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# DNA Information: Laws of Perception

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# Preface

The suggestion to write this booklet was provoked by our article published in one of the Springer journals and describing the DNA double helix as a coding device carrying two logically distinct types of information. The idea behind this is over a decade old. In the experiments carried out in mid-1990s together with Andrew Travers and Malcolm Buckle, we stumbled over a striking phenomenon indicating that during the injection of DNA binding proteins into a flowcell with surface-immobilized DNA fragments, the DNA molecules successively adopted different dynamic configurations. These distinct configurations were directly pertinent to regulation of genetic function and thus, embodied information, but in contrast to the genetic code, this information was not discrete, but rather continuous, as it depended by large on the distribution of torsional strain in the DNA molecule. To distinguish this latter from the digital genetic code, the continuous DNA information was subsequently dubbed analog code.

In principle, the relationship between the analog and digital DNA codes is akin to the relationship between the syntax and semantics of natural language. It occurred to me that a closer examination of this remarkable similarity between the most ancient coding device and the most recently invented means of social communication was worth trying. But how can one bridge so widely disparate phenomena? It was clear from the outset that the booklet would deal with information in a most broad sense, and that the definition of the term "information" would be crucial for the entire enterprise. I took advantage of Gregory Bateson's definition of information. In common sense, information is something that is transmitted, but Bateson maintained that for example, for the tax office an unpaid tax bill is also information, although in such a case, nothing is being transmitted.

In this booklet I argue that application of the double-coding principle of DNA information to various fields of scientific inquiry enables to relate widely disparate phenomena within a common exegetic framework, with a notable caveat that distinct types of information cannot be grasped simultaneously. This peculiarity can be fathomed by the Hindu concept of *Adhyasa,* describing oscillation of the mind due to ambiguity in identifying, whether an object on the road is a snake, or a rope. This phenomenon of oscillation of our perception obtains a deeper meaning with examples from natural science and especially, the indeterminacy principle of quantum physics. In all such cases one inference excludes the other, and this has in turn a genuine similarity to the problems caused by logical paradoxes. And as I try to show in this booklet, all this has something to do with our perception of time.

In a nutshell, this booklet is an attempt to show that the basic device of creating information in the living world, including our perception and social communication, is already provided in structural organisation of the DNA molecule, which alike the human mind, has a property of both, distinctness and wholeness to it. I surmise that it is this highly elaborate double coding mechanism with two structurally coupled codes mutually determining each other, which provides for the wholeness that no artificial device can ever attain.

I am grateful to Beatrice Menz for motivating me to write this booklet and to Jutta Lindenborn for her care and professional assistance. I am greatly indebted to my colleagues, especially Andrew Travers to whom I owe a lot, and the members of my laboratory for the countless discussions of many of the topics addressed in this booklet. I am grateful to Marc-Thorsten Hütt for his comments on regulatory networks, to Levan Muskhelishvili for helpful comments on the contents of the manuscript, and to Joel Wellbourne-Wood for editing the text. I owe a debt of gratitude to the late Vasil Makhaldiani for coining the term “optimal cooperation”. To his memory I dedicate this book.

Bremen Georgi Muskhelishvili

# Contents

# Chapter 1
# Introduction: Some Facts About Our Universe

> *Einstein: This is a purely human conception of the universe.*
> *Tagore: There can be no other conception. This world is a human world—the scientific view of it is also that of the scientific man.*
>
> —When Einstein met Tagore

**Abstract** The scientific “truths” appearing as coherent constructions connecting the scientifically verified observations by the rules of logic are always relative and never absolute. Furthermore, there is a generic limitation of the theories and abstract models of reality as such, which become overly conspicuous in the attempts to epitomize the process of life. This is simply because life is something most real and tangible to us. Strictly speaking it is our direct experience, such that life and perception are inseparable and therefore, the device of our perception yields the only model-free approach to the process of life. Only if we choose our perception as a guide and observe ourselves unobstructed by any preconceived ideas, we do not violate our own nature. Therefore, we shall get to grips with operation of a most ancient type of information-generating device materialized on this planet and relate its organizational logic to the operation of our perception.

**Keywords** Epistemology · Abstract knowledge · Perception · Information · Paradigm shifts · Distinction and directional choice · Animate and inanimate matter · Dissipative systems

The age of our Universe is estimated to be about 13.8 billion years. The time elapsed after the emergence of life on our planet approximately corresponds to the last quarter of this cosmic period. Human beings have been on stage for only about 0.1 % of the entire time since the origin of life, whereas the period of human civilization (ca. 6000 years) comprises about 2 % of the time elapsed after the emergence of “primitive” men. While our scientific data concerning the physical world grew exponentially during the last 100 years or so, the total matter made accountable by elementary particle physics comprises just a few percent of the entire known Universe. The rest, called “dark matter and energy,” remains unknown.

The human body is a universe on its own right. Whereas we all originate in a unique fertilized egg, our body contains about a hundred trillion of cells in total, and our intestine accumulates a tenfold excess of symbiotic (friendly) bacterial cells —the microbiota. Our brain—the assumed “hardware” of consciousness, engaged

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in trillions of communications—contains only 0.1 % of the body's total cells, of which we have about 200 different categories. Each single cell (except the red blood cells and gametes) harbors the same conglomerate of 46 chromosomes containing our genetic material—the DNA, which played an essential role in the evolution of life. Disorders such as cancer, diabetes, color blindness, autism, anxiety, dementia, schizophrenia (to name just a few), as well as our cognitive abilities and even our personality have been linked to the properties of the DNA. While the total length of the DNA sequence in each human cell nucleus is about 3.0 billion base pairs, the function of only a few percent of this sequence is known. The rest, by analogy, represents the "dark matter" of our "genetic universe."

## Information as a "Difference that Makes a Difference"

> *All experience is subjective.*
>
> Gregory Bateson

Perhaps it would not be too misleading to say that the introductory paragraph above contains some of the more or less deliberately chosen "facts" reflecting our present-day knowledge, provided as separate messages, or chunks of information. Of such chunks, we may know quite a few but certainly not all, as their number is overwhelming. And perhaps nobody would negate that both individually and also collectively we accumulate knowledge in our memory and its "extensions" as it were,—the libraries and servers, storing information that in principle, can be retrieved on demand (with the notable caveat that what we recall from our memory, is never exactly the same as it was before). Neither would it be an exaggeration to say, that nowadays, we literally feed on information. And while at least on some occasions we rely on our instinct, our instinctive behavior is thought to manifest acquired information, which by "internalisation" became constitutive over the evolutionary time (Jung 1968). However, instinctive behavior is not a human privilege, and if it recapitulates the most ancient information, we might wish to know, how a living being can generate information in the first place. And so it is, that this booklet is about the biological roots of information, and the ways it is inscribed in the central molecule of heredity—the double helical polymer of the DNA. In particular, it attempts to get to grips with operation of a possibly "simple" genetic system as an ancient type of information-generating device materialized on this planet and relate its organizational logic to the operation of our consciousness, which—unless otherwise stated—is regarded throughout this booklet primarily as *perception*.

For this undertaking, we need to clearly define the notion of "information" as we use it here in the first place. Literally, information is something that "in-forms" us. Gregory Bateson observed that in most general terms information could be defined as a "difference that makes a difference" (Bateson 1979). In other words, information is any difference that we can be made aware of. From this very general definition, it necessarily follows that as an antecedent of *information* we have to assume some kind of undifferentiated state, homogeneity or unity, within which *parts* can be discerned and perceived as different. It is then obvious that in turn, such discriminative perception implies a developed capacity of drawing distinctions (Maturana and Varela 1987).

## Abstract Knowledge *Versus* Direct Perception

> *We should keep in mind that life is not something abstract but something extremely individual.*
>
> Søren Kierkegaard

One may argue that among the various cultural traditions of exploring the world, scientific exploration is the main source of valid information available to us. The philosophical stance of science is grounded in the belief that information about the world lends itself to an uninvolved (that is, untouched by any internal or external influences) and unbiased (that is, exempted of any constraints or limitations) *objective* observer by serendipity. But how unbiased is the observer really, and how valid is the obtained information? Karl Popper, for example, maintained (as Darwin long before him) that an observation has to be for or against some kind of (preceding) hypothesis to be of any service (Popper 1972). For Ludwig Wittgenstein, the scientific inquiry belonged into the domain of so-called “language games,” meaning that the particular terms are justified only by the rules of their use in a given field of inquiry (Wittgenstein 1953). Similarly, it has been argued that the specific terms used in different fields of science and corresponding to disparate phenomena under their scope, are themselves decisively contributing to the explanatory power of the theory in which they figure, being thus true only by definition (Rosenberg 2000). Put another way, the answers to scientific questions are already decided by the choice of the framework in which they are asked (von Foerster and Pörksen 2013). Certainly there are general laws such as the law of gravity, which we perceive naturally (irrespective of its past, present and any future interpretations), but again this law is irrelevant for example, in molecular biology. Accordingly, the attempts to explain genetic phenomena by rules of gravitation are rare.

Furthermore, all scientific hypotheses and theories represent constructions of thought that are based on the rules of logic, whereas the universal propositions of logic themselves have no experiential basis but are given *a priori*, prompting Wittgenstein to describe logic as transcendental (Wittgenstein 1921). More specifically, logic as such is not about the truth, but rather about the true relationships,[1] and unless meaning is mapped to its propositions, logic itself contains no information whatsoever (Bateson 1979). Therefore, the scientific “truths” appearing as

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[1] Consider the logical expression “It is either raining or not.” This expression is always true, independent of the actual weather.

coherent constructions connecting the scientifically verified observations by the rules of logic are always relative and never absolute. And that is a good thing, because otherwise, the entire scientific enterprise would be doomed to stagnation.

Needless to say, science is a highly dynamic realm striving at vast generalizations and ultimately, at the construction of a *Theory of Everything*. However, it was observed that scientific theories, consolidated and passed over by generations of scientists in the form of global paradigms, periodically suffer a dramatic change (Kuhn 1973). This is perhaps inevitable, because all models and theories are products of our creativity, and creativity naturally proposes a change. Yet what primarily concerns us here is the generic limitation of the theories and abstract models of reality as such, which become overly conspicuous in the attempts to epitomize the process of life. This is simply because life is neither an abstract model, nor a theory, but rather something most real and tangible to us. Strictly speaking it is our direct experience, such that life and *perception* are inseparable and therefore, as a matter of fact, the device of our perception yields the only model-free approach to the process of life. Put in other words, only if we choose our perception as a guide and observe ourselves unobstructed by any preconceived ideas, we do not violate our own nature. Such a direct approach without any prejudiced notions, as to what the living beings are, is worth picking up as a starting point for a quest—at least to see how far we can go. In the following we shall, then, be primarily concerned with the operation of the basic device of our perception and its impact on *the way we observe*.

## Distinction and the Directionality of Choice

> *Our machine is so arranged that there are no separate places where different things can be experienced simultaneously.*
>
> G.I. Gurdjieff

It has been argued from ancient times that for a solitary mind incapable of perceiving with the consciousness of the others, it is impossible to decide with certainty whether the mind is in the world, or the world is in the mind. The obvious reason is that subjectively, we cannot tell whether the appearance of the world precedes the appearance of the consciousness, or other way around. Alas, no intellectual gymnastics can help us here, simply because the world and consciousness never appear in separation, as essentially they are *one* (Wittgenstein 1921). From this view, it is conceivable that the longing of Robison Crusoe for a soul mate (Friday) on his remote island was primarily dictated by the need of a witness ensuring him that the world does not perish when he falls asleep, for he could not prove it to himself. Certainly, Friday can be consoling, yet not of much help to decide on this matter, because he in turn needs a witness for himself. In fact, the posed question belongs to the so-called undecidable questions, for which the solutions vary with each epoch and creed, since no definite answer can be given (von Foerster and Pörksen 2013). And since without a witness, no one can answer this question decisively, all that one can do is to *believe*.

At this point, it is important to recognize that although this undecidability is a purely subjective condition, it does not entail a solipsist view, because this condition is *impersonal* and in that sense it is objective to an extent, as anything else can be. Objectivity, if anything, is a realm in which our subjective experiences overlap.

It is worth mentioning in passing that distinct attitudes to this constitutional undecidability inherent to our mental device are manifest in the polarity of the oriental and occidental worldviews, the former being more introspective and the latter more zealous about "outer world." Be it as it may, the unquestionable fact is that every day on awakening after a deep sleep from our mental and sensory deprivation, we become aware of the world (that is, we acquire perception) by an act of distinction between our "self" and the "world" (coming to the mind, for example, in form of a cup of coffee). And whereas this distinction splits, as it were, our catholic absence, we emerge as a totality of unity and distinction. For convenience, let us call this totality of unity and distinction the mind—notwithstanding all the various meanings that can be associated with this word.

Importantly, this *primeval* distinction between our "self" and the "world" is not to be confused with the philosophical/psychological *concepts* of self-consciousness, self-awareness or self-perception. The basic act of distinction, in whichever conceptual form we may wish to mold it, is itself neither an assumption, nor a hypothesis or concept, but simply our immutable everyday experience articulated already in the Upanishads. The fundamental nature of this experiential act is underscored by the fact that it could be readily employed as a foundational principle for a highly original mathematical calculus (Spencer Brown 1969), without any need of implicating the discourses of philosophy or psychology whatsoever. When taken as a verb, the word *distinction* does not mean anything more than an action word; what is especially important for us is the observational fact, that whenever we *enact* distinction, we can perceive one, and only one *selected* side of the distinction, be it between the subject and object, or between the objects; another side is always absent from our direct perception, although in the aftermath it is assumed to reside in the memory as an invisible connotation.

This peculiarity is exemplified in Fig. 1.1, which shows four pieces of dark chocolate. Note that the figure, at the same time, shows a white window. Note also, that it is impossible to see the four chocolate pieces and the window simultaneously. More compellingly, at any instant we can perceive only one side of the distinction, which we have chosen and on which we are focused *right now.*[2] The two sides of a distinction thus stand in a relationship of *perceptive exclusion.*[3]

Furthermore, since at any instant, we can perceive only one side of the distinction, our choice of a particular side inevitably imparts *directionality*. This is

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[2] This does not rule out that under certain circumstances we can perceive two events, e.g., two flashes of light, simultaneously. However, in such case the primary distinction we make is not of the nature of the events, but that of their simultaneity.

[3] A phenomenon akin to perceptive exclusion also occurs during the so-called "binocular rivalry," in which the visual perception alternates between two dissimilar stimuli imaged on corresponding regions of the two eyes (Blake and Logothetis 2002).

**Fig. 1.1** The chocolate window

**Fig. 1.2** A space divided by a *black line*

exemplified in Fig. 1.2, drawn in the style of George Spencer-Brown and showing a white space divided by a black line. By deliberately focusing attention on either the left or the right part of the divided space, it is easy to notice that our choice is associated with emergence of directionality due to our focus on the *selected* part. Let us take a further step and call *Yin* the black half of the divided circle depicted in Fig. 1.3.

By naming the selected side we thus fix the directionality. It is important to emphasize that the used signifier *Yin* itself does not reveal any property of the black hemisphere whatsoever. It is deliberately attached as a label; we could with equal success use, for example, the signifiers "*Me*" or "*Om*"). However, now we can reminisce on our choice and if asked, indicate the selected side by a shortcut, because the signifier *Yin* has been linked in our memory to a particular content. The elementary process of generating *information* can be thus described as an act of distinction associated with directional choice and naming. By operating in the realm of language, we are fortunate to be able of attaching unique labels (or "signifiers," to use a Saussurean term) to anything we observe, including complex formal expressions, as we will see later.

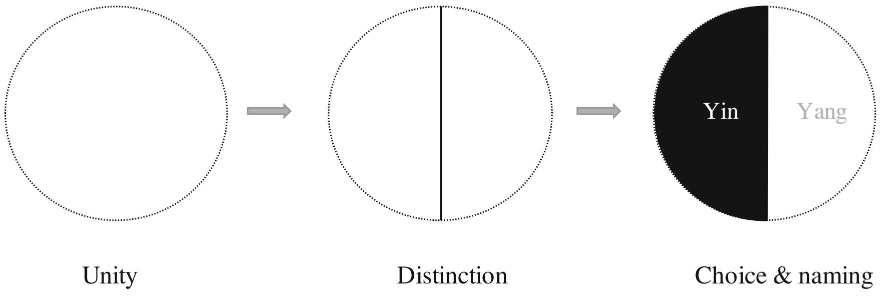

**Fig. 1.3** Creation of information by distinction, directional choice, and naming

## The Difference Between Animate and Inanimate Matter

Needless to say, although through memory shortcuts and "sensory adaptation" decreasing the sensitivity to a stimulus (Webster 2012), we are safe from making all the innumerable distinctions anew, they are omnipresent and inexhaustible while we are alive. However, neither the vast complexity of neural processes that are associated with the capacity of discrimination, nor the modulating effects of the psychosomatic context (Dehaene and Changeux 2011; Proulx et al. 2014) shall concern us here; what concerns us solely is the experiential act of distinction as such. Whenever the primeval distinction is enacted, all the other distinctions follow naturally by *reentry* (this term coined by George Spencer-Brown will be explained in detail later) of a distinction into distinction, with the only limitation to this process being the resolution capacity of our perception. It is obvious that making distinctions, as part of our everyday experience, is essential for our sensible behavior and eventually, our biological and social "survival." And sure enough, this is true not only for us. Indeed, it seems that any living being that can perceive its separation (isolation by boundaries) from the environment, is endowed with the capability to make distinctions (between the useful and dreadful) and directional choice (either flight or fight). In short, here we touch upon a characteristic of living matter that distinguishes it from inanimate matter in a fundamental way—with the notable exception of crystals. These latter can grow distinctly depending on their immediate environment. However, in contrast to living beings, the choice is not theirs but rather imposed externally by that very environment.

In general terms, the production of information by "drawing distinctions" can be imitated by physical systems that are capable of self-organization. Under the influence of external forces, such systems produce order from the disorder. On this view, even the closed physical systems (systems that do not exchange matter or energy with the environment), when tossed out of the equilibrium, are capable of producing order in the form of self-organizing spatiotemporal structures (so-called oscillons) as they evolve toward a final equilibrium (Gleiser 2013). This capacity, however, is especially conspicuous in the so-called *dissipative* systems. For example, when heat is applied to a plate with a thin layer of liquid, this leads to differential increase in the velocity of the molecules causing their motion along the temperature gradient in the liquid layer and thus creating *order* in form of a pattern of whirls (so-called "Benard rolls"). The process of "distinction" in this case is manifest as a sudden qualitative change in the behavior of system, or *bifurcation,* caused by threshold values of the physical parameters. Bifurcation is thus an emergent phenomenon resembling directional choice, whereby the order is produced by stabilizing one particular dynamic state, called an *attractor*.

When bifurcation emerges in form of splitting the symmetry of the apparently uniform chaos of Brownian motion, it is determined by influences that are *external* to the system. Nevertheless, dissipative systems show some autonomy in a sense that when an external constraint brings them out of the equilibrium, they may acquire a new "sensitivity." In the example above, the formation of Benard rolls results from the coherent vertical movement of the molecules due to the temperature gradient forcing the "warm" molecules to ascend from the heated floor, whereas gravitation drives the "cold" molecules toward the floor. In other words, while gravitation can be neglected at equilibrium, the change in the activity of the system (increased temperature) imparts sensitivity to gravitation (Prigogine 1988). As pointed out by Prigogine (and largely neglected by evolutionary theorists), this sensitivity of physical systems and its assimilation by living matter as a means of creating *information* is crucial for understanding the process of evolution. In the case of the Benard rolls, information is created in the form of regular *patterns* resulting from changing interactions between the two continuous variables, such as temperature and gravitation. Thus, in physical systems the capacity to "draw distinctions" and thus to self-organize, crucially depends on the threshold values of the *external* parameters, whereas in any living system the capacity to make distinction and directional choice is *internal*. Put another way, the faculty of perception in the living system appears as an *internalized* discrimination capacity. However, such a process of *internalization* obviously presupposes a prior organization of some kind of an *isolated unity* capable of internalization in the first place. But what does a "unity" actually mean? As we will see in the following chapters, the answer to this apparently simple question is anything but easy.

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# Chapter 2
# Problems of Logical Typing: The "One" and the "Unity"

> *Everything that is numbered depends on the one, and the one depends on nothing.*
>
> —Meister Eckhart

**Abstract** While we can count the oceans (or apples, elephants, money, etc.), we cannot do the same with the water (or sand, wind, temperature, etc.) in a meaningful way. However, we can instead measure the amount of water. It thus appears that we have to do with two, logically distinct types of information, one of which is discontinuous and subject to counting, whereas the other is continuous and subject to measuring. These accordingly correspond to the digital and analog information types, which respectively obey to the "on *or* off" and "more *or* less" logic. The distinction of logical types implies that these two types of information are in a relationship of perceptive exclusion, as evident in logical paradoxes. This problem of logical typing is ubiquitous, as it reflects our inherent incapacity to simultaneously perceive the discontinuity and continuity. The reality of this problem can be clearly traced back in the development of natural sciences. Most clearly however, the universality of the problem of logical typing revealed itself in the efforts to reduce the content of mathematical theories to formal logic.

**Keywords** One and unity · Logical types · Russel's paradox · Indeterminacy principle · Complementarity principle · Formal system · Gödel numbers · Genome · Proteome

According to Frege (1884), there is an essential difference between "0" and "1", and all the other numbers. While no quantity can be ascribed to "0", the peculiarity of "1" is that it appears in two guises, once as signifier of a *number*, and once as a notion of *unity*. Put another way, in the former case the word "one" is a proper *name*, whereas the same word "one" used as a *notion* unifies all items and/or processes that either have common features, or universal organization. For example, we may say that all five oceans on the Earth represent a *unity* (are *one*) by virtue of being water. The caveat is that while we can count the oceans (or apples, elephants, money, etc.), we cannot do the same with the water (or sand, wind, temperature, etc.) in a meaningful way. However, we can instead measure the amount of water. It thus appears that we have to do with two, logically distinct types of information,

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one of which is *discontinuous* and subject to counting, whereas the other is *continuous* and subject to measuring.[1] These accordingly correspond to the digital and analog information types, which respectively obey to the "on *or* off" and "more *or* less" logic (Wilden 1972). Again, as in the case of the chocolate window shown in Fig. 1.1, the distinction of logical types implies that these two types of information are in a relationship of perceptive exclusion, as illustrated in the examples of logical paradoxes below.

## Confusion of Logical Types Beget Paradoxes

One appropriate example of the phenomenon of perceptive exclusion is the Sorites (heap) paradox attributed to Eubulides of Miletus (Fig. 2.1). Eubulides is successively removing individual grains from a heap (of grains), asking each time whether the remainder is still a heap. While at first the answer is affirmative, at some later moment (latest when only one grain is left over) the answer becomes *no*. Note that a *heap* (as a unity of grains) belongs to the analog type of information, which is subject to measuring or weighing. The *grains* could also be counted individually and thus, belong to the digital information type as well. The monotonous process of grain removal masks the smooth transition between the logical types, whereas the request of Eubulides to see the heap and the grains as *one and the same* thing creates a paradox by virtue of perceptive exclusion.

Still better examples of the phenomenon of perceptive exclusion are given by the so-called "self-referential" paradoxes ("self-referential" in this case means a sentence referring to itself). Let us take the paradox of Epimenides: "A Cretan says, that all Cretans are liars". It follows that if he lies, he says truth, whereas if he says truth, he lies. It is easy to see, that the signifier "Cretan" appears once as a digital parameter (*one* unique "Cretan" making the utterance) and once as an analog parameter (regular member of the *class* of "Cretans" taken as a *unity*). So the sentence creates a paradox by imparting a double meaning to the signifier "Cretan". This amounts to saying that 1 (taken as number) is equal to 1 (taken as unity) and ultimately that digital = analog. Both of these are obviously false statements equating logically incompatible information types. Thus, the double informational content hidden in the unique signifier "Cretan" causes a paradox by virtue of oscillation of the distinction between the logically incompatible types (Bateson 1979).

This confusion is even more clearly apparent in the simplified version of the Liar paradox: "This sentence is false". In principle what is said here is that "This sentence is a false sentence". Now it can be seen that the term "this sentence",

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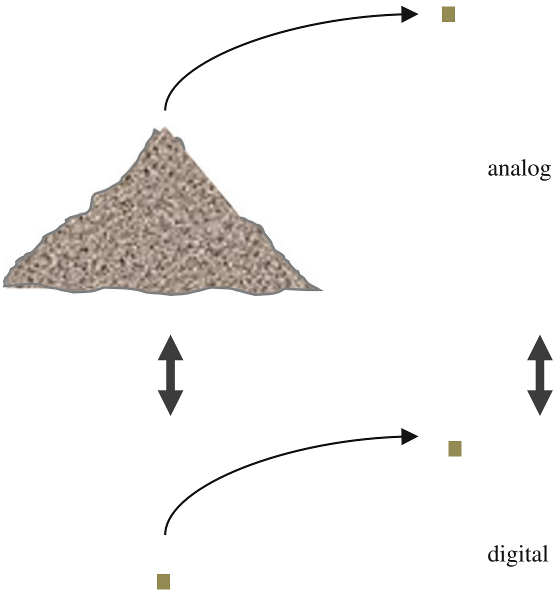
[1] At this point it is irrelevant that at sufficiently high resolution all the matter may appear corpuscular and thus regarded digital. We concern ourselves with the facts of immediate perception and not with abstract concepts of elementary particle physics.

**Fig. 2.1** Sorites paradox



which provides digital information (since *this* sentence is indicated uniquely), is equated to the term "false sentence", which provides analog information (since" false sentence" is a member of the class of all possible sentences). Thus again it is claimed that digital (sentence) = analog (sentence), and as we already know, this equation is false.

## Russell's Paradox

In a more subtle self-referential paradox constructed by Bertrand Russell, the assumption is that there are two kinds of classes of the things: those classes, which do not contain themselves as members and those that do. The former are called normal classes whereas the latter are non-normal. For example, a class of imaginable things itself is imaginable and so is a member of itself, thus being non-normal. Conversely a class of, let's say, gentleman, is not itself a gentleman and so does not contain itself as a member. Such a class would be a normal class. Now let us assume that N is a class of all normal classes. The question is whether N itself is normal or non-normal. If N is normal, it contains itself because by definition N is a class of all normal classes. However, the classes containing themselves are by definition non-normal. Now, if N is non-normal then it contains itself, but by definition N contains only normal classes. So it appears that if N is normal, then N is non-normal, and if N is non-normal, then N is normal.

Now let us take a look at what happens with logical typing in this paradox:

*Take a class N that contains all normal classes*

Notice that the signifier N defines a unique class, and so belongs to the digital information type. Now let us pose question:

*Is N normal or non-normal?*

Notice that the answer is sought by assuming the *membership* of N either in normal or non-normal classes. So we infer:

*If N (as unique class) is normal, then N (as member of a class) is non-normal*
*If N (as unique class) is non-normal, then N (as member of a class) is normal*

Note that while N, as a signifier of a unique class, provides digital information, the same signifier N taken as a member of a class (either normal or non-normal) is conveying analog information. Yet, although the signifier N on the right side of the two statements above is actually determined with regard to its analog property (membership in a class—which particular class does not matter) it appears (by definition) under the guise of a digital signifier. Therefore we shall write:

*If N (digital) is normal, then N (analog) is non-normal*
*If N (digital) is non-normal, then N (analog) is normal*

None of these sentences appear paradoxical any more because spelling out N once as analog and once as digital signifier abolishes the perceptive exclusion—independent of whether the sentences themselves make any sense or not. Thus again, the paradox is created by perceptive exclusion of two logically incompatible types of information, concealed under the guise of the same signifier, N.

## Bohr's Complementarity Principle

> *We have two contradictory pictures of reality; separately neither of them fully explains the phenomena of light, but together they do!*
>
> Albert Einstein

The problem of logical typing is ubiquitous, as it reflects our inherent capacity to perceive the distinction between *discontinuity* (digital information) and *continuity* (analog information). The reality of this problem can be clearly traced back in the development of natural sciences. For example, in classical mechanics the dynamic laws describe the interactions between discontinuous entities (such as, e.g., heavenly bodies or particles) governed by forces of attraction and repulsion that mainly depend on the distance between the unchanging entities. Thus, all matter is considered as digital. Yet from the very beginning this view had difficulties to account for the phenomena of, for example, the optics, which could be described better by the wave properties of the matter. Indeed, later on, the field theory put the emphasis on the structure of the space between the interacting entities (essentially, the wave properties of matter) rather than on the entities themselves, as most appropriate means for the description of optical and electrical phenomena. Since the intensity of a field is subject to continuous change, the concept of field embodies the analog property of the matter. As noted by Julian Barbour, the confrontation and reconciliation of the different worlds of particles and waves is one long ongoing saga. "It started with Kepler's optics, continued with the rival optical theories of Newton (particles) and Huygens, Euler, Young, and Fresnel (wave theory), and reached a first peak with Hamilton. It burst into life again in 1905 with Einstein's notion of the light quantum, then went through another remarkable transformation in Schrödinger's 1926 discovery of wave mechanics" (Barbour 1999). In other words, it appears that the emphasis on particular properties of the physical world oscillates according to changes of logical typing, that is, to idiosyncrasy of our observation.

In quantum physics the problem of logical typing can be made conspicuous with the example of Heisenberg's indeterminacy principle, stating that the more precisely the position of a particle is determined, the less precisely its momentum can be known, and vice versa. There are many accounts of this phenomenon but in any case, the unique position of a particle belongs to digital, whereas momentum (which is inversely proportional to the wavelength of the wave of a particle) to analog variables. The wave behavior (momentum) of a particle can be measured experimentally by bombarding it with a beam of photons, which in result become scattered, such that the momentum is determined by the energy of the scattered photons. The notable caveat is that with this measurement it is impossible to have better accuracy than with the momentum of a single photon. In turn, the position of a particle can be determined by deformation of the wave profile of an electromagnetic field in the presence of the particle and again, the accuracy cannot be greater than the wavelength of the given field. In short, the nature of the measuring device appears determinative for the observation. Observing in one way we obtain the probabilities for particle positions, whereas observing another way we obtain the probabilities for their momenta. This relationship embodies the uncertainty principle, because these two properties of a particle could not be measured simultaneously and with high accuracy (Anastopoulos 2008).

Put another way, the uncertainty principle appears to be an observational fact. Whereas there is no difficulty observing both the particle and wave properties of, for example, an electron separately, the problem arises when we are forced to conceive these properties simultaneously as *one and the same* thing. And even though we might invent new increasingly superb artifices to accurately measure both these (wave and particle) properties, by the virtue of perceptive exclusion we can nevertheless grasp these logically distinct types of information *only* in separation. This duality of perception motivated Bohr's ingenious notion of *complementarity,* purporting an existence of two mutually exclusive (essentially, analog, and digital) perspectives of the same phenomenon. These two mutually exclusive perspectives complement each other such that in parallel they exploit the full content of the phenomenon under the scope. Bohr argued, for example, that the measurement of the temperature of a system is incompatible with the knowledge of precise coordinates and velocity of the individual molecules, because temperature is defined as an average of these velocities taken together (Heisenberg 1969). To put it in our terms, the temperature is an analog component, whereas individual molecules represent digital components of the very same system, thus providing complementary information.

There is no question that our empirical concepts of matter necessarily depend on the technical instrumentation and resolution capacity of the experimental setup, and sure enough our interpretations of natural phenomena will change with technological progress, providing novel and increasingly powerful tools for experimentation. However, it must be obvious from all that has been said so far that the mysterious property of the matter to appear under different guises made so explicit by ingenious discoverers of the uncertainty principle is a constitutional and fundamental property of our perception, grasping the logically distinct types of information only in separation.

## Application of the Axiomatic Method to the Real World

> *Real is only the measurable.*
>
> Max Planck

Most clearly, the universality of the problem of logical typing revealed itself in strenuous efforts to reduce the content of mathematical theories to formal logic. This is perhaps because in contrast to experimental science, mathematics can operate using the “language” of the axiomatic method. For example, the entirety of elementary geometry can be founded on a limited number of *a priori* axioms that are accepted without proof, and serve as basic propositions from which numerous theorems can be derived. While the axioms of elementary geometry explicitly deal with the space, in the 19th century it was conjectured that in principle, any branch of mathematics could be founded on a limited set of axioms sufficient to deduce all the propositions in the given field. Such a system could be assumed consistent if it could be proved that it does not produce contradictory propositions (Nagel and Newman 2001). And although the final proof was lacking, it was expected (perhaps in keeping with the spirit of the time) that in principle, this was an achievable task. At the turn of the nineteenth century, David Hilbert made a remarkable attempt to provide an absolute proof of consistency by means of complete formalization of the axiomatic system. His idea was to drain the expressions of such a *formalized system* (FS) of all meaning and to regard them as empty signs. Put another way, the behavior of the (empty) signs in a formalized axiomatic system would be literally “exempted” from any dependence on their meaning, while still retaining the logical structure.

This approach can be explained by referring to the example of natural language, the syntactic and semantic properties of which provide logically different types of information. Syntax determines the structure of the rules of language and thus, the way in which the words are assembled in sentences, but it does not determine the meaning of the words. This latter is the task of the semantics. However, although the syntax itself is meaningless, it is nevertheless possible to describe the *different configurations* of the symbols and their relationships in a meaningful way. In the case of Hilbert's FS these would be the different configurations of the *strings of signs* in logical propositions. Unfortunately, this approach posed a methodological problem, because producing meaningful statements *about* the FS required a *metalanguage*. Furthermore, this latter language, to be able to talk *about* FS, had to be different from that of the FS. Thus, in order to provide his proof Hilbert had to construct a *metamathematical* language. In the following passage I shall refer to the brilliant book of Nagel and Newman (2001), which is dedicated to this subject, and shall illustrate the nature of a metamathematical statement by using an arithmetical formula:

$$1 + 1 = 2$$

This formula consists of arithmetical signs and shows their relationship. Now, if we write:

$$'1 + 1 = 2' \text{ is an arithmetical formula}$$

we will make a statement *about* the formula, which itself does not express an arithmetical fact and so belongs to *meta-mathematics*, because it confers a *meaning* to a certain string of arithmetical signs. In other words, the metamathematical statements contain the names and definitions used as *unique signifiers* of the formulas, but not the formulas themselves. Note that again, in the distinction of the arithmetical meaning of the formula $'1 + 1 = 2'$, and the metamathematical statement *about* it, we have a case of perceptive exclusion. If we use Bohr's metaphor this implies that these two languages to be consistent, have to be complementary in a similar way as are, for example, the temperature and the velocity of molecules in a physical system. Accomplishing this task is in no way trivial, and while Hilbert started the quest, the clarification of this question had to wait for about half a century for another ingenious mathematician—Kurt Gödel.

## Gödel's Formal System

> *Two propositions are opposed to each other, when there is no meaningful proposition that affirms them both.*
>
> L. Wittgenstein

Gödel elaborated on *Principia Mathematica*, a fundamental work carried out in the beginning of the twentieth century by Russell and Whitehead, who by using a comprehensive system of notation managed to convey mathematical meaning to the FS.

Put another way, they succeeded in matching the mathematical truths to logical relationships of the strings of empty signs in the FS. By doing so, they hoped to reduce (and thus facilitate) the proof of the consistency of any large mathematical system (in particular the *number theory*—a branch of pure mathematics operating with integers) to the proof of the consistency of formal logic itself.

Gödel used the accomplishments of *Principia Mathematica* to fine-tune his calculus such that the logical "syntax" of the FS could be systematically mapped to meaning (Nagel and Newman 2001). Notably, the *meaning* in this case is the arithmetical truth mapped to the logical proposition. The peculiarity of this mapping can be illustrated with the example of a particular musical rhythm in which numerous melodies can be "mapped", because the rhythm is not determinative of the melody. Now let us consider a natural rhythm, say for example, the wing beat of a flock of birds calling each other. Assuming that the birds have a particular (physiological) connection between the rhythm of the wing beat and calling frequency, the "melody" of calling would fit the wing beat best, giving it naturally a meaning. Note that by itself neither the calling belongs to the wing beat, nor the wing beat to calling (in fact, they both belong to the bird).

Gödel's logical system thus shows a similarity to natural language, in that it consists of two types of information—the syntax (formal logic) and the semantics (mathematical meaning). Furthermore, since the syntax and semantics of the FS matched each other precisely, meaningful statements could be produced. Ideally, the system would be expected to be both *consistent* and *complete*. Recall that the consistency of FS is provided if it is impossible to generate both a particular statement and its negation from its axioms. The demand of completeness of the FS means that its axioms should be able to produce all the logical truths that are expressible in the system.

## Gödel's Mapping

However to provide a proof of consistency of his system, Gödel, as Hilbert before, faced the necessity of elaborating a metamathematical language capable of making definite statements about the FS. In particular, he aimed at constructing meaningful metamathematical statements that could be mirrored in the logical expressions (strings of signs) of the FS. For this purpose Gödel employed an ingenious mapping procedure by assigning a *unique* number to each elementary sign, each formula (i.e., sequence of signs) and each proof (i.e., sequence of formulas) in the FS. These numbers, representing large integers, are essentially tags constructed in accordance with particular rules (which should not detain us here), enabling the translation of any sign, formula, or theorem of the FS into a specific (Gödel) number. Thus, on the one hand, this "arithmetization" of complex logical expressions of the FS simplified their handling, and on the other, the expressions could be readily retrieved (essentially by prime factorisation of large integers) from the Gödel numbers—simply because the method of their construction was known (Nagel and Newman 2001).

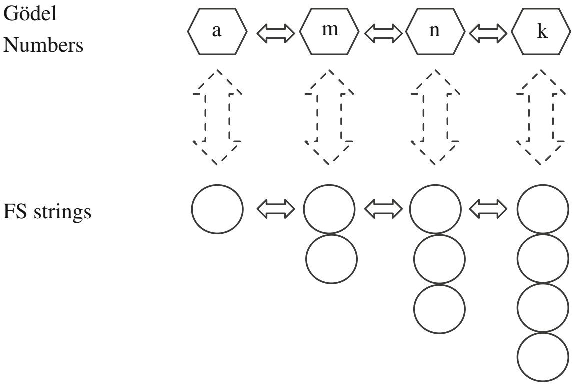


**Fig. 2.2** Gödel's mapping. The symbols and strings of the FS are converted in Gödel numbers according to particular rules (*vertical double arrows*). The strings of the FS (*connected circles*) as well as the Gödel numbers are related to each other by transformation rules and arithmetical relationships, respectively (*horizontal double arrows*). The relationships between the Gödel numbers can be mirrored in the relationships between the FS strings

Importantly, since in this way unique (Gödel) numbers were associated with variable signs and expressions of the FS, this offered the opportunity to construct metamathematical statements *about* the expressions of the FS using the *arithmetical relations* between their corresponding (Gödel) numbers. This was achieved by mapping of metamathematical statements (i.e., the arithmetical relationships between the Gödel numbers) on the relationships between the formulas and theorems (typographical properties of the strings of symbols) in the FS (Fig. 2.2). Gödel thus succeeded in constructing meaningful metamathematical statements about FS that could be accurately mirrored within the strings of the FS, showing that by using metamathematical language it is possible to teach the FS to speak about itself! However, he also found that his FS produced contradictory statements—a proposition and its negation, and so by definition was inconsistent.

In addition, Gödel managed to construct metamathematically correct statements that could be mirrored in the strings of the FS, but could not be derived from the axioms of the FS themselves. Gödel's inference was that the FS is incomplete. Moreover, he showed that this incompleteness is *essential,* because the FS could not be cured by any extensions—new formulas revealing the same defect of the "extended" FS could be constructed ad infinitum. Thus, it turned out that the formal system not only did not, but it essentially could not provide the anticipated result. Yet, Gödel's proof was a truly remarkable achievement of logical thinking—he decidedly demonstrated the inherent limitations of the axiomatic method in its ability to grasp the real world.

## Analogy Between the Formal System and the Genetic System

*Two descriptions are better than one.*

Gregory Bateson

Hofstadter (1979) observed that Gödel's logical construction shows a "profound kinship" to the logical organization of the genetic system. A brief outline of this similarity is important in order to understand why Gödel's mapping failed, especially in the light of the recent insights into the dual coding properties of DNA. While properties of DNA as the essential carrier of genetic information will be addressed in more detail in Chap. 4, it suffices to say here that in principle, according to the current conjecture (Muskhelishvili and Travers 2013), the variable mechanical stiffness and the corresponding three-dimensional configuration of the chromosomal DNA polymer represents the regulatory context, or the "syntax" of the genetic system. In turn, the unique genes expressing specific proteins involved in distinct cellular functions provide digital information and belong to the "semantic" component of the system that can be mapped on the DNA genome. The DNA molecule is thus a carrier of two types of information, akin to Gödel's logical system, in which arithmetical relationships between the Gödel numbers are mapped to the "typographical" strings of the formal expressions. Furthermore, the Gödel numbers and the formulas in the FS are related by arithmetical relationships and transformation rules, respectively. Similarly, the chromosomal genes are connected by means of the transcriptional regulatory network, whereas the expressed proteins are connected by means of the protein–protein interaction network. In both cases the mapping obtains a meaning by relation—to arithmetical truths in the former, and to true genetic functions in the latter.

Moreover, Hofstadter emphasized the analogy between the translation of the Gödel number(s) into the particular expression(s) for which it stands, and translation of the particular string of DNA sequence into the amino acid sequence of a protein. Indeed, the individual proteins, by analogy to Gödel numbers, conceal the method of their production from the DNA by an identical set of rules. It is now possible to see that mapping of metamathematics (arithmetical relationships between the Gödel numbers) onto the relationships between the logical expressions of the FS is analogous to the process of mapping the interactions between the proteins on functional communications between their cognate genes (Fig. 2.3).

That is all very well. However, despite this striking similarity of logical organization, we know that Gödel's FS is inconsistent and essentially incomplete, whereas we cannot readily say this about the genetic system of a self-reproducing cell. It can be rather said that in contrast to Gödel's FS, the information contained in the genetic system of a simple cell is consistent, because it always reproduces a cell and not something else, and it is also complete, as at any instant all the possible

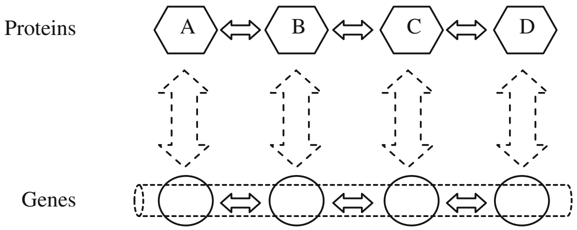


**Fig. 2.3** The information stored in the chromosomal genes (the chromosome is indicated by *dashed* tube and the genes by *circles*) is converted into the proteins (A, B, C, D) by processes of transcription and translation, whereas the proteins in turn affect the gene expression (*vertical double arrows*). The genes are related to each other by rules of transcriptional regulation, and proteins are related by protein–protein interactions in macromolecular complexes (*horizontal double arrows*)

enzymatic reactions and macromolecular interactions of a given cell are "derivable" from the particular organization of its genome.

## Differences of Logical Typing in the Formal and Genetic Systems

The essential difference between Gödel's FS and the genetic system becomes obvious if we analyze them in terms of logical typing. The "syntax" of the genetic system—three-dimensional configuration of the continuous DNA polymer—provides analog information regulating genetic activity and specifying the pattern of gene expression (Muskhelishvili et al. 2010; Travers et al. 2012). The expression pattern itself represents digital information because it comprises unique messenger RNA sequences, which are translated into proteins of unique three-dimensional structure.[2] However, a single messenger RNA can act as a template for multiple rounds of translation, such that the proteins are produced in a wide range of concentrations.

Notably, the entirety of all produced protein in the cell represents the cellular *proteome,* which as a whole is righteously seen as a carrier of analog information (von Neumann 1958), notwithstanding its substantial compositional variation. The latter is due to the homeostatic regulatory mechanisms ensuring that in the course of environmental changes the overall composition of the cellular proteome remains optimally balanced according to the given physiological state.

This means that the supply of each individual protein species in the proteome, including the abundant DNA binding architectural proteins that shape the

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[2] For the sake of simplicity the genetic effects of the noncoding RNAs are omitted, since this does not change the organizational logic of the genetic system.

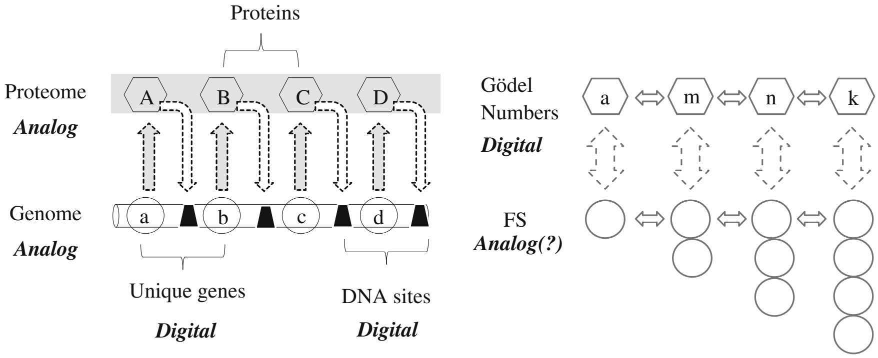

**Fig. 2.4** Differences of logical typing in the genetic system (*left panel*) and in Gödel’s FS (*right panel*). The proteome (*gray rectangle*) and the genome (*horizontal tube*) represent matching continuities, whereas the Gödel numbers and the FS strings do not. Specific DNA binding sites are indicated by the trapezoid areas

chromosomes, is instantly adjusted to the global cellular function. The changing composition of the DNA architectural protein components of the proteome directly modulates the chromosome configuration and thus mediates the transmission of information about the cellular physiological state to the genome. The coordinated impact of DNA architectural proteins on the three-dimensional structure, and hence the genetic activity of the chromosome, in turn feeds back into the proteome (Fig. 2.4, left panel).

This means that the organization of the genetic system is circular (Muskhelishvili et al. 2010). The circularity is achieved by perpetual conversion of analog information (chromosome configuration dynamics) into digital information (gene expression patterns), and back into analog information (the proteome). Yet also the proteome generates digital information via its DNA binding components interacting with specific DNA sites, which in turn determine the chromosomal configuration dynamics and thus close the circle. The crucial point is that the cellular proteome represents a compositionally coordinated variable *unity* corresponding to the genetic activity of the whole chromosome, whereby it is the “coalescence” of the two analog information types (chromosome configuration and proteome composition) that coordinates the global genetic activity. The digital components of the genetic system (i.e., specific pattern of expressed genes mirroring the chromosome configuration, and the specific pattern of occupied DNA binding sites mirroring the proteome composition) mediate the coordination of information flow between the two analog components, forming one indivisible unity. In short, both the consistency and completeness of the system, or better to say, its self-referentiality, is achieved by a perpetual interconversion of logically distinct information types (the explicit details of this conversion mechanism will be addressed in Chap. 4).

Logical typing in the FS is quite different (Fig. 2.4, right panel). For convenience, let us assume that the meaningless strings of the FS related by a set of transformation rules constitute a continuum providing analog information. Gödel translated these strings into unique (Gödel) numbers, which by definition provide digital information. Thus the situation appears analogous to the relationship between the global chromosomal configuration and the corresponding gene expression pattern. However, unlike the unique proteins, the unique Gödel numbers are not generated in different concentrations, such that there is no analog dimension to them. Furthermore, even though we assume that the purely logical structure of the FS represents some sort of a continuum or an operationally closed system (which, I guess, is a wrong assumption), the mathematical meanings conferred by Gödel to the strings of logical propositions in the FS represent discrete mathematical truths. Thus in fact, in Gödel's logical system, the digital information (unique Gödel number) is mapped onto digital information (explicit arithmetical meaning of a particular string of the FS), whereas in the genetic system the interconversion of digital information (that is, conversion of the effects of unique DNA binding sites into a specific pattern of gene expression) is coordinated by two coupled analog components—the proteome composition and the chromosome configuration. This means that in the "mapping" process of the genetic system everything is interdependent and obtains its true meaning only in the context of the coordinated whole. In contrast, whereas the arithmetical relationships between the Gödel numbers (that is, the statements of metamathematical language) can be mirrored in the FS, the mapping of each particular metamathematical statement is independent from that of the others. Since it appears that there is no limit to the extensions of the FS, and since most likely there can be no finite *universal* Gödel number (which by analogy to *proteome* could be called a *Gödelome*) to which *all* the other Gödel numbers could be equally related and thus coordinated as parts of a whole, the system will be prone to ambivalent formulas and mutually exclusive statements.

In other words the Gödel system, in contrast to the genetic system, lacks *unity,* which as we have argued above, is a prerequisite for engendering distinction and directional choice. Therefore in real world a creature having Gödel's FS as its brain would not survive. This also implies that any abstract logical system aided by the creative power of reason falls short of mirroring the organizational complexity of information stored in just a millimeter long DNA tape representing the "brain" of a simple unicellular organism.

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# Chapter 3
# Logical Typing and the Notion of Time in Biology

> *By the use of a clock the time concept becomes objective.*
> —Albert Einstein

**Abstract** Time is the most enigmatic "property" of our world but it seems that for the ancients, time has not been too much a quagmire. In the Orient time just did not exist—indeed, it is difficult to find any long-running account of the history of India. The same attitude has been observed not only in the old civilizations of the American continent and among the African Bushmen but interestingly also in ancient Greece. It thus appears that the notion of time as a dimension of objective reality distributed uniformly between the equally important past, present, and future is if not an invention, then at least an idiosyncrasy of the Western civilization, with its ingenious mastery of processes, and accordingly, the necessity of vast memorization and planning. However, time in biological systems appears in a guise quite different from that in mathematics or classical physics, where time is essentially transformed into space, enabling an equally efficient movement in both (past and future) directions. The peculiarity of the biological perception of time can be readily explained at the molecular level using a simplified model of the paradigmal *lac* operon of the bacterium *Escherichia coli.*

**Keywords** St. Augustine · Time-reversibility of physical laws · Perception of time · Lac operon · Biological unit of evolution · Replicator · Autopoiesis · Reductionist methodology

The peculiar organization of animate matter as an indivisible unity capable of drawing distinctions and meeting directional choice also implies a distinct relationship to time. Arguably, time is the most enigmatic and mind-boggling "property" of our world. Yet it seems that for the ancients, time has not been too much a quagmire. In the Orient time just did not exist—indeed, it is difficult to find any long-running account of the history of India, perhaps since traditionally, save the actual present, neither the past nor the future drew much attention there. The same attitude has been observed not only in the old civilizations of the American continent and among the African Bushmen (Keeney 2005), but interestingly also in ancient Greece, which was argued to have been poor in historians (Spengler 1923), yet vigorous in transforming the history (or myth) into literature. It thus appears that

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the notion of time as a dimension of objective reality distributed uniformly between the equally important past, present, and future—as we came to know it from the school—is if not an invention, then at least an idiosyncrasy of the Western civilization, with its ingenious mastery of processes, and accordingly, the necessity of vast memorization and planning. Nevertheless, as observed by McTaggart, historically many occidental thinkers including Spinoza, Kant, Hegel, and Schopenhauer questioned the objective reality of time (McTaggart 1908). Similar doubts were raised by Bergson (1913) and McTaggart himself, and more recently by such diverse thinkers as Krishnamurti and Maturana, and scientists such as Barbour (1999) and Lanza and Berman (2009), just to mention a few.

Although we cannot possibly delve into the nature of time here, we have to make it explicit that time in biological systems appears in a guise quite different from that in mathematics or classical physics, where time is essentially transformed into space, enabling an equally efficient movement in both (past and future) directions. In such a system the past and future time points can be juxtaposed and observed synchronously, or even in opposite succession. Comfortably, this time-reversibility also implies a symmetry exempting us from the need to invent separate laws for spatiotemporally distant events. The notion of reversible time presumably comes from studies of the heavenly bodies, as “the book of astronomy reads the same backward and forward,” (Wiener 1948) and essentially means that in such a conceptual system with static time, *all is given* at once. As every schoolboy knows, however, Heraclitus already noticed that we “cannot step twice into the same stream,” and we all know very well that in our perception no two moments of time can ever occur concurrently, as in reality the time is not thought but *lived* (Bergson 1913). It is a sobering fact that despite all our insights into history we cannot foretell our destiny, and from all the minute quantum physical data about the past and the actual present we cannot predict the future more than purely probabilistically. In fact, it seems that all living organisms are locked in the *present* such that save human beings, the past and future rarely burdens them. It is quite unlikely that, for example, a crocodile on a riverbank ponders on the past or concocts the future, much less does a simple bacterial cell. Fancy “travels” into the past and the future appear to be an exclusively human enterprise.

## Saint Augustine’s Conjecture

> *The senses burst out in the thoughts.*
>
> Meister Eckhart

But are the past and the future *real* at all? One of the lasting inquiries into the reality of the past and the future comes from Saint Augustine (*Confessiones*). Basically, he was suspicious that the past and future times can ever *be*, given that the former does not exist anymore, whereas the latter is not yet existent. Whenever the past and the future exist for us, they exist if, and only if, they are called into the present by memory and fantasy, respectively. In other words, there can be "present of past," "present of future," and "present of present." On the other hand, Augustine argues that time should have an extension, or else how could we measure it? Yet, this extension is not a movement of an external object, because we can still measure time when such an object is at rest. Neither can this extension be equated to the number of elements constituting an object, because any verse, for example, can be read faster or slower independent of the amount of syllables in it. The future, however, exists as anticipation, whereas the past exists as memory. Augustine thus concludes that time is a conversion of the anticipated (future) into the memory (past), such that the progressive shortening of anticipation extends the memory correspondingly, whereas the present is embodied in the process of conversion itself.

In other words, it appears that Augustine defines time as a direct perception of the interval between successive acts of distinction—of the initiation of an event and of its subsequent abolishment. This process can be fathomed with the help of the chocolate window shown in Fig. 1.1, by sequentially focusing attention first on the window, and then on the pieces of chocolate (or vice versa), whereby the passage of time can be grasped as the interval between the initial distinction of the window and the subsequent distinction of the chocolate pieces (abolishing the window). While our perception of time can be thus made conspicuous by perceiving the interval between the successive distinctions, the distinctions themselves can be seen as states of focused attention and *naming* of the distinguished objects—punctuation, so to speak—within an unceasing continuous process. It seems that without distinction there would be no change, and without change there would be no time, but perhaps eternity.

Unsurprisingly, the various notions of time more than often confound the logical types. One good example to illustrate this is the famous paradox of McTaggart (1908) considering two notions of time, whereby for our purpose it suffices to consider the notion asserting that the past, present, and future are incompatible properties. For example, if an event is past, it cannot be present. Indeed so! On the other hand any event has all these three properties: the extinction of dinosaurs was once future, then present, and now is past. That is right too, and so, we have a contradiction. However, from what we have said above it is clear that the past and the future (that is, the memory and the anticipation nurtured by the very same memory—as you can only project from what you do know) are both products of thought, whereas the present—in keeping with Augustine—is a direct experience of the interval between two consecutive distinctions. So this notion of time confounds the logical types, as memory and its future projections are always expressed in the form of thought images of *discrete* events and therefore, are both digital, whereas the present, as unceasing direct experience, has a quality of continuity or *duration* (Bergson 1913) and therefore, is an analog property. Thus in reality the tenses of grammar are not quite commensurate, as the past and the future can "exist" only when they are called into the present and perceived as an *actuality*.

## Time as an Interval Between Successive Distinctions

> *The secret of life is enjoying the passage of time.*
>
> James Taylor

By his focus on the interval between the consecutive acts of distinction, Augustine essentially provides the basic description of our perception of the "flow" of time, which we cannot deny exists in some analogous form in any animal also, or even in a bacterial cell—albeit in the form of succession of molecular interactions in the latter. In this respect—on the assumption that any biological organism is capable of drawing distinctions—we are on a par with any other living being.

This peculiarity of the biological perception of time can be readily explained at the molecular level using a simplified model of the paradigmal *lac* operon of the bacterium *Escherichia coli* (Fig. 3.1). The *lac* operon (*operon* is an assembly of several adjacent genes, the transcription of which starts from a single confined DNA sequence called the *promoter*) is producing proteins involved in lactose metabolism and is normally repressed by the Lac repressor (LacI), which tightly binds the *operator* site in the promoter region of the operon. Binding of LacI precludes the interaction of the transcription machinery (RNA polymerase enzyme) with the promoter and thus the expression of the operon. In the presence of sugar lactose in the medium, however, the operon is de-repressed. This is because lactose binds the LacI repressor affecting its structure such that the operator binding is impaired. The LacI repressor-lactose complex dissociates from the operator site and this enables the RNA polymerase to start transcription of the *lac* genes endowing the cell with the capacity to utilize lactose as an energy source. When the available lactose is exhausted, the LacI repressor-lactose complex is not formed any more, and the free repressor rebinds the promoter abolishing the *lac* operon transcription.

In the *lac* operon model we can clearly see a succession of distinctions at the molecular level. These distinctions are mediated by differential recognition of the *lac* operon promoter by the LacI repressor protein in the presence and absence of

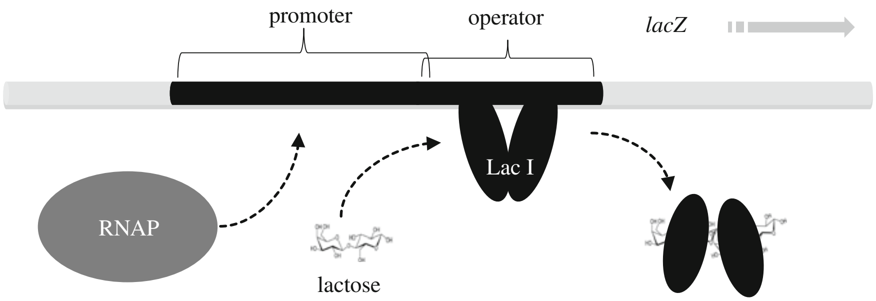

**Fig. 3.1** Regulation of the *lac* operon by the LacI repressor. Binding of lactose to LacI inactivates the repressor and enables the binding of RNA polymerase (RNAP) to the promoter and transcription of the *lac* genes (*lacZ* is the first gene in the operon)

lactose—one event leading to production of proteins for lactose utilization, and the other to cessation of their production. Here again, time appears as an interval between successive distinctions—perception of the initial event (presence of lactose), and its subsequent abolishment (absence of lactose). In the interval between these two distinctions the expression of the *lac* genes is mediated by the universal process of transcription, proceeding at an average pace of 50 base pairs per second. Because of this universality, we do not need to worry about the innumerable molecular interactions (distinctions, as it were) occurring in the process of transcription itself, otherwise we are ultimately doomed to slip into atomic and subatomic processes immaterial to our topic. Since the process of transcription is assumed to proceed at a fairly uniform rate in all kingdoms of life, it can be assumed a universal register in which time is *biologically inscribed.*[1]

Several lines of evidence are consistent with this notion. For example, during the *Escherichia coli* growth cycle, the spatiotemporal transcription of the chromosome corresponds to the distinction of alternating regimens of oxygen consumption (Sobetzko et al. 2012, 2013; Muskhelishvili and Travers 2013). In cyanobacteria also the circadian rhythms (oscillating biological temporal rhythms) appear to be regulated by the dynamics of chromosomal transcription (Woelfle et al. 2007; Vijayan et al. 2009). Furthermore, the respiratory oscillation of global transcription in the yeast chromosomes involves two gene superclusters, one for anabolic (biosynthetic) and another for catabolic (biodegradation) function, that are utilized successively during high and low oxygen uptake, respectively (Machne and Murray 2012). Such genome-wide oscillations of transcription are assumed to gate synchronous bursts of DNA replication, thus determining the “intervals” between the successive replication events (Klevecz et al. 2004). Finally, recent observations strongly suggest that transcription occurs in synchronous bursts, again in keeping with the function of this process as a molecular chronometer (Chong et al. 2014).

In contrast to microbes, the higher vertebrates carry out distinctions by virtue of highly developed sensory organs, connected to a neural system. Our sense organs transmit the perceived signals over large distances to the corresponding areas of the brain, integrating the response of vast amounts of cooperating cells carrying out individual distinctions, consolidation of which allows the sense organs to be instantly turned “on” in response to an external signal (Maturana and Varela 1987; Proulx et al. 2014). However, at the bottom all perception is physiologically realized at the level of individual cells responding to physical or chemical cues by modulating the gene transcription. The corollary is that the perception of time by drawing successive distinctions is an *intrinsic* property of any biological organism independent of its compositional complexity. Thus, although by developing the complex sensory organs our perception has “emancipated” itself, as it were, from

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[1] In principle, the cellular metabolism could also serve the purpose of inscribing biological time. However, the metabolic processes are much more variable in terms of both specificity and pace, but more importantly they are reversible, whereas the process of transcription is not.

the captivity of molecular distinctions, it is not independent of these latter but rather, has massively capitalized on them.

Importantly, the simple example of the *lac* operon makes it clear that it is the interval between the successive distinctions (process of *lac* gene expression), which gives physiological meaning to the distinction (of lactose availability) per se, rather than the other way around. This sounds trivial, yet underscores the limitations of the statistical mechanics approaches to living matter, where cells and organisms are examined as something akin to billiard balls interacting with each other, without any consideration of the interval between these interactions whatsoever. The point is that after the interaction, the billiard balls remain the same, whereas the biological systems do not.

From all the above mentioned we can define living systems as entities that, by means of the intervals delimited through the successive acts of distinction and directional choice (that is, acts of *in-formation*), perceive *intrinsic* time. This implies a unique *perceiver* possessing a quality of wholeness and again, the perception of wholeness, as we put it here, is not an abstract model or concept, but a basic fact of our experience. There is no question that all of us (with notable exception of schizophrenia patients) perceive ourselves as indivisible and unique human beings, and I surmise that our cult of personality largely expresses the collective acceptance of exactly this fact. While we are consciously aware of ourselves as isolated wholes, however, we do not necessarily attribute such conscious perception to a simple unicellular organism. Therefore, the major problem as we face it here is to understand the nature of the device endowing a most simple living cell with the capacity to behave as an indivisible, self-referential unity. Can evolution theory shelter us in resolving this matter?

## A Little Bit of Evolution Theory

> *Nothing in biology makes sense except in the light of evolution.*
>
> T. Dobzhansky

Needless to say, we cannot address the different facets of evolution theory even briefly here. In a nutshell, the evolution theory provides a conceptual framework for understanding the relationships between organisms and their surroundings, assuming that all life phenomena are shaped by natural selection favoring inheritable genetic changes that appear by chance and become fixed by selective pressure—provided they increase the competitive fitness of the organism(s) in the given environment (Meyr 1988). It should be noted in passing that notwithstanding the important role of spontaneous genetic change in the process of evolution, there are reasonable arguments in favor of the view that adaptive phenotypic changes often precede and even facilitate the genotypic changes (Bateson 1979; Maturana and Varela 1987). Indeed, phenotypic changes appear to be able to unmask a hidden genetic variability. One good example is the cavefish *Astyanax mexicanus,* in populations of which the morphological alterations of the eye size depend on the buffering function of the heat shock protein HSP90. This protein normally forestalls the appearance of vulnerable polymorphic variants, but the environmentally modulated stability of HSP90 can specify the penetrance of particular genetic traits (Rohner et al. 2013).

From its very outset, the evolution theory was stigmatized by a struggle between the Lamarckian view of the inheritance of acquired characteristics, assuming that the environment can directly affect the gene pool of an individual, and the classical view, postulating that new characters appear by means of the impartial process of natural selection acting upon a random genetic change. It is noteworthy that the classical evolution theory dealt primarily with the *vertical* genetic inheritance from parents to offspring as underlying the divergence and speciation (in form of a branching tree) of the plant and animal kingdoms taking place over the last half a billion of years or so. Inadvertently, it neglected the preceding evolution of the prokaryotes and bacteria in particular, which commenced about 4 billion years ago and resulted in the largest biomass on the present-day earth (Sapp 2003). Notably, in prokaryotes the *vertical* genetic inheritance, considered as the only form of inheritance in the classical theory, cannot be easily distinguished from horizontal inheritance (exchange of genetic material between the cells) due to highly efficient *lateral gene transfer* (Nelson-Sathi et al. 2015) that can be mediated by the processes of transformation, transduction, and conjugation. By virtue of the process of lateral gene transfer the evolution of prokaryotes is to a substantial degree Lamarckian, and resembles an expanding net, rather than a branching tree.

## The Essential Biological Unit of Evolution

One scourge of the evolution theory is the apparent ambiguity concerning the essential biological unit that is subject to natural selection: Is it a population of organisms, an individual organism, or perhaps a gene? Especially since theoretically, the benefits for the group can be seen in conflict with the benefits for the individual, and the benefits for the individual can be seen in conflict with the "common interest" of the genome (Leigh 2010). This problem is complicated further by ambiguities of definition. For example, population is loosely defined as a group of freely mating organisms belonging to one species and living in the same place at the same time. Although according to classical theory the environment cannot affect the gene pool of an individual organism, the environmental effects can modulate the population size and thus alter the gene pool available for selection (the so-called "random gene frequency drift"), with resultant stable inheritance and propagation of the new traits. Now, by proposition, evolution can be either Lamarckian or non-Lamarckian. Note that with the assumption that the selected biological unit is an individual organism in which the environment cannot affect the gene pool, the evolution would be non-Lamarckian. However, if we assume that the essential biological unit of selection is a population, then evolution would clearly be

Lamarckian, as the environment has a direct effect on the gene pool of the population (Bateson 1979). Note also that an organism and a population (of organisms) belong to different (respectively, digital and analog) logical types and that here, as in the logical paradoxes mentioned above, the truth of the proposition is contingent on logical typing.

Proponents of individual organisms as subjects of selection stumble over the ambiguity of the definition of an *organism*. For example, are the Lichens individual organisms or hybrids of two organisms (Algae and Fungi), and shall the numerous symbiotic organisms be treated as one indivisible entity? The unicellular flagellate protozoan *Myxotricha* harbors several different kinds of bacterial cells (Cleveland and Grimstone 1964). Interestingly, in this organism the flagella are not involved in propelling *Myxotricha,* but just steer it; the unidirectional movement is accomplished by coordinated undulations of many thousands of the *Spirochaetes* bacteria attached to the so-called brackets on the surface of *Myxotricha* cell, whereas some other rod-shaped bacterial species are intracellular, or adhere to the cell surface, such that a single *Myxotricha* is associated with over 100, 000 bacterial cells in total. Whereas the function of the numerous bacterial cells associated with a protozoan cell is not quite clear, their selective elimination by treatment with antibiotics can also kill their protozoan host. Shall we see such a protozoan as a unicellular, or perhaps a multicellular organism?

Organisms are often defined by a list of properties such as the ability to react to stimuli, grow, reproduce, etc. However, a description is not an explanation. More precisely, the organisms have been defined as integrated systems characterized by relations of cooperation and interdependence between the parts (Sapp 2003). But what exactly are the parts? In principle, the parts can be defined functionally by their “causal role in sustaining the existence of the whole” (Kauffman 2013). This means that to qualify something as a genuine “part” of the whole, it is advisable to evaluate its dispensability for the existence of the latter. Does a leg, for example, represent a part of the organism? Regarding its conspicuous function, it clearly does, but on the other hand, we all are familiar with the fact that many people can live without a leg quite happily (think of the Paralympics). True, an animal without a leg can live happily only in a zoo, and much less so in the wild, but nobody can live without a head (unless taken figuratively), be it in a zoo, or in the wild. Therefore, as an essential part sustaining the existence of the whole body, the head would certainly fare much better than a leg, but in such a case we have to admit an existence of parts of diverse essentiality and thus, eventually substitute the genuine parts (whatever they might be) by our *concepts* of the parts.

The notion of a *gene* is even more ambiguous: while in a simple bacterial organism it is possible to assign the property of a gene to a particular stretch of chromosomal DNA, in higher eukaryotes the RNA transcribed from a unique stretch of the DNA can be variably processed and translated into different proteins, making such assignments difficult. The term “gene” is thus often defined operationally depending on the context, evoking various notions that are featuring a gene either as a physical structure, or functional entity (Prohaska and Stadler 2008). Despite this ambiguity, the focus on a gene as an explicit biological unit of natural selection provoked wide attention, perhaps due to the posited extreme view maintaining that the organisms represent mere "vehicles" constructed by "selfish" genes for the purpose of facilitated propagation[2] (Dawkins 1976). However, it seems obvious that understanding of "selfish" behavior cannot miss some definition of the implicitly postulated "self", the actuality of which must logically precede any *selfish* behavior. Furthermore, the definition of a behavior as selfish is prone to errors of logical typing by itself. For example, an antelope on watch often separates from the group to keep an eye on the lurking predator, thus potentially exposing itself to danger. Now if we assume that the individual is an antelope, we may interpret this behavior as altruistic. However, if we assume that an individual is the group (a subpopulation) then we may wish to interpret this behavior as selfish (Maturana and Varela 1987).

## The Replicator Hypothesis and Errors of Logical Typing

The origin of the "selfish" behavior of a gene as a unit of natural selection has been proposed to have its roots in the so-called replicator molecules (Dawkins 1976). This conjecture seems to be a bit too hasty a jump, primarily because separately no particular molecule by itself, be it a replicator or not, appears to be either alive or possess any "self-ness". From all we have discussed above concerning the difference between animate and inanimate matter, it follows that in order to mimic the adaptive behavior of living matter, the replicator molecule(s) must be able to perceive the environmental alteration (make a distinction), react on it (meet directional choice), and change accordingly (become in-formed). In short, the replicator molecule must be acting as a self-referential unity capable of producing *information*. The same argument applies to self-replicating sets of autocatalytic molecules, which only catalyze particular types of reactions, and thus demonstrate purely deterministic behavior, unlike living matter (*cf* Kauffman 2013).

In contrast to the anonymous replicator, a *gene* is sensibly defined only via its phenotypic manifestations, associated with its function in the context of a living organism (Prohaska and Stadler 2008). This difference cannot be simply poured off, especially if the evolution theory is to be founded on "competition" between inanimate replicator molecules. Indeed, while inanimate matter may cooperate (think of the dissipative systems, or an avalanche), it cannot compete—this latter affair appears to be exclusively an undertaking of living beings. A river does not compete with the ebb and tide at its confluence with a sea, neither do the pebbles in

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[2] From this view it may appear surprising that the selfish genes of such remarkably intelligent vehicles as for example, Thomas of Aquinas, Immanuel Kant, and Søren Kierkegaard (to mention just a few illustrious ones), firmly denied any chance of propagation to themselves.

a sieve compete for the mesh, and if we let biological molecules compete with each other in a complex mixture, it is our complex skills as sentient living beings that enable the confrontation of isolated molecules in such a way as to imitate the process of life. In short, whenever the term competition makes sense *biologically*, it implies the capacity of discrimination between oneself and the others, and thus presupposes self-referential organization. The corollary is that to be tenable, any concept of evolution grounded in the replicator hypothesis has to take into account the exegetic gap between the organizational properties of inanimate and animate matter. This gap cannot be bridged by assumptions of an extraordinary fecundity and/or longevity of the replicator molecules, because as discussed above, the difference between inanimate and animate matter is that of *organization*, and not of quantity.

It is important to emphasize that by definition, the only thing a replicator can do is to replicate, whereas the process of replication is not tantamount to life. For example, some types of mammalian neurons can remain perfectly alive without any need of replication throughout the lifespan of an organism and far beyond (Magrassi et al. 2013). This means that in these dwelling neurons, over time no single molecule or even an atom is the same any more, whereas their organization is fully preserved. A more important circumstance, however, is that in fact a cell does not replicate, but rather reproduces itself. Whereas replication produces a copy, reproduction produces two unities of the same class (daughter cells having similar organization, but not necessarily identical structure) in a process akin to ordered fracture, rather than to copying. Furthermore, for a fracture to be *reproductive,* the involved unity must be organized in a distributed way- that is, it has to have *continuity* (think of a bar of chocolate, or of those plants that can be propagated by fractured branches), such that after the fracture both subunits independently retain the same original organization (Maturana and Varela 1987). Thus what we normally observe is that in any cell, as the simplest unit of life known to us, the replicator activity of a unique DNA molecule is inextricably coupled to a continuous membrane-bounded entity, preserving its class identity after its reproductive fracture.[3]

Be it all as it may, the crucial point relevant to our argumentation is that within the framework of both the "selfish gene" concept and the mathematically underpinned population genetics in general, the term "gene" is used explicitly to denote *digital* units of information and distribution frequencies thereof. It is perhaps not too misleading to draw an analogy between this attitude of exploring the relatedness of genomes, and linguistics approaches that assess the relatedness of different languages

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[3] From this view, the viruses having either DNA or RNA genomes packaged in proteinaceous shells are more akin to inanimate matter, as they acquire behavioral features characteristic of animate matter only after they become part of the cell and hitchhike on its biosynthetic machinery. Notably, whether the viruses evolutionarily preceded the cells, or whether they represent constituents of the genome that escaped from the primordial cells, remains an open question (see e.g. Forterre and Prangishvili 2009).

by "quantifying" the similarity of the semantically corresponding words, while disregarding the syntax (Searls 2002). The treatment of genes as independent entities neglects the fundamental fact that the genes obtain their natural "meanings" primarily as integral constituents of the physical chromosomes, the structural alterations of which provide *analog* information determinative for the genetic activity (Travers et al. 2012; Muskhelishvili and Travers 2013). To this end it is revealing that even the "parasitic" transposable elements (mobile genetic elements thought to be acquired by ancestral germ line cells via infection processes that took place millions of years ago) making up about 45 % of the human genome became "domesticated" and neofunctionalized according to the demands of the host genome, or were otherwise inactivated (Alzohairy et al. 2013). The corollary is that any evolution-theoretical constructions concerning the genes as purely digital entities—by analogy to Gödel's logical system—are doomed to be essentially incomplete. Indeed, recent studies suggest that the selective pressure is not on the genes, but rather on the relationship between genes, genetic regulation and DNA topology (Crozat et al. 2005; Woods et al. 2006; Fang et al. 2013). Notwithstanding the importance of gene frequencies in evolutionary change, as well as all the spectacular achievements of genetic engineering, whatever the individual genes may do, they normally do in the context of the germane chromosomal organization in which they have been *naturally selected*. As unique genes and the configuration dynamics of the chromosomal DNA, respectively, represent the digital and analog components of the same genetic entity (Muskhelishvili et al. 2010; Travers et al. 2012), no full understanding of the evolutionary process can be ever attained without grasping the device converting one logical type of DNA information into the other, thus integrating them into an indivisible unity.

From all these considerations it is obvious that whereas natural selection provides for evolutionary diversity by molding the organisms in different shapes according to the particular environmental pressures, it does not tell us much about the mechanisms rendering the inanimate matter a self-referential entity with an internalized capacity to draw distinctions and making directional choice. It is important to emphasize that what we explore here is exactly the peculiar *organization* of an indivisible unity, or wholeness as an experiential fact *given* by our direct perception, while we shall not concern ourselves with guesses (whatever educated) underlying its *creation*. Without undermining the exegetic power of evolution theory in the least, this means that there should be a clear distinction between the evolution of a primordial primitive organism from inanimate compounds as an indivisible self-referential entity on one hand, and the evolution of variable life forms from such a self-referential entity on the other. Notably, the former appears to be the problem of creating unity from a crowd, whereas the latter is quite the opposite. These two separate problems, each requiring its adequate methodology of exploration, are all too often cobbled together.

## A Little of Methodology

> *Those who investigate the phenomena of life… are crushed under a mass of facts, which they can describe but are incapable of defining in algebraic equations.*
>
> A. Carrel

Living systems, due to their overwhelming intricacy, appear more easily comprehensible when disengaged in parts than as a whole, with the caveat that their disengagement in parts is inevitably associated with irreversible loss of the very phenomenon under the scope—the process of life. In addition, while the disengagement may work quite well, the reconstruction of the whole appears much more problematic. Spectacular advances in molecular biology over the last 60 years reinforced the *reductionist* approach, intending to reconstruct the biological phenomena from molecular interactions. This attitude has a long tradition, being apparently rooted in the philosophy that reality can be measured with mathematical precision. Needless to say, the reductionist approach is useful, necessary, and often unavoidable, but it also has obvious limitations, which should not be overlooked. The assumption that a living organism can be reconstituted from underlying molecular interactions is based on the *belief* that an organism is made up of the sum of molecular interactions, as a machine. We shall not dwell on this questionable belief here. Suffice it to say, that a machine is something that is *designed* and *constructed*, whereas biological system is something *evolved* and *differentiated*. An organism, as a whole, is distinguished from its parts primarily by its *organization,* that imposes constraints on the communications between the parts in order to produce information required for the maintenance and reproduction of the whole (Wilden 1972). This means that while any deviations in the operation of a constructed machine over time such as, for example, an increase in the *degree of freedom* of its operating parts will inevitably compromise its function, the same effect can increase the operational flexibility of an organism (any music performer will confirm this). More so on an evolutionary timescale, it *must* be a bonus for an organism, as otherwise we would still walk on four legs. From a technical point of view, the important point is that reconstruction does not necessarily secure the restoration of organization. Structure and organization in general, and especially in biology, are notions conveying logically different types of information. A particular *structure* can be recognized by a characteristic relationship between its elements in space. For example, we can readily recognize a motionless snake by its characteristic structure. However, we cannot say whether it maintains its characteristic organization as living matter, unless it moves. This is because recognition is a unique event of distinction and therefore, recognition of structure essentially provides digital information. By contrast, *organization* implies a characteristic relationship of structural elements not only in space but also in time, such that these elements cannot be perceived simultaneously, but require successive distinctions. Organization is thus more akin to a process of certain (however infinitesimal) duration and therefore, conceals analog information. The corollary is that restoration of a structure implies reconstruction in space, whereas restoration of

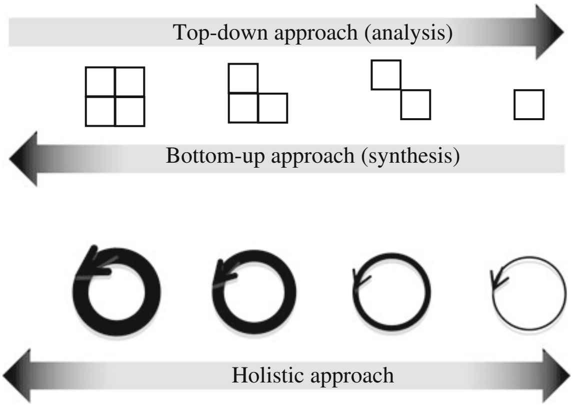

**Fig. 3.2** A schematic depiction of differences between the top-down, bottom-up, and holistic approaches. The change in the number of *squares* in the top-down and bottom-up approaches indicates the loss or gain of organizational complexity. In the holistic approach, the *circle* closing on itself indicates the self-referential organization of the living system, whereas the difference in the thickness of the *circle lines* indicates differences in compositional complexity, but not in organization. Adapted from Muskhelishvili and Travers (2013)

organization implies reconstruction both in space and time. To use a somewhat sloppy metaphor—for the final result it does not matter in which particular sequence a jigsaw puzzle will be assembled, but it can make a lot of difference whether a trigger will be pulled before or after loading a gun.

There are two major approaches based on the reductionist view—the top-down and bottom-up approaches. The top-down approach implies decomposition by moving from the most general level to the more detailed (analysis), and is occasionally confused with the holistic approach. In turn, the bottom-up approach entails ascendance from the detailed to the more general (synthesis). At bottom line, both approaches assume disparate levels of organizational complexity, and by virtue of this very assumption, both are essentially reductionist approaches (Fig. 3.2). In contrast, holistic approach assumes self-referentiality as an organizationally invariant characteristic of living matter, independent of its compositional and/or morphological complexity (Muskhelishvili and Travers 2013). Indeed, in terms of their basic organization, a unicellular bacterium and an elephant are very much the same—they are both alive.

## Autopoiesis

Self-referentiality as a fundamental characteristic of living systems is a focal point in the theory of autopoiesis, defining an organism as a closed circuit. In this theory living systems are observed as *operations* that produce the tools necessary for their operation (Maturana and Varela 1987). In such a system, therefore, the biological processes are streamlined primarily by the need for *internal cooperation* between the elements maintaining the self-reproductive capacity of the living entity that they constitute. Autopoiesis is thus conservative in terms of its demand for consistency of functions and relationships involved in the operation of the living system. A further important implication of the autopoiesis theory is that the living system is defined as "operationally closed". This means that all the changes in the system are only changes of an inner state, whereas the environment, instead of being instructive (as explicitly or implicitly assumed in the evolution theory), rather acts as a "catalyst" triggering the internal changes. Put another way, the changes resulting from the interactions between an operationally closed system and an environmental agent are "brought about by the disturbing agent, but determined by the structure of the disturbed system" (Maturana and Varela 1987). This means that by virtue of operational closure the organism is turned into an autonomous entity, the state of which is primarily determined by structural dynamics of its inherent organization. Since the entire range of structural rearrangements that can be triggered in a living system is delimited by its inherent structural plasticity, the organisms are said to be *structurally determined*. The corollary to this argument is that in principle, the environmental effects will become detrimental if, and only if they exceed the structural plasticity available to an organism.

However, living beings also strongly affect their surroundings (think only of global warming and pollution) and over a geological timeframe a tremendous influence on the environment has been exerted by plants, and still more by the most abundant and oldest organisms on Earth—bacteria. Accordingly, to explain adaptation, the autopoiesis theory substitutes the classical notion of natural selection by the notion of *natural drift*—a stochastic process of structural rearrangements occurring both in living systems, as well as in the environment, with concomitant maintenance of their *structural coupling*. Structural coupling can occur between the system and the environment, as well as between two (or more) living systems (whereby each represents an environment for the other), and is defined as the history of recurrent interactions leading to structural congruence (essentially coadaptation) between the interacting systems. Thus, in notable contrast to evolution theory, the autopoiesis theory considers the organism and the environment not in opposition, but rather in an ever-changing relationship of structural coupling. This notion pertains not only to the system and the environment, but also to two or more interacting systems, including the symbionts (Chandler et al. 2008), as well as the parasites and their host organisms (Zaman et al. 2014).

In the autopoiesis theory the notion of organizational invariance of living matter is embodied in the operational closure of the system. Correspondingly, instead of lineal causality (a causal chain is lineal if it does not return to the starting point), autopoiesis theory introduces circular causality (widely known from cybernetics), meaning that any event that crops up along the path of a closed circuit can act as an effector of all the subsequent events and thus ultimately, act upon itself. This circular organization of biological systems had already been recognized in the nineteenth century by Claude Bernard and became known as *homeostasis*—the capacity of an organism to maintain its internal milieu in balance through permanent self-correction. Such balance is conceivably also a characteristic of ecosystems, and perhaps the entire biosphere (Bateson 1979), with the notable (and regrettable) exception of what we can figuratively call the "humanosphere". It is noteworthy, that a long way before the dawn of cybernetics, Alfred Russell Wallace, the codiscoverer of the principle of natural selection, viewed the entire process of evolution as a cybernetic principle, writing to Darwin that "The action of this principle is exactly like that of the centrifugal governor of the steam engine, which checks and corrects any irregularities almost before they become evident; in that manner no unbalanced deficiency in the animal kingdom can ever reach any conspicuous magnitude because it would make itself felt at the very first step, by rendering existence difficult and extinction almost sure to follow" (Bateson 1979).

However, whereas the autopoiesis theory provides a holistic conceptual framework for exploration of biological systems, the mechanistic device sustaining the operational closure of the system, or put another way, the basic elements and relationships underlying the formation of an integrated unity such as a simple cell, remain largely unspecified. Which properties and relationships of the biological molecules underlie the propensity of a simple cell to act as an indivisible unity capable of creating information by means of distinction and directional choice? We have already mentioned in Chap. 2, that self-referentiality can be achieved by interconversion of two analog types of information (chromosomal configuration and proteome composition) mediated by digital components of the genetic system (unique gene sequences and DNA binding sites). To explain this apparently complex process in mechanistic terms, in the next chapter we have to delve a little deeper into the structural-organizational peculiarities of the best-understood and fairly simple genetic system of *Escherichia coli*—a friendly bacterium dwelling in our gut and normally preventing its colonization by pathogenic bacteria. In the following, it is important to keep in the mind that whenever we use the term *system* with regard to living matter, we mean an autopoietic system. However, for a nonbiologist reader it would suffice to read through the last section (*Chromosomal perception*) of the next chapter only, without suffering substantial losses in the understanding of the main message of this booklet.

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# Chapter 4
# Organization of the Genetic System: Proteins as Vehicles of Distinction

**Abstract** The transcriptional regulatory networks (TRNs) integrate all the known interactions between the numerous transcription factors and their target genes. However, in the TRN, the DNA sites mediating the effects of the transcription factors appear as purely static entities providing the unique "addresses" for their cognate binding proteins, whereas in fact all these gene regulatory interactions are embedded in the physical chromosome, and are modulated by its configuration dynamics. By virtue of its construction, the TRN lacks all information about the structural dynamics of the DNA and its role in regulating the genetic activity. Notably, a gene is a discontinuous entity that can be expressed or not, thus being subject to "on *or* off" logic and therefore, belonging to the digital information type. Conversely, the physicochemical properties of DNA are determined not by individual base pairs, but by the additive interactions of successive base steps. The thermodynamic stability and superhelical density of the DNA are by definition continuous variables subject to "more *or* less" logic and belong to analog information type. It is this latter information that largely determines the chromosomal configuration dynamics, interactions between the remote DNA sites, and ultimately, the expression of the linear genetic code. Analysis of genetic regulation is greatly facilitated by introducing a formalism, allowing the dissection, and quantification of the inputs of *digital* and *analog* control mechanisms.

**Keywords** DNA analog and digital codes · Analog and digital control · Transcriptional regulatory network · Heterarchical network · Regulons · Couplons · DNA supercoiling · Structural coupling · Reciprocal determination · Chromosome morphology

The major components of the genetic system are the proteins, RNA, and their encoding genes embedded in the chromosomal DNA polymer. We shall not elaborate on the RNA here which, notwithstanding its importance in the expression of the genetic code and increasingly recognized role in genetic regulation, has obvious limitations to serve as a major molecule of heredity, due to its peculiar structural properties (Travers and Muskhelishvili 2015). As to the proteins, it is perhaps not too misleading to say that in the eyes of most biologists they are much more "alive",

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than the DNA. This bias has understandable reasons. Proteins are extremely variable in their composition, three-dimensional structure, and biological activity, and participate in assemblies of large intra- and extracellular structures essential for cellular communications, metabolism, signal transduction, trafficking, recognition of "alien" molecules etc. The structural flexibility of the proteins and their propensity to unmask enzymatic activity by virtue of undergoing conformational changes during the molecular interactions makes them superior as vehicles for making distinctions. This property is encoded in the three-dimensional structure of the proteins. However, to explain why proteins alone cannot provide for the indivisible wholeness of living matter, it suffices to content ourselves with relevant ideas expounded in the classical work of Jacques Monod (1977).

Monod observed that the particular structures of the enzymes catalyzing various molecular reactions impart stereospecificity, aiding the selective recognition of their cognate substrates. For example, in the case of the enzyme fumarase catalyzing the interconversion of the fumaric and malic acid, the distinction made by the enzyme is due to the capacity of the three-dimensional structure of the catalytic center to interact stereospecifically (similar to a key and lock principle—but note that currently the preferred explanation is the *induced fit* mechanism, meaning that the initially weak interactions induce conformational changes in the enzyme with resultant strengthening of binding) with only one of the two isomers of the substrates available in nature. Monod inferred that enzymes possess information in the form of stereospecific receptors on their surface, proposing that the entire synthetic capacity of a cell can be explained on the basis of this general principle. However, he also correctly noticed that even though the enzymes would fulfill their role perfectly, the sum of their activities would just cause chaos unless they were somehow interdependent, thus being able to form a coherent whole. The enzymatic activity can be regulated by the so-called allosteric effectors, which are small molecules (including small RNAs) different from the enzymatic substrates that affect protein structure and activity, not by binding in the catalytic center, but elsewhere. It is noteworthy that susceptibility to allosteric regulation is not a privilege of the enzymes—in the previous chapter we have described the example of regulation of the *lac* operon by lactose, which acts as an allosteric regulator of the LacI repressor by changing the structure of the latter in order to reduce its affinity to the operator site.

Monod's conjecture was that since for an enzyme there is a possibility of binding numerous allosteric effectors, the activity of each enzyme could be potentially adjusted by allosteric effectors, thus coordinating the activity of the entire cellular proteome. However, it remains unclear *what* regulates the availability of the allosteric effectors themselves. Obviously, in order to fulfill their coordinating function, the availability of allosteric effectors (which themselves often appear as products of enzymatic reactions) must be coordinated in the first place. In this conjecture, the unity necessary to coordinate the independent components of the whole proteome is lacking. Thus despite being excellent vehicles for "drawing distinctions," the proteins alone cannot coordinate the behavior of the genetic system (neither by themselves, nor with the help of allosteric factors) any more than the Gödel numbers can coordinate the behavior of the formal system (as described in Chap. 2). The same argument applies to the numerous distinct small regulatory RNA molecules produced in the cell.

## Transcriptional Regulatory Network

The groundbreaking work of Jacob and Monod in the 1960s of the last century laid down the foundation for another mode of regulation of genetic activity, by proteins binding specific DNA sites. Since then, the genetic activity of any cell is believed be largely governed by an intricate system of genetic control mediated primarily by DNA binding proteins directly regulating gene expression—the transcription factors (TFs).[1] We are already familiar with one member of this wide and diverse family of proteins—the Lac I repressor, switching off the expression of the *lac* operon. Substantial data from dedicated studies over the last five decades in conjunction with the advance of bioinformatics tools enabled the construction of transcriptional regulatory networks (TRNs) integrating all the known interactions between the numerous TFs and their target genes (TGs). Generally speaking, the construction of a TRN is attempting to map cellular behavior to the organization and dynamics of the compiled TF-TG interactions. The TRN of *E. coli* (Salgado et al. 2013) is perhaps the most exhaustive compilation of all known functionally relevant interactions between the TFs and their specific binding sites in the genomic DNA. However, it is noteworthy that in the TRN the DNA sites mediating the effects of the TFs appear as purely static entities providing the unique "addresses" for their cognate binding proteins, whereas in fact all these gene regulatory interactions are embedded in the physical chromosome, and are modulated by its configuration dynamics. Thus by virtue of its construction, the TRN lacks all information about the structural dynamics of the DNA and its role in regulating the genetic activity.

The TRN is a hierarchically organized structure in which the TFs are connected to the TGs on individual basis, with the notable caveat that even for *E. coli* not all the genes and their functions are explicitly known, and in addition, the connectivity of the TRN is prone to changes with the acquisition of new experimental data (Beber et al. 2015a).

The global transcriptional regulators (abundant chromosome-associated proteins regulating large numbers of other genes) are on the top of the hierarchy, whereas the enzymes and structural proteins that are not known to regulate any other gene are at the bottom. Notably, the directional pairwise interactions between the TFs and TGs are unique, such that the TRN provides purely digital information.

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[1] We cannot elaborate here on the topic of various effects of small regulatory RNAs; for recent reviews see, e.g., Li and Izpisua Belmonte (2015), Ipsaro and Joshua-Tor (2015).

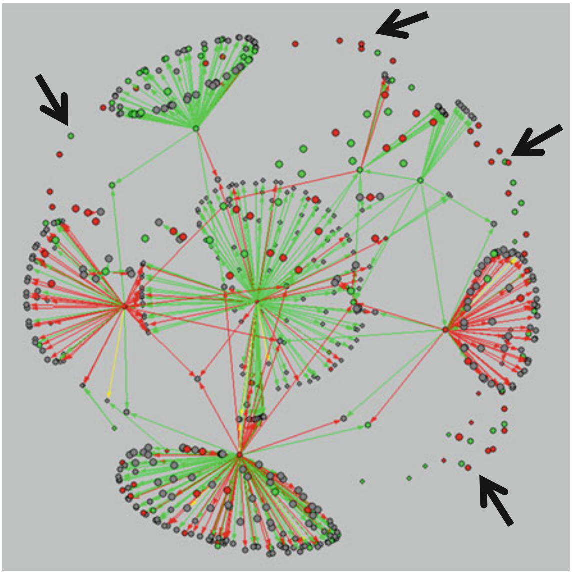


**Fig. 4.1** The effective TRN of *E. coli* corresponding to a snapshot of physiological state. Note that many genes (*colored circles*, with *red color* for repression and *green* for activation) appear without any connections to the others (indicated by *black arrows*). Courtesy Marcel Geertz

Therefore, by analogy to Gödel's FS, the information in the TRN is neither complete nor consistent. This is evident in the analyses of the *effective* transcript profiles, reflecting the experimentally derived "snapshots" of the cellular genetic activity, in which the expression of TFs may change without observable alterations of their putative TGs, and vice versa, the expression of TGs may be changed without observable alterations of their putative TFs (Fig. 4.1; Marr et al. 2008).

The interactions compiled in a hierarchical TRN are not only directional, but also sequential, thus implicating temporal order. By virtue of the hierarchical structure of the network, however, not all the nodes are interconnected, and therefore instead of reacting to perturbation as a unity, such a network can respond only in a fragmentary manner. This makes it obvious that the hierarchical structure of TRN is a poor model of the capacity of a cell to react to perturbations as an indivisible unity (Fig. 4.2). In principle, to be capable of reacting to the environmental signals as a unity, the structure of the TRN must be *heterarchical* (that is devoid of any major regulating entity—essentially circular), rather than hierarchical (Muskhelishvili et al. 2010).

## The Couplon Matrix

Whereas the TRNs compiled for both the prokaryotes and eukaryotes become more and more tightly interconnected with the acquisition of new data (Noversthern et al. 2011; Beber et al. 2015b), such networks remain purely digital. One possible way of integrating the digital and analog components of the genetic system in a

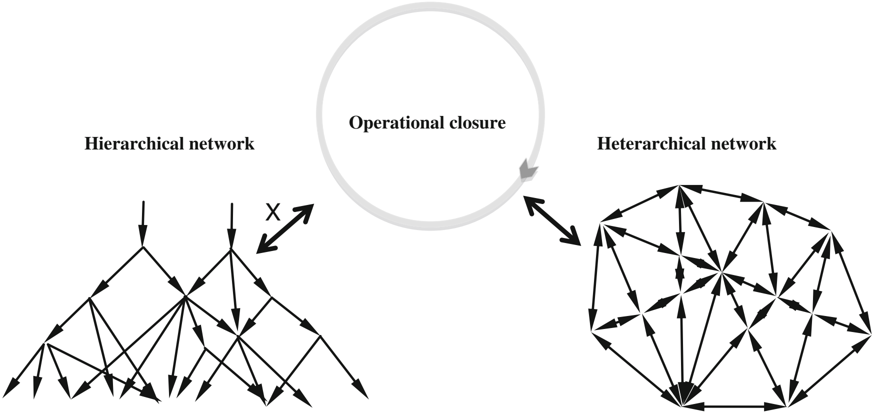
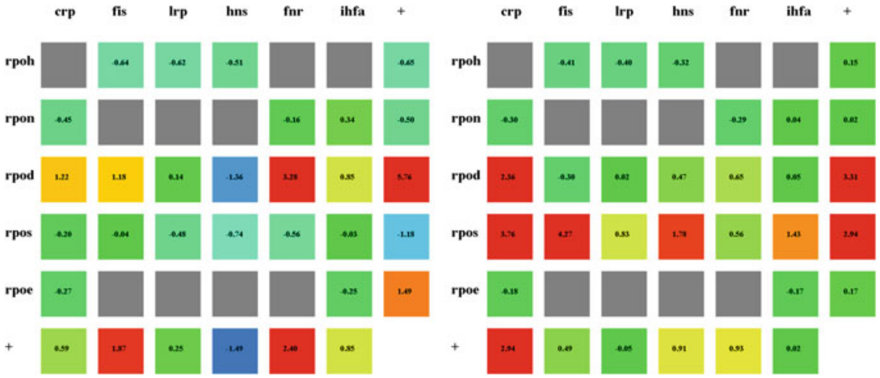


**Fig. 4.2** The difference between the hierarchical and heterarchical networks

heterarchical network is provided by the Couplon Matrix. Yet, to understand how this can be achieved, we have first to clearly distinguish the peculiar effects of the major components of the *E. coli* transcriptional regulation system. In general, the TFs regulate the accessibility of the gene promoters to the multisubunit RNA polymerase (RNAP) holoenzyme, which represents the basal cellular transcription machinery governing the genomic expression. The *E. coli* RNAP holoenzyme is a complex consisting of five subunits (α, β, β′, ω, and σ) in a specific stoichiometry, such that each RNAP contains two α subunits and only one of each of the other subunits. Furthermore, the σ subunit is exchangeable, such that in *E. coli* there can be different RNAP holoenzymes associated with one of the seven specific σ factors. Each of the σ factors endows the holoenzyme with distinct DNA recognition specificity, with the consequence that different holoenzymes selectively bind various gene promoters in the genome, where they can selectively interact with the TFs. Thus to a first approximation, the diversity of the genetic regulatory interactions largely ensues from the changing spatial organization of various combinations of the TFs and the different RNAP holoenzymes in the physical chromosome. The major problem is to understand the mechanism coordinating the spatiotemporal organization of these regulatory complexes in the chromosome, and their changes in adaptation to environmental clues. Notably, since the groups of genes responding to distinct σ factors carry out specific functions (Ishihama 2000), regulation of the RNAP σ factor composition during cellular growth enables flexible control of multiple functions by instantly adjusting the cellular functions to actual physiological needs.

The entire set of genes under the control of a particular TF or a σ factor is denoted as a *regulon*. Thus in *E. coli* there are seven different σ factor regulons in total, serving the recognition of at least 2000 specific promoter sites associated with the operons and isolated genes in the genome. The TF regulons are much more numerous, but most of the TFs are produced at low levels and regulate just a few genes, whereas several highly abundant nucleoid-associated proteins (NAPs) regulate plenty of genes. Therefore the NAPs, alike the σ factors, represent global (analog) regulators of gene expression, as they are produced in high (albeit different) concentrations, and interact with numerous sites in the genome. Taken together, the regulons of the NAPs and the σ factors comprise the entire bacterial genes and therefore, these regulons partially overlap—also in physical chromosomal space. These overlapping sets of regulons controlled by a specific couple of a particular NAP and a particular σ factor are dubbed couplons. Couplons represent entities relatively independent of the regulons (i.e., a couplon can be either activated or repressed without an activation or repression of the entire parent regulons) and comprise functionally related genes. The advantage of the couplons is that they enable monitoring of the information flow between the analog and digital components of the genetic system.

Couplons can be assembled in a matrix comprising sets of unique genes (representing digital units of the genetic system) coordinated by a specific pair of analog regulators (Fig. 4.3), whereby the latter become linked via the digital sets of the functionally related genes that are concertedly regulated. However, since there are numerous genes that are regulated by more than just one particular couple of a NAP and a σ factor, whenever such genes appear simultaneously in different couplons they connect the different pairs of analog regulators by couplon function (Geertz et al. 2011). Furthermore, the genes encoding the analog regulators (i.e., the σ factors and NAPs) are themselves members of the couplon matrix, such that ultimately the changes of the digital couplon patterns and the effects of the analog regulators are interdependent. The interdependence of the analog variables and digital patterns makes the couplon network heterarchical, that is to say, capable to respond to perturbations as a coordinated unity (Muskhelishvili et al. 2010).



| | crp | fis | lrp | hns | fnr | ihfa | + |
|---|---|---|---|---|---|---|---|
| rpoh | | -0.64 | -0.62 | -0.51 | | | -0.65 |
| rpon | -0.45 | | | | -0.16 | 0.34 | -0.50 |
| rpod | 1.22 | 1.18 | 0.14 | -1.36 | 3.28 | 0.85 | 5.76 |
| rpos | -0.20 | -0.04 | -0.48 | -0.74 | -0.56 | -0.03 | -1.18 |
| rpoe | -0.27 | | | | | -0.25 | 1.49 |
| + | 0.59 | 1.87 | 0.25 | -1.49 | 2.40 | 0.85 | |

| | crp | fis | lrp | hns | fnr | ihfa | + |
|---|---|---|---|---|---|---|---|
| rpoh | | -0.41 | -0.40 | -0.32 | | | 0.15 |
| rpon | -0.30 | | | | -0.29 | 0.04 | 0.02 |
| rpod | 2.36 | -0.30 | 0.02 | 0.47 | 0.65 | 0.05 | 3.31 |
| rpos | 3.76 | 4.27 | 0.83 | 1.78 | 0.56 | 1.43 | 2.94 |
| rpoe | -0.18 | | | | | -0.17 | 0.17 |
| + | 2.94 | 0.49 | -0.05 | 0.91 | 0.93 | 0.02 | |

**Fig. 4.3** The couplon matrix. The *left* and *right* panels show the activity of couplons (*red* for high, *blue* for low activity) observed in the transcript profiles of growing and stationary cells, respectively. Columns correspond to the regulons of global TFs, rows to the regulons of seven *E. coli* sigma (σ) factors. The *squares* represent different couplons. Note the increased activity of rpoD ($\sigma^{70}$) couplons compared to rpoS ($\sigma^S$) couplons during the growth (*left panel*) and activation of rpoS couplons on cessation of growth (*right panel*)

# Digital and Analog Control of Gene Expression

Explorations of genetic regulation are greatly facilitated by introducing a formalism, allowing the dissection and quantification of the inputs of different control mechanisms. For example, since the TRN connecting numerous dedicated TFs with their cognate TGs contains purely digital information, the transcriptional regulation exerted by TRN can be considered as *digital control*. Conversely, since the abundant DNA architectural proteins (such as e.g., the NAPs) exert continuous modulating effects on DNA topology and transcription, they act as analog regulators and thus exert *analog control*.

In practice, digital control can be measured by monitoring the ratios of the connected and isolated nodes in the network, so that:

$R = N$ connected/($N$ connected + $N$ isolated)

This value is determined for both the static and the *effective* TRNs, whereby the latter represent subnetworks emerging in the experimentally derived transcript profiles. The effective networks are obtained by mapping the expression profiles on the static TRN structure. They can be analyzed both as snapshots of particular physiological states, and also continuously, e.g., over the entire bacterial growth cycle (Beber et al. 2015b). It is obvious that at best any observed connectivity of the effective subnetworks can be commensurate to the connectivity in the corresponding fragment of the static TRN, but normally it will be lower. Nevertheless, it is possible to determine the significance of changes in the connectivity of an effective network by comparisons to a null model, that is to say, to connectivity of randomly derived networks of similar size (containing similar numbers of genes). In practice, the effective network is compared to $10^4$–$10^5$ of such random networks, so that the significance of connectivity deviation for any given effective network can be determined statistically by calculating the $Z$-scores (essentially, the number of standard deviations from the null model).

Remarkably, the same method can be applied to measurements of analog control but in this case, instead of a link between a TF and its TG, the links are made between the neighbor genes. The rationale is similar—the question asked is how many neighbor genes (starting from the immediately adjacent genes and continuously increasing the separation distance—normally up to 10–20 kbp in *E. coli*) show coherent expression changes in the experimentally derived transcript profile, compared to randomized expression patterns of similar size. In this way, gene proximity networks (GPNs) are generated, which are again compared to $10^4$–$10^5$ of random GPNs, so that the significance ($Z$-scores) of the given GPN can be determined statistically. For both the digital and analog control, the derived $Z$-scores are used as values measuring the control type confidence (CTC) for each type of control in any given transcript profile (Marr et al. 2008).

Measurements of CTC values in *E. coli* cells carrying mutations inactivating the genes encoding the abundant NAPs (*fis* and *hns)* yielded remarkable insights. FIS and HNS are global transcriptional regulators featured in the TRN as "hubs" connected to numerous target genes, so that intuitively their deletion is expected

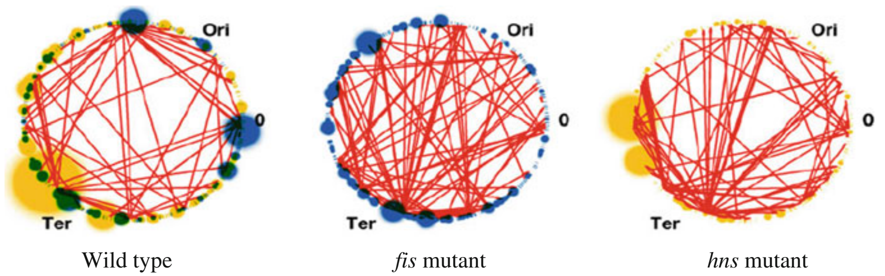


**Fig. 4.4** The relationship between digital control (*red lines*) and analog control (*blue* and *yellow spheres*) in the transcript profiles of the wild type and mutant *E. coli* strains. Note that the digital control is increased in the mutants at the expense of analog control (adapted from Marr et al. 2008)

to reduce the connectivity of the TRN. By contrast, instead of the expected decrease, the mutations inactivating *fis* and *hns* significantly increased the TRN connectivity (Fig. 4.4). Recall that despite being featured as hubs in the "digital" TRN, the NAPs are actually analog regulators affecting the genomic transcription by modulating the DNA supercoiling and chromosome dynamics. Furthermore, it was shown that in wild type cells, the global genomic transcription and metabolism are mainly under the control of analog regulators, such as DNA supercoiling and the NAPs, whereas the impact of TRN is negligible (Sonnenschein et al. 2011). These findings led to an important inference that in both the *fis* and *hns* mutants (and by extrapolation any other mutants lacking the abundant DNA architectural factors), the trade-off in gene communications due to absence of the "analog" chromosome-shaping effects of the NAPs is balanced by maximizing the "digital" TRN connections, in keeping with the self-referential organization of the genetic system (Marr et al. 2008).

## Two Types of Information in the DNA

In Chap. 2, we have mentioned that the syntactic and semantic properties of natural language provide logically different types of information, with the former determining the rules for the assembly of the words in sentences (i.e., the grammar), and the latter their meaning (i.e., the vocabulary). An important point is that neither the structural rules of language can determine the meanings of the words, nor is the vocabulary determinative for the structural rules of the language (i.e., syntax and semantics are not convertible). Thus, viewed as a coding system composed of two nonconvertible types of information, natural language is *not* self-referential. In contrast, the information harnessed by the genetic regulation system of a cell is self-referential, because it is able to perceive any internal changes of state and replenish its worn-out components, as well as sustain cellular (and thus its own) self-reproduction. We have also mentioned that this self-referential organization of the genetic system is based on the interconversion of logically distinct (analog and digital) types of information specifying each other reciprocally and thus constituting an indivisible *unity* (Muskhelishvili and Travers 2013). The fundamental question therefore is how this self-referential organization is encoded in the primary sequence of the DNA polymer.

As observed in Chap. 2, in addition to the linear genetic code (that is, the unique gene sequences written in distinct succession of individual letters), the primary sequence of the DNA also provides the three-dimensional information, by means of spatially ordered, three-dimensional supercoil structures, relevant to all DNA transactions including transcriptional control (Travers et al. 2012). Recall that despite the above-mentioned difficulties in the definition of the gene concept (see Chap. 3), we can assume that a gene, conceived as an isolated piece of linear code (no matter whether this isolation occurs at the level of transcription or posttranscriptional processing), is a discontinuous entity that can be expressed or not, thus being principally subject to "on *or* off" logic and therefore, belonging to the digital information type. Conversely, the physicochemical properties of DNA, as exemplified by supercoiling and mechanical stiffness, are determined not by individual base pairs, but by the additive interactions of successive base steps. Thus the thermodynamic stability and superhelical density of the DNA are by definition continuous variables subject to "more *or* less" logic and so belong to analog information type. It is this latter information that largely determines the chromosomal configuration dynamics, interactions between the remote DNA sites, and ultimately, the expression of the linear genetic code.

## DNA Supercoiling

The two antiparallel strands of the DNA double helix are normally intertwined in a right-handed sense, but under particular conditions certain sequences can also adopt a left-handed configuration, forming the so-called Z-form DNA (Fogg et al. 2012; Travers and Muskhelishvili 2015). This intertwining of the strands leads to formation of two grooves along the double helix, the width of which may vary with DNA form, but in the canonical B-form one groove is wider (major groove) than the other (minor groove). The DNA grooves differ not only in terms of their physical parameters but also in terms of their exposed chemically active "exocyclic" groups. However, under torsional stress, the axis of the double helix can also adopt a coiled configuration, generating DNA supercoils. DNA superhelicity is a topological parameter meaning that both in covalently closed circular DNA molecules characteristic of the bacterial genomes, or any linear eukaryotic chromosomes with anchored ends, the superhelical density is preserved under any conformational distortions, unless a nick is introduced into the DNA, such that one DNA strand is allowed to freely rotate around the other. This rotation is induced by release of DNA supercoiling energy due to either an excess or deficit of helical turns compared to the fully relaxed state. In the latter one, full turn of the DNA helix encompasses about 10.5 bps. Both the over- and underwinding of the DNA lead to change of the helical repeat (respectively less and more than 10.5 bps per one turn of the DNA helix). The introduced torsional strain leads to structural distortions demanding optimization of stacking interactions between the successive base steps, such that the over- and underwinding, respectively, generate positive and negative supercoils by deflections of the double-helical axis, relieving the "stacking discomfort" of the base steps. Numerically, the supercoiling of the DNA is described by linking number (Lk), representing the sum of the two geometric parameters: Twist (roughly the average inclination angle of the base pairs integrated over the entire polymer length), and Writhe (approximated by the average number of crossings of the DNA helical axis with itself). Whereas in the absence of strand breaks the Lk remains constant, the DNA polymer has an ability to partition the superhelicity between the Twist and Writhe (Tw <–> Wr).

Accordingly, any change in the Lk of a topologically closed DNA molecule is accommodated by compensatory changes of both parameters, albeit to different extents depending on the environmental conditions:

$$\Delta \mathrm{Lk} = \Delta \mathrm{Tw} + \Delta \mathrm{Wr}.$$

The linking number of a DNA molecule in a relaxed state ($\mathrm{Lk}_0$) is calculated as:

$$\mathrm{Lk}_0 = N/h$$

where N is the number of base pairs in the given DNA molecule, and *h* is the helical repeat (normally assumed to be 10.5 bps). In most organisms, the DNA is negatively supercoiled, meaning that globally it is underwound and so carries less supercoils (about 6 % of linking deficit), than in a relaxed state (this does not exclude an existence of locally overwound regions). The linking deficit (ΔLk) is calculated as:

$$\Delta \mathrm{Lk} = \mathrm{Lk}_0 \text{ - } \mathrm{Lk}$$

It is obvious that the linking deficit will strongly depend on the size of the molecule, making the definition somewhat cumbersome. The problem imposed by large variations of ΔLk values calculated for the DNA molecules of widely variable size, is obviated by introducing the term called superhelical density (σ), which is calculated as follows:

$$\sigma = \Delta \mathrm{Lk}/\mathrm{Lk}_0.$$

In spite of huge differences in size, the superhelical density of naturally occurring DNA molecules varies in a relatively narrow range from −0.01 (strongly relaxed) to −0.1 (hypernegatively supercoiled). The negative sign indicates that in most organisms (excluding some hyperthermophilic bacteria and archea thriving at temperatures close to the boiling point of water), the DNA is negatively supercoiled.

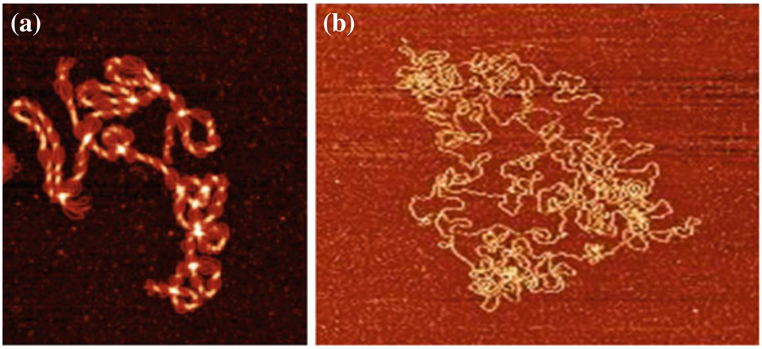


**Fig. 4.5** Atomic force microscopy (AFM) images of the highly negatively supercoiled (**a**) and relaxed (**b**) circular DNA molecules. Courtesy Aleksandre Japaridze (Japaridze 2015)

Both the global relaxation and hypernegative supercoiling are potentially detrimental because they, respectively, decrease and increase the chemical activity of the DNA, thus making it either too inert to react to the environmental changes, or too vulnerable to maintain its integrity under their influence. However, since the negatively supercoiled DNA (Fig. 4.5) is only slightly underwound, this facilitates the activities of the major enzymes such as, e.g., DNA and RNA polymerases, which utilize local unwinding of the DNA to initiate the essential processes of replication and transcription, respectively.

## The Role of Supercoiling in Shaping the DNA

The chromosomal configuration largely depends on the amount of superhelical tension stored in form of the coils, whereas DNA is found to generate a wide range of distinct structures stabilized in response to torsional stress. Importantly, the DNA is a heterogeneous polymer, and the partition between Twist and Writhe (i.e., preferred DNA geometry) is influenced by both the DNA base composition and the base sequence. The preferred configuration depends on the sign of the coils, as well as on the supercoiling level. For example, positively and negatively supercoiled DNAs form left-handed and right-handed crossovers, respectively. The left-handed crossovers appear to be stabilized by interactions between the negatively charged sugar–phosphate backbone of one DNA helix and the positively charged side-chains of bases (cytosine) in the major groove of another, whereas the less-stable right-handed crossovers involve the major groove—major groove interactions (Timsit and Varnai 2010). Accordingly, computational simulations of the molecular dynamics (MD) of supercoiled DNA also suggest that under excessive torsional stress, the right-handed (negative) coils are more easily denatured than the left-handed (positive) coils (Harris et al. 2008). The right- and left-handed crossovers thus not only have different stability, but also distinct local

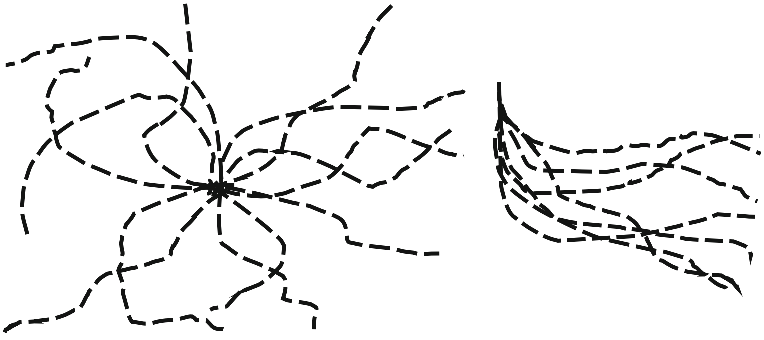


**Fig. 4.6** The configurational space depends on the flexibility of the DNA sequences. Highly flexible (isotropic) and less flexible (anisotropically bendable) DNA sequences (*left* and *right* panels, respectively) occupy different volumes of configurational space. Adapted from Muskhelishvili and Travers 2014

geometries that can be specifically recognized by DNA topoisomerases—enzymes removing or adding the DNA coils and thus homeostatically adjusting the supercoiling level, in order to optimize the function of the DNA replication, transcription, and recombination machineries (Menzel and Gellert 1983; Zechiedrich et al. 1990, 2000; Forterre and Gadelle 2009; Timsit 2011). Furthermore, depending on the environmental conditions, the different dinucleotide steps can adopt distinct preferred configurations, so that strategic arrangements of such flexible steps can impose a preferred bending directionality or *bending anisotropy* on a DNA sequence (Travers et al. 2012). For any DNA polymer of a given sequence, the entire repertoire of such structures defines the configurational space, which varies depending on the particular sequence organization (Fig. 4.6).

On average, the relatively stiff (GC-rich) and more flexible (AT-rich) DNA sequences will occupy different configurational spaces, and stabilize various structures so that ultimately the range of such structures will depend on the primary sequence organization of a given genome. Note that given the topological closure of the naturally occurring DNA molecules, the concept of finite volume of a configurational space can be seen as a molecular counterpart (at the genomic level) of the concept of *structural determination* of living systems, assumed in the autopoiesis theory and claiming that the entire range of structural rearrangements that can be triggered in the system is delimited by its inherent structural plasticity (see Chap. 3). Importantly, whereas the superhelical density of the DNA is an analog parameter, the various distinct three-dimensional DNA structures stabilized under particular states of superhelical density specify the binding pattern of regulatory proteins including the RNAP σ factors and the TFs (Kusano et al. 1996; Schneider et al. 1997/1999; Bordes et al. 2003; Ouafa et al. 2012; Brázdaa et al. 2012; Wei et al. 2014), so that ultimately the changes in superhelical density are directly transmitted to the gene regulatory machinery. As we will discuss below, the sequences with bending anisotropy, as well as easily deformable sequences, can serve not only as signatures

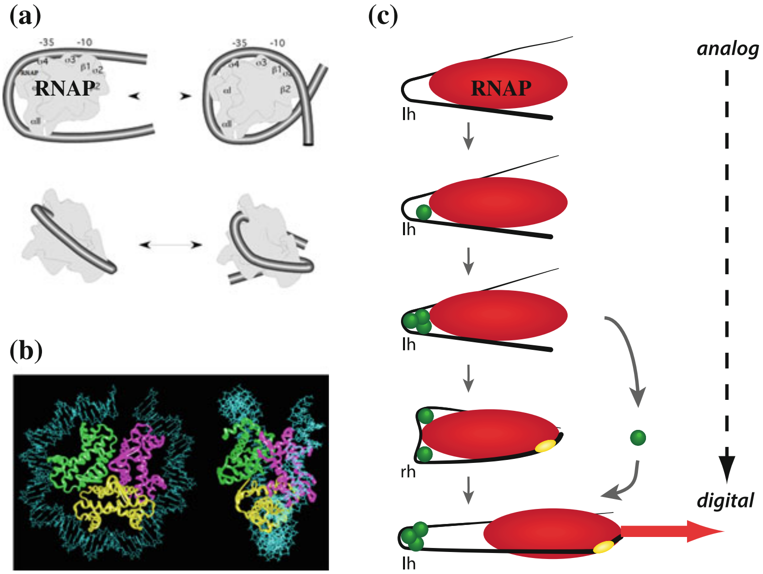


**Fig. 4.7** The mechanism of torsional transmission. **a** Binding of RNAP (gray object) constrains a bent loop, which can fluctuate between the planar (on the *left*) and writhed (on the *right*) configurations (*upper panel*—top view, *lower panel*—view from the apex of the loop; adapted from Muskhelishvili and Travers 2003). **b** Binding of a DNA bending transcription factor (*green*, *magenta* and *yellow*) on the inside of the loop stabilizes a particular configuration facilitating structural transitions in the complex (courtesy Thomas Hermann). **c** The torsional energy stored in the bent loop formed on binding of RNAP (*red oval*) is transmitted to the promoter sequence facilitating its untwisting (*yellow oval*) and transcription initiation (*red arrow*). Transmission of torque is enabled by fluctuation of the bent loop from the *left-handed* (lh) to *right-handed* (rh) configuration, assisted by differential binding of a TF (*green spheres*). Note that in this process the DNA 3D (analog) information is converted into linear (digital) information of the expressed gene. Adapted from Muskhelishvili and Travers 2013

for recognition, but also as repositories of supercoils relieving any excessive superhelical stress, as well as dynamic structural switches selectively channeling the torsional tension (Fig. 4.7) to facilitate the unwinding of individual gene promoters (Muskhelishvili et al. 1997; Travers and Muskhelishvili 1998; Hatfield and Benham 2002; Pemberton et al. 2002; Muskhelishvili and Travers 2003; Kouzine et al. 2014).

## Changes of Supercoiling and Digitalization of DNA Transactions

There is ample evidence that whereas the superhelical density determines the structural dynamics of the chromosomal DNA polymer, the structural dynamics and configuration of the chromosome in turn play a central role in genetic regulation, both in prokaryotes and eukaryotes (Travers and Muskhelishvili 2005; Naughton et al. 2013; Rao et al. 2014). The crucial point, however, is that the DNA superhelical density itself varies as a function of energy supply. In growing *E. coli* cells, the chromosomal DNA superhelicity changes depending on the metabolic state of the cell (McClellan et al. 1990; Hsieh et al. 1991; van Workum et al. 1996; Snoep et al. 2002; Sobetzko et al. 2012). This alteration of DNA topology modulates the chromosomal compaction and therefore the accessibility of gene promoters to the transcription machinery, including the transcription factors; hence this alteration modulates the genetic activity. We have mentioned above that this continuous mode of influence on the genetic activity, dubbed *analog* control, differs from the purely *digital* effects of interactions between the TFs and TGs (Marr et al. 2008), and that the analog control was found to be the predominant regulatory mode of the cellular metabolic activity (Sonnenschein et al. 2011). This is not surprising, given the direct dependence of the DNA superhelical density on the metabolic potential of the cell and especially, on the ATP/ADP ratio (van Workum et al. 1996). The energy of ATP, as the major energy source in the cell, is transmitted to the bacterial chromosome via the activity of DNA gyrase (Stuger et al. 2002), an enzyme introducing negative supercoils into the DNA in an ATP-dependent manner.

The activity of DNA gyrase thus directly links the cellular metabolism to the topology of DNA. The expression and activity of gyrase is in turn modulated by the NAPs, some of which directly bind the promoters of the gyrase genes, whereas others constrain the DNA supercoils and thus withdraw them, albeit temporally, from the free pool available to the gyrase enzyme (Bensaid et al. 1996; Malik et al. 1996; Schneider et al. 1997/1999; Keane and Dorman 2003). Excessive free supercoils generated by the activity of DNA gyrase or DNA translocases (see below) are removed by DNA-relaxing topoisomerases I and IV, so that the opposite effects of these enzymes and DNA gyrase keep the global supercoiling in a homeostatic balance (Menzel and Gellert 1983; Zechiedrich et al. 2000). Moreover, the genes of the topoisomerases themselves are also under a homeostatic control: DNA relaxation increases the gyrase production, whereas high superhelicity increases the production of the topoisomerases I and IV.

Storing supercoils in the form of higher order structures also plays an important role in relieving the torsional strain transiently induced by the processes of replication and transcription. The enzymatic machineries (replisomes and RNAPs), translocating along the DNA by successively untwisting the strands of the double helix, generate a force, such that positive supercoils are induced ahead and negative coils behind the moving enzymatic complexes (Liu and Wang 1987). Under such circumstances, easily deformable DNA sequences are supposed to act as sinks, withdrawing the excessive supercoils which would otherwise impede the translocation of enzymatic machineries (Travers and Muskhelishvili 2013). In short, the cumulative effects of DNA topoisomerases, NAPs, and DNA translocating enzymatic machineries determine the genomic distributions of the *effective* superhelicity that specifies the preferred local geometry of the chromosomal gene promoters (Travers and Muskhelishvili 2005; Blot et al. 2006), whereas the entire repertoire of such local structures in turn determines the binding pattern of the regulatory

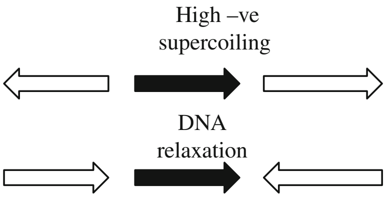


**Fig. 4.8** Spatial organization of the transcriptons (*white arrows*) determines the supercoiling preferences of the gene (*black arrow*) located in-between. The divergent (upper panel) and convergent (*lower panel*) orientation of the flanking transcriptions, respectively, increases and decreases the negative (−ve) supercoiling of the DNA in the region enclosing the gene by the Liu and Wang (1987) mechanism. Accordingly, the genes requiring high negative supercoiling and DNA relaxation for activation will, respectively, prefer divergent and convergent orientations of their immediate neighbors

proteins and ultimately, the expression of the linear genetic code. On this view, the local untwisting of the DNA sequences in the promoter regions during the transcription initiation represents the process of "digitalisation" of the analog information provided by the chromosomal supercoil dynamics. And since supercoling itself depends on the available metabolic energy, this energy availability is directly transmitted to the chromosomal gene transcription.

An additional means of harnessing the supercoil energy in the genome is the relative orientation of the transcription units (*transcriptons*). For example, divergently oriented transcriptons will supply a third intermediate transcripton located in-between them with high negative superhelicity, whereas convergently oriented transcriptons will supply the intermediate transcripton with positive superhelicity (Fig. 4.8). Thus the "digitalization" of the supercoil energy by local untwisting and activation of the neighbor transcriptions will be immediately relayed to the intermediate genes modulating their activity. This modulation will depend on the spatial orientation of the flanking transcriptons, and thus ultimately generate spatial patterns of coherently expressed genes, such as the GPNs mentioned above (Marr et al. 2008).

To summarize, the energy-dependent supercoil dynamics stabilizing the three-dimensional "recognition" signatures in the DNA mediate the conversion of the analog information of chromosomal supercoil dynamics into the digital pattern of genomic expression, which in turn specifies the composition of the proteome. As already mentioned above (Chap. 2), the latter determines the digital information of DNA binding site occupation by DNA architectural proteins that feeds back into the structural dynamics of the chromosome, thus closing the circle. The crucial point is that potentially, any local topological change induced in the chromosome by the actions of DNA topoisomerases or DNA translocases can be distributed in the entire topologically closed molecule and thus "perceived" by the polymer globally. It is exactly this mechanistic coupling between the local and global configurations of the topologically closed DNA molecule that endows it with the crucial property of wholeness, or unity.

## Structural Coupling and Reciprocal Determination

Whereas we have sketched the operational closure of the genetic system as a circular process converting the chromosomal supercoil dynamics into the gene expression patterns and vice versa, we still need to define the coordinating mechanism. An important insight was provided by the finding that during the *E. coli* growth cycle the changes in DNA topology and the composition of transcription machinery appear tightly coordinated, so that different sets of genes are transcribed by specific transcription machineries at a particular (optimal) superhelical density of the DNA (Geertz et al. 2011). This structural “fitting” between the DNA topology and the composition of transcription machinery has been termed structural coupling (Muskhelishvili et al. 2010), in allusion to Maturana and Varela’s notion of structural congruence emerging in the process of co-adaptation of two (or more) interacting systems (see *Autopoiesis* in Chap. 3). But how is this structural coupling sustained over the course of virtually permanent environmental change?

To a first approximation, the changing genetic activity during the *E. coli* growth cycle, is determined by the changing balance of the activity levels of the RNAP$\sigma^{70}$ and RNAP$\sigma^{S}$ holoenzymes (Ishihama 2000; Hengge-Aronis 2002). It was observed that the RNAP$\sigma^{70}$ and RNAP $\sigma^{S}$ holoenzymes prefer different supercoiling regimens for transcription (Kusano et al. 1996; Bordes et al. 2003; Geertz et al. 2011) and accordingly, their relative impacts in global transcription change with alterations in the topology of DNA and hence, the cellular metabolic state. More specifically, the RNAP$\sigma^{70}$ holoenzyme activity is higher under conditions of high negative superhelicity in rich medium during fast bacterial growth, and is inhibited by guanosine tetraphosphate (ppGpp), a small molecule accumulating with incipient starvation and assisting in the transition of the cells to stationary phase and growth cessation. Concomitantly, the RNAP$\sigma^{S}$ is activated, and the DNA is relaxed (Travers and Muskhelishvili 2005). However, it was also observed that an increased impact of RNAP$\sigma^{70}$ and RNAP $\sigma^{S}$ holoenzymes in the cell respectively increases and decreases the global negative superhelicity of the DNA (Geertz et al. 2011), implying that the changing composition of the transcription machinery is not only dependent on, but is also itself determinative of the topology of DNA. Accordingly, mutations of RNAP were found to induce adaptive changes in DNA topology and vice versa—experimentally induced changes of topology were found to affect the expression of the components of transcription machinery (Arnold and Tessman 1988; Drlica et al. 1988; Peter et al. 2004; Blot et al. 2006; Geertz et al. 2011). Finally, as mentioned above, both the configuration of chromosomal DNA and the composition of transcription machinery depend on the metabolic state of the cell (Balke and Gralla 1987; Ishihama 2000; Hengge-Aronis 2002; Ladurner 2009; Wellen et al. 2009) and, while being modulated by energy availability, these structurally coupled parameters in turn determine the organization of cellular metabolism (Blot et al. 2006; Conrad et al. 2010; Sonnenschein et al. 2011).

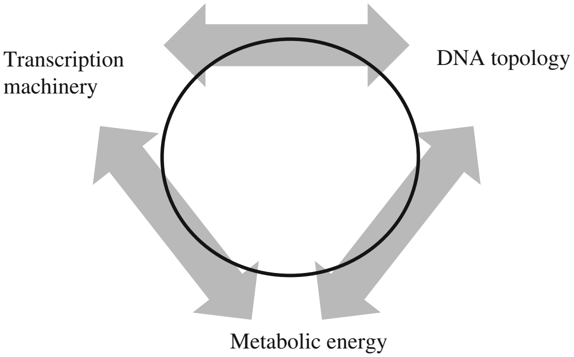


**Fig. 4.9** Sketch of the relationship of reciprocal determination between the elements of transcription machinery, the DNA topology determinants, and the cellular metabolism

Thus, the chromosomal DNA topology, the RNAP holoenzyme composition and the metabolism appear to stand in a relationship of reciprocal determination (Muskhelishvili et al. 2010). This means that alteration of any of the components of this integrated system will inevitably cause an adaptive alteration of the others, thus sustaining the structural coupling by always naturally producing the best-fitting combinations. This relationship of reciprocal determination renders the system circular, as prescribed by the requirement of self-referential organization (Fig. 4.9).

## The Spatiotemporal Model of Genetic Regulation

Once we have briefly described the circular relationships regulating the flow of genetic information in the cell, the remaining question is how these relationships are spatially and temporally organized in the chromosome. In this respect, a revealing recent observation made in the *E. coli* model system is that the spatial order of genes along the chromosomal replication origin (OriC) to terminus (Ter) axis correlates with their temporal expression during the growth cycle (Sobetzko et al. 2012). Importantly, the high negative superhelicity of the DNA observed early during the bacterial growth cycle activates the anabolic genes involved in biosynthetic processes, whereas relaxation of DNA on cessation of growth activates catabolic genes involved in the breakdown of molecules and energy release (Sobetzko et al. 2013). Furthermore, these two classes of genes differently respond to supercoiling (Blot et al. 2006) and occupy different regions of the genome. The former are preferentially clustered around the OriC, whereas the latter are closer to the Ter. In addition, the anabolic genes are on average more strongly transcribed, and utilize more GC-rich codons. The latter property is primarily due to a gradient

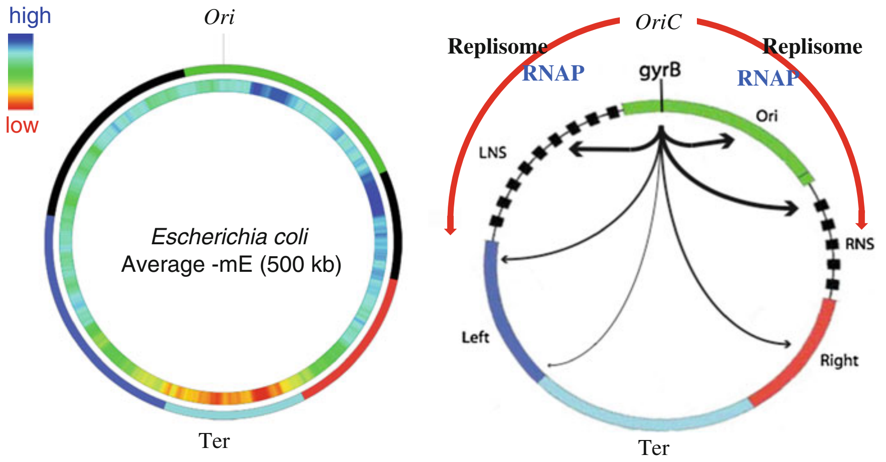


**Fig. 4.10** Gradient of DNA thermodynamic stability (*blue* for high, and *red* for low average negative melting energy; *inner circle* in the *left* panel), and the gradient of gyrase binding site frequences (*black curved arrows* in the *right* panel) in the *E. coli* genome. The chromosomal macrodomains (Valens et al. 2004) are color-coded (*Ori-green*, *Left-blue*, *Right-red*, *Ter-cyan* and the nonstructured LNS and RNS domains in *black*) and the direction of movement of the replisomes and RNAP molecules transcribing multiple ribosomal operons oriented from *OriC* toward Ter are indicated (*red arrows*)

of DNA thermodynamic stability (Fig. 4.10, left panel) along the OriC—Ter axis, featuring the GC-rich and GC-poor sequences in the OriC and Ter ends of the chromosome, respectively (Sobetzko et al. 2013). This gradient correlates with the frequency of GC-rich binding sites for DNA gyrase, the activating effect of which, on the chromosomal OriC end, becomes conspicuous in cells lacking HU, the main NAP constraining the negative supercoils, thus removing them from the free pool (Berger et al. 2010). HU is thought to act as a molecular governor smoothening the apparent supercoiling gradient along the OriC—Ter axis sustained by the DNA translocase activities of the replisomes and the RNAP molecules, the latter moving in trains along the exceptionally strong ribosomal operons oriented from OriC toward the Ter (Fig. 4.10, right panel). This co-orientation of replication and transcription is important for preserving the genomic integrity (Srivatsan et al. 2010) and since the process of translocation untwists and overtwists the DNA behind and in front of the enzymatic machineries, respectively (Liu and Wang 1987), it is thought that the chromosomal Ori end is overall more negatively supercoiled than the Ter end, especially during the frequent replication initiation events characteristic of fast bacterial growth (Travers and Muskhelishvili 2013). At this stage, the chromosomes are relatively expanded and demonstrate a characteristic accumulation of numerous RNAP molecules in the so-called *transcription foci,* engaging the strong ribosomal operons organized around the OriC end (Cabrera and Jin 2003), whereas the Ter end is largely silent. After the exhaustion of nutrients on transition to stationary phase, however, the transcription foci disassemble, the DNA becomes more relaxed, and the chromosomes become substantially compacted, with resultant repositioning of the OriC and Ter ends in close proximity to each other. This compaction is associated with silencing of the OriC end coordinately with cessation of the anabolic gene expression, and activation of the expression of catabolic genes in the chromosomal Ter end (Sobetzko et al. 2013).

Thus the chromosome appears to expand and shrink, or "breathe" so to speak, so that global regulation of gene expression during the growth cycle is ultimately determined by the spatial order and orientation of functionally distinct groups of genes along the OriC—Ter axis, in conjunction with coordinated changes in structural dynamics and the three-dimensional configuration of the chromosome.

## Chromosomal Perception

At this point it should be quite obvious that very much alike the *lac* operon described above (Chap. 3), at the level of the entire *E. coli* chromosome, there are also two successive distinctions—first of the presence of an energy source (oxygen and nutrients) in the medium, and subsequently of its exhaustion—that are mediated by alternative configurations of the chromosome, switching on and off the functionally different gene classes. However, there is one important difference. Whereas in the *lac* operon model, the promoter and the gene sequences are spatially and functionally separated, in the cellular chromosome the genomic "topography" appears inherently coupled to the genic "typography". Notwithstanding the fact that a promoter and a gene belong to logically different types of information (syntax and semantics, as it were), at the chromosomal level the distribution of physicochemical properties of the DNA polymer (analog information) and the spatial order of the genes (digital information) are structurally integrated in the primary sequence organization of the topologically closed chromosomal DNA molecule (Fig. 4.11). The self-referentiality of the system is achieved by the relationship of reciprocal determination between the two codes, one of which is specifying the chromosome configuration, and the other the composition of the proteome; the DNA processing and DNA architectural components of the proteome determine the gross chromosomal configuration via interactions with the chromosomal DNA binding sites, whereas the (thermo) dynamics of the chromosomal DNA polymer in turn determine the genomic expression pattern, and so the composition of the proteome.

By virtue of its topological closure in conjunction with conformational flexibility delimited by the primary sequence organization, the chromosomal DNA polymer appears to act as an indivisible unity "perceiving" the environmental changes by stabilizing particular (appropriate) dynamic configurations from the available configurational space. By means of these dynamic configurations, the DNA "draws distinctions," as it were, between changing environments. Since these particular distinctions (dynamic chromosome configurations) coordinate the genomic expression patterns, or "transcriptional responses," with particular environmental challenges, the DNA also "meets directional choice," and finally, it also "names" the

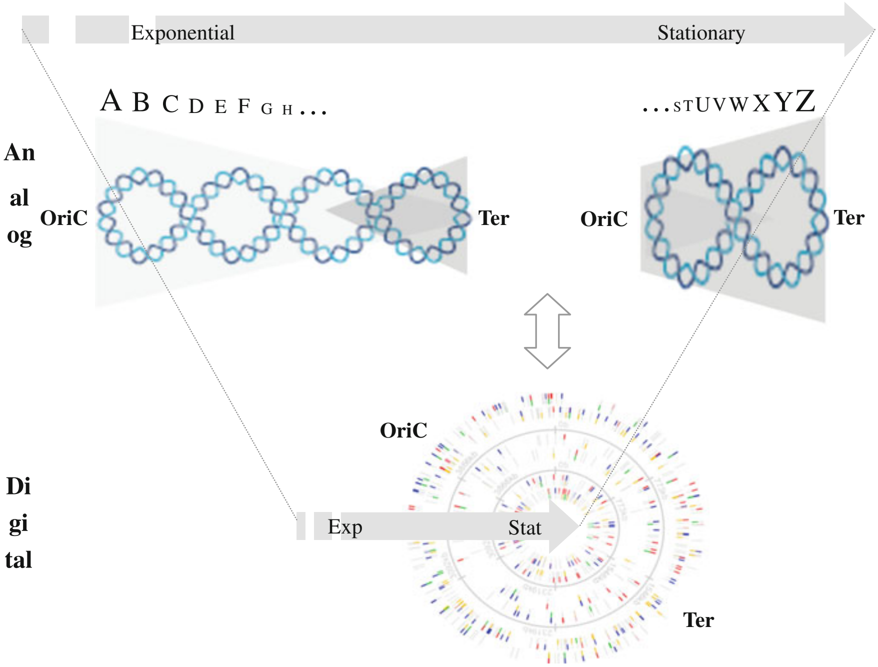


**Fig. 4.11** Spatiotemporal alteration of the chromosomal morphology determines the genomic expression pattern. The upper part (Analog) shows the change in the chromosome morphology (shrinkage) occurring on transition from the exponential growth to the stationary phase. The chromosome is depicted as a plectoneme. The light and dark gray triangles indicate the gradients of regulators of the growth and stationary phase, respectively, arranged spatially along the OriC->Ter axis and diffusing from their production sites according to the temporal order of expression. The chromosomal order of genes (letters) is indicated by alphabetical order (ABCDEFG… for OriC-proximal anabolic genes and regulators active during exponential growth, and …STUVWXYZ for Ter-proximal catabolic genes and regulators active during stationary phase; the gradually changing size of the letters approximates the temporal pattern of gene expression). Note that on shrinkage of the chromosome after transition to stationary phase, the levels of anabolic genes drop dramatically and the OriC end becomes silenced by the gradient of the stationary phase regulators (Sobetzko et al. 2012/2013). The *lower* part (Digital) shows the alteration of the transcript pattern on transition from the exponential growth to the stationary phase. The expressed genes are indicated as colored lines on the chromosomal wheels. *Blue* and *red color* of lines indicates the genes transcribed at high negative superhelicity and DNA relaxation, respectively. The *gray horizontal arrows* indicate the flow of time from the "initial distinction" of high oxygen pressure and nutrients in the medium and initiation of exponential growth (Exp), until the "final distinction" of their exhaustion and growth cessation in stationary phase (Stat). Adapted from Muskhelishvili and Travers (2014)

condition by aiding into the production of the corresponding proteomes "designated" to cope with the given environment. Thus, the dual coding capacity of the DNA endows it with both the self-referentiality, and the wholeness required for any living system—with the notable caveat that in isolation the DNA molecule by itself is not more alive than any other biological molecule.

Two consequences of the dual informational capacity of the DNA are of note. First, it is in keeping with the definition of an autopoietic system as an operationally closed circuit producing the tools required for its own operation (Maturana and Varela 1987) and reveals this operating principle at the molecular level of genetic organization, that is, at its very roots. Second, on this view the DNA does not appear as a simple *replicator* molecule any more, but rather as a cellular *reproduction governor*, with replication process being one essential function taking place in due time and under due conditions (recall, that neurons can dwell for a prolonged time without replication, but certainly not without self-reproduction—that is, without the continuous genetic activity required for replenishment of the worn-out components). As a matter of fact, the "self-referentiality" of the DNA can be realized only in the context of a cell through which it acts to receive its "selfness" in the first place, or else it would be lost. In short, the topologically closed DNA double helix operating within the confines of a simple cell demonstrates the same basic properties—capacity of distinction, directional choice and naming,—which we have observed as being fundamental for any living being, and first and foremost, for our conscious perception of the world.

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# Chapter 5
# Harnessing Energy and Information: Time-Irreversibility of Thermodynamics

**Abstract** According to Second Law of thermodynamics, the entropy of isolated thermodynamic systems can never decrease, because they unswervingly evolve toward the equilibrium, which is a state with maximum entropy. However, all the fundamental laws of physics are time-reversible and this means that the change of entropy has to be time-reversible too, yet that contradicts our observations. In keeping with the Second Law of thermodynamics, living systems "absorb", so to speak, order from the environment at the expense of increased entropy in the latter. However, since our perception always goes with distinction and naming, anything we can distinguish has first to appear in our perception before lending itself to destruction. On this view the Second Law is a reflection of the constitutional property of our perception, in which the distinction and naming of items produce order that necessarily precedes their eventual destruction. On this conjecture any individual organism appears as a genuine, albeit transient, entropy trap. Determination of the entropy of a living system acting as a transient entropy trap is very difficult, if possible at all, because definition of thermodynamic parameters requires equilibrium conditions, whereas in living systems the thermodynamic equilibrium can be attained only after their demise. Yet it appears that under given constraints, natural selection would stabilize the states of optimal cooperation between the interdependent elements of an operationally closed living system at the fastest possible entropy production rate.

**Keywords** Entropy · Perception · Time · Optimal cooperation · Organizational invariance · Maximization of entropy production rate · Energy-information conversion · Sociopolitical system

The regulation of the flow of genetic information outlined in the previous chapter is essentially founded on the particular relationship of interdependence between the discontinuous linear genetic code and the thermodynamic properties of the continuous DNA polymer. It is noteworthy that originally, thermodynamics concerned the transformations of heat into mechanical work and vice versa, but since eventually all the thermal phenomena have been reduced to motions of atoms and molecules, thermodynamics is considered a special branch of classical mechanics.

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In brief, thermodynamics deals with ensembles consisting of such large numbers of atoms and molecules that the details of their behavior are neglected, and only the average properties are accounted for. The difficulty of dealing with such large ensembles is circumvented by statistical character of the laws of thermodynamics, which without entering into the kinetic mechanism of a system can describe generation of disorder from order (increase of entropy) by using only a few continuous parameters such as temperature, pressure, volume etc., In short, thermodynamics exempt us from the need for exploring the behavior of the digital components of a system on the behalf of its analog parameters.

Importantly, according to the balance equation of the Second Law of thermodynamics, the entropy of isolated thermodynamic systems (i.e., systems not exchanging the heat and matter with the environment) can never decrease, because they unswervingly evolve toward the equilibrium, which is a state with maximum entropy. In general terms, entropy is defined as the degree of disorder, or the degree of a lack of correlation between the elements of a system, appearing as a lack of specific features, such as structures and patterns (Lesne 2013). Imagine, for example, a system consisting of two identical balls falling down on the floor. If they reach the floor simultaneously, they will also jump up simultaneously, but the following jumps will become more and more desynchronized, such that ultimately they will become entirely uncorrelated. The entropy of the system with balls would be low initially, and would become larger with increasing desynchronization, or in other words, the increasing degree of a lack of correlation between the jumps. Now imagine the same for a system of a billion balls, and add to that the changes of individual trajectories due to the collisions between the jumping balls. In such a system some of the balls would occasionally jump synchronously, but the probability that *all* the billion balls would jump up simultaneously would be incredibly low.

However, since all the fundamental laws of physics are time-reversible (that is, work symmetrically toward the future and the past) this means that the change of entropy has to be time-reversible too, yet that contradicts our observations. To use a metaphor of Roger Penrose's (Penrose 2011), while we can observe an egg cracking when it falls down from a table, we never observe the opposite (that is, a smashed egg assembling itself and jumping from the floor onto the table). In addition, if according to the theory entropy is symmetrical toward the future and the past, then we have trouble with explaining the past facts of the emergence of order. The theory has to assume occasional transient fluctuations, decreasing the entropy to the extent sufficient to produce such an unlikely and highly ordered process as for example, the phenomenon of life.

Ludwig Boltzmann, the founder of statistical mechanics in the second half of the nineteenth century, provided an apparent solution to this problem by defining entropy (S) statistically as the degree of disorder of a system proportional to the logarithm of the probability of given state:

$$S = k \log p$$

where $p$ is the probability of a given thermodynamic state, and $k$ the Boltzmann Constant. It follows that while a large number of dynamical states can correspond to the same thermodynamic state, the probability of a given state is related to the stability of each such dynamical state. The state of maximum entropy is most stable, meaning that there is vast number of dynamical states near the maximum entropy. Therefore, if the dynamical state of a system is altered, it most probably goes to another high entropy state. This is a simple consequence of the fact that such dynamical states—unless an external force is imposed on the system—are probabilistically much more abundant than the low entropy ones, although theoretically the ordered states are attainable too, yet with an extremely low probability. In short, Boltzmann's inference is that decrease of entropy is highly improbable, but it is possible. In other words, although it is very unlikely, provided sufficient observational time (perhaps comparable to the age of our universe) at some moment we might observe—to use the abovementioned examples—all the billion balls flying up simultaneously, or a smashed egg reassembling itself!

## The Nature of the Second Law

To produce a highly ordered universe as we observe it, the entropy should have been very small at the beginning. But what made entropy very small in the past? This mind-boggling question concerned Ludwig Boltzmann and the contemporary cosmologists alike. Let us take again Penrose's example of the smashed egg. He points out that if we roll an egg off the table and let it fall and crash on the floor, the entire sequel appears to us as a trivial fact comprehended without any problem (unless we roll an egg of a dinosaur in a Museum of Natural History), whereas the opposite (that is, reassembly of the smashed egg into an intact egg) would appear to us as pure magic. Why is it so, that the same sequel of events, once projected in the past and once in the future, appears once possible and once utterly impossible? Penrose's argument is that our universe started in an extraordinarily low entropy state, and as over the time the entropy progressively increases, it is just an *observational fact* that the Second Law of thermodynamics holds good. "Second Law holds no mystery, for our experience of the passage of time is dependent upon an increasing entropy as part of what constitutes our conscious feeling of the passage of time" (Penrose 2011). It is perhaps not too misleading to infer from this sentence that our psychological experience of the passage of time is such that the Second Law always holds true.

Essentially, this amounts to saying that the Second Law is a law of perception. As observed in Chap. 1, perception is the only way we can communicate with what we call the real world, and it embodies distinction, directional choice, and naming (generating information). Now as a matter of fact, a necessary condition for the possibility of perceiving a *smashed* egg is a prior knowledge of an *intact* egg. Although we can readily recognize the smashed egg on the floor even without seeing how it crashed, this recognition is inevitably associated with the perception of (an image of) an intact egg (actualised from the memory) as a prerequisite for the perception of a smashed egg. In other words, without knowing what an egg is, it is impossible to *know* it is smashed, any more than it is possible to perceive disorder before knowing the order, destruction before knowing construction, or death before knowing life. In this example, we first recognize an egg, and then, to put it in terms of Augustine, we perceive time by anticipating that the egg rolling off the table will fall on the floor and smash; we recognize it cracking, and we keep the memory of an intact egg when we see it smashed, or else how could we know it is smashed *egg*? Since our perception always goes with distinction and naming, anything we can distinguish (including eggs, books, continents, pets, and stars) has first to *appear* in our perception and be preserved at least for a while (such that we can name it) before lending itself to destruction. On this view the Second Law is a reflection of the constitutional property of our perception, in which the distinction and naming of items produce order (the state of low entropy, as it were), necessarily preceding their eventual destruction (increase of entropy). And if the Second Law is the law of perception, it becomes easily understandable why its application to the "space-ified" time with equivalent past, present, and future (adopted in physics and mathematics alike) generates a paradox—once more again, we have a case of confounded logical typing.

## Optimal Cooperation

> *When a living organism is penalized, by comparison with other members of its species, through losing the use of a particular organ or faculty, it is apt to respond to this challenge by specializing in the use of some other organ or faculty until it has secured an advantage over its fellows in this second field of activity to offset its handicap in the first.*
>
> Arnold J. Toynbee

According to the autopoiesis theory (Chap. 3), the entire range of structural rearrangements that can be triggered in an organism as an operationally closed system is delimited by its inherent structural plasticity. And it is reasonable to assume that despite the evolutionary unfolding in the structural complexity of living systems, any organism is *optimally* adapted to its peculiar environment within the constraints of its innate structural plasticity. Structural plasticity can be thus seen as an *operational freedom,* in utilizing a range of structures and processes available for coping with a challenge. The corollary is that although the organisms handicapped by genetic mutations appear occasionally in any population, as long as they can sustain their autopoiesis, their adaptation to the environment would be always optimal for the *given degree* of operational freedom. This simple principle can be illustrated on the example of a once eminent circus cripple from Tbilisi (aka Tiflis), who despite lacking both his arms became famous by running a show in which he, among other tricks, was taking meals using his feet! And in passing—he was married (so also the genetically handicapped jazz pianist Michel Petrucciani). This vivid example epitomizes (besides the maternal instinct, making women a good deal better than men) the natural flexibility of living organisms in maintaining their autopoiesis at the expense of compensatory structural changes that optimize their adaptation. Certainly, in this particular case of the circus cripple, there would be a trade off concerning for example, the capacity of eating and walking simultaneously, but the major challenge has been coped by the cripple optimally. Put another way, the assumption here is that neutralization of the negative impact is achieved naturally by *optimal cooperation* between the intact constituents of the challenged system.

By the same token, also in mutants of a unicellular organism, such as *E. coli*, the most probable state of the system will entail optimal cooperation between the interdependent variables within each *given* genetic context. Recent findings of mutually balancing effects of regulatory components of the genetic system are fully consistent with this notion (Marr et al. 2008). We mentioned in previous chapter that in *E. coli* the abundant NAPs modulating DNA topology and chromosomal shape exert "analog control" on transcription, whereas numerous dedicated transcription factors binding few high-affinity sites in promoter regions of specific genes exert "digital control". We also mentioned the finding that mutations of *fis* and *hns* genes encoding the global transcriptional regulators FIS and H-NS, instead of leading to an expected decrease, lead to a significantly increased connectivity of the transcriptional regulatory network (see Fig. 4.3). These findings are in keeping with the principle of optimal cooperation between the components of the genetic control system, suggesting that the impaired spatial communications mediated by the "analog" effects of the NAPs in the mutants are balanced by maximizing the "digital" network communications. The NAP mutations can be thus conceived as events increasing the entropy of the genetic regulatory system by impairing the chromosomal dynamics, which are compensated by "increasing order" in operation of another regulatory mode—the transcriptional network connectivity. Yet this comes at some cost, as the metabolic networks constrained in the mutants are less coherent (Sonnenschein et al. 2011).

Optimal cooperation is akin to purposeful, or "teleonomic", behavior of a living system, yet it has a simple explanation. In fact, optimal cooperation is a natural consequence of the relationship of reciprocal determination between the structurally coupled components of the cellular genetic system (see Fig. 4.9). This means that a change (e.g. a mutation) introduced in any of the interdependent components of the genetic system will automatically lead to readjustment of all the other components in order to optimize the impaired structural coupling. This in turn may lead to phenotypic changes. For example, the genetically engineered *E. coli* laboratory strains, in which the compromised regulatory function impairs the competitive growth fitness compared to wild type cells, may become superior in coping with antibiotics (Gerganova et al. 2015). Accordingly, previous studies carried out in "experimentally evolving" populations of *E. coli* also indicated that mutations harmful in one particular condition might be harmless, or even beneficial, in the other (Cooper and Lenski 2000). Definition of fitness is therefore always relative.

Can optimal cooperation between the components of the reorganized regulatory system in mutant cells be favored by entropy? Interestingly, it was observed that an ordered flow (of matter and energy) in a system would produce entropy *faster* than disordered flow, such that disordered flow would be less efficient at increasing the entropy as required by the balance equation of the Second Law of thermodynamics (Swenson and Turvey 1991; Mahulikar and Herwig 2004). For example, the highly coordinated behavior of heated liquid molecules generating the “dynamic order” of the Benard rolls discussed in Chap. 1, is thought be driven by a higher rate of heat transport (entropy production) as a consequence of increased dissipative surface. It follows that if in the mutant cells the *rate* of entropy production is maximized given the constraints, optimal cooperation between the elements of the challenged genetic system can generate sustainable new order driven by an increased rate of entropy production. The corollary is that under given constraints, natural selection would stabilize the states of optimal cooperation between the interdependent elements of an operationally closed autopoietic system at the fastest possible entropy production rate.

## Organizational Invariance

The principle of optimal cooperation explains how a heterarchical gene regulatory network can absorb, as it were, the changes induced by loss (or gain) of certain individual components and thus, sustain operational closure. In principle, this could be achieved via variable adaptation routes manifest in alternative states of the heterarchical network. However, as we have argued above, the crucial difference between living and physical systems resides in the self-referential organization of the former, and whatever the adaptation route, this organization cannot dwindle, as otherwise the autopoiesis of the system cannot be sustained. The corollary is that all living systems possess an *organizational invariance*, defined as the minimal degree of organization required for the maintenance of operational closure and ongoing autopoiesis. On this conjecture, let us assume that in analogy to the numerous dynamical states corresponding to the same thermodynamic state of a physical system, different degrees of operational freedom correspond to the same invariant organizational state (i.e., self-referentiality) of the living system. In such a case, the genetic system of any cell could be described by its characteristic range of operational freedom (with corresponding range of structural coupling) as a measure of its regulatory capacity. For example, the *totipotent* fertilized egg can produce all of the more than 200 different cell types of the human body, whereas differentiating cells progressively lose this potency. Thus, the egg can be assumed to have a higher operational freedom compared to the differentiated cells. Similarly, the *pluripotent* stem cells, which replenish the mature cells of the body, can be seen as having higher operational freedom than their differentiated progeny. Conversely, most of the cancerous cells progressively lose their differentiation traits, becoming increasingly more stem cell-like, reflected also in an increased similarity of their metabolic traits (Christofk et al. 2008; Apostolou and Hochedlinger 2013; Ito and Suda 2014). This process is accompanied by morphological changes and aberrant rearrangements of the genome, as well as acquisition of variable phenotypes, which is especially remarkable in the teratomas—highly variable tumors that can produce a mosaic of different tissues such as hair, teeth, bone, and also eyes and limbs. Therefore the cancer cells would possess higher operational freedom than their normal counterparts. Note that while the operational freedom of the system can both decrease (e.g. during cellular differentiation) and increase (e.g. during cancer cell progression), the organizational invariance (self-referentiality) is permanently sustained (albeit at the expense of increasing the thermodynamic entropy of the environment). Note also that this considerably complicates the interpretation of the problem with Penrose's example of the smashed egg. If the egg would also lose its organizational invariance by cracking (which is very likely), then even in the very unlikely case of its reassembly by a low entropy fluctuation, it would never hatch.

## Thermodynamics of Living Systems

Penrose maintains that the sun is a powerful low entropy force emitting the high-energy photons driving all diversity of life on our planet, which in turn—in keeping with the Second Law of thermodynamics—emits a much larger number of photons of lower energy (Penrose 2011). In principle, the entire process can be seen as conversion of solar energy into information implicit in the organization of vast diversity of living matter on this planet, from the first photosynthetic organisms directly utilizing the high-energy photons of the sun to generate organic compounds and oxygen, to the higher organisms utilizing oxygen and thriving on degradation of the organic compounds. In notable contrast to thermodynamically isolated physical systems, a biological organism is viewed as a thermodynamically open system, exchanging both matter and energy with its environment, and never attaining true equilibrium unless it deteriorates. Instead, it is said to be in steady state—an apparent equilibrium involving continuous, energy-driven replacement of the worn-out cellular components, and the maintenance of homeostasis. This is basically achieved by using the building blocks and metabolic energy obtained by degradation of the organic compounds derived from the environment. Erwin Schrödinger observed that in keeping with the Second Law of thermodynamics, living systems "absorb", so to speak, order from the environment at the expense of increased entropy in the latter (Schrödinger 1944). On this conjecture any individual organism appears as a genuine, albeit transient, energy or, perhaps better to say, entropy trap. It has been argued that the growth and survival of cells depends on the peculiar relationship between the so-called equilibrium and nonequilibrium hyperstructures, that is, the formation of large ordered aggregates of biomolecules of variable "fluidity", involved in the sustenance of different functions (Norris and Amar 2012). However, determination of the entropy of a living system acting as a *transient entropy trap* is very difficult, if possible at all (Wilden 1972; Lesne 2013). This is because definition of thermodynamic parameters requires equilibrium conditions, whereas as mentioned above, the living systems are very far from the thermodynamic equilibrium, which can be attained only after their demise.

It was Schrödinger's insight that in contrast to physical systems capable of producing order from disorder (especially conspicuous in the self-organizing capacity of the dissipative systems described in Chap. 1), living organisms produce order from order (Schrödinger 1944). Since the structure of DNA was not yet known, Schrödinger proposed that the biological order is produced from an immanent order concealed in some kind of an "aperiodic crystal" embodied in the chromosomes. He thus ascribed a high degree of internal organization to living system, foreshadowing the self-referential device based on the interdependent analog and digital codes of the DNA double helix that enable the conversion of the available energy into information (Muskhelishvili and Travers 2013). As we shall understand it now, this conversion is mediated by (i) "drawing distinctions" via distinct preferred configurations of the DNA dependent on the superhelical energy, and acting as three-dimensional signatures punctuating, as it were, the analog information in the genome, (ii)"meeting directional choice" by specifying the corresponding digital pattern of gene expression and, (iii) "naming" by producing the appropriate proteome with corresponding metabolic profile. The inference is that the cellular chromosome essentially acts as a thermodynamic machine mediating the conversion of energy into information.

## Conversion of Energy into Information in a Sociopolitical System

Since we observe the conversion of energy into information at the most basic level of the organization of life, can we observe the same process at far remote levels of the organization of living matter- let say, at the level of a sociopolitical system? I guess that anybody familiar with the history of the Lunar society will answer in an affirmative way by recalling the vivid example of the Soho manufactory (Uglow 2002) and the social differentiation contingent on the industrial revolution in the XVIII century Britain. But what about during ancient times, long before the invention of the steam engine and the governor?

A well-studied and lucid example of the influence of economics on the human community over a historical period is provided by the history of Iberia (aka Kartli), the ancient country of eastern Georgia. From the North and the South the country was delimited by the mountain ridges of Caucasus major and Caucasus minor respectively, and from the West by the sea, such that the country was isolated by natural borders on three sides, except the desertlike East. Investigations showed that the social organization of the early settlements (in the second half of the second millennium BC) was primarily determined by the physical geography, namely, by existence of numerous deep gorges offering protection from three sides, connected to a plain. Initially the settlements in the gorges were economically self-sufficient. These settlements had their chiefs, and otherwise any member was a free farmer. However, since the tribes dwelling in the mountain gorges were thriving mainly on

**Fig. 5.1** Dependence of the distribution of economical resources on the physical geography of the territory. The *pink color* indicates the agricultural valley producing fruits, vine and corn. The *gray* areas indicate the winter pastures, whereas the *yellow color* indicates the grass and flower-rich regions used as summer pastures. The *green color* indicates the mountainous regions enclosing the valley from the north (Caucasus major) and south (Caucasus minor). Courtesy D. Muskhelishvili

sheep farming, this required the sheep to be driven from mountain pastures to the plain in winter, and back from the plain to the mountain pastures in summer (Fig. 5.1). The sheep farmers provided fur and products of mining to the agricultural plain, which in turn provided salt, foods and vine, such that over the historical time the settlements in the plain and in the mountain gorges became economically interdependent. The intensification of trading and ensuing economical progress naturally led to unification of gorges into bigger political-economical entities connected to a larger strip of the plain, thus forming larger units—small kingdoms. These units were producing and exchanging different goods and this increasingly vigorous trade continued naturally until the united eastern Georgian state of Iberia was formed, in which the economical opportunities offered by the physical geography of the entire country—numerous mountainous gorges connected to a plain—were fully exhausted.

At this time (V century BC) the ruler was an autocratic king who unified the country and subdued the chiefs through his power. The latter became his beneficiaries, and received land from the king for their services, whereby initially this possession was not hereditary. Notably, in the unified country, the plain not only served as a thoroughfare connecting the gorges (the "Sheep Road"), but also as one of the trade routes of the trans-Caucasian "Silk Road", shuffling the goods between the West and East, and providing the country with substantial fines. The development of economics resulted in increased rivalry between the king and his beneficiaries, with the eventual establishment of a full-blown feudal state with a hereditary landholding system and concomitant diminution of free individual farmers at the expense of serfdom. Conversely, the weakening of economical ties by increased inner tensions in the feudal state (in the IX–X centuries), or by invasion (e.g. after eight sequential invasions of Timur the Lame devastating the country between the years 1386–1405), led to decomposition of the state into smaller units, and eventually into the very same isolated "primordial" gorges, which thus appear as natural physical-geographical entities, mediating the coupling between the economics and the sociopolitical organization on the historical scale (Muskhelishvili et al. 2012). In other words, in this example it can be seen clearly how the changing economics (available energy resources) are translated into the particular sociopolitical organization of a human community. It thus appears that the economical progress associated with harnessing the energy resources provided by a particular physical-geographical environment leads to differentiation of new social classes and correspondingly, entails emergence of new social communications (i.e., generates information), whereas social regress entails the return to primordial economics. To this end, there is an interesting parallel with cancer cells, in which the progressive autonomy and deafness to physiological signals of the organism entails not only the changes of morphology, but also recurrence of the primordial ways of deriving energy (Garber 2004; Trosko and Kang 2012). Thus in a sociopolitical system, in analogy to the genetic system, the availability of energy resources determines both the physical "configuration", and the generation of information in the system.

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# Chapter 6
# Social Communications and Logical Typing in the Social System

*Consciousness is never experienced in the plural, only in the singular.*
—Erwin Schrödinger

**Abstract** Social system represents an operationally closed system. The only operation that takes place in a social system is communication, and the operational closure ensues when the communications emerging from communications reproduce the difference between the system and the environment. In short, the system viewed as a difference reproduces itself by maintaining that very difference. However, social systems, seen as systems of communication, are not only self-referential, but also "foreign-referential." Since the difference between the two perspectives emerges within the confines of the same consciousness, the observer appears in two guises—once as a self-observer, and once as *foreigner* observing himself from a side in the context of a particular communication. Thus, the system oscillates between the self- and foreign-referentiality, and this inevitably creates a paradox. However, since the means of structural coupling between the consciousness and communication is the language, it can mediate between the unity (self-referentiality) and the difference (foreign-referentiality). There is a genuine similarity between the social and the genetic systems as information-producing devices. By the same token, there is a difference between the circuits of social communications and genetic information on one hand, and the Shannon information on the other.

**Keywords** Social systems · Communication · Self- and foreign-referentiality · Operational closure · Genetic system · Language · Proteome · Shannon information

We defined self-referentiality as a capacity of the living system to perceive itself as an isolated entity and correct its own behavior, and this definition is also pertinent to social systems. However, according to Niklas Luhmann (Luhmann 2002), who in the last quarter of the twentieth century provided perhaps the most remarkable insights into the nature of social systems, there is also an interesting difference. Again, we can touch only the relevant aspects of this comprehensive theory.

Luhmann maintains that social systems, seen as systems of communication, are not only self-referential, but also "foreign-referential" (for wanting of a better term

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to translate the German “Fremdreferenz”). This will be explained below; but first of all, it is noteworthy that Luhmann defines a system as an entity that can discriminate between itself and the environment, and from this he infers that a system essentially represents a *difference*, namely a difference between the system and the environment. Put another way, a system cannot be conceived of without drawing a distinction isolating it from its surroundings.

Second, Luhmann conceives of the social system as an operationally closed system, very much in line with Maturana and Varela’s notion of the autopoietic system (see Chap. 3). He maintains that the only operation that takes place in a social system is communication, and the operational closure ensues when the communications emerging from communications reproduce the difference between the system and the environment. In short, the system viewed as a difference reproduces itself by maintaining that very difference. So, to put this notion into the terms of this booklet, we may say that the (social) system is an entity operating via distinction, directional choice and naming, and reproducing itself by maintaining its capacity of drawing distinctions, making directional choice, and naming. And since this capacity entails generation of information (Chap. 1), it follows that a social system, alike any living system, is an information-generating entity, reproducing itself by maintaining its information-generating capacity.

Third, in his theory, Luhmann employs the notion of *reentry* (Spencer Brown 1969) of distinction into a distinction. The reentry occurs as a result of communication, because communication takes place when information is imparted to somebody, whereby this information can be about the system itself. In other words, while a system (let say, a sentient being) makes a distinction between itself and the environment (the primeval distinction, as we put it in Chap. 1), in the next step, it can communicate data *about* itself by copying, as it were, itself into itself (in principle, that is exactly what we do, when we talk *about* ourselves, for example, by disclosing the peculiarities of our character, or personality, to the others). This, in a nutshell, is what is meant by reentry here. Now, it is noteworthy that when a (sentient) system discriminates itself from the environment we may call it self-referential, whereas when it communicates with somebody *about* itself (observing itself from a side, as it were) we may call it foreign-referential. Although Luhmann puts a somewhat different meaning in the terms *self-* and *foreign-referential*, the crucial point is that the operation always remains intrinsic in a sense that the difference between the two perspectives emerges within the confines of the same consciousness. The observer appears in two guises—once as a self-observer, and once as *foreigner* observing himself from a side in the context of a particular communication. Thus, the system oscillates between the self- and foreign-referentiality, and this inevitably creates a paradox, because the initial distinction of the self, and the subsequent distinction of the self on *reentry* into the self, are not one and the same. Yet, we can resolve this apparent complication by recalling the blunder underlying the self-referential paradoxes (Chap. 2).

As Luhmann properly claims, both the self-referentiality and the foreign-referentiality occur in the same consciousness, so that in both cases the actual *observer* is the same. However, self-referentiality (i.e., perception of the self) manifests itself continuously and so provides analog information. In contrast, foreign-referentiality defines the person as a unique form (fixed in the instant communication context), and so provides digital information. Put in other words, the paradox emerges whenever the direct *perception* of the self (self-referentiality) is confounded with a *static image* of the self that is implanted, as it were, into oneself (foreign-referentiality). Thus, once more again, the paradox is created by oscillation of the mind between two logically incompatible types of information standing in a relationship of perceptive exclusion.

Although such blunders are far from being occasional, in most cases they do not cause insurmountable problems. The relationship between self-referentiality and foreign-referentiality is essentially a problem of mapping occurring for better or for worse. Sometimes it works, and sometimes not. However, in contrast to Gödel's mapping that as we have seen, fails fundamentally due to the lack of a coordinating unity, the self-referentiality and the foreign-referentiality are ultimately coordinated by the same *individual* mind. Yet, as we all know, their oscillation can cause problems of ethical character. Think, for example, of the consequences of the ridiculous fact that slaughter can make a man either a hero, or a criminal, depending on whether he is acting for the sake of foreign- or self-referentiality. This might be an extreme case but in fact, the implications of this oscillation are much wider, as they are omnipresent. Take a simple case of an accident involving a pedestrian immersed in his thoughts, and a hasting city biker crossing their ways during the rush hour. Although both might be aroused and hostile inwardly (that is, self-referentially), they can nonetheless arrange themselves by acting friendly foreign-referentially (otherwise, a friendly policemen can help). This is possible because social communications operate in the mode of foreign-referentiality. Whereas self-referentiality, seen as subjective introspection, cannot be directly communicated, the foreign-referentiality is a *form* produced by the discriminating mind that lends itself to verbal description and so, to communication. As mentioned above, foreign-referentiality is a result of reentry of a difference into the difference, which necessarily takes place during any communication and therefore, can attain different colorations contingent on the context of communication (e.g., our foreign-referential form will be different depending on whether we communicate with an easy bartender, or a frowning judge in the court). We thus slip in different forms, so to speak, which we adopt according to the constraints of the particular environment. The important point is that whereas these oscillations of perspective happen in the very same observer, the social system can "prescribe" the foreign-referentiality (in form of the default images and rules of behavior in which we, willy-nilly, plunge) and thus, has a potential to coordinate such perspectives. The corollary is that whenever the foreign-referentiality provides social security, we may deliberately and even enthusiastically stick to it, especially when we know that there are still some places on the globe where conformity is achieved by brainwashing and coercion. This also implies that for us, as sentient social beings, there is a fundamental necessity to keep a subtle balance between the self- and foreign-referentiality, as on the one extreme we usually obtain a frenzied, and on the other, a happy slave.

## Language as a Means of Structural Coupling

We mentioned above that in Luhmann's view, social communications represent an autopoietic system. The crucial point is that due to the operational closure inherent in autopoietic organization (Chap. 3), information is *not* transmitted from one system to the other (or from the environment to the system). Rather, the environment acts as a trigger of a change in a system, such that information (distinction, directional choice, and naming) is an exclusively system-internal affair. Indeed, if according to the common view information would be transmitted from a source to a recipient through a transmission channel (even if we assume that transmission is prone to errors due to a "noise" in a channel), we would have much fewer misunderstandings. The reader of this book is not absorbing ready-made information, but rather generates his own understanding (information) in response to induced perturbations in his own mental structure acting as triggers of thought. But then how can autopoietic systems, which by virtue of their operational closure are doomed to produce only intrinsic information and thus, create a meaning only for themselves, communicate? More specifically, what is the means of structural coupling between the consciousness and the communication?

The problem we are touching upon can be epitomized using Maturana and Varela's metaphor of a submarine pilot (Maturana and Varela 1987). The pilot, assumed to have seen nothing outside the submarine, operates the vehicle using a monitor indicating all the underwater objects with high precision on a coordinate system. By means of this indicator system the pilot can safely navigate the submarine through all the obstacles, which in reality may represent rocks, reefs or perhaps other vehicles. Now, while the pilot does not have even a slightest idea of what these obstacles really are (as he knows only the correlations between the indicator readings on the monitor), for an outside observer he appears as a skillful navigator maneuvering the submarine between the reefs and other obstacles on the see floor. The crucial point is that for the internal dynamics of the submarine states the environment does not exist in real representations of the world, as it exists for the outside observer. Conversely, for the outside observer the internal dynamics of the submarine states do not exist. And so once more again, since the topography of the see floor and the relationships between indicators do not share any objects or processes and yet, are perfectly coordinated, we have two complementary descriptions, and a problem of mapping. Put another way, we are in need of a mechanism of structural coupling explicating the observed coordinated behavior.

Luhmann argues that a similar relationship obtains between the operation of the consciousness and communication. He underscores that whereas consciousness is fundamentally grounded in perception (much more, than, e.g., in such a slippery thing, as *thinking*), communication itself is devoid of any capacity to perceive—it cannot see, hear, or feel. This means that as an operationally closed system, communication as such is fully independent of the happenings in the physical world (unless they are destructive) such as, for example, the interactions of the molecules in the body, the way of molding the tones into words, or the strength of the wind.

Indeed, no communication would be possible if we were compelled to account for all the physical, chemical, or biological processes taking place during communication. On the other hand, a communication without consciousness is sheer impossibility, as any communication is "filtered" by the consciousness. Yet consciousness itself is not communication. Thus we have a paradox, because in order to operate, communication has to block perception, and at the same time, it fully depends on the operation of the latter.

Luhmann's suggestion to escape this paradox is to observe the system as a totality of unity and difference. Now if we recall what we have said in Chap. 1 about the experience of the primeval distinction and the arousal of the mind, we may start to understand, why in Luhmann's view, the system appears as a totality of unity and difference. Luhmann argues that structural coupling between the consciousness and communication is a phenomenon that in principle can be related to both the unity and the difference, especially on the assumption that the means of structural coupling is the language. Language is double-edged, as it can be used both psychologically (i.e., as thinking) as well as communicatively, and thus, enables introspection and communication to remain apart, and operate separately. It is thus tempting to say that language operates at the interface of our self- and foreign-referentiality, mediating the conversion of the "impressed" into the "expressed."

But how can the process of communication lead to the establishment of social order? Since communication as an autopoietic system implies circular operation, Luhmann conjectures that in social systems the circularity is afforded by the relationship of "double contingency," as both the system (individual) and the environment (that is, another individual, or the society) influence each other mutually. More specifically, he sees the double contingency as the ability to generate complementary anticipations, such as, for example, "if you do what I want, I will do what you want" (Luhmann 2002). In fact, the communicative efforts of the one are dependent on those of the other, such that this interdependence can lead either to continuation, or cancelation of communication. From this view, the role of language, as a coding device understandable to both sides, is in "regulating" the double contingency, which by virtue of successive acts of confirmation or negation acts as a funnel, and so ultimately leads to the establishment of social order. This view is close to Maturana's notion that language primarily serves the purpose of coordination of behaviors (Maturana 1998). However, Luhmann does not imply any intentionality—he sees communication rather as an open-ended process subject to selection, very much in line with the process of natural selection in evolution theory.

## Similarities Between the Social and Genetic Systems

Luhmann discerns three necessary components forming a *unit act* of communication. The first component is *information*, which in this particular context represents the knowledge of the topic of communication, that is, its "aboutness." The second is an *announcement* (Mitteilung) of the information, and the third is the *understanding*.

Indeed, information cannot be triggered without announcement, and cannot be realized without understanding. Furthermore, Luhmann claims that for a communication to take place, there needs to be two. That is all right, but let us take for example a dream, in which we have a conversation with our dream image—who is the other there we communicate with? This does not mean to say that we have two selves, but communication is an inevitable result of our self-referential organization, for otherwise how could we correct our behavior? As a matter of fact, by our faculty of thinking we constantly communicate with ourselves. In this sense, reading a book also implies a communication with the (absent) author. Luhmann would perhaps argue that *sensu stricto* this is not a social communication, and he would be right, but this does not invalidate the argument, especially since we are not elaborating on the theory of social communications here, but rather on the ways living systems can generate information by means of distinction and directional choice. The crucial point is that any communication implies a distinction between the self- and the foreign-referentiality as a system-internal affair, and this distinction in our dream example, and during the regular (social) communication, is essentially all the same. To use a metaphor, whether we are playing tennis or squash, in both cases we are responding to the approaching ball.

From this perspective, there are interesting parallels between the composition of Luhmann's unit act of communication and the "unit act" of information as described in Chap. 1. Indeed, Luhmann's use of the term *information* is analogous to what we have called distinction, *announcement* is analogous to directional choice, and *understanding* is analogous to naming. In other words, Luhmann's unit of communication is analogous to the unitary process of creating information by distinction, directional choice, and naming. We have already underscored the analogy of this latter *experiential* process to the ability of the DNA, to "draw distinctions" by adopting distinct configurations corresponding to particular environments, making "directional choice" by determining the corresponding genomic expression pattern, and "naming" the physiological state by producing the state-specific proteome, capable of coping with the given environmental change. Another principal similarity is that the cellular proteome, alike the language, is also double-edged. It can interact with both the DNA (via its DNA binding components), and also with the environment (via the receptors and other sensory proteins, many of which are coincidently DNA binding factors). Accordingly, in its impact on the chromosome configuration, the proteome can be assumed to act in a self-referential mode, whereas by virtue of sensing environmental clues it acts in a foreign-referential mode. On this view, the proteome, in analogy to Luhmann's view of the role of the language, mediates the communication between the "outer" and "inner" world of a cell.

Furthermore, since according to Luhmann, the communication is a circular process that proceeds with continuous correction by agreement or disagreement (i.e., by saying *Yes* or *No*) to each communicated message, it clearly belongs to the digital type of information. Moreover, its operation mode resembles that of the digital components of the genetic system—unique genes and DNA binding sites. As we have outlined in Chap. 2 and detailed in Chap. 4, coordination of the cellular genetic

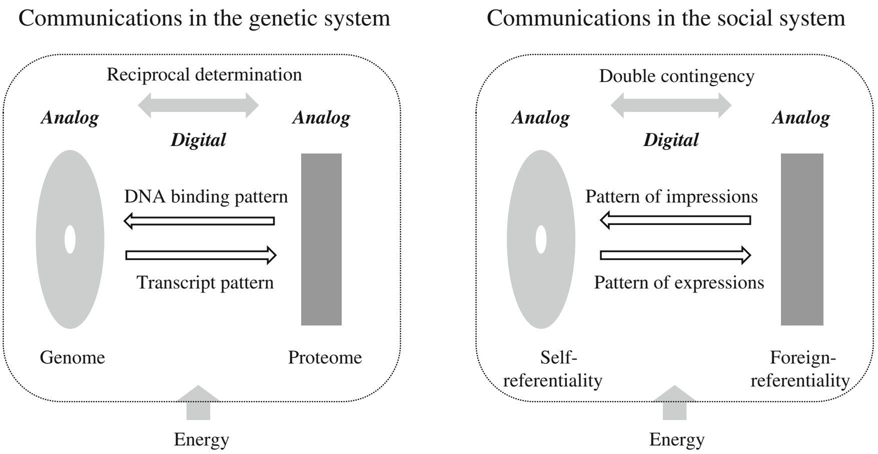

**Fig. 6.1** Similar organizational logic of the genetic (*left panel*) and social (*right panel*) communication systems

activity is achieved by a peculiar organization, in which two analog components (chromosome configuration and the proteome composition) are communicating via the digital components (unique genes and DNA binding sites). Similarly, in a social system, the coordination is achieved by two analog components—the self-referentiality (perception of wholeness) and foreign-referentiality (viewed here as the entire *class* of images in which we can possibly plunge and which in its entirety circumscribes what we call our *personality*). These analog components of the system communicate via the digital components—the announcement (expressions), and the understanding (impressions; see Fig. 6.1). Furthermore, the composition of the proteome and the form of foreign-referentiality in which we possibly slip are determined by particular states of the chromosome and the consciousness, respectively, and as no two different proteomes corresponding to different physiological states can be produced simultaneously, no two foreign-referential forms corresponding to different communication contexts can coexist. Finally, whereas the circularity of the genetic system is sustained by structural coupling and a relationship of reciprocal determination between the constituting elements producing the “physiological order” (see Fig. 6.1), in social systems the circularity is afforded by structural coupling via the language and relationship of “double contingency,” embodied in the interdependence of communicating entities and leading to the establishment of social order. And last but not least, whereas both these communication systems can ultimately thrive only at the expense of the energy derived—although one more and the other less directly—from the metabolism, both the social communications and genetic interactions lend themselves to the mechanism of (natural) selection (Luhmann 2002; Fang et al. 2013).

## Shannon Information

It is noteworthy that the notion of information employed throughout this booklet is at variance with the technical use of the term “information” as based on the information theory of Claude Shannon. At the same time, the Shannon information “circuit” has been likened to the flow of genetic information (e.g., Yockey 2000), and it is worthwhile therefore, to address the possible similarities and differences from the viewpoint of logical typing.

Shannon information circuits assume a sender of a signal, a signal transmission channel, and a receiver decoding the sent information (Fig. 6.2). In practice, transmission of a signal is mediated by some sort of physical conduct within a material medium and therefore, the signal is prone to various kinds of medium-dependent distortions, which are collectively called “noise.” These have been likened to genetic mutations (Yockey 2000), yet neither the genetic mutations, nor the technical problems associated with physical properties of the channel shall detain us here. What is important to us is the *way of interpreting* the signal, that is to say, the way of generating information.

The value of Shannon information ascribed to a signal depends on the degree of correlation between the received signals, and in this sense the definition of Shannon information and Boltzmann entropy show a notable similarity: the more the received signals are correlated, the lower the entropy and the less the information conveyed by the signal, whereas the larger the randomness of the signals, the larger the entropy, and so the conveyed information. In this latter case, given a channel

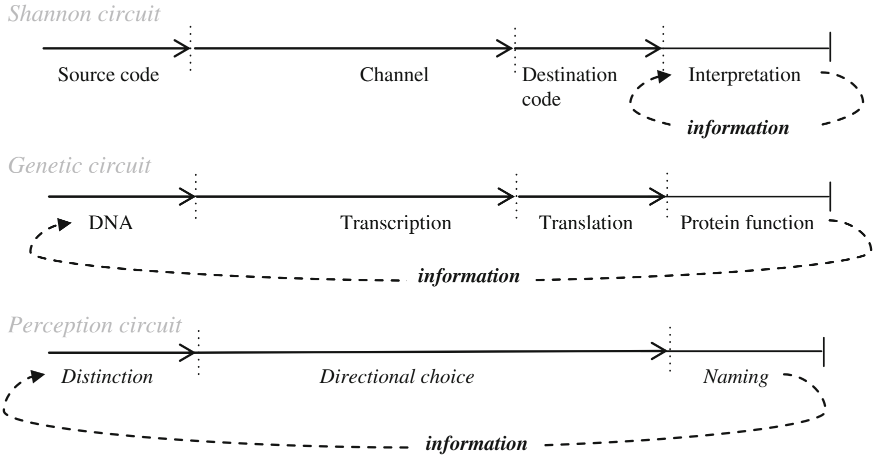

**Fig. 6.2** Comparison between the Shannon information circuit (**a**), the flow of genetic information (**b**), and perception (**c**). Note that the process of distinction, directional choice, and naming assumed as a unit act of information (**c**) occurs in the Shannon circuit at the level of the “interpretation” of the destination code by the signal receiver. In contrast, in both the genetic and perception circuits information is generated at the source

with constant transmission rate, any character can appear with equal probability at any instant of transmission, and so there is maximum uncertainty. In short, the information content of a signal is defined statistically with respect to the entire ensemble of possible signals that could be potentially received such that at bottom line, the mathematical measure of signal options, in the case of Shannon information, and physical options in the case of Boltzmann entropy, are similar (Deacon 2007). For this reason, by analogy to Boltzmann entropy, Shannon information is often defined as Shannon entropy, which thus defined, represents the *probability* of receiving the given signal among all possible signals in the ensemble. This point can be exemplified using a metaphor of a fisherman catching fish in a pond. If he catches the same sort of fish all the time, the information content will be minimal, and the entropy low, as he would expect to get the same kind of fish all the time. However, if all the fish he catches were different, the information content and so the Shannon entropy would be maximal.

Thus, in the Shannon circuit, information is viewed as some sort of encrypted message that is sent via a channel, and decoded on the receiver's end. Recall that by contrast, we defined information not as a transmitted *message*, but rather as a *process* of distinction, directional choice, and naming (Chap. 1).

The important difference between Shannon and the genetic, as well as the perception circuits, is that firstly, Shannon information represents a signal (or a pattern of signals), and is thus purely digital; there is no *analog-digital-analog* information conversion, as in the genetic circuit (Chap. 4), or in the social communication circuit as described above (see Fig. 6.1). Second, in the genetic system the *source* is represented by DNA, which both enacts the distinction, and also gets *informed* itself by changing its configuration in response to the metabolic function of the produced proteome. In other words, the DNA serves as both a source, and a receiver of the information. The same is true for consciousness, which produces information by reentry of the foreign-referential form into the same mind, as detailed above. By contrast, in Shannon circuit decoding of a signal does not influence the source. Again, this important difference can be fathomed using the metaphor of our fisherman. The kind of the fish caught by the fisherman *informs* him about the variety of fishes dwelling in the pond. However, depletion of the fishes may affect the ecosystem of the pond and thus *inform the pond* by causing, for example, overproduction of the prey on which the fish feed, which in turn may affect other parameters of the ecosystem. Yet all that change—besides the depletion of fishes—will go unnoticed for the fisherman.

Another important point is that whereas the entire Shannon signal detection circuit has a potential to convey information by transmitting a signal, it is "indifferent" to the *meaning* of the transmitted signal—it can be about anything. Therefore, the quantity of information (signals) needed by the receiver to properly identify the message requires an a priori knowledge of the set of all possible messages (Lesne 2013). Note that here once more, a meaning should be mapped to the pattern of received signals, to render the transmission *informative*. In principle, a meaning can be conveyed by interpretation of the *specific form* of the deviation from the random pattern of the signals. Since this specific form reflects specific constraints imposed on the system, in this way these constraints can be disclosed to the receiver (Deacon 2007). This means that information is *generated* in the interpretive receiver (Fig. 6.2), very much in line with the way outlined in Chap. 1. Therefore, the definition of information, as used throughout this booklet, would pertain to just the last part of the Shannon signal transmission chain—namely, the process of interpretive decoding. In short, what is actually transmitted is not information, but rather a signal acting as a *trigger* of information in the (sentient) receiver, who conveys meaning to the received signal by relating it to the set of possible signals and their probability distributions. This means that despite its unquestionable usefulness for technical applications, the Shannon information circuit, being purely digital alike Gödel's formal system, lacks the operational closure mediated by mutual conversion of logically distinct information types, and so, cannot provide an adequate instrument for grasping the intricacy of communications in the living system.

Recent studies, however, reveal that profound insights into the organization of DNA information can be obtained by integrated analyses of Shannon entropy and thermodynamic stability of the *Escherichia coli* genomic DNA (Nigatu et al. 2014). Let as take a sequence of three codons: GTG, CTG and GGA, which represent digital information, encoding three distinct amino acids respectively—valine, leucine and glycine. Each codon serves as a signal, and thus the frequency of its appearance in a sequence can be used to compute the Shannon entropy by comparing it with the entire ensemble of potentially possible codons. At the same time, these codons are characterized by different thermodynamic stabilities due to the stacking interactions between the base steps, such that for example, the GC steps will be on average more stable (have higher average negative melting energy) than the TA steps (Travers et al. 2012). This latter property is additive, and therefore belongs to the analog information type (see Chap. 4). The three codons- GTG, CTG, and GGA, can be thus written as eight dinucleotide steps, each characterized by different thermodynamic stability (GT, TG, GC, CT, TG, GG, GG, and GA). Nigatu et al. (2014) applied Boltzmann statistics to convert the computed DNA melting energies averaged across several base steps into probabilities. This made it possible to compare the Shannon entropy of the genomic sequence (that is, appearance of distinct signals corresponding to distinct codon frequencies in a sequence) with the distribution of thermodynamic stabilities of the dinucleotide steps in a chosen sequence block. The two parameters were found strongly anticorrelated around the chromosomal terminus of replication, with Shannon entropy being maximal, and thermodynamic stability minimal (Fig. 6.3). This means that the sequences around the terminus are more random and thermodynamically less stable, whereas the sequences around the origin of replication are less random and thermodynamically more stable (see also Fig. 4.10, *left panel*). There is a simple explanation of this relationship. The genetic code is "degenerate," meaning that many amino acids are encoded by several codons in which the third "wobble" position is occupied by a different base. For example, the amino acid leucine is encoded by four codons, CTC, CTG, CTT, and CTA. Note that the first two codons are GC-rich, whereas the last two are AT-rich. It turned out that GC-rich triplets encoding leucine (as well as many other abundant amino acids

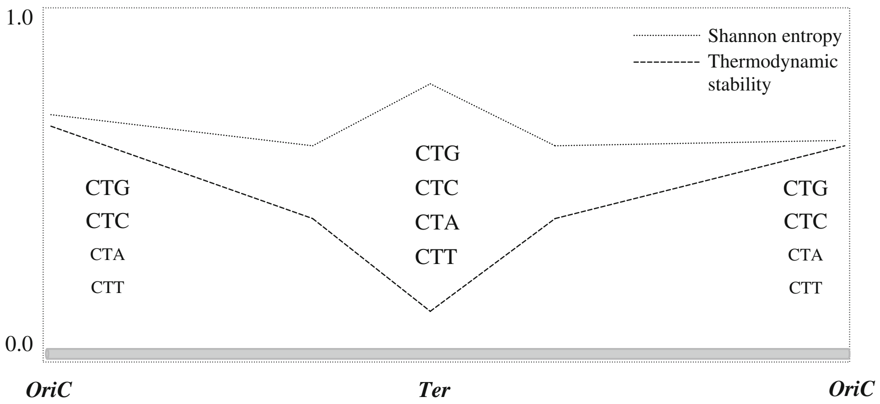

**Fig. 6.3** Relationship between the Shannon entropy and DNA thermodynamic stability in the *E. coli* genome. The ordinate indicates the arbitrary maximum (1.0) and minimum (0.0) values for both variables. The difference in the frequency of the codons encoding leucine (CTC, CTG, CTT, and CTA) in the genomic regions around the origin and terminus of replication is indicated by the difference in the size of the letters. Similar bias is observed for other abundant amino acids encoded by multiple codons. The chromosome linearized at OriC is indicated as a gray horizontal bar. Modified from Nigatu et al. (2014)

encoded by multiple codons) are used with high frequency in the genome region around the replication origin, whereas in the region around the terminus all four triplets are used with equal frequency. This organization enables equally frequent usage of leucine across the entire genome, despite the fact that the genes around the origin are more GC-rich. At the same time, the difference in thermodynamic stability of DNA in the chromosomal OriC and Ter ends facilitates stabilization of distinct supercoil structures implicated in genetic regulation of anabolic and catabolic genes enriched in the OriC and Ter ends, respectively (Chap. 4). The corollary is that in *E. coli* the analog DNA information responsible for the 3D structure (the "topography") of the chromosome is determinative of the spatial organization of the linear genetic code (the "typography"). And as we have outlined in Chap. 4, this peculiar organization of the primary DNA sequence provides a genuine device for the conversion of available supercoiling energy into the corresponding genomic expression and metabolic profile.

## Conclusion

> *The observer is the observed.*
>
> Jiddu Krishnamurti

In this booklet, we made an attempt to fathom the process of life based on the primary record of our direct perception of the world. Arguably, the emergence of perception preceded that of conscious thought, and it is noteworthy that although perhaps unusual at first glance, the perception-based approach to life is at least as old as the scriptures of the Vedanta. We observed that the first thing we can say about ourselves, as sentient beings, is that our consciousness appears as a split in the antecedent undiscriminating state being perceived, as a totality of unity and distinction, which we have conveniently called the mind. And whereas the arousal of the mind happens in a unit act of distinction, directional choice and naming, this act repeats itself over and over again by reentry of distinction into distinction. This unit act of distinction, directional choice, and naming, we have called *information*. The succession of perceived distinctions and intervals thereof generate an order, which we have called time. This property of generating intrinsic information and time is the basic difference between the animate and inanimate matter.

Obviously, the notion of information used in this booklet is at variance with the common assumption that information is something that can be transmitted. However, as mentioned by Heinz von Foerster, what can be transmitted is a signal. A signal is not information but is at best, provided it is understood, a trigger of information. Information is not a thing that can be bequeathed to somebody, but is rather a *form*, which we produce *in* ourselves in the process of creative thinking. From this view, memorization is not properly information, as it does not involve (or involves only superficially) creative thinking. Niklas Luhmann observed that thinking is a faculty that has to be learned. Indeed, any thinking person knows that creative thought comes from silence, and that pondering has to be cultivated. The pertinent question is whether the contemporary education system, with its emphasis on memorization, can meet this demand. In a tradesman's world, where education became an instruction to performance, the emphasis on memorization can, and indeed does, restrict thinking, and so the creativity. As mentioned already by Lyotard (1984), the old principle integrating the acquisition of knowledge with educational formation (Bildung) of the mind and personality is increasingly deteriorated, whereas the relationship between the provider and user of the knowledge is becoming similar to that between the producers and consumers of commodities. What is being taught nowadays is mainly how to solve the problem, but is never the way of how to find the right question in the first place (Smalheiser 2013). It is amazing that whereas the cultural tradition of thinking is perhaps the main treasure extended to the Western world by the philosophers of ancient Greece, recent studies suggest that contemporary men prefer to endure torture, rather than to think even for a few minutes (Wilson et al. 2014). The duty of thinking is apparently transferred to the computers, and to this end it is worth mentioning that since creative thought looms from the depth of our natural wholeness, no computation can provide a substitute for thinking, because no computer can ever possess this wholeness—except in a movie.

Be that as it may, an attentive reader may have noticed that our definition of the mind as a totality of unity and distinction is similar to Luhmann's definition of system. This is simply because, taken the terms of systems theory for granted, *the mind is the ultimate system*. It is the mind, emerging as the totality of unity and distinction, which endows us with the capacity to perceive both the continuity, as well as discreteness. For example, when we are asked who we are, we normally dub our name. Regardless of the contrasting *forms,* our name can be associated with in the mind of an olden friend and let say, a hospital administrator with thousands of patients in “stock” seeing the human beings as mere numbers, by dubbing our name we always expose our distinctness, and so to speak, *digitalise* ourselves. And we can do this exactly because our mind has the property of discreteness to it. However, it also has the impersonal property of incessant wholeness, enabling us to perceive the continuity, which we have dubbed *analog* information.

So then, we can define our mind as a totality of analog and digital information. This definition is instrumental insofar as it exposes the mind-system as a natural device for interconversion of logically distinct information types. By using examples from different fields we accordingly revealed that whenever science penetrates the unknown to considerable depth, as done by quantum theorists in physics, logicians in mathematics, and evolutionary theorists in biology, the world emerges as a mysterious blend of digital and analog features, causing blunders of logical typing. We have also observed that whenever we apply this “dual-coding” property of the mind to logical paradoxes, they can be readily resolved. Conversely, we observed that even the most brilliant logical thought fails to grasp reality if it employs only the digital, and omits the analog information. Furthermore, we observed that the genetic system of a relatively simple organism lending itself to detailed investigation and especially, the main molecule at the roots of life, the DNA, can be fully understood only as a system with dual-coding capacity. The chromosomes represent thermodynamic machines converting the supercoiling energy of the DNA into genetic information, and this capacity of transforming the energy into information is fundamental for the understanding of biological evolution and perhaps, also its spin-offs, such as the historical process of sociopolitical organization. Finally, we showed that communications in the social system disclose the same dual-coding pattern as genetic communications. But if our mind is a totality of unity and difference embodied, respectively, in our perception of analog and digital information types, is it surprising then that wherever we look, we see the very same thing? The ultimate instance to which *everything* is mapped is the mind. The corollary is that the natural laws are, in fact, the laws of perception (see also Lanza and Berman 2009).

Understanding of the mind-system as a device for conversion of logically distinct types of information is not an abstract model, but rather results directly from the primary record of our perception. It thus provides a strong incentive to our creativity by liberating our epistemology—to the extent deemed possible—from preoccupation with preconceived abstract models. One obvious advantage of this “holistic” approach is that it has a power to unify the phenomena from widely disparate research fields into a common exegetic framework. More specifically, it puts an emphasis on the interdependence and interconversion of analog and digital information types, reflecting different facets of the phenomena under study, enabling their holistic integration and hence, a more comprehensive understanding (Muskhelishvili and Travers 2013). And finally, if the reader could, by following the plot, find out a difference for himself that makes a difference, all this deliberation was perhaps of some service. Ultimately, it is all the matter of distinction and directional choice.

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