OPTIMAL DESIGNS FOR TWO-PARAMETER NONLINEAR MODELS WITH APPLICATION TO SURVIVAL MODELS

Maria Konstantinou, Stefanie Biedermann and Alan Kimber

Statistical Sciences Research Institute, University of Southampton

Abstract: Censoring occurs in many industrial or biomedical 'time to event' experiments. Finding efficient designs for such experiments can be problematic since the statistical models involved will usually be nonlinear, making the optimal choice of design parameter dependent. We provide analytical characterisations of locally D- and c-optimal designs for a class of models, thus reducing the numerical effort for design search substantially. We also investigate standadised maximin D- and c-optimal designs. We illustrate our results using the natural proportional hazards parameterisation of the exponential regression model. Different censoring mechanisms are incorporated and the robustness of designs against parameter misspecification is assessed.

Key words and phrases: c-optimality, D-optimality, proportional hazards, survival analysis.

1. Introduction

There is a large literature on optimal designs for nonlinear models but there is little reasearch on designs for models with potentially censored data. Ford, Torsney and Wu (1992) consider optimal designs for nonlinear models where the response is distributed as a member of the exponential family and Sebastiani and Settimi (1997) prove the optimality of these designs for a logistic regression model. Sitter and Torsney (1992) study D-optimal designs for generalised linear models with multiple design variables using the geometry of the design space in Ford, Torsney and Wu (1992), and Sitter and Torsney (1995) consider D- and c-optimal designs for binary response models with two design variables. However, neither paper considers the case where the data are subject to censoring.

Becker, McDonald and Khoo (1989) find D-optimal designs for proportional hazards models with one or two parameters and specified baseline hazard. They use geometric arguments and empirical values for the hazard to investigate how censoring affects the D-optimal designs for different shapes of the design region. López-Fidalgo, Rivas-López and Del Campo (2009) propose an algorithm to find D-optimal designs conditional on arrival time, where the design space is binary. They consider a two-parameter exponential regression model that requires constraints on the parameters. For recent results on accelerated life testing see, for example, Wu, Lin and Chen (2006) and McGree and Eccleston (2010).

Our research was motivated by the following problem. Let $T_1, \ldots, T_n$ be independent survival times of the n subjects in the experiment with $t_1, \ldots, t_n$ the corresponding observed values. Let α and β be the unknown model parameters. In survival models involving one explanatory variable, α relates to the baseline hazard whereas β describes how the hazard varies with the explanatory variable. Let $x_j \in \mathcal{X}$ be the experimental condition at which the jth observation is taken. In what follows, the design space $\mathcal{X}$ is either binary, with $\mathcal{X} = \{0, 1\}$, corresponding, for example, to two different treatments, or an interval, that is $\mathcal{X} = [u, v]$, corresponding, for example, to the doses of a drug.

The period of the experiment is the interval $[0, c]$. We consider two different types of censoring. Type I censoring corresponds to the situation where all subjects enter the study at the same time and are observed until time c or until failure, whichever is earlier. Survival times greater than c are therefore right-censored. Another relevant scenario is random censoring. The jth individual enters the study at a random time in $[0, c]$ which is independent of the survival time. Therefore the censoring time for this individual is also random. The example we shall use to illustrate our general results is the exponential regression model in its proportional hazards parameterisation, naturally used in survival analysis (see, for example, Collett (2003)), which is specified by the probability density function $f(t_j, x_j)$ with corresponding survivor function $S(t_j, x_j)$,

$$f(t_j, x_j) = e^{\alpha+\beta x_j} e^{-t_j e^{\alpha+\beta x_j}}, \quad S(t_j, x_j) = e^{-t_j e^{\alpha+\beta x_j}}, \qquad (t_j > 0) \qquad (1.1)$$

This parameterisation avoids the need to specify constraints on the parameters.

Optimal design is concerned with finding the experimental conditions at which measurements should be taken in order to draw the most precise conclusions. In what follows, we consider approximate designs of the form

$$\xi = \begin{Bmatrix} x_1 & \ldots & x_m \\ \omega_1 & \ldots & \omega_m \end{Bmatrix}, \ 0 < \omega_i \leq 1, \ \sum_{i=1}^{m} \omega_i = 1,$$

where the support points x_i, $i = 1, \dots, m$, $m \leq n$ are the distinct experimental conditions in the design and the weights ω_i represent the proportion of observations taken in the corresponding support point.

A recent trend in optimal design literature is to solve problems in more generality. Hedayat, Zhong and Nie (2004) characterise D-optimal designs for a class of two parameter models. However, these results are not applicable to many models such as model (1.1). Yang and Stufken (2009) consider Loewner optimality and a more general class of models. They obtain excellent results, showing that under some conditions, for each given design there is always a design from a simple class which is better in the Loewner sense. These results were generalised to models with more than two parameters by Yang (2010). Depending on the model, however, the conditions can be difficult to verify, even with symbolic computational software.

This paper aims to provide characterisations of D- and c-optimal designs under assumptions which are somewhat less restrictive and easier to verify than those in Yang and Stufken (2009) and which are satisfied by a large class of models, including model (1.1) for the censoring schemes considered. In section 2 we develop this approach for D-optimality. Section 3 contains the corresponding results for c-optimality when only the slope parameter β is of interest. The results are applied to model (1.1) with type I and random censoring in section 4. Section 5 provides analytical characterisations of the standardised maximin D- and c-optimal designs when a parameter space can be specified even when the locally optimal designs are not available in closed form. In section 6, we assess the robustness of locally optimal and parameter robust designs for model (1.1) and compare their efficiency with traditional designs currently in use. A brief discussion is given in section 7. The more technical proofs are in the appendix.

2. D-optimal designs

A D-optimal design maximises the determinant of the Fisher information $M(\xi, \alpha, \beta)$ with respect to the design, thereby minimising the volume of the confidence ellipsoid for the parameter estimators, so making the estimators as precise as possible. A design ξ^* is D-optimal if

$$\xi^* = \arg\max_{\xi} |M(\xi, \alpha, \beta)|.$$

We consider two-parameter models with Fisher information of the form

$$M(\xi,\alpha,\beta)=\sum_{i=1}^{m}\omega_i I(x_i,\alpha,\beta)=\sum_{i=1}^{m}\omega_i Q(\theta_i)\begin{pmatrix}1 & x_i\\ x_i & x_i^2\end{pmatrix}, \tag{2.1}$$

where $I(x_i,\alpha,\beta)$ is the Fisher information at the point x_i and $\theta_i=\alpha+\beta x_i$, which satisfy the conditions (a)-(d) below. Following Ford, Torsney and Wu (1992), an equivalent problem to maximising $|M(\xi,\alpha,\beta)|$ is to maximise the determinant of this matrix with x_i replaced by $\theta_i=\alpha+\beta x_i$, $i=1,\dots,m$ where $\beta\neq 0$, which will also be denoted $M(\xi,\alpha,\beta)$ in what follows. The parameter dependence of the design problem thus enters only via the transformed design space $\Theta=\alpha+\beta\mathcal{X}$ where $\beta\neq 0$. The assumptions are therefore given for $\theta\in\mathbb{R}$, so they are valid for all possible ranges for Θ.

(a) The function $Q(\theta)$ implicitly defined in (2.1) is positive for all $\theta\in\mathbb{R}$ and twice continuously differentiable.

(b) The function $Q(\theta)$ is strictly increasing on $\mathbb{R}$.

(c) The second derivative $g''(\theta)$ of the function $g(\theta)=2/Q(\theta)$ is an injective function.

(d) For any $s\in\mathbb{R}$, the function $r(\theta)=Q(\theta)(s-\theta)^2$ satisfies $r'(\theta)=0$ for exactly two values of $\theta\in(-\infty,s]$.

For the case of c-optimality we require the extra condition

(d1) : The function $\log Q(\theta)$ is concave for $\theta\in\mathbb{R}$.

which implies assumption (d) given that (a) and (b) hold. Our assumptions hold for Poisson, Gamma and Inverse Gamma regression models and for parametric proportional hazards models with a hazard function of the form

$$h(t)=e^{\alpha}g(t)e^{\beta x}, \tag{2.2}$$

where $e^{\alpha}g(t)$ is the baseline hazard.

To allow estimation of both parameters, a design must have at least two support points. For the binary design space $\mathcal{X}=\{0,1\}$ this means that both 0 and 1 are support points of the D-optimal design. From Lemma 5.1.3 in Silvey (1980), it then follows that the D-optimal design has equal weights.

For the rest of this section we will consider interval design spaces, $\mathcal{X}=[u,v]$. The locally D-optimal design for given α and β, on an arbitrary interval $[u,v]$, can be obtained from the locally D-optimal design on the interval $[0,1]$ for parameter values $\tilde{\alpha} = \alpha + \beta u$ and $\tilde{\beta} = \beta(v-u)$ by transforming its support points x_i^* via $z_i^* = u + (v-u)x_i^*$. Therefore without loss of generality we consider the design space $\mathcal{X} = [0,1]$. A tool for characterising D-optimal designs and for checking the D-optimality of a candidate design is the equivalence theorem (see, for example, Silvey (1980)).

Theorem 1. *A design ξ^* is D-optimal for a model with information matrix (2.1) if the inequality*

$$d(\xi^*, \alpha, \beta) = tr\{M^{-1}(\xi^*, \alpha, \beta) I(x, \alpha, \beta)\} \leq 2,$$

holds for all $x \in [0,1]$, with equality in the support points of ξ^*.

From Caratheodory's Theorem (see, for example, Silvey (1980)), there exists a D-optimal design with at most three support points. Lemma 1 shows that this number can be further reduced.

Lemma 1. *Let $\beta \neq 0$ and assumptions (a)-(c) be satisfied. Then the D-optimal design for a model with Fisher information (2.1) is unique and has two equally weighted support points.*

The proof of Lemma 1 is in the appendix. We next present the main result of this section, an analytical characterisation of D-optimal designs.

Theorem 2. *Let assumptions (a)-(d) be satisfied.*
(a) If $\beta > 0$, the design

$$\xi^* = \begin{Bmatrix} x_1^* & 1 \\ 0.5 & 0.5 \end{Bmatrix},$$

is D-optimal on $\mathcal{X}$, where $x_1^* = 0$ if $\beta < 2Q(\alpha)/Q'(\alpha)$. Otherwise x_1^* is the unique solution of the equation $\beta(x_1 - 1) + 2Q(\alpha + \beta x_1)/Q'(\alpha + \beta x_1) = 0$.
(b) If $\beta < 0$, the design

$$\xi^* = \begin{Bmatrix} 0 & x_2^* \\ 0.5 & 0.5 \end{Bmatrix},$$

is D-optimal on $\mathcal{X}$, where $x_2^* = 1$ if $\beta > -2Q(\alpha + \beta)/Q'(\alpha + \beta)$. Otherwise x_2^* is the unique solution of the equation $\beta x_2 + 2Q(\alpha + \beta x_2)/Q'(\alpha + \beta x_2) = 0$.

Theorem 2 (proved in the appendix) provides a complete classification of D-optimal designs. Depending on some easily verifiable conditions on the parameters, the design problem has been either reduced to an optimisation problem in one variable or solved entirely.

3. c-optimal designs

Often interest centers on estimating β while treating α as a nuisance parameter. For example, for model (1.1) β is a log hazard ratio. Therefore, an appropriate optimality criterion is c-optimality for β which minimises the asymptotic variance of the maximum likelihood estimator $\hat{\beta}$. Thus a design ξ^* is c-optimal for β if $(0\ \ 1)^T \in \text{range}(M(\xi^*, \alpha, \beta))$ and

$$\xi^* = \arg\min_{\xi} (0 \quad 1)\, M^{-}(\xi, \alpha, \beta) \begin{pmatrix} 0 \\ 1 \end{pmatrix}, \tag{3.1}$$

where M^- is a generalised inverse of the matrix M.
Lemma 2, which is proved in the appendix, shows that the c-optimal design for β is supported on two points.

Lemma 2. *For any real α, $\beta \neq 0$ and any model with Fisher information (2.1) there exists a c-optimal design for β with exactly two support points.*

From Pukelsheim and Torsney (1991), we obtain an expression for the optimal weights. A c-optimal design ξ^* for β with support points x_1^* and x_2^* is

$$\xi^* = \left\{ \begin{array}{cc} x_1^* & x_2^* \\ \frac{\sqrt{Q(\alpha+\beta x_2^*)}}{\sqrt{Q(\alpha+\beta x_1^*)}+\sqrt{Q(\alpha+\beta x_2^*)}} & \frac{\sqrt{Q(\alpha+\beta x_1^*)}}{\sqrt{Q(\alpha+\beta x_1^*)}+\sqrt{Q(\alpha+\beta x_2^*)}} \end{array} \right\}. \tag{3.2}$$

The design problem for $\mathcal{X} = \{0, 1\}$ has thus been solved completely. It remains to find the optimal support points when $\mathcal{X} = [u, v] \subset \mathbb{R}$. In this case, an analytical characterisation of the c-optimal designs for β for models with information matrix of the form (2.1) is given in Theorem 3, which is proved in the appendix.

Theorem 3. *Let assumptions (a)-(c) and (d1) be satisfied.*
(a) If $\beta > 0$, the design ξ^* with support points x_1^* and v and the optimal weights given in (3.2) is c-optimal for β, where $x_1^* = u$ if

$$\beta(u - v) + 2Q(\alpha + \beta u)/Q'(\alpha + \beta u) \left(1 + \sqrt{Q(\alpha + \beta u)}/\sqrt{Q(\alpha + \beta v)}\right) > 0. \tag{3.3}$$

Otherwise x_1^* is the unique solution of the equation

$$\beta(x_1 - v) + 2Q(\alpha + \beta x_1)/Q'(\alpha + \beta x_1) \left(1 + \sqrt{Q(\alpha + \beta x_1)}/\sqrt{Q(\alpha + \beta v)}\right) = 0. \tag{3.4}$$

(b) If $\beta < 0$, the design ξ^* with support points u and x_2^* and the optimal weights given in (3.2) is c-optimal for β, where $x_2^* = v$ if

$$\beta(u-v) - 2Q(\alpha+\beta v)/Q'(\alpha+\beta v)\left(1+\sqrt{Q(\alpha+\beta v)}/\sqrt{Q(\alpha+\beta u)}\right) < 0.$$

Otherwise x_2^* is the unique solution of the equation

$$\beta(u-x_2) - 2Q(\alpha+\beta x_2)/Q'(\alpha+\beta x_2)\left(1+\sqrt{Q(\alpha+\beta x_2)}/\sqrt{Q(\alpha+\beta u)}\right) = 0.$$

4. Application to an exponential regression model

In this section we apply the previous results to model (1.1) for an interval design space. We briefly discuss the special case of no censoring, corresponding to $c = \infty$, a study running for as long as necessary to record all survival times. From (1.1), the log-likelihood at x_j is $l(\alpha, \beta, x_j) = \alpha + \beta x_j - t_j e^{\alpha+\beta x_j}$ and thus the Fisher information at the point x_j is

$$I(x_j, \alpha, \beta) = \begin{pmatrix} 1 & x_j \\ x_j & x_j^2 \end{pmatrix},$$

since $E(T_j) = 1/e^{\alpha+\beta x_j}$. In this case the Fisher information is the same as for the linear model for independent identically distributed errors. The D-optimal design for this model is equally supported at the end points of the design space $\mathcal{X}$ (see, for example, Atkinson, Donev and Tobias (2007)) and coincides with the c-optimal design for β.

4.1. Type I censoring

In Type I censoring the censoring time c is fixed and common for all individuals. This occurs, for example, when all individuals have been recruited at the same time to a study of duration c. If the event of interest has not occurred by the end of the study the observation is right-censored. Let $Y_j = min\{T_j, c\}$ be the jth possibly censored observation and let T_j follow model (1.1). Then

$$E(Y_j) = \int_0^c y e^{\alpha+\beta x_j} e^{-y e^{\alpha+\beta x_j}}\, dy + cP(Y_j = c) = (1 - e^{-ce^{\alpha+\beta x_j}})/e^{\alpha+\beta x_j}, \quad (4.1)$$

and the log-likelihood at x_j is $l(\alpha, \beta, x_j) = \delta_j(\alpha + \beta x_j) - y_j e^{\alpha+\beta x_j}$, where δ_j is an event indicator which is zero if y_j is a censored observation and unity otherwise. Hence the Fisher information at x_j is

$$I(x_j, \alpha, \beta) = (1 - e^{-ce^{\alpha+\beta x_j}}) \begin{pmatrix} 1 & x_j \\ x_j & x_j^2 \end{pmatrix},$$

which yields (2.1) with $Q(\theta) = (1 - e^{-ce^{\theta}})$. It can be shown that assumptions (a)-(d) hold here. Hence Theorems 2 and 3 hold for Type I censoring.

4.2. Random censoring

Random censoring occurs, for example, if the jth individual enters the study at random time $Z_j \in [0, c]$, where Z_j is independent of the survival time T_j. Now the censoring time $C_j = c - Z_j$ for this individual is also random. We assume that $Z_1, \ldots, Z_n$ follow a uniform distribution on $[0, c]$, thus $C_1, \ldots, C_n$ also have a uniform distribution on $[0, c]$ with probability density function $f_c(c_j) = 1/c$. We observe $Y_j = min\{T_j, C_j\}$ where $E(Y_j|C_j = c_j)$ is given by the right hand side of (4.1) with c replaced by c_j. Thus

$$E(Y_j) = E(E(Y_j|C_j = c_j)) = \int_0^c (1 - e^{-c_j e^{\alpha+\beta x_j}})/ce^{\alpha+\beta x_j}\, dc_j$$
$$= \left(ce^{\alpha+\beta x_j} + e^{-ce^{\alpha+\beta x_j}} - 1\right)/ce^{2(\alpha+\beta x_j)},$$

and the log-likelihood at x_j is $l(\alpha, \beta, x_j) = \delta_j(-\log c + \alpha + \beta x_j) - y_j e^{\alpha+\beta x_j}$. Hence the Fisher information at point x_j is

$$I(x_j, \alpha, \beta) = \left(ce^{\alpha+\beta x_j} + e^{-ce^{\alpha+\beta x_j}} - 1\right)/ce^{\alpha+\beta x_j} \begin{pmatrix} 1 & x_j \\ x_j & x_j^2 \end{pmatrix}.$$

Again this is of the form (2.1) for $Q(\theta) = 1 + \left(e^{-ce^{\theta}} - 1\right)/ce^{\theta}$ and assumptions (a)-(d) and (d1) hold.

For $\beta > 0$ (< 0) the Q-functions above are increasing (decreasing) with x. Therefore from (3.2) the c-optimal weight corresponding to the smaller support point is greater (smaller) than the other weight if $\beta > 0$ (< 0). This means, for example, that more patients are allocated to the more effective dose. Note that the popular equal allocation rule leads to a suboptimal design.

5. Standardised optimal designs

The optimal designs found above depend on the model parameters which are unknown in practice. Nevertheless, in many practical situations some information about the parameter values can be provided by the experimenter. For example, α may determine the baseline hazard for a standard treatment. Hence precise knowledge of its value might be available, whereas for β the experimenter can specify a range of values for a clinically significant improvement with new treatment. We further assume that the experimenter has no preference for specific β-values and that the total duration of the study, c, is known.

Following Dette (1997) we seek designs that maximise the worst efficiencies with respect to the locally optimal designs over a range of parameter values. This allows us to construct robust designs which protect against the worst case scenario. Dette and Sahm (1998) compare a standardised and a nonstandardised maximum variance optimality criterion and show that in some cases the optimal designs based on the latter criterion may be inefficient. A design ξ^* maximising

$$\Phi(\xi) = \min \left\{ \tfrac{|M(\xi,\alpha,\beta)|}{|M(\xi^*_\beta,\alpha,\beta)|} \;\middle|\; \beta \in [\beta_0, \beta_1] \right\}, \tag{5.1}$$

is called a standardised maximin D-optimal design and a design ξ^* maximising

$$\Phi(\xi) = \min \left\{ \tfrac{(0 \quad 1) M^-(\xi^*_\beta,\alpha,\beta)\binom{0}{1}}{(0 \quad 1) M^-(\xi,\alpha,\beta)\binom{0}{1}} \;\middle|\; \beta \in [\beta_0, \beta_1] \right\}, \tag{5.2}$$

is called a standardised maximin c-optimal design for β, where ξ^*_β is the locally optimal design. Criteria (5.1) and (5.2) seek a design that maximises the worst D-efficiency and c-efficiency respectively, given by

$$eff_D(\xi) = \left(\frac{|M(\xi, \alpha, \beta)|}{|M(\xi^*_\beta, \alpha, \beta)|} \right)^{\frac{1}{2}}, \tag{5.3}$$

and

$$eff_c(\xi) = \frac{(0 \quad 1)\, M^-(\xi^*_\beta, \alpha, \beta)\binom{0}{1}}{(0 \quad 1)\, M^-(\xi, \alpha, \beta)\binom{0}{1}}. \tag{5.4}$$

For a binary design space the locally D-optimal design is equally supported at 0 and 1 for any parameter values, so no further investigation need be done. For an interval design space $\mathcal{X} = [0, 1]$, the following theorem provides an analytical characterisation of the standardised maximin D-optimal two point design for a given range of negative β-values and its proof is given in the appendix.

Theorem 4. *Let $\beta \in [\beta_0, \beta_1]$ where $\beta_1 < 0$, α be fixed and assumptions (a), (b) and (d1) be satisfied. The standardised maximin D-optimal two-point design is equally supported at points 0 and x^*_2 where $x^*_2 = 1$ if $\beta_0 > -2Q(\alpha+\beta_0)/Q'(\alpha+\beta_0)$. Otherwise x^*_2 is the solution of the equation*

$$Q(\alpha + \beta_0 x) Q(\alpha + \beta_1 x(\beta_1)) x(\beta_1)^2 = Q(\alpha + \beta_1 x) Q(\alpha + \beta_0 x(\beta_0)) x(\beta_0)^2, \tag{5.5}$$

where $x(\beta_0)$, $x(\beta_1)$ are the solutions of the equation $\beta x + 2Q(\alpha+\beta x)/Q'(\alpha+\beta x) = 0$, $0 < x \leq 1$ for β_0 and β_1 respectively.

Note that Theorem 4 applies when $\beta < 0$. The proof used in this case is not applicable when $\beta > 0$ and this is a topic for further investigation.

As shown in section 3, the locally c-optimal designs for β depend on the model parameters. Theorem 5, which is proven in the appendix, gives an analytical characterisation of the standardised maximin c-optimal design for β, for a binary design space.

Theorem 5. *Let $\beta \in [\beta_0, \beta_1]$, α be fixed and assumptions (a), (b) and (d1) be satisfied. Also let the design space be binary, that is $\mathcal{X} = \{0, 1\}$. The standardised maximin c-optimal two-point design is*

$$\xi^* = \begin{Bmatrix} 0 & 1 \\ \omega^* & 1 - \omega^* \end{Bmatrix},$$

where $\omega^* = (\omega(\beta_0) + \omega(\beta_1))/2$ and $\omega(\beta_0)$ and $\omega(\beta_1)$ is the optimal weight on zero for the locally c-optimal design for β given in (3.2) *for β_0 and β_1 respectively.*

6. Robustness analysis

In the following we assess the robustness of our designs by calculating their efficiency if the parameters have been misspecified. As a starting point we used the maximum likelihood estimates for α and β from the Freireich data (see Collett (2003)), -2.163 and -1.526 respectively, and $c = 30$. To compare the performance of an arbitrary design ξ to a locally D-optimal design ξ^* we use the D-efficiency (5.3), whereas for the comparison of ξ to a locally c-optimal design ξ^* we use the c-efficiency (5.4). Type I censoring is assumed throughout this numerical example for demonstration purposes.

6.1. Locally D-optimal designs

We consider locally D-optimal designs for a vector of parameter values $\boldsymbol{\gamma} = (\alpha, \beta)$. The value of the maximum likelihood estimator for α was used, whereas the β-values were chosen to have small, medium and large treatment effect. Table 6.1 gives the parameter vectors used and the corresponding D-efficiencies of the locally D-optimal designs when the parameter values are misspecified.

For the first three sets of parameter values the locally D-optimal design is the "standard design" supported at 0 and 1, with equal weights whereas ξ_{γ_3} is equally supported at 0 and 0.9. The "standard design" has high D-efficiency for all the values of the parameter vectors. The lowest efficiency, 0.900, is obtained

Table 6.1: D-efficiencies for some selected locally D-optimal designs

	Design			
Parameter vector	ξ_{γ_0}	ξ_{γ_1}	ξ_{γ_2}	ξ_{γ_3}
$\boldsymbol{\gamma_0} = (-2.163, -0.1)$	1	1	1	0.900
$\boldsymbol{\gamma_1} = (-2.163, -0.405)$	1	1	1	0.905
$\boldsymbol{\gamma_2} = (-2.163, -1.526)$	1	1	1	0.946
$\boldsymbol{\gamma_3} = (-2.163, -2.623)$	0.992	0.992	0.992	1

if the true value is $\boldsymbol{\gamma_0}$ and the experimenter has misspecified this value as $\boldsymbol{\gamma_3}$ and hence used the design ξ_{γ_3}. In other words if the experimenter has used design ξ_{γ_3} assuming a large treatment effect when the true effect is actually small, the D-efficiency is 0.9 which is quite satisfying. Hence ξ_{γ_3} seems to be a good alternative to the "standard design" if, for example, the experimenter does not want to expose the patients at the highest drug doses.

6.2. Locally c-optimal designs

For the same parameter vectors used in section 6.1, their locally c-optimal designs have support points 0 and 1. The weights were found using (3.2) and are shown in Table 6.2. The c-efficiencies of each of these designs were also calculated when the parameter values are misspecified and are presented in Table 6.3.

Table 6.2: Weights for some selected locally c-optimal designs

	Design			
Weight	ξ_{γ_0}	ξ_{γ_1}	ξ_{γ_2}	ξ_{γ_3}
ω_1	0.498	0.491	0.425	0.323
ω_2	0.502	0.509	0.575	0.677

Table 6.3: c-efficiencies for the locally c-optimal designs of Table 6.2

	Design			
Parameter vector	ξ_{γ_0}	ξ_{γ_1}	ξ_{γ_2}	ξ_{γ_3}
$\boldsymbol{\gamma_0}$	1	0.9998	0.9782	0.8772
$\boldsymbol{\gamma_1}$	0.9998	1	0.9824	0.8864
$\boldsymbol{\gamma_2}$	0.9787	0.9828	1	0.9552
$\boldsymbol{\gamma_3}$	0.8908	0.8991	0.9597	1

The locally c-optimal designs have high c-efficiencies for all the four sets of parameter values. The lowest efficiency, 0.8772, occurs when the assumed value is $\boldsymbol{\gamma_3}$ and the true value is $\boldsymbol{\gamma_0}$. Note that the design ξ_{γ_2}, which is locally c-optimal for a parameter value near the center of the parameter space, has a lowest efficiency of 0.9597 and hence is more robust than the other three designs.

6.3. Standardised maximin optimal designs

According to the analysis in section 5 we can find the standardised maximin D- and c-optimal designs for the range of β-values used above which are denoted by ξ_{γ_4} in both cases. We note that although here we consider the case of an interval design space all the locally c-optimal designs found in section 6.2 are supported at points 0 and 1 and so the result of Theorem 5 can be used.

The standardised maximin D-optimal design is supported at 0 and 0.993, with equal weights and is locally D-optimal for $\boldsymbol{\gamma_4} = (-2.163, -2.380)$, whereas the standardised maximin c-optimal design allocates 41.1% of the observations at the experimental point 0 and the rest at point 1, and is locally c-optimal for $\boldsymbol{\gamma_4} = (-2.163, -1.690)$. The minimum (median) efficiencies are 0.993 (0.993) for the D-optimal design and 0.969 (0.974) for the c-optimal design. For both of the above designs the minimum efficiencies are obtained at $\boldsymbol{\gamma_0}$ and $\boldsymbol{\gamma_3}$.

6.4. Cluster designs

This is a modification (see Biedermann and Woods (2011)) of the method introduced by Dror and Steinberg (2006). For each of 1000 parameter vectors, found by drawing 1000 β-values from a uniform distribution on the interval from -2.623 to -0.1, the locally D- and c-optimal designs were obtained. Then a clustering algorithm was applied where the cluster centroids are chosen as the support points and each weight is chosen to be proportional to the corresponding cluster size, reflecting the relative importance of each cluster.

The number of clusters for the D-optimal designs was chosen to vary from 2 to 6 and for each value the D-efficiency of a cluster design was calculated via (5.3) relative to each of the 1000 locally D-optimal designs. The two-point cluster design is equally supported at 0 and 1 whereas the rest of the cluster designs with more than two support points allocate half the observations at point 0, very little weight at points other than 0 and 1 and the rest at point 1. The minimum and median efficiencies are found to be the same for all the cluster designs (0.993 and 0.997 respectively) and this may be a result of the very low weight that all of our cluster designs give to experimental points other than 0 and 1.

The support points of the 1000 locally c-optimal designs are always 0 and 1, hence the cluster design must have two support points: 0 and 1. Also the clustering here was applied to *design* points, rather than *support* points as the support points of the locally c-optimal points have differing weights. The resulting cluster design allocates 43% of the observations at 0 and the rest at 1, and performs well as the minimum (median) efficiencies found via (5.4) are 0.956 (0.990).

6.5. Comparison of designs

First we compare the performance of the following 11 designs: the locally D-optimal designs $\xi_{\gamma_0}, \ldots, \xi_{\gamma_3}$, the standardised maximin D-optimal design ξ_{γ_4}, the cluster designs $\xi_1, \ldots, \xi_5$ and the equally spaced design ξ_0 with support points 0, 0.5, 1 and equal weights. The D-efficiency (5.3) of each of the above designs is calculated with respect to each of the 1000 locally optimal designs and the results are summarised in Figure 6.1. Designs ξ_0 and ξ_{γ_3} were omitted since they were clearly outperformed, although design ξ_{γ_3} was reasonably efficient.

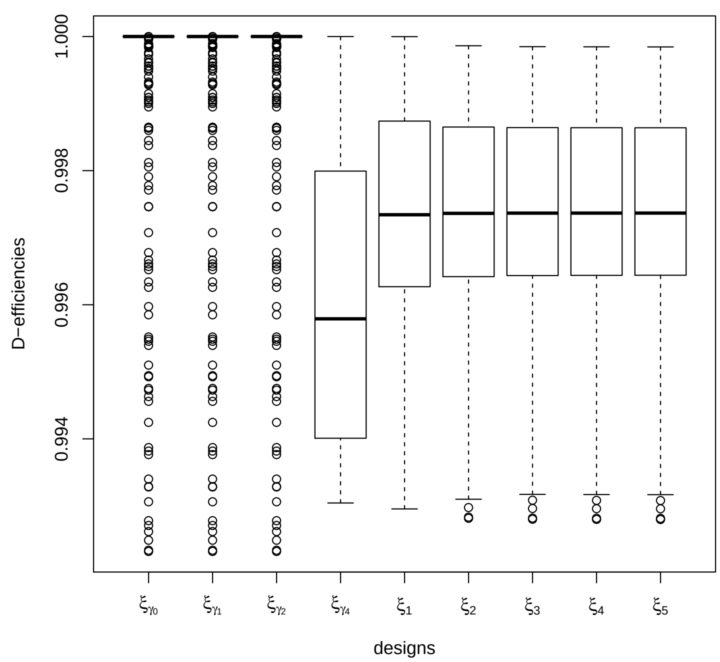

Figure 6.1: Boxplots of D-efficiencies calculated for 9 different designs for 1000 parameter vectors

Figure 6.1 shows that the standardised maximin D-optimal design ξ_{γ_4} has the highest minimum efficiency but lower median efficiency: there is a trade off between protecting against the worst case scenario and having a worse median efficiency. The cluster designs $\xi_2, \ldots, \xi_5$ with more than 2 support points are useful since they allow for linearity of the regression to be checked and do not perform worse than the two-point cluster design ξ_1. All cluster designs are good alternatives to locally optimal designs and perform similarly to the standardised maximin D-optimal design.

The locally c-optimal designs $\xi_{\gamma_0}, \ldots, \xi_{\gamma_3}$, the standardised maximin c-optimal design ξ_{γ_4} and the two-point cluster design ξ_1 are compared in Figure 6.2. Among the locally c-optimal designs only ξ_{γ_2} performs well across the parameter space. As for D-optimality, there is a trade off between best minimum efficiency and a lower median efficiency for the standardised maximin c-optimal design ξ_{γ_4}. Overall both ξ_{γ_4} and ξ_1 are good alternatives to the locally optimal designs.

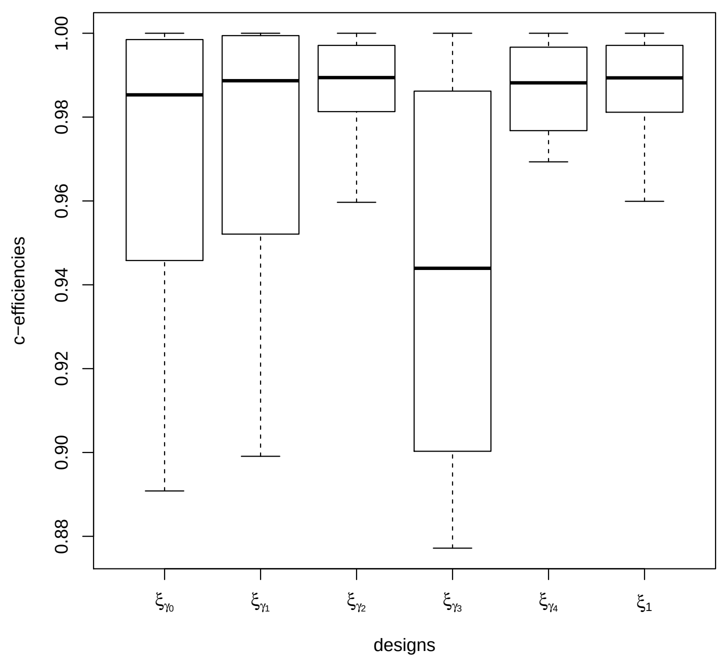

Figure 6.2: Boxplots of c-efficiencies calculated for 6 different designs for 1000 parameter vectors

7. Discussion

Survival models used in applications are usually nonlinear and hence the optimal designs depend on the unknown model parameters. To overcome this difficulty robust designs must be constructed which will perform well across a wide range of parameter values. Another difficulty in finding optimal designs for these applications is that the data are often subject to censoring.

For models with Fisher information of the form (2.1) that satisfy assumptions (a)-(d) and (d1) we have provided a complete classification of locally D- and c-optimal designs. Our assumptions are somewhat less restrictive and easier to check than those provided by Yang and Stufken (2009) and are satisfied by many models. Our results were then applied to the proportional hazards parameterisation of the exponential regression model (1.1), for the cases of Type I and random censoring. Under some conditions on the parameters the optimal design is not the "standard design" supported at 0 and 1 with equal weights, which is the one usually used in these experiments.

In order to construct robust designs we have found optimal designs based on standardised maximin criteria when there is some knowledge about the parameter values (that is a range of values is specified), which maximise the worst efficiency among all two-point designs. To the best of our knowledge, Theorem 4 is the first analytical characterisation of standardised maximin D-optimal designs in a situation where the locally D-optimal designs are not available in closed form. Additionally, cluster designs were built from the locally optimal designs for a specific set of parameter values and their computation was facilitated by our results for the locally optimal designs. In section 6 we have shown that good alternatives to the locally optimal designs are the cluster designs which in some cases (see D-optimality), have more than 2 support points, thereby enabling the linearity of the regression function to be checked.

Appendix

Proof of Lemma 1. Let α and $\beta > 0$ be fixed and $\alpha + \beta x = \theta$. The case where $\beta < 0$ can be shown analogously and is therefore not presented. From Theorem 1, we obtain that a D-optimal design ξ^* must satisfy the inequality

$$z(\theta) := z_1 + z_2\theta + z_3\theta^2 \leq 2/Q(\theta) =: g(\theta) \quad \forall \theta \in [\alpha, \alpha + \beta],$$

for some coefficients $z_1, z_2, z_3 \in \mathbb{R}$, with equality at the support points of ξ^*. Now suppose a D-optimal design has three support points, $\alpha \leq \theta_1 < \theta_2 < \theta_3 \leq \alpha + \beta$. Then $z(\theta_i) = g(\theta_i)$, $i = 1, 2, 3$. By Cauchy's mean value theorem, there exist points $\tilde{\theta}_i$, $i = 1, 2$ such that $\theta_1 < \tilde{\theta}_1 < \theta_2 < \tilde{\theta}_2 < \theta_3$ and $z'(\tilde{\theta}_i) = g'(\tilde{\theta}_i)$. Since $z(\theta) \leq g(\theta)$ on $[\alpha, \alpha + \beta]$, we also have $z'(\theta_2) = g'(\theta_2)$. By the mean value theorem, there exist points $\hat{\theta}_i$, $i = 1, 2$ such that $\tilde{\theta}_1 < \hat{\theta}_1 < \theta_2 < \hat{\theta}_2 < \tilde{\theta}_2$ and $z''(\hat{\theta}_i) = g''(\hat{\theta}_i)$. Now $z''(\theta)$ is constant, so can intersect with $g''(\theta)$ at most once on $[\alpha, \alpha+\beta]$, which contradicts the assumption of three support points. Hence a D-optimal design has exactly two support points, with equal weights.

Let ξ_1 and ξ_2 be two D-optimal designs. By log-concavity of the D-criterion, the design $\xi_3 = 0.5\xi_1 + 0.5\xi_2$ must also be D-optimal. However, if ξ_1 and ξ_2 are different, ξ_3 has more than two support points, which contradicts the result above. Hence the D-optimal design is unique. □

Proof of Theorem 2. We give a sketch of the proof for part (a). The proof of (b) follows along similarly using symmetry arguments and is therefore omitted.

Let $\beta > 0$. For a design with two support points $x_1, x_2 \in [0, 1]$, with $x_1 < x_2$, the determinant of (2.1) is increasing with x_2, regardless of the value of x_1, and therefore maximised for $x_2 = 1$. It remains to maximise the function

$$r(\alpha + \beta x_1) = Q(\alpha + \beta x_1)(x_1 - 1)^2, \quad 0 \leq x_1 < 1.$$

Using assumption (d), $r(\alpha+\beta x_1)$ has exactly two turning points on $(-\infty, 1]$, one of which is a minimum at $x_1 = 1$, hence the other one must be a maximum. If this maximum is attained outside the design space, $r(\alpha+\beta x_1)$ is maximised at $x_1 = 0$, which will then be the second support point of the D-optimal design. This occurs if and only $r'(\alpha + \beta x_1) < 0$ at $x_1 = 0$, which is equivalent to $\beta < 2Q(\alpha)/Q'(\alpha)$. Otherwise the point at which the maximum is attained will be the second support point. This is found by solving $r'(\alpha + \beta x_1) = 0$, which is equivalent to solving $\beta(x_1 - 1) + 2Q(\alpha + \beta x_1)/Q'(\alpha + \beta x_1) = 0$. □

Proof of Lemma 2. From Caratheodory's theorem, there exists a c-optimal design for β with at most two support points. We now assume that there exists an optimal design $\tilde{\xi}$ with only one support point $\tilde{\theta}$. For estimability we require that $(0 \;\; 1)^T$ is in the range of $M(\xi, \alpha, \beta)$, that is, there exists a vector $\eta = (\eta_1, \eta_2)^T \in \mathbb{R}^2$ such that

$$\begin{pmatrix} 0 \\ 1 \end{pmatrix} = Q(\tilde{\theta}) \begin{pmatrix} 1 & \tilde{\theta} \\ \tilde{\theta} & \tilde{\theta}^2 \end{pmatrix} \begin{pmatrix} \eta_1 \\ \eta_2 \end{pmatrix} \iff \begin{pmatrix} 0 = Q(\tilde{\theta})(\eta_1 + \eta_2\tilde{\theta}) \\ 1 = Q(\tilde{\theta})\tilde{\theta}(\eta_1 + \eta_2\tilde{\theta}) \end{pmatrix}, \qquad (7.1)$$

which yields a contradiction. □

Proof of Theorem 3. We give only a sketch of the proof of part (a). The proof of part (b) is similar and therefore omitted.

Let $\beta > 0$ and $x_1 < x_2$. Substituting the expressions for the optimal weights from (3.2), we obtain for the objective function defined in (3.1):

$$k(x_1, x_2) := \left(1/\sqrt{Q(\alpha + \beta x_1)} + 1/\sqrt{Q(\alpha + \beta x_2)}\right)^2 /(x_1 - x_2)^2.$$

Holding x_1 fixed, $k(x_1, x_2)$ is decreasing with x_2 and therefore attains its minimum in $[u, v]$ at the upper boundary v. Now $k(x_1, v)$ has exactly one turning point x_1^* on $(-\infty, v]$ and so there is at most one turning point in $[u, v]$, which is a minimum since $\lim_{x_1 \to -\infty} k(x_1, v) = \lim_{x_1 \to v} k(x_1, v) = \infty$. If $x_1^* \notin [u, v]$ the lower boundary, u, is the smaller support point. This occurs if and only if $k'(x_1, v) > 0$ at $x_1 = u$, which is equivalent to condition (3.3). Otherwise x_1^* is the smaller support point and can be found solving $k'(x_1, v) = 0$, which is equivalent to solving (3.4). □

Proof of Theorem 4. Using condition (d2) the function $\beta + 2Q(\alpha+\beta)/Q'(\alpha+\beta) := l(\beta)$ is increasing with β. Hence if $l(\beta_0) > 0$ then $l(\beta) > 0$ for all $\beta \in [\beta_0, \beta_1]$ and using part (b) in Theorem 2 the locally D-optimal design ξ_β^* is equally supported at points 0 and 1 for all $\beta \in [\beta_0, \beta_1]$. Hence the standardised maximin D-optimal design is also supported at 0 and 1 with equal weights.

Now let $l(\beta_0) \leq 0$. Since $l(\beta)$ is increasing with β there exists $\beta^* \in (\beta_0, \beta_1]$ such that $l(\beta) > 0$ for all $\beta \geq \beta^*$. Again using part (b) in Theorem 2 the locally D-optimal design ξ_β^* is equally supported at points 0 and x_β where $x_\beta = 1$ for $\beta \geq \beta^*$. Otherwise x_β is the solution of the equation

$$\beta x_\beta + 2Q(\alpha + \beta x_\beta)/Q'(\alpha + \beta x_\beta) = 0, \quad 0 < x_\beta \leq 1. \tag{7.2}$$

From (5.3) the D-efficiency of a two-point design ξ equally supported at 0 and x is given by

$$eff_D(\xi) = \left(\frac{Q(\alpha + \beta x)x^2}{Q(\alpha + \beta x_\beta)x_\beta^2}\right)^{\frac{1}{2}} := (u(x, \beta))^{\frac{1}{2}}.$$

For $\beta \geq \beta^*$, $x_\beta = 1$ and for fixed $0 < x \leq 1$

$$\frac{du(x, \beta)}{d\beta} = x^2/Q^2(\alpha + \beta)\left[Q'(\alpha + \beta x)xQ(\alpha + \beta) - Q(\alpha + \beta x)Q'(\alpha + \beta)\right],$$

which is non-positive for all $\beta \in [\beta^*, \beta_1]$ using condition (d2). Hence for fixed x, $u(x, \beta)$ is minimised at β_1.

For $\beta < \beta^*$ and fixed $0 < x \leq 1$, solving $\frac{du(x,\beta)}{d\beta} = 0$ is equivalent to solving

$$\beta x + 2Q(\alpha + \beta x)/Q'(\alpha + \beta x) = 0,$$

using equation (7.2). This has a unique solution β such that $x_\beta = x$. So the function $\beta \to u(x, \beta)$ is unimodal for fixed x and it is minimised at β_0 or β_1. We note that if $l(\beta_1) \leq 0$ then for all $l(\beta) \leq 0$ and x_β is the solution of equation (7.2). Following the same arguments as in the above case for fixed $0 < x \leq 1$, the function $\beta \to u(x, \beta)$ is unimodal and minimised at β_0 or β_1. Hence the standardised maximin design can be found by maximising

$$\Phi(\xi) = \min\left\{u(x, \beta_0), u(x, \beta_1)\right\}.$$

This maximisation can be divided into maximisation over the sets

$$M_< := \left\{x \in (0,1] \,\middle|\, u(x, \beta_0) < u(x, \beta_1)\right\}$$
$$M_> := \left\{x \in (0,1] \,\middle|\, u(x, \beta_0) > u(x, \beta_1)\right\}$$
$$M_= := \left\{x \in (0,1] \,\middle|\, u(x, \beta_0) = u(x, \beta_1)\right\}$$

Now assume that the standardised maximin D-optimal design is in the set $M_<$ and so we must maximise the function $u(x, \beta_0)$. Taking its first derivative with respect to x and equating it to zero yields

$$\beta_0 x + 2Q(\alpha + \beta_0 x)/\beta Q'(\alpha + \beta_0 x) = 0 \Rightarrow x = x(\beta_0).$$

Hence $(u(x(\beta_0), \beta_0))^{\frac{1}{2}} = 1 < (u(x(\beta_0), \beta_1))^{\frac{1}{2}}$ which is a contradiction. Following similar arguments for set $M_>$ also leads to a contradiction and so the standardised maximin D-optimal design can be found by solving $u(x, \beta_0) = u(x, \beta_1)$ which is equivalent to solving

$$Q(\alpha + \beta_0 x)Q(\alpha + \beta_1 x(\beta_1))x(\beta_1)^2 = Q(\alpha + \beta_1 x)Q(\alpha + \beta_0 x(\beta_0))x(\beta_0)^2.$$

□

Proof of Theorem 5. For a binary design space the c-optimal weights ω_β and $1 - \omega_\beta$ for β are defined in (3.2). From (5.4) the c-efficiency of a design ξ with support points 0 and 1 and weights ω and $1 - \omega$ respectively is

$$eff_c(\xi) = \omega(1 - \omega)/((1 - \omega)(\omega_\beta)^2 + \omega(1 - \omega_\beta)^2) := u(\omega, \omega_\beta)$$

and the standardised maximin c-optimal criterion is

$$\Phi(\xi) = \min\left\{u(\omega, \omega_\beta) \;\middle|\; \omega_\beta \in [\omega_{\beta_0}, \omega_{\beta_1}]\right\}$$

For fixed ω the function $\omega_\beta \to u(\omega, \omega_\beta)$ is unimodal and the standardised maximin design ω^* is in $M_=$. Hence we can find ω^* by solving the equation $u(\omega, \omega(\beta_0)) = u(\omega, \omega(\omega_1))$ which yields $\omega^* = (\omega(\beta_0) + \omega(\beta_1))/2$. □

References

Atkinson, A. C., Donev, A. N. and Tobias, R. D. (2007). *Optimum Experimental Designs, with SAS.* Oxford: Oxford University Press.

Becker, N., McDonald, B. and Khoo, C. (1989). Optimal designs for fitting a proportional hazards regression model to data subject to censoring. *Australian Journal of Statistics* **31**, 449-468.

Biedermann, S. and Woods, D. C. (2011). Optimal designs for generalized nonlinear models with application to second-harmonic generation experiments. *Applied Statistics* **60**, 281-299.

Collett, D. (2003). *Modelling Survival Data in Medical Research.* Chapman and Hall/CRC.

Dette, H. (1997). Designing experiments with respect to 'standardized' optimality criteria. *J. Roy. Statist. Soc. Ser. B* **59**, 97-110.

Dette, H. and Sahm, M. (1998). Minimax optimal designs in nonlinear regression models. *Statist. Sinica* **8**, 1249-1264.

Dror, H. A. and Steinberg, D. M. (2006). Robust experimental design for multivariate generalized linear models. *Technometrics* **48**, 520-529.

Ford, I., Torsney, B. and Wu, C. F. J. (1992). The use of a canonical form in the construction of locally optimal designs for non-linear problems. *J. Roy. Statist. Soc. Ser. B* **54**, 569-583.

Hedayat, A. S., Zhong, J. and Nie, L. (2004). Optimal and efficient designs for 2-parameter nonlinear models. *J. Statist. Plann. Inference* **124**, 205-217.

López-Fidalgo, J., Rivas-López, M. J. and Del Campo, R. (2009). Optimal designs for Cox regression. *Statist. Neerlandica* **63**, 135-148.

McGree, J. M. and Eccleston, J. A. (2010). Investigating design for survival models. *Metrika* **72**, 295-311.

Pukelsheim, F. and Torsney, B. (1991). Optimal weights for experimental designs on linearly independent support points. *Ann. Statist.* **19**, 1614-1625.

Sebastiani, P. and Settimi, R. (1997). A note on D-optimal designs for a logistic regression model. *J. Statist. Plann. Inference* **59**, 359-368.

Silvey, S. D. (1980). *Optimal Designs: An Introduction to the Theory for Parameter Estimation.* Chapman and Hall, London.

Sitter, R. R. and Torsney, B. (1992). *D*-optimal designs for generalized linear models. Technical Report No. 211, Technical Report Series of the Laboratory for Research in Statistics and Probability, Carleton University, Ottawa, Canada.

Sitter, R. R. and Torsney, B. (1995). Optimal designs for binary response experiments with two design variables, *Statist. Sinica* **5**, 405-419.

Wu, S. J., Lin, Y. P. and Chen, Y. J. (2006). Planning step-stress life test with progressively type I group-censored exponential data. *Statist. Neerlandica* **60**, 46-56.

Yang, M. and Stufken, J. (2009). Support points of locally optimal designs for nonlinear models with two parameters. *Ann. Statist.* **37**, 518-541.

Yang, M. (2010). On the de la Garza phenomenon. *Ann. Statist.* **38**, 2499-2524.

Southampton Statistical Sciences Research Institute, University of Southampton, University Road, Southampton SO17 1BJ, United Kingdom

E-mail: mk21g09@southampton.ac.uk

E-mail: S.Biedermann@southampton.ac.uk

E-mail: A.C.Kimber@southampton.ac.uk