus the retention of patterns and processes with some modification, analysis of the basis of developmental processes, comparative development from genes to species, and several others. Some, but not all, of these approaches employ hierarchical analyses and attempt to form integrative conclusions. And yet Evo-devo is perhaps unusually amenable to integrative and hierarchical approaches for several reasons:

1. New molecular and genetic tools, and diverse methods of analysis, facilitate the investigation of processes that were formerly "black boxes."
2. Conceptual advances in several subfields of biology (and chemistry, physics, computer science, and sociology) directly affect progress in dissecting both development and evolution (e.g., epigenesis, phylogenetic reconstruction, etc.).
3. There is a new and refreshing open-mindedness to broadening the practice of science beyond one or a few dominant research perspectives.

This expansion, in retrospect, was and is led, in many ways, by Evo-devo and its practitioners because of their focus on understanding the evolution of development and the significance of development to understanding evolution, including the conservation of genes and characters, as well as the molecular genetic changes that affect gene frequency and phenotypic modifications. Reductionism—in the

sense of focusing on the explanatory significance of lower levels of organization—is not antithetic to integration but is a part of it. Reductionism examines upward causation primarily; relatively rarely, but increasingly, it incorporates downward causation through the avenue of genomics.

A selective review of the literature allows us to examine the degree to which hierarchical and integrative approaches were facilitated *by* Evo-devo or whether such approaches actually facilitated what we now perceive as the "field" of Evo-devo. Which came first, the conscious adoption of synthetic approaches, or did attempts at synthesis generate integrative approaches? Historically, biology was more "unified," having split into ever-finer subunits ('fields') over time. At the moment there is a real movement to reassociate the different parts of biology with each other, but questions remain about its prospects. Does Dollo's Law (an organ, once evolved, cannot return to the ancestral state) apply to systems of thought? Can "reversal" (toward a more unified biology) happen given the diversification of tools, ideals, goals, and ways of thinking in the life sciences? It is ironic that Evo-devo is often labeled a "new field" when in many ways it is a return to a broader, more reticulated view of biological science. I will first consider the nature of hierarchies and integration, with special attention to their conceptualization around the time Evo-devo began to coalesce. Then I will examine current thinking and assess the degree to which ideas about and practices of hierarchical and integrative approaches have influenced the development of Evo-devo and the degree to which they are manifested in research today. Finally, in light of these considerations, I will discuss the strengths and weaknesses of contemporary Evo-devo, especially in terms of its progress over the past few decades and its scientific leadership as an exemplar field of biology.

## 18.2 Hierarchies in Biology: From 1981 to the Present

Let us first examine the notion of hierarchies in biology, and how they could be understood as elements of research programs, rather than being descriptions of interactions (e.g., social or food chain hierarchies). Although the literature on biological hierarchies is large, and interesting ideas have emerged over time, these discussions have gained little attention from most practicing researchers and consequently had short half-lives. Korn (2002, 199) summarized this problem:

> The study of hierarchies has passed through periods of enthusiasm followed by years of inactivity with little resolution achieved… About all that has been agreed upon is that hierarchies are composed of discrete levels (Weiss 1971) and a variety of types make it difficult to find common features (von Bertalanffy 1952).

Vrba and Eldredge (1984, 146) were similarly pessimistic:

> Hierarchy is a central phenomenon of life. Yet it does not feature as such in traditional biological theory… We urge that interlevel causation should feature centrally in explanatory hypotheses of evolution… A general theory of biology is a theory of hierarchical levels—how they arise and interact.

Grene (1987, 505) examined the history of the usage of the term "hierarchy," and found that biological discussion about hierarchies "has been simmering. . .with a "variety of meanings"" for more than a century. She noted that each field of biology has its own hierarchical perspective even though "the same word keeps turning up," but that these diverse perspectives appear anchored in two basic types of hierarchies: (a) the dynamics of levels of organization, and the constraints and controls involved; and, (b) the classification or structural arrangement of levels, in which control of upper and/or lower levels is not involved. In addition to these basic types, Grene concluded that "it is the flow of information both horizontally and vertically that makes the organism an integrated, working whole." I will return to the significance of this implication—that hierarchies should be considered with regard to the centrality of the organism—below (Sect. 18.2.3).

Although this debate about hierarchies was vigorous through the 1980s, it waned in the 1990s despite the fact that many held that "hierarchies are able to render complexity tractable" (Valentine and May 1996). But that tractability rarely resulted from broad conceptual attempts to bridge distinct hierarchies or all levels of organization, so many researchers resorted to developing hierarchies *within* a level (e.g. metabolic pathways, Ravasz et al. 2002) or *across* two or three of the most closely associated "levels." Broader syntheses were usually not attempted, if not actively discouraged.

### *18.2.1 Kinds of Hierarchies*

Valentine and May (1996) described several kinds of hierarchies of biological organization and the problems inherent in their definition and exploration. These include:

1. Somatic hierarchies—"constitutive" hierarchies that describe ranks of entities that form the bodies of organisms (particle to individual).
2. Ecological hierarchies—"aggregative" hierarchies, usually with ranks from individual to biosphere. Including enzymes and cells is inappropriate because these components do not exhaustively represent their entire rank (see Eldredge and Salthe 1984).
3. Taxonomic hierarchies—"aggregative" hierarchies, including that proposed by Linnaeus (1758).
4. Genetic and genealogical hierarchies—those that deal with the information used in heredity (codon/gene/gene pools, organism/species, etc.).

Valentine and May (1996) saw several problems in employing any of these kinds of hierarchies. For example, somatic hierarchies that include the gene as a rank below the cell, which is not uncommon, are problematic because the gene is one of many molecular entities at the same hierarchical level (rather than a level in-and-of-itself)—cells are not collections of genes. Furthermore, the genetic hierarchy—the collective for genes is the genome—is usually disregarded (Valentine and May 1996).

Ecological hierarchies are often based on a series of processes but since the processes do not form ranks, there is not a hierarchy but instead a sequence. Gene hierarchies are erected to correspond variously to a taxonomic hierarchy, an ecological hierarchy, or a somatic hierarchy, and thus the units and/or ranks are variably inclusive.

Another framework for biological hierarchies is presented by Love (2006), who discussed two relevant kinds: compositional (scalar) hierarchies that deal with part-whole relationships, and procedural (control or organizational) hierarchies that deal with "process dependence." Love pointed out that both kinds could be considered across generations (evolutionary time) and within a generation (developmental time). Regrettably, this framework has received little attention from Evo-devo practitioners, despite its organizational and descriptive potential. Love's particular interest is the origin of evolutionary novelty, which involves changes across the entire biological hierarchy (Shubin and Marshall 2000). Grene's (1987) framework for hierarchies was also dual, as was that of Eldredge (1982), especially in terms of research into patterns and processes of macroevolution. Given that macroevolutionary inquiry involves determining how new features (innovations and novelties) developed, Eldredge's discussion and others (e.g., Jablonski 2007) are of significance to Evo-devo and introduce a paleontological perspective or deep-time framework to the interaction of development and evolution. Eldredge's articulation of a new macroevolutionary theory based on hierarchical approaches continues to gain attention among those interested in evolution above the species level, particularly among paleontologists, but among other organismal biologists as well. For example, Gregory (2004) used a macroevolutionary framework and hierarchy theory to evaluate the massive variation in genome sizes among organisms, even within lineages (the "C-value paradox"). His highly integrative approach illustrates the potential that applications of hierarchy theory hold for evolutionary questions, including those involving development.

### *18.2.2 Properties and Uses of Biological Hierarchies*

What value, then, is there in using hierarchical approaches to analyze biological problems, such as those typical of Evo-devo? Hierarchical analysis has several useful properties when construed in its "pure" sense. A hierarchy is a nested series of relationships with emergent properties at different levels that influence other levels—this characterization both facilitates analysis and opens new questions. Pattee (1969, 161) defined a hierarchy as "a descending arrangement of constraints that is associated with increasing "strengths,"" presaging the use of such terms in evolution and development. Lauder (1981, 1982) recognized several emergent organizational properties, such as structural complexity, repetition of parts, and the decoupling of primitively constrained systems. All of these require explanation in development and evolution, as well as functional morphology. Salthe (1985, 1993) reviewed the conceptual basis of hierarchical systems in evolution, but failed to garner attention from most evolutionary biologists. A number of morphologists criticized the "synthetic theory of evolution" because it lacked an organismal

perspective that was connected to multiple hierarchical levels and the causal interactions among them (e.g., Olson 1960, 1965; reviews by Waisbren 1988; Wake 1992; Love 2006, 2007). Gould (1980, 129) with his usual prescience, captured the sentiment succinctly:

> A general theory of evolution would be rooted in a hierarchical view of nature, and will possess a common body of causes and constraints, but will recognize that they work in characteristically different ways in the material of different levels... The new theory will restore to biology a concept of organism.

But even Gould was not taken seriously; no "new theory" based on a hierarchical view emerged. However, concepts and uses of hierarchies continue to creep in from considerations related to the complexity of biology, especially as displayed in both development and evolution.

Eldredge (1982, 43 et seq.) asserts that the "recognition of the hierarchical structure of large-scale biological systems constitutes an alternative epistemology for approaching natural complexity." The epistemology to which he compares a hierarchical approach is reductionism, which he finds "deeply inculcated in nearly all disciplines." But he emphasizes that "patterns of constraint and causality flow upward and downward," so a hierarchical approach has heuristic value. For Eldredge, the organism is the fundamental entity and is central to both genealogical and economic hierarchies, but his focus is on "biological hierarchies above the organism level" (Eldredge and Salthe 1984; Eldredge 1985; Eldredge and Grene 1992; Salthe 1985). This is unsurprising given that Eldredge is writing in a context shaped by macroevolutionary investigation.

### *18.2.3 Centrality of the Organism*

Gould's (1980) claim that biology lost its "concept of organism" is significant, and only occasionally championed (see Wagner, Chap. 15, this volume). The concept of "levels of biological organization" usually emphasizes increasing complexity from molecule to cell, from cell to organ, and so on up through a hierarchy (organism, population/community, ecosystem). However, most research on "organization" usually *accepts* or takes for granted the organism and investigates levels below or above it, rather than integrating across multiple levels inclusive of the organism.

The hierarchical organization of organisms, in terms of both infra- and supra-levels, has rarely been given sustained attention, let alone actively integrated (but see Riedl 1978; Wake and Larson 1987; Mittenthal and Baskin 1992; Stork 1992; Wagner and Laubichler 2001; Wake 2001, 2008). There have been several calls for an organism-centered approach to the examination of complexity and scales of interactions (e.g. MacMahon et al. 1978; Wake 1990, 2003, 2008; and the paleontologists and morphologists referred to previously). The usual rationale for these calls is that the organism seems to be a "pivotal" level for comprehending the significance of different levels of organization and their interactions. Furthermore, the internal and

external organization of organisms can then be assessed hierarchically and the emergent properties have a conceptual anchor-point for evaluating their relevance. Grene (1987), in the context of her assessment of hierarchies in biology, stresses the distinction between two different evolutionary hierarchies—the genealogical and the ecological (both being "control" hierarchies). The genealogical hierarchy pertains to reproduction "via the transfer of information," and the ecological with interactions "or the economics of transactions in, with, and of organisms." This is not dissimilar to Vrba and Eldredge's (1984) perspective. But organisms, even though they are targets of selection, are usually considered to just be "vehicles of reproduction." Grene (1987) argues that environment-related factors typically have been construed only as affecting the means to reproduction. This criticism introduces new questions without providing a structure for answering them, but Grene's point, almost casually inserted, is crucial: "it is the flow of information both horizontally and vertically that makes the organism an integrated, working whole" (Grene 1987, 505). That construct, if more explicitly adopted, would make the organism theoretically central again because it constitutes the "whole."

The focus on "levels" alone apart from their significance to the whole organism remains a major concern, especially for Evo-devo. The "evo" part has not been pervasive enough to overcome this lack of integration, and is itself parsed into separate components, such as population genetics, phylogenetics, etc. At the same time, the "devo" part now emphasizes the genetic and molecular basis for development, rather than thinking about whole organisms, let alone how ecology, behavior, and other factors can effect changes in development. I return to this problem below (Sect. 18.5).

## 18.3 Integrative Biology: From 1981 to the Present

In the 1980s, as Evo-devo was developing, so was "integrative biology." In fact, Evo-devo is an instantiation of a kind of integrative biology. But ideas about integrating approaches, techniques, and fields of biology with each other—and with mathematics, chemistry, and physics—have surfaced many times over the last 50 years. Recent, and influential, examples from the period of Evo-devo's inception include Olson and Miller's landmark book *Morphological Integration* (1958), Arnold's paper entitled "Morphology, performance, and fitness" (1983), which called for the integration of structure, measures of performance, and the genetics of evolutionary fitness (thereby establishing a new research paradigm), and Wainwright and Reilly's *Ecological Morphology: Integrative Organismal Biology* (1994) that emphasized "eco-morphology" in a manner parallel to what one finds in Evo-devo. But many scientists were, and are, *integrative* biologists because of the way they practice their science, without being deliberate or even conscious of it as a perspective or design. "Oh, I do that" is a common response when integrative approaches are mentioned.

The use of the label "integrative biology" has become pervasive, but there have been few attempts to give it coherence, definition, and substance. For example, many

university departments and institutes (and foundations) have adopted the term, usually for organizational changes that brought together researchers of diverse expertise. Several "new" departments that were fusions of traditional Zoology and Botany departments now call themselves "Integrative Biology" (at least one because the Dean thought the taxon-based terms were "old-fashioned"). I, as a consequence of chairing a nascent Department of Integrative Biology during its formal emergence and developing a program in integrative biology for an international non-governmental organization (NGO), attempted to provide a conceptual framework for integrative biology in a series of papers. I was motivated to do so when the new Department of Integrative Biology became labeled the "Department of Left-over Biology" by biologists in other departments who thought only they explored the "cutting edge." Therefore, I argued that, integrative biology presents both a philosophy and a mechanism for the incorporation of expertise from different but relevant fields of science to be brought to bear on complex questions. I claim that integrative biology is both an attitude and an approach that includes both diversity and inclusiveness. It can deal with questions across all levels of biological organization, and it requires a hierarchical approach to the exploration of complex questions/problems, the use of multiple techniques, and novel but relevant analyses... depending on the question being asked (Wake 2001, 2004).

> Integrative biology is a label frequently used to describe various forms of cross-disciplinary and multitaxon research... generates new information and new ideas by bringing diverse expertise to problems, so that individual and institutional expertise becomes broader and more explanatory (Wake 2008, 349).

Inherent to integrative approaches and conclusions is the precept that the question being asked determines the nature of the approach and the expertise that is required (see Wake 1990, 2001, 2004, 2008; Brigandt and Love 2010; Brigandt 2010).

"Integrative biology" continues to have many different definitions (Wake 1998, 2001; Ripoll et al. 1998; Pennisi 2000; Lakhotia 2001)—multidisciplinarity includes the use of multiple techniques and/or taxa in conjunction with hierarchical approaches to questions, but also provides a set of general principles and a coherent framework, as well as a new attitude toward the practice of science (see Wake 2003, 2008).[1] Several recent attempts to define or characterize "integrative biology" have been too narrowly topical: e.g., labeling "systems biology" merely the integration of biology, technology, computation and medicine via a cross-disciplinary team of researchers (Alberghina and Westerhoff 2005). Efforts to integrate biology with nanotechnology, chemistry, physics, epidemiology, traditional knowledge, medicine, engineering, i.e., biology with only one of each of these areas, or the attempt to mesh fields of biology with each other to deal with particular questions, are typical of this overly narrow approach.

But how, and why, is Evo-devo integrative? Love (2003) examined the way the meshing of evolution and development has taken place around the concept of evolutionary innovation. He adapts Dullemeijer's (1980) idea of two options for

[1] See van der Steen 1990; Love 2008, regarding multidisciplinarity versus interdisciplinarity.

bringing disciplines together—one is a comparison of the disciplines such that the two are brought together as a single structure, the other is a consideration of the significance of the concepts of the two disciplines for each other. Love calls the first option "disciplinary integration", and the second "conceptual synthesis".[2] The point of difference between the options is that the former merges two disciplines into a new one "with the individuality of the original parts being lost or effaced" and the latter blends the two such that a new entity is formed that does not dissolve the individuality of the two disciplines, but transforms it so that a new entity results. In such an analysis, Evo-devo is a "disciplinary synthesis" (as part of a complete taxonomy: Love 2003) that is much more than a fusion of fields or an amalgamation of perspectives, but rather a unification of a range of approaches (genomic to organismal to populational to selection) in the service of comprehending evolutionary change. In attempting unification, Evo-devo draws on several subfields of biology to derive its own set of methods, approaches and questions (see Hall 1999). Such an approach also characterizes such new fields as biomechanics/robotics, whose conceptual development has similar characteristics.

But what are the characteristics of the nascent disciplinary synthesis of evolution and development? Some examples include:

1. The continued emergence of newer, faster means of gathering data.
2. The utilization of new tools for data integration.
3. The recognition and incorporation of phylogenetic hypotheses, depending on the question (see Wagner and Laubichler 2004).

The pervasiveness of integration across different hierarchical levels of analysis is becoming more obvious. It is illustrated in quite different ways; e.g., Gilbert and Bolker (2001, 1) state that "signal transduction pathways. . .integrate embryonic development. . .both within species and between species." Gass and Bolker (2003, 260) comment that organisms are "the integration of partially independent, interacting units and several hierarchical levels," which highlights the centrality of the organism. New schemes for organizing information are developing, such as bio-ontologies, as tools for integration in biology (Leonelli 2008).

## 18.4 Where Does Hierarchical and Integrative Thinking Stand Currently in Evo-devo, and Biology Generally?

New tools and methods of analysis facilitate mechanistic approaches to "emergent properties"—what they are, how they arise and interact, and what "upward" and "downward causation" really mean. This is a real advance in the 30 years since Vrba and Eldredge (1984) looked at approaches to thinking about evolutionary patterns and processes as hierarchical structures with emergent properties, and helps to

[2] This differs structurally from Love's (2006) framework for hierarchies, but has the same philosophical underpinning.

explain why those approaches have not been extensively utilized until now. The ability to identify and explore mechanisms, rather than phenomena, has produced new understanding of "being and becoming," and how change can take place.

The science, especially in Evo-devo, is expanding from a handful of "model systems" (but with them as a base; see Bolker 1995) to investigate the interactions, maintenance, and changes in biological diversity at many levels of organization, and how those levels influence each other. This is facilitated by the new ability to examine and even integrate elements of the large bodies of data (molecular, genomic, ecological, behavioral, etc.) that are being generated. Ever-increasing computer capacity and new, expanded database frameworks and analytical tools facilitate multi-level examination of patterns and processes of development and evolution. However, the current tendency to label any species that appears amenable to the study of development (or other biological processes) a "model organism" without attention to what it is a "model" for, or why it is a model, let alone one from which conclusions are generalizable, is not productive (Ankeny and Leonelli 2011). Most researchers still work primarily at levels of the biological hierarchy that constitute only a subset, and rarely is the "centrality of the organism" observed. (Not that I think all levels can be explored at once, but cognizance of the influence of levels upon each other, especially with regard to the "wholeness" of the organism, could be maintained.) At the same time, the capacity of Evo-devo to expand from studying a handful of model systems to the full investigation of biological diversity has great potential now that so many molecular and even ecological and analytical tools are available.

Integrative (and integrated) approaches demonstrably generate new insights into the nature of *complexity* in biology. There are many approaches to *being* integrative, both philosophically and pragmatically. The training of students is becoming more integrative—it is typically centered in a sub-discipline with a thematic focus, but fosters awareness of the techniques and ideas of other parts of biology, physics, engineering, social sciences, etc., as appropriate to diverse questions. The US National Science Foundation's Integrated Graduate Education and Research Training (IGERT) program is a major effort to implement such training. Students learn that, depending on the questions being addressed, having multiple inputs of expertise contributes to a deeper understanding of a problem and its possible resolution, as well as its impact on and interactions with related issues. As a consequence, more of science is accessible to practitioners because of the resulting attitudes about collaborative research. Furthermore, computer-generated access to the literature makes rapid searches and information assimilation possible (i.e., the "literature explosion" is not so foreboding).

Pragmatic effects of the adoption of an integrative paradigm, at least in theory, include new kinds of institutional and financial support, as both academic institutions and funding agencies are recognizing—or at least claiming to recognize—that integrative and integrated approaches are useful, if not essential, to the analysis of biological complexity. Consequently, intellectual and financial support for more broadly based research is promised. Unfortunately, many units, programs, and agencies still stop at simply labeling themselves "Integrative XXXX" without

producing new ways of thinking about old (or new) questions. Additionally, there has been a proliferation of journals that support integrative biology, including *Integrative Biology*, *Integrative and Comparative Biology*, *Integrative Zoology*, *OMICS: A Journal of Integrative Biology*, *Communicative and Integrative Biology*, *International Journal of Integrative Biology*, *Journal of Integrative Plant Biology*, and *Issues in Integrative Studies* (to cite just a few), so communication that emphasizes these approaches has cachet.

## 18.5 What Is Still Missing in the Current Practice of Evo-devo?

Duboule (2010) criticized Evo-devo as being a transitory research enterprise because it is the product of two different disciplines that are based on different epistemological foundations, the fusion of which leads to "an unstable equilibrium." He is convinced that the field lacks a clear definition about what it covers, and that it needs a uniformly accepted set of guidelines about its research aims. Evo-devo is characterized as a "conflicting *ménage*" of developmental geneticists (apparently restricting development to that narrow realm) and population geneticists (apparently equated with evolutionary biology). The extension of this (false, in my opinion) dichotomy is the claim that development "is a science of recurrence. . . (with) a fixed timeframe," but that evolutionary science uses exactly opposing, linear premises so recurrence is not possible and, therefore, evolution lacks a clear timeframe and predictable results. This is an interesting view, almost an indictment. Duboule thinks that a "theoretical antagonism" characterizes Evo-devo, but it might diminish as the mechanisms of development are fully understood (i.e., when the forms that occur can be predicted). Somehow, this achievement will reshape our understanding of macroevolution. As Duboule asserts, it is an open question whether it will take another hundred years for developmental biology to turn evolutionary biology into a predictive science, in large part by increasing our ability to predict environmental conditions.

It is not difficult to see the basis for Duboule's difficulty with perceiving Evo-devo as an approach with a future. From the 1980s on, there have been tremendous advances: (i) a better understanding of genes and patterns that are shared; (ii) the analysis of gene expression in various species establishing correlations between gene activities and change in form; (iii) the use of new animal models; and, (iv) the development of some new concepts. However,

> Evo-devo research extends from simply 'PCRing' a trendy gene from a weird animal, up to the most sophisticated molecular genetic approaches dealing with the evolution of gene function and regulation. Yet the experiments are always within the general context of homology. (Duboule 2010, 489)

By accepting this narrow view of Evo-devo research, Duboule (and others who share it) constrain the field to one small part of its real activity and broader potential.

Unfortunately, many in the field perpetuate this view because of the predominance of attention given to advances in the molecular-genetic understanding of processes in early ontogeny. There is often limited regard for extant Evo-devo research at other levels of the hierarchy of biological organization. That research often uses genetic "tools" developed in the context of early development, but it asks very different questions and investigates "emergent properties" by exploring the manifold interactions of development and evolution. There are many types of Evo-devo research, including life history evolution, diversification in reproductive modes (fusing development and evolution in time, space, parentage, and genetic though phylogenetic lineage properties), and courtship behavior-copulation-fertilization-maintenance (or not) on the continuum of developing embryos in their internal and external environmental contexts. These areas are not often represented at the Evo-devo table currently dominated by the molecular geneticists, thought their inclusion would enrich the science. At the same time, some molecular geneticists, genomicists, and allied practitioners, as well as developmental and evolutionary biologists, are beginning to ask broader questions that relate their concepts and tools to questions of development and evolution at other levels of biological organization.

I assert—*pace* Duboule—that it is the *absence* of a "clear definition of the field" and a body of "commonly accepted guidelines" for research that facilitates the expansion of Evo-devo. The field of Evo-devo *sensu lato* is able to adopt techniques and ideas from much of biology (and other sciences) as they become available for application to understanding complexity. With scientists asking broader questions and establishing wider-ranging intellectual frameworks and research programs, a greater elaboration and diversity of hierarchical exploration and integration will result.

### *18.5.1 Why Has "Evo-devo" Led the Conceptual Expansion of the Integration of Biology?*

The question, though important, is not easy to answer. Some aspects are apparent. Developmental biology became enlivened with advances in molecular biology, genomics, and systems theory, and its practitioners started asking questions about the evolution of organisms and their parts, and then added additional dimensions of study. The black boxes that can now be opened using diverse tools illustrate the capacity to work at several levels of hierarchical organization so that new (and old) questions can be approached. The enlightened "marriage" of development and evolution facilitated the exploration of a diversity of wide-reaching black boxes, and the recognition of like practices at different levels of the biological hierarchy. For example, network analysis in cell–cell signaling can inform organismal interactions, which could thereby inform the nature of ecological food web networks.

By demonstrating that integration produces new insights and concepts, Evo-devo biologists have expanded their horizons, and those of biologists with

other specialties, such that a new and better informed search for general principles, involving hierarchical approaches to the nature of complexity, is occurring. In fact, counter to Duboule's criticism, Evo-devo is *more* than just a fusion of development and evolution or an incorporation of the two perspectives. It is an attempt to unify diverse approaches at several hierarchical levels to examine the nature of evolutionary change. Evo-devo has its own sets of constitutive questions, but the research agenda is broad (Hall 1999; Love 2006).

Evo-devo is a core element in various current pragmatic and intellectual expansions of science, such as "Eco-evo-devo" and its extension into medicine, epigenetics, and a host of biological interactions (see Gilbert and Epel 2009). Gilbert and Epel have provided a roadmap by which Evo-devo, and science in general, can expand both its intellectual contributions and its application to real-world problems like complexity. The introduction of Evo-devo into other subfields of biology (e.g., ecology, physiology, immunology, behavior, and systematics) broadens and enriches those arenas by facilitating the generation of new questions and new approaches. Similarly, the inclusion of development in paleontology at many levels is resulting in new understandings of evolutionary pattern and process, and not only in the analysis of macroevolution, as studies of extinct and extant taxa inform each other (e.g. Hall 2002, 2007; Shubin et al. 1997, 2009). Because of its ability to encompass and combine, Evo-devo continues to manifest an integrative and synthetic perspective, which provides intellectual leadership and reciprocity in developing new ways to do the science that will enlighten our understanding of the complexity of life.

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# Chapter 19
# Development and Evolution: The Physics Connection

**Stuart A. Newman**

## 19.1 Introduction

To assert that living systems are material entities, plainly subject to the laws of physics and chemistry, has been uncontroversial since at least the beginning of the twentieth century. The veneration of Gregor Mendel (1822–1884) and Charles Darwin (1809–1882) as founding figures of modern biology is to a great extent due to their positing materialist explanations for two of the most salient features of organisms: the transmission of distinctive within-type features across generations and the transformation of types over time.

Organisms are composed of complex materials, making the variation of biological form ultimately a problem of physics. For Isaac Newton (1643–1727), who established the dominant physical paradigm of the eighteenth century, matter was inert and inertial, changing its form and position in a continuous fashion, and only when acted on by external forces. Jean-Baptiste de Lamarck (1744–1829), Johann Wolfgang von Goethe (1749–1832), and Étienne Geoffroy Saint-Hilaire (1772–1844) attempted to formulate "laws of form" based on speculative extensions of the prevailing physics. Both the chemistry and physics of middle-scale ("mesoscale") matter soon underwent major advances, however. Figures such as John Dalton (1766–1844), Joseph Louis Gay-Lussac (1778–1850), Claude-Louis Navier (1785–1836), and Sadi Carnot (1796–1832) established a scientific foundation for qualitative transformations in the composition and state of materials, which provided countless examples of abrupt transitions in the composition and form of parcels of matter. The older Newtonian picture, however, persisted as the signature of materialism through the late nineteenth into the twentieth century, not with standing advances in physics in the interim (Newman and Bhat 2011).

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Darwin's theory of evolutionary change embodied this Newtonian incrementalist materialism (see Weber and Depew 1996). The correspondence between the gradual refinements featured by natural selection and the highly successful industrial paradigm of trial-and-error fabrication of metal machine tools, dies and molds likely contributed to the theory's early acceptance. It also established an intellectual habit of avoiding the role of development in evolution because if the only relevant changes in an object's form are gradual, then how the object originated, its degrees of freedom, and the limits of its possible deformations can be side-stepped. This aspect of Darwin's theory is used to this day for impugning critics of the standard model; anyone who would not acknowledge that every complex biological character arose gradually, under adaptive selection, must be irrationally uncomprehending of the "universal acid" of Darwin's "dangerous idea" (Dennett 1995; see also Dawkins 1996).

Darwin's incrementalism could only survive its harnessing to Mendel's genetics in the Modern Synthesis by embedding them both in a populational framework that expunged the saltationism implicit in many of Mendel's experimental results (Provine 2001). The focus of the theory became alleles of small effect or quantitative trait loci. Although Darwin's doctrine of pangenesis and embrace of the inheritance of acquired characteristics provided ample space for behavioral and environmental (i.e., non-genetic) influences on variation, this was often condescendingly dismissed as the rare stumbles of a great man.

Even though embryology increasingly provided support for both discontinuities and conditionality of the phenotype-genotype relationship, the synthesis architects forged a view of organismal form on the basis of the machine-like expression of "information" contained in genomes, with small changes in this information mapping onto small changes in an organism's phenotype. By the mid-twentieth century, the new field of developmental biology—influenced by the successes of molecular genetics and the parallel rise of digital computers—came to endorse, in theory if not in practice, the information-based notion of the "genetic program" (Kay 2000).

The agenda of evolutionary developmental biology (Evo–devo), which began to assume its modern form at the 1981 Dahlem conference on evolution and development (Bonner 1982), is concerned both with the evolution of developmental mechanisms and the role of developmental processes in setting the trajectory of evolutionary change. Once this perspective, with its associated set of issues, was identified, it was bound to destabilize the Modern Synthesis for reasons related to the history outlined above. In particular, gradualism could no longer be privileged over saltationism in considering the range of variation consistent with given genotypes and small variations thereof—modern developmental biology and life history studies disclosed unforeseen complexities in genotype-phenotype mappings. And, in addition, it was no longer possible to ignore the physical forces and effects pertaining to living materials, e.g., cell aggregates and tissues. The earlier "information" model of the genome placed no constraints on biological form and function, so long as it resulted from a sequence of changes each of which met some marginally superior adaptive role. If, on the contrary, phenotypic jumps and morphological novelties resulting from developmental rerouting were possible, the actual physical processes that mold tissues and induce switching among the multidimensional biochemical

states that characterize cell types were strong candidates for major causal and constraining factors of organismal form and function.

Even before physics had advanced to the point of being able to account, in principle, for the forms and patterns of developing tissues, several prescient scientists had recognized its potential to explain the origination of morphological motifs and thus introduce a predictive component to evolutionary theory. William Bateson (1861–1926) proposed that certain tissues exhibited oscillatory excitations that could cause them to organize into segmental and other repeating patterns (Bateson and Bateson 1928; Newman 2007). D'Arcy Wentworth Thompson (1860–1948) suggested that viscous flow and environmentally induced mechanical deformation, among other physical factors, could explain the shapes of organisms and morphological transformations between different species (Thompson 1942). The embryologist E. E. Just described the animal egg as a purely physical system that was nonetheless "self-acting, self-regulating and self-realizing" (Just 1939, 237; Newman 2009). One implication of these views—that much biological form was nonadaptive—had no place in the emerging standard model, however, and these figures were relegated to the scientific margins during their lifetimes.

By the 1970s, when my colleagues and I, along with several other groups, began our attempts to integrate new findings from the cell and molecular biology of developing systems with the physics of condensed, chemically and mechanically excitable materials, mesoscale physics had advanced to a level barely imagined by Bateson, Thompson, and Just. In the following sections I will review some work in this vein from circa 1981 and the post-Dahlem period, and its influence on concepts of the evolutionary role of physical processes and mechanisms. The presentation will be divided into four phases in the development of Evo–devo, characterized by scientific themes that successively received new or intensified attention during the past four decades.

## 19.2 Phase I: Physical Mechanisms of Embryogenesis

### *19.2.1 Oscillations and Somitogenesis*

One area of major progress in the 1950s and 1960s in the study of dynamical systems of the middle scale, such as chemical reaction networks, was the theory of nonlinear oscillations; chaos theory, developed in the 1970s, was just one of its many fruits (Minorsky 1962; Epstein and Pojman 1998). Oscillations could occur in any "excitable" (i.e., reactive, energy-storing) system, living or nonliving, in which there was an appropriate balance of positive and negative feedback interactions. The principles that emerged from this area of research were quickly applied to a variety of biological questions (Winfree 1980; Goldbeter 1996). Where the phenomena described were metabolic processes like glycolysis (Boiteaux et al. 1975) or pulsatile chemical signaling by the social amoeba *Dictyostelium discoidum*

(Goldbeter and Segel 1977), there was little scientific resistance since the study of metabolism had long been a province of chemistry, a field for which dynamics was integral. More controversial, since it related to morphology, was the proposal of an oscillatory mechanism for the generation of somites, paired blocks of tissue that emerge in a sequential cranio-caudal direction during vertebrate embryogenesis (Cooke and Zeeman 1976). According to this mechanism, cells in the presomitic tissue oscillate in a synchronized fashion with their periodically changing cell state (the clock) acting as a "gate" for the action of a front of potentially changed cell behavior that sweeps along the embryo's length (the wavefront). The interaction of these two factors was predicted mathematically to generate a segmental pattern.

Possibly because of the conviction that embryonic development was a programmed machine-like process that had little in common with the conditional (i.e., producing outcomes subject to physically defined parameters), environment-sensitive aggregation of *Dictyostelium*, the clock-and-wavefront model, an embodiment of William Bateson's proposed vibratory mechanism for segmentation, was similarly ignored. Then, in the late 1990s, Olivier Pourquié and his colleagues presented compelling experimental evidence for a formally similar mechanism for somitogenesis. It involved a demonstrable intracellular biochemical clock, the components of which included the transcriptional switching factor Hes1 and a wavefront consisting of a gradient of the morphogen FGF8 with its source at the embryo's tail tip (Palmeirim et al. 1997). The dynamics of interaction of these factors were somewhat different from those predicted by Cooke and Zeeman: the periodic "sweeping" effect is due to the clock, which is phase-shifted in a continuous fashion along the length of the embryo, not to the wavefront, which is relatively static. Nonetheless, it is clear, as Bateson, and Cooke and Zeeman, predicted, that a tissue-based oscillator underlies somitogenesis. That the associated developmental mechanism is a conditional physical process rather than a machine-like programmatic one is demonstrated by its ability to account for the increase in number of segments in snakes, for example, by evolutionary alterations in the ratio of parameters characterizing the interaction of the clock and wavefront (Gomez and Pourquié 2009).

### *19.2.2 The Turing Mechanism in Limb Development*

Like several other research groups in the 1970s (Gierer and Meinhardt 1972; Kauffman et al. 1978), we were intrigued by the potential explanatory power of the reaction-diffusion mechanisms explored by the mathematician Alan Turing in his paper titled "The chemical basis of morphogenesis" (Turing 1952). Although he had some predecessors in this line of research (Kolmogorov et al. 1937; Rashevsky 1948), Turing showed in a particularly accessible fashion that a balance of positive and negative feedbacks in an open chemical system (essentially identical to networks that generate temporal oscillations), coupled with differences in the rates of diffusion of the key reactive molecules, could defy the expectation that everything

evens out under the influence of diffusion and instead (self-)organize into stable, nonuniform concentration patterns, often exhibiting periodicities.

Because a prominent aspect of the vertebrate limb is the quasi-periodic arrangement of its skeletal elements, we attempted to understand its development in terms of a Turing-type mechanism. The most widely discussed model for this phenomenon at the time was one that incorporated the physical process of molecular diffusion (Crick 1970), but relied heavily on the genetic information paradigm (Summerbell et al. 1973). In particular, all the details of the resulting skeletal pattern depended on the "interpretation" of a simple diffusion gradient based on a presumed point-by-point internal representation of the developing limb in the organism's genome (Wolpert 1971).

Our approach was to model the capacity of the limb's mesenchymal tissue to exhibit formal properties similar to Turing's chemical reaction-diffusion system. By incorporating what was known in the late 1970s about the cell and molecular biology of the formation of precartilage mesenchymal condensations, we were able to show that a succession of skeletal patterns with increasing numbers of parallel elements would be predicted to form under experimentally ascertained changes in the size and shape of the undifferentiated distal tip of the limb bud (Newman and Frisch 1979).

The relation between the actual course of development of a chicken limb and that predicted by a more recent version of our reaction-diffusion model (Zhu et al. 2010) is shown in Fig. 19.1. Isolated and dissociated limb bud tissue can reconstitute limb-like skeletal patterns in vivo (Zwilling 1964; Ros et al. 1994), and nodular patterns of

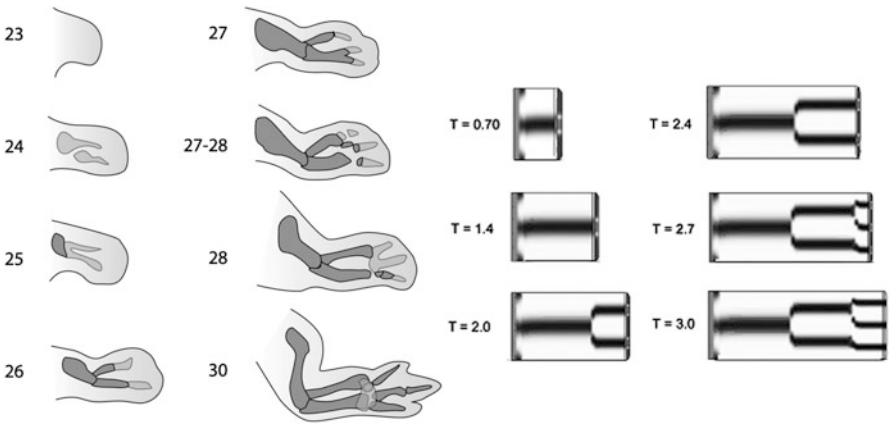



**Fig. 19.1** Simulation of chicken wing development. (*Left*) Developmental progression of the chicken forelimb between days 3 and 7 of development (indicated by the corresponding Hamburger-Hamilton stages). Early cartilage, including precartilage condensations, is shown in *light gray*; definitive cartilage is shown in *dark gray*. (*Right*) A sequence of snapshots from a simulation of normal limb development based, on a Turing-type reaction–diffusion model. The transitions between different numbers of elements in successively appearing regions of the simulated limb, which occur in the development of the actual limb, are primarily the result of the changing size and shape of the spatial domain within which the reaction-diffusion system operates. Time in the simulation is in arbitrary linear units (Adapted from Zhu et al. 2010)

cartilage with similar spacing statistics in vitro (Kiskowski et al. 2004; Christley et al. 2007). These phenomena, as well as aspects of the skeletal patterns of mutant and fossil limbs, find ready explanation in the self-organizational capacity of Turing-type reaction–diffusion mechanisms (Miura et al. 2006; Zhu et al. 2010), and our predictions have been borne out in a recent study using gene manipulation in mice (Sheth et al. 2012). Studies of a variety of partly self-organizing developmental systems over the past 30 years, however, have shown that unlike purely chemical reaction-diffusion systems, which have been experimentally confirmed to form patterns by Turing's mechanism (Castets et al. 1990; Ouyang and Swinney 1991), "reaction" and "diffusion" in the developing embryo can often represent complex biosynthetic response and transport functions (Kondo and Miura 2010). While thus only formally similar to chemical reaction and molecular diffusion, these interacting processes produce patterns that resemble those of the purely chemical systems.

## 19.3 Phase II: "Generic" and "Genetic" Mechanisms of Development

If embryos could take form using "generic" physical processes, such as biochemical oscillations, reaction-diffusion patterning, and thermodynamically driven phase separation of differentially adhesive cell populations (Steinberg 1978), to which living tissues were susceptible in common with nonliving malleable, excitable, media, how were such forms inherited? And if genes were (and are) not the exclusive medium of the inheritance of form, what was the relationship between gene regulatory mechanisms and the physical processes highlighted above, and how has it changed over the course of evolution?

Since animal life cycles typically involve a gametic phase, it has been standard to think that what is passed on to the next generation at this reproductive bottleneck is simply DNA, and (for the more mechanistically broad-minded) patterns of methylation and organized ooplasms that influence its expression. But the physical world is also part of every organism's inheritance. Moreover, contrary to common belief, this does not affect every parcel of matter or cluster of cells in a uniform fashion (Newman 2011a). Solids do not flow and liquids do not bounce, despite existing in the same environment.

Specific gene products in the developing embryo help to mobilize different physical effects—surface tension, viscosity, elasticity, phase separation, solidification—and the evolution of developmental regulatory genes cannot be understood apart from the physical effects they directly or indirectly mobilize. Thus, gametes convey not just genes but the processes that are inescapably mobilized when the genes become expressed (Newman 2011a).

All mechanisms of development, generic or otherwise, therefore involve organization and transformation of materials in which gene products play a prominent part. But it also became clear in the 1970s and 1980s that this was not the whole

story. A burst of research during this period enabled by the new technologies of gene cloning and sequencing, and then genetic engineering of multicellular organisms, established that animal development was accompanied, and indeed apparently orchestrated, by programmed expression of gene activity regulated according to a hierarchical logic (Davidson 1976, 1986).

Taking account of the compelling narratives emerging from both the physical and genetic lines of developmental biological research, we suggested that there was a complementarity between generic and genetic mechanisms of pattern formation and morphogenesis (Newman and Comper 1990). "Genetic" in this case did not simply mean employing genes; as noted above, all developmental mechanisms fit this description. Nor did it mean not employing physics: all biological mechanisms are subject to the laws of physics and chemistry. Rather, "genetic mechanisms" of development referred to hierarchical programs of gene expression and other ontogenetic consequences of highly intricate molecular organization that do not bear any straightforward relationship to organizational processes of nonliving materials.

Our complementarity proposal addressed an emerging paradox. Gene manipulation methods newly available in the 1980s were beginning to show that key developmental control genes, even those at the apex of regulatory hierarchies, were often dispensable (Hülskamp et al. 1989; Zimmer and Gruss 1989) or nearly so (reviewed in Shastry 1995). These findings were difficult to reconcile with the accepted incrementalist scenario for the evolution of these elaborate mechanisms, in which each piece of the puzzle was presumed to be selected for its marginal adaptive advantage. The principle that every genetic difference between related organisms makes a phenotypic difference, or at least did so at some point in evolutionary history, seemed inconsistent with findings that individual, or groups of, regulatory genes may be centrally involved in developmental processes that also occur equally well without them. Even if redundancy and compensatory action were involved, these results suggested a more fluid relationship between genes and form than that advocated by the Modern Synthesis and genetic program models.

The generic/genetic duality indicated a way out of this conundrum through a revised understanding of the relationship between genes and form (Newman and Comper 1990). The idea was that developmental mechanisms represented evolving composites of generic and genetic processes. Specifically, we suggested that the morphological motifs of body plans and organ forms were established early in evolution by generic physical mechanisms whose organizing effects were inescapable in the sense that they were inherent to the materials involved.[1] Then, over time, selective pressures to stabilize and make routine the development of generically originated forms that found success in the original or other ecological settings would lead to the accumulation of genetic circuitry and pathways that facilitated

[1] This aspect of the concept contained echoes of William Bateson and D'Arcy Thompson, as well as the anti-adaptationism of Stephen Jay Gould and Richard Lewontin (e.g., Gould and Lewontin 1979).

construction of these forms.[2] Ultimately, the developmental need for the generic physical mechanism could be partly or even largely bypassed. The physical mechanisms mobilized by the genetic circuitry in these more complex contexts would have decreasing resemblance to those of purely physical systems.[3]

One much-discussed example will illustrate this idea. The identification of regulatory genes of the segmentation pathway in embryos of the fruit fly *Drosophila melanogaster* and the visualization of their spatial expression patterns disclosed striking seven-stripe patterns of "pair-rule" gene mRNAs and proteins at the stage at which the embryo is a syncytium and the transcription factor products are in principle free to diffuse between the nuclear sites of production of their mRNAs (Carroll and Scott 1985; Frasch et al. 1987). The resemblance of these stripes to ones predicted to be formed by a Turing-type reaction-diffusion mechanism led some to initially conclude that this was precisely the basis of this early developmental step. Once it became clear, however, that individual pair-rule stripes were in some cases actually specified by dedicated promoters responsive to position-specific combinations of other factors (Goto et al. 1989; Stanojevic et al. 1991), the notion of a generic patterning mechanism for these stripes was almost universally abandoned (Akam 1989).

Our proposal of a progressive supersession of generic mechanisms by genetic ones suggests a different interpretation of the "inelegant" (Akam 1989) generation of the elegant pair-rule stripe patterns: the primordial mechanism of stripe formation in long germ-band insects such as *Drosophila* was indeed a Turing-type reaction-diffusion mechanism, but this pattern was "captured" over time (in part through promoter duplication) by the more reliable non-generic molecular hierarchy that is seen in present-day forms (Newman 1993; Salazar-Ciudad et al. 2001).

This and other plausible cases of morphologically elaborate forms originating by the action of generic physical mechanisms, and only later coming under the control of complex genetic mechanisms, implied evolutionary scenarios that ran counter to the expectations of Darwinian models. In particular, the rapid early diversification of animal phyla and the stability of morphological types once established (congruent with paleontological findings difficult to accommodate in the standard model), were readily explained by this alternative view of the relationship between genes and form (Newman 1992, 1994).

## 19.4 Phase III: The Autonomization of Form

Our "physico-genetic" view of the development and evolution of animal form attempted to avoid both naïve physicalism and genetic determinism. Its major features were: (i) organisms are both physical entities and repositories of genetic

[2] This aspect reflected the insights of C. H. Waddington and I. I. Schmalhausen on canalization and stabilizing selection, respectively (Waddington 1942; Schmalhausen 1949).

[3] In many cases, however, it is possible to discern the continued efficacy of the originating physical mechanisms in present-day organisms (see Forgacs and Newman 2005).

information; (ii) development, as the reorganization and transformation of living matter, makes use of the morphogenetic and pattern forming capabilities of meso-scale physics, but the more purely generic physical effects were more prominent earlier in the evolution of a body plan or organ form; and, (iii) once a functionally successful or adequate form arises, natural selection, under the premium of breeding true and developing reliably, promotes the evolution of stabilizing genetic mechanisms that protect developmental pathways against perturbations by external factors like temperature and pressure (both osmotic and hydrostatic), which might affect the outcomes of generic physical processes.

This view seems to imply that over the course of evolution organismal body plans and organ forms should tend towards the condition of "genetic machines" that late twentieth century mainstream evolutionary and developmental biology appeared to maintain they always had been (e.g., Yuh et al. 1998). But research on comparative developmental biology, particularly as it came to be informed by genomics, had more surprises to offer.

The problem of homology, for example, had puzzled morphologists (e.g., Richard Owen) well before Darwin advanced his theory of evolution. What was the relationship, for instance, between the body segments of different animals that may (humans, snakes) or may not (mice, flies) have had a recent common ancestor, or among the distinct elements of the vertebrate limb? The discovery of the pan-phyletic employment of homeobox-containing genes for similar developmental functions in the 1980s (Lobe and Gruss 1989) encouraged gene-based definitions of homology (Holland et al. 1996). These quickly led to new conceptual difficulties, not least of which were the conflation of homology with analogy and the failure to take account of the rewiring of genetic networks that occurs during evolution (Raff 1996; Bolker and Raff 1996; Minelli 1998; see Müller 2007). Nevertheless, assigning evolutionary relationships to different biological structures on the basis of a privileged set of developmental regulatory genes continues to be a popular theme in evolutionary biology under the rubric of "deep homology" (Shubin et al. 2009).

Even before the discovery of the homeobox, Pere Alberch recognized that, insofar as development was underlain by physical mechanisms, ideas of homology based solely on common descent (whether morphological or genetic) could not be sustained. This is because these notions assumed an orderliness of embryogenesis by which corresponding stages in the embryos of different species could be placed into correspondence with one another. But physical mechanisms of morphogenesis could be mobilized in different sequences in different lineages (Alberch 1985).

Even though they are adequate determinants of form, however, physical mechanisms have difficulty accounting for important aspects of biological specificity. While a physical mechanism such as reaction-diffusion could help explain why a reduced-size limb in an evolutionary lineage would suffer the abrupt loss of a digit, it could not determine *which* digit would be lost (Alberch and Gale 1983; Alberch 1985). Such specificity is a function of a lineage's evolutionary history wherein elements became individualized and differentiated from each other, rather than (as would be generated by purely generic physical mechanisms), simply equivalent modules.

To address this inertial aspect of evolved form (referred to as "burden" by Riedl 1978), Gunter Wagner proposed a "biological homology concept" in which pathways of gene activity and interaction constrain the production of individualized parts of the phenotype (Wagner 1989). These "epigenetic traps" limit the possible phenotypic effects of genetic variation, "even though they became established by genetic variation and gene substitution in the first place" (Wagner 1989, p. 66).

Based on work summarized above on physical causation in development, Gerd Müller and I presented an extension of the biological homology concept (Müller and Newman 1999). We suggested that the evolution of the morphological phenotype proceeds in three stages: *generation*, *integration* and *autonomization*. In the first stage, novel morphological motifs are produced by the action of generic physical processes acting on multicellular aggregates or parcels of tissue. The mechanisms of innovation include generic physical determinants that are relevant to the origination of new body plans in ancient clusters of "developmentally naïve" cells (i.e., cells with no evolutionary history in a developing system; Newman and Müller 2000; Newman et al. 2006), but also that act on the "developmentally sophisticated" tissues of more evolved organisms (Müller 1990). We referred to these as *epigenetic* mechanisms, in the classical sense of mobilizing intrinsic generative properties of tissues, rather than the narrower one of chemical modifications to DNA (Müller and Newman 2003). Such epigenetic mechanisms tend to yield trends in the evolutionary trajectories of morphological outcomes which are predictable from the inherent material properties of the tissues (Newman and Müller 2005). Recurrent morphological motifs generated in this fashion would appear as "homoplasies" (Wake 1991).

During the second stage of the proposed evolutionary scenario, the adaptive utility of the novelty—insofar as it exists—places a premium on genetic variants in which the novel structure becomes generated by developmental processes that are independent of the conditionality of physical determination. This leads to the novel constructional unit becoming integrated into the developmental repertoire of the organism by what Waddington termed genetic assimilation (Waddington 1961).

In the final stage of the evolution of a morphological unit it becomes independent not only of its originating conditions, but also of the gene expression networks mobilized at the initiating step. Once the unit or element has been sufficiently well integrated into the organism's ontogeny, there is no reason why it must continue to be generated in the same manner. Autonomization arises from genetic changes and rewiring of circuits ("developmental systems drift": True and Haag 2001) that may leave a structure unchanged, or nearly so, while altering the means of its developmental realization. Striking examples of this are seen when comparing endomesoderm specification (Lin et al. 2009) and vulva development (Kiontke et al. 2007) in different nematode species, and optic vesicle formation in Medaka and zebrafish (Furutani-Seiki and Wittbrodt 2004). Once integrated and autonomized, a novelty would be less likely to undergo dramatic morphological changes as a result of changes in genetic architecture. The evolutionarily stable structure would now be susceptible to the kind of incremental fine-tuning featured in the gradualist scenarios of the Modern Synthesis (Müller and Newman 2005).

This framework provides a rational basis for homologizing structures in related lineages. The relationship between homologues is partly one of common origin and common ancestry, although sister groups that have homologous structures need not have been descended from a common ancestor that also had that structure (Alberch 1985). It is, in addition, partly one of common developmental mechanisms, although what is common to the mechanisms may have little to do with the precise genes employed.

A question posed at the beginning of this section concerned whether the proposed evolutionary trajectory away from the generic physical determination of form and towards non-generic, hierarchical modes of development led embryos to become the genetic machines or computers of some standard narratives. The answer from the perspective of autonomization is clearly no—forms, not genes, become increasingly important in determining evolutionary trajectories. Furthermore, as indicated by the conservation of morphological phenotypes in the face of gene knockouts and developmental systems drift, developmental systems retain their dynamicity over phylogenetic time scales despite the fact that genetics and physics become increasingly intertwined.

## 19.5 Phase IV: Dynamical Patterning Modules: Entrenched Associations Between Gene Products and Physical Processes

Beginning in the 1990s there was increasing recognition that all animal phyla implemented their developmental processes using a common set of proteins, products of what has been termed the "developmental-genetic toolkit" (see Carroll et al. 2004). These "tools" included transcription factors, some relatively specific to certain metazoan cell types and others associated with positional differences within unitary tissues, as well as molecules involved in cell-cell aggregation (cadherins, collagen) and signal transduction (Wnts, Notch, BMPs). Duboule and Wilkins suggested that the majority of these gene products were invented before the Cambrian explosion "for specialized, terminal cell differentiations rather than for the earliest steps in basic patterning" (Duboule and Wilkins 1998). This prediction was amply borne out a decade later when the genomic sequence of *Monosiga brevicollis*, a unicellular choanoflagellate representative of an extant sister clade of Metazoa, became available (King et al. 2008).

Though they did not originally evolve to mediate multicellular development, this is precisely what these molecules now do in animal embryos. Moreover, many of them perform their functions to surprisingly similar ends given the phylogenetic distances involved. For example, transcription factors Pax6 and Nkx2.5 act early in the developmental pathway of eyes and hearts, respectively, in both mice and fruit flies, and Dlx helps specify the distal ends of developing limbs in these same organisms. No one had previously thought mammalian and insect eyes or limbs

were anything but analogous, and the common ancestor of chordates and arthropods did not even bear limbs. And even if hearts could be traced to a common bilaterian ancestor, the conservation of the genes in the developmental pathway over more than a half billion years of subsequent evolution was not what the standard evolutionary narrative would have predicted (Newman 2006).

The challenge to our physical-genetic hypothesis for the generation of metazoan body plans was that it contained no implication concerning the level of molecular conservation seen in the developmental-genetic toolkit (Newman 1994). Generic physical processes such as adhesion, diffusion, lateral inhibition (i.e., the enforcement by a cell on its neighbors of an alternative cell state), and so forth, are expected to be indifferent to the specific identity of molecular components they interface with so long as those components harness the relevant physics. Cell adhesion proteins have to be sticky, morphogens have to be released and not irreversibly bind to extracellular materials, and mechanisms for alternation of cell fates require some kind of switching mechanism. For this reason (under the standard assumption that diversification of phyla took place by the accumulation of many microevolutionary steps—"phyletic gradualism"), each of the mechanisms employed in the physical-genetic model should have had many different molecular embodiments since the appearance of the Metazoa more than 600 Ma ago.

But like the cell type- and region-specific transcription factors mentioned above, and equally surprisingly, the products of the genes specifying basic multicellular morphogenetic and patterning functions (the "interaction toolkit") are highly conserved: cadherins and collagens mediate associations among cells in all animal embryos; the Wnt pathway mediates changes in the shape or surface polarity of embryonic cells of nearly all animal phyla, with emergent morphological or topological consequences at the tissue level (Newman and Bhat 2008); the Notch pathway acts (via its nuclear switching factor Hes1) to mediate segmentation in phyla as evolutionarily separated as arthropods (Schoppmeier and Damen 2005) and vertebrates (Dequéant and Pourquié 2008); secreted morphogens of the hedgehog, BMP and FGF families, and a few others, mediate nonlocal cell-to-cell communication in all animal embryos (Lander 2007).

There have been attempts to accommodate these striking findings of molecular conservation to the phyletic gradualism of the Modern Synthesis; for example, perhaps it was the regulatory portions of the toolkit genes that evolved gradually (Carroll 2000). But morphological gradualism itself is no longer tenable: evidence has mounted that the abrupt appearance of disparate animal phyla in the late Precambrian and early Cambrian fossil beds (Conway Morris 2006; Budd 2008; Shen et al. 2008) is not an artifact of fossil recovery, but was truly compressed in time (Rokas et al. 2005; Peterson et al. 2008).

Certainly the outcome (with respect to the genes utilized) of the physical generation/origination of forms would have been different if phyletic gradualism had been a valid concept. But the physical-genetic hypothesis does not require gradualism. If the unicellular antecedents of the Metazoa contained most of the interaction toolkit genes, as now appears to be the case (King et al. 2008; Abedin and King 2008; Manning et al. 2008; Sebé-Pedrós et al. 2010), then,

by virtue of their entering into multicellular aggregates, their gene products would automatically mobilize physical processes and effects characteristic of the increased scale of such aggregates and the fact that they comprise discrete, independently mobile subunits (i.e., cells) (Newman and Bhat 2008).

The change to a multicellular context has numerous consequences (Newman and Bhat 2008): (i) while surface tension does not determine the shapes of individual cells, it does determine the shape of a cell aggregate; (ii) cell aggregates containing surface-polarized cells can spontaneously acquire internal lumens; (iii) aggregates containing distinct populations of cells with different adhesive strengths will spontaneously sort out into separate layers; (iv) aggregates of cells that each contain the same biochemical oscillator will spontaneously undergo synchronization, so that the cell state (with respect to the oscillating component) will be globally coordinated across the cell mass; and, (v) cells that secrete diffusible molecules, when present in an aggregate, can act as sources of gradients that pattern neighboring cells, or, when interacting with synchronized oscillating cells, control segmentation.

Physical origination processes are naturally saltational (i.e., nonlinear) and orthogenetic (i.e., similar morphological motifs are expected to occur in independent lineages). These early-established structural themes would constitute a "developmental burden" for subsequent evolution (Riedl 1978), giving them the property of "generative entrenchment" (Wimsatt 1986; Wimsatt and Schank 2004). Because the physical mechanisms involved are sensitive to external conditions, these processes are also naturally plastic. But physically based plasticity would be expected to decline as integration and autonomization, due to stabilizing and canalizing selection (Waddington 1942; Schmalhausen 1949), set in.

The capacities of the products of the ancestral unicellular counterparts to the molecules of the metazoan interaction toolkit to facilitate the mobilization of a range of distinct and relatively independent physical processes in multicellular aggregates, can been schematized into "dynamical patterning modules" (DPMs) (Newman 2010; Newman and Bhat 2008, 2009; Fig. 19.2). The most fundamental of the DPMs is *ADH* (cell–cell adhesion). Genes specifying several members of the most commonly employed cell-cell adhesion proteins are present in the non-colonial choanoflagellate *M. brevicollis* (Abedin and King 2008). What was required, therefore, in order to "invent" the corresponding DPM was a genetic or environmental change that turned the originally nonhomophilic cell surface proteins into homophilic ones. Once this occurred, *ADH*, by mediating aggregate formation, would have set in motion the early developmental-evolutionary trajectory of the Metazoa.

It is evident that these early associations of gene products and physical processes would have been among the most indispensible causal factors of animal development. If diversification happened quickly, as proposed here, the phyla would have immediately set out on their separate evolutionary paths with identical developmental-genetic toolkits (embodied in the DPMs) but different morphotypes (Newman 2011b). Over time, as the phyla's characteristic morphological motifs became integrated into body plans and organ forms, the toolkit would have become increasingly entrenched. Even as some morphological building blocks became partially unmoored from their originating conditions (autonomization), the most

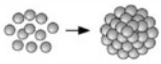
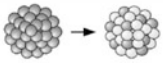
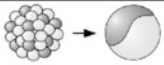
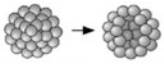
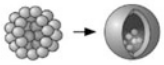
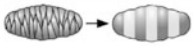
| DPM | molecules | physics | evo-devo role | effect |
|---|---|---|---|---|
| ADH | cadherins | adhesion | multicellularity |  |
| LAT | Notch | lateral inhibition | coexistence of alternative cell states |  |
| DAD | cadherins | differential adhesion | phase separation; tissue multilayering |  |
| $POL_a$ | Wnt | cell surface anisotropy | topological change; interior cavities |  |
| $POL_p$ | Wnt | cell shape anisotropy | tissue elongation |  |
| ECM | chitin; collagen | stiffness; dispersal | tissue solidification; elasticity; EMT |  |
| OSC | Wnt + Notch | chemical oscillation | segmentation; periodic patterning |  |
| MOR | TGF-β/BMP; FGF; Hh | diffusion | pattern formation |  |
| TUR | MOR + Wnt + Notch | dissipative structure | segmentation; periodic patterning |  |

**Fig. 19.2** Key dynamical patterning modules (DPMs), their respective molecular constituents and physical principles, roles in evolution and development, and schematic representations of the main morphological motif they generate. Each DPM is assigned a three-letter acronym. *ADH* cell-cell adhesion, *LAT* lateral inhibition, *DAD* differential adhesion, $POL_a$ cell polarity (apicobasal), $POL_p$ cell polarity (planar), *ECM* extracellular matrix, *OSC* biochemical oscillation, *MOR* morphogen, *TUR* Turing-type reaction-diffusion system. This list of DPMs is not exhaustive. DPMs that refer to individual cell functions such as the *POL*s and *OSC*, are to be understood as designating the multicellular consequences of those functions (Based on Newman and Bhat 2008. See Newman and Bhat 2008, 2009 for additional details)

plausible rewirings of developmental pathways would have involved novel deployments of DPMs, which in present-day organisms typically retain the same associations of physical effects and specific toolkit molecules on the basis of which they first came into existence.

## 19.6 Conclusions

The legacy of Dahlem 1981 is multifaceted, but there is general agreement that the emphasis on the role of developmental mechanisms in generating morphological variation and thus influencing the pathways of evolution was a prominent and influential theme (Love 2006). Our physico-genetic perspective on the

connection between evolution and development has led us to conclusions at odds with the Modern Synthesis, though our framework finds support from findings by investigators working within Evo–devo employing different paradigms from ours:

(i) Morphological evolution does not necessarily track genetic evolution; large-scale morphological change can occur with a minimum of genetic change, while morphology can be static despite extensive genetic change (e.g., Kuraku and Meyer 2008; Cardoso et al. 2009)
(ii) Phenotypic change can precede associated genotypic change (e.g., West-Eberhard 2003; Palmer 2004).
(iii) Macroevolutionary change can be very rapid (e.g., Rokas et al. 2005).
(iv) Saltation is an expected mode of evolution; gradualist adaptive scenarios are not needed to transition from one complex morphology to another (e.g., Erwin 2000; Minelli et al. 2009; Chouard 2010).
(v) Homoplasy is expected to be common; some morphological motifs are recurrent and even predictable, and do not necessarily arise by selection for functional adaptation (e.g., Conway Morris 2003; Seaver 2003; Grazhdankin 2004; Jaekel and Wake 2007).
(vi) Evolution is not uniformitarian; developmental mechanisms at the origin of many morphological motifs were different in kind from those of present-day organisms (e.g., Davidson and Erwin 2009).
(vii) Morphological plasticity was greater at early stages of the evolution of body plans and organ forms than at later stages (e.g., Coates and Clack 1990; Webster 2007).

I suggest that these observations, all of which are puzzling from the viewpoint of the Darwinian model, flow logically from the physical-genetic framework. Darwin's theory, immersed in the scientific culture of its time, committed itself to gradualism as the only acceptable form of material change under the doctrine of *Natura non facit saltum*. Though the Modern Synthesis also embraced this metaphysics, we now know much more about physical processes and their role in generating living structures than we did in the mid-twentieth century. The intellectual ferment around integrating development with evolutionary theory that Dahlem 1981 both represented and promoted is coming to fruition in a broader understanding of the causal basis of life's varied forms.

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# Chapter 20
# The Interaction of Research Systems in the Evo-devo Juncture

**Elihu M. Gerson**

## 20.1 Formation of the Evo-devo Juncture

In order to understand the emergence and development of the Evo-devo juncture, it is necessary to take into account its historical background (Laubichler and Maienschein 2007). Research in what is now Evo-devo inherited a strained relationship between developmental biology and cytogenetics that had developed early in the twentieth century. This debate centered on the relative roles of the cell nucleus and cytoplasm in governing the transmission of genetic information across generations (Sapp 1987). In addition, the reaction against the conceptual and measurement inadequacies of the classical program of comparative embryology (Gould 1977) made it difficult to reinstitute a program of research that sought connections among macroevolution and development.

In the late 1970s and early 1980s, evolutionary research was dominated, as it is today, by the Modern Synthesis that formed in the late 1930s and 1940s (Mayr and Provine 1980; Smocovitis 1996). The Synthesis brought together several different specialties, including systematics, cytogenetics, population genetics, and paleontology. These specialties were integrated by a common theoretical focus: a modified version of Darwin's theory of adaptation and speciation. The Synthesis was notable for its exclusion of several specialties, especially development, but also morphology, ecology, and behavior (Gerson 2007). Research on development and on evolution, for the most part, proceeded independently of one another in the years after World War II. The work of the few researchers that attempted to connect the two areas was dismissed or isolated.

At the same time, the study of development was undergoing a series of changes that transformed it into the modern specialty of developmental biology. The scope of the field expanded from a primary concern with aspects of species-typical

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embryonic development to include problems related to growth, regeneration, and the full life cycle. This trend was signaled by the formation of the Society for Developmental Biology in 1939 and implied a broadening of investigative concerns—from a focus on the development of particular species to topics that cut across taxa, such as growth and regeneration (e.g., Oppenheimer 1966; Gilbert 1991, 2003, 2011).

Evo-devo emerged in late 1970s and early 1980s when several different lines of research began to raise questions about the split between developmental and evolutionary biology. Gould and Lewontin (1979), for example, questioned the all-sufficiency of externally controlled adaptation in shaping differences among species, and argued that developmental constraints limited what natural selection could accomplish. In the course of developing this argument, Gould wrote a book that included an extended history of the conceptual split between development and evolution (Gould 1977). This book stimulated a movement that generated a series of studies exploring the conceptual and theoretical connections between development, morphology, and evolution, especially macroevolution (e.g., Alberch et al. 1979; Alberch 1980, 1982, 1985; Maynard Smith et al. 1985; Shubin and Alberch 1986; Wake 1978; McNamara 1997). A second strand of research significant to Evo-devo emerged in the mid-1960s when the re-invigoration of functional morphology opened up the possibility of improved connections between evolutionary and developmental thought, since morphology had traditionally had close ties with both specialties (e.g., Bock and von Wahlert 1965; Goodwin et al. 1983; Love 2003).

Since the 1960s and 1970s, progress in cell biology and in molecular biology has had a massive impact on the formation and development of specialties in the juncture (Beurton et al. 2000; Carroll et al. 2001; Gerhart and Kirschner 1997; Kirschner and Gerhart 2005). Major advances in developmental genetics occurring in the early 1980s, which offered significant hope for an improved understanding of evolution, were especially important. The most prominent of these was the discovery of the homeotic genes that control the pattern of relationships among body segments (Gehring 1998). These discoveries, and others that soon followed, were crucial to the development of Evo-devo because these genes—fundamental to the most basic organization of the organism—appeared across many metazoan taxa. The implication was that such gene-complexes first appeared in the common ancestor of metazoans, which must have been a very ancient lineage. Their great importance to the study of developmental genetics aside, such broadly distributed genes offered a way to tie development to large-scale and long-term evolutionary trends across clades of bilaterians. The study of phylogeny thus acquired a respectable empirical basis outside of paleontology for the first time since the beginning of the twentieth century.

Thus, the early 1980s saw a convergence of two different intersections occurring between evolutionary biology on the one hand, and developmental biology on the other. From one side, the intersection of paleontology, systematics, morphology, and macroevolution were reconnected to developmental concerns by the rehabilitation of the idea of heterochrony and related topics. From the other side, molecular

genetics and cell biology provided developmental biology with a powerful new set of tools for studying early development, and the results of this work offered important insights into macroevolution.

During the 1980s and 1990s, these separate but overlapping intersections coalesced and elaborated to form the Evo-devo juncture. The Dahlem conference of 1981 was a major impetus to this process. The proceedings of the Dahlem conference were organized by "levels," i.e., the physical scale of phenomena: molecular, cellular, life cycle, and evolutionary. At the time of the conference, the specialties involved at these different scales were clearly ready to talk to one another, but their integration was, as yet, not very far advanced. Over the next three decades, there was progress toward integration among several of the intersecting specialties, most notably between molecular genetics, cell biology, and early development. Other intersections came together more slowly, if at all. As a result, Evo-devo has not achieved anything like a full integration among the specialties participating in the juncture. Rather, work in the juncture is still heavily based in the traditional concerns of its constituent lines of research, and many potentially fruitful lines of joint effort are still at arm's length.

The Evo-devo juncture does not include every line of research harboring a joint interest in development and evolution. For example, Donald Anderson wrote a substantial monograph comparing development across numerous invertebrate groups (Anderson 1973). This work was carried out in the style of classical comparative embryology, and did not make use of ideas from modern cell biology or molecular genetics (which was still in its infancy at the time). There is also a tradition of research in comparative vertebrate reproductive biology that brings together concerns from developmental biology, endocrinology, behavior studies, ecology, and other specialties to focus on a variety of problems, such as masculinization in some species of mammals (e.g., Place and Glickman 2004; Glickman et al. 2005). Participants consider neither of these approaches a part of Evo-devo, and there is no effective contact between them.

In order to understand how and why some parts of the Evo-devo juncture have moved toward a fuller integration while other lines of research have remained relatively distant, it will help to consider this question as one of understanding Evo-devo in terms of the organization of research work. To do this, some sociological concepts will prove helpful.

## 20.2 Research Systems

In order to understand the phenomenon of Evo-devo institutionally, we have to focus on the ways that specific research programs interact with one another rather than the level of broad research specialties, such as genetics or developmental biology. To do this, we need to be able to discuss the characteristics of *research systems*. The idea of a research system is motivated by the insight that sustained reliable production requires persistent organized effort, i.e., a "going concern."

Successful research programs require not just individual scientists but an organized complex of people, equipment, ideas, and other resources. Thus, a research system is an organized effort devoted to a problem or group of closely related problems, and embodied in one or more laboratories or other concrete research organizations. A research system pulls together a set of technical concerns in the form of models, techniques, useful concepts, procedures for dealing with data, and a group of people, as well as the resources they need to carry out studies and interpret their results. Versions of this view of research organization have been developed independently under different names many times in recent years (e.g., "laboratory system", Griesemer and Wade 1988; "breeder reactor", Kohler 1994; "experimental system", Rheinberger 1997; "package", Gerson 1998; "research ensemble", Hackett et al. 2004; "machine to make a future", Rabinow and Dan-Cohen 2005; and, "agencement", Callon et al. 2007).

A research system is a way of detecting and exerting systematic control over aspects of nature in order to answer questions about them. It does this in four major ways. First, it marks and tracks phenomena (Griesemer 2007). Research systems are the means to do this reliably and systematically. Second, research systems control variation in order to make it more comprehensible. They restrict or eliminate some variation ("noise") so as to make phenomena of interest clearer. They reveal, retain, or amplify some variation ("signal") so as to make tracking more convenient. Third, research systems metabolize anomalies (Wimsatt 1987). Because research systems organize and maintain pertinent expertise, data, and tools, they can investigate anomalies systematically as they arise. These investigations lead to revisions in the research system in order to prevent similar incongruities from occurring in the future. Thus, research systems grow and develop by detecting failures and incorporating fixes for them. Fourth, research systems systematically organize the work needed to bring together everything needed to solve research problems. They also articulate the different kinds of technical and administrative expertise required to carry out the research. In doing so, they juxtapose and concinnate multiple actors, materials, and ideas so as to produce or control phenomena of interest.

Research systems exhibit many properties of interest. Some of these properties mark significantly different approaches to topics in the Evo-devo juncture. These include differences in focus, mode and style of research, and variations in problem strategy.

### *20.2.1 Focus*

Some research in biology focuses on a particular group of organisms, such as birds or salamanders. Other research focuses on particular analytical problems such as inheritance, relations among species, development, reproduction, and so on. The two different foci have co-existed since the early twentieth century, although there is a long-term trend toward prioritization of analytical problems, sometimes at the expense of research on particular taxa (Gerson 1998).

### *20.2.2 Mode of Research*

Several different broad approaches to the conduct of research have developed since the emergence of organized empirical inquiry in early modern times. Crombie (1988, 1994) referred to these as "styles." Here I mention three such broad approaches or *modes* of research, slightly modified from Crombie's discussion: the comparative-historical, analysis of mechanisms, and abstract formalism. Of these, the first two are of great importance in understanding the formation and persistence of the Evo-devo juncture.

The comparative-historical mode generates concrete descriptions, classifications, and relations among them. It depends heavily on analogy as a means of ampliative inference, and produces scenarios and parallels (i.e., homologies) as theoretical products. It relies largely on fieldwork and specimen collections to assemble and analyze data. This mode organizes concepts in terms of part/whole relations and as versions (i.e., series and sequences of taxa). It values criteria of robustness, consilience, classificatory adequacy, and completeness of description as standards of evaluation. Systematics, morphology, classical comparative embryology, biogeography, and paleontology are among the specialties that have traditionally adopted the comparative-historical approach, which was the dominant mode of research in much of the life sciences in the nineteenth century.

Mechanism analysis generates relatively concrete models and explications of part-whole relations. It depends heavily on idealization as a means of ampliative inference, and produces models and scenarios as theoretical products. It relies on iterated trials, troubleshooting, and the analysis of "edge cases" to collect and analyze data. This mode organizes concepts in terms of part-whole relations and sequences of operation. It values criteria of robustness and verification as standards of evaluation. Cell and developmental biology since World War II, genetics, and many branches of physiology have been among the specialties that have relied heavily on mechanism analysis.

The formal mode generates abstract laws (ideally expressed mathematically) and predictions about the states of variables. It depends heavily on abstraction as a means of ampliative inference, producing laws and formal relations among variables as theoretical products. It relies on assays and controlled experiments to collect and analyze data. This mode organizes concepts in terms of kinds and their instances. It values criteria of verification, prediction, generality, and conceptual simplicity as standards of evaluation. Relatively few specialties in the life sciences have made extensive use of the formal mode. Among the specialties that contribute to the Evo-devo juncture, some branches of ecology and population genetics exemplify this mode.

Typically, research programs or specialties have been dominated by a single mode of research, with others playing a relatively minor role. For some specialties, this has changed over time; a long-term shift from comparative-historical to mechanism analysis has been characteristic of the life sciences since the beginning of the 20th century. Nevertheless, the comparative-historical approach remains

important, not only for specialties such as paleontology that have always relied upon it heavily, but also for specialties such as molecular genetics (Strasser 2010, 2011).

### *20.2.3 Style*

Every approach to research requires scientists to make many specific commitments about the ways they allocate resources. Each hypothesis, for example, implies certain kinds of data collection and analysis, and each technique requires certain materials and tools. The decision to adopt one approach rather than another, in turn, is guided by styles of research. Styles are abstract commitments used to organize other, relatively concrete, commitments. Styles typically appear as general philosophical or methodological positions; e.g., focusing on structural rather than functional considerations, or preferring the construction of formal models to the detailed description and analysis of particular cases. Any such pattern of commitments can serve to frame a line of research problems, such as German genetics in the inter-war years (Harwood 1993).

Styles of research are only loosely associated with particular research modes, problems, techniques, and findings. Thus, they are compatible with many different investigative projects. Particular research systems are informed by the styles they adopt, but the particulars of their work are settled by many other factors. Stylistic conflicts within a line of research are routine. Stylistic commitments often appear as alternative sides of familiar philosophical and methodological debates.

The structural and processual styles are different ways of formulating questions about patterns of organization. The distinction between an emphasis on form or structure versus change or process is a familiar one in Evo-devo research, as well as some of the specialties that contribute to it, such as genetics and developmental biology (Amundson 2005).

Another style contrast that has been important in the formation and organization of the Evo-devo juncture is the distinction between integrative and partitioning approaches (Gerson 1998, 2007). The contrast between partitioning and integrative styles arises from different strategies for locating causes. The partitioning style searches for causes in the relationships among constituent parts and processes of a phenomenon. In order to find out how something works or what it is made of, then: (a) take it apart; (b) study each component part or process; and, (c) study how the components fit or act together. In contrast, the integrative style searches for causes in the relationships between phenomena and their contexts. In order to find out how something works or what kind of thing it is: (a) observe and classify the way it responds to different situations; (b) classify the situations according to some ordering principle; and, (c) construct a rule that associates changes in the phenomenon with changes in the situation.

Another important style arises from alternative ways of conceptualizing phenomena. For example, some researchers are concerned primarily with parts

and wholes, while others are concerned primarily with instances and kinds (Gerson 2007). Morphologists, cell biologists, and developmental biologists have traditionally been concerned with parts, wholes, and their relationships. Population biologists, in contrast, have traditionally considered individual organisms as instances of particular kinds of classes, such as populations or species.

### *20.2.4 Variations in Problem Structure and Strategy*

There are many ways to pose problems, and each offers advantages and disadvantages with respect to the functions of a research system. For example, developmental biologists are concerned typically with variation within species over time, while population geneticists are more typically concerned with variation within and between populations. There is no necessary conflict between these two concerns; actual organisms and populations vary in both ways. But differences in problem structure can make it difficult to form effective connections between two systems. For example, research systems can frame their questions in ways that apply to many taxa or only a few. Some are concerned with a limited number of phenomena or variables; others encompass a large number of variables. Some research systems are set up to avoid restrictions on the number of variables, so that the number is (at least potentially) very large, or even infinite (e.g., those based in traditional natural history). Other research systems sharply restrict the number of variables they are willing to consider. Pantin (1968) and Rip (1982) used this criterion as a way of distinguishing among specialties. Many other ways of organizing problems and problem-agendas (Love 2008) are possible.

Research systems have many other properties not discussed here. Among the most important of these are the different ways in which models, procedures for working with data, and categorizing and interpreting observations are formed and change. Where these properties are compatible with one another, integration of different research systems is relatively simple; where they are not easily reconciled, integration becomes difficult.

## 20.3 Relations Among Research Systems in the Evo-devo Juncture

The notion of a research system provides us with some of the analytical tools we need to understand both the successes and failures of specialty integration that characterize the Evo-devo juncture. For complete integration to occur in an intersection of research systems, there must be a relatively good match among many of their properties. In particular, the problems of two different lines of work must come to be seen as a single problem. This can occur when new insights lead to

a conceptual reorganization. It can also occur when new techniques allow a reframing of problems. The techniques of molecular genetics, for example, enabled a reframing of the notion of gene expression while simultaneously enabling a novel kind of experimental access to embryogenesis (e.g., Burian 1997; Morange 2000). Two lines of research with a history of antagonism (e.g., Sapp 1987) were thus recast as complementary and closely allied.

The emergence of molecular genetics has enabled a second set of close alliances in the Evo-devo juncture. Because the genes that organize development appear in many taxa that are only distantly related, they provide a basis for constructing phylogenies as well as studying embryogenesis. This enables another set of alliances between developmental genetics on the one hand, and macroevolutionary research in paleontology and systematics on the other.

This system of alliances is one of the principal threads of the Evo-devo juncture, tying together its two main sides conceptually. The system rests on a common set of ideas about genes and their expression that has grown up since the early 1980s. These ideas provide the basis of a partial integration of multiple specialties that leaves the separate problems of the specialties intact. These ideas, as embodied in a variety of research systems, cut across traditional specialty boundaries, and act as a substrate or matrix that binds different research programs together.

Another prominent example of this process is the use of model organisms as a kind of common "background knowledge" for multiple specialties composing Evo-devo's research programs. The detailed knowledge that comes from routinely dealing with a single organism, including the husbandry necessary for the organisms to live, reproduce, and develop, serves to link multiple research systems. The common body of knowledge built up by working with a single organism serves to anchor and scaffold the work of framing and organizing research on Evo-devo problems, especially those that cut across specialty and stylistic boundaries. The accumulation of knowledge and experience with model organisms thus serves to create a kind of infrastructure that provides many scientists with the benefits of using a common facility, which they could not afford to construct and maintain for themselves. This constitutes a kind of partial integration of the research systems (but not necessarily the specialties) that use the model organism. Model organisms are thus platforms (Evans et al. 2006), which can serve as a basis for many different complementary efforts—a *de facto* set of standard arrangements and resources that serve as a substrate or scaffold to focus commitments.

Recent years have seen an increasing number of experimental techniques and associated instruments that require very high levels of specialized knowledge to acquire, maintain, and employ properly. Advanced kinds of laser microscopy, flow cytometry, immunohistochemistry, and other techniques all require developing the skills and knowledge used to address problems in many different research systems. These techniques, and the equipment they require, form the basis of another kind of partial integration that frequently cuts across specialty as well as research system boundaries. Partial integration occurs in virtue of their use of common techniques in a way that is analogous to, if narrower than, the partial integration provided by the use of model organisms.

Another coordinative arrangement that offers many of the same advantages as model organisms is the use of model *taxa*. For example, David Wake's systematic use of salamanders as a group of species has supported an extraordinary range of studies in evolutionary biology, morphology, and development (e.g., Wake 2009; see Griesemer, Chap. 13, this volume). This focus on a single clade allows scientists from many specialties to apply methods of comparative analysis to work on many different problems, often based in part on access to collections (Sunderland 2012).

Compatibilities in the properties of research systems make for relatively simple integrative trajectories. Technical and administrative changes often alter intersections; they can change or even eliminate impediments to integration. Thus, the overall integration of a specialty or juncture can improve over time. Since these changes are not systematic, the changes in degree of integration are unpredictable. Compatibilities among research systems are almost always partial. For example, two research systems may share use of particular data collection technologies but differ in their problem structures, models, mode, and other properties. The more that two research systems share properties in this sense, the more likely they are to integrate in practice, at least to some degree. The branches of genetics provide an example of multiple sub-specialties that are highly integrated.

Shifts in the characteristics of one research system can lead to improved compatibility with complementary research systems, and thus trigger the recognition that integration is feasible. Thus, for example, the long-term historical trend that has shifted many lines of work from comparative-historical to mechanism-oriented approaches has made it easier for the Evo-devo juncture to emerge and develop. Similarly, the long-term shift in focus from taxon-orientation to analytic problems has made it easier for lines of research in the Evo-devo juncture to integrate. Conversely, different properties of research systems can lead to different ways of framing and organizing research, which in turn can lead to incompatibilities. Such incompatibilities can make it difficult or impossible for researchers from different specialties to make use of one another's tools, models, and observations in a useful way. They also may find collaboration on particular projects to be difficult, and hence not as attractive.

Some kinds of shifts involve relatively few complex changes to the research system, while others are more difficult. Differences among research systems committed to alternative modes of research can be difficult to resolve if they require complex shifts, especially if multiple research systems are involved. For example, incompatibilities among data strategies are relatively easy to resolve, while those based on stylistic conflicts can be very difficult. The presence of common criteria of assessment (e.g., a joint commitment to theoretical simplicity) can be a major aid to reconciliation. Since differences between styles are by definition differences in evaluation criteria, stylistic differences can be very persistent. Intersections where research systems are incompatible or competitive can become the sites of prolonged debates and conflicts.

## 20.4 Institutional Constraints on Integration of Research Systems

The broad institutional context in which research takes place developed in the U.S. around the turn of the twentieth century (Veysey 1965; Geiger 1986, 1993; Gerson 1998). Over the course of the twentieth century, and especially since World War II, the number of research specialties has been increasing rapidly. In part, this is due to the growth of funds and facilities for research, but it also has come from the development of many sub-specialties that have appeared as the expansion of knowledge defines an ever-larger number of research problems to be solved. This same expansion also has generated an exponential increase in the actual and potential number of intersections among specialties. This growth is beginning to strain the system of research institutions, and the Evo-devo juncture is affected by some of these strains.

Specialties, and the research systems that make them up, are embodied in organizations that have limits and agendas that shape what researchers can do. Specialties organize learned associations to support and promote their work, and arrange to have journals published. Universities and other organizations provide space, utilities, and administrative services for their efforts. Educational programs prepare and certify the next generation of researchers. Sponsors provide funds for research projects and programs. Regulators constrain the use of reagents, live animals, the collection of specimens, and many other aspects of research. Hobbyists provide popular support and often collect data; recently, they also provide computing resources to data reduction and analysis. Commercial firms often donate or subsidize specialized materials and instruments, and provide useful technical support and education as well. All these arrangements support the work of the specialties and provide them with a relatively stable environment in which they can flourish. By these means, a steady stream of funds and other resources generates findings, new problems, and publications that help to justify existing funds and facilities, as well providing the funding and rationale for more researchers, students, and new research projects.

A fully developed specialty is well connected to all of these arrangements. On the other hand, intersections among specialties ordinarily do not have the clear institutional connections that established specialties do, especially early in their lives. They must therefore devote time and effort to building up these arrangements, or find a way to take advantage of established programs and organizations. Research systems that span two or more specialties, such as Evo-devo, encounter all the usual costs and benefits of working in the larger system, but they also encounter some additional difficulties that stem from their boundary-crossing position.

Evo-devo has developed much of the organizational apparatus of an established specialty, but some important gaps remain. The juncture has acquired several textbooks that cover the area (e.g., Raff and Kaufman 1983, 2nd. ed. 1991; Hall 1992; Raff 1996; Minelli 2003, 2009), and conferences and workshops to present new work, and provide in-service training, are frequent. Short courses at places like the Marine Biological Laboratory and the Cold Spring Harbor Laboratory are routine.

A formal association to represent and promote Evo-devo has yet to be organized, nor are there sections representing Evo-devo concerns within the structure of either the Society for Developmental Biology or the Society for the Study of Evolution, the principal associations serving developmental biology and evolutionary biology. On the other hand, the Society for Integrative and Comparative Biology (SICB), a major association emphasizing comparative biology, has a division of Evolutionary Developmental Biology. This division is the most important learned association for Evo-devo.

SICB's Division of Evolutionary Developmental Biology also sponsors *Evolution & Development*, a journal established in 1999 to represent the common concerns of the juncture. The *Journal of Experimental Zoology (Molecular and Developmental Evolution*), and *Development, Genes and Evolution* also serve as publication outlets for research in the area. Articles reporting Evo-devo research also find a ready home in other journals.

It is relatively easy to establish a new laboratory or research center in a host organization.[1] Evo-devo is thus established on many campuses. Establishing new degree programs and departments is far more difficult than establishing laboratories, learned associations, and journals. A new intersection among sub-specialties can develop in a few months, perhaps over a few years. Establishing new courses and degree programs often takes years; universities are slow to establish new open-ended programs that consume resources, and that might not prove broadly accepted among other specialties. In addition, standardized tests such as the GRE and the MCAT impose *de facto* requirements on curricula, and these tests recognize and incorporate new discoveries at their own pace. Perhaps most important, acquiring an advanced degree is not the end but the beginning of a career, and it may take a long time for a new specialty to be recognized in the hiring practices of university departments.

Additional problems for interdisciplinary research appear in the organizations that house research and supply the requisite administrative services. The need to teach standard courses to many undergraduates means that the internal structure of departments typically favors large, long-established specialties rather than smaller, newer, and hybrid ones (Campbell 1969; Gerson 2009). Specialties are sometimes housed in different departments, which adds a layer of administrative costs to cooperative arrangements among the specialties recognized in the organization's structure. To some degree, this is inevitable—a host organization must divide up its work according to some scheme, and disciplinary boundary lines have been an obvious and useful way of doing it since the end of the nineteenth century (Gerson 1998). But the growth in sub-specialty and intersection numbers over the past few decades has meant that the traditional department structure of universities, museums, and other basic research organizations has become detached from the everyday work of their resident specialties. A department of zoology or evolutionary biology in the early twenty-first century covers (at least in principle) many

[1] The correct emphasis here is on "relatively," not "easy."

organized specialties, and hundreds or even thousands of their lines of work and the intersections among them. The relationship between host organizational structures and research programs is thus a loose one, and departments have become little more than bookkeeping devices for their host organizations.

As the number of specialties in the biological sciences has grown, and academic departments have grown and re-organized with them, a clear trend has emerged that favors having two large departments on a campus. These have responsibility for many specialties, and may even be organized into sub-departments or divisions with responsibilities for a smaller range of research problems, such as genetics or ecology. This particular trend poses some problems for Evo-devo. Many of these large departments have clustered into two major groups, typically covering something like evolution, ecology, and systematics on the one hand, and molecular and cell biology on the other. This division tends to crosscut major parts of the Evo-devo juncture, inserting an administrative barrier into the midst of efforts to coordinate work in the juncture. Moreover, the position of the barrier is inconsistent across hosts. One university might house its developmental research in a department of organismal biology, along with morphology; another might house it with cell and molecular biology; and a third might house it with evolution and ecology. Moreover, some relevant specialties may be housed in schools of medicine, public health, veterinary medicine, agriculture, or forestry. And, of course, most paleontology research is housed in departments of geology. These institutional arrangements suggest that Evo-devo research will be split across multiple departments indefinitely.

The inconsistencies among organizational arrangements make it difficult to develop standardized ways of dealing with inconsistencies across departments. In turn this means that every inter-organizational joint venture or career move implies a degree of retraining and adjustment. Establishing cooperative projects based in the same department is easier than establishing research systems that span department, school, university, or national boundaries. More generally, the farther apart two research organizations are in the space of organizational hierarchies, the more layers of management, policy, and regulation must be satisfied before two groups can work together.

Sponsors' policies can also present difficulties for interdisciplinary research. Sponsors may be slow to recognize the significance of an emerging intersection. For sponsors, as with other hosts that house many research programs, there is no arrangement of boundaries among organizational units that will not make some otherwise suitable research project "fall through the cracks" of the organization, and thus fail to receive support. Interdisciplinary programs are more likely to suffer this fate if the sponsor is organized around the conventional pattern of specialties. Interdisciplinary research proposals must thus be "tailored" to meet the expectations of disciplinary specialists, who are less likely to appreciate the subtleties of the interdisciplinary argument made by the proposal.

Even where these difficulties do not arise, the sponsor's administrative requirements can put interdisciplinary work at a disadvantage. For example, many sponsors put limits on the size of a proposal, in order to keep down the burden on reviewers.

Interdisciplinary proposals must explain their projects in ways accessible to referees from multiple specialties. The proposals thus cannot assume that referees are familiar with all the technicalities involved in a proposal. Space that might be used to deal with relatively advanced issues must therefore be devoted to explanations for referees who are not familiar with all the relevant details. This puts multi-specialty proposals at a disadvantage. Disadvantages for multi-specialty projects also arise from stylistic or other incompatibilities between proposals and their referees. These increase as the number and variety of referees increase.

In summary, hosts, sponsors, and other organizations that anchor research inevitably impose burdens on it as well. These burdens are likely to be more troublesome for interdisciplinary projects, which predominate in junctures. The incompatibilities among research systems that come about as the result of mismatches between the research and its anchoring organizations discourage communication and collaboration among researchers. It makes collaboration across specialty boundaries more difficult because this collaboration increases risks to funding, publication, and tenure as well as other opportunities. They also discourage the recruitment of researchers into new specialties.

The effect of each of these constraints is probably small by itself; they may discourage a few projects directly, but often most can be carried out despite the additional difficulties. But the cumulative effect of many small disruptions and barriers to cross-specialty and collaborative research is probably significant. Research involving multiple specialties, organizations, and research systems will be done less often, more slowly, and more expensively than research carried out within the limits of established arrangements (National Academy of Sciences 2004). Small barriers to communication can maintain significant differences across lines of work.

## 20.5 Conclusion: The State of the Evo-devo Juncture

From the above considerations, we can draw several conclusions about the state of the Evo-devo juncture (see also M. Wake, Chap. 18, this volume). First, progress in molecular and cell biology has enabled many new relations among the specialties that made up the nascent Evo-devo juncture in the early 1980s. This work has formed a major system of alliances among genetics, developmental biology, and macroevolution. In doing so, it has transformed debates about the extent and nature of the Modern Synthesis that were prominent in the early 1980s. This progress also has encouraged a great deal of partial integration among the specialties in the juncture. Model organisms are one important basis of partial integration, providing common knowledge and skills across multiple research systems that themselves span multiple specialties. Adoption of the same styles in multiple research systems provides another basis for partial integration among programs that might not otherwise have any good reason for interacting. Cell biology's successful marriage of structural and processual views (Bechtel 2006) is a model of how to reconcile

stylistic differences in life science. Similarly, evolutionary biologists have begun to think explicitly about working with both comparative and mechanism perspectives simultaneously (e.g., Autumn et al. 2002). The use of common technologies in multiple research systems also provides a basis for correction and cooperative effort among research systems largely independent of their problem structures, theoretical models, and concepts. These events suggest that it might be possible to develop ways of forming alliances between approaches with different styles and foci.

Despite real progress, important problems requiring further interdisciplinary alliances still exist. The notion of heterochrony, for example, which was at the center of the early Evo-devo juncture, does not seem to be at the center of current research (Hanken, Chap. 4, this volume); understanding its underlying mechanisms at the cellular or molecular level remains to be achieved. Similarly, inputs to development from the environment have not been an important part of Evo-devo research, although concern with phenotypic plasticity has gained attention in recent years (e.g., West-Eberhard 2003). Integration of Evo-devo concerns with ecological thinking is in its infancy (Gilbert and Epel 2009; Hall et al. 2004), and represents a significant set of problems and a potential major expansion of the juncture in coming years. The absence of embryonic forms in the fossil record makes it difficult to achieve closer integration of paleontology with developmental biology. Instead, the integration is indirect, via the traditionally close relationships both specialties have had with morphology. Within this framework, there are some promising studies (e.g., Wagner and Gauthier 1999), but there does not appear to be a sustained intersection as yet.

The pattern of partial integration among research systems is the "glue" that holds the juncture together. These partial integrations serve to connect multiple specialties in complex and durable ways without encouraging a full merger of specialties. At the same time, the many different problems, focuses, modes, and styles of the research systems that make up the juncture ensure that there are real incentives to maintain independence among technical approaches to Evo-devo. The segmenting tendencies are supported and reinforced by the difficulties of working smoothly within the system of anchoring organizations. The juncture thus has an apparently stable basis of continuity that does not depend on the formation of a fully integrated specialty. Hence, even if Evo-devo is not a fully formed discipline in its own right, it is clearly a successful and durable part of the biological sciences. As a consequence, it is well placed to serve as a type specimen for further research on the organization of junctures and the integration of specialties.

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# Chapter 21
# Evo-devo as a Trading Zone

**Rasmus Grønfeldt Winther**

## 21.1 Introduction

Evolutionary developmental biology (Evo-devo) is philosophically fascinating because of its plurality of scientific "cultures" of practice and theory that continue making progress towards a better understanding of complex biological reality. Through an examination of a variety of the scientific cultures pertinent to Evo-devo, I show here that Evo-devo can be usefully understood as a *trading zone* (Galison 1997). That is, it is constituted by a variety of disciplines, styles, and paradigms negotiating heavily with one another. I am concerned with the differences, interactions, and relative openness and flexibility of these cultures. When are the cultures acting—individually or collectively—in ways that further research empirically, theoretically, and ethically? When do they become imperialistic, in the sense of excluding and subordinating other cultures? I wish to explore some of the key assumptions standing behind, under, and within each. Such presuppositions ground the concepts, methods, and models of each culture. They are also an integral aspect of the broader norms, forms of communication, and shared meanings and behaviors of each culture. The goal of this chapter is to identify six

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cultures of Evo-devo (three styles and three paradigms) and provide an initial *assumption archaeology*[1] of their internal structure, and mutual relations, through the concept of a trading zone. My main excavation site is Bonner (1982), a founding text of Evo-devo and product of the 1981 Dahlem conference on evolution and development. Possible future work and limitations of my analysis are sketched in the conclusion.

What exactly is a trading zone? Peter Galison developed the concept in *Image and Logic* (1997) to describe the interactions between two traditions of instrument-building and experimentation in microphysics: those using bubble chambers to form images of sub-atomic interactions, and those employing detectors arrayed around the particle collision event itself, arranged according to logical electrical circuit diagrams, to produce statistical patterns of the spatiotemporal appearance of diverse kinds of particles. Theorists also met these instrument-makers and experimentalists in this trading zone. What is the relation among researchers and among traditions?

> Two groups can agree on rules of exchange even if they ascribe utterly different significance to the objects being exchanged; they may even disagree on the meaning of the exchange process itself. Nonetheless, the trading partners can hammer out a *local* coordination despite vast *global* differences. In an even more sophisticated way, cultures in interaction frequently establish contact languages, systems of discourse that can vary from the most function-specific jargons, through semispecific pidgins, to full-fledged creoles rich enough to support activities as complex as poetry and metalinguistic reflection. (Galison 1997, 783)

A pidgin is a first-generation "hybrid" language. A creole is a pidgin that has been learned by a new generation of speakers and thereby nativized; it is a full-fledged language. Interactions of various degrees of richness and texture can thus be established in trading zones. Following Galison, the coordination among cultures need only be spatiotemporally local and hardly implies agreement: "...in any exchange, the two subcultures may altogether disagree about the implications of the equivalencies established, the nature of the information exchanged, or the epistemic status of the coordination" (Galison 1997, 806). The often incomplete—yet powerful—trading zone dynamics identified by Galison are at work in Evo-devo. For instance, the trading zone of Evo-devo is approaching the articulation of a creole through concepts such as "gene regulatory networks" and "cell signaling" that are readily understood by workers across different cultures. Moreover, there is an exchange of molecular tools and methodologies among mechanism and mathematical modeling styles. The trading zone concept provides insight into the structure, function, and historical dynamics of Evo-devo.

[1] In a forthcoming book, I develop a critical *assumption archaeology* (my term, following Michel Foucault 1966, 1969; Ian Hacking 2002; Michael Friedman 1999), which explores methods for identifying different types of assumptions (e.g., ontological, theoretical). One aim of this philosophical methodology is to investigate opportunities for collaboration of theories that make different (perhaps even conflicting) assumptions. The dialogue and self-reflexivity through which such collaboration can happen—and in which the philosopher can play a significant role—occurs in what is called an *integration platform* (Winther under contract).

In addition to the features characterized by Galison, a trading zone can be further described as a *richly overlapping domain* in which scientific cultures at different levels of abstraction interact. Disciplines, styles, and paradigms (i.e., three types of culture, each at a particular level of abstraction) interact across and within distinct levels of abstraction. Possible types of inter-cultural relations within a level can be understood in terms of different dimensions, including: (1) collaboration and competition; (2) mutual understanding and reliable translation, on the one hand, and misunderstanding, miscommunication, and incommensurability, on the other hand; and, (3) integration and fragmentation. Across levels there are complex relations of guidance (e.g., styles *guide* paradigms) and instantiation (e.g., a paradigm *instantiates* one or more styles). Understanding trading zones as richly overlapping domains provides a fine-grained tool for dissecting these manifold relations and their consequences, both within Evo-devo and elsewhere. Moreover, Evo-Devo is an important example of how science can progress through a radical plurality of perspectives and cultures.

This chapter is organized as follows. First, I explore three styles: mathematical modeling, mechanism, and history. After providing a general analysis of the concept of styles, I detail the basic components and properties of each style and locate their signature in the 1982 Dahlem volume (paying more attention to an assumption archaeology of the mathematical modeling style). Next, I analyze the concept of paradigm and initiate an archaeology of three paradigms relevant to Evo-devo: adaptationism, structuralism, and cladism. This analysis characterizes three specific paradigm cultures that often (and ideally) collaborate, understand one another, or are integrated. Finally, I explore the complex anatomy and physiology of Evo-devo as a trading zone, inviting a final reflection on the concept itself.

## 21.2 Styles in Evo-devo: Mathematical Modeling, Mechanism, and History

Styles of scientific research are very general ways of doing science, of "finding things out" (Hacking 2009). The concept was introduced by historian A.C. Crombie.

> The scientific movement brought together in its common restriction to answerable questions a variety of styles of scientific argument, of scientific methods of inquiry, demonstration and explanation, diversified by their subject-matters, by general conceptions of nature, by presuppositions about scientific validity and cogency, and by scientific experience of the interaction of programmes with realizations. (Crombie 1994, vol 1, 83)

Hacking, who has articulated the concept over the last three decades, notes:

> Every style of reasoning introduces a great many novelties including new types of: objects; evidence; sentences, new ways of being a candidate for truth or falsehood; laws, or at any rate modalities; possibilities. One will also notice, on occasion, new types of classification and new types of explanations. (Hacking 2002, 189)

Following these descriptions, styles provide overarching theoretical and experimental ways of doing science, and of viewing objects and processes in nature. The *standard view* of styles identifies six types: (1) deductive (postulation or axiomatic), (2) experimental, (3) analytical-hypothetical (hypothetical modeling), (4) taxonomic, (5) probabilistic, and (6) evolutionary (historical derivation or genealogy)[2] (Crombie 1994; Hacking 2002, 2009; Kwa 2011; cf. Pickstone 2001).

There are many other ways to identify and classify styles, such as: (1) "causal-mechanical" theorizing of German embryologists and fact-finding of American embryologists in the early twentieth century (Maienschein 1991), (2) "analysis: synthesis" and "palaetiology" in the nineteenth century (Elwick 2007), and (3) "formal" and "compositional" biology (Winther 2006a). These distinctions of style were developed for particular purposes, unrelated to the central aim of the standard view of understanding science in general. There are also classifications of styles in disciplines outside of the biological sciences (e.g., Davidson 2001; Forrester 1996). Although ongoing research explores how these styles relate to each other and to the standard view, I will not adjudicate among these classifications. Instead, I argue that biological styles are both more specific (i.e., smaller domain of application) and more concrete (i.e., more, substantive assumptions) than the standard view implies, though connections with the six generalized styles remain salient. Three biological styles are identified and discussed in this section.

1. *mathematical modeling*: the analytical-hypothetical "Galilean style" that Edmund Husserl, Noam Chomsky, and Steven Weinberg also wrote about, together with probability and statistics. It can be seen as the first and fifth, and probably the third, styles combined around the notion of a mathematical model (see Winther 2012)
2. *mechanism*: a style essential to biology, thanks to Descartes, Claude Bernard, and others. More generally, it is associated with ubiquitous, if at times problematic, forms of reductionism. This style is also a particular sort of modeling: the non-mathematical part of the analytical-hypothetical style.
3. *history*: a *bona fide* standard view style.

### *21.2.1 Mathematical Modeling Style*

The mathematical modeling style, as expressed in the biological sciences, is not primarily about proving conjectures through deduction from axioms (the first style of the standard view). Rather, it aims at abstracting, idealizing, and generalizing a *mathematical model* for a particular set of objects and processes that express regularities and obey causal rules. The process of generating, evaluating, and using the model can be articulated in terms of five sequential activities: (1) *setting up*,

[2] The first terms are Kwa's. When present, second terms are Crombie's and third terms are Hacking's.

(2) *manipulating*, (3) *explaining*, (4) *objectifying,* and (5) *pluralizing* (the *SMEO-P* account, narrated in Winther 2006b, c, under contract).

1. A model is set up by measuring and observing empirical phenomena, and in the context of a theoretical background. We set up initial equations in a language (e.g., differential equations, geometrical patterns, probability equations) with a syntax (derivation rules) and semantics (parameters, variables, and functions with real-world meanings and mappings) appropriate to the problem (i.e., the language's pragmatics is respected).
2. Manipulating the initial equations with the derivation rules, which include idealizations, heuristics, and approximations permitted by the internal demands of the model, can lead to surprising results (e.g., unexpected equilibrium conditions).
3. Models can explain real-world phenomena when they identify causes, processes, and mechanisms, increase our understanding, or provide greater integration and unification of our scientific knowledge.
4. Objectifying is a concern about how models export and impose their assumptions about the world, and about the modeling process. This fourth step has been completed when researchers consider model assumptions as independent of the model and present in nature itself.[3] One function of an assumption archaeology is to track the epistemic and social processes associated with objectifying.
5. Since objectifying can result in pernicious reification (as well as generative explanation), a powerful additional, fifth step is often taken—pluralize. Here assumptions, data, methods, and representations are compared across mathematical models in order to assess the strengths and weaknesses of each model, and to search for robust assumptions and results (on "robustness analysis" see Weisberg 2006; Wimsatt 2007).

My *SMEO-P* account helps analyze and troubleshoot the mathematical modeling process. Many mathematical languages and methods are used when modeling in the biological sciences. Moreover, statistical theory (together with experimentation) is invariably used to compare model and data. In short, the mathematical modeling style is ubiquitous to the life sciences, including Evo-devo. It is immediately evident in the 1982 Dahlem volume. Three levels of biological hierarchy will be considered: genetic, morphogenetic, and life history.

First, Stuart Kauffman's Boolean logic genetic networks have been important in inspiring, if not directing, a significant amount of research on complexity and self-organization. One of his first papers set the formal tone in the late 1960s, which were watershed years for theoretical biology (Kauffman 1969). In the 1982 Dahlem volume, he added a short section to the group report by Dawid on "Genomic Change and Morphological Evolution." In his section ("General Properties of Interacting Systems of Large Numbers of Genes"), Kauffman noted how "Given certain assumptions about the rules of regulatory interactions, these model genetic

[3] For a discussion of Richard Levins and Richard Lewontin's analyses of objectifying model assumptions, see Winther 2006c.

regulatory systems spontaneously crystallize ordered patterns of gene expression" (Bonner 1982, 34). These assumptions include a connectivity $K$ of exactly two—i.e., any gene is connected to two other genes. Moreover, any gene was either on or off (1 or 0), so for 10,000 genes there were $2^{10,000}$ possible states. For that number of genes, Kauffman's simulations indicated approximately 100 sets of gene expression patterns (with some slight variation within each set). Each of these coordinated patterns was then argued to "correspond to a single cell type" (Bonner 1982, 34). While the assumption of $K = 2$ may be questioned, as may the very notion of "cell type,"[4] of interest here is the fact that Kauffman employed abstract mathematics to articulate a predictive and explanatory research project (see also Lewin 1996).

Let us turn to the morphogenetic level. The role of morphogens in development was studied and modeled by various scientists at the 1981 Dahlem conference, including Lewis Wolpert, David Raup, and Hans Meinhardt. In an earlier paper by Meinhardt (Meinhardt and Gierer 1980), cited in the "Adaptive Aspects of Development" group report, he had outlined a plethora of ways in which local and global concentrations of morphogens of various sorts (e.g., inductive, inhibitory, fast- or slow-diffusing) could give rise to different morphological phenomena (e.g., compartments, cell differentiation, and stripes). A useful table ("Reactions which lead to pattern formation") is in the 1982 Dahlem volume (reproduced here as Table 21.1). In the text, the group report on "Adaptive Aspects of Development" (authors include J.T. Bonner, H. Meinhardt, R.A. Raff, and S.C. Stearns) states:

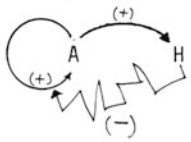
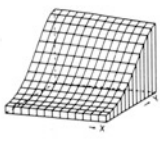
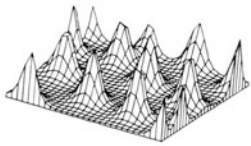
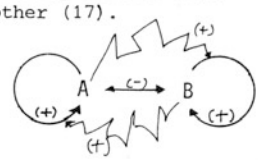
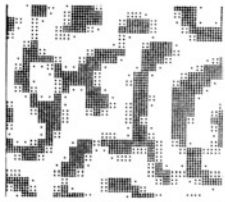
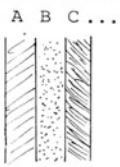
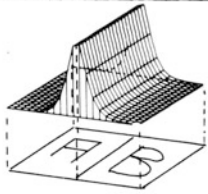
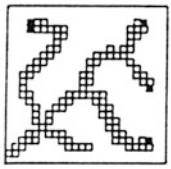
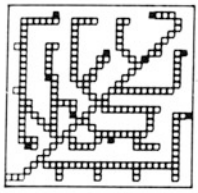
> Table 1 shows the kinds of patterns that are generated by mathematical models of the behavior of substances that are postulated to affect differentiation. This table teaches two important and general lessons. Many patterns typically seen in development can be generated by a few simple and realistic models. Furthermore, different patterns can be produced by changes in the parameters of one model. (Bonner 1982, 218)

Mathematical models have explanatory and predictive power. The complexity of developmental patterns can be reduced to a "few simple and realistic models." This is a strong statement, and may be too strong in two senses. First, there may be a *reification fallacy* occurring here, an abstract-concrete conflation (i.e., step 4 of the *SMEO-P* account). This is a common bias and error in mathematical modeling practices—the abstract model is confused with, and imposed on, the concrete world (Winther 2006b, c, 2008, 2011, 2014a, b, under contract). Here is the problem: mathematical models cannot *themselves* "generate" physical patterns. Yet, mathematical modeling and model objectifying is useful and productive, as long as we are careful to avoid pernicious reification and not insist on the absolute truth of the model. Second, the claim that a toolkit of a few simple models explains most developmental patterns, and that any one of those models can satisfy the explanatory burden of a broad gamut of developmental patterns places an extraordinary amount of explanatory leverage on just a few models. An *explanatory stress*

[4] Kauffman (1993) argues that there are 256 cell types, or $2^8$. But consider B cells of the mammalian immune system. Each human being literally makes millions of new sorts of B cells every day, each with a distinct external protein chain signature. Should these be considered different cell types?

**Table 21.1** Some of the different ways morphogens can act in morphogenesis (Bonner 1982, 219)

TABLE 1 - Reactions which lead to pattern formation (15-17).

| Type of reaction | Pattern which can be generated |
|---|---|
| 1. Local autocatalysis and long-range inhibition (15).   |  Graded concentration profiles  Bristle-like pattern |
| 2. Long-range activation of states which locally exclude each other (17).   |      Stripe-like arrangement of two or more states. |
| 3. Cooperation of compartments. Cell type A produces, e.g., a precursor, cell type B the final product (16). |   A pattern centered over the common boundary is formed. Used to organize subfields such as limbs |
| 4. Local elongation (15), see type 1, and: local maximum causes cell differentiation, differentiated structure repels the maximum. |   Long elongated structures such as veins, tracheae or nerves |

(overextending explanatory resources; trying to explain too much with too little) may be at play here. "Simple and realistic models" may explain some aspects of certain phenomena and regularities, but care must be taken in assessing exactly how and what is being explained. In explaining stripes with these models, do we explain the causal processes underlying relative location and size? Do we explain the physiology of the cell types and the chemical composition of the morphogens in which stripes are instantiated? Are we still explaining or providing grounds for

predicting changes in stripe patterns if we vary animal species or individual genotype? Mathematical modeling in the complex, multi-causal, and empirical life sciences is a powerful tool, but the possibilities of reification fallacies and explanatory stresses means that we must be critically aware of the nature and locations of its limits (Winther 2008, 2011, 2014a, b, under contract).

The mathematical modeling style is also employed in life history theory, which addresses an even higher level of the biological hierarchy. The temporal sequencing and duration of the major milestones in the growth and development of individual organisms is here investigated (e.g., sexual maturity, age at first reproductive event, age of death, and number of offspring). Stephen Stearns' solo essay in the 1982 Dahlem volume, "The Role of Development in the Evolution of Life Histories" (237–258) highlighted three important points about life history theory. First, it "emerged in the 1960s out of the dual traditions of comparative demography and population regulation." Indeed, it was the "second attempt" at formulating a "predictive quantitative theory of evolution—population genetics was the first." Second, Stearns correctly argues that all disciplines and theories contain simplifying assumptions: "whereas population genetics underrates the organism, life history theory underrates the gene. The simplifications of one field are the complexities of the other." Third, the way forward in 1981 (and in 2010; see Stearns, Chap. 6, this volume) was for each field to stop ignoring the other, and to pay attention to development. After all, "developmental mechanisms could connect population genetics with life history theory to form a predictive theory of evolution more powerful than either" (Bonner 1982, 238–239). In essence, Stearns was advocating that Evo-devo become a trading zone, in which various disciplines and other scientific cultures would interact and negotiate theories, instruments, and concepts.

Let us continue the assumption archaeology by examining how the mathematical modeling style remains operative today, influencing ongoing work in Evo-devo at each of the three levels of biological hierarchy described above. With respect to gene regulatory networks, Kauffman and Eric Davidson's research programs are ongoing (e.g., see Huang et al. 2009 for gene regulatory networks and the Evo-devo of cancer; see also Winther 2008, 2009a, 2011). Other biologists interested in Evo-devo (and more broadly in Systems Theory) have incorporated mathematical gene networks (e.g., Alon 2003; Álvarez-Buylla et al. 2007; Junker and Schreiber 2008). At the morphogenetic level, Stuart Newman and Karl Niklas display the mathematical modeling style in their work on the evolution and development of tetrapod limb and plant body plans, respectively (see Newman, Chap. 19, this volume; Niklas, Chap. 2, this volume). Newman and his co-authors build on Alan Turing's (1952) powerful insights of a "reaction-diffusion" system. Morphogenesis is modeled using differential equations with parameters estimating morphogen concentrations as well as cell movement, number, differentiation, aggregation, and adhesion (Newman and Müller 2005; Forgacs and Newman 2005; see Winther 2011). Niklas' investigations concern both morphogenesis as well as life history and the "adaptive aspects of development" (e.g., Niklas 1994, 2000).

> Regardless of this phytocentric bias, my thesis is that the participants of the 1981 Dahlem conference knew that neither biomechanics nor allometry *sensu stricto* could provide mechanistic explanations for the phenomena that occupied their attention because these disciplines lacked mathematical formulations that could make their observational consequences explicit. (Niklas, Chap. 2, this volume)

Niklas attempts to harness the resources of "biomechanics, allometry and network theory" in order "to answer some of the important questions raised during the 1981 Dahlem conference." Note also that he, like most careful mathematical modelers, is well aware of "the intrinsic limitations imposed when using these tools" (Niklas, Chap. 2, this volume). Finally, it is worth noting that mathematical work on life history theory and "adaptive aspects of development" has further broadened, and helped give rise to a new field, Eco-evo-devo (ecological and evolutionary developmental biology; e.g., Gilbert and Epel 2008).

### *21.2.2 Mechanism Style*

The mechanism style takes a functional system and breaks it down in order to understand how it works. The functional system may itself be part of a larger system—i.e., it may be a module (Winther 2001, 2005). Of which (types of) parts does the system consist? How do these parts behave, and what do they cause each other to do? What are the basic theoretical principles governing the parts, as well as the system as a whole?[5] The mechanism style searches for and constitutes mechanisms using four overarching strategies: (1) *analysis*, (2) *physicochemical (PC) reduction*, (3) *causal surgery*, and (4) *mechanism transplantation*.

1. To analyze is to break down or decompose. Analysis is the identification and abstraction of both the parts of a system and the behaviors of those parts. Once analyzed, the parts (and part-behaviors) of a system can be suitably articulated into a mechanism. For Robert Cummins, analysis is both the disarticulation of a system into parts ("componential analysis") and the disarticulation of system capacities into part capacities ("functional analysis") (Cummins 1983, 28ff). For Nancy Cartwright, "the analytical method" in physics is: "to understand what happens in the world, we take things apart into their fundamental pieces" (Cartwright 1999, 83). To analyze is to disarticulate, disarm, disassociate, cut, and divide.
2. Physicochemical (PC) reduction amounts to explaining and understanding biological phenomena, regularities, and principles using physicochemical phenomena, regularities, and principles. In particular, it is a reduction of the (hierarchical and complex) biological level to the principles of physics and chemistry, as well as of biophysics and biochemistry.[6] This strategy concerns *explanations*.

[5] See Valadez Blanco (2011) and Winther (2011) for recent discussions.

[6] For recent work on reduction in the biological sciences, see Wimsatt (2007), Brigandt and Love (2008), and Winther (2009a).

Marcel Weber calls this form of reduction "explanatory heteronomy" (Weber 2005, Chap. 2). Under a broad interpretation, PC-reduction is also very close to the "explanatory reduction" of classical genetics to molecular genetics (and its principles) defended by Sarkar (1998). Molecular genetics is here interpreted as part of biochemistry. PC-reduction is concerned with the reduction of abstract principles and explanations, not of parts and components.

3. To engage in causal surgery is to intervene in a system by removing or controlling the effects of certain parts, and thereby studying how other parts react to that intervention. Such active, experimental intervention is the foundation of how we learn about the behaviors of parts. This strategy concerns *actions carried out for understanding*. For Judea Pearl "intervention as surgery" is causal analysis discussed in terms of a generalized path analysis, with its regression equations and diagrams (Pearl 2000, 346ff, Winther 2014b). Carl Craver (2007) prefers to call this "ideal intervention": "an *ideal* intervention I on X with respect to Y is a change in the value of X that changes Y, if at all, *only via* the change in X" (96). Causal surgery provides us with insight into the workings of the system.
4. Mechanism transplantation is the ultimate test of our understanding and causal surgery capacities. When we can move a part, or a collection of parts, into a new context and have them behave in (close to) the way we predicted, we have verified that our comprehension is accurate. This strategy is about *actions carried out for material construction*: "to control a situation we reassemble the pieces, we reorder them so they will work together to make things happen as we will" (Cartwright 1999, 398). For a purpose different but not unrelated to mine, Ian Hacking writes: "We are completely convinced of the reality of electrons when we regularly set out to build—and often enough succeed in building—new kinds of device that use various well-understood causal properties of electrons to interfere in other more hypothetical parts of nature" (Hacking 1983, 265). In other words, we transplant a part (an electron) into new causal contexts (e.g., machines) and validate that it behaves in the same way.

Each of these strategies is important to the mechanism style. Arguably, only the first three are necessary to identify and understand a mechanism, but the fourth is required to control and construct a mechanism. These strategies are also part and parcel of how we *characterize* a mechanism—that is, a "mechanism" is something that can be, and has been, analyzed, PC-reduced, and so forth.

How is mechanism discussed in the 1982 Dahlem volume articles? It is often used synonymously with *causal process*. For instance, "evolutionary", "developmental", and "genetic" mechanisms are appealed to throughout the volume (e.g., metamorphosis is a mechanism; Bonner 1982, 226). These causal processes are intended to be explanatory. Let us look at just two examples, and apply the four strategies discussed above.

First, the last group report on "The Role of Development in Macroevolutionary Change" (authors include P. Alberch, B.C. Goodwin, S.J. Gould, A. de Ricqlès, G.P. Wagner, and D.B. Wake) states: "perhaps such homeostatic mechanisms are the key to understanding why stasis is encountered in phylogeny" (Bonner 1982, 287).

The group is appealing to developmental systems as "resilient to environmental and genetic perturbations" and as a possible explanatory processes for long-term stasis of species in phylogeny, under the punctuated equilibrium model of Eldredge and Gould. The broad system of a species (i.e., a species-as-an-individual) is analyzed into one of its parts: the development of individual organisms. While analysis is employed, PC-reduction may not be. Causal surgery on, and transplantation of, homeostatic mechanisms is difficult to imagine, but it would not be impossible to set up experiments for the role of developmental homeostasis in speciation, perhaps through chemical or temperature shock that perturbs otherwise robust canalization. A second example—"diffusion-reaction mechanism"—is observable in Wolpert (Bonner 1982, 183) and the last group report (290–293). (This is the mechanism that was modeled mathematically in the above section.) Morphogenic gradients, and cell-type and tissue/organ formation can be measured biochemically. Parts are identified, complex processes are (partly) reduced to physicochemical principles, experimental causal surgery can be carried out, and transplantation into other species is possible. The four mechanism strategies are also satisfied for the "genetic mechanisms" determining "heterochronic shifts" (Bonner 1982, 2) or the "specification of body pattern" (192). Further assumption archaeology of the mechanism style in Evo-devo today (e.g., David Stern's research program on *cis*-regulatory elements in Drosophilids; Stern and Orgogozo 2009) would shed light on the power of causal and experimental analysis, and on the rich relations of this style to other styles.

### *21.2.3 History Style*

The history style in the biological sciences aims to present the narrative or biography of a part, placing it in its organizational and causal whole; this biography is justified by a phylogeny (see Winther 2006a, 2011). Here we consider two general sorts of parts: (1) a part of an organism, and, (2) a species as a part of a clade and an ecosystem.

Consider first a part of an organism. There is a well-known narrative about the evolution of the inner ear in mammals from the first two gill arches—the "visceral arches"—of agnathans ("jawless" fish) *via* the throat skeleton and stapes of early tetrapods (Radinsky 1987; Olivier Rieppel, personal communication). In this biography of the inner ear, the "central subject" (Hull 1989) of the narrative is placed in the context of the organism. The historically changing dynamics and topological organization of the inner ear with respect to surrounding organs and tissues are investigated, recognized, and weaved into the biography. Moreover, the central subject's changing functions (and associated selective pressures) are also explored and incorporated into the narrative. Form and function are intertwined; comparative morphology, functional morphology, and life-history theory are integrated (Wake 1979; Winther 2006a, b). A phylogeny—the abstracted and postulated

ancestor-descendant relations—is the necessary theoretical background to this morphological and functional biography. In order to trace the changing content and context of the central subject, we must know the history of the species in which it is found.

Second, consider the narrative of an entire species. It also is articulated in a specific context—its clade and ecosystem. The species' biography includes (i) who it came from (its ancestors) and who it gave rise to (its descendants), and (ii) to whom it is related in a nested manner (its clade). Depending on the philosophy of systematics, (i) and (ii) are related (e.g., process cladism, many Bayesian schools) or utterly distinct (e.g., pattern cladism) matters (Hull 1988; De Queiroz 1988; Sober 2008). Furthermore, the biography includes an account of the selective and ecological pressures to which the species is subject. A given species' history and environment are necessary components for telling a justified and coherent narrative of a species.

In the 1982 Dahlem volume, considerations of history and systematics are sparse and phylogenetic reconstruction is dramatically undertheorized. There is no mention of cladism or cladistics (see below, Sect. 21.3). The term "classification" is rarely used, and then only for the classification of mutations (Bonner 1982, 196; e.g., "homeotic mutations") or "styles of heterochrony" (334). The term "phylogeny" is a little more frequent, but is used in a vague and general manner. The only drawn phylogenies (97) are highly abstract (and now quaint) representations of deuterostome and protostome relationships, indicating the presence or absence of metamerism. Phylogenies are significantly more standardized and formalized today. Even the term "history" is almost absent (apart from its use in "life-history"). "Systematics" is used only once, almost ironically, in Alberch's contribution. The explicit use of, and reflection about, the history style is absent, which is curious for at least three reasons: (1) some of the biologists at the 1981 Dahlem conference (e.g., Raff, de Ricqlès, Wagner, and Wake) did phylogenetic work then and subsequently; (2) the history style became very important to Evo-devo subsequently; and, (3) the "cladistic wars" were raging in nearby professional contexts.

In light of the above observations, a range of interpretations is possible, so I informally surveyed some of those who had been present at the 1981 Dahlem conference for their recollections. All of those whom I surveyed ($n = 5$) agreed that there was no explicit discussion of phylogeny, classification, systematics, or history at the workshop. But they disagreed as to why. Some felt that historical considerations were not deemed important by the participants of a workshop focused explicitly on developmental mechanisms rather than on technical issues in phylogenetic reconstruction (i.e., *phylogeny was not part of the problem* view). Others thought that history was indeed judged to be significant, and was seen as an indispensable part of the attempt to incorporate mechanism, constraint, and heterochrony/allometry into evolutionary theory, but that history either was already a "core principle" not requiring special attention or the correct general outline of a single phylogeny was already at hand, and further work would not change that outline significantly, a position also found in Dobzhansky (1937) (both of these can be summarized as *we already have the admittedly important phylogeny*).

The importance of history for Evo-devo was not fully appreciated by many of those present at the 1981 Dahlem conference and may hint that mechanism and constraint were overemphasized.[7]

## 21.3 Paradigms in Evo-devo: Structuralism, Adaptationism, and Cladism

A classic analysis of another type of scientific culture is Kuhn's "paradigms". Paradigms are also frameworks or ways of looking at the world. They are guided by styles, and nested within them; they are more specific than styles, or even than style hybrids. Paradigms employ particular methods and theories, are motivated by certain questions and meanings, and emphasize (as well as reify) specific sorts of objects and processes.

There is no simple definition of the concept in Kuhn's work. But Kuhn's (1970 [1962]) first use of it stated that paradigms stemmed from the "classics of science," especially the work of great theoretical innovators, including Aristotle, Ptolemy, Newton, Lavoisier, and Lyell. The term is polysemous, and Kuhn used it to mean at least:

1. A specific and standard *exemplar*, including a new mathematical procedure (e.g., "Maxwell's mathematization of the electromagnetic field") or experimental set-up (e.g., "Lavoisier's application of the balance," 23).
2. The *general framework* ("disciplinary matrix", 1969 postscript, 182) with various components, including: laws and symbolic generalizations (e.g., $F = ma$), ontological assumptions, values (e.g., theoretical/epistemic virtues, such as simplicity and scope), and exemplars.
3. The *sociological community* embedding and co-constituting the paradigm. While Kuhn distinguished theoretical and experimental practices and products from the community of origin within which they were shared, this third sense of paradigm appeals directly to the composition and practices of the social group in order to individuate a paradigm (see Masterman (1970) on "sociological paradigms.")

Under a paradigm's guidance, "normal science," with its associated activity of "puzzle-solving," occurs. Most of science is normal, but anomalies do accumulate. When there are too many, or the anomalies are too significant (or both), a crisis ensues. The resolution of a crisis is often a revolution, with the adoption of a new

[7] A more complete archaeology of the history style would require further investigation of the way history, and cladism in particular, became incorporated into Evo-devo. This would include looking at ways in which initially open and exploratory theory became stabilized into standardized computer platforms and molecular biotechnology that could produce phylogenies at industrial scales.

paradigm. On rare occasions, a crisis can defuse with the old paradigm declaring victory.

Thus, paradigms are frameworks constituting and periodizing the historical scientific process. They consist of (1) symbolic generalizations, (2) ontological assumptions, (3) values, (4) exemplars, (5) sociological communities, and also, I argue, (6) specific theories and experiments, (7) acceptable research questions, and (8) (partly reified) objects and processes (see Winther 2012). Analyzing these paradigm components is one burden of an assumption archaeology. I now will characterize three operative paradigms in Evo-devo by pointing to their components (ignoring exemplars since they were not pertinent to the 1981 Dahlem conference). My treatment is not balanced: the relation between adaptationism and structuralism will be explored; the cladism paradigm will only be sketched.

### *21.3.1 Adaptationism Paradigm*

The adaptationism paradigm holds that "the fit" between organism and environment is the most important problem in evolution. Moreover, natural selection is considered the strongest explanatory principle in evolutionary theory. Adaptationism is associated with a variety of theoretical and experimental methods (e.g., game theory and optimality modeling), and objects and processes (e.g., atomized adaptations, as well as directional, disruptive, and correlated selection). Here is a formulation from Gould and Lewontin (1979):

> [Adaptationism] regards natural selection as so powerful and the constraints upon it so few that direct production of adaptation through its operation becomes the primary cause of nearly all organic form, function, and behavior (584–585).

Gould and Lewontin's well-known critique of the "adaptationist programme" (or "Panglossian paradigm") focused on how this paradigm was imperialistic in its exclusion and subordination of other explanations and paradigms (e.g., structuralism and history). Moreover, they accused the paradigm of frequently committing a reification fallacy. That is, adaptationist thinking first postulates atomized traits, and subsequently believes in their true and independent existence (cf. John Dewey's "the philosophic fallacy," discussed in Winther 2014a). Indeed, the maintenance in natural populations of these traits is now seen as requiring explanation. The move from postulation to objectification is a reification. However, the adaptationism paradigm is also creative and generative, and remains (and was always) operative and relevant. Indeed, it highlights important aspects of the natural world, while its perceived competitor paradigm—structuralism—emphasizes others. Ultimately, these two paradigms act collaboratively in the Evo-devo trading zone.

Adaptationism is a paradigm with the theories and methods, objects and processes, and ontological assumptions mentioned above, and more. But one can also be an adaptationist with respect to distinct sorts of questions. It might be useful to explore the multidimensionality of the paradigm, rather than just its core. It is in this

multidimensionality that the collaborative aspects of the paradigm come to the fore. Godfrey-Smith (2001) distinguishes between *empirical*, *methodological*, and *explanatory* adaptationism. Empirical adaptationism focuses on the causal ubiquity of natural selection. This interpretation of adaptationism answers "natural selection" to the question: what is the most important and prevalent evolutionary causal factor? Methodological adaptationism focuses not on nature, but on research programs—"adaptation is a good 'organizing concept' for evolutionary research." (337) This kind of adaptationism answers "adaptation" to the question: which phenomenon or concept is best for organizing our perspective on nature? Explanatory adaptationism also focuses on science, but this time on what is interesting—design and adaptedness "are the *big questions*, the amazing facts in biology." (336) In short, these three interpretations of adaptationism focus, respectively, on nature, the structure of research, and the explanatory interest of research. Godfrey-Smith's analysis provides a nuanced picture of the multidimensionality and flexibility of adaptationism. When research commits to all three interpretations, to the exclusion of other questions, adaptationism becomes *imperialist*. When research adopts one or another kind, but remains open to other different types of questions, adaptationism is *collaborative*.

The adaptationism paradigm, as it gets used in Evo-devo and elsewhere, is guided by all three styles (Sect. 21.2). Mathematical modeling is commonplace. The "calculus and algebra of frequencies" is essential to a paradigm concerned with fitness and changes in relative gene frequencies. Mechanistic analyses identify the objective (rather than reified) characters to which we ascribe adaptation; mechanistic investigations also "increase the strength of inferences regarding the evolutionary history of characters and their adaptive consequences" (Autumn et al. 2002, 383). The history style is necessary for stating which characters are derived, and might thereby be present due to (possibly strong) selective forces.

### *21.3.2 Structuralism Paradigm*

The structuralism paradigm emphasizes the development and organization of kinds of parts of a system typically understood as self-organizing. Parts—or rather kinds or equivalence classes of parts—are connected and mutually dependent in complex and hierarchical ways. This paradigm often appeals to both mathematical laws of development and physicochemical morphogenetic mechanisms, and is guided by mathematical modeling, history, and mechanism styles. This paradigm has a long tradition in the post-Darwinian English-speaking world, starting with William Bateson, D'Arcy Thompson, and Joseph Woodger in the early twentieth century, and continuing through to many of the participants at the 1981 Dahlem conference. This tradition is the *sociological paradigm* (see above, Sect. 21.3) of structuralism. Structuralism has roots in the transcendental morphology of Goethe and St. Hilaire, and even in Kant's view of the organism as a purposive whole, as defended in his third Critique, *Kritik der Urteilskraft*.

The structuralism paradigm has multiple components. With respect to *form*, Olivier Rieppel writes: "structuralism comprehends biological structures in terms of constituent elements and their relations to each other" (Rieppel 1990, 299). Both the parts and the relations among them are critical. D'Arcy Thompson warns against focusing exclusively on the parts: "As we analyse a thing into its parts or into its properties, we tend to magnify these, to exaggerate their apparent independence, and to hide from ourselves (at least for a time) the essential integrity and individuality of the composite whole" (1961 [1917], 262). Structuralism's commitments to emergence, complexity, and non-linearity are in contrast with the atomism, reductionism, and additivity of adaptationism. With respect to developmental and morphogenetic *process*, Alberch's contribution to the 1982 Dahlem volume identifies "three interacting levels":

> Level 1—the genome itself is compartmentalized and highly integrated. . . Level 2—There are second order interactions among enzymes and proteins which interact and assemble themselves according to physicochemical laws. . . . Level 3—Tissues can also interact in complex ways and according to sets of well-defined rules. (Bonner 1982, 320)

Note the appeal to "laws" and "rules" in this three-tiered nested division of form (i.e., parts and part-organization) and process (i.e., development and morphogenesis). Indeed, under the structuralism paradigm evolution itself is sometimes redefined: "evolution can be viewed as the process of phenotypic transformations resulting from the genetically mediated perturbations of these basic developmental parameters through phylogeny" (322). The meanings of key terms can change across paradigms (Amundson 2005).

Structuralism has all the hallmarks of a paradigm in the 1982 Dahlem volume. It has a variety of theoretical and experimental methods (e.g., the mathematical and biochemical/cellular identification of a few simple rules of development and morphogenesis) and objects and processes (e.g., constraints). Exemplars include limb bud development and morphogenetic gradients/positional information, which were discussed extensively (e.g., "the Cellular Basis of Morphogenetic Change" group report, authored by, among others, J.C. Gerhart, C. Nüsslein-Volhard, G.F. Oster, G.S. Stent, and L. Wolpert, and Wolpert's solo contribution, "Pattern Formation and Change"). Values include simple and unified explanations, and an attention to the whole organism rather than to atomized parts (see Wagner, Chap. 15, this volume). Ontological assumptions include definitions of evolution and process, as well as an emphasis on what requires explanation—i.e., the integration rather than the design of organisms.

The three styles guide structuralism in a different manner from how they guide adaptationism. The mathematics of structuralism is analytical geometry and the "calculus of space." Transformations in space, grounded in physicochemical mechanisms of temporal morphogenesis, are essential. Some structuralism is anti-historical (e.g., Brian Goodwin), but much structuralism appeals to the historical (meta-)transformations of developmental transformations. Phylogenetic information is necessary to make meaningful statements about how changes in form and process happen over long-term evolution.

### *21.3.3 Adaptationism and Structuralism: Collaborations ca. 1982*

Many controversies in the life sciences are "relative significance disputes" (Beatty 1997), in part because multiple types of causes must be taken into account to explain complex systems. I distinguish between two forms of relative significance disputes: *zero-sum* and *complementarity*. These are associated, respectively, with *imperialist* and *collaborative* interpretations of a paradigm. I contend that Lewontin and Gould critiqued only a zero-sum, imperialist version of adaptationism. We can comprehend these two related distinctions more deeply by looking at adaptationism in its various guises in the 1982 Dahlem volume. First, there is an explicit critique of imperialist adaptationism in the last group report on "the role of development in macroevolutionary change," which was written by researchers such as Alberch, Goodwin, Gould, Wake, and Wagner. In discussing the "theories of evolutionary genetics", which rely on natural selection, the group report states:

> Yet for many of the changes that we know did occur in evolution, it is difficult to discern what must have been their relation to adaptation, and we should examine the possibility that they resulted from components of systems of developmental, architectural, and functional constraints (cite to Gould and Lewontin 1979). (Bonner 1982, 295)

Underlying this critique is a zero-sum perspective: changes and characters arise either through adaptation or through constraints. Selection and constraints are mutually exclusive and collectively exhaustive causal factors. When the adaptationist paradigm is seen as an imperialist foe, it is common for its critics to endorse a zero-sum perspective and claim that *some*—indeed *many*—evolutionary changes require explanations that appeal to internal factors, rather than to natural selection. Gould continues this form of critique in his 1982 solo chapter.

However, a different attitude focusing on the complementarity of causal factors, and on collaborative adaptationism, is also present in the volume. In his chapter, Alberch writes: "internal correlations and constraints might impose directional change and they can be a mechanism for the origin of new morphologies and for drastic structural rearrangements that open up a new adaptive realm for the organism" (Bonner 1982, 330). Here, constraints interact with adaptive demands, and the two factors (and explanations) are interpreted as complementary rather than as zero-sum. Adaptationism is understood as collaborative rather than imperialist. The group report on "Adaptive Aspects of Development" also emphasizes collaborative adaptationism. The group insists on adaptation being "inherently comparative" (215) in two senses: an adaptive developmental pattern is comparatively better than others in a given environment, and an adaptive developmental pattern has an environment in which it is best, compared to other environments. Gould and Lewontin's critique is mentioned, as are worries about "epistemological difficulties" of the concept of adaptation, such as "circularity, teleology, or unfalsifiability" (216). However, the group argues, if the comparative notion of adaptation is taken to heart, these difficulties can be lessened. Moreover, comparative analyses of adaptation ground predictions and "provide[. . .] an observational setting that is

the logical equivalent of experiment and control" (216–7). The group's adoption of a complementarity perspective emphasizes emergent and non-linear causal (and explanatory) interaction between selection and constraint. The structuralism paradigm collaborates with the adaptationism paradigm by making explicit the dynamics underlying "evolutionary opportunity" and "flexibility" (217) with which selection may act. Despite this potential for complementarity, the ongoing relation between structuralism and adaptationism, in Evo-devo and elsewhere, is a complex love-hate relationship.

One final analytical point regarding language in the context of relative significance disputes is worth making. Under the former zero-sum perspective and dynamics, concepts such as "constraints" and "selection" are typically used with radically different—and perhaps incommensurable—meanings by adaptationists and structuralists (e.g., see analysis in Amundson 2005). Distinct languages flourish on different discursive islands. In contrast, according to the attitude of complementarity, at least some discursive market places exist to hash out shared meanings across paradigms. Creoles can emerge in the collaborations of trading zones.

### *21.3.4 Cladism Paradigm*

The cladism paradigm holds that taxonomies must reflect the evolutionary process as captured in phylogenetic trees, and that parsimony is the best method for inferring such trees, called cladograms. In order for our classifications to be natural and objective, they must refer to the systematizations captured in cladograms, which show a nested clade structure. One central aim of cladism is thus to provide natural phylogenetic classifications. As Darwin (1859 [1964], 420) wrote: "all true classification is genealogical." Following Mishler (2009), and the work of David Hull (e.g., Hull 1988), Elliott Sober (e.g., Sober 2008), and others, it can be argued that cladism is a paradigm that was born in the work of Willi Hennig and continues in a robust fashion with a range of methods for character analysis, phylogenetic inference, and naming (see also De Queiroz 1988; Doolittle 1999; Winther 2009b). The cladism paradigm was not evident at the 1981 Dahlem conference, but through an increasing emphasis on phylogenetic reconstruction, it has come to play an important role in Evo-devo research (e.g., Wagner 2000; Hall and Olson 2003). Therefore, even though adaptationism, structuralism, and cladism are all operative in Evo-devo today, only the first two were clearly evident in 1981, whereas the influence of cladism for conceptualizing the relationship between development and evolution was no more than immanent.

## 21.4 Evo-devo as a Trading Zone

Evo-devo is an ambitious, integrative, and interdisciplinary domain. Its problems and questions are multi-faceted. The biological reality it explores is complex. As a consequence, Evo-devo requires the operation of many styles and paradigms,

which in turn demands bringing together a variety of cultures. Other domains are undoubtedly also trading zones in this sense (e.g., genomics and climate modeling), but Evo-devo is philosophically interesting because it brings together some of the greatest theoretical questions of biology pertinent to function, form, process, and history. It cannot be understood without knowledge of a broad diversity of the most advanced theories and experiments in the biological sciences. Evo-devo trades across cultures and, precisely because it does so, we can identify a trading zone at its intersection of multiple, complex levels of abstraction (e.g., styles and paradigms).

Adaptationism and structuralism are negotiating intensely in the trading zone of Evo-devo. In the past, there was primarily segregation. Different national and philosophical contexts tended to stress one paradigm to the detriment of the other (e.g., Germanic contexts are more structuralist, Anglo-American more adaptationist). Moreover, evolutionary questions usually have been asked within the adaptationism paradigm, and developmental questions within the structuralism paradigm. Tools also differ radically: mathematical modeling has been common to adaptationism, mechanism to structuralism. (Here the difference is smaller as each paradigm also employs the other style.) Evo-devo has provided a locus where collaboration, mutual understanding, and integration between adaptationism and structuralism can and does occur—they are no longer allowed to ignore each other. Indeed, it is a mistake to critique Evo-devo *tout court* from the (imperialist) adaptationism often found in evolutionary genetics (e.g., Hoekstra and Coyne 2007). Mathematical modeling tools (e.g., simulations, closed-form analytical equations, and statistical tests), as well as instruments and experimental protocols from molecular biology and biochemistry, are shared across paradigms within Evo-devo. For instance, genomics and developmental biology have influenced standard evolutionary theory, as seen in the research programs of Scott Gilbert and Günter Wagner. Moreover, mathematics from evolutionary genetics is used to understand development in Maynard-Smith and Szathmáry (1995) and Michod (1999). Sometimes the inter-paradigm dynamics are collaborative and integrative, and mutual understanding occurs, particularly when explanatory labor is divided. At other times, miscommunication, incommensurability, and fragmentation are rampant, especially when terms exhibit different meanings or tools and theories have explicitly different goals and content. All of this is exactly what we would expect from an active trading zone. And let us not forget competition and fighting—a shared perspective with common aims and questions is still being built. But the key point is that these paradigms will continue meeting and interacting in the Evo-devo trading zone.

The cladism paradigm has been integrated into Evo-devo. This was not evident in 1982. History was understood to be a core principle by many at the Dahlem meeting, but the relevance or possibilities for success of the nascent cladistic revolution in the 1970s and early 1980s were not evident. Today, phylogenetic reconstruction is commonplace in Evo-devo and elsewhere. The large-scale phylogenetic branching patterns of metazoans had to be tested and redrawn (Raff, personal communication). If adaptation is "inherently comparative" (Bonner 1982, 215), then a correct phylogeny with which to formulate comparisons of potentially

adaptive characters across taxa is necessary. And if, as Gould claims, "development has a special 'relevance' to macroevolution insofar as it imposes styles of evolution departing from the extreme Darwinian notion that virtually all change is a result of natural selection working on a spectrum of small, random variation" (Bonner 1982, 337), then a correct phylogeny is necessary to determine the overall macroevolutionary pattern and thereby show where developmental "styles of evolution" may be operating. Every hypothesis, or set of hypotheses, concerning adaptation or developmental pattern requires a referent phylogeny in order to be testable. Due to the internal logic of Evo-devo, the cladism paradigm became intertwined with adaptationism and structuralism. The meeting and rich negotiation of these three paradigms occurred for the first time in Evo-devo. It may even be definitional of Evo-devo to say that it is the trading zone where these three paradigms negotiate, sometimes without success, but often with high pay-off.

Styles are self-vindicating in that they produce and stabilize their own culture (Hacking 2009). There is a vicious side to this: the methods can become an end in themselves and lose their relevance and empirical adequacy, such as when the ongoing articulation of mathematical modeling becomes the ultimate goal rather than its application to biological phenomena. But there is also a useful side. Styles can mature, develop tools and theories, and grow stronger when they meet and interact. This is especially true given the questions and goals of Evo-devo. Consider the collaborative relationship between the mathematical modeling and mechanism styles. The first is "theoretical", the second "experimental." In many studies, the former makes predictions and tells us where to look. Mathematics can only hint at underlying causal mechanism. Causal surgery is necessary to identify these. History (built with molecular *and* morphological data, e.g., Winther 2009b) can predict the taxa in which we might expect to find a mechanism acting. But again, only actual searching will reveal the mechanism. Thus, theoretical predictions are produced by math and history, but verification through actual mechanism identification and characterization is ultimately required.

Finally, there are the relationships between styles and paradigms in a trading zone. Each paradigm is guided by each style. In other words, there are many-to-many relations between styles and paradigms. More specifically, styles are *multiply realized* in distinct paradigms. The latter instantiate the former—paradigms express all the assumptions of styles, and also are more specific. We saw in Sect. 21.3.3 how structuralism and adaptationism each coordinated the three styles in unique ways. The complex trading zone is such that the different styles are negotiated in distinct manners for each paradigm.

To summarize, in this chapter I have argued that Evo-devo is a trading zone. The method of assumption archaeology can help us understand how three paradigms and three styles interact intensely. They overlap richly within and across levels of abstraction. A specific trading interaction may be between just two cultures, but a trading zone is a domain of interaction among multiple cultures, at several related levels of abstraction. Competition exists. Many deep rifts, misunderstandings, and miscommunications remain. The cultures are still sometimes fragmented. But collaboration, mutual understanding, and integration are in

progress and desirable. I have descriptively identified Evo-devo as a trading zone and undertaken assumption archaeologies of some of its foundational assumptions.

Many outstanding matters, and possible limitations, remain. What are the institutions and instruments, goals and costs/benefits, associated with each culture (see Gerson, Chap. 20, this volume)? How might the cultures here excavated ca. 1982 transform over time? A complete assumption archaeology requires analytical angles from sociology, history, political science, economics, and ethics. Moreover, possible limitations of my analysis must be considered. Might these cultures evaporate or disappear—or crosscut too richly to individuate—if and when we perform micro-sociological and detailed historical studies of the different individuals, labs, and "cultural" contexts involved? If so, does this disprove my paper's thesis that Evo-devo *is* a trading zone? What else might Evo-devo, broadly construed, then be—a "domain" à la Shapere (1977), a "scene of inquiry" with "questions" à la Jardine (2000), etc.? Finally, pivotal normative questions remain. Which institutional, political, experimental, theoretical, and ethical constellations should and must be in place to achieve mutual understanding and integration? Is synthesis worthwhile? Where do we want the busy and blooming trading zone of Evo-devo to go, today and tomorrow?

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