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

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## Appendix

**Proof of Lemma 1.** Let $\alpha$ 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 $\xi^*$ 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 $\xi^*$.

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 $\xi_1$ and $\xi_2$ 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 $\xi_1$ and $\xi_2$ are different, $\xi_3$ 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 applied to the Elfving set, Elfving (1952), there exists a $c$-optimal design for $\beta$ 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 $(0 \quad 1)^T$ 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

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

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 (d1) the function $\beta+2Q(\alpha+\beta)/Q'(\alpha+\beta):=l(\beta)$ is increasing with $\beta$. 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 $\xi_\beta^*$ 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 $l(\beta_0)\le 0$. Since $l(\beta)$ is increasing with $\beta$ there exists $\beta^*\in(\beta_0,\beta_1]$ such that $l(\beta)>0$ for all $\beta\ge\beta^*$. Again using part (b) in Theorem 2 the locally $D$-optimal design $\xi_\beta^*$ is equally supported at points 0 and $x(\beta)$ where $x(\beta)=1$ for $\beta\ge\beta^*$. Otherwise $x(\beta)$ is the solution of the equation

$$\beta x(\beta)+2Q(\alpha+\beta x(\beta))/Q'(\alpha+\beta x(\beta))=0, \quad 0<x(\beta)\le 1. \qquad (2)$$

From (5.3) the $D$-efficiency of a two-point design $\xi$ 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 (d1). Hence for fixed $x$, $u(x,\beta)$ is minimised at $\beta_1$.

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 (2). This has a unique solution $\beta$ such that $x(\beta) = x$. So the function $\beta \to u(x,\beta)$ is unimodal for fixed $x$ and it is minimised at $\beta_0$ or $\beta_1$. We note that if $l(\beta_1) \leq 0$ then for all $l(\beta) \leq 0$ and $x(\beta)$ is the solution of equation (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 $\beta_0$ or $\beta_1$. 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 $\omega(\beta)$ and $1-\omega(\beta)$ for $\beta$ are defined in (3.2). From (5.4) the $c$-efficiency of a design $\xi$ with support points 0 and 1 and weights $\omega$ 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 $\omega$ the function $\omega(\beta) \to u(\omega, \omega(\beta))$ is unimodal and the standardised maximin design $\omega^*$ is in $M_=$. Hence we can find $\omega^*$ by solving the equation $u(\omega, \omega(\beta_0)) = u(\omega, \omega(\beta_1))$ which yields $\omega^* = (\omega(\beta_0) + \omega(\beta_1))/2$. □