Contributions to Statistics

Joachim Kunert
Christine H. Müller
Anthony C. Atkinson *Editors*

mODa 11 - Advances in Model-Oriented Design and Analysis

Proceedings of the 11th International Workshop in Model-Oriented Design and Analysis held in Hamminkeln, Germany, June 12-17, 2016

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Preface

This volume contains articles based on presentations at the 11th workshop on model-oriented data analysis and optimum design (mODa) in Hamminkeln-Dingden, Germany, during June 2016. The 11th workshop was organized by the Department of Statistics of the TU Dortmund and supported by the Collaborative Research Center "Statistical modeling of nonlinear dynamic processes" (SFB 823) of the German Research Foundation (DFG).

The mODa series of workshops focuses on nonstandard design of experiments and related analysis of data. The main objectives are:

- To promote new advanced research areas as well as collaboration between academia and industry.
- Whenever possible, to provide financial support for research in the area of experimental design and related topics.
- To give junior researchers the opportunity of establishing personal contacts and working together with leading researchers.
- To bring together scientists from different statistical schools – particular emphasis is given to the inclusion of scientists from Central and Eastern Europe.

The mODa series of workshops started at the Wartburg near Eisenach in the former GDR in 1987 and has continued as a tri-annual series of conferences. The locations and dates of the former conferences are as follows:

- mODa 1: Eisenach, former GDR, 1987,
- mODa 2: St. Kyrik, Bulgaria, 1990,
- mODa 3: Peterhof, Russia, 1992,
- mODa 4: Spetses, Greece, 1995,
- mODa 5: Luminy, France, 1998,
- mODa 6: Puchberg/Schneeberg, Austria, 2001,
- mODa 7: Heeze, The Netherlands, 2004,
- mODa 8: Almagro, Spain, 2007,
- mODa 9: Bertinoro, Italy, 2010,
- mODa 10: Łagów Lubuski, Poland, 2013.

The articles in this volume provide an overview of current topics in research on experimental design. The topics covered by the papers are:

- designs for treatment combinations (Atkinson; Druilhet; Grömping and Bailey),
- randomisation (Bailey; Ghiglietti; Shao and Rosenberger),
- computer experiments (Curtis and Maruri-Aguilar; Ginsbourger, Baccou, Chevalier and Perales),
- designs for nonlinear regression and generalized linear models (Amo-Salas, Jiménez-Alcázar and López-Fidalgo; Burclová and Pázman; Cheng, Majumdar and Yang; Mielke; Radloff and Schwabe),
- designs for dependent data (Deldossi, Osmetti and Tommasi; Gauthier and Pronzato; Prus and Schwabe),
- designs for functional data (Aletti, May and Tommasi; Zang and Großmann),
- adaptive and sequential designs (Borrotti and Pievatolo; Hainy, Drovandi and McGree; Knapp; Lane, Wang and Flournoy),
- designs for special fields of application (Bischoff; Fedorov and Xue; Graßhoff, Holling and Schwabe; Pepelyshev, Staroselskiy and Zhigljavsky),
- foundations of experimental design (Müller and Wynn; Zhigljavsky, Golyandina and Gillard).

In this time of Big Data, it is often not emphasized in public discourse that experimental design remains extremely important. The mODa series of workshops wishes to raise public awareness of the continuing importance of experimental design. In particular, the papers from various fields of application show that experimental design is not a mathematical plaything, but is of direct use in the sciences.

Since the first workshop in Eisenach, optimal design for various situations has been at the heart of the research covered by mODa. Sequential design is another long-standing topic in the mODa series. It is clear that computer experiments, designs for dependent data, and functional data become increasingly feasible. For causal inference in particular, old-fashioned methods like randomization, blinding, and orthogonality of factors remain indispensable. In addition to the importance of the research covered here, we think that the articles in this volume show the beauty of mathematical statistics, which should not be forgotten.

For the editors, it was a pleasure reading these research results. We would like to thank the authors for submitting such nice work and for providing revisions in time, wherever a revision was necessary. Last, but not least, we want to thank the referees who provided thoughtful and constructive reviews in time, helping to make this volume a fine addition to any statistician's bookshelves.

Dortmund, Germany

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On Applying Optimal Design of Experiments when Functional Observations Occur

Giacomo Aletti, Caterina May, and Chiara Tommasi

Abstract In this work we study the theory of optimal design of experiments when functional observations occur. We provide the best estimate for the functional coefficient in a linear model with functional response and multivariate predictor, exploiting fully the information provided by both functions and derivatives. We define different optimality criteria for the estimate of a functional coefficient. Then, we provide a strong theoretical foundation to prove that the computation of these optimal designs, in the case of linear models, is the same as in the classical theory, but a different interpretation needs to be given.

1 Introduction

In many statistical contexts data have a functional nature, since they are realizations from some continuous process. For this reason functional data analysis is an interest of many researchers. Reference monographs on problems and methods for functional data analysis are, for instance, the books of [6, 12] and [7].

Even in the experimental context functional observations can occur in several situations. In the literature many authors have already dealt with optimal design for experiments with functional data (see, for instance, [1, 3, 9, 10, 13, 14, 16]). Sometimes the link between the infinite-dimensional space and the finite-dimensional projection is not fully justified and may unknowingly cause errors. In this work we offer a theoretical foundation to obtain the best estimates of the functional coefficients and the optimal designs in the proper infinite-dimensional space, and its finite-dimensional projection which is used in practice.

When dealing with functional data, derivatives may provide important additional information. In this paper we focus on a linear model with functional response and multivariate (or univariate) predictor. In order to estimate the functional coefficient,

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we exploit fully the information provided by both functions and derivatives, obtaining a strong version of the Gauss-Markov theorem in the Sobolev space H^1.

Since our goal is precise estimation of the functional coefficients, we define some optimality criteria to reach this aim. We prove that the computation of the optimal designs can be obtained as in the classical case, but the meaning of the of A- and D- criteria cannot be traced back any more to the confidence ellipsoid. Hence we give the right interpretation of the optimal designs in the functional context.

2 Model Description

We consider a linear regression model where the response y is a random function which depends on a vector (or scalar) known variable $\mathbf{x}$ through a functional coefficient, which needs to be estimated. Whenever n experiments can be performed the model can be written in the following form, for $t \in \tau$,

$$y_i(t) = \mathbf{f}(\mathbf{x}_i)^T \boldsymbol{\beta}(t) + \varepsilon_i(t) \qquad i = 1, \dots, n, \tag{1}$$

where $y_i(t)$ denote the response curve for the i-th value of the regressor $\mathbf{x}_i$; $\mathbf{f}(\mathbf{x}_i)$ is a p-dimensional vector of known functions; $\boldsymbol{\beta}(t)$ is an unknown p-dimensional functional vector; $\varepsilon_{ij}(t)$ is a zero-mean error process. This model is a functional response model described, for instance, in [7].

In a real world setting, the functions $y_i(t)$ are not directly observed. By a smoothing procedure from the original data, the investigator can reconstruct both the functions and their derivatives, obtaining $y_i^{(f)}(t)$ and $y_i^{(d)}(t)$, respectively. Hence we can assume that the model for the reconstructed functional data is

$$\begin{cases} y_i^{(f)}(t) = \mathbf{f}(\mathbf{x}_i)^T \boldsymbol{\beta}(t) + \varepsilon_i^{(f)}(t) \\ y_i^{(d)}(t) = \mathbf{f}(\mathbf{x}_i)^T \boldsymbol{\beta}'(t) + \varepsilon_i^{(d)}(t) \end{cases} \qquad i = 1, \dots, n, \tag{2}$$

where all the n couples $\{\varepsilon_i^{(f)}(t), \varepsilon_i^{(d)}(t)\}$ are zero-mean identically distributed processes, each process being independent of all the other processes, with $E(\|\varepsilon_{ij}^{(f)}(t)\|_{L^2}^2 + \|\varepsilon_{ij}^{(d)}(t)\|_{L^2}^2) < \infty$.

Note that the investigator might reconstruct each function $y_i^{(f)}(t)$ and its derivative $y_i^{(d)}(t)$ separately. In this case, the terms of the second equation of (2) are not the derivative of the terms of the first equation. The particular case when $y_i^{(d)}(t)$ is obtained deriving $y_i^{(f)}(t)$ is the most simple situation in model (2) and can be seen as model (1).

Let us consider an estimator $\hat{\boldsymbol{\beta}}(t)$ of $\boldsymbol{\beta}(t)$, formed by p random functions in the Sobolev space $H^1 = H^1(\tau)$. Recall that a function $g(t)$ is in H^1 if $g(t)$ and its derivative function $g'(t)$ belongs to L^2. Moreover, H^1 is a Hilbert space with inner product

$$\begin{aligned}\langle g_1(t), g_2(t)\rangle_{H^1} &= \langle g_1(t), g_2(t)\rangle_{L^2} + \langle g_1'(t), g_2'(t)\rangle_{L^2}\\ &= \int g_1(t)g_2(t)dt + \int g_1'(t)g_2'(t)dt, \qquad g_1(t), g_2(t) \in H^1.\end{aligned}$$

Definition 1 We define the H^1-*generalized covariance matrix* $\Sigma_{\hat{\boldsymbol{\beta}}}$ of $\hat{\boldsymbol{\beta}}(t)$ as the $p \times p$ matrix whose (l_1, l_2)-th element is

$$E\langle \hat{\beta}_{l_1}(t) - \beta_{l_1}(t), \hat{\beta}_{l_2}(t) - \beta_{l_2}(t)\rangle_{H^1}. \tag{3}$$

Definition 2 In analogy with classical settings, we define the H^1-functional best linear unbiased estimator (H^1-BLUE) as the estimator with minimal (in the sense of Loewner Partial Order) H^1-generalized covariance matrix (3), in the class of the linear unbiased estimators of $\boldsymbol{\beta}(t)$.

Given a couple $\{y^{(f)}(t), y^{(d)}(t)\} \in L^2 \times L^2$, a linear continuous operator on H^1 may be defined as follows

$$\phi(h) = \langle y^{(f)}, h\rangle_{L^2} + \langle y^{(d)}, h'\rangle_{L^2}, \qquad \forall h \in H^1.$$

From the Riesz representation theorem, there exists a unique $\tilde{y} \in H^1$ such that

$$\langle \tilde{y}, h\rangle_{H^1} = \langle y^{(f)}, h\rangle_{L^2} + \langle y^{(d)}, h'\rangle_{L^2}, \qquad \forall h \in H^1. \tag{4}$$

Definition 3 We call $\tilde{y} \in H^1$ in (4) the *Riesz representative* of the couple $(y^{(f)}(t), y^{(d)}(t)) \in L^2 \times L^2$.

This definition will be useful to provide a nice expression for the functional OLS estimator $\hat{\boldsymbol{\beta}}(t)$. Actually the Riesz representative synthesizes, in some sense, the information of both $y^{(f)}(t)$ and $y^{(d)}(t)$ in H^1.

The *functional OLS estimator* for the model (2) is

$$\begin{aligned}\hat{\boldsymbol{\beta}}(t) &= \arg\min_{\boldsymbol{\beta}(t)} \left(\sum_{i=1}^{n} \|y_i^{(f)}(t) - \mathbf{f}(\mathbf{x}_i)^T \boldsymbol{\beta}(t)\|_{L^2}^2 + \sum_{i=1}^{n} \|y_i^{(d)}(t) - \mathbf{f}(\mathbf{x}_i)^T \boldsymbol{\beta}'(t)\|_{L^2}^2 \right)\\ &= \arg\min_{\boldsymbol{\beta}(t)} \sum_{i=1}^{n} \left(\|y_i^{(f)}(t) - \mathbf{f}(\mathbf{x}_i)^T \boldsymbol{\beta}(t)\|_{L^2}^2 + \|y_i^{(d)}(t) - \mathbf{f}(\mathbf{x}_i)^T \boldsymbol{\beta}'(t)\|_{L^2}^2 \right).\end{aligned}$$

The quantity

$$\|y_i^{(f)}(t) - \mathbf{f}(\mathbf{x}_i)^T \boldsymbol{\beta}(t)\|_{L^2}^2 + \|y_i^{(d)}(t) - \mathbf{f}(\mathbf{x}_i)^T \boldsymbol{\beta}'(t)\|_{L^2}^2$$

resembles

$$\|y_i(t) - \mathbf{f}(\mathbf{x}_i)^T \boldsymbol{\beta}(t)\|_{H^1}^2,$$

because $y_i^{(f)}(t)$ and $y_i^{(d)}(t)$ reconstruct $y_i(t)$ and its derivative function, respectively. The functional OLS estimator $\hat{\boldsymbol{\beta}}(t)$ minimizes, in this sense, the sum of the H^1-norm of the unobservable residuals $y_i(t) - \mathbf{f}(\mathbf{x}_i)^T \boldsymbol{\beta}(t)$.

3 Infinite and Finite-Dimensional Results

This section contains the fundamental theoretical results for estimation of functional linear models given in Sect. 2; they can be proved as particular cases of the theorems contained in [2].

Theorem 1 *Given the model in* (2),

(a) the functional OLS estimator $\hat{\boldsymbol{\beta}}(t)$ can be computed by

$$\hat{\boldsymbol{\beta}}(t) = (F^T F)^{-1} F^T \tilde{\mathbf{y}}(t), \tag{5}$$

where $\tilde{\mathbf{y}}(t) = \{\tilde{y}_1(t), \dots, \tilde{y}_n(t)\}$ is the vector whose components are the Riesz representatives of the replications, and $F = [\mathbf{f}(\mathbf{x}_1), \dots, \mathbf{f}(\mathbf{x}_n)]^T$ is the $n \times p$ design matrix.

(b) The estimator $\hat{\boldsymbol{\beta}}(t)$ is unbiased and its generalized covariance matrix is

$$\Sigma_{\hat{\boldsymbol{\beta}}} = \sigma^2 (F^T F)^{-1},$$

where $\sigma^2 = E(\|y_i(t) - \mathbf{f}(\mathbf{x}_i)^T \boldsymbol{\beta}(t)\|_{H^1}^2)$.

The functional OLS estimator obtained in Theorem 1 by means of the Riesz representatives is also the best linear unbiased estimator in the Sobolev space, as stated in the next theorem, which is a functional version of the well known Gauss-Markov theorem.

Theorem 2 *The functional OLS estimator $\hat{\boldsymbol{\beta}}(t)$ for the model* (2) *is a H^1-functional BLUE, when the Riesz representatives of the eigenfunctions of the error terms are independent.*

In a real world context, we work with a finite dimensional subspace $\mathscr{S}$ of H^1. Let $S = \{w_1(t), \dots, w_N(t)\}$ be a base of $\mathscr{S}$. Without loss of generality, we may assume that $\langle w_h(t), w_k(t)\rangle_{H^1} = \delta_h^k$, where δ_h^k is the Kronecker delta symbol, since a Gram-Schmidt orthonormalization procedure may always be applied. More precisely, given any base $\tilde{S} = \{\tilde{w}_1(t), \ldots, \tilde{w}_N(t)\}$ in H_1, the corresponding orthonormal base is given by:

for $k = 1$, define $w_1(t) = \frac{\tilde{w}_1(t)}{\|\tilde{w}_1(t)\|_{H^1}}$,

for $k \geq 2$, let $\hat{w}_k(t) = \tilde{w}_k(t) - \sum_{h=1}^{n-1} \langle \tilde{w}_k(t), w_h(t) \rangle_{H^1} w_h(t)$, and $w_k(t) = \frac{\hat{w}_k(t)}{\|\hat{w}_k(t)\|_{H^1}}$.

With this orthonormalized base, the projection $\tilde{y}(t)_{\mathscr{S}}$ on $\mathscr{S}$ of the Riesz representative $\tilde{y}(t)$ of the couple $\{y^{(f)}(t), y^{(d)}(t)\}$ is given by

$$\begin{aligned}
\tilde{y}(t)_{\mathscr{S}} &= \sum_{k=1}^{N} \langle \tilde{y}(t), w_k(t) \rangle_{H^1} \cdot w_k(t) \\
&= \sum_{k=1}^{N} \left(\langle y^{(f)}(t), w_k(t) \rangle_{L^2} + \langle y^{(d)}(t), w_k'(t) \rangle_{L^2} \right) w_k(t),
\end{aligned} \tag{6}$$

where the last equality comes from the definition (4) of the Riesz representative. Now, if $\mathbf{m}_l = (m_{l,1}, \ldots, m_{l,n})^T$ is the l-th row of $(F^T F)^{-1} F^T$, then

$$\begin{aligned}
\langle \hat{\boldsymbol{\beta}}_l(t), w_k(t) \rangle_{H^1} &= \sum_{i=1}^{n} \langle m_{l,i} y_i(t), w_k(t) \rangle_{H^1} \\
&= \sum_{i=1}^{n} m_{l,i} \langle y_i(t), w_k(t) \rangle_{H^1}, \qquad \text{for any } k = 1, \ldots, N, \\
\hat{\boldsymbol{\beta}}_l(t)_{\mathscr{S}} &= \mathbf{m}_l^T \mathbf{y}(t)_{\mathscr{S}},
\end{aligned}$$

hence $\hat{\boldsymbol{\beta}}(t)_{\mathscr{S}} = (F^T F)^{-1} F^T \mathbf{y}(t)_{\mathscr{S}}$.

Let us note that, even if the Riesz representative (4) is implicitly defined, its projection on $\mathscr{S}$ can be easily computed by (6). From a practical point of view, the statistician can work with the data $\{y_{ij}^{(f)}(t), y_{ij}^{(d)}(t)\}$ projected on a finite linear subspace $\mathscr{S}$ and the corresponding OLS estimator $\hat{\boldsymbol{\beta}}(t)_{\mathscr{S}}$ is the projection on $\mathscr{S}$ of the obtained H^1-OLS estimator $\hat{\boldsymbol{\beta}}(t)$. As a consequence of Theorem 2, $\hat{\boldsymbol{\beta}}(t)_{\mathscr{S}}$ is also H^1-BLUE in $\mathscr{S}$, since it is unbiased and the projection is linear. For the projection, it is crucial to take a base of $\mathscr{S}$ which is orthonormal in H^1.

It is straightforward to prove that the estimator (5) becomes

$$\hat{\boldsymbol{\beta}}(t) = (F^T F)^{-1} F^T \mathbf{y}^{(f)}(t),$$

in two cases: when we do not take into consideration $y^{(d)}$, or when $y^{(d)} = y'^{(f)}$. In both cases, from the results obtained, $\hat{\boldsymbol{\beta}}$ is an L^2-BLUE. To our knowledge, this is the most common situation considered in the literature.

4 Optimal Designs

Assume we work in an experimental setup. Therefore, $\mathbf{x}_i$, with $i = 1, \dots, n$, are not observed auxiliary variables; they can be freely chosen by an experimenter on the design space $\mathscr{X}$. The set of experimental conditions $\{\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_n\}$ is called an exact design. A more general definition is that of a continuous design, as a probability measure ξ with support on $\mathscr{X}$ (see, for instance, [8]). The choice of ξ may be made with the aim of obtaining accurate estimates of the model functional parameters.

From Theorem 2, $\hat{\boldsymbol{\beta}}(t)$ given in (5) is the H^1-BLUE for the model (2). This optimal estimator can be further improved by a "clever" choice of the design. By analogy with the criteria proposed in the finite-dimensional theory (see for instance, [4, 11, 15]) we define a *functional optimal design* as a design which minimizes an appropriate convex function of the generalized covariance matrix $\Sigma_{\hat{\boldsymbol{\beta}}}$ given in Definition 1. In particular, we define the following optimality criteria.

Definition 4 A *functional D-optimum* design is a design ξ_D^* which minimizes $\det(\Sigma_{\hat{\boldsymbol{\beta}}})$; a *functional A-optimum* design is a design ξ_A^* which minimizes $trace(\Sigma_{\hat{\boldsymbol{\beta}}})$; a *functional E-optimum* design is a design ξ_E^* which minimizes the maximum eigenvalue of $\Sigma_{\hat{\boldsymbol{\beta}}}$.

Observe that Definition 4 may be applied also in the case of functional non-linear models. When we deal in particular with models (1) or (2), part (b) of Theorem 1 shows that

$$\Sigma_{\hat{\boldsymbol{\beta}}} \propto (F^T F)^{-1},$$

and, from the definition of continuous design,

$$F^T F \propto \int_{\mathscr{X}} \mathbf{f}(\mathbf{x})\mathbf{f}(\mathbf{x})^T d\xi(\mathbf{x}).$$

Hence we have proved that, in the case of models (1) and (2), a functional optimal design can be computed as in the classical theory.

4.1 Interpretation

We describe here the meaning of the optimality criteria given by Definition 4 in the functional context. Observe that these interpretations are strongly connected to the definition of generalized covariance matrix given in Definition 1.

4.1.1 Functional D-Optimum Designs

Let $\hat{\boldsymbol{\beta}}(t)$ be an unbiased estimator for a functional parameter $\boldsymbol{\beta}(t)$ having H^1-generalized covariance matrix $\Sigma_{\hat{\boldsymbol{\beta}}}$ according to Definition 1. Then, for $\boldsymbol{\theta}$ in R^p, the equation

$$\boldsymbol{\theta}^T\, \Sigma_{\hat{\boldsymbol{\beta}}}\, \boldsymbol{\theta} \leq \text{constant} \tag{7}$$

defines an ellipsoid of R^p such that the linear combinations

$$\boldsymbol{\theta}^T\, \hat{\boldsymbol{\beta}}(t) = \sum_{i=1}^{p} \theta_i\, \hat{\beta}_i(t), \tag{8}$$

with $\boldsymbol{\theta}$ in the ellipsoid (7), have H^1-generalized variance bounded by the same arbitrary constant:

$$\Sigma_{\boldsymbol{\theta}^T \hat{\boldsymbol{\beta}}} = E(\| \sum_{i=1}^{p} \theta_i\, \hat{\beta}_i(t) - \sum_{i=1}^{p} \theta_i\, \beta_i(t) \|_{H^1}^2) \leq \text{constant}.$$

A functional D-optimum design maximizes the volume of ellipsoid (7) and hence the estimate of $\boldsymbol{\beta}(t)$ is more accurate since the "volume" of linear combinations $\sum_{i=1}^{p} \theta_i\, \hat{\beta}_i(t)$ with bounded variance is greater.

4.1.2 Functional A-Optimum Designs

A functional A-optimum design minimizes the trace of $\Sigma_{\hat{\boldsymbol{\beta}}}$; it can be proved that this is equivalent to minimizing

$$\int_{\|\boldsymbol{\theta}\| \leq 1} \boldsymbol{\theta}^T\, \Sigma_{\hat{\boldsymbol{\beta}}}\, \boldsymbol{\theta}\; d\boldsymbol{\theta}\,.$$

Observe that $\boldsymbol{\theta}^T\, \Sigma_{\hat{\boldsymbol{\beta}}}\, \boldsymbol{\theta}$ is the H^1-generalized variance of the linear combinations (8). In other words, a functional A-optimum design minimizes the mean H^1-generalized variance of the linear combinations $\sum_{i=1}^{p} \theta_i\, \hat{\beta}_i(t)$ with coefficients on the unit ball $\|\boldsymbol{\theta}\| \leq 1$. We are able to prove that this can be also achieved with coefficients on the unit sphere $\|\boldsymbol{\theta}\| = 1$.

4.1.3 Functional E-Optimum Designs

Finally, the E-optimality criterion has the following interpretation: a functional E-optimum design minimizes the maximum H^1-generalized variance of the linear combinations $\sum_{i=1}^{p} \theta_i\, \hat{\beta}_i(t)$ with the constraint $\|\boldsymbol{\theta}\| \leq 1$ or $\|\boldsymbol{\theta}\| = 1$.

5 Future Developments

The advantages of applying the theory discussed in this paper are shown in [2] in a real example, where a linear model with functional response and vectorial predictor is used for an ergonomic problem, as proposed in [13]. To forecast the motion response of drivers within a car (functional response), different locations are chosen (experimental conditions). The original, non-optimal design adopted provides a D-efficiency equal to 0.3396; this D-efficiency is raised to 0.9779 through a numerical algorithm for optimal designs.

Regression models with functional variables can cover different situations: we can have functional responses, or functional predictors, or both. In this work we have considered optimal designs for the case of functional response and non-functional predictor. A future goal is to develop the theory of optimal designs also for the scenarios with functional experimental conditions (see also [5]).

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Optimal Designs for Implicit Models

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Abstract In this paper the tools provided by the theory of the optimal design of experiments are applied to a model where the function is given in implicit form. This work is motivated by a dosimetry problem, where the dose, the controllable variable, is expressed as a function of the observed value from the experiment. The best doses will be computed in order to obtain precise estimators of the parameters of the model. For that, the inverse function theorem will be used to obtain the Fisher information matrix. Properly the D-optimal design must be obtained directly on the dose using the inverse function theorem. Alternatively a fictitious D-optimal design on the observed values can be obtained in the usual way. Then this design can be transformed through the model into a design on the doses. Both designs will be computed and compared for a real example. Moreover, different optimal sequences and their D-effiencies will be computed as well. Finally, c-optimal designs for the parameters of the model will be provided.

1 Introduction

This paper is focused on the case of nonlinear models where the explanatory variable is expressed as a function of the dependent variable or response and this function is not invertible. That is, we consider the model

$$y = \eta(x, \theta) + \varepsilon, \quad \varepsilon \sim N(0, \sigma), \tag{1}$$

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where y is the dependent variable, x is the explanatory variable, θ is the vector of parameters of the model and $\mu(y, \theta) = \eta^{-1}(x, \theta)$ has a known expression, but a mathematical expression of $\eta(x, \theta)$ is not available. The challenge of this situation is to find optimal experimental designs for the explanatory variable when the expression of the function $\eta(x, \theta)$ is unknown. This situation is presented in a dosimetry study which will be used as case study in this work. Firstly, the description of the case study and a general introduction to the theory of Optimal Experimental Design is given. In Sect. 2 the inverse function theorem is applied to compute the information matrix. Finally, in Sect. 3 D-optimal designs are computed and compared for the case study proposed. Moreover, arithmetic and geometric optimal sequences, c-optimal designs and their D-effiencies are computed.

1.1 Case Study Background

The use of digital radiographs has been a turning point in dosimetry. In particular, radiochromic films are very popular nowadays because of their near tissue equivalence, weak energy dependence and high spatial resolution. In this area, calibration is frequently used to determine the right dose. The film is irradiated at known doses for building a calibration table, which will be used to fit a parametric model, where the dose plays the role of the dependent variable. The nature of this model is phenomenological since the darkness of the movie is only known qualitatively. An adjustment is necessary to filter noise and interpolate the unknown doses.

Ramos-García and Pérez-Azorín [9] used the following procedure. The radiochromic films were scanned twice. The first scanning was made when a pack of films arrived and the second 24 h after being irradiated. With the two recorded images the optical density, *netOD*, was calculated as the base 10 logarithm of the ratio between the means of the pixel values before (PV_0) and after (PV) the irradiation. They used patterns formed by 12 squares of $4 \times 4\,\text{cm}^2$ irradiated at different doses. This size is assumed enough to ensure the lateral electronic equilibrium for the beam under consideration. A resolution of 72 pp, without color correction and with 48-bit pixel depth was used for the measurements. The pixel values were read at the center of every square. Then, the mean and standard error were calculated. The authors assumed independent and normally distributed errors with constant variance as well as we do in this paper.

To adjust the results to the calibration table the following model was used:

$$netOD = \eta(D, \theta) + \varepsilon,$$

where D is the dose and the error ε will be assumed normally distributed with mean zero and constant variance, σ^2. The expression of the function $\eta(D, \theta)$ is unknown but the mathematical expression of the inverse is known

$$\eta^{-1}(D, \theta) = \mu(netOD, \theta) = \alpha\; netOD + \beta\; netOD^{\gamma},\; D \in [0, B], \tag{2}$$