Contributions to Statistics

Dariusz Uciński
Anthony C. Atkinson
Maciej Patan *Editors*

# mODa 10 – Advances in Model-Oriented Design and Analysis

## Proceedings of the 10th International Workshop in Model-Oriented Design and Analysis Held in Łagów Lubuski, Poland, June 10–14, 2013

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*The volume is dedicated to Alessandra Giovagnoli and Anatoly Zhigljavsky on the occasion of their birthdays (70 and 60)*

# Preface

This volume contains a substantial number of the papers presented at the MODA 10 workshop in Łagów Lubuski, Poland, in June 2013; MODA here stands for *Model Oriented Data Analysis and Optimal Design*. Design of experiments (DOE) constitutes a powerful statistics-based methodology playing a major role in the knowledge discovery process in science and engineering. Data collection issues, including DOE, are at least as important as data analysis since they determine how much information data contain. No statistical modelling or analysis methods can extract information which the data do not contain, whereas a poor analysis can always be corrected later. Thus, haphazard experimentation may be very wasteful of resources, lead to needless repetition, poor inference and, where human subjects are concerned, may be ethically unsound.

The subject began in an agricultural context, but the theory and practice of DOE have become important in many scientific and technological fields, ranging from optimal designs for dynamical models in pharmacological research, to designs for industrial experimentation, to designs of simulation experiments in environmental risk management, to name but a few. DOE has become even more important in recent years, because of the increased speed of scientific developments, the complexity of the systems currently under investigation and the continuously increasing pressure on businesses, industries and scientific researchers to reduce product and process development times. This increased competition requires ever increasing efficiency in experimentation, thus necessitating new statistical designs.

A model-oriented view on DOE, which is the pivot of the MODA meetings, assumes some knowledge of the form of the data-generating process. It naturally leads to the so-called optimum design of experiments. This approach has the potential to revolutionize experimental programs of drug development and testing. Standard methods of DOE are no longer adequate and research into new ways of planning clinical and non-clinical trials for dose-finding is receiving close attention. In turn, applications of DOE in engineering often deal with large scale and highly complex systems where time and/or space are inevitable components. These applications may involve models in the form of ordinary differential, differential algebraic or partial differential equations. The underlying design space can be a class of input sequences

(time-domain analysis), a range of frequencies (frequency domain), a range of sampling intervals (sampling strategies), or a set of spatial sensor locations. As a result, factors continuously changing in time and/or space (e.g., temperature, pressure) can be taken into account. Relevant application areas are as diverse as control engineering, analytical chemistry, air sampling, atmospheric science and geophysical surveys.

Surprisingly, for a long time, the resources devoted to research on DOE have been rather limited. Partly, this was because the developments in different application areas and in different branches of mathematics had led to a fragmentation of the theory and practice of DOE. Leading European experts on DOE therefore decided to form the MODA group to bring together the different approaches, primarily through organizing special workshops. The initiative was a success and the scope of MODA rapidly expanded to countries far beyond Europe, including the USA, South Africa and India. MODA meetings are known for their friendly atmosphere, leading to fruitful discussions and collaboration. Since the beginning, they have also been aimed at giving junior researchers the opportunity of establishing personal contacts and work together with leading researchers. In order to guarantee a high-scientific level, participation is only by invitation of the board and meetings take place every third year. The proceedings are always published before the date of the meeting, to allow detailed and intelligent discussion.

Here is the list of previous MODA conferences:

1. Eisenach, former GDR, 1987
2. St. Kyrik monastery, Bulgaria, 1990
3. Petrodvorets, Russia, 1992
4. Spetses, Greece, 1995
5. Marseilles, France, 1998
6. Puchberg/Schneeberg, Austria, 2001
7. Heeze, The Netherlands, 2004
8. Almagro, Spain, 2007
9. Bertinoro, Italy, 2010

Organization of the 10-th anniversary edition of the workshop has been conferred to the University of Zielona Góra in Poland, which hosts an active group of researchers at the Institute of Control and Computation Engineering, who are concerned with optimum experimental design for spatiotemporal processes. The workshop itself takes place in Łagów Lubuski, a small, picturesque town with much charm and atmosphere attracting artists and intellectuals. It is a long tradition of MODA workshops that they are organized in such relatively isolated places, far from the hustle and bustle of big cities. As this book clearly demonstrates, the present meeting once more brings together researchers from all over the world. These papers have undergone a complete review to ensure that contributions were significant and the manuscripts remain of high quality and clarity.

The papers presented in this volume cover a large spectrum of topics that are all well aligned with the scope of the workshop. They have been arranged in alphabetical order of author, but some patterns of topics emerge. A breakdown is as follows:

1. The most common theme is that of clinical trials. This arises both in the papers by Biswas, Banerjee and Mandal and, in the form of dose finding studies, in

the papers by Flournoy, Galbete, Moler and Plo, by Magnusdottir, by Gao and Rosenberger and by Dragalin, as well as that by Ghiglietti and Paganoni.
2. Designs for linear and non-linear mixed-effects models are developed in the papers by Prus and Schwabe, and by Mielke and Schwabe, while an approximation of the information matrix in a similar setting is advanced by Leonov.
3. Lifetime experiments with exponential distribution and censoring feature in the contribution by Müller. Calibration designs for an extended Rasch-Poisson counts model are outlined by Graßhoff, Holling and Schwabe. Optimal designs for log-linear regression test models are refined by Wang, Pepelyshev and Flournoy.
4. The papers by Ginsbourger, Durrande, and Roustant, as well as by Chevalier, Ginsbourger, Bect and Molchanov describe improved designs for computer experiments.
5. The topic of the paper by Atkinson and Bogacka is discrimination between models. Designs for model selection are also considered by Skubalska-Rafajłowicz and Rafajłowicz.
6. The paper by Pázman and Pronzato deals with regularized optimality criteria for experimental design. In turn, some new information criteria are proposed in the paper by Ferrari and Borrotti.
7. Algorithmic issues are thoroughly treated in the context of the KL-optimality criterion by Aletti, May and Tommasi, or in the more general case of minimax criteria by Nyquist. A related problem of numerically constructing optimal designs using the functional approach is studied by Melas, Krylova and Uciński. A new technique of generating optimal designs by means of simulation tapping into approximate Bayesian computation is proposed by Hainy, Müller and Wynn.
8. Finally, a number of papers are strongly application-driven. Thus, Bischoff focuses on checking linear regression models taking time into account. Fackle-Fornius and Wänström construct minimax designs for contingent valuation experiments. Choice experiments for measuring how the attributes of goods or services influence preference judgments are studied by Großmann. Coetzer and Haines put forward designs for response surface models involving multiple mixture and process variables. Rafajłowicz and Rafajłowicz determine optimum input signals for processes modelled by partial differential equations. Designs for correlated observations in spatial models are exposed by Pepelyshev.

In our personal opinion, the papers in this volume make notable contributions to the state of the art in the field of model-based optimum experimental design. We hope the reader will share our point of view and find this volume very useful. We would like to acknowledge all the authors for their efforts in submitting high-quality papers. Last, but not least, we are also very grateful to the reviewers for their thorough and critical reviews of the papers within the short stipulated time.

Zielona Góra, Poland

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# A Convergent Algorithm for Finding KL-Optimum Designs and Related Properties

**Giacomo Aletti, Caterina May, and Chiara Tommasi**

**Abstract** Among optimality criteria adopted to select best experimental designs to discriminate between different models, the KL-optimality criterion is very general. A KL-optimum design is obtained from a minimax optimization problem on an infinite-dimensional space. In this paper some important properties of the KL-optimality criterion function are highlighted and an algorithm to construct a KL-optimum design is proposed. It is analytically proved that a sequence of designs obtained by iteratively applying this algorithm converges to the set of KL-optimum designs, provided that the designs are regular. Furthermore a regularization procedure is discussed.

## 1 Introduction

One of the goals of optimum experimental design theory is the selection of the best experimental conditions to discriminate between competitive models. Among the optimality criteria proposed in the literature for discrimination purposes, the KL-optimality criterion (introduced in López-Fidalgo et al. 2007) is very general. Actually, it can be applied to any distribution and includes as a particular case the optimality criterion introduced by Uciński and Bogacka (2004) when models are Gaussian, which is in turn a generalization of the T-optimality criterion for homoscedastic errors given in Atkinson and Fedorov (1975a, 1975b). A KL-optimum design maximizes the power function for a discrimination test in the worst case (see

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López-Fidalgo et al. 2007, for details). Furthermore, the KL-criterion has been extended to discriminate between several models (Tommasi 2007) and has been used in compound criteria for the double goal of discrimination and estimation of models (Tommasi 2009; May and Tommasi 2012).

The analytical construction of KL-optimum designs is possible only in a few cases. In practice, KL-optimum designs are obtained through iterative procedures (Fedorov and Hackl 1997). In this paper the first-order algorithm to find a KL-optimum design is presented in more detail than in López-Fidalgo et al. (2007) and its convergence is proved in the setting of probability measures, that is, in an infinite-dimensional space. To this end, some classical results of the minimax literature (see, e.g., Polak 1997) are adapted to the infinite-dimensional case.

The paper is organized as follows. In Sect. 2 some important properties of KL-optimum designs are given, together with the notational setting and the main definitions. Section 3 is devoted to presenting the algorithm and a proof of its convergence for regular designs is given. In Sect. 4 a regularization problem is discussed to include the cases when the minimum (in the maximin problem related to the KL-criterion) is not unique. Final comments in Sect. 5 conclude the work.

## 2 Notation and Some Properties of the KL-Optimum Designs

Let an experimental design $\xi$ be a probability distribution having support on a compact experimental domain $\mathscr{X}$ in $\mathbb{R}^q$, $q \geq 1$. Consider two statistical models, that is, two parametric families of conditional distributions $f_1(y|x;\beta_1)$ and $f_2(y|x;\beta_2)$, where $\beta_1 \in \Theta_1$, $\beta_2 \in \Theta_2$, and $\Theta_i$ are open subsets of $\mathbb{R}^{d_i}$, $i = 1, 2$. Denote by

$$\mathscr{I}(x, \beta_1, \beta_2) = \int_{\mathscr{Y}} \log \frac{f_1(y|x;\beta_1)}{f_2(y|x;\beta_2)} \, f_1(y|x;\beta_1) \, \mathrm{d}y \tag{1}$$

the Kullback-Leibler divergence between $f_1(y|x;\beta_1)$ and $f_2(y|x;\beta_2)$, assuming that $f_1(y|x;\beta_1)$ is the "true" model. In order to discriminate between $f_1(y|x;\beta_1)$ and $f_2(y|x;\beta_2)$, the design $\xi$ may be selected by maximizing the KL-optimality criterion function (López-Fidalgo et al. 2007),

$$I_{2,1}(\xi;\beta_1) = \inf_{\beta_2 \in \Theta_2} \int_{\mathscr{X}} \mathscr{I}(x, \beta_1, \beta_2) \, \mathrm{d}\xi(x). \tag{2}$$

For a given value $\beta_1 \in \Theta_1$, the criterion (2) is the minimum Kullback-Leibler distance between the two models averaged on the experimental design $\xi$. Equivalently, the criterion function (2) is the minimum Kullback-Leibler distance between the two joint distributions associated with a response variable $Y$ and an experimental condition $X$, that is $f_1(y|x;\beta_1)\xi(x)$ and $f_2(y|x;\beta_2)\xi(x)$.

From now on, the value of the parameter of the first model $\beta_1 \in \Theta_1$ is assumed to be known and therefore it is omitted in the notation.

A design $\xi$ is *regular* if the set

$$\Omega_2(\xi) = \left\{ \tilde{\beta}_2 : \tilde{\beta}_2(\xi) = \arg \min_{\beta_2 \in \Theta_2} \int_{\mathscr{X}} \mathscr{I}(x, \beta_2)\, \xi(\mathrm{d}x) \right\} \tag{3}$$

is a singleton. Otherwise $\xi$ is called *singular*.

The KL-criterion function $I_{2,1}(\xi)$ defined in (2) has the following properties:

**Concavity** The KL-criterion function $I_{2,1}(\xi)$ is concave, as proved in Tommasi (2007).

**Upper Semi-continuity** Assume that the Kullback-Leibler divergence $\mathscr{I}(x, \beta_2)$ defined in (1) is continuous with respect to $x$. Endow the set $\Xi$ of probability distributions $\xi$ with support $\mathscr{X} \subset \mathbb{R}^q$ with a metric $d_w$ which metrizes the weak convergence on $\mathscr{X}$. Since $\mathcal{X}$ is compact, the metric space $(\Xi, d_w)$, which is an infinite-dimensional space, is complete and compact, as a consequence of Prokhorov's Theorem. In May and Tommasi (2012) it is proved that the KL-criterion function

$$I_{2,1} : (\Xi, d_w) \to [0, +\infty)$$

is upper semi-continuous. This property guarantees the existence of a KL-optimum design

$$\xi^* \in \arg \max_{\xi} I_{2,1}(\xi). \tag{4}$$

**Continuity (Under Suitable Conditions)** The KL-criterion function is not continuous in general (a counter-example is provided in Aletti et al. 2012). Despite this fact, Aletti et al. prove that, under mild conditions, $I_{2,1} : (\Xi, d_w) \to [0, +\infty)$ is also continuous.

## 3 Convergent Algorithm

In this section an iterative procedure generated by an ascendant algorithm is proposed to construct a KL-optimum design $\xi^*$. Following Luenberger and Ye (2008), an *algorithm* **Alg** is a map defined on a space **S** that assigns to every point $\mathbf{s} \in \mathbf{S}$ a subset of **S**. It is clear that, unlike the case where **Alg** is a point-to-point mapping, a sequence generated by the algorithm **Alg** cannot, in general, be predicted solely from knowledge of the initial point $\mathbf{s}_0$.

Let $\Gamma$ be the set that we wish to reach with an algorithm **Alg**. A continuous real-valued function Z on **S** is said to be an *ascendant function* for $\Gamma$ and **Alg** if it satisfies

(i) if $\mathbf{s} \notin \Gamma$ and $\mathbf{t} \in \mathbf{Alg}(\mathbf{s})$, then $Z(\mathbf{t}) > Z(\mathbf{s})$;
(ii) if $\mathbf{s} \in \Gamma$ and $\mathbf{t} \in \mathbf{Alg}(\mathbf{s})$, then $Z(\mathbf{t}) \geq Z(\mathbf{s})$.

When there is such a function, the algorithm is said to be ascendant.

The algorithm $\mathbf{Alg}_{KL}$ here proposed to construct the KL-optimum design is obtained by composing the following point-to-set maps:

$\mathbf{Map_1}$: $\Xi \hookrightarrow \Xi \times \Theta_2$, defined by $\mathbf{Map_1}(\xi) = (\xi, \Omega_2(\xi))$, where $\Omega_2(\xi)$ is defined in (3);[1]
$\mathbf{Map}_{\mathscr{X}}$: $\Theta \hookrightarrow \mathscr{X}$, defined by $\mathbf{Map}_{\mathscr{X}}(\beta) = \{x \in \mathscr{X} : x = \arg\max_{s \in \mathscr{X}} \mathscr{I}(s, \beta)\}$;
$\mathbf{Map_\xi}$: $(\Xi \times \mathscr{X}) \hookrightarrow \Xi$, defined by $\mathbf{Map_\xi}(\xi, x) = \{\xi' \in \Xi : \xi' = (1-\alpha)\xi + \alpha\delta_x$ for some $0 \le \alpha \le 1$ such that $I_{2,1}(\xi') = \max_{\alpha \in [0,1]} I_{2,1}[(1-\alpha)\xi + \alpha\delta_x]\}$, where $\delta_x$ denotes the distribution which concentrates the whole mass at $x$.

Referring to the natural definition of point-to-set mapping obtained by composing two point-to-set mappings (Luenberger and Ye 2008), let $\mathbf{Map_2} : \Xi \times \Theta_2 \hookrightarrow \Xi$ be defined by

$$\mathbf{Map_2}(\xi, \beta) = \mathbf{Map_\xi}\big[\xi, \mathbf{Map}_{\mathscr{X}}(\beta)\big].$$

The algorithm $\mathbf{Alg}_{KL} : \Xi \hookrightarrow \Xi$ is finally given by

$$\mathbf{Alg}_{KL}(\xi) = \mathbf{Map_2}\big[\mathbf{Map_1}(\xi)\big].$$

Assume that $\mathscr{I}(x, \beta_2)$ defined in (1) is continuous with respect to $(x, \beta_2)$ and $I_{2,1}(\xi)$ is continuous (see Sect. 2). Provided that the algorithm explores regular designs, a sequence of designs obtained by iteratively applying $\mathbf{Alg}_{KL}$ converges to the set of KL-optimum designs, as stated in the following theorem.

**Theorem 1** *Let $\xi_0 \in \Xi$ such that its sub-level $\{\xi \in \Xi : I_{2,1}(\xi) \ge I_{2,1}(\xi_0)\}$ is compact. For any $n$, let $\xi_{n+1} \in \mathbf{Alg}_{KL}(\xi_n)$. If $\xi_n$ is a sequence of regular designs, then the limit of any converging subsequence of $\xi_n$ is a KL-optimum design. In particular, if the optimum $\xi^*$ is unique, $\xi_n \to \xi^*$.*

To prove the result, the fundamental idea is that, as a consequence of Theorem 1 of López-Fidalgo et al. (2007), $I_{2,1}(\xi)$ is an ascendant function for the set of KL-optimal designs and $\mathbf{Alg}_{KL}$. Hence it is possible to apply the Global Convergent Theorem for ascendant algorithms. A detailed proof is provided in the Appendix.

Note that the algorithm proposed here coincides with the first-order algorithm described in López-Fidalgo et al. (2007) except for the choice of the sequence $\{\alpha_n\}$, which is not fixed in advance, but is instead obtained by maximizing the KL-criterion function in $\mathbf{Map_\xi}$.

## 4 Regularization

The numerical procedure described in Sect. 3 converges provided that the designs $\xi_n$ where the algorithm moves are regular. If this is not the case, Fedorov and Hackl

[1] When $\Omega_2(\xi)$ is empty, replace it with $\{\tilde{\beta}_2 : \int_{\mathscr{X}} \mathscr{I}(x, \tilde{\beta}_2)\,\xi(\mathrm{d}x) \le \inf_{\beta_2 \in \Theta_2} \int_{\mathscr{X}} \mathscr{I}(x, \beta_2)\,\xi(\mathrm{d}x) + \varepsilon\}$, for an arbitrary $\varepsilon > 0$.

(1997) suggest to regularize the problem, i.e., using the function

$$I_\gamma(\xi) = I_{2,1}\big[(1-\gamma)\xi + \gamma\tilde{\xi}\big]$$

instead of $I_{2,1}(\xi)$, where $0 < \gamma < 1$ and $\tilde{\xi}$ is a regular design. Let $\xi_1 = (1-\gamma)\xi + \gamma\tilde{\xi}$. Then $I_\gamma(\xi) = I_{21}(\xi_1)$. It is straightforward to prove that the new criterion function $I_\gamma(\xi)$ is also concave and continuous.

The algorithm described in Sect. 3 may be then readapted to $I_\gamma(\xi)$ instead of $I_{2,1}(\xi)$ in the following way:

1. $\mathbf{Map_1} : \Xi \hookrightarrow \Xi \times \Theta_2$ is now replaced by $\mathbf{Map_1}(\xi) = (\xi, \Omega_2(\xi_1))$;
2. $\mathbf{Map_\xi} : (\Xi \times \mathscr{X}) \hookrightarrow \Xi$ is now replaced by $\mathbf{Map_\xi}(\xi, x) = \{\xi' \in \Xi : \xi' = (1-\alpha)\xi + \alpha\delta_x$ for some $0 \le \alpha \le 1$ such that $I_\gamma(\xi') = \max_{\alpha\in[0,1]} I_\gamma[(1-\alpha)\xi + \alpha\delta_x]\}$.

Note that, at least in the class of generalized linear models, any design with a non-singular Fisher information matrix is regular according to the definition given in Sect. 2. Therefore, if $\tilde{\xi}$ is regular, then so is $\xi_1$ (the proof is available from the authors). For these models, it is then guaranteed that the readapted algorithm moves on regular designs. In addition, Theorem 1 may be specialized for this algorithm, obtaining a sequence $\xi_n$ converging to the set of optimum designs for $I_\gamma(\xi)$

$$\xi^*_\gamma \in \arg\max_\xi I_\gamma(\xi),$$

instead of the set of KL-optimum designs $\xi^*$. The following derivations show that $I_{2,1}(\xi^*_\gamma)$ approximates $I_{2,1}(\xi^*)$, justifying the regularization procedure.

For any given $\tilde{\xi}$ and $\gamma$, let

$$\Xi_\gamma = \big\{\eta : \eta = (1-\gamma)\xi + \gamma\tilde{\xi}, \xi \in \Xi\big\} \subseteq \Xi$$

and $I_\gamma : \Xi \to \mathbb{R}$ is equivalent to $I_{2,1} : \Xi_\gamma \to \mathbb{R}$. Thus

$$\max_{\xi\in\Xi} I_\gamma(\xi) = \max_{\eta\in\Xi_\gamma} I_{2,1}(\eta) \le \max_{\xi\in\Xi} I_{2,1}(\xi)$$

and so $I_{2,1}(\xi^*) \ge I_\gamma(\xi^*_\gamma)$.

From the concavity of $I_{2,1}(\xi)$, we get

$$I_\gamma\big(\xi^*\big) = I_{2,1}\big[(1-\gamma)\xi^* + \gamma\tilde{\xi}\big] \ge (1-\gamma)I_{2,1}\big(\xi^*\big) + \gamma I_{2,1}(\tilde{\xi}).$$

Thus

$$I_{2,1}\big(\xi^*\big) - I_\gamma\big(\xi^*\big) \le \gamma\big[I_{2,1}\big(\xi^*\big) - I_{2,1}(\tilde{\xi})\big].$$

Since $\xi^*_\gamma$ is the maximum of $I_\gamma(\xi)$, $I_{2,1}(\xi^*) - I_\gamma(\xi^*_\gamma) \le I_{2,1}(\xi^*) - I_\gamma(\xi^*)$ and so

$$I_{2,1}\big(\xi^*\big) - I_\gamma\big(\xi^*_\gamma\big) \le \gamma\big[I_{2,1}\big(\xi^*\big) - I_{2,1}(\tilde{\xi})\big].$$

From the definition of $I_\gamma(\xi)$ the last inequality can be rewritten as

$$0 \le I_{2,1}\big(\xi^*\big) - I_{2,1}\big[(1-\gamma)\xi^*_\gamma + \gamma\tilde{\xi}\big] \le \gamma\big[I_{2,1}\big(\xi^*\big) - I_{2,1}(\tilde{\xi})\big].$$

Thus, if $\gamma$ is a small value, the design $(1-\gamma)\xi^*_\gamma + \gamma\tilde{\xi}$ is *almost* KL-optimum and therefore $\xi^*_\gamma$ is *almost* KL-optimum since $I_{2,1}(\xi)$ is continuous. This result motivates the use of a regularization procedure.

## 5 Final Comments

In the present work an iterative procedure to find KL-optimum designs is proposed. A detailed proof is provided of the convergence of a sequence generated by the algorithm to the set of KL-optimum designs. This analytical result holds when the algorithm moves on regular designs. Introduction of the regularization procedure ensures that the algorithm can be always successfully applied.

When an algorithm is used in practice, a finite number of iterations are generated to approximate an optimum design. A stopping rule may be developed for the algorithm described here, following the method proposed in López-Fidalgo et al. (2007). The stopping rule may also be extended from the regular case to the general case by means of the discussed regularization.

## Appendix

The convergence of the algorithm is studied by means of the property of closeness of point-to-set maps (Luenberger and Ye 2008), which is a generalization of the classical concept of continuity.

**Lemma 1** $\int_{\mathscr{X}} \mathscr{I}(x,\beta_2)\,\mathrm{d}\xi(x)$ *is continuous in* $(\xi,\beta_2)$.

*Proof* Take $(\xi_n,\beta_n) \to (\xi,\beta)$. We have

$$\begin{aligned}
&\left|\int_{\mathscr{X}} \mathscr{I}(x,\beta)\mathrm{d}\xi(x) - \int_{\mathscr{X}} \mathscr{I}(x,\beta_n)\mathrm{d}\xi_n(x)\right| \\
&\quad\le \left|\int_{\mathscr{X}} \mathscr{I}(x,\beta)\mathrm{d}\xi(x) - \int_{\mathscr{X}} \mathscr{I}(x,\beta)\mathrm{d}\xi_n(x)\right| \\
&\qquad + \left|\int_{\mathscr{X}} \mathscr{I}(x,\beta)\mathrm{d}\xi_n(x) - \int_{\mathscr{X}} \mathscr{I}(x,\beta_n)\mathrm{d}\xi_n(x)\right| \\
&\quad\le \left|\int_{\mathscr{X}} \mathscr{I}(x,\beta)\big[\mathrm{d}\xi(x) - \mathrm{d}\xi_n(x)\big]\right| + \int_{\mathscr{X}} \big|\mathscr{I}(x,\beta) - \mathscr{I}(x,\beta_n)\big|\mathrm{d}\xi_n(x) \\
&\quad\le A + \max_{x\in\mathscr{X}} \big|\mathscr{I}(x,\beta) - \mathscr{I}(x,\beta_n)\big|.
\end{aligned}$$

From the definition of weak convergence, it follows that $A \to 0$ as $\xi_n \to \xi$, since $\mathscr{I}$ is continuous in $x$ and $\mathscr{X}$ is compact. To prove that $\max_{x\in\mathscr{X}} |\mathscr{I}(x,\beta) - \mathscr{I}(x,\beta_n)| \to 0$ as $\xi_n \to \xi$, take a converging sequence $\beta_n \to \beta$ and define the function $h_n(x) = \max_{x\in\mathscr{X}} |\mathscr{I}(x,\beta_n) - \mathscr{I}(x,\beta)|$. Let $\hat{x}_n$ be a maximum point: $\hat{x}_n \in \arg_{x\in\mathscr{X}} \max h_n(x)$. Since $\mathscr{X}$ is compact, from any subsequence of $(\hat{x}_n)_n$, we can extract a converging subsequence $\hat{x}_{n_k} \to \hat{x}$. Hence

$$\begin{aligned} h_{n_k}(\hat{x}_{n_k}) &= \left|\mathscr{I}(\hat{x}_{n_k},\beta_{n_k}) - \mathscr{I}(\hat{x}_{n_k},\beta)\right| \\ &\le \left|\mathscr{I}(\hat{x}_{n_k},\beta_{n_k}) - \mathscr{I}(\hat{x},\beta)\right| + \left|\mathscr{I}(\hat{x},\beta) - \mathscr{I}(\hat{x}_{n_k},\beta)\right|. \end{aligned}$$

The continuity of $\mathscr{I}$ with respect to both the variables concludes the proof. □

**Corollary 1** *The map* $\mathbf{Map_1}$ *is closed.*

*Proof* Let $\xi_n \to \xi$, $\beta_n \in \Omega_2(\xi_n)$ and $\beta_n \to \beta$. We must prove that $\beta \in \Omega_2(\xi)$. By Lemma 1, we have that, for $n$ sufficiently large,

$$\int_{\mathscr{X}} \mathscr{I}(x,\beta_n)\mathrm{d}\xi_n(x) \le \varepsilon + \int_{\mathscr{X}} \mathscr{I}(x,\beta)\mathrm{d}\xi(x).$$

Moreover, since $I_{2,1}$ is a continuous function, then $I_{2,1}(\xi) \le \varepsilon + I_{2,1}(\xi_n)$ (again for $n$ sufficiently large). Therefore, since $I_{2,1}(\xi_n) = \int_{\mathscr{X}} \mathscr{I}(x,\beta_n)\mathrm{d}\xi_n(x)$, we get

$$I_{2,1}(\xi) \le \varepsilon + I_{2,1}(\xi_n) = \varepsilon + \int_{\mathscr{X}} \mathscr{I}(x,\beta_n)\mathrm{d}\xi_n(x) \le 2\varepsilon + \int_{\mathscr{X}} \mathscr{I}(x,\beta)\mathrm{d}\xi(x).$$

The arbitrary choice of $\varepsilon$ ensures that $I_{2,1}(\xi) = \int_{\mathscr{X}} \mathscr{I}(x,\beta)\mathrm{d}\xi(x)$. □

**Lemma 2** *The map* $\mathbf{Map}_{\mathscr{X}}$ *is closed.*

*Proof* First note that $\mathbf{Map}_{\mathscr{X}}(\beta) \neq \emptyset$ for any $\beta$, since $\mathscr{X}$ is compact and $\mathscr{I}$ is continuous. Now, let $\beta_n \to \beta$, $x_n \in \mathbf{Map}_{\mathscr{X}}(\beta_n)$ and $x_n \to x$. By definition, $\mathscr{I}(x_n,\beta_n) \ge \mathscr{I}(s,\beta_n)$ for any $n$ and $s$. The desired result is a consequence of the continuity of $\mathscr{I}$. □

The following lemma extends the closedness of line search algorithms in an infinite-dimensional space.

**Lemma 3** *The map* $\mathbf{Map}_{\boldsymbol{\xi}}$ *is closed.*

*Proof* Let $(\xi_n, x_n) \to (\xi, x)$, $\xi_n' \in \mathbf{Map}_{\boldsymbol{\xi}}(\xi_n, x_n)$ and $\xi_n' \to \xi'$. We need to prove that $\xi' \in \mathbf{Map}_{\boldsymbol{\xi}}(\xi, x)$. For any $n$, define

$$K_n = \left\{(1-\alpha)\xi_n + \alpha\delta_{x_n} \text{ for some } 0 \le \alpha \le 1\right\}.$$

Since

$$d\big[(1-\alpha)\xi_n + \alpha\delta_{x_n}, (1-\alpha)\xi + \alpha\delta_x\big] \le (1-\alpha)d(\xi_n, \xi) + \alpha|x_n - x|,$$

we have that $d(K_n, K) \to 0$, where $K = \{(1-\alpha)\xi + \alpha\delta_x \text{ for some } 0 \le \alpha \le 1\}$.

Since $\xi'_n \in K_n$, it follows that

$$d\big(\xi', K\big) \le d\big(\xi', \xi'_n\big) + d\big(\xi'_n, K_n\big) + d(K_n, K) \to 0,$$

which implies $\xi' \in K$, that is, $\xi' = (1-\alpha')\xi + \alpha'\delta_x$ for some $\alpha' \in [0, 1]$.

By the definition of $\xi'_n$, we have that $I_{2,1}(\xi'_n) \ge I_{2,1}[(1-\alpha)\xi_n + \alpha\delta_{x_n}]$ for any $\alpha \in [0, 1]$. Letting $n \to \infty$, we get

$$I_{2,1}\big(\xi'\big) \ge I_{2,1}\big[(1-\alpha)\xi + \alpha\delta_x\big].$$

Thus $I_{2,1}(\xi') \ge \max_{\alpha\in[0,1]} I_{2,1}[(1-\alpha)\xi + \alpha\delta_x]$, and hence $\xi' \in \mathbf{Map}_{\boldsymbol{\xi}}(\xi, x)$. □

**Corollary 2** *The map* $\mathbf{Map_2}$ *is closed.*

*Proof* By Lemmas 2 and 3, the maps $(\xi, \beta) \xrightarrow{(\mathrm{Id}, \mathbf{Map}_{\mathscr{X}})} (\xi, \mathbf{Map}_{\mathscr{X}}(\beta))$ and $(\xi, \mathbf{Map}_{\mathscr{X}}(\beta)) \xrightarrow{\mathbf{Map}_{\boldsymbol{\xi}}} \mathbf{Map_2}(\xi, \beta)$ are closed. Since $\Xi \times \mathscr{X}$ is compact, the composition of the closed point-to-set mappings

$$(\xi, \beta) \xrightarrow{(\mathrm{Id}, \mathbf{Map}_{\mathscr{X}})} \big(\xi, \mathbf{Map}_{\mathscr{X}}(\beta)\big) \xrightarrow{\mathbf{Map}_{\boldsymbol{\xi}}} \mathbf{Map_2}(\xi, \beta)$$

is closed (see Luenberger and Ye 2008, p. 205, Cor. 1). □

*Proof of Theorem 1* From Lemma 1, Lemma 2 and Luenberger and Ye (2008, Cor. 2, p. 205), it follows that $\mathbf{Alg}_{KL}$ is closed. Moreover, as a consequence of Theorem 1 of López-Fidalgo et al. (2007), it is simple to prove that $I_{2,1}(\xi)$ is an ascent function for the set of KL-optimal designs and $\mathbf{Alg}_{KL}$. Finally, it is sufficient to apply the Global Convergence Theorem for ascendant algorithms in Luenberger and Ye (2008, p. 206). □

## References


Aletti, G., May, C., Tommasi, C.: Properties of the KL-optimality criterion. arXiv:1212.3556 (2012)

Atkinson, A.C., Fedorov, V.V.: The design of experiments for discriminating between two rival models. Biometrika **62**, 57–70 (1975a)

Atkinson, A.C., Fedorov, V.V.: Optimal design: experiments for discriminating between several models. Biometrika **62**, 289–303 (1975b)

Fedorov, V.V., Hackl, P.: Model-Oriented Design of Experiments. Springer, New York (1997)

López-Fidalgo, J., Tommasi, C., Trandafir, P.C.: An optimal experimental design criterion for discriminating between non-normal models. J. R. Stat. Soc. B **69**, 231–242 (2007)

Luenberger, D.G., Ye, Y.: Linear and Nonlinear Programming, 3rd edn. Springer, New York (2008)
May, C., Tommasi, C.: Model selection and parameter estimation in non-linear nested models: A sequential generalized DKL-optimum design. Stat. Sin. (2012). doi:10.5705/ss.2012.258
Polak, E.: Optimization; Algorithms and Consistent Approximations. Springer, New York (1997). doi:10.1007/978-1-4612-0663-7
Tommasi, C.: Optimal designs for discriminating among several non-normal models. In: López-Fidalgo, J., Rodríguez-Díaz, J.M., Torsney, B. (eds.) mODa 8—Advances in Model-Oriented Design and Analysis, pp. 213–220. Physica-Verlag, Heidelberg (2007). doi:10.1007/978-3-7908-1952-6_27
Tommasi, C.: Optimal designs for both model discrimination and parameter estimation. J. Stat. Plan. Inference **139**, 4123–4132 (2009). doi:10.1016/j.jspi.2009.05.042
Uciński, D., Bogacka, B.: T-optimum designs for multiresponse dynamic heteroscedastic models. In: Di Bucchianico, A., Läuter, H., Wynn, H.P. (eds.) mODa 8—Advances in Model-Oriented Design and Analysis, pp. 191–199. Physica-Verlag, Heidelberg (2004)

# Robust Experimental Design for Choosing Between Models of Enzyme Inhibition

**Anthony C. Atkinson and Barbara Bogacka**

**Abstract** Models for enzyme inhibition form a family of extensions of the Michaelis-Menten model to two explanatory variables. We present four-point locally Ds-optimum designs for discriminating between competitive and non-competitive models of inhibition and explore the sensitivity of the designs to the values of the two nonlinear parameters in the model. We evaluate combinations of pairs of locally optimum designs. A robust design is found with six support points that has high minimum and average efficiencies over all considered parameter values.

## 1 Introduction

Enzymes are organic catalysts. In a typical enzyme kinetics reaction enzymes bind substrates and turn them into products. In the absence of inhibition the reaction rate is represented by the standard Michaelis-Menten model $v = V[S]/(K_m + [S])$, where $V$ denotes the maximum velocity of the reaction, $[S]$ is the concentration of the substrate and $K_m$ is the Michaelis-Menten constant—the value of $[S]$ at which half of the maximum velocity $V$ is reached (Michaelis and Menten 1913).

Enzyme inhibitors are molecules that decrease the activity of enzymes. In order to model such behaviour, the Michaelis-Menten model is extended to include the effect of inhibitor concentration $[I]$. Two important mechanisms are competitive and non-competitive inhibition; see, for example, Segel (1993). Our paper presents a method of constructing robust experimental designs for discriminating between the mechanisms.

The two models, which have a similar structure, are introduced in Sect. 2. They may be combined in a single four-parameter model with parameter of combination $\lambda$

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(Atkinson 2011). The locally Ds-optimum designs of Atkinson (2012) yield efficient estimates of $\lambda$ and provide a method of discriminating between the models. However, these locally optimum designs depend on the values of two of the parameters in the combined model. In Sect. 3 we find the minimum and average efficiencies of these designs over a set $\Theta$ of parameter values. The combination of pairs of locally optimum designs in Sect. 4 yields our robust design with an increased number of support points that has greatly improved minimum efficiency over $\Theta$.

## 2 Models for Enzyme Inhibition and the Design Criterion

The velocity equation for *Competitive Inhibition* is

$$v = V[S]/\{K_m(1 + [I]/K_{ic}) + [S]\}. \tag{1}$$

For *Non-competitive Inhibition* the model is

$$v = V[S]/\{(K_m + [S])(1 + [I]/K_{in})\}, \tag{2}$$

where $K_{ic}$ and $K_{in}$ are the inhibition constants.

The nonlinear models (1) and (2) have some structure in common. Atkinson (2011) suggests combining the two models into the single four-parameter model

$$v = V[S]/[K_m\{1 + [I]/K_\lambda\} + [S]\{1 + (1 - \lambda)[I]/K_\lambda\}]. \tag{3}$$

When $\lambda = 1$ the model is that for competitive inhibition and $K_\lambda = K_{ic}$, whereas, for $\lambda = 0$, $K_\lambda = K_{in}$ and we obtain non-competitive inhibition.

An experimental design involves the choice of substrate and inhibitor concentrations $x_i = ([S]_i, [I]_i)^{\mathrm{T}}$ at which measurements are to be taken. Interest is in precise estimation of $\lambda$, with the other three parameters being treated as nuisance parameters. We use Ds-optimality and investigate the robustness of designs to the values of the nuisance parameters. The linearized model in partitioned form is

$$y_i = \psi^{\mathrm{T}} f(x_i) + \varepsilon_i = \psi_1^{\mathrm{T}} f_1(x_i) + \psi_2^{\mathrm{T}} f_2(x_i) + \varepsilon_i, \tag{4}$$

where $\psi^{\mathrm{T}} = (\psi_1^{\mathrm{T}} \ \psi_2^{\mathrm{T}})$ is a $p$-dimensional vector of all parameters and $\psi_1$ is $s \times 1$. We assume $\varepsilon_i \sim \mathcal{N}(0, \sigma^2)$. For the design measure $\xi$ putting weight $w_i$ at the design point $x_i$ in the design region $\mathcal{X}$, the information matrix for $\psi$ for a design with $n$ support points can be written in the partitioned form, with blocks given by

$$M_{jk}(\xi) = \sum_{i=1}^{n} w_i f_j(x_i) f_k^{\mathrm{T}}(x_i), \quad j, k = 1, 2. \tag{5}$$

The covariance matrix for the estimator of $\psi_1$ is then

$$A^{-1}(\xi) = \{M_{11}(\xi) - M_{12}(\xi) M_{22}^{-1}(\xi) M_{12}^{\mathrm{T}}(\xi)\}^{-1}. \tag{6}$$

The Ds-optimum design for $\psi_1$ in the linear model (4) maximizes the determinant $|A(\xi)|$.

We linearize the model by Taylor series expansion. The information matrix is now a function of the vector of partial derivatives

$$f\left(x_i, \psi^0\right) = \left.\frac{\partial v(x_i, \psi)}{\partial \psi}\right|_{\psi^0} \tag{7}$$

of the response function with respect to the parameters $\psi$, often called the parameter sensitivities, where $\psi^0$ is a prior point estimate of the parameters. Optimum designs for this linearized model are called *locally-optimum* and depend, often strongly, on the value of $\psi^0$.

In our example the model is nonlinear, $\psi_1 = \lambda$ and $s = 1$, so that the locally Ds-optimum design maximizes $A(\xi, \psi^0)$. Throughout we will be interested in approximate designs in which the weights $w_i$ are not constrained to be ratios of integers.

## 3 Design Sensitivity

Bogacka et al. (2011) find analytical expressions for locally D-optimum designs for several enzyme inhibition models including (1) and (2). However, Ds-optimum designs have to be found numerically. We base our numerical results on those for the system Dextrometorphan-Sertraline used by Bogacka et al. (2011) in which the rectangular design region is $\mathscr{X} = [0, [S]_{\max}] \times [0, [I]_{\max}]$, with $[S]_{\max} = 30$ and $[I]_{\max} = 40$. Bogacka et al. (2011) took parameter values $K_m^0 = 4.36$ and $K_{ic}^0 = 2.58$ with the value of $V$ arbitrary. Our value of $\lambda^0$ was 0.8, since Atkinson (2012) demonstrates that this provides efficient locally optimum designs whether $\lambda = 0$ or 1. In (3) the inhibition coefficient is written as a general value $K_\lambda$. Atkinson (2011) argues that it is necessary to choose parameter values which are appropriate for modelling the same physical phenomenon, whichever component model is used. This is achieved by taking $K_\lambda$ in (3) equal to $(2 - \lambda)K_{ic}$, so that $K_\lambda^0 = 1.2K_{ic}^0$. Since $V$ occurs linearly in (3), we take the arbitrary value $V^0 = 10$. The parameter sensitivities required in the calculations are given by Atkinson (2011).

We calculated the optimum designs by numerical optimization using an unconstrained Quasi-Newton method with parameter transformation to satisfy the constraints on the design points and weights required for experimental designs (Atkinson et al. 2007, Sect. 9.5). For the design region used in this paper, and for all parameter values considered, the Ds-optimum designs for $\lambda$ have the form

$$\xi^* = \left\{ \begin{array}{cccc} ([S]_{\max}, [I]_{\min}) & (s_2, [I]_{\min}) & ([S]_{\max}, i_3) & (s_4, i_4) \\ w_1 & w_2 & w_3 & w_4 \end{array} \right\}, \tag{8}$$

so that they can be found by a seven-dimensional numerical search, provided this structure holds. That this structure holds and that the optimum design had been

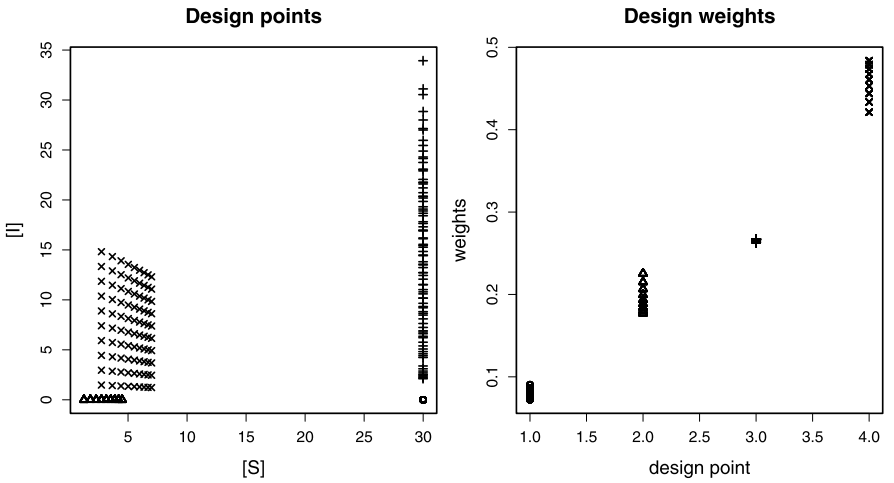


**Fig. 1** 90 locally Ds-optimum designs for elements of $\Theta$. *Left-hand panel*, clustering of support points in $\mathscr{X}$; symbols $\circ$, $\triangle$, $+$ and $\times$ respectively denote $x_1$, $x_2$, $x_3$ and $x_4$. *Right-hand panel*, design weights

found for each case was checked by using the equivalence theorem (Atkinson et al. 2007, Sect. 10.3) over a grid of 81 $\times$ 81 points in $\mathscr{X}$.

To investigate the dependence of designs on the values of the two parameters in (3) let $\theta^{\mathrm{T}} = (K_{ic}, K_m)$. We take a grid of values $\theta_j \in \Theta$ defining the set $\Theta$ at all pairs such that

$$K_{ic} = (0.5, 1.0, \ldots, 5) \quad \text{and} \quad K_m = (2, 3, \ldots, 10). \tag{9}$$

There are therefore ten values of $K_{ic}^0$ and nine of $K_m^0$. The scatter of design points in $\mathscr{X}$ for the 90 locally optimum designs is shown in the left-hand panel of Fig. 1.

There is an appreciable structure in these designs which follows in part from (8). All designs have the same first support point $([S]_{\max}, [I]_{\min}) = (30, 0)$. There are 9 values of $s_2$ and of $s_4$, the variations in both of which therefore depend only on the value of $K_m^0$. The 90 values of $i_3$ range from 2.12 to 33.94 whereas those for $i_4$ have a maximum of 14.83.

The design weights in the right-hand panel are less dependent on the prior values $\theta_j^0$. The minimum value is 0.048, so that, in this example, the Ds-optimum designs are not singular. However, Youdim et al. (2010) show that the Ds-optimum design for $K_{ic}$ in (1) has only two points of support. Such singular designs are useful in calculating the efficiencies of practically useful designs.

To assess the designs requires the efficiency of $\xi_{\mathrm{S}}^i$, the optimum design found for prior $\theta_i^0$, evaluated at parameter $\theta_j \in \Theta$. Since $s = 1$, we define the efficiency as

$$\mathrm{Eff}_{\mathrm{s}}(i, j) = A\big(\xi_{\mathrm{S}}^i, \theta_j\big) / A\big(\xi_{\mathrm{S}}^j, \theta_j\big). \tag{10}$$

To assess each design we look at the minimum and average value of $\mathrm{Eff}_{\mathrm{s}}(i, j)$.

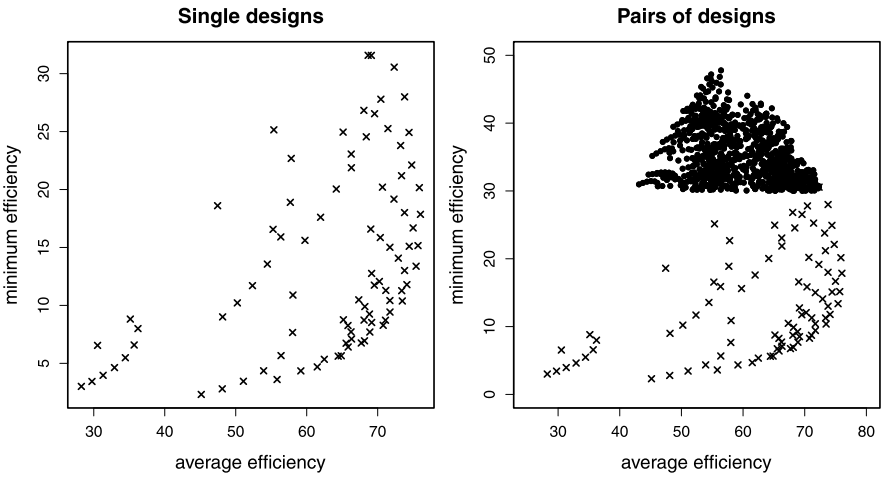


**Fig. 2** *Left-hand panel*: Minimum and average efficiencies (×) over $\Theta$ for the 90 locally Ds-optimum designs. *Right-hand panel*: the same with the addition of efficiencies for selected pairs of locally optimum designs (•)

**Table 1** Average and minimum efficiencies of six of the locally Ds-optimum designs shown in Fig. 2. $K_{ic}^{min}$ and $K_m^{min}$ are the parameter values at which each design has its minimum efficiency

| Design | $K_{ic}^0$ | $K_m^0$ | Efficiency % | | $K_{ic}^{min}$ | $K_m^{min}$ |
|---|---|---|---|---|---|---|
| | | | Average | Minimum | | |
| 1 | 2.5 | 5.0 | 76.03 | 17.86 | 0.5 | 10.0 |
| 2 | 2.5 | 6.0 | 75.87 | 20.16 | 0.5 | 10.0 |
| 3 | 1.5 | 4.0 | 68.65 | 31.58 | 0.5 | 10.0 |
| 4 | 1.5 | 5.0 | 69.11 | 31.58 | 5.0 | 2.0 |
| 5 | 0.5 | 10.0 | 28.25 | 3.01 | 5.0 | 2.0 |
| 6 | 5.0 | 2.0 | 45.14 | 2.32 | 0.5 | 10.0 |

These efficiencies are plotted in the left-hand panel of Fig. 2 with properties of six selected designs displayed in Table 1. Again there is some structure in the plot reflecting the grid of parameter values. Desirable designs will have both a high average efficiency and a high minimum efficiency. It is clear from the figure that there is a trade off, amongst the locally-optimum designs in the top right-hand corner of the figure, between average and minimum efficiency over $\Theta$.

Some numerical details are in Table 1. The first two designs, for priors in the centre of the parameter range, are those with the highest average efficiency, 76.03 and 75.87 %. The second two designs, for smaller values of $K_{ic}^0$, have lower average efficiencies, 68.65 and 69.11 %, but higher minimum efficiencies; 31.58 % for both designs, rather than 17.86 and 20.16 %. The last two designs in the table, for parameter prior values on the boundary of $\Theta$, have the lowest minimum efficiencies of those in Fig. 2.

**Table 2** Six-point robust Ds-optimum design; a combination of locally optimum designs for parameter values (3.5, 4.0) and (0.5, 4.0). Left-hand panel, numerical; right-hand panel, notational from (8)

| $[S]$ | $[I]$ | $w$ | $[S]$ | $[I]$ |
|---|---|---|---|---|
| 30.000 | 0.000 | 0.083 | $[S]_{\max}$ | $[I]_{\min}$ |
| 2.304 | 0.000 | 0.207 | $s_2$ | $[I]_{\min}$ |
| 30.000 | 20.195 | 0.133 | $[S]_{\max}$ | $i_{31}$ |
| 30.000 | 2.885 | 0.133 | $[S]_{\max}$ | $i_{32}$ |
| 4.414 | 9.738 | 0.222 | $s_4$ | $i_{41}$ |
| 4.414 | 1.391 | 0.222 | $s_4$ | $i_{42}$ |

The designs considered can be extended by including Bayesian-optimum designs over suitable prior distributions. For example, for a uniform distribution over the nine-point prior $[1, 2.5, 4] \times [3, 6, 9]$ which almost spans $\Theta$, the design has four support points with the structure of (8); the average efficiency for this design is 75.12 %, similar to those of Designs 1 and 2 in Table 1, although the minimum is higher at 24.07. To find designs with higher minimum efficiencies we generate designs with more support points.

## 4 Robust Designs

The last two columns of Table 1 given the parameter values for which the minimum efficiency occurs for each locally optimum design. For four of the designs, these are (0.5, 10) and for the other two (5.0 and 2.0). Both are extreme points of $\Theta$, yielding designs 5 and 6 in the table for which the minimum efficiency is smallest. The designs with high efficiencies are locally optimum for more central values of the prior values of the parameters. This suggests that a combination of locally optimum designs for central and extreme points in $\Theta$ will have a relatively high minimum efficiency.

The right hand-panel of Fig. 2 repeats the plot of minimum and average efficiencies of the 90 locally optimum designs and adds the efficiencies for all those pairs of locally optimum designs for which the minimum efficiency is greater than 30 %. As the plot shows, there are numerous designs with a minimum efficiency higher than the maximum value of 31.58 in Table 1. The design with the highest minimum efficiency, 47.78 %, has an average efficiency of 56.43. The numerical results for the design are given in the left-hand panel of Table 2 with notational expressions in the right-hand panel.

Because of the structure of the locally optimum designs shown in (8), the equally weighted combination of two designs only has six points of support. Points 1 and 2 have full weight whereas points 3 and 4 in (8) are divided between two points, although the values of $s_4$ are the same for the two parts of the two divided support points. The design is the combination of those for prior parameter values (3.5, 4.0) and (0.5, 4.0), not as extreme as those giving the minimum efficiencies in Table 1. However the three values of efficiency below 48 % for this design all occur at extremes of $\Theta$: (5.0, 10.0), (5.0, 2.0) and (0.5, 10.0).

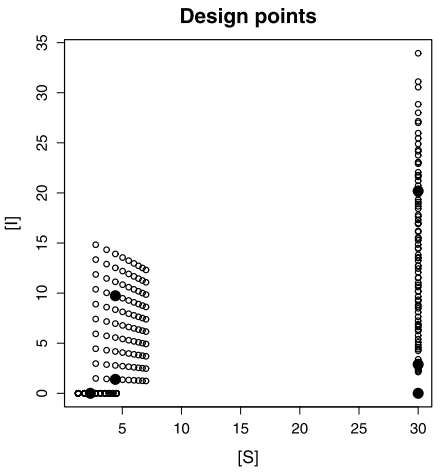


**Fig. 3** The six support points of the robust design, •, and the points, ∘, of the 90 locally Ds-optimum designs for elements of $\Theta$

## 5 Discussion

The combination of two locally optimum designs has led to a design with increased minimum efficiency. If a design with higher average efficiency but lower minimum efficiency is required, another design from the boundary in Fig. 2 could be used.

It is informative to look at the robust design points in the context of the locally optimum designs (8). Figure 3 repeats the left-hand panel of Fig. 1 with the addition of the points of the robust design. We see that the value of $s_2$ lies in the centre of the range of values for the locally optimum designs, the two values of $i_3$ almost span the range of locally optimum values and that there is a medium and extreme value of $i_4$, but not of $s_4$.

Intuitively some of the properties of the robust design are clear, such as an increase in the number of support points relative to the locally-optimum design. However it is not immediate from Fig. 1 which points should be divided. Dror and Steinberg (2006) find robust designs through the clustering of the support points of locally optimum designs, a procedure echoed in Fig. 3. D-optimality is used by Woods et al. (2006) to find robust designs for generalized linear models over link functions and parameters.

We have found designs which provide a compromise between the value of the average and minimum efficiencies. Calculation of the maximin design that maximizes the minimum efficiency is complicated by the non-convexity of the objective function. Recent results are given by Biedermann et al. (2011) for additive models. Dette et al. (2007) provide an equivalence theorem for maximin designs and apply it to a one parameter problem. King and Wong (2000) provide an algorithm for the construction of maximin designs.

Finally, we note that if only one model is of interest, T-optimum designs (Atkinson and Fedorov 1975) maximize the non-centrality parameter of the F-test for departures from that model. See Wiens (2009) for recent developments. However, since either model may be true, compound T-optimum designs are required (Atkinson 2008, Sect. 4) which maximize a function of the non-centrality parameters for

departures from each model. Atkinson (2012) finds, for the parameter values of Bogacka et al. (2011), that the individual T-efficiencies for the T-optimum design are 3–4 % higher than those for the Ds-optimum design. In some cases T-optimum designs can be difficult to compute (but see Dette and Titoff 2008) so that Ds-optimum designs may be a useful surrogate.

## References

Atkinson, A.C.: DT-optimum designs for model discrimination and parameter estimation. J. Stat. Plan. Inference **138**, 56–64 (2008)

Atkinson, A.C.: Some optimum designs for building enzyme inhibition kinetic models. J. Stat. Theory Pract. **10**, 143–162 (2011)

Atkinson, A.C.: Optimum experimental designs for choosing between competitive and non-competitive models of enzyme inhibition. In: Communications in Statistics—Theory and Methods, pp. 2283–2296 (2012). doi:10.1080/03610926.2011.593720

Atkinson, A.C., Fedorov, V.V.: The design of experiments for discriminating between two rival models. Biometrika **62**, 57–70 (1975)

Atkinson, A.C., Donev, A.N., Tobias, R.D.: Optimum Experimental Designs, with SAS. Oxford University Press, Oxford (2007)

Biedermann, S., Dette, H., Woods, D.C.: Optimal design for additive partially nonlinear models. Biometrika **98**, 449–458 (2011). doi:10.1093/biomet/asr001

Bogacka, B., Patan, M., Johnson, P., Youdim, K., Atkinson, A.C.: Optimum designs for enzyme inhibition kinetic models. J. Biopharm. Stat. **21**, 555–572 (2011). doi:10.1080/10543406.2010.489979

Dette, H., Titoff, S.: Optimal discrimination designs. Ann. Stat. **37**, 2056–2082 (2008)

Dette, H., Haines, L.M., Imhof, L.A.: Maximin and Bayesian optimal designs for regression models. Stat. Sin. **17**, 463–480 (2007)

Dror, H.A., Steinberg, D.M.: Robust experimental design for multivariate generalized linear models. Technometrics **48**, 520–529 (2006). doi:10.1198/004017006000000318

King, J., Wong, W.K.: Minimax D-optimal designs for the logistic model. Biometrics **56**, 1263–1267 (2000)

Michaelis, L., Menten, M.: Die Kinetik der Invertinwirkung. Biochem. Z. **49**, 333–369 (1913)

Segel, I.H.: Enzyme Kinetics: Behavior and Analysis of Rapid Equilibrium and Steady-State Enzyme Systems, 2nd edn. Wiley, New York (1993)

Wiens, D.P.: Robust discrimination designs. J. R. Stat. Soc. B **71**, 805–829 (2009)

Woods, D.C., Lewis, S.M., Eccleston, J.A., Russell, K.G.: Designs for generalized linear models with several variables and model uncertainty. Technometrics **48**, 284–292 (2006)

Youdim, K.A., Atkinson, A.C., Patan, M., Bogacka, B., Johnson, P.: Potential application of D-optimal designs in the efficient investigation of cytochrome P450 inhibition kinetic models. Drug Metab. Dispos. **38**, 1019–1023 (2010). doi:10.1124/dmd.110.033142

# Checking Linear Regression Models Taking Time into Account

**Wolfgang Bischoff**

**Abstract** Linear regression models are usually checked by a lack-of-fit (LOF) test to be sure that the model is at least approximately true. In many practical cases data can only be sampled sequentially. Such a situation can appear in industrial production when goods are produced one after the other. So as time goes by, the mean may also depend on time, i.e., the mean is not only a function of the covariates, but it may be also a function of time. This dependence over time is difficult to detect by a conventional LOF test. Tests based on the residual partial sum process are then more suitable. Therefore, in such a situation we suggest applying both an LOF test, e.g., the F-test, and a test based on the residual partial sum process, e.g., a test of Kolmogorov type. When the linear regression model is not rejected by either test, least squares estimation can be used to estimate the parameters of the linear regression model. For the situation just discussed, we are here interested in a design with which we can efficiently run the two tests and estimate the linear model. Usually, classical optimal designs and LOF-optimal designs do not have these properties.

## 1 Introduction

It is popular to describe input-output relationships by linear regression models. There are at least two reasons to sample data for such models: (i) in order to estimate the linear regression model and (ii) in order to check the linear regression model by a lack-of-fit (LOF) test. In many cases data cannot be sampled at the same time. They are sampled one after the other. Therefore time can exert an influence on the observations, i.e., on the output. Hence, the $i$-th output (observation) $y_i$ may not depend on only the input variable (covariate) $x_i \in [a, b] \subseteq \mathbb{R}$. The $i$-th observation $y_i$ may also depend on the time point $t_i \in [0, 1]$ at which the observation is taken. An example of such a situation is industrial production when goods are produced one

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after another. There it is of strong interest to understand the input-output relationship of the production process. Production processes, however, deteriorate as time goes by. Usually, at what time point the process begins getting worse is unknown. Therefore the production process of goods is controlled continuously over time. In this paper we assume that only the mean of the observations may depend on time. Accordingly, the variances and covariances do not depend on time.

A deviation of the mean function over time is difficult to detect by a lack-of-fit (LOF) test. Therefore we suggest applying a second test that is able to detect changes occurring over time. Such tests are based on the residual partial sum process. In this paper we consider the F-test as the LOF test and as the second test a test of Kolmogorov type based on the residual partial sum process. If neither test rejects the model, then the linear regression model can be estimated by least squares.

Classical optimal designs for estimating parameters of a linear model, such as $D$-optimal designs, are often unsuitable for checking the fit of the model, unless extra terms are included in the model specifically for model testing. On the other hand, uniform designs are LOF-optimal under certain assumptions described below. But they are not very efficient for estimating the parameters of a linear regression model. Moreover, as opposed to $D$-optimal designs, uniform designs cannot detect some interesting deviations over time. Therefore, we are looking for a design that does not have the disadvantages of $D$-optimal designs and uniform designs. Loosely speaking, we are looking for designs which are efficient to:

(i) Check the linear regression model (input-output model) by the F-test;
(ii) Check the constancy of the mean function (of the input-output model) over time by a test of Kolmogorov type based on the residual partial sum process and
(iii) Estimate the parameters of the linear regression model by least squares.

The next section contains some preliminaries. Then in Sect. 3 the problems just mentioned are discussed in more detail. In the last section a simulation study is presented illustrating our discussion.

## 2 Preliminaries

We consider $n+1$ observations, $n \in \mathbb{N}$. So input variables (covariates) $x_1, \ldots, x_{n+1}$ can be arbitrarily chosen from the experimental region $[a, b]$, a real compact interval. Then according to the time point $t_i$ of the observation $y_i$, we have $n+1$ design points $(x_i, t_i) \in [a, b] \times [0, 1]$. We assume that the observations are taken equidistantly over time, i.e., $t_1 = 0, t_2 = 1/n, t_3 = 2/n, \ldots, t_n = 1$. Therefore the general model for the observations can be formulated by

$$y_i = y\left(x_i, \frac{i-1}{n}\right) = f(x_i) + g\left(\frac{i-1}{n}\right) + \varepsilon_i, \quad i = 1, \ldots, n+1, \tag{1}$$

where $x_i \in [a, b]$, $f : [a, b] \to \mathbb{R}$ is the unknown input-output regression function and $g : [0, 1] \to [0, \infty)$ describes deviations of the mean over time with $g(0) = 0$.

We assume that $g$ does not depend on the covariate $x$. In the example of the production process, for instance, $g$ describes how the production is getting worse. If larger values of $g$ correspond to deteriorated production, then it is appropriate to assume additionally that $g$ is non-decreasing when the product is not improved during the whole time of production [0, 1].

Furthermore, let $\varepsilon_i$, $i = 0, 1, \ldots, n$, be independent with $\mathrm{E}(\varepsilon_i) = 0$, $\mathrm{Var}(\varepsilon_i) = \sigma^2$. Under the null-hypothesis we assume a linear regression model without deviations of the mean over time

$$H_0 : f = \sum_{j=1}^{d} f_j \beta_j, \quad g \equiv 0, \tag{2}$$

where $f_1, \ldots, f_d : [a, b] \to \mathbb{R}$ are $d$ linearly independent known regression functions, and $\beta_1, \ldots, \beta_d \in \mathbb{R}$ are unknown parameters.

## 3 Good Designs

Our goal is to find efficient designs for the three claims stated in Sect. 1. Let us discuss these three claims in detail.

### *3.1 Lack-of-Fit (LOF) Test*

It is well-known that the F-test is the most powerful invariant test for testing linear alternatives under normally distributed errors. Therefore it is also popular to use the F-test as a lack-of-fit test for linear regression models against arbitrary alternatives. Let $\tilde{\lambda}$ be the uniform distribution on $[a, b]$, i.e., $\tilde{\lambda} = \frac{1}{\lambda([a,b])}\lambda$, where $\lambda$ is the Lebesgue measure, let $BV([a, b]) = \{h : [a, b] \to \mathbb{R} \mid h \text{ has bounded variation}\}$ and let $c > 0$. Then a meaningful set of alternatives for the mean of the input-output linear regression model can be expressed by

$$\mathscr{F}_c := \left\{ \sum_{i=1}^{d} f_i \beta_i + h \;\middle|\; h \in BV_c\big([a, b]\big), \beta_i \in \mathbb{R}, i = 1, \ldots, d \right\}, \tag{3}$$

where $BV_c([a, b]) = \{h \in BV([a, b]) | \int_{[a,b]} h^2 \, \mathrm{d}\tilde{\lambda} \geq c, \int_{[a,b]} f_i h \, \mathrm{d}\tilde{\lambda} = 0, i = 1, \ldots, d\}$. Note that the following considerations and results do not depend on the constant $c > 0$. Wiens (1991) showed that the uniform design $\tilde{\lambda}$ is LOF-optimal, which means that, given the F-test, the uniform design maximizes the smallest power in a certain class $\mathscr{F}_c$ of alternatives. Biedermann and Dette (2001) generalized this result and proved Wiens' result for other LOF tests. Bischoff (2010) showed that the class of alternatives (considered in both papers) must be restricted to, for instance, $\mathscr{F}_c$.

We shall use the F-test as a lack of fit test in our simulation study in Sect. 4.

### 3.2 Test for $g = 0$

Residual partial sum processes are useful to detect changes over time. Let

$$r\left(x_i, \frac{i-1}{n}\right) := y\left(x_i, \frac{i-1}{n}\right) - \sum_{j=1}^{d} f_j(x_i)\hat{\beta}_j, \quad 1 \le i \le n+1, \tag{4}$$

be the $i$-th least squares residual given the linear regression model under $H_0$, where $\hat{\beta}_1, \ldots, \hat{\beta}_d$ are the least squares estimates of the mean parameters of the linear regression model. Let $r_{n+1} = (r(x_1, 0), r(x_2, 1/n), \ldots, r(x_{n+1}, 1))^\top \in \mathbb{R}^{n+1}$ be the vector of least squares residuals. Here $r_{n+1}$ is embedded in the space $C[0,1]$ of continuous functions on $[0,1]$ by the partial sum operator

$$\begin{aligned} &T_{n+1} : \mathbb{R}^{n+1} \longrightarrow C[0,1], \\ &\mathbf{a} = (a_1, \ldots, a_{n+1})^\top \mapsto T_{n+1}(\mathbf{a})(z) \\ &\quad = \sum_{i=1}^{[(n+1)z]} a_i + \big((n+1)z - \big[(n+1)z\big]\big) a_{[(n+1)z]+1}, \quad z \in [0,1], \end{aligned}$$

where $[s] = \max\{m \in \mathbb{N}_0 \mid m \le s\}$ and $\sum_{i=1}^{0} a_i = 0$.

The stochastic process $\frac{1}{\hat{\sigma}\sqrt{n+1}} T_{n+1}(r_{n+1})$ is called the residual partial sum process, where $\hat{\sigma}$ is a consistent estimator of $\sigma$. MacNeill (1978a, 1978b) showed that the residual partial sum process converges weakly in $C[0,1]$ to a Gaussian process as $n \to \infty$ and derived its asymptotic distribution if $x_i = t_i = (i-1)/n \in [0,1]$, $i = 1, \ldots, n+1$. Bischoff (1998), see also (Bischoff 2002) for a geometrical approach, generalized this result to an arbitrary design $x_i = t_i \in [0,1]$, $i = 1, \ldots, n+1$, i.e., when it is not assumed that $t_1, \ldots, t_{n+1}$ are chosen equidistantly. The limit process is useful to develop asymptotic tests for detecting changes over time by using, e.g., tests of Kolmogorov(-Smirnov) or Cramér-von Mises types.

In Sect. 4 we use a test of Kolmogorov type based on the partial sum process to check whether deviations over time occur.

### 3.3 Estimation of the Parameters $\beta_1, \ldots, \beta_d$

We estimate the mean parameter vector $\beta = (\beta_1, \ldots, \beta_d)^\top$ of the linear regression model by the least squares estimates $\hat{\beta} = (\hat{\beta}_1, \ldots, \hat{\beta}_d)^\top$ under $H_0$. A good design should be used for the input variables $x_1, \ldots, x_n$ to get an efficient estimator of $\beta$. In this paper we consider $D$-optimal designs. Classical optimal designs for estimating the parameters of a linear model, however, are often unsuitable for applying an LOF test. This is true, for example, for polynomial regression. Therefore uniform designs which are LOF-optimal are more popular. On the other hand, uniform designs are not very efficient for estimating the unknown parameters.

To take into consideration these concerns, Bischoff and Miller (2006a, 2006b, 2006c, 2010) suggest taking one part of the design points to enable an LOF test for checking the assumed model with a given power, see Sect. 3.1. Then the remaining design points are determined in such a way that the whole design is as good as possible (according to a specific criterion) for estimating the unknown parameters of interest. We call such designs optimally $p$-LOF-test-efficient, where $p$ gives the percentage of the input variables $x_1, \ldots, x_{n+1} \in [a, b]$ chosen as an LOF-optimal design, i.e., in our context as the uniform design. In Bischoff and Miller (2010) the general form of $D$-optimally $p$-LOF-test-efficient designs for polynomial regression models is determined. But note that such designs for polynomial regression of order greater than 2 are difficult to determine. Bischoff (2008) constructs easy to calculate $p$-LOF-test-efficient designs that are highly efficient for estimation of the unknown parameters.

In Sect. 4 we compare $D$-optimal, LOF-optimal (i.e., uniform) and $D$-optimally $p$-LOF-test-efficient designs for $p = 1/2$ in a simulation study when $H_0$ is a straight-line regression model.

## 4 Comparison of the Three Designs

By a simulation study we compare the designs discussed above for the input values $x_1, \ldots, x_n \in [a, b]$ when the linear model under $H_0$ is a straight-line regression model. Accordingly, our null-hypothesis is given by

$$H_0 : f(x) = \beta_0 + \beta_1 x, \quad x \in [a, b]; \qquad \beta_0, \beta_1 \in \mathbb{R} \quad \text{arbitrary but fixed; } g \equiv 0. \tag{5}$$

To simplify the notation, we assume that the number $n + 1$ of observations is $n + 1 = 4m$, $m \in \mathbb{N}$. Moreover, the problem is simplified by assuming $x_1 \leq \cdots \leq x_n$ which is in some practical situations a necessary assumption. Thus we consider the following three designs:

1. $D$-optimal design for the straight-line regression model:

$$(x_1, t_1) = (a, 0), \quad \ldots, \quad (x_{2m}, t_{2m}) = \left(a, \frac{2m-1}{n-1}\right),$$

$$(x_{2m+1}, t_{2m+1}) = \left(b, \frac{2m}{n-1}\right), \quad \ldots, \quad (x_n, t_n) = (b, 1).$$

2. LOF-optimal design: uniform design with two observations at each design point in order to be able to use the F-test as the lack-of-fit test, i.e.,

$$(x_1, t_1) = (a, 0), \qquad (x_2, t_2) = \left(a, \frac{1}{n-1}\right),$$

$$(x_3, t_3) = \left(a + \frac{b-a}{2m-1}, \frac{2}{n-1}\right),$$

$$(x_4,t_4)=\left(a+\frac{b-a}{2m-1},\frac{3}{n-1}\right),\qquad (x_5,t_5)=\left(a+\frac{2(b-a)}{2m-1},\frac{4}{n-1}\right),$$
$$(x_6,t_6)=\left(a+\frac{2(b-a)}{2m-1},\frac{5}{n-1}\right),\quad \ldots,$$
$$(x_{n-3},t_{n-3})=\left(a+\frac{(2m-2)(b-a)}{2m-1},\frac{n-4}{n-1}\right),$$
$$(x_{n-2},t_{n-2})=\left(a+\frac{(2m-2)(b-a)}{2m-1},\frac{n-3}{n-1}\right),$$
$$(x_{n-1},t_{n-1})=\left(b,\frac{n-2}{n-1}\right),\qquad (x_n,t_n)=(b,1).$$

3. $D$-optimally 1/2-LOF-efficient design for the straight-line regression model:

$$(x_1,t_1)=(a,0),\quad \ldots,\quad (x_m,t_m)=\left(a,\frac{m-1}{n-1}\right),$$
$$(x_{m+1},t_{m+1})=\left(a,\frac{m}{n-1}\right),\qquad (x_{m+2},t_{m+2})=\left(a+\frac{b-a}{2m-1},\frac{m+1}{n-1}\right),$$
$$(x_{m+3},t_{m+3})=\left(a+\frac{2(b-a)}{2m-1},\frac{m+2}{n-1}\right),\quad \ldots,$$
$$(x_{3m-3},t_{3m-3})=\left(a+\frac{(2m-4)(b-a)}{2m-1},\frac{3m-4}{n-1}\right),$$
$$(x_{3m-2},t_{3m-2})=\left(a+\frac{(2m-3)(b-a)}{2m-1},\frac{3m-3}{n-1}\right),$$
$$(x_{3m-1},t_{3m-1})=\left(a+\frac{(2m-2)(b-a)}{2m-1},\frac{3m-2}{n-1}\right),$$
$$(x_{3m},t_{3m})=\left(b,\frac{3m-1}{n-1}\right),$$
$$(x_{3m+1},t_{3m+1})=\left(b,\frac{3m}{n-1}\right),\quad \ldots,\quad (x_n,t_n)=(b,1).$$

## *4.1 Basis of Our Simulation*

In our simulation we consider two alternatives:

$$K_1: f(x)+g_1(t)=\frac{1}{2}+\frac{1}{2}x+\mathbf{1}_{(1/3,1]}(t),\quad x,t\in[0,1],$$

**Table 1** Power of the F-test for two alternatives and three designs

| | Alternative $K_1$ | Alternative $K_2$ |
|---|---|---|
| $D$-optimal | – | – |
| LOF-optimal | 0.44 | 0.05 |
| $D$-optimal 1/2-LOF-efficient | 0.39 | 0.05 |

**Table 2** Power of the Kolmogorov-type test for two alternatives and three designs

| | Alternative $K_1$ | Alternative $K_2$ |
|---|---|---|
| $D$-optimal | 0.99 | 0.54 |
| LOF-optimal | 0.94 | 0.05 |
| $D$-optimal 1/2-LOF-efficient | 0.87 | 0.17 |

where $f(x) = \frac{1}{2} + \frac{1}{2}x$, $x \in [0, 1]$ is a straight line, $\mathbf{1}_{(1/3,1]}$ is the indicator function of $(1/3, 1]$, i.e., $\mathbf{1}_{(1/3,1]}(t)$ is 1 if $t \in (1/3, 1]$ and 0 otherwise, and

$$K_2 : f(x) + g_2(t) = \frac{1}{2} + \frac{1}{2}x + \frac{1}{2}t, \quad x, t \in [0, 1].$$

Both alternatives have deviations of the mean over time and there is no deviation of the mean with respect to the input variable $x$. Furthermore, for the error variables $\varepsilon_i$ we took normally distributed random variables with zero mean and standard deviation $\sigma = 0, 2$. We chose $m = 10$, i.e., $n = 40$ observations. All tests were constructed for the null hypothesis $H_0$ given by (5) with a significance level of 0.05. We took 10000 repetitions for each observation.

## *4.2 Simulation Results for the F-Test*

We consider the F-test for the null hypothesis $H_0$ given in (5). Table 1 shows the power of the F-test for the two alternatives $K_1$ and $K_2$ and the three designs under the null-hypothesis $H_0$. For the straight-line regression the $D$-optimal design cannot detect any deviation from the model. The two other designs can detect a certain part of the alternative $K_1$. The alternative $K_2$ has a deviation in the form of a straight line over time. Therefore it is impossible to detect it by a lack-of-fit test. Recall that the significance level is 0.05.

## *4.3 Simulation Results for the Kolmogorov-Type Test*

Table 2 shows the power of the test of Kolmogorov type based on the residual partial sum process for the two alternatives $K_1$ and $K_2$ and the three designs under the null-hypothesis of straight-line regression. The $D$-optimal design is best for detecting these deviations. The uniform (LOF-optimal) design cannot detect the

alternative $K_2$. (Note again that the significance level is 0.05.) The $D$-optimally $1/2$-LOF-efficient design can detect both alternatives with less power than the $D$-optimal design. This power can, of course, be increased by using a larger number of observations and putting these at the design points of the $D$-optimal design. It is impossible to increase the power for the uniform design when the alternative $K_2$ is specified.

## *4.4 Conclusion*

The $D$-optimally $1/2$-LOF-efficient design is the only one of the three investigated designs that can detect all deviations considered in this paper. Additionally, it is much more efficient for estimating $\beta$ than the uniform design. Its power can be improved if the design points at $a$ and at $b$ can be uniformly distributed on the time interval $[0, 1]$. In that case it can be shown that each deviation $g(t)$ can be detected if the number $n$ of observations is large enough.

By checking the model using two tests we get an inflation of the significance level. For the $D$-optimally $1/2$-LOF-efficient design we then have an overall significance level of 0.08.

## References

Biedermann, S., Dette, H.: Optimal designs for testing the functional form of a regression via nonparametric estimation techniques. Stat. Probab. Lett. **52**, 215–224 (2001)

Bischoff, W.: A functional central limit theorem for regression models. Ann. Stat. **26**, 1398–1410 (1998)

Bischoff, W.: The structure of residual partial sums limit processes of linear regression models. Theory Stoch. Process. **8**, 23–28 (2002)

Bischoff, W.: $D$-optimally lack-of-fit-test-efficient designs and related simple designs. Aust. J. Stat. **37**, 245–253 (2008)

Bischoff, W.: An improvement in the lack-of-fit optimality of the (absolutely) continuous uniform design in respect of exact designs. In: Giovagnoli, A., Atkinson, A.C., Torsney, B., May, C. (eds.) mODa 9—Advances in Model-Oriented Design and Analysis, pp. 33–40. Physica-Verlag, Heidelberg (2010)

Bischoff, W., Miller, F.: Optimal designs which are efficient for lack of fit tests. Ann. Stat. **34**, 2015–2025 (2006a)

Bischoff, W., Miller, F.: Efficient lack of fit designs that are optimal to estimate the highest coefficient of a polynomial. J. Stat. Plan. Inference **136**, 4239–4249 (2006b)

Bischoff, W., Miller, F.: Lack-of-fit-efficiently optimal designs to estimate the highest coefficient of a polynomial with large degree. Stat. Probab. Lett. **76**, 1701–1704 (2006c)

Bischoff, W., Miller, F.: $D$-optimally lack-of-fit-test-efficient designs with an application to a fertilizer-response-relationship. J. Stat. Appl. **5**, 119–137 (2010)

MacNeill, I.B.: Properties of sequences of partial sums of polynomial regression residuals with applications to test for change of regression at unknown times. Ann. Stat. **6**, 422–433 (1978a)

MacNeill, I.B.: Limit processes for sequences of partial sums of regression residuals. Ann. Probab. **6**, 695–698 (1978b)

Wiens, D.P.: Designs for approximately linear regression: two optimality properties of uniform design. Stat. Probab. Lett. **12**, 217–221 (1991)

# Optimal Sample Proportion for a Two-Treatment Clinical Trial in the Presence of Surrogate Endpoints

**Atanu Biswas, Buddhananda Banerjee, and Saumen Mandal**

**Abstract** The use of surrogate endpoints is a very popular practice in medical research when true endpoints are expensive or only available after a long time. Here we obtain an optimal proportion of allocation among two competing treatments based on both true and surrogate endpoints. As the optimum true-surrogate sample proportion obtained by minimizing the variance of the estimated parametric function, e.g., the treatment difference, lies on a boundary in parameter space, we obtain cost optimized choices for these parameters. These are further used in a two-stage optimization for the proportion of allocation to the two treatments.

## 1 Introduction

Many clinical outcomes are such that the response variables are often difficult or highly expensive to measure, or the responses are delayed, whilst short-term measurements are needed for inferential and administrative purposes. Consequently, in medical studies to evaluate the effects of treatments or exposures on the true endpoint, a closely related variable with lower cost and/or available earlier can be used as a surrogate response. Surrogate endpoints are increasingly used in medical science and, consequently, statistical procedures are needed for their efficient use.

In a trial of treatments for osteoporosis, reduction in the fracture rate is the true endpoint, whereas the bone mineral density is treated as the surrogate endpoint. A change in the CD4 cell count in a randomized trial is considered as a surrogate for survival time in a study of HIV. Again, damage to the heart muscle due to myocardial infarction can be accurately assessed by arterioscintography, which is an expensive

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procedure. Consequently, the peak cardiac enzyme level in the blood stream, which is more easily obtainable, is used as a surrogate measure of heart vascular damage (Wittes et al. 1989).

A statistical definition of, and validation criteria for, surrogate endpoints, were first introduced by Prentice (1989). If a test based on surrogate endpoints to compare the treatments is equivalent to the test constructed by true endpoints, then the surrogate is a valid surrogate. See Banerjee and Biswas (2011) and the references therein for a detailed discussion. In the present paper we are not trying to judge the validity of a surrogate. We assume that the surrogates considered are already validated.

We consider two treatments $A$ and $B$, with both the true and surrogate endpoints being binary. It has been observed by many authors that the proportion of validation samples (i.e., true endpoints) relative to the surrogate endpoints, say $\rho$, plays a crucial role in the associated inference. Quite often the experimenter can control this proportion by controlling the cost or time (which is also measured in terms of cost). In particular, with two treatments, we need two such proportions $\rho_A$ and $\rho_B$ for the two treatments, where $\rho_A$ is the proportion of the true response to the total number of surrogate responses from $A$-treated patients and $\rho_B$ is similarly defined for $B$-treated patients. The optimal choice of $\rho_A$ and $\rho_B$ may be a key design issue. Note that if we consider $\rho_A = \rho_B$, we will have one less parameter, but only a restricted set up. Here we study the more general case where $\rho_A$ and $\rho_B$ are allowed to be different. This may be justified as the success probabilities (and hence variances) of the two treatments are different. In addition, with two treatments, the proportion of patients treated by a particular treatment, say treatment $A$, denoted by $\eta$, is another important design parameter. The best value of $\eta$ is widely studied in optimal response-adaptive design literature, but without any surrogate. This is another important design issue in the surrogate-augmented set up. Thus, the design problem is the simultaneous choice of the three parameters, $(\eta, \rho_A, \rho_B)$. In the present paper, our objective is to address this issue.

The rest of the paper is organized as follows. In Sect. 2, we discuss the structure of the problem and the notation. Section 3 describes the improvement of variance by using surrogate endpoints. The optimization problem is discussed in Sect. 4. Section 5 concludes the paper.

## 2 Genesis and Structure of Surrogate Endpoints

We consider two treatments with binary true endpoints and also binary surrogate endpoints. Begg and Leung (2000) pointed out that, for binary endpoints, the probability of concordance is an indicator of association between true and surrogate endpoints. Banerjee and Biswas (2011, 2012a, 2012b) explored and established this fact more formally. Suppose $n_A$ and $n_B$ patients are allotted to treatments $A$ and $B$, respectively, but we get only $m_A$ and $m_B$ true endpoints along with all surrogate endpoints within the stipulated time frame or cost limit, where $m_t \ll n_t$, $t = A, B$. Let $Z$ be the indicator variable equal to 1 or 0 according to whether or not treatment

**Table 1** True-surrogate frequency table

| True | Surrogate | | Total |
|---|---|---|---|
| | $W_t = 1$ | $W_t = 0$ | |
| $Y_t = 1$ | $m_{t11}$ | $m_{t10}$ | $Y_{tT}$ |
| $Y_t = 0$ | $m_{t01}$ | $m_{t00}$ | $m_t - Y_{tT}$ |
| Total | $W_{tT}$ | $m_t - W_{tT}$ | $m_t$ |

$A$ is allocated to the patient. Denote by $Y_t$ and $W_t$ the true and surrogate endpoints for treatment $t$, $t = A$ or $B$. All these endpoints are either 1 or 0 for success or failure, respectively. Let $p_t = P(Y_t = 1)$ be the success probability by the true endpoint for treatment $t$. Furthermore, set

$$P(W_t = 1|Y_t = 1) = \pi_{t1}, \qquad P(W_t = 0|Y_t = 0) = \pi_{t0}, \tag{1}$$

which are the *sensitivity* and *specificity* of the $2 \times 2$ table for treatment $t$ where the true and surrogate responses are in the two margins. Consequently, the success probabilities by the surrogate responses for the treatments are,

$$r_t = P(W_t = 1) = (1 - \pi_{t0}) + (\pi_{t1} + \pi_{t0} - 1)\, p_t.$$

The data corresponding to treatment $t$ can be represented as in Table 1, where $Y_{tT} = \sum_{i=1}^{m_t} Y_{t,i}$ and $W_{tT} = \sum_{i=1}^{m_t} W_{t,i}$. We also write $W_{tS} = \sum_{i=m_t+1}^{n_t} W_{t,i}$. If any marginal total is zero, it is customary to add 0.5 to each of the marginals. Banerjee and Biswas (2011, 2012a, 2012b) considered similar data structures.

In order to compare the two competing treatments, we focus on a function of their success probabilities $(p_A, p_B)$. Moreover, to estimate $p_A$ and $p_B$, we first estimate the sensitivity and the specificity between the true and the surrogate endpoints for individual treatments. This helps to capture the dependence between the true and the surrogate endpoints. So, typically we have a six-parameter set up.

## 3 Estimators and Their Variances

Consider the likelihood for treatment $t$,

$$\begin{aligned} L(\xi_t) = &\binom{m_t}{y_{tT}} p_t^{y_{tT}} q_t^{m_t - y_{tT}} \binom{y_{tT}}{m_{t11}} \pi_{t1}^{m_{t11}} (1 - \pi_{t1})^{y_{tT} - m_{t11}} \\ &\times \binom{m_t - y_{tT}}{m_{t01}} (1 - \pi_{t0})^{m_{t01}} \pi_{t0}^{m_{t00}} \binom{n_t - m_t}{w_{tS}} r_t^{w_{tS}} (1 - r_t)^{n_t - m_t - w_{tS}}, \end{aligned} \tag{2}$$

where $\xi_t = (p_t, \pi_{t1}, \pi_{t0})$ and $q_t = 1 - p_t$. The Fisher information matrix is $\mathbf{I}(\xi_t)$ and the $(1, 1)$-th element of $[\mathbf{I}(\xi_t)]^{-1}$, denoted by $[\mathbf{I}(\xi_t)]_{11}^{-1}$, gives the asymptotic variance of $\widehat{p}_t$. Furthermore, write $m_t/n_t = \rho_t \in (0, 1]$. But $\rho_t = 0$ only when $m_t = 0$, indicating no true response is available. This is of no statistical interest. Using

$m_t = \rho_t n_t$, we get $\mathbf{I}(\xi_t) = n_t \boldsymbol{I}_{\xi_t}(\rho_t)$ and hence $\text{Var}(\widehat{p}_t) = V_{\xi_t}(\rho_t)$, the variance in the presence of surrogate endpoints, is given by

$$\begin{aligned} V_{\xi_t}(\rho_t) &= n_t^{-1}\left[\boldsymbol{I}_{\xi_t}(\rho_t)\right]_{11}^{-1} \\ &= m_t^{-1}\rho_t\left[\boldsymbol{I}_{\xi_t}(\rho_t)\right]_{11}^{-1} \\ &= m_t^{-1} p_t q_t \left\{u_t + (1-u_t)\rho_t\right\} \\ &= m_t^{-1} p_t q_t G_{\xi_t}(\rho_t), \end{aligned} \tag{3}$$

where

$$u_t = \frac{q_t \pi_{t0}(1-\pi_{t0}) + p_t \pi_{t1}(1-\pi_{t1})}{r_t(1-r_t)}$$

and

$$G_{\xi_t}(\rho_t) = u_t + (1-u_t)\rho_t = \rho_t + (1-\rho_t)u_t. \tag{4}$$

The proportion of the reduced variance using surrogate endpoints to estimate $p_A - p_B$, the treatment difference (TD), is a plane in three dimensions given by

$$G_{TD}(\rho_A, \rho_B) = \frac{m_A^{-1} p_A q_A G_{\xi_A}(\rho_A) + m_B^{-1} p_B q_B G_{\xi_B}(\rho_B)}{m_A^{-1} p_A q_A + m_B^{-1} p_B q_B}, \tag{5}$$

and, for $\rho_A = \rho_B = \rho$ we get the line along the diagonal of that plane given by

$$G_{TD}(\rho) = \rho + (1-\rho)\left\{\frac{n_A^{-1} p_A q_A u_A + n_B^{-1} p_B q_B u_B}{n_A^{-1} p_A q_A + n_B^{-1} p_B q_B}\right\}. \tag{6}$$

This has been studied in detail by Banerjee and Biswas (2012b). In the present paper we use this expression to find optimal sample proportions. A plot of $G(\cdot)$ against common $\rho$ is given in Fig. 1 for $\xi_A = (p_A, \pi_{A1}, \pi_{A0}) = (0.7, 0.2, 0.3)$ and $\xi_B = (p_B, \pi_{B1}, \pi_{B0}) = (0.8, 0.2, 0.5)$ (we follow the same parameter specification for next diagrams as well). ML can be used for estimation, which is iterative for the problem under consideration. For a practical implementation of the surrogate-augmented procedure, Banerjee and Biswas (2011) used EM-based estimates of $p_A$ and $p_B$. Alternative estimates based on conditional expectations are (Banerjee and Biswas 2012a)

$$\widehat{p}_t = \widehat{\mathbf{Y}}_t / n_t = n_t^{-1}\left\{Y_{tT} + \frac{m_{t11}}{W_{tT}} W_{tS} + \frac{m_{t10}}{m_t - W_{tT}}(n_t - m_t - W_{tS})\right\}.$$

Here the three terms within the brace on the right-hand side correspond to the observed number of successes from the true responses, the estimate of the true successes out of $W_{tS}$ surrogate successes for which the true responses are unobserved, and the estimate of true successes out of $(n_t - m_t - W_{tS})$ surrogate failures for which the true responses are unobserved. The expression is the same as the E-step of the

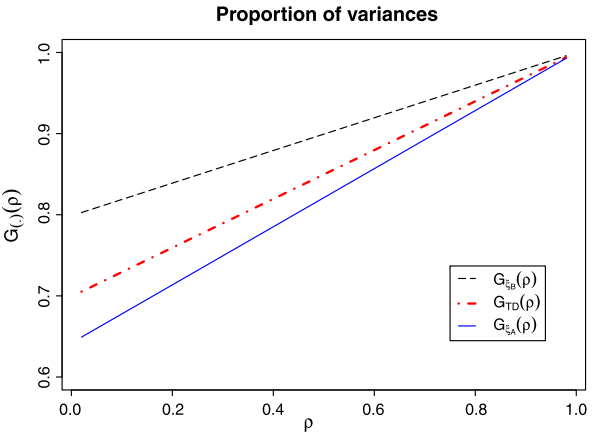


**Fig. 1** $G_{\xi_A}(\rho)$, $G_{\xi_B}(\rho)$ and $G_{TD}(\rho)$ against common $\rho$

EM algorithm. Detailed simulation studies show that the behavior of this estimator is almost similar to the MLE (Banerjee and Biswas 2012a).

## 4 Optimal Proportion of Allocation

Note that we have assumed that the true endpoints are much more expensive than the surrogate endpoints. Accordingly, we want to minimize some function of true endpoints, in general, say

$$m_A\Psi_A + m_B\Psi_B = n_A\rho_A\Psi_A + n_B\rho_B\Psi_B = \left\{\eta\rho_A\Psi_A + (1-\eta)\rho_B\Psi_B\right\}n, \tag{7}$$

to estimate the treatment difference, $p_A - p_B$, for a fixed variance, where $n = n_A + n_B$ and $\eta = n_A/n$, the proportion of patients allocated to treatment $A$. Here $\Psi_A$ and $\Psi_B$ are suitable weights assigned to the observed true endpoints. We consider a set up where we can control $\eta$ and also $\rho_A, \rho_B$. In fact, the choice of $\rho_A, \rho_B$ is a matter of cost. Thus the optimization problem involves an optimal choice of $(\eta, \rho_A, \rho_B)$. If $\Psi_A = \Psi_B = 1$ in the objective function (7), we minimize the total number of observed true samples. On the other hand, if $\Psi_A = q_A, \Psi_B = q_B$, we minimize the total number of expected failures from the available true responses. Again, if $\Psi_A = q_A/\rho_A, \Psi_B = q_B/\rho_B$, we minimize the total number of expected failures from all of the patients although we may not observe all of them. The variance of the estimator of treatment difference, $p_A - p_B$, in the surrogate augmented set up is kept equal to some preassigned positive quantity $V$, i.e.,

$$m_A^{-1}p_Aq_AG_{\xi_A}(\rho_A) + m_B^{-1}p_Bq_BG_{\xi_B}(\rho_B) = V. \tag{8}$$

Then the optimal proportion of allocation to treatment $A$ is given by

$$\eta_{\text{opt},1} = \frac{\rho_B\sqrt{p_Aq_AG_{\xi_A}(\rho_A)/\Psi_A}}{\rho_B\sqrt{p_Aq_AG_{\xi_A}(\rho_A)/\Psi_A} + \rho_A\sqrt{p_Bq_BG_{\xi_B}(\rho_B)/\Psi_B}}. \tag{9}$$

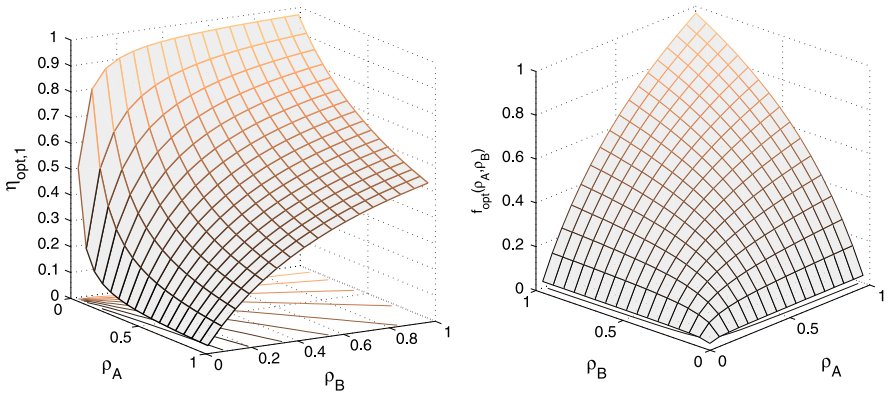


**Fig. 2** Dependence of $\eta_{\text{opt},1}$ (**a**), and $f_{\text{opt}}$ (**b**) on $\rho_A$ and $\rho_B$

See Rosenberger et al. (2001) for the derivation of the solution to such an optimization problem. The plot of $\eta_{\text{opt}}$ against $(\rho_A, \rho_B)$ is shown in Fig. 2(a) for $p_A = 0.7$, $p_B = 0.8$, and $\Psi_A = \Psi_B$. It is immediate that the optimal number of true endpoints required is

$$\begin{aligned} m_{\text{opt}} &= m_A(\eta_{\text{opt},1}) + m_B(\eta_{\text{opt},1}) \\ &= n\rho_A\rho_B \frac{\sqrt{p_A q_A G_{\xi_A}(\rho_A)/\Psi_A} + \sqrt{p_B q_B G_{\xi_B}(\rho_B)/\Psi_B}}{\rho_B\sqrt{p_A q_A G_{\xi_A}(\rho_A)/\Psi_A} + \rho_A\sqrt{p_B q_B G_{\xi_B}(\rho_B)/\Psi_B}} \\ &= n f_{\text{opt}}(\rho_A, \rho_B), \end{aligned} \tag{10}$$

which is a symmetric function of $(\rho_A, \rho_B)$. Moreover, it attains its optimal value at the vertices of a unit square. A plot of $f_{\text{opt}}$ against $(\rho_A, \rho_B)$ is given in Fig. 2(b), with the same parameter values as for Fig. 2(a). Thus, no more optimization of $f_{\text{opt}}$ is possible except at boundary values.

Optimization with respect to the cost constraint to obtain $\rho_t$, $t = A, B$, is discussed by Banerjee and Biswas (2012b) as follows. Assume that the cost per surrogate sample is $c_1$ and that of the true endpoint is $c_2$. For any treatment $t = A, B$, the total cost $C$ is constant, and it can be written as $C = c_1 n_t + c_2 m_t$. Consequently,

$$m_t^{-1} = C^{-1}\{c_1\rho_t^{-1} + c_2\}. \tag{11}$$

The variance in the presence of surrogate endpoints is

$$\begin{aligned} V_{\xi_t}(\rho_t) &= m_t^{-1} p_t q_t \{u_t + (1-u_t)\rho_t\} \\ &= \frac{p_t q_t}{C}\{c_1\rho_t^{-1} + c_2\}\{u_t + (1-u_t)\rho_t\} \\ &= \left\{\frac{p_t q_t}{C}\right\}\left\{\frac{u_t c_1 + [u_t c_2 + (1-u_t)c_1]\rho_t + (1-u_t)c_2\rho_t^2}{\rho_t}\right\}. \end{aligned} \tag{12}$$

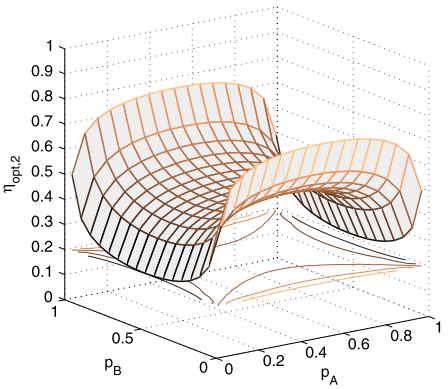


**Fig. 3** Dependence of $\eta_{\text{opt},2}$ after the second stage of optimization on $p_A$ and $p_B$

This gives $\rho_t^{\text{opt}} = \sqrt{\frac{u_t c_1}{(1-u_t)c_2}}$ if and only if $\rho_t^{\text{opt}} \in (0, 1)$. Hence, in that case,

$$V_{\xi_t}^{\text{opt}}(\rho_t) = \frac{p_t q_t}{C}\left(\sqrt{u_t c_2} + \sqrt{(1-u_t)c_1}\right)^2.$$

Studying the function $V_{\xi_t}(\rho_t)$ when $c_1 = 0$ is equivalent to studying $G_{\xi_t}(\rho_t)$ over $\rho_t$; the minimum is attained as $\rho_t \to 0$, which is easy to observe. When $\rho_t^{\text{opt}} > 1$, the minimum is attained at the extreme bound 1. Note that here we assume the same cost $C$ for each of the two treatments. We could easily consider the situation when the costs for the two treatments are different, say $C_A$ for treatment $A$ and $C_B$ for treatment $B$. The procedure would be similar. Here no attention was paid to the choice of $\eta$. However, we suggest to plug-in these cost-optimized choices of $\rho_A, \rho_B$ in (9) to obtain the cost-optimized optimal choice of $\eta$ as

$$\eta_{\text{opt},2} = \left(1 + \frac{\sqrt{u_B c_2} + \sqrt{(1-u_B)c_1}}{\sqrt{u_A c_2} + \sqrt{(1-u_A)c_1}}\sqrt{\frac{p_B q_B \Psi_A}{p_A q_A \Psi_B}}\right)^{-1}. \tag{13}$$

This is a two-fold optimized value of $\eta$. A plot of such two-fold optimal $\eta_{\text{opt},2}$ against $(p_A, p_B)$ is given in Fig. 3 for $\Psi_A = \Psi_B$.

## 5 Conclusion

Optimal allocation design for a two-treatment problem is well studied in the literature, but assuming only true endpoints. Here we discussed a scenario where surrogate endpoints are present along with true endpoints. Our objective was to compare the competing treatments when both the true and surrogate endpoints are binary. First, we obtained the optimal allocation proportion for both of the treatments as a function of treatment parameters as well as the true-surrogate sample ratio. We then obtained the optimum true-surrogate sample ratio in the cost constraint setup and used it for further second stage optimization for the proportion of allocations to the

treatments. This approach should be extended to other types of true and surrogate responses (categorical, continuous) and also to the presence of covariates. These may be topics of further research.

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## References

Banerjee, B., Biswas, A.: Estimating treatment difference for binary responses in the presence of surrogate end points. Stat. Med. **30**, 186–196 (2011)

Banerjee, B., Biswas, A.: Odds ratio for $2 \times 2$ tables: Mantel-Haenszel estimator, profile likelihood and presence of surrogate responses. Indian Statistical Institute Tech. Report No. ASD/2012/11 (2012a). Available at www.isical.ac.in/~asu/pub.html

Banerjee, B., Biswas, A.: Variance and sample size reduction using surrogate end-points. Tech. Report No. ASD/2012/12, Indian Statistical Institute (2012b). Available at www.isical.ac.in/~asu/pub.html

Begg, C.B., Leung, D.H.Y.: On the use of surrogate endpoints in randomized trials. J. R. Stat. Soc. A **163**, 15–28 (2000)

Prentice, R.L.: Surrogate endpoints in clinical trials: definition and operational criteria. Stat. Med. **8**, 431–440 (1989)

Rosenberger, W.F., Stallard, N., Ivanova, A., Harper, C.N., Ricks, M.L.: Optimal adaptive design for binary response trials. Biometrics **57**, 909–913 (2001)

Wittes, J., Lakatos, E., Probstfield, J.: Surrogate endpoints in clinical trials: cardiovascular disease. Stat. Med. **8**, 415–425 (1989)

# Estimating and Quantifying Uncertainties on Level Sets Using the Vorob'ev Expectation and Deviation with Gaussian Process Models

**Clément Chevalier, David Ginsbourger, Julien Bect, and Ilya Molchanov**

**Abstract** Several methods based on Kriging have recently been proposed for calculating a probability of failure involving costly-to-evaluate functions. A closely related problem is to estimate the set of inputs leading to a response exceeding a given threshold. Now, estimating such a level set—and not solely its volume—and quantifying uncertainties on it are not straightforward. Here we use notions from random set theory to obtain an estimate of the level set, together with a quantification of estimation uncertainty. We give explicit formulae in the Gaussian process set-up and provide a consistency result. We then illustrate how space-filling versus adaptive design strategies may sequentially reduce level set estimation uncertainty.

## 1 Introduction

Reliability studies increasingly depend on complex deterministic simulations. A problem that is often at stake is to identify, from a limited number of evaluations of $f : D \subset \mathbb{R}^d \mapsto \mathbb{R}$, the level set of "dangerous" configurations $\Gamma_f = \{x \in D : f(x) \geq T\}$, where $T$ is a given threshold. In such a context, it is commonplace to predict quantities of interest relying on a surrogate model for $f$. This approach was popularized in the design and analysis of computer experiments (Santner et al. 2003; Rasmussen and Williams 2006; Forrester et al. 2008). In the Kriging frame-

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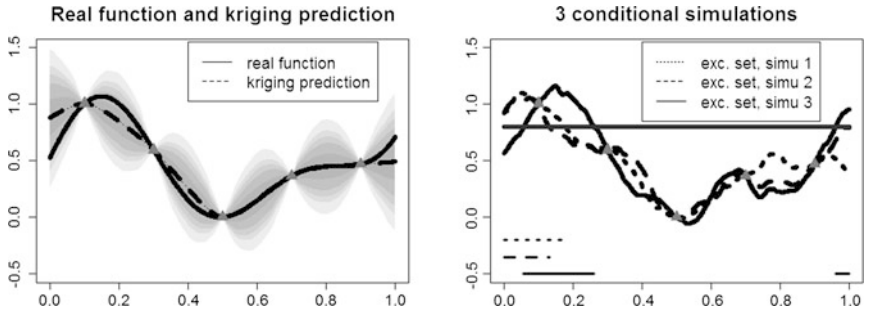


**Fig. 1** Conditional simulations of level sets. *Left*: the Kriging model obtained from five evaluations of a $1d$ function. *Right*: three GP conditional simulations, leading to three different level sets. Here the threshold is fixed as $T = 0.8$

work, several works have already been proposed for reliability problems (see, e.g., Bect et al. 2012; Picheny et al. 2010; Ranjan et al. 2008; Dubourg 2011, and the references therein). However, the quantity of interest is usually the *volume* of $\Gamma_f$, and none of the methods explicitly reconstructs $\Gamma_f$ itself.

An illustrative example for this issue is given in Fig. 1. A Kriging model is built from five evaluations of a $1d$ function (left panel). Three level set realisations (with $T = 0.8$) are obtained from conditional simulations of a Gaussian process (GP). The focus here is on summarizing the conditional distribution of excursion sets using *ad hoc* notions of expectation and deviation from the theory of random sets. We address this issue using an approach based on the Vorob'ev expectation (Baddeley and Molchanov 1998; Molchanov 2005).

In Sect. 2 we present the Vorob'ev expectation and deviation for a closed random set. In Sect. 3 we then give analytical expressions for these quantities in the GP framework. In addition, we give a consistency result regarding the convergence of the Vorob'ev expectation to the actual level set. To the best of our knowledge, this is the first Kriging-based approach focusing on the level set itself, and not solely, its volume. Our results are illustrated on a test case in Sect. 4.

## 2 The Vorob'ev Expectation and Deviation in Random Set Theory

Random variables are usually defined as measurable maps from a probability space $(\Omega, \mathcal{G}, \mathbb{P})$ to some measurable space, such as $(\mathbb{R}, \mathscr{B}(\mathbb{R}))$ or $(\mathbb{R}^d, \mathscr{B}(\mathbb{R}^d))$. However, in the last decades there has been a growing interest in set-valued random elements and, in particular, in *random closed sets* (Molchanov 2005).

**Definition 1** Let $\mathscr{F}$ be the family of all closed subsets of $D$. A map $X : \Omega \mapsto \mathscr{F}$ is called a *random closed set* if, for every compact set $K$ in $D$,

$$\left\{\omega : X(\omega) \cap K \neq \emptyset\right\} \in \mathcal{G}. \tag{1}$$

As mentioned in Molchanov (2005), this definition basically means that, for any compact $K$, one can always say, when observing $X$, whether or not it hits $K$. Defining the expectation of a random set is far from being straightforward. Different candidate notions of expectation from the random set literature are documented in Molchanov (2005, Chap. 2), with a major development on the *selection expectation*. Some alternative expectations mentioned in Molchanov (2005) include the *linearisation approach*, the *Vorob'ev expectation*, the *distance average*, the *Fréchet expectation*, and the *Doss and Herer expectations*.

In the present work we focus on the Vorob'ev expectation, which is based on the intuitive notion of a coverage probability function. Given a random closed set $X$ over a space $D$ with a $\sigma$-finite measure $\mu$ ($D \subset \mathbb{R}^d$ and $\mu = \mathrm{Leb}_d$, say), $X$ is associated with a random field $(\mathbf{1}_X(x))_{x\in D}$. The coverage function is defined as the expectation of this binary random field:

**Definition 2** (Coverage function and $\alpha$-quantiles of a random set) The function

$$p_X : x \in D \mapsto \mathbb{P}(x \in X) = \mathrm{E}\big[\mathbf{1}_X(x)\big] \tag{2}$$

is called the *coverage function* of $X$. The *$\alpha$-quantiles* of $X$ are the level sets of $p_X$,

$$Q_\alpha := \big\{x \in D : p_X(x) \geq \alpha\big\}, \quad \alpha \in (0, 1]. \tag{3}$$

Note that in (2), the expectation is taken with respect to the set $X$ and not to the point $x$. In Fig. 1 (right panel) we plotted three conditional realizations of the random set $X := \{x \in [0, 1], \xi(x) \geq T\}$, where $\xi$ is a GP. The $\alpha$-quantile of Definition 2 can be seen as the set of points having a (conditional, in Fig. 1) probability of belonging to $X$ greater than or equal to $\alpha$. This definition is particularly useful here as, now, the so-called Vorob'ev expectation of the random set $X$ will be defined as a "well-chosen" $\alpha$-quantile of $X$.

**Definition 3** (Vorob'ev expectation) Assuming that $\mathrm{E}[\mu(X)] < \infty$, the *Vorob'ev expectation* of $X$ is defined as the $\alpha^*$-quantile of $X$, where $\alpha^*$ is determined from

$$\mathrm{E}\big[\mu(X)\big] = \mu(Q_{\alpha^*}) \tag{4}$$

if this equation has a solution, or in general, from the condition

$$\mu(Q_\beta) \leq \mathrm{E}\big[\mu(X)\big] \leq \mu(Q_{\alpha^*}) \quad \text{for all } \beta > \alpha^*. \tag{5}$$

Throughout this paper, an $\alpha^*$ satisfying the condition of Definition 3 will be referred to as a *Vorob'ev threshold*.

*Property 1* For any measurable set $M$ with $\mu(M) = \mathrm{E}[\mu(X)]$, we have

$$\mathrm{E}\big[\mu(Q_{\alpha^*} \Delta X)\big] \leq \mathrm{E}\big[\mu(M \Delta X)\big], \tag{6}$$

where $A \Delta B$ denotes the symmetric difference between sets $A$ and $B$. The quantity $\mathrm{E}[\mu(Q_{\alpha^*} \Delta X)]$ is called *Vorob'ev deviation*.

The Vorob'ev expectation thus appears as a global minimizer of the deviation, among all closed sets with volume equal to the average volume of $X$. A proof can be found in Molchanov (2005, p. 193). In the next section, we shall use these definitions and properties for our concrete problem, where the considered random set is a level set of a GP.

## 3 Conditional Vorob'ev Expectation for Level Sets of a GP

In this section, we focus on the particular case where the random set (denoted by $X$ in the previous section) is a level set

$$\Gamma := \{x \in D : \xi(x) \geq T\} \tag{7}$$

of a GP $\xi$ above a given threshold $T \in \mathbb{R}$. Once $n$ evaluation results $\mathscr{A}_n := ([x_1, \xi(x_1)], \ldots, [x_n, \xi(x_n)])$ are known, the main object of interest is then the conditional distribution of the level set $\Gamma$ given $\mathscr{A}_n$. We propose to use the Vorob'ev expectation and deviation to capture and quantify the variability of the level set $\Gamma$ conditionally on the available observations $\mathscr{A}_n$.

### *3.1 Conditional Vorob'ev Expectation and Deviation*

In the simple Kriging GP set-up (see, e.g., Chilès and Delfiner 1999), we know the marginal conditional distributions of $\xi(x)|\mathscr{A}_n$:

$$\mathscr{L}\big(\xi(x)|\mathscr{A}_n\big) = \mathscr{N}\big[m_n(x), s_n^2(x)\big], \tag{8}$$

where $m_n(x) = \mathrm{E}(\xi(x)|\mathscr{A}_n)$ and $s_n^2(x) = \mathrm{var}(\xi(x)|\mathscr{A}_n)$ are respectively the *simple Kriging* mean and variance functions. The coverage probability function and any $\alpha$-quantile of $\Gamma$ can be straightforwardly calculated (given $\mathscr{A}_n$) as follows.

*Property 2* (i) The coverage probability function of $\Gamma$ is

$$p_n(x) := \mathbb{P}(x \in \Gamma|\mathscr{A}_n) = \mathbb{P}\big(\xi(x) \geq T|\mathscr{A}_n\big) = \Phi\left(\frac{m_n(x) - T}{s_n(x)}\right), \tag{9}$$

where $\Phi(\cdot)$ denotes the c.d.f. of the standard Gaussian distribution.

(ii) For any $\alpha \in (0, 1]$, the $\alpha$-quantile of $\Gamma$ (conditional on $\mathscr{A}_n$) is

$$Q_{n,\alpha} = \{x \in D : m_n(x) - \Phi^{-1}(\alpha)s_n(x) \geq T\}. \tag{10}$$

(iii) For any $\alpha \in (0, 1]$, the $\alpha$-quantile of $\Gamma$ can also be seen as the excursion set above $T$ of the Kriging quantile with level $1 - \alpha$.

From Property 2, one can see that the Vorob'ev expectation is in fact the excursion set above $T$ of a certain Kriging quantile. In applications, an adequate Vorob'ev threshold value can be determined by tuning $\alpha$ to a level $\alpha_n^*$ such that $\mu(Q_{n,\alpha_n^*}) = \mathrm{E}(\mu(\Gamma)|\mathscr{A}_n) = \int_D p_n(x)\mu(\mathrm{d}x)$. This can be done through a simple dichotomy.

Once the Vorob'ev expectation is calculated, the computation of the Vorob'ev deviation $\mathrm{E}(\mu(Q_{n,\alpha_n^*}\Delta\Gamma)|\mathscr{A}_n)$ does not require simulation of $\Gamma$. Indeed,

$$\begin{aligned}\mathrm{E}\big(\mu(Q_{n,\alpha_n^*}\Delta\Gamma)|\mathscr{A}_n\big) &= \mathrm{E}\left(\int_D (\mathbf{1}_{x\in Q_{n,\alpha_n^*}, x\notin\Gamma} + \mathbf{1}_{x\notin Q_{n,\alpha_n^*}, x\in\Gamma})\mu(\mathrm{d}x)|\mathscr{A}_n\right)\\ &= \int_{Q_{n,\alpha_n^*}} \mathrm{E}(\mathbf{1}_{x\notin\Gamma}|\mathscr{A}_n)\mu(\mathrm{d}x) + \int_{Q^c_{n,\alpha_n^*}} \mathrm{E}(\mathbf{1}_{x\in\Gamma}|\mathscr{A}_n)\mu(\mathrm{d}x)\\ &= \int_{Q_{n,\alpha_n^*}} \big[1 - p_n(x)\big]\mu(\mathrm{d}x) + \int_{Q^c_{n,\alpha_n^*}} p_n(x)\mu(\mathrm{d}x). \qquad (11)\end{aligned}$$

In Sect. 4 we present an example of computation of the Vorob'ev expectation and deviation. Before that, in the next subsection, we provide a consistency result for the case where observations of $\xi$ progressively fill the space $D$.

## 3.2 Consistency Result

Let us consider a (zero-mean, stationary) GP $Z$ and a deterministic sequence of sampling points $x_1, x_2, \ldots$, such that $s_n^{\max} \triangleq \sup_{x\in D} s_n \to 0$ (this holds, e.g., for any space-filling sequence, assuming that the covariance function is merely continuous). We denote by $\alpha_n^*$ the Vorob'ev threshold selected for the first $n$ sampling points, and by $\kappa_n = \Phi^{-1}(\alpha_n^*)$ and $Q_{n,\alpha_n^*} \subset D$ the corresponding quantile and Vorob'ev expectation. Our goal here is to prove that the Vorob'ev expectation is a consistent estimator of the true excursion set $\Gamma$, in the sense that $\mu(Q_{n,\alpha_n^*}\Delta\Gamma) \to 0$ for some appropriate convergence mode. To this end, we shall consider a slightly modified estimator $Q_{n,\alpha_n^*}$, where the choice of the Vorob'ev threshold $\alpha_n^*$ is constrained in such a way that $|\kappa_n| \le \kappa_n^{\max}$, for some deterministic sequence of positive constants $\kappa_n^{\max}$.

**Proposition 1** *Assume that* $\mu(D) < +\infty$ *and* $\kappa_n^{\max} = O(\sqrt{|\log s_n^{\max}|})$. *Then*

$$\mathrm{E}\big(\mu(Q_{n,\alpha_n^*}\Delta\Gamma)\big) = O\Big(s_n^{\max}\sqrt{\big|\log s_n^{\max}\big|}\Big).$$

*As a consequence,* $\mu(Q_{n,\alpha_n^*}\Delta\Gamma) \to 0$ *for the convergence in mean.*

*Proof* The result has been proven in Vazquez and Piera-Martinez (2006, 2007) in the special case $\kappa_n^{\max} = 0$ (i.e., with $\alpha_n^* = 1/2$). We follow their proof very closely.

Let us first rewrite the probability of misclassification at $x \in D$ as

$$\mathrm{E}\big(\mathbf{1}_{Q_{n,\alpha_n^*}\Delta\Gamma}(x)\big) = \mathrm{E}\big(\mathbf{1}_{p_n(x)\geq\alpha_n^*}\big[1-p_n(x)\big] + \mathbf{1}_{p_n(x)<\alpha_n^*}p_n(x)\big), \tag{12}$$

and consider the events

$$E_n^+ = \big\{m_n(x) \geq T + w_n(x)\big\}, \qquad E_n^- = \big\{m_n(x) \geq T - w_n(x)\big\},$$

where $w_n(x)$ is a deterministic sequence that will be specified later. Let us assume that $\kappa_n^{\max} s_n(x) = O[w_n(x)]$, uniformly in $x$. Then we have

$$|\kappa_n| s_n(x) \leq \kappa_n^{\max} s_n(x) \leq C w_n(x)$$

for some $C > 1$ (without loss of generality), and thus

$$\mathbf{1}_{p_n(x)\geq\alpha_n^*} = \mathbf{1}_{m_n(x)\geq T+\kappa_n s_n(x)} \leq \mathbf{1}_{|m_n(x)-T|\leq C w_n(x)} + \mathbf{1}_{E_n^+}.$$

As a consequence, noting that $[m_n(x) - T]/s_n(x) \geq w_n(x)/s_n(x)$on $E_n^+$, we obtain

$$\begin{aligned}\mathbf{1}_{p_n(x)\geq\alpha_n^*}\big[1-p_n(x)\big] &\leq \mathbf{1}_{|m_n(x)-T|\leq C w_n(x)} + \mathbf{1}_{E_n^+}\big[1-p_n(x)\big] \\ &\leq \mathbf{1}_{|m_n(x)-T|\leq C w_n(x)} + \Psi\left(\frac{w_n(x)}{s_n(x)}\right),\end{aligned}$$

where $\Psi$ denotes the standard normal complementary c.d.f. Proceeding similarly with the second term in (12), we get

$$\mathrm{E}\big(\mathbf{1}_{Q_{n,\alpha_n^*}\Delta\Gamma}(x)\big) \leq 2\left(\Psi\left(\frac{w_n(x)}{s_n(x)}\right) + \mathbb{P}\big[\big|m_n(x) - T\big| \leq C w_n(x)\big]\right).$$

Using the tail inequality $\Psi(u) \leq \frac{1}{u\sqrt{2\pi}}\exp(-\frac{1}{2}u^2)$, and observing that $\mathrm{var}[m_n(x)] \geq s_0^2 - (s_n^{\max})^2 \geq s_0^2/4$ for $n$ larger than some $n_0$ that does not depend on $x$, we have

$$\mathrm{E}\big(\mathbf{1}_{Q_{n,\alpha_n^*}\Delta\Gamma}(x)\big) \leq \sqrt{\frac{2}{\pi}}\left[\frac{s_n(x)}{w_n(x)}\exp\left(-\frac{1}{2}\frac{w_n^2(x)}{s_n^2(x)}\right) + 4C\frac{w_n(x)}{s_0}\right]. \tag{13}$$

Finally, taking $w_n(x) = \sqrt{2}s_n(x)\sqrt{|\log s_n(x)|}$ as in Vazquez and Piera-Martinez (2006), we have indeed $\kappa_n^{\max} s_n(x) = O[w_n(x)]$ uniformly in $x$, and from (13) we deduce that

$$\mathrm{E}\big(\mathbf{1}_{Q_{n,\alpha_n^*}\Delta\Gamma}(x)\big) = O\left(s_n^{\max}\sqrt{\big|\log s_n^{\max}\big|}\right)$$

uniformly in $x$. The result follows by integrating with respect to $\mu$ over $D$. □

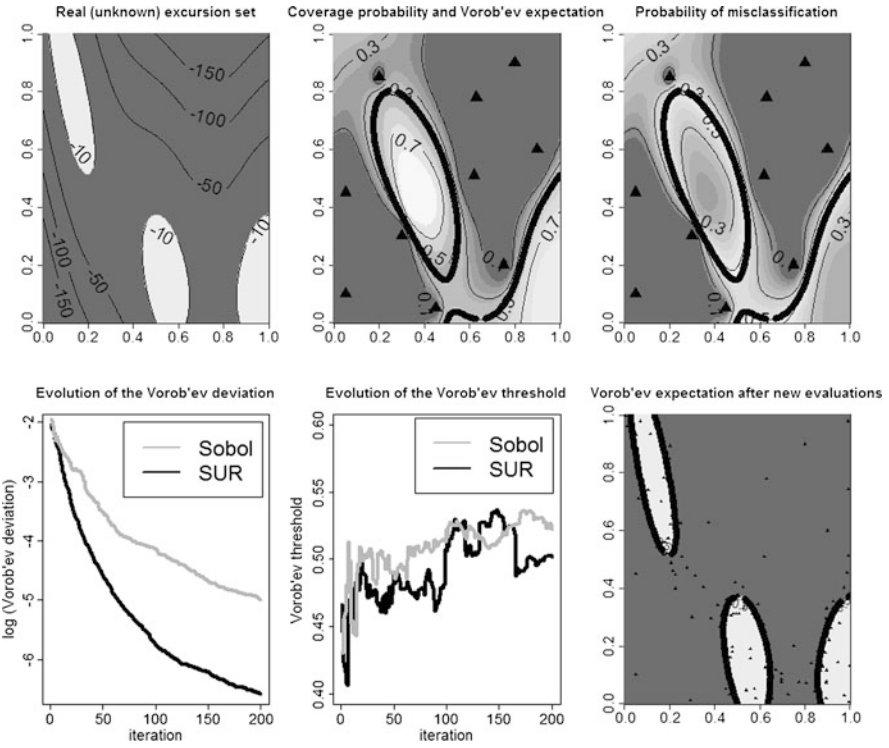


**Fig. 2** *Top left*: level set of a $2d$ function. *Middle*: coverage probability function after 10 evaluations of $f$. *Top right*: $\mathrm{E}(\mathbf{1}_{Q_{n,\alpha_n^*}\Delta\Gamma}(\cdot))$. *Bottom left*: decrease in the Vorob'ev deviation when new points are added (2 strategies). *Middle*: evolution of $\alpha^*$. *Bottom right*: new Vorob'ev expectation (SUR strategy)

## 4 Application to Adaptive Design for Level Set Estimation

Here we present a two-dimensional example on the foregoing notions and results. We consider the Branin-Hoo function, with variables normalised so that the domain $D$ is $[0,1]^2$. We multiply the function by a factor of $-1$ and we are interested in the set $\{x \in D : f(x) \geq -10\}$. Figure 2 (top) gives the real level set and the coverage probability function obtained from $n = 10$ observations. The covariance parameters of the Gaussian process used for Kriging are assumed to be known. The measure $\mu$ is the uniform measure on $D = [0,1]^2$ and the current Vorob'ev deviation is $\mathrm{E}(\mu(Q_{n,\alpha_n^*}\Delta\Gamma)|\mathscr{A}_n) \approx 0.148$. All the integrals are calculated using the KrigInv R package (Chevalier et al. 2012b) with a Sobol' Quasi Monte-Carlo sequence of 10000 points.

In Fig. 2 (bottom plots) one can see the evolution of the Vorob'ev deviation and threshold when new points are added. Two different strategies are tested: a simple space filling strategy (with, again, the Sobol' sequence) and a so-called Stepwise Uncertainty Reduction (SUR) strategy, aiming at reducing the variance of $\mu(\Gamma)$

(see, Bect et al. 2012, criterion $J_{4,n}^{\mathrm{SUR}}$, or Chevalier et al. 2012a for more details). We observe that the SUR strategy manages to reduce quickly the Vorob'ev deviation (bottom left plot) and that the Vorob'ev expectation obtained after the new evaluations matches with the true level set. However, note that the consistency of the adaptive approach is not guaranteed by Proposition 1 as the latter only holds for a deterministic space filling sequence. Further research is needed to establish an extension of Proposition 1 to adaptive settings.

## 5 Conclusion

In this paper we proposed the use of random set theory notions, the Vorob'ev expectation and deviation, to estimate and quantify uncertainties on a level set of a real-valued function. This approach has the originality of focusing on the set itself, rather than solely on its volume. When the function is actually a GP realization, we proved that the Vorob'ev deviation converges to zero under infill asymptotics, with some mild conditions. However, the final example illustrates that a space-filling approach based on a Sobol' sequence may not be optimal for level set estimation, as it clearly was outperformed by an adaptive strategy dedicated to volume of excursion estimation. In future work, we plan to investigate sampling criteria and adaptive strategies dedicated to uncertainty reduction in the particular context of set estimation.

## References

Baddeley, A., Molchanov, I.: Averaging of random sets based on their distance functions. J. Math. Imaging Vis. **8**, 79–92 (1998)

Bect, J., Ginsbourger, D., Li, L., Picheny, V., Vazquez, E.: Sequential design of computer experiments for the estimation of a probability of failure. Stat. Comput. **22**, 773–793 (2012)

Chevalier, C., Bect, J., Ginsbourger, D., Vazquez, E., Picheny, V., Richet, Y.: Fast parallel Kriging-based stepwise uncertainty reduction with application to the identification of an excursion set. http://hal.inria.fr/hal-00641108/en (2012a)

Chevalier, C., Picheny, V., Ginsbourger, D.: KrigInv: Kriging-based Inversion for Deterministic and Noisy Computer Experiments. http://CRAN.R-project.org/package=KrigInv. R package version 1.3 (2012b)

Chilès, J.P., Delfiner, P.: Geostatistics: Modeling Spatial Uncertainty. Wiley, New York (1999)

Dubourg, V.: Métamodèles adaptatifs pour l'analyse de fiabilité et l'optimisation sous contrainte fiabiliste. Ph.D. thesis, Université Blaise Pascal et Institut Français de Mécanique Avancée (2011)

Forrester, A.I.J., Sóbester, A., Keane, A.J.: Engineering Design via Surrogate Modelling: A Practical Guide. Wiley, Chichester (2008)

Molchanov, I.: Theory of Random Sets. Springer, London (2005)

Picheny, V., Ginsbourger, D., Roustant, O., Haftka, R.T., Kim, N.H.: Adaptive designs of experiments for accurate approximation of target regions. Journal of Mechanical Design **132** (2010). doi:10.1115/1.4001873

Ranjan, P., Bingham, D., Michailidis, G.: Sequential experiment design for contour estimation from complex computer codes. Technometrics **50**, 527–541 (2008)

Rasmussen, C.R., Williams, C.K.I.: Gaussian Processes for Machine Learning. MIT Press, Cambridge (2006)
Santner, T.J., Williams, B.J., Notz, W.: The Design and Analysis of Computer Experiments. Springer, Berlin (2003)
Vazquez, E., Piera-Martinez, M.: Estimation of the volume of an excursion set of a Gaussian process using intrinsic Kriging. http://arxiv.org/abs/math/0611273 (2006)
Vazquez, E., Piera-Martinez, M.: Estimation du volume des ensembles d'excursion d'un processus Gaussien par Krigeage intrinsèque. In: 39ème Journées de Statistiques, Angers, France (2007)

# Optimal Designs for Multiple-Mixture by Process Variable Experiments

**Roelof L.J. Coetzer and Linda M. Haines**

**Abstract** In industry many processes include mixture components some or all of which are themselves made up of other sub-components and typically these variables are subject to lower and upper constraints. Process variables which may change the effect of the blending properties of the mixture components on the response of interest may also be involved. In this paper response surface models in more than two sets of mixture variables, including multiple-mixtures and sub-compositions, in combination with process variables are developed and attendant $D$-optimal designs are constructed. The work is motivated by an industrial problem involving the modelling of a coal gasification process.

## 1 Introduction

Experiments for mixtures have been extensively researched and models and attendant designs for settings involving crossed mixtures and, separately, mixture-of-mixtures are well documented (Cornell 2002). However experiments involving multiple mixtures, i.e., both crossed mixtures and mixtures-of-mixtures, together with process variables have received little, if any, attention in the literature. In the present study an example of such a multiple mixture-process variable experiment taken from industry is introduced and the issues relating to model building and design construction are investigated.

## 2 Problem Setting

The amount of gas produced in a coal gasification plant depends crucially on the distribution of the size of the coal particles, on the composition of the coal feed and

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of the ash, which is a sub-component of the coal, and on a number of process variables. To be specific, the particle size distribution (PSD) is specified by proportions of fine, medium and coarse particles (Coetzer and Keyser 2003). The coal properties are characterized by a mixture of carbon, ash and small amounts of other elements, including nitrogen and sulphur, and inherent moisture. In the present preliminary study interest is restricted to a mixture of the three key components of the coal, namely carbon, ash and the remainder, termed "other". The ash comprises a mixture of metal and other oxides which can be broadly and conveniently classified into three groups, namely acid, base and the rest. Finally, the process variables comprise the oxygen load and the amount of carbon dioxide in the raw gas which is fed into the plant. All the mixture and process variables so identified are constrained to lie in restricted ranges which can be inferred from historical data. The challenge is to formulate a model for the amount of gas produced based on the mixture and process variables and to recommend designs which can be implemented in order to estimate the parameters of the proposed model as precisely as possible.

## 3 Model Building

The proportions of fine, medium and coarse particles in the coal are denoted by $x_1, x_2$ and $x_3$ respectively with $\sum_{i=1}^{3} x_i = 1$, the proportions of carbon, other and ash in the coal by $c_1, c_2$ and $c_3$ respectively with $\sum_{j=1}^{3} c_j = 1$ and the proportions of acid, base and the rest in the sub-component ash by $a_1, a_2$ and $a_3$, respectively, with $\sum_{k=1}^{3} a_k = 1$. Feasible regions for the PSD and the coal and ash mixtures are given by

$$\begin{aligned} D_{psd} &= \{(x_1, x_2, x_3) : \ 0.106 < x_1 < 0.54, 0.393 < x_2 < 0.882, \\ &\qquad 0.011 < x_3 < 0.206\}, \\ D_{coal} &= \{(c_1, c_2, c_3) : \ 0.5035 < c_1 < 0.6285, 0.12883 < c_2 < 0.2382, \\ &\qquad 0.189 < c_3 < 0.3090\}, \\ D_{ash} &= \{(a_1, a_2, a_3) : \ 0.602 < a_1 < 0.917, 0.096 < a_2 < 0.238, \\ &\qquad 0.066 < a_3 < 0.181\} \end{aligned}$$

and are displayed as polytopes in the 3-dimensional simplex in Figs. 1(a), (b) and (c), respectively. The two process variables, oxygen and carbon dioxide, are denoted by $z_1$ and $z_2$ respectively and are coded to lie between 0 and 1 to give the design region $D_z = [0, 1] \times [0, 1]$.

The response surface model for the amount of gas produced in the plant can be formulated broadly as

$$y = F(x, c, a, z) + e,$$

where $y$ denotes the yield, $F(\cdot)$ is a deterministic function of the vectors of proportions $x = (x_1, x_2, x_3)$, $c = (c_1, c_2, c_3)$ and $a = (a_1, a_2, a_3)$ and of the process

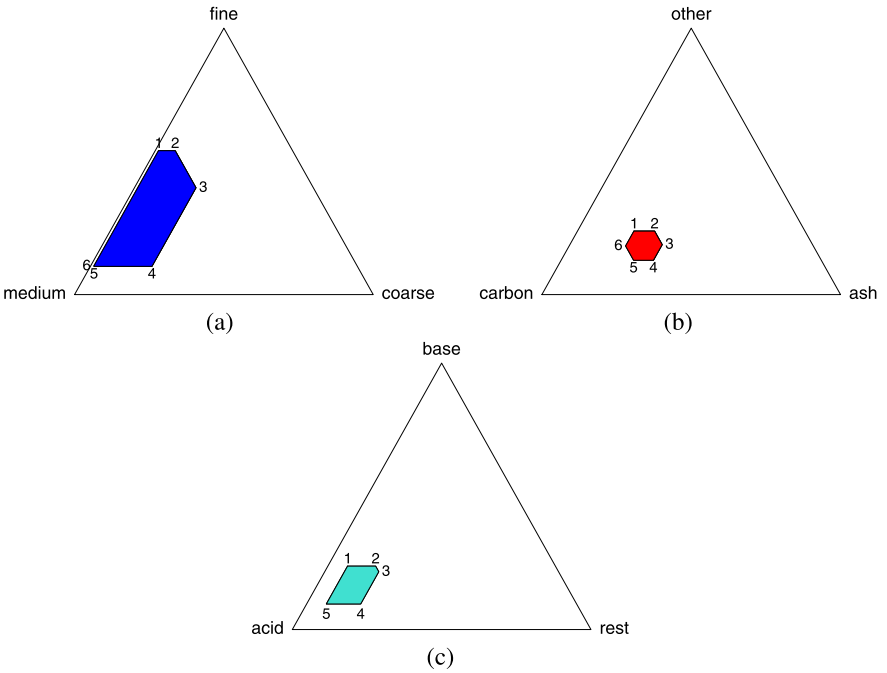


**Fig. 1** Feasible regions for the mixtures (**a**) particle size, (**b**) coal composition and (**c**) ash

variables $z = (z_1, z_2)$ and $e$ represents an independent error term with mean 0 and variance $\sigma^2$. The component of the model involving the mixtures is built up from the three linear Scheffé polynomials

$$f(x) = \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 = \sum_{i=1}^{3} \beta_i x_i,$$

$$g(c) = \gamma_1 c_1 + \gamma_2 c_2 + \gamma_3 c_3 = \sum_{j=1}^{3} \gamma_j c_j,$$

$$h(a) = \delta_1 a_1 + \delta_2 a_2 + \delta_3 a_3 = \sum_{k=1}^{3} \delta_k a_k,$$

relating to the PSD, coal and ash, respectively, and the process variables are then introduced into the resultant multiple mixture model. Note that $\beta_i$, $\gamma_j$ and $\delta_k$with $i, j, k = 1, 2, 3$ represent unknown parameters.

The component of the global model which incorporates PSD and coal can be formulated immediately as a mixture-by-mixture or crossed mixture (Didier et al. 2007; Borges et al. 2007) and is specified by the product of the appropriate linear

Scheffé polynomials, that is by $f(x)g(c)$. The formulation of a combined model for the coal and its sub-component ash is however a little more delicate. Thus it is possible to invoke the mixture-of-mixtures setting of Cornell and Ramsey (1998) and to introduce a coal-ash building block as the multiple Scheffé model specified by $g(c)h(a)$ with 9 unknown parameters. However it is also possible to invoke the major-minor model for mixtures with subcomponents which was introduced into the literature recently by Kang et al. (2011) and which circumvents the issue of crossed terms involving the subcomponent being present in the model when the sub-component itself is absent. The major-minor model for coal and ash can then be formulated as

$$\gamma_1 c_1 + \gamma_2 c_2 + \gamma_3 c_3 h(a) = \gamma_1 c_1 + \gamma_2 c_2 + c_3(\delta_{31} a_1 + \delta_{32} a_2 + \delta_{33} a_3)$$

and involves the five unknown parameters, $\gamma_1, \gamma_2$ and $\delta_{3k}, k = 1, 2, 3$. Two models for the PSD and the coal and ash mixtures can now be built. Specifically, the multiple Scheffé model for coal and its subcomponent ash can be crossed with that for PSD to give the model specified by

$$F_{XCA(MS)}(x, c, a) = f(x)g(c)h(a) = \sum_{i=1}^{3}\sum_{j=1}^{3}\sum_{k=1}^{3}\gamma_{ijk} x_i c_j a_k$$

with 27 unknown parameters, $\gamma_{ijk}, i, j, k = 1, 2, 3$. Alternatively the major-minor model for coal and ash can be crossed with the PSD mixture model to give the formulation

$$F_{XCA(MM)}(x, c, a) = \sum_{i=1}^{3}\sum_{j=1}^{2}\beta_{ij} x_i c_j + c_3 \sum_{i=1}^{3} x_i(\delta_{i31} a_1 + \delta_{i32} a_2 + \delta_{i33} a_3)$$

with 15 unknown parameters, $\beta_{ij}, i = 1, 2, 3, j = 1, 2$ and $\delta_{i3k}, i, k = 1, 2, 3$. Both these models can now be incorporated into multiple mixture models involving the process variables of the form

$$F_m(x, c, a, z) = F^{(0)}_{XCA(m)}(x, c, a) + \sum_{l=1}^{2} z_l F^{(l)}_{XCA(m)}(x, c, a) \quad \text{for } m = MS, MM$$

with a total of 81 parameters for the crossed coal-ash model and 45 for the coal-ash major-minor model. The notation for the identifiable parameters in these models is specified by the superscripts 0 and $l = 1, 2$ in the formulations for $F_{XCA(m)}$.

## 4 D-Optimal Designs

Designs, both approximate and exact, which maximize the information matrix associated with the parameters of the full response surface models, that is $D$-optimal

**Table 1** Extreme vertices of the polytopes $D_{psd}$, $D_{coal}$ and $D_{ash}$ are numbered in accord with the numbering in Figs. 1(a), (b) and (c), respectively

| | $x_1$ | $x_2$ | $x_3$ |
|---|---|---|---|
| $v_1^{(x)}$ | 0.540 | 0.449 | 0.011 |
| $v_2^{(x)}$ | 0.540 | 0.393 | 0.067 |
| $v_3^{(x)}$ | 0.401 | 0.393 | 0.206 |
| $v_4^{(x)}$ | 0.106 | 0.688 | 0.206 |
| $v_5^{(x)}$ | 0.106 | 0.882 | 0.012 |
| $v_6^{(x)}$ | 0.107 | 0.882 | 0.011 |

| | $c_1$ | $c_2$ | $c_3$ |
|---|---|---|---|
| $v_1^{(c)}$ | 0.5728 | 0.2382 | 0.1890 |
| $v_2^{(c)}$ | 0.5035 | 0.2382 | 0.2583 |
| $v_3^{(c)}$ | 0.5035 | 0.1875 | 0.3090 |
| $v_4^{(c)}$ | 0.56217 | 0.12883 | 0.3090 |
| $v_5^{(c)}$ | 0.6285 | 0.12883 | 0.24267 |
| $v_6^{(c)}$ | 0.6285 | 0.1825 | 0.1890 |

| | $a_1$ | $a_2$ | $a_3$ |
|---|---|---|---|
| $v_1^{(a)}$ | 0.238 | 0.696 | 0.066 |
| $v_2^{(a)}$ | 0.238 | 0.602 | 0.160 |
| $v_3^{(a)}$ | 0.217 | 0.602 | 0.181 |
| $v_4^{(a)}$ | 0.096 | 0.723 | 0.181 |
| $v_5^{(a)}$ | 0.096 | 0.838 | 0.066 |

designs, are now sought. For ease of construction, and since only linear Scheffé polynomials are invoked in the mixture components of the separate models, the designs are assumed to be based on the extreme vertices and centroids of the feasible regions for PSD, coal and ash together with appropriate points $(z_1, z_2)$ in the design region for the process variables, $D_z$. The extreme vertices of the feasible regions for the mixtures are conveniently summarized in Table 1.

## *4.1 Approximate Designs*

The construction of approximate $D$-optimal designs which allocate weights $w_u$ to the distinct support points $(x_u, c_u, a_u, z_u), u = 1, \ldots, d$, where $0 < w_u < 1$ with $\sum_{u=1}^{d} w_u = 1$ is now discussed. Such designs, while not of immediate practical use, provide valuable pointers to the nature and benchmarks for the efficiency of their exact $D$-optimal counterparts. Design construction is based on a proposition of Kang et al. (2011) for the formulation of approximate $D$-optimal designs for crossed mixtures and proceeds stepwise, mirroring the building of the model as described in Sect. 3.

Building block $D$-optimal designs for the PSD and for the coal and ash mixtures, taken separately and specified by the linear Scheffé polynomials $f(x), g(c)$ and $h(a)$ respectively, are first introduced. Thus the approximate $D$-optimal design for the model for PSD alone is based on four of the extreme vertices of the feasible region $D_{psd}$ and is given by

$$\xi_X^\star = \begin{Bmatrix} v_1^{(x)} & v_3^{(x)} & v_4^{(x)} & v_6^{(x)} \\ 0.2919 & 0.2081 & 0.2081 & 0.2919 \end{Bmatrix}$$

and, similarly, that for ash alone is based on four of the extreme vertices of $D_{ash}$ and is specified by

$$\xi_A^\star = \begin{Bmatrix} v_1^{(a)} & v_3^{(a)} & v_4^{(a)} & v_5^{(a)} \\ 0.2695 & 0.2305 & 0.2305 & 0.2695 \end{Bmatrix}.$$

In contrast, $D$-optimal designs for the coal mixture alone were somewhat unusual. Specifically, two $D$-optimal designs, each based on five of the six extreme vertices of the feasible region $D_{coal}$, were obtained, namely

$$\xi^{\star}_{C1} = \left\{ \begin{matrix} v_1^{(c)} & v_2^{(c)} & v_3^{(c)} & v_4^{(c)} & v_5^{(c)} \\ 0.3099 & 0.0446 & 0.2802 & 0.0629 & 0.3024 \end{matrix} \right\}$$

and

$$\xi^{\star}_{C2} = \left\{ \begin{matrix} v_1^{(c)} & v_2^{(c)} & v_4^{(c)} & v_5^{(c)} & v_6^{(c)} \\ 0.0632 & 0.3049 & 0.3076 & 0.0455 & 0.2788 \end{matrix} \right\}.$$

Clearly, designs with weights on the support points which are a convex combination of the weights for $\xi^{\star}_{C1}$ and $\xi^{\star}_{C2}$, as, e.g., the near-equireplicate design

$$\xi^{\star}_{CE} = \left\{ \begin{matrix} v_1^{(c)} & v_2^{(c)} & v_3^{(c)} & v_4^{(c)} & v_5^{(c)} & v_6^{(c)} \\ 0.1864 & 0.1749 & 0.1399 & 0.1854 & 0.1738 & 0.1396 \end{matrix} \right\},$$

are also $D$-optimal.

Approximate $D$-optimal designs for the PSD-coal-ash crossed mixture model with deterministic component $F_{XCA(MS)}(x, c, a)$ now follow immediately. Specifically, following a proposition of Kang et al. (2011), an approximate $D$-optimal design for a crossed mixture model is a crossed design, that is a design which crosses the $D$-optimal designs of the individual mixtures. Thus, in the present case, the requisite designs for the crossed mixture model, denoted by $\xi^{\star}_X \otimes \xi^{\star}_C \otimes \xi^{\star}_A$, comprise support points $(v_r^{(x)}, v_s^{(c)}, v_t^{(a)})$ with the corresponding weights being products of the weights $w_r^{(x)}$, $w_s^{(c)}$ and $w_t^{(a)}$ associated with the extreme vertices $v_r^{(x)}$, $v_s^{(c)}$ and $v_t^{(a)}$ of the individual $D$-optimal designs for PSD, coal and ash respectively, that is with weights $w_{rst} = w_r^{(x)} \times w_s^{(c)} \times w_t^{(a)}$ where $r, s = 1, \ldots, 6, t = 1, \ldots, 5$. A suite of approximate $D$-optimal designs based on 80 and on 96 support points can thus be constructed.

The construction of approximate $D$-optimal designs for the multiple mixture model for which PSD is crossed with coal and ash as major-minor components, that is for the model specified by $F_{XCA(MM)}(x, c, a)$, is not straightforward. In particular $D$-optimal designs for the major-minor mixture model comprising coal and ash alone do not follow immediately from the individual $D$-optimal designs for those components and must be constructed independently. A careful algorithmic search over all designs with points taken from the crossed extreme vertices of the feasible regions $D_{coal}$ and $D_{ash}$, that is from the 30 points of the form $(v_r^{(c)}, v_t^{(a)})$ for $r = 1, \ldots, 6$ and $t = 1, \ldots, 5$, yielded approximate $D$-optimal designs for the coal-ash major-minor mixture model with a minimum support of 12 points. Two of these designs are presented in Table 2. Note again that designs with weights which are a convex combination of the weights of the 12-point $D$-optimal designs, denoted generically by $\xi^{\star}_{CA(MM)}$, are also $D$-optimal. It now follows immediately from the proposition of Kang et al. (2011) that approximate $D$-optimal designs for the complete PSD crossed coal-ash major-minor mixture model are crossed designs of the

**Table 2** Approximate $D$-optimal designs for the coal-ash major-minor mixture model based on 12 support points specified by the pairs of vertices $(v_r^{(c)}, v_t^{(x)})$ with attendant weight $w_{rt}$

| $v_r^{(c)}$ | $v_t^{(x)}$ | $w_{rt}$ | | $v_r^{(c)}$ | $v_t^{(x)}$ | $w_{rt}$ |
|---|---|---|---|---|---|---|
| 1 | 1 | 0.0575 | | 1 | 1 | 0.1331 |
| 2 | 3 | 0.0464 | | 1 | 3 | 0.0199 |
| 2 | 4 | 0.1115 | | 1 | 5 | 0.0592 |
| 2 | 5 | 0.0646 | | 2 | 4 | 0.0593 |
| 3 | 1 | 0.1418 | and | 3 | 3 | 0.1555 |
| 4 | 3 | 0.1159 | | 3 | 4 | 0.0299 |
| 4 | 4 | 0.0884 | | 3 | 5 | 0.1320 |
| 4 | 5 | 0.1312 | | 4 | 1 | 0.1310 |
| 5 | 1 | 0.0679 | | 4 | 5 | 0.0511 |
| 6 | 3 | 0.0728 | | 5 | 1 | 0.0396 |
| 6 | 4 | 0.0246 | | 5 | 3 | 0.0204 |
| 6 | 5 | 0.0774 | | 5 | 4 | 0.1690 |

general form $\xi_X^\star \otimes \xi_{CA(MM)}^\star$. It should be noted here that the $D$-optimality of all of the above designs was confirmed, albeit numerically, by invoking the appropriate equivalence theorem.

The construction of approximate $D$-optimal designs for models which include both mixture and process variables is now addressed. A small scale investigation for the PSD-process variable setting was undertaken and the design which puts equal weights on the basic approximate $D$-optimal design $\xi_X^\star$ replicated at the factorial points of the process variable region $D_z$, that is at $(0, 0), (1, 0), (0, 1), (1, 1)$, was found to be $D$-optimal. It is therefore tempting to extend this notion to the more general case and to take crossed multiple mixture-with-process variable $D$-optimal designs to be $D$-optimal. This somewhat opportunistic strategy is adopted here. However, it should be emphasized that numerical confirmation of the construction proved to be computationally intensive and was not performed.

## *4.2 Exact Designs*

Exact $D$-optimal designs for multiple mixture and process variable models with observations taken at small numbers of support points are required in practice (Atkinson et al. 2007). The construction of such designs can be expedited, albeit in a somewhat *ad hoc* manner, by drawing on the results for the corresponding approximate $D$-optimal designs. Specifically near-optimal exact designs for the complete models are assumed to comprise exact designs for the multiple mixture models alone, that is for the models specified either by $F_{XCA(MS)}(x, c, a)$ or by $F_{XCA(MM)}(x, c, a)$, repeated the same number of times at the four factorial points of $D_z$. In addition,

**Table 3** Percentage $D$-efficiencies, denoted by $DE_{MS}$ and $DE_{MM}$, for the multiple mixture models specified by $F_{XCA(MS)}(x, c, a)$ and $F_{XCA(MM)}(x, c, a)$ with numbers of parameters 15 and 27, respectively, for a range of $n$ values ($a$ indicates too few points for estimation)

| $n$ | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 75 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|
| $DE_{MS}$ | $a$ | $a$ | $a$ | 3.7 | 14.1 | 37.1 | 59.9 | 65.1 | 74.2 | 84.7 |
| $DE_{MM}$ | 18.8 | 58.3 | 75.4 | 81.1 | 87.1 | 89.8 | 92.6 | 93.2 | 97.6 | 98.5 |

the support points of exact designs for the mixture models alone are assumed to come from the crossed support points of the individual approximate $D$-optimal designs for the PSD and the coal and ash mixtures, giving a total of $6 \times 4 \times 4 = 96$ candidate points. Near-exact $n$-point designs for the multiple mixture models with $n \leq 100$ can then be obtained by implementing a Fedorov exchange procedure at surprisingly reasonable computational cost.

The near-optimal designs for the models with coal and ash crossed and with coal and ash as major-minor components have very different patterns but, for brevity, details are not given here. The $D$-efficiency of the near-optimal exact designs relative to the corresponding approximate $D$-optimal designs is of more immediate interest and results for a representative range of $n$ values are summarized in Table 3. It is clear that designs with minimal support are not efficient but that $D$-efficiency increases rapidly with increasing $n$. Thus designs for the coal-ash major-minor component model based on 50 points are highly efficient whereas for models incorporating the multiple Scheffé component for coal and ash at least 75 points are required for the efficiency to be considered acceptable.

## 5 Conclusions

Models for an experiment involving multiple mixture and process variables have been developed and the attendant approximate $D$-optimal and exact near-$D$-optimal designs constructed. Model building proceeds stepwise and is mirrored in design construction. The approach can be readily extended to large-scale industrial experiments but some care is clearly required in obtaining designs for individual mixtures, as for example the mixture of coal in the present study, and, more importantly, for the major-minor mixture model components in the overall model.

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## References

Atkinson, A.C., Donev, A.N., Tobias, R.: Optimum Experimental Designs, with SAS. Oxford University Press, Oxford (2007)

Borges, C., Bruns, R., Almeida, A.A., Scarminio, I.S.: Mixture–mixture design for the fingerprint optimization of chromatographic mobile phases and extraction solutions for Camellia sinensis. Anal. Chim. Acta **595**, 28–37 (2007)

Coetzer, R.L.J., Keyser, M.J.: Experimental design and statistical evaluation of a full-scale gasification project. Fuel Process. Technol. **80**, 263–278 (2003)

Cornell, J.A.: Experiments with Mixtures: Designs, Models, and the Analysis of Mixture Data. Wiley, New York (2002)

Cornell, J.A., Ramsey, P.J.: A generalized mixture model for categorized-components problems with an application to a photoresist-coating experiment. Technometrics **40**, 48–61 (1998)

Didier, C., Etcheverrigaray, M., Kratje, R., Goicoechea, H.C.: Crossed mixture design and multiple response analysis for developing complex culture media used in recombinant protein production. Chemom. Intell. Lab. Syst. **86**, 1–9 (2007)

Kang, L., Roshan, J.V., Brenneman, W.A.: Design and modeling strategies for mixture-of-mixtures experiments. Technometrics **53**, 125–136 (2011)

# Optimal Design of Experiments for Delayed Responses in Clinical Trials

**Vladimir Dragalin**

**Abstract** The efficiency of optimal experimental designs when the primary endpoint is immediate is well documented. Often, however, in the practice of clinical trials there will be a delay in the response of clinical interest. Since few patients will have experienced the endpoint in the early stages of a trial, there may be little information that can be used in making a decision to modify the trial's course. But almost always, the clinical efficacy endpoint will be measured at early time points and these measurements might be correlated with, and predictive for, the primary long-term endpoint. The focus of the definitive analysis is still the primary clinical endpoint and not these short-term endpoints. The latter may be used just as an estimate of potential treatment effect and can enhance the interim decision of dropping a treatment arm or changing the treatment allocation. The research questions are: what is the optimal number of measurements per patient and what are the optimal time intervals between these measurements? A major benefit of modeling relationships between early and late endpoints is that it makes for stronger interim assessments of long-term endpoints and therefore improves the efficiency of adaptive designs.

## 1 Motivating Study

A motivation for this research was a dose ranging study in subjects with mild to moderate Alzheimer's disease. The primary objective of this study was to investigate the dose response relationship of a new drug as assessed at 12 months after initiation of treatment on the primary endpoint, the Alzheimer Disease Assessment Scale-Cognitive sub-score (ADAS-Cog).

For 80 % power, a conventional parallel group design would require 64 subjects per group to detect a difference of 3 units in the mean change from baseline in the primary endpoint with a standard deviation of 6 units. Instead of running a conventional dose ranging study with a total of 256 patients equally randomized to three doses (Low, Medium, and High) of the new drug and placebo, we considered an

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adaptive dose ranging study in which up to eight doses of the new drug could be investigated for better estimation of the dose response relationship, but using the same total of 256 patients. The efficiency was expected from using an adaptive design at several interim analyses during the enrollment period in order to change the patient allocation ratios according to the D-optimality criterion. The challenge was that the time to the primary endpoint—a change from baseline in ADAS-Cog at 52 weeks—was too long and in the planned 36 month enrollment period very few patients would have the completed treatment period at the interim analyses. To implement the adaptations using a shorter-term endpoints, let us say, the change from baseline on ADAS-Cog at 12 weeks, is also risky because different doses may have different time profiles of the mean change from baseline in ADAS-Cog.

The research questions are: (i) How to use these short-term measurements to improve the estimation of mean dose response parameters at interim analyses and improve the adaptive design efficiency? (ii) By how much this efficiency can be improved? (iii) How many short-term endpoints are optimal, if an additional cost per observation is considered? (iv) What are the optimal time locations for these observations to be taken?

In Sect. 2, we introduce the model for the primary endpoint as a parsimonious sigmoid Emax dose-response model. This model has been used in many publications on adaptive dose ranging designs, see, e.g., Thomas (2006), Dragalin et al. (2007), Leonov and Miller (2009), Padmanabhan and Dragalin (2009), Dragalin et al. (2010). We consider also a parametric model for the time-profile of the repeated measurements per patient. Such a model was introduced recently by Fu and Manner (2010); see also Li and Fu (2011). Locally optimal designs and information matrices for these special non-linear mixed effects models are defined in Sect. 3. A cost for repeated measurements is proposed by Gagnon and Leonov (2005) and the optimality criterion is maximized taking into account both the cost for patient recruitment and the cost incurred in taking a single measurement. Additional technical details in implementing adaptive versions of the optimal designs in this situation are presented in Sect. 4.

## 2 Model for the Primary Efficacy Endpoint

Let $Y$ be a continuous primary efficacy endpoint. Patients have a staggered entry in the trial and can be allocated to one of the available doses from a set of doses $\mathscr{D} = \{d_1, d_2, \ldots, d_D\}$. The density function of the efficacy endpoint $Y$ for a patient allocated to dose $d$ depends on $d$ and $\theta$, where $\theta = (\theta_1, \ldots, \theta_p)$ is the vector of unknown parameters. It is often assumed that the dose-response relationship will be sigmoid in nature. This is a highly flexible nonlinear model that captures the essential features of many dose-response relationships such as an apparent threshold dose below which little, if any, treatment effect is observed, an approximately log-linear dose versus mean treatment effect at higher doses, and sometimes a plateau or ceiling effect at relatively high doses.

The mean of the response, $E_\theta(Y|d)$, at a given dose $d$ for the sigmoid Emax model is

$$f(d,\theta) = \theta_1 + (\theta_2 - \theta_1)\frac{d^{\theta_4}}{d^{\theta_4} + \theta_3^{\theta_4}}, \tag{1}$$

where $\theta_1$ denotes the mean response at the zero dose, $\theta_2$ is the asymptote of the mean response at the infinite dose, $\theta_3$ is the dose that corresponds to a mean response halfway between the minimum and maximum treatment effect (sometimes called also $ED_{50}$), and $\theta_4$ is the slope parameter controlling the steepness of the curve. Note that by changing the values of $\theta_1$ and $\theta_2$ and the sign of $\theta_4$, the same model can be used to describe both monotonically increasing and decreasing dose-response curves. The model provides adequate approximation for many families of parametric monotone dose-response models (see, e.g., Thomas 2006; Dragalin et al. 2010).

In many clinical trials there will be a delay before obtaining the primary efficacy response; in our motivating example of Alzheimer disease ADAS-Cog or Clinical Dementia Rating scale Sum of Boxes (CDR-SB) score are typically measured after 12 months on treatment. Other examples with similar delays include the Disease Activity Score (DAS28) in Rheumatoid Arthritis, glycated hemoglobin (HbA1c) in Diabetes, CD4 counts or viral load in HIV, etc. However, the patients can be measured for the same endpoint at several time points before the end of treatment, for example at month 3 and month 6. These measurements will hopefully be correlated with, and predictive of, the primary long-term endpoint.

Therefore, we assume that each patient $j$ can provide measurements at time points $t_{jk}$ taken from the time interval $[0, T]$, where $0 \le t_{j1} < t_{j2} < \cdots < t_{jk_j} \le T$. We further assume that the efficacy response at time $t_{jk}$ for patient $j$ allocated to dose $d_i$ has the form

$$Y_{ijk} = \left[f(d_i,\theta) + s_{ij} + \varepsilon_{ijk}\right]\frac{1 - \mathrm{e}^{\beta t_{jk}}}{1 - \mathrm{e}^{\beta T}}, \tag{2}$$

where $f(d_i,\theta)$ is the underlying mean dose response (the primary long-term) from (1) and $s_{ij}$ is the subject $j$ random effect. We can rewrite (2) and set $\gamma_k = \{1 - \mathrm{e}^{\beta t_{jk}}\}/\{1 - \mathrm{e}^{\beta T}\}$, the mean proportional improvement from time point $t_{jk}$ to the final time point $T$ that depends on the single unknown parameter $\beta$, with $\varepsilon_{ijk}$ the measurement error associated with the observation at time $t_{jk}$. Furthermore, it is assumed that $s_{ij} \sim \mathcal{N}(0, \tau^2)$, $\varepsilon_{ijk} \sim \mathcal{N}(0, \sigma^2)$, $\mathrm{Cov}(\varepsilon_{ijk}, s_{ij}) = \mathrm{Cov}(\varepsilon_{ijk}, \varepsilon_{ij'k'}) = 0$. Notice that the coefficient of variation for $Y_{ijk}$ is constant over time $t_{jk}$, which is common in biological experiments (Shargel et al. 2004; Fu and Manner 2010).

## 3 Designs and Information Matrices

An individual design $\zeta_K$ for a patient with $K$ repeated measurements can be naturally defined as a $K$-dimensional vector of time points $(t_1, t_2, \ldots, t_K)$, such that

$0 \le t_1 < \cdots < t_K = T$. Then the vector of observations for patient $j$ on dose $d_i$ with the individual design $\zeta_K$,

$$\mathbf{Y}_{ij} = (Y_{ij1}, Y_{ij2}, \ldots, Y_{ijK}),$$

has a multivariate normal distribution with mean

$$\eta_i(\zeta_K, \theta, \beta) = f(d_i, \theta)\gamma(\zeta_K, \beta) \tag{3}$$

and covariance

$$\mathrm{Cov}(\mathbf{Y}_{ij}) = \Sigma(\zeta, \beta) = \tau^2 \Gamma_K^\top \Gamma_K + \sigma^2 \mathrm{diag}\{\gamma_1^2, \gamma_2^2, \ldots, \gamma_K^2\},$$

where $\Gamma_K = \gamma(\zeta_K, \beta) = (\gamma_1, \gamma_2, \ldots, \gamma_K)$.

A closed-form solution for the Fisher information matrix $\mu(\zeta, \vartheta)$ for $\vartheta = (\theta_1, \theta_2, \theta_3, \theta_4, \beta)$ of an individual design $\zeta$ exists (see, e.g., Muirhead 1982, Chap. 1) with elements

$$\mu_{ab}(\zeta, \vartheta) = \frac{\partial \eta(\zeta, \vartheta)}{\partial \vartheta_a} \Sigma^{-1}(\zeta, \beta) \frac{\partial \eta^\top(\zeta, \vartheta)}{\partial \vartheta_b} + \frac{1}{2}\mathrm{tr}\left[\Sigma^{-1}(\zeta, \beta)\frac{\partial \Sigma(\zeta, \beta)}{\partial \vartheta_a}\Sigma^{-1}(\zeta, \beta)\frac{\partial \Sigma(\zeta, \beta)}{\partial \vartheta_b}\right], \quad a, b = 1, \ldots, 5. \tag{4}$$

If $\tau^2$ and $\sigma^2$ are also unknown, (4) remains valid with the addition of partial derivatives with respect to the variance components. Of course, $\mu(\zeta, \vartheta)$ depends on $d$ but, for notational simplicity, $d$ is dropped here.

Consider now a population design $\xi$ with $m$ different doses $x_1, \ldots, x_m \in \mathscr{D}$

$$\xi = \begin{Bmatrix} x_1, \ldots, x_m \\ w_1, \ldots, w_m \end{Bmatrix},$$

with $0 < w_i < 1$ and $\sum w_i = 1$. This means that according to the population design $\xi$, patients are randomized to $m$ design doses proportionally to the weights $w_1, \ldots, w_m$.

Patients on each dose may be allocated to $R$ distinct individual designs $\zeta_1, \ldots, \zeta_R$, with relative allocation ratios $v_1, \ldots, v_R$, such that $\sum_{r=1}^R v_r = 1$. We will denote such an allocation scheme as $\Xi$. Because of the usual double-blinding requirements in clinical trials, patients at different doses should be allocated to the individual designs $\zeta_r$ for their repeated measurements according to the same scheme. For example, if the allocation scheme to the individual designs consists of two ($R = 2$) such designs, say, $\zeta_1 = (0, t_{11}, T)$ and $\zeta_2 = (0, t_{21}, t_{22}, T)$, with 3- and 4-time points, respectively, and $v_1 = 0.6$ and $v_2 = 0.4$, then 60 % of patients will be measured at baseline ($t = 0$), final time point ($t = T$), and one intermediate time $0 < t_{11} < T$, while the other 40 % will be measured at baseline, final time point, and two intermediate time points $0 < t_{21} < t_{22} < T$. However, this allocation scheme

should be applied for all doses. Otherwise, it will be known at what dose a patient is treated.

The normalized information matrix for such a scheme at dose $x_i$ is

$$I_i(\Xi, \vartheta) = \sum_{r=1}^{R} v_r \mu_i(\zeta_r, \vartheta), \tag{5}$$

where the index $i$ for $\mu$ stands for the information matrix calculated for dose $x_i$.

In this setting we will call the pair $(\xi, \Xi)$ a combined design. The normalized information matrix for the combined design $(\xi, \Xi)$ is then defined as

$$M(\xi, \Xi, \vartheta) = \sum_{i=1}^{m} w_i I_i(\Xi, \vartheta). \tag{6}$$

It is rather straightforward to define optimization criteria depending on the normalized information matrix, in particular the D-optimality criterion

$$\Psi\big(M(\xi, \Xi, \vartheta)\big) = \log\det\big[M(\xi, \Xi, \vartheta)\big], \tag{7}$$

to construct numerical algorithms for the optimal designs, and to derive their properties (see, e.g., Atkinson et al. 2007; Fedorov and Hackl 1997).

For example, a design $(\xi^*, \Xi^*)$ is D-optimal if and only if

$$\mathrm{tr}\big[I_i(\Xi, \vartheta) M^{-1}\big(\xi^*, \Xi^*, \vartheta\big)\big] \le p \tag{8}$$

for all doses $x_i$ and all individual designs $\Xi$, where $p = \dim(\vartheta)$. Moreover, the equality in (8) is attained at all support points of the optimal design.

As an illustration, let us consider the example of a sigmoid Emax model from Dragalin et al. (2007) with parameters $\vartheta = (3, 15, 400, 4, -2)$ and the dose space $\mathscr{D} = \{0(100)1000\}$. We assume $\tau = 0.5$ and $\sigma = 1$. The D-optimal design with a single post-baseline measurement at week 52, i.e., $\zeta_0 = (0, 52)$ has support points at doses 0, 300, 500, 1000 with equal weights $w = 1/4$. We will use this design as a benchmark in comparison with D-optimal designs with the individual designs $\zeta_1 = (0, 12, 52)$ and $\zeta_2 = (0, 12, 26, 52)$. The relative D-efficiency in estimating $(\theta_1, \ldots, \theta_4)$, defined as the scaled (1/4) ratio of the determinants of the inverse information matrix of $\zeta_0$ versus $\zeta_1$ and $\zeta_2$ is 1.18 and 1.61, respectively.

## *3.1 Cost-Constrained Designs*

Obviously, taking more measurements per patient provides additional information and increases the precision of parameter estimators. However, the number of measurements per patient usually needs to be restricted because of monetary cost and other logistical reasons. Therefore, it is reasonable to take the cost of repeated measurements into account at the trial design stage. Suppose that the cost of recruiting

a patient in the study is $c_1$ and the cost of obtaining a measurement per patient at a given time point is $c_2$. Then the cost for an individual design $\zeta_r$ with $K_r$ time points is $c_1 + K_r c_2$. The total cost for a trial with $N$ patients randomized according to a combined design $(\xi, \Xi)$ is

$$C_N(\xi, \Xi) = N\left(c_1 + c_2 \sum_{r=1}^{R} v_r K_r\right).$$

If we denote by $M_N(\xi, \Xi, \vartheta) = N \times M(\xi, \Xi, \vartheta)$ the total information about $\vartheta$ in such a trial, then the cost-normalized information matrix can be defined as

$$\tilde{M}_C(\xi, \Xi, \vartheta) = M_N(\xi, \Xi, \vartheta)/C_N(\xi, \Xi) = \sum_{i=1}^{m} w_i \sum_{r=1}^{R} \tilde{v}_r \tilde{\mu}_i(\zeta_r, \vartheta)$$

$$= \sum_{i=1}^{m} w_i \tilde{I}_i(\Xi, \vartheta),$$

where $\tilde{I}_i(\Xi, \vartheta)$ is the cost-normalized information matrix for $\vartheta$ under the allocation strategy $\Xi$ with

$$\tilde{v}_r = v_r \frac{c_1 + c_2 K_r}{C(\Xi)}, \qquad \tilde{\mu}_i(\zeta_r, \vartheta) = \frac{\mu_i(\zeta_r, \vartheta)}{c_1 + c_2 K_r},$$

$C(\Xi) = c_1 + c_2 \sum_{r=1}^{R} v_r K_r$.

Then the cost-constrained D-optimal design is the pair $(\tilde{\xi}^*, \tilde{\Xi}^*)$ maximizing

$$\log\det\left[M(\xi, \Xi, \vartheta)/C(\Xi)\right] \tag{9}$$

and (8) in the above equivalence statement should be replaced by

$$\mathrm{tr}\left[I_i(\Xi, \vartheta) M^{-1}\left(\tilde{\xi}^*, \tilde{\Xi}^*, \vartheta\right)\right] \le p \frac{C(\Xi)}{C(\tilde{\Xi}^*)}. \tag{10}$$

Note that while (7) can be viewed as maximization of information per one observation, the optimization problem (9) provides the maximization of information per cost unit. A similar approach was considered by Dragalin and Fedorov (2006) for penalized optimal designs with a more general non-linear cost (penalty) function.

As an illustration, let us consider again the example before (5): assume that the optimal allocation scheme $\Xi^*$ assigns 60 % of patients to an individual design with 3-time points and 40 % to a design with 4-time points when there are no extra costs incurred in taking a measurement and in recruiting a patient. Therefore, the number of patients $n_1$ and $n_2$ allocated to the individual designs $\zeta_1$ and $\zeta_2$, respectively, should satisfy $n_1/n_2 = 0.6/0.4 = 1.5$. Now suppose that $c_1 = 5$ and $c_2 = 0.5$ and the optimal cost-based design $\tilde{\Xi}^*$ also has $\tilde{v}_1 = 0.6$ for a 3-time point individual design and $\tilde{v}_2 = 0.4$ for a 4-time point design. However, now the number of patients $n_1$ and $n_2$ allocated to the individual design $\tilde{\zeta}_1$ and $\tilde{\zeta}_2$, respectively, should satisfy $n_1/n_2 = \{0.6 \times (5 + 3 \times 0.5)\}/\{0.4 \times (5 + 4 \times 0.5)\} = 1.39$.

## 4 Adaptive Designs

The designs considered in the previous section are locally optimal designs, i.e., they depend on the unknown parameter $\vartheta$. For practical use, we apply their adaptive implementation (see, e.g., Dragalin and Fedorov 2006; Dragalin et al. 2007, 2010). The steps are: (i) we start with an initial design randomizing the first $N_0$ patients; (ii) an interim analysis is conducted after $N_0$ patients have been enrolled and the unknown parameter is estimated as $\hat{\vartheta}_0$ using all available data; (iii) the design for the next $N_1$ patients is derived using the augmented locally optimal design $[\xi(\hat{\vartheta}_0), \Xi(\hat{\vartheta}_0)]$; (iv) these iterative steps are repeated in several stages until the total number of patients $N$ are enrolled. Applying the methodology developed in Pronzato (2010), we can show that the information matrix evaluated at the current estimated value of the parameter strongly converges to the matrix of the D-optimal design for the unknown true value of the parameter.

## References

Atkinson, A.C., Donev, A.N., Tobias, R.D.: Optimum Experimental Designs with SAS. Oxford University Press, Oxford (2007)

Dragalin, V., Fedorov, V.V.: Adaptive designs for dose-finding based on efficacy-toxicity response. J. Stat. Plan. Inference **136**, 1800–1823 (2006)

Dragalin, V., Hsuan, F., Padmanabhan, S.K.: Adaptive designs for dose-finding studies based on sigmoid Emax model. J. Biopharm. Stat. **17**, 1051–1070 (2007)

Dragalin, V., Bornkamp, B., Bretz, F., Miller, F., Padmanabhan, S.K., Perevozskaya, I., Pinheiro, J., Smith, J.R.: A simulation study to compare new adaptive dose-ranging designs. Stat. Biopharm. Res. **2**, 487–512 (2010)

Fedorov, V., Hackl, P.: Model-Oriented Design of Experiments. Springer, Berlin (1997)

Fu, H., Manner, D.: Bayesian adaptive dose-finding studies with delayed responses. J. Biopharm. Stat. **20**, 1055–1070 (2010)

Gagnon, R., Leonov, S.: Optimal population designs for PK models with serial sampling. J. Biopharm. Stat. **15**, 143–163 (2005)

Leonov, S., Miller, S.: An adaptive optimal design for the Emax model and its application in clinical trials. J. Biopharm. Stat. **19**, 360–385 (2009)

Li, W., Fu, H.: Bayesian optimal adaptive designs for delayed-response dose-finding studies. J. Biopharm. Stat. **21**, 888–901 (2011)

Muirhead, R.: Aspects of Multivariate Statistical Theory. Wiley, New York (1982)

Padmanabhan, S.K., Dragalin, V.: Adaptive Dc-optimal designs for dose finding based on a continuous efficacy endpoint. Biom. J. **52**, 836–852 (2009)

Pronzato, L.: One-step ahead adaptive D-optimal design on a finite design space is asymptotically optimal. Metrika **71**, 219–238 (2010)

Shargel, L., Wu-Pong, S., Yu, A.B.C.: Applied Biopharmaceutics & Pharmacokinetics, 5th edn. McGraw-Hill Medical, New York (2004)

Thomas, N.: Hypothesis testing and Bayesian estimation using a sigmoid Emax model applied to sparse dose-response designs. J. Biopharm. Stat. **16**, 657–677 (2006)

# Construction of Minimax Designs for the Trinomial Spike Model in Contingent Valuation Experiments

**Ellinor Fackle-Fornius and Linda Wänström**

**Abstract** This paper concerns design of contingent valuation experiments when interest is in knowing whether respondents have positive willingness to pay and, if so, if they are willing to pay a certain amount for a specified good. A trinomial spike model is used to model the response. Locally D- and c-optimal designs are derived and it is shown that any locally optimal design can be deduced from the locally optimal design for the case when one of the model parameters is standardized. It is demonstrated how information about the parameters, e.g., from pilot studies, can be used to construct minimax and maximin efficient designs, for which the best guaranteed value of the criterion function or the efficiency function is sought under the assumption that the parameter values are within certain regions. The proposed methodology is illustrated on an application where the value of the environmentally friendly production of clothes is evaluated.

## 1 Introduction

Contingent valuation experiments (CVEs) are frequently used to estimate the value of non-market goods and services, such as environmental resources. The assessment of the willingness to pay (WTP) in the population is a primary objective when conducting a CVE. In the CVE respondents are presented with a hypothetical scenario under which a good or a service is to be offered and then exposed to a bidding scenario, consisting of one or more bids (Hanemann 1984; Hanemann and Kanninen 1999). Standard models for binary data, e.g., the logistic model, are often used. However, a major drawback with these models is that negative WTP is allowed for, which is often implausible. Also, a large proportion of individuals may have zero

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WTP. The trinomial spike model specifically accounts for this possibility. The trinomial response falls into one of three categories depending whether the respondent rejects any positive cost, has positive WTP but rejects the bid, or accepts the bid. The spike model is basically a truncated version of the logistic model with support only for positive bid values, with a discrete probability at zero that models the probability that an individual has zero WTP. Various spike models are described in Kriström (1997).

The design issues, when planning a CVE, involve selecting the number of bids (design points), the sizes of the bids (support of the design), as well as the allocation of respondents to each bid (design weights). We consider here the theory of continuous designs (Kiefer 1974; Silvey 1980; Fedorov and Hackl 1997; Atkinson et al. 2007) such that the number allocated to each design point is not restricted to be an integer. If required, the actual number of respondents is approximated in proportion to the optimal design weights. A suitable optimality criterion corresponding to the objectives of the CVE has to be chosen. For the objective to determine the distribution of the WTP in the population, D-optimality is reasonable. The c-optimality criterion is better suited for estimation of a function of the model parameters, e.g., median WTP.

A problem with optimal designs for non-linear models is the parameter-dependence issue. One could use a single best guess of the true parameter values yielding a locally optimal design. However, such designs are rarely robust to departures from this guess. Another approach would be to specify a prior distribution over the parameter space and use it to derive an optimal on-the-average (or Bayesian) design (Chaloner and Verdinelli 1995). However, it may be difficult to decide on the prior distribution. Sequential methods (Wu 1985) are also a possibility but sometimes unrealistic for practical reasons.

For the application to CVEs we propose to use a minimax approach. It is particularly suitable when there is information available from pilot studies. The first step is to construct a region of plausible parameter values, on the basis of the available information, and then seek a design that is robust within this region. The minimax design protects against a worst-case scenario as the parameters are varied in the specified region. The worst case may be defined directly by any of the standard criteria, to achieve, e.g., minimax D-optimality or minimax c-optimality (King and Wong 2000; Berger et al. 2000). Another alternative is to use the efficiency of the design in relation to the locally optimal design as the criterion. The resulting design will then be maximin efficient (Dette 1997; Imhof 2001; Dette et al. 2006). However, except for some special cases, numerical methods are needed to derive those designs. Moreover, there are often computational difficulties involved. This is a reason why minimax/maximin efficient designs have seen a limited use in practice so far. We implement the H-algorithm described in Nyquist (2013) which facilitates the construction of the designs.

The outline of the paper is as follows. Section 2 describes the trinomial spike model and Sect. 3 presents locally optimal designs. The minimax approach is described in Sect. 4 and we demonstrate how minimax and maximin efficient designs are derived based on data from a CVE to estimate WTP for the environmentally

friendly production of clothes. Some concluding remarks are given in the final section.

## 2 The Trinomial Spike Model

In the setup described in Kriström et al. (1992), two questions are asked: if the respondent accepts *any* positive cost and if the respondent accepts a bid $A$. The bids are allowed to be any positive real number. Thus the design space is $\mathbb{R}^+$. The trinomial response $Y = (Y_0, Y_1, Y_2)$ is classified either as "zero WTP", "positive WTP less than $A$" or "positive WTP at least $A$". The probability that a randomly selected individual accepts a bid $A$ is modelled via the logistic function as $\pi_2(A) = P(WTP \geq A) = e^{\beta_0+\beta_1 A}/(1 + e^{\beta_0+\beta_1 A})$, $\beta_1 < 0$. The probability that a randomly selected individual has zero WTP is not related to the bid size and is defined as $\pi_0 = P(WTP = 0) = (1 + e^{\beta_0})^{-1}$. The mean WTP for the trinomial spike model is $\mu = -\ln(1 + e^{\beta_0})/\beta_1$ and the median of the WTP is $\rho = -\beta_0/\beta_1$ if $\beta_0 > 0$, and zero otherwise.

Let $\pi(A) = [\pi_0, \pi_2(A)]^\top$ and $\theta = (\beta_0, \beta_1)^\top$. Then we have

$$D = \frac{\partial \pi(A)}{\partial \theta} = \begin{pmatrix} -\pi_0(1-\pi_0) & 0 \\ \pi_2(A)[1-\pi_2(A)] & A\pi_2(A)[1-\pi_2(A)] \end{pmatrix}$$

and

$$V = \operatorname{cov}\begin{pmatrix} Y_0 \\ Y_2 \end{pmatrix} = \begin{pmatrix} \pi_0(1-\pi_0) & -\pi_0\pi_2(A) \\ -\pi_0\pi_2(A) & \pi_2(A)[1-\pi_2(A)] \end{pmatrix}.$$

For a continuous design $\xi$ with $n$ support points $A_1, \ldots, A_n$ and weights $\xi(A_i)$, $i = 1, \ldots, n$ the $2 \times 2$ information matrix is

$$\begin{aligned} &M(\xi, \theta) \\ &\quad = \sum_{i=1}^{n} \xi(A_i) D_i^\top V_i^{-1} D_i \\ &\quad = \sum_{i=1}^{n} \xi(A_i)(1-\pi_0) \begin{pmatrix} [1-\pi_2(A_i)][\pi_0+\pi_2(A_i)] & A_i\pi_2(A_i)[1-\pi_2(A_i)] \\ A_i\pi_2(A_i)[1-\pi_2(A_i)] & \frac{A_i^2\pi_2(A_i)[1-\pi_2(A_i)]^2}{1-\pi_0-\pi_2(A_i)} \end{pmatrix} \end{aligned} \tag{1}$$

$M^{-1}(\xi, \theta)$ is proportional to the asymptotic covariance matrix of the maximum likelihood estimator of $\theta$. A measure of the variability of a prediction at a point $A$ is given by the standardized predictor variance function

$$d(A, \xi, \theta) = \operatorname{tr}\big[m(A, \theta) M(\xi, \theta)^{-1}\big],$$

where $m(A, \theta)$ is the information from a design with unit mass at $A$.

**Table 1** Locally D-optimal ($\xi_D^*$) and c-optimal designs ($\xi_c^*$) for different values of $\beta_0$

| $\beta_0$ | $\pi_0$ | $\xi_D^*$ | $\beta_0$ | $\pi_0$ | $\xi_D^*$ | $\xi_c^*$ |
|---|---|---|---|---|---|---|
| −4 | 0.98 | 1.609 (1) | 1 | 0.27 | 2.652 (1) | 1.656 (1) |
| −2 | 0.88 | 1.703 (1) | 2 | 0.12 | 3.292 (1) | 2.425 (1) |
| −1 | 0.73 | 1.858 (1) | 4 | 0.02 | 3.133 (0.331)<br>5.310 (0.669) | 4.124 (1) |
| 0 | 0.5 | 2.165 (1) | | | | |

## 3 Locally Optimal Designs

A D-optimal design yields a minimal generalized variance, and thereby the smallest possible asymptotic confidence region for the parameters by minimization of the criterion function $\ln\det M(\xi,\theta)^{-1}$. By the General Equivalence Theorem of Kiefer and Wolfowitz (1960) a D-optimal design $\xi^*$ satisfies $d(A,\xi^*,\theta)\le 2$ for all $A>0$, with equality at the support points.

Assume that the design $\widetilde{\xi}^*$ with support points $\{A_i^*\}$ is locally D-optimal for the parameter vector $\widetilde{\theta}=(\beta_0,-1)^\top$. Let $\xi^*$ be as $\widetilde{\xi}^*$ with support points $\{-A_i^*/\beta_1\}$. Observing that $\pi_2(-A/\beta_1)$ for $\theta$ is equal to $\pi_2(A)$ for $\widetilde{\theta}$, from (1) it can be deduced that

$$\det\bigl[M\bigl(\widetilde{\xi}^*,\widetilde{\theta}\bigr)^{-1}\bigr]=\beta_1^2\det\bigl[M\bigl(\xi^*,\theta\bigr)^{-1}\bigr].$$

This implies that $\xi^*$ is locally D-optimal for $\theta$. Thus, once the optimal design is found for $\widetilde{\theta}=(\beta_0,-1)^\top$, the optimal design for any value of $\beta_1$ can easily be determined.

D-optimal designs for selected values of $\beta_0$ with $\beta_1=-1$ are shown in Table 1. These were obtained numerically and verified using the general equivalence theorem. In most cases the D-optimal design consists of just one point. Note however that all respondents are asked if they are willing to accept *any* positive cost in addition to being asked if they accept the bid $A$. That is, there are effectively two design points in these designs. Therefore, singularity is not an issue with the one-point designs here. When the probability of zero WTP, $\pi_0$, is close to zero, not much information is gained from the zero point and the D-optimal design consists of two design points.

Sometimes the objective is to estimate some function $g(\theta)$ of the parameters as precisely as possible, for instance when the primary interest is to estimate the median of the WTP, rather than the complete response curve. A c-optimal design minimizes the approximate variance of $g(\widehat{\theta})$: $c^\top M(\xi,\theta)^{-1}c$, where $c$ is a $p$-vector. For nonlinear $g(\theta)$, $c=\partial g(\theta)/\partial\theta$ and so for estimation of $\rho$, $c^\top=(-1/\beta_1,\beta_0/\beta_1^2)$ if $\beta_0>0$. The standardized predictor variance is then

$$d_c(A,\xi,\theta)=\operatorname{tr}\bigl[m(A,\theta)M(\xi,\theta)^{-1}c\bigl(c^\top M(\xi,\theta)^{-1}c\bigr)c^\top M(\xi,\theta)^{-1}\bigr]$$

and analogous conditions for c-optimality are obtained from the general equivalence theorem. As in the D-optimal case, it can be shown that the criterion function for

$\widetilde{\theta}$ is proportional to the criterion function for $\theta$ after the transformation to $-A/\beta_1$. Table 1 gives examples of c-optimal designs for estimation of $\rho$. We consider here only cases where $\beta_0 > 0$, that is, where $\rho > 0$, in order for the variance approximation to be justified. The support points of the c-optimal designs differ from those of the corresponding D-optimal designs.

**Application: Environmentally Friendly Clothes Data** A pilot CVE in which the purpose was to estimate WTP for environmentally friendly clothes was conducted in Levinson (2010). The data obtained from this study can be used to estimate the model parameters which in turn can be used as a basis for the design of the experiment. For a more detailed description of the application, but with not so much focus on theoretical issues, see Fornius and Wänström (2012). For the data from this pilot study the maximum likelihood parameter estimates were found to be $\widehat{\theta} = (1.4899, -0.0242)^\top$. Assuming these estimates are the true model parameters, the one point design at $A = 122$ SEK is locally D-optimal, while the one point design at $A = 84$ SEK is locally c-optimal for estimation of $\rho$. However, there is uncertainty in these parameter values and there is no guarantee that the locally optimal design is robust for other values. Instead, we examine the minimax and maximin efficient designs.

## 4 Minimax and Maximin Efficient Designs

To construct a minimax or maximin efficient design, a parameter subset $\Theta_0 \subset \Theta$ containing plausible values of $\theta$ needs to be specified. $\Theta_0$ is here defined as a rectangular region $\Theta_0 = [\beta_0^L, \beta_0^U] \times [\beta_1^L, \beta_1^U]$, where $\beta_0^{L/U}$ and $\beta_1^{L/U}$ are selected by the experimenter. These values can, e.g., be based on confidence intervals for the parameters from a pilot study, expert knowledge or theoretical considerations. The minimax design is then found as the minimum over the set of all designs of

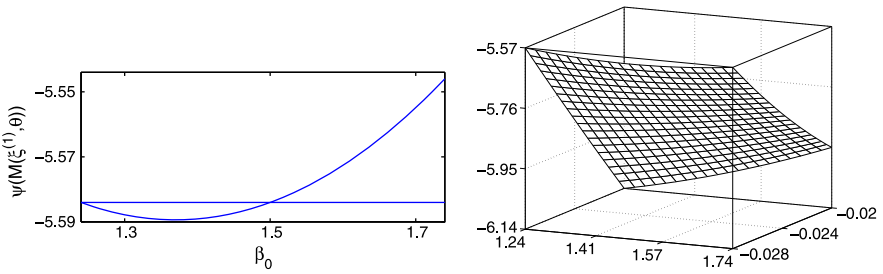
$$\max_{\theta \in \Theta_0} \psi\left[M(\xi, \theta)^{-1}\right],$$

where $\psi[\cdot]$ is the chosen criterion function. The efficiency of a design with respect to the locally optimally design $\xi^*$ is defined as

$$\text{eff}(\xi, \theta) = \left(\frac{\psi[M(\xi, \theta)]}{\psi[M(\xi^*, \theta)]}\right)^{\frac{1}{p}},$$

where $p$ is the number of parameters and the maximin efficient design maximizes $\min_{\theta \in \Theta_0} \text{eff}(\xi, \theta)$.

**The H-Algorithm** The H-algorithm given in Nyquist (2013) builds on a relation between minimax designs and optimum on-the-average designs. Let $\gamma$ be a prior distribution for $\theta$. A design $\xi^\gamma$ is optimum on-the-average with respect




(a) (b)

**Fig. 1** Panel (**a**) displays $\psi[M(\xi^{(1)}, \theta)]$ plotted over $\beta_0$ for $\beta_1 = -0.028$; $B(\xi^{(1)}, \pi^{(1)}) = -5.58$ is indicated by the *horizontal line*. Panel (**b**) displays $\psi[M(\xi^{(2)}, \theta)]$ plotted over $\Theta_0$, with the maximum value $B(\xi^{(2)}, \pi^{(2)}) = -5.57$

to $\gamma$ if it minimizes $B(\xi, \gamma) = E_\theta\{\psi[M(\xi, \theta)^{-1}]\}$ over all possible designs. It is shown in Nyquist (2013) that if $\gamma_0$ is a distribution with support only for points $\theta \in \Theta_0$, and if $\xi^0$ is an optimum on-the-average design with respect to $\gamma_0$ such that $\psi[M(\xi^0, \theta)^{-1}] \leq B(\xi^0, \gamma_0)$ for all $\theta \in \Theta_0$, then under general regularity conditions, $\xi^0$ is a minimax design with respect to $\Theta_0$. This changes the problem of finding a minimax design to the problem of finding a prior distribution $\gamma_0$, which is the *least favourable distribution* (l.f.d.), and the associated optimum on-the-average design. An l.f.d. $\gamma_0$ has support only for $\theta$, where $\psi[M(\xi^0, \theta)^{-1}] = B(\xi^0, \gamma_0)$.

To construct a minimax design, begin by setting $k = 1$, and generate an initial distribution $\gamma^{(k)}$. Determine the design $\xi^{(k)}$ which is optimal on-the-average with respect to $\gamma^{(k)}$. Check if $\psi\{M(\xi^{(k)}, \theta)^{-1}\} \leq B(\xi^{(k)}, \gamma^{(k)})$ holds for all $\theta \in \Theta_0$. If the condition is met, stop and conclude that $\gamma^{(k)}$ is the l.f.d. and that $\xi^{(k)}$is the minimax design. Otherwise, add mass to $\gamma^{(k)}$ where $\psi[M(\xi^{(k)}, \theta)^{-1}]$ is maximized, and decrease mass accordingly elsewhere. The amount of mass to be added to this point should be such that $B(\cdot)$ is increased. Then set $k$ to $k + 1$ and determine a new optimum on-the-average design and so on; see Nyquist (2013) for details.

To obtain a maximin efficient design, seek instead an l.f.d. $\gamma_0$ with the associated optimum on-the-average design $\xi^0$ such that $\text{eff}(\xi^0, \theta) \geq B(\xi^0, \gamma_0) = E_\theta[\text{eff}(\xi^0, \theta)]$ for all $\theta \in \Theta_0$.

On the basis of the parameter estimates for the data presented in Sect. 3, approximate 95 percent confidence intervals for the parameters (separately) are given by $(1.24, 1.74)$ for $\beta_0$, and $(-0.028, -0.020)$ for $\beta_1$. Therefore, let the region of plausible parameter values be $\Theta_0 = [1.24, 1.74] \times [-0.028, -0.02]$. Take as $\gamma^{(1)}$ a distribution with unit mass at $\theta = (1.24, -0.028)$. For D-optimality, the optimum on-the-average design $\xi^{(1)}$ consists of one point at $A = 98$. But the checking condition is not met, see Fig. 1(a). Also note that mass should be added to $\theta = (1.74, -0.028)$. For $\gamma^{(2)} = \{(1.24, -0.028), (1.74, -0.028); 0.5, 0.5\}$ the one point design at $A = 107$ is optimum on the average. The checking condition is now met, see Fig. 1(b). Therefore we conclude that $\gamma^{(2)}$ is the l.f.d. and the minimax D-optimal design is found. By following analogous steps, the maximin D-efficient design is found to be a one-point design at $A = 125$, see Table 2. Other examples of

**Table 2** Minimax D-optimal designs ($\xi_{\mathrm{D}}^{0}$) and maximin D-efficient designs ($\xi_{\mathrm{D\text{-}eff}}^{0}$) with respect to some parameter regions $\Theta_0 = [\beta_0^L, \beta_0^U] \times [\beta_1^L, \beta_1^U]$

| $\beta_0^L$ | $\beta_0^U$ | $\beta_1^L$ | $\beta_1^U$ | $\xi_{\mathrm{D}}^{0}$ | l.f.d. | $\min_{\Theta_0} \mathrm{eff}_{\mathrm{D}}$ | $\max_{\Theta_0} \psi_{\mathrm{D}}$ | $\xi_{\mathrm{D\text{-}eff}}^{0}$ | l.f.d. | $\min_{\Theta_0} \mathrm{eff}_{\mathrm{D}}$ | $\max_{\Theta_0} \psi_{\mathrm{D}}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1.24 | 1.74 | −0.028 | −0.02 | 107 (1) | 1.24, −0.028 (0.5)<br>1.74, −0.028 (0.5) | 0.8732 | $3.787 \cdot 10^{-3}$ | 125 (1) | 1.24, −0.028 (0.47)<br>1.74, −0.02 (0.53) | 0.9503 | $4.167 \cdot 10^{-3}$ |
| 1 | 2 | −0.028 | −0.02 | 107 (1) | 1, −0.028 (0.5)<br>2, −0.028 (0.5) | 0.8237 | $4.012 \cdot 10^{-3}$ | 127 (1) | 1, −0.028 (0.52)<br>2, −0.02 (0.48) | 0.9241 | $4.583 \cdot 10^{-3}$ |
| 1.24 | 1.74 | −0.04 | −0.01 | 75 (1) | 1.24, −0.04 (0.5)<br>1.74, −0.04 (0.5) | 0.3588 | $7.749 \cdot 10^{-3}$ | 90 (0.61)<br>290 (0.39) | 1.24, −0.04 (0.35)<br>1.74, −0.022 (0.19)<br>1.74, −0.01 (0.46) | 0.7324 | 0.01412 |
| 1 | 2 | −0.04 | −0.01 | 75 (1) | 1, −0.04 (0.5)<br>2, −0.04 (0.5) | 0.3114 | $8.183 \cdot 10^{-3}$ | 85 (0.56)<br>180 (0.07)<br>290 (0.37) | 1, −0.04 (0.34)<br>2, −0.022 (0.24)<br>2, −0.01 (0.42) | 0.7125 | 0.01566 |

**Table 3** Minimax c-optimal designs ($\xi_c^0$) and maximin c-efficient designs ($\xi_{c\text{-eff}}^0$) for estimation of the median of the WTP with respect to some parameter regions $\Theta_0 = [\beta_0^L, \beta_0^U] \times [\beta_1^L, \beta_1^U]$

| $\beta_0^L$ | $\beta_0^U$ | $\beta_1^L$ | $\beta_1^U$ | $\xi_c^0$ | l.f.d. | $\min_{\Theta_0} \text{eff}_c$ | $\max_{\Theta_0} \psi_c$ | $\xi_{c\text{-eff}}^0$ | l.f.d. | $\min_{\Theta_0} \text{eff}_c$ | $\max_{\Theta_0} \psi_c$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1.24 | 1.74 | −0.028 | −0.02 | 110 (1) | 1.74, −0.02 (1) | 0.8391 | $9.038 \cdot 10^3$ | 90 (1) | 1.24, −0.028 (0.62)<br>1.74, −0.02 (0.38) | 0.9301 | $9.742 \cdot 10^4$ |
| 1 | 2 | −0.028 | −0.02 | 122 (1) | 2, −0.02 (1) | 0.7822 | $9.203 \cdot 10^3$ | 127 (1) | 1, −0.028 (0.52)<br>2, −0.02 (0.48) | 0.9241 | $9.353 \cdot 10^4$ |
| 1.24 | 1.74 | −0.04 | −0.01 | 222 (1) | 1.74, −0.01 (1) | 0.0670 | $3.615 \cdot 10^4$ | 75 (0.61)<br>250 (0.39) | 1.74, −0.04 (0.43)<br>1.74, −0.022 (0.13)<br>1.74, −0.01 (0.44) | 0.6867 | $5.281 \cdot 10^4$ |
| 1 | 2 | −0.04 | −0.01 | 244 (1) | 2, −0.01 (1) | 0.0350 | $3.681 \cdot 10^4$ | 82 (0.61)<br>265 (0.39) | 2, −0.04 (0.42)<br>2, −0.022 (0.17)<br>2, −0.01 (0.41) | 0.6466 | $5.738 \cdot 10^4$ |

$\Theta_0$ are also given in the table as well as the minimum efficiency and the maximum value of the criterion of the designs within $\Theta_0$. Table 3 shows corresponding results for c-optimality, all having different design points compared with D-optimality, while the structures of the designs and l.f.d.s are similar. Comparing the minimax and maximin efficient designs, the support points are different. In addition, the latter may have more support points. Also, the l.f.d.s differ. The minimum efficiency is always higher for the maximin efficient designs and sometimes by a remarkable amount. On the other hand, the maximum value of the criterion is always worse for the maximin efficient designs.

## 5 Concluding Remarks

Locally optimal designs for the trinomial spike model have been derived and consist of one point in most of the cases. The locally optimal design for any parameter $\beta_1$ is shown to be easily transformed from the locally optimal design for $\beta_1 = -1$. Construction of minimax and maximin efficient designs via the H-algorithm has been demonstrated based on pilot data for a CVE. The minimax designs consist of one point for each of the considered parameter subsets while the maximin efficient designs sometimes have more support points. The associated l.f.d.s have support on the boundary of the rectangular parameter regions. The minimum efficiency and maximum value of the criterion within the region of plausible parameters were examined. The results show considerable advantage of the maximin efficient designs when it comes to efficiency while the opposite applies when comparing the maximum criterion values. Choosing between the two types of criteria, one has to decide which is most important, to protect against a low efficiency or against a high (generalized) variance.

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## References

Atkinson, A., Donev, A., Tobias, R.: Optimum Experimental Designs, with SAS. Oxford University Press, New York (2007)

Berger, M., Joy King, C., Wong, W.: Minimax D-optimal designs for item response theory models. Psychometrika **65**, 377–390 (2000)

Chaloner, K., Verdinelli, I.: Bayesian experimental design: a review. Stat. Sci. **10**, 273–304 (1995)

Dette, H.: Designing experiments with respect to 'standardized' optimality criteria. J. R. Stat. Soc. B **59**, 97–110 (1997)

Dette, H., Lopez, I.M., Rodriguez, I.M.O., Pepelyshev, A.: Maximin efficient design of experiment for exponential regression models. J. Stat. Plan. Inference **136**, 4397–4418 (2006)

Fedorov, V.V., Hackl, P.: Model-Oriented Design of Experiments. Springer, New York (1997)

Fornius, E.F., Wänström, L.: Minimax optimal designs of contingent valuation experiments: Willingness to pay for environmentally friendly clothes (2012, submitted)

Hanemann, W.M.: Welfare evaluations in contingent valuation experiments with discrete responses. Am. J. Agric. Econ. **66**, 332–341 (1984)

Hanemann, W.M., Kanninen, B.: The statistical analysis of discrete-response cv data. In: Bateman, I.J., Willis, K.G. (eds.) Valuing Environmental Preferences: Theory and Practice of the Contingent Valuation Method in the USA, EC, and Developing Countries, pp. 302–441. Oxford University Press, Oxford (1999)

Imhof, L.A.: Maximin designs for exponential growth models and heteroscedastic polynomial models. Ann. Stat. **29**, 561–576 (2001)

Kiefer, J.: General equivalence theory for optimum designs (approximate theory). Ann. Stat. **2**, 849–879 (1974)

Kiefer, J., Wolfowitz, J.: The equivalence of two regression problems. Can. J. Math. **12**, 363–366 (1960)

King, J., Wong, W.K.: Minimax D-optimal designs for the logistic model. Biometrics **56**, 1263–1267 (2000)

Kriström, B.: Spike models in contingent valuation. Am. J. Agric. Econ. **79**, 1013–1023 (1997)

Kriström, B., Nyquist, H., Haneman, W.M.: Dichotomous choice contingent valuation experiment: A mixed distribution approach. Working Paper, Department of Economics, University of Umeå, Sweden (1992)

Levinson, E.: "Green clothes"—a survey of people's willingness to pay for environmentally friendly clothes. Master's thesis, Sustainable Enterprising, Stockholm University (2010)

Nyquist, H.: Convergence of an algorithm for constructing minimax designs. In: Uciński, D., Atkinson, A., Patan, M. (eds.) mODa 10—Advances in Model-Oriented Design and Analysis, pp. 187–194. Physica-Verlag, Heidelberg (2013)

Silvey, S.D.: Optimal Design. Chapman & Hall, London (1980)

Wu, C.F.J.: Asymptotic inference from sequential design in a nonlinear situation. Biometrika **72**, 553–558 (1985)

# Maximum Entropy Design in High Dimensions by Composite Likelihood Modelling

**Davide Ferrari and Matteo Borrotti**

**Abstract** In maximum entropy sampling (MES), a design is chosen by maximizing the joint Shannon entropy of parameters and observations. However, when the conditional parametric model of the response contains a large number of covariates, the posterior calculations in MES can be challenging or infeasible. In this work, we consider the use of composite likelihood modelling to break down the complexity of the full likelihood and code the original optimization problem into a set of simple partial likelihood problems. We study the optimality behaviour of the composite likelihood sampling approach as the number of design variables grows using both asymptotic analysis and numerical simulations.

## 1 Introduction

Let $\Xi$ be a set of possible experiments and $\xi = (x_1, \ldots, x_p) \in \Xi$ denote an experiment. The experimental response is an $n$-dimensional random vector $Y$ in $\mathscr{Y}$. The distribution of the response, denoted by $p(y|\xi, \theta)$, depends on the possible experiment $\xi$ and the value of a parameter vector $\theta \in \theta = \Theta$ in $\Omega$. The parameter $\theta$ has a prior distribution $p(\theta)$ which is assumed to be independent of the experiment $\xi$. In maximum entropy sampling (MES), the optimal experiment is chosen from the set of experiments $\Xi$, by maximizing the amount of information measured as the negative Shannon entropy. For a random vector $X$ with pdf or pmf $p(x)$, the Shannon entropy is defined by $H(X) = -\mathrm{E}_X\{\log p(X)\}$. Lindley (1956) proposed choosing the experiment $\xi$ by maximizing the expected information gain, $\mathrm{E}_Y\, H(\Theta|Y, \xi) - H(\Theta)$, where the first term represents the average information on

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the parameter, given the experiment $\xi$. Since the second term does not depend on $\xi$, the above task is equivalent to maximizing

$$\mathrm{E}_Y\, H(\Theta|Y,\xi) = \int_{\mathscr{Y}}\int_{\Omega} p(\theta|y,\xi)\log p(\theta|y,\xi)\, f(y)\,\mathrm{d}\theta\,\mathrm{d}y. \tag{1}$$

Computation of the posterior distribution poses well-known issues when the complexity of the sampling distribution $Y$ given $\Theta$ is high. Traditional approaches to MES often rely on asymptotic approximations of the posterior near the Maximum Likelihood Estimate (MLE) $\hat{\theta}$ of $\theta$. The posterior can be approximated as $\Theta|y,\xi \sim N\{\hat{\theta}, I(\hat{\theta},\xi)^{-1}\}$, where the covariance matrix is given by the inverse of the expected Fisher information matrix $I(\hat{\theta},\xi) = -\mathrm{E}_Y\,\nabla^2_\theta \log p(y|\theta,\xi)$. For a multivariate normal variable $Z \sim N(\mu,\Sigma)$, the entropy is $H(Z) = \log\det\Sigma$, which depends only on the covariance $\Sigma$. Therefore, for large samples, (1) can be approximated by the criterion function

$$L(\xi) = -\mathrm{E}_Y \log\det I(\hat{\theta},\xi) = -\mathrm{E}_\Theta \log\det I(\Theta,\xi), \tag{2}$$

where the second equality follows from consistency of the MLE and expectation is now over the prior distribution of $\Theta$. Another approach to asymptotically approximating Shannon entropy maximization is the minimax distance design (Johnson et al. 1990). The two designs are equivalent only under a specific condition on $\Sigma$.

In this paper, we propose a new criterion to compute optimal designs called pairwise maximum entropy sampling (P-MES). We consider partial likelihoods for the data, $p(y|\theta_i,x_i)$, $i=1,\ldots,p$, and $p(y|\theta_{ij},x_i,x_j)$, $i>j$, depending only on one and two predictors, respectively. The parameters $\theta_i \in \Omega_i$ and $\theta_{ij} \in \Omega_{ij}$ are subsets of the original parameter vector and typically $\Omega_i \subset \Omega_{ij} \subset \Omega$. The P-MES criterion is defined by the maximization of

$$\mathrm{E}_Y\, H_c(\Theta|Y,\xi) = \sum_{i<j} \mathrm{E}_Y\, H_2(\Theta|Y,x_i,x_j) - (p-1)\sum_i \mathrm{E}_Y\, H_1(\Theta|Y,x_i), \tag{3}$$

where $H_2$ and $H_1$ are entropy functions depending on the partial posterior distributions $p(\theta_{ij}|y,x_i,x_j)$ and $p(\theta_i|y,x_i)$. Similarly to MES, a consistent asymptotic approximation to (3) is given by

$$L^{(P)}(\xi) = \sum_{i<j} \mathrm{E}_\Theta \log\det I_{ij}(\Theta,x_i,x_j) - (p-1)\sum_i \mathrm{E}_\Theta \log\det I_i(\Theta,x_i), \tag{4}$$

where $I_i$ and $I_{ij}$ denote the expected Fisher information for marginal and pairwise models. Further, we show that when $p$ increases, $L^{(P)}(\xi)$ converges to $L(\xi)$. This implies that, in large problems with many variables, the designs selected by P-MES tend to coincide with those provided by MES.

## 2 Hoeffding Scores and P-MES

The second-order Hoeffding projection of $Y$ onto $Z_1, \ldots, Z_p$ is defined by

$$P^*Y = \sum_{i<j} P_{ij}Y - \sum_{i=1}^{p} P_i Y, \tag{5}$$

where $P_i Y = E(Y|Z_i)$ and $P_{ij}Y = E(Y|Z_i, Z_j) - E(Y|Z_i) - E(Y|Z_j)$. Such a decomposition gives the best approximation of sums of functions of two variables at a time (Van der Vaart 1998). In this paper, we use the Hoeffding decomposition to project the parameter vector $\Theta$ onto the covariate space $\Xi$. In particular,

$$P^* \log p(\Theta|y) = \sum_{i<j} \log p(\Theta|y, x_i, x_k) - (p-1) \sum_{i} \log p(\Theta|y, x_i).$$

Taking the expectation of the above quantity with respect to $\Theta$ gives (3). It represents a special case of the composite likelihood function studied by Cox and Reid (2004), with their parameter $a$ set to be equal to 1. Formula (5) is common in composite likelihood approaches (Varin et al. 2011). Lindsey et al. (2011) and Varin et al. (2011) describe the use of pairwise Hoeffding scores to define composite likelihood objects. In the context of parameter estimation, Lindsey et al. (2011) show the optimality of (5) under independence conditions on the parameter vector.

Next, we study the relationship between MES and P-MES under sparsity conditions. Given a random vector $\mathbf{Z}$, let $\mathbf{Z}_{-j}$ denote the vector without the $j$-th component and define

$$S_p(\mathbf{Z}) = \frac{1}{p}\sum_{j=1}^{p} M(Z_j, \mathbf{Z}_{-j}) = \frac{1}{p}\sum_{j=1}^{p} \mathrm{E}_{\mathbf{Z}}\left\{\log \frac{p(\mathbf{Z})}{p(Z_j)p(\mathbf{Z}_{-j})}\right\}, \tag{6}$$

where $M$ denotes the mutual information between $Z_j$ and $\mathbf{Z}_{-j}$. The quantity $S_p$ is interpreted as a measure of sparsity as it computes the average information loss when breaking the dependence with respect to each individual component. We have $S_p(\mathbf{Z}) = 0$ if all the components are mutually independent. Next, we show the equivalence of MES and P-MES, when the sparsity of the parameter vector increases with the number of variables.

**Proposition 1** *Let* $\Theta = (\theta_1, \ldots, \theta_p)^\top$ *and assume that given* $Y$ *the elements of* $\Theta$ *depend only on elements of* $\xi$ *with the same index. If* $\mathrm{E}_Y[S_p(\Theta|Y, \xi)] \to 0$, *as* $p \to \infty$, *uniformly on* $\Xi$, *then* $\sup_{\xi\in\Xi} |L(\xi) - L^{(P)}(\xi)| \to 0$, *as* $p \to \infty$.

If the sparsity increases, the difference between the MES and P-MES criteria becomes negligible. This property turns out to be useful when the number of parameters is large and calculations involved in MES can be challenging. In practice, optimization of MES is usually feasible only in relatively small problems where $p$

is not too large. When $p$, $n$ and the complexity of the likelihood model are large, then the calculations become challenging because of the large size of the design space and non-linearity of the objective function. In fact, the objective function (3) is separable with respect to pairs $(x_i, x_j)$ and maximization can be achieved by the following set of quasi-Newton updates:

$$\hat{x}_i^{(s+1)} = \hat{x}_i^{(s)} - \hat{H}_i^{-1}\left\{\nabla_{x_i} L_{ij}\left(\hat{x}_i^{(s)}, \hat{x}_j^{(s)}\right)\right\}, \quad i = 1, \ldots, p, \tag{7}$$

where

$$L_{ij}^{(p)}(x_i, x_j) = \sum_{j=1}^{p} \mathrm{E}_Y\, H_2(\Theta|Y, x_i, x_j) - (p-1)\left\{\mathrm{E}_Y\, H_1(\Theta|Y, x_i) + \mathrm{E}_Y\, H_1(\Theta|Y, x_j)\right\}$$

and $H_i$ is a suitable approximation of the $n \times n$ Hessian $H_i = \nabla_{x_i}^2 L_{ij}^{(p)}(x_i, x_j)$. In the preliminary numerical comparisons in the next sections, when $x_i$, $i = 1, \ldots, p$, are discrete and the size of the design space is small, we employ exact enumeration of the design space. When the size of the design space is moderate or large, maximization is achieved by a genetic algorithm (GA) (Goldberg 1989). The GA is an optimization method inspired by the process of natural evolution and generates solutions using particular techniques such as selection, crossover and mutation. Currently, we are developing an exact enumeration algorithm for high-dimensional problems by a branch-and-bound approach (Ko et al. 1995).

## 3 Numerical Analysis

In this section, we compare MES and P-MES approaches by a numerical study based on an example proposed by Sebastiani and Wynn (2000). We consider the normal regression model $Y|(\xi, \theta) \sim N_n(X\theta, \Sigma_1)$, where $\Sigma_1$ is a known matrix. We assume that $\Theta \sim N_p(\theta_0, R^{-1})$ with $\theta_0$ and $R$ known and independent of the design $\xi$. The goal is to find an optimal design point $\xi$, i.e., a design matrix that maximize $\mathrm{E}_Y\, H(\Theta|Y, \xi)$.

To measure the difference between the MES and P-MES solutions, we employ two measures of discrepancy. The first measure is the Hamming distance, i.e., the number of different entries in the two design matrices. The second measure is the number of identical vectors.

We compare the two approaches for various choices of $p$ and $n$. Particularly, we consider $n = 1, 2, 3$ and $p = 3, 6, 9$. The order of the correlation among variables, $r$, is set as $p/3$. If $p = 3$, then $r = 1$ and $R$ is set as the identity matrix. If $p = 6$ then $r = 2$, meaning that only two variables are correlated with correlation $\rho$, where $\rho = 0.1$ or $0.9$.

**Table 1** Minimum Hamming distance between optimal P-MES and MES solutions. The brackets contain the number of equal vectors (experimental points)

| | $p=3$ | $p=6$ | $p=9$ | | |
|---|---|---|---|---|---|
| | no correlation | $\rho=0.1$ | $\rho=0.9$ | $\rho=0.1$ | $\rho=0.9$ |
| $n=1$ | 0 (1) | 0 (1) | 0 (1) | 0 (1) | 0 (1) |
| $n=2$ | 0 (2) | 1 (1) | 0 (2) | – | – |
| $n=3$ | 0 (3) | – | – | – | – |

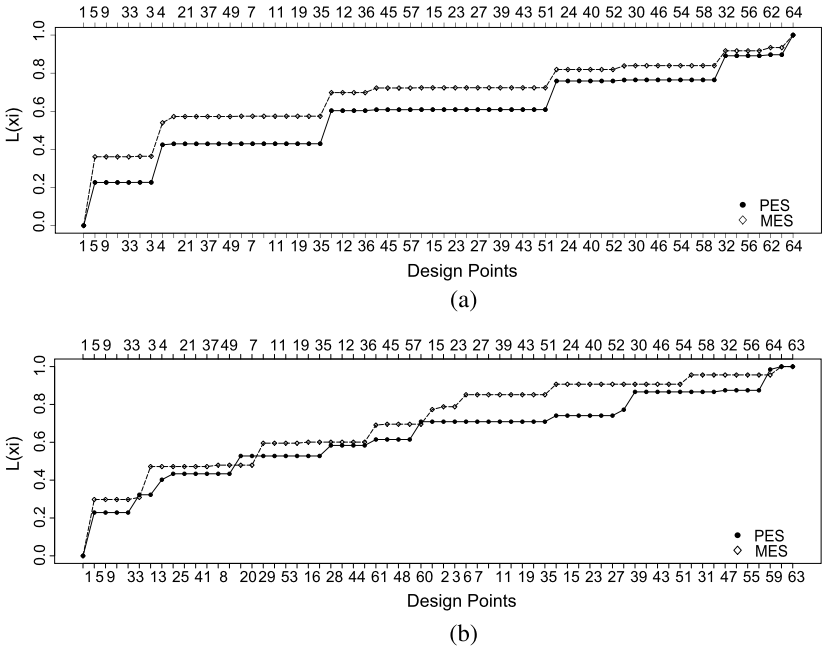


**Fig. 1** Single-point experiment for $n=1$ and $p=6$: (**a**) $\rho=0.1$ and (**b**) $\rho=0.9$. *Bottom horizontal line* reports the ordered design point according to the value of MES. *Top horizontal line* reports the ordered design point according to the value of P-MES

In almost all cases P-MES and MES find the same optimal design matrix but with different neighbouring solutions (see Table 1). An example is shown in Fig. 1 where the experimental points are ordered according to the value $L(\xi)$ calculated by P-MES and MES in the case of $n=1$, $p=6$ with $\rho=0.1$ and $\rho=0.9$. In only one case do the two approaches find different optimal solutions with a common design point (row) and Hamming distance equal to 1 ($n=2$, $p=6$ and $\rho=0.1$).

## 4 Case of $p$ Greater than $n$

We investigate the efficiency of P-MES when $p$ is larger than $n$, for both discrete and continuous covariates.

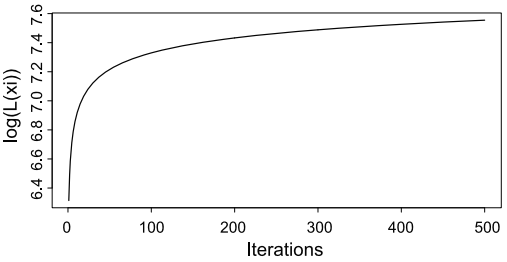


**Fig. 2** Behaviour of the response optimized by the quasi-Newton approach based on P-MES principles

## *4.1 Discrete Covariates*

We consider $p = 12$ and $n = 4$ and the worst case when all the parameters are correlated with $r = p = 12$ and $\rho = 0.1, 0.9$. To optimize the response surface we implemented a genetic algorithm. We computed 20 Monte-Carlo runs using randomly chosen starting points for the optimization. A run was stopped after the censoring time $T = 30$.

Our genetic algorithm is based on tournament selection, one-point crossover and a mutation operator with probability $p = 0.05$. In the selection operator the size of the tournament is 4. There are two tournaments and in each tournament we select the design matrix with the highest response. A one-point crossover is randomly selected and then the new children are created in accordance with this point and the selected parents.

In 20 runs, the largest value of MES is obtained twice resulting in two different design matrices. In this case ($p = 12$, $n = 4$ and $\rho = 0.1$) MES has two optimal solutions. P-MES reaches the same maximum value in 14 runs out of 20. In the case of $\rho = 0.9$ MES proposes 20 different design matrices with the same value of MES. P-MES reaches the same maximum value but it proposes different design matrices.

## *4.2 Continuous Covariates*

We set $n$ and $p$ equal to 4 and 12, respectively. The correlation matrix $R$ has elements $0.7^{|i-j|}, i, j = 1, \ldots, p$. We apply a quasi-Newton approach where the design matrix is selected using the P-MES criterion, and carry out Monte-Carlo simulations, using different initial matrices. At each step the algorithm improves significantly on the previous solution, and the optimization procedure moves consistently towards the optimal region of the search space. Figure 2 shows the behaviour of P-MES iteration by iteration.

The design matrices selected at each step of the optimization procedure are also evaluated with MES. We observe that while increasing the P-MES values, we also obtain increasingly larger values for the MES criterion. This suggests that, if the

complexity of the problem increases, the MES and P-MES criteria could find a similar path towards regions of optimality.

## Appendix

*Proof of Proposition 1.* Let $\mathbf{Z} = (Z_1, \ldots, Z_p)$ be a $p$-dimensional random vector with distribution $p(\mathbf{z})$. Singer (2004) shows that if $Z_j$ is independent of $Z_k$ for any $j \neq k$, then $p(\mathbf{z}) = \tilde{p}(\mathbf{z})^{(p)} = \prod_{|E|<p} p_E(\mathbf{z}_E)^{q_E}$, where $E$ is a set in the power set of indexes $\mathscr{P} = \{1, 2, \ldots, \{1, 2\}, \ldots, \{1, \ldots, p\}\}$, $|E|$ is the cardinality of the set $E$, $q^E = (-1)^{p+1-|E|}$, and $p_E$ denotes the distribution of $\mathbf{Z}_E \subset \mathbf{Z}$. Without loss of generality, we start from $\theta_1$, $\theta_2$ and $\theta_3$ and write

$$\log p(\theta_1, \theta_2, \theta_3 | y, \xi) = \log \tilde{p}(\Theta | y, \xi)^{(2)} + \log p(\theta_1 | \theta_2, \theta_3, y, \xi) - \log p(\theta_1 | \theta_2, y, \xi).$$

Recursively applying the formula by Singer (2004) for $3 \leq k \leq p$, gives

$$\log p(\Theta | y, \xi) = \log \tilde{p}(\Theta | y, \xi)^{(p)} + \log \left\{ \frac{p(\Theta |, y, \xi)}{p(\Theta_{-p} | y, \xi) p(\theta_p | y, \xi)} \right\}. \tag{8}$$

By summing over all such decompositions and taking the expectation with respect to $\Theta | Y, \xi$, we obtain

$$pH(\Theta | y, \xi) = p \, \mathrm{E}_\Theta \log \tilde{p}(\Theta | y, \xi)^{(p)} + \sum_{j=1}^{p} \mathrm{E}_\Theta \log \left\{ \frac{p(\Theta |, y, \xi)}{p(\Theta_{-j} | y, \xi) p(\theta_p | y, \xi)} \right\},$$

which implies $L(\xi) = \mathrm{E}_Y \, H(\Theta | Y, \xi) = L^{(p)}(\xi) + S_p(\Theta | Y, \xi)$. Finally, by our sparsity assumption, the last summand converges to zero as $p \to \infty$.

## References


Cox, D.R., Reid, N.: A note on pseudolikelihood constructed from marginal densities. Biometrika **91**, 729–737 (2004)

Goldberg, D.E.: Genetic Algorithms in Search, Optimization and Machine Learning. Kluwer Academic, Boston (1989)

Johnson, M.E., Moore, L.M., Ylvisaker, D.: Minimax and maximin distance design. J. Stat. Plan. Inference **26**, 131–148 (1990)

Ko, C.W., Lee, J., Queyranne, M.: An exact algorithm for maximum entropy sampling. Oper. Res. **43**, 684–691 (1995)

Lindsey, D.V.: On a measure of the information provided by an experiment. Ann. Math. Stat. **27**, 986–1005 (1956)

Lindsey, B.G., Yi, G.Y., Sum, J.: Issues and strategies in the selection of composite likelihoods. Stat. Sin. **21**, 71–105 (2011)

Sebastiani, P., Wynn, H.P.: Maximum entropy sampling and optimal Bayesian experimental design. J. R. Stat. Soc. B **62**, 145–157 (2000)
Singer, A.: Maximum entropy formulation of the Kirkwood superposition approximation. J. Chem. Phys. **121**, 3657–3666 (2004)
Van der Vaart, A.W.: Asymptotic Statistics. Cambridge University Press, New York (1998)
Varin, C., Reid, N., Firth, D.: An overview of composite likelihood methods. Stat. Sin. **21**, 5–42 (2011)

# Randomization Based Inference for the Drop-The-Loser Rule

**Nancy Flournoy, Arkaitz Galbete, José Antonio Moler, and Fernando Plo**

**Abstract** In the framework of clinical trials, legal and ethical restrictions make a population model unrealistic for sampling. Randomization tests are a viable alternative to classical inference. Their theoretical properties depend heavily on the random rule used to allocate patients to treatments, so that Ad-Hoc theoretical studies are necessary for each allocation design. In this paper, we obtain theoretical results for randomization tests when the drop-the-loser rule is used.

## 1 Introduction

Consider establishing the superiority of one *treatment* with respect to another. A *treatment* can be an industrial procedure, a new surgical procedure, a new pharmaceutical product, etc. Herein randomization refers to the random allocation of individuals participating in a controlled clinical trial where the efficacy of a treatment, say *treatment 1*, is compared with a control treatment, say *treatment 2*. We assume also that the responses are immediate and dichotomous with success probabilities $p_1$ and $p_2$, respectively.

The use of randomization in the context of clinical trials is studied and vindicated in Rosenberger and Lachin (2002). However, it has been a controversial topic

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among statisticians as can be seen in Kempthorne (1977) and the references therein. Nowadays, the use of randomization is firmly established in protocols for designing clinical trials and this is accepted even by non-randomizers; see, for instance Aickin (2001).

A controversial topic now is the use of randomization tests as the inferential procedure to be applied under randomized allocations; see Basu (1980) and the comments that follow that paper. In Rosenberger and Lachin (2002, Chap. 7), randomization based inference (RBI) is considered more adequate than a population model for analyzing clinical trials because, among other reasons, random sampling of patients from a target population is hard to accept. Randomization tests are also known as permutation tests, rerandomization tests and exact tests (Good 1993). They were first proposed in a pioneering work by Fisher (1935). The experiment is known in the statistical literature as *The Lady Tasting Tea*.

Pesarin and Salmaso (2010, Chap. 1), discuss classical criticisms about the use of permutation tests and present their adequacy under different conditions. They also provide an updated revision on permutation tests. In Sect. 1.3, they claim that a heuristic approach to constructing permutation tests, based on intuitive reasoning, is the most commonly adopted approach for *non-complex statistical designs* (Edgington 1987; Good 1993). The heuristic approach is also followed in our paper, as in Pesarin and Salmaso (2010, Sect. 1.8), for a similar problem.

Edgington (1987, p. 1), describes RBI as follows: Given the experimental data, $\mathbf{x}$, a statistic $T(\mathbf{x})$ is computed. Then, the data are permuted repeatedly in a manner consistent with the random assignment procedure, and the statistic is computed for each of the resulting data permutations. Suppose that a one-sided significance test with significance level $\alpha$ is applied to accept or reject a null hypothesis. As usual, the null hypothesis for a randomization test is that there is no difference in the observed outcomes whatever the allocation. RBI proceeds by computing the probability that the random assignment procedure provides a permutation for which the test statistic is greater than the observed value $T(\mathbf{x})$. In other words, the p-value associated with $T(\mathbf{x})$ is computed. If this probability is smaller than $\alpha$, the null hypothesis is rejected.

RBI is conditional on the responses obtained and requires calculating the value of the test statistic for each permutation of the assignments that is consistent with the allocation procedure, and also, with the probability of each assignment. Depending on the sample size and on the allocation method, complete enumeration of all the permutations can be infeasible. This is one of the principal drawbacks of RBI. However, several procedures allow one to avoid complete enumeration for small-to-moderate samples. For instance, in Hollander and Peña (1988) and Mehta et al. (1988), an algorithm shortens the calculations and both Plamadeala and Rosenberger (2012, Sect. 1.6) and Pesarin and Salmaso (2010) use Monte-Carlo techniques to approximate the exact p-values. For large sample sizes, a central limit theorem for the test statistic $T$ is one way to approximate the p-value; see, for instance, Rosenberger and Lachin (2002, Chap. 14). Asymptotic results are also useful in sequential monitoring techniques (Zhang et al. 2007).

Another important statistical issue when randomization tests are used concerns the use of conditional or unconditional tests. Assume that $n$ individuals participate

in the trial. Let $N_{n1}$ be the number of patients randomly allocated to treatment $A$ and assume that $N_{n1} = n_1$. When a conditional randomization-based test is applied, the p-value of $T(\cdot)$ is obtained under the condition that $N_{n1} = n_1$. Otherwise, we say that an unconditional test has been applied.

Observe that $n_1$ can reach 0 or $n$, or be close to them, specially when $n$ is small. The use of conditional tests is advised by Cox (1982) when the number of patients allocated to each treatment is ancillary. This is the case for Efron's design (Efron 1971) where the present allocation depends only on the previous allocations of patients. More precisely, by tossing a biased-coin with a fixed probability $p_0 > 1/2$, the patient is allocated to the underrepresented treatment. Allocation is random when there is balance between treatments. However, with response-driven adaptive designs, the distribution of $N_{n1}$ depends on the success probabilities and, so, it is not ancillary and the use of a conditional test is not justified with Cox's arguments.

There exists a wide catalogue of response-driven designs in the literature (Hu and Rosenberger 2006). Primary classes are the biased-coin designs and the urn designs. In Rosenberger and Lachin (2002, Sect. 11.4), an overview of RBI for response-driven designs is provided but most of the references focus on the randomized play-the-winner rule. As can be observed in a comparative study of several response-adaptive designs in Rosenberger and Hu (2004), the play-the-winner rule is not competitive among them. There, two designs are outstanding due to their good compromise between ethics and inference. One of them is the biased coin design presented in Hu and Zhang (2004) for $\gamma = 2$. The other one is the urn design introduced in Ivanova (2003) which is named *drop the loser rule* (*DTL design* in the sequel).

In a comparative study with a wider range of response-adaptive designs (Flournoy et al. 2012), both designs remain advantageous for their ethical and inferential properties. In Flournoy et al. (2012), graphics are used to position at once several response-adaptive designs with respect to an ethical and an inferential criteria.

In this paper, for space limitations, we will focus only on permutation test statistics based on the sum of responses when the DTL design is used to allocate patients. Our principal target is to calculate p-values for those test statistics. For this purpose, we provide an efficient algorithm which makes it computationally feasible to obtain p-values for the test statistic that provides the difference of successes between both treatments.

In Sect. 2, the DTL design is described. Notation and asymptotic results under the population model are also given for the DTL design. In Sect. 3 necessary mathematical formalisms are given for handling the DTL design when patient responses are assumed known. Then, an algorithm to obtain exact p-values for a basic test statistic is provided. The paper closes with some final comments.

## 2 Response Adaptive Designs. DTL Rule

In a randomized clinical trial, patients arrive sequentially and are randomly allocated to a treatment. In order to allocate the presenting patient randomly, several rules can

be applied. Three kinds of allocation designs can be distinguished depending on the previous information that is used to determine the allocation of the patient. If no previous information is used, we have a completely randomized design, for instance, allocation by tossing a coin. If the dependence is only on the previous allocations, the rule is adaptive, as in Efron (1971). Finally, if the dependence also includes the previous responses the rule is response-adaptive, as is the DTL rule that was introduced in Ivanova (2003).

The DTL rule is an urn design that works as follows. Initially the urn contains $w$ balls of each type 1 and type 2 and one ball of type 0, which in the literature is also called an immigration ball. When a patient arrives, extract a ball from the urn. If the ball is of type 0, no treatment is assigned and one ball of type 1 and one ball type 2 are added into the urn. If the ball is not of type 0, the treatment associated with the ball drawn is assigned. If the treatment is successful, the ball is replaced in the urn; otherwise, the ball is not replaced. The number of type 1 balls in the urn after the $m$-th replacement and the total number of balls are denoted, respectively, by $W_m$ and $T_m$. So $W_0 = w$ and $T_0 = 2w + 1$. Observe that, due to the presence of a type 0 ball, the number of replacements is not necessarily equal to the number of patients.

In order to express the model mathematically, we need to introduce some notation. For extraction $m$, $m = 1, 2, \ldots$, $\varphi_m$ is a random variable which equals 1 when a ball of type 1 is drawn, $-1$ when the ball is of type 2 and 0 when the ball is of type 0.

Let $\{\tau_m\}_{m\geq 0}$ be a sequence of stopping times which represent, for each $m$, the number of patients allocated up to the $m$-th replacement. Observe that if $\tau_0 = 0$ then, for $m \geq 1$, $\tau_m = \sum_{i=1}^{m} \varphi_i^2$.

The responses of the $k$-th patient to treatment $j = 1, 2$ are denoted by $Z_{kj}$. We assume that these responses are immediate. Obviously, this is a mathematical formalism because only one response is observed. But this notation will be useful to establish the following assumption which is needed in this section:

(**A1**) For each $j$, $j = 1, 2$, and $k = 1, 2, \ldots$, we assume that $\{Z_{kj}\}$ is a sequence of independent and identically distributed random variables.

Finally, let $\mathscr{F}_m = \sigma(\varphi_i, Z_{\tau_i 1}, Z_{\tau_i 2} : i = 1, \ldots, m)$ denote the natural sigma algebra generated by all the previous allocations and responses up to the $m$-th replacement. Then

$$P(\varphi_{m+1} = 1|\mathscr{F}_m) = W_m/T_m, \qquad P(\varphi_{m+1} = 0|\mathscr{F}_m) = 1/T_m. \tag{1}$$

Let $\Delta_m = \sum_{i=1}^{m} \varphi_i$ represent the imbalance between the number of patients allocated to each treatment at the $m$-th replacement. Observe that $N_{m1}$ and $N_{m2}$, the number of patients allocated to treatment 1 and treatment 2 up to and including the $m$-th replacement, can be expressed as $N_{m1} = \sum_{i=1}^{m}(\varphi_i + \varphi_i^2)/2$ and $N_{m2} = \sum_{i=1}^{m}(\varphi_i^2 - \varphi_i)/2$. So, the number of type 0 balls drawn up to the $m$-th replacement is $N_{m0} = m - N_{m1} - N_{m2}$.

Zhang et al. (2011) have recently presented theoretical properties for a wide range of urn models under a unified approach called immigrated urn models. In

addition to this, applications of immigrated urn models in clinical trials are also studied under the assumption of a population model. The DTL design is a particular immigrated urn model for which the expected number of added balls in each step, according to the outcome of a treatment, is less than the number of drawn balls, which is 1. Then, from Zhang et al. (2011), among many more theoretical properties for some stochastic processes associated with the DTL design, central limit theorems for the success proportions in each treatment are obtained. These establish the theoretical basis for using classical test statistics for the equality of treatments.

In the following section we assume that the patients' responses are known. In such a situation, the population model which must be assumed for direct application of the results in Zhang et al. (2011), no longer holds.

## 3 Randomization Based Inference for the DTL Design

The underlying idea in RBI is that given the responses of the patients, under the null hypothesis of no difference between treatments, the only randomness in the process is due to the allocation of patients. So that, in order to make inferences we must obtain the conditional probability distribution of the test statistic given the responses for any allocation that can possibly be made with the DTL design. We introduce some notation in order to give a formal presentation of RBI tools.

Let $\mathbf{a}_n := (a_1, a_2, \ldots, a_n)$ contain the responses of $n$ patients participating in the experiment. In this section we assume that this vector is known. To reflect this dependence, we include a superscript $\mathbf{a}$ in the notation of Sect. 2. Then, $\varphi_m^{\mathbf{a}}$ is the random variable which points to the type of ball of the $m$-th extraction, given the responses available up to the $(m-1)$-th replacement. The number of patients treated up to the $m$-th replacement is equal to the number of times that a type 0 ball has not been drawn.

Observe that variables $\tau_m$, $\Delta_m$, $N_{m1}$ and $N_{m2}$ are obtained using the random variable $\varphi_m$. We add the superscript $\mathbf{a}$ to these random variables to mark their dependence on $\mathbf{a}$.

Let $S_n$ be the difference between the number of successes in the two treatments once $n$ patients have responded under the DTL rule. Observe that a type 0 ball can be extracted in each step and this implies that the number of extractions of type 0 balls between two allocations is an unbounded random variable. It will be helpful to define $S_m^*$, the difference between the number of successes up to and including the $m$-th extraction: $S_m^* := \sum_{i=1}^{m} a_{\tau_i} \varphi_i^{\mathbf{a}}$.

We are going to take $S_n$ to be the permutation test statistic for studying the equality of treatments. This choice responds to the arguments given in Sect. 2.5 in Pesarin and Salmaso (2010) where test statistics based on sums of responses are advised. Our target now is to obtain an algorithm for finding the exact value of $P(S_n = s)$ for any $s$ in the interval $[-n, n]$.

Observe that the event $\{S_n = s\}$ is equal to a union of disjoint events indexed by $m \geq n$:

$$P(S_n = s) = \sum_{m=n}^{\infty} P\big(S_m^* = s, \tau_m^{\mathbf{a}} = n, \varphi_m^{\mathbf{a}} \neq 0\big). \tag{2}$$

The following technical proposition will be crucial for computing the exact p-values of the randomization test based on the $S_n$ statistic for the DTL design.

**Proposition 1** *Assume that the DTL design is applied and that n patients have been allocated to two treatments by means of the DTL design. Let* $\mathbf{a} := (a_1, a_2, \ldots, a_n)^\top$ *denote the sequence of responses. Consider for each replacement* $m \geq 1$ *the random variables* $\varphi_m^a$, $\Delta_m^{\mathbf{a}}$ *and* $\tau_m^{\mathbf{a}}$ *defined as before. Then,*

$$P\big(S_m^* = s, \tau_m^{\mathbf{a}} = n, \varphi_m^{\mathbf{a}} \neq 0\big), \quad -n \leq s \leq n,$$

*can be calculated with a recursion formula with initial values*

$$P\big(S_1^* = 0, \tau_1^{\mathbf{a}} = 0, \Delta_1^{\mathbf{a}} = 0\big) = \frac{1}{2w+1},$$

$$P\big(S_1^* = 0, \tau_1^{\mathbf{a}} = 1, \Delta_1^{\mathbf{a}} = -1\big) = P\big(S_1^* = 0, \tau_1^{\mathbf{a}} = 1, \Delta_1^{\mathbf{a}} = 1\big) = (1 - a_1)\frac{w}{2w+1},$$

$$P\big(S_1^* = -1, \tau_1^{\mathbf{a}} = 1, \Delta_1^{\mathbf{a}} = -1\big) = P\big(S_1^* = 1, \tau_1^{\mathbf{a}} = 1, \Delta_1^{\mathbf{a}} = 1\big) = a_1\frac{w}{2w+1}.$$

*Proof* Observe that for each extraction $m \geq 1$ we have

$$\begin{aligned} &P\big(S_m^* = s, \tau_m^{\mathbf{a}} = k, \Delta_m^{\mathbf{a}} = i, \varphi_m^{\mathbf{a}} = r\big) \\ &\quad = P\big(\varphi_m^{\mathbf{a}} = r | S_{m-1}^* = s - a_k r, \tau_{m-1}^{\mathbf{a}} = k - r^2, \Delta_{m-1}^{\mathbf{a}} = i - r\big) \\ &\qquad \times P\big(S_{m-1}^* = s - a_k r, \tau_{m-1}^{\mathbf{a}} = k - r^2, \Delta_{m-1}^{\mathbf{a}} = i - r\big). \end{aligned} \tag{3}$$

On the other hand, from the dynamics of the urn, for each extraction $m$, we have that

$$T_m^{\mathbf{a}} = 2w + 1 + 2m - 3\tau_m^{\mathbf{a}} + \sum_{j=1}^{\tau_m^{\mathbf{a}}} a_j, \qquad 2W_m^{\mathbf{a}} = T_m^{\mathbf{a}} - 1 + S_m^* - \Delta_m^{\mathbf{a}}.$$

Consequently, for $r = 1$, $r = 0$ or $r = -1$ we can explicitly express

$$P\big(\varphi_m^{\mathbf{a}} = r | S_{m-1}^* = l_1, \tau_{m-1}^{\mathbf{a}} = l_2, \Delta_{m-1}^{\mathbf{a}} = l_3\big) = \frac{r^2(l_1 - l_3) + r(T_{m-1}^{\mathbf{a}} - 1) + 2}{2T_{m-1}^{\mathbf{a}}}. \tag{4}$$

Finally, a recursion is obtained by plugging (4) into (3) and observing that

$$P\big(S_m^* = s, \tau_m^{\mathbf{a}} = n, \varphi_m^{\mathbf{a}} = r\big) = \sum_{i=-n}^{n} P\big(S_m^* = s, \tau_m^{\mathbf{a}} = n, \Delta_m^{\mathbf{a}} = i, \varphi_m^{\mathbf{a}} = r\big).$$

□

**Table 1** Proportion of times that the null hypothesis is rejected with the test statistic $S_n$ in a randomization test in 10000 replications of the DTL rule

| $p_1$ | $p_2$ | $n$ | | |
|---|---|---|---|---|
| | | 25 | 50 | 100 |
| 0.9 | 0.3 | 0.679 | 0.986 | 1 |
| 0.9 | 0.5 | 0.347 | 0.759 | 0.987 |
| 0.9 | 0.7 | 0.096 | 0.306 | 0.607 |
| 0.7 | 0.3 | 0.323 | 0.728 | 0.971 |
| 0.7 | 0.7 | 0.018 | 0.017 | 0.017 |

When randomization is made with the DTL design, Proposition 1 and Eq. (2) allow us to obtain exact calculations of p-values when RBI is used with the test statistic $S_n$.

*Remark 1* Proposition 6 in Sect. 2.5 of Pesarin and Salmaso (2010) gives a formal argument, based on asymptotic tools, for choosing a permutation test as an alternative to the classical parametric test. Assuming the population model, when a response-adaptive design is used for allocations, and $S_{ni}$ is the total number of successes with treatment $i$, $i = 1, 2$ then $(S_{n1}, S_{n2}, N_{n1})$ are jointly sufficient for estimating $p_1$ and $p_2$ (Rosenberger and Lachin 2002, p. 193), where $n$ is the sample size. So a good estimator of $p_1 - p_2$ is $T_n := S_{n1}/N_{n1} - S_{n2}/N_{n2}$. Let $T_n^{\mathbf{a}}$ be the difference between success proportions for each treatment when the $n$ patients have been allocated with the DTL rule. Reasoning as in (2), it follows that if $T_m^{*\mathbf{a}}$ is the difference of success proportions up to and including extraction of the $m$-th ball, then

$$\begin{aligned} P\left(T_n^{\mathbf{a}} = t\right) &= \sum_{m=n}^{\infty} \sum_{k=0}^{n} P\left(T_m^{*\mathbf{a}} = t, \Delta_m^{\mathbf{a}} = 2k - n, \tau_m^{\mathbf{a}} = n, \varphi_m^{\mathbf{a}} \neq 0\right) \\ &= \sum_{m=n}^{\infty} \sum_{k=0}^{n} P\left(S_m^{*} = r(k), \Delta_m^{\mathbf{a}} = 2k - n, \tau_m^{\mathbf{a}} = n, \varphi_m^{\mathbf{a}} \neq 0\right), \end{aligned} \tag{5}$$

where $r(k) = (2t \times k \times (n-k) - (n-2k)\sum_{i=1}^{n} a_i)/n$. Now, using Proposition 1, any p-value for the distribution of $T_n^{\mathbf{a}}$ can be obtained.

In Table 1, a simulation study of the power of the permutation test with $S_n$ is presented. The distribution of $S_n$ changes with the sequence of responses. So, in each replication of the clinical trial, we obtain a p-value which indicates if the null hypothesis must be rejected and, finally, we obtain the proportion of simulations in which the null has been rejected. This is not exactly the power function that is well established in the parametric setting. But it is the usual procedure used to study power in RBI studies Good (1993, e.g., Sect. 13.7).

## 4 Final Comments

Sections 2 and 3 can be replicated for other response-adaptive designs. However, Proposition 1 should be adapted to the adaptive-response allocation rule because, in this case, its proof heavily relies on the dynamics of the DTL design. If the long run distribution of the permutation test statistic is deemed reliable, it is more practical to use it than the exact distribution to characterize the randomization test. This motivates interest in obtaining central limit theorems. These kind of studies follow the paradigmatic results on central limit theorems that were obtained in this context in the seminal paper of Smythe and Wei (1983). Conditions on the set of responses that appear in Smythe and Wei can be quite stringent for any vector **a**.

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## References

Aickin, M.: Randomization, balance, and the validity and efficiency of design-adaptive allocation methods. J. Stat. Plan. Inference **94**, 97–119 (2001)
Basu, D.: Randomization analysis of experimental data: The Fisher randomization test. J. Am. Stat. Assoc. **75**, 575–595 (1980)
Cox, D.R.: A remark on randomization in clinical trials. Util. Math. **21A**, 245–252 (1982)
Edgington, E.S.: Randomization Tests. Dekker, New York (1987)
Efron, B.: Forcing a sequential experiment to be balanced. Biometrika **58**, 403–417 (1971)
Fisher, R.A.: The Design of Experiments. Oliver & Boyd, Edinburgh (1935)
Flournoy, N., Haines, L.M., Rosenberger, W.: A graphical method for comparing response-adaptive randomization procedures. Under revision. Available at http://www.newton.ac.uk/preprints/NI12009.pdf
Good, P.: Permutation Tests. Springer, New York (1993)
Hollander, M., Peña, E.: Nonparametric tests under restricted treatment-assignment rules. J. Am. Stat. Assoc. **83**, 1144–1151 (1988)
Hu, F., Rosenberger, W.F.: The Theory of Response-Adaptive Randomization in Clinical Trials. Wiley, New York (2006)
Hu, F., Zhang, L.: Asymptotic properties of doubly adaptive biased coin designs for multitreatment clinical trials. Ann. Stat. **32**, 268–301 (2004)
Ivanova, A.: A play-the-winner-type urn design with reduced variability. Metrika **58**, 1–13 (2003)
Kempthorne, O.: Why randomize? J. Stat. Plan. Inference **1**, 1–25 (1977)
Mehta, C.R., Patel, N.R., Wei, L.J.: Constructing exact significance tests with restricted randomization rules. Biometrika **75**, 295–302 (1988)
Pesarin, F., Salmaso, L.: Permutation Tests for Complex Data, Theory, Applications and Software. Wiley, Chichester (2010)
Plamadeala, V., Rosenberger, W.F.: Sequential monitoring with conditional randomization tests. Ann. Stat. **40**, 30–44 (2012)
Rosenberger, W.F., Hu, F.: Maximizing power and minimizing treatment failures in clinical trials. Clin. Trials **1**, 141–1477 (2004)
Rosenberger, W.F., Lachin, J.M.: Randomization in Clinical Trials. Theory and Practice. Wiley, New York (2002)

Smythe, R.T., Wei, L.J.: Significance tests with restricted randomization design. Biometrika **70**, 496–500 (1983)
Zhang, Y., Rosenberger, W.F., Smythe, R.T.: Sequential monitoring of randomization tests: stratified randomization. Biometrics **63**, 865–872 (2007)
Zhang, L., Hu, F., Cheung, S.H., Chan, W.S.: Immigrated urn models—theoretical properties and applications. Ann. Stat. **39**, 643–671 (2011)

# Adaptive Bayesian Design with Penalty Based on Toxicity-Efficacy Response

**Lei Gao and William F. Rosenberger**

**Abstract** The penalized local *D*-optimal design is introduced by Dragalin and Fedorov (J. Stat. Plan. Inference 136:1800–1823, 2006). We extend the method to the Bayesian realm for the bivariate Gumbel model. Then we conduct a simulation study to compare our method with the trade-off methods of Thall and Cook (Biometrics 60:684–693, 2004). Various measures are employed to present a thorough understanding of both the methods. Our method is more favorable in terms of consistency across simulations and information gain.

## 1 Introduction

The ultimate goal of dose finding studies is to understand the relationship between doses and responses. The relationship, sometimes nonlinear, can be discovered by parametric and nonparametric methods. The parametric approach is preferred when the relation can be approximated by a parametric model and the sample size is small, such as early phase clinical trials. For parametric models, statisticians have control over how much information can be gained, in terms of the precision of parameter estimation. An ideal goal is to maximize the parameter estimation precision even on a limited sample. Examples of designs that optimize the dose-response information are introduced by Perevozskaya et al. (2003) and Dragalin and Fedorov (2006), among others. In these designs, doses are allocated in such a way that a function of the Fisher information matrix is optimized.

Univariate models are appropriate for modeling toxicity or efficacy, separately as in phase I or II trials. However, sometimes there are both toxicity and efficacy responses, which can be accommodated by bivariate response modeling. Two candidate bivariate models are the Cox model and Gumbel model as illustrated by Dragalin and Fedorov (2006). The common thread to designing experiments under all these models is the optimization of a function of the Fisher information matrix.

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In addition to maximizing the information gain, a difficulty arises from ethical considerations. A design may be optimal for efficiency or precision, but it may also allocate participants at a high dose level with high toxicity. Therefore, achieving a balance between the information gain and participants' protection becomes important in these designs. There are some methods to address this problem: the restricted dose space method (Mats et al. 1998) sets an upper bound for the dose; the local penalty function method (Dragalin and Fedorov 2006) penalizes high doses with high toxicity and low doses with low efficacy through a penalty function. The philosophy in the constrained and penalized methods is to maximize the information gain over a restricted space. From a different point of view, Thall and Cook (2004) consider desirability contours as trade-offs between efficacy and toxicity to protect patients. The doses with high desirabilities are those with low toxicity and high efficacy. Their philosophy is to maximize the desirability by sequentially assigning patients to the most desirable dose. Therefore, an interesting question is which design philosophy has better performance with respect to important outcome measures.

To answer the question, we extend the penalized method to the Bayesian realm and carry out a simulation study of our penalized approach and the trade-off approach in a setting similar to that used by Thall and Cook (2004). The two methods are compared on various measures with respect to desirability and information gain. The paper is organized as follows. In Sect. 2, we introduce the bivariate Gumbel model and present the Bayesian $D$-optimality criterion. In Sect. 3, we introduce the adaptive design in a clinical setting. Then we include the simulation study details, discuss measures, and present the results in Sect. 4.

## 2 Bivariate Gumbel Model

The Gumbel model is a bivariate extension of the logistic model. In a Gumbel model, we have a pair of binary responses $(Y, Z)$, where $Y = 1$ indicates efficacy and $Z = 1$ indicates toxicity. They equal zero otherwise. Let $x$ denote a transformed dose level in some dose space $\mathscr{X}$ and $\alpha$ a parameter to characterize the correlation between toxicity and efficacy. We define the function (Dragalin and Fedorov 2006)

$$G(y,z) = F(y)F(z)\big\{1+\alpha\big[1-F(y)\big]\big[1-F(z)\big]\big\}, \quad -\infty < y,z < +\infty,\ |\alpha| < 1,$$

and $F(y)$ is the logistic function $F(y) = 1/(1+\mathrm{e}^{-y})$. We follow Thall and Cook (2004) by assuming a quadratic dose efficacy effect $x_E = \mu_E + \beta_{E1}x + \beta_{E2}x^2$, and a linear dose toxicity effect $x_T = \mu_T + \beta_T x$. Then the cell probabilities, $p_{yz} = Pr(Y = y, Z = z)$, form a multinomial distribution given by

$$\begin{aligned} p_{11} &= G(x_E, x_T), & p_{10} &= F(x_E) - G(x_E, x_T),\\ p_{01} &= F(x_T) - G(x_E, x_T), & p_{00} &= 1 - G(x_E, +\infty) - G(+\infty, x_T)\\ & & &\quad + G(x_E, x_T). \end{aligned}$$

The Fisher information matrix $I(x;\theta)$ can be obtained in the same fashion as in Dragalin and Fedorov (2006).

In clinical trials, a design is a discrete measure on a dose space $\mathscr{X}$:

$$\xi = \begin{pmatrix} x_1 & x_2 & \cdots & x_{n-1} & x_n \\ w_1 & w_2 & \cdots & w_{n-1} & w_n \end{pmatrix}, \tag{1}$$

where $x_i$'s are doses and $w_i$'s are corresponding weights with sum one. The single point design at $x$ is denoted by $\delta_x$. The Fisher information matrix for the design $\xi$ in (1) is $M(\xi;\theta) = \sum_i w_i I(x_i;\theta)$.

To gain maximal information, the locally $D$-optimal design minimizes the volume of the asymptotic variance ellipsoid, which is inversely proportional to the determinant of the Fisher information matrix,

$$\Phi(\xi,\theta) = \left|M^{-1}(\xi;\theta)\right|, \tag{2}$$

over a design space $\Xi$. Chaloner and Larntz (1989) extended the two parameter local optimal designs to the Bayesian realm, where the model parameters are allowed to vary according to prior distributions. Assume that $\theta$ follows a prior distribution $\Theta(\eta)$ and $\pi(\theta|\mathscr{D};\eta)$ is a posterior distribution given data $\mathscr{D}$. The Bayesian $D$-optimality criterion maximizes

$$\Psi(\xi) = \mathrm{E}_{\theta|\pi} \log \Phi(\xi,\theta) = \int \log \Phi(\xi,\theta)\pi(\theta|\mathscr{D};\eta)\,\mathrm{d}\theta. \tag{3}$$

We use "$E_{\theta|\pi}$" to denote the conditional expectation under the posterior distribution $\pi$ throughout the paper.

To protect patients from being assigned to too high or too low doses, Dragalin and Fedorov (2006) introduce the penalty function $c(x;\theta) = [p_{10}(x,\theta)]^{-1}[1 - p_{01}(x,\theta) - p_{11}(x,\theta)]^{-1}$, to encourage efficacious doses and penalize toxic ones. The total cost is $C(\xi;\theta) = \sum_i w_i c(x_i;\theta)$.

To incorporate Dragalin and Fedorov's penalized method into the Bayesian realm, we observe that the penalty function cannot be arbitrary. The extension can be made when the penalty function can be factored as the product of functions of doses $x$ and functions of the local parameter $\theta$, or when it does not depend on the local parameter. In our design, we choose the penalty function to be $c(x;\theta_\pi)$, by substituting the mean of the posterior distribution $\theta_\pi$ for $\theta$.

As in Dragalin and Fedorov (2006), the penalized Bayesian $D$-optimality solves the following equation:

$$\xi^* = \arg\min_{\xi} E_{\theta|\pi} \log \Phi\left\{\frac{M(\xi;\theta)}{C(\xi;\theta_\pi)}\right\}. \tag{4}$$

If we consider the derivative of $\Phi$ along a single point design $\delta_x$, then we can define the directional derivative $\phi$ by $\phi(x,\xi;\theta) = \mathrm{tr}[I(x;\theta)M^{-1}(\xi;\theta)]$.

The generalized equivalence theorem can be modified as the equivalence of the following three conditions:

1. $\xi^* = \arg\min_\xi E_{\theta|\pi} \log \Phi[M(\xi;\theta)/C(\xi;\theta_\pi)]$;

2. $\xi^* = \arg\min_\xi \max_x E_{\theta|\pi}[\phi(x,\xi;\theta) - \frac{c(x;\theta_\pi)}{C(x;\theta_\pi)}p]$;
3. $E_{\theta|\pi}\frac{C(x;\theta_\pi)}{c(x;\theta_\pi)}\phi(x,\xi^*;\theta) \le p, \forall x \in \mathscr{X}$. Equality is attained at the design points.

Atkinson et al. (2007) included a comprehensive treatment of the generalized equivalence theorem for local cases. Chaloner and Larntz (1989) considered Bayesian cases. Dragalin and Fedorov (2006) considered penalized cases.

## 3 Bayesian Adaptive Design with Penalty Function

In practice, we do not have accurate information on the true parameter values. Therefore we have to implement a design wisely so that we can estimate the parameter efficiently. Adaptive designs can serve this purpose well. Instead of assigning all patients at the same time, we assign them one by one as we maximize the optimality criterion (2) at each step.

Suppose our dose space is $\mathscr{X}$, either discrete or continuous. We identify the optimal weights of doses based on the prior information. To do this, we implement the penalized method and substitute the mean of the priors as the local parameter. After the initial $n_0$ doses are allocated, we need a sequential procedure to approximate the optimality in (4). Instead of using the first-order algorithm (Dragalin and Fedorov 2006), we use the idea proposed by Haines et al. (2003). Specifically, suppose the posterior distribution $\pi_n$ can be inferred through previous responses at step $n$. Then we choose the next dose as

$$x_{n+1} = \arg\min_x E_{\theta|\pi_n}\Phi\left(\frac{\sum_{i=1}^n I(x_i;\theta) + I(x;\theta)}{n+1}\frac{1}{\sum_{i=1}^n c(x_i;\theta_{\pi_n}) + c(x;\theta_{\pi_n})}\right). \tag{5}$$

As the above steps are iteratively processed, the adaptive design is expected to converge to its corresponding optimum design (not the one in (4)) and give precise parameter estimation. Roy et al. (2003) proved the convergence of the Bayesian sequential procedure for the location-scale family, in both unconstrained and constrained cases. However, the convergence of (5), as a "best intention design", is yet to be determined.

Thall and Cook (2004) proposed a different Bayesian adaptive design by introducing a desirability function that measures the distance between any toxicity-efficacy probability pair $(p_{01} + p_{11}, p_{10} + p_{11})$ to the pair (0,1). The algorithm starts from the lowest dose and escalates through steps. At each step, a cohort of three patients is assigned to the dose with the highest desirability according to the posterior information. If the expected toxicity is higher than a critical value, the algorithm stops. Thall and Cook (2004) show that the trade-off algorithm assigns the most patients to the most desirable dose. However, because the efficiency of estimation is not their primary concern, yet their algorithm does rely on parameter estimation, the trade-off method may not be robust to model misspecification. As a result, the algorithm may not be efficient compared with our algorithm with respect to participant protection.

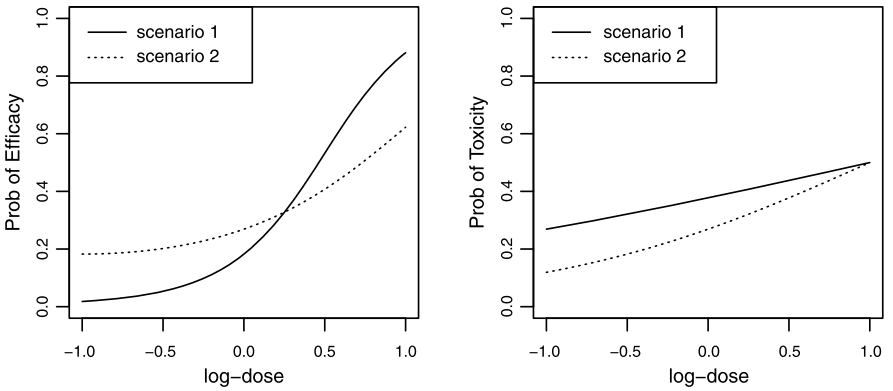


**Fig. 1** Probability of efficacy (*left*) and toxicity (*right*), over the design region for Scenarios 1 and 2. The probability of efficacy increases rapidly in Scenario 1. The probability of toxicity increases at similar rates in both the scenarios

## 4 Monte Carlo Simulation and Results

In this Monte Carlo study, we compare our penalized method with the trade-off method. We choose a similar setting to Thall and Cook (2004) in which the design sample size is 36 and the initial sample size is 3. We assume the dose-response curve follows a Gumbel model with true parameter $\theta_0 = (-1.5, 3, 0.5, -0.5, 0.5, 0.5)$ in Scenario 1 and $(-1, 1, 0.5, -1, 1, 0.5)$ in Scenario 2. The prior distribution is chosen almost the same as in Thall and Cook (2004): $\mu_E, \beta_{E1}, \beta_{E2}, \mu_T$ and $\beta_T$ are independently normally distributed with means and standard deviations $(-1.496, 1.113)$ for $\mu_E$, $(1.180, 0.069)$ for $\beta_{E1}$, $(0.149, 1.192)$ for $\beta_{E2}$, $(-0.619, 0.941)$ for $\mu_T$ and $(0.587, 1.659)$ for $\beta_T$. The different setting is the correlation parameter $\alpha$, which is assumed to follow a uniform distribution on $[-1, 1]$. All parameters are independently distributed. Because there are six parameters, it is computationally infeasible to compute six-dimensional integrations over the posterior distribution. Thus we employ Monte Carlo methods to approximate the expectations in a six-dimensional space. Specifically, we generate two chains, each with 5000 $\theta$'s, and approximate the expectation by the average.

The raw dose $d$ is transformed to $x$ in the same way as in Thall and Cook (2004): $x_i = \log(d_i) - \text{mean}(d)$. Therefore, the dose space $\mathscr{X}$ consists of $-0.79$, $-0.10$, 0.30 and 0.59 instead of the four raw doses, 0.25, 0.5, 0.75 and 1. We use the same desirability function as that defined by Thall and Cook (2004) and obtain their desirabilities as $-0.194$, $-0.137$, 0.021 and 0.161 in Scenario 1 and 0.002, 0.031, 0.080 and 0.109 in Scenario 2. Their probabilities of efficacy and toxicity are $(0.027, 0.290)$, $(0.142, 0.366)$, $(0.368, 0.414)$ and $(0.611, 0.449)$ in Scenario 1 and $(0.186, 0.143)$,$(0.250, 0.249)$,$(0.343, 0.332)$ and $(0.442, 0.399)$ in Scenario 2. The true parameters are chosen so that the efficacy increases faster than toxicity in Scenario 1, and they have comparable increasing rate in Scenario 2, as shown in Fig. 1.

We implement 5000 simulations for each scenario. As shown in Sect. 3, one simulation of the penalized algorithm starts by assigning 3 patients to the lowest dose for a fair comparison. Then we begin the iteration after a few steps. Specifically, we estimate the posterior distribution based on the responses and the prior using MCMC. Then we assign the next patient to an optimal dose as in (5). Also we obtain the bivariate response for each patient according to the true model. We continue the iterations until all 36 patients are assigned. The trade-off algorithm is implemented in the same manner as in Thall and Cook (2004).

The two algorithms will be compared on measures from two categories, one related to information gain and the other related to toxicity and efficacy trade-off desirability. Because there are incomplete trials in the trade-off algorithm when the algorithm stops before all patients are assigned, we simulate 5000 complete trials and compare them with the penalized method on the following measures:

1. Expected number of toxicities, i.e., events of $Z = 1$, denoted by "Toxicity";
2. Expected number of efficacies, i.e., events of $Y = 1$, denoted by "Efficacy";
3. Expected number of efficacies but not toxicities, i.e., events of $Y = 1$ and $Z = 0$, denoted by "Eff-Tox";
4. Expected average desirabilities across four doses, denoted by "Desirability" (larger is better);
5. Expected number of patients assigned to the dose with the highest desirability, denoted by "DesHigh";
6. Expected precision, $\log |M(\xi, \theta_0)|^{-1/6}$, denoted by "Precision" (smaller is better);
7. Expected total cost, $C(\xi, \theta_0)$, denoted by "Cost" (smaller is better);
8. Expected information loss per unit cost, $|M(\xi, \theta_0)|^{1/6}/C(\xi, \theta_0)$, denoted by "Info/Cost" (larger is better).

Note that desirability is defined in Thall and Cook (2004). Also, the last three measures are used in Dragalin and Fedorov (2006). The trade-off design (Thall and Cook 2004) is expected to assign most participants to the most desirable dose. On the other hand, the penalized design (Dragalin and Fedorov 2006) is expected to achieve a high Info/Cost ratio, which balances the parameter estimation precision and the ethical cost.

As for the simulation results, we have 5498 simulations in Scenario 1 and 5271 simulations in Scenario 2 until the trade-off algorithm produces 5000 complete trials in each scenario. Table 1 includes the results of the two methods for Scenario 1 and Table 2 for Scenario 2. They perform similarly with respect to protecting the patients, since they yield similar values for Toxicity, Efficacy and Eff-Tox. For desirability considerations, the trade-off method is expected to outperform the penalized method. However, the penalized method performs better by putting more patients on the dose with highest desirability in both scenarios. The penalized method also achieves a higher average desirability than the trade-off method in Scenario 1. When it comes to the precision measure, the penalized method performs better with more estimation information (or a low Precision value) and less cost as expected. As a result, the penalized method has larger and better Info/Cost ratios. Note that our penalized method has smaller Monte-Carlo variation and performs more consistently

**Table 1** Summary of Monte-Carlo simulations for Scenario 1. The mean and standard deviation of the measures defined in Sect. 4 across the 5000 complete trials are listed for each method

| Measure | Penalized | | Trade-off | |
|---|---|---|---|---|
| | mean | (sd) | mean | (sd) |
| Toxicity | 14.69 | (2.80) | 14.51 | (2.61) |
| Efficacy | 15.36 | (3.33) | 14.40 | (4.89) |
| Eff-Tox | 7.78 | (2.92) | 7.24 | (2.58) |
| Desirability | 0.012 | (0.005) | 0.0079 | (0.019) |
| DesHigh | 22.04 | (5.16) | 17.55 | (10.03) |
| Precision | 29.48 | (2.68) | 33.78 | (3.57) |
| Cost | 14.13 | (0.198) | 18.83 | (9.12) |
| Info/Cost | 0.0024 | (0.0002) | 0.0018 | (0.0005) |

**Table 2** Summary of Monte-Carlo simulations for Scenario 2. The mean and standard deviation of the measures defined in Sect. 4 across the 5000 complete trials are listed for each method

| Measure | Penalized | | Trade-off | |
|---|---|---|---|---|
| | mean | (sd) | mean | (sd) |
| Toxicity | 10.68 | (2.47) | 11.03 | (2.69) |
| Efficacy | 11.85 | (2.96) | 12.07 | (3.37) |
| Eff-Tox | 7.1 | (2.44) | 7.34 | (3.54) |
| Desirability | 0.016 | (0.004) | 0.017 | (0.006) |
| DesHigh | 16.40 | (6.49) | 14.9 | (10.30) |
| Precision | 57.46 | (4.56) | 68.83 | (7.01) |
| Cost | 7.17 | (1.11) | 7.40 | (0.20) |
| Info/Cost | 0.0025 | (0.0004) | 0.0020 | (0.0002) |

due to more efficient parameter estimation. Overall, the penalized method performs more stably and provides more information than the trade-off method. The effect is amplified when efficacy increases faster than toxicity.

## 5 Conclusion

We propose a Bayesian version of the adaptive design of Dragalin and Fedorov (2006) to penalize doses with too high toxicity or too low efficacy. The penalized method is compared with the trade-off method in Thall and Cook (2004) in two simulation scenarios. The penalized method performs better when it comes to information gain. It also assigns more patients to the most desirable dose. The penalized method performs more consistently by having a smaller Monte-Carlo simulation variation. The advantage is pronounced when the efficacy increases at a higher rate than toxicity.

There are some limitations to our study. First, we assume the true toxicity-efficacy relation arises from a Gumbel model. However, such a parametric model may fail to represent the toxicity-efficacy relationship. Also, most of the measures are only applicable to complete trials. Here, a portion of incomplete trials due to the trade-off algorithm stopping rules are excluded from the comparison. In addition, we do not have a scenario in which the toxicity increases at a high rate, because the stopping rule would generate too many incomplete trials leading to an inappropriate comparison.

Future work may include flexible modeling which can handle complex toxicity-efficacy relations. Also, the penalized method can be incorporated with a stopping rule to improve the protection of participants. Next, measures that are applicable to incomplete cases should be introduced for the evaluation. With these added features, simulations of more scenarios would be tested.

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## References

Atkinson, A.C., Donev, A.N., Tobias, R.: Optimum Experimental Design, with SAS. Oxford University Press, Oxford (2007)

Chaloner, K., Larntz, K.: Optimal Bayesian design applied to logistic regression experiments. J. Stat. Plan. Inference **21**, 191–208 (1989)

Dragalin, V., Fedorov, V.: Adaptive designs for dose-finding based on efficacy-toxicity response. J. Stat. Plan. Inference **136**, 1800–1823 (2006)

Haines, L.M., Perevozskaya, I., Rosenberger, W.F.: Bayesian optimal designs for phase I clinical trials. Biometrics **50**, 591–600 (2003)

Mats, V.A., Rosenberger, W.F., Flournoy, N.: Restricted optimality for phase I clinical trials. In: Flournoy, N., Rosenberger, W.F., Wong, W.K. (eds.) New Developments and Applications in Experimental Design, pp. 50–61. Institute of Mathematical Statistics, Hayward (1998)

Perevozskaya, I., Rosenberger, W.F., Haines, L.M.: Optimal design for the proportional odds model. Can. J. Stat. **31**, 225–235 (2003)

Roy, A., Ghosal, S., Rosenberger, W.F.: Convergence properties of sequential Bayesian *D*-optimal designs. J. Stat. Plan. Inference **139**, 425–440 (2003)

Thall, P.F., Cook, J.D.: Dose-finding based on efficacy-toxicity trade-offs. Biometrics **60**, 684–693 (2004)

# Randomly Reinforced Urn Designs Whose Allocation Proportions Converge to Arbitrary Prespecified Values

**Andrea Ghiglietti and Anna Maria Paganoni**

**Abstract** There are many randomization procedures in clinical trials in which the proportion of patients allocated to treatments converges to a fixed value. Many of these procedures, like those targeting the optimal Neyman allocation, are not adaptive designs and the limiting proportion of allocations is independent of the treatment behavior. In this work we construct a response adaptive design, described in terms of a two-colour urn model, targeting fixed asymptotic allocations that are a function of treatment performances. We prove some asymptotic results for the process of colours generated by the urn and for the process of its composition. Applications to sequential clinical trials and connections with response-adaptive design of experiments are considered. Additionally, we report simulation studies concerning the power function of a hypothesis testing procedure that naturally arises from this statistical framework.

## 1 Introduction

Consider a clinical trial with two competing treatments $R$ and $W$, say. We introduce a new response adaptive design, described in terms of an urn model, targeting any asymptotic allocation fixed in advance (Aletti et al. 2013). In a clinical setting, adaptive designs are attractive because they aim to achieve two simultaneous goals, concerning both statistical and ethical points of view: (a) collecting evidence to determine the superior treatment, and (b) increasing the allocation of units to the superior treatment. For a complete literature review on response adaptive designs, see Hu and Rosenberger (2006).

A wide class of response-adaptive randomized designs is based on urn models, because it is a classical tool to guarantee a randomized device (Cheung et al.

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2006; Rosenberger 2002), to balance the allocations (Baldi Antognini and Giannerini 2007) or to construct designs which asymptotically assign all subjects to the best treatment (Muliere et al. 2006; Flournoy and May 2009). In general, these designs model the experiment with an urn containing balls of different colours, each one associated with a specific treatment. The urn is sampled sequentially and the patients are assigned to the treatments according to the sampled colours. In the *two-colour Randomly Reinforced Urn* (RRU) studied in Muliere et al. (2006), after any allocation the urn is reinforced by a random quantity of balls having the same colour as the sampled one. In Muliere et al. (2006) it was proved that RRU design is a randomized device able to target the optimal treatment (i.e., the urn proportion of the colour related to the superior treatment converges almost surely to one). Because of its degenerate limit, the traditional asymptotic theory cannot be applied straightforwardly to the RRU. Specific asymptotic results for the RRU design are studied in Flournoy and May (2009). We present the *Modified Randomly Reinforced Urn* design (MRRU) introduced in Aletti et al. (2013). This model changes the reinforcement scheme of the RRU model in order asymptotically to target any allocation proportion in $(0, 1)$. In Ghiglietti and Paganoni (2012) we compare statistical properties of the MRRU design with the RRU design. Other papers have described urn models that can target any desired allocation. For instance, in Cheung et al. (2011) a general class of immigrated urn models with this feature is presented and some related asymptotic results are detailed.

In Sect. 2 the MRRU model introduced in Aletti et al. (2013) is described. Then, in Sect. 3 we conduct an analysis of the statistical properties of a usual hypothesis test in the MRRU setting. We end the paper with a short conclusion.

## 2 The Modified Randomly Reinforced Urn Model

We consider two probability distributions $\mu_R$ and $\mu_W$ with supports contained in $[\alpha, \beta]$, where $0 \leq \alpha \leq \beta < +\infty$ and a sequence $(U_n)_n$ of independent uniform random variables on $(0, 1)$. We will interpret $\mu_R$ and $\mu_W$ as the laws of the responses to treatments $R$ and $W$, respectively. We assume that both the means $m_R = \int_\alpha^\beta x\, \mu_R(\mathrm{d}x)$ and $m_W = \int_\alpha^\beta x\, \mu_W(\mathrm{d}x)$ are strictly positive. Visualize an urn initially containing $r_0$ balls of colour $R$ and $w_0$ balls of colour $W$. Set

$$R_0 = r_0, \qquad W_0 = w_0, \qquad Z_0 = \frac{R_0}{D_0}.$$

At time $n = 1$, a ball is sampled from the urn. Its colour is $X_1 = \mathbf{1}_{[0,Z_0]}(U_1)$, a random variable with Bernoulli $(Z_0)$ distribution. Let $M_1$ and $N_1$ be two independent random variables with distributions $\mu_R$ and $\mu_W$, respectively. Assume that $X_1, M_1$ and $N_1$ are independent. Next, if the sampled ball is $R$, it is replaced in the urn together with $X_1 M_1$ balls of the same colour if $Z_0 < \eta$, where $\eta \in (0, 1)$ is a suitable parameter. Otherwise, the urn composition does not change. If the sampled ball is $W$, it is replaced in the urn together with $(1 - X_1)N_1$ balls of the same

colour if $Z_0 > \delta$, where $\delta < \eta \in (0, 1)$ is a suitable parameter. Otherwise, the urn composition does not change. Consequently, we can update the urn composition in the following way:

$$R_1 = R_0 + X_1 M_1 \mathbf{1}_{[Z_0 < \eta]}, \qquad W_1 = W_0 + (1 - X_1) N_1 \mathbf{1}_{[Z_0 > \delta]}, \qquad Z_1 = \frac{R_1}{D_1}.$$

Now iterate this sampling scheme. Thus, at time $n + 1$, given the sigma-field $\mathscr{F}_n$ generated by $X_1, \ldots, X_n, M_1, \ldots, M_n$ and $N_1, \ldots, N_n$, let $X_{n+1} = \mathbf{1}_{[0, Z_n]}(U_{n+1})$ be a Bernoulli$(Z_n)$ random variable and, independently of $\mathscr{F}_n$ and $X_{n+1}$, assume that $M_{n+1}$ and $N_{n+1}$ are two independent random variables with distributions $\mu_R$ and $\mu_W$, respectively. Set

$$\begin{aligned} R_{n+1} &= R_n + X_{n+1} M_{n+1} \mathbf{1}_{[Z_n < \eta]}, \\ W_{n+1} &= W_n + (1 - X_{n+1}) N_{n+1} \mathbf{1}_{[Z_n > \delta]}, \\ Z_{n+1} &= \frac{R_{n+1}}{D_{n+1}}. \end{aligned}$$

We thus generate two infinite sequences $(X_n)_{n \in \mathbb{N}}$ and $(Z_n)_{n \in \mathbb{N}}$ of random variables, representing the colour of the ball sampled from the urn and the proportion of balls of colour $R$, respectively.

In Aletti et al. (2013, Theorem 3.1) the following asymptotic convergence result is proved:

**Theorem 1** *The sequence of proportions $(Z_n)_{n \in \mathbb{N}}$ of the urn process converges almost surely to the following limit*:

$$\lim_{n \to \infty} Z_n = \begin{cases} \eta & \text{if } \int_\alpha^\beta x \, \mu_R(\mathrm{d}x) > \int_\alpha^\beta x \, \mu_W(\mathrm{d}x), \\ \delta & \text{if } \int_\alpha^\beta x \, \mu_R(\mathrm{d}x) < \int_\alpha^\beta x \, \mu_W(\mathrm{d}x). \end{cases} \tag{1}$$

The urn proportion process $(Z_n)_{n \in \mathbb{N}}$ converges to a value which depends on the unknown means of the reinforcement distributions. This aspect characterizes the adaptive nature of the design based on the urn model. In particular, this modified urn model generates a process $(Z_n)_{n \in \mathbb{N}}$ that converges to one of the values $\{\delta, \eta\}$, according to which reinforcement presents the distribution with the greater mean. When $m_R = m_W$ we do not have an explicit form for the asymptotic distribution of the urn proportion $Z_n$. Nevertheless, we know that $(Z_n)_{n \in \mathbb{N}}$ converges to a random variable $Z_\infty$ whose distribution has no atoms and its support is $S_\infty = [\delta, \eta]$.

## 3 Response-Adaptive Designs and Classical Statistical Tools

We introduce a classical hypothesis test to compare the response means of two treatments using data accrued during the trial. The aim of this section is to discuss the

statistical properties obtained by applying a response-adaptive design (such as the urn model described in Sect. 2), in comparison with a classical procedure. We deal with the statistical hypothesis test

$$H_0 : m_R - m_W = 0 \quad \text{vs.} \quad H_1 : m_R - m_W \neq 0. \tag{2}$$

In a classical framework we can compute the critical region and the power curve of the test. Let us fix some parameters:

- $n_{0,R}$ and $n_{0,W}$: sample sizes of patient responses to treatments $R$ and $W$, respectively;
- $\alpha$: significance level;
- $\Delta_0$: smallest mean difference detected with high power;
- $\beta_0$: minimum power for the mean difference of $\pm\Delta_0$.

Once we have defined the proportion $p_0$ of patients allocated to treatment $R$, it is easy to find the correct sample size $n_0$ which allows the test to satisfy the properties required by the parameters. We have the following critical region:

$$R_\alpha = \left\{ |\overline{M}_{n_{0,R}} - \overline{N}_{n_{0,W}}| > \sqrt{\frac{\sigma_R^2}{n_{0,R}} + \frac{\sigma_W^2}{n_{0,W}}}\, z_{\frac{\alpha}{2}} \right\}, \tag{3}$$

where $\overline{M}_{n_{0,R}} = \sum_{i=1}^{n_{0,R}} M_i/n_{0,R}$ and $\overline{N}_{n_{0,W}} = \sum_{i=1}^{n_{0,W}} N_i/n_{0,W}$. The region introduced in (3) defines a test with level $\alpha$ that is exact in the case of Gaussian reinforcements, and asymptotic in the case of continuous reinforcement, not necessarily Gaussian. Moreover, we obtain the power of the test (3) as a function of the real mean difference $\Delta = m_R - m_W$ (see Fig. 1 in the case of equal variances),

$$\beta(\Delta) = P\left( Z < -z_{\frac{\alpha}{2}} - \frac{\Delta}{\sqrt{\frac{\sigma_R^2}{n_{0,R}} + \frac{\sigma_W^2}{n_{0,W}}}} \right) + P\left( Z > z_{\frac{\alpha}{2}} - \frac{\Delta}{\sqrt{\frac{\sigma_R^2}{n_{0,R}} + \frac{\sigma_W^2}{n_{0,W}}}} \right). \tag{4}$$

Define $n_0$ as the total sample size of the classical test $\mathscr{T}_0$ and $p_0$ as the corresponding proportion of patients allocated to the treatment $R$, i.e., $n_0 = n_{0,R} + n_{0,W}$ and $p_0 = n_{0,R}/n_0$. If we want a test with same features (the level $\alpha$ and the minimum power $\beta_0$ for the mean difference of $\pm\Delta_0$), but of better performance, we could modify the proportion of assignments or the sample size. The test $\mathscr{T}_0$ can be identified in the space $((0,1) \times \mathbb{N})$, that we will call the *proportion-sample size* space, by the couple $(p_0, n_0)$. Any other test $\mathscr{T}$ will be represented by a point $(\rho, n)$ in the same space. The goal of this section is to point out regions in this space characterizing tests with performances better than $\mathscr{T}_0$. A test $\mathscr{T}$ will be considered strictly better than $\mathscr{T}_0$ if it satisfies two conditions:

(a) $\mathscr{T}$ has a power function uniformly higher than the power function of $\mathscr{T}_0$;
(b) $\mathscr{T}$ assigns to the worst treatment fewer patients than $\mathscr{T}_0$ does.

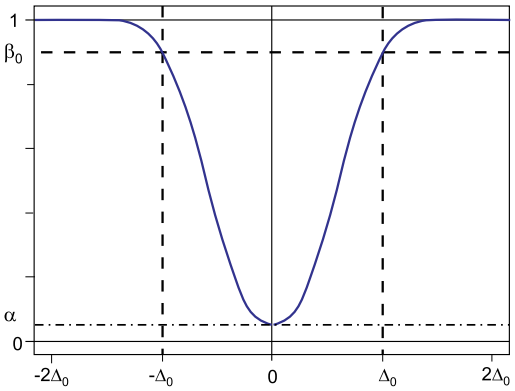


**Fig. 1** The power function $\beta : \mathbb{R} \to [0, 1]$ of the test defined in (3) in the case of $\alpha = 0.05$ and $\beta_0 = 0.9$

Let $\beta_{\mathscr{T}_0}$ and $\beta_{\mathscr{T}}$ respectively be the power functions of tests $\mathscr{T}_0$ and $\mathscr{T}$. To achieve the condition (a), we impose

$$\beta_{\mathscr{T}}(\Delta) \geq \beta_{\mathscr{T}_0}(\Delta), \quad \forall \Delta \in \mathbb{R} \quad \Leftrightarrow \quad \frac{\sigma_M^2}{n\rho} + \frac{\sigma_N^2}{n(1-\rho)} \leq \frac{\sigma_M^2}{n_0 p_0} + \frac{\sigma_N^2}{n_0(1-p_0)}. \quad (5)$$

If we denote by $p_{\text{opt}}$ the optimal allocation proportion $\sigma_M/(\sigma_M + \sigma_N)$, we can rewrite the previous inequality in a more suitable form:

$$\frac{{p_{\text{opt}}}^2}{n\rho} + \frac{(1-p_{\text{opt}})^2}{n(1-\rho)} \leq \frac{{p_{\text{opt}}}^2}{n_0 p_0} + \frac{(1-p_{\text{opt}})^2}{n_0(1-p_0)}. \quad (6)$$

The above condition divides the *proportion-sample size* space into two regions. The boundary is computed by imposing equality and expressing the sample size $n$ as a function of the proportion $\rho$:

$$n_\beta(\rho) = \left(\frac{p_{\text{opt}}^2}{\rho} + \frac{(1-p_{\text{opt}})^2}{1-\rho}\right)\left(\frac{p_{\text{opt}}^2}{n_0 p_0} + \frac{(1-p_{\text{opt}})^2}{n_0(1-p_0)}\right)^{-1}. \quad (7)$$

We refer to this function as $n_\beta$, since it is defined by imposing the condition related to the power of the tests. This relationship between $\rho$ and $n$ is visualized in Fig. 2 by a dashed line. Every point upon this line identifies a test $\mathscr{T}$ having a power higher than $\mathscr{T}_0$. On the other hand, points behind the dashed line represent tests with a power lower than $\mathscr{T}_0$. It is easy to see that the function $n_\beta : (0, 1) \to (0, \infty)$ is unbounded for proportions close to zero and to one, and it has a global minimum for $\rho = p_{\text{opt}}$. This seems reasonable because $p_{\text{opt}}$ is the allocation proportion which requires fewest patients to get any fixed value of power. Besides, the further the proportion $\rho$ from $p_{\text{opt}}$ is, the more patients are necessary to attain this power. Specifically, the minimum lies on a very interesting curve, which is uniquely identified by the parameters of the classical test. Define $g_{\min} : (0, 1) \to (0, \infty)$ as the

function associated with that curve. Then, we are able to express it in analytic form

$$g_{\min}(x) = n_0\left(\frac{x^2}{p_0} + \frac{(1-x)^2}{1-p_0}\right)^{-1}, \quad \forall x \in (0,1). \tag{8}$$

The curve is represented in Fig. 2 by a dotted line. The functions $n_\beta$ and $g_{\min}$ intersect at two points (in general, they are different) denoted by $M$ and $Q$. The point $M$ is the minimum of the function $n_\beta$ and it corresponds to the optimal allocation proportion

$$M = \left(p_{\text{opt}},\ n_0\left(\frac{p_{\text{opt}}^2}{p_0} + \frac{(1-p_{\text{opt}})^2}{1-p_0}\right)^{-1}\right). \tag{9}$$

The point $Q$ is the maximum of the function $g_{\min}$ and it corresponds to the features of the classical test $\mathscr{T}_0$: $Q = (p_0, n_0)$. The points $M$ and $Q$ coincide when $p_0 = p_{\text{opt}}$, i.e., when the test $\mathscr{T}_0$ uses the optimal allocation proportion. In this case, the curves are tangent at $M$ (or $Q$). Moreover, there are other relevant points highlighted by the function $g_{\min}$. In fact, the curve starts at $X_{W,0} = (0, n_0(1-p_0))$ and ends at $X_{R,0} = (1, n_0 p_0)$. The ordinates of points $X_{W,0}$ and $X_{R,0}$ tell us how many patients have been allocated by the test $\mathscr{T}_0$ to the treatments $W$ and $R$, respectively.

For the condition (b) we have to distinguish two different cases:

- If $m_R > m_W$ then the superior treatment is $R$ and the condition to be imposed is

$$n(1-\rho) < n_0(1-p_0) \quad \Rightarrow \quad \rho > 1 - \frac{n_0}{n}(1-p_0). \tag{10}$$

- If $m_R < m_W$ then the superior treatment is $W$ and the condition to be imposed is

$$n\rho < n_0 p_0 \quad \Rightarrow \quad \rho < \frac{n_0}{n} p_0. \tag{11}$$

Both of these relationships are marked with bold solid lines in the plane $(\rho, n)$. Under each one of these lines, alternatively, the first or the second condition is verified. In conclusion, we divide the space $(\rho, n)$ into three regions:

- Region $A$: tests $\mathscr{T}$ having greater power and fewer patients allocated to treatment $R$ than $\mathscr{T}_0$.
- Region $B$: tests $\mathscr{T}$ having greater power and more patients allocated to both the treatments.
- Region $C$: tests $\mathscr{T}$ having greater power and fewer patients allocated to treatment $W$ than $\mathscr{T}_0$.

A good way to design a better test could be to choose new parameters $(\rho, n)$ in the region $A$ if $m_R < m_W$, or otherwise, in the region $C$ if $m_R > m_W$. Naturally, which mean is greater constitutes information which is not available before the experiment begins. This is the purpose of the trial and so is unknown at the design stage. For this reason, it may be useful to adopt an adaptive response design to construct the test. In particular, when we apply the urn model described in Sect. 2, we have to assign the

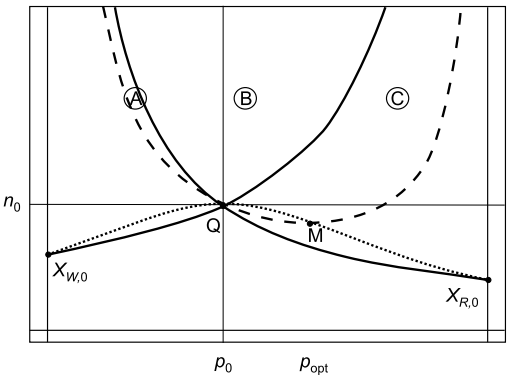


**Fig. 2** The regions $A$, $B$ and $C$, in the *proportion-sample size* plane, for a particular choice of parameters. The *dashed line* represents the function $n_\beta$. It separates the test $\mathscr{T}$ with power $\beta_{\mathscr{T}}(\Delta) > \beta_{\mathscr{T}_0}(\Delta)$ from the test with power $\beta_{\mathscr{T}}(\Delta) < \beta_{\mathscr{T}_0}(\Delta)$. *Solid lines* separate the tests according on the number of patients allocated to the treatments $R$ and $W$, with respect of $n_{0,R}$ and $n_{0,W}$, the sample sizes of $\mathscr{T}_0$. The *dotted line* represents the function $g_{\min}$

parameters $\delta$ and $\eta$ some values such that $(\delta, n) \in A$ and $(\eta, n) \in C$, with $n$ denoting the total number of draws by the urn. Define the quantities $N_R(n) = \sum_{i=1}^{n} X_i$ and $N_W(n) = \sum_{i=1}^{n}(1 - X_i)$, representing the numbers of patients allocated by the urn to the treatments $R$ and $W$, respectively. Note that, in this case, the sample sizes are random variables. Proposition 3.1 in Aletti et al. (2013) implies that the critical region (12) defines a test with the asymptotic level $\alpha$

$$R_\alpha = \left\{ |\overline{M}_{N_R(n)} - \overline{N}_{N_W(n)}| > \sqrt{\frac{\sigma_R^2}{N_R(n)} + \frac{\sigma_W^2}{N_W(n)}}\, z_{\frac{\alpha}{2}} \right\}. \tag{12}$$

## 4 Conclusion

In this work, we have made a statistical study of the classical hypothesis test that compares the mean responses of two competing treatments. These analyses concern the performance of different tests, in terms of power and in terms of the number of subjects assigned to the inferior treatment. As mentioned in Sect. 1, both these aspects are very important in a clinical setting. Given any test $\mathscr{T}_0$, identified by a point $(p_0, n_0)$ in the *proportion-sample size* space, we studied how to construct a test $\mathscr{T}$ that provides greater power and assigns fewer patients to the worse treatment. Hence, assuming the knowledge of which treatment is superior, we identified the region in which it is more convenient to choose the new test $\mathscr{T}$. Naturally, the knowledge of which treatment has the greater mean response is the purpose of the trial, so we suggest adopting an adaptive response design, like the MRRU design. An ongoing project is to exploit the asymptotic results reported in Ghiglietti and

Paganoni (2012) in order to compute the probability of detecting a point $\mathscr{T}$ in the right region.

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## References

Aletti, G., Ghiglietti, A., Paganoni, A.M.: A modified randomly reinforced urn design. J. Appl. Probab. **50** (2013, forthcoming). [Available as Mox-report 32/2011, Politecnico di Milano. http://mox.polimi.it/it/progetti/pubblicazioni/quaderni/32-2011.pdf]

Baldi Antognini, A., Giannerini, S.: Generalized Polya urn designs with null balance. J. Appl. Probab. **44**, 661–669 (2007)

Cheung, S.H., Zhang, L.-X., Hu, F.: Asymptotic theorems of sequential estimation-adjusted urn models. Ann. Appl. Probab. **16**, 340–369 (2006)

Cheung, S.H., Zhang, L.-X., Hu, F., Wai, S.C.: Immigrated Urn Models—theoretical properties and applications. Ann. Stat. **39**, 643–671 (2011)

Flournoy, N., May, C.: Asymptotic theorems of sequential estimation-adjusted urn models. Ann. Stat. **37**, 1058–1078 (2009)

Ghiglietti, A., Paganoni, A.M.: Statistical properties of two-colour randomly reinforced urn design targeting fixed allocations (2012). Available as Mox-report 48. Politecnico di Milano. http://mox.polimi.it/it/progetti/pubblicazioni/quaderni/48-2012.pdf

Hu, F., Rosenberger, W.F.: The Theory of Response-Adaptive Randomization in Clinical Trials. Wiley, New York (2006)

Muliere, P., Paganoni, A.M., Secchi, P.: A randomly reinforced urn. J. Stat. Plan. Inference **136**, 1853–1874 (2006)

Rosenberger, W.F.: Randomized urn models and sequential design. Seq. Anal. **21**, 1–28 (2002)

# Kernels and Designs for Modelling Invariant Functions: From Group Invariance to Additivity

**David Ginsbourger, Nicolas Durrande, and Olivier Roustant**

**Abstract** We focus on kernels incorporating different kinds of prior knowledge on functions to be approximated by Kriging. A recent result on random fields with paths invariant under a group action is generalised to combinations of composition operators, and a characterisation of kernels leading to random fields with additive paths is obtained as a corollary. A discussion follows on some implications on design of experiments, and it is shown in the case of additive kernels that the so-called class of "axis designs" outperforms Latin hypercubes in terms of the IMSE criterion.

## 1 Introduction

Models based on Random Fields (RFs), and especially on Gaussian RFs, have been increasingly used in the last decades for designing and analysing costly deterministic experiments (Santner et al. 2003; Rasmussen and Williams 2006). In most popular implementations of such models, a constant or linear trend and a stationary covariance kernel are assumed. However, there seems to be an enormous potential in designing kernels reflecting different kinds of prior knowledge. Recently, classes of kernels leading to RFs with additive paths have been considered in Durrande et al. (2012) and Duvenaud et al. (2011). Calling $f \in \mathbb{R}^D$ [$D = \prod_i^d D_i$ where $D_i \subset \mathbb{R}$ $(1 \leq i \leq d)$] additive when there exists $f_i \in \mathbb{R}^{D_i}$ $(1 \leq i \leq d)$ such

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that $\forall \mathbf{x} = (x_1, \ldots, x_d) \in D,\ f(\mathbf{x}) = \sum_{i=1}^{d} f_i(x_i)$, it was shown by Durrande et al. (2012) that

**Proposition 1** *If a centred RF $Z$ possesses a kernel of the form*

$$k\big(\mathbf{x}, \mathbf{x}'\big) = \sum_{i=1}^{d} k_i\big(x_i, x_i'\big), \tag{1}$$

*where the $k_i$'s are arbitrary positive definite kernels over the $D_i$'s, then $Z$ is additive up to a modification, i.e., there exists a random field $A$ with paths which are additive functions and such that $\forall \mathbf{x} \in D, \mathbb{P}(Z_{\mathbf{x}} = A_{\mathbf{x}}) = 1$.*

Are the kernels of the form $k(\mathbf{x}, \mathbf{x}') = \sum_{i=1}^{d} k_i(x_i, x_i')$ the only ones giving birth to RFs with additive paths? For a different question, Ginsbourger et al. (2012) proposed a characterization of kernels which associated centred RFs have their trajectories invariant under the action of a finite group. Let $G$ be a finite group acting on $D$ via

$$\Phi : (\mathbf{x}, g) \in D \times G \longrightarrow \Phi(\mathbf{x}, g) = g \cdot \mathbf{x} \in D.$$

**Proposition 2** *$Z$ has invariant paths under $\Phi$ (up to a modification) if and only if $k$ is argumentwise invariant*: $\forall \mathbf{x} \in D, \forall g \in G, k(g \cdot \mathbf{x}, \cdot) = k(\mathbf{x}, \cdot)$.

In Sect. 2 we show that both Propositions 1 and 2 are subcases of a general result on RFs invariant under the class of *combination of composition operators*, defined below. As a corollary, a characterization of kernels leading to RFs with additive paths is given in Sect. 3, and it is shown that having the form of Eq. (1) is not necessary. Sections 4 and 5 are dedicated to a discussion on the design of experiments for RF models with invariant kernels, with examples in the additive case.

## 2 Invariances and Combinations of Composition Operators

### 2.1 Composition Operators and Their Combinations

**Definition 1** Let us consider an arbitrary function $v : \mathbf{x} \in D \longrightarrow v(\mathbf{x}) \in D$. The *composition operator $T_v$ with symbol $v$* is defined as

$$T_v : f \in \mathbb{R}^D \longrightarrow T_v(f) := f \circ v \in \mathbb{R}^D.$$

*Remark 1* Such operators can be extended naturally to random fields indexed by $D$:

$$T_v(Z)_{\mathbf{x}} := Z_{v(\mathbf{x})}, \quad \forall \mathbf{x} \in D.$$

**Definition 2** We call a *combination of composition operators with symbols* $v_i \in D^D$ *and weights* $\alpha_i \in \mathbb{R}$ $(1 \le i \le q)$ the operator

$$T = \sum_{i=1}^{q} \alpha_i T_{v_i}.$$

## 2.2 Invariance Under a Combination of Composition Operators

**Proposition 3** *Let $Z$ be a centred RF with kernel $k$. Then $k$ is T-invariant, i.e.,*

$$T\big[k\big(\cdot, \mathbf{x}'\big)\big] = k\big(\cdot, \mathbf{x}'\big), \quad \forall \mathbf{x}' \in D \tag{2}$$

*if and only if $Z$ equals $T(Z)$ up to a modification, i.e.,*

$$\mathbb{P}\big[Z_{\mathbf{x}} = T(Z)_{\mathbf{x}}\big] = 1, \quad \forall \mathbf{x} \in D.$$

*Proof* (Sufficiency) Let us fix arbitrary $\mathbf{x}$ and $\mathbf{x}'$. Since $Z_{\mathbf{x}}$ is a modification of $T(Z)_{\mathbf{x}}$, we have $\operatorname{cov}(Z_{\mathbf{x}}, Z_{\mathbf{x}'}) = \operatorname{cov}[T(Z)_{\mathbf{x}}, Z_{\mathbf{x}'}] = \operatorname{cov}(\sum_{i=1}^{q} \alpha_i Z_{v_i(\mathbf{x})}, Z_{\mathbf{x}'})$, so that

$$k\big(\mathbf{x}, \mathbf{x}'\big) = \sum_{i=1}^{q} \alpha_i k\big(v_i(\mathbf{x}), \mathbf{x}'\big) = T\big[k\big(\cdot, \mathbf{x}'\big)\big](\mathbf{x}).$$

(Necessity) Using $T[k(\cdot, \mathbf{x}')] = k(\cdot, \mathbf{x}')$, $\forall \mathbf{x}' \in D$, and $\operatorname{var}[T(Z)_{\mathbf{x}}] = \operatorname{cov}[Z_{\mathbf{x}}, T(Z)_{\mathbf{x}}] = \operatorname{var}(Z_{\mathbf{x}})$, we get $\operatorname{var}[Z_{\mathbf{x}} - T(Z)_{\mathbf{x}}] = 0$. Since $Z$ is centred, so is $T(Z)$, and hence $Z_{\mathbf{x}} \overset{\text{a.s.}}{=} T(Z)_{\mathbf{x}}$. □

*Example 1* (Case of group-invariance) $T(f)(\mathbf{x}) = \sum_{i=1}^{\#G} \frac{1}{\#G} f[v_i(\mathbf{x})]$ with $v_i(\mathbf{x}) := g_i.\mathbf{x}$ $(1 \le i \le \#G)$ leads to $\Phi$-invariant $Z$ if and only if $k$ is argumentwise invariant.

# 3 Kernels Characterizing Centered Fields with Additive Paths

## 3.1 Additivity as Invariance Under a Combination of Compositions

**Proposition 4** *Assuming $\mathbf{a} \in D$, a function $f : D \to \mathbb{R}$ is additive if and only if $f$ is invariant under the following combination of composition operators*:

$$T(f)(\mathbf{x}) = \sum_{i=1}^{d} f\big[v_i(\mathbf{x})\big] - (d-1) f\big[v_{d+1}(\mathbf{x})\big] \quad (\mathbf{x} \in D), \tag{3}$$

*where* $v_i(\mathbf{x}) := (a_1, \ldots, a_{i-1}, \underbrace{x_i}_{i\text{-th coordinate}}, a_{i+1}, \ldots, a_d)$, *and* $v_{d+1}(\mathbf{x}) := \mathbf{a}$.

*Proof* (Sufficiency) This follows from $T(f) = f$, $f(\mathbf{x}) = \sum_{j=1}^{d} f_j(x_j)$ with $f_j(x_j) := f[v_j(\mathbf{x})] - \frac{d-1}{d} f(\mathbf{a})$.

(Necessity) $f(\mathbf{x}) = \sum_{j=1}^{d} f_j(x_j)$ implies $f[v_i(\mathbf{x})] = f_i(x_i) + \sum_{j=1, j\neq i}^{d} f_j(a_j)$, and so

$$\begin{aligned} T(f)(\mathbf{x}) &= \sum_{i=1}^{d} f\big[v_i(\mathbf{x})\big] - (d-1) f(\mathbf{a}) \\ &= \sum_{i=1}^{d} f_i(x_i) + \underbrace{\sum_{i=1}^{d} \sum_{\substack{j=1 \\ j\neq i}}^{d} f_j(a_j) - (d-1) f(\mathbf{a})}_{0} = f(\mathbf{x}). \end{aligned}$$

□

### 3.2 Kernels Characterizing Centred Fields with Additive Paths

**Corollary 1** *A centred RF $Z$ possessing a covariance kernel $k$ has additive paths (up to a modification) if and only if $k$ is a positive definite kernel of the form*

$$\boxed{k\big(\mathbf{x}, \mathbf{x}'\big) = \sum_{i=1}^{d} \sum_{j=1}^{d} k_{ij}\big(x_i, x'_j\big).} \tag{4}$$

*Proof* If $Z$ has additive paths up to a modification, there exists an RF $(A_{\mathbf{x}})_{\mathbf{x}\in D}$ with additive paths such that $\mathbb{P}(Z_{\mathbf{x}} = A_{\mathbf{x}}) = 1$, $\forall \mathbf{x} \in D$, and so $Z$ and $A$ have the same covariance kernel. Now, $A$ having additive paths, Proposition 4 implies that $A_{\mathbf{x}} = \sum_{i=1}^{d} A_{v_i(\mathbf{x})} - (d-1) A_{v_{d+1}(\mathbf{x})} = \sum_{i=1}^{d} A^i_{x_i}$, where $A^i_{x_i} := A_{v_i(\mathbf{x})} - \frac{(d-1)}{d} A_{v_{d+1}(\mathbf{x})}$, so (4) holds with $k_{ij}(x_i, x'_j) := \mathrm{cov}(A^i_{x_i}, A^j_{x'_j})$. Conversely, from Proposition 3, we know that it suffices for $Z$ to have additive paths that $k(\cdot, \mathbf{x}')$ is additive $\forall \mathbf{x}' \in D$. For a kernel $k$ such as in Eq. (4) and an arbitrary $\mathbf{x}' \in D$, setting

$$\forall x_i \in D_i, \quad \widetilde{k}_i\big(x_i, \mathbf{x}'\big) := \sum_{j=1}^{d} k_{ij}\big(x_i, x'_j\big) \quad (1 \leq i \leq d),$$

we get $k(\mathbf{x}, \mathbf{x}') = \sum_{i=1}^{d} \widetilde{k}_i(x_i, \mathbf{x}')$, $\forall \mathbf{x} \in D$, and so $k(\cdot, \mathbf{x}')$ is additive. □

## 4 Kriging-Equivalent Designs: Generalities and Invariant Case

We now focus on cases where two designs, $X \in D^n$ and $X' \in D^{n'}$, bring the same information on $Z$. We first give general results, and then specialize to invariant RFs.

**Definition 3** $X'$ and $X$ are said to be *Kriging-equivalent*, which is denoted by $X' \equiv X$, iff the Kriging mean and variance of $Z$ based on $\{Z_{\mathbf{x}}, \mathbf{x} \in X\}$ or $\{Z_{\mathbf{x}'}, \mathbf{x}' \in X'\}$ coincide.

In particular two equivalent designs lead to the same Integrated Mean Squared Error (IMSE). We now give a sufficient condition for two designs to be equivalent.

**Proposition 5** *If* $\text{span}(Z_{\mathbf{x}'}, \mathbf{x}' \in X') = \text{span}(Z_{\mathbf{x}}, \mathbf{x} \in X)$, *then* $X' \equiv X$.

*Proof* Kriging is characterized by the *linear* conditional expectations $E_L(Z_{\mathbf{u}}|Z_{\mathbf{x}}, \mathbf{x} \in X)$ and $E_L(Z_{\mathbf{u}}Z_{\mathbf{v}}|Z_{\mathbf{x}}, \mathbf{x} \in X)$ ($\mathbf{u}, \mathbf{v}$ in $D$), and hence depends only on $\text{span}(Z_{\mathbf{x}}, \mathbf{x} \in X)$. □

*Remark 2* If $Z$ is also Gaussian, the equality of the two linear spans guarantees that the whole conditional processes $Z|Z_{\mathbf{x}}, \mathbf{x} \in X$ and $Z|Z_{\mathbf{x}'}, \mathbf{x}' \in X'$ have the same distribution. In particular, conditional simulations performed with $X$ or $X'$ coincide.

**Corollary 2** (Exchangeability condition) *Assume that* $\exists \mathbf{x}' \notin X$, $Z_{\mathbf{x}'} = \sum_{\mathbf{x} \in X} \alpha_{\mathbf{x}} Z_{\mathbf{x}}$, *with* $\alpha_{\mathbf{x}} \neq 0, \forall \mathbf{x} \in X$. *Then* $\forall \mathbf{x} \in X$, $X - \{\mathbf{x}\} + \{\mathbf{x}'\} \equiv X \equiv X + \{\mathbf{x}'\}$.

*Remark 3* The condition "$\alpha_{\mathbf{x}} \neq 0, \forall \mathbf{x} \in X$" is one way to guarantee that the dimension of $\text{span}(Z_{\mathbf{x}}, \mathbf{x} \in X)$ does not decrease when exchanging $Z_{\mathbf{x}}$ for $Z_{\mathbf{x}'}$.

**Corollary 3** (Invariant kernels) *Let us consider a combination of composition operators* $T = \sum_{j=1}^{q} \alpha_j T_{v_j}$, *with* $\forall j = 1, \ldots, q, \alpha_j \neq 0$, *and assume that* $k$ *is* $T$*-invariant. For* $\mathbf{x} \in D$, *write* $X_v(\mathbf{x}) := (v_1(\mathbf{x}), \ldots, v_q(\mathbf{x}))$. *Then for* $j = 1, \ldots, q$, *we have*

$$X_v(\mathbf{x}) \equiv X_v(\mathbf{x}) - \{v_j(\mathbf{x})\} + \{\mathbf{x}\} \equiv X_v(\mathbf{x}) + \{\mathbf{x}\}.$$

*Proof* This results from the fact that $T(Z) = Z$ (Proposition 3) and Corollary 2. □

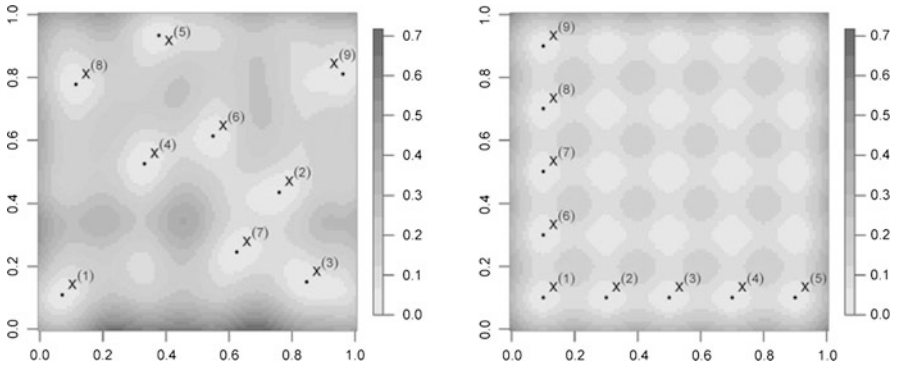
*Example 2* (Equivalent designs for additive kernels) Let us assume that $Z$ is 2-dimensional, with an additive kernel $k$, and consider a *rectangle* design:

$$X = \{\mathbf{x}^{(1)} = (a_1, a_2), \mathbf{x}^{(2)} = (b_1, a_2), \mathbf{x}^{(3)} = (a_1, b_2), \mathbf{x}^{(4)} = (b_1, b_2)\},$$

with $\mathbf{a}, \mathbf{b} \in D, \mathbf{a} \neq \mathbf{b}$. Then, all three-point designs contained in $X$ are equivalent to $X$:

$$(\mathbf{x}^{(1)}, \mathbf{x}^{(2)}, \mathbf{x}^{(3)}) \equiv (\mathbf{x}^{(1)}, \mathbf{x}^{(2)}, \mathbf{x}^{(4)}) \equiv (\mathbf{x}^{(1)}, \mathbf{x}^{(3)}, \mathbf{x}^{(4)}) \equiv (\mathbf{x}^{(2)}, \mathbf{x}^{(3)}, \mathbf{x}^{(4)}) \equiv X.$$

Indeed, consider the operator $T$ defined by $T(f)(\mathbf{x}) = f(a_1, x_2) + f(x_1, a_2) - f(a_1, a_2)$, as in Proposition 4 ($d = 2$). Relying on this proposition, $k$ is $T$-invariant. The result follows by applying Corollary 3 with $q = 3$ ($\alpha_1 = \alpha_2 = 1, \alpha_3 = -1$) and $\mathbf{x} = (b_1, b_2)$.




(a) (b)

**Fig. 1** MSE for two nine-point designs: (**a**) nine-point LHS design, (**b**) nine-point axis design. The univariate kernels are Matérn 5/2 with parameters $\sigma^2 = 1$, $\theta = 0.2$. For the (scrambled) LHS, the IMSE is $I = 0.196$ whereas for the axis design $I = 0.116$

*Example 3* (Equivalent designs for a group-invariant kernel) The case where $Z$ is invariant under the action of a group $G$ is degenerate since the condition $T(Z)_{\mathbf{x}} = Z_{\mathbf{x}}$ is equivalent to: $\forall g \in G$, $Z_{\mathbf{x}} = Z_{g.\mathbf{x}}$. Then it follows directly from Definition 3 that replacing one point in $X$ by any other point of its orbit gives an equivalent design:

$$\left(\mathbf{x}^{(1)}, \ldots, \mathbf{x}^{(n)}\right) \equiv \left(g_1 \cdot \mathbf{x}^{(1)}, \ldots, g_n \cdot \mathbf{x}^{(n)}\right), \quad \forall g_1, \ldots, g_n \in G.$$

## 5 On Choosing Designs for RF Models with an Additive Kernel

Example 2 shows that additive kernels may lead to points with zero variance outside the design. For LHS designs, such a configuration cannot occur (assuming, e.g., strict positive definiteness for at least one of the underlying univariate kernels) since points of the design are never aligned vertically, nor horizontally. On the other hand, designs where points are distributed parallel to the axis with a shared point at the intersection, hereafter called "axis designs", take advantage of this property since they imply zero variance on a whole grid. This property is illustrated in Fig. 1.

Figure 2 compares, for different values of the number of points $n$, the IMSE of all possible LHS designs with that of an axis design. In all cases, the space is divided into an appropriate number of square cells ($n^2$ for the LHS and $(\frac{n-1}{2} + 1)^2$ for the axis design) and the design points are located at the centres of some cells. It appears that, except for $n = 3$, the tested configurations are always in favour of the axis design. As the total number of possible LHS is $n!$ for $d = 2$, it was practically infeasible to run the exhaustive comparison for more than 9 points. However, the right panel of Fig. 2 shows the comparison between 100 maximin LHS designs generated with the *lhs* R package (Carnell 2009) and the axis designs for various values of the dimension $d$. As advocated in Loeppky et al. (2009), the number of points is taken

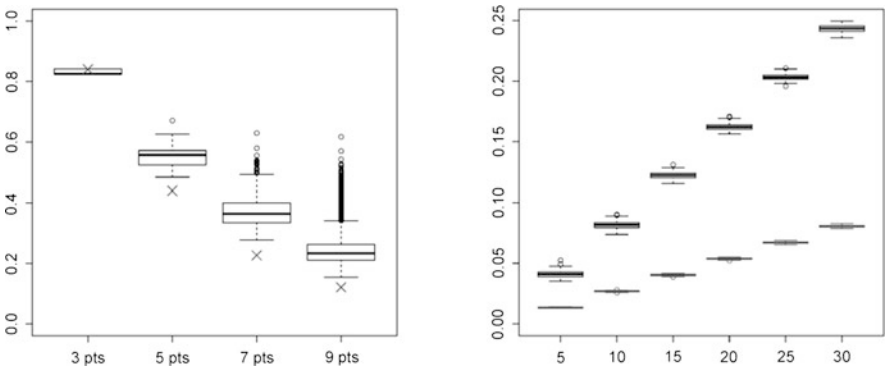



**Fig. 2** Comparisons of the IMSE of LH designs and axis designs: (**a**) influence of $n$ for $d = 2$; all possible LHS are enumerated and the integral in the IMSE expression is approximated by a Riemann sum based on $51^2$ points; the *crosses* represent the IMSE of axis designs; (**b**) influence of $d$ with $n = 10 \times d + 1$; 100 maximin-LHS (*upper* series) are compared with the axis design (*bottom* series). The variability in the IMSE of axis designs is due to the use of Monte Carlo methods for integration. In both cases, the settings of the covariance are the same as in Fig. 1

of the order of 10 times the dimension: $n = 10 \times d + 1$. The graph suggests that the axis designs become more and more superior to LHS as the dimension increases. These numerical investigations show that axis designs seem particularly adapted for fitting additive Kriging models.

However, axis designs are likely to perform poorly for nonadditive functions since they do not fill the space. Fortunately, a direct application of Corollary 2 shows that any design point can be moved to any other point where it induces a zero variance without introducing any change in the resulting Kriging equations. A straightforward application of this property is that the points distributed over one axis can be scattered in an LHS fashion without modifying the IMSE. This approach is illustrated in Fig. 3. If the function to be approximated has an additive component but also some interaction terms, the design presented in the right panel may efficiently capture not only the additive component but also the interaction terms.

## 6 Concluding Remarks and Perspectives

Although (generalized) additive models (Hastie and Tibshirani 1990) and related sparsity assumptions for high-dimensional data seem to have reached a golden age, the science of designing kernels adapted for high-dimensional Kriging is still in its infancy. In a recent article, Durrande et al. (2012) proposed a particular kind of kernel leading to centred RFs with additive paths. Following their lead, we give here a complete characterization of such kernels. This characterization appears in fact as a particular case of a property involving so-called combinations of composition operators. This property also generalizes another recent characterization of covariance

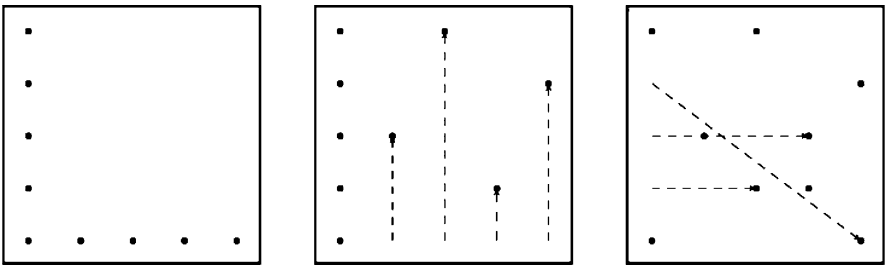


**Fig. 3** Example of Kriging-equivalent modifications of a design in the additive case. The axis design is transformed into the sum of a five-point LHS design and another five-point LHS design deprived of one point. These three designs lead to identical Kriging models when using a kernel satisfying Eq. (4)

kernels leading to RFs with paths invariant under the action of a finite group on the index set (Ginsbourger et al. 2012).

Some implications concerning the design of experiments are discussed, and it is illustrated with an empirical study that the so-called class of *axis designs* outperforms Latin hypercubes in terms of the IMSE for most configurations (for $n > 3$) in the case of an additive kernel. Furthermore, thanks to a proven exchangeability property in the case of Kriging modelling with an invariant kernel, axis designs can be modified so as to lead to better performance when interactions exist, while preserving exactly the same features as the axis design in the additive case.

Future work includes an extended study of optimal designs for Kriging with an invariant kernel. In addition, further generalisations of the present result on combination of composition operators may be worth looking at for better understanding what kind of prior knowledge can (or cannot) be injected into an RF model (in the Gaussian or in the general case), and how to practically implement kernels (Roustant et al. 2012) incorporating given functional properties, with adapted parameter estimation procedures.

## References

Carnell, R.: lhs: Latin Hypercube Samples. R package version 0.5 (2009)

Durrande, N., Ginsbourger, D., Roustant, O.: Additive covariance kernels for high-dimensional Gaussian process modeling. Ann. Fac. Sci. Toulouse **21**, 481–499 (2012). http://hal.inria.fr/hal-00446520/en

Duvenaud, D., Nickisch, H., Rasmussen, C.: Additive Gaussian processes. In: Proc. 25th Annual Conference on Neural Information Processing Systems 2011 (2011). http://nips.cc/Conferences/2011/

Ginsbourger, D., Bay, X., Roustant, O., Carraro, L.: Argumentwise invariant kernels for the approximation of invariant functions. Ann. Fac. Sci. Toulouse **21**, 501–527 (2012). http://hal.archives-ouvertes.fr/hal-00632815/

Hastie, T., Tibshirani, R.: Generalized Additive Models. Chapman & Hall/CRC, Boca Raton (1990)

Loeppky, J., Sacks, J., Welch, W.: Choosing the sample size of a computer experiment: a practical guide. Technometrics **51**, 366–376 (2009)

Rasmussen, C.R., Williams, C.K.I.: Gaussian Processes for Machine Learning. MIT Press, Cambridge (2006)

Roustant, O., Ginsbourger, D., Deville, Y.: Two R packages for the analysis of computer experiments by Kriging-based metamodeling and optimization. J. Stat. Softw. **51**, 1–55 (2012). http://www.jstatsoft.org/v51/i01

Santner, T., Williams, B., Notz, W.: The Design and Analysis of Computer Experiments. Springer, New York (2003)

# Optimal Design for Count Data with Binary Predictors in Item Response Theory

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**Abstract** The Rasch Poisson counts model (RPCM) allows for the analysis of mental speed which represents a basic component of human intelligence. An extended version of the RPCM, which incorporates covariates in order to explain the difficulty, provides a means for modern rule-based item generation. After a short introduction to the extended RPCM we develop locally $D$-optimal calibration designs for this model. To this end the RPCM is embedded in a particular generalized linear model. Finally, the robustness of the derived designs is investigated.

## 1 Introduction

Reasoning, memory, creativity and mental speed are among the most important factors of human intelligence (Jäger 1984). Mental speed refers to the human ability to carry out mental processes, required for the solution of a cognitive task, at variable rates or increments of time. Usually, mental speed is measured by elementary tasks with low cognitive demands in which the speed of response is primary. As Rasch (1960) already showed in his classical monograph, elementary cognitive tasks can be analyzed by the so-called Rasch Poisson counts model. Other successful applications of this model have been published by, e.g., Jansen (1997) and Verhelst and Kamphuis (2009).

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Typical items measuring mental speed can be differentiated by task characteristics or rules that correspond to cognitive operations to solve an item. The kind and amount of task characteristics influence the difficulty of the items. The task characteristics can be used to predict the task difficulty analogously to linear logistic models for reasoning items (Graßhoff et al. 2010).

## 2 Poisson Model for Count Data

According to the Rasch Poisson count model, the number of correct answers is assumed to follow a Poisson distribution with intensity $\lambda = \theta\sigma$, where $\theta$ is the ability of the test person and $\sigma$ is the easiness of the test item. Obviously, the (expected) number of correct answers will increase simultaneously with the ability of the person and the easiness of the task.

In the following, we consider the calibration step for the test items, when the ability of the test person is assumed to be known. The dependence of the easiness of an item on the rules may then be specified by a Poisson regression (Poisson ANOVA) model with exponential link.

More formally, the number of correct answers $Y(\mathbf{x})$ is Poisson distributed with intensity $\lambda(\mathbf{x};\beta) = \theta \exp(\mathbf{f}(\mathbf{x})^\top \beta)$, where $\mathbf{x}$ is the experimental setting ("rules"), which may be chosen from a specific experimental region $\mathscr{X}$, $\sigma = \exp(\mathbf{f}(\mathbf{x})^\top \beta)$ is the easiness of the item, $\mathbf{f} = (f_1, \ldots, f_p)^\top$ is a vector of known regression functions, and $\beta \in \mathbb{R}^p$ the vector of unknown parameters to be estimated.

As rules may be applied or not, we will focus on the situation of a $K$-way layout with binary explanatory variables $x_k$, where $x_k = 1$, if the $k$-th rule is applied, and $x_k = 0$ otherwise. In particular, if $x_k = 0$ for all rules $k$, a basic item is presented. The experimental setting is then $\mathbf{x} = (x_1, \ldots, x_k) \in \{0, 1\}^K$. As we assume no interactions, the vector of regression functions is $\mathbf{f}(\mathbf{x}) = (1, x_1, x_2, \ldots, x_k)^\top$, and the parameter vector $\beta$ consists of a constant term $\beta_0$ and $K$ main effects $\beta_k$. Thus $p = K + 1$ and the expected response equals the intensity $\lambda(\mathbf{x};\beta) = \theta \exp(\beta_0 + \sum_{k=1}^K \beta_k x_k)$.

## 3 Information and Design

For a single observation the Fisher information is $\mathbf{M}(\mathbf{x};\beta) = \lambda(\mathbf{x};\beta)\mathbf{f}(\mathbf{x})\mathbf{f}(\mathbf{x})^\top$, which depends on the particular setting $\mathbf{x}$ and additionally on $\beta$ through the intensity. Consequently, the normalized information matrix equals $\mathbf{M}(\xi;\beta) = \frac{1}{N}\sum_{i=1}^N \mathbf{M}(\mathbf{x}_i;\beta)$ for an exact design $\xi$ consisting of $N$ design points $\mathbf{x}_1, \ldots, \mathbf{x}_N$. For analytical ease we shall make use of approximate designs $\xi$ with mutually different design points $\mathbf{x}_1, \ldots, \mathbf{x}_n$, say, and the corresponding (real valued) weights $w_i = \xi(\{\mathbf{x}_i\}) \geq 0$ with $\sum_{i=1}^n w_i = 1$ in the spirit of Kiefer (1974). This approach seems appropriate, as typically the number $N$ of items presented may be

quite large. The information matrix is then more generally defined as $\mathbf{M}(\xi;\beta) = \sum_{i=1}^{n} w_i \lambda(\mathbf{x}_i;\beta)\mathbf{f}(\mathbf{x}_i)\mathbf{f}(\mathbf{x}_i)^\top$.

As is common in generalized linear models, the information matrix and, hence, optimal designs will depend on the parameter vector $\beta$. For measuring the quality of a design, we will use the popular $D$-criterion. More precisely, a design $\xi$ will be called locally $D$-optimal at $\beta$ if it maximizes the determinant of the information matrix $\mathbf{M}(\xi;\beta)$.

In the present situation the intensity and, hence, the information is proportional to $\theta$ and $\exp(\beta_0)$ such that $\mathbf{M}(\xi;\beta) = \theta\exp(\beta_0)\mathbf{M}_0(\xi;\beta)$, where $\mathbf{M}_0(\xi;\beta)$ is the information matrix in the standardized situation $\theta = 1$ and $\beta_0 = 0$. Thus for a fixed person only $\det(\mathbf{M}_0(\xi;\beta))$ has to be optimized. Throughout the remainder of the paper, and without loss of generality, we will assume the standardized case ($\theta = 1$, $\beta_0 = 0$). If more than one test person is involved, then the same optimal design has to be applied to each of them. When the choice of the test persons is at the disposal of the examiner, the person with the highest ability provides the most information.

## 4 Two Way-Layout with Binary Predictors

Before starting the case of a two-way layout we notice that for the situation of only one rule ($K = 1$) the $D$-optimal design assigns equal weights $w_i^* = 1/2$ to the only two possible settings $x_1 = 1$ of application of the rule and $x_2 = 0$ of the basic item independently of $\beta$, as all (regular) designs are saturated.

Our main focus, however, is on $K = 2$ binary explanatory variables, where the number of parameters equals $p = 3$. Here the four possible settings are $\mathbf{x}_1 = (1,1)$, where both the rules are applied, $\mathbf{x}_2 = (1,0)$ and $\mathbf{x}_3 = (0,1)$, where either only the first or the second rule is used, respectively, and $\mathbf{x}_4 = (0,0)$ for the basic item. Hence, any design $\xi$ is completely determined by the corresponding weights $w_1,\ldots,w_4$. In what follows, we denote by $\lambda_i = \lambda(\mathbf{x}_i;\beta)$ the related intensities. Then the information matrix of a design $\xi$ results in

$$\mathbf{M}(\xi;\beta) = \begin{pmatrix} \sum_{i=1}^{4} w_i\lambda_i & w_1\lambda_1 + w_2\lambda_2 & w_1\lambda_1 + w_3\lambda_3 \\ w_1\lambda_1 + w_2\lambda_2 & w_1\lambda_1 + w_2\lambda_2 & w_1\lambda_1 \\ w_1\lambda_1 + w_3\lambda_3 & w_1\lambda_1 & w_1\lambda_1 + w_3\lambda_3 \end{pmatrix}$$

with the determinant equal to

$$\begin{aligned}\det\big(\mathbf{M}(\xi;\beta)\big) = {} & w_1w_2w_3\lambda_1\lambda_2\lambda_3 + w_1w_2w_4\lambda_1\lambda_2\lambda_4 \\ & + w_1w_3w_4\lambda_1\lambda_3\lambda_4 + w_2w_3w_4\lambda_2\lambda_3\lambda_4.\end{aligned}$$

Candidates for optimal designs will be either saturated designs on any three of these settings with the corresponding weights $w_i = 1/3$ or "true" four-point designs with suitable positive weights for all four settings. As we will see later, all these cases may occur depending on the values of the effect sizes $\beta_1$ and $\beta_2$ of the two rules. For the saturated designs denote by $\xi_{ij}$ the equally weighted three-point design on the setting $(i,j)$ and its two adjacent settings $(i,1-j)$ and $(1-i,j)$

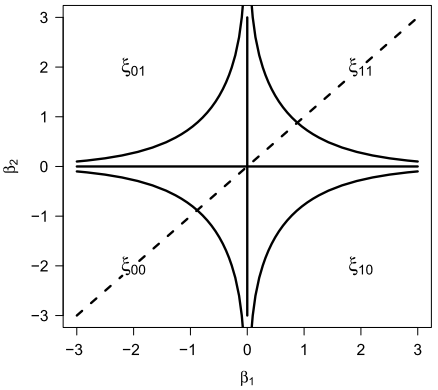


**Fig. 1** Dependence of locally $D$-optimal designs on $(\beta_1, \beta_2)$

for $i, j = 0, 1$. For example $\xi_{00}$ is the equally weighted design on $(0, 0)$, $(0, 1)$ and $(1, 0)$.

In the present application it is reasonable to investigate the case $\beta_1 \leq 0$ and $\beta_2 \leq 0$, as it is to be expected that the application of a rule increases the difficulty and, hence, decreases the easiness of an item. Other parameter constellations can be treated by symmetry considerations.

Russell et al. (2009) treated the situation of continuous predictors. From their result we may conclude that in our setting the design $\xi_{00}$, which avoids the most difficult item, is locally $D$-optimal for $\beta_1 = \beta_2 = -2$.

For other non-positive values of $\beta_1$ and $\beta_2$ we can derive that the design $\xi_{00}$ is locally $D$-optimal if and only if $\lambda_2\lambda_3\lambda_4 - \lambda_1\lambda_2\lambda_4 - \lambda_1\lambda_3\lambda_4 - \lambda_1\lambda_2\lambda_3 \geq 0$ by the celebrated equivalence theorem, see, e.g., Silvey (1980). This condition is fulfilled if and only if $\beta_2 \leq \log((1-\exp(\beta_1))/(1+\exp(\beta_1)))$. Otherwise, a "true" four-point design will be optimal.

By considerations of equivariance, similar conditions can be derived for the other sign combinations in $\beta$, and we can state that some saturated design is locally $D$-optimal if and only if $\beta_1 \neq 0$ and $|\beta_2| \geq \log((\exp(|\beta_1|) + 1)/(\exp(|\beta_1|) - 1))$.

In Fig. 1 the parameter regions of $\beta_1$ and $\beta_2$ are depicted, where the saturated designs are locally $D$-optimal. From this picture it can be seen that saturated designs are optimal if the effect sizes are large, and then that level combination is avoided, which results in the lowest intensity. Conversely, for the interior diamond shaped region, where $|\beta_2| < \log((\exp(|\beta_1|) + 1)/(\exp(|\beta_1|) - 1))$, a "true" four-point design will be locally $D$-optimal. Similar results have been obtained by Yang et al. (2012) for binary response. In the case of vanishing effects, $\beta_1 = \beta_2 = 0$, the information matrix coincides with the corresponding linear model of a two-way layout, and the equally weighted design is optimal with weights $w_i = 1/4$ on all four level combinations $\mathbf{x}_1, \ldots, \mathbf{x}_4$ (Cox 1988).

Next we consider two particular parameter constellations, where either one of the effect sizes vanishes or where the two effect sizes are equal. For the first case we assume $\beta_1 = 0$, which corresponds to the vertical axis in Fig. 1. The intensity $\lambda(\mathbf{x}; \beta)$ is constant in the first component, $\lambda_1 = \lambda_3 = \exp(\beta_2)$ and $\lambda_2 = \lambda_4 = 1$.

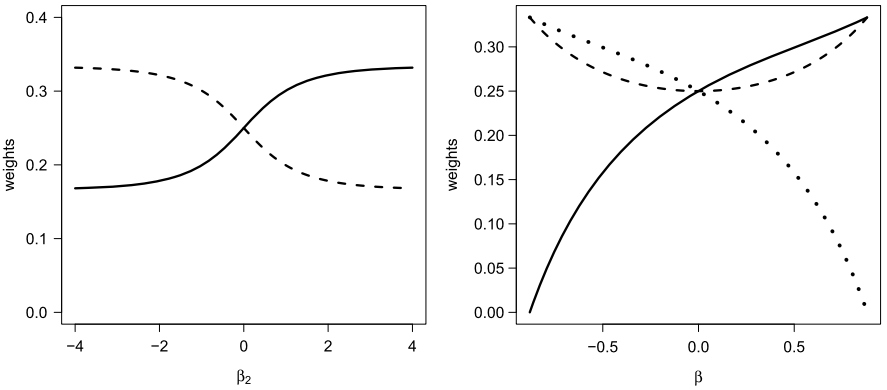


**Fig. 2** *Left panel*: optimal weights $w_1^* = w_3^*$ (*solid line*) and $w_2^* = w_4^*$ (*dashed line*) for $\beta_1 = 0$. *Right panel*: $w_1^*$ (*solid line*), $w_2^* = w_3^*$ (*dashed line*) and $w_4^*$ (*dotted line*) for $\beta_1 = \beta_2 = \beta$

According to Theorem 1 in Graßhoff et al. (2004) we obtain an optimal product-type design $\xi^*$ defined by $\xi^*(\mathbf{x}) = \xi_2^*(x_2)/2$ and the marginal weight $v^* = \xi_2^*(1)$ maximizes $v(1-v)(1+(\lambda_1-1)v)$. If, additionally, $\beta_2 = 0$, then $\lambda_1 = 1$ and the optimal marginal weight equals $v^* = 1/2$, from which we recover the optimality of the equally weighted four-point design. If $\beta_2 \neq 0$, then $\lambda_1 \neq 1$ and the optimal weight can be calculated as

$$v^* = \frac{1}{2} + \frac{\tau - 2\sqrt{\tau^2 - 3}}{6(\exp(\beta_2/2) - \exp(-\beta_2/2)},$$

where $\tau = \exp(\beta_2/2) + \exp(-\beta_2/2)$. Note that $1/3 < v^* < 2/3$. Consequently, we get $1/6 < w_i^* < 1/3$ as $w_1^* = w_3^* = v^*/2$ and $w_2^* = w_4^* = (1-v^*)/2$. The left panel of Fig. 2 exhibits these weights as functions of $\beta_2$. The weights $w_1^* = w_3^*$ for $\mathbf{x}_1 = (1,1)$ and $\mathbf{x}_3 = (0,1)$ decrease as $\beta_2 \to -\infty$, i.e., if these items become more difficult. Hence, more observations should be allocated to the other items $\mathbf{x}_2 = (1,0)$ and $\mathbf{x}_4 = (0,0)$ with lower difficulty. The case $\beta_2 = 0$ can be treated analogously.

Another parameter constellation where we can explicitly determine the optimal weights is the situation of equally sized effect sizes, $|\beta_2| = |\beta_1|$. In particular, we consider the case $\beta_2 = \beta_1 = \beta$, which is relevant for our application and which corresponds to the dashed line in Fig. 1. Here the intensities are $\lambda_1 = \exp(2\beta)$, $\lambda_2 = \lambda_3 = \exp(\beta)$ and $\lambda_4 = 1$. Owing to symmetry considerations with respect to swapping the factors, we can conclude that the optimal weights satisfy $w_2^* = w_3^*$. The saturation condition above leads to $|\beta| \geq \log(\sqrt{2}+1) \approx 0.881$. Hence, for $\beta \leq -\log(1+\sqrt{2})$ the design $\xi_{00}$ is locally $D$-optimal, while for $\beta \geq \log(1+\sqrt{2})$ this is true for the design $\xi_{11}$. For the intermediate case, $|\beta| < \log(1+\sqrt{2})$, the determinant is optimized by

$$w_2^* = w_3^* = \frac{4\gamma + 2\sqrt{\gamma^2+12}}{3(4-\gamma^2)},$$

where $\gamma = \exp(\beta) + \exp(-\beta) - 4$, and

$$w^*_{1,4} = \frac{1}{2} - w^*_2 \pm \frac{1}{4}\big(\exp(\beta) - \exp(-\beta)\big)w^*_2.$$

The right panel of Fig. 2 presents the dependence of the weights of the locally $D$-optimal designs on $\beta$. The passage from an optimal design with four points to an optimal saturated design takes place continuously in the weights at the critical values $\beta = \pm\log(1+\sqrt{2})$, and the symmetry properties of the optimal weights become evident from the picture. Again the equally weighted four-point design can be recovered to be optimal for the case of vanishing effects ($\beta = 0$). The case $\beta_2 = -\beta_1$ can again be treated analogously by symmetry considerations.

## 5 Robustness

Locally $D$-optimal designs may show poor performance if false initial values are specified for the parameters. Therefore, a sensitivity analysis has to be performed, and we shall compare the efficiency of a saturated design with that of the equally weighted four-point design, which is optimal for $\beta_1 = \beta_2 = 0$. The $D$-efficiency of a design $\xi$ is defined by $\mathrm{eff}(\xi;\beta) = (\det(\mathbf{M}(\xi;\beta))/\det(\mathbf{M}(\xi^*_\beta;\beta)))^{1/p}$, where $\xi^*_\beta$ denotes the locally $D$-optimal design at $\beta$ and $p$ is the dimension of the parameter vector (here $p = 3$).

In particular, we consider again the saturated design $\xi_{00}$. In the left panel of Fig. 3 the efficiency is exhibited for the situation of one vanishing effect ($\beta_1 = 0$). The efficiency of the saturated design $\xi_{00}$ (solid line) tends to 1 as $\beta_2 \to -\infty$ and tends to 0 as $\beta_2 \to +\infty$. The efficiency of the equally weighted four-point design (dashed line) drops from 1 for $\beta_2 = 0$, where this design is locally optimal, to $(27/32)^{1/3} \approx 0.945$, when $|\beta_2|$ tends to infinity. In the right panel of Fig. 3 the efficiency is plotted for equal effect sizes ($\beta_2 = \beta_1 = \beta$). The saturated design $\xi_{00}$ is locally $D$-optimal and, hence, has the efficiency 1 for $\beta \le -\log(1+\sqrt{2})$. If $\beta$ increases beyond this critical value, the efficiency of $\xi_{00}$ decreases, and for $\beta \ge \log(1+\sqrt{2})$ the efficiency equals $\exp(-2\beta)^{1/3}$, which finally drops down to 0. For the efficiency of the equally weighted four-point design we observe again the value of 1 at $\beta = 0$ and a lower bound of 3/4, which is approached for $|\beta| \to \infty$. Thus the equally weighted four-point design seems to be essentially more robust to misspecifications of the parameter values than the saturated designs.

Finally, we note that the equally weighted four-point design is maximin efficient for symmetric parameter regions, which follows from a corresponding result in Graßhoff and Schwabe (2008), as this design is the only invariant design with respect to permutations of the levels. Similar arguments may also establish that the equally weighted four-point design is also optimal for weighted ("Bayesian") criteria, when the weight function is symmetric in the parameters.

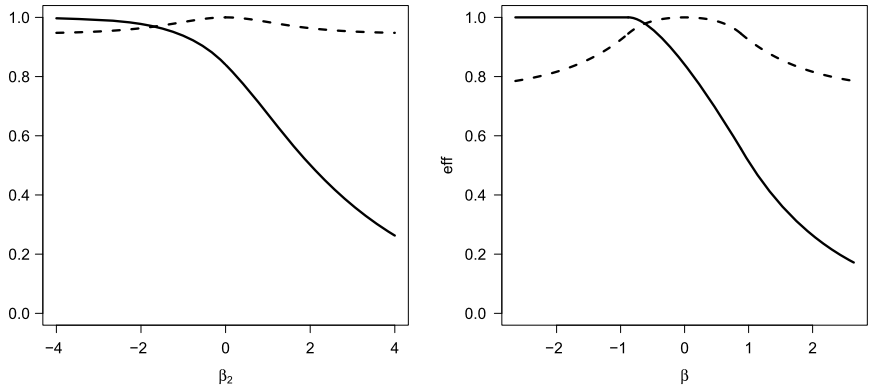


**Fig. 3** Efficiencies of the saturated design $\xi_{00}$ (*solid line*) and the equally weighted four-point design (*dashed line*). *Left panel*: $\beta_1 = 0$. *Right panel*: $\beta_1 = \beta_2 = \beta$

## 6 Conclusion

In this article we developed locally $D$-optimal designs for the Rasch Poisson counts model including two binary explanatory variables. If the effect sizes are large, saturated designs proved to be optimal. However, this condition implies, at least, a ratio of $(1 + \sqrt{2})^2 \approx 5.83$ between the highest and the lowest intensity. Such a ratio is quite unrealistic in our applications of the RPCM for rule-based testing of mental speed. Hence, four-point designs will mostly be required for the corresponding calibration studies.

For two particular parameter constellations optimal weights have been derived. For these cases it has been shown that uniform four-point designs are very robust. Since rule-based tests of mental speed often include more than two task characteristics, we will, as a next step, develop locally $D$-optimal designs for the RPCM with $K > 2$ binary explanatory variables.

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## References

Cox, D.R.: A note on design when response has an exponential family distribution. Biometrika **75**, 161–164 (1988)

Graßhoff, U., Schwabe, R.: Optimal design for the Bradley-Terry paired comparison model. Stat. Methods Appl. **17**, 275–289 (2008)

Graßhoff, U., Großmann, H., Holling, H., Schwabe, R.: Design optimality for main effects in linear paired comparison models. J. Stat. Plan. Inference **126**, 361–376 (2004)

Graßhoff, U., Holling, H., Schwabe, R.: Optimal designs for linear logistic test models. In: Givovagnoli, A., Atkinson, A., Torsney, B. (eds.) mODa 9—Advances in Model-Oriented Design and Analysis, pp. 97–104. Physica-Verlag, Berlin (2010)

Jäger, A.: Intelligenzstrukturforschung: Konkurrierende Modelle, neue Entwicklungen. Perspektiven **35**, 21–35 (1984)
Jansen, M.: Rasch's model for reading speed with manifest explanatory variables. Psychometrika **62**, 393–409 (1997)
Kiefer, J.: General equivalence theory for optimum designs (approximate theory). Ann. Stat. **2**, 849–879 (1974)
Rasch, G.: Probabilistic Models for Some Intelligence and Attainment Tests. Danish Institute for Educational Research, Copenhagen (1960)
Russell, K., Woods, D., Lewis, S., Eccleston, J.: D-optimal designs for Poisson regression models. Stat. Sin. **19**, 721–730 (2009)
Silvey, D.: Optimal Design. Chapman & Hall, London (1980)
Verhelst, N.D., Kamphuis, F.H.: A Poisson-Gamma model for speed tests. Tech. Rep. 2009-2, Cito, Arnhem (2009)
Yang, J., Mandal, A., Majumdar, D.: Optimal designs for two-level factorial experiments with binary response. Stat. Sin. **22**, 885–907 (2012)

# Differences between Analytic and Algorithmic Choice Designs for Pairs of Partial Profiles

**Heiko Großmann**

**Abstract** Choice experiments are widely used for measuring how the attributes of goods or services influence preference judgments. To this end, a suitable experimental design is used to combine attribute levels into options or profiles and to further arrange these into choice sets. Often incomplete descriptions of the options, which are known as partial profiles, are used in order to reduce the amount of information respondents need to process. For the situation where the choice sets are pairs, where only the main effects of the attributes are of interest and where the attributes fall into two groups such that all attributes within a group have the same number of levels, optimal designs which were obtained analytically are compared with algorithmically generated designs. For the situations considered, there are sometimes substantial differences between the efficiencies of the two types of design.

## 1 Introduction

Choice experiments mimic situations where individuals face a decision between a number of competing real or, more frequently, hypothetical options. The goal is to find out why, for example, certain products are preferred over others and to quantify the influence of the dimensions or attributes which characterize the choice alternatives. Individuals are asked to consider several choice sets and to pick the, usually, most preferred option from each choice set. More details about this type of experiment, methods of analysis and examples of applications can be found in Louviere et al. (2000) and Train (2003).

After identifying the attributes and levels which are deemed to represent the most important characteristics of the, say, products of interest, an integral part of a choice experiment is the design of the choice sets. This amounts to generating so-called profiles or, more technically, vectors of attribute level combinations which represent the choice options and to arranging the profiles into choice sets of a, typically,

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fixed size. Usually the two steps are interrelated and the profiles and choice sets are created simultaneously. Choice sets of size two, three or four appear to be most commonly used in practice. In this paper, only paired comparisons are considered, that is choice experiments with choice sets of size two. General results about the design of these experiments have been presented by Graßhoff et al. (2004) and Street and Burgess (2007), among others.

The number of attributes is one of the dimensions which have an effect on the complexity of the choice task (Caussade et al. 2005). High task complexity is associated with a greater amount of information that needs to be processed. If the task is too demanding, individuals may resort to simplifying response strategies when making their preference judgments, such as considering only the most important attributes. The assumption common to many choice models that the effects of the attributes combine linearly becomes questionable when such strategies are applied.

One approach which attempts to avoid the possibly detrimental effects of high task complexity uses so-called partial profiles (Chrzan 2010) where, within every choice set, only the levels of a few of the attributes are allowed to change. For example, in a choice experiment with five attributes, the partial profiles in every given choice set may differ in only three of the attributes, while the levels of the remaining two attributes are held constant across all the alternatives in the set. In practice, often then only the attributes which are not fixed are shown.

Although the name 'partial profiles' was only coined later, designs for experiments involving such profiles appear to have been considered first in Green (1974). That paper presents some general ideas, but does not consider the efficiency of the designs. Optimality results and constructions for pairs of partial profiles when all attributes have the same number of levels and only the main effects are to be estimated are given in Graßhoff et al. (2004). Extensions to situations with different numbers of levels are presented in Großmann et al. (2006, 2009). The first of these papers derives the general form of the information matrix of optimal designs and proves a sufficient condition for optimality, while the second paper gives constructions of exact optimal designs for the case where there are two groups of attributes such that within each group the number of levels is constant. An optimal design algorithm for generating partial profile choice designs with choice sets of any size is described in Kessels et al. (2011). A version of this algorithm is implemented in the JMP10 software (JMP 2012).

In what follows, some simple experiments are considered, where the choice sets are pairs of partial profiles. As in Großmann et al. (2009) it is assumed that only the main effects of the attributes are to be estimated and, moreover, that the attributes fall into two groups with the same number of levels within each group. In this setting, optimal designs which were obtained analytically are compared with designs that were generated algorithmically by using the JMP10 software.

## 2 Designs for Pairs of Partial Profiles

### 2.1 Model and Information Matrix

A common model for choice experiments is the multinomial logit or, in short, MNL model. For an experiment with $N$ choice sets $C_n$, $n = 1, \ldots, N$, each of which contains $m$ options $\mathbf{x}_{n,1}, \ldots, \mathbf{x}_{n,m}$, this model assumes that the probability of choosing $\mathbf{x}_{n,i}$ from $C_n$ is given by

$$P(\mathbf{x}_{n,i}; C_n) = \frac{\exp[\mathbf{f}(\mathbf{x}_{n,i})^\top \beta]}{\sum_{j=1}^{m} \exp[\mathbf{f}(\mathbf{x}_{n,j})^\top \beta]}, \tag{1}$$

where $\mathbf{f}$ is a vector of known regression functions and $\beta$ a vector of unknown parameters. Every option $\mathbf{x}_{n,i}$ is a vector whose components are the levels of $K$ attributes, which here are assumed to be qualitative factors with a finite number of levels. The levels of an attribute with $u$ levels are represented by the integers $1, 2, \ldots, u$. For an exact design $\xi$ with $N$ choice sets $C_1, \ldots, C_N$ the information matrix, normalized by the number of choice sets, is equal to

$$\mathbf{M}(\xi, \beta) = \frac{1}{N} \sum_{n=1}^{N} \mathbf{X}_n^\top \big(\mathrm{Diag}(\mathbf{p}_n) - \mathbf{p}_n \mathbf{p}_n^\top\big) \mathbf{X}_n, \tag{2}$$

where $\mathbf{X}_n$ is a matrix with rows $\mathbf{f}(\mathbf{x}_{n,1})^\top, \ldots, \mathbf{f}(\mathbf{x}_{n,m})^\top$. Further, $\mathbf{p}_n$ is a column vector with elements $P(\mathbf{x}_{n,1}; C_n), \ldots, P(\mathbf{x}_{n,m}; C_n)$. In what follows, designs are compared in terms of the $D$-optimality criterion, which aims to maximize the determinant of the information matrix.

Only choice sets of size $m = 2$, that is pairs, are considered. In this case the probability in (1) of choosing the first option $\mathbf{x}_{n,1}$ from the pair $C_n$ can be written as $P(\mathbf{x}_{n,1}; C_n) = \exp[(\mathbf{f}(\mathbf{x}_{n,1}) - \mathbf{f}(\mathbf{x}_{n,2}))^\top \beta] / (1 + \exp[(\mathbf{f}(\mathbf{x}_{n,1}) - \mathbf{f}(\mathbf{x}_{n,2}))^\top \beta])$, which shows that standard logistic regression with appropriately coded explanatory variables can be used to estimate the model parameters.

The information matrix in (2) depends on the unknown parameter vector $\beta$. However, for the purpose of deriving optimal or efficient designs, the assumption $\beta = \mathbf{0}$ is frequently made, which means that every option has the same probability of being chosen from a choice set. Sometimes the corresponding designs are called utility-neutral (Kessels et al. 2011). Under this assumption, for every exact design $\xi$ where $C_1, \ldots, C_N$ are pairs of alternatives it follows that

$$\mathbf{M}(\xi, \mathbf{0}) = \frac{1}{4N} \mathbf{X}^\top \mathbf{X} = \frac{1}{4} \mathbf{M}(\xi),$$

where $\mathbf{X}$ with rows $(\mathbf{f}(\mathbf{x}_{n,1}) - \mathbf{f}(\mathbf{x}_{n,2}))^\top$ is the design matrix and $\mathbf{M}(\xi)$ the normalized information matrix for the linear paired comparison model

$$Y(\mathbf{x}_{n,1}, \mathbf{x}_{n,2}) = \big(\mathbf{f}(\mathbf{x}_{n,1}) - \mathbf{f}(\mathbf{x}_{n,2})\big)^\top \beta + \varepsilon. \tag{3}$$

Thus designs which are $D$-optimal for the model (3) are also optimal for the MNL model with choice sets of size $m = 2$.

For experiments which use partial profiles, the number $S < K$ of attributes for which the options in a choice set can have different levels and which is also known as the profile strength (Graßhoff et al. 2004) is determined prior to generating the design. For pairs of partial profiles the design region $\mathscr{X}^*(S)$ for the model (3) is then the set of all ordered pairs $(\mathbf{x}_{n,1}, \mathbf{x}_{n,2})$ which have different levels for exactly $S$ of the attributes.

## 2.2 Two Groups of Factors

In applications, several of the $K$ attributes often share the same number of levels. In the simplest case, after a possible reordering, each of the first $1 \leq K_1 < K$ attributes possesses $u_1$ levels and each of the remaining $K_2 = K - K_1$ attributes has $u_2$ levels, where $u_1 < u_2$. If the levels of these attributes are effects-coded, then the vector of regression functions for option $\mathbf{x}_{n,i}$ can be represented as $\mathbf{f}(\mathbf{x}_{n,i}) = (\mathbf{f}_1(\mathbf{x}_{n,i})^\top, \ldots, \mathbf{f}_K(\mathbf{x}_{n,i})^\top)^\top$, where for $k = 1, \ldots, K_1$ and $i = 1, 2$ the component $\mathbf{f}_k(x_{n,i})$ is a column vector of length $q_1 = u_1 - 1$. If the $k$-th element $x_{n,i,k}$ of $\mathbf{x}_{n,i}$ is smaller than $u_1$, then $\mathbf{f}_k(x_{n,i})$ has a 1 in position $x_{n,i,k}$ and all other components are equal to zero. Otherwise, if $x_{n,i,k} = u_1$, then $\mathbf{f}_k(x_{n,i}) = -\mathbf{1}_{q_1}$, that is all components of the vector are equal to $-1$. The $K_2$ attributes with $u_2$ levels are coded similarly. There are then $p = K_1 q_1 + K_2 q_2$ model parameters in total, where $q_2 = u_2 - 1$.

The pairs in $\mathscr{X}^*(S)$ can be classified according to their type. More precisely, for a given profile strength $S < K$ a set of pairs is of type $(n_1, n_2)$, where $n_1 + n_2 = S$, if for every pair $(\mathbf{x}_1, \mathbf{x}_2)$ in the set the profiles have different levels for $n_1$ attributes with $u_1$ levels and for $n_2$ attributes with $u_2$ levels. For the case of two groups of factors it can be shown (Großmann et al. 2009) that there exist $D$-optimal designs which use at most two different types of pairs. Table 1 distinguishes five cases (a)–(e) and gives the types of pairs which form the support of a $D$-optimal approximate design $\xi$ in each case. The corresponding weights can be found in Großmann et al. (2009). The information matrix in the model (3) of such an optimal design $\xi$ is block-diagonal and under effects-coding equal to

$$\mathbf{M}(\xi) = \begin{pmatrix} c_1(\mathbf{I}_{K_1} \otimes \mathbf{M}_{u_1}) & \mathbf{0} \\ \mathbf{0} & c_2(\mathbf{I}_{K_2} \otimes \mathbf{M}_{u_2}) \end{pmatrix}, \tag{4}$$

where $\mathbf{M}_{u_i} = \frac{2}{u_i - 1}(\mathbf{I}_{u_i - 1} + \mathbf{1}_{u_i - 1}\mathbf{1}_{u_i - 1}^\top)$ for $i = 1, 2$. In the cases (a)–(d) of Table 1 the constants $c_1$ and $c_2$ in (4) are equal to $c_1 = q_1 S/p$ and $c_2 = q_2 S/p$, respectively, whereas in case (e) the constants are $c_1 = 1 - (K - S)/K_1$ and $c_2 = 1$.

By using Hadamard and weighing matrices, $D$-optimal exact designs with practical numbers of pairs can be constructed which use only the types of pairs in Table 1. For each of the above cases (a)–(e) several constructions are presented in Großmann et al. (2009). An example of an optimal design with $N = 24$ pairs for $K_1 = 3$, $K_2 = 2$, $u_1 = 2$, $u_2 = 4$ and $S = 3$, which provides an illustration of case (e), is shown in the left panel of Table 2. In the table, an asterisk $(*)$ indicates an attribute level that is held constant in a pair. Since the constant levels have no effect on the

**Table 1** Types $(n_1, n_2)$ of pairs used by $D$-optimal partial profile designs for two groups

| Case | Conditions | Pair type |
|---|---|---|
| (a) | $K_1, K_2 \geq S$ | $(S, 0)$ and $(0, S)$ |
| (b) | $K_2 \geq S > K_1$ | $(K_1, S - K_1)$ and $(0, S)$ |
| (c) | $K_1 \geq S > K_2$ and $q_2 S < p$ | $(S - K_2, K_2)$ and $(S, 0)$ |
| (d) | $S > K_1, K_2$ and $q_2 S < p$ | $(K_1, S - K_1)$ and $(S - K_2, K_2)$ |
| (e) | $S > K_2$ and $q_2 S \geq p$ | $(S - K_2, K_2)$ |

**Table 2** Partial profile designs with $N = 24$ pairs for $K_1 = 3$, $K_2 = 2$, $u_1 = 2$, $u_2 = 4$ and $S = 3$

| Pair | Optimal design | Pair | JMP10 design |
|---|---|---|---|
| 1 | ((2, ∗, ∗, 2, 2), (1, ∗, ∗, 1, 1)) | 1 | ((1, 1, 2, 2, 4), (2, 1, 2, 3, 2)) |
| 2 | ((2, ∗, ∗, 3, 3), (1, ∗, ∗, 1, 1)) | 2 | ((1, 2, 1, 1, 3), (1, 1, 2, 1, 3)) |
| 3 | ((∗, 2, ∗, 4, 4), (∗, 1, ∗, 1, 1)) | 3 | ((1, 2, 1, 4, 4), (2, 2, 1, 1, 4)) |
| 4 | ((∗, 2, ∗, 3, 3), (∗, 1, ∗, 2, 2)) | 4 | ((1, 1, 1, 2, 3), (1, 2, 2, 1, 3)) |
| 5 | ((∗, ∗, 2, 4, 4), (∗, ∗, 1, 2, 2)) | 5 | ((2, 2, 1, 2, 2), (1, 2, 1, 3, 1)) |
| 6 | ((∗, ∗, 2, 4, 4), (∗, ∗, 1, 3, 3)) | 6 | ((2, 2, 2, 4, 1), (1, 1, 2, 3, 1)) |
| 7 | ((1, ∗, ∗, 2, 1), (2, ∗, ∗, 1, 2)) | 7 | ((2, 2, 2, 3, 2), (2, 2, 1, 1, 1)) |
| 8 | ((1, ∗, ∗, 3, 1), (2, ∗, ∗, 1, 3)) | 8 | ((2, 2, 2, 2, 4), (2, 2, 1, 1, 2)) |
| 9 | ((∗, 1, ∗, 4, 1), (∗, 2, ∗, 1, 4)) | 9 | ((1, 1, 2, 1, 3), (1, 2, 2, 2, 1)) |
| 10 | ((∗, 1, ∗, 3, 2), (∗, 2, ∗, 2, 3)) | 10 | ((1, 1, 2, 2, 2), (2, 2, 2, 2, 1)) |
| 11 | ((∗, ∗, 1, 4, 2), (∗, ∗, 2, 2, 4)) | 11 | ((2, 2, 1, 3, 3), (1, 1, 2, 3, 3)) |
| 12 | ((∗, ∗, 1, 4, 3), (∗, ∗, 2, 3, 4)) | 12 | ((1, 1, 2, 3, 1), (2, 1, 1, 3, 4)) |
| 13 | ((1, ∗, ∗, 1, 2), (2, ∗, ∗, 2, 1)) | 13 | ((1, 1, 1, 2, 3), (2, 2, 1, 2, 1)) |
| 14 | ((1, ∗, ∗, 1, 3), (2, ∗, ∗, 3, 1)) | 14 | ((2, 1, 1, 4, 1), (2, 2, 1, 1, 3)) |
| 15 | ((∗, 1, ∗, 1, 4), (∗, 2, ∗, 4, 1)) | 15 | ((2, 2, 1, 1, 4), (1, 2, 2, 1, 1)) |
| 16 | ((∗, 1, ∗, 2, 3), (∗, 2, ∗, 3, 2)) | 16 | ((2, 1, 2, 1, 3), (1, 2, 1, 1, 3)) |
| 17 | ((∗, ∗, 1, 2, 4), (∗, ∗, 2, 4, 2)) | 17 | ((2, 1, 1, 3, 1), (1, 1, 1, 3, 1)) |
| 18 | ((∗, ∗, 1, 3, 4), (∗, ∗, 2, 4, 3)) | 18 | ((2, 2, 2, 1, 3), (1, 1, 2, 1, 4)) |
| 19 | ((2, ∗, ∗, 1, 1), (1, ∗, ∗, 2, 2)) | 19 | ((2, 1, 2, 1, 4), (2, 1, 1, 3, 3)) |
| 20 | ((2, ∗, ∗, 1, 1), (1, ∗, ∗, 3, 3)) | 20 | ((2, 1, 2, 4, 3), (2, 2, 1, 4, 2)) |
| 21 | ((∗, 2, ∗, 1, 1), (∗, 1, ∗, 4, 4)) | 21 | ((2, 2, 1, 2, 2), (1, 2, 2, 3, 2)) |
| 22 | ((∗, 2, ∗, 2, 2), (∗, 1, ∗, 3, 3)) | 22 | ((1, 1, 1, 1, 4), (1, 2, 2, 2, 4)) |
| 23 | ((∗, ∗, 2, 2, 2), (∗, ∗, 1, 4, 4)) | 23 | ((2, 2, 1, 3, 4), (2, 1, 2, 3, 3)) |
| 24 | ((∗, ∗, 2, 3, 3), (∗, ∗, 1, 4, 4)) | 24 | ((2, 2, 2, 4, 2), (1, 2, 1, 2, 2)) |

optimality of the designs, the '∗' symbols which occur in the same position in the two options of a pair can be replaced with any of the levels of the corresponding attribute.

Großmann et al. (2009) also report the parameters needed for constructing optimal partial profile designs with at most $N = 100$ pairs for all situations with $4 \leq K \leq 6$ attributes in two groups with $2 \leq u_1 \leq 4$ and $u_1 < u_2 \leq 5$ levels and profile strength $S = 2$ or $S = 3$. The corresponding designs are available on the Internet at http://www.maths.qmul.ac.uk/~hg/PP2G/.

## 3 Efficiency Comparison

Optimal design algorithms for generating partial profile designs for experiments with choice sets of any size, for any number of attributes and levels, and arbitrary profile strength are presented in Kessels et al. (2011). These can be used to generate utility-neutral designs, that is under the assumption $\beta = \mathbf{0}$, but also allow the specification of a distribution for the model parameters at the design stage. In this section only designs for $\beta = \mathbf{0}$ are considered.

The algorithms generalize ideas of Green (1974) and proceed in two stages. First, the attributes that are held constant in the choice sets are determined and, secondly, the levels of the attributes that can change are computed. When the so-called unrestricted algorithm (Kessels et al. 2011) is used, then in some choice sets the number of attributes that do change can be smaller than the intended profile strength. A version of this unrestricted algorithm is implemented in the JMP10 software and in this section for the case of two groups of attributes we compare the designs in Großmann et al. (2009) with the corresponding utility-neutral designs generated by the software. The second design in Table 2 is one example. It should be noted that instead of using asterisks to indicate constant levels, the software produces designs which have levels for all attributes.

For all designs in Table 2 of Großmann et al. (2009) with $K = 4$ or $K = 5$ attributes, the corresponding utility-neutral JMP10 designs were generated by selecting the options to ignore the prior information and to ignore the prior variance. Moreover, the number of randomly chosen starting designs was set to thirty in all cases. Since in some of the examples in Kessels et al. (2011) two thousand random starts were used, this number appears to be very small. The reason for choosing a small number of random starts is, however, that although for small designs the algorithm runs very quickly, for some larger examples several hours were needed to generate the designs.

Table 3 reports $D$-efficiency values of the JMP10 designs, which are computed in the usual way as the $p$-th root, where $p = K_1q_1 + K_2q_2$ is the number of model parameters, of the ratio of the determinant of the information matrix of the algorithmic design divided by the determinant of the information matrix of the optimal design. The latter matrix is the one in (4) with constants $c_1$ and $c_2$ given earlier. For convenience, in the table the efficiency values are reported as percentages. It should be noted that the software does not appear to routinely provide the efficiency of the designs and that all values in Table 3 were computed outside JMP10. The 'ID' column gives the name of the construction in Table 1 of Großmann et al. (2009) that

**Table 3** Efficiency of designs generated by JMP10 software

| $K$ | $K_1$ | $K_2$ | $u_1$ | $u_2$ | $S$ | ID | Pairs | $D$-Efficiency (%) |
|---|---|---|---|---|---|---|---|---|
| 4 | 1 | 3 | 2 | 3 | 3 | b4 | 42 | 92.60 |
| 4 | 2 | 2 | 2 | 3 | 2 | a1 | 18 | 89.44 |
| 4 | 2 | 2 | 2 | 3 | 3 | e1 | 12 | 85.17 |
| 4 | 2 | 2 | 2 | 4 | 2 | a1 | 16 | 75.45 |
| 4 | 2 | 2 | 2 | 4 | 3 | e1 | 24 | 83.32 |
| 4 | 2 | 2 | 2 | 5 | 2 | a1 | 50 | 77.15 |
| 4 | 2 | 2 | 2 | 5 | 3 | e1 | 40 | 78.93 |
| 4 | 2 | 2 | 3 | 4 | 2 | a1 | 60 | 93.76 |
| 4 | 2 | 2 | 3 | 5 | 2 | a1 | 90 | 90.26 |
| 4 | 3 | 1 | 2 | 3 | 2 | c2 | 30 | 93.36 |
| 4 | 3 | 1 | 2 | 3 | 3 | e2 | 36 | 93.51 |
| 4 | 3 | 1 | 2 | 4 | 2 | e1 | 12 | 76.56 |
| 4 | 3 | 1 | 2 | 4 | 3 | e2 | 72 | 90.42 |
| 4 | 3 | 1 | 2 | 5 | 2 | e1 | 60 | 73.38 |
| 4 | 3 | 1 | 3 | 4 | 2 | c2 | 54 | 94.27 |
| 5 | 1 | 4 | 2 | 3 | 3 | b3 | 36 | 90.94 |
| 5 | 2 | 3 | 2 | 3 | 2 | a2 | 24 | 82.69 |
| 5 | 2 | 3 | 2 | 3 | 3 | b2 | 96 | 93.00 |
| 5 | 2 | 3 | 2 | 4 | 2 | a2 | 44 | 78.97 |
| 5 | 2 | 3 | 2 | 5 | 2 | a2 | 70 | 75.53 |
| 5 | 3 | 2 | 2 | 3 | 2 | a3 | 42 | 88.89 |
| 5 | 3 | 2 | 2 | 3 | 3 | c2 | 28 | 89.49 |
| 5 | 3 | 2 | 2 | 4 | 2 | a3 | 18 | 70.21 |
| 5 | 3 | 2 | 2 | 4 | 3 | e1 | 24 | 74.28 |
| 5 | 3 | 2 | 3 | 4 | 2 | a3 | 72 | 92.62 |
| 5 | 3 | 2 | 3 | 4 | 3 | c2 | 96 | 93.71 |
| 5 | 4 | 1 | 2 | 3 | 2 | c1 | 36 | 92.27 |
| 5 | 4 | 1 | 2 | 3 | 3 | e1 | 24 | 89.81 |
| 5 | 4 | 1 | 2 | 4 | 2 | c1 | 28 | 78.28 |
| 5 | 4 | 1 | 2 | 4 | 3 | e1 | 24 | 84.21 |
| 5 | 4 | 1 | 2 | 5 | 2 | e1 | 40 | 68.89 |
| 5 | 4 | 1 | 2 | 5 | 3 | e1 | 40 | 78.97 |

was used to generate the optimal design. A letter in a name, such as `b3`, refers to the corresponding case in Table 1 and the number to one of the available constructions for that case.

The highest efficiency in the table is 94.27 %, but there are several cases where the efficiency of the algorithmic design is well below 80 %. One referee pointed out that in all such cases the difference between $u_2$ and $u_1$ is greater than or equal

to two. There are, however, also situations where $u_2 - u_1 \geq 2$ and the efficiency is greater than 90 %. When the optimal design uses construction `e1`, the efficiency of the JMP10 design tends to be relatively low. This is of some interest, since the constants $c_1$ and $c_2$ in (4) for case (e) in Table 1 are different from the corresponding values in the other cases (a)–(d).

The results in Table 3 may be explained in part by the fact that the algorithm tries to achieve 'attribute balance' (Kessels et al. 2011, 2012) when choosing the attributes whose levels are held constant, without taking into account the numbers of levels, whereas the optimal designs in Großmann et al. (2009) do not possess this property. Kessels et al. (2012) therefore suggest selecting the constant attributes by means of a weighted criterion, where the weights depend on the numbers of levels and their form is motivated by the results of Graßhoff et al. (2004) and Großmann et al. (2009).

## 4 Concluding Remarks

The efficiency comparison in the current paper appears to indicate that there is still scope for improving design algorithms for choice experiments involving partial profiles. It should be emphasized however that the findings reported here should not be overgeneralized. The comparisons are only for the very specific situation of pairs and two groups of attributes with different numbers of levels. Moreover, the number of starting designs for the algorithm was relatively small and increasing that number will probably give more efficient designs. Both reviewers of the paper recommended at least 1000 random starts. While this is possible for small examples, it does not seem to be practical when there are, say, about eighty choice sets. Here for reasons of uniformity thirty random starts were used in all examples, despite which the program sometimes ran for several hours. It should also be noted that the default number of starting designs in the JMP10 software appears to be even smaller than thirty, so that users who stick to the default option will only use a few starting designs.

The optimal designs used in the comparison require very specific numbers of pairs and hence are much less widely applicable than those that can be provided by algorithms such as the JMP10 implementation of the method in Kessels et al. (2011). Still, it appears that these designs provide a useful benchmark for assessing the performance of design algorithms. The constructions in Großmann et al. (2009) can be modified to generate smaller designs which still possess a block-diagonal information matrix giving rise to a type of algorithm which is quite different from standard approaches. It is hoped to report these ideas elsewhere.

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## References

Caussade, S., Ortúzar, J.de D., Rizzi, L.I., Hensher, D.A.: Assessing the influence of design dimensions on stated choice experiments. Transp. Res. **39B**, 621–640 (2005)

Chrzan, K.: Using partial profile choice experiments to handle large numbers of attributes. Int. J. Mark. Res. **52**, 827–840 (2010)

Graßhoff, U., Großmann, H., Holling, H., Schwabe, R.: Optimal designs for main effects in linear paired comparison models. J. Stat. Plan. Inference **126**, 361–376 (2004)

Green, P.E.: On the design of choice experiments involving multifactor alternatives. J. Consum. Res. **1**, 61–68 (1974)

Großmann, H., Holling, H., Graßhoff, U., Schwabe, R.: Optimal designs for asymmetric linear paired comparisons with a profile strength constraint. Metrika **64**, 109–119 (2006)

Großmann, H., Graßhoff, U., Schwabe, R.: Approximate and exact optimal designs for paired comparisons of partial profiles when there are two groups of factors. J. Stat. Plan. Inference **139**, 1171–1179 (2009)

JMP, Version 10. SAS Institute Inc., Cary, NC (1989–2012)

Kessels, R., Jones, B., Goos, P.: Bayesian optimal designs for discrete choice experiments with partial profiles. J. Choice Model. **4**, 52–74 (2011)

Kessels, R., Jones, B., Goos, P.: A comparison of partial profile designs for discrete choice experiments with an application in software development. Research Paper 2012-004, University of Antwerp, Faculty of Applied Economics (2012)

Louviere, J.J., Hensher, D.A., Swait, J.D.: Stated Choice Methods: Analysis and Application. Cambridge University Press, Cambridge (2000)

Street, D.J., Burgess, L.: The Construction of Optimal Stated Choice Experiments: Theory and Methods. Wiley, Hoboken (2007)

Train, K.E.: Discrete Choice Methods with Simulation. Cambridge University Press, Cambridge (2003)

# Approximate Bayesian Computation Design (ABCD), an Introduction

**Markus Hainy, Werner G. Müller, and Henry P. Wynn**

**Abstract** In this paper we propose a new technique of generating optimal designs by means of simulation. The method combines ideas from approximate Bayesian computation and optimal design of experiments and allows great flexibility in the employed criteria and models. We illustrate the idea by a simple expository example.

## 1 Introduction

We are concerned with improving data collecting schemes where one has at least part control over the experimental conditions by methods of *optimum experimental design*. Furthermore, we focus on cases where a probability model for the investigated phenomenon is not easily available and the situation lends itself naturally to a recently popularized simulation technique called *approximate Bayesian computing (ABC)*. This is not the only way in which our method should be distinguished from the seminal work on simulation-based design by Peter Müller (Müller 1999; Müller et al. 2004).

In Bayesian experimental design it is natural to deal with a design criterion by averaging it over the parameter values with respect to the prior distribution (Chaloner and Verdinelli 1995). However, the perspective can be reversed by computing the criterion with respect to the posterior distribution of the parameters and then averaging the criterion over the marginal distribution of the data. The posterior distribution summarizes the knowledge about the parameters after observing the data. Thus,

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if the average criterion with respect to the posterior distribution is at least as large as the criterion with respect to the prior distribution, this reflects some notion of learning from the observations.

## 2 Bayesian Learning and Simulation Based Design

Let $\pi(\theta)$ be the probability density function (pdf) of the prior distribution of the parameters $\theta \in \Theta$ and $\pi(y|\theta, \xi)$ denote the pdf of the probability model of the data $y \in \mathscr{Y}$ for some given design $\xi \in \Xi$, which can be chosen by the experimenter. It is usually assumed that the prior of $\theta$ does not depend on the design. The pdf of the marginal distribution of $y$ follows from $\pi(y|\xi) = \int_{\theta\in\Theta} \pi(y|\theta, \xi)\pi(\theta)\,\mathrm{d}\theta$. The corresponding posterior distribution of $\theta$ is denoted by $\pi(\theta|y, \xi)$.

The aim of Bayesian optimal design is to maximize the design criterion

$$U(\xi) = \mathrm{E}_{y|\xi}\left\{\Phi\left[\pi(\theta|y,\xi)\right]\right\} = \int_{y\in\mathscr{Y}} \Phi\left[\pi(\theta|y,\xi)\right]\pi(y|\xi)\,\mathrm{d}y \tag{1}$$

with respect to $\xi$; $\Phi[\pi(\theta|y, \xi)]$ denotes a functional of the posterior distribution of $\theta$. Examples of general functionals $\Phi(\cdot)$ are, e.g., quantiles (probability regions) or the mode of the posterior $\pi(\theta|y, \xi)$. If

$$\Phi\left[\pi(\theta|y,\xi)\right] = \int_{\theta\in\Theta} u(y,\theta,\xi)\pi(\theta|y,\xi)\,\mathrm{d}\theta, \tag{2}$$

and $u(\cdot)$ is regarded as a utility function (here for the simplicity of the posterior), then $U(\xi)$ is called the expected utility function. In this case the problem of finding $\xi^* = \arg\max_\xi U(\xi)$ is referred to as a problem of *expected utility maximization* (cf., e.g., Müller 1999).

From, e.g., Ginebra (2007), it follows that the class of functionals $\Phi$ such that, for all $\pi(\theta)$ and $\pi(y|\theta, \xi)$,

$$U(\xi) \geq \Phi\left[\pi(\theta)\right] \tag{3}$$

is the class of convex functionals: $\Phi[(1-\alpha)\pi_1 + \alpha\pi_2] \leq (1-\alpha)\Phi(\pi_1) + \alpha\Phi(\pi_2)$. Convex functionals can be interpreted as measures of dispersion because they take on their largest values over outlying regions. For highly informative experiments, the posterior distributions are very peaked. Moreover, the peak and therefore the form of the posterior distribution change considerably if $y$ changes by a non-negligible amount. Convex functionals tend to attribute higher values to "extreme" posterior distributions, which provide a lot of information about $\theta$. Thus the expectation $U(\xi) = \mathrm{E}_{y|\xi}\{\Phi[\pi(\theta|y, \xi)]\}$, where $\Phi(\cdot)$ is any convex functional, is a measure of the experiment's average information about $\theta$, see Ginebra (2007). The most common measure of information is Fisher information. Therefore, (3) states that the expected information of the experiment is at least as high as the prior information.

If it is feasible to compute $U(\xi)$ for all possible designs $\xi$, a standard maximization algorithm can be employed to find $\xi^* = \arg\max_\xi U(\xi)$. This computation,

however, can be a challenging task. Usually it involves the evaluation of integrals or sums. If the integrals are analytically intractable and numerical integration routines do not work, Monte Carlo simulation strategies can be applied in a framework of stochastic optimization.

For a range of standard problems $\Phi[\pi(\theta|y,\xi)]$ can be evaluated explicitly. However, for cases where $\pi(\theta|y,\xi)$ is hard to evaluate or, at least, the integral over $y$ in (1) is expensive to compute, more refined simulation-based methods are needed. If it is possible to calculate $\Phi[\pi(\theta|y,\xi)]$ or estimate it by $\hat{\Phi}[\pi(\theta|y,\xi)]$ for all values of $y$, one can perform Monte Carlo integration over the draws $\{y^{(i)},\ i=1,\ldots,G\}$:

$$\hat{U}(\xi) = \frac{1}{G}\sum_{i=1}^{G} \hat{\Phi}\left[\pi\left(\theta|y^{(i)},\xi\right)\right] \tag{4}$$

and proceed by some maximization of $\hat{U}(\xi)$. For the estimation of $\hat{\Phi}[\pi(\theta|y,\xi)]$ we propose to employ a recently popularized special simulation-based technique called *approximate Bayesian computing*.

## 3 ABCD

ABC, sometimes referred to as *likelihood-free* methods, can be applied if simulating the data from the probability model is feasible for every parameter $\theta$. For instances where it has been successfully applied, see Sisson and Fan (2011).

The simplest case is likelihood-free rejection sampling. The goal is to sample from the posterior distribution $\pi(\theta|y)$. This is done by drawing the parameters from the prior distribution, $\theta \sim \pi(\theta)$, drawing a variable $y'$ from the probability model, $y' \sim \pi(y|\theta)$, and accepting $\theta$ if $y' \approx y$. Thus, direct sampling from the posterior distribution is replaced by sampling from the prior distribution. The efficiency of this approach depends crucially on the similarity between the posterior and the prior distribution, i.e., the information gain of the posterior compared with the prior distribution.

More generally, the original posterior target distribution $\pi(\theta|y)$ is replaced by the marginal of the augmented distribution

$$\pi_{ABC}\left(\theta, y'|y\right) \propto \pi_{\varepsilon}\left(y|y',\theta\right)\pi\left(y'|\theta\right)\pi(\theta).$$

The variable $y'$, which is sampled together with $\theta$, is added to the posterior arguments. Integrating over $y'$ leads to the original posterior distribution if $\pi_{\varepsilon}(y|y',\theta)$ is a point mass at the point $y'=y$. Since this event has a very small probability for higher-dimensional discrete distributions and probability zero in the case of continuous distributions, a compromise has to be found between exactness and practicality by adjusting the "narrowness" of $\pi_{\varepsilon}(y|y',\theta)$. In this case $\pi_{\varepsilon}(y|y',\theta)$ is usually assumed to be a smoothing kernel density function: $\pi_{\varepsilon}(y|y',\theta) = (1/\varepsilon)K\{[|T(y') - T(y)|]/\varepsilon\}$, where $T(\cdot)$ is some low-dimensional statistic of $y$ and $y'$, respectively.

If the statistic is a sufficient statistic for the parameters of the probability model, we obtain the same distribution if we integrate out $T(y')$ as if we integrate out $y'$ itself. The parameter $\varepsilon$ controls the tightness of $\pi_\varepsilon(y|y', \theta)$. Popular choices for $K(\cdot)$ are uniform, Gaussian, or Epanechnikov kernels.

Linear functionals of the form (2) are the most common class of functionals and thus deserve particular attention. In this case (1) can be written as

$$U(\xi) = \int_{y \in \mathscr{Y}} \int_{\theta \in \Theta} u(y, \theta, \xi) \pi(y|\theta, \xi) \pi(\theta) \, \mathrm{d}\theta \, \mathrm{d}y. \tag{5}$$

As in the general case (1), the explicit evaluation or numerical integration of the linear functional expression (5) may not be possible. However, in most practical cases there is some effective way to sample from the prior distribution $\pi(\theta)$ and from the probability model for the data $\pi(y|\theta, \xi)$. If a sample $\{y^{(i)}, \theta^{(i)}, \ i = 1, \ldots, G\}$ can be obtained with little computational effort, one straightforward way to compute $U(\xi)$ is to perform Monte Carlo integration:

$$\hat{U}(\xi) = \frac{1}{G} \sum_{i=1}^{G} u\big(y^{(i)}, \theta^{(i)}, \xi\big).$$

Practical applications of simulation-based optimal design have mainly focused on linear functionals because it is relatively simple to sample the data and the parameters and to compute the design criterion via Monte Carlo integration.

In the linear functional case, it is also possible to pursue the simulation based optimal design approach originally proposed by Müller (1999); the integrand in (5) is regarded as a joint distribution of the variables $y, \theta$, and $\xi$. MCMC methods are used to estimate this joint distribution. The mode of the marginal distribution of $\xi$ gives the optimal design. Therefore this approach jointly addresses the estimation as well as the optimization problem. An MCMC-based variant of design optimization without likelihoods is alluded to in Hainy et al. (2012). A comprehensive account of ABC methods for MCMC is given in Sisson and Fan (2011).

In contrast, our ABCD method (4) does not employ an MCMC step, and therefore allows simple and effective treatment of complex models and nonlinear optimality criteria. It presents two major challenges. First, one needs draws from the marginal distribution of $y$, which may not be directly available. Second, $\Phi[\pi(\theta|y, \xi)]$ is a functional of the posterior distribution, so one needs an innovative method for fast evaluation of criteria based on the posterior distribution. ABC methods, however, suggest a way of dealing with both problems. A sample $S = \{(y'^{(i)}, \theta^{(i)}), \ i = 1, \ldots, G\}$ can be obtained in the usual way of first drawing $\theta^{(i)}$ from the prior distribution and then drawing $y'^{(i)}$ from the probability model. Draws of the posterior distribution of $\theta$ for a particular $y' = y$ are obtained by retaining those elements of $S$ where the draws of $y'$ are close to $y$, i.e., $y'^{(i)} \in N_\varepsilon(y)$, where $N_\varepsilon(y)$ denotes an $\varepsilon$-neighbourhood around $y$.

We summarize ABCD in abbreviated form:

1. Choose a design $\xi$.

2. Draw $\{\theta\}$ values from the prior distribution $\pi(\theta)$.
3. For every sample parameter value draw from $\pi(y|\theta, \xi)$ hence producing a sample $\{y'\}$ from the joint distribution of $y$ and $\theta$.
4. For every $y$ from the marginal distribution $\pi(y|\xi)$ collect the $\theta$ for which $y'$ lies in a neighbourhood $N_\varepsilon(y)$.
5. Approximate the criterion $\Phi$ using these neighbourhood $\theta$ values.
6. Approximate $U(\xi)$ by Monte-Carlo integration (Eq. (4)).
7. Repeat Steps 1–6 for each $\xi$ during an optimization procedure.

## 4 An Expository Example

We apply the standard linear regression model, so we assume that

$$\pi(y|\theta, X) = \mathcal{N}\big(X\theta, \sigma^2 I_N\big).$$

That is, the expected value of the dependent variable is a linear combination of the parameter values $\theta \in \Theta \subseteq \mathbb{R}^k$ and depends on the design through the design matrix $X = [f(x_1), \ldots, f(x_N)]^T$, where $f(\cdot)$ is a $k$-dimensional function of the design variables $x_i \in [-1, 1]$. The $N$ observations are assumed to be normally distributed, independent, and homoscedastic with known variance $\sigma^2$. Furthermore, the parameters $\theta$ follow the prior normal distribution

$$\pi(\theta) = \mathcal{N}\big(\theta_0, \sigma^2 R^{-1}\big).$$

Define $M = X^T X$. Then the posterior distribution of the parameters $\theta$ is

$$\pi(\theta|y, X) = \mathcal{N}\big[(M + R)^{-1}\big(X^T y + R\theta_0\big), \sigma^2 (M + R)^{-1}\big].$$

We take

$$\Phi\big[\pi(\theta|y, X)\big] = \int_{\theta\in\Theta} \log\left[\frac{\pi(\theta|y, X)}{\pi(\theta)}\right]\pi(\theta|y, X)\,\mathrm{d}\theta,$$

so we have a linear functional of the posterior with utility function $u(y, \theta, X) = \log[\pi(\theta|y, X)] - \log[\pi(\theta)]$. The expected utility for a specific design $X$ is the expected gain in Shannon information (Chaloner and Verdinelli 1995):

$$U(X) = \int_{y\in\mathcal{Y}} \left\{\int_{\theta\in\Theta} \log\left[\frac{\pi(\theta|y, X)}{\pi(\theta)}\right]\pi(\theta|y, X)\,\mathrm{d}\theta\right\}\pi(y|X)\,\mathrm{d}y$$

Since $\iint \log[\pi(\theta)]\pi(\theta|y, X)\pi(y|X)\mathrm{d}\theta\mathrm{d}y = \int \log[\pi(\theta)]\pi(\theta)[\int \pi(y|\theta, X)\mathrm{d}y]\mathrm{d}\theta$ does not depend on $X$, it is sufficient to compute

$$U^*(X) = \int_{y\in\mathcal{Y}} \left\{\int_{\theta\in\Theta} \log\big[\pi(\theta|y, X)\big]\pi(\theta|y, X)\,\mathrm{d}\theta\right\}\pi(y|X)\,\mathrm{d}y. \tag{6}$$

For our particular model, the integral can be computed analytically. It is

$$U^*(X) = -\frac{k}{2}\log(2\pi) - \frac{k}{2} + \frac{1}{2}\log\det\left[\sigma^{-2}(M+R)\right],$$

which has the same maximum as the criterion for $D_B$ optimality, $\Psi(X) = \det[M+R]$ (Atkinson et al. 2007). Note that the $D_B$-optimal design depends neither on $\sigma^2$ nor on the prior mean $\theta_0$. We examine the performance of the ABCD algorithm on our toy example. This little exercise is meant to assess the usefulness and limitations of the algorithm. It is not difficult to obtain the exact solution for our example, making it easy to check the results.

The following setting was used: the predictor is a quadratic in one factor, i.e.

$$X = \begin{pmatrix} 1 & x_1 & x_1^2 \\ \vdots & \vdots & \vdots \\ 1 & x_N & x_N^2 \end{pmatrix}.$$

The continuous optimal design for this problem puts equal weights of $1/3$ on the three design points $-1$, 0, and 1, see Atkinson et al. (2007). Likewise, if the number of trials of an exact design is divisible by three, then at the optimal design $1/3$ of the trials are set to $-1$, 0, and 1, respectively. Therefore, if we want to select $N = 1$ trial and if the prior information matrix $R$ is chosen to represent prior information equivalent to two observations taken at the design points $-1$ and 1, respectively, i.e., $R = f(-1)f^T(-1) + f(1)f^T(1) = (1,-1,1)^T(1,-1,1) + (1,1,1)^T(1,1,1)$, then it is optimal to set the trial to 0.

We solve this example following our general ABCD algorithm. Thus, for every design point $x$ that we investigate we independently generate a sample $\{y^{(i)}, i = 1,\ldots,G\}$ from the marginal distribution of $y$ and a sample $S = \{y'^{(j)}, \theta^{(j)}, j = 1,\ldots,H\}$ from the joint distribution of $y$ and $\theta$. Let $J_\varepsilon(i) = \{j \in \{1,\ldots,H\} : y'^{(j)} \in N_\varepsilon(y^{(i)})\}$ be the subset of indices of those elements of $S$ for which $y'^{(j)}$ lies in a neighbourhood of $y^{(i)}$. For every $y^{(i)}$ we compute

$$\hat{\Phi}\left[\pi\left(\theta|y^{(i)}, X\right)\right] = \frac{1}{|J_\varepsilon(i)|}\sum_{j\in J_\varepsilon(i)} \log\left[\pi\left(\theta^{(j)}|y^{(i)}, X\right)\right]$$

to estimate the inner integral in (6). In the one-dimensional case the neighbourhood is defined to be $N_\varepsilon(y) = [y - \varepsilon/2, y + \varepsilon/2]$. In our simple example we know the analytical form of $\pi(\theta|y, X)$, so we can just plug $\theta^{(j)}$ and $y^{(i)}$ into

$$\log\left[\pi(\theta|y,X)\right] = -\frac{1}{2}\log(2\pi) + \frac{1}{2}\log\det\left[\sigma^{-2}(M+R)\right] - \frac{1}{2\sigma^2}(\theta-\tilde{\theta})^T(M+R)(\theta-\tilde{\theta}),$$

where $\tilde{\theta} = (M+R)^{-1}(X^T y + R\theta_0)$.

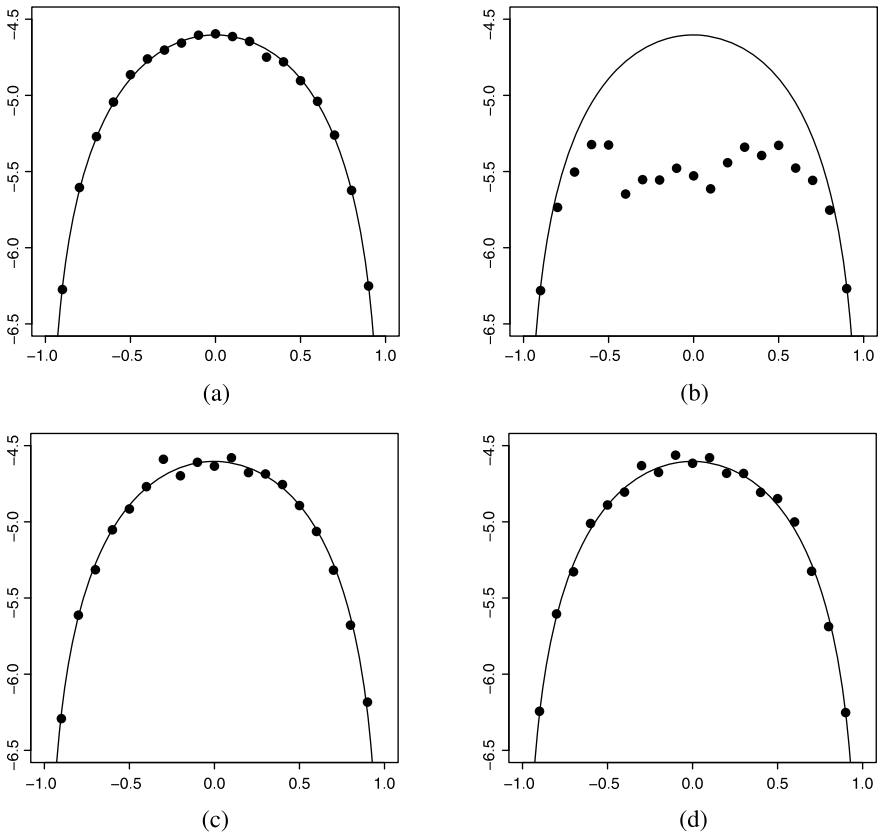


**Fig. 1** $\hat{U}(x)$ (*dots*) and $U(x)$ (*solid line*) for baseline setting with $G = 1000$, $H = 10000$, and small $\varepsilon$ (**a**); setting with high $\varepsilon$ (**b**); setting with $H = 1000$ (**c**); setting with $G = 100$ (**d**)

Finally, the outer integral is computed by averaging $\hat{\Phi}[\pi(\theta|y^{(i)}, X)]$ over the draws $\{y^{(i)}\}$ as stated in (4).

The results are shown for four settings. The first setting, which gives rather accurate approximations, uses $G = 1000$, $H = 10000$, and $\varepsilon = (\max_j\{y'^{(j)}\} - \min_j\{y'^{(j)}\})/1000$. The other three settings are meant to display the effects of decreasing the simulation numbers and expanding the neighbourhood. In the second setting, $\varepsilon$ is increased to $\varepsilon = (\max_j\{y'^{(j)}\} - \min_j\{y'^{(j)}\})/100$ while $G$ and $H$ have the same values as in the first setting. In the third setting, $H$ is changed to $H = 1000$, all other parameters being equal to the first setting. Finally, in the fourth setting $G$ is reduced to $G = 100$ while the other parameters are the same as in the first setting. The approximate criterion values $\hat{U}(x)$ were computed over a regular grid on the line segment $[-1, 1]$ with a spacing of 0.1 in order to assess the goodness of the approximations in the different parts of the design space. Figure 1 shows the approximated criterion values (dots) along with the true criterion values for all possible $x \in [-1, 1]$ (solid line) for all settings.

The first setting clearly succeeds in delivering reasonably accurate approximations to $U(x)$. When $\varepsilon$ is too large, such that the approximation is too imprecise, this has a much more severe effect on the accuracy of the results than using simulation numbers which are too small. In all three suboptimal settings, the random variation of the approximations around the true value is increased compared to the first setting. The large neighbourhood additionally introduces a considerable downward bias to the approximations. This example illustrates the paramount importance of high simulation numbers and, in particular, of small neighbourhoods for the accuracy of the ABCD results. There is a need to develop algorithms which provide accurate results while keeping the computational costs manageable.

## 5 Outlook

All these considerations demonstrate that approximate Bayesian computing offers a wide range of new opportunities for solving general optimum design problems. Particularly, for complicated models with non-evaluable and intractable likelihood functions such as models in population genetics (Marjoram et al. 2003) or models for spatial extremes, where there is no closed-form version of the multivariate extreme value distribution for dimensions greater than two (Erhardt and Smith 2012), there is a need to employ likelihood-free methods. Also, up to now, there have been no satisfying solution concepts for adaptive design problems for non-trivial models. ABCD promises to provide a universally applicable way to solve such problems. The basic ideas sketched above are still in an early stage of development and there are many possibilities for further refinements, which we intend to address in future papers.

Simulation-based approaches can be of great value to optimal experimental design whenever other methods fail to deliver useful results or are too inefficient, particularly when the design criterion is nonlinear. The use of ABC techniques further expands the range of possible applications to design problems that were intractable before. ABCD could thus become a standard solution method whenever circumstances require it.

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## References

Atkinson, A.C., Donev, A.N., Tobias, R.D.: Optimum Experimental Designs, with SAS. Oxford University Press, New York (2007)

Chaloner, K., Verdinelli, I.: Bayesian experimental design: a review. Stat. Sci. **10**, 273–304 (1995). doi:10.1214/ss/1177009939

Erhardt, R.J., Smith, R.L.: Approximate Bayesian computing for spatial extremes. Comput. Stat. Data Anal. **56**, 1468–1481 (2012). doi:10.1016/j.csda.2011.12.003

Ginebra, J.: On the measure of the information in a statistical experiment. Bayesian Anal. **2**, 167–212 (2007). http://ba.stat.cmu.edu/journal/2007/vol02/issue01/ginebra.pdf

Hainy, M., Müller, W.G., Wagner, H.: Simulation-based $D_B$-optimal designs: conception and implementation issues. In: Komárek, A., Nagy, S. (eds.) Proceedings of the 27th International Workshop on Statistical Modelling, pp. 537–542. Charles University of Prague, Prague (2012)

Marjoram, P., Molitor, J., Plagnol, V., Tavaré, S.: Markov chain Monte Carlo without likelihoods. Proc. Natl. Acad. Sci. USA **100**, 15,324–15,328 (2003). doi:10.1073/pnas.0306899100

Müller, P.: Simulation based optimal design. In: Bernardo, J.M., Berger, J.O., Dawid, A.P., Smith, A.F.M. (eds.) Bayesian Statistics, vol. 6, pp. 459–474. Oxford University Press, New York (1999). http://citeseerx.ist.psu.edu/viewdoc/summary?doi=10.1.1.131.3004

Müller, P., Sansó, B., De Iorio, M.: Optimal Bayesian design by inhomogeneous Markov chain simulation. J. Am. Stat. Assoc. **99**, 788–798 (2004). doi:10.1198/016214504000001123

Sisson, S.A., Fan, Y.: Likelihood-free Markov chain Monte Carlo. In: Brooks, S.P., Gelman, A., Jones, G., Meng, X.L. (eds.) Handbook of Markov Chain Monte Carlo, Handbooks of Modern Statistical Methods, pp. 319–341. Chapman & Hall/CRC Press, Boca Raton (2011)

# Approximation of the Fisher Information Matrix for Nonlinear Mixed Effects Models in Population PK/PD Studies

**Sergei Leonov and Alexander Aliev**

**Abstract** We discuss different types of approximations of the individual Fisher information matrix used in population optimal design software tools and describe a Monte-Carlo option in the PkStaMp library which constructs optimal sampling schemes for population pharmacokinetic (PK) and pharmacodynamic (PD) studies.

## 1 Introduction

Optimal design of experiments for population PK/PD studies has received considerable attention in the statistical literature and software development over the last decade. Starting from 2007, various population optimal design software tools were discussed and compared at the annual PODE workshop (Population Optimum Design of Experiments). Details on the software comparison were presented by Mentré et al. (2007, 2011); see also Leonov and Aliev (2012).

Aliev et al. (2012) described the PkStaMp library for constructing locally D-optimal designs for population compartmental PK and PK/PD models. The focus of this paper is on the Monte-Carlo option for the calculation of the individual Fisher information matrices which are of essential interest for designing population studies.

## 2 Model and Fisher Information Matrix

The model of observations used in the PkStaMp library is given by

$$y_{ij} = \eta(x_{ij}, \gamma_i) + \varepsilon_{ij}, \quad i = 1, \ldots, N, \ j = 1, \ldots, k_i, \tag{1}$$

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where $\{x_{ij}\}$ are times of taking PK or PD measurements $\{y_{ij}\}$ for patient $i$; $k_i$ is the number of measurements for patient $i$; $N$ is the total number of patients in the study; $\eta(x, \gamma)$ is the response function (e.g., drug concentration at time $x$) which is assumed to be known up to the unknown parameters $\gamma$. Individual response parameters $\gamma_i$ (rate constants, clearances, volumes) are assumed to be independently sampled from a given population distribution, either normal, $\gamma_i \sim \mathcal{N}(\gamma^0, \Omega)$, or log-normal,

$$\gamma_{il} = \gamma_l^0 \mathrm{e}^{\zeta_{il}}, \qquad \gamma_0 = \left(\gamma_1^0, \ldots, \gamma_{m_\gamma}^0\right)^\top, \qquad \zeta_i = (\zeta_{i1}, \ldots, \zeta_{im_\gamma})^\top \sim \mathcal{N}(\mathbf{0}, \Omega), \tag{2}$$

where $m_\gamma$ is the dimension of the vector of response parameters; $l = 1, \ldots, m_\gamma$. Residual errors $\varepsilon_{ij}$ have additive and proportional components of variability,

$$\varepsilon_{ij} = \varepsilon_{1,ij} + \varepsilon_{2,ij}\eta(x_{ij}, \gamma_i), \tag{3}$$

where $\varepsilon_{1,ij}, \varepsilon_{2,ij}$ are random variables with zero mean, such that vectors $\varepsilon_{1,i} = (\varepsilon_{1,i}, \ldots, \varepsilon_{1,ik_i})^\top$ and $\varepsilon_{2,i'} = (\varepsilon_{1,i'}, \ldots, \varepsilon_{1,i'k_{i'}})^\top$ are mutually independent for all $i, i'$, and

$$\mathrm{E}\left(\varepsilon_{1,i}\varepsilon_{1,i}^\top\right) = \sigma_A^2 I_{k_i}, \qquad \mathrm{E}\left(\varepsilon_{2,i}\varepsilon_{2,i}^\top\right) = \sigma_P^2 \mathbf{I}_{k_i},$$

where $\mathbf{I}_k$ denotes a $(k \times k)$-identity matrix. By $\theta = (\gamma^0, \Omega; \sigma_A^2, \sigma_P^2)$ we denote the combined vector of model parameters, and by $m$ its length.

Let $\mu(\mathbf{x}, \theta)$ be the Fisher information matrix of a $(k \times 1)$-sequence $\mathbf{x}$ of sampling times, and let $\mathbf{M}(\xi, \theta)$ be the normalized Fisher information matrix of the continuous design $\xi = \{(\mathbf{x}_u, w_u)\}$,

$$\mathbf{M}(\xi, \theta) = \sum_u w_u \mu(\mathbf{x}_u, \theta), \tag{4}$$

where $\sum_u w_u = 1$. In the PkStaMp library we minimize the $D$-optimality criterion,

$$\xi^* = \arg\min_\xi \left|\mathbf{M}^{-1}(\xi, \theta)\right|, \tag{5}$$

where sequences $\mathbf{x}_u$ in (4) belong to a pre-specified design region $\mathbb{X}$. We implement the first-order optimization algorithm with forward and backward steps; for details, see Fedorov and Hackl (1997, Chap. 3), Fedorov et al. (2007) and Leonov and Aliev (2012), formulae (9)–(12).

The individual Fisher information matrix $\mu(\mathbf{x}, \theta)$ for nonlinear mixed models like (1) does not have a closed-form expression. To approximate $\mu(\mathbf{x}, \theta)$, we use the following formula which is exact for normally distributed random variables with mean $\eta_0$ and variance $\mathbf{S}$:

$$\tilde{\mu}_{\alpha\beta}(\mathbf{x}, \theta) = \frac{\partial \eta_0^\top}{\partial \theta_\alpha}\mathbf{S}^{-1}\frac{\partial \eta_0}{\partial \theta_\beta} + \frac{1}{2}\,\mathrm{tr}\left[\mathbf{S}^{-1}\frac{\partial \mathbf{S}}{\partial \theta_\alpha}\mathbf{S}^{-1}\frac{\partial \mathbf{S}}{\partial \theta_\beta}\right], \quad \alpha, \beta = 1, \ldots, m; \tag{6}$$

see Magnus and Neudecker (1988). To approximate $\eta_0$ and $\mathbf{S}$ in the above formula, the first-order Taylor expansion is utilized. In particular, the mean response of the

observations $\{y_{ij}\}$ is approximated by $\eta_0 = \mathrm{E}_{\varepsilon,\gamma}(y_{ij}) \approx \eta(x_{ij}, \theta)$, where $\mathrm{E}_{\varepsilon,\gamma}$ denotes the expectation with respect to the distribution of $\varepsilon_{ij}$ and $\gamma_i$, and the formula (3) leads to the following presentation for normally distributed $\gamma_i$:

$$\mathbf{S}(\mathbf{x}, \theta) \simeq \mathbf{F}\Omega\mathbf{F}^\top + \sigma_P^2 \operatorname{diag}\left[\eta(\mathbf{x}, \theta)\eta^\top(\mathbf{x}, \theta) + \mathbf{F}\Omega\mathbf{F}^\top\right] + \sigma_A^2\mathbf{I}_k, \tag{7}$$

where $\eta(\mathbf{x}, \theta) = [\eta(x_1, \theta), \ldots, \eta(x_k, \theta)]^\top$, and $\mathbf{F} = \mathbf{F}(\mathbf{x}, \gamma^0) = [\partial\eta(\mathbf{x}, \theta)/\partial\gamma_\alpha]|_{\gamma=\gamma^0}$ is a $(k \times m_\gamma)$ matrix of partial derivatives of $\eta(\mathbf{x}, \theta)$ with respect to response parameters $\gamma^0$. Note that while in (7) we use the notation $\eta(\mathbf{x}, \theta)$, under the first-order approximation the mean response depends only on response parameters $\gamma^0$ and does not depend on the variance parameters $\{\Omega, \sigma^2\}$. This explains the dimension of the matrix $\mathbf{F}$ (Aliev et al. 2012, Sect. 2.5). For log-normally distributed $\gamma_i$ as in (2), the matrix $\Omega$ on the right-hand side of (7) has to be replaced with

$$\tilde{\Omega} = \operatorname{diag}\left(\gamma^0\right)\Omega\operatorname{diag}\left(\gamma^0\right), \tag{8}$$

where $\operatorname{diag}(\mathbf{a})$ denotes a diagonal matrix with diagonal elements equal to either $a_{ll}$ when $\mathbf{a}$ is a square matrix, or $a_l$ when $\mathbf{a}$ is a vector.

As described by Aliev et al. (2012) and Leonov and Aliev (2012), the design region $\mathbb{X}$ in the PkStaMp library is a discrete set of candidate sampling sequences $\mathbf{x}_s$. Therefore, the forward step of the first-order optimization algorithm presents a finite optimization problem. Note also that the calculation of individual information matrices (via the first-order approximation or any other option) is performed only once, prior to running the optimal design algorithm and, therefore, does not affect the algorithm's running time.

## 3 Approximation Options

In 2009–2011 participants of PODE workshop used a one-compartment model with first-order absorption and linear elimination as a benchmark test to compare different software tools:

$$\eta(x, \gamma) = \frac{DK_a}{V(K_a - K_e)}\left(\mathrm{e}^{-K_e x} - \mathrm{e}^{-K_a x}\right), \tag{9}$$

where $D$ is a single dose administered at time $x = 0$; $K_a$ and $K_e$ are absorption and elimination rate constants, respectively; $V$ is the volume of distribution, and $\gamma = (K_a, K_e, V)^\top$ is the vector of response parameters. The model was parameterized via clearance $CL$, so that $K_e = CL/V$. It was assumed that the individual response parameters $\gamma_i = (K_{ai}, CL_i, V_i)$ are log-normally distributed as in (2) with the population mean $\gamma^0 = (1, 0.15, 8)$ and the diagonal population variance-covariance matrix $\Omega = \operatorname{diag}(\omega_r^2) = \operatorname{diag}(0.6, 0.07, 0.02)$, and $\sigma_A^2 = 0$, $\sigma_P^2 = 0.01$ in (3). The combined vector of parameters for this example was

$$\theta = \left(K_a^0, CL^0, V^0; \omega_{K_a}^2, \omega_{CL}^2, \omega_V^2; \sigma_P^2\right)^\top = (1, 0.15, 8; 0.6, 0.07, 0.02; 0.01). \tag{10}$$

The goal was to compare the coefficients of variation $CV_s = \sqrt{[\mu^{-1}(\mathbf{x},\theta)]_{ss}/N}/\theta_s$, for the 8-sample sequence $\mathbf{x} = (0.5, 1, 2, 6, 24, 36, 72, 120)$ hours, where $N = 32$ was the number of patients in the earlier study.

To validate approximate formulae, Monte-Carlo simulations were performed by members of the PODE community using two software packages for parameter estimation: NONMEM (Beal and Sheiner 1992) and MONOLIX (Laveille and Mentré 2006; Lixoft 2011). Specifically, sample estimates of the coefficients of variation were reported for the one-compartment model (9) and a more complex example of the combined PK/PD model of hepatitis C viral dynamics; for details, see Mentré et al. (2011). After the first round of comparisons for the model (9), (10), all population design tools produced similar coefficients of variation for all model parameters except the absorption rate $K_a$: $CV(K_a) = 0.052$ for PkStaMp, while $CV(K_a) = 0.139$ for most other tools. Simulations in both NONMEM and MONOLIX resulted in estimates $CV(K_a) \in [0.12, 0.13]$. The observed differences required a closer look at how calculations have been implemented in different tools, and the following explanation was found.

The matrix $\tilde{\mu}$ in (6) can be partitioned as

$$\tilde{\mu}(\mathbf{x},\theta) = \begin{Bmatrix} \mathbf{A} & \mathbf{C} \\ \mathbf{C}^\top & \mathbf{B} \end{Bmatrix}, \quad \mathbf{A} = \mathbf{A}_1 + \mathbf{A}_2, \mathbf{A}_1 = \mathbf{F}^\top \mathbf{S}^{-1} \mathbf{F}, \tag{11}$$

$$\mathbf{A}_{2,\alpha\beta} = \frac{1}{2} \mathrm{tr}\left[ \mathbf{S}^{-1} \frac{\partial \mathbf{S}}{\partial \theta_\alpha} \mathbf{S}^{-1} \frac{\partial \mathbf{S}}{\partial \theta_\beta} \right], \quad \alpha, \beta = 1, \ldots, m_\gamma; \tag{12}$$

$$\mathbf{C}_{\alpha\beta} = \frac{1}{2} \mathrm{tr}\left[ \mathbf{S}^{-1} \frac{\partial \mathbf{S}}{\partial \theta_\alpha} \mathbf{S}^{-1} \frac{\partial \mathbf{S}}{\partial \theta_\beta} \right], \quad \alpha = 1, \ldots, m_\gamma, \beta = m_\gamma + 1, \ldots, m; \tag{13}$$

$$\mathbf{B}_{\alpha\beta} = \frac{1}{2} \mathrm{tr}\left[ \mathbf{S}^{-1} \frac{\partial \mathbf{S}}{\partial \theta_\alpha} \mathbf{S}^{-1} \frac{\partial \mathbf{S}}{\partial \theta_\beta} \right], \quad \alpha, \beta = m_\gamma + 1, \ldots, m,$$

see, e.g., Retout and Mentré (2003). Thus block $\mathbf{A}$ represents partial derivatives with respect to response parameters ("typical values" in NONMEM nomenclature), block $\mathbf{B}$ represents partial derivatives with respect to variance parameters, and block $\mathbf{C}$ contains mixed derivatives. Several software developers used a so-called "reduced" option by making $\mathbf{A}_2 = \mathbf{0}$ and $\mathbf{C} = \mathbf{0}$ in (11), while in PkStaMp we used the first-order approximation (7), (8) and a so-called "full option", i.e., the full matrix $\tilde{\mu}(\mathbf{x},\theta)$ in (11). These differences led to quite visible differences in the elements of the information matrix $\tilde{\mu}$ which correspond to the absorption rate $K_a$. Once the initial settings were made identical, the output results coincided for all software tools. However, questions remained about which approximation option is preferable.

As noted in Leonov and Aliev (2012), the use of the first-order approximation for log-normally distributed random variables may lead to a substantial distortion of the distribution, in particular when elements of the variance-covariance matrix $\Omega$ are not small. This was exactly the case for the absorption rate $K_a$ in the model (9) where $\omega^2_{K_a} = 0.6$: the first-order approximation led to $\mathrm{E}(K_{ai}) \approx 1$, $\mathrm{Var}(K_{a,i}) \approx 0.6$,

while the exact mean and variance of log-normally distributed random variable $\gamma_i = K_{a,i}$ were 1.35 and 1.5, respectively. For more discussion on linearization options, see Mielke and Schwabe (2010).

Obviously, one can use higher-order approximation for the response $\eta$ and variance $\mathbf{S}$. In particular, if one uses the second-order approximation of the response function $\eta(x, \gamma_i)$ in the vicinity of $\gamma^0$, then for normally distributed $\gamma_i$

$$\mathrm{E}_{\varepsilon,\gamma}\big[\eta(x,\gamma_i)\big] \approx \eta\big(x,\gamma^0\big) + \frac{1}{2}\,\mathrm{tr}\big[\mathbf{H}\big(x,\gamma^0\big)\Omega\big], \tag{14}$$

where $\mathbf{H}(x, \gamma^0)$ is the matrix of second-order partial derivatives of the response function, $\mathbf{H}(x, \gamma^0) = [\partial^2\eta(x,\gamma)/\partial\gamma_\alpha\partial\gamma_\beta]|_{\gamma=\gamma^0}$. The first-order approximation (7) for the variance matrix $\mathbf{S}$ utilizes first-order derivatives $\mathbf{F}$ of the response $\eta$, so calculation of the derivatives of $\mathbf{S}$ in (6) requires second-order derivatives of $\eta$. Thus, with the second-order approximation (14), one will require fourth-order derivatives of the response function $\eta$ which numerically is rather cumbersome.

### 3.1 Monte-Carlo Option

One of the possible ways of avoiding numerical approximation as in (7), (8) or (14), is to calculate the mean $\eta_0$ and variance $\mathbf{S}$ via Monte-Carlo simulations at each candidate sampling sequence $\mathbf{x}$:

- Generate $L$ independent realizations of response parameters $\gamma_i$ from a given distribution, $i = 1, \ldots, L$.
- Generate values $\mathbf{Y}_i = \{y_{ij}\}$ according to (1) and (3).
- Calculate the empirical mean and variance

$$\begin{aligned}
\widehat{\eta}_0 = \widehat{\eta}(\mathbf{x},\theta) = \widehat{\mathrm{E}}_\theta(\mathbf{Y}) &= \frac{1}{L}\sum_{i=1}^{L}\mathbf{Y}_i,\\
\widehat{\mathbf{S}} = \widehat{\mathbf{S}}(\mathbf{x},\theta) = \widehat{\mathrm{Var}}_\theta(\mathbf{Y}) &= \frac{1}{L-1}\sum_{i=1}^{L}(\mathbf{Y}_i - \widehat{\eta}_0)(\mathbf{Y}_i - \widehat{\eta}_0)^\top.
\end{aligned} \tag{15}$$

- Use the formula (6) to calculate $\tilde{\mu}(\mathbf{x}, \theta)$ with values $\{\widehat{\eta}_0, \widehat{\mathbf{S}}\}$ from (15).

The described Monte-Carlo approach eliminates the need to calculate second- and higher-order derivatives of the response and variance functions. Note, however, that this approach still relies on the normal approximation (6).

### 3.2 Stepsize for Numerical Differentiation

To calculate partial derivatives in (6), we use central difference approximations: for the function $g(\theta)$ of scalar argument $\theta$,

**Table 1** Coefficients of variation (%), model (9), (10); various approximation options

| Parameters | $K_a$ | CL | V | $\omega^2_{K_a}$ | $\omega^2_{CL}$ | $\omega^2_V$ | $\sigma$ |
|---|---|---|---|---|---|---|---|
| From PODE 2009–2011 comparison | | | | | | | |
| Reduced version | 13.9 | 4.74 | 2.76 | 25.8 | 25.6 | 30.3 | 5.58 |
| NONMEM, FOCE | 13.6 | 4.93 | 2.72 | 26.6 | 26.1 | 32.4 | |
| MONOLIX | 13.8 | 4.76 | 2.76 | 28.1 | 26.5 | 30.8 | 5.52 |
| Monte-Carlo option | | | | | | | |
| $h = 0.015, L = 10^6$ | 10.7 | 4.23 | 2.86 | 21.3 | 24.9 | 35.7 | 7.10 |
| $h = 0.019, L = 10^6$ | 10.6 | 4.16 | 2.76 | 20.2 | 24.7 | 34.9 | 7.18 |
| $h = 0.001, L = 10^6$ | **3.21** | 4.28 | **0.54** | **6.66** | 24.7 | 36.3 | 6.78 |

$$g'(\theta) = \frac{g(\theta + h) - g(\theta - h)}{2h} + O\left(h^2\right) + \frac{rg(\theta)}{h}, \tag{16}$$

where $r$ is a round-off error of order $10^{-16}$ for double precision. The best approximation is obtained when the second and the third terms on the right-hand side of (16) have the same order of magnitude, i.e. $h \sim r^{1/3}$. For the implementation of the first-order approximation in PkStaMp library, we traditionally used $h \in [10^{-4}, 10^{-3}]$. This selection worked well because the third term on the right-hand side of (16) was negligible.

For the Monte-Carlo option, rather small values of the stepsize $h$ may lead to substantial distortion due to the stochastic error which is introduced in the calculation of $\hat{\eta}_0$ and $\hat{\mathbf{S}}$ in (15). Indeed, consider the model (1), (3) with $\sigma_A^2 = 0$, as in the example (9), (10). Then the standard deviation of $\hat{\eta}$ is of order $\sigma_P \eta(x, \theta)/\sqrt{L}$. Thus, the optimal stepsize $h$ can be obtained from the balance relation

$$h^2 \sim \frac{\sigma_P \eta(x, \theta)}{h\sqrt{L}}, \quad \text{or } h \sim \left[\sigma_P \eta(x, \theta)\right]^{1/3} L^{-1/6}. \tag{17}$$

Note now that $\sigma_P = 0.1$ for our example of the one-compartment model, and $\eta(x, \theta)$ is within the range $[0, 8]$ for the majority of parameter values; cf. Fig. 1 in Leonov and Aliev (2012). Therefore if $L = 10^6$, reasonable values of $h \in [0.05, 0.1]$. Note also that the stepsize $h$ may need adjustment depending on parameter values. For our example, in order to make $h$ not too small, we parameterized the model (3) via the standard deviation $\sigma_P$ (not variance $\sigma_P^2$) which allowed us to use values of $h$ close to 0.02. Another option is to take different values of $h$ for different parameters to calculate partial derivatives.

Table 1 and Fig. 1 present coefficients of variation, in % (or relative standard errors RSE) for the model (9), (10) where we used $L = 10^6$ for the three scenarios of Monte-Carlo simulations. Also shown are results for the reduced and full versions of the approximation of the matrix $\tilde{\mu}(\mathbf{x}, \theta)$ in (11), and results of the simulations in NONMEM and MONOLIX; see Mentré et al. (2011). The Monte-Carlo option with modestly sized $h$ (0.015 or 0.019) produce RSEs of the parameter $K_a$ which

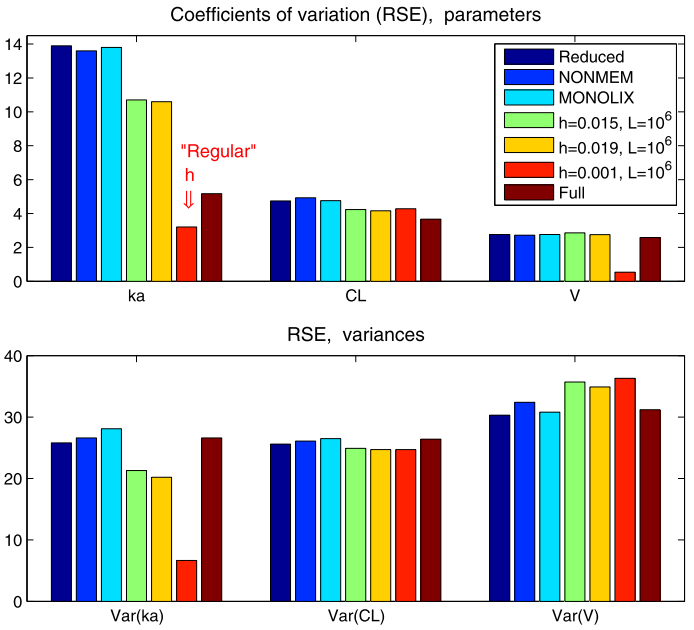


**Fig. 1** Coefficients of variation in % (relative standard errors, RSE). Order of *bars*, from *left* to *right*: reduced, NONMEM, MONOLIX; $h = \{0.015, 0.019, 0.001\}$; full

are closer to the results of the simulations in NONMEM and MONOLIX than for the full option. On the other hand, a traditionally "small" value $h = 0.001$ leads to significant distortion of the results; see values highlighted in boldface in Table 1 and the corresponding bars in Fig. 1 (the sixth bar from the left for $K_a$, $V$ and $\mathrm{Var}(K_a)$).

## 4 Discussion

The Monte-Carlo option described in this paper is straightforward to implement and takes seconds to compute for $L = 10^6$. The reduced option for the approximation of the Fisher information matrix performed well in the examples considered. Mielke and Schwabe (2010) in their Sect. 4 provide an example where taking into account the second term on the right-hand side of the approximation (6)—or, equivalently, the term $\mathbf{A}_2$ in (11)—leads to overestimation of the information and underestimation of the variance. However, the reduced option also disregards the submatrix $\mathbf{C}$ in (11) for which we do not have an explanation (formal or heuristic). Still more work is needed for better understanding of the advantages and disadvantages of the various approximation options.

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## References

Aliev, A., Fedorov, V., Leonov, S., McHugh, B., Magee, M.: PkStaMp library for constructing optimal population designs for PK/PD studies. Commun. Stat., Simul. Comput. **41**, 717–729 (2012)

Beal, S.L., Sheiner, L.B.: NONMEM User's Guide. NONMEM Project Group. University of California, San Francisco (1992)

Fedorov, V.V., Hackl, P.: Model-Oriented Design of Experiments. Springer, New York (1997)

Fedorov, V.V., Gagnon, R., Leonov, S., Wu, Y.: Optimal design of experiments in pharmaceutical applications. In: Dmitrienko, A., Chuang-Stein, C., D'Agostino, R. (eds.) Pharmaceutical Statistics Using SAS. A Practical Guide, pp. 151–195. SAS Press, Cary (2007)

Laveille, M., Mentré, F.: Estimation of population pharmacokinetic parameters of saquinavir in HIV patients with the MONOLIX software. J. Pharmacokinet. Pharmacodyn. **34**, 229–249 (2006)

Leonov, S., Aliev, A.: Optimal design for population PK/PD models. Tatra Mt. Math. Publ. **51**, 115–130 (2012)

Magnus, J.R., Neudecker, H.: Matrix Differential Calculus with Applications in Statistics and Econometrics. Wiley, New York (1988)

Mentré, F., Duffull, S., Gueorguieva, I., Hooker, A., Leonov, S., Ogungbenro, K., Retout, S.: Software for optimal design in population pharmacokinetics and pharmacodynamics: a comparison. In: Abstracts of the Annual Meeting of the Population Approach Group in Europe (PAGE) (2007). ISSN 1871-6032. Available via http://www.page-meeting.org/?abstract=1179

Mentré, F., Nyberg, J., Ogungbenro, K., Leonov, S., Aliev, A., Duffull, S., Bazzoli, C., Hooker, A.: Comparison of results of the different software for design evaluation in population pharmacokinetics and pharmacodynamics. In: Abstracts of the Annual Meeting of the Population Approach Group in Europe (PAGE) (2011). ISSN 1871-6032. Available via http://www.page-meeting.org/default.asp?abstract=2066

Mielke, T., Schwabe, R.: Some considerations on the Fisher information in nonlinear mixed effects models. In: Giovagnoli, A., Atkinson, A.C., Torsney, B. (eds.) mODa 9—Advances in Model-Oriented Design and Analysis, pp. 129–136. Physica-Verlag, Berlin (2010)

Lixoft: MONOLIX documentation. Available via http://www.lixoft.net/monolix/overview/ (2011)

Retout, S., Mentré, F.: Further developments of the Fisher information matrix in nonlinear mixed effects models with evaluation in population pharmacokinetics. J. Biopharm. Stat. **13**, 209–227 (2003)

# c-Optimal Designs for the Bivariate Emax Model

**Bergrun Tinna Magnusdottir**

**Abstract** This paper explores c-optimal design problems for non-linear, bivariate response models. The focus is on bivariate dose response models, one response being a primary efficacy variable and the other a primary safety variable. The aim is to construct designs that are optimal for estimating the dose that gives the best possible combination of effects and side-effects.

## 1 The Bivariate Emax Model

Understanding of the dose-response relationship is among the most important and challenging problems in drug development. In dose finding studies a primary response variable is usually defined and modelled. Various dose-response models have been suggested. Among the most successful models for modeling a continuous response variable is the Emax model. It is of the form

$$\text{Response(dose)} = E_0 + E_{\max}\frac{\text{dose}}{\text{dose} + ED_{50}} + \varepsilon, \tag{1}$$

where $\varepsilon \sim \mathcal{N}(0, \sigma^2)$. For a detailed discussion of this model and its mechanistic properties see, e.g., Holford and Sheiner (1981) and Goutelle et al. (2008). When interest is not in the placebo response, it might be reasonable to assume $E_0 = 0$. The model used in this paper is the Emax model including only the two parameters $ED_{50}$ and $E_{\max}$. The problem of deriving optimal designs for the two parameter Emax model has been investigated by several authors see, for example, López-Fidalgo and Wong (2002).

In the early phases of drug development (Phase I) the focus is on safety and the primary response variable is a safety variable. In later phases (Phases II and III) the focus is shifted towards efficacy and the primary response variable is an efficacy variable. In spite of this traditional division into safety and efficacy studies, it is often useful to study efficacy and safety simultaneously. Examples are found in, e.g.,

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Thall and Russell (1998) or Ouellet et al. (2009). Several authors have discussed the construction of optimal designs when simultaneously considering binary efficacy and safety variables (Li et al. 1995; Dragalin and Fedorov 2006). Here the focus is on continuous efficacy and safety variables. Dragalin et al. (2008) also discuss the construction of optimal designs when both the efficacy and safety variables are continuous, but both their model and the aim of their study are different from what is assumed here.

The idea in this paper is to consider both efficacy and safety simultaneously and extend the Emax model to two dimensions, one for a primary efficacy variable, $Z_1$, and one for a primary safety variable, $Z_2$. High values of $Z_1$ are here assumed to indicate a positive effect while high values of $Z_2$ indicate a negative effect. An example of a primary efficacy variable is the decrease (from a baseline) in systolic blood pressure, measured in millimeters of mercury (mmHg). An example of a primary safety variable is increased sleep latency from baseline, measured in minutes. The bivariate Emax model is hereby defined as follows:

$$Z_1 = E_{\max}\frac{x}{x + ED_{50}} + \varepsilon_1, \qquad Z_2 = S_{\max}\frac{x}{x + SD_{50}} + \varepsilon_2 \tag{2}$$

where $(\varepsilon_1, \varepsilon_2) \sim \mathcal{N}_2[0, \Sigma(\sigma_1, \sigma_2, \rho)]$. Further, let $\theta = (ED_{50}, E_{\max}, SD_{50}, S_{\max})$ and $\Omega = (\sigma_1, \sigma_2, \rho)$. In this paper $\Sigma$ is assumed to be known while $\theta$ needs to be estimated. Note that $x$ represents the dose of a drug, so naturally it is assumed that $x \in \chi = [0, \infty[$. $E_{\max}$ represents the maximal achievable effect from the drug and $S_{\max}$ the maximal realizable side-effect. $ED_{50}$ and $SD_{50}$ represent the doses that give half of the maximal effect and side-effect, respectively. Hence $ED_{50}, SD_{50} > 0$. For explicitness it is also assumed here that $E_{\max}, S_{\max} > 0$. In this paper a simplified version of the bivariate Emax model, referred to as the simple bivariate model, is also explored. There it is assumed that the maximal effect and side-effect equal one so that

$$Z_1 = \frac{x}{x + ED_{50}} + \varepsilon_1, \qquad Z_2 = \frac{x}{x + SD_{50}} + \varepsilon_2,$$

where $(\varepsilon_1, \varepsilon_2) \sim \mathcal{N}_2(0, \Sigma)$, $\theta = (ED_{50}, SD_{50})$, and $ED_{50}, SD_{50} > 0$ as before.

## 2 The Clinical Utility Index (CUI)

The Clinical Utility Index (CUI) is a tool for multiattribute decision making in drug development. The term and the use of the CUI are relatively new, but its application is steadily growing. For a good historical overview of the CUI see, e.g., Carrothers et al. (2011). The CUI combines different aspects regarding the quality of the new drug. After receiving the drug, the patient might experience several different effects and side-effects. These are measured on different scales and are of different importance to the patient. The CUI combines these multidimensional aspects into a single metric. Each possible scenario is given a CUI value for ranking; the higher the CUI, the better. A patient taking an anti-diabetic drug might prefer his normal dose to a

new, higher, dose that would lead to an 0.5 % extra reduction in HbA1c but with an increased risk for hypoglycemia. The normal dose would then be assigned to a higher CUI value than the new dose. In this paper we consider only one primary efficacy variable, $Z_1$, and one primary safety variable, $Z_2$, but it is straightforward to generalize and include more efficacy, safety and possible other variables of importance such as an increased cost for a higher dose.

The form and derivation of the CUI should be considered separately for each drug under investigation. The most common approach is however to use a linear combination of the different response variables. This is the approach discussed by Carrothers et al. (2011) and the one that is covered here. For the dose-response models in this paper the CUI is defined as

$$\mathrm{CUI}(x) = k_1 Z_1 - k_2 Z_2. \tag{3}$$

A negative sign is here assigned to the side-effect because high values of $Z_2$ indicate a negative effect. Since the response variables are usually measured on different scales, Carrothers et al. (2011) suggest that all response variables be first transformed onto the same scale, which they call utility, with range from 0 to 1. Then weights, here $k_1$ and $k_2$, are assigned to the response variables depending on their relative importance. For a detailed example of how a linear CUI has been used in practice see Ouellet et al. (2009). The most desirable dose for a population of patients is the one that maximizes E[CUI]. It is straightforward to show that if such a positive dose exists then, for the bivariate Emax model, it is

$$\begin{aligned} g(\theta) &:= \max_{x>0} \mathrm{E}\big[\mathrm{CUI}(x)\big] \\ &= \frac{\sqrt{k_1 ED_{50} E_{\max} k_2 SD_{50} S_{\max}}(ED_{50} - SD_{50}) - ED_{50} SD_{50}(k_1 E_{\max} - k_2 S_{\max})}{k_1 ED_{50} E_{\max} - k_2 SD_{50} S_{\max}}. \end{aligned} \tag{4}$$

For the simple bivariate model this simplifies to

$$g(\theta) := \max_{x>0} \mathrm{E}\big[\mathrm{CUI}(x)\big] = \frac{\sqrt{k_1 ED_{50} k_2 SD_{50}}(ED_{50} - SD_{50}) - ED_{50} SD_{50}(k_1 - k_2)}{k_1 ED_{50} - k_2 SD_{50}}. \tag{5}$$

## 3 Locally c-Optimal Designs

A design is denoted here by $\xi = \{x_1, x_2, \ldots, x_n; w_1, w_2, \ldots, w_n\}$. For dose finding studies the $x_i$'s represent the doses, i.e., the amount of the drug (in mg) and $w_i$ denotes the proportion of the participants that receive dose $x_i$. Here $n$ is the number of different study groups and $N$ denotes the number of participants. Finally, $\chi$ denotes the design space. The design that allocates all observations to one design point, $x$,

is denoted by $\xi_x$ and the standardized information matrix is denoted by $M$. For the bivariate Emax model the one-point standardized information matrix is

$$M(\xi_x) = \frac{1}{(1-\rho^2)} \times \begin{pmatrix} \frac{1}{\sigma_1^2}\frac{E_{\max}^2 x^2}{(x+ED_{50})^4} & \frac{1}{\sigma_1^2}\frac{-E_{\max}x^2}{(x+ED_{50})^3} & \frac{\rho}{\sigma_1\sigma_2}\frac{-E_{\max}S_{\max}x^2}{(x+ED_{50})^2(x+SD_{50})^2} & \frac{\rho}{\sigma_1\sigma_2}\frac{E_{\max}x^2}{(x+ED_{50})^2(x+SD_{50})} \\ * & \frac{1}{\sigma_1^2}\frac{x^2}{(x+ED_{50})^2} & \frac{\rho}{\sigma_1\sigma_2}\frac{S_{\max}x^2}{(x+ED_{50})(x+SD_{50})^2} & \frac{\rho}{\sigma_1\sigma_2}\frac{-x^2}{(x+ED_{50})(x+SD_{50})} \\ * & * & \frac{1}{\sigma_2^2}\frac{S_{\max}^2 x^2}{(x+SD_{50})^4} & \frac{1}{\sigma_2^2}\frac{-S_{\max}x^2}{(x+SD_{50})^3} \\ * & * & * & \frac{1}{\sigma_2^2}\frac{x^2}{(x+SD_{50})^2} \end{pmatrix}$$

and for the simple bivariate model it is

$$M(\xi_x) = \frac{1}{(1-\rho^2)} \begin{pmatrix} \frac{1}{\sigma_1^2}\frac{x^2}{(x+ED_{50})^4} & \frac{\rho}{\sigma_1\sigma_2}\frac{-x^2}{(x+ED_{50})^2(x+SD_{50})^2} \\ * & \frac{1}{\sigma_2^2}\frac{x^2}{(x+SD_{50})^4} \end{pmatrix}.$$

In what follows, it is assumed that $M$ is an invertible matrix.

In this paper, the focus is on c-optimal designs which are appropriate when the objective of the study is to estimate some function, $g(\theta)$, of the parameters in the model. Let $\hat{\theta}$ denote the maximum likelihood estimator of the parameters in a non-linear, bivariate response model such as the bivariate Emax model (2). For a non-linear function, $g(\theta)$, a design is c-optimal if it minimizes the asymptotic variance of $g(\hat{\theta})$, which equals

$$\Psi = \nabla g(\theta)^\top M(\xi)^{-1} \nabla g(\theta). \tag{6}$$

$\Psi$ is referred to as the criterion function. A general problem with optimal designs for non-linear models is that they depend on the true value of the unknown parameters, $\theta$. The optimal designs constructed in this paper are locally optimal and assume prior values for $\theta$. For dose finding studies, the prior is based on data from preclinical and early clinical trials as well as data from competitor drugs.

**Theorem 1** (General Equivalence Theorem, GET) *Suppose $\xi$ is a design such that $M(\xi)^{-1}$ exists. Then $\xi$ is locally c-optimal with respect to a non-linear function of the model parameters, $g(\theta)$ if, and only if,*

$$\nabla g^\top M(\xi)^{-1} M(\xi_x) M(\xi)^{-1} \nabla g \leq \nabla g^\top M(\xi)^{-1} \nabla g, \quad \forall x \in \chi. \tag{7}$$

*Further, equality holds the design points $x \in \{x_1, \ldots, x_n\}$.*

The proof is given in the Appendix. Note that $\Psi$ in (6) is a special case of the linear criterion, $\Psi = \mathrm{tr}\{AM^{-1}\}$. Fedorov (1972) sets up the framework for optimal designs that minimize the linear criterion in the multi-response setting.

## 4 Designs for Estimating the Most Desirable Dose of a Drug

The designs derived in this section are optimal for estimating the most desirable dose of a drug, provided that such a positive dose exists and that the models and the CUI, introduced in Sects. 1 and 2, are reasonable assumptions. Specifically, the designs are locally c-optimal with respect to the functions in (4) and (5) and depend on the parameter vector $(\theta, \Omega, k_1, k_2)$. First note that, without loss of generality, one of the variance parameters $\sigma_1$, say, can be set to one. This is true for all bivariate models with error terms following the bivariate normal distribution.

**Theorem 2** *Assume that* $\xi = \{x_1, \ldots, x_n; w_1, \ldots, w_n\}$ *is locally c-optimal for the bivariate Emax model with parameters* $\theta = (ED_{50}, E_{\max}, SD_{50}, S_{\max})$ , $k = (k_1, k_2)$ *and* $\Omega = (\sigma_1, \sigma_2, \rho)$, *i.e.,* $\xi$ *minimizes* $\Psi = \nabla g^\top M^{-1} \nabla g$. *If* $a, b, c, d \in \mathbb{R}\backslash\{0\}$, *then*

1. $\xi$ *is locally c-optimal for the same model but with one or more of the following changes for the parameters*
   (i) $k = (ak_1, ak_2)$,
   (ii) $\Omega = (b\sigma_1, b\sigma_2, \rho)$,
   (iii) $\theta = (ED_{50}, cE_{\max}, SD_{50}, cS_{\max})$.
2. $\xi^* = \{dx_1, \ldots, dx_n; w_1, \ldots, w_n\}$ *is locally c-optimal for the same model but with*
   (iv) $\theta = (dED_{50}, E_{\max}, dSD_{50}, S_{\max})$.

*Proof*

(i) $\nabla g(\theta, k_1, k_2) = \nabla g(\theta, ak_1, ak_2)$ and $M$ does not depend on $k$.
(ii) $M(\xi, \sigma_1, \sigma_2) = b^2 M(\xi, b\sigma_1, b\sigma_2)$ and $\nabla g$ does not depend on $\Omega$.
(iii) $\Psi(\xi, ED_{50}, E_{\max}, SD_{50}, S_{\max}) = c^2 \Psi(\xi, ED_{50}, cE_{\max}, SD_{50}, cS_{\max})$.
(iv) $\Psi(\xi, ED_{50}, E_{\max}, SD_{50}, S_{\max}) = \frac{1}{d^2} \Psi(\xi^*, dED_{50}, E_{\max}, dSD_{50}, S_{\max})$. □

Theorem 2 implies that, without loss of generality, 4 out of 9 parameters for the bivariate Emax model can be set equal to one. If $\xi$ is known to be locally c-optimal for the model with parameters $\theta = (ED_{50}, 1, SD_{50}, S_{\max}/E_{\max})$ then Theorem 2(iii) yields that $\xi$ is also locally c-optimal for the model with parameters $\theta = (ED_{50}, E_{\max}, SD_{50}, S_{\max})$. For the simple bivariate model it can analogously be assumed that $\sigma_1 = k_1 = ED_{50} = 1$. Below are formulae for deriving some locally c-optimal designs for the simple bivariate model. The proof is provided in the Appendix. Note that if $k_1 = k_2$ then the restriction $SD_{50} > ED_{50}$ is necessary. Otherwise, the side-effects would always outweigh the effects.

**Corollary 1** *Let* $\sigma_1^2 = \sigma_2^2$, $k_1 = k_2$ *and* $\rho = 0$. *Then, for the simple bivariate model,*

(i) $\xi = \{\sqrt{ED_{50}SD_{50}}; 1\}$ *is locally c-optimal when* $SD_{50}/ED_{50} \in ]1, (5 + \sqrt{21})/2]$.
(ii) $\xi = \{ED_{50}, SD_{50}; 0.5, 0.5\}$ *is locally c-optimal as* $SD_{50}/ED_{50} \to \infty$.

For the bivariate Emax model the design space, $\chi$, needs to be restricted or some design weight is necessarily assigned to an infinitely high dose. Some locally c-optimal designs for the design space $\chi = [0, 500]$ are provided in Tables 1 and 2.

**Table 1** Locally c-optimal designs $\xi = \{x_1, 500; w_1, 1 - w_1\}$ for the bivariate Emax model with respect to $g(\theta)$ in (4). Here $\chi = [0, 500]$, $ED_{50} = 1$, $SD_{50} = 2$, $\sigma_1^2 = \sigma_2^2$ and $\rho = 0$

| $\frac{S_{\max}}{E_{\max}}$ $(\frac{k_2}{k_1} = 1)$ | 1 | 0.9 | 0.8 | 0.7 | 0.6 |
|---|---|---|---|---|---|
| $x_1$ | 1.1078 | 0.7436 | 0.8234 | 0.9701 | 1.1030 |
| $w_1$ | 0.3944 | 0.4074 | 0.4713 | 0.5285 | 0.5720 |
| $\frac{k_2}{k_1}$ $(\frac{S_{\max}}{E_{\max}} = 1)$ | 1 | 0.9 | 0.8 | 0.7 | 0.6 |
| $x_1$ | 1.1078 | 0.7374 | 0.7871 | 0.8719 | 0.9423 |
| $w_1$ | 0.3944 | 0.4157 | 0.4845 | 0.5387 | 0.5774 |

**Table 2** Locally c-optimal designs $\xi = \{x_1, x_2, 500; w_1, w_2, 1 - w_1 - w_2\}$ for the bivariate Emax model with respect to $g(\theta)$ in (4). Here $\chi = [0, 500]$, $ED_{50} = 1$, $k_1 = k_2$ and $E_{\max} = S_{\max}$. If the design point $x_2$ is not specified then $x_1$ and 500 are the only design points

| $SD_{50}$ | | $\rho$ $(\frac{\sigma_2^2}{\sigma_1^2} = 1)$ | | | | $\frac{\sigma_2^2}{\sigma_1^2}$ $(\rho = 0)$ | | |
|---|---|---|---|---|---|---|---|---|
| | | −0.5 | 0 | 0.5 | 0.9 | 0.5 | 1.5 | 3 |
| 2 | $x_1$ | 1.0793 | 1.1078 | 1.0972 | 0.4985 | 0.8437 | 1.3875 | 2.1699 |
| | $w_1$ | 0.2800 | 0.3944 | 0.5118 | 0.4883 | 0.3702 | 0.4160 | 0.4670 |
| | $x_2$ | | | | 4.9811 | | | |
| | $w_2$ | | | | 0.3639 | | | |
| 3 | $x_1$ | 1.2704 | 1.2833 | 0.8407 | 0.4626 | 0.9356 | 1.6057 | 1.7091 |
| | $w_1$ | 0.3723 | 0.4903 | 0.4736 | 0.5111 | 0.4555 | 0.5197 | 0.3929 |
| | $x_2$ | | | 6.0010 | 5.6854 | | | 6.3070 |
| | $w_2$ | | | 0.2220 | 0.4213 | | | 0.2684 |
| 4 | $x_1$ | 1.4553 | 1.1358 | 0.7026 | 0.4815 | 1.0312 | 1.1128 | 1.0766 |
| | $w_1$ | 0.4188 | 0.4582 | 0.4704 | 0.5197 | 0.4956 | 0.4124 | 0.3433 |
| | $x_2$ | | 6.5538 | 7.6651 | 6.3468 | | 7.2480 | 8.9210 |
| | $w_2$ | | 0.1282 | 0.3411 | 0.4305 | | 0.2700 | 0.5557 |
| 5 | $x_1$ | 1.3371 | 0.9347 | 0.6662 | 0.5040 | 0.9375 | 0.9327 | 0.9287 |
| | $w_1$ | 0.3933 | 0.4353 | 0.4767 | 0.5232 | 0.4831 | 0.4016 | 0.3420 |
| | $x_2$ | 7.2388 | 8.7514 | 8.6498 | 7.0101 | 8.5842 | 8.8849 | 9.1612 |
| | $w_2$ | 0.0889 | 0.2548 | 0.3853 | 0.4343 | 0.0786 | 0.3833 | 0.6213 |

These designs are derived by informative guessing and numerical minimization of $\Psi$ in (6). It is easy to use Theorem 1 to verify that the designs in Tables 1 and 2 are indeed locally c-optimal.

## 5 Discussion

Table 2 indicates that two design points are sufficient as long as $1 < SD_{50}/ED_{50} < c$, where c is some constant. Otherwise, if $SD_{50}/ED_{50} > c$ then an additional design point is needed. Table 2 also indicates how the variance-covariance parameters influence the designs. The larger $\rho$ and $\sigma_2^2/\sigma_1^2$, the smaller $c$ for which the statement above holds. A study where the two responses are negatively correlated (for a fixed dose) needs, in this setting, fewer or as many design points as when the two responses are positively correlated. Moreover, a study where the variance for the primary safety variable is large compared with the variance for the primary efficacy variable needs as many or more design points than if this were the other way round. In the present paper the variance-covariance parameters are assumed to be known. It is of interest to analyze further the impact of these parameters and the uncertainty that arises when they are unknown. The work in this paper is part of a larger study (Magnusdottir 2012).

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## Appendix

**Lemma 1** (Pázman 1986) *Let $\phi(x,\xi)$ stand for the derivative of $\Psi$ in the direction $\xi_x$ and let $\Psi$ be a general criterion function to be minimized. A design, $\xi$, is locally optimal with respect to $\Psi$ if and only if $\phi(x,\xi) \geq 0$, $\forall x \in \chi$. This further implies that $\phi(x,\xi) = 0$ for $x \in \{x_1, \ldots, x_n\}$.*

*Proof of Theorem 1* First note that the directional derivative can be written of the form $\phi(x,\xi) = \mathrm{tr}(\frac{\partial \Psi}{\partial M(\xi)}(M(\xi_x) - M(\xi)))$ (Pázman 1986). We have

$$\frac{\partial \Psi}{\partial M(\xi)} = \frac{\partial}{\partial M(\xi)}\left(\nabla g(\theta)^\top M(\xi)^{-1} \nabla g(\theta)\right) = -M(\xi)^{-1}\nabla g(\theta)\nabla g(\theta)^\top M(\xi)^{-1}.$$

From the above we get

$$\begin{aligned}\phi(x,\xi) &= \mathrm{tr}\left(-M(\xi)^{-1}\nabla g(\theta)\nabla g(\theta)^\top M(\xi)^{-1}\left(M(\xi_x) - M(\xi)\right)\right) \\ &= \nabla g(\theta)^\top M(\xi)^{-1}\nabla g(\theta) - \nabla g(\theta)^\top M(\xi)^{-1} M(\xi_x) M(\xi)^{-1}\nabla g(\theta).\end{aligned}$$

Now

$$\begin{aligned}\phi(x,\xi) \geq 0 \quad \Leftrightarrow \quad & \nabla g(\theta)^\top M(\xi)^{-1} M(\xi_x) M(\xi)^{-1}\nabla g(\theta) \\ & \leq \nabla g(\theta)^\top M(\xi)^{-1}\nabla g(\theta).\end{aligned}$$

□

*Proof of Corollary 1* (i) Let $s := SD_{50}/ED_{50} > 1$, $\theta_s = (1, s)$ and $\xi_s = \{\sqrt{s}; 1\}$. Theorem 1 gives that $\xi_2$ is locally c-optimal iff $f(x) := x^2(\frac{1}{s(x+1)^4} + \frac{s}{(x+s)^4}) \leq \frac{2}{(\sqrt{s}+1)^4}$, $\forall x \in \chi$. Equality holds when $x = \sqrt{s}$ and it is easy to show that this point is a local maximum given that $s \in ]1, \frac{7+3\sqrt{5}}{2}[$ ($f'(\sqrt{s}) = 0\ \forall s \in \chi$ and $f''(\sqrt{s}) < 0 \Leftrightarrow s \in ]\frac{7-3\sqrt{5}}{2}, \frac{7+3\sqrt{5}}{2}[$). Now $f'(x) = 2x(x - \sqrt{s})(x + \sqrt{s})g(x)/((x + s)^5(x + 1)^5)$, where $g(x)$ is a polynomial of degree 4. If $s \in ]1, \frac{5+\sqrt{21}}{2}]$ then all coefficients of $g(x)$ are negative and hence $x = \sqrt{s}$ is a global maximum. This means that $\xi_s$ is locally c-optimal for this interval and thus $\xi = \{ED_{50}\sqrt{s}; 1\} = \{\sqrt{ED_{50}SD_{50}}; 1\}$ is locally c-optimal for the model with $\theta = ED_{50}\theta_s = (ED_{50}, SD_{50})$ given that $SD_{50}/ED_{50} \in ]1, \frac{5+\sqrt{21}}{2}]$. (ii) Let $s := SD_{50}/ED_{50}$, $\theta_s = (1, s)$ and $\xi_s = \{1, s; 0.5, 0.5\}$. Theorem 1 implies that $\xi_2$ is locally c-optimal iff

$$\left(\frac{32(s+1)^4}{16s^2 + (s+1)^4}\right)^2 \frac{sx^2}{4}\left(\frac{1}{(x+1)^4} + \frac{s^2}{(x+s)^4}\right) \leq \frac{16s(s+1)^4}{16s^2 + (s+1)^4}, \quad \forall x \in \chi,$$

which is equivalent to

$$\frac{16(s+1)^4}{16s^2 + (s+1)^4} x^2\left(\frac{1}{(x+1)^4} + \frac{s^2}{(x+s)^4}\right) \leq 1, \quad \forall x \in \chi. \tag{8}$$

The left-hand side of (8) tends to $16x^2/(x+1)^4$ as $s \to \infty$. Finally, $16x^2/(x+1)^4 \leq 1, \forall x \in \chi$. This gives that $\xi_s$ is locally c-optimal and thus $\xi = \{ED_{50}, ED_{50}s; 0.5, 0.5\} = \{ED_{50}, SD_{50}; 0.5, 0.5\}$ is locally c-optimal for the model with $\theta = (ED_{50}, ED_{50}s) = (ED_{50}, SD_{50})$ as $SD_{50}/ED_{50} \to \infty$. □

## References


Carrothers, T.J., Hodge, F.L., Korsan, R.J., Poland, W.B., Dykstra, K.H.: Decision-making in drug development: application of a clinical utility index. AAPS J. **1**, 85–107 (2011)

Dragalin, V., Fedorov, V.: Adaptive designs for dose-finding based on efficacy-toxicity response. J. Stat. Plan. Inference **136**, 1800–1823 (2006)

Dragalin, V., Fedorov, V., Wu, Y.: Two-stage design for dose-finding that accounts for both efficacy and safety. Stat. Med. **27**, 5156–5176 (2008)

Fedorov, V.V.: Theory of Optimal Experiments. Academic Press, New York (1972)

Goutelle, S., Maurin, M., Rougier, F., Barbaut, X., Bourguignon, L., Ducher, M., Maire, P.: The Hill equation: a review of its capabilities in pharmacological modelling. Fundam. Clin. Pharmacol. **22**, 633–648 (2008)

Holford, N.H.G., Sheiner, L.B.: Understanding the dose-effect relationship: clinical application of pharmacokinetic-pharmacodynamic models. Clin. Pharmacokinet. **6**, 429–453 (1981)

Li, Z., Durham, S.D., Flournoy, N.: An adaptive design for maximization of a contingent binary response. In: Flournoy, N., Rosenberger, W.F. (eds.) Adaptive Designs. IMS Lecture Notes—Monograph Series, vol. 25, pp. 179–196. Institute of Mathematical Statistics, Hayward (1995)

López-Fidalgo, J., Wong, W.K.: Design issues for the Michaelis-Menten model. J. Theor. Biol. **215**, 1–11 (2002)

Magnusdottir, B.T.: Optimal design problems for the bivariate Emax model. Research Report, Department of Statistics, Stockholm University (2012)

Ouellet, D., Werth, J., Parekh, N., Feltner, D., McCarthy, B., Lalonde, R.L.: The use of a clinical utility index to compare insomnia compounds: a quantitative basis for benefit-risk assessment. Clin. Pharmacol. Ther. **85**, 277–282 (2009)

Pázman, A.: Foundations of Optimum Experimental Design. Reidel, Dordrecht (1986)

Thall, P.F., Russell, K.E.: A strategy for dose-finding and safety monitoring based on efficacy and adverse outcomes in phase I/II clinical trials. Biometrics **54**, 251–264 (1998)

# On the Functional Approach to Locally D-Optimum Design for Multiresponse Models

**Viatcheslav B. Melas, Lyudmila A. Krylova, and Dariusz Uciński**

**Abstract** D-optimum experimental designs are investigated for a multiresponse kinetic model of two consecutive first-order reactions. The model is nonlinear and consists of a set of ordinary differential equations. We demonstrate how the functional approach can be adapted to numerically construct optimal designs in this setting.

## 1 Introduction

Optimal designs are usually found either in closed form or, more often, using well-known numerical algorithms (Atkinson et al. 2007). An effective alternative could be the so-called "functional approach" developed and refined by Melas (2006). Its basic idea is to treat the support points and weights of the optimal design as implicit functions of some judiciously selected auxiliary parameters. These functions can be represented by means of power series and then the problem reduces to numerical computation of a sufficiently large number of their most significant terms.

The functional approach has been successfully applied to linear and nonlinear regression models and various design criteria, including minimax and Bayesian ones. This paper makes a start on its use in the design of optimal experiments for multiresponse dynamic models whose evolution is described by systems of ordinary differential equations. We motivate our work by an example drawn from chemical kinetics, which also serves as a device to illustrate the effectiveness of the approach.

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## 2 Problem Formulation

Consider a simple chemical reaction which is, however, sufficiently rich to illustrate our ideas. In the model for two consecutive first-order reactions $A \overset{\theta_1}{\to} B \overset{\theta_2}{\to} C$, we start, at $t = 0$, with concentrations $[A](0;\theta) = 1$ and $[B](0;\theta) = [C](0;\theta) = 0$ of three reactants. The change over time of these is governed by the kinetic ordinary differential equations (Atkinson et al. 2007, p. 270) which have the closed-form solution

$$\begin{cases} [A](t;\theta) = \mathrm{e}^{-\theta_1 t}, \\ [B](t;\theta) = \left( -\dfrac{\theta_1 \mathrm{e}^{-(\theta_1-\theta_2)t}}{\theta_1-\theta_2} + \dfrac{\theta_1}{\theta_1-\theta_2} \right) \mathrm{e}^{-\theta_2 t}, \\ [C](t;\theta) = 1 - [A](t;\theta) - [B](t;\theta). \end{cases} \tag{1}$$

We assume that the observations in a given time interval $T = [0, t_f]$ consist of simultaneous measurements of the three components, i.e.,

$$y_i = \eta(t_i,\theta) + \varepsilon_i, \quad t_i = 1, \ldots, N,$$

where $\eta(t;\theta) = ([A](t;\theta), [B](t;\theta), [C](t;\theta))^{\mathsf{T}}$, $t_i \in T$, $i = 1, \ldots, N$, $\varepsilon_i$ stands for measurement noise, $\mathrm{E}\{\varepsilon_i\} = 0$, $\mathrm{E}\{\varepsilon_i \varepsilon_j^{\mathsf{T}}\} = R\delta_{ij}$, $\delta_{ij}$ is the Kronecker delta, $R \in \mathbb{R}^{3\times 3}$ is assumed to be known. This means that the observations at different time moments are not correlated, but there may be correlations between individual response components for the same time moment.

Allowing replicated measurements, we consider continuous designs of the form

$$\xi = \left\{ \begin{matrix} t_1, & \ldots, & t_k \\ w_1, & \ldots, & w_k \end{matrix} \right\}, \tag{2}$$

where the support points $t_i$ do not coincide, and $w_i$ denote the corresponding weights, with $k$ not being fixed. Then the corresponding information matrix can be written as

$$M(\xi;\theta) = \sum_{i=1}^{k} w_i \left( \frac{\partial \eta}{\partial \theta}(t_i,\theta) \right)^{\mathsf{T}} R^{-1} \frac{\partial \eta}{\partial \theta}(t_i,\theta). \tag{3}$$

Our goal is to determine locally D-optimum designs for the regression function $\eta(t,\theta)$. To this end, the functional approach (Melas 2006) is going to be exploited.

## 3 Main Analytical Results

We start by partitioning the matrix $R^{-1}$ as

$$R^{-1} = \begin{pmatrix} Q & h \\ h^{\mathsf{T}} & q \end{pmatrix},$$

where $Q \in \mathbb{R}^{2\times 2}$, $h \in \mathbb{R}^2$, $q \in \mathbb{R}$. We then define $W$ as the matrix function

$$W(R) = Q - hd^{\mathsf{T}} - dh^{\mathsf{T}} + qdd^{\mathsf{T}},$$

with $d = (1, 1)^{\mathsf{T}}$.

For notational simplicity, the derivatives of the responses with respect to parameters will be denoted by

$$f_1(t;\theta) = \frac{\partial \eta_1(t,\theta)}{\partial \theta_1}, \qquad f_2(t;\theta) = \frac{\partial \eta_2(t,\theta)}{\partial \theta_1}, \qquad f_3(t;\theta) = \frac{\partial \eta_2(t,\theta)}{\partial \theta_2}. \tag{4}$$

For similar reasons, we set

$$\widetilde{X}(t) = \begin{pmatrix} f_1(t) & f_2(t) & -f_1(t) - f_2(t) \\ 0 & f_3(t) & -f_3(t) \end{pmatrix}, \qquad X(t) = \begin{pmatrix} f_1(t) & f_2(t) \\ 0 & f_3(t) \end{pmatrix}.$$

It is easy to check that

$$\widetilde{X}(t)R^{-1}\widetilde{X}^{\mathsf{T}}(t) = X(t)WX^{\mathsf{T}}(t).$$

The matrix product on the right-hand side thus produces a positive-definite matrix.

For any design $\xi$ of the form (2) the Fisher information matrix (3) becomes

$$M(\xi) = \sum_{i=1}^{k} w_i \widetilde{X}(t_i)R^{-1}\widetilde{X}^{\mathsf{T}}(t_i) = \sum_{i=1}^{k} w_i X(t_i)WX^{\mathsf{T}}(t_i).$$

Observe that for $k = 1$, i.e., for a one-point design $\xi = \delta_{t_0} = \{ {}^{t_0}_{1} \}$, we get

$$\det\bigl[M(\delta_{t_0})\bigr] = \det(W)\bigl\{\det\bigl[X(t_0)\bigr]\bigr\}^2 = \det(W) f_1^2(t_0) f_3^2(t_0). \tag{5}$$

**Lemma 1** (Equivalence Theorem) *A design $\xi^\star$ is a D-optimum one for the considered model iff $\varphi(t, \xi^*) \le 2$, $\forall t \in T$, where*

$$\varphi(t,\xi) = \operatorname{tr}\bigl[WX^{\mathsf{T}}(t)M^{-1}(\xi)X(t)\bigr].$$

The proof is standard (see, e.g., Uciński 2005) and is therefore omitted.

It is easily seen that D-optimum designs depend on the unknown values of $\theta_1$ and $\theta_2$. Therefore, we focus on construction of a locally D-optimum design using their prior point estimates. By abuse of notation, we use the same letters $\theta_1$ and $\theta_2$ for these arbitrarily selected values.

Observe that if we multiply both $\theta_1$ and $\theta_2$ by a constant and scale the time variable by dividing it by the same constant, the model (1) does not change. Therefore, without loss of generality, we can assume that $\theta_1 + \theta_2 = 2$. Whenever $\theta_1 + \theta_2 = c \neq 2$, the support points of the optimal designs which are going to be determined in what follows should be simply multiplied by $2/c$.

Introduce the parameter $\Delta = 1 - \theta_1$, which yields $\theta_1 = 1 - \Delta$ and $\theta_2 = 1 + \Delta$. The support points and the corresponding weights of the D-optimum design $\xi$ will

thus be treated as functions of $\Delta$. The idea is to study the problem for $\Delta = 0$, which is less complicated, and then expand the solution in a power series for arbitrary $\Delta$.

Observe that, as $\Delta \to 0$, we have

$$f_1(t) \to -t\mathrm{e}^{-t}, \qquad f_2(t) \to \left(t - \frac{t^2}{2}\right)\mathrm{e}^{-t}, \qquad f_3(t) \to -\frac{t^2}{2}\mathrm{e}^{-t}.$$

Therefore, $M(\xi)$ has a continuous extension to the case of $\theta_1 = \theta_2 = 1$.

Set

$$\bar{X}(t) = \lim_{\Delta\to 0} X(t;\theta)\big|_{\substack{\theta_1=1-\Delta\\ \theta_2=1+\Delta}} = \begin{pmatrix} -t\mathrm{e}^{-t} & (t-\frac{t^2}{2})\mathrm{e}^{-t} \\ 0 & -\frac{t^2}{2}\mathrm{e}^{-t} \end{pmatrix},$$

$$\bar{M}(\xi) = \sum_{i=1}^{k} w_i \bar{X}(t) W \bar{X}^{\mathsf{T}}(t_i).$$

Furthermore, define

$$W = \begin{pmatrix} a & b \\ b & c \end{pmatrix}, \quad \gamma = \gamma(R) = \frac{ac + c^2 - 2bc}{ac - b^2},$$

$$\Psi(t;\gamma) = \mathrm{e}^{-2t+3}\left[\gamma\left(y^2 - y\right)^2 + 2y^3\right], \quad \text{where } y = \frac{2}{3}t,$$

$$t_{1,2}(\gamma) = \frac{7}{4} - \frac{3}{2\gamma} \pm \sqrt{\left(\frac{7}{4} - \frac{3}{2\gamma}\right)^2 - \frac{3}{2}}.$$

Let $\gamma^\star$ denote any solution of the equation

$$\max_{i=1,2} \Psi\left[t_i(\gamma);\gamma\right] = 2 \tag{6}$$

subject to

$$\gamma > \bar{\gamma} = \frac{3}{2}\left(\frac{7}{4} - \sqrt{\frac{3}{2}}\right)^{-1}. \tag{7}$$

**Theorem 1** *Assume that $t_f \geq 3/2$ and $\Delta = 0$. Equation (6) has a unique solution $\gamma^\star$ satisfying (7). What is more, the D-optimum design has only one support point iff*

$$\gamma(R) \leq \gamma^\star. \tag{8}$$

*It then has the form $\delta_{t_0} = \left\{ {}^{t_0}_{1} \right\}$, where $t_0 = 3/2$. For $\gamma(R) > \gamma^\star$ the optimal design has two support points.*

Note that the numerical solution of (6) subject to (7) gives $\gamma^\star \approx 2.872$.

**Table 1** Optimal designs $\xi^{\text{opt}}$ determined numerically for various $\Delta$: $t_1$ and $t_2$ are optimal support points with optimal weights $w$ and $1-w$, respectively

| $\Delta$ | $t_1$ | $t_2$ | $w$ | $\det[M(\xi^{\text{opt}})]$ |
|---|---|---|---|---|
| 0.01 | 1.50504 | 1.50504 | 1 | 0.02118 |
| 0.10 | 1.55456 | 1.55456 | 1 | 0.02114 |
| 0.50 | 1.93755 | 1.93755 | 1 | 0.01944 |
| 0.80 | 2.99853 | 2.99853 | 1 | 0.01356 |
| 0.85 | 3.60919 | 3.60919 | 1 | 0.01170 |
| 0.90 | 3.11325 | 7.61392 | 0.48351 | 0.00994 |
| 0.99 | 3.61443 | 85.92849 | 0.41614 | 0.00919 |

*Proof* By definition, a one-point D-optimum design $\delta_{t_0} = \left\{ \begin{smallmatrix} t_0 \\ 1 \end{smallmatrix} \right\}$ must maximize (5), which implies $t_0 = 3/2$. In this case we see that $\varphi(t, \delta_{t_0}) = \Psi(t; \gamma)$.

The derivative of $\Psi(t; \gamma)$ with respect to $t$ is

$$\frac{\mathrm{d}\Psi(t;\gamma)}{\mathrm{d}t} = -\frac{32}{81}\mathrm{e}^{-2t+3}t\left(t-\frac{3}{2}\right)\left[\gamma\left(t^2-\frac{7}{2}t+\frac{3}{2}\right)+3t\right]. \tag{9}$$

For $\gamma$ not satisfying (7) it becomes zero for $t > 0$ only at $t = t_0 = 3/2$, where $t \mapsto \varphi(t, \delta_{t_0})$ attains its maximum equal to 2. From Lemma 1 it then follows that the one-point design $\delta_{3/2}$ is the unique D-optimal design.

If (7) is satisfied, then the derivative (9) becomes zero at points $t_0$, $t_1(\gamma)$ and $t_2(\gamma)$ and it can be verified that the function $\gamma \mapsto \max_{i=1,2} \Psi[t_i(\gamma); \gamma]$ is monotonically increasing. Accordingly, Eq. (6) has a unique solution $\gamma^*$ and for $\gamma > \gamma^*$ we have $\varphi(t, \xi_{t_0}) > 2$ for $t = t_1(\gamma)$ or $t = t_2(\gamma)$.

By Lemma 1 the optimal design in this case cannot be one-point. On the other hand, that the number of support points of the optimal design in this case must not exceed two results from the Chebyshev property of the system of functions defined as products of exponentials and monomials, cf. Dette and Melas (2011). □

## 4 Computational Results

Consider first the case when $R$ is the identity matrix. Theorem 1 implies that for $\Delta = 0$ the optimal design has one support point and is of the form $\delta_{3/2}$. For $\Delta > 0$ it may have two or even three support points; Carathéodory's Theorem makes it possible to restrict attention to designs with no more than three support points.

The results of a numerical search for D-optimum designs using Maple are reported in Table 1 (optimal designs are denoted by $\xi^{\text{opt}}$). For $\Delta \in [0, 0.85]$ the optimal design has only one support point. From (5) we see that the determinant of the corresponding information matrix is $3(f_1 f_3)^2$, where $f_1$ and $f_3$ are given by (4). Substituting $\theta_1 = 1 - \Delta$ and $\theta_2 = 1 + \Delta$, we obtain

$$f_1 = -t\mathrm{e}^{(\Delta-1)t}, \qquad f_3 = (1-\Delta)\mathrm{e}^{-(1+\Delta)t}\left(\frac{1-\mathrm{e}^{2\Delta t}}{4\Delta^2}+\frac{t}{2\Delta}\right).$$

In order to find a D-optimal design for this case, it is enough to solve the equation

$$g(t, \Delta) = 0, \tag{10}$$

where $g(t, \Delta) = \partial \det M(t, \Delta)/\partial t$. This gives

$$(1 - 2t + 2\Delta t)\mathrm{e}^{2\Delta t} - 1 - 4\Delta t + 2t + 4\Delta t^2 = 0. \tag{11}$$

We shall consider the optimal support point $t^\star$ as a function of $\Delta$. Equation (11) makes it possible to determine the coefficients of the expansion of $t^\star(\Delta)$ in the Taylor series about $\Delta = 0$. Denote by $t^\star_{(i)}$ the $i$-th coefficient of this expansion, i.e.,

$$t^\star(\Delta) = \sum_{i=0}^{\infty} t^\star_{(i)} \Delta^i.$$

From Theorem 1, we see that $t^\star(0) = t^\star_{(0)} = 3/2$.

Consider now the Jacobi matrix of Eq. (10) (here it reduces to a scalar):

$$J(t, \Delta) = \frac{\partial^2}{\partial t^2} \det M(t, \Delta).$$

Expanding $J(t, \Delta)$ in a series of $\Delta$ up to the sixth order, we get

$$J(t, \Delta) = 12\mathrm{e}^{-4t}t^6 + \frac{45}{2}\mathrm{e}^{-4t}t^4 - 36\mathrm{e}^{-4t}t^5 + (\dots)\Delta + O\big(\Delta^2\big).$$

Substituting $t^\star_{(0)} = 3/2$, we obtain the limit of $J[t(\Delta), \Delta]$ as $\Delta \to 0$:

$$J_{(0)} = -\frac{729}{32}\,\mathrm{e}^{-6}.$$

Exploiting the recurrence formulae from Melas (2006), it may be concluded that

$$t_{(s)} = -J_{(0)}^{-1}\big\{g\big[t_{\langle s-1\rangle}(\Delta), \Delta\big]\big\}_{(s)}, \quad s = 1, 2, \dots,$$

where $t_{\langle n\rangle}(\Delta) = \sum_{i=0}^{n} t_{(i)}\Delta^i$, $g[t(\Delta), \Delta]_{(s)}$ being the $s$-th coefficient in the expansion of $g[t(\Delta), \Delta]$ in the Taylor series about $\Delta = 0$. Implementing this in Maple, we get

$$t^\star(\Delta) = \frac{3}{2} + \frac{1}{2}\Delta + \frac{5}{12}\Delta^2 + \frac{16}{45}\Delta^3 + \frac{697}{2160}\Delta^4 + \frac{173}{567}\Delta^5 + \cdots.$$

As $\Delta \to 0$, the determinant of the information matrix for the design $\xi = \left\{ \begin{smallmatrix} t^\star \\ 1 \end{smallmatrix} \right\}$ tends to $\frac{2187}{256}\mathrm{e}^{-6} \approx 0.0211759$ (this agrees with the numerical results of Table 1).

Let us investigate how the quality of the above approximation to the D-optimum design $\xi^\star$ depends on the number of expansion coefficients. Let $\xi^{\langle n\rangle}$ be the approximate design constructed based on $n$ coefficients of the expansion. Set $t^\star =$

**Table 2** Accuracy of designs constructed by the functional approach

| $\Delta$ | $n$ | $t^{\langle n\rangle}$ | $\det M(t^{\langle n\rangle})$ | $t^\star$ | $\varphi(t^\star, \xi^{\langle n\rangle})$ | $\det M(t^\star)$ |
|---|---|---|---|---|---|---|
| 0.1 | 1 | 1.5500 | 0.0211 | 1.5566 | 2.0000 | 0.0211 |
| 0.1 | 2 | 1.5541 | 0.0211 | 1.5547 | 2.0000 | 0.0211 |
| 0.5 | 5 | 1.9283 | 0.0194 | 1.9386 | 2.0000 | 0.0194 |
| 0.5 | 7 | 1.9352 | 0.0194 | 1.9378 | 2.0000 | 0.0194 |
| 0.8 | 15 | 2.9347 | 0.0135 | 3.0893 | 2.0019 | 0.0135 |
| 0.8 | 25 | 2.9877 | 0.0135 | 3.0130 | 2.0000 | 0.0135 |
| 0.8 | 30 | 2.9941 | 0.0135 | 3.0043 | 2.0000 | 0.0135 |
| 0.85 | 10 | 3.1610 | 0.0114 | 5.6376 | 2.1450 | 0.0087 |
| 0.85 | 30 | 3.5692 | 0.0117 | 3.9830 | 2.0016 | 0.0115 |
| 0.85 | 40 | 3.5989 | 0.0117 | 3.6841 | 2.0000 | 0.0117 |
| 0.9 | 30 | 4.7017 | 0.0095 | 8.5400 | 2.1238 | 0.0068 |

$\arg\max_t \varphi(t, \xi^{\langle n\rangle})$. For comparison, the last row of Table 2 contains the results for $\Delta = 0.9$. In this case, the one-point design is not D-optimal. The reason for the observed change in the number of support points is that for $\Delta \approx 1$ the multiresponse model behaves much like a single-response model.

For the designs found for $\Delta = 0.87, 0.88, \ldots, 0.999$ the condition $\varphi(t, \xi^{\mathrm{opt}}) \le 2$ is satisfied with great accuracy for any two-point design from Table 1. The maximum of the function $\varphi(t, \xi^{\mathrm{opt}})$ is attained at points $\tilde{t}_1$ and $\tilde{t}_2$ such that $\tilde{t}_1 \approx t_1, \tilde{t}_2 \approx t_2$. Note that the one-point design $\delta_{3/2}$ which is locally D-optimum for $\Delta = 0$ has efficiency 0.998 for $\Delta = 0.1$, efficiency 0.919 for $\Delta = 0.5$ and 0.662 for $\Delta = 0$.

Consider now the case where for $\Delta = 0$ the optimal design has two support points. To this end, assume that $R$ is such that

$$W(R) = \begin{pmatrix} 102 & 10 \\ 10 & 1 \end{pmatrix}. \tag{12}$$

It is easy to see that $\gamma(R) = 83/2$ does not satisfy (8).

For $\Delta \to 0$ we numerically find the limit optimal two-point design with

$$t_1^{\mathrm{opt}} = 0.6490, \qquad t_2^{\mathrm{opt}} = 2.3295, \qquad w^{\mathrm{opt}} = 0.4936.$$

Treating the support points $t_1$, $t_2$ and the weight $w$ as functions of $\Delta$, we recurrently find the respective coefficients of the expansion of these functions in the Taylor series about $\Delta = 0$ (several of them are included in Table 3).

Using 20 coefficients of the expansion around $\Delta = 0$, we find the design at point $\Delta = 0.2$:

$$t_1^{\langle 20\rangle}(0.2) = 0.5874, \qquad t_2^{\langle 20\rangle}(0.2) = 2.1088, \qquad w^{\langle 20\rangle}(0.2) = 0.4639.$$

The optimal design found numerically has the form

$$t_1^{\mathrm{opt}} = 0.5861, \qquad t_2^{\mathrm{opt}} = 2.1097, \qquad w^{\mathrm{opt}} = 0.4651.$$

**Table 3** Several coefficients of the expansions about $\Delta = 0$ for $R$ satisfying (12): $t_{1(i)}$ and $t_{2(i)}$ signify coefficients for the optimal support points; $w_{(i)}$ are coefficients for the weight of the support point $t_1$

| $i$ | $t_{1(i)}$ | $t_{2(i)}$ | $w_{(i)}$ |
|---|---|---|---|
| 0 | 0.6490 | 2.3295 | 0.4936 |
| 1 | −0.1988 | −0.9830 | −0.0612 |
| 2 | −0.5395 | −0.3998 | −0.2424 |
| 3 | −0.2033 | −1.6464 | −0.6302 |
| 4 | 0.5075 | 1.9346 | −1.2363 |

In turn, at point $\Delta = 0.4$ we get the following design:

$$t_1^{\langle 20\rangle}(0.4) = 0.4944, \qquad t_2^{\langle 20\rangle}(0.4) = 1.8880, \qquad w^{\langle 20\rangle}(0.4) = 0.3191.$$

The optimal design found numerically has the form

$$t_1^{\mathrm{opt}} = 0.4942, \qquad t_2^{\mathrm{opt}} = 1.8874, \qquad w^{\mathrm{opt}} = 0.3190.$$

Thus the achieved accuracies are at least $5 \times 10^{-3}$.

## 5 Conclusion

The obtained theoretical and numerical results demonstrate that the functional approach combined with the equivalence theorem makes it possible to approximate locally optimal designs for the nonlinear model considered with quite high accuracy. We intend to continue this line of research towards models described by systems of ordinary differential equations which do not have closed-form solutions for responses.

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## References

Atkinson, A.C., Donev, A.N., Tobias, R.D.: Optimum Experimental Designs with SAS. Oxford University Press, Oxford (2007)

Dette, H., Melas, V.B.: A note on the de la Garza phenomenon for locally optimal designs. Ann. Stat. **44**, 617–628 (2011)

Melas, V.B.: Functional Approach to Optimal Experimental Design. Springer, New York (2006)

Uciński, D.: Optimal Measurement Methods for Distributed Parameter System Identification. CRC Press, Boca Ration (2005)

# Sample Size Calculation for Diagnostic Tests in Generalized Linear Mixed Models

**Tobias Mielke and Rainer Schwabe**

**Abstract** Intra-cluster correlations have to be taken into account for calculating the stochastic behaviour of estimators in diagnostic studies with repeated measurements on individuals. One approach of inducing the intra-cluster correlation is provided by generalized linear mixed models. In these models the inverse of the Fisher information matrix is important as the asymptotic covariance of the maximum likelihood estimator which is necessary for determining the required sample size of statistical tests. We illustrate the dependence of the sample size on different approximations of the Fisher information matrix through an example of the proof of non-inferiority in medical diagnostic studies.

## 1 Introduction

Generalized linear mixed effects models can be applied in diagnostic studies to take account of possible intra-individual dependencies. The observations within one individual are assumed to follow a common response structure, which is described by an individual parametric model. The individual parameters specifying these models are assumed to vary across the whole population with some distribution defined by population parameters. These parameters, or functions thereof, are of interest in clinical studies. However, the likelihood function in mixed effects models generally contains integrals which cannot be simplified into a closed form. As a consequence, estimators of the population parameters are also not obtainable as closed-form expressions, nor is the inverse of the Fisher information matrix. This inverse is customarily used in designing experiments as the asymptotic covariance matrix of the maximum likelihood estimator. Approximations to the Fisher information are therefore needed. Experimental designs based on such approximations (Waterhouse 2005; Niaparast

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2010; Waite et al. 2012) may however be of limited efficiency with respect to the true model.

In Sect. 2 we introduce the binomial response model considered here with subject specific success probabilities. A related testing problem is presented in Sect. 3 and an example on the impact of different information approximations on the required sample size in diagnostic studies is given in Sect. 4. Section 5 summarizes our findings and proposes further areas of study.

## 2 Model

Diagnostic methods are applied in order to study the presence of certain diseases in individuals. For $N$ individuals let $x_{ij} \in \{0, 1\}$, $j = 1, \ldots, m$ and $i = 1, \ldots, N$, describe the presence of a particular disease in component $j$ of the $i$-th individual, where the value $x_{ij} = 1$ indicates an existing disease. The values of $x_{ij}$ are unknown at the planning stage of the study and might be considered as realizations of binomial random variables $X_{ij}$ with success probabilities $p$, such that the proportion of individuals with exactly $l$ diseased objects is given by

$$\omega_l := \binom{m}{l} p^l (1-p)^{m-l}.$$

The exact determination of the disease status $x_{ij}$ in the objects is generally impossible. Diagnostic methods yield insights into the disease status, but include some errors. Diagnostic test results are modelled as realizations of zero-one valued random variables $Y_{kij}$, which describe the judgments in the $k$-th study group for the $j$-th component in individual $i$. Measures for the appropriateness of diagnostic tests are given by the sensitivity and the specificity. The sensitivity describes the probability of declaring a diseased object as diseased:

$$\pi_k := P(Y_{kij} = 1 | X_{ij} = 1),$$

whereas the specificity denotes the probability of declaring a non-diseased object as non-diseased:

$$\tau_k := P(Y_{kij} = 0 | X_{ij} = 0).$$

The sensitivity and specificity will generally depend on the treatment group $k$ and the individual $i$, but are assumed to be independent of the compartment $j$. One way to model the dependence of sensitivity and specificity on the individual is provided by including individual effects in the model for the probability of observing positive diagnostic test results. It is common to employ a generalized linear model with the logit link function:

$$\operatorname{logit}\big(P(Y_{kij} = 1 | X_{ij} = x_{ij})\big) = f(x_{ij})^\top \theta_{i;k} = \theta_{1;i;k} + \theta_{2;i;k} x_{ij},$$

where $f(x_{ij}) = (1, x_{ij})^\top$. The parameter vectors $\theta_{i;k}$ are assumed to be normally distributed random variables with uncorrelated components:

$$\theta_{i;k} \sim \mathcal{N}(\theta_k, D), \tag{1}$$

where $D = \mathrm{diag}(d_1, d_2)$, $d_1 > 0$, $d_2 > 0$, $i = 1, \ldots, N$.

The model for the observations $Y_{ki} = (Y_{ki1}, \ldots, Y_{kim})$ is hence a generalized linear mixed model. The log-likelihood results for individual $i$ and realizations $y_{ki} = (y_{ki1}, \ldots, y_{kim})$, given values of the disease status $x_i = (x_{i1}, \ldots, x_{im})$ and a design matrix $F_i := (f(x_{i1}), \ldots, f(x_{im}))^\top$ in

$$l(\theta; y_{ki}, x_i) = \ln\left(\int_{\mathbb{R}^2} \exp\left[ y_{ki}^\top F_i \theta_i - \sum_{j=1}^{m} \ln\left(1 + \exp\left[f(x_{ij})^\top \theta_i\right]\right)\right] \phi_{\theta_{i;k}}(\theta_i)\, \mathrm{d}\theta_i\right),$$

where $\phi_{\theta_{i;k}}$ is the corresponding normal density to (1) for the individual parameter vector.

A closed-form representation of the likelihood function for the present model is not obtainable. Approaches in statistical programs aim at optimizing the true likelihood by maximizing an approximated likelihood with the use of Laplace approximations or MCMC-methods. These provide estimators of the population parameters $\theta_k$ that behave similar to the maximum likelihood estimator $\widehat{\theta}_k$, which is under some regularity conditions asymptotically normally distributed as

$$\sqrt{N}(\widehat{\theta}_k - \theta_k) \xrightarrow{\mathcal{L}} \mathcal{N}\left(0, \mathbf{M}_{\theta_k}^{-1}\right), \quad (N \to \infty)$$

with the inverse of the standardized Fisher information $\mathbf{M}_{\theta_k}$ as the asymptotic covariance. The problem of the missing formula for the likelihood function carries forward to the calculation of the Fisher information matrix, which is defined as the covariance of the score function (Mielke 2011)

$$\begin{aligned}\mathbf{M}_{\theta_k} &:= \sum_{j=0}^{m} \omega_j E\left(\frac{\partial l(\theta_k; Y_{ki}, x_j)}{\partial \theta_k} \frac{\partial l(\theta_k; Y_{ki}, x_j)}{\partial \theta_k^\top}\right) \\ &= D^{-1} - D^{-1} E\left(\mathrm{Var}(\theta_{i;k} | Y_{ki})\right) D^{-1},\end{aligned}$$

where here and in the following $x_j = (x_{j1}, \ldots, x_{jm})$ is defined with $x_{jl} = 1$, $l \le j$ and $x_{jl} = 0$ otherwise. The dependence of the Fisher information on the prevalence of the disease is contained in the weights $\omega_j$.

Various approaches to approximating the Fisher information matrix might be applied based on this representation. Approximations of the conditional density of $\theta_{i;k}$ for given realizations $y_{ki}$ and fixed numbers of diseased objects $x_i$:

$$f_{\theta_{i;k}|Y_{ki}=y_{ki}}(\theta_i) = \frac{\exp(y_{ki}^\top F_i \theta_i - \sum_{j=1}^{m} \ln(1 + \exp[f(x_{ij})^\top \theta_i])) \phi_{\theta_i}(\theta_i)}{\int_{\mathbb{R}^2} \exp(y_{ki}^\top F_i \theta_i - \sum_{j=1}^{m} \ln(1 + \exp[f(x_{ij})^\top \theta_i])) \phi_{\theta_i}(\theta_i)\, \mathrm{d}\theta_i} \tag{2}$$

can be derived by applying a Laplace approximation to the denominator integral and a second order Taylor approximation to the exponents in the numerator term. The application of the same support point $\widetilde{\theta}_{i;k}$ for the approximations of the denominator and the numerator results in a normal density as an approximation of the conditional distribution (Mielke 2011). We are here only interested in the approximation of the conditional variance, which is approximated with the described approach on the conditional density by

$$\operatorname{Var}(\theta_{i;k}|Y_{ki} = y_{ki}) \approx \left(D^{-1} + F_i^\top C_{\widetilde{\theta}_{i;k}} F_i\right)^{-1},$$

where

$$C_{\widetilde{\theta}_{i;k}} := \operatorname{diag}\left(\frac{\exp(f(x_{i1})^\top \widetilde{\theta}_{i;k})}{(1+\exp(f(x_{i1})^\top \widetilde{\theta}_{i;k}))^2}, \ldots, \frac{\exp(f(x_{im})^\top \widetilde{\theta}_{i;k})}{(1+\exp(f(x_{im})^\top \widetilde{\theta}_{i;k}))^2}\right).$$

Different approximations of the conditional variance result in a dependence of this approach on the support point $\widetilde{\theta}_{i;k}$. Approximations of the Fisher information matrix can be computed by

$$\begin{aligned}\mathbf{M}_{\theta_k} &= D^{-1} - D^{-1} E\left(\operatorname{Var}(\theta_{i;k}|Y_{ki})\right) D^{-1} \\ &\approx E\left(D^{-1} - D^{-1}\left(D^{-1} + F_i^\top C_{\widetilde{\theta}_{i;k}} F_i\right)^{-1} D^{-1}\right) = E\left(F_i^\top \left(C^{-1}_{\widetilde{\theta}_{i;k}} + F_i D F_i^\top\right)^{-1} F_i\right).\end{aligned}$$

A frequently applied approximation of the Fisher information matrix in mixed effects models is obtained by the application of the mean $\theta_k$ of the individual parameter vectors as a support point of the approximation and corresponds to the Longford approximation (Waterhouse 2005):

$$\mathbf{M}_{1;\theta} := \sum_{j=0}^{m} \omega_j F_j^\top \left(C^{-1}_{\theta_k} + F_j D F_j^\top\right)^{-1} F_j.$$

This approximation does not depend in any way on the possible outcomes $y_{ki}$. A more refined approximation of the conditional density is given by applying the complete Laplace approximation, which approximates the conditional mean by the mode of the joint density for given observations $y_{ki}$. This was proposed by Breslow and Clayton (1993) and, in much the same manner, in nonlinear mixed effects models by Nyberg (2011). The limited number of possible outcomes $y_i \in \{0, 1\}^m$ in the generalized linear mixed model considered here allows the computation of the modes $\theta^*_{i;k}$ of the expression (2) and hence the approximation of the Fisher information using these support points:

$$\mathbf{M}_{2;\theta} := \sum_{j=0}^{m} \omega_j \sum_{l=1}^{2^m} F_j^\top \left(C^{-1}_{\theta^*_{i;k}} + F_j D F_j^\top\right)^{-1} F_j P(Y_{ki} = y_l | X_i = x_j),$$

where the values of

$$P(Y_{ki} = y_l | X_i = x_j) = \int_{\mathbb{R}^2} \exp\left[ y_l^\top F_j \theta_i - \sum_{i'=1}^{m} \ln\left(1 + \exp\left[ f(x_{ji'})^\top \theta_i \right]\right) \right] \phi_{\theta_{i;k}}(\theta_i)\, \mathrm{d}\theta_i$$

are approximated using Laplace approximations.

A third alternative for approximating the Fisher information based on the above approximation of the conditional variance was presented by Mielke (2011) for nonlinear mixed effects models. The individual parameter vectors $\theta_{i;k}$ are applied as support points of the Laplace approximation in this approach and the Fisher information is approximated by the mean of the resulting matrices:

$$\mathbf{M}_{3;\theta} := \sum_{j=0}^{m} \omega_j E_{\theta_{i;k}} \left( F_j^\top \left( C_{\theta_{i;k}}^{-1} + F_j D F_j^\top \right)^{-1} F_j \right).$$

Waite et al. (2012) state that for large numbers $N$ of individuals the approximation $\mathbf{M}_{3;\theta}$ will coincide with the approximation $\mathbf{M}_{2;\theta}$. This result does not hold in general, as the distribution of support points $\theta_{i;k}^*$ will not coincide with the distribution of the individual parameters $\theta_{i;k}$.

An alternative approach for estimating $\theta_k$ is given by the Quasi-likelihood estimator $\widehat{\theta}_{QL}$, minimizing the least squares function for observed $y = (y_{k1}, \ldots, y_{kN})$:

$$L_{QL}(\theta; y) := \sum_{i=1}^{N} \left( y_{ki} - E_\theta(Y_{ki}) \right)^\top \mathrm{Cov}_{\theta_0}(Y_{ki})^{-1} \left( y_{ki} - E_\theta(Y_{ki}) \right) \to \min_{\theta \in \mathbb{R}^p}.$$

Here $\theta_0$ is an iteratively updated guess of $\theta_k$. The theory of least-squares estimation provides the asymptotic normality of the estimator $\widehat{\theta}_{QL}$:

$$\sqrt{N}(\widehat{\theta}_{QL} - \theta_k) \xrightarrow{\mathscr{L}} \mathscr{N}\left(0, \mathbf{M}_{4;\theta}^{-1}\right)$$

with the quasi-information

$$\mathbf{M}_{4;\theta} := \sum_{j=0}^{m} \omega_j \frac{\partial E(Y_{ki} | X_i = x_j)^\top}{\partial \theta_k} \mathrm{Cov}_\theta(Y_{ki} | X_i = x_j)^{-1} \frac{\partial E(Y_{ki} | X_i = x_j)}{\partial \theta_k^\top}.$$

The quasi information provides a lower bound to the Fisher information matrix and might be used for designing experiments in generalized linear mixed models (Niaparast 2010).

Note that in the present example the Fisher information matrix can be computed numerically due to a limited number of possibly different outcomes.

## 3 Statistical Testing Problem

Aim of diagnostic studies might be the proof of non-inferiority in the sensitivity and specificity of the endpoints. A treatment $k$ is called non-inferior to a treatment $k'$ if the following inequalities are fulfilled for given non-inferiority margins $\delta_\pi$ and $\delta_\tau$:

$$\pi_k > \pi_{k'} - \delta_\pi \quad \text{and} \quad \tau_k > \tau_{k'} - \delta_\tau .$$

The intersection-union test can be applied to prove the non-inferiority with the global null-hypotheses:

$$H_0 : \pi_k \leq \pi_{k'} - \delta_\pi \quad \text{or} \quad \tau_k \leq \tau_{k'} - \delta_\tau ,$$

which is rejected at a level of $\alpha$ if the two hypotheses

$$H_{01} : \pi_k \leq \pi_{k'} - \delta_\pi \quad \text{and} \quad H_{02} : \tau_k \leq \tau_{k'} - \delta_\tau$$

are both rejected by level $\alpha$-tests (Berger 1982). Our aim is the calculation of the minimal sample size for attaining a power of $1-\beta$ in the case of the equality of both the endpoints in the two-treatment groups. The $\Delta$-Method is applied for deriving the asymptotic statistical model of the estimators of sensitivity and specificity.

Write

$$\widehat{\pi}_k := \frac{\exp(\widehat{\theta}_{1;k} + \widehat{\theta}_{2;k})}{1 + \exp(\widehat{\theta}_{1;k} + \widehat{\theta}_{2;k})}, \qquad \widehat{\tau}_k := \frac{1}{1 + \exp(\widehat{\theta}_{1;k})}.$$

Then the asymptotic normality of the maximum likelihood estimator follows:

$$\sqrt{N_k}\left(\begin{pmatrix}\widehat{\pi}_k \\ \widehat{\tau}_k\end{pmatrix} - \begin{pmatrix}\pi_k \\ \tau_k\end{pmatrix}\right) \xrightarrow{\mathscr{L}} \mathscr{N}\big(0, \Lambda_{\theta_k} \mathbf{M}_{\theta_k}^{-1} \Lambda_{\theta_k}^\top\big), \quad (N_k \to \infty)$$

where

$$\Lambda_{\theta_k} := \begin{pmatrix} \frac{\exp(\theta_{1;k}+\theta_{2;k})}{(1+\exp(\theta_{1;k}+\theta_{2;k}))^2} & \frac{\exp(\theta_{1;k}+\theta_{2;k})}{(1+\exp(\theta_{1;k}+\theta_{2;k}))^2} \\ -\frac{\exp(\theta_{1;k})}{(1+\exp(\theta_{1;k}))^2} & 0 \end{pmatrix}.$$

We assume that each individual is assigned to exactly one treatment group. The estimators for $\theta_k$ and $\theta_{k'}$ are hence independent. The non-inferiority is asymptotically proven if, with $c_1{=}(1,0)^\top$ and $c_2{=}(0,1)^\top$ and group sizes $N_k$ and $N_{k'}$, we get

$$T_i := \frac{c_i^\top \left(\left(\begin{smallmatrix}\widehat{\pi}_k \\ \widehat{\tau}_k\end{smallmatrix}\right) - \left(\begin{smallmatrix}\widehat{\pi}_{k'} \\ \widehat{\tau}_{k'}\end{smallmatrix}\right) + \left(\begin{smallmatrix}\delta_\pi \\ \delta_\tau\end{smallmatrix}\right)\right)}{\sqrt{c_i^\top \left(\frac{1}{N_k} \Lambda_{\widehat{\theta}_k} \mathbf{M}_{\widehat{\theta}_k}^{-1} \Lambda_{\widehat{\theta}_k}^\top + \frac{1}{N_{k'}} \Lambda_{\widehat{\theta}_{k'}} \mathbf{M}_{\widehat{\theta}_{k'}}^{-1} \Lambda_{\widehat{\theta}_{k'}}^\top\right) c_i}} > z_{1-\alpha} \quad \text{for both } i = 1, 2.$$

The group sizes $N_k$ and $N_{k'}$ are supposed to coincide for equal parameters $\theta_k = \theta_{k'}$ and the minimal $N$ fulfilling

$$1 - \beta \leq P_{\theta_k = \theta_{k'}}(T_1 > z_{1-\alpha} \cap T_2 > z_{1-\alpha})$$

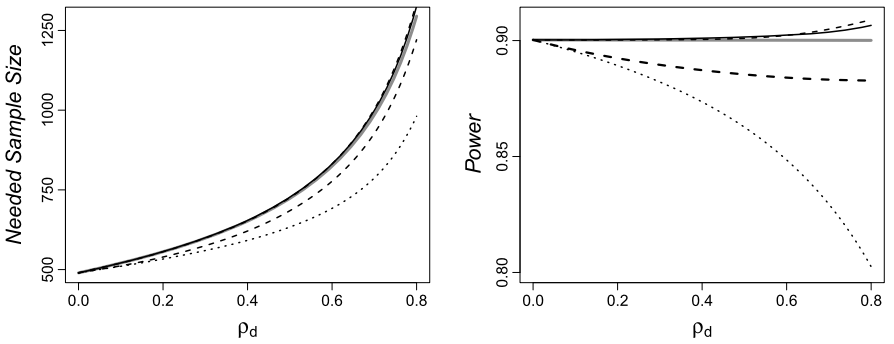


**Fig. 1** Sample sizes. *Grey*: $\mathbf{M}_{\theta}$; *dotted*: $\mathbf{M}_{1,\theta}$; *dashed*: $\mathbf{M}_{2,\theta}$; *long-dash*: $\mathbf{M}_{3,\theta}$; *solid*: $\mathbf{M}_{4,\theta}$

can be calculated numerically to determine the required treatment group sizes.

## 4 Example

We consider the particular example of a diagnostic study for a contrast agent in medical imaging. Each observed individual has $m = 8$ liver segments, which are assumed either to be diseased ($x_{ij} = 1$) or non-diseased ($x_{ij} = 0$). The prevalence was assumed to be given by $P(X_{ij} = 1) = 0.1$. Per individual only one contrast agent is administered and computer tomography results by one reader are obtained $y_{ki} = (y_{ki1}, \ldots, y_{ki8})$ for each individual. For planning purposes, we assume for both treatment groups the same sensitivity and specificity. The non-inferiority margins were given as $\delta_{\pi} = 0.1$ and $\delta_{\tau} = 0.05$. The individual parameters are considered to be normally distributed with specified means $\theta_k = \theta_{k'} = (-1.75, 2.35)^{\top}$. The parameters $\theta_{1;i;k}$ are assumed to vary within the population with a variance $d_1$, whereas $\theta_{2;i;k}$ is considered not to vary ($d_2 = 0$).

Figure 1 presents the required sample sizes for proving non-inferiority in dependence on the variance parameter $d_1$ with a given power $1 - \beta = 0.9$. The required sample size was computed for different values of the ratio

$$\rho_d = \frac{d_1}{1 + d_1} \in (0, 1),$$

such that all possible values of the inter-individual variance are mapped on the interval (0, 1). The required sample size for proving non-inferiority strongly depends in the observed scenarios on the inter-individual variances. The frequently applied approach to approximating the Fisher information matrix with the use of the mean of the individual parameter vectors ($\mathbf{M}_{1;\theta}$) might provide non-sufficient sample sizes. For large inter-individual variances $d_1$ extreme individual parameter values are more likely and are not sufficiently taken into account when computing the matrix $\mathbf{M}_{1;\theta}$.

The expected information $\mathbf{M}_{3;\theta}$ and the quasi-information $\mathbf{M}_{4;\theta}$ provide good approximations to the true Fisher information matrix and the required sample size in the present example.

## 5 Discussion

Various approaches to approximating the Fisher information in generalized linear mixed effects models were shortly presented and their influence on the required sample size for proving non-inferiority in a diagnostic study was examined in an example. The frequently applied information approximation $\mathbf{M}_{1;\theta}$ provided non-sufficient sample sizes for the desired power. The computationally harder approximations $\mathbf{M}_{2;\theta}$, $\mathbf{M}_{3;\theta}$ and $\mathbf{M}_{4;\theta}$ suggested sample sizes which were much closer to the one computed by numerically evaluating the Fisher information. The results can be generalized to multivariate equivalence tests and relative non-inferiority margins. Further considerations are needed for studying the dependence of the treatment group sizes on potential inter-individual variance.

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## References

Berger, R.L.: Multiparameter hypothesis testing and acceptance sampling. Technometrics **24**, 295–300 (1982)

Breslow, N.E., Clayton, D.G.: Approximate inference in generalized linear mixed models. J. Am. Stat. Assoc. **88**, 9–25 (1993)

Mielke, T.: Approximations of the Fisher information for construction of efficient experimental designs in nonlinear mixed effects models. Ph.D. thesis, Otto-von-Guericke-University Magdeburg (2011)

Niaparast, M.: Optimal designs for mixed effects Poisson regression models. Ph.D. thesis, Otto-von-Guericke University Magdeburg (2010)

Nyberg, J.: Practical optimal experimental design in drug development and drug treatment using nonlinear mixed effects models. Ph.D. thesis, Uppsala University (2011)

Waite, T.W., Woods, D.C., Waterhouse, T.H.: Designs for generalized linear models with random block effects. Working Paper M12/01 Methodology S3RI, University of Southampton (2012)

Waterhouse, T.H.: Optimal experimental design for nonlinear and generalised linear models. Ph.D. thesis, University of Queensland (2005)

# D-Optimal Designs for Lifetime Experiments with Exponential Distribution and Censoring

**Christine H. Müller**

**Abstract** The Kiefer-Wolfowitz approach is used to construct D-optimal designs for lifetime experiments with exponential distribution and censoring. If the expected lifetime is simply the reciprocal of the stress, then the optimal design does not depend on the unknown parameter and the censoring. However, the situation is more complicated for the more frequent assumption that the logarithm of the expected lifetime is linear in the stress. Conditions are given here where the locally D-optimal designs for experiments with censoring coincide with those in the classical approach of normally distributed errors. In particular, this is the case when the censoring variable is not too small and the slope of the regression is not too large.

## 1 Introduction

Often the expected lifetime $\mathrm{E}(T(s))$ of a product depends on the stress $s$ via a given link function. Here it is assumed that this function is known up to a parameter vector $\theta$. We assume that $N$ lifetime experiments at different stress levels $s_n \in \mathscr{S}$ for $n = 1, \ldots, N$ are executed and that the lifetime $T_n$ of the product will be observed in each lifetime experiment. However, if the stress is too low, then often the lifetime cannot be observed since the time up to the event, the 'death', is too long. Therefore usually a time $c$ is fixed at which the lifetime experiment is stopped. Then the only information is that the product has survived the time $c$. Such observations are the so-called censored observations. It is clear that the censored observations should also be used in an analysis of lifetime data. Therefore define

$$Y_n := \begin{cases} T_n & \text{if } T_n \le c, \\ c & \text{if } T_n > c, \end{cases} \quad \text{and} \quad D_n := \begin{cases} 1 & \text{if } T_n \le c, \\ 0 & \text{if } T_n > c. \end{cases}$$

Then $(Y_1, D_1, s_1), \ldots, (Y_N, D_N, s_N)$ constitutes the available information, where $D_n$ is the censoring variable. Let $t_n$, $y_n$, and $d_n$ be the realizations of $T_n$, $Y_n$ and $D_n$ respectively and $y_* = (y_1, \ldots, y_N)^\top$, $d_* = (d_1, \ldots, d_N)^\top$, $s_* = (s_1, \ldots, s_N)^\top$. The

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likelihood function is then given by (see, e.g., Klein and Moeschberger 2003, p. 75)

$$L_\theta(y_*, d_*, s_*) := \prod_{n=1}^{N} f_{\theta,s_n}(y_n)^{d_n} S_{\theta,s_n}(y_n)^{1-d_n},$$

where $f_{\theta,s}$ is the lifetime distribution density at stress $s$ and

$$S_{\theta,s}(t) := \int_t^\infty f_{\theta,s}(u)\,\mathrm{d}u$$

is the survival function at time $t$ and stress $s$.

There is a large body of literature on planning and analysis of lifetime experiments due to their importance in practice. Often the planning concerns only the construction of sampling plans (Liang et al. 2012) or the censoring mechanism by removing units after some failure events (Park and Ng 2012; Tsai and Lin 2010; Wu and Huang 2010). In other cases (Barriga et al. 2008), the planning concerns the analysis of a specific lifetime experiment. Only a few papers deal with the optimal planning of the stress variables. Bai and Chung (1991) consider the construction of optimal two-point designs for experiments where the number of failures up to a given time point is observed. They use the Poisson distribution to model the number of failures. Ahmad et al. (2006) numerically determine locally optimal designs $\alpha e_{s_1} + (1-\alpha)e_{s_2}$ with $s_1 \in (s_0, s_2)$, where $s_0$ and $s_2$ are given, if the lifetime is modelled by the exponential Weibull distribution. However, they assume that only the scale parameter of the exponential Weibull distribution is unknown and that the lifetime is measured in $k$ units. Bai and Chung (1991) as well Ahmad et al. (2006) do not use equivalence theorems (Kiefer and Wolfowitz 1960; Fedorov 1971) for constructing D- and A-optimal designs. D-optimal designs for lifetime experiments are developed by Das and Lin (2011). But they assume a lognormal distribution for the lifetime and taking the logarithm of the lifetime they can use the usual theory for normally distributed observations. Their new contribution is the assumption of correlated errors.

To the best of the author's knowledge, there are only a very few papers using the Kiefer and Wolfowitz (1960) or Fedorov (1971) equivalence theorems for constructing D- and A-optimal designs for censored observations or lifetime experiments. López-Fidalgo and Garcet-Rodríguez (2011) derive optimal designs when the independent variable is censored. But in lifetime experiments, as considered in this paper, the dependent variable is censored. Pal and Mandal (2009) construct optimal designs for the stress strength reliability $P(X < Y|Z)$ where both the stress $X$ and the strength $Y$ have an exponential distribution. The approach most similar to that of this paper is given by López-Fidalgo et al. (2009), who consider the case where the censoring variable varies in an interval and the design space is $\{0, 1\}$.

As in López-Fidalgo and Garcet-Rodríguez (2011), López-Fidalgo et al. (2009) and Pal and Mandal (2009), we consider here the exponential distribution which is the simplest lifetime distribution so that

$$f_{\theta,s}(t) = \lambda_\theta(s)\exp\bigl(-\lambda_\theta(s)t\bigr)$$

is the lifetime density. Here the link function $\lambda_\theta : \mathscr{S} \to (0, \infty)$ is known up to the parameter vector $\theta$. The expected lifetime is then

$$E_\theta(T_n) = \frac{1}{\lambda_\theta(s_n)}.$$

Simple reasonable functions for $\lambda_\theta$ are the following:

$$\lambda_\theta(s) = \theta s, \quad \theta \in (0, \infty), \tag{1}$$

$$\lambda_\theta(s) = \exp(\theta_0 + \theta_1 s), \quad \theta = (\theta_0, \theta_1)^\top \in \mathbb{R} \times (0, \infty). \tag{2}$$

Both functions ensure that the expected lifetime is decreasing with increasing stress $s$. The function given by (1) provides an infinite lifetime if there is no stress while the function (2) is more flexible with a finite expected lifetime for no stress. The function (2), also used in Ahmad et al. (2006), means that the logarithm of the expected lifetime is linear which is an assumption often used by engineers (see, e.g., Haibach 2006, p. 25).

We consider here the problem of constructing optimal designs of the stress levels for the maximum likelihood estimator of $\theta$,

$$\widehat{\theta} := \arg\max_\theta L_\theta(y_*, d_*, s_*).$$

In Sect. 2, the information matrix for this estimator is given. Section 3 deals then with the optimal design for $\lambda_\theta$ given by (1) and Sect. 4 provides locally D-optimal designs for $\lambda_\theta$ given by (2).

## 2 The Information Matrix

Since the survival function for the exponential distribution satisfies $S_{\theta,s}(t) = \exp(-\lambda_\theta(s)t)$, the loglikelihood function has the form

$$\begin{aligned}\log L_\theta(y_*, d_*, s_*) &= \sum_{d_n=1} \big(\log \lambda_\theta(s_n) - \lambda_\theta(s_n) y_n\big) + \sum_{d_n=0} \big(-\lambda_\theta(s_n) c\big) \\ &= \sum_{n=1}^N l(\theta, t_n, s_n)\end{aligned}$$

with

$$l(\theta, t, s) := \big(\log \lambda_\theta(s) - \lambda_\theta(s)t\big) 1_{[0,c]}(t) - \lambda_\theta(s) c 1_{(c,\infty)}(t).$$

The maximum likelihood estimator $\widehat{\theta}$ is a solution to

$$\sum_{n=1}^N \dot{l}(\widehat{\theta}, t_n, s_n) = 0,$$

where

$$\dot{l}(\theta,t,s) := \frac{\partial}{\partial\theta} l(\theta,t,s) = \frac{\partial}{\partial\theta}\lambda_\theta(s)\left[\left(\frac{1}{\lambda_\theta(s)} - t\right)1_{[0,c]}(t) - c1_{(c,\infty)}(t)\right].$$

Also set

$$\begin{aligned}\ddot{l}(\theta,t,s) &:= \frac{\partial}{\partial\theta}\dot{l}(\theta,t,s)\\ &= \frac{\partial^2}{\partial^2\theta}\lambda_\theta(s)\left[\left(\frac{1}{\lambda_\theta(s)} - t\right)1_{[0,c]}(t) - c1_{(c,\infty)}(t)\right]\\ &\quad + \frac{\partial}{\partial\theta}\lambda_\theta(s)\frac{\partial}{\partial\theta}\lambda_\theta(s)^\top\left(-\frac{1}{\lambda_\theta(s)^2}\right)1_{[0,c]}(t).\end{aligned}$$

Note that for any $\lambda > 0$ we have

$$\int_0^c \left(\frac{1}{\lambda} - t\right)\lambda\,\mathrm{e}^{-\lambda t}\,\mathrm{d}t - c\int_c^\infty \lambda\,\mathrm{e}^{-\lambda t}\,\mathrm{d}t = 0, \tag{3}$$

$$\int_0^c \left(\frac{1}{\lambda} - t\right)^2\lambda\,\mathrm{e}^{-\lambda t}\,\mathrm{d}t + c^2\int_c^\infty \lambda\,\mathrm{e}^{-\lambda t}\,\mathrm{d}t = \frac{1}{\lambda^2}\left(1-\mathrm{e}^{-\lambda c}\right). \tag{4}$$

Equation (3) implies $E_\theta[\dot{l}(\theta,T_n,s_n)] = 0$ for all stress levels $s_n$ so that the maximum likelihood estimator is not biased. If the stress is a random variable $S$ with distribution $\delta$ and the conditional distribution of the lifetime $T$ given $S = s$ is an exponential distribution with parameter $\lambda_\theta(s)$, then (3) and (4) imply

$$\begin{aligned}&E_\theta\left(\dot{l}(\theta,T,S)\dot{l}(\theta,T,S)^\top\right)\\ &\quad = \int \frac{1}{\lambda_\theta(s)^2}\left(1-\mathrm{e}^{-\lambda_\theta(s)c}\right)\frac{\partial}{\partial\theta}\lambda_\theta(s)\frac{\partial}{\partial\theta}\lambda_\theta(s)^\top\delta(\mathrm{d}s) = -E_\theta\left[\ddot{l}(\theta,T,S)\right].\end{aligned}$$

If the design measure $\delta_N = \sum_{n=1}^N e_{s_n}$, where $e_s$ is the Dirac measure at $s$, converges to the design measure $\delta$ then the maximum likelihood estimator has an asymptotic normal distribution with variance $E_\theta[\dot{l}(\theta,T_n,s_n)\dot{l}(\theta,T_n,s_n)^\top]^{-1}$, i.e.,

$$\sqrt{N}(\widehat{\theta}-\theta) \overset{N\to\infty}{\longrightarrow} \mathcal{N}\left(0, I_\theta(\delta)^{-1}\right),$$

where

$$I_\theta(\delta) := \int \frac{1}{\lambda_\theta(s)^2}\left(1-\mathrm{e}^{-\lambda_\theta(s)c}\right)\frac{\partial}{\partial\theta}\lambda_\theta(s)\frac{\partial}{\partial\theta}\lambda_\theta(s)^\top\delta(\mathrm{d}s)$$

is the information matrix at the design $\delta$ (see, e.g., Schervish 1995, p. 421–428).

## 3 Optimal Designs if $\lambda_\theta(s) = \theta s$

Here the information is

$$I_\theta(\delta) = \int \frac{1}{\theta^2}\left(1 - \mathrm{e}^{-\theta s c}\right)\delta(\mathrm{d}s).$$

Since $1 - \mathrm{e}^{-\theta s c}$ is strictly increasing in $s$, the information is maximized if the design puts all its mass on the largest possible value for the stress, i.e., the optimal design on a design region $\mathscr{S} = [S_l, S_u]$ uses only the upper value $S_u$. However, as soon as there is no censoring, i.e., $c = \infty$ it does not matter which stress levels are used.

## 4 Locally D-Optimal Designs if $\lambda_\theta(s) = \exp(\theta_0 + \theta_1 s)$

Setting

$$x_\theta(s) := \sqrt{1 - \mathrm{e}^{-\exp(\theta_0+\theta_1 s)c}}\begin{pmatrix}1\\ s\end{pmatrix} = \sqrt{1 - \mathrm{e}^{-k\exp(\theta_1 s)}}\begin{pmatrix}1\\ s\end{pmatrix}$$

with $k := c\exp(\theta_0)$, the information matrix can be expressed here by

$$I_\theta(\delta) = \int \left(1 - \mathrm{e}^{-k\exp(\theta_1 s)}\right)\begin{pmatrix}1 & s\\ s & s^2\end{pmatrix}\delta(\mathrm{d}s) = \int x_\theta(s)x_\theta(s)^\top\delta(\mathrm{d}s).$$

To derive locally D-optimal two-point designs on $[0, S_u]$, let $0 \le s_1 < s_2 \le S_u$ and set $X_\theta := (x_\theta(s_1), x_\theta(s_2))^\top$. Then $\delta_{s_1,s_2} := \frac{1}{2}e_{s_1} + \frac{1}{2}e_{s_2}$, where $e_s$ is the Dirac measure at $s$, is D-optimal within all designs with support $s_1$ and $s_2$ since with the equivalence theorem for D-optimality (Kiefer and Wolfowitz 1960) we have

$$x_\theta(s_i)^\top I_\theta(\delta_{s_1,s_2})^{-1}x_\theta(s_i) = u_i^\top X_\theta\left(\frac{1}{2}X_\theta^\top X_\theta\right)^{-1}X_\theta^\top u_i = 2$$

for $i = 1, 2$ (here $u_i$ denotes the $i$-th unit vector in $\mathbb{R}^2$). The determinant of the information matrix for a design $\delta_{s_1,s_2}$ is given by

$$\det\left(I_\theta(\delta_{s_1,s_2})\right) = \frac{1}{4}\left(1 - \mathrm{e}^{-k\exp(\theta_1 s_1)}\right)\left(1 - \mathrm{e}^{-k\exp(\theta_1 s_2)}\right)[s_2 - s_1]^2.$$

**Theorem 1** *Let $k := c\exp(\theta_0) > 0$. Then $\delta_{0,S_u} = \frac{1}{2}e_0 + \frac{1}{2}e_{S_u}$ is a D-optimal design within all two-point designs on $\mathscr{S} = [0, S_u]$ if and only if $\theta_1 \le \frac{2}{kS_u}(\mathrm{e}^k - 1)$.*

*Proof* Since $1 - \mathrm{e}^{-k\exp(\theta_1 s)}$ is strictly increasing in $s$, $\det(I_\theta(\delta_{s_1,s_2}))$ is maximized with respect to $s_2 \in (s_1, S_u]$ for any given $s_1 \in [0, S_u]$ if and only if $s_2 = S_u$. Therefore we have only to determine $s \in [0, S_u]$ so that $\det(I_\theta(\delta_{s,S_u}))$ is maximized. This is equivalent to maximizing

$$g(s) = \left(1 - \mathrm{e}^{-k\exp(\theta_1 s)}\right)[S_u - s]^2.$$

Since we have

$$g'(s) = \mathrm{e}^{-k\exp(\theta_1 s)}\, k\theta_1 \exp(\theta_1 s)[S_u - s]^2 - 2\big(1 - \mathrm{e}^{-k\exp(\theta_1 s)}\big)[S_u - s],$$

$\delta_{0,S_u}$ can be D-optimal only if

$$0 \geq g'(0) = \mathrm{e}^{-k}\, k\theta_1 S_u^2 - 2\big(1 - \mathrm{e}^{-k}\big)S_u \quad \Longleftrightarrow \quad \mathrm{e}^{-k}\, k\theta_1 S_u \leq 2\big(1 - \mathrm{e}^{-k}\big).$$

This is equivalent to $\theta_1 \leq \frac{2}{kS_u}\,\mathrm{e}^k(1 - \mathrm{e}^{-k}) = \frac{2}{kS_u}(\mathrm{e}^k - 1)$. Hence $\delta_{0,S_u}$ is not D-optimal if $\theta_1 > \frac{2}{kS_u}(\mathrm{e}^k - 1)$. To prove that $\delta_{0,S_u}$ is indeed a D-optimal two-point design for $\theta_1 \leq \frac{2}{kS_u}(\mathrm{e}^k - 1)$, it is sufficient to prove that $g$ is strictly decreasing on $[0, S_u]$. To show $g'(s) < 0$, we need the monotonicity of some auxiliary functions:

(a) For $h_1(k) := 1 - \mathrm{e}^k + k\,\mathrm{e}^k - k^2\,\mathrm{e}^k$ we have

$$h_1'(k) = -\,\mathrm{e}^k + \mathrm{e}^k + k\,\mathrm{e}^k - 2k\,\mathrm{e}^k - k^2\,\mathrm{e}^k = -k\,\mathrm{e}^k - k^2\,\mathrm{e}^k < 0,$$

so that $h_1$ is strictly decreasing for $k > 0$. Since obviously $h_1(0) = 0$, we get $h_1(k) < 0$ for all $k > 0$.

(b) Now consider $h_2(k) := \frac{2}{k}(\mathrm{e}^k - 1) - 1 - 2\,\mathrm{e}^k$. The l'Hôpital rule yields $\lim_{k\downarrow 0} h_2(k) = -1$. Then $h_2(k) < 0$ for all $k \geq 0$ follows with (a) from

$$h_2'(k) = -\frac{2}{k^2}\big(\mathrm{e}^k - 1\big) + \frac{2}{k}\,\mathrm{e}^k - 2\,\mathrm{e}^k = 2k^2 h_1(k) < 0.$$

(c) $\theta_1 \leq \frac{2}{kS_u}(\mathrm{e}^k - 1)$ and (b) imply for $g_1(s) := \theta_1[S_u - s] - 1 - 2\,\mathrm{e}^{k\exp(\theta_1 s)}$

$$\begin{aligned} g_1(0) &= \theta_1 S_u - 1 - 2\,\mathrm{e}^k \\ &\leq \frac{2}{kS_u}\big(\mathrm{e}^k - 1\big)S_u - 1 - 2\,\mathrm{e}^k = \frac{2}{k}\big(\mathrm{e}^k - 1\big) - 1 - 2\,\mathrm{e}^k = h_2(k) < 0 \end{aligned}$$

for all $k \geq 0$. Owing to

$$g_1'(s) = -\theta_1 - 2\,\mathrm{e}^{k\exp(\theta_1 s)}\, k\theta_1 \exp(\theta_1 s) < 0,$$

we have $g_1(s) < 0$ for all $k \geq 0$, $s \geq 0$.

(d) $\theta_1 \leq \frac{2}{kS_u}(\mathrm{e}^k - 1)$ implies for $g_2(s) := k\theta_1 \exp(\theta_1 s)[S_u - s] + 2 - 2\,\mathrm{e}^{k\exp(\theta_1 s)}$

$$g_2(0) = k\theta_1 S_u + 2 - 2\,\mathrm{e}^k \leq k\frac{2}{kS_u}\big(\mathrm{e}^k - 1\big)S_u + 2 - 2\,\mathrm{e}^k = 2\,\mathrm{e}^k - 2 + 2 - 2\,\mathrm{e}^k = 0.$$

Moreover, with (c) we obtain

$$\begin{aligned} g_2'(s) &= k\theta_1^2 \exp(\theta_1 s)[S_u - s] - k\theta_1 \exp(\theta_1 s) - 2\,\mathrm{e}^{k\exp(\theta_1 s)}\, k\theta_1 \exp(\theta_1 s) \\ &= k\theta_1 \exp(\theta_1 s)\big[\theta_1[S_u - s] - 1 - 2\,\mathrm{e}^{k\exp(\theta_1 s)}\big] = k\theta_1 \exp(\theta_1 s) g_1(s) < 0 \end{aligned}$$

so that $g_2$ is strictly decreasing starting from a value $g_2(0) \leq 0$, which implies $g_2(s) < 0$ for all $k > 0$, $s > 0$.

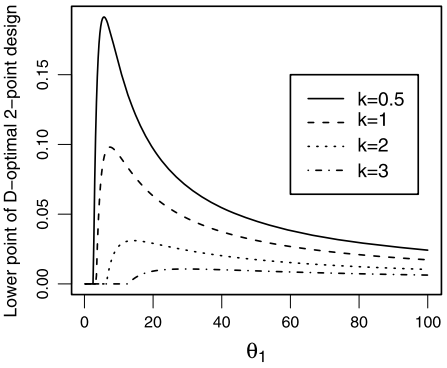


**Fig. 1** Lower points $s(\theta_1, k)$ of the D-optimal two-point designs on [0, 1]

(e) Finally, we have

$$\begin{aligned} g'(s) &= [S_u - s]\,\mathrm{e}^{-k\exp(\theta_1 s)}\big[k\theta_1\exp(\theta_1 s)[S_u - s] + 2\big] - 2[S_u - s] < 0 \\ &\iff \quad \mathrm{e}^{-k\exp(\theta_1 s)}\big[k\theta_1\exp(\theta_1 s)[S_u - s] + 2\big] < 2 \\ &\iff \quad k\theta_1\exp(\theta_1 s)[S_u - s] + 2 < 2\,\mathrm{e}^{k\exp(\theta_1 s)} \quad \iff \quad g_2(s) < 0, \end{aligned}$$

so that (d) proves the assertion. □

To prove that $\delta_{0,S_u}$ is D-optimal within all designs on $\mathscr{S} = [0, S_u]$, the property

$$\begin{aligned} 2 &\geq x_\theta(s)^\top I_\theta(\delta_{0,S_u})^{-1} x_\theta(s) \\ &= \frac{2}{S_u^2}\big(1 - \mathrm{e}^{-k\exp(\theta_1 s)}\big)\left(\frac{(S_u - s)^2}{1 - \mathrm{e}^{-k}} + \frac{s^2}{1 - \mathrm{e}^{-k\exp(\theta_1 S_u)}}\right) \end{aligned} \tag{5}$$

must be shown for all $s \in [0, S_u]$ according to Kiefer and Wolfowitz (1960) where equality holds for $s = 0$ and $s = S_u$. The equality is indeed always met for $s = 0$ and $s = S_u$. Set

$$q(s) := \big(1 - \mathrm{e}^{-k\exp(\theta_1 s)}\big)\left(\frac{(S_u - s)^2}{1 - \mathrm{e}^{-k}} + \frac{s^2}{1 - \mathrm{e}^{-k\exp(\theta_1 S_u)}}\right).$$

A necessary condition for the D-optimality of $\delta_{0,S_u}$ is then $q'(0) \leq 0$.

**Lemma 1** *We have $q'(0) \leq 0$ if and only if $\theta_1 \leq \frac{2}{kS_u}(\mathrm{e}^k - 1)$.*

Hence the condition $\theta_1 \leq \frac{2}{kS_u}(\mathrm{e}^k - 1)$ implies not only that $\delta_{0,S_u}$ is a locally D-optimal design within all two-point designs on $[0, S_u]$, but also the necessary condition for the D-optimality of $\delta_{0,S_u}$ within all designs on [0, 1]. Several plots of $q(s)$ for different values of $\theta_1$ and $k$ with $\theta_1 \leq \frac{2}{kS_u}(\mathrm{e}^k - 1)$ showed that $q$ is first decreasing and then increasing on $[0, S_u]$ so that (5) should be satisfied. However, the author has not been able to prove it so far.

As soon as $\theta_1 > \frac{2}{kS_u}(e^k - 1)$, the locally D-optimal two-point design is of the form $\delta_{s(\theta_1,k),S_u}$ with $0 < s(\theta_1, k) < S_u$. The lower points $s(\theta_1, k)$ depending on $\theta_1$ are shown in Fig. 1 for $k = 0.5, 1, 2, 3$ and $S_u = 1$. The condition $\theta_1 > \frac{2}{kS_u}(e^k - 1)$ is in particular satisfied if $k$ is small. The quantity $k := c \exp(\theta_0)$ is small if the censoring variable $c$ or the regression parameter $\theta_0$ is small. A small $\theta_0$ means a high expected lifetime at $s = 0$, which provides a high probability of censoring. Then it is reasonable to make observations at higher stress levels $s(\theta_1, k) > 0$ so that the probability of censoring is smaller. But since $\frac{2}{kS_u}(e^k - 1) \geq \frac{2}{S_u}$ for all $k \geq 0$, the censoring variable as well as $\theta_0$ have no influence on the D-optimal design as soon as $\theta_1 \leq \frac{2}{S_u}$. The condition $\theta_1 > \frac{2}{kS_u}(e^k - 1)$ is also satisfied if $\theta_1$ is large. In this case, the expected lifetime decreases so rapidly with growing stress that observations at $s(\theta_1, k) > 0$ provide more information than at 0 where observations are censored with higher probability.

## References


Ahmad, N., Islam, A., Salam, A.: Analysis of optimal accelerated life test plans for periodic inspection: the case of exponentiated Weibull failure model. Int. J. Qual. Reliab. Manag. **23**, 1019–1046 (2006)

Bai, D.S., Chung, S.W.: An optimal design of accelerated life test for exponential distribution. Reliab. Eng. Syst. Saf. **31**, 57–64 (1991)

Barriga, G.D.C., Ho, L.L., Cancho, V.G.: Planning accelerated life tests under Exponentiated-Weibull-Arrhenius model. Int. J. Qual. Reliab. Manag. **25**, 636–653 (2008)

Das, R.N., Lin, D.K.J.: On D-optimal robust designs for lifetime improvement experiments. J. Stat. Plan. Inference **141**, 3753–3759 (2011)

Fedorov, V.V.: Design of experiments for linear optimality criteria. Theory Probab. Appl. **16**, 189–195 (1971)

López-Fidalgo, J., Garcet-Rodríguez, S.: Optimal experimental designs when an independent variable is potentially censored. Statistics **45**, 143–154 (2011)

López-Fidalgo, J., Rivas-López, M.J., del Campo, R.: Optimal designs for Cox regression. Stat. Neerl. **63**, 135–148 (2009)

Haibach, E.: Betriebsfestigkeit. Verfahren und Daten zur Bauteilberechnung. Springer, Berlin (2006)

Kiefer, J., Wolfowitz, J.: The equivalence of two extremum problems. Can. J. Math. **12**, 363–366 (1960)

Klein, J.P., Moeschberger, M.L.: Survival Analysis: Techniques for Censored and Truncated Data. Springer, New York (2003)

Liang, T., Chen, L.-S., Yang, M.-C.: Efficient Bayesian sampling plans for exponential distributions with random censoring. J. Stat. Plan. Inference **142**, 537–551 (2012)

Pal, M., Mandal, N.K.: Optimum designs for stress strength reliability. J. Indian Soc. Agric. Stat. **63**, 305–310 (2009)

Park, S., Ng, H.K.T.: Missing information and an optimal one-step plan in a Type II progressive censoring scheme. Stat. Probab. Lett. **82**, 396–402 (2012)

Schervish, M.J.: Theory of Statistics. Springer, New York (1995)

Tsai, T.-R., Lin, C.-W.: Acceptance sampling plans under progressive interval censoring with likelihood ratio. Stat. Pap. **51**, 259–271 (2010)

Wu, S.-J., Huang, S.-R.: Optimal progressive group-censoring plans for exponential distribution in presence of cost constraint. Stat. Pap. **51**, 431–443 (2010)

# Convergence of an Algorithm for Constructing Minimax Designs

**Hans Nyquist**

**Abstract** In nonlinear regression, optimal designs of experiments generally depend on unknown parameters. One approach to deal with this problem is to use the minimax criterion for choosing a design. However, constructing minimax designs has shown to be numerically intractable in many applications. The H-algorithm is a new iterative algorithm that utilizes the relation between minimax designs and optimum on-the-average designs based on a least favorable distribution. It is also fairly easy to apply this algorithm in applications. In this paper, the H-algorithm is described and its convergence properties are discussed.

## 1 Introduction

An optimum design of an experiment is defined as a design that minimizes some function of the information matrix. This ensures that the inferences drawn from the experiment are made as precise as possible. A common difficulty with nonlinear models is that the information matrix depends on unknown parameters of the model. Therefore, the criterion function may in general depend on unknown quantities. There are a number of approaches to deal with the parameter dependence. One alternative, known as the minimax approach, is defined by minimizing the maximum of the criterion function, where the maximum is taken as the parameters are varied over a specified subset of the parameter space. Minimax procedures are, however, known to be numerically intractable and difficult to construct. Consequently, they have not been used in practice except in a few cases (Sitter 1992; Müller 1995; King and Wong 1998, 2004; Müller and Pazman 1998; Noubiap and Seidel 2000; Imhof 2001; Dette et al. 2006; Fackle-Fornius and Nyquist 2012).

A new algorithm for construction of minimax designs is indicated in Nyquist (2012). The aim of this paper is to describe this algorithm in more detail and to discuss its convergence properties. Notation and the design problem are introduced in the next section while the algorithm and its convergence are presented in Sect. 3. Numerical examples and some concluding remarks are given in two final sections.

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## 2 The Statistical Problem

Let $Y$ be the response variable from an experiment with a probability density function $f(y; x, \theta)$, $x$ being a $q$ vector of known explanatory variables representing the experimental conditions and $\theta$ a $p$ vector of unknown parameters. Assume that $x$ belongs to a design region $\chi$ such that

A1 $\chi$ is a compact subset of $\mathbb{R}^q$, $x \in \chi \subset \mathbb{R}^q$.

A design $\xi$ is defined as a discrete probability measure on $\chi$. With $n$ support points, a design is written as

$$\xi = \begin{Bmatrix} x_1 & x_2 & \cdots & x_n \\ \omega_1 & \omega_2 & \cdots & \omega_n \end{Bmatrix},$$

where $\omega_j$, $j = 1, 2, \ldots, n$, are design weights such that $\sum_{x \in \chi} \xi(x) = \sum_{j=1}^{n} \omega_j = 1$, $0 \leq \omega_j \leq 1$. Furthermore, $\omega_j N$ independent observations are to be taken on $Y$ at the conditions $x_j$, $N$ being the total number of observations. The focus here is on continuous designs, originally proposed by Kiefer (see, e.g., Kiefer 1974) for which the number of observations at a specific experimental condition is not restricted to be an integer. The set of all possible designs is denoted by $\Xi$. Thus, $\Xi$ is the convex set of all probability measures with supporting sets belonging to $\chi$. Furthermore, it is assumed that $\theta$ belongs to a parameter space $\Theta \subset \mathbb{R}^p$.

The usual regularity conditions on inference are assumed. In particular, the standardized information matrix is defined as

$$M(\xi, \theta) = \sum_{x \in \chi} \xi(x) m(x, \theta), \tag{1}$$

where $m(x, \theta)$ is the contribution to the information matrix from one observation, i.e., the expectation of the squared score function.

A criterion $\psi(M)$ for assessing the quality of a design is defined such that better designs are represented by smaller values of the criterion and an optimal design minimizes the criterion. In general, it is assumed that

A2 $\psi$ is a strictly convex and differentiable real-valued function defined on the set of symmetric $p \times p$ matrices and bounded from below.

Since the standardized information matrix in general depends on the design $\psi$ and the parameters $\theta$, $\psi$ can be considered as a mapping from the design space as well as from the parameter space into the set of real numbers, $\psi : \Xi \times \Theta \curvearrowright \mathbb{R}$. In the sequel, the simplified notation $\psi(\xi, \theta) = \psi(M(\xi, \theta))$ is used. Furthermore, it is assumed that

A3 $\psi(\xi, \theta)$ is continuous as a function of $\theta$.

In many cases where the criterion depends on unknown parameters, an optimal design cannot be used in practice. If a particular value of $\theta$ is plausible, a locally optimal design $\xi^\theta$ can be constructed so that it minimizes the criterion function

for this particular value on $\theta$. A design that is optimal for one value of $\theta$ can be reasonably good also for some other values on $\theta$ but may as well show a severe non-robustness to departures from the specified value of $\theta$. If a set of possible values of $\theta$ is available, the optimum on-the-average approach (Fedorov and Hackl 1997) can be applied. In this approach the criterion is evaluated at plausible parameter values and weighted by a probability measure $\pi$, the measure having support in the parameter space $\Theta$. The resulting weighted criterion is thus

$$B(\xi, \pi) = \int_{\Theta} \psi(\xi, \theta) \, \mathrm{d}\pi(\theta). \tag{2}$$

A design $\xi^{\pi}$ is optimum on the average with respect to the prior $\pi$ if it minimizes $B$ over the set of all possible designs

$$B\left(\xi^{\pi}, \pi\right) = \min_{\xi \in \Xi} B(\xi, \pi). \tag{3}$$

It is convenient to use the notation $B(\pi) = B(\xi^{\pi}, \pi)$. Note that $B(\pi)$ is concave.

Assumptions A1 and A2 ensure that there exist locally optimal designs and optimum on-the-average designs. Also, there exist a number of algorithms for construction of these designs, although they are known to be slow in some applications (Atkinson et al. 2007; Berger and Wong 2009).

The minimax approach to design construction offers another possibility to take care of the problem of dependence on unknown parameters (Fedorov and Hackl 1997). A minimax design is constructed so that it avoids a bad performance as long as the parameter vector is in a specified subset $\Theta_0$ of the parameter space, $\Theta_0 \subset \Theta$. It is assumed that

A4 $\Theta_0$ is a compact subspace of $\Theta$.

A design $\xi^0$ is minimax with respect to $\Theta_0$ if it minimizes $\max_{\theta \in \Theta_0} \psi(\xi, \theta)$,

$$\max_{\theta \in \Theta_0} \psi\left(\xi^0, \theta\right) = \min_{\xi \in \Xi} \max_{\theta \in \Theta_0} \psi(\xi, \theta). \tag{4}$$

Define $\Pi_0$ as the set of distributions with support only on points in $\Theta_0$. It is possible to show that $\max_{\theta \in \Theta_0} \psi(\xi, \theta) = \max_{\pi \in \Pi_0} B(\xi, \pi)$ and, hence, (4) is equivalent to

$$\max_{\pi \in \Pi_0} B\left(\xi^0, \pi\right) = \min_{\xi \in \Xi} \max_{\pi \in \Pi_0} B(\xi, \pi) \tag{5}$$

(see, e.g., Nyquist 2012). A prior distribution $\pi_0$ with the property that

$$\min_{\xi \in \Xi} B(\xi, \pi_0) = \max_{\pi \in \Pi_0} \min_{\xi \in \Xi} B(\xi, \pi) \tag{6}$$

is called a least favorable distribution with respect to $\Pi_0$.

**Theorem 1** *Suppose that $\xi^0$ is an optimum on-the-average design with respect to $\pi_0 \in \Pi_0$ and that $\psi(\xi^0, \theta) \leq B(\pi_0)$ for all $\theta \in \Theta_0$. Then*

(i) $\min_{\xi\in\Xi}\max_{\pi\in\Pi_0} B(\xi,\pi) = \max_{\pi\in\Pi_0}\min_{\xi\in\Xi} B(\xi,\pi) = B(\pi_0)$,
(ii) $\pi_0$ *is a least favorable distribution with respect to* $\Pi_0$, *and*
(iii) $\xi^0$ *is a minimax design with respect to* $\Theta_0$.

*Proof* From the inequality

$$\max_{\pi^*\in\Pi_0} B\big(\xi,\pi^*\big) \geq \min_{\xi^*\in\Xi} B\big(\xi^*,\pi\big), \quad \forall\xi\in\Xi,\ \forall\pi\in\Pi_0, \tag{7}$$

it follows that

$$\min_{\xi\in\Xi}\max_{\pi\in\Pi_0} B(\xi,\pi) \geq \max_{\pi\in\Pi_0}\min_{\xi\in\Xi} B(\xi,\pi). \tag{8}$$

On the other hand, from the assumptions of the theorem, we have

$$\begin{aligned}\min_{\xi\in\Xi}\max_{\pi\in\Pi_0} B(\xi,\pi) &\leq \max_{\pi\in\Pi_0} B\big(\xi^0,\pi\big) = \max_{\theta\in\Theta_0}\psi\big(\xi^0,\theta\big) \leq B(\pi_0)\\ &= \min_{\xi\in\Xi} B(\xi,\pi_0) \leq \max_{\pi\in\Pi_0}\min_{\xi\in\Xi} B(\xi,\pi),\end{aligned} \tag{9}$$

and hence, there are just equalities in (8) and (9) and the theorem follows. □

The theorem indicates that, under some conditions, a design that is optimum on-the-average with respect to a least favorable distribution is also a minimax design. This is utilized in the H-algorithm for constructing minimax designs, which is described in the next section. Furthermore, it can be shown (Nyquist 2012) that if $\pi_0$ is a least favorable distribution, $\xi^0$ is an associated optimum on-the-average design, and

$$\min_{\xi\in\Xi}\max_{\pi\in\Pi_0} B(\xi,\pi) = \max_{\pi\in\Pi_0}\min_{\xi\in\Xi} B(\xi,\pi) = B(\pi_0),$$

then $\pi_0$ has support only at points $\theta$ such that $\psi(\xi^0,\theta) = B(\pi_0)$. It is therefore reasonable to assume that $\pi_0$ is a discrete measure. Thus, throughout the paper only discrete measures are considered so that $0 \leq \pi(\theta) \leq 1$ and $B(\xi,\pi) = \sum_\theta \pi(\theta)\psi(\xi,\theta)$. In particular, it is assumed that

A5 A least favorable distribution with respect to $\Pi_0$ is discrete.

## 3 The H-Algorithm

The H-algorithm for construction of minimax designs is proposed by Nyquist (2012). The algorithm is iterative and utilizes the relations between a minimax design and an optimum on-the-average design for a least favorable distribution. Given an initial prior distribution, an optimum on-the-average design is constructed. At each subsequent iteration of the algorithm, the prior distribution is updated and the associated optimum on-the-average design is constructed. This is continued until the prior distribution can be confirmed to be a least favorable distribution and the

associated optimum on-the-average design is a minimax design. The iterations of the algorithm can be described as follows:

**Step 0**: Set initial values as $\ell = 1$ and $B(\pi^{(0)}) = -\infty$. Define a grid of step lengths $H = \{h_t; 0 = h_0 < h_1 < \cdots < h_T \leq 1\}$. Generate an initial prior distribution $\pi^{(1)}$, construct an optimum on-the-average design with respect to $\pi^{(1)}$, $\xi^{(1)}$, and evaluate $B(\pi^{(1)})$.

**Step 1**: Check if

$$\psi\big(\xi^{(\ell)}, \theta\big) \leq B\big(\pi^{(\ell)}\big), \quad \forall \theta \in \Theta_0. \tag{10}$$

If the condition is met, stop and conclude that $\pi^{(\ell)}$ is a least favorable distribution and that $\xi^{(\ell)}$ is a minimax design. Otherwise, continue to Step 2.

**Step 2**: Let $\theta^{(\ell)}$ maximize $\psi(\xi^{(\ell)}, \theta)$ over $\Theta_0$ and let $\delta^{(\ell)}$ be the probability distribution that assigns unit mass to $\theta^{(\ell)}$.

**Step 3**: Generate $T$ new priors as $\pi_t^{(\ell+1)} = (1 - h_t)\pi^{(\ell)} + h_t\delta^{(\ell)}$. For each new prior, construct an optimum on-the-average design with respect to $\pi_t^{(\ell+1)}$, $\xi_t^{(\ell+1)}$, and evaluate $B(\pi_t^{(\ell+1)})$, $t = 1, \ldots, T$. Define $\xi^{(\ell+1)}$ as the design associated with the largest $B(\pi_t^{(\ell+1)})$.

**Step 4**: Check if

$$B\big(\pi^{(\ell+1)}\big) \geq B\big(\pi^{(\ell)}\big). \tag{11}$$

If the condition is not met, then make the grid of step lengths $H$ denser and repeat Step 3. Otherwise, set $\ell$ as $\ell + 1$ and go to Step 1.

**Theorem 2** *The sequence $\{B(\pi^{(\ell)})\}$ defined by the H-algorithm converges. Denote the limit by $B(\pi_0)$. If, in addition, $\psi(\xi^0, \theta) \leq B(\pi_0)$ for all $\theta \in \Theta_0$, then the sequence $\{\xi^{(\ell)}\}$ converges to a minimax design $\xi^0$ and the sequence $\{\pi^{(\ell)}\}$ converges to a least favorable distribution $\pi_0$.*

*Proof* Let $\pi^{(\ell)}$ be a prior distribution and $\xi^{(\ell)}$ an associated optimum on-the-average design. Since $\psi(\xi^{(\ell)}, \theta)$ as a function of $\theta$ is assumed to be continuous (A3) and $\Theta_0$ is assumed to be compact (A4), there exists a $\theta^{(\ell)}$ that maximizes $\psi(\xi^{(\ell)}, \theta)$. Now, the set of prior distributions $\pi_t^{(\ell+1)} = (1 - h_t)\pi^{(\ell)} + h_t\delta^{(\ell)}$, $h_t \in H$, yield

$$\begin{aligned} B\big(\xi, \pi_t^{(\ell+1)}\big) &= \sum_{\theta \in \Theta_0} \pi_t^{(\ell+1)}(\theta)\psi(\xi, \theta) \\ &= (1 - h_t) \sum_{\theta \in \Theta_0} \pi_t^{(\ell)}(\theta)\psi(\xi, \theta) + h_t\delta^{(\ell)}(\theta)\psi(\xi, \theta). \end{aligned}$$

For each $h_t$ there exists an optimum on-the-average design, $\xi_t^{(\ell+1)}$, that minimizes $B(\xi, \pi_t^{(\ell+1)})$ and there exists a $h_t \in H$ that maximizes $B(\pi_t^{(\ell+1)})$. Denote by $\pi^{(\ell+1)}$ and $\xi^{(\ell+1)}$ the prior and the associated design that maximizes $B(\pi_t^{(\ell+1)})$, respectively. Obviously, $B(\pi^{(\ell+1)}) \geq B(\pi_{h=0}^{(\ell+1)}) = B(\pi^{(\ell)})$, so that the sequence

$\{B(\pi^{(\ell)})\}$ is non-decreasing. Since $B(\pi)$ is concave, the sequence attains a maximum at $B(\pi_0)$, say. If, in addition, as is assumed by the theorem, $\psi(\xi^0, \theta) \leq B(\pi_0)$ for all $\theta \in \Theta_0$, then the conditions in Theorem 1 are satisfied. Hence, it is concluded that $\xi^0$ is a minimax design with respect to $\Theta_0$ and that $\pi_0$ is a least favorable distribution with respect to $\Pi_0$. □

## 4 Numerical Examples

*Example 1* (Non-linear model with additive error term) Consider the one parameter Michaelis-Menten model for describing the velocity of an enzymatic reaction

$$y = \frac{x}{\theta + x} + \varepsilon. \tag{12}$$

The information for $\theta$ is the scalar

$$M(\xi, \theta) = \sum_{j=1}^{n} \omega_j \frac{x_j^2}{(\theta + x_j)^4} \tag{13}$$

and a suitable criterion is the asymptotic variance $\psi(\xi, \theta) = M^{-1}(\xi, \theta)$. Assume that $\Theta_0 = \{\theta; 1 \leq \theta \leq 2\}$. For construction of a minimax design a grid of step lengths is set to $h_1 = 0.25$, $h_2 = 0.5$, $h_3 = 0.75$, and $h_4 = 1.0$. The initial prior distribution, $\pi^{(1)}$, assigns unit mass to $\theta = 1$. The associated optimum on-the-average design, $\xi^{(1)}$, is equivalent to the locally optimal design with $\theta = 1$ and is the one point design that assigns all design weight to $x = 1$. In the first step of the H-algorithm, it is found that $B(\pi^{(1)}) = 16$ and the maximum of the criterion function $\psi(\xi^{(1)}, \theta)$ is 81, which appears to $\theta^{(1)} = 2$. Hence, the maximum value of $\psi(\xi^{(1)}, \theta)$ exceeds $B(\pi^{(1)})$ and it is concluded that $\xi^{(1)}$ is not a minimax design.

In the third step of the H-algorithm, a set of new priors is generated. $\pi_1^{(2)}$ assigns mass 0.75 to $\theta = 1$ and mass 0.25 to $\theta = 2$, $\pi_2^{(2)}$ assigns mass 0.5 to both these points, $\pi_3^{(2)}$ assigns mass 0.25 to $\theta = 1$ and mass 0.75 to $\theta = 2$, and $\pi_4^{(2)}$ assigns unit mass to $\theta = 2$. The associated optimum on-the-average designs, $\xi_t^{(2)}$, and the values $B(\pi_t^{(2)})$ are reported in Table 1. As can be seen, $B(\pi_t^{(2)})$ is maximized for $t = 4$, and $\xi^{(2)}$ is defined as the design that assigns all design weight to $x = 2$. In the first step of next iteration, it is found that the maximum of $\psi(\xi^{(2)}, \theta)$ as a function of $\theta$ is 64, which equals $B(\pi^{(2)})$. Since the condition in Step 1 is satisfied, the iteration stops and Theorem 1 is used to verify that $\pi^{(2)}$ is a least favorable distribution and that $\xi^{(2)}$ is a minimax design.

*Example 2* (Logistic regression) Consider the logistic regression model with linear predictor

$$\eta = \theta_2(x - \theta_1) \tag{14}$$

**Table 1** Results from the first iteration in Example 1

| $t$ | $\pi_t^{(2)}(1)$ | $\pi_t^{(2)}(2)$ | $x_t^{(2)}$ | $B(\pi_t^{(2)})$ |
|---|---|---|---|---|
| 0 | 1.00 | 0.00 | 1.0000 | 16.0000 |
| 1 | 0.75 | 0.25 | 1.0435 | 19.9979 |
| 2 | 0.50 | 0.50 | 1.1271 | 26.5465 |
| 3 | 0.25 | 0.75 | 1.3355 | 38.7690 |
| 4 | 0.00 | 1.00 | 2.0000 | 64.0000 |

and assume it is believed that the true parameter values are in the set $\Theta_0 = \{(\theta_1, \theta_2) \mid 0.5 \le \theta_1 \le 1.5,\ 4 \le \theta_2 \le 5\}$. Using the H-algorithm, a minimax design based on the D-criterion will now be constructed. The H-algorithm is initialized by setting the grid of step lengths as $h_1 = 0.2$, $h_2 = 0.4$, $h_3 = 0.6$, $h_4 = 0.8$, and $h_5 = 1.0$, and the initial prior distribution, $\pi^{(1)}$, assigns mass 0.25 to the four corners of $\Theta_0$. The resulting optimum on-the-average design is the three-point design

$$\xi^{(1)} = \begin{Bmatrix} 0.26 & 1.00 & 1.74 \\ 0.275 & 0.450 & 0.275 \end{Bmatrix}$$

with $B(\pi^{(1)}) = 3.691$ and the maximum of the criterion function $\psi(\xi^{(1)}, \theta)$ is 3.806, appearing at $\theta^{(1)} = (1, 5)$. It is therefore concluded that $\xi^{(1)}$ is not a minimax design and that the prior should be modified by adding mass at $(\theta_1, \theta_2) = (1, 5)$, the amount of which being determined by the step lengths. The step length that results in the largest value on $B$ is $h_1$ that assigns equal mass to points $(0.5, 4)$, $(0.5, 5)$, $(1.5, 4)$, $(1.5, 5)$, and $(1, 5)$, and the optimum on-the-average design is the four-point design

$$\xi^{(2)} = \begin{Bmatrix} 0.31 & 0.90 & 1.10 & 1.69 \\ 0.272 & 0.228 & 0.228 & 0.272 \end{Bmatrix},$$

with a modest increase in the $B$-value, $B(\pi^{(2)}) = 3.695$.

The maximum of the criterion function $\psi(\xi^{(2)}, \theta)$ is 3.79 so that $\xi^{(2)}$ is not a minimax design. The maximum appears at two points, $\theta^{(2)} = (0.5, 5)$ and $\theta^{(2)} = (1.5, 5)$, respectively. This suggests that mass in the prior distribution should be added to these two points. The prior is therefore updated as

$$\pi_t^{(3)} = (1 - h_t)\pi^{(2)} + h_t(\delta_{(0.5,5)} + \delta_{(1.5,5)})/2. \tag{15}$$

The step length $h_5 = 1.0$ maximizes the $B$-value, resulting in the prior that assigns mass 0.5 to points $(0.5, 5)$ and $(1.5, 5)$. The associated optimum on-the-average design is the three-point design

$$\xi^{(3)} = \begin{Bmatrix} 0.287 & 1.00 & 1.713 \\ 0.2675 & 0.4650 & 0.2675 \end{Bmatrix}.$$

This time the maximum of $\psi(\xi^{(3)}, \theta)$ equals $B(\pi^{(3)}) = 3.773$ so that it is concluded that $\xi^{(3)}$ is a minimax design and the iteration stops.

## 5 Conclusions

An algorithm for constructing minimax designs has been presented and its convergence properties have been discussed. A proof of convergence to a minimax design is based on the assumption of a discrete least favorable prior distribution. With some more regularity assumptions it would be possible to relax this assumption. However, since the least favorable distribution has support only at points where the criterion as a function of the model parameters has maxima, it is reasonable to assume a discrete prior. Two numerical examples illustrate the application of the algorithm. While these examples are fairly simple, the algorithm has successfully been used for constructing designs for more complicated models (Fackle-Fornius and Wänström 2012) and design criteria, including a maximin criterion of estimation efficiency.

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## References

Atkinson, A.C., Donev, A.N., Tobias, R.D.: Optimum Experimental Designs, with SAS. Oxford University Press, New York (2007)

Berger, M.P.F., Wong, W.K.: An Introduction to Optimal Designs for Social and Biomedical Research. Wiley, Chichester (2009)

Dette, H., Martinez Lopez, I., Ortiz Rodriguez, I.M., Pepelyshev, A.: Maximin efficient design of experiment for exponential regression models. J. Stat. Plan. Inference **136**, 4397–4418 (2006)

Fackle-Fornius, E., Nyquist, H.: Optimal allocation to treatment groups under variance heterogeneity. Research Report, Department of Statistics, Stockholm University (2012)

Fackle-Fornius, E., Wänström, L.: Minimax optimal designs of contingent valuation experiment: willingness to pay for environmentally friendly clothes. Working paper, Department of Statistics, Stockholm University (2012)

Fedorov, V.V., Hackl, P.: Model-Oriented Design of Experiments. Springer, New York (1997)

Imhof, L.A.: Maximin designs for exponential growth models and heteroscedastic polynomial models. Ann. Stat. **29**, 561–576 (2001)

Kiefer, J.: General equivalence theory for optimum designs (approximate theory). Ann. Stat. **2**, 849–879 (1974)

King, J., Wong, W.K.: Optimal minimax designs for prediction in heteroscedastic models. J. Stat. Comput. Simul. **69**, 371–383 (1998)

King, J., Wong, W.K.: Optimal designs for the power logistic model. J. Stat. Comput. Simul. **74**, 779–791 (2004)

Müller, C.: Maximin efficient designs for estimating nonlinear aspects in linear models. J. Stat. Plan. Inference **44**, 117–132 (1995)

Müller, C., Pazman, A.: Applications of necessary and sufficient conditions for maximin efficient designs. Metrika **48**, 1–19 (1998)

Noubiap, R.F., Seidel, W.: A minimax algorithm for constructing optimal symmetrical balanced designs for a logistic regression model. J. Stat. Plan. Inference **91**, 151–168 (2000)

Nyquist, H.: Conditions for minimax designs. Working paper, Stockholm University (2012)

Sitter, R.: Robust designs for binary data. Biometrics **48**, 1145–1155 (1992)

# Extended Optimality Criteria for Optimum Design in Nonlinear Regression

**Andrej Pázman and Luc Pronzato**

**Abstract** Among the major difficulties that one may encounter when estimating parameters in a nonlinear regression model are the non-uniqueness of the estimator, its instability with respect to small perturbations of the observations and the presence of local optimizers of the estimation criterion. We show that these estimability issues can be taken into account at the design stage, through the definition of suitable design criteria. Extensions of $E$, $c$ and $G$-optimality criteria will be considered, which, when evaluated at a given $\theta^0$ (locally optimal design), account for the behavior of the model response $\eta(\theta)$ for $\theta$ far from $\theta^0$. In particular, they ensure some protection against close-to-overlapping situations where $\|\eta(\theta) - \eta(\theta^0)\|$ is small for some $\theta$ far from $\theta^0$. These extended criteria are concave, their directional derivative can be computed, and necessary and sufficient conditions for optimality (Equivalence Theorems) can be formulated. They are not differentiable, but a relaxation based on maximum-entropy regularization is proposed to obtain concave and differentiable alternatives. When the design space is finite and the set of admissible $\theta$ is discretized, their optimization forms a linear programming problem.

## 1 Introduction

We consider a nonlinear regression model with observations

$$y_i = y(x_i) = \eta(x_i, \bar{\theta}) + \varepsilon_i, \quad i = 1, \ldots, N,$$

where the errors $\varepsilon_i$ satisfy $\mathrm{E}(\varepsilon_i) = 0$, $\mathrm{var}(\varepsilon_i) = \sigma^2$ and $\mathrm{cov}(\varepsilon_i, \varepsilon_j) = 0$ for $i \neq j$, $i, j = 1, \ldots, N$, and $\bar{\theta} \in \Theta$, a compact subset of $\mathbb{R}^p$ such that $\Theta \subset \overline{\mathrm{int}(\Theta)}$, the

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closure of int($\Theta$). In a vector notation, we write

$$\mathbf{y} = \eta(\bar{\theta}) + \varepsilon, \quad \text{with } \mathrm{E}(\varepsilon) = \mathbf{0}, \mathrm{var}(\varepsilon) = \sigma^2 \mathbf{I}_N, \tag{1}$$

where $\eta(\theta) = \eta_X(\theta) = (\eta(x_1, \theta), \ldots, \eta(x_N, \theta))^\top$, $\mathbf{y} = (y_1, \ldots, y_N)^\top$, $\varepsilon = (\varepsilon_1, \ldots, \varepsilon_N)^\top$ and $X$ is the exact design $(x_1, \ldots, x_N)$. We suppose that $\eta(x, \theta)$ is twice continuously differentiable with respect to $\theta \in \mathrm{int}(\Theta)$ for any $x \in \mathscr{X}$ compact. We shall consider design measures $\xi$, which correspond to probability measures on $\mathscr{X}$. The information matrix for the design $X$ at $\theta$ is

$$\mathbf{M}_\theta(X) = \sum_{i=1}^{N} \frac{\partial \eta(x_i, \theta)}{\partial \theta} \frac{\partial \eta(x_i, \theta)}{\partial \theta^\top}$$

and we have $\mathbf{M}_\theta(\xi) = \int_{\mathscr{X}} [\partial \eta(x, \theta)/\partial \theta][\partial \eta(x, \theta)/\partial \theta^\top] \xi(\mathrm{d}x)$. Denoting by $\xi_N$ the empirical design measure associated with $X$, $\xi_N = (1/N) \sum_{i=1}^{N} \delta_{x_i}$ with $\delta_x$ the delta measure at $x$, we have $\mathbf{M}_\theta(X) = N \mathbf{M}_\theta(\xi_N)$.

The set of all hypothetical means of the observed vectors $\mathbf{y}$ in the sample space $\mathbb{R}^N$ forms the expectation surface $\mathbb{S}_\eta = \{\eta(\theta) : \theta \in \Theta\}$. Since $\eta(\theta)$ is supposed to have continuous first and second-order derivatives in int($\Theta$), $\mathbb{S}_\eta$ is a smooth surface in $\mathbb{R}^N$ with a (local) dimension given by $r = \mathrm{rank}[\partial \eta(\theta)/\partial \theta^\top]$. If $r = p$ (which means full rank), the model (1) is called regular. In regular models with no overlapping of $\mathbb{S}_\eta$, i.e., when $\eta(\theta) = \eta(\theta')$ implies $\theta = \theta'$, the LS estimator

$$\hat{\theta} = \hat{\theta}_{LS}^N = \arg\min_{\theta \in \Theta} \|\mathbf{y} - \eta(\theta)\|^2$$

is uniquely defined, since as soon as the distributions of errors $\varepsilon_i$ have probability densities (in the standard sense) it can be proven that $\eta[\hat{\theta}_{LS}^N(\mathbf{y})]$ is unique with probability one, see Pázman (1984) and Pázman (1993, p. 107). However, there is still a positive probability that the function $\theta \longrightarrow \|\mathbf{y} - \eta(\theta)\|^2$ has a local minimizer different from the global one when the regression model is intrinsically curved in the sense of Bates and Watts (1980), i.e., when $\mathbb{S}_\eta$ is a curved surface in $\mathbb{R}^N$, see Demidenko (1989, 2000). Moreover, a curved surface can "almost overlap"; that is, there may exist points $\theta, \theta'$ such that $\|\theta' - \theta\|$ is large but $\|\eta(\theta') - \eta(\theta)\|$ is small (or even equals zero in the case of strict overlapping). This phenomenon may cause serious difficulties in parameter estimation, leading to instabilities of the estimator, and one should thus attempt to reduce its effects by choosing an adequate experimental design. Note that putting restrictions on curvature measures is not enough: consider the case $\dim(\theta) = 1$ with the overlapping $\mathbb{S}_\eta$ formed by a circle of arbitrarily large radius and thus arbitrarily small curvature.

Important and precise results are available concerning the construction of subsets of $\Theta$ where such effects are guaranteed not to occur, see, e.g., Chavent (1983, 1990, 1991). However, their exploitation for choosing adequate designs is far from straightforward. Also, the construction of designs with restricted curvature, as proposed by Clyde and Chaloner (2002), is based on the curvature measures of Bates and Watts (1980) and uses derivatives of $\eta(\theta)$ at a certain $\theta$. This local approach

is unable to catch the problem of overlapping for two points that are distant in the parameter space.

The aim of this paper is to present new optimality criteria for optimum design in nonlinear regression models that may reduce such effects, especially overlapping, and are at the same time closely related to classical optimality criteria like $E$, $c$ or $G$-optimality (in fact, they coincide with those criteria when the regression model is linear).

## 2 Extended (Globalized) E-Optimality

### 2.1 Extended E-Optimality Criterion

Consider the design criterion

$$\phi_{eE}(\xi) = \phi_{eE}(\xi;\theta) = \min_{\theta' \in \Theta} \left\{ \left\| \eta(\cdot,\theta') - \eta(\cdot,\theta) \right\|_{\xi}^{2} \left( K + \left\| \theta' - \theta \right\|^{-2} \right) \right\}$$

to be maximized with respect to the design measure $\xi$, where $K$ is some positive tuning constant (to be chosen in advance) and $\|\cdot\|_\xi$ denotes the norm in $\mathscr{L}_2(\xi)$; that is, $\|\phi\|_\xi = [\int_{\mathscr{X}} \phi^2(x)\xi(\mathrm{d}x)]^{1/2}$ for any $\phi \in \mathscr{L}_2(\xi)$.

Notice that in a nonlinear regression model $\phi_{eE}(\cdot)$ depends on the value chosen for $\theta$ and can thus be considered as a local optimality criterion. On the other hand, the criterion is global in the sense that it depends on the behaviour of $\eta(\cdot,\theta')$ for $\theta'$ far from $\theta$. We could remove this (limited) locality by considering $\phi_{MeE}(\xi) = \min_{\theta\in\Theta} \phi_{eE}(\xi)$, but this will not be considered in what follows.

For a linear regression model with $\eta(\theta) = \mathbf{F}(X)\theta + \mathbf{v}(X)$ and $\Theta = \mathbb{R}^p$, we have $\min_{\theta'\in\Theta, \|\theta'-\theta\|^2=\delta} \|\eta(\theta') - \eta(\theta)\|^2 = \min_{\theta'\in\Theta, \|\theta'-\theta\|^2=\delta} (\theta'-\theta)^\top [N\mathbf{M}(\xi_N)](\theta' - \theta) = N\delta\lambda_{\min}[\mathbf{M}(\xi_N)]$, so that $\phi_{eE}(\xi) = \lambda_{\min}[\mathbf{M}(\xi)]$ for any $K \geq 0$, which corresponds to the $E$-optimality criterion. For a nonlinear regression model with no overlapping $\phi_{eE}(\xi;\theta)$ can be made arbitrarily close to $\lambda_{\min}[\mathbf{M}_\theta(\xi)]$ by choosing $K$ large enough; $\phi_{eE}(\cdot)$ can thus be considered as an *extended E-optimality criterion*. At the same time, choosing $K$ not too large ensures some protection against $\|\eta(\theta') - \eta(\theta)\|$ being small for some $\theta'$ far from $\theta$ for a $\phi_{eE}$-optimum design $\xi^*_{eE}$. Note that $\xi^*_{eE}$ is necessarily non-degenerate, i.e., $\mathbf{M}(\xi^*_{eE})$ is nonsingular.

### 2.2 Properties of $\phi_{eE}(\cdot)$

The criterion $\phi_{eE}(\cdot)$ is the minimum of linear functions of $\xi$ and is thus *concave*: for all $\xi, \nu \in \Xi$, the set of design measures on $\mathscr{X}$, for all $\alpha \in [0,1]$, for all $\theta \in \Theta$, $\phi_{eE}[(1-\alpha)\xi + \alpha\nu] \geq (1-\alpha)\phi_{eE}(\xi) + \alpha\phi_{eE}(\nu)$. It is also *positively homogeneous*: $\phi_{eE}(a\xi) = a\phi_{eE}(\xi)$ for all $\xi \in \Xi$, $\theta \in \Theta$ and $a > 0$. Its concavity implies the existence of directional derivatives and we have the following, see, e.g., Dem'yanov and Malozemov (1974):

**Theorem 1** *For any $\xi, \nu \in \Xi$, the directional derivative of the criterion $\phi_{eE}(\cdot)$ at $\xi$ in the direction $\nu$ is given by*

$$F_{\phi_{eE}}(\xi;\nu) = \min_{\theta' \in \Theta_\theta(\xi)} \left\{ \left\| \eta(\cdot,\theta') - \eta(\cdot,\theta) \right\|_\nu^2 \left( K + \left\| \theta' - \theta \right\|^{-2} \right) \right\} - \phi_{eE}(\xi),$$

*where*

$$\Theta_\theta(\xi) = \left\{ \theta' \in \Theta : \left\| \eta(\cdot,\theta') - \eta(\cdot,\theta) \right\|_\xi^2 \left( K + \left\| \theta' - \theta \right\|^{-2} \right) = \phi_{eE}(\xi) \right\}.$$

We can write $F_{\phi_{eE}}(\xi;\nu) = \min_{\theta' \in \Theta_\theta(\xi)} \int_{\mathcal{X}} \Psi_{eE}(x,\theta',\xi)\nu(\mathrm{d}x)$, where

$$\Psi_{eE}(x,\theta',\xi) = \left( K + \left\| \theta' - \theta \right\|^{-2} \right) \times \left\{ \left[ \eta(x,\theta') - \eta(x,\theta) \right]^2 - \left\| \eta(\cdot,\theta') - \eta(\cdot,\theta) \right\|_\xi^2 \right\}, \tag{2}$$

and a necessary and sufficient condition for the optimality of a design measure $\xi_{eE}^*$ for the criterion $\phi_{eE}(\cdot)$ is that $\sup_{\nu \in \Xi} F_{\phi_{eE}}(\xi^*;\nu) \le 0$. One should notice that $\sup_{\nu \in \Xi} F_{\phi_{eE}}(\xi^*;\nu)$ is not generally obtained for $\nu$ equal to a one-point (delta) measure, which prohibits the usage of classical vertex-direction algorithms for optimizing $\phi_{eE}(\cdot)$. This is why a regularized version $\phi_{eE,\lambda}(\cdot)$ of $\phi_{eE}(\cdot)$ is considered below, with the property that $\sup_{\nu \in \Xi} F_{\phi_{eE,\lambda}}(\xi;\nu)$ is obtained when $\nu$ is the delta measure $\delta_{x^*}$ at some $x^* \in \mathcal{X}$ (depending on $\xi$).

## 2.3 Maximum-Entropy Regularization of $\phi_{eE}(\cdot)$

The criterion $\phi_{eE}(\cdot)$ can be equivalently defined by

$$\phi_{eE}(\xi) = \min_{\mu \in \mathcal{M}(\Theta)} \int_\Theta \left\{ \left\| \eta(\cdot,\theta') - \eta(\cdot,\theta) \right\|_\xi^2 \left( K + \left\| \theta' - \theta \right\|^{-2} \right) \right\} \mu(\mathrm{d}\theta'),$$

where $\mathcal{M}(\Theta)$ denotes the set of probability measures on $\Theta$. We use the approach of Li and Fang (1997) and regularize $\phi_{eE}(\xi)$ through a penalization of measures $\mu$ having small (Shannon) entropy, with a penalty coefficient $1/\lambda$ that sets the amount of regularization introduced. We then obtain the regularized criterion

$$\phi_{eE,\lambda}(\xi) = -\frac{1}{\lambda} \log \int_\Theta \exp\left\{ -\lambda H_E(\xi,\theta') \right\} \mathrm{d}\theta', \tag{3}$$

where

$$H_E(\xi,\theta') = \left\| \eta(\cdot,\theta') - \eta(\cdot,\theta) \right\|_\xi^2 \left( K + \left\| \theta' - \theta \right\|^{-2} \right). \tag{4}$$

This criterion satisfies $\lim_{\lambda \to \infty} \phi_{eE,\lambda}(\xi) = \phi_{eE}(\xi)$ for any $\xi \in \Xi$ and convergence is uniform when $\Theta$ is a finite set. Moreover, $\phi_{eE,\lambda}(\cdot)$ is concave. Its directional

derivative at $\xi$ in the direction $\nu$ is

$$F_{\phi_{eE,\lambda}}(\xi;\nu)=\frac{\int_{\mathscr{X}}\int_{\Theta}\exp\{-\lambda H_E(\xi,\theta')\}\Psi_{eE}(x,\theta',\xi)\mathrm{d}\theta'\nu(\mathrm{d}x)}{\int_{\Theta}\exp\{-\lambda H_E(\xi,\theta')\}\mathrm{d}\theta'}, \tag{5}$$

with $\Psi_{eE}(x,\theta',\xi)$ given by (2). It is also differentiable (unlike $\phi_{eE}(\cdot)$) and a necessary and sufficient condition for the optimality of $\xi^*$ maximizing $\phi_{eE,\lambda}(\cdot)$ is that $\sup_{x\in\mathscr{X}}\int_{\Theta}\exp\{-\lambda H_E(\xi^*,\theta')\}\Psi_{eE}(x,\theta',\xi^*)\mathrm{d}\theta'\le 0$. In order to facilitate computations, the integrals on $\theta'$ in (3, 5) can be replaced by finite sums.

### *2.4 A Solution via Linear Programming*

When $\Theta$ is finite, i.e., $\Theta=\{\theta^{(1)},\theta^{(2)},\ldots,\theta^{(m)}\}$, $\phi_{eE}(\xi)$ can be written as $\phi_{eE}(\xi)=\min_{j=1,\ldots,m}H_E(\xi,\theta^{(j)})$, with $H_E(\xi,\theta')$ given by (4). If the design space $\mathscr{X}$ is finite too, $\mathscr{X}=\{x^{(1)},x^{(2)},\ldots,x^{(q)}\}$, then the determination of an optimal design measure for $\phi_{eE}(\cdot)$ amounts to the determination of a scalar $\gamma$ and of a vector of weights $\mathbf{w}=(w_1,w_2,\ldots,w_q)^\top$ such that $\mathbf{c}^\top[\mathbf{w}^\top,\gamma]^\top$ is maximized, with $\mathbf{c}=(0,0,\ldots,0,1)^\top$ and $\mathbf{w}$ and $\gamma$ satisfying the constraints

$$\sum_{i=1}^{q}w_i=1,$$
$$w_i\ge 0,\quad i=1,\ldots,q,$$
$$\sum_{i=1}^{q}w_i\left[\eta\left(x^{(i)},\theta^{(j)}\right)-\eta\left(x^{(i)},\theta\right)\right]^2\left(K+\left\|\theta^{(j)}-\theta\right\|^{-2}\right)\ge\gamma,\quad j=1,\ldots,m.$$

## 3 Extended (Globalized) c-Optimality

Define $\phi_{ec}(\xi)=\min_{\theta'\in\Theta}\{\|\eta(\cdot,\theta')-\eta(\cdot,\theta)\|_\xi^2(K+|h(\theta')-h(\theta)|^{-2})\}$, with $K$ being some positive constant. When $\eta(x,\theta)$ and the scalar function $h(\theta)$ are both linear in $\theta$, we get

$$\phi_{ec}(\xi)=\min_{\theta'\in\Theta,\mathbf{c}^\top(\theta'-\theta)\neq 0}\frac{(\theta'-\theta)^\top\mathbf{M}(\xi)(\theta'-\theta)}{[\mathbf{c}^\top(\theta'-\theta)]^2}$$

and therefore $\phi_{ec}(\xi)=[\mathbf{c}^\top\mathbf{M}^-(\xi)\mathbf{c}]^{-1}$, which justifies consideration of $\phi_{ec}(\xi)$ as an *extended c-optimality criterion*. Again, for large $K$, $\phi_{ec}(\xi)$ can be approximated by $[\mathbf{c}^\top\mathbf{M}^{-1}(\xi,\theta)\mathbf{c}]^{-1}$, whereas choosing $K$ not too large ensures some protection against $\|\eta(\cdot,\theta')-\eta(\cdot,\theta)\|_\xi^2$ being small for some $\theta'$ such that $h(\theta')$ is significantly different from $h(\theta)$. The criterion $\phi_{ec}(\cdot)$ is concave and positively homogeneous. Its concavity implies the existence of directional derivatives.

**Theorem 2** *For any $\xi, \nu \in \Xi$, the directional derivative of the criterion $\phi_{ec}(\cdot)$ at $\xi$ in the direction $\nu$ is given by*

$$F_{\phi_{ec}}(\xi;\nu) = \min_{\theta' \in \Theta_{\theta,c}(\xi)} \left\{ \left\| \eta\left(\cdot,\theta'\right) - \eta(\cdot,\theta) \right\|_{\nu}^2 \left(K + \left| h\left(\theta'\right) - h(\theta) \right|^{-2}\right) \right\} - \phi_{ec}(\xi),$$

*where*

$$\Theta_{\theta,c}(\xi) = \left\{ \theta' \in \Theta : \left\| \eta\left(\cdot,\theta'\right) - \eta(\cdot,\theta) \right\|_{\xi}^2 \left(K + \left| h\left(\theta'\right) - h(\theta) \right|^{-2}\right) = \phi_{ec}(\xi) \right\}.$$

A necessary and sufficient condition for the optimality of $\xi^*$ maximizing $\phi_{ec}(\cdot)$ is that $\sup_{\nu \in \Xi} F_{\phi_{ec}}(\xi^*;\nu) \le 0$. A regularized version of $\phi_{ec}(\cdot)$ can be obtained through maximum-entropy regularization

$$\phi_{ec,\lambda}(\xi) = -\frac{1}{\lambda} \log \int_{\Theta} \exp\left\{ -\lambda H_c\left(\xi,\theta'\right) \right\} \mathrm{d}\theta', \tag{6}$$

where $H_c(\xi,\theta') = \|\eta(\cdot,\theta') - \eta(\cdot,\theta)\|_{\xi}^2 (K + |h(\theta') - h(\theta)|^{-2})$. The regularized criterion $\phi_{ec,\lambda}(\cdot)$ is concave and differentiable with respect to $\xi$. Its directional derivative at $\xi$ in the direction $\nu$ is

$$F_{\phi_{ec,\lambda}}(\xi;\nu) = \frac{\int_{\mathcal{X}} \int_{\Theta} \exp\{-\lambda H_c(\xi,\theta')\} \Psi_{ec}(x,\theta',\xi) \mathrm{d}\theta' \nu(\mathrm{d}x)}{\int_{\Theta} \exp\{-\lambda H_c(\xi,\theta')\} \mathrm{d}\theta'}, \tag{7}$$

where

$$\begin{aligned} \Psi_{ec}\left(x,\theta',\xi\right) = {} & \left(K + \left| h\left(\theta'\right) - h(\theta) \right|^{-2}\right) \\ & \times \left\{ \left[ \eta\left(x,\theta'\right) - \eta(x,\theta) \right]^2 - \left\| \eta\left(\cdot,\theta'\right) - \eta(\cdot,\theta) \right\|_{\xi}^2 \right\}. \end{aligned}$$

A necessary and sufficient condition for the optimality of $\xi^*$ maximizing $\phi_{ec,\lambda}(\cdot)$ is that $\sup_{x \in \mathcal{X}} \int_{\Theta} \exp\{-\lambda H_c(\xi^*,\theta')\} \Psi_{ec}(x,\theta',\xi^*) \mathrm{d}\theta' \le 0$. Again, in order to facilitate computation, the integrals in (6) and (7) can be replaced by finite sums. A linear programming solution can be obtained when both $\Theta$ and $\mathcal{X}$ are finite, following an approach similar to that in Sect. 2.

## 4 Extended (Globalized) G-Optimality

Following the same lines as above, we can also define an extended $G$-optimality criterion by

$$\phi_{GG}(\xi) = \min_{\theta' \in \Theta} \left[ \left\| \eta\left(\cdot,\theta'\right) - \eta(\cdot,\theta) \right\|_{\xi}^2 \left\{ K + \frac{1}{\max_{x \in \mathcal{X}} [\eta(x,\theta') - \eta(x,\theta)]^2} \right\} \right]$$

with $K$ some positive constant. The fact that this corresponds to the $G$-optimality criterion for a linear model can easily be seen, noticing that in the model (1) with

$\eta(x,\theta) = \mathbf{f}^\top(x)\theta + v(x)$ we have

$$\left\{ \sup_{x\in\mathscr{X}} \frac{N}{\sigma^2} \operatorname{var}\left[\mathbf{f}^\top(x)\hat{\theta}_{LS}^N\right] \right\}^{-1}$$
$$= \inf_{x\in\mathscr{X}} \inf_{\mathbf{u}\in\mathbb{R}^p, \mathbf{u}^\top\mathbf{f}(x)\neq 0} \frac{\mathbf{u}^\top\mathbf{M}(X)\mathbf{u}}{[\mathbf{f}^\top(x)\mathbf{u}]^2}$$
$$= \inf_{\mathbf{u}\in\mathbb{R}^p, \mathbf{u}^\top\mathbf{f}(x)\neq 0} \left[ \mathbf{u}^\top\mathbf{M}(X)\mathbf{u} \left\{ K + \frac{1}{\max_{x\in\mathscr{X}}[\mathbf{f}^\top(x)\mathbf{u}]^2} \right\} \right].$$

Directional derivatives can be computed and a regularized version can be constructed similarly to the cases of extended $E$ and $c$-optimality. An optimal design can be obtained by linear programming when $\Theta$ and $\mathscr{X}$ are both finite.

## 5 Example

The model response is given by

$$\eta(\mathbf{x},\theta) = \theta_1\{\mathbf{x}\}_1 + \theta_1^3\big(1-\{\mathbf{x}\}_1\big) + \theta_2\{\mathbf{x}\}_2 + \theta_2^2\big(1-\{\mathbf{x}\}_2\big), \quad \theta = (\theta_1,\theta_2)^\top,$$

with $\mathbf{x}\in\mathscr{X} = [0,1]^2$ and $\{\mathbf{x}\}_i$ denoting the $i$-th component of $\mathbf{x}$. We consider local designs for $\theta^0 = (1/8, 1/8)^\top$. The classical $D$ and $E$-optimal designs are supported on three and two points respectively,

$$\xi_D^*\big(\theta^0\big) \simeq \left\{ \begin{pmatrix}0\\1\end{pmatrix} \quad \begin{pmatrix}1\\0\end{pmatrix} \quad \begin{pmatrix}1\\1\end{pmatrix} \right\}, \qquad \xi_E^*\big(\theta^0\big) \simeq \left\{ \begin{pmatrix}0\\1\end{pmatrix} \quad \begin{pmatrix}1\\0\end{pmatrix} \right\}.$$
$$0.4134 \qquad 0.3184 \qquad 0.2682 \qquad\qquad 0.5113 \qquad 0.4887$$

We replace integrals by finite sums in (3) and (5), and consider regular grids $\mathscr{G}(\rho, M)$ formed of $M$ points uniformly distributed on a circle centered at $\theta^0$ with radius $\rho$. When $\Theta = \bigcup_{i=1}^{20} \mathscr{G}(0.1i, 100)$, $K = 0.01$ and $\lambda = 10^3$, the optimal design for $\phi_{eE,\lambda}$ is

$$\xi_{eE}^*\big(\theta^0\big) \simeq \left\{ \begin{pmatrix}0\\0\end{pmatrix} \quad \begin{pmatrix}1\\0\end{pmatrix} \quad \begin{pmatrix}1\\1\end{pmatrix} \right\}.$$
$$0.2600 \qquad 0.3575 \qquad 0.3825$$

Figure 1 presents a plot of the function

$$\delta\in\mathbb{R}^+ \longrightarrow E_{\eta,\theta^0}^{\xi}(\delta) = \min_{\theta'\in\Theta, \|\theta'-\theta^0\|^2=\delta} \big\|\eta\big(\cdot,\theta'\big) - \eta\big(\cdot,\theta^0\big)\big\|_\xi^2$$

for the three designs $\xi_D^*$, $\xi_E^*$ and $\xi_{eE}^*$. The minimum of $\|\eta(\cdot,\theta') - \eta(\cdot,\theta^0)\|_\xi$, say for $\|\theta'-\theta^0\| > 1$, is 0.131 for $\xi_{eE}^*$ and only 0.082 for $\xi_D^*$. It is zero for $\xi_E^*$ since the parameters are only locally estimable for this design.

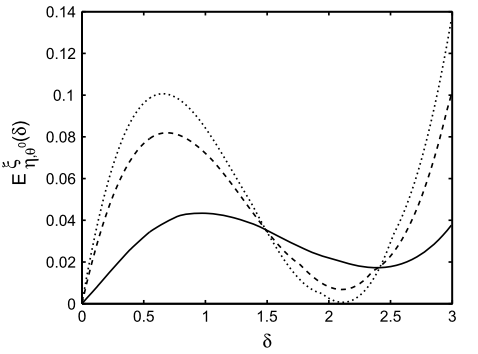


**Fig. 1** Plot of the function $E^{\xi}_{\eta,\theta^0}(\cdot)$ for the three designs $\xi^*_D$ (*dashed line*), $\xi^*_E$ (*dotted line*) and $\xi^*_{eE}$ (*solid line*)

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## References

Bates, D., Watts, D.: Relative curvature measures of nonlinearity. J. R. Stat. Soc. B **42**, 1–25 (1980)

Chavent, G.: Local stability of the output least square parameter estimation technique. Mat. Appl. Comput. **2**, 3–22 (1983)

Chavent, G.: A new sufficient condition for the wellposedness of non-linear least-square problems arising in identification and control. In: Bensoussan, A., Lions, J.L. (eds.) Analysis and Optimization of Systems, pp. 452–463. Springer, Heidelberg (1990)

Chavent, G.: New size × curvature conditions for strict quasiconvexity of sets. SIAM J. Control Optim. **29**, 1348–1372 (1991)

Clyde, M., Chaloner, K.: Constrained design strategies for improving normal approximations in nonlinear regression problems. J. Stat. Plan. Inference **104**, 175–196 (2002)

Demidenko, E.: Optimization and Regression. Nauka, Moscow (1989). (In Russian)

Demidenko, E.: Is this the least squares estimate? Biometrika **87**, 437–452 (2000)

Dem'yanov, V., Malozemov, V.: Introduction to Minimax. Dover, New York (1974)

Li, X.S., Fang, S.C.: On the entropic regularization method for solving min-max problems with applications. Math. Methods Oper. Res. **46**, 119–130 (1997)

Pázman, A.: Nonlinear least squares—uniqueness versus ambiguity. Math. Oper.forsch. Stat., Ser. Stat. **15**, 323–336 (1984)

Pázman, A.: Nonlinear Statistical Models. Kluwer Academic, Dordrecht (1993)

# Optimal Design for Multivariate Models with Correlated Observations

**Andrey Pepelyshev**

**Abstract** The methodology proposed in Zhigljavsky et al. (J. Am. Stat. Assoc. 105:1093–1103, 2010) is studied in the case of multivariate models with correlated observations. A numerical procedure for constructing asymptotically optimal and exact designs is proposed. It is shown that exact $n$-point designs generated from these asymptotic designs for any desired $n$ have very good efficiency. The performance of the procedure is illustrated in the case of spatial models.

## 1 The Statement of the Problem

Consider the common linear regression model

$$y(x) = \theta_1 f_1(x) + \cdots + \theta_m f_m(x) + \varepsilon(x), \quad x \in \mathbb{X} \subset \mathbb{R}^d, \tag{1}$$

where the functions $f_1(x), \ldots, f_m(x)$ are linearly independent and continuous, the random error field $\varepsilon(x)$ has the zero mean with the covariance kernel $K(x, x') = \mathrm{E}[\varepsilon(x)\varepsilon(x')]$, the parameters $\theta_1, \ldots, \theta_m$ are unknown and the explanatory variable $x$ varies in a compact design space $\mathbb{X}$. Suppose that $N$ observations $y_1, \ldots, y_N$ can be taken at experimental conditions $x_1, \ldots, x_N$ to estimate the parameters in the model (1). The problem of experimental design for this model has been studied amongst others by Bickel and Herzberg (1979), Müller (2000), Näther (1985), Pázman (2010), Sacks and Ylvisaker (1966, 1968) and by Zhigljavsky et al. (2010).

If the covariance kernel is known, then the vector of parameters can be estimated by the weighted least-squares method as

$$\hat{\theta} = \left(\mathbf{X}^\top \Sigma^{-1} \mathbf{X}\right)^{-1} \mathbf{X}^\top \Sigma^{-1} Y,$$

where $\mathbf{X} = (f_i(x_j))_{j=1,\ldots,N}^{i=1,\ldots,m}$, $Y = (y_1, \ldots, y_N)^\top$, and $\Sigma = (K(x_i, x_j))_{i,j=1,\ldots,N}$. Note that $\hat{\theta}$ is the best linear unbiased estimate (BLUE) of $\theta = (\theta_1, \ldots, \theta_m)^\top$. The

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covariance matrix of the BLUE is given by

$$\mathrm{Var}(\hat{\theta}) = \left(\mathbf{X}^\top \Sigma^{-1} \mathbf{X}\right)^{-1}.$$

An exact experimental design $\xi_N = \{x_1, \ldots, x_N\}$ is a collection of $N$ points from the design space $\mathbb{X}$. A design $\xi_N$ is called $D$-optimal if it minimizes the determinant of the covariance matrix. Since it is difficult to find optimal designs explicitly (Dette et al. 2008a; Harman and Štulajter 2010; Kiseľák and Stehlík 2008), several algorithms have been proposed for the numerical construction of exact optimal designs (see Brimkulov et al. 1980; Fedorov and Müller 2007; Müller and Pázman 1999, 2003; Uciński and Atkinson 2004).

Although the optimal exact $N$-point designs for different $N$ typically contain different points, these designs have a unified pattern of the location of points. This pattern can be identified through an asymptotic consideration as follows. We rewrite the design as a probability measure $\xi_n = \{x_1, \ldots, x_n; 1/n, \ldots, 1/n\}$. Then we expect that the sequence of designs $\xi_n$ converges to some limiting probability measure $\xi$, which, as $n$ increases, can be treated as the density pattern of the location of the points.

Interpretation of the design $\xi$ and the method of generating exact designs from $\xi$ differ from classical ones for uncorrelated observations because, if one realization of a stochastic field is observed, then no replication of design points is allowed. For the model (1) exact designs are obtained from $\xi$ as a collection of quantiles $Q(0), Q(1/(N-1)), Q(2/(N-1)), \ldots, Q(1)$, where $Q(x)$ is the quantile function of $\xi$ (see Näther 1985; Zhigljavsky et al. 2010). If $d > 1$, a rough way of obtaining exact designs is by independent sampling from the distribution of $\xi$ and an accurate way is by the procedure proposed in Sect. 3. We also note that the asymptotically optimal design $\xi$ is a convenient tool for identifying regions of the design space that are preferable for observation and those that are not.

## 2 Asymptotically Optimal Design

Finding an asymptotically optimal design that minimizes the covariance matrix of the BLUE is an extremely difficult problem. Therefore, we consider the ordinary least squares estimate (LSE) which has a covariance matrix allowing a simple formulation in terms of a probability measure (see Dette et al. 2011; Näther 1985). Note that we can consider the design problem for the LSE, rather than the one for the BLUE because the optimal design for the LSE is sufficiently efficient relative to that for the BLUE. This efficiency can then be verified numerically.

The covariance matrix for the LSE has the form

$$D(\xi) = M^{-1}(\xi) B(\xi, \xi) M^{-1}(\xi),$$

where $\xi$ is either an exact design or a probability measure and

$$M(\xi) = \int_{\mathbb{X}} f(u) f^\top(u) \xi(\mathrm{d}u), \tag{2}$$

$$B(\xi,\xi)=\int_{\mathbb{X}}\int_{\mathbb{X}} K(u,v)f(u)f^{\top}(v)\xi(\mathrm{d}u)\xi(\mathrm{d}v). \tag{3}$$

The asymptotically $D$-optimal design for the LSE minimizes the determinant of $D(\xi)$ among the class of probability measures such that the matrix $M(\xi)$ is not singular.

The necessary condition for $D$-optimality can be derived from the positivity of the directional derivative in an explicit way as follows (see Dette et al. 2011 for details).

**Theorem 1** *Let $\xi^*$ be any $D$-optimal design. Then for all $x\in\mathbb{X}$ we have*

$$d\big(x,\xi^*\big)\le b\big(x,\xi^*\big), \tag{4}$$

*where*

$$d(x,\xi)=f^{\top}(x)M^{-1}(\xi)f(x)$$

*and*

$$b(x,\xi)=\mathrm{tr}\big(B^{-1}(\xi,\xi)B(\xi,\xi_x)\big)=f^{\top}(x)B^{-1}(\xi,\xi)\int K(u,x)f(u)\xi(\mathrm{d}u),$$

*with $\xi_x=\{x,1\}$ the Dirac measure. Moreover, there is equality in (4) for $\xi^*$ for almost all $x$.*

Numerical computation of optimal designs for a common linear regression model (1) with a given correlation function can be performed by an extension of the multiplicative algorithm proposed in Dette et al. (2008b) for the case of non-correlated observations. Note that the proposed algorithm constructs a discrete design which can be considered as an approximation to a design which satisfies the necessary optimality conditions of Theorem 1. By choosing a fine discretization $\{x_1,\dots,x_n\}$ of the design space $\mathbb{X}$ and running the algorithm long enough, the approximation error can be made rather small.

Let $\xi^{(r)}=\{x_1,\dots,x_n;w_1^{(r)},\dots,w_n^{(r)}\}$ denote the design at the $r$-th iteration. Then the updating rule for the weights has the form

$$w_i^{(r+1)}=\frac{w_i^{(r)}(\psi(x_i,\xi^{(r)})-\beta_r)}{\sum_{j=1}^n w_j^{(r)}(\psi(x_j,\xi^{(r)})-\beta_r)},\quad i=1,\dots,n, \tag{5}$$

where $\beta_r$ is a tuning parameter, $0\le\beta_r<\min_i\psi(x_i,\xi^{(r)})$, $\psi(x,\xi)=d(x,\xi)/b(x,\xi)$, that leads to the so-called multiplicative algorithm for the case of correlated observations. The condition (4) takes the form $\psi(x,\xi^*)\le 1$ for all $x\in\mathbb{X}$. The rule (5) means that at the next iteration the weight of a point $x=x_j$ increases if the condition (4) does not hold at this point. Numerical experience shows that 20 iterations of the multiplicative algorithm are sufficient for finding a good approximation to the optimal design.

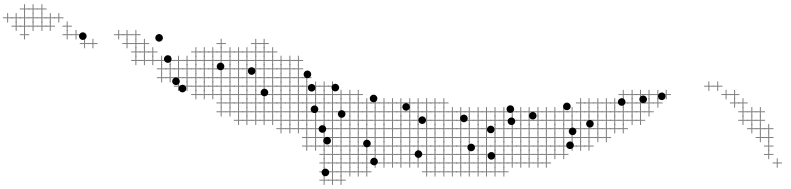

**Fig. 1** The Südliche Tullnerfeld in Lower Austria and the monitoring network

## 3 Computing Exact Designs from Asymptotically Optimal Designs

An exact $N$-point design can be obtained by independent sampling from the asymptotically optimal design $\xi$. However, such exact designs could be not very good due to randomness, especially for small $N$. Therefore, we propose the following procedure of approximating the probability measure $\xi$ by $N$ points.

For given $N$, we choose a discretization $x_1, \dots, x_n$ such that $n$ is much larger than $N$. Let $\xi = \{x_1, \dots, x_n; w_{1(1)}, \dots, w_{n(1)}\}$ be the asymptotically optimal design calculated by the multiplicative algorithm. Then we compute $N$ points $x'_1, \dots, x'_N$ of the exact design in $N$ iterations where the $k$-th iteration has the following form:

- Find an index $\tau$ such that $w_{\tau(k)}$ is maximal, i.e., $w_{\tau(k)} = \max_j w_{j(k)}$.
- Set $x'_k = x_\tau + \varepsilon$, where $\varepsilon$ is a random variable with zero mean and very small variance.
- Define $w_{\tau(k+1)} = w_{\tau(k)} - 1/N$ and $w_{j(k+1)} = w_{j(k)}$ for all $j \neq \tau$.
- If $w_{\tau(k+1)} < 0$, then set $w_{\tau(k+1)} = 0$. The weights of points in a neighborhood of $x_\tau$ should then be decreased so that $\sum_{j=1}^n w_{j(k+1)} = (N-k)/N$. That is, we take the points that are nearest to $x_\tau$ and decrease the weights at them.

## 4 Application to Spatial Models

As an example, we consider the design problem for a water-quality monitoring network in the Südliche Tullnerfeld in Lower Austria, which was previously studied in Müller (2000, 2005), Müller and Pázman (1999). The network existed in the period 1992–1997 and consisted of 36 measurement stations represented by the points in Fig. 1. The intersection of the grid with the Südliche Tullnerfeld is shown in Fig. 1 by crosses, giving 485 crosses in total.

We consider the linear regression model given by $f(x) = (1, x_{[1]}, x_{[2]})^\top$, where $x = (x_{[1]}, x_{[2]}) \in \mathbb{R}^2$. We also consider two correlation functions: the isotropic spherical correlation function

$$K_1(x, x'; \theta) = \begin{cases} \theta_1 + \theta_2, & \|x - x'\| = 0, \\ \theta_2(1 - 1.5\|x - x'\|/\theta_3 + 0.5\|x - x'\|^3/\theta_3^3), & 0 < \|x - x'\| < \theta_3, \\ 0, & \|x - x'\| > \theta_3 \end{cases}$$

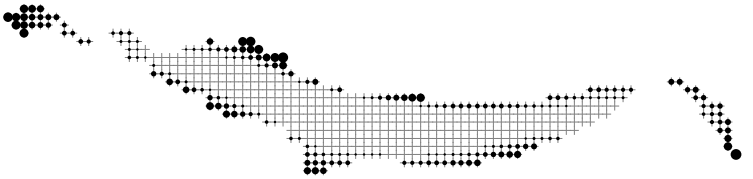

**Fig. 2** The design $\xi^{(20)}$ obtained by the multiplicative algorithm for the linear model and the spherical correlation function with $\theta = (4.89, 1.86, 0.81)$. The size of points is proportional to weights

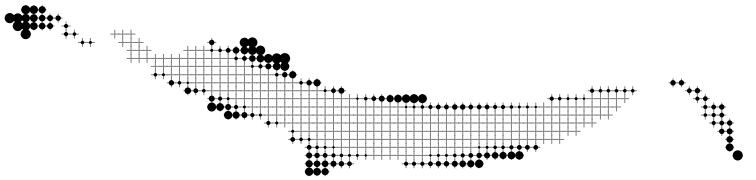

**Fig. 3** The design $\xi^{(20)}$ obtained by the multiplicative algorithm for the linear model and the Gaussian correlation function with $\theta = (4.89, 1.86, 0.5)$

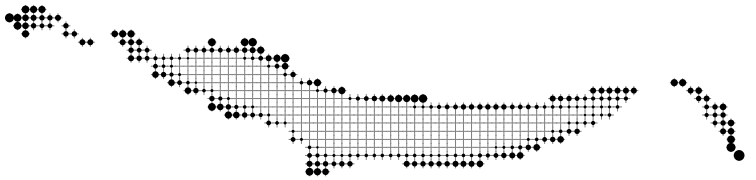

**Fig. 4** The design $\xi^{(20)}$ obtained by the multiplicative algorithm for the linear model and the spherical correlation function with $\theta = (4.89, 1.86, 0.4)$

and the Gaussian correlation function $K_2(x, x'; \theta) = \theta_1 \delta_0(\|x - x'\|) + \theta_2 \exp(-\|x - x'\|^2/\theta_3^2)$, where $\delta_0$ is the delta-function. We depict the design $\xi^{(20)}$ computed by the multiplicative algorithm for these correlation functions in Figs. 2 and 3. We can see that these designs have the same pattern when the correlation functions are rather similar in the sense that $\max_{x,x'} |K_1(x, x') - K_2(x, x')|$ is small. We also note that the positive weights are for points mostly near the boundary of the design space.

In Figs. 2, 4 and 5 we depict designs $\xi^{(20)}$ computed for the spherical correlation function with different parameters. We can see that the optimal design for $\theta = (4.89, 1.86, 0.4)$ is more uniform near the boundary while the optimal design for $\theta = (4.89, 1.86, 1.6)$ has several strict modes.

We now study exact designs generated by the asymptotically optimal design in terms of $\Psi(\xi_N) = [\mathrm{Var}(\hat{\theta})]^{1/3} = \sqrt[3]{(\mathbf{X}^\top \Sigma^{-1} \mathbf{X})^{-1}}$. In Fig. 6 we depict exact $N$-point designs $\xi_N$ for $N = 20, 25, 30$ and 36. We find that $\Psi(\xi_{20}) = 5.39$, $\Psi(\xi_{25}) = 4.56$, $\Psi(\xi_{30}) = 4.15$ and $\Psi(\xi_{36}) = 3.67$.

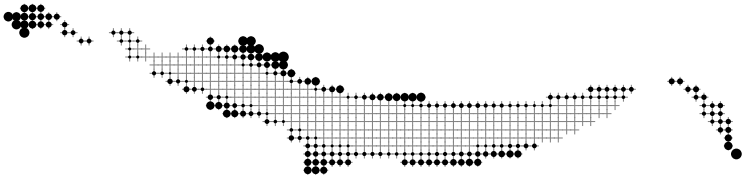

**Fig. 5** The design $\xi^{(20)}$ obtained by the multiplicative algorithm for the linear model and the spherical correlation function with $\theta = (4.89, 1.86, 1.6)$


**Fig. 6** The exact designs $\xi_{20}, \xi_{25}, \xi_{30}$ and $\xi_{36}$ generated by the design $\xi^{(20)}$ for the linear model and the spherical correlation function with $\theta = (4.89, 1.86, 0.81)$

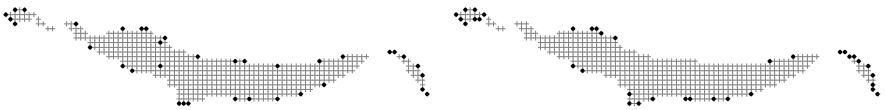

**Fig. 7** The exact designs $\xi^*_{D,36,r}$ (*left*) and $\xi^*_{D,36,a}$ (*right*) computed by the Brimkulov algorithm when the initial design is random and one generated from the asymptotically optimal density, respectively, for the linear model and the spherical correlation function with $\theta = (4.89, 1.86, 0.81)$

Exact designs generated from the asymptotically optimal design can be optimized by the Brimkulov algorithm (Brimkulov et al. 1980). In Fig. 7 we show two designs obtained by this algorithm. Let $\xi^*_{D,36,r}$ denote the design computed by the Brimkulov algorithm when the initial design is random. The design $\xi^*_{D,36,r}$ is shown in Müller (2005) for which $\Psi(\xi^*_{D,36,r}) = 3.55$, that is just slightly smaller than $\Psi(\xi_{36}) = 3.67$. Let $\xi^*_{D,36,a}$ denote the design computed by the Brimkulov algorithm when the initial design is generated from the asymptotically optimal density. We obtain $\Psi(\xi^*_{D,36,a}) = 3.39$ that is smaller than $\Psi(\xi^*_{D,36,r})$. Finally, we note $\Psi(\xi_{m.n.}) = 6.93$ where $\xi_{m.n.}$ corresponds to the real monitoring network depicted in Fig. 1. Thus, optimal location of measurement stations can double the estimation accuracy.

## 5 Conclusion

In the present paper we studied asymptotically optimal designs which can be useful in several ways. First, practitioners can more easily identify the general pattern of optimal allocation of points using the optimal density rather than using some exact designs. Second, the weights of points indirectly show how informative observations at these points can be. As a result, points with small weights can be removed from further consideration. Note that the problem of detection of points giving zero information for the BLUE is investigated in Pázman (2010). Third, algorithms for computing exact designs often converge to a better design when starting from an exact design computed from the asymptotically optimal design, rather than when starting from an arbitrary exact design.

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## References

Bickel, P.J., Herzberg, A.M.: Robustness of design against autocorrelation in time I: Asymptotic theory, optimality for location and linear regression. Ann. Stat. **7**, 77–95 (1979)

Brimkulov, U.N., Krug, G.K., Savanov, V.L.: Numerical construction of exact experimental designs when the measurements are correlated. Zavod. Lab. **36**, 435–442 (1980) (in Russian)

Dette, H., Kunert, J., Pepelyshev, A.: Exact optimal designs for weighted least squares analysis with correlated errors. Stat. Sin. **18**, 135–154 (2008a)

Dette, H., Pepelyshev, A., Zhigljavsky, A.: Improving updating rules in multiplicative algorithms for computing *D*-optimal designs. Comput. Stat. Data Anal. **53**, 312–320 (2008b)

Dette, H., Pepelyshev, A., Zhigljavsky, A.: Optimal design for linear models with correlated observations. Preprint, Ruhr-University, Bochum (2011)

Fedorov, V.V., Müller, W.G.: Optimum design for correlated processes via eigenvector expansions. In: Lopez-Fidalgo, J., Rodriguez-Diaz, J.M., Torsney, B. (eds.) mODa 8—Advances in Model-Oriented Design and Analysis. Contributions to Statistics, pp. 57–66. Physica-Verlag, Heidelberg (2007)

Harman, R., Štulajter, F.: Optimal prediction designs in finite discrete spectrum linear regression models. Metrika **72**, 281–294 (2010)

Kiseľák, J., Stehlík, M.: Equidistant and *D*-optimal designs for parameters of Ornstein-Uhlenbeck process. Stat. Probab. Lett. **78**, 1388–1396 (2008)

Müller, W.G.: Collecting Spatial Data, 2nd edn. Physica-Verlag, Heidelberg (2000)

Müller, W.G.: A comparison of spatial design methods for correlated observations. Environmetrics **16**, 495–505 (2005)

Müller, W.G., Pázman, A.: An algorithm for the computation of optimum designs under a given covariance structure. Comput. Stat. **14**, 197–211 (1999)

Müller, W.G., Pázman, A.: Measures for designs in experiments with correlated errors. Biometrika **90**, 423–434 (2003)

Näther, W.: Effective Observation of Random Fields. Teubner, Leipzig (1985)

Pázman, A.: Information contained in design points of experiments with correlated observations. Kybernetika **46**, 771–783 (2010)

Sacks, J., Ylvisaker, N.D.: Designs for regression problems with correlated errors. Ann. Math. Stat. **37**, 66–89 (1966)

Sacks, J., Ylvisaker, N.D.: Designs for regression problems with correlated errors; many parameters. Ann. Math. Stat. **39**, 49–69 (1968)
Uciński, D., Atkinson, A.C.: Experimental design of time-dependent models with correlated observations. Stud. Nonlinear Dyn. Econom. **8**, 13 (2004)
Zhigljavsky, A., Dette, H., Pepelyshev, A.: A new approach to optimal design for linear models with correlated observations. J. Am. Stat. Assoc. **105**, 1093–1103 (2010)

# Optimal Designs for the Prediction of Individual Effects in Random Coefficient Regression

**Maryna Prus and Rainer Schwabe**

**Abstract** In this note we propose optimal designs for (i) the prediction of the individual responses as well as for (ii) the individual deviations from the population mean response in random coefficient models. If the mean population parameters are unknown, which is typically the case, the mean squared errors for (i) and (ii) do not coincide and the design optimization leads to substantially different results. For simplicity, we consider the case where all individuals are treated in the same way. If the population parameters were known, Bayesian optimal designs would be optimal (Gladitz and Pilz in Statistics 13:371–385, 1982). While the optimal design for the prediction of the individual responses differ from the Bayesian optimal design proposed in the literature (see Prus and Schwabe in Optimal Design of Experiments—Theory and Application: Proceedings of the International Conference in Honor of the Late Jagdish Srivastava, 2011), the latter designs remain optimal if only the individual deviations from the mean response are of interest.

## 1 Introduction

Random coefficient regression models, which incorporate variations between individuals, are becoming more and more popular in many fields of application, especially in biosciences. The problem of optimal designs for estimation of the mean population parameters in these models has been widely considered and many theoretical and practical solutions are available in the literature. More recently, prediction of the individual response as well as of the individual deviations from the population mean response has attracted greater interest in order, for example, to create individualized medication and individualized medical diagnostics or to provide information for individual selection in animal breeding. The frequently applied theory developed by Gladitz and Pilz (1982) requires prior knowledge of the population

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parameters and can be useful when pilot experiments are available. In this note we consider the practically more relevant situation where the population parameters are unknown.

The paper is organized as follows: In Sect. 2 the model is specified and the prediction of individual effects is introduced. Section 3 provides some theoretical results for the determination of optimal designs, which are illustrated in Sect. 4 by a simple example. The final section contains some discussion and presents conclusions.

## 2 Model Specification and Prediction

In the general case of random coefficient regression models the observations are assumed to result from a hierarchical (linear) model. At the individual level the $j$th observation of individual $i$ is given by

$$Y_{ij} = \mathbf{f}(x_{ij})^\top \boldsymbol{\beta}_i + \varepsilon_{ij}, \quad x_{ij} \in \mathscr{X}, j = 1, \ldots, m_i, i = 1, \ldots, n, \tag{1}$$

where $n$ denotes the number of individuals, $m_i$ is the number of observations on individual $i$, $\mathbf{f} = (f_1, \ldots, f_p)^\top$ is the vector of known regression functions, and $\boldsymbol{\beta}_i = (\beta_{i1}, \ldots, \beta_{ip})^\top$ is the individual parameter vector specifying the individual response. The experimental settings $x_{ij}$ may be chosen from a given experimental region $\mathscr{X}$. Within an individual the observations are assumed to be uncorrelated given the individual parameters. The observational errors $\varepsilon_{ij}$ have zero mean, $\mathrm{E}(\varepsilon_{ij}) = 0$, and are homoscedastic with common variance $\mathrm{Var}(\varepsilon_{ij}) = \sigma^2$.

At the population level the individual parameters $\boldsymbol{\beta}_i$ are assumed to have an unknown population mean $\mathrm{E}(\boldsymbol{\beta}_i) = \boldsymbol{\beta}$ and a given covariance matrix $\mathrm{Cov}(\boldsymbol{\beta}_i) = \sigma^2\mathbf{D}$. All individual parameters and all observational errors are assumed to be uncorrelated.

The model can be alternatively represented in the following form:

$$Y_{ij} = \mathbf{f}(x_j)^\top \boldsymbol{\beta} + \mathbf{f}(x_j)^\top \mathbf{b}_i + \varepsilon_{ij} \tag{2}$$

by separation of the random individual deviations $\mathbf{b}_i = \boldsymbol{\beta}_i - \boldsymbol{\beta}$ from the mean response $\boldsymbol{\beta}$. Here these individual deviations $\mathbf{b}_i$ have zero mean $\mathrm{E}(\mathbf{b}_i) = 0$ and the same covariance matrix $\mathrm{Cov}(\mathbf{b}_i) = \sigma^2\mathbf{D}$ as the individual parameters.

We consider the particular case where the number of observations as well as the experimental settings are the same for all individuals ($m_i = m$ and $x_{ij} = x_j$). Moreover, for simplicity, we assume that the covariance matrix $\mathbf{D}$ is regular. The singular case is briefly addressed in the discussion.

In the following we investigate both the predictors of the individual parameters $\boldsymbol{\beta}_1, \ldots, \boldsymbol{\beta}_n$ and of the individual deviations $\mathbf{b}_1, \ldots, \mathbf{b}_n$. These predictors are also sometimes called estimators of the random parameters or deviations, respectively. In particular, the prediction of $\boldsymbol{\beta}_i$ can be viewed as an empirical Bayes estimation problem.

As shown by Prus and Schwabe (2011), the best linear unbiased predictor $\hat{\boldsymbol{\beta}}_i$ of the individual parameter $\boldsymbol{\beta}_i$ is a weighted average of the individualized estimate $\hat{\boldsymbol{\beta}}_{i;\mathrm{ind}} = (\mathbf{F}^\top\mathbf{F})^{-1}\mathbf{F}^\top\mathbf{Y}_i$, based on the observations at individual $i$, and the estimator of the population mean $\hat{\boldsymbol{\beta}} = (\mathbf{F}^\top\mathbf{F})^{-1}\mathbf{F}^\top\bar{\mathbf{Y}}$,

$$\hat{\boldsymbol{\beta}}_i = \mathbf{D}\big(\big(\mathbf{F}^\top\mathbf{F}\big)^{-1} + \mathbf{D}\big)^{-1}\hat{\boldsymbol{\beta}}_{i;\mathrm{ind}} + \big(\mathbf{F}^\top\mathbf{F}\big)^{-1}\big(\big(\mathbf{F}^\top\mathbf{F}\big)^{-1} + \mathbf{D}\big)^{-1}\hat{\boldsymbol{\beta}}. \tag{3}$$

Here $\mathbf{F} = (\mathbf{f}(x_1), \ldots, \mathbf{f}(x_m))^\top$ denotes the individual design matrix, which is equal for all individuals, $\mathbf{Y}_i = (\mathbf{Y}_{i1}, \ldots, \mathbf{Y}_{im})^\top$ is the observation vector for individual $i$, and $\bar{\mathbf{Y}} = \frac{1}{n}\sum_{i=1}^n \mathbf{Y}_i$ is the average response across all individuals.

It is worthwhile mentioning that the estimator of the population mean may be represented as the average $\hat{\boldsymbol{\beta}} = \frac{1}{n}\sum_{i=1}^n \hat{\boldsymbol{\beta}}_{i;\mathrm{ind}}$ of the individualized estimates and hence does not require the knowledge of the dispersion matrix $\mathbf{D}$, whereas the predictor of the individual parameter $\boldsymbol{\beta}_i$ does.

The performance of the prediction (3) may be measured in terms of the mean squared error matrix of $(\hat{\boldsymbol{\beta}}_1^\top, \ldots, \hat{\boldsymbol{\beta}}_n^\top)^\top$. Using results of Henderson (1975) it can be shown that this mean squared error matrix is a weighted average of the corresponding covariance matrix in the fixed effects model and the Bayesian one,

$$\mathrm{MSE}_\beta = \sigma^2\left(\left(\mathbf{I}_n - \frac{1}{n}\mathbf{1}_n\mathbf{1}_n^\top\right) \otimes \big(\mathbf{F}^\top\mathbf{F} + \mathbf{D}^{-1}\big)^{-1} + \left(\frac{1}{n}\mathbf{1}_n\mathbf{1}_n^\top\right) \otimes \big(\mathbf{F}^\top\mathbf{F}\big)^{-1}\right), \tag{4}$$

where $\mathbf{I}_n$ is the $n \times n$ identity matrix, $\mathbf{1}_n$ is an $n$-dimensional vector of ones and "$\otimes$" as usual denotes the Kronecker product of matrices. Note that this representation differs from that given by Fedorov and Hackl (1997, Sect. 5.2).

Similarly, the best linear unbiased predictor $\hat{\mathbf{b}}_i = \hat{\boldsymbol{\beta}}_i - \hat{\boldsymbol{\beta}}$ of the individual deviation $\mathbf{b}_i$ can be alternatively represented as a scaled difference

$$\hat{\mathbf{b}}_i = \mathbf{D}\big(\big(\mathbf{F}^\top\mathbf{F}\big)^{-1} + \mathbf{D}\big)^{-1}(\hat{\boldsymbol{\beta}}_{i;\mathrm{ind}} - \hat{\boldsymbol{\beta}}) \tag{5}$$

of the individualized estimate $\hat{\boldsymbol{\beta}}_{i;\mathrm{ind}}$ from the estimated population mean $\hat{\boldsymbol{\beta}}$. The corresponding mean squared error matrix of the prediction of individual deviations $(\hat{\mathbf{b}}_1^\top, \ldots, \hat{\mathbf{b}}_n^\top)^\top$ can be written as a weighted average of the covariance matrix of the prediction in the Bayesian model and the dispersion matrix $\mathbf{D}$ of the individual effects

$$\mathrm{MSE}_b = \sigma^2\left(\left(\mathbf{I}_n - \frac{1}{n}\mathbf{1}_n\mathbf{1}_n^\top\right) \otimes \big(\mathbf{F}^\top\mathbf{F} + \mathbf{D}^{-1}\big)^{-1} + \left(\frac{1}{n}\mathbf{1}_n\mathbf{1}_n^\top\right) \otimes \mathbf{D}\right). \tag{6}$$

Note that in the case of a known population mean $\boldsymbol{\beta}$, which was considered by Gladitz and Pilz (1982), the mean squared error matrix for the prediction of individual parameters coincides with that for the prediction of individual deviations and equals $\sigma^2\,\mathbf{I}_n \otimes (\mathbf{F}^\top\mathbf{F} + \mathbf{D}^{-1})^{-1}$.

## 3 Optimal Design

The mean squared error matrix of a prediction depends crucially on the choice of the observational settings $x_1, \ldots, x_m$, which can be chosen by the experimenter to minimize the mean squared error matrix and which constitute an exact design. Typically the optimal settings will not necessarily all be distinct. Then a design

$$\xi = \begin{pmatrix} x_1, \ldots, x_k \\ w_1, \ldots, w_k \end{pmatrix} \tag{7}$$

can be specified by its distinct settings $x_1, \ldots, x_k$, $k \leq m$, say, and the corresponding numbers of replications $m_1, \ldots, m_k$ or the corresponding proportions $w_j = m_j/m$.

For analytical purposes we make use of approximate designs in the sense of Kiefer (see, e.g., Kiefer 1974) for which the integer condition on $mw_j$ is dropped and the weights $w_j \geq 0$ may be any real numbers satisfying $\sum_{j=1}^{k} m_j = m$. For these approximate designs the standardized information matrix for the model without individual effects ($\boldsymbol{\beta}_i \equiv \boldsymbol{\beta}$, i.e. $\mathbf{D} = \mathbf{0}$) is defined as

$$\mathbf{M}(\xi) = \sum_{j=1}^{k} w_j \mathbf{f}(x_j)\mathbf{f}(x_j)^\top = \frac{1}{m}\mathbf{F}^\top\mathbf{F}. \tag{8}$$

Further, for notational convenience, we introduce the standardized covariance matrix of the random effects $\boldsymbol{\Delta} = m\mathbf{D}$. With this notation we may define the standardized mean squared error matrices as

$$\mathrm{MSE}_\beta(\xi) = \left(\mathbf{I}_n - \frac{1}{n}\mathbf{1}_n\mathbf{1}_n^\top\right) \otimes \left(\mathbf{M}(\xi) + \boldsymbol{\Delta}^{-1}\right)^{-1} + \left(\frac{1}{n}\mathbf{1}_n\mathbf{1}_n^\top\right) \otimes \mathbf{M}(\xi)^{-1} \tag{9}$$

for the prediction of the individual parameters and

$$\mathrm{MSE}_b(\xi) = \left(\mathbf{I}_n - \frac{1}{n}\mathbf{1}_n\mathbf{1}_n^\top\right) \otimes \left(\mathbf{M}(\xi) + \boldsymbol{\Delta}^{-1}\right)^{-1} + \left(\frac{1}{n}\mathbf{1}_n\mathbf{1}_n^\top\right) \otimes \boldsymbol{\Delta} \tag{10}$$

for the prediction of the individual deviations. For any exact design $\xi$ all $mw_j$ are integers. Then the matrices $\mathrm{MSE}_\beta(\xi)$ and $\mathrm{MSE}_b(\xi)$ coincide with the mean squared error matrices (4) and (6), respectively, up to a multiplicative factor $\sigma^2/m$.

In this paper we focus on the criterion of integrated mean squared error (IMSE) of prediction, which is defined as

$$\mathrm{IMSE}_\beta = \int_{\mathscr{X}} \mathrm{E}\left[\sum_{i=1}^{n} \left(\hat{\mu}_i(x) - \mu_i(x)\right)^2\right] \nu(\mathrm{d}x) \tag{11}$$

for individual parameters, where $\hat{\mu}_i(x) = \mathbf{f}(x)^\top\hat{\boldsymbol{\beta}}_i$ and $\mu_i(x) = \mathbf{f}(x)^\top\boldsymbol{\beta}_i$ respectively denote the predicted and true individual response and the integration is with respect to a given weight distribution $\nu$ (typically uniform) on the design region $\mathscr{X}$.

Using (9), the standardized IMSE-criterion $\Phi_\beta = \frac{m}{\sigma^2}\mathrm{IMSE}_\beta$ can be represented as

$$\Phi_\beta(\xi) = (n-1)\,\mathrm{tr}\left[\left(\mathbf{M}(\xi) + \boldsymbol{\Delta}^{-1}\right)^{-1}\mathbf{V}\right] + \mathrm{tr}\left[\mathbf{M}(\xi)^{-1}\mathbf{V}\right], \tag{12}$$

which is a weighted sum of the IMSE-criterion in the fixed effects model and the Bayesian IMSE-criterion, where $\mathbf{V} = \int_{\mathscr{X}} \mathbf{f}(x)\mathbf{f}(x)^\top \nu(\mathrm{d}x)$ is the "information" of the weight distribution $\nu$ and "tr" denotes the trace of a matrix.

With the general equivalence theorem (see, e.g., Silvey 1980) we may obtain the following characterization of an optimal design.

**Theorem 1** *The approximate design $\xi^*$ is IMSE-optimal for the prediction of individual parameters if and only if*

$$\begin{aligned}&\mathbf{f}(x)^\top\left[(n-1)\left(\mathbf{M}\left(\xi^*\right) + \boldsymbol{\Delta}^{-1}\right)^{-1}\mathbf{V}\left(\mathbf{M}\left(\xi^*\right) + \boldsymbol{\Delta}^{-1}\right)^{-1} + \mathbf{M}\left(\xi^*\right)^{-1}\mathbf{V}\mathbf{M}\left(\xi^*\right)^{-1}\right]\mathbf{f}(x)\\ &\quad\le \mathrm{tr}\left[\left((n-1)\left(\mathbf{M}\left(\xi^*\right) + \boldsymbol{\Delta}^{-1}\right)^{-1}\mathbf{M}\left(\xi^*\right)\left(\mathbf{M}\left(\xi^*\right) + \boldsymbol{\Delta}^{-1}\right)^{-1} + \mathbf{M}\left(\xi^*\right)^{-1}\right)\mathbf{V}\right]\end{aligned} \tag{13}$$

*for all $x \in \mathscr{X}$.*

*For any experimental setting $x_j$ of $\xi^*$ with $w_j > 0$ equality holds in (13).*

The IMSE-criterion of prediction for the individual deviations is given by

$$\mathrm{IMSE}_b(\xi) = \int_{\mathscr{X}} \mathrm{E}\left[\sum_{i=1}^{n}\left(\hat{\mu}_i^b(x) - \mu_i^b(x)\right)^2\right]\nu(\mathrm{d}x), \tag{14}$$

where $\hat{\mu}_i^b(x) = \mathbf{f}(x)^\top\hat{\mathbf{b}}_i$ and $\mu_i^b(x) = \mathbf{f}(x)^\top\mathbf{b}_i$ denote the predicted and the true individual response deviation from the population mean, respectively. Using (10), the standardized IMSE-criterion $\Phi_b = \frac{m}{\sigma^2}\mathrm{IMSE}_b$ can be written as

$$\Phi_b(\xi) = (n-1)\,\mathrm{tr}\left[\left(\mathbf{M}(\xi) + \boldsymbol{\Delta}^{-1}\right)^{-1}\mathbf{V}\right] + \mathrm{tr}\left[\boldsymbol{\Delta}\mathbf{V}\right]. \tag{15}$$

The first term in (15) coincides with the criterion function of the Bayesian IMSE-criterion and the second term is constant. Hence, Bayesian IMSE-optimal designs are also IMSE-optimal for the prediction of individual deviations. The characterization of IMSE-optimal designs is given by the corresponding equivalence theorem for Bayes optimality.

**Theorem 2** *The approximate design $\xi^*$ is IMSE-optimal for the prediction of individual deviations if and only if*

$$\begin{aligned}&\mathbf{f}(x)^\top\left(\mathbf{M}\left(\xi^*\right) + \boldsymbol{\Delta}^{-1}\right)^{-1}\mathbf{V}\left(\mathbf{M}\left(\xi^*\right) + \boldsymbol{\Delta}^{-1}\right)^{-1}\mathbf{f}(x)\\ &\quad\le \mathrm{tr}\left[\left(\mathbf{M}\left(\xi^*\right) + \boldsymbol{\Delta}^{-1}\right)^{-1}\mathbf{M}\left(\xi^*\right)\left(\mathbf{M}\left(\xi^*\right) + \boldsymbol{\Delta}^{-1}\right)^{-1}\mathbf{V}\right]\end{aligned} \tag{16}$$

*for all $x \in \mathscr{X}$.*

*For any experimental setting $x_j$ of $\xi^*$ with $w_j > 0$ equality holds in (16).*

## 4 Example

To illustrate our results, we consider the model $Y_{ij} = \beta_{i1} + \beta_{i2} x_j + \varepsilon_{ij}$ of a straight line regression on the experimental region $\mathscr{X} = [0, 1]$, where the settings $x_j$ can be interpreted as time or dosage. We assume uncorrelated components such that the covariance matrix $\mathbf{D} = \operatorname{diag}(d_1, d_2)$ of the random effects is diagonal with entries $d_1$ and $d_2$ for the variance of the intercept and slope, respectively. To exhibit the differences in the design criteria, the variance of the intercept is assumed to be small, $d_1 < 1/m$.

According to Theorems 1 and 2, the IMSE-optimal designs only take observations at the endpoints $x = 0$ and $x = 1$ of the design region, as the sensitivity functions, given by the left-hand sides of inequalities (13) and (16), are polynomials of degree 2 in $x$. Hence, the optimal design $\xi^*$ is of the form

$$\xi_w = \begin{pmatrix} 0 & 1 \\ 1-w & w \end{pmatrix}, \tag{17}$$

and only the optimal weight $w^*$ has to be determined. For designs $\xi_w$ the criteria (12) and (15) are evaluated with $\delta_k = m\, d_k$ to get

$$\Phi_\beta(\xi_w) = \frac{1}{3}\left( \frac{(n-1)(3\delta_1 + \delta_2 + \delta_1\delta_2)}{(\delta_1+1)(w\delta_2+1) - w^2\delta_1\delta_2} + \frac{1}{w(1-w)} \right), \tag{18}$$

$$\Phi_b(\xi_w) = \frac{1}{3}\left( \frac{(n-1)(3\delta_1 + \delta_2 + \delta_1\delta_2)}{(\delta_1+1)(w\delta_2+1) - w^2\delta_1\delta_2} + 3\delta_1 + \delta_2 \right). \tag{19}$$

To obtain numerical results, the number of individuals and the number of observations at each individual are fixed as $n = 100$ and $m = 10$. For the variance $d_1$ of the intercept we use the value 0.001. Figure 1 illustrates the dependence of the optimal weight $w^*$ on the rescaled variance parameter $\rho = d_2/(1 + d_2)$, which in a way mimics the intraclass correlation and has the advantage of being bounded, so that the whole range of slope variances $d_2$ can be shown. The optimal weight for the prediction of individual parameters increases with the slope variance $d_2$ from 0.5 for $d_2 \to 0$ to about 0.91 for $d_2 \to \infty$. For $d_1 < 1/m$ the Bayesian optimal design, which is also optimal for the prediction of individual deviations, has optimal weight $w^* = 1$ for all positive values of $d_2$ and is thus singular.

In Fig. 2 the efficiencies $\operatorname{eff}(\xi) = \Phi(\xi_{w^*})/\Phi(\xi)$ are plotted for the optimal design $\xi_{0.5}$ in the fixed effects model without individual effects and for the naive equidistant design $\bar{\xi}$, which assigns weights $1/m$ to $m$ settings $x_j = (j-1)/(m-1)$. For the prediction of individual parameters the efficiency of the design $\xi_{0.5}$ decreases from 1 for $d_2 \to 0$ to approximately 0.60 for $d_2 \to \infty$, whereas $\bar{\xi}$ shows an overall lower performance going down to 0.42 for large $d_2$.

For the prediction of individual deviations the efficiency of both designs reveals a bathtub shaped behavior with limiting efficiency of 1 for $d_2 \to 0$ or $d_2 \to \infty$. This is due to the fact that all regular designs are equally good for small $d_2$ and equally bad for large $d_2$, since the criterion function (15) behaves like $\operatorname{tr}(\boldsymbol{\Delta}\mathbf{V})$ for $d_2 \to \infty$ independently of $\xi$. The minimal efficiencies are 0.57 for $\xi_{0.5}$ and 0.43 for $\bar{\xi}$.

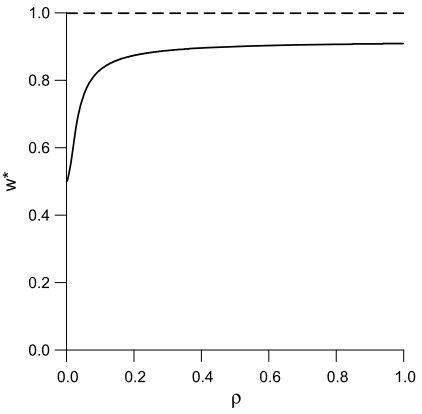


**Fig. 1** Optimal weights $w^*$ for the prediction of individual parameters (*solid line*) and for the prediction of individual deviations (*dashed line*) as functions of $\rho = d_2/(1 + d_2)$

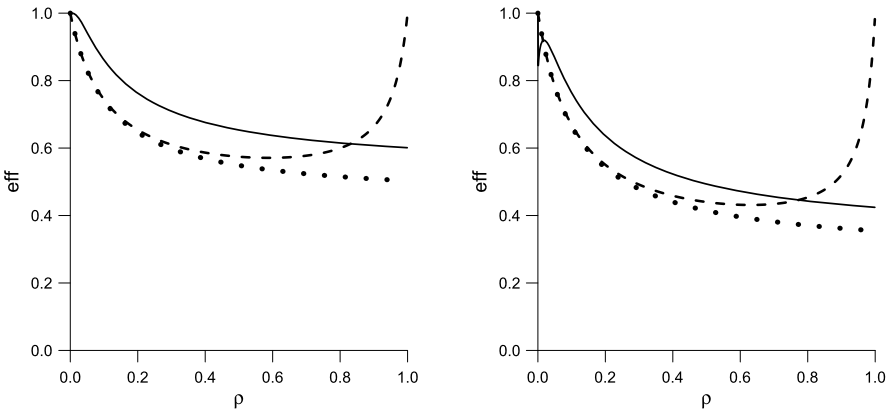


**Fig. 2** Efficiency of $\xi_{0.5}$ (*left panel*) and $\bar{\xi}$ (*right panel*) for the prediction of individual parameters (*solid line*), individual deviations (*dashed line*) and for the Bayesian IMSE-criterion (*dotted line*) as functions of $\rho = d_2/(1 + d_2)$

It is worthwhile mentioning that, although the design optimization seems to be the same for the prediction of the deviations and for the Bayesian criterion, the corresponding efficiencies may differ. For the sake of completeness these are also plotted in Fig. 2. This difference is due to the second (constant) term in (15), which is added to the Bayesian criterion.

It should also be noted that the present efficiencies cannot be interpreted as savings or additional needs in terms of sample sizes as in fixed effect models.

## 5 Discussion and Conclusions

We have pointed out similarities and differences between the mean squared error, the IMSE-criterion and the corresponding optimal designs for the prediction of individ-

ual responses and individual deviations compared with that for Bayesian estimation. The IMSE-criterion is seen to be a weighted average of its Bayesian and standard counterparts in the case of prediction of individual parameters and hence it defines a compound criterion. For the prediction of individual deviations, Bayesian optimal designs retain optimality but the criteria differ by an additive constant.

A generalization of the present results to singular dispersion matrices $\mathbf{D}$ is straightforward, although there is no Bayesian counterpart in that case and the formulae become less appealing. Such singular dispersion matrices occur naturally if only parts of the parameter vector are random and some linear combinations are constant across the population. In particular, in the case of a random intercept model, when all other parameters are fixed, an optimal design for the prediction of the individual response curves can be obtained as the optimal one in the corresponding model without individual effects (Prus and Schwabe 2011), while for prediction of the individual deviations any design will be optimal.

The method proposed can be directly extended to other linear design criteria as well as to the class of $\Phi_q$-criteria based on the eigenvalues of the mean squared error matrix. The design optimality presented here is formulated for approximate designs, which in general cannot be exactly realized. However, these optimal approximate designs can serve as a benchmark for candidate exact designs, obtained for instance by appropriate rounding of the optimal weights. Constructions, which allow different individual designs, will be a subject of future research. In particular, the case of sparse sampling where the number of observations per individual is less than the number of parameters is going to be investigated.

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## References

Fedorov, V., Hackl, P.: Model-Oriented Design of Experiments. Springer, New York (1997)

Gladitz, J., Pilz, J.: Construction of optimal designs in random coefficient regression models. Statistics **13**, 371–385 (1982)

Henderson, C.R.: Best linear unbiased estimation and prediction under a selection model. Biometrics **31**, 423–477 (1975)

Kiefer, J.: General equivalence theory for optimum designs (approximate theory). Ann. Stat. **2**, 849–879 (1974)

Prus, M., Schwabe, R.: Optimal designs for individual prediction in random coefficient regression models. In: Melas, V., Nachtmann, G., Rasch, D. (eds.) Optimal Design of Experiments—Theory and Application: Proceedings of the International Conference in Honor of the Late Jagdish Srivastava, pp. 122–129. Center of Experimental Design, University of Natural Resources and Life Sciences, Vienna (2011)

Silvey, S.D.: Optimal Design. Chapman & Hall, London (1980)

# D-Optimum Input Signals for Systems with Spatio-Temporal Dynamics

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**Abstract** Our aim is to provide optimality conditions for D-optimum input signal design in linear systems described by partial differential equations. They are derived using the variational approach. We also reveal the space-time structure of optimal input signals. As a by-product, we derive optimality conditions for input signals in systems described by ordinary differential equations.

## 1 Introduction

The old paradigms concerning parameter estimation of systems described by partial differential equations (PDEs) assumed that input signals can act at a finite number of spatial points only and that one can observe system states at another finite set of spatial points. They have become obsolete in recent years, since industrial and infra-red cameras, MRI and CT provide information which can be considered as observations that are continuous in space. High energy lasers, acting as moving sources, microwave heating and shape changing materials (e.g., piezo-electric bonds) can be modelled as spatially distributed sources. For these reasons, we consider the problem of selecting spatio-temporal input signals for parameter estimation in PDEs from observations that are available at each point of a spatial domain. Even if we are not able to provide observations and actuation at each spatial point, our results provide a lower bound for the attainable estimation accuracy.

The related problem of sensor allocation has received much attention (Rafajłowicz 1978, 1981) including results on moving sensor trajectories (Uciński 2005; Patan 2012). Results on topics similar to those considered here can be found in Rafajłowicz (1983, 2011), where mainly frequency-domain synthesis is discussed. Partial results on the time-domain synthesis can be found in Rafajłowicz (1989) and Rafajłowicz and Skubalska-Rafajłowicz (2011). In this paper we provide results that

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differ from those above since we obtain the optimality conditions directly, using the variational approach. As a result, we provide a simple algorithm for input signal design when one parameter is estimated.

## 2 Problem Statement

Denote by $q(x,t)$ the system state[1] at time $t$ and at spatial point $x \in \Omega \subset \mathbb{R}^d$, where $\Omega$ is a bounded and open spatial domain with smooth boundary $\Gamma$. Consider the following class of PDEs:

$$\kappa \ddot{q}(x,t) + \mu \dot{q}(x,t) = A_x(\bar{a})\, q(x,t) + U(x,t), \quad x \in \Omega, \tag{1}$$

where $\dot{q}(x,t) = \partial q(x,t)/\partial t$, $A_x(\bar{a})$ is an elliptic operator that depends on a vector of unknown[2] constant parameters. When $\kappa = 1$, we have a hyperbolic PDE. For $\kappa = 0$, (1) is parabolic. The boundary conditions for (1) on $\Gamma$ are included in the definition of $A_x(\bar{a})$. We assume zero initial conditions $q(x,\,0) = 0$, $x \in \Omega$ and, additionally, $\dot{q}(x,0) = 0$, if the term $\ddot{q}(x,t)$ is present. $U(x,t)$ is an input signal. Observations for estimating $\bar{a}$ are made over the interval $(0,\,T]$ and have the form $Y(x,t) = q(x,t;\bar{a}) + \varepsilon(x,t)$, $x \in \Omega$, $t \in [0,\,T]$, where $\varepsilon(x,t)$ is a spatiotemporal white noise process with unit variance. The Fisher information matrix (FIM) is given by

$$\mathbb{M}_T(U) = \int_\Omega \int_0^T \nabla_a q(x,t;\bar{a})\, \nabla_a^\top q(x,t;\bar{a})\, \mathrm{d}t\, \mathrm{d}x.$$

Our main problem is to find a D-optimal control with constrained energy, i.e.,

$$U^* = \arg\min_U \det\left[\mathbb{M}_T^{-1}(U)\right] \quad \text{subject to} \quad \int_\Omega \int_0^T U^2(x,t)\, \mathrm{d}t\, \mathrm{d}x \le 1, \tag{2}$$

where the admissible $U$ are elements of the space of continuous functions $C\{(\Omega \cup \Gamma) \times [0,\,T]\}$ that are also square integrable. The problem of the existence of optimal solutions is solved in Sect. 3 for a wide class of PDEs.

## 3 Auxiliary Problem: Optimal Input Signal for ODE Parameter Estimation

**Formulation** Consider the system described by the Ordinary Differential Equation (ODE)

$$\frac{\mathrm{d}^r y(t)}{\mathrm{d}t^r} + a_{r-1} \frac{\mathrm{d}^{r-1} y(t)}{\mathrm{d}t^{r-1}} + \cdots + a_0\, y(t) = a_r\, u(t), \quad t \in (0,\,T], \tag{3}$$

[1] We shall also write $q(x,t;\bar{a})$ to indicate its dependence on unknown parameters $\bar{a}$.

[2] Here we treat $\mu$ as a known parameter, but it can also be included as an unknown parameter.

with zero initial conditions, where $y(t)$ is the output and $u(t)$ is the input signal. The solution $y(t;\,\bar{a})$ of (3) depends on the vector $\bar{a} = [a_0,\, a_1, \ldots,\, a_r]^\top$ of unknown parameters. The observations have the form $\Upsilon(t) = y(t;\,\bar{a}) + \varepsilon(t)$, $t \in [0,\, T]$, where $\varepsilon(t)$ is zero-mean and uncorrelated Gaussian white noise.

It can be shown (Goodwin and Payne 1977), that the FIM $\mathbf{M}_T(u)$ for estimating $\bar{a}$ has the form $\mathbf{M}_T(u) = \int_0^T \nabla_a y(t;\bar{a})\,[\nabla_a y(t;\bar{a})]^\top \,\mathrm{d}t$, where $\nabla_a y(t;\bar{a})$ depends on $u(\cdot)$ through (3). Define $\mathscr{U}_0 = \{u : \int_0^T u^2(t)\,\mathrm{d}t \le 1,\ \det[\mathbf{M}_T(u)] > 0\}$. Our auxiliary problem is to find $u^* \in \mathscr{U}_0 \cap C[0,\, T]$ for which $\min_{u\in\mathscr{U}_0} \det[\mathbf{M}_T^{-1}(u)]$ is attained, where $C[0,\, T]$ is the space of continuous functions in the closed interval $[0,\, T]$. The linearity of (3) implies $\mathbf{M}_T(u) = \int_0^T \int_0^T H(\tau,\, \nu;\, \bar{a})\, u(\tau)\, u(\nu)\,\mathrm{d}\tau\,\mathrm{d}\nu$, where $H(\tau,\, \nu;\, \bar{a}) \stackrel{\text{def}}{=} \int_0^T \bar{k}(t-\tau;\bar{a})\,\bar{k}^\top(t-\nu;\bar{a})\,\mathrm{d}t$, while the $r \times 1$ vector of sensitivities $\bar{k}(t;\bar{a}) \stackrel{\text{def}}{=} \nabla_a g(t;\bar{a})$ is defined through the impulse response of the ODE (3), denoted by $g(t;\bar{a})$. We have $g(t;\bar{a}) = 0$ for $t < 0$. In our problem, the existence of feedback is not explicitly allowed, but one can incorporate its presence by modifying the definition of $\bar{k}(t;\bar{a})$ as shown in Rafajłowicz and Rafajłowicz (2011).

**Gâteaux Differential** Note that $\mathbf{M}_T(\varsigma\, u) = \varsigma^2\, \mathbf{M}_T(u)$ for arbitrary $\varsigma \in \mathbb{R}$ and $\log[\det(\cdot)]$ is strictly convex. Hence, $\int_0^T (u^*)^2(t)\,\mathrm{d}t = 1$. For $\gamma \in \mathbb{R}$ being the Lagrange multiplier, define $L(u,\gamma) = \log[\det(\mathbf{M}_T(u))] - \gamma\,(\int_0^T u^2(t)\,\mathrm{d}t - 1)$. Let $u^* \in \mathscr{U}_0 \cap C[0,\, T]$ be a solution to the auxiliary problem and let $u_\varepsilon(t) = u(t) + \varepsilon\, f(t)$, where $f \in C[0,\, T]$ is arbitrary. Then, equating the Gâteaux differential of $L$ to zero we obtain

$$\left.\frac{\partial L(u_\varepsilon,\, \gamma)}{\partial\, \varepsilon}\right|_{\varepsilon=0} = 2 \int_0^T f(\nu)\left[\int_0^T \ker\big(\tau,\, \nu,\, u^*\big)\, u^*(\tau)\,\mathrm{d}\tau - \gamma\, u^*(\nu)\right]\mathrm{d}\nu = 0\,,$$

where, for $u \in \mathscr{U}_0$, we define the kernel $\ker(\tau,\, \nu,\, u) \stackrel{\text{def}}{=} \mathrm{trace}[\mathbf{M}_T^{-1}(u)\, H(\tau,\, \nu,\, \bar{a})]$. This condition holds for any $f \in C[0,\, T]$. Thus, the fundamental lemma of the calculus of variations implies that $u^*$ is an eigenfunction of the following integral operator:

$$\int_0^T \ker\big(\tau,\, \nu,\, u^*\big)\, u^*(\tau)\,\mathrm{d}\tau = \gamma\, u^*(\nu). \tag{4}$$

This equation is nonlinear with respect to $u^*$, but it is expedient to consider a family of associated linear eigenvalue problems. Specifically, for any fixed $u \in \mathscr{U}_0$, we seek eigenfunctions $\phi(\nu, u)$ and eigenvalues $\mu(u)$ that depend on a selected $u$ and satisfy

$$\int_0^T \ker(\tau,\, \nu,\, u)\, \phi(\nu, u)\,\mathrm{d}\nu = \mu(u)\, \phi(\tau, u). \tag{5}$$

The kernel $\ker(\tau,\, \nu,\, u)$ is symmetric and nonnegative definite. There exists a sequence of orthonormal eigenfunctions $\phi_k(\tau, u)$ and nonnegative eigenvalues $\mu_k(u)$, $k = 1, 2, \ldots$ for which (5) holds (Yosida 1981). From (4) we know that for

$k = 1, 2, \ldots$ we have $u^*(\tau) = \phi_k(\tau, u^*)$ and $\mu_k(u^*) = \gamma$. We note that $\|u^*\| = \int_0^T (u^*(\tau))^2 \, \mathrm{d}\tau = 1$. Multiplying both the sides of (4) by $u^*$ and integrating, we obtain $\gamma = (r+1) = \dim(\bar{a})$. Additionally, for any fixed $u \in \mathscr{U}_0$ such that $\|u\| = 1$,

$$r + 1 = \operatorname{trace}\left[\mathbf{M}_T^{-1}(u)\, \mathbf{M}_T(u)\right] = \int_0^T \int_0^T \ker(\tau, \nu, u)\, u(\tau)\, u(\nu)\, \mathrm{d}\tau\, \mathrm{d}\nu \le \mu_{\max}(u),$$

where $\mu_{\max}(u)$ denotes the largest eigenvalue among $\mu_k(u)$, $k = 1, 2, \ldots$. This implies that also $\inf_{u \in \mathscr{U}_0} \mu_{\max}(u) \ge (r+1)$ and we know that the infimum is attained for $u = u^*$, since for some $k$, $\mu_k(u^*) = \gamma = (r+1)$.

**Corollary 1** *If $u^* \in \mathscr{U}_0 \cap C[0, T]$ is a solution to the auxiliary problem, then* (i) $\gamma = \mu_{\max}(u^*) = (r+1)$ *and $u^*$ is the eigenfunction of* (4) *that corresponds to this eigenvalue, and* (ii) $\inf_{u \in \mathscr{U}_0} \max_{k=1,2,\ldots} \mu_k(u) = (r+1)$.

*Remark 1* The above conditions are necessary for the optimality of $u^*$. If $T < 2\sqrt{\gamma} - 1 = 2\sqrt{r+1} - 1$, then these conditions are also sufficient for the optimality of $u^*$. The proof is based on the second variation of $L(u, \gamma)$.

*Example 1* Consider the system $\ddot{y}(t) + 2\xi\, \dot{y}(t) + \omega_0^2\, y(t) = \omega_0\, u(t)$ with a known resonance frequency $\omega_0$ and estimated damping parameter $\xi$, $\dot{y}(0) = 0$, $y(0) = 0$. Its sensitivity has the form $k(t; \xi) = -t \exp(-\xi t) \sin(\omega_0 t)$, $t > 0$. The eigenfunction corresponding to the largest eigenvalue of $H(\tau, \nu; \xi)$ was calculated numerically and depicted in Fig. 1 (left) for $T = 2.5$ and grid step size 0.005.

## 4 Input Signals for Estimating Parameters in PDEs

**Assumptions** We need additional assumptions concerning the class of considered PDEs:

$$\kappa \ddot{q}(x,t) + \mu\, \dot{q}(x,t) = A_x(\bar{a})\, q(x,t) + U(x,t), \quad x \in \Omega, \tag{6}$$

which should be accompanied by boundary conditions that are included in the description of the domain of $A_x(\bar{a})$, denoted by $\mathscr{D}(A_x) \subset L^2(\Omega)$, where $L^2(\Omega)$ is the class of square-integrable functions with inner product $\langle f, g \rangle = \int_\Omega f(x)\, g(x)\, \mathrm{d}x$. We admit operators $A_x$ of the form

$$A_x(\bar{a})\, q(x,t) = \sum_{i=1}^{R} a_i\, P_x^{(i)}\, q(x,t),$$

where $P_x^{(i)}$, $i = 1, \ldots, R$ are differential operators with respect to spatial variables such that

(A1) $A_x$ is symmetric, i.e., $\forall f,\, g \in L_2(\Omega)$: $\langle A_x(\bar{a})\, f,\, g \rangle = \langle f,\, A_x(\bar{a})\, g \rangle$ and is positive definite, i.e., $\forall f, \in L_2(\Omega)\ f \neq 0 \Rightarrow \langle f,\, A_x(\bar{a})\, f \rangle > 0$.

(A2) The eigenfunctions $v_1(x), v_2(x), \ldots$ of $A_x(\bar{a})$ do not depend on $\bar{a}$ (it suffices that each $v_k$ is simultaneously the eigenfunction of all $P_x^{(i)}$). Then the eigenvalues $\lambda_k(\bar{a})$ of $A_x(\bar{a})$ are linear functions of $\bar{a}$, i.e., $\lambda_k(\bar{a}) = \bar{b}_k^\top \bar{a}$, $A_x(\bar{a})\, v_k = -\lambda_k(\bar{a})\, v_k$ for some known vectors $\bar{b}_k$, $k = 1, 2, \ldots$.

(A3) $v_k$, $k = 1, 2, \ldots$, form a complete orthonormal basis of $L_2(\Omega)$. If multiple eigenvalues appear, then the eigenfunctions having the same eigenvalue can be orthonormalized (Yosida 1981) and in all formulas below we assume that this was done.

**Partial Modal Decomposition** In order to characterize the solution, we express the solution of (6) as $q(x, t, \bar{a}) = \sum_{k=1}^{\infty} v_k(x)\, y_k(t, \bar{a})$, where the $y_k(t)$'s are the solutions of

$$\kappa\, \ddot{y}_k(t, \bar{a}) + \mu\, \dot{y}_k(t, \bar{a}) = -\lambda_k(\bar{a})\, y_k(t, \bar{a}) + \tilde{u}_k(t), \tag{7}$$

$\tilde{u}_k(t) \stackrel{\text{def}}{=} \int_\Omega U(x, t)\, v_k(x)\, \mathrm{d}x$, $\dot{y}_k(0) = y_k(0) = 0$. Thus, the eigenfunctions $v_k$'s of $A_x$ play the role of spatial modes. The completeness in $L_2(\Omega)$ and orthogonality of eigenfunctions $v_k$ allow us to reformulate our problem. Define $\tilde{u}_k(t) = \langle U(\cdot, t), v_k \rangle$. Then the constraint (2) reads as $\sum_{k=1}^{\infty} \int_0^T \tilde{u}_k^2(t)\, \mathrm{d}t \le 1$, while the FIM is $\mathbb{M}_T(U) = \sum_{k=1}^{\infty} \int_0^T \nabla_a y_k(t, \bar{a})\, \nabla_a^\top y_k(t, \bar{a})\, \mathrm{d}t$. Denote by $I_k(t, \bar{a})$ the impulse response of (7). Then $\nabla_a y_k(t, \bar{a}) = \int_0^T \nabla_a I_k(t - \tau, \bar{a})\, \tilde{u}_k(\tau)\, \mathrm{d}\tau$. Summarizing, the FIM can be expressed as

$$\mathbb{M}_T(U) = \sum_{k=1}^{\infty} \int_0^T \int_0^T H_k(\tau, \nu, \bar{a})\, \tilde{u}_k(\tau)\, \tilde{u}_k(\nu)\, \mathrm{d}\tau\, \mathrm{d}\nu, \tag{8}$$

where $H_k(\tau, \nu, \bar{a}) \stackrel{\text{def}}{=} \int_0^T \nabla_a I_k(t - \tau, \bar{a})\, \nabla_a^\top I_k(t - \nu, \bar{a})\, \mathrm{d}t$, $k = 1, 2, \ldots$. We can explore the structure of the FIM even further. Note that $\nabla_a I_k(t, \bar{a}) = \bar{b}_k\, \rho_k(t, \bar{a})$. Hence, $H_k(\tau, \nu, \bar{a}) = \bar{b}_k\, \bar{b}_k^\top\, c_k(\tau, \nu, \bar{a})$, where $c_k(\tau, \nu, \bar{a}) \stackrel{\text{def}}{=} \int_0^T \rho_k(t - \tau, \bar{a})\, \rho_k(t - \nu, \bar{a})\, \mathrm{d}t$, while for $\delta(t)$ denoting the Dirac delta we get

$$\ddot{I}_k(t, \bar{a}) + \mu\, \dot{I}_k(t, \bar{a}) = -\lambda_k(\bar{a})\, I_k(t, \bar{a}) + \delta(t),$$

$$\ddot{\rho}_k(t, \bar{a}) + \mu\, \dot{\rho}_k(t, \bar{a}) = -\lambda_k(\bar{a})\, \rho_k(t, \bar{a}) - I_k(t),$$

with zero initial conditions. Note that we cannot select one mode and optimize its input signal. The reason is that $H_k(\tau, \nu, \bar{a}) = \bar{b}_k\, \bar{b}_k^\top\, c_k(\tau, \nu, \bar{a})$ is a rank-one matrix.

**Proposition 1** *The necessary condition for $M_T(U)$ to be nonsingular is that at least $R$ of $\tilde{u}_k(t) = \langle U(\cdot, t), v_k \rangle \neq 0$ on subintervals of $(0, T)$ having nonzero lengths.*

Thus, we are forced to consider (8) as a whole. However, we can partition the energy of input signals among modes and select their excitations. To this end, define $u_k(t) = \tilde{u}_k(t)/\sqrt{\alpha_k}$, where $\alpha_k = \|\tilde{u}_k\|^2$.

**Proposition 2** *Under* (A1)–(A3), *the problem* (1)–(2) *is equivalent to finding* $\alpha_k > 0$, $\sum_{k=1}^{\infty} \alpha_k \le 1$ *and* $u_k(t)$, $k = 1, 2, \ldots$, *which maximize the determinant of*

$$M_T(U) = \sum_{k=1}^{\infty} \int_0^T \int_0^T \alpha_k \, H_k(\tau, \nu, \bar{a}) \, u_k(\tau) \, u_k(\nu) \, \mathrm{d}\tau \, \mathrm{d}\nu, \quad \|u_k(\cdot)\|^2 = 1.$$

*Denote by* $\alpha_k^*$ *and* $u_k^*$, $k = 1, 2, \ldots$, *the solution of the above problem. Then the solution of problem* (2) *can be expressed as*

$$U^*(x, t) = \sum_{k=1}^{\infty} \sqrt{\alpha_k^*} \, v_k(x) \, u_k^*(t). \tag{9}$$

Note that $\log\{\det[M_T(U)]\}$ is convex with respect to the $\alpha_k$'s. Our aim is to provide conditions for the optimality of $\alpha_k^*$ and $u_k^*$, $k = 1, 2, \ldots$. Assume that $U^*$ is an optimal solution and $U_\varepsilon(x, t) = U^*(x, t) + \varepsilon \, u(t) \, v_j(x)$ for some $j = 1, 2, \ldots$ and $u \in C[0, T]$. Define $\mathscr{L}(U, \bar{\gamma}) = \log\{\det[M_T(U)]\} - \sum_{k=1}^{\infty} \alpha_k \gamma_k \, (\|u_k(\cdot)\|^2 - 1)$. Then

$$\left.\frac{\partial \mathscr{L}(U_\varepsilon, \bar{\gamma})}{\partial \varepsilon}\right|_{\varepsilon=0} = 2\alpha_j^* \int_0^T u(\nu) \left[ \int_0^T \ker_j\big(\tau, \nu, U^*\big) \, u_j^*(\tau) \, \mathrm{d}\tau - \gamma_j \, u_j^*(\nu) \right] \mathrm{d}\nu, \tag{10}$$

where $\alpha_j^* \, u_j^*(t) = \langle U^*(\cdot, t), v_j \rangle$,

$$\ker_j\big(\tau, \nu, u_j^*\big) \stackrel{\text{def}}{=} \operatorname{trace}\big[M_T^{-1}\big(U^*\big) \, H_j(\tau, \nu, \bar{a})\big] = \zeta_j\big(U^*, T\big) \, c_j(\tau, \nu, \bar{a}),$$

and $\zeta_j(U^*, T) \stackrel{\text{def}}{=} \bar{b}_j^\top \, M_T^{-1}(U^*) \, \bar{b}_j$. The expression in (10) is zero for every $u \in C[0, T]$ and for every $j = 1, 2, \ldots$. Hence, if $U^*$ is optimal, then the excitation $u_j^*$ of the $j$-th mode is an eigenfunction of the integral equation

$$\zeta_j\big(U^*, T\big) \int_0^T c_j(\tau, \nu, \bar{a}) \, u_j^*(\tau) \, \mathrm{d}\tau = \gamma_j \, u_j^*(\nu) \quad (j = 1, 2, \ldots). \tag{11}$$

From (i) in Corollary 1 it follows that $u_j^*$ corresponds to the largest eigenvalue of (11), denoted by $\gamma_{\max}^{(j)}$, when it is considered as the linear eigenvalue problem with treated $\zeta_j(U^*, T)$ as a constant.

The kernel $\ker_j$ is symmetric and positive definite. It depends on $U^*$ only through the constant $\zeta_j(U^*, T) > 0$. This fact is crucial, since we are able to determine the eigenfunctions of (11) without knowing $U^*$. Furthermore, given $j$ we can determine its largest eigenvalue and the corresponding eigenfunction. To this end, it suffices to find the largest eigenvalue $\eta_{\max}^{(j)}$ and the corresponding eigenfunction $\phi_{\max}^{(j)}(t)$, $(\|\phi_{\max}^{(j)}\| = 1)$, of $\int_0^T c_j(\tau, \nu, \bar{a}) \, \varphi(\tau) \, \mathrm{d}\tau = \eta \, \varphi(\nu)$. Note that $\gamma_{\max}^{(j)} = \zeta_j(U^*, T) \, \eta_{\max}^{(j)}$, $j = 1, 2, \ldots$.

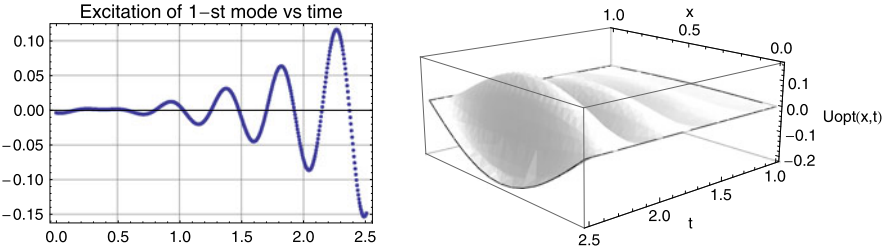


**Fig. 1** *Left panel*—excitation of the first mode by the optimal input signal, *right panel*—space-time optimal input wave in Example 2

**Proposition 3** *Under* (A1)–(A3), *if* $U^*$ *is a D-optimal input signal, then it can be expressed in the modal form* (9) *with* $u_k^*(t) = \phi_{\max}^{(k)}(t)$ *and* $\alpha_k^*$ *selected in such a way that they are maximizers, over all* $\alpha_k \geq 0$*'s,* $\sum_{k=1}^{\infty} \alpha_k \leq 1$, *of the criterion*

$$\max_{\alpha_1, \alpha_2, \ldots} \log \det \left[ \sum_{k=1}^{\infty} \alpha_k \, \zeta_k\big(U^*, T\big) \, \eta_{\max}^{(k)} \, \bar{b}_k \, \bar{b}_k^{\top} \right]. \tag{12}$$

This result almost completely characterizes the spatio-temporal structure of the optimal input signal, including excitations of each spatial mode. The only ingredients that are not explicitly stated are the $\alpha_k^*$'s indicating allocation of energy between modes. For fixed $U^*$ one can repeat the proof of the Kiefer-Wolfowitz theorem.

**Corollary 2** *If* $U^*$ *is optimal, then the following condition holds*:

$$\max_{k=1,\,2,\ldots} \eta_{\max}^{(k)} \left[ \bar{b}_k^{\top} \, M_T^{-1}\big(U^*\big) \, \bar{b}_k \right]^2 = R = \dim(\bar{a}). \tag{13}$$

Proposition 3 and Corollary 2 provide necessary optimality conditions. Under the same additional assumption as in Remark 1, they are also sufficient.

As for a numerical procedure to solve (13), applying the Carathēodory theorem, we infer that in (12) it suffices to select at most $R\,(R+1)/2$ terms (we cannot say which of them, since $\zeta_k(U^*, T)$'s depend on $U^*$). The eigenvalues of PDEs decay very rapidly, so we can consider only several first modes. The condition (13) looks familiar (except raising $\bar{b}_k^{\top} \, M_T^{-1}(U^*) \bar{b}_k$ to a power of 2). Formally, the Wynn-Fedorov algorithm applies (Wynn 1970; Fedorov 1972), but this deserves more study.

*Example 2* (Hyperbolic case) Consider damped vibrations described by

$$\frac{\partial^2 q(x,t)}{\partial t^2} + 2\,\xi \, \frac{\partial q(x,t)}{\partial t} + a \, \frac{\partial^2 q(x,t)}{\partial x^2} = U(x,t),$$

$x \in (0,1)$, $q(0,t) = q(1,t) = 0$, where $a$ is an unknown parameter. In this case it suffices to excite the first mode of the system $v_1(x) = \sin(\pi\, x)/\sqrt{\pi}$ by a signal which is proportional to $t \, \exp(\xi\, t) \sin(\sqrt{a}\, t)$. Its structure is shown in Fig. 1.

*Example 3* (Parabolic case) Consider the heat equation with unknown parameters $a_1$ and $a_2$:

$$\frac{\partial q(x,t)}{\partial t} + a_1 \frac{\partial^2 q(x,t)}{\partial x^2} + a_2 q(x,t) = U(x,t),$$

$x \in (0,1)$, $q(0,t) = q(1,t) = 0$. The structure of the optimal input signal involves two modes, $v_1(x) = \sin(\pi x)/\sqrt{\pi}$ and $v_2(x) = \sin(2\pi x)/\sqrt{\pi}$, each excited by an exponentially growing function of time, but the influence of the second one is rather weak.

## 5 Conclusions

Under several simplifying assumptions we have established that optimal input signals are sums of excitations, which are products of natural modes in space and exponentials or exponentially growing sinusoids with natural system frequencies in time. As in optimum experimental design for regression models nonlinear in the parameters, here the optimal $u^*$ also depends on estimated parameters. There are well known ways of circumventing this difficulty (Atkinson et al. 2007).

The results are presented for the D-optimality criterion, but they can readily be generalized to the A-optimality, general L-optimality and Lp-optimality criteria.

## References

Atkinson, A.C., Donev, A.N., Tobias, R.D.: Optimum Experimental Designs, with SAS. Oxford University Press, New York (2007)

Fedorov, V.V.: Theory of Optimal Experiments. Academic Press, New York (1972)

Goodwin, G.C., Payne, R.L.: Dynamic System Identification. Experiment Design and Data Analysis. Academic Press, New York (1977)

Patan, M.: Optimal Sensor Network Scheduling in Identification of Distributed Parameter Systems. Springer, Berlin (2012)

Rafajłowicz, E.: Design of experiments for eigenvalue identification in the static distributed systems. Syst. Sci. **4**, 349–361 (1978)

Rafajłowicz, E.: Design of experiments for eigenvalue identification in distributed parameter systems. Int. J. Control **34**, 1079–1094 (1981)

Rafajłowicz, E.: Optimal experiment design for identification of linear distributed-parameter systems. IEEE Trans. Autom. Control **28**, 806–808 (1983)

Rafajłowicz, E.: Time-domain optimization of input signals for distributed-parameter systems identification. J. Optim. Theory Appl. **60**, 67–79 (1989)

Rafajłowicz, E.: Lecture presented at The Isaac Newton Institute. Cambridge (2011). Available via http://www.newton.ac.uk/programmes/DAE/seminars/072014001.html

Rafajłowicz, E., Rafajłowicz, W.: $(n+r)D$ systems and their control with reduced sensitivity to parametric uncertainties. In: Bachelier, O., Galkowski, K., Rogers, E. (eds.) Proc. 7th Int. Workshop on Multidimensional (nD) Systems, September 5th–7th, 2011, Poitiers (2011). Available via IEEE Xplore

Rafajłowicz, E., Skubalska-Rafajłowicz, E.: On optimal space-time excitation structures for parameter estimation in linear partial differential equations. In: Melas, V., Nachtmann, G., Rasch, D. (eds.) Optimal Design of Experiments—Theory and Application, Vienna, Austria, pp. 130–145 (2011)

Uciński, D.: Optimal Measurement Methods for Distributed Parameter System Identification. CRC Press, Boca Raton (2005)

Wynn, H.P.: The sequential generation of D-optimal experimental designs. Ann. Math. Stat. **41**, 1055–1064 (1970)

Yosida, K.: Functional Analysis. Springer, Heidelberg (1981)

# Random Projections in Model Selection and Related Experimental Design Problems

**Ewa Skubalska-Rafajłowicz and Ewaryst Rafajłowicz**

**Abstract** We propose a method for selecting terms to be included into a regression model, when a part of the primary candidates is specified (e.g., the main effects), and discuss related experimental design problems. A distinctive feature here is a deficit in the admissible number of experiments in comparison with a much larger number of candidate terms. We apply a large number of random projections of candidate terms to eliminate spurious terms. The design problem is solved for a linear regression with a very large number of interactions.

## 1 Introduction and Problem Statement

Unlike those in the present paper, most of the methods for selecting terms to be included into a regression function, including backward stepwise rejection and all subset regression as well as the Lasso (Tibshirani 1996) require more observations than candidate terms. Methods that are based on penalizing too many terms, such as information criteria, cross-validation or the bootstrap (see Konishi and Kitagawa 2008 for these and other criteria) either require candidate models to be nested or lead to the need for comparing all the subsets of candidate terms. A rarely considered aspect is experimental design for model selection. Exceptions include Du Mouchel and Jones (1994), Dette and Kwiecien (2005), Titterington (2000), Atkinson et al. (2007) and Dean and Lewis (2006) and communications on model discrimination (Uciński and Bogacka 2005; Lopez-Fidalgo et al. 2005; Agboto et al. 2010). Our problem statement is closest in spirit to the one by Atkinson et al. (2007, Chap. 20). There are also some relationships with group testing (Lewis and Dean 2001) (see also Morris 2006 for a survey of group testing approaches). Notice, however, that in Lewis and Dean (2001) the grouping is done according to factor levels, while here we propose grouping by random mixing of regression terms.

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It is worth noticing that random projections of a large number of regression terms considered here are also quite different from the deterministic projections of design points that are considered in Tsai et al. (2000). We also point out that, unlike Satterthwaite (1959), we randomize model terms, but not the experimental design itself. Clearly, our approach does not preclude the randomization of run order.

We assume that, for given design points $\mathbf{x}_i \in \mathbb{R}^d$, $i = 1, 2, \ldots, n$, the observations are $y_i = (\mathbf{a}^0)^\top \mathbf{v}(\mathbf{x}_i) + \sum_{j=1}^{K} b_j w_{k(j)}(\mathbf{x}_i) + \varepsilon_i$, $i = 1, 2, \ldots, n$, where $\mathbf{a}^0 \in \mathbb{R}^r$ is a vector of unknown parameters and $\mathbf{v}(\mathbf{x}) = [v_1(\mathbf{x}), v_2(\mathbf{x}), \ldots, v_r(\mathbf{x})]^\top$ a vector of known functions $v_l : \mathbb{R}^d \to \mathbb{R}$, $l = 1, 2, \ldots, r$ that are linearly independent in a certain compact set $\mathbb{X} \subset \mathbb{R}^d$. We let $w_k : \mathbb{R}^d \to \mathbb{R}$, $k = 1, 2, \ldots, \widetilde{K}$ be a collection of given, linearly independent functions in $\mathbb{X}$ that form the vector $\mathbf{w} : \mathbb{R}^d \to \mathbb{R}^{\widetilde{K}}$, $\mathbf{w}(\mathbf{x}) = [w_1(\mathbf{x}), w_2(\mathbf{x}), \ldots, w_{\widetilde{K}}]^\top$, but we know neither which, nor how many of them, appear in our regression function. Thus, $b_j$'s and $K$ are also unknown, but we expect that $K$ is essentially smaller than the length $\widetilde{K}$ of $\mathbf{w}$. The observations $y_i$ contain additive i.i.d. random errors $\varepsilon_i$, $i = 1, 2, \ldots, n$. For formal derivations we assume that $\varepsilon_i \sim \mathcal{N}(0, \sigma_\varepsilon^2)$, although some parts of the results concerning the experimental design do not rely on this assumption.

Let $\mathbf{V}$ denote the $r \times n$ matrix $[\mathbf{v}(\mathbf{x}_1), \mathbf{v}(\mathbf{x}_2), \ldots, \mathbf{v}(\mathbf{x}_n)]$. As is frequently appropriate in practice, we assume that $n$ is (much) smaller than $r + \tilde{K}$. Our aim is to propose a method of selecting terms from $\mathbf{w}(\mathbf{x})$ to be included in the regression function, assuming that the terms contained in $\mathbf{v}(\mathbf{x})$ are prime candidates, e.g., the main effects in a linear model. Simultaneously, our primary aim is to propose an approach to selecting experimental designs that are well suited to our model selection approach.

## 2 Randomly Projected Regression and Experimental Design

### *2.1 Random Projections of Model Terms and Their Selection*

Details of the proposed method are presented in Skubalska-Rafajłowicz and Rafajłowicz (2012). Due to space limitations, we here provide only the main ideas. Our starting point is the model[1]

$$\bar{y}(\mathbf{x}, \mathbf{a}, \beta, \mathbf{s}) = \mathbf{a}^\top \mathbf{v}(\mathbf{x}) + \beta \mathbf{s}^\top \mathbf{w}(\mathbf{x}), \tag{1}$$

where $\mathbf{a} \in \mathbb{R}^r$, $\beta \in \mathbb{R}$, $\mathbf{s} \in \mathbb{R}^{\widetilde{K}}$ is drawn at random by the experimenter: $\mathbf{s} \sim \mathcal{N}(\mathbf{0}, \sigma_s^2 \mathbf{I}_{\widetilde{K}})$, $\sigma_s > 0$, $\mathbf{I}_{\widetilde{K}}$ is the $\widetilde{K} \times \widetilde{K}$ identity matrix. For fixed $\mathbf{s}$, estimates $\hat{\mathbf{a}}$

[1] The model (1) resembles a model that was proposed by Cook and Weisberg (2004). A fundamental difference is that here $\mathbf{s}$ is selected at random and only $\beta$ is estimated, while in Cook and Weisberg (2004) both $\beta$ and $\mathbf{s}$ are estimated. See Skubalska-Rafajłowicz and Rafajłowicz (2012) for further discussion and references.

and $\hat{\beta}$ of the parameters $\mathbf{a}$ and $\beta$ are obtained by ordinary least squares (OLS), i.e.,

$$\min_{\mathbf{a},\beta} \sum_{i=1}^{n} \big[y_i - \bar{y}(\mathbf{x}, \mathbf{a}, \beta, \mathbf{s})\big]^2. \tag{2}$$

Then we test $H_0 : \beta = 0$ using the $t$-test, a new $\mathbf{s} \sim \mathcal{N}(\mathbf{0}, \sigma_s^2 \mathbf{I}_{\widetilde{K}})$ is drawn, and (2) and the test are repeated $q$ times, say. If $H_0$ were rejected a sufficient number of times ($0.2q$, say, cf. Donoho and Jin 2004, for explanation) we would conclude that $\mathbf{w}(\mathbf{x})$ may contain terms that are worth introducing into the model (otherwise, STOP). In order to identify such terms, $\mathbf{w}(\mathbf{x})$ will be repeatedly partitioned (roughly) in half in further derivations. The corresponding left and right parts will be denoted by $\mathbf{w}_L(\mathbf{x})$, $\mathbf{w}_R(\mathbf{x})$, $\mathbf{w}_{LL}(\mathbf{x})$, $\mathbf{w}_{LR}(\mathbf{x})$, $\mathbf{w}_{RL}(\mathbf{x})$, $\mathbf{w}_{RR}(\mathbf{x})$ etc. In subsequent steps the following models will be used:

$$\bar{\bar{y}}(\mathbf{x}, \mathbf{a}, \beta_L, \beta_R, \mathbb{S}) = \mathbf{a}^\top \mathbf{v}(\mathbf{x}) + \beta_L \mathbf{s}_L^\top \mathbf{w}_L(\mathbf{x}) + \beta_R \mathbf{s}_R^\top \mathbf{w}_R(\mathbf{x}), \tag{3}$$

$$\bar{\bar{\bar{y}}}(\mathbf{x}, \mathbf{a}, \beta_{LL}, \beta_{LR}, \ldots) = \mathbf{a}^\top \mathbf{v}(\mathbf{x}) + \beta_{LL} \mathbf{s}_{LL}^\top \mathbf{w}_{LL}(\mathbf{x}) + \beta_{LR} \mathbf{s}_{LR}^\top \mathbf{w}_{LR}(\mathbf{x}), \tag{4}$$

where $\mathbf{a} \in \mathbb{R}^r$, $\beta_L, \beta_R \in \mathbb{R}$, $\mathbf{s}_L, \mathbf{s}_R \in \mathbb{R}^{\widetilde{K}//2}$, $\mathbb{S} \stackrel{\text{def}}{=} [\mathbf{s}_L, \mathbf{s}_R]$, $\mathbf{w}_1(\mathbf{x}), \mathbf{w}_2(\mathbf{x}) \in \mathbb{R}^{\widetilde{K}//2}$ and $\widetilde{K}//2 = \widetilde{K}/2$ if $\widetilde{K}$ is even, and otherwise, $\widetilde{K}//2$ is the largest integer less than $\widetilde{K}/2$ for $\mathbf{w}_L(\mathbf{x})$ vectors and the smallest integer larger than $\widetilde{K}/2$ for $\mathbf{w}_R(\mathbf{x})$ vectors. The same convention is used for further subdivisions $\mathbf{w}_{LL}(\mathbf{x})$, $\mathbf{w}_{LR}(\mathbf{x})$, etc., and for random vectors $\mathbf{s}_L, \mathbf{s}_R \sim \mathcal{N}(\mathbf{0}, \sigma_s^2 \mathbf{I}_{\widetilde{K}//2})$, assuming that they have the same dimensions as the corresponding vectors $\mathbf{w}_L(\mathbf{x})$, $\mathbf{w}_R(\mathbf{x})$, $\mathbf{w}_{LL}(\mathbf{x})$, $\mathbf{w}_{LR}(\mathbf{x})$. Furthermore, we assume that random vectors $\mathbf{s}_L, \mathbf{s}_R, \mathbf{s}_{LL}, \mathbf{s}_{LR}$, etc., are mutually independent.

To fix ideas, consider the model (3). We formulate the hypotheses $H_{0L} : \beta_L = 0$ and $H_{0R} : \beta_R = 0$. For fixed $\mathbf{s}_L$ and $\mathbf{s}_R$, we find $\hat{\mathbf{a}}$, $\hat{\beta}_L$ and $\hat{\beta}_R$ by OLS $\min_{\mathbf{a},\beta_I,\beta_R} \sum_{i=1}^{n} [y_i - \bar{\bar{y}}(\mathbf{x}_i, \mathbf{a}, \beta_L, \beta_R, \mathbb{S})]^2$ and the $t$ test is applied for $\hat{\beta}_L$ and $\hat{\beta}_R$. Again, $\mathbf{s}_L$ and $\mathbf{s}_R$ are drawn at random and the above OLS and $t$ tests are repeated 100 times, say. Simultaneously, we increment counters, denoted by $c_L$ (resp. $c_R$), each time when $H_{0L} : \beta_L = 0$ (resp. $H_{0R} : \beta_R = 0$), is rejected. If, for a preselected threshold $0 < \theta < 1$, we have $c_L < \theta q$ and $c_R < \theta q$, then STOP—there are no additional terms to be introduced into the model. Otherwise, if $c_L \geq \theta q$ and $c_L > c_R$, we split $\mathbf{w}_L(\mathbf{x})$ in half and repeat the above steps for the model (4) (or its 'right' counterpart). Simultaneously, if also $c_R \geq \theta q$, we keep $\mathbf{w}_R(\mathbf{x})$ terms as prospective for further consideration, otherwise we skip $\mathbf{w}_R(\mathbf{x})$ in further steps. If our algorithm reaches the stage that $\mathbf{w}_{LR,\ldots,RL}(\mathbf{x})$ contains only one element, we add it, after the $t$ test, to the list of candidates to be introduced to our model. If the list of prospective terms is not empty, we enter it as a new $\mathbf{w}(\mathbf{x})$ list and repeat the entire procedure. Finally, we have a list of candidates that is used as the extension of $\mathbf{v}(\mathbf{x})$. The parameters of the extended regression are re-estimated and undergo $t$ tests and/or other standard procedures for model validation.

## 2.2 Experimental Design

The matrix of normal equations corresponding to (3) has the form

$$\mathbf{M}_{\mathbb{S}} = \begin{bmatrix} \mathbf{V}\mathbf{V}^{\top} & \mathbf{m}_L(\mathbb{S}) & \mathbf{m}_R(\mathbb{S}) \\ \mathbf{m}_L^{\top}(\mathbb{S}) & m_{LL}(\mathbb{S}) & m_{LR}(\mathbb{S}) \\ \mathbf{m}_R^{\top}(\mathbb{S}) & m_{LR}(\mathbb{S}) & m_{RR}(\mathbb{S}) \end{bmatrix}, \tag{5}$$

where $m_{LL}(\mathbb{S}) \stackrel{\text{def}}{=} \sum_{i=1}^{n} \mathbf{w}_L^{\top}(\mathbf{x}_i)\mathbf{s}_L\mathbf{s}_L^{\top}\mathbf{w}_L(\mathbf{x}_i)$, $\mathbf{m}_L(\mathbb{S}) \stackrel{\text{def}}{=} \sum_{i=1}^{n} \mathbf{s}_L^{\top}\mathbf{w}_L(\mathbf{x}_i)\mathbf{v}(\mathbf{x}_i)$, $m_{RR}(\mathbb{S}) \stackrel{\text{def}}{=} \sum_{i=1}^{n} \mathbf{w}_R^{\top}(\mathbf{x}_i)\mathbf{s}_R\mathbf{s}_R^{\top}\mathbf{w}_R(\mathbf{x}_i)$, $\mathbf{m}_R(\mathbb{S}) \stackrel{\text{def}}{=} \sum_{i=1}^{n} \mathbf{s}_R^{\top}\mathbf{w}_R(\mathbf{x}_i)\mathbf{v}(\mathbf{x}_i)$, while for the mixed element we have $m_{LR}(\mathbb{S}) \stackrel{\text{def}}{=} \sum_{i=1}^{n} \mathbf{s}_L^{\top}\mathbf{w}_L(\mathbf{x}_i)\mathbf{s}_R^{\top}\mathbf{w}_R(\mathbf{x}_i)$.

From now on, $\mathrm{E}_{\mathbb{S}}[\mathbf{M}_{\mathbb{S}}]$, i.e. the expectation of $\mathbf{M}_{\mathbb{S}}$ with respect to $\mathbb{S}$, plays the role of the information matrix.[2] The assumed properties of $\mathbf{s}_L$ and $\mathbf{s}_R$ immediately imply that

$$\mathrm{E}_{\mathbb{S}}[\mathbf{M}_{\mathbb{S}}] = \begin{bmatrix} \mathbf{V}\mathbf{V}^{\top} & \mathbf{0} & \mathbf{0} \\ \mathbf{0}^{\top} & \sigma_s^2 \sum_{i=1}^{n} \|\mathbf{w}_L(\mathbf{x}_i)\|^2 & 0 \\ \mathbf{0}^{\top} & 0 & \sigma_s^2 \sum_{i=1}^{n} \|\mathbf{w}_R(\mathbf{x}_i)\|^2 \end{bmatrix},$$

where $\|\cdot\|$ is the Euclidean norm. For simplicity, in what follows we set $\sigma_s = 1$. As is customary in experimental design (Atkinson et al. 2007), we pass from discrete designs $\mathbf{x}_i$, $i = 1, 2, \ldots, n$ to approximate designs $\xi(\mathbf{x})$, which are probability measures on a compact set $\mathbb{X} \subset \mathbb{R}^d$. The class of all such measures will be denoted by $\Xi(\mathbb{X})$. For $\xi \in \Xi(\mathbb{X})$, we shall denote by $\mathbf{M}(\xi)$ the counterpart of $\mathbf{E}_{\mathbb{S}}[\mathbf{M}_{\mathbb{S}}]$ that can expressed as:

$$\mathbf{M}(\xi) = \begin{bmatrix} \int_{\mathbb{X}} \mathbf{v}(\mathbf{x})\mathbf{v}^{\top}(\mathbf{x})\xi(\mathrm{d}\mathbf{x}) & \mathbf{0} & \mathbf{0} \\ \mathbf{0}^{\top} & W_L(\xi) & 0 \\ \mathbf{0}^{\top} & 0 & W_R(\xi) \end{bmatrix}, \tag{6}$$

where $W_L(\xi) \stackrel{\text{def}}{=} \int_{\mathbb{X}} \|\mathbf{w}_L(\mathbf{x})\|^2 \xi(\mathrm{d}\mathbf{x})$, $W_R(\xi) \stackrel{\text{def}}{=} \int_{\mathbb{X}} \|\mathbf{w}_R(\mathbf{x})\|^2 \xi(\mathrm{d}\mathbf{x})$.

We consider the D-optimum experimental design problem (Atkinson et al. 2007), i.e., finding a design $\xi^* \in \Xi(\mathbf{x})$ that maximizes the determinant of $\mathbf{M}(\xi)$ over $\xi \in \Xi(\mathbf{x})$. It is well known that for $\mathbf{v}(\mathbf{x})$ and $\mathbf{w}(\mathbf{x})$ continuous in $\mathbb{X}$ it suffices to look for optimal designs in the class of all probability measures with finite supports $\kappa_1, \kappa_2, \ldots, \kappa_m$ and attached nonnegative weights $p_1, p_2, \ldots, p_m$, $\sum_{j=1}^{m} p_j = 1$, interpreted as frequencies of applying input $\kappa_j$'s. Note that $m$ is also a decision variable and we do not require the $np_j$ to be integers. As a direct consequence of the equivalence theorem (Atkinson et al. 2007) we obtain

[2] Strictly speaking, $\mathbf{M}_{\mathbb{S}}$ is the Fisher information matrix for fixed $\mathbb{S}$ subject to the hypothesis that $b_j^0 = 0$, $j = 1, 2, \ldots, K$.

**Corollary 1** *A design $\xi^* \in \Xi(\mathbb{X})$ is D-optimal for estimating parameters* $\mathbf{a}$, $\beta_L$, $\beta_R$ *in the model* (3) *if, and only if, for*

$$\phi\big(\mathbf{x}, \xi^*\big) \stackrel{\text{def}}{=} \mathbf{v}^\top(\mathbf{x}) M_{\mathbf{v}}^{-1}\big(\xi^*\big)\mathbf{v}(\mathbf{x}) + \frac{\|\mathbf{w}_L(\mathbf{x})\|^2}{W_L(\xi^*)} + \frac{\|\mathbf{w}_R(\mathbf{x})\|^2}{W_R(\xi^*)},$$

*we have*

$$\sup_{\mathbf{x}\in\mathbb{X}} \phi\big(\mathbf{x}, \xi^*\big) = r + 2, \tag{7}$$

*where* $\mathbf{M}_{\mathbf{v}}(\xi) \stackrel{\text{def}}{=} \int_{\mathbb{X}} \mathbf{v}(\mathbf{x})\mathbf{v}^\top(\mathbf{x})\xi(d\mathbf{x})$. *The supremum in* (7) *is attained at the support points of* $\xi^*$.

To determine such designs numerically, we can apply the Wynn-Fedorov algorithm (Atkinson et al. 2007). Designs that are optimal in the above sense may cause problems in our case for the following reasons:

- from the theory of D-optimal designs we know that there exists a D-optimal design with no more than $(r+2)(r+3)/2$ support points, but this number can be prohibitively large (e.g., 153 points for $r = 15$),
- there is no guarantee that a parameter corresponding to each individual term in $\mathbf{w}(\mathbf{x})$ is identifiable in conjunction with $\mathbf{a}$, which is a prerequisite for their selection.

Below we describe how these difficulties can be alleviated with a minor loss in design efficiency. Details are presented for linear regression with possible interactions, but the idea can be extended to more complicated cases.

## 2.3 Design for Linear Regression with Possible Interactions

Consider a regression linear in the factors with possible interactions. In our convention $\mathbf{v}(\mathbf{x}) = [1, x^{(1)}, x^{(2)}, \ldots, x^{(d)}]^\top$, $r = d + 1$ and we treat the main effects as prime candidates to be present in the model. Let us assume the need for the presence of the second-order or higher-order interactions is not established and therefore we place them in the vector $\mathbf{w}(\mathbf{x}) = [x^{(1)}x^{(2)}, x^{(2)}x^{(3)}, \ldots, x^{(d-1)}x^{(d)}]^\top$ of length $\tilde{K}$. We halve this vector into $\mathbf{w}_L(\mathbf{x})$ and $\mathbf{w}_R(\mathbf{x})$ with lengths $\tilde{K}_L = \tilde{K}//2$ and $\tilde{K}_R = \tilde{K}//2$, respectively, such that $\tilde{K}_L + \tilde{K}_R = \tilde{K}$. As a candidate for the experimental design in $\mathbb{X} = [-1, 1]^d$ we take designs with support at the points of a fractional factorial design $2^{d-f}$ with $f \geq 1$ selected in such a way that

- $2^{d-f}$ is the smallest integer larger than $r + 2 = d + 3$, if this design is expected to be applied directly in the experiment,
- in the absence of any two-factor or higher-order interactions, the estimates of $\mathbf{a}$ (main effects) are unbiased, i.e., we select the so-called main-effect design (Atkinson et al. 2007, p. 79). As $p_j$'s we take $1/2^{d-f}$ and denote such a design by $\tilde{\xi}$.

**Corollary 2** *If* $\mathbf{v}(\mathbf{x})$ *contains only main effects, and possibly a constant term, and* $\mathbf{w}(\mathbf{x})$ *contains only interactions of two or more factors* (*but not necessarily all of them*), *then the optimality condition* (7) *holds for the design* $\tilde{\xi}$.

The proof is provided in Skubalska-Rafajłowicz and Rafajłowicz (2012). Note that the optimality condition for $\tilde{\xi}$ also holds for further subdivisions of $\mathbf{w}_L(\mathbf{x})$ and/or $\mathbf{w}_R(\mathbf{x})$, with obvious changes in the lengths $\tilde{K}_L$ and $\tilde{K}_R$. This design, although formally D-optimal, is not sufficient for our purposes. The reason is that a large number of interaction terms are not identifiable, because—by construction of $\tilde{\xi}$—they are all equal to $+1$ (or all equal to $-1$) for all the support points,[3] which precludes the possibility of their estimation when they appear as single terms in the last stage of subdivisions of $\mathbf{w}_L(\mathbf{x})$ or $\mathbf{w}_R(\mathbf{x})$.

As the next step in constructing an acceptable design, we consider the design $\xi_{\text{mix}}$, which is a convex combination of $\tilde{\xi}$ and the design $\xi_u(\mathbf{x}) = 1/2^d$ that is uniform in $\mathbb{X} = [-1, 1]^d$, i.e., $\xi_{\text{mix}} = (1-\gamma)\tilde{\xi} + \gamma\xi_u$, where $0 < \gamma < 1$ is selected by the experimenter.

**Corollary 3** *For simplicity, let us assume, that* $\mathbf{w}(\mathbf{x})$ *contains only second-order interactions. Then, under the same assumptions as in Corollary* 2, $M(\xi_{\text{mix}})$ *is a diagonal matrix with* $(d+3)$ *diagonal entries, where the first is* 1, *the next d entries have the form* $(1-\gamma)+\gamma/3 = 1-2\gamma/3$ *and the last two are equal to* $(1-\gamma)\tilde{K}_L + \gamma\tilde{K}_L/3^4$ *and* $(1-\gamma)\tilde{K}_R + \gamma\tilde{K}_R/3^4$, *respectively.*

*The D-efficiency with respect to a D-optimal, but not satisfactory, design* $\tilde{\xi}$ *is*

$$D_{\text{eff}}(d,\gamma) \stackrel{\text{def}}{=} \left\{ \frac{|M(\xi_{\text{mix}}|}{|M(\tilde{\xi})|} \right\}^{\frac{1}{(d+3)}} = (1-\gamma 80/81)^{\frac{2}{d+3}} (1-2\gamma/3)^{\frac{d}{d+3}}, \tag{8}$$

*where* $\lim_{d\to\infty} D_{\text{eff}}(d,\gamma) = 1-2\gamma/3$ *and the dependence on* $\gamma$ *is almost linear for moderate* $d$.

The proof is based on direct calculations using the fact that $M(\xi_u)$ is also diagonal (Skubalska-Rafajłowicz and Rafajłowicz 2012). The result also holds when higher-order interactions are involved, but then other multipliers of $\gamma$ in (8) appear. It is worth noticing that, even for problems of a moderate size, the D-efficiency of $\xi_{\text{mix}}$ is large, e.g., for $d = 10$ and $\gamma = 0.25$ the D-efficiency of $\xi_{\text{mix}}$ is at least 0.83.

The final step in constructing designs suitable for our purposes is to approximate the uniform design in $[0, 1]^d$ by an implementable one. To this end, one can select a design from a large variety of so-called quasi-random sequences. We propose to approximate $\xi_u$ by Hammersley sequences (see Niederreiter 1992) since they are well known and already proved their usefulness as experimental designs for nonparametric regression (Rafajłowicz and Schwabe 2006).

[3] One can consider the Plackett and Burman designs for estimating main effects, but in our opinion they share the same drawback.

**Table 1** Left panel: results of testing our algorithm when two terms should be entered into the model. Right panel: the results of testing the forward stepwise regression when the same two terms should be entered into the model. Heading codes: 2 OK—two proper terms were included, 2 OK+—two proper terms were included plus spurious terms (maximum 4 in 100 runs), 1 OK—one proper term was found, None—neither of the two proper terms was included

| $\sigma_\varepsilon$ | 2 OK | 2 OK+ | 1 OK | None | Total |
|---|---|---|---|---|---|
| 0.75 | 41 | 8 | 44 | 7 | 100 |
| 0.5 | 77 | 12 | 11 | 0 | 100 |

| $\sigma_\varepsilon$ | 2 OK | 2 OK+ | 1 OK | None | Total |
|---|---|---|---|---|---|
| 0.75 | 0 | 6 | 81 | 6 | 100 |
| 0.5 | 0 | 6 | 92 | 2 | 100 |

As for a suggested experimental design, consider model selection by random projections when the regression is linear in its main effects, plus possible interactions. An experimental design that we suggest is the convex combination of $\tilde{\xi}$ and points generated by the Hammersley method with equal weights. Select $\gamma$ near 0.5, if we expect many interaction terms and $\gamma$ closer to 0.25, if the number of interaction terms is expected to be smaller. Such designs are highly D-efficient, e.g., for the design used in our simulations for $\gamma = 0.25$ we have $D_{\text{eff}} = 0.92$, while for $\gamma = 0.5$ drops to $D_{\text{eff}} = 0.73$, assuming $\sigma_s = 1$.

### *2.4 Simulations*

We consider a linear model with main effects and possible interactions of all pairs and triples of factors, $d = 10$, $r = \dim[\mathbf{v}(\mathbf{x})] = d + 1 = 11$, $\tilde{K} = \dim[\mathbf{w}(\mathbf{x})] = 165$ and we have only $n = 50$ observations at our disposal that are obtained using a $2^{10-5}$ fractional factorial design plus 18 elements of the Hammersley sequence $\sigma_s = 3$, $\sigma_\varepsilon = 0.5$ or 0.75 (see Table 1, left panel). Two terms, contained in $\mathbf{w}(\mathbf{x})$, have to be included in the regression, namely, $x(2)x(7)$ and $x(3)x(6)$ with coefficients 2.5, while $(\mathbf{a}^0)^\top = [1, 1, \ldots, 1]$. The results seem to be satisfactory, since we had three and a half times more terms to be considered than observations. Note that for $\sigma_\varepsilon = 0.5$ the proper two terms were found in 89 % of cases, while for larger errors ($\sigma_\varepsilon = 0.75$), at least one proper term was identified in 93 % of cases. The same simulations were repeated using the classical forward stepwise regression method. The results are much worse (Table 1, right panel). The same pattern (or even worse for the stepwise forward method) appears, when pairs other than $x(2)x(7)$ and $x(3)x(6)$ are selected for inclusion in the model. On the other hand, the time of calculation for the stepwise regression was much less than for the proposed method (2 seconds vs. 30), but our method is much more reliable in detecting proper terms.

## 3 Concluding Remarks

An important feature of the proposed approach is the dimensionality reduction that comes from random projections of candidate regression terms. The idea of using random projections for this purpose was introduced by the first author in Skubalska-

Rafajłowicz (2011) in the context of the usually even larger models arising in the identification of nonlinear time series. This aspect, as well as bounds on the probabilities of properly selecting all necessary terms, while avoiding introducing spurious ones, are beyond the scope of the present paper.

## References

Agboto, V., Li, W., Nachtsheim, C.: Screening designs for model discrimination. J. Stat. Plan. Inference **140**, 766–780 (2010)

Atkinson, A.C., Donev, A.N., Tobias, R.D.: Optimum Experimental Designs, with SAS. Oxford University Press, Oxford (2007)

Cook, R.D., Weisberg, S.: Partial one-dimensional regression models. Am. Stat. **58**, 110–116 (2004)

Dean, A.M., Lewis, S.M.: Screening methods for experimentation. In: Industry, Drug Discovery, and Genetics. Springer, New York (2006)

Dette, H., Kwiecien, R.: Finite sample performance of sequential designs for model identification. J. Stat. Comput. Simul. **75**, 477–495 (2005)

Donoho, D., Jin, J.: Higher criticism for detecting sparse heterogeneous mixtures. Ann. Stat. **32**, 962–994 (2004)

Du Mouchel, W., Jones, B.: A simple Bayesian modification of D-optimal designs to reduce dependence on an assumed model. Technometrics **36**, 37–47 (1994)

Konishi, S., Kitagawa, G.: Information Criteria and Statistical Modeling. Springer, New York (2008)

Lewis, S.M., Dean, A.M.: Detection of interactions in experiments on large numbers of factors (with discussion). J. R. Stat. Soc. B **63**, 633–672 (2001)

Lopez-Fidalgo, J., Dette, H., Zhu, W.: Optimal designs for discriminating between heteroscedastic models. In: Proc. of the 5th St Petersburg Workshop on Simulation, pp. 429–436. NII Chemistry Univ. Publ., St. Petersburg (2005)

Morris, M.D.: An overview of group factor screening. In: Dean, A.M., Lewis, S.M. (eds.) Screening Methods for Experimentation in Industry, Drug Discovery, and Genetics, pp. 191–207. Springer, New York (2006)

Niederreiter, H.: Random Number Generation and Quasi-Monte Carlo Methods. SIAM, Philadelphia (1992)

Rafajłowicz, E., Schwabe, R.: Halton and Hammersley sequences in multivariate nonparametric regression. Stat. Probab. Lett. **76**, 803–812 (2006)

Satterthwaite, F.E.: Random balance experimentation. Technometrics **1**, 111–137 (1959)

Skubalska-Rafajłowicz, E.: Experiments with Neural Network for Modeling of Nonlinear Dynamical Systems: Design Problems. Lecture presented at the Isaac Newton Institute, Cambridge (2011). Available. http://www.newton.ac.uk/programmes/DAE/seminars/072010301.html

Skubalska-Rafajłowicz, E., Rafajłowicz, E.: Appendix to Random projections in regression model selection and corresponding experiment design problems. Technical Report (2012). Available http://swing.ict.pwr.wroc.pl/~ewa/raf/index.html

Tibshirani, R.: Regression analysis and selection via the Lasso. J. R. Stat. Soc. B **58**, 267–288 (1996)

Titterington, D.M.: Optimal design in flexible models, including feed-forward networks and nonparametric regression (with discussion). In: Atkinson, A.C., Bogacka, B., Zhigljavsky, A. (eds.) Optimum Design 2000, pp. 261–273. Kluwer, Dordrecht (2000)

Tsai, P.-W., Gilmour, S.G., Mead, R.: Projective three-level main effects designs robust to model uncertainty. Biometrika **87**, 467–475 (2000)

Uciński, D., Bogacka, B.: T-optimum designs for discrimination between two multivariate dynamic models. J. R. Stat. Soc. B **67**, 3–18 (2005)

# Optimal Design for the Bounded Log-Linear Regression Model

**HaiYing Wang, Andrey Pepelyshev, and Nancy Flournoy**

**Abstract** Wang and Flournoy (2012) developed estimation procedures for the bounded log-linear regression model, an alternative to the four parameter logistic model which has a bounded response with non-homogeneous variance. In the present paper, we prove that an optimal design that minimizes an information-based criterion requires at most five design points including the two boundary points of the design space. The $D$-optimal design does not depend on the two parameters representing the boundaries of the response, but it does depend on the variance of the error. Furthermore, if the error variance is known and bigger than a certain constant, we prove that the $D$-optimal design is the two-point design supported at boundary points with equal weights. Numerical examples are provided.

## 1 The Statement of the Problem

Consider the bounded log-linear regression model defined by

$$\log\left(\frac{B-Y}{Y-A}\right) = a + bx + \varepsilon, \tag{1}$$

or equivalently,

$$Y = B - \frac{B-A}{1+\mathrm{e}^{-(a+bx+\varepsilon)}}, \tag{2}$$

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where $\varepsilon \sim N(0, \sigma^2)$, $a$, $b$, $\sigma$, $A$ and $B$ are unknown parameters, $x$ is a non-random covariate, $x \in \mathbb{X}$ and $Y$ is the response. Note that model (1) is closely related to the four parameter logistic (4PL) model. The inferential procedure for model (1), together with a discussion of its advantages over the 4PL model can be found in Wang and Flournoy (2012).

For estimating $\theta = (a, b, \sigma, A, B)$ by the local maximum likelihood method, the Fisher information matrix based on a single observation at $x$ is

$$I(\theta, x) = \begin{bmatrix} I_{11} & 0 & I_{13} \\ 0 & I_{22} & I_{23} \\ I_{13}^\top & I_{23}^\top & I_{33} \end{bmatrix},$$

where

$$I_{11} = \frac{1}{\sigma^2}\begin{bmatrix} 1 & x \\ x & x^2 \end{bmatrix}, \qquad I_{13} = -\frac{1}{\sigma^2(B-A)}\begin{bmatrix} 1+\delta\,\mathrm{e}^{c} & 1+\delta\,\mathrm{e}^{-c} \\ (1+\delta\,\mathrm{e}^{c})x & (1+\delta\,\mathrm{e}^{-c})x \end{bmatrix},$$

$$I_{22} = \frac{2}{\sigma^2}, \qquad I_{23} = \frac{2\delta}{\sigma(B-A)}\left[-\mathrm{e}^{c},\ \mathrm{e}^{-c}\right],$$

$$I_{33} = \begin{bmatrix} \frac{\delta^4\,\mathrm{e}^{2c}}{(B-A)^2} + \frac{1+2\delta\,\mathrm{e}^{c}+\delta^4\,\mathrm{e}^{2c}}{\sigma^2(B-A)^2} & -\frac{1}{(B-A)^2} + \frac{2+\delta\,\mathrm{e}^{c}+\delta\,\mathrm{e}^{-c}}{\sigma^2(B-A)^2} \\ -\frac{1}{(B-A)^2} + \frac{2+\delta\,\mathrm{e}^{c}+\delta\,\mathrm{e}^{-c}}{\sigma^2(B-A)^2} & \frac{\delta^4\,\mathrm{e}^{2c}}{(B-A)^2} + \frac{1+2\delta\,\mathrm{e}^{-c}+\delta^4\,\mathrm{e}^{-2c}}{\sigma^2(B-A)^2} \end{bmatrix},$$

$c = a + bx$ and $\delta = \mathrm{e}^{\sigma^2/2}$; see Wang and Flournoy (2012) for derivation of $I(\theta, x)$.

Denote by $\xi = \{x_i, w_i\}_1^K$ an approximate design, where $w_i > 0$ is the design weight at the point $x_i$ and $\sum_{i=1}^K w_i = 1$. Under the design $\xi$, the average information matrix for $\theta$ is

$$M_\xi(\theta) = \sum_{i=1}^{K} w_i\, I(\theta, x_i). \tag{3}$$

We consider optimality criteria that minimize a statistically meaningful convex functional of this information matrix. In the rest of the paper we assume that the design space is defined such that $c = a + bx \in [l, u]$.

## 2 Main Results

### *2.1 The Case of Unknown σ*

In the following theorem we obtain an upper bound for the number of support points of optimal designs that improves on the classical upper bound based on Carathéorody's theorem (Carathéodory 1911; Steinitz 1913).

**Theorem 1** *An optimal design that minimizes an information based criterion for model* (1) *is supported at no more than* 5 *design points. In addition, the optimal design is always supported at the boundary points of the design space.*

*Proof* Reformulating the design problem in terms of $c$, rather than $x$, we rewrite the design as $\xi = \{c_i, w_i\}_1^K$. By matrix manipulation, the matrix $I(\theta, x)$ has the form $I(\theta, c) = P_\theta C_c P_\theta^\top$, where

$$C_c = \begin{bmatrix} 1 & c & 0 & \mathrm{e}^{c} & \mathrm{e}^{-c} \\ c & c^2 & 0 & c\,\mathrm{e}^{c} & c\,\mathrm{e}^{-c} \\ 0 & 0 & \frac{1}{2\sigma^2} & \mathrm{e}^{c} & -\mathrm{e}^{-c} \\ \mathrm{e}^{c} & c\,\mathrm{e}^{c} & \mathrm{e}^{c} & (\sigma^2+1)\delta^2\,\mathrm{e}^{2c} & \frac{1-\sigma^2}{\delta^2} \\ \mathrm{e}^{-c} & c\,\mathrm{e}^{-c} & -\mathrm{e}^{-c} & \frac{1-\sigma^2}{\delta^2} & (\sigma^2+1)\delta^2\,\mathrm{e}^{-2c} \end{bmatrix}$$

and

$$P_\theta = \frac{1}{\sigma} \begin{bmatrix} 1 & 0 & 0 & 0 & 0 \\ \frac{-a}{b} & \frac{1}{b} & 0 & 0 & 0 \\ 0 & 0 & 2\sigma & 0 & 0 \\ \frac{-1}{B-A} & 0 & 0 & \frac{-\delta}{B-A} & 0 \\ \frac{-1}{B-A} & 0 & 0 & 0 & \frac{-\delta}{B-A} \end{bmatrix}.$$

Using the notation from Yang (2010), we define $\Psi_1(c) = \mathrm{e}^{-2c}$, $\Psi_2(c) = \mathrm{e}^{-c}$, $\Psi_3(c) = c\,\mathrm{e}^{-c}$, $\Psi_4(c) = c$, $\Psi_5(c) = \mathrm{e}^{c}$, $\Psi_6(c) = c^2$, $\Psi_7(c) = c\,\mathrm{e}^{c}$ and $\Psi_8(c) = \mathrm{e}^{2c}$. As described by Yang (2010), we find $f_{1,1} = -2\,\mathrm{e}^{-2c}$, $f_{2,2} = \mathrm{e}^{c}/2$, $f_{3,3} = 1$, $f_{4,4} = -2\,\mathrm{e}^{c}$, $f_{5,5} = 6\,\mathrm{e}^{c}$, $f_{6,6} = -\mathrm{e}^{-c}/3$, $f_{7,7} = -3\,\mathrm{e}^{c}$, $f_{8,8} = 24\,\mathrm{e}^{c}$ and $F = \prod_{i=1}^{8} f_{i,i} = 288\,\mathrm{e}^{2c} > 0$. Therefore, by Theorem 2 in Yang (2010), any optimal design based on the Fisher information matrix is supported at no more than $8/2 + 1 = 5$ points including two boundary points. □

Note that $C_c$ is independent of the boundary parameters $A$ and $B$, and $P_\theta$ does not involve $c$. Thus, the $D$-optimal design does not depend on the boundary parameters $A$ and $B$.

We now study numerically the sharpness of the derived upper bound. We focus on $D$-optimality for all our numerical studies. Since the $D$-optimal design does not depend on $A$ and $B$, without loss of generality we define $A = 0$ and $B = 10$. We assume that the design interval is $\mathbb{X} = [-2, 2]$. Suppose that $a = 0$ and $b = 1$. Straightforward calculus gives the $D$-optimal designs: $\xi_{2p}^* = \{(-2, 0.5), (2, 0.5)\}$ for $\sigma = 1$; $\xi_{3p}^* = \{(-2, 0.41), (0, 0.18), (2, 0.41)\}$ for $\sigma = 0.4$ $\xi_{4p}^* = \{(-2, 0.26), (-0.94, 0.24), (0.94, 0.24), (2, 0.26)\}$ for $\sigma = 0.1$. In Fig. 1 the sensitivity function $d(x, \xi^*, \theta) = \mathrm{tr}\{I(\theta, x) M_{\xi^*}(\theta)^{-1}\}$ is depicted for these three designs. Note that the $D$-optimality of the computed designs is confirmed by the equivalence theorem. We have not found cases when the $D$-optimal design is supported at 5 points.

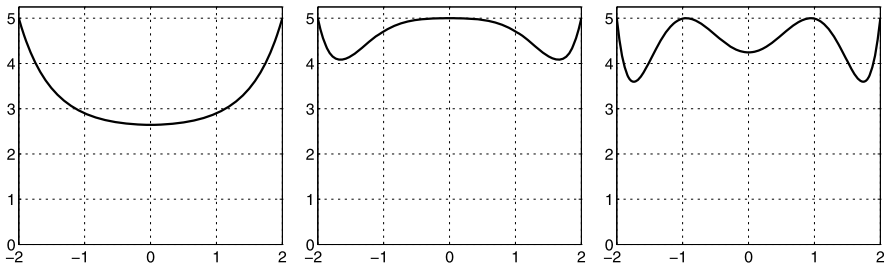

**Fig. 1** The sensitivity function $d(x, \xi^*, \theta)$ for the model (1) with unknown $\sigma$ in three cases. *Left*: $\sigma = 1$; *middle*: $\sigma = 0.4$; *right*: $\sigma = 0.1$

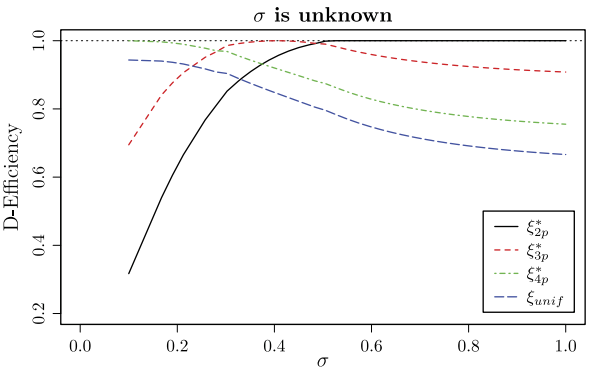


**Fig. 2** Values of $\{\det M_\xi(\theta)/\det M_{\xi^D}(\theta)\}^{1/5}$ (the $D$-efficiency of design $\xi$) for the model (1) with unknown $\sigma$ as a function of $\sigma$ when $\xi$ is $\xi^*_{2p}$, $\xi^*_{3p}$, $\xi^*_{4p}$ and $\xi_{\text{unif}}$, $A = 0$, $B = 10$

Now we evaluate the asymptotic efficiency of designs $\xi^*_{2p}$, $\xi^*_{3p}$, $\xi^*_{4p}$, the uniform design $\xi_{\text{unif}} = \{(-2, 0.2), (-1, 0.2), (0, 0.2), (1, 0.2), (2, 0.2)\}$ and the $D$-optimal designs under different values of $\sigma$. Figure 2 displays the asymptotic efficiency of $\xi^*_{2p}$, $\xi^*_{3p}$, $\xi^*_{4p}$ and $\xi_{\text{unif}}$ relative to the $D$-optimal design. It is seen that $\xi^*_{2p}$ is optimal when $\sigma$ is large, whereas $\xi^*_{3p}$ and $\xi^*_{4p}$ are each optimal only at one value of $\sigma$. Note that the $D$-efficiency of $\xi_{\text{unif}}$ is about 0.9 for small $\sigma$ and 0.7 for large $\sigma$.

For finite sample sizes, we compare the mean squared error (MSE) for each parameter estimate under different designs by simulation. When sample sizes are small, the MLE may not exist, see Wang and Flournoy (2012). For these cases, the smallest and largest observations are used as estimators of $A$ and $B$. We consider the two-point design, the uniform design and a design in which design points are randomly taken from a continuous uniform distribution on $\mathbb{X} = [-2, 2]$. The last we call the random design. Table 1 presents the relative MSE of each parameter estimate calculated from 1000 repetitions of the simulation. The two-point design outperforms the other two designs for most scenarios. It does not perform well for estimating $\sigma$ when $\sigma = 0.5$. The two-point design is not optimal in this scenario.

**Table 1** Values of $MSE(e_k^\top \hat{\theta}|\xi_{2p}^*)/MSE(e_k^\top \hat{\theta}|\xi) \times 100$, the relative performance for estimating individual parameters in the model (1) with unknown $\sigma$ in cases when $\xi$ is the uniform design and the random design of size $n$, $K = 5$. "NS" is the number of cases where a consistent solution to the likelihood equation cannot be found for the given design and "NST" is the number of cases with no consistent solution for the two-point design among 1000 repetitions of the simulation

| Design | | $a$ | $b$ | $\sigma$ | $A$ | $B$ | NS | NST |
|---|---|---|---|---|---|---|---|---|
| $\sigma = 1.0$ | | | | | | | | |
| Uniform | $n = 20$ | 98.5 | 44.6 | 105.2 | 39.8 | 40.8 | 252 | 263 |
| | $n = 40$ | 98.3 | 50.6 | 113.5 | 39.2 | 44.7 | 11 | 16 |
| | $n = 80$ | 96.3 | 53.7 | 117.9 | 45.7 | 43.2 | 0 | 0 |
| Random | $n = 20$ | 76.5 | 29.9 | 86.0 | 21.7 | 19.3 | 293 | 263 |
| | $n = 40$ | 74.5 | 31.9 | 89.3 | 22.2 | 21.4 | 10 | 16 |
| | $n = 80$ | 89.0 | 30.7 | 100.6 | 22.6 | 20.7 | 0 | 0 |
| $\sigma = 0.5$ | | | | | | | | |
| Uniform | $n = 20$ | 139.3 | 88.4 | 270.6 | 74.6 | 77.0 | 66 | 175 |
| | $n = 40$ | 131.4 | 108.6 | 283.4 | 87.2 | 92.8 | 4 | 27 |
| | $n = 80$ | 120.1 | 114.2 | 249.8 | 90.6 | 101.8 | 0 | 0 |
| Random | $n = 20$ | 79.0 | 47.6 | 174.2 | 33.5 | 32.0 | 108 | 175 |
| | $n = 40$ | 83.5 | 55.4 | 181.8 | 40.5 | 43.2 | 16 | 27 |
| | $n = 80$ | 94.5 | 57.8 | 182.4 | 44.4 | 43.0 | 0 | 0 |

## 2.2 The Case of Known σ

When $\sigma$ is known, there are four unknown parameters and the matrix $C_c$ in the Fisher information matrix reduces to

$$C_c = \begin{bmatrix} C_{c11} & C_{c12} \\ C_{c21} & \Sigma_c \end{bmatrix},$$

where

$$C_{c11} = \begin{bmatrix} 1 & c \\ c & c^2 \end{bmatrix}, \qquad C_{c21} = C_{c12}^\top = (\mathbf{Z}_c, c\mathbf{Z}_c), \qquad \mathbf{Z}_c = (\mathrm{e}^c, \mathrm{e}^{-c})^\top,$$

$$\Sigma_c = \begin{bmatrix} (\sigma^2+1)\delta^2\,\mathrm{e}^{2c} & (1-\sigma^2)/\delta^2 \\ (1-\sigma^2)/\delta^2 & (\sigma^2+1)\delta^2\,\mathrm{e}^{-2c} \end{bmatrix}.$$

Using arguments from the proof of Theorem 1, we can show that an optimal design that minimizes an information based criterion for this model is also supported at no more than 5 points.

In the following theorem we explicitly derive $D$-optimal designs in some cases.

**Theorem 2** *For model* (1) *with known* $\sigma$, *there exists a constant* $\zeta < 9$ *such that if* $(\sigma^2+1)\,\mathrm{e}^{\sigma^2} > \zeta$ *the D-optimal design* $\xi^*$ *is the two-point design supported at the boundary points with equal weights.*

*Proof* From the extended general equivalence theorem in White (1973), it suffices to show that $\sup_{c\in[l,u]} d(c,\xi^*,\theta) = 4$. Note that

$$\mathrm{tr}\big\{I_c(\theta)M_{\xi^*}(\theta)^{-1}\big\} = \mathrm{tr}\big\{P_\theta C_c P_\theta^\top \big(P_\theta A P_\theta^\top\big)^{-1}\big\} = \mathrm{tr}\big(A^{-1}C_c\big),$$

where $A = (C_l + C_u)/2$, and $C_l$ and $C_u$ have the same form as $C_c$ with $c$ replaced by $l$ and $u$, respectively. Thus, we need to prove that $\sup_{c\in[l,u]} \mathrm{tr}(A^{-1}C_c) = 4$. By tedious calculation, we have $\mathrm{tr}\{(C_l - C_u)(C_l + C_u)^{-1}\} = 0$, which implies that $\mathrm{tr}(A^{-1}C_l) = \mathrm{tr}(A^{-1}C_u) = 4$.

Now we will prove that $\mathrm{tr}(A^{-1}C_c)$ reaches its maximum at the boundary points $l$ and $u$. By direct calculation, we obtain

$$\begin{aligned}\mathrm{tr}\big(A^{-1}C_c\big) &= 2\frac{(c-l)^2+(c-u)^2}{(l-u)^2} + \mathrm{tr}\big(D^{-1}\Gamma_c\big)\\ &\quad + \frac{\mathrm{tr}(D^{-1}\{(u-c)(\mathbf{Z}_l-\mathbf{Z}_c)-(c-l)(\mathbf{Z}_u-\mathbf{Z}_c)\}^{\otimes 2})}{(l-u)^2}\\ &\le 2 + \mathrm{tr}\big(D^{-1}\Gamma_c\big) + \mathrm{tr}\big(D^{-1}\kappa\big),\end{aligned}$$

where $\kappa = \{2(u-c)^2(\mathbf{Z}_l-\mathbf{Z}_c)^{\otimes 2} + 2(c-l)^2(\mathbf{Z}_u-\mathbf{Z}_c)^{\otimes 2}\}/(l-u)^2$, $\Gamma_c = \Sigma_c - \mathbf{Z}_c\mathbf{Z}_c^\top$, $D = (\Gamma_l+\Gamma_u)/2$, $\Gamma_l$ and $\Gamma_u$ has the same form as $\Gamma_c$ with $c$ replaced by $l$ and $u$, respectively, and $M^{\otimes 2} = MM^\top$ for any matrix $M$.

Note that $\mathrm{tr}(D^{-1}\kappa) + \mathrm{tr}(D^{-1}\Gamma_c) = 2$ at the boundary $l$ or $u$. Consequently, we need to show that $\mathrm{tr}(D^{-1}\kappa) + \mathrm{tr}(D^{-1}\Gamma_c)$ or, equivalently, $\mathrm{tr}(D^*\kappa) + \mathrm{tr}(D^*\Gamma_c)$ achieves its maximum at boundary points $l$ or $u$, where

$$D^* = \frac{1}{2}\begin{bmatrix}\phi(\mathrm{e}^{-2l}+\mathrm{e}^{-2u}) & 2\psi\\ 2\psi & \phi(\mathrm{e}^{2l}+\mathrm{e}^{2u})\end{bmatrix}$$

is the co-factor matrix of $D$, and $\phi = (\sigma^2+1)\delta^2 - 1$ and $\psi = \{1+\delta^2-\sigma^2\}/\delta^2 > 0$.

By direct calculation, it follows that

$$\begin{aligned}\mathrm{tr}\big(D^*\kappa\big) &\le 2\phi\frac{(u-c)^2}{(l-u)^2}\big(\mathrm{e}^{2l}+\mathrm{e}^{2u}\big)\big(\mathrm{e}^{-c}-\mathrm{e}^{-l}\big)^2\\ &\quad + 2\phi\frac{(c-l)^2}{(l-u)^2}\big(\mathrm{e}^{-2l}+\mathrm{e}^{-2u}\big)\big(\mathrm{e}^{c}-\mathrm{e}^{u}\big)^2\\ &= \Delta_1 + \Delta_2\end{aligned}$$

and

$$\mathrm{tr}\big(D^*\Gamma_c\big) = \frac{\phi^2}{2}\big\{\big(\mathrm{e}^{-2l}+\mathrm{e}^{-2u}\big)\mathrm{e}^{2c} + \big(\mathrm{e}^{2l}+\mathrm{e}^{2u}\big)\mathrm{e}^{-2c}\big\} - 2\psi^2.$$

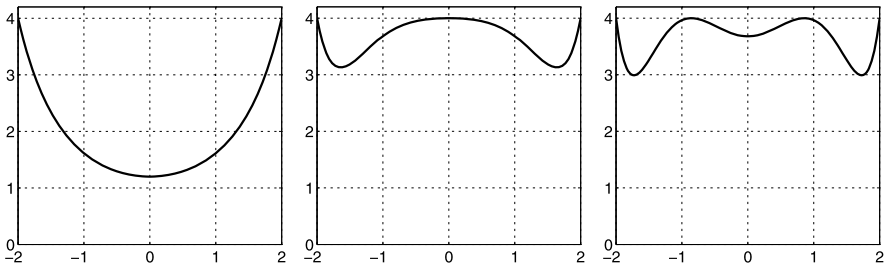

**Fig. 3** The sensitivity function $d(x, \xi^*, \theta)$ for the model (1) with known $\sigma$ in three cases. *Left*: $\sigma = 1$. *Middle*: $\sigma = 0.2$. *Right*: $\sigma = 0.1$

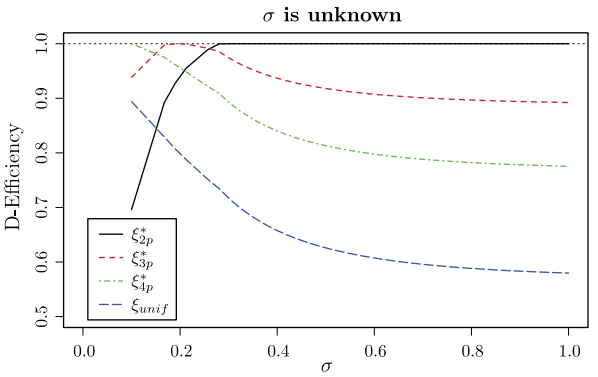


**Fig. 4** Values of $\{\det M_\xi(\theta)/\det M_{\xi^D}(\theta)\}^{1/4}$ (the $D$-efficiency of design $\xi$) for the model (1) with known $\sigma$, different $\sigma$ and cases when $\xi$ is $\xi^*_{2p}$, $\zeta^*_{3p}$, $\zeta^*_{4p}$ and $\xi_{\text{unif}}$, $A = 0$, $B = 10$

Note that if $\Delta_i < \text{tr}(D^*\Gamma_l)/2 - \text{tr}(D^*\Gamma_c)/2$ for $c \in (l, u)$, $i = 1, 2$, then it follows that $\text{tr}(D^*\kappa) + \text{tr}(D^*\Gamma_c)$ achieves its maximum at $c = l$. This is true because $\Delta_i$ vanishes at the two boundary points, $i = 1, 2$.

By direct calculation, we obtain

$$\frac{1}{2}\{\text{tr}(D^*\Gamma_l) - \text{tr}(D^*\Gamma_c)\} = \frac{\phi^2}{4}(e^{2l} + e^{2u})\{1 - e^{2(x-u)}\}(e^{-2l} - e^{-2x}). \quad (4)$$

Thus, assuming $\phi \geq 8$, to prove that $\Delta_1 < \text{tr}(D^*\Gamma_l)/2 - \text{tr}(D^*\Gamma_c)/2$, we need

$$\frac{(u-c)^2}{(l-u)^2} \leq \{1 - e^{2(c-u)}\}\frac{1 + e^{l-c}}{1 - e^{l-c}}. \quad (5)$$

The inequality (5) is true if $\{1 - e^{2(c-u)}\}(1 + e^{l-c})/(1 - e^{l-c}) > 1$. Otherwise, we have $2e^{l-c} < e^{2(c-u)} + e^{l+c-2u} < 2e^{2(c-u)}$, which implies $(l + 2u)/3 < c$.

**Table 2** Values of $MSE(e_k^\top \hat{\theta}|\xi_{2p}^*)/MSE(e_k^\top \hat{\theta}|\xi) \times 100$, the relative performance of estimating individual parameters for the model (1) with known $\sigma$ in cases when $\xi$ is the uniform design and the random design of size $n$, $K = 5$. "NS" is the number of cases where a consistent solution to the likelihood equation cannot be found for the given design and "NST" is the number of cases of no consistent solution for the two-point design among 1000 repetitions of simulation

| Design | | $a$ | $b$ | $A$ | $B$ | NS | NST |
|---|---|---|---|---|---|---|---|
| $\sigma = 1.0$ | | | | | | | |
| Uniform | $n = 20$ | 96.5 | 40.6 | 35.3 | 35.3 | 0 | 0 |
| | $n = 40$ | 98.6 | 45.2 | 33.7 | 37.3 | 0 | 0 |
| | $n = 80$ | 96.3 | 48.5 | 40.7 | 38.6 | 0 | 0 |
| Random | $n = 20$ | 74.2 | 28.5 | 19.6 | 17.6 | 4 | 0 |
| | $n = 40$ | 75.4 | 31.2 | 20.8 | 19.7 | 0 | 0 |
| | $n = 80$ | 90.3 | 30.9 | 21.9 | 21.1 | 0 | 0 |
| $\sigma = 0.5$ | | | | | | | |
| Uniform | $n = 20$ | 120.9 | 42.4 | 47.4 | 44.0 | 20 | 13 |
| | $n = 40$ | 129.0 | 49.0 | 46.2 | 49.1 | 0 | 1 |
| | $n = 80$ | 118.4 | 53.6 | 50.8 | 53.0 | 0 | 0 |
| Random | $n = 20$ | 75.0 | 32.0 | 21.9 | 19.3 | 23 | 13 |
| | $n = 40$ | 81.6 | 33.5 | 24.5 | 23.4 | 0 | 1 |
| | $n = 80$ | 94.6 | 34.9 | 27.4 | 26.4 | 0 | 0 |

Thus, if $u - l < 1$, by the mean-value theorem we then have

$$\{1 - \mathrm{e}^{2(c-u)}\}\frac{\mathrm{e}^{c-l}+1}{\mathrm{e}^{c-l}-1} > 2(u-c)\,\mathrm{e}^{\frac{2(l-u)}{3}}\,\frac{2}{e(c-l)} > \frac{4(u-c)}{\mathrm{e}^2(c-l)}$$
$$> \frac{1}{3}\,\frac{(u-c)}{(u-l)} > \frac{(u-c)^2}{(l-u)^2}.$$

If $u - l \geq 1$, we obtain $\{1-\mathrm{e}^{2(c-u)}\}(\mathrm{e}^{c-l}+1)/(\mathrm{e}^{c-l}-1) > \{1-\mathrm{e}^{2(c-u)}\}$. Let $h(c) = \{1-\mathrm{e}^{2(c-u)}\} - (u-c)/\{3(l-u)\}$. Then $h''(c) = -4\,\mathrm{e}^{2(c-u)} < 0$ and, therefore, $h(x)$ is convex. Note that $h(u) = 0$ and $h\{(l+2u)/3\} = 8/9 - \mathrm{e}^{2(l-u)/3} \geq 8/9 - \mathrm{e}^{-2/3} > 0$ and, thus, $h(c) > 0$ for $c \in [(l+2u)/3, u]$. □

We now investigate the dependence of the $D$-optimal design on $\sigma$. As previously, we suppose that $A = 0$, $B = 10$, $\mathbb{X} = [-2, 2]$, $a = 0$ and $b = 1$. Then we obtain the $D$-optimal designs: $\xi_{2p}^* = \{(-2, 0.5), (2, 0.5)\}$ for $\sigma = 1$; $\zeta_{3p}^* = \{(-2, 0.425), (0, 0.15), (2, 0.425)\}$ for $\sigma = 0.2$ and $\zeta_{4p}^* = \{(-2, 0.33), (-0.86, 0.17), (0.86, 0.17), (2, 0.33)\}$ for $\sigma = 0.1$. In Fig. 3 we depict the sensitivity function $d(x, \xi^*, \theta)$ for these three designs. We observe that $d(x, \xi^*, \theta) \leq 4$ for all $x \in \mathbb{X}$ which proves the $D$-optimality. Note that the $D$-optimal design is a two-point design if $\sigma > 0.31$ (for $a = 0$ and $b = 1$). The relative asymptotic efficiency graphs

given in Fig. 4 for the case of known $\sigma$ are similar to the case when $\sigma$ is unknown. However, the design $\xi_{2p}^*$ is $D$-optimal for a larger range of $\sigma$.

Table 2 reports finite sample comparisons. The two point design dominates the other designs when $\sigma = 1.0$. When $\sigma = 0.5$, the uniform design provides better accuracy for estimating only the parameter $a$ and the two point design is preferable for estimating the other parameters.

## References

Carathéodory, C.: Über den Variabilitätsbereich der Fourierschen Konstanten von positiven harmonischen Funktionen. Rend. Circ. Mat. Palermo **32**, 193–217 (1911)

Steinitz, E.: Bedingt konvergente Reihen und konvexe Systeme. J. Reine Angew. Math. **143**, 128–175 (1913)

Wang, H., Flournoy, N.: Inference on a new sigmoid regression model with unknown support and unbounded likelihood function. NI12001-DAE, http://www.newton.ac.uk/preprints/NI12001.pdf (2012)

White, L.V.: An extension of the general equivalence theorem to nonlinear models. Biometrika **60**, 345–348 (1973)

Yang, M.: On the de la Garza phenomenon. Ann. Stat. **38**, 2499–2524 (2010)

# Index




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Contributions to Statistics, DOI 10.1007/978-3-319-00218-7,


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