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A computer tool for a minimax criterion in binary response and heteroscedastic simple linear regression models

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ABSTRACT

Background and objective: Binary response models are used in many real applications. For these models the Fisher information matrix (FIM) is proportional to the FIM of a weighted simple linear regression model. The same is also true when the weight function has a finite integral. Thus, optimal designs for one binary model are also optimal for the corresponding weighted linear regression model. The main objective of this paper is to provide a tool for the construction of MV-optimal designs, minimizing the maximum of the variances of the estimates, for a general design space.
Methods: MV-optimality is a potentially difficult criterion because of its nondifferentiability at equal variance designs. A methodology for obtaining MV-optimal designs where the design space is a compact interval $[a, b]$ will be given for several standard weight functions.
Results: The methodology will allow us to build a user-friendly computer tool based on Mathematica to compute MV-optimal designs. Some illustrative examples will show a representation of MV-optimal designs in the Euclidean plane, taking a and b as the axes. The applet will be explained using two relevant models. In the first one the case of a weighted linear regression model is considered, where the weight function is directly chosen from a typical family. In the second example a binary response model is assumed, where the probability of the outcome is given by a typical probability distribution.
Conclusions: Practitioners can use the provided applet to identify the solution and to know the exact support points and design weights.

1. Introduction

Pioneering and comprehensive work in the area of minimax designs includes Elfving [1]. He uses minimax designs, that is, E-optimal designs, aiming to minimize the maximum of the variances of any unitary linear combination of the parameters. Dette, Heiligers and Studden [2] generalized the minimax criterion to any norm over a euclidean space [2]. The MV-optimal criterion considers the ℓ_1-norm, therefore it minimizes the largest of the variances of the parameter estimates of the model. MV-optimality is a potentially difficult, but

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meaningful, criterion because of its nondifferentiability at equal variance (EV) designs. Ford [3] proved some general results for this criterion, specifically, he found the directional derivative, a key tool for checking the MV-optimality of a design. Later Jacroux [4] called it MV-optimality and used it for block designs. López-Fidalgo [5] determined the gradient of this criterion function on a partition of the information matrix space, specifically, in the regions where the criterion function is differentiable. Dette [6] further considered a minimax criterion of standardized variances. Uddin [7] computed MV-optimal block designs when observations within each block are correlated. Hedayat and Yang [8] and Hedayat and Zheng [9] used MV-optimality as a convenient criterion for comparing test treatments with a control treatment using crossover designs and provided sufficient conditions for a crossover design to be simultaneously A-optimal and MV-optimal. Yan and Locke [10] generalized these results to the situation in which subject effects are assumed to be random. Kounias and Chalikias [11] used MV-optimal repeated measurement designs when a treatment–period interaction exists.

Binary response models are of much interest in a variety of areas, where optimal designs have been computed. From optimal experimental design theory, these nonlinear models can be seen as weighted linear regression models when the square root of the weight function has a finite integral ([12,13], Proposition 5.1). Thus, we consider the problem of finding minimax designs for a weighted linear regression model. Much of the research on binary regression models has been focused on D-optimality for the Logistic model. The Probit model has also been figured and a few results have been given for the Double Exponential, Double Reciprocal, complementary Log–Log or skewed Logit models [14]. Myers, Myers and Carter [15] focused on the average prediction variance for the Logistic model. Sitter and Torsney [16] considered two variables for Logit and Probit models and gave D- and c-optimal designs. As is well known, these models are nonlinear, so the information matrix depends on the parameters. Some authors have considered sequential designs as a solution to this problem of parameter dependence [17,18]. Some other authors have used a Bayesian approach [19–21]. Scazzero and Ord [22] computed D-optimal designs for the Logistic model with restrictions on the design weights. Burridge and Sebastiani [23] provided D-efficient designs not depending on the parameters. Haines [24] showed a geometric framework for computing Bayesian and minimax designs for the logistic models with known slope and Agin and Chalonr [21] gave an analytical approach to the problem introduced by Haines [24] comparing the results. King and Wong [25] introduced a new criterion minimizing the largest determinant of the inverse of the information matrix on the parametric space and provided an algorithm for the Logistic model. Mathew and Sinha [26] optimized some functions of the parameters for the Logistic model. Zocchi and Atkinson [27] considered the more complex case of multinomial Logistic models. Biedermann, Dette and Pepelyshev [28] provided optimal designs for percentile estimation of a quantal response curve considering a maximin criterion leading to robust designs. Dose–response problems frequently involve binary response models either for measuring efficacy or toxicity. There is an extensive literature of optimal designs for particular dose–response models [29,30].

López-Fidalgo, Torsney and Ardanuy [13], Torsney and López-Fidalgo [31,32] reported MV-optimal designs for symmetric weight functions and symmetric intervals, for simple linear regression in a general interval and demonstrated numerically that for every compact interval $[a, b]$ there is always a 2-point MV-optimal design for the Logistic model and gave the whole picture for different regions in the semi-plane $b > a$, where a c_1-, a c_2- or an EV-optimal design is MV-optimal. Hereafter, we denote by c_j-optimal, the c-optimal design for the j-th parameter. Dette and Sahm [33] gave a method for computing MV-optimal designs for two different parametrizations of binary regression models. Using invariant properties the corresponding standardized SMV-optimal designs are derived easily. Some results for implementing this method computationally were given by López-Fidalgo and Tommasi [34]. López-Fidalgo and Wong [35] and Imhof, López-Fidalgo and Wong [36] compared MV- and SMV-optimal designs for binary response models.

In this paper we obtain MV-optimal designs for a binary response model, considered as a weighted linear regression model. In particular, the results of López-Fidalgo, Torsney and Ardanuy [13] and Torsney and López-Fidalgo [32] are generalized for a general non-symmetric interval, as well as for a class of weight functions typically used in biomedical sciences (Probit, Normal density, Double Exponential and Double Reciprocal). One of the novelties of the present work is to provide the nature of EV-optimal designs with three support points that appear when the Double Exponential or Double Reciprocal is considered. Moreover, the Equivalence Theorem for MV-optimality defined here takes into account the cases where the criterion is differentiable or not. Despite the interest on the MV-optimality criterion for binary response models, we have noted a lack of user-friendly software. We develop an *applet* for obtaining MV-optimal designs. The user/practitioner needs only to specify the weighting function (or a pdf) and the interval for the design variable. Recently, some software has been developed around optimal design of experiments in different platforms such as MATLAB or R [37–41]. For MV-optimality, Tommasi and López-Fidalgo [42] provided a practical procedure to implement computationally some standardized minimax designs for some particular binary response models.

The outline of the paper is as follows. Section 2 outlines definitions and background on minimax criteria and the models considered in this work. Then, the design problem is introduced and an Equivalence Theorem for MV-optimality criteria is provided. In Section 3 we describe the structure of MV-designs. In Section 4 the user-friendly *applet* is presented. The utility of the *applet* is illustrated with two examples. Section 5 concludes with a discussion.

2. Theoretical background

2.1. *Optimal design theory*

The theory of optimal experimental design provides tools for computing good designs from different points of view. A model relating uncorrelated observations (responses), $y_1, \ldots, y_n$ with some explanatory variables with the corresponding values $x_1, \ldots, x_n$ that are under the control of the experimenter is defined through a pdf,

$f(y_i, x_i; \theta), i = 1, \ldots, n,$

where θ is the vector of parameters to be estimated. The set of values $x_1, \ldots, x_n$, selected from a design space χ, is usually called an *exact experimental design of size n*. Some of these values may be repeated, e.g., when there are k different values, say $x_1, \ldots, x_k$, without loss of generality. This suggests the definition of a finite discrete probability distribution assigning to each point a weight proportional to the number of replicates. Using this idea Kiefer [43] introduced the concept of an *approximate* design, ξ, as any probability measure defined on a design space χ, where the design points may be chosen. The per observation *Fisher information matrix* associated to an approximate design ξ is,

$$M(\xi) = \int_\chi I(x)\xi(dx), I(x) = \mathrm{E}\left(\frac{-\partial^2 L(\theta)}{\partial \theta^2}\right), \tag{1}$$

where $L(\theta)$ is the log-likelihood function. For non-linear models this matrix depends on the parameters.

Caratheodory's theorem applied to the space of symmetric matrices allows restrictions to finite designs,

$$\xi = \begin{Bmatrix} x_1 & \ldots & x_k \\ p_1 & \ldots & p_k \end{Bmatrix},$$

where $\xi(x_i) = p_i$ defines the mass probability function. A realizable design has to be "approximated" to $n_i \approx n \times p_i$ replicates for the i-th experiment.

The inverse of the FIM is asymptotically proportional to the covariance matrix of the estimates of the parameters of the model. Thus, a criterion function can be defined on the FIM, $\Phi[M(\xi)]$, paying attention to one aspect to be optimized. A design minimizing Φ is called Φ-optimal. With some mild properties and convexity of Φ, the so called General Equivalence Theorem (GET) establishes that a design, ξ^*, is Φ-optimal if, and only if:

$$\partial\Phi[M(\xi^*), M(\xi)] \geq 0, \quad \xi \in \Xi, \tag{2}$$

where Ξ is the set of all designs and $\partial\Phi[M, N]$ is the usual directional derivative of Φ at M in the direction of $N - M$. There is a more friendly version of the theorem for differentiable criteria, but that is not the case in this paper.

An important tool to measure the performance of a design, ξ, from the point of view of a criterion, Φ, is given by its efficiency relative to the optimum ξ^*:

$$eff_\Phi(\xi) = \frac{\Phi[M(\xi^*)]}{\Phi[M(\xi)]}.$$

If the criterion is positively homogeneous then there is a statistical interpretation of this *efficiency* in the percentage of the saving of sample size to attain the same results with the optimal design. A lower bound for the efficiency of any design ξ is:

$$1 + \frac{\min_{\xi' \in \Xi} \partial\Phi[M(\xi), M(\xi')]}{\Phi[M(\xi)]}. \tag{3}$$

From now on the design will be omitted in the matrix if it does not lead to confusion.

2.2. *Minimax criteria*

Dette, Heiligers and Studden [2] generalized the minimax criterion of Elfving [1] to any norm over the Euclidean space,

$$\Phi_{|\,|}[M(\xi)] = \max\{c^\top M^{-1}(\xi)c : c \in \mathbb{R}^m, |c| = 1\},$$

where $M(\xi)$ is the per observation FIM under a design ξ over a compact set χ. In particular, for the ℓ_1-norm, $|c|_1 = \sum_{i=1}^m |c_i|$ we have the MV-optimality criterion,

$$\Phi_{|\,|_1}[M(\xi)] = \max_i e_i^\top M^{-1}(\xi)e_i \propto \max_i \mathrm{var}_\xi(\hat{\theta}_i) = \Phi_{MV}[M(\xi)],$$

where $\theta_i, i = 1, 2, \ldots, m$, are the model parameters. Then, the MV-optimal design minimizes the largest of the variances of the parameter estimates of the model.

2.3. *Weighted linear regression and binary response model*

We consider the weighted linear regression model:

$$E(y) = \gamma\sqrt{w(x)} + \delta x\sqrt{w(x)}, \mathrm{var}(y) = 1, x \in [a, b] \tag{4}$$

where y is a response variable, x is a design variable restricted to the interval $[a, b]$, and γ, δ are unknown parameters.

From the design point of view this model is equivalent to several models. On the one hand, it is equivalent to an heteroscedastic simple regression model with $\mathrm{var}(y) = 1/w(x)$. On the other hand, it is equivalent to the nonlinear regression model for a binary response v,

$$E(v) = F(\alpha + \beta z), \mathrm{var}(v) = F(\alpha + \beta z)[1 - F(\alpha + \beta z)]. \tag{5}$$

Under the parameter dependent linear transformation $x = \alpha + \beta z$ local D-optimal and c-optimal design problems transform to equivalent design problems for the above linear model [12]. Then the FIM for this nonlinear model is the information matrix of model (4). For this, $w(x)$ is of the form:

$$w(x) = \frac{f^2(x)}{F(x)[1 - F(x)]} \tag{6}$$

where $F(x)$ is a cdf and $f(x)$ is the corresponding pdf. The function $f(x)$ is symmetric if, and only if $w(x)$ is symmetric. In proposition 5.1 López-Fidalgo, Torsney and Ardanuy [13] established the necessary conditions, namely, $w(x) \geq 0$ and $\int_{-\infty}^{\infty} \sqrt{w(x)}dx < \infty$, for $w(x)$ to identify a binary regression weight with the form (6). In such cases the cdf is $F(x) = \frac{1}{2}\left[1 - \cos\left(\int_{-\infty}^{x} \sqrt{w(z)}dz\right)\right]$.

Then we consider in this paper several choices of $f(x)$, the Logistic, Normal (i.e., Probit regression), Double Exponential and Double Reciprocal. Moreover we consider other weight functions which occur in the literature on weighted linear regression. These are often of the form $w(x) \propto f(x)$, where $f(x)$ is a probability density function. Specifically, we provide results using, as $w(x)$, the symmetric Normal density. In Section 4, for illustrating the use and results of our computer tool and for showing its potential, we use as weighting functions the Double Exponential, from the category of weight functions obtained with a given $f(x)$, and the Normal as a direct value of $w(x)$.

Note that for many weight functions including the above there need to be no restrictions on a, b. In the case of $w(x)$ as (6) the widest possible choice of $[a, b]$, say χ_w, will be the sample space of the random variable with pdf $f(x)$. For instance $\chi_w = \mathbb{R}$ in the case of the Logistic distribution. Both of the functions $\sqrt{w(x)}$ and $x\sqrt{w(x)}$ converge to zero as $x \to \pm\infty$.

2.4. MV-optimal design problem

The design problem for the MV-criterion under model (4) is to find for all $[a, b]$ the probability measure ξ on $[a, b]$ which solves:

$$\min_{\xi} \max\left\{\mathrm{var}_{\xi}(\hat{\gamma}), \mathrm{var}_{\xi}\left(\hat{\delta}\right)\right\}.$$

Let X denote a random variable with probability measure ξ. Then the FIM is:

$$M = \begin{pmatrix} E_{\xi}[w(X)] & E_{\xi}[Xw(X)] \\ E_{\xi}[Xw(X)] & E_{\xi}[X^2 w(X)] \end{pmatrix}$$

and

$$\mathrm{var}_{\xi}(\hat{\gamma}) \propto \frac{E_{\xi}[X^2 w(X)]}{\det M} = c_1^{\top} M^{-1} c_1,$$

$$\mathrm{var}_{\xi}\left(\hat{\delta}\right) \propto \frac{E_{\xi}[w(X)]}{\det M} = c_2^{\top} M^{-1} c_2,$$

where $c_1^{\top} = (1, 0)$, and $c_2^{\top} = (0, 1)$. Then

$$\Phi_{MV}(M) = \max\left\{\frac{E_{\xi}[(X^2 w(X))]}{\det M}, \frac{E_{\xi}[w(X)]}{\det M}\right\}.$$

Remark 2.1. Denoting $\rho = Corr\left(\hat{\gamma}, \hat{\delta}\right)$ we can establish the relationships,

$$\det M = E_{\xi}[w(X)] E_{\xi}[X^2 w(X)][1 - \rho^2],$$
$$c_1^{\top} M^{-1} c_1 = \{E_{\xi}[w(X)](1 - \rho^2)\}^{-1},$$
$$c_2^{\top} M^{-1} c_2 = \{E_{\xi}[X^2 w(X)](1 - \rho^2)]\}^{-1}.$$

Remark 2.2.

1. *If $[a, b] \subseteq [-1, 1]$ then MV-optimality is the same as c_2-optimality.*
2. *If $b \le -1$ or $a \ge 1$ then MV-optimality is the same as c_1-optimality.*
3. *In other cases Equal Variances designs must be checked. The MV-optimal design will be an EV-optimal design if the common value of the two c-criteria at this design is smaller than their values at each other's optimal design; i.e., than the value of the c_1-criterion at the c_2-optimal design and vice versa.*

2.5. General conditions of MV-optimality

Ford [3] found the directional derivative of Φ_{MV} at M in the direction of $N - M$ to be:

$$\partial\Phi_{MV}(M, N) = \{M^{-1} - M^{-1} N M^{-1}\}_{ss},$$

where $\{M^{-1}\}_{ss}$ is the biggest diagonal element of M^{-1}. For example, if the second entry of the diagonal of M^{-1} is the biggest one, then $ss = 22$ and the directional derivative will be $\{M^{-1} - M^{-1} N M^{-1}\}_{22}$. If there are r coincident biggest diagonal elements in M^{-1}, say $ss_1, \ldots, ss_r$, then $ss = \arg\min_{ss_i} \{M^{-1} N M^{-1}\}_{ss_i}$. We will say that a matrix N has the ss_j property if,

$$\partial\Phi_{MV}(M, N) = \{M^{-1} - M^{-1} N M^{-1}\}_{ss_j}.$$

For instance, if M is a 2×2 matrix with equal diagonal elements with $\{M^{-1}\}_{11} = \{M^{-1}\}_{22}$ then $ss = \arg\min\left[\{M^{-1} N M^{-1}\}_{11}, \{M^{-1} N M^{-1}\}_{22}\right]$. Note that, if N has equal diagonal elements both terms have the same value. That criterion function is not differentiable at EV-optimal designs. But it is differentiable at non-equal variance designs, because MV-optimality is the same as c-optimality for $c = c_1$ or $c = c_2$ (see Remark 2.2). The c-optimality problem has been considered in Ford, Torsney and Wu [12] for several weight functions.

Theorem 2.1. (Equivalence theorem for MV-optimality)*Assume model (4). According to the GET (2), in order to check the optimality of an information matrix M of a design ξ, it is necessary to check the directional derivative, $\partial\Phi_{MV}(M, N)$, for $N \in \mathcal{M}$. The directional derivative must be non-negative for optimal designs.*

1. *If Φ_{MV} is differentiable at M (i.e., different diagonal elements) we need only calculate $\partial\Phi_{MV}(M, N)$ for N given by 1-point design information matrices $M_x = vv^{\top}$, $v^{\top} = \left(\sqrt{w(x)}, x\sqrt{w(x)}\right)$.*

$$\partial\Phi_{MV}(M, M_x) = \begin{cases} \dfrac{f}{df - e^2} - \dfrac{w(x)(f - ex)^2}{(df - e^2)^2} & \text{if } \xi \text{ is } c_1 - \text{optimal}, \\[2ex] \dfrac{d}{df - e^2} - \dfrac{w(x)(dx - e)^2}{(df - e^2)^2} & \text{if } \xi \text{ is } c_2 - \text{optimal}, \end{cases}$$

where $M = \begin{pmatrix} d & e \\ e & f \end{pmatrix}$. This must be greater than or equal to zero for all $x \in [a, b]$.

2. *If Φ_{MV} is not differentiable at M (equal diagonal elements, i.e., EV), we need to calculate the directional derivative for $N \in \mathcal{M}$ which are the generators of the convex sets $\mathcal{M}_{ss_i}$, $i = 1, \ldots, m$, of the matrices with the ss_j property and which are feasible optimal solutions. In our case, for two types of generators of $\mathcal{M}_{ss_1}$ and $\mathcal{M}_{ss_2}$, that is*
   (a) *For 1-point design information matrices $M_x = vv^{\top}$, $v^{\top} = \left(\sqrt{w(x)}, x\sqrt{w(x)}\right)$.*

$$\partial\Phi_{MV}(M, M_x) = \begin{cases} \dfrac{d}{d^2 - e^2} - \dfrac{w(x)(d - ex)^2}{(d^2 - e^2)^2} & \text{if } x^2 > 1, \\[2ex] \dfrac{d}{d^2 - e^2} - \dfrac{w(x)(dx - e)^2}{(d^2 - e^2)^2} & \text{if } x^2 < 1, \end{cases}$$

Table 1 – Weighting functions considered (see (6) for *f*(*x*)) and critical values for the support points of optimal designs, b^* (c-optimal), b^{**} (2-point EV-optimal) and b^{***} (3-point EV-optimal).

Name	$w(x)$ or $f(x)$	b^*	b^{**}	b^{***}
Normal	$w(x)=\exp(-x^2/2)$	1.414	1	–
Logistic	$f(x)=\frac{\exp(-x)}{[1+\exp(-x)]^2}$	2.399	1	–
Probit	$f(x)=\frac{1}{\sqrt{2\pi}}\exp\left(\frac{-x^2}{2}\right)$	1.575	1	–
Double Exponential	$f(x)=\frac{1}{2}\exp(-\lvert x\rvert)$	1.841	1	1.594
Double Reciprocal	$f(x)=\frac{1}{2}(1+\lvert x\rvert)^{-2}$	1.618	1	1.414

where $M=\begin{pmatrix} d & e\\ e & d\end{pmatrix}$. *This must be greater than or equal to zero for all* $x \in [a, b]$.

(b) *For N corresponding to a 2-point EV design,* $N=\begin{pmatrix} g & h\\ h & g\end{pmatrix}$

$$\partial\Phi_{MV}(M,N)=\frac{(d,e)\begin{pmatrix} d-g & h\\ h & -g-d\end{pmatrix}\begin{pmatrix} d\\ e\end{pmatrix}}{(d^2-e^2)^2}.$$

This must be greater than or equal to zero for $|x_1|\le 1, |x_2|\ge 1$ *and* $x_1, x_2 \in [a, b]$.

Proof.

1. If the matrix M has different diagonal elements then $M(\xi)^{-1}_{11} > M(\xi)^{-1}_{22}$ when ξ is the c_1-optimal design or, vice versa, $M(\xi)^{-1}_{22} > M(\xi)^{-1}_{11}$ when it is the c_2-optimal design. Then $\partial\Phi_{MV}(M,N)$ is $\{M^{-1}-M^{-1}NM^{-1}\}_{11}$ or $\{M^{-1}-M^{-1}NM^{-1}\}_{22}$.
2. When matrix M has equal diagonal elements ($d = f$), we shall compute the directional derivative in the direction of $N - M$, for any information matrix

$$N=\sum_j p_j w(x_j)\begin{pmatrix} 1\\ x_j\end{pmatrix}(1,x_j),\quad \xi=\begin{Bmatrix} x_1 & \cdots & x_k\\ p_1 & \cdots & p_k\end{Bmatrix}.$$

Then, the matrix $M^{-1}NM^{-1}$ has equal diagonal elements if $\sum_j p_j w(x_j)(x_j^2-1)=0$, regardless of the elements of M. Therefore the weights of the design have to satisfy the following equations,

$$\sum_j p_j = 1,\quad \sum_j d_{x_j} p_j = 0,$$

where $d_x = w(x)(x^2-1)$. The generators correspond to the vertices of the simplex defined above. By a linear programming reasoning the Basic Feasible Solutions have exactly 2 nonzero components, that is, 2- and possibly 1-point designs. In particular the design weights are

$$p_1=\frac{d_{x_2}}{d_{x_2}-d_{x_1}} \text{ and } p_2=\frac{d_{x_1}}{d_{x_1}-d_{x_2}}. \tag{7}$$

But $p_1, p_2 > 0$ if $|x_2|>1, |x_1|<1$. In this case,

$$E[w(X)]=E[X^2w(X)]=w(x_1)w(x_2)(x_2^2-x_1^2)/D,$$
$$E[Xw(X)]=w(x_1)w(x_2)(x_1x_2+1)(x_2-x_1)/D,$$

where $D=d_{x_2}-d_{x_1}$.

3. MV-optimal designs

It is known that there exists an MV-optimal design with 2 or 3 support points in the case of 2 parameter models, perhaps none of them symmetric. Sitter and Wu [14] considered a bimodal weight function which needs 4 points for a symmetric design. In this work several classes of weight functions, all unimodal, are considered. But we note that López-Fidalgo and Tommasi [34] provided an example where a unimodal symmetric weight function for the particular parametrization $f(y=1,x;\theta)=F[\beta(x-\mu)]$ needs 4-points for a MV-optimal symmetric design. Since the interval is not symmetric we no longer focus on symmetric designs.

In the following we establish the structure of MV-optimal designs based on the structure of c- and EV-optimal designs on each interval $[a, b]$, that is, the number of support points of the design and what they are.

Assuming model (4), when the MV-optimal design is a c-optimal design, it has two support points on the interval $[a, b]$. Ford, Torsney and Wu [12] using theorem 3.1.4 of Fellman [44] showed that these two support points are a fixed pair of points, the same for any c. Their structure is as follows:

$$\text{Supp}\{\xi_c^*\}=\begin{cases}\{a^*,b^*\} & a\le a^*<b^*\le b\\ \{a,\min\{b,b^*(a)\}\} & a^*\le a<b^*\le b\\ \{\max\{a,a^*(b)\},b\} & a\le a^*<b\le b^*\\ \{a,b\} & a^*\le a<b\le b^*\end{cases} \tag{8}$$

where $\text{Supp}(\xi_c^*)$ denotes the set of support points of the c-optimal design ξ_c^*; and, assuming $\chi_w=[A,B]$, where A and B are chosen as large as necessary in absolute value, a^*, b^* are the support points on χ_w; $b^*(a)$ is the upper support point on $[a, B]$; $a^*(b)$ is the lower support point on $[A, b]$. The values of $b^*(a^*=-b^*)$ for the weights considered in this paper can be seen in Table 1, obtained from Ford, Torsney and Wu [12]. It is important to stress that if a c-optimal design is to be a

MV-optimal design it must ensure estimation of both parameters and so it has at least two support points.

When the MV-optimal design is an EV-optimal design, it may have two or three support points on the interval $[a, b]$. We found empirically that weight functions that are differentiable at 0 have only two support points. On the other hand, there are weight functions that depend on x only through $|x|$ and so there are not differentiable. Then, they have a vertex at $x = 0$ and the optimal designs put some positive weight at zero.

The structure of the support points for a 2-point EV-optimal designs is similar to that of the c-optimal designs with a double star,

$$\mathrm{Supp}\{\xi^{*}_{2EV}\} = \begin{cases} \{a^{**}, b^{**}\} & a \le a^{**} < b^{**} \le b \\ \{a, \min\{b, b^{**}(a)\}\} & a^{**} \le a < b^{**} \le b \\ \{\max\{a, a^{**}(b)\}, b\} & a \le a^{**} < b \le b^{**} \\ \{a, b\} & a^{**} \le a < b \le b^{**} \end{cases} \tag{9}$$

where a^{**}, b^{**}, $a^{**}(b)$ and $b^{**}(a)$ have the same meaning as above. López-Fidalgo, Torsney and Ardanuy [12] calculated the values of $b^{**}(a^{**} = -b^{**})$ for different models (see Table 1).

The structure of the support points for a 3-point EV-optimal design is as follows:

$$\mathrm{Supp}\{\xi^{*}_{3EV}\} = \begin{cases} \{a^{***}, m^{***}, b^{***}\} & a \le a^{***} < b^{***} \le b \\ \{a, m^{***}, \min\{b, b^{***}(a)\}\} & a^{***} \le a < b^{***} \le b \\ \{\max\{a, a^{***}(b)\}, m^{***}, b\} & a \le a^{***} < b \le b^{***} \\ \{a, m^{***}, b\} & a^{***} \le a < b \le b^{***} \end{cases} \tag{10}$$

where m^{***} is a middle support point between the other two support points and the meaning of a^{***}, b^{***}, $a^{***}(b)$ and $b^{***}(a)$ is similar to the previous design structures. The value for b^{***} $(a^{***} = -b^{***})$ for the models considered in this work is shown in Table 1. Note that the middle support point will be zero for the weight function with a vertex at zero, as is said above.

Remark 3.1. *In practice, the first case of c-optimality, $\mathrm{Supp}\{\xi^{*}_{c}\} = \{a^{*}, b^{*}\}$, is never MV-optimal. Finally, consider the last case of 2-point EV-optimal designs, $\mathrm{Supp}\{\xi^{*}_{2EV}\} = \{a, b\}$, and 3-point EV-optimal designs, $\mathrm{Supp}\{\xi^{*}_{3EV}\} = \{a, m^{***}, b\}$. Neither are the MV-optimal design.*

Remark 3.2. *Regarding the mass probability function $\xi(x_i) = p_i$, or design weights (do not confuse with the weight function), there is a well known result for c-optimality:*

$$p_i = \frac{|x_i|}{|x_1| + |x_2|}, i = 1, 2, \tag{11}$$

where $(x_1, x_2) = \mathrm{Supp}\{\xi^{*}_{c}\}$.

For a 2-point EV-optimal design the optimal design weights can be seen in (7). For a 3-point EV-optimal design the following reasoning can be used. We wish to find a design, if it exists, on $[a, b]$ which minimizes the two variances subject to them being equal. Let us assume a 3-point EV design,

$$\begin{Bmatrix} l & m & u \\ p_l & p_m & p_u \end{Bmatrix}.$$

The EV constraint implies that the weights must satisfy the two equations:

$$\begin{cases} p_l + p_m + p_u = 1 \\ d_l p_l + d_m p_m + d_u p_u = 0. \end{cases}$$

where $d_i = w(i)(i^2 - 1), i = l, m, u$. Let $r_{ij} = d_i/(d_i - d_j)$. Using linear programming terminology there are three basic solutions to these equations,

$$\begin{pmatrix} p_l \\ p_m \\ p_u \end{pmatrix} = \begin{pmatrix} r_{ml} \\ r_{lm} \\ 0 \end{pmatrix}, \begin{pmatrix} r_{ul} \\ 0 \\ r_{lu} \end{pmatrix}, \begin{pmatrix} 0 \\ r_{um} \\ r_{mu} \end{pmatrix}.$$

Further if $p_i > 0, i = l, m, u$ then (p_l, p_m, p_u) must be a convex combination of just two Basic Feasible Solutions (BFS), namely those basic solutions with nonnegative components. Thus any search can be restricted to these convex combinations. Given symmetry considerations only three cases need to be taken into account. In each case there are only two BFS,

1. *Case1: $l \le -1 \le m \le 1 \le u$. In this case the second vector of weights is infeasible.*
2. *Case2: $-1 \le l \le m \le 1 \le u$. In this case the first vector of weights is infeasible.*
3. *Case3: $-1 \le l \le 1 \le m \le u$. In this case the third vector of weights is infeasible.*

To find MV-optimal designs for all design intervals $[a, b]$, it helps to recall the solution for $w(x) = 1$ [31]. Considering a and b as the axes, the relationship of (a, b) to two loci of points determines which design is MV-optimal. These are the circle of radius 2 and the hyperbolas $ab = 1$ and $ab = -1$ (see Fig. 2 in Torsney and López-Fidalgo [31]). In the case of weighted regression, corresponding boundaries will again be crucial in (potentially) determining when the MV-optimal design changes from a c-optimal to an EV-optimal design. In particular, c_1-optimal designs produce 2-point EV-optimal designs on the curve $h(a)/|a| = -h(b)/|b|$ and c_2-optimal designs produce 2-point EV-optimal designs on the curve $h(a) = -h(b)$, where $h(x) = (x^2 - 1)\sqrt{w(x)}$. To these, however we must add the "curves" $a^{*}(b)$, $b^{*}(a)$, $a^{**}(b)$, $b^{**}(a)$, $a^{***}(b)$ and $b^{***}(a)$. These render parts of the EV boundaries as irrelevant. They cut away areas of the semi-plane $\{(a, b) : a \le b\}$ since designs have fixed support points in these areas. An example of this, for the Logistic weight, can be seen in Torsney and López-Fidalgo ([32], Figs. 1 and 2).

In the next Section we will introduce a computer tool under which a graph with all the previous curves ($h(a)/|a| = -h(b)/|b|$, $h(a) = -h(b)$, $a^{*}(b)$, $b^{*}(a)$,...) is shown for each weight function considered (see Fig. 1). These functions partition the semi-plane into regions in which the supports of either c_1-optimal or c_2-optimal or EV-optimal designs of 2 or 3 support points are identified. The corresponding graphs for the MV-optimal designs in respect of the cases Normal and Double Exponential are shown in Fig. 3. Comparing Figs. 1 and 3 (left), both for the Normal case, it can be seen that parts of some curves are irrelevant in respect of the support of the MV-optimal design. Fig. 2 shows the plot of the Normal case provided by the applet

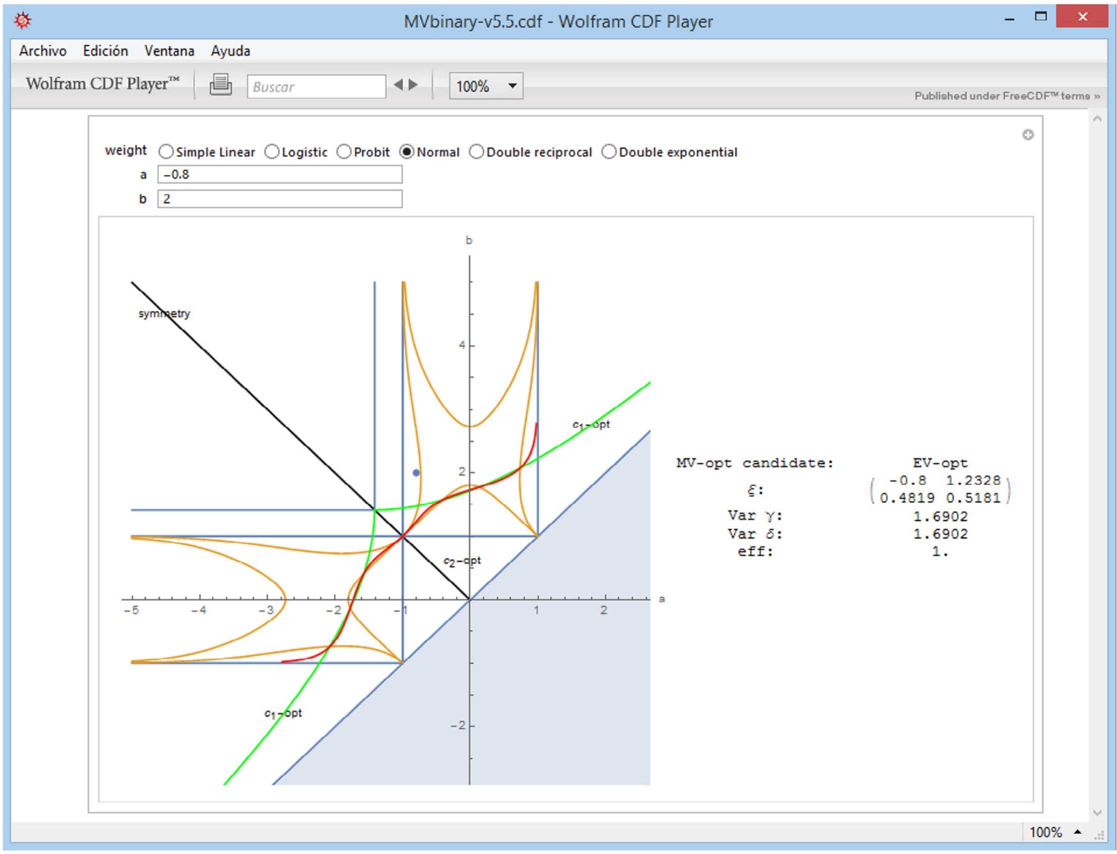

Fig. 1 – Initial output of the applet. MV-optimal design for model (4) considering the Normal density as weight function on a design space $\chi = [-0.8, 2]$.

after detailing all the curves described above. This can be useful for the practitioner in order to see the location of the design interval in the space with respect to the curves/boundaries that indicate possible changes on the nature of the support points of MV-optimal designs.

4. Computer tool

An *applet*/computer tool has been developed for obtaining MV-optimal designs. It has been implemented in Mathematica, but practitioners/users can use it in an interactive and friendly environment, because it is a stand-alone file. It is only necessary to download, the *applet* named "MVbinary" from the website http://areaestadistica.uclm.es/oed/index.php/computer-tools/ and the free CDF Player from wolfram.com available for Windows, Mac and Linux platforms.

The *applet* with a set of default options runs automatically when the user opens it (see Fig. 1). The options the practitioners can modify are:

- The weight function: Simple Linear, Logistic, Probit, Normal, Double Reciprocal or Double Exponential.
- The design space $\chi = [a, b]$.

The output contains:

- A graph of the semi-plane which considers a and b as the axes. Moreover, it depicts a point representing the chosen interval, the boundaries indicating possible changes from c_1- or c_2- to EV-optimal designs and the boundaries indicating possible changes in the support points (see Figs. 1 and 2 for more details).
- Information about the MV-optimal design: the type of optimal design (c_1-, c_2- or EV-, labeled as "candidate"), the design itself (the support points and the corresponding design weights), the two variances of the two parameter estimates of the model and the MV-efficiency.

Remark 4.1. *The candidate design with a MV-efficiency equal to 1 is the MV-optimal design.*

The procedure of the *applet* is as follows:

1. Given the weight function and the interval $[a, b]$ the two support points for c- and 2-point EV-optimal designs according to (8) and (9) are obtained.

Remark 4.2. *The c_1- and c_2-optimal designs have the same 2 support points.*

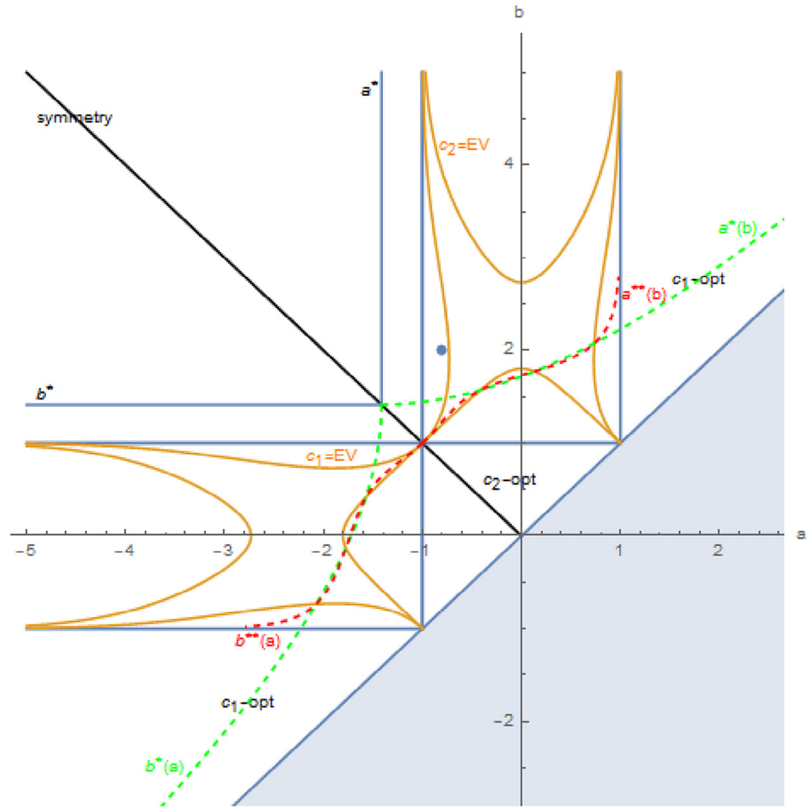

Fig. 2 – All potential boundaries for the Normal density. Solid curves are for boundaries between c_1- or c_2- and EV-optimal designs. Dashed curves refer to $a^*(b)$, $b^*(a)$, $a^{**}(b)$ and $b^{**}(a)$.

2. Computes the corresponding FIM for each design type, depending on the weights.
3. Obtains the design weights p for c_1-, c_2- and 2-point EV-optimal designs according to (11) and (7), respectively.
4. Computes the variances of the 2 parameter estimates for the 3 candidate designs.
5. Compares the largest variance of the 3 designs and chooses the design with minimum value. That is the MV-candidate.

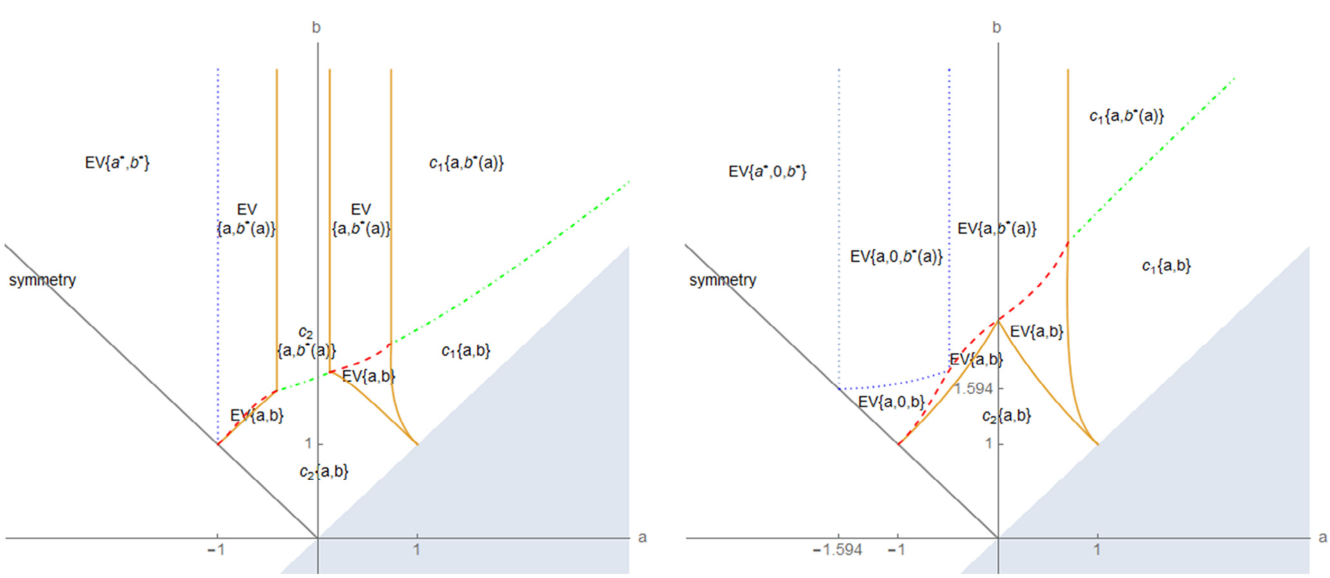

Fig. 3 – Nature and supports (within brackets) of the MV-optimal designs using the Normal density (left) and Double Exponential (right), for different intervals [a, b]. Continuous curves correspond to c-optimal designs with equal variances. Dashed curves are $b^*(a)$ (–·–), $b^{**}(a)$ (– – –) and $b^{***}(a)$ (…). Vertical dotted straight lines show other changes in the support points. There are symmetrical results with respect to $a = -b$ for the lower triangular region.

6. Computes the MV-efficiency of the MV-candidate design using directional derivatives, that is, checks the Equivalence Theorem (Theorem 2.1). If the efficiency is 1, the candidate is the MV-optimal design (see Remark 4.1). Otherwise a 3-point EV-optimal design with the structure given in (10) should be considered.

Remark 4.3. *Only for the Double Exponential and Double Reciprocal have we found MV-optimal design with 3 support points.*

4.1. Illustrative cases

The weight functions considered, $w(x)$, can be divided into two groups, depending on its differentiability at 0. The following weight functions which are differentiable at 0 will be considered in the computer tool: Simple Linear case, Normal Density, Logistic and Probit Regression. On the other hand, there are weight functions that depend on x only through $|x|$. Then, they have a vertex at $x = 0$ where they are not differentiable. Then we can see that some optimal designs put some weight at zero. We consider in this group the Double Exponential and the Double Reciprocal. For illustrating the use of the *applet* we consider here two cases, one of each type: the normal density and the Double Exponential binary regression. Moreover, these cases represent the two points of view of the model, as a weighted linear regression and as a binary response model, respectively (see Section 2.3). Thus we are showing an example using a $w(x)$ and an example using a $f(x)$. In Table 1 the weighting functions are displayed.

In Theorem 5.1 of López-Fidalgo, Torsney and Ardanuy [13] the MV-optimal design is found for any symmetric interval [–b, b] using several weight functions. With the *applet* provided in this paper it is possible to find the MV-optimal design for any interval [a, b].

4.1.1. Normal density case

It can be seen that no more than 2-point designs are needed for this weight function. The MV-optimal design for any design space χ that contains the interval [–1, 1] is the EV-optimal design:

$$\begin{Bmatrix} -1 & 1 \\ 0.5 & 0.5 \end{Bmatrix}.$$

From the theoretical results of Section 2.4 (see Remark 2.2) it is known that the MV-optimal design for a design space $\chi \subseteq [-1,1]$ is the c_2-optimal design. Its support points are the end-points of the interval. When $a > 1$ or $b < -1$ it is the c_1-optimal design which is MV-optimal but the support points are not the end-points for all possible intervals (see Fig. 3). In fact, for a fixed value of $a > 1$, the MV-optimal design for all design spaces $[a, b]$ with $b > b^*(a)$ will be the same, namely the c_1-optimal design with support points a and $b^*(a)$.

The remaining question concerns the MV-optimal design for the region $b > 1$ and a between –1 and 1 and its "complement" with respect to the straight line $y = -x$, that is, $a < -1$ and b between –1 and 1. Practitioners can use the *applet* to identify the solution and to know the exact support points and design weights. As a summary Fig. 3 shows the nature and support points of MV-optimal designs. Some particular examples are shown in Table 2. It can be observed that the c_1- and c_2-optimal design regions are larger than those provided by the theoretical result (see Remark 2.2).

Table 2 – Comparison of MV-optimal designs for the Normal and Double Exponential cases.

Design space	Normal case	Double Exponential case
[–1.7, 2]	EV: $\begin{Bmatrix} -1 & 1 \\ 0.5 & 0.5 \end{Bmatrix}$	EV: $\begin{Bmatrix} -1.594 & 0 & 1.594 \\ 0.4258 & 0.1484 & 0.4258 \end{Bmatrix}$
[–1.2, 2]	EV: $\begin{Bmatrix} -1 & 1 \\ 0.5 & 0.5 \end{Bmatrix}$	EV: $\begin{Bmatrix} -1.2 & 0 & 1.6183 \\ 0.3952 & 0.1176 & 0.4872 \end{Bmatrix}$
[–0.8, 2]	EV: $\begin{Bmatrix} -0.8 & 1.2328 \\ 0.4819 & 0.5181 \end{Bmatrix}$	EV: $\begin{Bmatrix} -0.8 & 0 & 1.6949 \\ 0.3696 & 0.0679 & 0.5625 \end{Bmatrix}$
[–0.3, 2]	c_2: $\begin{Bmatrix} -0.3 & 1.6088 \\ 0.3487 & 0.6513 \end{Bmatrix}$	EV: $\begin{Bmatrix} -0.3 & 2 \\ 0.2891 & 0.7109 \end{Bmatrix}$
[0.1, 2]	c_2: $\begin{Bmatrix} 0.1 & 1.7606 \\ 0.3159 & 0.6841 \end{Bmatrix}$	c_2: $\begin{Bmatrix} 0.1 & 2 \\ 0.2286 & 0.7714 \end{Bmatrix}$
[0.8, 2]	c_1: $\begin{Bmatrix} 0.8 & 2 \\ 0.5191 & 0.4809 \end{Bmatrix}$	c_1: $\begin{Bmatrix} 0.8 & 2 \\ 0.5558 & 0.4442 \end{Bmatrix}$

4.1.2. Double exponential binary regression case

For this case $F(x)$, $f(x)$ and hence $w(x)$ depend on x only through $|x|$ (see Table 1). The locus of points $\left(\sqrt{w(x)}, x\sqrt{w(x)}\right)$, i.e., the Elfving set, is similar to the Logistic case but it has a vertex at $x = 0$. This means in practice that some optimal designs put weight at zero. As a matter of fact, all the EV- and MV-optimal designs with 3 support points are obtained by putting weight at zero (see (10)).

Unlike the previous case, there is a new key value $b^{***} = 1.594$ (see Table 1). This key point distinguishes the cases where the 3-point EV-optimal designs have and do not have fixed support points. When the design space contains the interval $[-1.594, 1.594]$ the MV-optimal design is the EV-optimal design:

$$\begin{Bmatrix} -1.594 & 0 & 1.594 \\ 0.4258 & 0.1484 & 0.4258 \end{Bmatrix}.$$

Now the remaining region (removing the theoretical cases of regions of c_1- and c_2-optimal designs, see Remark 2.2) is larger than the previous case, and we have more possibilities as is pointed out previously. For every point of that region, the *applet* computes the c_1, c_2 and 2-point EV-optimal designs (if this latter case exists). If all of them have MV-efficiency less than 1, the 3-point EV-optimal design is considered. Some results are shown in Table 2 and Fig. 3 summarizes the nature and the structure of MV-optimal designs.

5. Discussion

In the graphs shown in the *applet* a symmetry in the boundaries can be easily seen. This symmetry is with respect to the straight line $y = -x$, as we previously said and it is pointed out in the applet. But, it is not the only perspective of symmetry in this work. Symmetry in the designs means something different. For example, the designs for the normal case with design space [−0.8, 2] and its "symmetric" interval, namely [−2, 0.8], are the same subject to exchanging support points (signs) and weights.

The paper of Dette [6] proposes an alternative class of design criteria for dealing with the problem of different scales of magnitude in design variables. Modifying MV-optimality for this purpose leads to a criterion function of the kind,

$$\min_{\xi} \max\left\{\mathrm{var}_{\xi}(\hat{\gamma}), \mathrm{var}_{\xi}\left(d^{\top}\hat{\theta}\right)\right\}, \quad \text{with} \quad \hat{\theta}^{\top} = \left(\hat{\gamma}, \hat{\delta}\right)$$
$$\text{and} \quad d^{\top} = (d_1, d_2).$$

The methods used here could be directly applied to the case $d_1 = 0$, $d_2 = R$, with EV-optimal designs becoming designs with a variance ratio of R. More generally the above criterion is equivalent to the general case [a, b], that has been considered here.

A natural extension of this work is to implement in the *applet* weight functions such as: Beta, $w(x) = (1 - x^2)^{\gamma - 1}, x \in [-1, 1], \gamma > 0$; Potential, $w(x) = |x|^k, k > 0$; or other relevant weighting functions in the literature.

Simple linear regression has been considered in (5). The theory and ideas of the paper may be applied to any other linear model, e.g. $F(\alpha + \beta x + \gamma x^2)$, which leads to a similar FIM of model (4). Once the number of parameters is greater than two, analytic expressions are no longer available and numerical computation is needed and then with a particular difficulty in checking the equivalence theorem. For instance, for three parameters, differentiability fails when any pair of variances or all the three are equal and this introduces an important level of difficulty.

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