INTRODUCTION

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.

The aim of this work is to provide analytical characterisations of D- and c-optimal designs under assumptions which are easily verifiable and satisfied by a large class of models including models which are widely used in survival analysis. We also investigate standardised maximin D- and c-optimal designs when a range of parameter values is provided.

CLASS OF MODELS

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

\[ M(\xi,\alpha,\beta) = \sum_{i=1}^{m} \omega_i J(x_i,\alpha,\beta) = \sum_{i=1}^{m} \omega_i Q(\xi,\alpha,\beta), \]

where \(x_1,\ldots,x_m\) are support points taking values in the design space \(X\), \(\omega_i\) is the proportion of observations collected on \(x_i, \alpha, \beta\) and \(\xi\) are the model parameters and \(Q(\xi)\) satisfies the following conditions:

(a) \(Q(\xi)\) is positive for all \(\xi \in \mathbb{R}\) and twice continuously differentiable.

(b) \(Q(\xi)\) is strictly increasing on \(\mathbb{R}\).

(c) The second derivative \(\xi^2(\xi) = 2 Q(\xi)\) is an injective function.

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

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

(d1): The function log \(Q(\xi)\) is concave for \(\xi \in \mathbb{R}\), which implies (d) given that (a) and (b) hold. Our assumptions hold, for example, for the Poisson, Gamma and Inverse Gamma regression models and for parametric proportional hazards models with a hazard function of the form

\[ h(t) = e^{t^\xi}(t)^{\alpha-1}, \]

where \(e^t\xi(\xi)\) is the baseline hazard.

D-OPTIMAL DESIGNS

In the case of a binary design space \(X = \{0,1\}\) the D-optimal design is equally supported at points 0 and 1. Because of the invariance property of D-optimal designs, for design spaces that are intervals we can choose the design space to be \(X = \{0,1\}\) without loss of generality.

We showed that the D-optimal design is unique and has two equally weighted support points. The following theorem provides a complete classification of D-optimal designs.

Theorem 1 Let assumptions (a)-(d) be satisfied.

(a) If \(\beta > 0\), the design

\[ \mathcal{L}^* = \left\{ \frac{x^*}{0.5} \right\}, \]

is D-optimal on \(X\), where \(x^* = 0\) if \(\beta < 2Q(\alpha)/Q'(\alpha)\). Otherwise \(x^*_1\) is the unique solution of \(\beta(x^*_1-1) + 2Q(\alpha + \beta x_1)/Q'(\alpha + \beta x_1) = 0\).

(b) If \(\beta < 0\), the design

\[ \mathcal{L}^* = \left\{ 0 \right\}, \]

is D-optimal on \(X\), where \(x^*_1 = 1\) if \(\beta > -2Q(\alpha + \beta x_1)/Q'(\alpha + \beta x_1)\). Otherwise \(x^*_1\) is the unique solution of \(\beta x_2 + 2Q(\alpha + \beta x_2)/Q'(\alpha + \beta x_2) = 0\).

APPLICATION TO AN EXPONENTIAL REGRESSION MODEL

The exponential regression model is specified by

\[ f(t) = e^{(\alpha + \beta t)}(t > 0), \]

where \(t_1,\ldots,t_n\) are observed survival times in a study of duration \(c\). Thus survival times greater than \(c\) are right-censored. We consider Type I censoring for which the censoring time \(c\) is fixed and common for all the units and random censoring where each unit has a censoring time \(C_i\) which is assumed to be a random variable.

C-OPTIMAL DESIGNS

We consider c-optimal designs for estimating the parameter \(\beta\). We show that there exists a c-optimal design for estimating \(\beta\) with exactly two support points and optimal weights given by

\[ \mathcal{L}^* = \left\{ \frac{x^*_1}{0.5} \right\}, \]

The design problem for the binary design space \(X = \{0,1\}\) has thus been solved completely. An analytical characterisation of the c-optimal designs for \(\beta\) on the interval \([u,v]\) is given in Theorem 2.

Theorem 2 Let assumptions (a)-(c) and (d1) be satisfied.

(a) If \(\beta > 0\), the design \(\mathcal{L}^*\) with support points \(x^*_1\) and \(v\) and the optimal weights given in (2) is c-optimal for \(\beta\), where \(x^*_1 = u\) if \(\beta(u - v) + 2Q(\alpha + \beta u)/Q'(\alpha + \beta u)\left(1 + \sqrt{Q'(\alpha + \beta v)}/\sqrt{Q'(\alpha + \beta v)}\right) > 0\).

Otherwise \(x^*_1\) is the unique solution of the equation

\[ \beta(x^*_1 - v) + 2Q(\alpha + \beta x_1)/Q'(\alpha + \beta x_1)\left(1 + \sqrt{Q'(\alpha + \beta v)}/\sqrt{Q'(\alpha + \beta v)}\right) = 0 \]

(b) If \(\beta < 0\), the design \(\mathcal{L}^*\) with support points \(u\) and \(x^*_1\) and the optimal weights given in (2) is c-optimal for \(\beta\), where \(x^*_1 = v\) if \(\beta(u - v) - 2Q(\alpha + \beta v)/Q'(\alpha + \beta v)\left(1 + \sqrt{Q'(\alpha + \beta v)}/\sqrt{Q'(\alpha + \beta v)}\right) < 0\).

Otherwise \(x^*_1\) is the unique solution of the equation

\[ \beta(x^*_1 - v) - 2Q(\alpha + \beta x_1)/Q'(\alpha + \beta x_1)\left(1 + \sqrt{Q'(\alpha + \beta v)}/\sqrt{Q'(\alpha + \beta v)}\right) = 0 \]

STANDARDISED MAXIMIN DESIGNS

Precise knowledge of the \(\alpha\)-value and a range of \(\beta\)-values might be available. Following Dette (1997) we find designs maximising the worst efficiencies with respect to the locally optimal designs over a range of parameter values. Theorems 3 and 4 provide analytical characterisations of standardised maximin D- and c-optimal 2-point designs.

Theorem 3 Let \(\beta \in [\beta_0, \beta_1]\) with \(\beta_0 < 0\). The standardised maximin D-optimal two-point design is equally supported at 0 and \(x^*_2\) where \(x^*_2 = 1\) if \(\beta_0 > -2Q(\alpha + \beta_1)/Q'(\alpha + \beta_1)\). Otherwise \(x^*_2\) is the solution of

\[ Q'(\alpha + \beta_0)x(\alpha + \beta_0)/Q'(\alpha + \beta_1)x(\alpha + \beta_1) = 2Q(\alpha + \beta_0)x(\alpha + \beta_0)/Q'(\alpha + \beta_1)x(\alpha + \beta_1), \]

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

Theorem 4 Let \(\beta \in [\beta_0, \beta_1]\) and \(X = \{0,1\}\). The standardised maximin c-optimal two-point design is supported at 0 and 1 where \(\omega_0 = (\omega(\beta_0) + \omega(\beta_1))/2\) is the weight on 0 and \(\omega(\beta_0)\) and \(\omega(\beta_1)\) is the optimal weight on 0 given in (2) for \(\beta_0\) and \(\beta_1\) respectively.

ROBUSTNESS ANALYSIS

We compare the performance of locally optimal, standardised maximin and cluster designs (Biedermann and Woods, 2011) by calculating their efficiency with respect to 1000 parameter vectors.

REFERENCES


