Efficient design of experiment for exponential regression models

Holger Dette
Ruhr-Universität Bochum
Fakultät für Mathematik
44780 Bochum , Germany
holger.dette@ruhr-uni-bochum.de

Ignacio Martinez Lopez
Departamento de Estadistica
y Matematica Aplicada
Universidad de Almeria
4120 Almeria, Spain
ijmartin@ual.es

Isabel M. Ortiz Rodriguez
Departamento de Estadistica
y Matematica Aplicada
Universidad de Almeria
4120 Almeria, Spain
iortiz@ual.es

Andrey Pepelyshev
St. Petersburg State University
Department of Mathematics
St. Petersburg, Russia
andrey@ap7236.spb.edu

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Abstract

In this paper robust and efficient designs are derived for several exponential decay models. These models are widely used in chemistry, pharmacokinetics or microbiology. We propose a maximin approach, which determines the optimal design such that a minimum of the D-efficiencies (taken over a certain range for the nonlinear parameters) becomes maximal. Analytic solutions are derived if optimization is performed in the class of minimal supported designs. In general the optimal designs with respect to the maximin criterion have to be determined numerically and some properties of these designs are also studied.

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1 Introduction

Exponential regression models are widely used in subject areas such as biology, chemistry, pharmacokinetics or microbiology. For example in microbiology these models are usually applied for

describing growth and death of microorganisms, dose-response analysis and risk assessment (Coleman, Marks, 1998), and kinetics of metabolite production. These models are also incorporated in the numerous models in predictive microbiology for describing effects of temperature (Geeraerd et al, 2000). Other applications of exponential regression models include pharmacokinetics [see Landaw and DiStefano (1984)], biology [see Liebig (1988), or Krug and Liebig (1988)] or toxicology [Becka and Urfer (1993, 1996)]. Several applications involving more complicated exponential regression models can be found in Cobaleda et al. (1994), Alvarez et al. (2003) or Pruitt and Kamau (1993).
An appropriate choice of the experimental conditions can improve the quality of statistical inference substantially and therefore many authors have discussed the problem of designing experiments for exponential regression models. Usually optimal or efficient designs maximize an appropriate function of the Fisher information matrix in the particular model and this matrix depends on the nonlinear parameters of the model. Numerous authors investigate local optimal designs [see Melas (1978), Han and Chaloner (2003) or Dette, Melas and Pepelysheff (2003)], which assume some prior guess for the unknown parameters in the regression model [see Chernoff (1953)]. Because this approach is not necessarily robust with respect to a misspecification and may result in an inefficient design several authors use a Bayesian approach to obtain robust designs [see Mukhopadhyay and Haines (1994), Dette and Neugebauer (1997) or Han and Chaloner (2003) among others]. The Bayesian methodology requires the specification of a prior distribution for the nonlinear parameters in the models. As an alternative for the construction of robust designs, we propose in this paper a maximin approach based on the D-optimality criterion, which only requires the specification of a certain range for the unknown parameter of the model. This method determines a design, which maximizes a minimum of D-efficiencies [see Müller (1995), Dette (1997), Imhof (2001)] and is motivated by the fact that in some cases practitioners will have difficulties to specify a prior distribution for the unknown parameter, especially if this is multidimensional.
We will concentrate on the exponential regression model

$$E(Y|t) = \eta(t,\theta) = a + be^{-\lambda t}, \quad D(Y|t) = \sigma^2 \tag{1.1}$$

and several simplifications, where the explanatory variable t varies in the design space

$$\mathcal{T} = [t_{\min}, t_{\max}] \subset \mathbb{R},$$

$\theta = (a, b, \lambda)^T$ is a vector of unknown parameters ($\lambda > 0$) and different measurements are assumed to be independent. This model has applications in agricultural sciences, where it is called Mitscherlichs growth law ($b < 0$) and used for describing the relation between the yield of a crop and the amount of fertilizer [see Box and Lucas (1959)]. In fisheries research this model is called Bertalanffy growth curve ($b < 0$) and used for the description of the length of a fish in dependence of its age [see Ratkowsky (1983, 1990)]. The model (1.1) contains several sub-models which are also widely used. For example, the model

$$E(Y|t) = \eta(t,\theta) = a + e^{-\lambda t} \tag{1.2}$$

is obtained from (1.1) assuming that $b = 1$ and model (1.1) reduces to

$$E(Y|t) = \eta(t,\theta) = a(1 - e^{-\lambda t}), \tag{1.3}$$

if it is assumed that $b = -a$. These models are often used for analyzing the growth of crops [see Liebig (1988) or Krug and Liebig (1988)]. A further simplification appears if the parameter a is known to be 0 which yields the model

$$E(Y|t) = \eta(t, \theta) = be^{-\lambda t}. \tag{1.4}$$

The regression model (1.4) has applications in pharmacokinetics [see Landaw and DiStefano (1984)]. Local D- and c-optimal designs for the model (1.1) and the sub-models (1.2) and (1.4) have been recently found in Han and Chaloner (2003), some Bayesian D-optimal designs for these models are given in Dette and Neugebauer (1997).
It is the purpose of the present paper to complete these results by presenting some optimal designs for the models (1.1) - (1.4) with respect to a maximin efficiency criterion. In Section 2 we state some preliminary notation and general results on maximin efficient designs. The definition of the maximin optimality criterion requires the knowledge of the local D-optimal designs, which are given in Section 3 (for most but not for all of the models under consideration, these designs are available from the literature). Section 4 is devoted to the problem of constructing maximin optimal designs. Optimal designs supported on a minimal number of points are determined explicitly, but the answer to the question if these designs are optimal within in the class of all designs depends on the size of the range specified for the parameter. In the case where the minimal supported designs are not optimal, the maximin optimal designs are found numerically. Finally some of the proofs are given in an appendix in Section 5.

2 Maximin efficient designs

Following Kiefer (1974) we call any probability measure ξ with finite support on the interval $\mathcal{T}$ an (approximate) design. The support points give the locations where observations have to be taken, while the masses correspond to the relative proportions of total observations to be taken at the particular points. If the distribution of Y in (1.1) is normal then the Fisher information matrix of a design ξ in one of the models (1.1) - (1.4) is defined by

$$M(\xi, \theta) = \int_{\mathcal{T}} f(t, \theta) f^T(t, \theta) d\xi(t), \tag{2.1}$$

where

$$f(t, \theta) = \frac{\partial \eta}{\partial \theta}(t, \theta) \tag{2.2}$$

is the vector of partial derivatives of the regression function. It is easy to see that in general the Fisher information matrix depends on the parameters a, b, λ. In the exponential regression models (1.1) - (1.4) these matrices can easily be calculated and are given by

$$M(\xi, \theta) = \int_{\mathcal{T}} \begin{bmatrix} 1 & \mathrm{e}^{-\lambda t} & -bt\mathrm{e}^{-\lambda t} \\ \mathrm{e}^{-\lambda t} & \mathrm{e}^{-2\lambda t} & -bt\mathrm{e}^{-2\lambda t} \\ -bt\mathrm{e}^{-\lambda t} & -bt\mathrm{e}^{-2\lambda t} & b^2t^2\mathrm{e}^{-2\lambda t} \end{bmatrix} \mathrm{d}\xi(t) \tag{2.3}$$

for the model (1.1),

$$M(\xi, \theta) = \int_{\mathcal{T}} \begin{bmatrix} 1 & -t\mathrm{e}^{-\lambda t} \\ -t\mathrm{e}^{-\lambda t} & t^2\mathrm{e}^{-2\lambda t} \end{bmatrix} \mathrm{d}\xi(t) \ , \tag{2.4}$$

for the model (1.2),

$$(2.5) \qquad M(\xi,\theta) = \int_{\mathcal{T}} \begin{bmatrix} (1-\mathrm{e}^{-\lambda t})^2 & at(1-\mathrm{e}^{-\lambda t})\mathrm{e}^{-\lambda t} \\ at(1-\mathrm{e}^{-\lambda t})\mathrm{e}^{-\lambda t} & a^2t^2\mathrm{e}^{-2\lambda t} \end{bmatrix} \mathrm{d}\xi(t)$$

for the model (1.3), and

$$(2.6) \qquad M(\xi,\theta) = \int_{\mathcal{T}} \begin{bmatrix} \mathrm{e}^{-2\lambda t} & -tb\mathrm{e}^{-2\lambda t} \\ -tb\mathrm{e}^{-2\lambda t} & b^2t^2\mathrm{e}^{-2\lambda t} \end{bmatrix} \mathrm{d}\xi(t)$$

for the model (1.4).
A local optimal design maximizes an appropriate function of the information matrix [see Silvey (1980) or Pukelsheim (1993)], which is called optimality criterion. There are numerous optimality criteria proposed in the literature to discriminate between competing designs and we restrict ourselves to the famous D-optimality criterion. A design is called local D-optimal if it maximizes

$$(2.7) \qquad \det M(\xi,\theta).$$

Local D-optimal designs have been found for some of the models (1.1) - (1.4) [see Dette and Neugebauer (1996,1997) and Han and Chaloner (2003)]. Note that the implementation of local optimal designs in practice requires a prior guess for the unknown parameter, which is rarely available in real experiments. Because statistical inference based on a local optimal design might be very sensitive with respect to a misspecification of this preliminary guess, several alternative procedures have been proposed in the literature to obtain designs, which are on the one hand efficient for parameter estimation and on the other hand robust with respect to misspecifications of the unknown parameter θ [see Pronzato and Walter (1985) or Chaloner and Verdinelli (1995)]. In the present paper we will use an alternative approach to obtain efficient and robust designs for the exponential regression models (1.1) - (1.4), which is based on the maximin concept.
To be precise assume that the regression function η under consideration contains m unknown parameters, i.e. $\theta \in \mathbb{R}^m$ and let ξ_θ^D denote a local D-optimal design, i.e. the design which maximizes (2.7) under the assumption that θ is the 'true' parameter. For a given design ξ the D-efficiency of ξ (with respect to the local optimal design) is defined by

$$(2.8) \qquad \mathrm{eff}_D(\xi,\theta) = \sqrt[m]{\frac{\det M(\xi,\theta)}{\det M(\xi_\theta^D,\theta)}},$$

[see Pukelsheim (1993)] and a design ξ^* is called standardized maximin D-optimal (with respect to Θ) if it maximizes the worst D-efficiency, i.e.

$$(2.9) \qquad \min_{\theta\in\Theta} \mathrm{eff}_D(\xi,\theta) \to \max_{\xi},$$

where $\Theta \subset \mathbb{R}^m$ is a given set of possible values for the parameter θ, which has to be specified by the experimenter [see Müller (1995), Dette (1997) or Imhof (2001)].
Note that the optimality criterion (2.9) is not differentiable and as a consequence the problem of determining standardized maximin D-optimal designs is not trivial. This difficulty is also reflected

in the following equivalence theorem for this type of optimality criterion [see Dette, Haines and Imhof (2003)] which gives a characterization of standardized maximin D-optimal designs.

Theorem 2.2. *A design ξ^* is standardized maximin D-optimal if and only if there exists a probability distribution π_ω on the set $\mathcal{N}(\xi^*) \subseteq \Theta$ such that the inequality*

$$\int_{\mathcal{N}(\xi^*)} f(t,\theta)^T M^{-1}(\xi^*,\theta) f(t,\theta)\; d\pi_w(\theta) \;\leq\; m \tag{2.10}$$

holds for all $t \in \mathcal{T}$, where the set $\mathcal{N}(\xi^*)$ is defined by

$$\mathcal{N}(\xi^*) = \left\{\theta \in \Theta \mid \operatorname{eff}_D(\xi^*,\theta) = \min_{\theta\in\Theta} \operatorname{eff}_D(\xi^*,\theta)\right\}. \tag{2.11}$$

Moreover, there is equality in (2.10) for all support points of ξ^*.

The distribution π_ω is called least favourable prior. Note also that the definition of the standardized maximin D-optimality criterion requires the knowledge of the local D-optimal designs ξ_θ^D, or at least knowledge of the value of the optimal determinant $\det M(\xi_\theta^D,\theta)$. For this reason we give in the next section some results on local D-optimal designs for the models introduced in Section 1.

3 Local optimal designs

It is easy to see from the representation of the information matrices (2.3) - (2.6) that local D-optimal designs for the exponential regression models (1.1) - (1.4) do not depend on the parameters a, b. For this reason the local D-optimal designs will be denoted by ξ_λ^D throughout this paper. We start with a simple auxiliary result, which relates local D-optimal designs on different design spaces and simplifies the calculation of local D-optimal designs substantially. The proof is straightforward and therefore omitted.

Lemma 3.1.
a) *Assume that $\mu \in \mathbb{R}$. In the models (1.1) and (1.4) the local D-optimal designs ξ_λ^D and $\tilde{\xi}_\lambda^D$ on the design spaces $\mathcal{T} = [t_{\min}, t_{\max}]$ and $\tilde{\mathcal{T}} = [t_{\min} - \mu, t_{\max} - \mu]$ are related by the transformation $t \to t + \mu$, that is*

$$\xi_\lambda^D(t) = \tilde{\xi}_\lambda^D(t+\mu)$$

b) *Assume that $\gamma > 0$. In the models (1.1) - (1.4) the local D-optimal designs ξ_λ^D and $\tilde{\xi}_\lambda^D$ on the design spaces $\mathcal{T} = [t_{\min}, t_{\max}]$ and $\tilde{\mathcal{T}} = [\frac{t_{\min}}{\gamma}, \frac{t_{\max}}{\gamma}]$ are related by the transformations $t \to \gamma t$, $\lambda \to \gamma\lambda$ that is*

$$\xi_\lambda^D(t) = \tilde{\xi}_{\gamma\lambda}^D(\gamma t)$$

Note that the first part of Lemma 3.1 does not apply to the exponential regression model (1.2) and (1.3). In the following we will restrict ourselves to the interval

$$[t_{\min}, t_{\max}] = [0, T]\ ,$$

which is most important from a practical point of view. For model (1.1) and (1.4) the local D-optimal designs on a general interval are obtained by a linear transformation [for model (1.2) and (1.3) see the examples below]. The following Lemma specifies the local D-optimal designs on the interval $[0, T]$ for the exponential regression models introduced in Section 1.

Lemma 3.2.

(a) *The local D-optimal design for the exponential regression model (1.1) on the interval* $[0, T]$ *is given by*

$$\xi_\lambda^D = \begin{pmatrix} 0 & t_D^* & T \\ 1/3 & 1/3 & 1/3 \end{pmatrix},$$

where the point t_D^* *is defined by*

$$t_D^* = \frac{1}{\lambda} - \frac{Te^{-\lambda T}}{1 - e^{-\lambda T}}. \tag{3.1}$$

(b) *The local D-optimal design for the exponential regression model (1.2) on the interval* $[0, T]$ *is given by*

$$\begin{pmatrix} 0 & t_D^* \\ 1/2 & 1/2 \end{pmatrix} , \tag{3.2}$$

where $t_D^* = \min\{1/\lambda, T\}$.

(c) *The local D-optimal design for the exponential regression model (1.3) on the interval* $[0, T]$ *is given by*

$$\begin{pmatrix} t_D^* & T \\ 1/2 & 1/2 \end{pmatrix} ,$$

where the point t_D^* *is defined by (3.1)*

(d) *The local D-optimal design for the exponential regression model (1.4) on the interval* $[0, T]$ *is given by the design (3.2).*

Example 3.3.

(a) It follows from Lemma 3.1 that local D-optimal designs on the interval $[t_{\min}, t_{\max}]$ for the models (1.1) and (1.4) are obtained from the designs on the interval $[0, t_{\max} - t_{\min}]$ by the transformation $t \to t + t_{\min}$. For example, the local D-optimal design for the exponential regression model (1.1) puts equal masses at the points $t_{\min}$, $t_{\max}$ and

$$t_{\min} + \frac{1}{\lambda} - \frac{(t_{\max} - t_{\min})e^{-\lambda(t_{\max}-t_{\min})}}{1 - e^{-\lambda(t_{\max}-t_{\min})}} = \frac{1}{\lambda} + \frac{t_{\min}e^{-\lambda t_{\min}} - t_{\max}e^{-\lambda t_{\max}}}{e^{-\lambda t_{\min}} - e^{-\lambda t_{\max}}}$$

[see Han and Chaloner (2003)].

(b) For the model (1.2) the local D-optimal design on the interval $[t_{\min}, t_{\max}]$ has equal masses at the points t_0 and t_1, where

$$t_0 = t_{\min} \ , \quad t_1 = t_{\max}$$

if $1/\lambda \notin \mathcal{T}$ and

$$t_0 = 1/\lambda \ , \quad t_1 = \text{argmax}_{t \in \{t_{\min}, t_{\max}\}} \{-te^{-\lambda t}\}$$

if $1/\lambda \in \mathcal{T}$ [see Han and Chaloner (2003)].

(c) For the model (1.3) the local D-optimal design on the interval $[t_{\min}, t_{\max}]$ with $t_{\min} > 0$ has equal masses at the points t_0 and $t_{\max}$, where $t_0 = t_{\min}$ if $t_{\min} > t_D^*$, $t_0 = t_D^*$ if $t_{\min} < t_D^*$ and the point t_D^* is defined in (3.1).

4 Standardized maximin D-optimal designs

The determination of standardized maximin D-optimal designs is usually substantially more difficult, because in contrast to the local D-optimal designs discussed in Section 3 the number of support points of the standardized maximin D-optimal designs is not necessarily equal to the number of parameters in the regression model. Nevertheless some simplification of the optimization problem is possible. For this recall the definition of the information matrices in (2.3) - (2.6), then it is easy to see that the D-efficiency (2.8) of any design depends only on the parameter λ. We reflect this fact using the notation $\mathrm{eff}_D(\xi, \lambda)$ for the efficiency and

$$\min_{\lambda \in \Lambda} \mathrm{eff}_D(\xi, \lambda) \tag{4.1}$$

for the optimality criterion (2.9), where Λ is an interval in the positive real line, that is $\Lambda = [\lambda_1, \lambda_2]$. The standardized maximin D-optimal design (for the set Λ) is denoted by ξ_Λ^D. Moreover an analogue of Lemma 3.1 is readily available.

Lemma 4.1.

(a) *Assume that $\mu \in \mathbb{R}$. In the models (1.1) and (1.4) the standardized maximin D-optimal designs ξ_Λ^D and $\tilde{\xi}_\Lambda^D$ on the design spaces $\mathcal{T} = [t_{\min}, t_{\max}]$ and $\tilde{\mathcal{T}} = [t_{\min} - \mu, t_{\max} - \mu]$ are related by the transformation $t \to t + \mu$, that is*

$$\xi_\Lambda^D(t) = \tilde{\xi}_\Lambda^D(t + \mu).$$

(b) *Assume that $\gamma > 0$ and define $\gamma\Lambda = [\gamma\lambda_1, \gamma\lambda_2]$. In the models (1.1) - (1.4) the standardized maximin D-optimal designs ξ_Λ^D and $\tilde{\xi}_\lambda^D$ on the design spaces $\mathcal{T} = [t_{\min}, t_{\max}]$ and $\tilde{\mathcal{T}} = [\frac{t_{\min}}{\gamma}, \frac{t_{\max}}{\gamma}]$ are related by the transformation $t \to \gamma t$, $\lambda \to \gamma\lambda$, that is*

$$\xi_\Lambda^D(t) = \tilde{\xi}_{\gamma\Lambda}^D(\gamma t).$$

4.1 Minimal supported designs

We begin our investigations by optimizing the criterion (2.9) in the class of all minimal supported designs. Throughout this paper we call an optimal design with k support points an optimal k-point design.

Theorem 4.2.

(a) *The standardized maximin D-optimal three point design for the exponential regression model (1.1) on the interval $[0, T]$ is given by*

$$\xi_\Lambda^D(t^*) = \begin{pmatrix} 0 & t^* & T \\ 1/3 & 1/3 & 1/3 \end{pmatrix},$$

where the point t^* is defined as the unique solution of the equation

$$\mathrm{eff}_D(\xi_\Lambda^D(t), \lambda_1) \; = \; \mathrm{eff}_D(\xi_\Lambda^D(t), \lambda_2) \tag{4.2}$$

and

$$\mathrm{eff}_D(\xi_\Lambda^D(t), \lambda) \; = \; \frac{(1 - e^{-\lambda T}) t e^{-\lambda t} - (1 - e^{-\lambda t}) T e^{-\lambda T}}{(1 - e^{-\lambda T})(\frac{1}{\lambda} + \frac{T}{1 - e^{\lambda T}}) e^{-1 - \frac{\lambda T}{1 - e^{\lambda T}}} - (1 - e^{-1 - \frac{\lambda T}{1 - e^{\lambda T}}}) T e^{-\lambda T}} \tag{4.3}$$

(b) *The standardized maximin D-optimal two point design for the exponential regression model (1.2) on the interval* $[0, T]$ *is of the form*

$$(4.4) \qquad \xi_\Lambda^D = \begin{pmatrix} 0 & t^* \\ 1/2 & 1/2 \end{pmatrix},$$

where the point t^* *satisfies*

$$t^* = \begin{cases} \dfrac{\log \lambda_2 - \log \lambda_1}{\lambda_2 - \lambda_1} & \text{if } T > \dfrac{1}{\lambda_1} \\[2ex] \dfrac{\log(T\lambda_2) + 1 - T\lambda_1}{\lambda_2 - \lambda_1} & \text{if } \dfrac{1}{\lambda_2} \le T \le \dfrac{1}{\lambda_1} \\[2ex] T & \text{if } T < \dfrac{1}{\lambda_2} \end{cases}$$

(c) *The standardized maximin D-optimal two point design for the exponential regression model (1.3) on the interval* $[0, T]$ *is given by*

$$\xi_\Lambda^D(t^*) = \begin{pmatrix} t^* & T \\ 1/2 & 1/2 \end{pmatrix},$$

where the point t^* *is defined as the unique solution of (4.2) and (4.3).*

(d) *The standardized maximin D-optimal two point design for the exponential regression model (1.4) on the interval* $[0, T]$ *is given by the design (4.4).*

It follows from the proof of Theorem 4.2 that in all cases the non-trivial support point t^* of the standardized maximin D-optimal design $\xi_\Lambda^D(t^*)$ is determined as the unique solution of the equation

$$\text{eff}(\xi_\Lambda^D(t^*), \lambda_1) = \text{eff}(\xi_\Lambda^D(t^*), \lambda_2).$$

Note also the equations for the model (1.1) and (1.3) are identical. As a consequence we obtain the following statement.

Corollary 4.3. *Let* $u^*(\lambda_1, \lambda_2)$ *denote the unique solution of the equation (4.2) and*

$$\xi_\Lambda^D = \begin{pmatrix} u^*(\lambda_1, \lambda_2) & T \\ 1/2 & 1/2 \end{pmatrix}$$

denote the standardized maximin D-optimal two-point design for the exponential regression model (1.3) with respect to the interval $\Lambda = [\lambda_1, \lambda_2]$, *then the design*

$$\begin{pmatrix} 0 & u^*(\lambda_1, \lambda_2) & T \\ 1/3 & 1/3 & 1/3 \end{pmatrix}$$

is the standardized maximin D-optimal three-point design for the exponential regression model (1.1) (with respect to the interval $\Lambda = [\lambda_1, \lambda_2]$*).*

Remark 4.4. Note that Theorem 4.2 does not guarantee that the minimal supported designs are in fact standardized maximin D-optimal within the class of all designs. This property has to be checked by an application of the equivalence Theorem 2.2. However, it follows from the proof of Theorem 4.2 that the least favourable distribution π_ω required for the inequality (2.10) is supported on the set $\{\lambda_1, \lambda_2\}$. The corresponding weights can then easily be determined by the fact that there must be equality in (2.10) for the support points of the standardized maximin D-optimal design. Thus the global optimality of the minimal supported standardized maximin D-optimal designs for the models (1.1) - (1.4) can easily be checked by an application of Theorem 2.2 using a prior supported on the boundary of Λ.

Example 4.5. Consider the exponential regression model (1.2) and assume that the parameters λ_1 and λ_2 specified by the experimenter satisfy $T > \frac{1}{\lambda_1}$. It then follows from Theorem 4.2 that the best two point design (with respect to the standardized maximin criterion), say ξ^*, has equal masses at the points 0 and

$$t^* = \frac{\log \lambda_2 - \log \lambda_1}{\lambda_2 - \lambda_1} .$$

By Theorem 2.2 the design ξ^* is a standardized maximin D-optimal design within the class of all designs if and only if there exists a prior π_ω supported on the set $\mathcal{N}(\xi^*)$ defined in (2.11) such that the inequality

$$g(t, \lambda_1, \lambda_2) = \int_{[\lambda_1, \lambda_2]} f^T(t, \lambda) M^{-1}(\xi^*, \lambda) f(t, \lambda) \pi_\omega(d\lambda) \leq 2 \tag{4.5}$$

is satisfied, where there is equality for the support points 0 and t^*. It also follows from the proof of Theorem 4.2 that $\mathcal{N}(\xi^*) = \{\lambda_1, \lambda_2\}$. For the calculation of the least favourable distribution

$$\pi_\omega = \left\{ \begin{array}{cc} \lambda_1 & \lambda_2 \\ w_0 & w_1 \end{array} \right\}$$

with $w_1 = 1 - w_0$, we note that a straightforward calculation yields for the function $g(t, \lambda_1, \lambda_2)$ defined in (4.5)

$$\begin{aligned} g(t, \lambda_1, \lambda_2) &= \int_{\lambda_1}^{\lambda_2} \left(2 + 4\left(g_1^2(t, \lambda) - g_1(t, \lambda)\right)\right) \pi_\omega(d\lambda) \\ &= w_0 \left(2 + 4g_1^2(t, \lambda_1) - 4g_1(t, \lambda_1)\right) + (1 - w_0)\left(2 + 4g_1^2(t, \lambda_2) - 4g_1(t, \lambda_2)\right) \end{aligned}$$

where $g_1(t, \lambda) = e^{\lambda(t^* - t)} t (t^*)^{-1}$. By Theorem 2.2 this function must satisfy $g(0, \lambda_1, \lambda_2) = 2 = g(t^*, \lambda_1, \lambda_2)$ and $g'(t^*, \lambda_1, \lambda_2) = 0$, which yields

$$w_0(1 - \lambda_1 t^*) + (1 - w_0)(1 - \lambda_2 t^*) = 0.$$

With the notation $k = \frac{\lambda_1}{\lambda_2} \in (0, 1]$ we obtain $t^* = -\log k / (\lambda_2(1 - k))$ and the weights of the least favourable distribution are given by

$$w_0 = \frac{1}{1 - k} + \frac{1}{\log k} , \quad w_1 = \frac{k}{k - 1} - \frac{1}{\log k}.$$

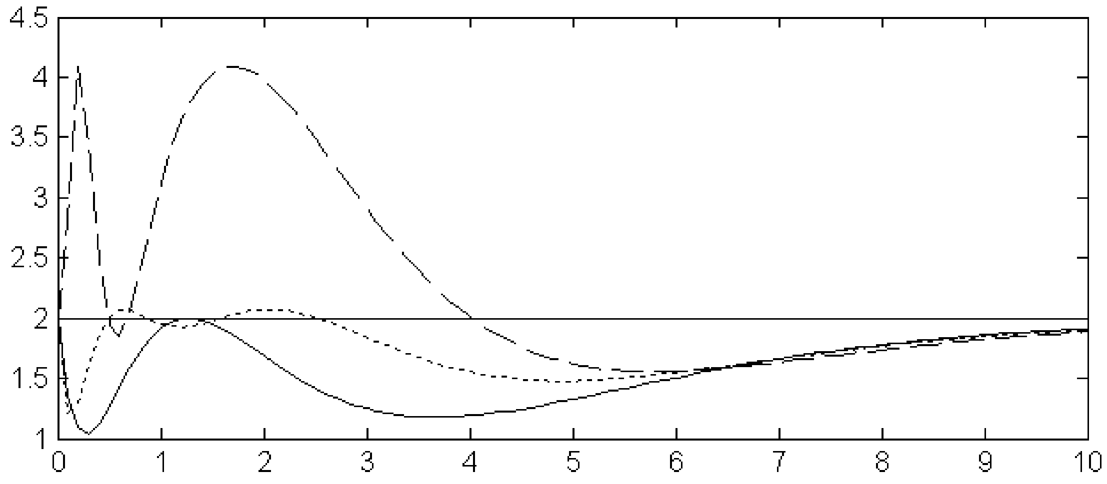

Figure 1: *The function $g(t, \lambda_1, \lambda_2)$ for the standardized maximin D-optimal two-point design ξ^* in the regression model $a + e^{-\lambda t}$ for the cases $\Lambda = [0.6, 1]$ (solid line), $\Lambda = [0.6, 2]$ (dotted line), $\Lambda = [0.6, 5]$ (dashed line).*

In Figure 4.1 we present plots of the function $g(t, \lambda_1, \lambda_2)$ for the cases $\Lambda = [0.6, 1]$, $\Lambda = [0.6, 2]$ and $\Lambda = [0.6, 5]$. The standardized maximin D-optimal two point design has equal masses at the set $\{0, 1.28\}$, $\{0, 0.86\}$ and $\{0, 0.48\}$, respectively. We observe that two point designs are only globally standardized maximin D-optimal in the first case, and that standardized maximin D-optimal designs with respect to larger parameter spaces require more than two support points. We finally note that it follows by numerical calculations that the two point standardized maximin D-optimal design coincides with the standardized maximin D-optimal design within the class of all design if and only if

$$0.342 < \frac{\lambda_1}{\lambda_2} < 1.$$

Remark 4.6. It can be shown numerically, that for the model (1.4) with $T > \frac{1}{\lambda_1}$ the two point standardized maximin D-optimal design is optimal within the class of all designs if and only if

$$0.292 < \frac{\lambda_1}{\lambda_2} < 1.$$

For the models (1.1) and (1.3) similar bounds exist, but these bounds depend on the length T of the design space and are not given here for the sake of brevity.

4.2 Maximin optimal designs

It is indicated in the previous paragraph that in general standardized maximin D-optimal designs for exponential regression models have to be found numerically and their optimality has to be confirmed by an application of Theorem 2.2. Note that a check of the inequality requires the determination of the least favourable distribution [see Example 4.5]. A formal difficulty is that there is no bound on the number of support points of a standardized maximin D-optimal design.

Table 1: *Standardized maximin D-optimal designs for the exponential regression model $a + e^{-\lambda t}$ for various sets $\Lambda = [\Lambda_1, \lambda_2]$. The table shows the support points and weights of the optimal design and the minimal efficiency over the interval $\Lambda = [\lambda_1, \lambda_2]$.*

λ_1	λ_2	t_1	t_2	t_3	t_4	w_1	w_2	w_3	w_4	min eff
0.6	1	0	1.28			0.5	0.5			0.9680
0.6	1.5	0	1.02			0.5	0.5			0.9015
0.6	2	0	0.65	1.83		0.45	0.33	0.22		0.8493
0.6	2.5	0	0.53	1.68		0.44	0.31	0.25		0.8372
0.6	3	0	0.47	1.53		0.43	0.30	0.26		0.8259
0.6	4	0	0.38	1.34		0.43	0.30	0.27		0.8049
0.6	5	0	0.28	0.92	1.92	0.40	0.25	0.22	0.13	0.7899
0.5	1	0	1.39			0.5	0.5			0.9421
0.4	1	0	1.53			0.5	0.5			0.9015
0.3	1	0	1.31	3.67		0.45	0.33	0.22		0.8493
0.2	1	0	1.40	4.60		0.43	0.30	0.26		0.8259
0.1	1	0	1.23	4.21	10.00	0.38	0.22	0.23	0.17	0.7810

Table 2: *Standardized maximin D-optimal designs for the exponential regression model $be^{-\lambda t}$ for various $\Lambda = [\Lambda_1, \lambda_2]$. The table shows the support points and weights of the optimal design and the minimal efficiency over the interval $\Lambda = [\lambda_1, \lambda_2]$.*

λ_1	λ_2	t_1	t_2	t_3	w_1	w_2	w_3	min eff
0.6	1	0	1.28		0.5	0.5		0.9680
0.6	1.5	0	1.02		0.5	0.5		0.9015
0.6	2	0	0.86		0.5	0.5		0.8372
0.6	2.5	0	0.49	1.68	0.47	0.35	0.18	0.8007
0.6	3	0	0.39	1.67	0.46	0.35	0.20	0.7875
0.6	4	0	0.32	1.46	0.45	0.34	0.20	0.7678
0.6	5	0	0.27	1.31	0.45	0.34	0.21	0.7501
0.5	1	0	1.39		0.5	0.5		0.9421
0.4	1	0	1.53		0.5	0.5		0.9015
0.3	1	0	1.72		0.5	0.5		0.8372
0.2	1	0	1.16	5.01	0.46	0.35	0.20	0.7875
0.1	1	0	1.41	7.37	0.45	0.35	0.21	0.7345

Usually the number of support points depends on the size of the parameter space Λ [see also the numerical examples given below].
A solution to this problem is to start with the determination of a minimal supported standardized maximin D-optimal design and to check the optimality by an application of Theorem 2.2. If the design is not standardized maximin D-optimal the procedure is repeated, where the number of support points in the class of designs under investigation is increased by 1. The calculation of the least favourable distribution in the application of Theorem 2.2 is performed similarly. If the optimality of a k-point standardized maximin D-optimal design has to be checked by Theorem 2.2, then it follows from Pshenichnyi (1971) that there exists a least favourable distribution associated with the standardized maximin optimal design which is based on at most $2k$ support points. The second part of Theorem 2.2 shows that there must be equality at the support points of the standardized maximin D-optimal design and therefore yields a system of $2k-2$ equations for the determination of the least favourable distribution (if only one or two of the boundary points are not contained in the support of the candidate designs, Theorem 2.2 yields $2k-1$ or $2k$ equations, respectively). It follows from the equivalence Theorem 2.2 that the least favourable distribution corresponding to the standardized maximin D-optimal design has at least 2 support points. Therefore for a given standardized maximin D-optimal k-point design we start determining a two point prior using the (at least) $2k-2$ conditions provided by Theorem 2.2. We use this prior to check the optimality of the k point design [see also Example 4.5]. If the inequality (2.10) is not satisfied, we increase the number of support points of the prior and repeat this procedure.

In all our examples this procedure terminates after a few steps and the standardized maximin D-optimal designs were found numerically. In the following we present some of our results for the design space $[0, 10]$ and some selected parameter spaces $\Lambda = [\lambda_1, \lambda_2]$. We begin our investigations with the models (1.2) and (1.4), for which the local D-optimal designs are identical. The corresponding standardized maximin D-optimal designs are given in Table 1 and 2 for various values of λ_1 and λ_2. We observe that for a small length of the interval Λ two point designs are standardized maximin D-optimal and that in this case the maximin optimal designs in the models (1.2) and (1.4) are identical [see also Theorem 4.2]. However, for larger parameter spaces the standardized maximin D-optimal designs are supported on more than two points and the designs in the models (1.2) and (1.4) are not identical any more. For example, if $\Lambda = [0.6, 2]$ a three point design is standardized maximin D-optimal for the model (1.2), while the two-point design from Theorem 4.2(d) is still standardized maximin D-optimal for the model (1.4). We observe a minimal efficiency over the range Λ of at least 73%, even in the ratio λ_2/λ_1 is 10. Thus the standardized maximin D-optimal designs yield reasonable D-efficiencies over the full parameter space Λ. Of course the efficiency of the designs is increased if the length of the interval is decreased.
Table 3 and 4 show the corresponding results for the exponential regression model (1.1) and (1.3). Note that for the minimal supported designs the interior support point of the standardized maximin D-optimal two-point design for the model (1.3) coincides with the interior support point of the standardized maximin D-optimal three-point design for the model (1.1) [see Corollary 4.3]. If the standardized maximin D-optimal design is supported on more points this relation does not hold any more. Again the standardized maximin D-optimal designs yield good D-efficiencies for a broad range of the parameter λ (in the displayed cases the minimal efficiency is at least 78%).
We finally investigate the performance of the standardized maximin D-optimal designs for the model (1.1) in the three sub-models (1.2) - (1.4). Note that the designs for model (1.1) have at least three support points. Consequently, the application of these designs for parameter estimation

Table 3: *Standardized maximin D-optimal designs for the exponential regression model* $a(1-e^{-\lambda t})$ *for various sets* $\Lambda = [\Lambda_1, \lambda_2]$. *The table shows the support points and weights of the optimal design and the minimal efficiency over the interval* $\Lambda = [\lambda_1, \lambda_2]$.

λ_1	λ_2	t_1	t_2	t_3	t_4	w_1	w_2	w_3	w_4	min eff
0.6	1	1.27	10			0.5	0.5			0.9696
0.6	1.5	1.01	10			0.5	0.5			0.9041
0.6	2	0.71	1.91	10		0.35	0.19	0.46		0.8507
0.6	2.5	0.51	1.81	10		0.27	0.29	0.43		0.8314
0.6	3	0.45	1.67	10		0.27	0.30	0.43		0.8192
0.6	4	0.36	1.46	10		0.26	0.32	0.43		0.7966
0.6	5	0.30	1.34	10		0.25	0.32	0.43		0.7765
0.6	6	0.25	1.07	1.82	10	0.23	0.22	0.13	0.41	0.7607
0.5	1	1.37	10			0.5	0.5			0.9469
0.4	1	1.48	10			0.5	0.5			0.9148
0.3	1	1.62	10			0.5	0.5			0.8719
0.2	1	1.34	3.79	10		0.31	0.24	0.45		0.8375
0.1	1	1.25	4.40	10		0.26	0.31	0.43		0.8193

Table 4: *Standardized maximin D-optimal designs for the exponential regression model* $a + be^{-\lambda t}$ *for various sets* $\Lambda = [\Lambda_1, \lambda_2]$. *The table shows the support points and weights of the optimal design and the minimal efficiency over the interval* $\Lambda = [\lambda_1, \lambda_2]$.

λ_1	λ_2	t_1	t_2	t_3	t_4	t_5	w_1	w_2	w_3	w_4	w_5	min eff
0.6	1	0	1.27	10			0.33	0.33	0.33			0.9797
0.6	1.5	0	1.01	10			0.33	0.33	0.33			0.9350
0.6	2	0	0.60	1.95	10		0.32	0.22	0.17	0.29		0.9110
0.6	2.5	0	0.51	1.77	10		0.31	0.21	0.18	0.29		0.9038
0.6	3	0	0.45	1.61	10		0.31	0.21	0.19	0.29		0.8967
0.6	4	0	0.36	1.44	10		0.31	0.21	0.20	0.29		0.8833
0.6	5	0	0.26	0.94	1.97	10	0.30	0.18	0.14	0.11	0.27	0.8738
0.5	1	0	1.37	10			0.33	0.33	0.33			0.9643
0.4	1	0	1.48	10			0.33	0.33	0.33			0.9424
0.3	1	0	1.34	3.26	10		0.32	0.25	0.11	0.31		0.9170
0.2	1	0	1.17	3.85	10		0.31	0.21	0.19	0.29		0.9061
0.1	1	0	1.25	4.27	10		0.31	0.21	0.19	0.29		0.8985

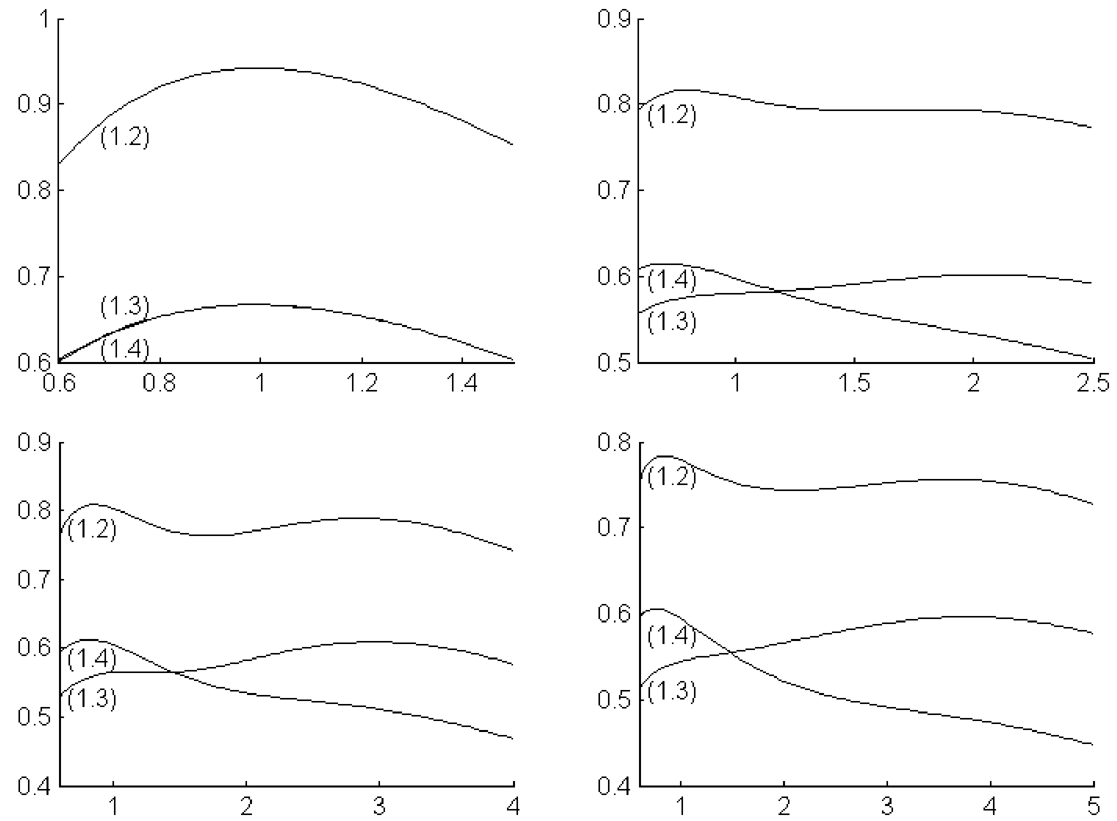

Figure 2: *D-efficiencies of the standardized maximin D-optimal design ξ_Λ^D for the model (1.1) in the exponential regression models (1.2), (1.3), (1.4), where* $\Lambda = [0.6, 1.5]$, $[0.6, 2.5]$, $[0.6, 4]$, $[0.6, 5]$.

in the models (1.2) - (1.4) with two parameters gives the experimenter the additional flexibility to perform a goodness-of-fit test regarding the model assumptions. In Figure 2 we display the D-efficiencies of the standardized maximin D-optimal design for the model (1.1) in the three sub-models. We consider four cases for the set of parameters, namely $\Lambda = [0.6, 1.5]$, $[0.6, 2.5]$, $[0.6, 4]$, $[0.6, 5]$. We observe that the standardized maximin D-optimal designs from model (1.1) yield reasonable D-efficiencies in the exponential regression model (1.2) (between 80%-90%), while the D-efficiencies of these designs in the models (1.3) - (1.4) are substantially smaller. Thus if standardized maximin D-optimal designs from model (1.1) are used in model (1.2), these designs allow for some goodness-of-fit testing against the model (1.1), without loosing too much efficiency for estimating the parameters in the model (1.2). On the other hand some more care is necessary with the application of the standardized maximin D-optimal designs from model (1.1) in the sub-models (1.3)-(1.4), because the loss of efficiency for the estimation of the parameters in these two-dimensional sub-models can be substantial.

5 Appendix: Proofs

5.1 Proof of Lemma 3.2.

The cases (a), (b) and (d) have been proved by Han and Chaloner (2003) and it remains to show the assertion (c). In a first step we prove that the local D-optimal design is supported at two points. In a second step we show that the right boundary point T of the design space is a support point of the local D-optimal design. For this let $t_1, \ldots, t_n$ denote the different support points of a local D-optimal design ξ_λ^D. Because the information matrix of ξ_λ^D should be non singular we obtain $n \geq 2$. Due to the equivalence theorem for the D-optimality criterion [see Kiefer (1974)] it follows that the design ξ_λ^D is local D-optimal if and only if the inequality

$$g(t) = f^T(t,\theta) M^{-1}(\xi_\lambda^D, \theta) f(t,\theta) \leq 2$$

holds for all $t \in [0,T]$, where the vector $f(t,\theta)$ is defined by

$$f(t,\theta) = (1 - e^{-\lambda t}, ate^{-\lambda t})^T,$$

and there is equality for all support points of ξ_λ^D, that is $g(t_i) = 2$, $i = 1, \ldots, n$. Note that g is nonnegative and a linear combination of the functions $\{1, e^{-\lambda t}, te^{-\lambda t}, e^{-2\lambda t}, te^{-2\lambda t}, t^2 e^{-2\lambda t}\}$. Moreover $g(0) = 0$,

$$g(t) \to c,$$

and $g(t) \to \infty$ if $t \to \infty$ and $t \to -\infty$, respectively. This implies that the function g' has at least $2n-1$ roots [note that $g'(t_i) = 0$ for $i = 1, \ldots n-1$, $g'(0) = 0$ and that there must exist n points $\nu_1, \ldots, \nu_n$ such that $t_1 < \nu_1 < t_2 < \ldots < \nu_{n-1} < t_n \leq \nu_n$ and $g'(\nu_i) = 0$ for $i = 1, \ldots, n$]. Corresponding to the size of the limit c there appear two situations for the n support points $t_1 < \ldots < t_n$ of the D-optimal design

1. If $t_n = T$, then the function g' has at least $2n-1$ zeros at the points t_i, ν_i, $i = 1, \ldots, n-1$ and at the point 0.

2. If $t_n < T$, then the function g' has at least $2n+1$ zeros at the points t_i, ν_i, $i = 1, \ldots, n$ and the point 0.

On the other hand the functions $\{1, e^{-\lambda t}, te^{-\lambda t}, e^{-2\lambda t}, te^{-2\lambda t}, t^2 e^{-2\lambda t}\}$ generate a Chebyshev system on the real line [see Karlin and Studden (1966)] and consequently $g(t) - 2$, which is a linear combination of these functions, cannot have more than 5 roots. This implies $n = 2$ and proves the assertion regarding the number of support points of the local D-optimal design.
By a standard argument [see Silvey (1980)] the weights of the 2-point D-optimal design are equal to 1/2. Now let

$$\xi_{t_1,t_2} = \begin{pmatrix} t_1 & t_2 \\ 1/2 & 1/2 \end{pmatrix}$$

be a 2-point design with arbitrary support points, $t_2 > t_1$ then we have

$$\frac{\partial}{\partial t_2} \left(\sqrt{\det M(\xi_{t_1,t_2})} \right) \;=\; a/2 \left(\lambda t_1 e^{-\lambda t_2} e^{-\lambda t_1} + (1 - e^{-\lambda t_1})(\lambda t_2 - 1) e^{-\lambda t_2} \right) > 0 \;,$$

which implies $\det M(\xi_{t_1,t_2}) < \det M(\xi_{t_1,T})$. Consequently a design ξ_{t_1,t_2} with $t_2 < T$ is not D-optimal, and a direct maximization shows that the maximum $\det M(\xi_{t_1,T})$ with respect to t_1 is attained at the point $t_1 = t_D^*$ defined in (3.1). □

5.2 Proof of Lemma 4.1.

The statement (a) of Lemma 4.1 follows from the following identities

$$\frac{\det \int_{\mathcal{T}} I(t)\xi(dt)}{\det \int_{\mathcal{T}} I(t)\xi_\lambda^D(dt)} = \frac{\det \int_{\tilde{\mathcal{T}}} I(t-\mu)\xi(d(t-\mu))}{\det \int_{\tilde{\mathcal{T}}} I(t-\mu)\xi_\lambda^D(d(t-\mu))} = \frac{\det \int_{\tilde{\mathcal{T}}} I(t)\xi(d(t-\mu))}{\det \int_{\tilde{\mathcal{T}}} I(t)\tilde{\xi}_\lambda^D(dt)} ,$$

where

$$I(t) = I(t,\lambda) = f(t,\lambda)f^T(t,\lambda).$$

denotes the Fisher information at the point t. Similarly, assertion (b) is obtained from

$$\frac{\det \int_{\mathcal{T}} I(t,\lambda)\xi(dt)}{\det \int_{\mathcal{T}} I(t,\lambda)\xi_\lambda^D(dt)} = \frac{\det \int_{\tilde{\mathcal{T}}} I(t\gamma,\lambda)\xi(d(t\gamma))}{\det \int_{\tilde{\mathcal{T}}} I(t\gamma,\lambda)\xi_\lambda^D(d(t\gamma))} = \frac{\det \int_{\tilde{\mathcal{T}}} I(t,\gamma\lambda)\xi(d(t\gamma))}{\det \int_{\tilde{\mathcal{T}}} I(t,\gamma\lambda)\tilde{\xi}_{\gamma\lambda}^D(dt)}$$

$\square$

5.3 Proof of Theorem 4.2.

We restrict ourselves to a proof of part (b). All other cases are treated similarly. For an arbitrary two-point design

$$\xi_{t_1,t_2,w} = \begin{pmatrix} t_1 & t_2 \\ w & 1-w \end{pmatrix}$$

with $t_2 > t_1$ we calculate the determinant of the information matrix (2.3) and obtain

$$\det M(\xi_{t_1,t_2,w}) = w(1-w)(t_2e^{-\lambda t_2} - t_1e^{-\lambda t_1})^2$$

It is now easy to see that for any $t_1 > 0$

$$\det M(\xi_{t_1,t_2,w}) < \det M(\xi_{0,t_2,w})$$

Consequently a design $\xi_{t_1,t_2,w}$ with $t_1 > 0$ cannot be standardized maximin D-optimal. By a standard argument [see Silvey (1980)] the weights of the standardized maximin D-optimal two point design are equal to $1/2$. Thus the standardized maximin D-optimal two point design is of the form $\xi_t = \xi_{0,t,1/2}$ and we have to solve problem

$$\min_{\lambda\in[\lambda_1,\lambda_2]} \text{eff}(\xi_t,\lambda) \to \max_{t>0}$$

Assume that t^* is a solution of this optimization problem and define $\xi^* = \xi_{t^*}$. We now have to consider the different cases separately

(i) Consider first the case $T > 1/\lambda_1$. It is easy to see that for fixed t the function $\text{eff}(\xi_t,\lambda) = \lambda te^{-\lambda t}$ has at most one local maximum with respect to $\lambda > 0$. Consequently

$$\min_{\lambda\in[\lambda_1,\lambda_2]} \text{eff}(\xi_t,\lambda) = \min_{\lambda\in\{\lambda_1,\lambda_2\}} \text{eff}(\xi_t,\lambda).$$

Suppose that the minimum for the standardized maximin D-optimal design is attained in the point λ_1. Then it follows that $t^* = 1/\lambda_1$ and from the representation

$$e^{-1} = \text{eff}(\xi^*,\lambda_1) = \min_{\lambda\in\{\lambda_1,\lambda_2\}} \text{eff}(\xi^*,\lambda) = \min\{e^{-1}, he^{-h}\} = he^{-h}$$

where $h = \frac{\lambda_2}{\lambda_1}$. But this is a contradiction to the well known inequality $he^{-h} < e^{-1}$.
By a similar argument it follows that the minimum of the function $\text{eff}(\xi^*, \lambda)$ cannot be attained at the point λ_2. Consequently, we obtain the equation $\text{eff}(\xi_t, \lambda_1) = \text{eff}(\xi_t, \lambda_2)$, which is equivalent to

$$\lambda_1 te^{-\lambda_1 t} = \lambda_2 te^{-\lambda_2 t}.$$

and determines the point t^* uniquely, that is

$$t^* = \frac{\log \lambda_2 - \log \lambda_1}{\lambda_2 - \lambda_1}.$$

(ii) Secondly, consider the case $T < 1/\lambda_2$, then it follows from the discussion of Section 3 that the local D-optimal design ξ_λ^D has equal weights at the points 0 and T and does not depend on the parameter λ. Consequently, this design is also the standardized maximin D-optimal two-point design and $\text{eff}(\xi^*, \lambda) \equiv 1$ for all $\lambda \in [\lambda_1, \lambda_2]$.
(iii) Finally we consider the case $1/\lambda_2 \leq T \leq 1/\lambda_1$, where a direct calculation shows that $t^* \geq 1/\lambda_2$. The same arguments as in the first part of the proof show that t^* is a solution of the equation $\text{eff}(\xi_t, \lambda_1) = \text{eff}(\xi_t, \lambda_2)$, which reduces for the case under consideration to

$$\frac{te^{-\lambda_2 t}}{1/(e\lambda_2)} = \frac{te^{-\lambda_1 t}}{Te^{-\lambda_1 T}}.$$

A straightforward calculation shows that the solution of this equation is given by

$$t^* = \frac{\log(\lambda_2 T) + 1 - \lambda_1 T}{\lambda_2 - \lambda_1} ,$$

which satisfies $t^* \geq 1/\lambda_2$ and proves the assertion of Theorem 4.2 for the case (b). □

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