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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Editors
Prof. Dariusz Uciński
Institute of Control and Computation Engineering
University of Zielona Góra
Zielona Góra, Poland

Dr. Maciej Patan
Institute of Control and Computation Engineering
University of Zielona Góra
Zielona Góra, Poland

Prof. Anthony C. Atkinson
Department of Statistics
London School of Economics
London, UK

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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

Dariusz Uciński
Anthony C. Atkinson
Maciej Patan

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- The University of Zielona Góra (http://www.uz.zgora.pl)
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Dariusz Uciński
Anthony C. Atkinson
Maciej Patan
Editors

Contents

Contributors

Giacomo Aletti ADAMSS Center & Dipartimento di Matematica, Università degli Studi di Milano, Milan, Italy

Alexander Aliev Institute for Systems Analysis, Russian Academy of Sciences, Moscow, Russia

Anthony C. Atkinson Department of Statistics, London School of Economics, London, UK

Buddhananda Banerjee Applied Statistics Unit, Indian Statistical Institute, Kolkata, India

Julien Bect Supélec Sciences des Systèmes, EA4454 (E3S), SUPELEC, Plateau de Moulon, Gif-sur-Yvette cedex, France

Wolfgang Bischoff Faculty of Mathematics and Geography, Catholic University Eichstätt–Ingolstadt, Eichstätt, Germany

Atanu Biswas Applied Statistics Unit, Indian Statistical Institute, Kolkata, India

Barbara Bogacka School of Mathematical Sciences, Queen Mary University of London, London, UK

Matteo Borrotti Department of Environmental Science, Informatics and Statistics, European Centre for Living Technology, Cá Foscari University of Venice, Venice, Italy

Clément Chevalier Institute of Mathematical Statistics and Actuarial Science, University of Bern, Bern, Switzerland

Roelof L.J. Coetzer Sasol Technology, Sasolburg, South Africa

Vladimir Dragalin Aptiv Solutions, Durham, NC, USA

Nicolas Durrande Department of Computer Science, The University of Sheffield, Sheffield, UK

Ellinor Fackle-Fornius Department of Statistics, Stockholm University, Stockholm, Sweden

Davide Ferrari Department of Mathematics and Statistics, The University of Melbourne, Parkville, VIC, Australia

Nancy Flournoy Department of Statistics, University of Missouri, Columbia, MO, USA; University of Missouri, Columbia, MO, USA

Arkaitz Galbete Universidad Pública de Navarra, Pamplona, Spain

Lei Gao Department of Statistics, George Mason University, Fairfax, VA, USA

Andrea Ghiglietti Dipartimento di Matematica "F. Brioschi", Politecnico di Milano, Milan, Italy

David Ginsbourger Institute of Mathematical Statistics and Actuarial Science, University of Bern, Bern, Switzerland; Institute of Mathematical Statistics and Actuarial Science, University of Bern, Bern, Switzerland

Ulrike Graßhoff Institut für Mathematische Stochastik, Otto-von-Guericke-Universität Magdeburg, Magdeburg, Germany; Psychologisches Institut IV, Westfälische Wilhelms-Universität Münster, Münster, Germany

Heiko Großmann School of Mathematical Sciences, Queen Mary University of London, London, UK

Linda M. Haines Department of Statistical Sciences, University of Cape Town, Rondebosch, South Africa

Markus Hainy Department of Applied Statistics, Johannes Kepler University of Linz, Linz, Austria

Heinz Holling Psychologisches Institut IV, Westfälische Wilhelms-Universität Münster, Münster, Germany

Lyudmila A. Krylova Department of Statistical Simulation, St. Petersburg State University, St. Petersburg, Russia

Sergei Leonov AstraZeneca, Wilmington, DE, USA

Bergrun Tinna Magnusdottir Department of Statistics, Stockholm University, Stockholm, Sweden

Saumen Mandal Department of Statistics, University of Manitoba, Winnipeg, MB, Canada

Caterina May Dipartimento DiSEI, Università del Piemonte Orientale, Novara, Italy

Viatcheslav B. Melas Department of Statistical Simulation, St. Petersburg State University, St. Petersburg, Russia

Tobias Mielke Institute for Mathematical Stochastics, Otto-von-Guericke University, Magdeburg, Germany

Ilya Molchanov Institute of Mathematical Statistics and Actuarial Science, University of Bern, Bern, Switzerland

José Antonio Moler Universidad Pública de Navarra, Pamplona, Spain

Christine H. Müller Faculty of Statistics, TU University Dortmund, Dortmund, Germany

Werner G. Müller Department of Applied Statistics, Johannes Kepler University of Linz, Linz, Austria

Hans Nyquist Department of Statistics, Stockholm University, Stockholm, Sweden

Anna Maria Paganoni Dipartimento di Matematica "F. Brioschi", Politecnico di Milano, Milan, Italy

Andrej Pázman Department of Applied Mathematics and Statistics, Faculty of Mathematics, Physics and Informatics, Comenius University, Bratislava, Slovakia

Andrey Pepelyshev Faculty of Mathematics, St. Petersburg State University, St. Petersburg, Russia; Institute of Statistics, RWTH Aachen University, Aachen, Germany

Fernando Plo Universidad de Zaragoza and BIFI, Zaragoza, Spain

Luc Pronzato Laboratoire I3S, CNRS/Université de Nice–Sophia Antipolis, Sophia Antipolis, France

Maryna Prus Institute for Mathematical Stochastics, Otto-von-Guericke University, Magdeburg, Germany

Ewaryst Rafajłowicz Institute of Computer Engineering Control and Robotics, Wrocław University of Technology, Wrocław, Poland

Wojciech Rafajłowicz Institute of Computer Engineering Control and Robotics, Wrocław University of Technology, Wrocław, Poland

William F. Rosenberger Department of Statistics, George Mason University, Fairfax, VA, USA

Olivier Roustant FAYOL-EMSE, LSTI, Ecole Nationale Supérieure des Mines de Saint-Etienne, Saint-Etienne, France

Rainer Schwabe Institut für Mathematische Stochastik, Otto-von-Guericke-Universität Magdeburg, Magdeburg, Germany; Institute for Mathematical Stochastics, Otto-von-Guericke University, Magdeburg, Germany

Ewa Skubalska-Rafajłowicz Institute of Computer Engineering Control and Robotics, Wrocław University of Technology, Wrocław, Poland

Chiara Tommasi Dipartimento DEMM, Università degli Studi di Milano, Milan, Italy

Dariusz Uciński Institute of Control and Computation Engineering, University of Zielona Góra, Zielona Góra, Poland

HaiYing Wang Department of Statistics, University of Missouri, Columbia, MO, USA

Linda Wänström Division of Statistics, Department of Computer and Information Science, Linköping University, Linköping, Sweden

Henry P. Wynn Department of Statistics, London School of Economics, London, UK

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

G. Aletti (✉)
ADAMSS Center & Dipartimento di Matematica, Università degli Studi di Milano,
Via Saldini 50, 20133 Milan, Italy
e-mail: giacomo.aletti@unimi.it

C. May
Dipartimento DiSEI, Università del Piemonte Orientale, Via Perrone 18, 28100 Novara, Italy
e-mail: caterina.may@eco.unipmn.it

C. Tommasi
Dipartimento DEMM, Università degli Studi di Milano, Via Conservatorio 7, 20122 Milan, Italy
e-mail: chiara.tommasi@unimi.it

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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 ξ 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 Θ_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 ξ 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 ξ. 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 ξ is *regular* if the set

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

is a singleton. Otherwise ξ 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 Ξ of probability distributions ξ 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 (Ξ, 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

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

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 ξ^*. 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 Γ 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 Γ 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 $\mathbf{Map}_{\mathscr{X}}(\beta) = \{x \in \mathscr{X} : x = \arg\max_{s \in \mathscr{X}} \mathscr{I}(s, \beta)\}$;
$\mathbf{Map}_{\boldsymbol{\xi}}$: $(\Xi \times \mathscr{X}) \hookrightarrow \Xi$, defined by $\mathbf{Map}_{\boldsymbol{\xi}}(\xi, x) = \{\xi' \in \Xi : \xi' = (1-\alpha)\xi + \alpha\delta_x$ 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 δ_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

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

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, β_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 ξ_n is a sequence of regular designs, then the limit of any converging subsequence of ξ_n is a KL-optimum design. In particular, if the optimum ξ^* 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 $\mathbf{Map}_{\boldsymbol{\xi}}$.

4 Regularization

The numerical procedure described in Sect. 3 converges provided that the designs ξ_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

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

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. $\mathbf{Map_1} : \varXi \hookrightarrow \varXi \times \varTheta_2$ is now replaced by $\mathbf{Map_1}(\xi) = (\xi, \varOmega_2(\xi_1))$;
2. $\mathbf{Map_\xi} : (\varXi \times \mathscr{X}) \hookrightarrow \varXi$ is now replaced by $\mathbf{Map_\xi}(\xi, x) = \{\xi' \in \varXi : \xi' = (1-\alpha)\xi + \alpha\delta_x$ 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 ξ_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 ξ_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 ξ^*. 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 γ, let

$$\varXi_\gamma = \left\{\eta : \eta = (1-\gamma)\xi + \gamma\tilde{\xi}, \xi \in \varXi\right\} \subseteq \varXi$$

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

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

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

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

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

Thus

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

Since ξ^*_γ 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

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

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 γ is a small value, the design $(1-\gamma)\xi_\gamma^* + \gamma\tilde{\xi}$ is *almost* KL-optimum and therefore ξ_γ^* 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 (ξ,β_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 ε 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 β, 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 ξ'_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 $(\xi, \mathbf{Map}_{\mathscr{X}}(\beta)) \xrightarrow{\mathbf{Map}_{\xi}} \mathbf{Map_2}(\xi, \beta)$ are closed. Since $\Xi \times \mathscr{X}$ is compact, the composition of the closed point-to-set mappings

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

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). □

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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 λ

A.C. Atkinson (✉)
Department of Statistics, London School of Economics, London WC2A 2AE, UK
e-mail: a.c.atkinson@lse.ac.uk

B. Bogacka
School of Mathematical Sciences, Queen Mary University of London, London E1 4NS, UK
e-mail: b.bogacka@qmul.ac.uk

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