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Locally Optimal Designs for Some Dose–Response Models With Continuous Endpoints

Yi Zhai and Zhide Fang*

Biostatistics Program, Louisiana State University Health Sciences Center, New Orleans, Louisiana, 70112, USA

Abstract

We consider the problem of constructing static (or non-sequential), approximate optimal designs for a class of dose response models with continuous outcomes. We obtain conditions for a design being D -optimal or c -optimal. The designs are locally optimal in that they depend on the model parameters. The efficiency studies show that these designs have high efficiency when the misspecification of the initial values of model parameters is not severe. A case study indicates that using an optimal design may result in a significant saving of resources.

Key words and phrases

Dose-Response; D -optimality; c -optimality; Efficiency; Toxicology

1 Introduction

In the field of risk assessment, in addition to binary endpoint (response) such as showing response or not at a dose level, the toxicological observations may be continuous, taking values in some interval. For example, in a developmental toxicity study of ethylene glycol (Price *et al.*, 1985), ethylene glycol was administered at different dose levels to laboratory pregnant mice and then continuous endpoints (fetal weights following sacrifice) were recorded to study the adverse effects of the developmental toxicant on the fetal weight. In this paper we consider dose-response models with continuous endpoints only.

When analyzing the data generated from a toxicological study with continuous endpoints, Slob (2002) pointed out that several restrictions should be imposed in the dose-response models for the outcomes. Specifically, such models should prevent negative responses and the existence of dose-threshold. Note that a model with a threshold may be insufficient to explain the variability in experimental units when the endpoint (response) is continuous, taking values in some interval. Furthermore, it would be appropriate if the models include parameters that will represent the relative sensitivity between different populations and/or the difference in sensitivity of the subjects (or efficacy of the chemical). Based on these concerns and others, a general dose-response model should have mean response, $\eta(x, \theta) = ag(x/b)$, where a , b are positive, unknown parameters, and g is a univariate function with

*Corresponding author, zfang@lsuhsc.edu.

$g(0) = 1$, which can be achieved by functions such as exponential function. In addition, the models should be sufficiently curved to level off and/or change more at higher doses (to imitate the threshold-like responses). Thus the dose level x may have an order, d , higher than one. The choice of function g gives us options to model dose-response data from different experiments.

In this paper we will consider the optimal design problem for some dose-response models (defined later) with continuous endpoints. Assume that one observes, with additive, uncorrelated, homoscedastic errors, a response variable $Y(x)$ with expectation,

$$E(Y|x) = \eta(x, \boldsymbol{\theta}), \quad (1)$$

where x represents dose level taking values in design space $\mathcal{X} = [x_L, x_U]$, $0 < x_L < x_U < \infty$. The p -dimensional vector $\boldsymbol{\theta}$ is the collection of unknown model parameters, to be estimated. Suppose that N subjects are tested at dose levels: $x_1, x_2, \dots, x_N$, which are not necessarily distinct. Without loss of generality, let $x_1, x_2, \dots, x_n$ be the distinct dose levels and r_i be the number of subjects tested at x_i , then a design, denoted as ξ , is defined as the probability measure placing mass $w_i = r_i/N$ on x_i , $i = 1, 2, \dots, n$, where the sum of r_i is N . For the model (1), the Fisher's information matrix of a design ξ , whose inverse is proportional to the asymptotic covariance matrix of the parameter estimates (see, for example, Silvey, 1980), is given by the following:

$$M(\xi, \boldsymbol{\theta}) = E_{\xi} \left(\frac{\partial \eta(x, \boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \right) \left(\frac{\partial \eta(x, \boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \right)^T = \sum_{i=1}^n w_i q(x_i, \boldsymbol{\theta}) q^T(x_i, \boldsymbol{\theta}),$$

where $q(x, \boldsymbol{\theta})$ denotes the vector derivative of $\eta(x, \boldsymbol{\theta})$ with respect to $\boldsymbol{\theta}$. Generally, by some strongly monotonic continuous map: $z = \gamma(x, \boldsymbol{\theta}) \in \mathcal{Z} = [z_L, z_U]$, where z -bounds correspond to x -bounds respectively, the information matrix can be decomposed as

$$M(\xi, \boldsymbol{\theta}) = Q(\boldsymbol{\theta}) \left(\sum_{i=1}^n w_i L(\boldsymbol{\theta}, z_i) \right) Q^T(\boldsymbol{\theta}), \quad (2)$$

for some $(p \times p)$ matrices Q and L . Note that Q is nonsingular and free of ξ . The elements of matrix $L(\boldsymbol{\theta}, z)$ may depend on $\boldsymbol{\theta}$ directly or indirectly through the mapping $z = \gamma(x, \boldsymbol{\theta})$. Note that this decomposition enables us to consider only the designs with the number of support points less than certain integer when seeking the optimal design (Theorem 2 in Yang, 2010).

For the model (1), constructing an optimal design is to seek the set of $\{(x_i, w_i)\}_{i=1}^n$ such that the corresponding design has the largest information matrix (or the smallest inverse of information matrix) in the Loewner partial order (see, for example, Pukelsheim, 2006). We assume $n \geq p$ so that the information matrix is invertible. Generally, it is impossible to find such design because of the complexity of optimality in Loewner partial order and the fact that w_i is a multiple of N^{-1} . Thus, the criteria for optimality are usually defined as some

scalar functions of the information matrix. For example, D -, A -optimal designs minimize $|M^{-1}(\xi, \theta)|$, $\text{tr}(M^{-1}(\xi, \theta))$ respectively, while c -optimal design minimizes $c^T M^{-1}(\xi, \theta) c$ for some known vector c . And we extend the definition of design to the approximate design that allows w_i to vary continuously in $[0, 1]$ regardless of N . The ways to implement an approximate design can be found in Chapter 12 of Pukelsheim (2006).

Furthermore, as showed in (2), the information matrix in nonlinear regression model usually depends on the unknown parameters, which complicates the construction of design. One way to handle this problem is to obtain initial estimates from the preliminary data or guess the true values of parameters, and then search for the locally optimal designs (Chernoff, 1953). Other methods, such as Bayesian and minimax procedures, can also be applied. Given a prior distribution $\pi(\theta)$ on θ , a Bayesian optimal design for nonlinear regression model minimizes the expected loss (for example, $\int \log |M^{-1}(\xi, \theta)| d\pi(\theta)$ for Bayesian D -optimality) of using an experimental design. See Chaloner (1993), Mukhopadhyay and Haines (1995), Dette and Neugebauer (1996, 1997), Dette and Wong (1996, 1998), and Fang and Wiens (2004) for more details and examples. Minimax approach constructs design which minimizes the maximum, over the parameter space, of the loss. For D -optimality, this is equivalent to maxmin design which maximizes the minimum of the information (see, for example, Imhof, 2001). But We will focus on locally optimal designs in this paper.

The dose-response (nonlinear) models considered here has the following general form of the expectation (that is, $g(t) = \exp(t^d)$),

$$\eta(x, \theta) = a \exp \left(\left(\frac{x}{b} \right)^d \right), \quad (3)$$

where $\theta = (a, b, d)^T$, is a vector of parameters with a being background parameter, b being dose factor, and d being power to mimic threshold-like responses. Obviously, $a > 0$ and represents the endpoint value at dose level 0. It is assumed that $d \geq 1$ so that the rate of change in response at dose level 0 is not infinite. As a parameter reflecting the efficacy of the chemical, b is assumed to be positive. Detailed discussion about the motivation of this model can be found in Slob (2002). In real-life data analysis, this model has been adopted to fit the relationship between increasing relative liver weight and dose (OECD, 2006), and used in a dose responding study for anti-anxiety drug where the endpoint is the change from baseline in an anxiety scale at the end of the study (Pinheiro et al., 2006). Note that if $d = 1$, the true parameter lies on the boundary of the parameter space. Statistical inference may be constructed based on extended maximum likelihood estimate, of which asymptotic behavior is presented by Fisher information. See, for example, Feng and McCulloch (1992) and Self and Liang (1987), for more details.

The model can be simplified for some special situations. For example, we can set $a = 1$, if different populations can be considered equally sensitive, and assume

$$\eta(x, \theta) = \exp\left(\left(\frac{x}{b}\right)^d\right), \quad (4)$$

or $b=1$, if suitable data are available so that the dose factor can be directly estimated, with the expected response at x as

$$\eta(x, \theta) = a \exp(x^d). \quad (5)$$

Many results have been published for the locally optimal designs for dose-response (nonlinear) regression models. Different optimality criteria, response functions, methods of design construction are used in these works. See, for example, Silvey (1980), Ford et al. (1989), Dette and Neugebauer (1997), Han and Chaloner (2003), Dette et al. (2006, 2008, 2010), Yang (2010), Fedorov and Leonov (2014), and others for more details. While exponential models with fixed order d have widely been investigated in design literature, we consider d in models (3) – (5) as an unknown parameter in this paper.

The setup of the paper is as follows. We present the results on locally optimal designs for above models in Section 2. In Section 3, we study the efficiency of optimal designs with misspecified initial values of parameters. A case study is given in Section 4.

2 Locally Optimal Designs

In this section, we will construct locally D -optimal and c -optimal designs for models (3) – (5) separately. Theorem 2 in Yang (2010) plays an important role in determining the number of support points of the optimal designs. Thus, we state the theorem here for readers' convenience. Specifically, rename all distinct elements of matrix $L(\theta, z)$ in (2): $\phi_{l,s}, 1 \leq l \leq s \leq p$, to $\phi_1, \dots, \phi_k$ such that ϕ_k is one of $\phi_{l,s}, 1 \leq l \leq s \leq p$, and there is no $\phi_{l,s} = \phi_k, l < s$. If $\phi_1, \dots, \phi_k$ are infinitely differentiable and $f_{l,l}, 1 \leq l < k$, have no zero value on $[z_L, z_U]$, where

$$f_{l,s} = \begin{cases} \phi'_l(z) & s = 1, l = 1, \dots, k, \\ \left(\frac{f_{l,s-1}(z)}{f_{s-1,s-1}(z)} \right)' & 2 \leq s \leq k, s \leq l \leq k, \end{cases} \quad (6)$$

then for any design ξ , there exists a design ξ^* with at most $(\lfloor \frac{k}{2} \rfloor + 1)$ support points such that $M(\xi, \theta) \leq M(\xi^*, \theta)$, that is, ξ^* is not inferior to ξ in Loewner ordering, where $\lfloor \cdot \rfloor$ represents the greatest integer function. Specifically,

1. if k is odd and $\prod_{l=1}^k f_{l,l}(z) < 0$ (or > 0), then ξ^* is supported on at most $(k+1)/2$ points, including z_L (or z_U);
2. if k is even and $\prod_{l=1}^k f_{l,l}(z) < 0$, then ξ^* is supported on at most $k/2$ points;

3. if k is even and $\prod_{l=1}^k f_{l,l}(z) > 0$, then ξ^* is supported on at most $k/2 + 1$ points, including z_L and z_U .

The benefit of applying this theorem is that we may restrict our search for optimal design to a subclass of designs with at most $(\lfloor \frac{k}{2} \rfloor + 1)$ support points. This will greatly simplify the proof for analytical solution or reduce the computational time for numerical solution.

2.1 Designs for $a = 1$ model

For the model (4), the parameter vector becomes $\theta = (b, d)^T$. Let $z = t(x) = (\frac{x}{b})^d \in [z_L, z_U]$, a strictly increasing function of $x \in [x_L, x_U]$. Then the gradient vector can be written as

$$q(t^{-1}(z), \theta) = ze^z \left(-\frac{d}{b}, \frac{1}{d} \log z \right)^T.$$

Thus, in the expression (2) of the information matrix, we have $Q(\theta) = \text{diag}(-\frac{d}{b}, \frac{1}{d})$, and

$$L(\theta, z) = \begin{pmatrix} z^2 e^{2z} & z^2 e^{2z} \log z \\ z^2 e^{2z} \log z & z^2 e^{2z} \log^2 z \end{pmatrix}.$$

For $i = 1, 2, 3$, let $\phi_i(z)$ be the $(i, s)^{th}$ element of $L(\theta, z)$, $i = I + s - 1$, $I = 1, 2, 3$. Then, by (6) and some algebraic operations, we can show that for $z > 0$,

$$f_{1,1} = \phi'_1(z) = 2(1+z)ze^{2z} > 0,$$

$$f_{2,2} = \left(\frac{\phi'_2(z)}{\phi'_1(z)} \right)' = \frac{2+3z+2z^2}{2z(1+z)^2} > 0,$$

$$f_{3,3} = \left(\left(\frac{\phi'_3(z)}{\phi'_1(z)} \right)' / \left(\frac{\phi'_2(z)}{\phi'_1(z)} \right)' \right)' = \frac{2(6z^4 + 15z^3 + 18z^2 + 13z + 4) + (z^3 + 4z^2 + 2z) \log z}{z(2+3z+2z^2)^2} > 0.$$

Thus the product of these functions is positive and $k = 3$. By the argument under Section 2, the locally D -optimal and c -optimal designs for model (4) are both supported on at most two design points, including the right end point of the design interval.

2.1.1 Locally D -optimal designs—It is well known that if the number of supports of D -optimal design is the same as that of parameters, the design has equal weights. Thus, we have the following theorem.

Theorem 1: Assume model (4). Given parameters b and d , the locally D -optimal design puts equal weights on design points: $\max\{x_1^*, x_L\}$, and x_U , where x_1^* is the unique solution of

$$d\left(\left(\frac{x_1}{b}\right)^d + 1\right) = \log^{-1}\left(\frac{x_U}{x_1}\right). \quad (7)$$

Note that the induced design interval is $[z_L, z_U] = [(x_L/b)^d, (x_U/b)^d]$. We prove the theorem in z , then use the bijective map between x and z to get the equation in the theorem.

Proof of Theorem 1: Based on the argument before the theorem, we only consider the designs with the form,

$$\xi = \begin{pmatrix} z_1 & z_U \\ 0.5 & 0.5 \end{pmatrix}.$$

Thus, the determinant of the information matrix is a univariate function of z_1 :

$$|M(\xi, \theta)| \propto \left(z_1 z_U e^{\left(\frac{z_1 + z_U}{\log z_U - \log z_1} \right)^2} \right)^2.$$

Denote the right hand side of the equation as $\varphi(z_1)$. Since

$$\frac{\partial}{\partial z_1} \log \varphi(z_1) = \frac{2}{z_1} \left(1 + z_1 - \frac{1}{\log z_U - \log z_1} \right),$$

it is straightforward to show that for $z_1 \in (0, z_U)$, the second derivative of $\varphi(z_1)$ is negative and

$$\lim_{z_1 \rightarrow 0} \frac{\partial}{\partial z_1} \log \varphi(z_1) = \infty, \quad \lim_{z_1 \rightarrow z_U} \frac{\partial}{\partial z_1} \log \varphi(z_1) = -\infty.$$

Hence, $\varphi(z_1)$ has a unique stationary point $z_1^* \in (0, z_U)$. Now if $z_1^* > z_L$, then the locally D -optimal design has support points z_1^* and z_U . If $z_1^* < z_L$, then $\frac{\partial}{\partial z_1} \log \varphi(z_1) < 0$ for $z_1 \in (z_L, z_U)$. This implies that the locally D -optimal design has support points z_L and z_U . Using the map between x and z , we have the conclusion in the theorem.

As an example, we take $x_U = 10$, and present the values of x_1^* for different sets of (b, d) in Table 1. Note that the map between x and z has been used to obtain the table. It is clear that for a fixed d , the locally D -optimal design tends to have both boundary points as the support points when b becomes larger. This makes sense because under such situation the model (when $d = 1$) is very close to a simple linear model for which the D -optimal design puts

equal weights on the boundaries of the design interval. Furthermore, the right hand side of (7) is a strictly increasing function of x_1 , independent of b and d . Given x_1 , the left hand side of (7) decreases as b increases, and increases as d increases. These imply that x_1^* is decreasing in b for fixed d and increasing in d for fixed b . The results in Table 1 are consistent to the analytical conclusion.

2.1.2 Locally c -optimal designs—To determine the support points of locally c -optimal design, we applied Elfving's Theorem (see Elfving (1952), Chernoff (1953, 1972) for details). Denote $c = (c_1, c_2)^T$, where $c_1^2 + c_2^2 \neq 0$, and $\lambda = \frac{c_2}{c_1}$ ($= \infty$, if $c_1 = 0$). Note that we construct c -optimal design for estimating individual parameters if one of c_i is zero.

Theorem 2: If z_0 is the solution to the equation

$$\frac{z_U e^{z_U} \log z_U + z_0 e^{z_0} \log z_0}{z_U e^{z_U} + z_0 e^{z_0}} = \frac{\log z_0 + z_0 \log z_0 + 1}{z_0 + 1}, \quad (8)$$

and $z_0 \in (z_L, z_U)$, let $z_1 = z_0$, otherwise let $z_1 = z_L$. If $-(d^2/b)\lambda \notin (\log z_1, \log z_U)$, then the locally c -optimal design is supported on z_1 and z_U , with corresponding weights

$$w_1 = \frac{z_U e^{z_U} - \delta}{z_1 e^{z_1} + z_U e^{z_U}} \text{ and } w_2 = 1 - w_1, \text{ where}$$

$$\delta = \frac{dz_1 z_U e^{z_1} e^{z_U} (\log z_U - \log z_1)}{d^2 \lambda (z_1 e^{z_1} + z_U e^{z_U}) + b(z_1 e^{z_1} \log z_1 + z_U e^{z_U} \log z_U)}.$$

Proof: For $z \in [z_L, z_U]$, given the gradient vector of the response, denote the curve in st -plane as $\mathcal{S} = \{(s, t) : s = -dz e^z / b, t = z e^z \log z / d\}$ and $-\mathcal{S}$ as its reflection about the origin. By some algebraic operations, we have that

$$\frac{\partial^2 t}{\partial s^2} = \frac{b^2}{d^3} \frac{z^2 + z + 1}{z(1+z)^3 e^z} > 0,$$

that is, the curve $\mathcal{S}$ is concave (or $-\mathcal{S}$ is convex) and thus the slope of the curve is decreasing (or increasing). If $z_L < z_0$, then the Elfving set, the convex hull of $\mathcal{S} \cup -\mathcal{S}$, has a straight-line boundary linking $A = (-dz_U e^{z_U} / b, z_U e^{z_U} \log z_U / d)$, and a tangential point on $-\mathcal{S}$, say $B = (-dz_0 e^{z_0} / b, z_0 e^{z_0} \log z_0 / d)$, $z_L < z_0 < z_U$. The value of z_0 can be determined by equating the slope of the line to the derivative of $-\mathcal{S}$ at B , that is, by the equation (8) in the theorem. Otherwise, the Elfving set has a straight-line boundary linking one end point of $\mathcal{S}$, say $A = (-dz_U e^{z_U} / b, z_U e^{z_U} \log z_U / d)$, and the end point $B = (dz_L e^{z_L} / b, -z_L e^{z_L} \log z_L / d)$, of $-\mathcal{S}$.

Now, since the ray connecting the origin and the point (c_1, c_2) has slope λ , then, if $-(d^2/b)\lambda \notin (\log z_L, \log z_U)$, the ray will penetrate the Elfving set at some point inside the above straight-line boundary. Thus, the cross point is a convex combination of the two end points of the straight-line. This and the Elfving's method prove the theorem.

Note that for (8), there always exists a solution $z_0 \in (0, z_U)$. A special case is $c = (0, 1)^T$, that is, we consider the locally c -optimal design for estimating the parameter d . Then $\lambda = \infty$, so the condition in Theorem 2 holds, and the locally c -optimal design puts weight

$$w_1 = \frac{z_U e^{z_U}}{z_U e^{z_U} + z_1 e^{z_1}} \quad (\text{note that } \delta = 0) \text{ at } z_1. \text{ Some examples of locally } c\text{-optimal design (in}$$

original design space) are given in Table 2. Furthermore, for illustrative purpose, we present the Elfving set and the ray (vertical axis) in Figure 1 when $b = d = 1$.

If $-(d^2/b)\lambda \in (\log z_L, \log z_U)$, the ray representing c will not penetrate the Elfving set at a convex combination of two points in $\mathcal{S}$ and $-\mathcal{S}$ but at a single point in $z = \exp\left(-\frac{d^2}{b}\lambda\right)$. This implies that the c -optimal design has only one support point, which is not practical in reality because the information matrix is not invertible. We comment that this does not contradict with Theorem 2 in Yang (2000), which states that for any design ξ with invertible information matrix, there exists a design ξ_1 with two support points (one is the right end point of the design interval) that is better than ξ in that $c^T M^{-1}(\xi_1)c < c^T M^{-1}(\xi)c$. The design ξ_1 can be further improved to have lower loss, $c^T M^{-1}(\xi_1)c$, if we put more weights on $z = \exp\left(-\frac{d^2}{b}\lambda\right)$ and less weight on z_U . Repeat the process, the limit of these designs will be the c -optimal design with single support point $z = \exp\left(-\frac{d^2}{b}\lambda\right)$, as obtained from Elfving's Theorem.

Consider the locally c -optimal design for estimating b , that is, $c = (1, 0)^T$ and $\lambda = 0$, where c represents the horizontal axis. This ray will penetrate the curve $\mathcal{S}$ if the interval $[z_L, z_U]$ covers 1 for any b and d . In this case, the c -optimal design will put all the weight at $z = 1$, which is an infeasible design. Otherwise, when the interval does not cover 1, the intersection point of the ray will be a convex combination of two points so we still can apply Theorem 8.

2.2 Designs for $b = 1$ model

In this subsection, we construct locally optimal design for Model (5). Similar to Section 2.1, we check Theorem 2 in Yang (2010) so as to consider a smaller class of designs only. With the map $z = x^d$ (the induced design space $\mathcal{Z}$ having bounds $z_L = x_L^d, z_U = x_U^d$), we obtain the gradient vector as $q(z) = e^{\mathcal{Z}}(1, az \log z/d)^T$, and the information matrix, in the form of (2), with $Q(\theta) = \text{diag}(1, a/d)$ and

$$L(\theta, z) = \begin{pmatrix} e^{2z} & ze^{2z} \log z \\ ze^{2z} \log z & z^2 e^{2z} \log^2 z \end{pmatrix}.$$

Let $\phi_1(z) = e^{2z}$, $\phi_2(z) = ze^{2z} \log z$, and $\phi_3(z) = z^2 e^{2z} \log^2 z$. It is easy to verify that (see Appendix for explicit expressions of $f_{i,s}(z)$)

$$f_{1,1}(z) = \phi'_1(z) = 2e^{2z} > 0,$$

$$f_{2,2}(z) = \left(\frac{\phi'_2(z)}{\phi'_1(z)} \right)' = \frac{1}{2z} + \log z + 1 > 0.$$

But $f_{3,3}(z) = \left(\left(\frac{\phi'_3(z)}{\phi'_1(z)} \right)' / \left(\frac{\phi'_2(z)}{\phi'_1(z)} \right)' \right)'$ changes sign in $\mathbb{R}^+$. It can be shown that $f_{3,3}(e^{-1}) = 0$.

Numerically we obtain another zero as $z_0 \approx 0.0275$, and find that $f_{3,3}(z) < 0$ when $z \in (z_0, e^{-1})$, or > 0 otherwise. Thus the locally D - and c -optimal designs have two supports points, including z_L if $\mathcal{Z} \subset (z_0, e^{-1})$, or z_U if $\mathcal{Z} \subset (0, z_0) \cup (e^{-1}, \infty)$.

2.2.1 Locally D -optimal designs—For the model (5) and a design ξ with support points $z_1 < z_2$ and weights $w_1 = w_2 = 0.5$, we have

$$|M(\xi, \theta)| \propto e^{(2z_1 + 2z_2)} (z_2 \log z_2 - z_1 \log z_1)^2.$$

Denote the right hand side as $\varphi_2(z_1, z_2)$.

Theorem 3

1. If $z_L > e^{-1}$, then the locally D -optimal design has supports $z_2 = z_U$, and $z_1 = \max\{z_L, z_1^*\}$, where $z_1^* \in (e^{-1}, z_U)$ is the unique solution to the equation

$$(1 + z) \log z = z_U \log z_U - 1. \quad (9)$$

2. If $[z_L, z_U] \subset (0, z_0) \cup (z_0, e^{-1})$, then the locally D -optimal design puts equal weights on $z_1 = z_L$, and $z_2 = z_U$.

Proof: The proof is straightforward. Based on the argument before Section 2.2.1, for 1), we have $z_2 = z_U$, and by equating the derivative of $\log \varphi_2(z, z_U)$ to zero we obtain the equation (9). Let $h_1(z) = (1 + z) \log z$. The fact that the function $h_2(z) = z \log z$ has the global minimum value, $-e^{-1}$, at $z = e^{-1}$ implies that if $z_U > z_L > e^{-1}$, we have

$$h_1(e^{-1}) = -(1 + e^{-1}) < z_U \log z_U - 1 < h_1(z_U).$$

Thus, the equation (9) has at least one solution within (e^{-1}, z_U) . The uniqueness is due to the fact that the derivative of $h_1(z)$ is greater than zero, for $z > 0$. The second part of 1) can be proved similarly. The claim in 2) is due to the fact that $\varphi_2(z_L, z_2)$ is an increasing function of $z_2 \in [z_L, z_U]$ when $z_U < e^{-1}$.

For the design spaces not listed in the theorem, we cannot assert that locally D -optimal designs have exactly two support points. However, it is interesting to report that the support points of the minimally supported locally D -optimal designs are characterized by the curve, $\{(z_1, z_2) : z_1 < z_2, z_1 \log z_1 = z_2 \log z_2\}$.

Assume the design space with $z_L < e^{-1}$. If $z_1 \log z_1 > z_2 \log z_2$, we have $z_1 < e^{-1}$. This and the fact that $h_1(z) = (1+z) \log z$ is an increasing function imply that

$$1 + \log z_1 < z_2 \log z_2 - z_1 \log z_1 < 0 \Rightarrow \frac{\partial}{\partial z_1} \log \varphi_2 < 0, \text{ the first design point should be } z_1 = z_L.$$

Thus, it is easy to show that

- i. for the design space with $z_L < z_U < e^{-1}$, the minimally supported locally D -optimal design is supported at the boundary points.

Now consider the design space with $z_L < e^{-1} < z_U$. Denote $z_L^* (> e^{-1})$ as a value satisfying $z_L \log z_L = z_L^* \log z_L^*$. Then we have a unique stationary point, z_2^* , of $\log \varphi_2(z_L, z)$ within (e^{-1}, z_L^*) . That is, the function φ_2 has a local maxima at the point (z_L, z_2^*) . Similarly, if $z_1 \log z_1 < z_2 \log z_2$, we have $z_2 > e^{-1}$, and another local maxima at (z_1^*, z_U) , where $z_1^* \in (e^{-1}, z_U)$, determined by $\frac{\partial}{\partial z_1} \log \varphi_2(z_1, z_U) = 0$.

Thus, for the design space with $z_L < e^{-1} < z_U$,

- ii. when $\varphi_2(z_1^*, z_U) > \varphi_2(z_L, z_2^*)$, the minimally supported locally D -optimal design puts equal weight on z_1^* , and z_U ;
- iii. when $\varphi_2(z_1^*, z_U) < \varphi_2(z_L, z_2^*)$, the minimally supported locally D -optimal design puts equal weight on z_L and z_2^* if $z_2^* < z_U$. When $z_2^* > z_U$, the support points are z_L and z_U if $\varphi_2(z_L, z_U) > \varphi_2(z_1^*, z_U)$, or z_1^* and z_U otherwise.

In Table 3, we provide some examples of minimally supported locally D -optimal designs with different x -design spaces. Note that, after transformed to z , the design interval covers e^{-1} if $d = 1$, and both $z_0 \approx 0.0275$ and e^{-1} if $d > 1$. Furthermore, those in the left panel belong to case (ii), with z_U being one support point and those in the right panel belong to (iii), with z_L being one point.

Note that one can apply the celebrated Equivalence Theorem (Kiefer and Wolfowitz, 1960) to check whether these designs are locally D -optimal. If $d(x, \xi) = q^T(z)M^{-1}(\xi, \theta)q(z) - 2$, where $z = x^d$, $x \in \mathcal{X}$, with equality being held at the design points, the design is locally D -optimal. As examples, in Figure 2 we take $d = 1$ (so that $z = x$) and present the plots of $d(x, \xi)$ for two designs with the design spaces not discussed in Theorem 3. In the left panel we assume $\mathcal{X} = [0.001, 1]$, and the minimally supported locally D -optimal design ξ_1 puts equal mass in $x_1 = 0.517$ and 1. The plot verifies that the design is locally D -optimal. With $\mathcal{X} = [0.001, 0.3]$, the right panel indicates that the minimally supported D -optimal design ξ_2 supported at 0.001 and 0.3, is locally D -optimal.

2.2.2 Locally c -optimal designs—We use the same technique as that in Section 2.1.2 to construct locally c -optimal design. For the purpose of simplicity, we consider the case of $c = (0, 1)^T$ only. In such case, the values of the model parameter a and d will not affect the location where the ray connecting the origin and the point $(0, 1)$ penetrates the convex hull in terms of z . Therefore, the optimal design does not depend on the linear parameter a , but depends on d through the transformation $z = x^d$. Thus, for simplicity, we can use $(e^z, ze^z \log z)$, for all $z > 0$, to substitute the gradient vector, and have a straight-line that passes through the origin and is tangent to $\mathcal{S}$ and $-\mathcal{S}$ at $z = e^{-1}$ (see Figure 3), indicating that locally c -optimal designs, similar to locally D -optimal designs, may be characterized by the value $z = e^{-1}$.

The results on locally c -optimal designs are presented in the following theorem. The conclusion about the number of support points is stronger than that discussed at the beginning of Section 2.2.

Theorem 4: Assume z -design space $[z_L, z_U] \subset [0, +\infty)$, and $c = (0, 1)^T$.

1. Suppose $z_L > e^{-1}$, and z^* is the solution of the equation,

$$\frac{z^* e^{z^*} \log z^* + z_L e^{z_L} \log z_L}{e^{z^*} + e^{z_L}} = z_L \log z_L + \log z_L + 1, \quad (10)$$

then the locally c -optimal design has support points $z_1 = z_L, z_2 = z_U$ if $z_U < z^*$, or $z_1 = z^{**}, z_2 = z_U$ if $z_U > z^*$, where z^{**} is the solution of the equation

$$\frac{z_U e^{z_U} \log z_U + z^{**} e^{z^{**}} \log z^{**}}{e^{z_U} + e^{z^{**}}} = z^{**} \log z^{**} + \log z^{**} + 1. \quad (11)$$

The corresponding weights are $w_1 = \frac{e^{z_2}}{e^{z_1} + e^{z_2}}, w_2 = 1 - w_1$.

2. Suppose $z_L < e^{-1}$, and denote z' as the unique solution of the equation

$$\frac{z_L e^{z_L} \log z_L + z e^z \log z}{e^{z_L} + e^z} = z \log z + \log z + 1. \quad (12)$$

Furthermore, let z'' be the largest solution of the equation

$$\frac{z e^z \log z + z' e^{z'} \log z'}{e^z + e^{z'}} = z' \log z' + \log z' + 1. \quad (13)$$

Then, the locally c -optimal design is supported at $z_1 = z^{**}$, $z_2 = z_U$ if $z_U > z''$, with z^{**} being determined by (11); or at $z_1 = z_L$, $z_2 = z'$ if $z_U \in (z', z'')$; or at $z_1 = z_L$, $z_2 = z_U$ if $z_U < z'$. The corresponding weights are $w_1 = \frac{e^{z_2}}{e^{z_1} + e^{z_2}}$, $w_2 = 1 - w_1$.

Proof: We prove Part 2) only. The proof for Part 1) is similar.

The equation (12) indicates that the tangent line to $-\mathcal{J}$ at the point $B(-e^{z'}, -z' e^{z'} \log z')$ passes through $A(e^{z_L}, z_L e^{z_L} \log z_L)$, the left end point of the curve $\mathcal{J}$. The line AB has equation (13), which intersects with $\mathcal{J}$ at A and $(-e^{z''}, z'' e^{z''} \log z'')$. If $z_U > z''$, then the upper boundary of the Elfving set pass through $(e^{z_U}, z_U e^{z_U} \log z_U)$ and is tangent to $-\mathcal{J}$ at the point determined by z^{**} from equation (11). By Elfving's Theorem, we obtain the conclusion.

If $z_U \in (z', z'')$, the upper boundary of the Elfving set is the tangent line of $-\mathcal{J}$ passing through $A(e^{z_L}, z_L e^{z_L} \log z_L)$. Thus the locally c -optimal design is supported at z_L, z' .

If $z_U < z'$, no tangent line to $-\mathcal{J}$ intersects with $\mathcal{J}$. The upper boundary of the Elfving set is a line connecting two points: $(-e^{z_U}, -z_U e^{z_U} \log z_U)$ and $(e^{z_L}, z_L e^{z_L} \log z_L)$. Hence, by Elfving's Theorem, the locally c -optimal design is supported at z_L, z_U . The corresponding weights are also determined by Elfving's theorem.

Some examples of locally c -optimal designs are presented in Table 4 for different sample spaces. These reflect the different cases in Theorem 4.

2.3 Designs for the three-parameter model

For the model (3), we have only obtained partial results for locally D -optimal design due to the complexity of the information matrix. With the transformation $z = (x/b)^d$ and some algebraic operations, we have the matrix,

$$L(\theta, z) = \begin{pmatrix} e^{2z} & ze^{2z} & ze^{2z} \log z \\ ze^{2z} & z^2 e^{2z} & z^2 e^{2z} \log z \\ ze^{2z} \log z & z^2 e^{2z} \log z & z^2 e^{2z} \log^2 z \end{pmatrix},$$

for the information matrix (2). The following theorem indicates that the locally D -optimal design has three support points for some special design space.

Theorem 5—Let the induced design space be $\mathcal{Z} = [z_L, z_U]$, and z_{00} (≈ 2.562) be the largest solution of the equation,

$$4z^3 - 14z^2 + 10z - 1 = 0.$$

Then the locally D -optimal design for the model (3) has three support points if $\mathcal{Z} \subset (z_0, \infty)$. Furthermore, if we restrict ourselves to the minimally supported designs, the locally D -optimal design for the model (3) has

1. z_U as one support point, and
2. if $z_U - z_L < 1$, then the locally D -optimal design is supported at z_L , z_U and z_2 , a solution of the equation

$$\frac{z_L \left(\log \frac{z_U}{z_L} + 1 \right) + z_U \left(\log \frac{z_U}{z} - 1 \right)}{z z_L \log \left(\frac{z}{z_L} \right) + z z_U \log \left(\frac{z_U}{z} \right) - z_L z_U \log \left(\frac{z_U}{z_L} \right)} = -1. \quad (14)$$

Proof: From the matrix $L(\theta, z)$, taking $\phi_1(z) = e^{2z}$, $\phi_2(z) = ze^{2z}$, $\phi_3(z) = z^2 e^{2z}$, $\phi_4(z) = ze^{2z} \log z$, $\phi_5(z) = z^2 e^{2z} \log z$, and $\phi_6(z) = z^2 e^{2z} \log^2 z$, we have $f_{1,1}(z) = 2e^{2z}$, $f_{2,2}(z) = 1$, $f_{3,3}(z) = 2$, $f_{4,4}(z) = \frac{1-z}{2z^3}$, $f_{5,5}(z) = \frac{-2z^2 + 4z - 1}{(1-z)^2}$, and

$$f_{6,6}(z) = \frac{(z-1)(4z^3 - 14z^2 + 10z - 1)}{z(-2z^2 + 4z - 1)^2}.$$

Obviously, the product of $f_{i,i}(z)$ is greater than zero if $\mathcal{Z} \subset (z_0, \infty)$, which, by the Theorem 2 in Yang (2010), implies that the locally D -optimal design has three support points.

Now consider design ξ with three supports, z_1 , z_2 , z_3 , and weights $w_1 = w_2 = w_3 = 1/3$. Assume $z_L = z_1 < z_2 < z_3 = z_U$, and $\varphi_3(z_1, z_2, z_3) = \log |M(\xi, \theta)|$. Then, we have

$$\varphi_3(z_1, z_2, z_3) = 2(z_1 + z_2 + z_3) + \log \left(z_1 z_2 \log \frac{z_2}{z_1} + z_2 z_3 \log \frac{z_3}{z_2} - z_1 z_3 \log \frac{z_3}{z_1} \right)^2.$$

For any $z_1, z_2 < z_3$, due to the facts that the function $h_2(z) = z \log z$ is convex and that $h_3(z) = z(1 + \log \frac{z_3}{z})$ is increasing in $(0, z_3)$, it is easy to show that $\varphi_3(z_1, z_2, z_3)$ is increasing in z_3 , and thus z_U is one support point.

The left bound, z_L , is also a design point when $z_U - z_L < 1$, because

$$\frac{\partial}{\partial z_1} \varphi_3(z_1, z_2, z_U) = 2 \left(1 - \frac{z_U \left(\log \frac{z_U}{z_1} - 1 \right) - z_2 \left(\log \frac{z_2}{z_1} - 1 \right)}{z_1 z_2 \log \frac{z_2}{z_1} + z_2 z_U \log \frac{z_U}{z_2} - z_1 z_U \log \frac{z_U}{z_1}} \right) < 0,$$

for any $z_1 < z_2 < z_U$.

In fact, let $h_4(z_2)$ be the difference of the numerator and the denominator of the second term within the parenthesis. Then $h_4(z_U) = 0$. If $z_U - z_L < 1$, we have $h'_4(z_2) = (z_U - z_1 - 1)/z_2 < 0$. Thus, for $z_2 \in (z_1, z_U)$,

$$h'_4(z_2) < h'_4(z_1) = z_U \log(z_1) - z_U \log(z_U) + (z_U - z_1) < 0.$$

Hence, $h_4(z_2) > h_4(z_U) = 0$. This and the fact that both the numerator and the denominator are positive in (z_L, z_U) imply that $\frac{\partial}{\partial z_1} \varphi_3(z_1, z_2, z_U) < 0 \Rightarrow z_L$ is a design point. For 2), the other design point is determined by solving $\frac{\partial}{\partial z_2} \varphi_3(z_L, z_2, z_U) = 0$, that is, the equation (14). This completes the proof.

We comment that the solution of the equation (14) is unique (proof omitted), and that for the case 1) in Theorem 5, the other two design points, z_1, z_2 , can be obtained by solving the equations that the derivatives of $\varphi_3(z_1, z_2, z_U)$ with respect to z_1, z_2 are equal to 0 separately. Note that z_1 may or may not be z_L . The optimal designs in original x -design space can be obtained correspondingly through the inverse transformation.

3 Efficiency for Parameter Misspecification

As demonstrated in previous section, the optimal designs for non-linear dose-response models generally depend on the unknown parameters. Thus, to implement such designs, one needs to estimate/guess the true values of parameters based on preliminary data or historical knowledge. In this section, we investigate the efficiencies of the designs constructed when the parameters are incorrectly specified.

Assume that $\boldsymbol{\theta}^*$ is the vector of true parameters, and ξ_D^* and ξ_c^* are related D -optimal and c -optimal designs. Let $\xi_D(\boldsymbol{\theta})$ and $\xi_c(\boldsymbol{\theta})$ be the locally D - and c -optimal designs separately for the initial guess of $\boldsymbol{\theta}$. Then, we study the relative efficiency of these locally optimal designs through the D -efficiency defined as

$$\text{eff}_D = \left(\frac{|M(\xi_D(\boldsymbol{\theta}), \boldsymbol{\theta}^*)|}{|M(\xi_D^*, \boldsymbol{\theta}^*)|} \right)^{1/p},$$

and the c -efficiency defined as

$$\text{eff}_c = \frac{{}_c^T M^{-1}(\xi_c^*, \boldsymbol{\theta}^*)_c}{{}_c^T M^{-1}(\xi_c(\boldsymbol{\theta}), \boldsymbol{\theta}^*)_c},$$

where p is the dimension of vector $\boldsymbol{\theta}$. Higher efficiency indicates that the misspecification of the parameters has less effect on the performance of the locally optimal design.

We use model (4) and related designs for illustration. Assume $\theta^* = (b^*, d^*)^T = (10, 2)^T$, and the x -design space $\mathcal{X} = [0, 10]$. Then, $\xi_D^*(7.192) = 0.5 = \xi_D^*(10)$. In Table 5, we present the efficiencies of locally D -optimal designs (the efficiencies for locally c -optimal designs presented in parentheses, $c = (0, 1)^T$) for different initial values of two parameters. We observe that 1) the D -efficiency is greater than 0.9 if the parameter misspecification is not severe ($0.8 \leq b/b^*, d/d^* \leq 1.25$); 2) we do not lose much D -efficiency if both parameters are misspecified to the same direction (less than 4% if both $b/b^*, d/d^*$ are the same and between 0.5 and 2). However, the loss in efficiency becomes large if two parameters are misspecified to opposite directions, especially when b is small and d is large. Note that we have very similar observations when the true parameters are $b^* = 20, d^* = 1.5$ (results not shown).

Furthermore, in Figure 4, we plot the change of efficiency of locally D -optimal design against one parameter ranging from half to double of true value of the parameter, when another parameter is correctly specified. We observe that the loss of D -efficiency for b is higher for parameter underestimation than for overestimation. The drop in D -efficiency for d in either direction is dramatic since the response is more sensitive to a power increase.

For the efficiency of locally c -optimal design, where $c = (0, 1)^T$, we have similar observations as those for locally D -optimal design, and similar plots (not shown) as those in Figure 4. Generally, locally c -optimal design loses more efficiency than D -optimal when parameters are misspecified.

4 Case study

In this section we consider a clinical dose-finding study for anti-anxiety drug (Pinheiro et al., 2006) to demonstrate the benefit of using optimal designs from Section 2.1. The original considerations for the study led to a design with dose levels 0, 10, 25, 50, 100 and 150, and a total sample size of 300 patients being equally allocated to each of the six parallel treatment (dose) groups. That is,

$$\xi_s = \begin{pmatrix} 0 & 10 & 25 & 50 & 100 & 150 \\ 1/6 & 1/6 & 1/6 & 1/6 & 1/6 & 1/6 \end{pmatrix}.$$

We will investigate the performance of the design ξ_s , by calculating its relative D -efficiency and c -efficiency with respect to the locally optimal designs:

$$\text{Rel-eff}_D(\xi_s) = \left(\frac{|M(\xi_s, \theta)|}{|M(\xi_D^*, \theta)|} \right)^{1/2}, \quad \text{Ref-eff}_c(\xi_s) = \frac{c^T M^{-1}(\xi_s, \theta) c}{c^T M^{-1}(\xi_c^*, \theta) c},$$

for different initial values of θ .

In Table 6, with the dose range $\mathcal{X} = [0, 150]$, and certain initial values of b and d , we present the corresponding locally D -optimal and c -optimal designs, where $c = (0, 1)^T$, and the relative efficiencies of ξ_s . A message from the table is that the experimenter can save resource by using optimal designs. Using the case of $(b, d) = (100, 1)$ as an example, we see

that the experimenter would require only about one half as many patients to obtain the same level of accuracy, should an optimal design have been employed.

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Appendix

In the model (5), let $\phi_1(z) = e^{2z}$, $\phi_2(z) = ze^{2z} \log z$ and $\phi_3(z) = z^2 e^{2z} \log^2 z$. Then

$$f_{1,1}(z) = \phi_1'(z) = 2e^{2z},$$

$$f_{2,1}(z) = \phi_2'(z) = e^{2z}(1 + \log z + 2z \log z),$$

$$f_{2,2}(z) = \left(\frac{f_{2,1}(z)}{f_{1,1}(z)} \right)' = \frac{1}{2z} + \log z + 1,$$

$$f_{3,1}(z) = \phi_3'(z) = 2ze^{2z} \log z(\log z + z \log z + 1),$$

$$f_{3,2}(z) = \left(\frac{f_{3,1}(z)}{f_{1,1}(z)} \right)' = (1 + 2z) \log^2 z + (2z + 3) \log z + 1,$$

$$\begin{aligned} f_{3,3}(z) &= \left(\frac{f_{3,2}(z)}{f_{2,2}(z)} \right)' = \frac{2 \log^2 z + \left(\frac{2}{z} + 6 \right) \log z + 2 + \frac{3}{z}}{\frac{1}{2z} + \log z + 1} - \frac{\left(\frac{1}{z} - \frac{1}{2z^2} \right) \left[(1 + 2z) \log^2 z + (2z + 3) \log z + 1 \right]}{\left(\frac{1}{2z} + \log z + 1 \right)^2} \\ &= \frac{4z^2 \log^3 z + (12z^2 + 6z + 1) \log^2 z + (12z^2 + 12z + 5) \log z + (4z^2 + 6z + 4)}{2 \left(\frac{1}{2} + z \log z + z \right)^2}. \end{aligned}$$

Let $u = \log(z) + 1$, and δ denote the function in the numerator of $f_{3,3}$. Then $\delta(u) = u(4u^2 e^{2u-2} + 6ue^{u-1} + u + 3)$. Since $\frac{\delta(u)}{u}$ is a strictly increasing function, $\delta(u)$ has two zeros, -2.592 and 0 . Hence, $f_{3,3}(z)$ has two zeros, 0.0275 and e^{-1} .

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Figure 1.
The convex hull of $\mathcal{S} \cup -\mathcal{S}$ when $b = d = 1$ and $\mathcal{L} = (0, 1)$.

Figure 2.
The plots of $d(x, \xi)$ for the two minimally supported locally D -optimal designs.

Figure 3.

Plot of $S \cup -S$, where $S = \{(s, t) : s = e^z, t = ze^z \log z\}$, $\mathcal{Z} = (0, 1]$.

Figure 4. Plot of D -efficiency of locally D -optimal design versus the initial value of parameter b (left) or d (right). In the left panel, d takes the true value of 2, and in the right panel, b takes the true value of 10.

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Table 1

The values of x^*_I for fixed q and d .

I_{x^*}		I_{x^*}		I_{x^*}	
b	d	b	d	b	d
5	1	6.466	10	1	1
		5.174	20	1	1
5	2	8.863	10	2	2
		7.193	20	2	2
5	3	9.595	10	3	3
		8.027	20	3	3

Table 2

Locally c -optimal designs when $c = (0, 1)^T$ and $\mathcal{X} = [0, 10]$.

b	d	x_1	w_1	x_2	w_2
5	1	5.591	0.812	10	0.188
5	2	8.529	0.804	10	0.196
5	3	9.477	0.794	10	0.206
20	1	3.448	0.801	10	0.199
20	2	5.570	0.793	10	0.207
20	3	6.650	0.788	10	0.212

Table 3

Some minimally supported locally D -optimal designs for Model (5).

d	$\mathcal{X} = [\mathbf{0.2}, \mathbf{1}]$			$\mathcal{X} = [\mathbf{0.2}, \mathbf{x}_U]$		
	$\mathbf{x}_1(z_1)$	$\mathbf{x}_2(z_2)$	$\mathbf{x}_U(z_U)$	$\mathbf{x}_1(z_1)$	$\mathbf{x}_2(z_2)$	$\mathbf{x}_U(z_U)$
1	0.517 (0.571)	1 (1)	0.5 (0.5)	0.2 (0.2)	0.385 (0.385)	
2	0.719 (0.517)	1 (1)	0.7 (0.49)	0.2 (0.04)	0.680 (0.462)	
3	0.803 (0.518)	1 (1)	0.8 (0.512)	0.2 (0.008)	0.794 (0.501)	

Table 4

Examples of locally c -optimal designs when $c = (0, 1)^T$.

z_1	z_2	w_1	w_2
1	2	1	0.269
0	1	0.461	0.368
0	0.45	0	0.395
0	0.2	0	0.450

Table 5
Efficiencies of locally D -optimal (c -optimal in parentheses) designs with (mis-)specified initial parameter values.

	d/d^*						
	0.5	0.75	0.8	1	1.25	1.5	2
0.5	0.968 (0.899)	0.943 (0.841)	0.907 (0.750)	0.727 (0.406)	0.505 (0.162)	0.334 (0.062)	0.139 (0.010)
0.75	0.878 (0.665)	0.999 (0.995)	1.000 (0.999)	0.962 (0.891)	0.864 (0.652)	0.749 (0.439)	0.533 (0.184)
0.8	0.861 (0.629)	0.995 (0.982)	0.999 (0.998)	0.979 (0.938)	0.904 (0.742)	0.810 (0.542)	0.620 (0.268)
$\frac{b}{b^*}$							
1	0.806 (0.520)	0.967 (0.900)	0.980 (0.939)	1 (1)	0.982 (0.944)	0.943 (0.835)	0.851 (0.617)
1.25	0.756 (0.435)	0.931 (0.805)	0.949 (0.854)	0.990 (0.971)	0.999 (0.998)	0.986 (0.955)	0.934 (0.809)
1.5	0.721 (0.381)	0.903 (0.740)	0.924 (0.791)	0.977 (0.933)	0.999 (0.997)	0.996 (0.985)	0.956 (0.868)
2	0.676 (0.320)	0.869 (0.663)	0.893 (0.718)	0.958 (0.883)	0.994 (0.981)	0.999 (0.995)	0.968 (0.900)

Table 6

Efficiencies of ξ_s , compared to locally D -, c -optimal designs (values in parentheses are weights).

(b, d)	D -optimal design	c -optimal design	Rel-eff $_D$	Rel-eff $_c$
(50, 1)	109.67, 150 (0.5, 0.5)	99.00, 150 (0.808, 0.192)	0.3740	0.3234
(50, 2)	141.95, 150 (0.5, 0.5)	139.63, 150 (0.793, 0.207)	0.0210	0.0011
(50, 3)	148.16, 150 (0.5, 0.5)	147.64, 150 (0.786, 0.214)	1.4e-6	7e-12
(100, 1)	88.16, 150 (0.5, 0.5)	73.94, 150 (0.813, 0.187)	0.4707	0.4544
(100, 2)	122.92, 150 (0.5, 0.5)	115.05, 150 (0.811, 0.189)	0.2847	0.1941
(100, 3)	136.54, 150 (0.5, 0.5)	132.45, 150 (0.806, 0.194)	0.1216	0.0365
(300, 1)	66.11, 150 (0.5, 0.5)	51.71, 150 (0.199, 0.201)	0.5356	0.5141
(300, 2)	95.25, 150 (0.5, 0.5)	83.55, 150 (0.793, 0.207)	0.4036	0.3577
(300, 3)	109.14, 150 (0.5, 0.5)	99.74, 150 (0.788, 0.212)	0.3414	0.2795