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Optimal dose calibration in radiotherapy

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ABSTRACT

In this paper, the tools provided by the theory of Optimal Experimental Design are applied to a nonlinear calibration model. This is motivated by the need of estimating radiation doses using radiochromic films for radiotherapy purposes. The calibration model is in this case nonlinear and the explanatory variable cannot be worked out explicitly from the model. In this case an experimental design has to be found on the dependent variable. For that, the inverse function theorem will be used to obtain an information matrix to be optimized. Optimal designs on the response variable are computed from two different perspectives, first for fitting the model and estimating each of the parameters and then for predicting the proper dose. While the first is a common point of view in a general context of the Optimal Experimental Design, the latter is actually the main objective of the calibration problem for the practitioners and algorithms for computing these optimal designs are also provided.

The optimal designs obtained have just three different points in their support, but practitioners usually demand for more support points. Thus, a methodology for computing space-filling designs is also provided when the support points are forced to follow some mathematical rule, such as arithmetic or geometric sequences. Cross efficiencies of all these designs are computed in order to show their ability for different goals.

1. Introduction

Calibration models are used in many scientific and industrial fields. They have been studied widely, e.g. by Osborne (1991). It means a different perspective from a standard experimental regression model. In particular, the calibration process is made in two steps. First, for known values of the explanatory variable, the response is measured and the parameters of the model are fitted. Then, on a second stage, in order to calibrate a particular value of the explanatory variable, the response is computed using the inverse function of the model and after that the right value of the explanatory variable to be used is predicted. Thus, while for a standard regression model, generally the main concern is the estimation of the parameters of the model or the prediction of the response at some values of the explanatory variable, for a calibration model the main concern is to provide the most accurate prediction of the explanatory variable in order to get a desired specific value for the response, e.g a specific area properly irradiated.

Optimal designs for calibration models have been rarely considered in the literature. Kitsos (1992), provided a procedure in a simple case when the explicit expression of the inverse model can be obtained and the outline becomes traditional. Francois et al. (2004) computed optimal designs for inverse prediction in calibration models and presented two criteria, G_I–optimality and V_I–optimality. The aims of these criteria are the same than G- and V-optimality, but for the case of inverse prediction. Biedermann et al. (2011) considered a similar problem for indirect observations through a second variable and shows how a uniform design performs quite well for this purpose. Finally, Amo-Salas et al. (2016) presented a previous work in this field, which is detailed and extended in this paper from the perspective of calibration. In that paper the authors gave the theory for non–invertible functions of calibration, although the nominal values considered allowed obtaining a closed–form expression for the inverted model (Ramos-García and Pérez-Azorín (2013)). In this work a case study with more general nominal values is considered (Reinhardt et al. (2012)). Then, the aim of this paper is the study of nonlinear models where the explanatory variable is expressed as a function of the dependent variable and this function has not a closed–form for its inverse, even for the nominal values of the parameters. This study is presented from two perspectives, firstly it is focused on the estimation of the parameters of the model and then on the final goal is prediction of the explanatory variable.

One of the fields where the calibration has an important role is dosimetry. 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

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high spatial resolution. In this area, calibration is frequently used to determine the right dose in radiotherapy for a specific treatment. A film is first irradiated at known doses for building a calibration table, which will be used to fit a parametric model, where now the dose plays the role of the dependent variable.

In this paper a case study from Reinhardt et al. (2012) will be used to illustrate the procedure. They considered the case of dose verification in highly conformal radiation therapy taking advantage of the high spatial resolution offered by radiochromic films such as Gafchromic EBT, EBT2 or the new generation of these films EBT3. A comparison of dose response curves of different EBT2 film batches and a single EBT3 film lot was made in that paper. Response curves were fit according to the Dosimetric GafChromic films literature. In particular, Devic et al. (2004) states that "a suitable function for a given system i) it has to be monotonically increasing; ii) it has to go through zero, and finally iii) it has to give the minimum relative uncertainty for the fitting parameters." Based on these criteria they have chosen the family of functions of the form

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

where

$$\eta^{-1}(Dose, \theta) = \mu(netOD, \theta) = \alpha\ netOD + \beta\ netOD^{\gamma},$$
$$Dose \in \mathscr{X}_{Dose} = [0, B]. \quad (1)$$

The error ε will be assumed normally distributed with mean zero and constant variance, σ^2, and $\theta = (\alpha, \beta, \gamma)^T$ are unknown parameters to be estimated using the Least Squares procedure (LSE), actually the Maximum Likelihood Estimates (MLE) in this case of normality.

Devic et al. (2004) gave some hints for the third term, in particular for the parameter γ. This term tries to account for the nonlinear dose response. The power γ was treated by Devic et al. (2004) as parameter and it was varied from 0.5 to 5.0 with a step of 0.5. For a given film type/densitometer combination, the γ value leading to a minimal overall uncertainty was retained. They have also tried to leave the power γ as a fitting parameter and observed that the sum of residuals would improve negligibly, if at all, by (for the best case) 0.2%. However, the consideration of a new fitting parameter has introduced higher fit uncertainties by 1%–2% in their analysis.

Higueras et al. (2020) computed optimal designs for a calibration dosimetry model that can be inverted for any values of the parameters and therefore there is a closed–form expression for the prediction of the dose. Then the optimality criterion to be used is minimizing the variance of this prediction, which is the so called c–optimality criterion.

The main contributions of this paper are basically two. On the one hand Amo-Salas et al. (2016) considered the case of a nominal value of $\gamma_0 = 2$. Although γ remains still unknown this assumption simplifies very much the problem. Actually this makes the problem computationally much simpler since the explanatory variable can be worked out explicitly. In this paper we afford this through the inverse function theorem at each step of the computations. On the other hand, the two (inverse) criteria introduced by Francois et al. (2004) are used here, again for a non-invertible function. The algorithms provided make the computations possible in this case.

This work is structured as follows, in Section 2 the inverse function theorem is used to obtain the expression of the Fisher Information Matrix (FIM), which is needed for computing optimal designs. This work considers both, estimating the parameters of the model (Section 3) and calibrating the explanatory variable of the radiation dose (Section 4) and for both situations optimal designs are computed using a study case from Reinhardt et al. (2012). Moreover, optimal space–filling designs are computed in both cases for reaching the requirements of the common practice.

2. Optimal experimental design for calibration

Let a general model be

$$y = \eta(x, \theta) + \varepsilon, \quad \varepsilon \sim N(0, \sigma), \quad (2)$$

where y is the dependent variable, x is the explanatory variable, θ is the vector of parameters of the model and $\eta(x, \theta)$ is an unknown function with $\mu(y, \theta) = \eta^{-1}(x, \theta)$ explicitly known. The challenge here is to find optimal designs for the explanatory variable when the expression of the function $\eta(x, \theta)$ is unknown and possibly nonlinear in the parameters.

An *exact experimental design of size n* consists of a collection of points $x_i,\ i = 1, ..., n$, in a given compact *design space*, $\mathscr{X}_x$. Some of these points may be repeated and a probability measure can be defined assigning to each different point the proportion of times it appears in the design. This leads to the idea of extending the definition of experimental design to any probability measure (*approximate design*). From the optimal experimental design point of view we can restrict the search to discrete designs of the type

$$\xi = \begin{Bmatrix} x_1 & x_2 & \dots & x_k \\ p_1 & p_2 & \dots & p_k \end{Bmatrix},$$

where $x_i,\ i = 1, ..., k$ are the support points and $\xi(x_i) = p_i$ is the proportion of experiments to be made at point x_i. Thus, $p_i \geq 0$ and $\sum_{i=1}^{k} p_i = 1$. In practice this design means realizing $n_i \simeq n \times p_i$ experiments for a particular value, x_i, of the explanatory variable(s).

For the exponential family of distributions the FIM of a design ξ is given by

$$M(\xi, \theta) = \sum_{x \in \mathscr{X}_x} I(x, \theta)\xi(x), \quad (3)$$

where $I(x, \theta) = \frac{\partial \eta(x, \theta)}{\partial \theta} \frac{\partial \eta(x, \theta)}{\partial \theta^T}$ is the FIM at a particular point x. It is evaluated at some nominal value of θ. This is actually the FIM of a linear model with regressors $\frac{\partial \eta(x, \theta)}{\partial \theta}$. The nominal value usually represents the best guess for the parameters vector θ at the beginning of the experiment.

It can be proved that the inverse of this matrix is asymptotically proportional to the covariance matrix of the parameter estimators. An optimality design criterion, $\Phi[M(\xi, \theta)]$, aims to minimize the covariance matrix in some sense and therefore the inverse of the information matrix. For simplicity $\Phi(\xi)$ will be used instead of $\Phi[M(\xi, \theta)]$. In this paper two popular criteria, D– and c-optimality, as well as two calibration-oriented criteria, G_I- and V_I-optimality, will be considered.

The D-optimality criterion minimizes the volume of the confidence ellipsoid of the parameters and it is given by $\Phi_D(\xi) = \det M^{-1/m}(\xi, \theta)$, where m is the number of parameters in the model. The c-optimality criterion is used to estimate a linear combination of the parameters, say $c^T\theta$, and it is defined by $\Phi_c(\xi) = c^T M^-(\xi, \theta)c$, where the superscript $^-$ stands for the generalized inverse class of the matrix. Although the generalized inverse is unique only for nonsingular matrices the value of $c^T M^-(\xi, \theta)c$ is invariant for any member of the generalized inverse class if and only if $c^T\theta$ is estimable with the design ξ.

Francois et al. (2004) computed optimal designs for inverse prediction in calibration models and presented two criteria, G_I- and V_I-optimality. The aims of these criteria are the same that $G-$ and $V-$optimality, that is minimizing the maximum and the average prediction variance respectively, but when the interest is in inverse prediction. These criteria will be detailed in Section 4 as well as the algorithms for computing the optimal designs. These criterion functions are convex and non-increasing. A design that minimizes one of these functions, say Φ, over all the designs defined on $\mathscr{X}_x$ is called a $\Phi-$optimal design, or more specifically, a D-, c-, G_I- or V_I-optimal design.

The goodness of a design, ξ, is measured by its efficiency, defined by

$$\text{eff}_\Phi(\xi) = \frac{\Phi(\xi^*)}{\Phi(\xi)},$$

where ξ^* is the $\Phi-$optimal design.

This efficiency can be multiplied by 100 and be reported in percentage. If the function has a homogeneity property there is a practical statistical interpretation. Thus, if the efficiency of a design is 50% this means that the design needs to double the total number of observations to perform as well as the optimal design.

In order to check the optimality of a design the General Equivalence Theorem (GET) can be used (Kiefer and Wolfowitz, 1960; Whittle, 1973) for a more general version. This theorem is valid for approximate designs and convex criteria. It is quite useful also for building efficient algorithms for computing optimal designs. Let $\psi(x, \xi)$ be the Frechet directional derivative in the direction of a one-point design at x,

$$\psi(x, \xi) = \lim_{\varepsilon \to 0^+} \frac{\Phi((1-\varepsilon)M(\xi, \theta) + \varepsilon I(x, \theta)) - \Phi(M(\xi, \theta))}{\varepsilon}.$$

This function is frequently called the sensitivity function. The GET states that under some conditions of the criterion function, $\psi(x, \xi)$ achieves its minimum value, zero, at the support points of the optimal design.

This theorem provides also a bound for the Φ–efficiency of a design, ξ,

$$\text{eff}_\Phi(\xi) \geq 1 + \frac{\min_x \psi(x, \xi)}{\Phi(\xi)}.$$

For D-optimality $\psi(x, \xi^*) = m - \frac{\partial \eta(x,\theta)}{\partial \theta^T} M^{-1}(\xi, \theta) \frac{\partial \eta(x,\theta)}{\partial \theta}$.

For c-optimality the Elfving's graphic method (Elfving, 1952) can be used to construct the optimal design and this will not be needed. The G_I- optimal criterion is not differentiable and for V_I-optimality the sensitivity function will be given in Section 4.

More details on the theory of optimal experimental designs may be found, e.g., by Pazman (1986); Fedorov and Hackl (1997); Atkinson et al. (2007).

2.1. Inverse function theorem for computing the FIM

The experiments are designed for the explanatory variable, x, which is assumed under the control of the experimenter. However, in this work it is considered that $\eta(x, \theta)$ is unknown and invertible within the design space. Nevertheless, the expression of the inverse with respect to x, $\mu(y, \theta) = \eta^{-1}(x, \theta)$, is known. Therefore the FIM, which is given by (3), is defined in terms of y instead of x. In particular, for a specific point the FIM is

$$I(x, \theta) = \frac{\partial \eta(x, \theta)}{\partial \theta} \frac{\partial \eta(x, \theta)}{\partial \theta^T}.$$

We can calculate the FIM in terms of the response variable y through the inverse function theorem and the chain rule for differentiating composed functions. In particular, differentiating the equation

$$x = \mu(y, \theta) = \mu(\eta(x, \theta), \theta),$$

we obtain

$$0 = \left(\frac{\partial \mu(y, \theta)}{\partial y}\right)_{y=\eta(x,\theta)} \frac{\partial \eta(x, \theta)}{\partial \theta} + \left(\frac{\partial \mu(y, \theta)}{\partial \theta}\right)_{y=\eta(x,\theta)}.$$

Then

$$\frac{\partial \eta(x, \theta)}{\partial \theta} = -\left(\frac{\partial \mu(y, \theta)}{\partial y}\right)^{-1}_{y=\eta(x,\theta)} \left(\frac{\partial \mu(y, \theta)}{\partial \theta}\right)_{y=\eta(x,\theta)}. \quad (4)$$

For simplicity of notation the last expression will be called $f(x)$.

This result allows the computation of the FIM and therefore optimal designs on x may be obtained. This is the same model to be used for designing variable y in the inverse model being heteroscedastic instead of homoscedastic, that is with non–constant variance

$$\left(\frac{\partial \mu(y, \theta)}{\partial y}\right)^2.$$

This is meaningful since if the response is considered as the mean model plus some error with constant variance, then the mean model for the explanatory variable could be approximated by the inverse of the original mean plus a different error, now with a non–constant variance coming from the transformation of the model. Summarizing this idea, heteroscedasticity needs to be considered when the calibration model is adjusted. Assuming otherwise constant variance may introduce important biases. This adds some complexity, not only for estimating the parameters of the model, but also for outlining the optimal design procedure.

3. Designs for best fitting the model

The model proposed by Reinhardt et al. (2012) is being considered for the case study. In this model, the function $\eta(Dose, \theta)$ is unknown but its inverse is known and defined by Equation (1). Using Equation (4), we obtain

$$f(netOD) = \frac{\partial \eta(Dose, \theta)}{\partial \theta} = \frac{-1}{\alpha_0 + \beta_0 \gamma_0 \eta(Dose, \theta)^{\gamma_0 - 1}} \begin{pmatrix} \eta(Dose, \theta) \\ \eta(Dose, \theta)^{\gamma_0} \\ \beta_0 \eta(Dose, \theta)^{\gamma_0} \log(\eta(Dose, \theta)) \end{pmatrix},$$

where α_0, β_0, γ_0 are some nominal values assumed for the parameters to compute the optimal design. The function $f(netOD)$ is considered here as a function of $netOD$ since mathematical expression of $\eta(Dose, \theta)$ is not known and it will be considered as the inverse of $\mu(netOD, \theta)$. Thus, the FIM for a design ξ is

$$M(\xi; \theta_0) = \sum_i \xi(Dose_i) I(Dose_i, \theta_0),$$

where $\theta_0^T = (\alpha_0, \beta_0, \gamma_0)$, $netOD$ has been replaced by $\eta(Dose, \theta)$ and

$$I(Dose, \theta_0) = \frac{1}{(\alpha_0 + \beta_0 \gamma_0 \eta^{\gamma_0 - 1})^2} \begin{pmatrix} \eta & \eta^{\gamma_0+1} & \beta_0 \eta^{\gamma_0+1} \log(\eta) \\ \eta^{\gamma_0+1} & \eta^{2\gamma_0} & \beta_0 \eta^{2\gamma_0} \log(\eta) \\ \beta_0 \eta^{\gamma_0+1} \log(\eta) & \beta_0 \eta^{2\gamma_0} \log(\eta) & \beta_0^2 \eta^{2\gamma_0} \log^2(\eta) \end{pmatrix}, \quad (5)$$

where η denotes $\eta(Dose, \theta)$ for simplicity of notation.

Although the optimal design is computed on $Dose$ the function of the original model $\eta(Dose, \theta)$ is unknown, then this function is replaced by $netOD$ in Equation (5). Using the results of Reinhardt et al. (2012), the estimated parameters for radiochromic new generation films EBT3 (in particular the F06110902 film lot and radiation type Proton, Table 1) are being considered as nominal values: $\alpha_0 = 8.32$, $\beta_0 = 49.91$ and $\gamma_0 = 2.6$. Just for some values of γ_0 the inverse function can be computed analytically, otherwise it has to be computed numerically when needed, what makes the problem much more demanding from a computational point of view. The design space on the $netOD$, $\mathcal{X}_{netOD} = [0, b] = [0,0.45]$, corresponds to the design space for the dose, $\mathcal{X}_{Dose} = [0, B] = [0,10.00]$.

3.1. D-optimal designs

In order to compute the $D-$optimal design and due to the number of parameters, a three–point design with equal weights in the support points will be assumed, say $Dose_1$, $Dose_2$ and $Dose_3$ with weights 1/3. The D-optimal is computed on the variable $netOD$ using matrix (5) and then transformed into a design on the variable $Dose$. The determinant of the information matrix for a general three–point design supported on $netOD_1$, $netOD_2$ and $netOD_3$ with weights 1/3 at each point is computed and maximized in the interval $\mathcal{X}_{netOD} = [0, b] = [0,0.45]$. The obtained design, ξ_D^{netOD}, shown in Table 1, is actually D-optimal. Fig. 1 (left) shows

Table 1
Optimal designs (support points and weights within parenthesis when it is the case). The last point of all the designs, either 0.45 or 10, is ommited. The efficiencies of the approximate designs are computed with respect to the D-optimal design except the efficiencies for the c-optimal designs that are the c-efficiencies of the D-optimal design. For the sequences the efficiencies are computed with respect to the corresponding criterion, either D, V_I or G_I, for the optimal approximate design. Superscripts *Ar* and *Ge* stand for arithmetic an geometric optimal designs.

	netOD		*Dose*		Efficiency
Design	Support points (weights)		Support points (weights)		%
ξ_D	0.09 (1/3)	0.27 (1/3)	0.80 (1/3)	3.90 (1/3)	100
$\tilde{\xi}_D$	0.13 (1/3)	0.33 (1/3)	1.33 (1/3)	5.54 (1/3)	87
ξ_α	0.06 (0.78)	0.27 (0.16)	0.54 (0.78)	4.00 (0.16)	53
ξ_β	0.29 (0.48)		4.45 (0.48)		0.3
ξ_γ	0.06 (0.41)	0.27 (0.40)	0.54 (0.41)	4.00 (0.40)	81
ξ_{G_I}	0.13 (0.06)	0.33 (0.30)	1.33 (0.06)	5.54 (0.30)	59
ξ_{V_I}	0.09 (0.19)	0.29 (0.46)	0.84 (0.19)	4.41 (0.46)	93
ξ_D^{Ar}	0.07 0.15	0.22 0.30 0.37	0.60 1.50	2.80 4.60 6.90	84
ξ_D^{Ge}	0.07 0.10	0.15 0.21 0.31	0.60 0.90	1.50 2.60 4.90	85
$\xi_{G_I}^{Ar}$	0.23 0.27	0.31 0.36 0.41	2.90 3.90	5.00 6.40 8.10	37
$\xi_{G_I}^{Ge}$	0.22 0.26	0.30 0.34 0.39	2.80 3.60	4.50 5.80 7.60	29
$\xi_{V_I}^{Ar}$	0.10 0.17	0.240.31 0.38	0.90 1.80	3.20 4.90 7.10	83
$\xi_{V_I}^{Ge}$	0.13 0.17	0.21 0.27 0.35	1.30 1.80	2.60 3.90 6.20	73

$$m - \psi(netOD, \xi_D^{netOD}) = \frac{\partial \eta(Dose, \theta)}{\partial \theta^T} M^{-1}(\xi_D^{netOD}, \theta) \frac{\partial \eta(Dose, \theta)}{\partial \theta}$$

for the design obtained using the transformation of the theorem of the inverse function. It is lower than the number of parameters, $m = 3$, and therefore the sensitivity function, $\psi(netOD, \xi_D^{netOD}) \geq 0$. The equivalence theorem states this design is actually D-optimal.

Transforming the three points through the function (1), with the previous nominal values of the parameters,

$$Dose = 8.32 \times netOD + 49.91 \times netOD^{2.6},$$

the D-optimal design on variable *Dose*, ξ_D^{Dose}, is shown in Table 1. These are the designs (points and weights) related to the Dose, applied in practice for the calibration procedure.

Now a design for *netOD* is computed in the usual way for the function $\mu(netOD, \theta)$ in order to compare it with the previous one and check the loss of efficiency. This is the wrong way of computing it since the roles of the independent and the dependent variables are actually exchanged. In particular the variance term is considered constant in this way missing the heteroscedasticity induced by inverting the model. Then, *netOD* is considered as the explanatory variable and after computing the D-optimal design for *netOD*, we obtain the transformed design for *Dose*. That is, we are assuming $\mu(netOD, \theta)$ as the function of the original model. Using the previous nominal values, the D-optimal design, say $\tilde{\xi}_D^{netOD}$ is given in Table 1.

Fig. 1 (right) shows that

$$m - \psi(netOD, \tilde{\xi}_D^{netOD}) = \frac{\partial \mu(netOD, \theta)}{\partial \theta^T} M^{-1}(\tilde{\xi}_D^{netOD}, \theta) \frac{\partial \mu(netOD, \theta)}{\partial \theta}$$

is lower than the number of parameters, $m = 3$, and therefore the sensitivity function is greater than or equal to zero. The equivalence theorem states this design is actually D-optimal. At this point a design for the response, *Dose*, can be obtained by transforming again the design points using the equation from the model $\mu(netOD, \theta)$ (Table 1).

Apparently this design is quite different from the correct one, e.g. the first and the second points are sensitively larger than the originals. But the efficiency provides better information to compare this design with respect to the right one, ξ_D^{Dose},

$$\text{eff}_D(\tilde{\xi}_D^{Dose}) = \left(\frac{\Phi_D(\xi_D^{Dose})}{\Phi_D(\tilde{\xi}_D^{Dose})} \right)^{\frac{1}{3}} = 0.868,$$

which means, in this particular case, a moderate loss of efficiency of a little less than 15%. This suggests that it is important the use of the right expression of $f(netOD)$ for computing the optimal design. In the following sections the designs obtained will be computed directly for *netOD* using the transformed expression of $f(netOD)$ and then transforming it back to designs on *Dose*.

For the computation of optimal designs it is necessary to guess some initial parameters (nominal values). In order to asses how sensitive this choice is a study for D-optimality has been performed as an example. For measuring the impact of a wrong choice of the nominal values of the parameters the efficiency of the computed design (with the nominal values) has been obtained with respect to different possible true values of the parameters in a neighborhood of the nominal values $\alpha_0 = 8.32$, $\beta_0 = 49.91$, $\gamma_0 = 2.6$. Fig. 2 shows the efficiencies of the D–optimal design for the nominal values of the parameters with respect to different possible true values of the parameters. The design is very robust for the linear parameters α and β, but much care has to be taken for choosing a right nominal value of γ. After a true value $\gamma = 4$ the efficiency starts to drop quickly. This information is important for the experimenter in order to choose the appropriate nominal values. Similar results can be obtained for the other criteria considered in the paper, but they are not shown to avoid been too repetitive.

3.2. c–optimal designs

Frequently the interest is not in estimating all of the parameters of the model, but some linear combination. A particular case is when there is special interest in estimating just one particular parameter. For example, in the case considered here, there is special interest in γ. As mentioned above the Elfving's method is a graph procedure for calculating c-optimal designs. Although the method can be applied to any

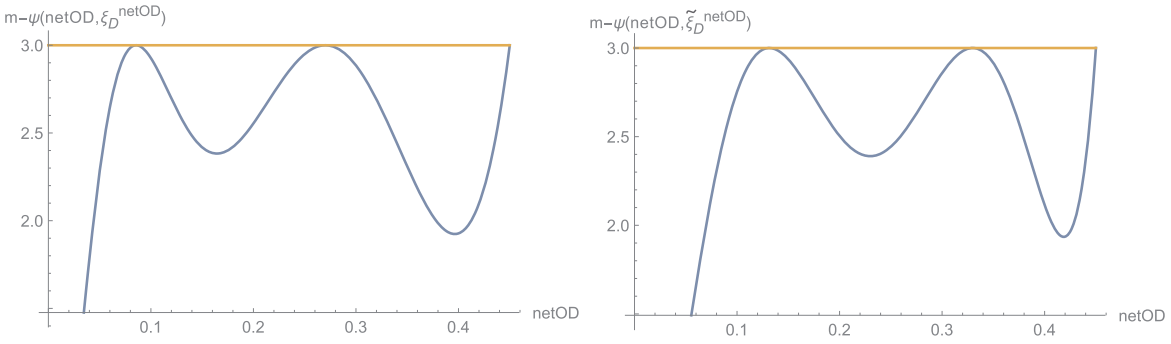

Fig. 1. Sensitivity function for ξ_D^{netOD} (left) and $\tilde{\xi}_D^{netOD}$ (right) designs.

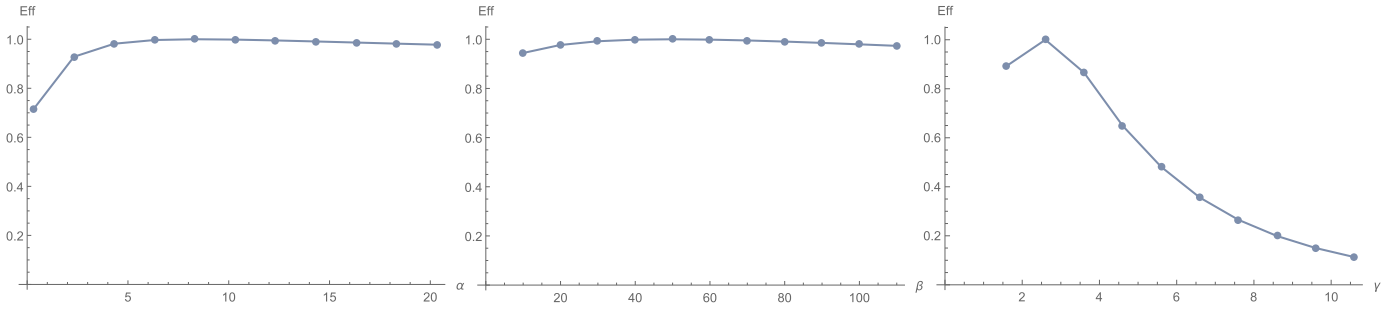

Fig. 2. Efficiencies of the D–optimal design for the nominal values of the parameters with respect to different possible true values of α (left), *beta* (center) y *gamma* (right).

number of parameters it is not easily visualized for more than two parameters. López-Fidalgo and Rodríguez-Díaz (2004) proposed a computational procedure for finding c-optimal designs using Elfving's method for more than two dimensions. Harman and Jurik (2008); Bartroff (2011) have also developed these idea.

In the example considered in this paper there are three parameters and the Elfving locus, convex hull of $f(\mathscr{X}_{netOD}) \cup -f(\mathscr{X}_{netOD})$, where $f(x)$ comes from Equation (4), is hard to be visualized (Fig. 3). Computing the intersection point of the boundary with the straight line defined by vector c for the case of two parameters is rather simple, but for more parameters, even just three, it is not affordable or too difficult. Thus, the procedure detailed by López-Fidalgo and Rodríguez-Díaz (2004) is being applied here. The idea is simple although the formalization is a bit tedious. Once one has the Elfving locus all it is needed is to find the

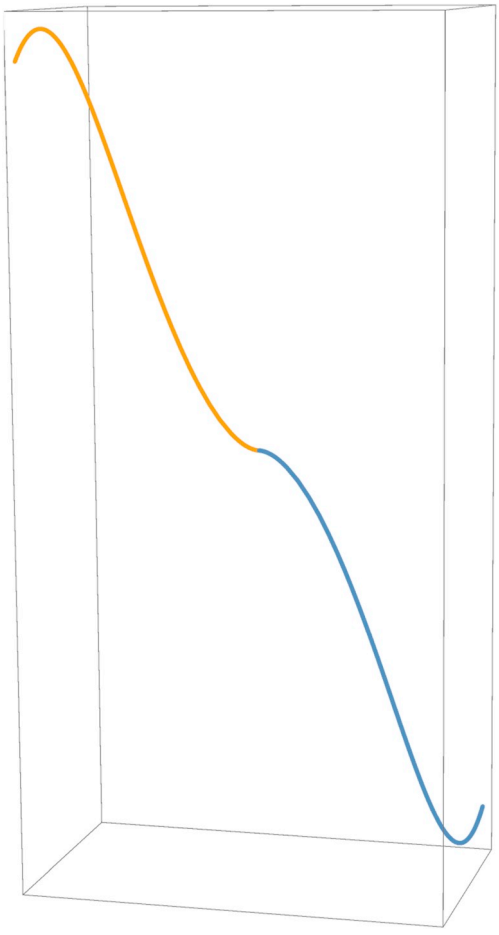

Fig. 3. Curves $f(\mathscr{X}_{netOD}) \cup -f(\mathscr{X}_{netOD})$ for the Elfving's locus, properly scaled to detect the shape details.

intersection of the line defined by vector c (assuming the objective is to estimate $c^T\theta$) with the boundary of this set. The two possible points are just symmetric and produce the same design. This point is a convex combination of at most m points of the set $f(\mathscr{X}_{netOD}) \cup -f(\mathscr{X}_{netOD})$. Those points will be the support points of the c-optimal design and the coefficients of the convex combination will be the weights of the design.

The procedure takes into account that any of the non–null components of a generic point satisfying the conditions of the Elfving locus can be considered as objective function. The only exceptions are the null components of vector c. This point has to be a convex combination of no more than m support points of the set $f(\mathscr{X}_{netOD}) \cup -f(\mathscr{X}_{netOD})$. Thus, a generic point of this type depends on m different points and $m-1$ different coefficients. Now they must satisfy that they are in the straight line defined by c, so the point must be ρc, for some scalar ρ. This gives m linear (in the coefficients) equations with the extra ρ. Solving the linear system on the coefficients they will disappear. Thus, the objective function is any of the components of the point such that $c_i \neq 0$, which depends just on the m points of the design. This is now a standard optimization problem with a number of algorithms and software available for computing the optimum.

In this section c-optimal designs will be computed for estimating each of the parameters in the example considered. The procedure is being explained in more detail for the computation of the c-optimal design for γ, i.e., corresponding to the vector $c^T = (0,0,1)$.

The c-optimal design will be of the form:

$$\xi = \begin{Bmatrix} t & s & u \\ 1-\lambda-\delta & \lambda & \delta \end{Bmatrix},$$

corresponding to a point on the boundary of the Elfving's locus as well as on the line defined by $c^T = (0,0,1)$. A point in the Elfving's locus has to be a convex combination of, at least, three points of $f(\mathscr{X}_{netOD}) \cup -f(\mathscr{X}_{netOD})$. Apart from symmetric situations there are two possibilities. Either the three points come from $f(\mathscr{X}_{netOD})$ (equivalently from $-f(\mathscr{X}_{netOD})$), that is,

$$(x_1, x_2, x_3)^T = (1-\lambda-\delta)f(t) + \lambda f(s) + \delta f(u)$$

or two come from $f(\mathscr{X}_{netOD})$ and one from $-f(\mathscr{X}_{netOD})$ (symmetrically two come from $-f(\mathscr{X}_{netOD})$ and one from $f(\mathscr{X}_{netOD})$), that is,

$$(x_1, x_2, x_3)^T = (1-\lambda-\delta)f(t) + \lambda f(s) - \delta f(u).$$

Fig. 3 shows the point will be of the second kind. At the same time they must be on the line defined by $c^T = (0,0,1)$. Thus, for the second case,

$$(1-\lambda-\delta)f(t) + \lambda f(s) - \delta f(u) = \rho(0,0,1)^T.$$

The equations coming from the two first components give the values of λ and δ as a function of the three points,

$$(1-\lambda-\delta)f_1(t) + \lambda f_1(s) - \delta f_1(u) = 0,$$

$$(1-\lambda-\delta)f_2(t) + \lambda f_2(s) - \delta f_2(u) = 0,$$

that is

$$\lambda(t, s, u) = \frac{f_1(u)f_2(t) - f_1(t)f_2(u)}{f_1(u)(f_2(t) - f_2(s)) - f_1(t)(f_2(s) + f_2(u)) + f_1(s)(f_2(t) + f_2(u))},$$

$$\delta(t, s, u) = \frac{f_1(s)f_2(t) - f_1(t)f_1(u)}{f_1(u)(f_2(t) - f_2(s)) - f_1(t)(f_2(s) + f_2(u)) + f_1(s)(f_2(t) + f_2(u))},$$

where

$$f^T(x) = \left(-\frac{x}{\alpha + \beta\gamma x^{-1+\gamma}}, -\frac{x^\gamma}{\alpha + \beta\gamma x^{-1+\gamma}}, -\frac{\beta\gamma\, x^\gamma \log x}{\alpha + \beta\gamma x^{\gamma-1}}\right).$$

Plugging (6) into the third component the function

$$x_3(t, s, u) = (1 - \lambda(t, s, u) - \delta(t, s, u))f_3(t) + \lambda(t, s, u)f_3(s) - \delta(t, s, u)f_3(u)$$

has to be maximized subject to $t, s, u \in \mathcal{X}_{netOD} = [0,0.45]$. The maximum is reached at $t^* = 0.06$, $s^* = 0.27$, $u^* = 0.45$. The weights are them obtained from Equation (6),

$$1 - \lambda(t^*, s^*, u^*) - \delta(t^*, s^*, u^*) = 0.41, \quad \lambda(t^*, s^*, u^*) = 0.40,$$
$$\delta(t^*, s^*, u^*) = 0.19.$$

Thus, the c-optimal designs before, ξ_γ^{netOD}, and after, ξ_γ^{Dose}, the transformation, are given in Table 1. This is the best design to estimate the parameter γ. Proceeding in a similar way the best designs for estimating α and β are computed. Since the c-optimal design for estimating β is a singular two–point design, and therefore the D–efficiency is zero, the c-efficiencies of the D-optimal design are shown in Table 1 instead of the D–efficiencies. The c-optimal designs for the parameters α and γ have the same support points but different weights, this implies that the D-optimal design has a efficiency greater than 80% for estimating γ but for estimating α that efficiency decreases and it is close to 50%. The c-efficiency of the D-optimal design for estimating parameter β is too low due to fact that the c-optimal design is singular. In all cases the designs (points and weights) applied in practice for the calibration procedure are those related to the Dose in the right hand side of Table 1. For instance, the D-optimal design is 0.80 (1/3), 3.90 (1/3), 10 (1/3). Thus, if we have the chance to realize $n = 30$ experiments a third of them, that is 10 experiments, will be performed for each of the doses 0.80, 3.90 and 10. If n is not a multiple of 3 then some compromise has to be made distributing the leftover replicates.

3.3. Space–filling designs with more than 3 points

Generally, the experimenters do not like designs with few and extreme points. For instance, the design used by Reinhardt et al. (2012) was the collection of equidistant points between 0.2 and 8 using steps of 0.5, that is

{0.2, 0.7, 1.2, 1.7, 2.2, 2.7, 3.2, 3.7, 4.2, 4.7, 5.2, 5.7, 6.2, 6.7, 7.2, 7.7}

for the doses. Using equation (1) the design is transformed into

{0.024, 0.077, 0.12, 0.16, 0.19, 0.22, 0.24, 0.26, 0.28, 0.30, 0.32, 0.34, 0.35, 0.37, 0.38, 0.39}

for *netOD*. The D-efficiency of this design is about 51%. But this design can be very much improved still keeping the requirements of the practitioners. If an exact design with a number of points, say n, is searched then three different, but replicated in some way, points are going to be found always. If more than three different points are wanted then the search has to be forced to a sequence of points following some particular rule, such as an arithmetic or geometric sequence. It is worthy to explain here that this has nothing to do with sequential or adaptive designs. That is the reason they are called space–filling designs since they try to be spread along the design space. In these cases, the D-optimal design can be used as a reference measure of the goodness of the space–filling design considered. López-Fidalgo and Wong (2002) optimized different types of sequences according to D-optimality, including arithmetic, geometric, harmonic and an arithmetic inverse of the trend model. In this section, D-optimal space–filling designs are computed and compared in order to analyze these designs because we knew by personal communication with our physicists collaborators that there was particular interest in them.

The target are exact designs of the type

$$\xi_n = \{Dose_1, Dose_2, ..., Dose_n\},$$

after a transformation from a design on *netOD*.

Each of the two sequences may follow some pattern, e.g. arithmetic or geometric rules. The FIM is computed as:

$$M(\xi_n, \theta) = \frac{1}{n}\sum_i I(Dose_i, \theta) = \frac{1}{n}\sum_i f(netOD_i)f^T(netOD_i).$$

Space–filling designs of size $n = 6$ will be considered in this paper, although the main idea remains for any sample size. Arithmetic and geometric sequences are being considered in the sense explained in what follows. In all the cases appropriate interesting efficiencies will be obtained.

3.3.1. Arithmetic sequences

Taking into account the last point of the design space $\mathcal{X}_{netOD} = [0, b]$ is always in the support of the D-optimal design, the arithmetic sequence will be forced to end at the right extreme of the interval,

$$b(1 - r),\ b\left(1 - r\frac{n-2}{n-1}\right),\ ...,b\left(1 - r\frac{2}{n-1}\right),\ b\left(1 - r\frac{1}{n-1}\right),\ b; \quad r \in (0,1).$$

Just r will be free and it will be optimized. The FIM for this sequence assuming equal weights at each point, i.e. $1/n$, is

$$M(\xi_n, \theta) = \frac{1}{n}\sum_{i=1}^{n} I(Dose_i, \theta) = \frac{1}{n}\sum_{i=1}^{n} f\left(b\left(1 - r\frac{n-i}{n-1}\right)\right)f^T\left(b\left(1 - r\frac{n-i}{n-1}\right)\right).$$

A ratio of $r^* = 0.84$ maximizes the determinant as it is shown in Fig. 4 (left). The arithmetic D-optimal sequences on *netOD* and *Dose*, ξ_D^{Ar}, as well as its D-efficiency are shown in Table 1.

3.3.2. Geometric sequences

We consider geometric sequences starting at the last point, $b = 0.45$, going backwards,

$$r^{n-1}b,\ ...,r^2b,\ rb,\ b.$$

The ratio, r, has to be optimized. The FIM for a design of this type is

$$M(\xi_n, \theta) = \frac{1}{n}\sum_i I(Dose_i, \theta) = \frac{1}{n}\sum_{i=1}^{n} f(r^{n-i}b)f^T(r^{n-i}b).$$

Fig. 4 (right) shows the ratio $r^* = 0.69$ maximizes the determinant. The geometric D-optimal designs (on *netOD* and *Dose*) and its D-efficiency are shown in Table 1. In spite of the designs for both sequences are different the efficiencies are quite similar and high. The reason could be related to the presence of the end-point of the design space, 0.45, in these designs and that the first support point of the sequences, 0.07 is close to the first support point of the D-optimal design, 0.09.

Again, in all cases the designs (points and weights) applied in practice for the calibration procedure are those related to the Dose in the right hand side of Table 1.

Arithmetic and geometric sequences can be considered on the *Dose* as well offering slightly different results.

4. Optimal designs for estimating the right dose

In previous sections the main concern of the experimental design was the precise estimation of the parameters of the model. But the main interest in calibration, from the point of view of the practitioners, is the precise prediction (calibration) of the explanatory variable. Thus, optimal designs in the explanatory variable should be computed to minimize the variance of the prediction in this variable. As mentioned

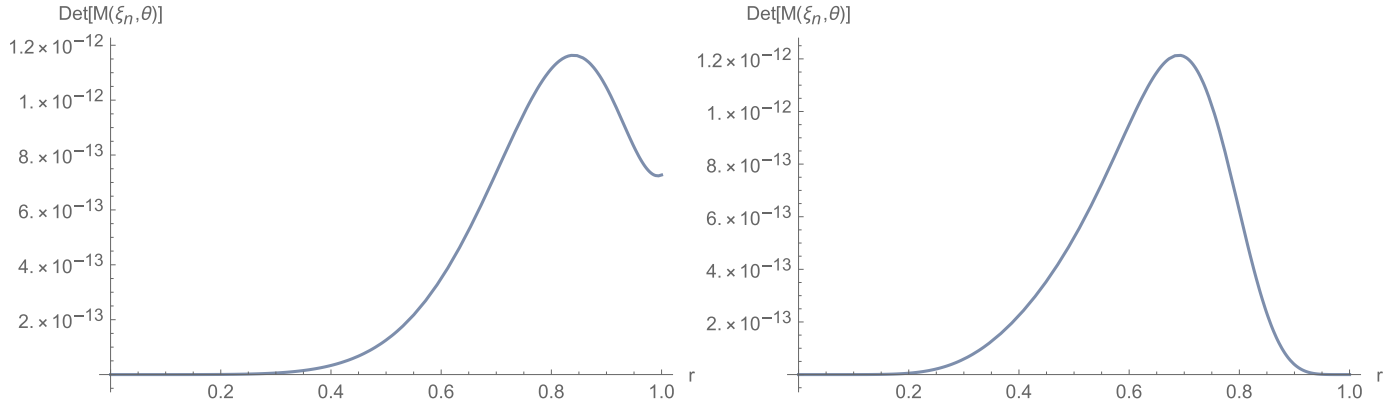

Fig. 4. Determinant of the FIM for an arithmetic (left) and a geometric sequence (right) on *netOD* in function of *r*.

in the introduction, Francois et al. (2004) computed optimal designs for inverse prediction in calibration models, in the particular case where the function of the model is known and invertible. They presented two criteria, G_I-optimality and V_I-optimality in this paper. The aims of these criteria are the same that G- and V-optimality, but for inverse prediction. In this section, we adapt these criteria to the problem faced in this work.

Taking into account that the explanatory variable *Dose* is modelled by the function $\mu(netOD, \theta)$, the variance of the prediction of *Dose* given a value of *netOD* is

$$Var(\hat{Dose}) = \frac{\partial \mu(netOD, \theta)}{\partial \theta^T} M^{-1}(\xi, \theta) \frac{\partial \mu(netOD, \theta)}{\partial \theta}.$$

Then, from this definition of the variance of the explanatory variable we can define the following criteria,

$$\Phi_{G_I}(\xi) = \max_{netOD \in \mathcal{X}_{netOD}} Var(\hat{Dose})$$

$$\Phi_{V_I}(\xi) = \int_{\mathcal{X}_{netOED}} Var(\hat{Dose})\, d(netOD),$$

Both criteria can be optimized in *netOD* and the optimal design in this variable will be transformed to the optimal design in *Dose* following the procedure used in previous sections.

4.1. Computation of G_I- optimal designs

For computing the G_I-optimal design the following Algorithm is proposed.

Algorithm 1.

Step 1. Select an initial design ξ_0 supported on at least three different points.
Step 2. Let ξ_s be the design obtained at step *s*. Determine

$$netOD_s = \arg \max_{netOD \in \mathcal{X}_{netOD}} \frac{\partial \mu(netOD, \theta)}{\partial \theta^T} M^{-1}(\xi_s, \theta) \frac{\partial \mu(netOD, \theta)}{\partial \theta}.$$

Step 3. Let $\xi_{s+1} = (1 - \alpha_s)\xi_s + \alpha_s \xi_{netOD_s}$, where ξ_{netOD_s} is a one-point design with, e.g. $\alpha_s = 1/(s + 4)$, or some optimized step satisfying the conditions $\alpha_s \to 0$, $\sum_s \alpha_s = \infty$.
Step 4. If

$$\frac{\Phi_{G_I}(\xi_s) - \Phi_{G_I}(\xi_{s+1})}{\Phi_{G_I}(\xi_s)} < \delta',$$

where δ' is the given bound for the improvement of the criterion function, then STOP. Otherwise, set $s + 1 \leftarrow s + 2$ and go to Step 2.

Using this Algorithm the G_I- optimal design obtained on *netOD* and the transformed design are given in Table 1, as well as its D-efficiency. The designs (points and weights) applied in practice for the calibration procedure are those related to the Dose in the right hand side of the table.

4.2. Computation of V_I-optimal designs

For computing the V_I-optimal designs, firstly the sensitivity function is calculated in order to define the Algorithm. The sensitivity function for V_I-criterion is

$$\psi\left(Dose, \xi\right) = \int_{\mathcal{X}_{netOD}} \left(\frac{\partial \mu}{\partial \theta^T} M^{-1}\left(\xi, \theta\right) \frac{\partial \mu}{\partial \theta} - \right.$$

$$\left. - \left(\frac{\partial \mu}{\partial \theta}\right) M^{-1}(\xi, \theta) \frac{\partial \eta(Dose, \theta)}{\partial \theta} \frac{\partial \eta(Dose, \theta)}{\partial \theta^T} M^{-1}(\xi, \theta) \frac{\partial \mu}{\partial \theta^T} \right) d(netOD),$$

where $\mu \equiv \mu(netOD, \theta)$ for space saving.

Algorithm 2.

Step 1. Select an initial design ξ_0 supported on at least three different points.
Step 2. Let ξ_s be the design obtained at step *s* and compute

$$netOD_s = \arg \min_{netOD \in \mathcal{X}_{netOD}} \psi(\mu(netOD, \theta), \xi_s).$$

Step 3. Define $\xi_{s+1} = (1 - \alpha_s)\xi_s + \alpha_s \xi_{netOD_s}$, where ξ_{netOD_s} is a one-point design with, e.g. $\alpha_s = 1/(s + 4)$, or some optimized step satisfying the conditions $\alpha_s \to 0$, $\sum_s \alpha_s = \infty$.
Step 4. If

$$1 + \frac{\min_{netOD \in \mathcal{X}_{netOD}} \psi(\mu(netOD, \theta), \xi_{s+1})}{\Phi_{V_I}(\xi_{s+1})} > \delta,$$

where δ is the given efficiency aimed, then STOP. Otherwise, set $s + 1 \leftarrow s + 2$ and go to Step 2.

With this Algorithm the V_I-optimal design obtained on *netOD*, the transformed design and its D-efficiency are shown in Table 1. In order to show how the algorithm works the first iteration of the algorithm is described in detail for the study case.

$$\psi(\mu(netOD, \theta), \xi_s)$$
$$= \frac{y^{5.2}((a_1 \log(y) - a_2)\log(y) - a_3) - a_4 y^{3.6} - a_5 y^{3.6} \log(y) + a_6 y^{3.2} + a_7 y^{1.6} - a_8 y^2 + a_9}{(a_{10} y^{1.6} + a_{11})^2},$$

where $a_1, \ldots, a_{11}$ are specific numbers varying at each iteration of the

Algorithm, not written to avoid a larger formula. The minimum of this function is reached at $netOD_1 = 0.45$.

$$\xi_1 = \begin{Bmatrix} 0.1 & 0.25 & 0.4 & 0.45 \\ 1/4 & 1/4 & 1/4 & 1/4 \end{Bmatrix}.$$

Step 1. The initial design is $\xi_0 = \begin{Bmatrix} 0.1 & 0.25 & 0.4 \\ 1/3 & 1/3 & 1/3 \end{Bmatrix}$.
Step 2. The sensitivity function for this design is
Step 3. Then a new design is generated, $\xi_1 = 3/4\,\xi_0 + 1/4\,\xi_{netOD_1}$, where ξ_{netOD_1} is a one–point design at $netOD_1 = 0.45$. This new design means just adding one new point with the same weight as the other,
Step 4. A bound of the **efficiency** is then

$$1 + \frac{\min_{netOD \in \mathscr{X}_{netOD}} \psi(netOD, \xi_4)}{\Phi_{V_I}(\xi_4)} = 1 + \frac{-707.97}{694.41} = -0.019 < \delta = 0.999.$$

It is a really poor bound since it is even negative and we know the efficiency must be always positive. The reason is that we are still very far from the optimal design. Thus, a new iteration has to be done in the same way until the bound for the efficiency will be near 1 enough. Fig. 5 shows the behavior of these bound along the iterations of the Algorithm. We can appreciate there is a fast convergence although not monotonic.

At each iteration of the algorithm a new point is added to the design. After that we remove those points with a very small weight or we replace points very near by the mean of them adding their corresponding weights. This is a typical technique in the computation of optimal designs since it is well known that the actual optimal design has no many more different points in its support than the number of parameters to be estimated.

Again, the designs (points and weights) applied in practice for the calibration procedure are those related to the Dose in the right hand side of the table. It is remarkable the difference between the D-efficiency of the V_I- and G_I-optimal design. Thus, while the efficiency for the estimation of the parameters of the model is about 60% with G_I-optimality, the V_I-optimal design is a suitable design both for estimation and for prediction.

4.3. A note on the convergence of the algorithms for G_I and V_I–optimality

As seen in Section 2.1 the calibration model takes to a transformed model that is heteroscedastic but the variance of the predictions of the explanatory variable are considered in these two criteria. In order to make it more clear a general situation is considered. Let $f(y) = g(y)/w(y)$ as in (4), where the three functions depend also on θ.

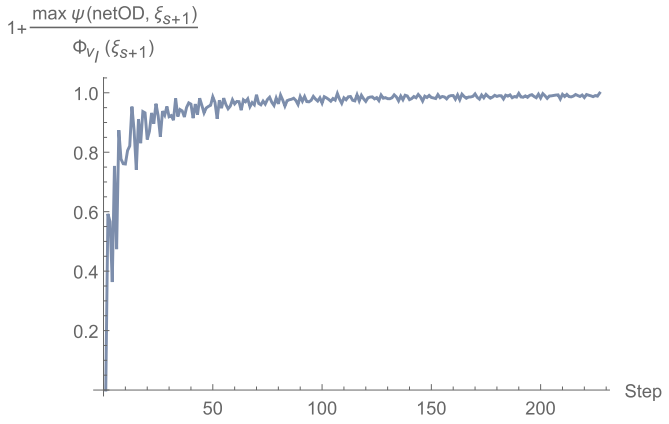

Fig. 5. Convergence of the Algorithm for teh V_I–optimal design.

The parameters are omitted here for brevity taking also into account the nominal values will be provided from the beginning. Then the information matrix of a design is built with f,

$$M(\xi, \theta) = \sum_{y \in \mathscr{X}_y} f(y) f^T(y) \xi(y).$$

V_I–optimality is again a type of V–optimality with a different measure, in particular the Lebesgue measure multiplied by $w^2(y)$,

$$\Phi_{V_I}(M(\xi, \theta)) = \int_{\mathscr{X}_y} g^T(y) M_g^{-1}(\xi) g(y) w^2(y) dx,$$

and therefore the convergence of the Algorithm is known.

For G_I–optimality the convergence is not so simple. The G_I–optimality criterion is defined as

$$\Phi(M(\xi, \theta)) = \max_{y \in \mathscr{X}_y} g^T(y) M^{-1}(\xi) g(y)$$

$$= \max_{y \in \mathscr{X}_y} w^2(y) f^T(y) M^{-1}(\xi) f(y)$$

$$= \max_{y \in \mathscr{X}_y} w^2(y) d(y, \xi),$$

where $d(y, \xi) = f^T(y) M^{-1}(\xi) f(y)$ is proportional to the variance of the prediction of the response as usual. This criterion is different from G–optimality in the factor $w^2(y)$. It is convex and if $w^2(\cdot)$ is continuous in the compact set $\mathscr{X}_y$ then there exists an optimal design $\xi^\star$ with $\Phi^\star = \Phi(\xi^\star) > -\infty$. Our empirical results seem to lead to an optimal design.

4.4. Space–filling designs

Following the procedure of Section 3.3 designs with 6 points have been computed also for these criteria. They are shown in Table 1 with their efficiencies with respect to the criterion considered, G_I- optimality and V_I-optimality. The designs (points and weights) applied in practice for the calibration procedure are those related to the Dose in the right hand side of the table. We can see how these space–filling designs are better for V_I-optimality than for G_I- optimality, where the efficiencies are lower than 40%.

All of the designs in Table 1 were more efficient than the sequence used by the researchers. In particular, Table 2 shows the efficiencies of the design used by the practitioners with respect to the computed designs in this paper. This stresses the importance of using a good design.

4. Conclusions and further work

By using the Inverse Function Theorem, optimal designs were computed on the dependent variable for estimating the parameters of the model and for the prediction of the independent variable considering a dosimetry model. From the perspective of the estimation of the parameters, the D-optimal design was computed directly on the response variable and then it was transformed into a design on the explanatory variable. This is not the proper design to be computed and may displayed an important loss of efficiency as is the case in our example with respect to the right one. The transformed model actually becomes heteroscedastic. This needs to be considered when the calibration model is adjusted in order to avoid mispecification of the right model. Optimal designs for estimating each parameter of the model were also computed. This allowed to measure how efficient was the D-

Table 2
Efficiencies of the experimental design used in practice with respect to different criteria.

Criterion	D	G_I	V_I	C_1	C_2	C_3
Efficiency	0.51	0.07	0.34	0.19	0.18	0.24

optimal design for estimating each of them, displaying a good efficiency for estimating parameter γ but neither for α nor for β.

Taking into account that this model has calibration purposes, the G_I- and V_I-optimal designs have been computed in order to optimize the inverse prediction. Moreover, algorithms for computing them are provided in this paper.

The main contribution of this work is to establish the methodology for computing optimal designs when the function of the model is given as a function of the response variable and there is not a closed-form available for its inverse. This situation is common with calibration models as the dosimetry model considered in this work. Thus, the optimal designs computed cover different aims from the estimation of the parameters of the model to the maximization of the precision of the measured dose.

CRediT authorship contribution statement

Jesús López-Fidalgo: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft, Writing - review & editing, Funding acquisition, Supervision. **Mariano Amo-Salas:** Conceptualization, Methodology, Software, Formal analysis, Writing - original draft, Writing - review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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