Efficient experimental designs for sigmoidal growth models

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Abstract

For the Weibull- and Richards-regression model robust designs are determined by maximizing a minimum of D- or D_1-efficiencies, taken over a certain range of the non-linear parameters. It is demonstrated that the derived designs yield a satisfactory solution of the optimal design problem for this type of model in the sense that these designs are efficient and robust with respect to misspecification of the unknown parameters. Moreover, the designs can also be used for testing the postulated form of the regression model against a simplified sub-model.

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1 Introduction

Sigmoidal growth curves are widespread tools for analyzing data from processes arising in various fields. Such curves are increasing functions with an inflection point after which the growth rate decreases to approach asymptotically a finite value. Numerous mathematical functions have been proposed for modelling sigmoidal curves. Typical applications include subject areas such as biology [see Landaw and DiStefano (1984)], chemistry, pharmacokinetics [see Liebig (1988), or Krug and Liebig (1988)], toxicology [Becka and Urfer (1996), Becka, Bolt, Urfer (1993)] or microbiology [see Coleman, Marks (1998)]. An appropriate choice of the experimental conditions can improve the quality of statistical inference substantially. Although optimal designs for non-linear regression models have been discussed by many authors, much less attention has been paid to the problem of designing experiments for sigmoidal regression models.
In non-linear models the Fisher information matrix of the maximum likelihood estimator depends on the unknown parameters and for this reason optimal designs, which maximize some function of

the Fisher information matrix are difficult to implement in practice. Many authors concentrate on local optimal designs, where it is assumed that a preliminary guess for the unknown parameters is available [see Chernoff (1953) or Silvey (1980)]. Most local optimal designs for non-linear regression models have been criticized for two reasons. First these designs are not necessarily robust with respect to a misspecification of the non-linear parameters in the model. Secondly they advice the experimenter to take observations only at a few different points. The number of these points usually coincides with the number of parameters in the regression model and as a consequence these designs are not applicable for testing the goodness-of-fit of the assumed model.

Several proposals have been made to obtain robust designs with respect to misspecification of the parameters [see Pronzato and Walter (1985), Chaloner and Verdinelli (1995), Müller (1995), Dette (1997), Imhof (2001) or Dette and Biedermann (2003)], but less literature is available to address the possibility of model checking in the construction of optimal designs. In linear models some suggestions can be found in Stigler (1971) or Studden (1982) in the context of a polynomial regression model, who suggested to embed the postulated model in an extended model (usually a polynomial of larger degree) and to construct an optimal design for testing the postulated against the extended model. Discrimination designs for polynomial regression models in a more general context have been discussed in Dette (1990, 1995), but not much literature seems to be available in the context of non-linear models. Atkinson and Fedorov (1975) proposed the T-optimality criterion, which adapts Stigler's idea to the nonlinear setup. However, their criterion is local and therefore not necessarily robust with respect to a misspecification of the unknown parameters. Recently, Dette, Melas and Wong (2004) considered the Michaelis-Menten model and constructed robust and efficient designs, which can on the one hand be used for testing this model against an extension (called EMAX model) and are on the other hand robust with respect to misspecification of the non-linear parameters.

It is the purpose of the present paper, to demonstrate that this approach is more broadly applicable and useful for the construction of efficient and robust designs in nonlinear models for several objects. For this we consider two commonly used sigmoidal regression models and its corresponding extension. The first model under consideration is the exponential regression model

$$\eta(t,\theta) = a - be^{-\lambda t} \tag{1.1}$$

(with $\theta = (a, b, \lambda)$), which is called von Bertalanffy growth curve or Mitscherlichs growth law. Numerous authors studied optimal designs for this model from various points of view [see Dette and Neugebauer (1997) and Han and Chaloner (2004) for example]. Most of these optimal designs are three-point designs and can for this reason not be used for testing the goodness-of-fit of the postulated model. For this purpose we consider the Weibull regression model

$$\eta(t,\theta) = a - be^{-\lambda t^h} \tag{1.2}$$

(here $\theta = (a, b, \lambda, h)$), which is an extension of the model (1.1). The Weibull model is also widely used for describing sigmoidal growth [see e.g. Ratkowsky (1983), Zeide (1993) or Vanclay and Skovsgaard (1997) among many others]. Our goal is to construct an optimal experimental design for model (1.1) and (1.2) which fulfills at least three requirements.

(1) The design should allow to test the hypothesis

$$H_0 \ : \ h = 1 \quad vs \quad H_1 : h \neq 1 \tag{1.3}$$

in the extended model (1.2).

(2) The design should be efficient for the estimation of the parameters in the regression models (1.1) and (1.2).

(3) The design should be robust with respect to misspecification of the non-linear parameters in the regression models.

The second pair of sigmoidal growth models, where a similar question is considered, is given by the logistic regression model

$$\eta(t,\theta) = \frac{a}{1+be^{-\lambda t}} \tag{1.4}$$

(with $\theta = (a, b, \lambda)$), and the Richards-regression model

$$\eta(t,\theta) = \frac{a}{(1+be^{-\lambda t})^h} \tag{1.5}$$

(here $\theta = (a, b, \lambda, h)$). The models (1.2) and (1.5) are serious competitors to the models (1.1) and (1.4), respectively, and therefore it is desirable to incorporate in the construction of an experimental design the flexibility to test the hypothesis (1.3) in the regression models (1.2) or (1.5).
Our first approach for the construction of efficient designs is based on the classical D-optimality criterion and maximizes the determinant of the (asymptotic) covariance matrix of the least squares estimator for the parameters in the extended model. The second method is based on the D_1-optimality criterion and determines the design such that the asymptotic variance of the least squares estimator for the parameter h in the extended model is minimal. Because all models are non-linear the optimal designs depend on the unknown parameters in the extended and corresponding sub-model. In Section 2 we determine local optimal designs, which require an initial guess of the unknown parameters [see Chernoff (1953)]. These designs are rather sensitive with respect to the choice of the initial parameters and we construct in Section 3 standardized maximin optimal designs [see Müller (1995), Dette (1997), Imhof (2001) or Imhof and Wong (2000)], which maximize the minimum D- or D_1-efficiency over a certain range of parameters. It is demonstrated that these designs are on the one hand quite efficient for discrimination between the basic model and its extension and on the other hand efficient for the estimation of the parameters. We also compare the performance of these designs with the uniform design, which is commonly used in these models. For the sake of brevity we present a detailed discussion for the model (1.1) and (1.2) and discuss the situation of the Richards-regression model (1.5) more briefly. Some conclusions are given in Section 4, while the proofs of our results are technical and therefore deferred to the Appendix.

2 Local optimal designs

2.1 Preliminaries

Let $[0, T]$ denote the experimental region and assume that for each $t \in [0, T]$ an observation Y could be made, where different observations are assumed to be independent with the same variance, say $\sigma^2 > 0$, and expectation

$$E[Y|t] = \eta(t, \theta) \ , \tag{2.1}$$

where $\eta(t, \theta)$ is either the function in (1.2) or (1.5). Following Kiefer (1974) we call any probability measure

$$\xi = \begin{pmatrix} t_1 & \dots & t_n \\ w_1 & \dots & w_n \end{pmatrix} \tag{2.2}$$

with finite support $t_1, \dots, t_n \in [0, T]$, $t_i \neq t_j$ $(i \neq j)$ and masses $w_i > 0$, $\sum_{i=1}^n w_i = 1$ an experimental design. We assume that the design ξ has at least four support points, and denote by

$$M(\xi, \theta) = \int_0^T f(t, \theta) f^T(t, \theta) d\xi(t) \tag{2.3}$$

the information matrix of the design ξ for the model (2.1), where

$$f(t, \theta) = \frac{\partial \eta}{\partial \theta}(t, \theta) = (f_1(t, \theta), \dots, f_m(t, \theta))^T \tag{2.4}$$

is the vector of partial derivatives of the conditional expectation $E[Y|t]$ with respect to the parameter θ. If N is the total sample size, the experimenter takes approximately $n_i \approx N w_i$ observations at the point t_i $(i = 1, \dots, n)$ such that $\sum_{i=1}^n n_i = N$. It is well known [see Jennrich (1969)] that under regularity assumptions, the asymptotic covariance matrix of the least squares estimator $\hat{\theta}$ for the parameter θ in the model (2.1) is given by the matrix

$$\frac{\sigma^2}{N} M^{-1}(\xi, \theta).$$

A local optimal design maximizes an appropriate function of the information matrix $M^{-1}(\xi, \theta)$ and there are numerous optimality criteria which can be used to discriminate among competing designs [see Silvey (1980) or Pukelsheim (1993)]. In the present paper we restrict ourselves to the D- and D_1-optimality criterion.

For a fixed θ a local D-optimal design maximizes the determinant $|M(\xi, \theta)|$, while the local D_1-optimal design maximizes

$$\left(e_4^T M^{-1}(\xi, \theta) e_4\right)^{-1} = \frac{|M(\xi, \theta)|}{|\tilde{M}(\xi, \theta)|}, \tag{2.5}$$

where $e_4^T = (0, 0, 0, 1) \in \mathbb{R}^4$ and the matrix $\tilde{M}$ is obtained from M by deleting the last row and column.

2.2 Local optimal designs for the Weibull regression model

Recall the definition of the Weibull and the exponential regression model in (1.2) and (1.1), respectively. For the model (1.2) we have $\theta = (a, b, \lambda, h)$ and a straightforward calculation yields for the vector of partial derivatives in (2.4)

$$f(t, \theta) = f(t, a, b, \lambda, h) = (1, -e^{-\lambda t^h}, b t^h e^{-\lambda t^h}, b \lambda t^h \ln(t) e^{-\lambda t^h})^T. \tag{2.6}$$

With our first result we establish some basic properties of local D- and D_1-optimal designs in the Weibull regression model (1.2), which facilitate their numerical calculation.

Lemma 2.1. *The local D- or D_1-optimal design in the Weibull regression model (1.2) does not depend on the parameters a and b. Moreover, let $t_i(\lambda, h, T)$ denote a support point of a local D- or D_1-optimal design on the interval $[0, T]$, then*

$$\begin{aligned} t_i(\lambda, h, T^h) &= (t_i(\lambda, 1, T))^h, \\ t_i(r\lambda, 1, T) &= \frac{1}{r}\, t_i(\lambda, 1, rT) \end{aligned}$$

for any $r > 0$. The weights of the local D- or D_1-optimal design do not depend on the parameter h and the factor r.

Note that we are interested in efficient designs for discriminating between the models (1.2) and (1.1). Because this is most difficult if the parameter h is close to 1 we assume $h = 1$ throughout this paper. This choice is also partially motivated by Lemma 2.1 which relates local D- or D_1-optimal designs in the Weibull regression model (1.2) for different values of h. An important further consequence of Lemma 2.1 is that it is sufficient to calculate local D- or D_1-optimal designs on a fixed design space for various values of λ, where the remaining parameters a, b, h have been fixed. Local optimal designs on a different design space or with respect to a different specification of the parameters can then easily be calculated by a non-linear transformation. Our next result is of some theoretical interest and the main tool for the calculation of the D_1-optimal design.

Lemma 2.2. *For any $T > 0$ the functions $1, -e^{-\lambda t}, te^{-\lambda t}, t\ln(t)e^{-\lambda t}$ form a Chebyshev system on the interval $[0, T]$.*

It is well known [see Karlin and Studden (1966), Theorem II, 10.2] that if the system of functions $\{f_1, \ldots, f_m\}$ is a Chebyshev system on the interval $[0, T]$, then there exists a unique function

$$\sum_{i=1}^{m} p_i^* f_i(t) = p^{*T} f(t), \tag{2.7}$$

with the following properties

(2.8)
(i) $|p^{*T} f(t)| \leq 1 \quad \forall\, t \in [0, T]$
(ii) there exist m points $t_1^* < \ldots < t_m^*$ such that $p^{*T} f(t_i) = (-1)^{i-1}$, $i = 1, \ldots, m$.

The function $p^{*T} f(t)$ is called Chebyshev polynomial, and the points t_i^* are called Chebyshev points. It turns out that in many cases the Chebyshev points are the support points of c-optimal designs, i.e. designs minimizing $c^T M^{-1}(\xi, \theta)c$ for a given vector $c \in \mathbb{R}^m$. In fact the following result shows that the Chebyshev points of the system $\{1, -e^{-\lambda t}, te^{-\lambda t}, t\ln(t)e^{-\lambda t}\}$ are the support points of the local D_1-optimal design in the Weibull regression model.

Theorem 2.3. *A D_1-optimal design in the Weibull regression model (1.2) is uniquely determined and supported at 4 points, say $t_1^* < t_2^* < t_3^* < t_4^*$. The support points are the Chebyshev points* *corresponding to the system* $\{1, -e^{-\lambda t}, te^{-\lambda t}, t\ln(t)e^{-\lambda t}\}$. *Moreover,* $t_1^* = 0$, $t_4^* = T$ *and the corresponding weights* $w_1^*, \ldots, w_4^*$ *can be obtained explicitly as*

$$w^* = (w_1^*, \ldots, w_4^*)^T \;=\; \frac{JF^{-1}e_4}{\mathbf{1}_4 JF^{-1}e_4}, \tag{2.9}$$

where the matrixes F *and* J *are defined by*

$$F = (f(t_1^*, \theta), f(t_2^*, \theta), f(t_3^*, \theta), f(t_4^*, \theta)),$$

$J = \mathrm{diag}(1, -1, 1, -1)$, *respectively, and* $\mathbf{1}_4 = (1, 1, 1, 1)^T$.

It follows from (2.8) and Theorem 2.3 that the Chebyshev points t_2^*, t_3^* can be found as a solution of the system of equations

$$\begin{array}{ccc} \psi(0) = 1 & \psi(t_2) = -1 & \psi(t_3) = 1 \\ \psi(T) = -1 & \psi'(t_2) = 0 & \psi'(t_3) = 0 \end{array}$$

with respect to the parameters $t_2, t_3, p = (p_1, p_2, p_3, p_4)^T$, where $\psi(t) = p^T f(t, \theta)$. Some D_1-optimal designs for the Weibull regression model (1.2) are given in Table 1 for the design space $[0, T] = [0, 10]$. We observe that the support points of these designs depend sensitively on the parameter λ while there are less changes in the weights.
The determination of local D-optimal designs is a little more complicated. We begin our discussion with a result on minimally supported local D-optimal design. Throughout this paper a local optimal design found in the subclass of k-point designs is called local optimal k-point design ($k \in \mathbb{N}$).

Lemma 2.4. *The local* D*-optimal* 4*-point design for the Weibull regression model (1.2) with* $h = 1$ *on the interval* $[0, T]$ *is uniquely determined and has equal masses at the points* 0, t_2^*, t_3^* *and* T. *The nontrivial support are the (uniquely determined) points maximizing the function*

$$\begin{aligned} \Phi(t_2, t_3, \lambda) \;=\; & (Tt_2 \ln(T/t_2) - t_3 t_2 \ln(t_3/t_2) - Tt_3 \ln(T/t_3))\, e^{-\lambda(t_2+t_3+T)} \\ & -Tt_2 \ln(T/t_2) e^{-\lambda(t_2+T)} + t_3 t_2 \ln(t_3/t_2) e^{-\lambda(t_2+t_3)} + Tt_3 \ln(T/t_3) e^{-\lambda(t_3+T)}. \end{aligned} \tag{2.10}$$

Lemma 2.5. *Any local* D*-optimal design in the Weibull regression model (1.2) on the interval* $[0, T]$ *contains the bounds of the design space in its support.*

We were not able to prove that the local D-optimal design in the Weibull regression model (1.2) is always supported at only four points. However, our numerical results strongly suggest that this is indeed the case. We have calculated the best local D-optimal 4 point designs by maximizing the function in (2.10) with respect to the points t_2 and t_3. The optimality of the derived designs within the class of all designs was verified by the equivalence theorem of Kiefer and Wolfowitz (1960). We did not find any case where the best 4-point design is not local D-optimal. In Table 2 we show some representative local D-optimal designs. Optimal designs on different design spaces can easily be obtained by the transformation given in Lemma 2.1. We observe again that the local D-optimal designs are rather sensitive with respect to changes in the parameter λ.

2.3 Local optimal designs in the Richards-regression model

We now briefly mention the corresponding results for the Richards-regression model defined by (1.5). In this case we have $\theta = (a, b, \lambda, h)$ and a straightforward calculation yields for the vector of partial derivatives in (2.4)

$$(2.11) \qquad f(t,\theta) = \left(\frac{1}{(1+be^{-\lambda t})^h}, -\frac{ahe^{-\lambda t}}{(1+be^{-\lambda t})^{h+1}}, \frac{ahbte^{-\lambda t}}{(1+be^{-\lambda t})^{h+1}}, -\frac{a\ln(1+be^{-\lambda t})}{(1+be^{-\lambda t})^h} \right)^T .$$

Theorem 2.6.
(a) The local D- or D_1-optimal design in the Richards-regression model (1.5) does not depend on the parameters a. Moreover, let $t_i(b, \lambda, h, T)$ denote a support point of a local D- or D_1-optimal design on the interval $[0, T]$, then

$$t_i(b, r\lambda, 1, T) \;=\; \frac{1}{r}\; t_i(b, \lambda, 1, rT)$$

for any $r > 0$. The weights of the local D- or D_1-optimal design do not depend on the factor r.

(b) For any $T > 0$ the system defined by (2.11) is a Chebyshev system on the interval $[0, T]$. The D_1-optimal design in the Richards-regression model (1.5) is uniquely determined and supported at 4 points, say $t_1^* < t_2^* < t_3^* < t_4^*$. The support points are the Chebyshev points corresponding to the system (2.11). Moreover, $t_4^* = T$ and the corresponding weights $w_1^*, \ldots, w_4^*$ can be obtained explicitly by formula (2.9) where the vector (2.11) is used instead of (2.6).

(c) The local D-optimal 4-point design in the Richards-regression model (1.5) on the interval $[0, T]$ is uniquely determined and has equal masses at four points t_1^*, t_2^*, t_3^* and T.

In Table 3 and 4 we show some representative local D_1- and D-optimal designs (where $h = 1$). Note that for the Richards-regression models the local optimal designs depend on two parameters, namely b and λ. In all our numerical examples the local D-optimal designs are supported at four points, but a rigorous proof seems to be difficult. We observe again that the local optimal designs are rather sensitive with respect to changes in the parameters b and λ.

3 Standardized maximin D- and D_1-optimal designs

Note that the local D- and D_1-optimal designs derived in the previous sections are not necessarily robust with respect to the choice of initial values of the unknown parameters. In some cases the loss of efficiency caused by a misspecification of the parameters in the local optimality criteria can be substantial. A more robust approach to this problem is to, in some sense, quantify the uncertainty in those parameters and to incorporate this additional information into the formulation of suitable optimality criteria. This has been achieved in practice through the introduction of the concepts of Bayesian and maximin optimality. In the present paper we will use the last named approach for the construction of robust and efficient designs in the non-linear regression models (1.2) and (1.5), which was proposed by Müller (1995) and Dette (1997). Our decision for the maximin approach is motivated for two reasons. First it is our experience that in many cases the experimenter has difficulties to specify an appropriate prior distribution, which is necessary for the definition of the

Bayesian optimality criterion. Secondly, if the experimenter uses a noninformative prior (as the uniform distribution) in the Bayesian optimality criterion it is demonstrated in Braess and Dette (2005) that the standardized maximin optimal designs usually have more different support points than Bayesian optimal designs with respect to such priors. As a consequence these designs are more useful for testing the regression model against any deviations from the model assumptions. To be precise let Ω be a set of plausible values for the parameter θ. We call a design ξ^* standardized maximin D-optimal with respect to the set Ω if it maximizes the worst D-efficiency,

$$\min_{\theta \in \Omega} \mathrm{eff}_D(\xi, \theta), \tag{2.12}$$

where

$$\mathrm{eff}_D(\xi, \theta) = \sqrt[m]{\frac{\det M(\xi, \theta)}{\det M(\xi_D^*(\theta), \theta)}}, \tag{2.13}$$

$\xi_D^*(\theta)$ is the local D-optimal design and $m = 4$ is the number of parameters in the extended regression model. Similarly, a design ξ^* is called standardized maximin D_1-optimal with respect to Ω if it maximizes the worst D_1-efficiency

$$\min_{\theta \in \Omega} \mathrm{eff}_4(\xi, \theta) \ , \tag{2.14}$$

where

$$\mathrm{eff}_4(\xi, \theta) = \frac{e_4^T M^{-1}(\xi_4^*(\theta), \theta) e_4}{e_4^T M^{-1}(\xi, \theta) e_4} \tag{2.15}$$

and $\xi_4^*(\theta)$ is the local D_1-optimal design. It is easy to see that the weights of a 4-point standardized maximin D-optimal design have to be equal. The optimality of a given design with respect to one of the introduced optimality criteria can easily be checked by the following equivalence theorem [see Dette, Haines and Imhof (2004)].

Theorem 3.1. *A design ξ^* is standardized maximin D-optimal if and only if there exists a distribution π^* on the set*

$$N(\xi^*) = \Big\{ \tilde{\theta} \in \Omega \ \Big| \ \mathrm{eff}_D(\xi^*, \tilde{\theta}) = \min_{\theta \in \Omega} \mathrm{eff}_D(\xi^*, \theta) \Big\}.$$

such that the inequality

$$\int_{N(\xi^*)} f^T(t, \theta) M^{-1}(\xi^*, \theta) f(t, \theta) d\pi^*(\theta) \leq m, \tag{2.16}$$

holds for all $t \in [0, T]$. Moreover, there is equality in (2.16) for all support points of the standardized maximin D-optimal design.
A design ξ^* is standardized maximin D_1-optimal if and only if there exists a distribution $\tilde{\pi}^*$ on the set

$$\tilde{N}(\xi^*) = \Big\{ \tilde{\theta} \in \Omega \ \Big| \ \mathrm{eff}_4(\xi^*, \tilde{\theta}) = \min_{\theta \in \Omega} \mathrm{eff}_4(\xi^*, \theta) \Big\}.$$

such that

$$\int_{\tilde{N}(\xi^*)} \frac{e_4^T M^{-1}(\xi^*,\theta) f^T(t) f(t) M^{-1}(\xi^*,\theta) e_4}{e_4^T M^{-1}(\xi^*,\theta) e_4} d\tilde{\pi}^*(\theta) \leq 1 \tag{2.17}$$

holds for all $t \in [0,T]$. Moreover, there is equality in (2.17) for all support points of the standardized maximin D_1-optimal design.

In general the determination of standardized maximin D- and D_1-optimal designs is a very hard problem and can only be done numerically in all cases of practical interest. For our numerical calculation we first looked at standardized maximin optimal 4-point designs. The optimality of the best 4-point designs was checked by an application of Theorem 3.1. If the optimality of a minimally supported design could be established, the procedure is terminated. Otherwise we increase the number of support points and determine the standardized maximin optimal design within the class of all 5-points designs. This procedure is repeated until it terminates (this usually happens after a few steps). In the following we consider the Weibull and Richards-regression model separately.

3.1 Efficient and robust designs for the Weibull regression model

Recall the definition of the exponential and Weibull regression model in (1.1) and (1.2). In the following we are interested in a robust (with respect to misspecification of the parameters) design, which is on the one hand efficient for discriminating between the models (1.1) and (1.2) and yields on the other hand precise parameter estimates in both models. The proof of the next result follows by the same arguments as given in the proof of Lemma 2.1 and is therefore omitted.

Lemma 3.2. *The standardized maximin D- or D_1-optimal design in the Weibull regression model (1.2) does not depend on the parameters a and b. Moreover, if $t_i^*(\lambda_1,\lambda_2,h,T)$ denote the support points of the standardized maximin D- or D_1-optimal design, where the minimum is taken with respect to the interval $\lambda \in [\lambda_1,\lambda_2]$, then*

$$\begin{aligned} t_i^*(\lambda_1,\lambda_2,h,T^h) &= \left(t_i^*(\lambda_1,\lambda_2,1,T)\right)^h, \\ t_i^*(r\lambda_1,r\lambda_2,1,T) &= \frac{1}{r}\, t_i^*(\lambda_1,\lambda_2,1,rT) \end{aligned}$$

for any $r > 0$. The weights of the the standardized maximin D- or D_1-optimal design do not depend on the parameter h and the factor r.

Similar arguments as presented in Section 2 show that the bounds of the design space $[0,T]$ are always support points of the standardized maximin D- and D_1-optimal design.

Lemma 3.3. *Any standardized maximin D- or D_1-optimal design in the Weibull regression model (1.2) contains the bounds of the design space in its support.*

Lemma 3.2 allows us to consider parameter spaces of the form

$$\Omega = \{1\} \times \{1\} \times [\lambda_1,\lambda_2] \times \{1\}$$

in the standardized maximin optimality criteria (2.12) and (2.14) (note that we assume $h = 1$ addressing the most difficult case with respect to the problem of testing the hypotheses (1.3)). Therefore we briefly call the designs standardized maximin optimal with respect to the interval $[\lambda_1, \lambda_2]$ in the following.

In Table 5 we present some standardized maximin D-optimal designs for the Weibull regression model on the interval $[0, 10]$ with respect to various intervals $[\lambda_1, \lambda_2]$, i.e. we choosed $\theta = (a, b, \lambda, h)^T \in \Omega = \{1\} \times \{1\} \times [\lambda_1, \lambda_2] \times \{1\}$ in the optimality criterion (2.12). Optimal designs with respect to other design spaces can be obtained by an application of Lemma 3.2. We observe that the number of support points is increasing with the length of the interval $[\lambda_1, \lambda_2]$. For example, if $[\lambda_1, \lambda_2] = [0.6, 4]$, the standardized maximin D-optimal design for the Weibull model (1.2) has 6 support points. The table also shows the minimum D-efficiency over the interval $[\lambda_1, \lambda_2]$. This minimal efficiency corresponds to the worst case calculated over the interval $[\lambda_1, \lambda_2]$ and is at least 90%. Consequently, standardized maximin D-optimal designs are rather robust (with respect to misspecification of the initial parameter λ) and efficient for the estimation of the parameters in the Weibull regression model (1.2).

The corresponding results for the standardized maximin D_1-optimal designs can be found in Table 6. In this case the minimum D_1-efficiency of the standardized maximin D_1-optimal designs is approximately 65%. This indicates that the standardized maximin D_1-optimal designs are more sensitive with respect to the specification of the interval $[\lambda_1, \lambda_2]$ than the standardized maximin D-optimal designs.

We continue our discussion with a comparison of the standardized maximin optimal designs with respect to their performance for the estimation of the parameters in the non-linear regression models (1.1) and (1.2). For this we introduce for two designs, say ξ_1 and ξ_2, the quantity

$$C_i(\xi_1, \xi_2, \theta) = C_i(\xi_1, \xi_2, \lambda) = \frac{e_i^T M^{-1}(\xi_1, \lambda) e_i}{e_i^T M^{-1}(\xi_2, \lambda) e_i}, \tag{2.18}$$

where e_i denotes the ith unit vector in $\mathbb{R}^4$ ($i = 1, \ldots, 4$) and $M(\xi, \lambda) = M(\xi, \theta)$ with $\theta = (1, 1, \lambda, 1)$. Note that the variance of the maximum likelihood estimate for the parameter $e_i^T \theta$ in the Weibull regression model is (asymptotically) proportional to $e_i^T M^{-1}(\xi_1, \theta) e_i$, if observations are taken according to the design ξ_1. Therefore the design ξ_2 is more efficient than the design ξ_1 for the estimation of the ith parameter if and only if $C_i(\xi_1, \xi_2, \lambda) > 1$. In Table 7 we compare the standardized maximin D- and D_1-optimal designs with respect to their performance of estimating the individual parameters in the Weibull regression model (1.2) for some representative values of the parameter λ. The corresponding results for the exponential regression model (1.1) can be found in Table 8. We can see from Table 7 that the standardized maximin D-optimal design ξ_D^* is substantially more efficient for estimating the parameter a, b, λ in the Weibull regression model than the standardized maximin D_1-optimal design $\xi_{D_1}^*$. The differences are substantial and at least 65%. On the other hand the design $\xi_{D_1}^*$ is more efficient for estimating parameters h than the design ξ_D^*, which is obvious by its construction. However, the improvement in the variance of the estimate for the parameter h by choosing the standardized maximin D_1-optimal design $\xi_{D_1}^*$ is usually smaller (approximately 10%) compared to the loss of efficiency for estimating the other parameters. From Table 8 we see that the performance of the standardized maximin optimal designs in the reduced model (1.1) is very similar. In the exponential regression model (1.1) the standardized maximin D-optimal design ξ_D^* from the Weibull model is substantially more efficient for estimating parameters a, b, λ than the standardized maximin D_1-optimal design.

We finally investigate the performance of the standardized maximin D-optimal design from the Weibull model (1.2) in the sub-model (1.1). For this purpose we show in Table 9 the values C_i for the standardized maximin D-optimal design ξ_D^* from the Weibull model (1.2) and the standardized maximin D-optimal design $\tilde{\xi}_D^*$ from the sub-model model (1.1). We observe that the optimal design from the extended model yields sufficiently accurate estimates in the reduced model (1.1) (note that we are comparing with respect to the best design in this model). Summarizing our results we recommend to use standardized maximin D-optimal designs in the Weibull regression model (1.2) for the following reasons:

(1) Standardized maximin D-optimal designs are very efficient for a rather broad range of the non-linear parameters in the model.

(2) Standardized maximin D-optimal designs have approximately 90% efficiency for testing the model (1.1) against (1.2).

(3) Standardized maximin D-optimal designs are also very efficient for the estimation of the parameters in the reduced model (1.1) (the efficiency with respect to the standardized maximin D-optimal design for the reduced model is approximately 80%).

(4) Standardized maximin D-optimal designs often advice the experimenter to take observations at a large number of different locations. For this reason these designs can also be used for testing the postulated model (1.2) against models with more than four parameters by means of a goodness-of-fit test.

Example 3.4. We briefly re-design an experiment in order to demonstrate the potential benefits of using standardized maximin D-optimal designs for the analysis with the Weibull-regression model. For this we reanalyze the data presented in Ratkowsky (1983), p. 88, which shows the water content of bean root cells (Y) versus the distance from tip (t). We fitted the Weibull regression model (1.1) to this data and the results are depicted in Table 10.
The parameter estimates are given by $\hat{a} = 21.104$, $\hat{b} = 19.815$, $\hat{\lambda} = 0.0018$ and $\hat{h} = 3.180$, while estimate of the variance is obtained as $\hat{\sigma}^2 = 0.364$. The design used in the experiment is a uniform design with 15 observations on the interval $[0.5, 14.5]$ while the standardized maximin D-optimal design with respect to the interval $[\lambda_1, \lambda_2] = [0.0003, 0.0033]$ is supported at 6 points and given by

$$\begin{pmatrix} 0.5 & 4.8242 & 7.3427 & 9.7347 & 11.854 & 14.5 \\ 0.2354 & 0.1618 & 0.1861 & 0.0956 & 0.1197 & 0.2014 \end{pmatrix} \tag{2.19}$$

and this design has a minimal D-efficiency of 89.9%. The performance of the two designs is illustrated in Table 11, where we show the quantities

$$D_{ii} = e_i^T M_i^-(\xi, \hat{a}, \hat{b}, \hat{\lambda}, \hat{h}) e_i \quad i = 1, \ldots, 4 \tag{2.20}$$

which are proportional the asymptotic variances of the maximum likelihood estimates for the parameters a, b, λ and h, respectively. We observe a substantial improvement in the variance of the estimates for the parameters a and b (between 25 - 35%), a moderate decrease in the variance of the estimate $\hat{h}$ (10%) and essentially no difference with respect to the estimation of the parameter λ.

Because the quantities D_{ii} are based on the asymptotic theory we also performed a small simulation study to investigate if these considerations can be transferred to a finite sample sizes. For this we generated $N = 15$ observations according to the Weibull regression model with $a = 21.1, b = 19.8, \lambda = 0.0018, h = 3.18, \sigma = 0.603$ and normally distributed errors using the design (2.19). In other words we took 4,2,3,1,2 and 3 observations at the points given in (2.19). We used 600 simulation runs to estimate the variances of the least squares estimates for the parameters a, b, λ and h. The results (multiplied with the factor N/σ^2) are displayed in the second row of Table 11 and confirm the superiority of the standardized maximin D-optimal design in the finite sample situation.

3.2 Efficient and robust design for the Richards-regression model

In this section we briefly investigate the performance of standardized maximin D_1- and D-optimal designs in the Richards-regression model (1.5). Note that the minimum in the optimality criterion now has to be taken over a two dimensional space of the form

$$\Omega = \{1\} \times [b_1, b_2] \times [\lambda_1, \lambda_2] \times \{1\} \tag{2.21}$$

and as a consequence the calculation of the optimal designs is substantially more difficult. We present some representative results for the D_1- and D-optimality criterion in Table 13 and 12, respectively. Again we observe that the standardized maximin D-optimal designs are rather efficient for a broad range of the parameters (the minimal D-efficiency in the set Ω is at least 87%) while the standardized maximin D_1-optimal designs are more sensitive with respect to the choice of the set Ω.

A final comparison of the standardized maximin optimal designs with respect to their performance for estimating the individual parameters in model (1.5) and (1.4) is given in Table 14 and 15, respectively. The conclusions are very similar as for the Weibull model. In the Richards regression model (1.5) both designs are comparable, where the D-optimal designs are substantially more efficient for estimating the parameter a. The other parameters are usually better estimated by the standardized D_1-optimal design (but the differences are less than 10%). However, in the reduced model (1.4) the standardized maximin D-optimal design yields substantially smaller variances of all parameter estimates than the standardized maximin D_1-optimal design. For these reasons we also recommend the application of standardized maximin D-optimal designs for inference in the Richards regression model.

4 Conclusions

In this paper we have investigated a strategy which takes two objectives in the construction of optimal designs for nonlinear regression models into account. First, the designs should be robust with respect to a misspecification of the unknown parameters in the sense that they yield reasonable efficiencies for the estimation of the parameters in the assumed model. Secondly, the constructed designs should give the experimenter the flexibility do check the postulated model assumptions with reasonable efficiency.

For this purpose we propose to consider an extended model, which reduces for a special choice of the parameters to the model under consideration. In this extended model we use a maximin approach to find optimal designs which are robust with respect to misspecification and study the performance of the resulting designs in the extended and original model. We concentrate on two models: the exponential model (where the extension is the Weibull model) and the logistic regression model (where the extension is the Richards-regression model). The D-optimality and D_1-optimality criterion are considered, where the lastnamed criterion is particularly useful for discriminating between the assumed model and its extension. It is demonstrated that standardized maximin D-optimal designs yield a satisfactory solution to the problem. These designs are usually very efficient for model discrimination. They also allow precise estimation of all coefficients in the original model and in the extended model. The latter property is of particular importance if the assumed model will be rejected by means of a goodness-of-fit test. The standardized maximin D_1-optimal designs are slightly more efficient for model discrimination but have substantially lower efficiencies for estimating the remaining parameters in the extended model and all parameters in the assumed model. For this reason the application of standardized maximin D-optimal designs from the extended model are recommended. We also note that these designs usually have a large number of support points which gives the experimenter the possibility to test the postulated form of the regression model against several other alternatives.

5 Appendix: Proofs

Proof of Lemma 2.1. Note that $|M(\xi, a, b, \lambda, h)| = b^4 |M(\xi, 1, 1, \lambda, h)|$ by elementary properties of the determinant and consequently local D- or D_1-optimal designs do not depend on the parameters a and b. Let $I(x, \lambda, h) = f(x, 1, 1, \lambda, h) f^T(x, 1, 1, \lambda, h)$. The remaining statement of the Lemma follows from identities

$$\det \int_0^{T^h} I(t, \lambda, h) d\xi(t) = \frac{1}{h^2} \det \int_0^{T^h} I(t^h, \lambda, 1) d\xi(t) = \frac{1}{h^2} \det \int_0^{T} I(t, \lambda, 1) d\xi(t^{1/h})$$

and

$$\det \int_0^{T} I(t, r\lambda, 1) d\xi(t) = \frac{1}{r^2} \det \int_0^{T} I(rt, \lambda, 1) d\xi(t) = \frac{1}{r^2} \det \int_0^{rT} I(t, \lambda, 1) d\xi(t/r).$$

□

Proof of Lemma 2.2. Let $g(t) = p^T f(t)$ be an arbitrary linear combination of the functions $1, -e^{-\lambda t}, te^{-\lambda t}, t\ln(t)e^{-\lambda t}$, then it is easy to see that the function $(g'(t)e^{\lambda t})'' = const\,(1 + \lambda t)/t^2$ does not have any roots in the interval $[0, T]$. Consequently, the function $g(t)$ has at most 3 roots, which proves the Chebyshev property for system of functions $1, -e^{-\lambda t}, te^{-\lambda t}, t\ln(t)e^{-\lambda t}$. □

Proof of Theorem 2.3. The proof follows by a standard argument from Lemma 2.2 . To be precise note that Lemma 2.2 shows that the functions $1, e^{-\lambda t}, te^{-\lambda t}, t\ln(t)e^{-\lambda t}$ form a Chebyshev system on the interval $[0, T]$. By similar arguments as given in the proof of this lemma the functions $1, e^{-\lambda t}, te^{-\lambda t}$ form also a Chebyshev system on $[0, T]$. Consequently,

$$\begin{vmatrix} 1 & 1 & 1 & 0 \\ e^{-\lambda x_1} & e^{-\lambda x_2} & e^{-\lambda x_2} & 0 \\ x_1 e^{-\lambda x_1} & x_2 e^{-\lambda x_2} & x_3 e^{-\lambda x_3} & 0 \\ x_1 \ln(x_1) e^{-\lambda x_1} & x_2 \ln(x_2) e^{-\lambda x_2} & x_3 \ln(x_3) e^{-\lambda x_3} & 1 \end{vmatrix} = \begin{vmatrix} 1 & 1 & 1 \\ e^{-\lambda x_1} & e^{-\lambda x_2} & e^{-\lambda x_3} \\ x_1 e^{-\lambda x_1} & x_2 e^{-\lambda x_2} & x_3 e^{-\lambda x_3} \end{vmatrix} \neq 0$$

for all $0 \leq x_1 < x_2 < x_3 \leq T$, and we obtain from Theorem 7.7 (Chap X) in Karlin and Studden (1966) that the local D_1-optimal design is supported at the Chebyshev points. Finally, the assertion regarding the weights of the local D_1-optimal design follows from Pukelsheim and Torsney (1991). $\Box$

Proof of Lemma 2.4. By standard arguments the weights of a local D-optimal 4-point design are equal [see Silvey (1980)]. Note that the determinant of the information matrix in the Weibull regression model (1.2) of a 4-point design with equal weights at the points $t_1, \ldots, t_4$ is given by

$$M(\xi, \theta) \;=\; \Big(\frac{1}{4}\Big)^4 [\tilde{\phi}(t_1, t_2, t_3, t_4)]^2,$$

where the function

$$\tilde{\phi}(t_1, t_2, t_3, t_4) = \det(f(t_1, \theta), f(t_2, \theta), f(t_3, \theta), f(t_4, \theta)) \tag{2.22}$$

is positive for any $t_1 < t_2 < t_3 < t_4$ due to the Chebyshev property of the components of the vector $f(t, \theta) = (1, -e^{-\lambda t}, te^{-\lambda t}, t\ln(t)e^{-\lambda t})^T$. Fix t_1, t_2, t_3 and consider the function $\psi_4(t) = \tilde{\phi}(t_1, t_2, t_3, t)$. Calculating the first derivative yields $\psi_4'(t) > 0$ and consequently the function ψ_4 is strictly increasing. Similarly the function $\psi_1(t) = \tilde{\phi}(t, t_2, t_3, t_4)$ is decreasing with respect to $t < t_1$ (calculate the first derivative and check $\psi_1'(t) < 0$). Consequently the bounds of the design space are support points of the local D-optimal design.
For a 4-point design containing 0 and T as support point it follows that

$$\begin{aligned}
\Phi(t_2, t_3, \lambda) \;&=\; \tilde{\phi}(0, t_2, t_3, T) \\
&=\; (Tt_2 \ln(T/t_2) - t_3 t_2 \ln(t_3/t_2) - Tt_3 \ln(T/t_3))\, e^{-\lambda(t_2+t_3+T)} \\
&\quad\; -Tt_2 \ln(T/t_2)e^{-\lambda(t_2+T)} + t_3 t_2 \ln(t_3/t_2)e^{-\lambda(t_2+t_3)} + Tt_3 \ln(T/t_3)e^{-\lambda(t_3+T)}.
\end{aligned}$$

Note that the equation

$$\frac{\partial \Phi}{\partial t_2}(t_2, t_3) = 0$$

has only one root in the interval $t_2 \in (0, t_3)$ and that the equation

$$\frac{\partial \Phi}{\partial t_3}(t_2, t_3) = 0$$

has only one root in the interval $t_3 \in (t_2, T)$. Consequently the system of these two equations has only one solution and the local D-optimal 4-point design is unique. $\Box$

Proof of Lemma 2.5. Let ξ be k-point design with weights $w_1, \ldots, w_k$ at the support points $t_1 < t_2 < \ldots < t_k$. Due to the Cauchy-Binet formula

$$\det M(\xi, \theta) = \sum_{1 \leq i_1 < i_2 < i_3 < i_4 \leq k} w_{i_1} w_{i_2} w_{i_3} w_{i_4} [\tilde{\phi}(t_{i_1}, t_{i_2}, t_{i_3}, t_{i_4})]^2,$$

where the function $\tilde{\phi}$ is defined in (2.22). It follows from the proof of Lemma 2.4 that $\det M(\xi, \theta)$ is decreasing with respect to the smallest support point t_1 and increasing with respect the largest support t_k. Consequently, the support of any D-optimal design contains the boundary points 0 and T of the experimental domain. $\square$

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Table 1: *Some local D_1-optimal designs in the Weibull regression model (1.2) with design space* $[0, 10]$.

λ	t_1	t_2	t_3	t_4	w_1	w_2	w_3	w_4
0.1	0	1.129	5.959	10	0.268	0.403	0.233	0.097
1	0	0.292	1.839	10	0.229	0.364	0.271	0.136
5	0	0.058	0.368	10	0.229	0.364	0.272	0.136

Table 2: *Some local D-optimal designs in the Weibull regression model (1.2) with design space* $[0, 10]$. *The optimal design has equal masses at the four support points.*

λ	t_1	t_2	t_3	t_4
0.1	0	1.320	5.560	10
0.5	0	0.665	3.096	10
5	0	0.070	0.330	10

Table 3: *Some local D_1-optimal designs in the Richards-regression model (1.5) on the interval* $[0, 10]$, *($t_1 = 0, t_4 = T = 10$).*

b	λ	t_2	t_3	w_1	w_2	w_3	w_4
0.2	0.1	2.099	6.998	0.171	0.336	0.330	0.164
0.2	1	0.496	2.171	0.173	0.323	0.327	0.177
0.2	5	0.099	0.435	0.173	0.322	0.327	0.177
5	0.1	3.125	7.960	0.193	0.347	0.310	0.150
5	1	1.491	3.634	0.291	0.275	0.274	0.161
5	5	0.299	0.729	0.291	0.274	0.274	0.161

Table 4: *Some local D-optimal designs in the Richards-regression model (1.5) on the interval* $[0, 10]$. *The optimal design has equal masses at the four support points* ($t_1 = 0, t_4 = 10$).

b	λ	t_2	t_3
0.2	0.1	2.334	6.708
0.2	1	0.560	2.019
0.2	5	0.112	0.404

b	λ	t_2	t_3
5	0.1	3.425	7.725
5	1	1.587	3.418
5	5	0.318	0.685

Table 5: *Some standardized maximin D-optimal designs in the Weibull regression model (1.2) with respect to the interval* $[\lambda_1, \lambda_2]$. *The design space is the interval* $[0, 10]$.

λ_1	λ_2	t_1	t_2	t_3	t_4	t_5	t_6	w_1	w_2	w_3	w_4	w_5	w_6	min eff
0.6	1	0	0.44	2.08	10			0.25	0.25	0.25	0.25			0.9710
0.6	2.5	0	0.21	0.82	2.39	10		0.24	0.19	0.20	0.15	0.21		0.9149
0.6	4	0	0.13	0.51	1.46	3.11	10	0.23	0.16	0.20	0.12	0.11	0.19	0.8951
0.5	1	0	0.48	2.23	10			0.25	0.25	0.25	0.25			0.9504
0.1	1	0	0.50	1.92	5.27	10		0.24	0.19	0.19	0.16	0.22		0.9153

Table 6: *Some standardized maximin* D_1*-optimal designs in the Weibull regression model (1.2) with respect to the interval* $[\lambda_1, \lambda_2]$. *The design space is the interval* $[0, 10]$.

λ_1	λ_2	t_1	t_2	t_3	t_4	t_5	t_6	w_1	w_2	w_3	w_4	w_5	w_6	min eff
0.6	1	0	0.38	2.22	10			0.24	0.37	0.26	0.13			0.8498
0.6	2	0	0.23	0.96	2.65	10		0.23	0.31	0.19	0.17	0.10		0.6946
0.6	4	0	0.13	0.48	1.34	2.97	10	0.22	0.24	0.21	0.13	0.11	0.09	0.6284
0.5	1	0	0.40	2.00	3.51	10		0.23	0.36	0.19	0.09	0.12		0.7689
0.1	1	0	0.48	1.93	5.26	10		0.24	0.31	0.20	0.16	0.10		0.6816

Table 7: *Comparison of standardized maximin D- and* D_1*-optimal designs for the Weibull regression model with respect to the interval* $[\lambda_1, \lambda_2]$. *The design space is* $[0, 10]$ *and the table shows the efficiencies* $C_i = C_i(\xi^*_{D_1}, \xi^*_D, \lambda)$ *defined by (2.18) in model (1.2) for various values of* $\lambda \in [\lambda_1, \lambda_2]$.

		$\lambda = \lambda_1$				$\lambda = (\lambda_1 + \lambda_2)/2$				$\lambda = \lambda_2$			
λ_1	λ_2	C_1	C_2	C_3	C_4	C_1	C_2	C_3	C_4	C_1	C_2	C_3	C_4
0.6	1	1.86	1.47	1.21	0.82	1.87	1.47	1.34	0.85	1.87	1.47	1.52	0.95
0.6	1.5	1.99	1.60	1.25	0.91	1.71	1.42	1.35	0.88	1.47	1.26	1.27	0.87
0.6	2	2.01	1.61	1.24	0.93	1.63	1.36	1.30	0.87	1.42	1.22	1.18	0.88

Table 8: *Comparison of standardized maximin D- and* D_1*-optimal designs for the Weibull regression model with respect to the interval* $[\lambda_1, \lambda_2]$. *The design space is* $[0, 10]$ *and the table shows the efficiencies* $C_i = C_i(\xi^*_{D_1}, \xi^*_D, \lambda)$ *defined by (2.18) in model (1.1) for various values of* $\lambda \in [\lambda_1, \lambda_2]$.

		$\lambda = \lambda_1$			$\lambda = (\lambda_1 + \lambda_2)/2$			$\lambda = \lambda_2$		
λ_1	λ_2	C_1	C_2	C_3	C_1	C_2	C_3	C_1	C_2	C_3
0.6	1	1.83	1.35	1.33	1.73	1.24	1.37	1.57	1.15	1.30
0.6	1.5	1.90	1.42	1.34	1.53	1.16	1.24	1.35	1.10	1.08
0.6	2	1.94	1.48	1.32	1.49	1.15	1.17	1.33	1.10	1.00

Table 9: *Comparison of standardized maximin D-optimal designs ξ_D^* for the Weibull model (1.2) and standardized maximin D-optimal designs $\tilde{\xi}_D^*$ for the sub-model model (1.1). The design space is $[0, 10]$ and the table shows the quantities $C_i = C_i(\tilde{\xi}_D^*, \xi_D^*, \lambda)$ in the model (1.1).*

		$\lambda = \lambda_1$			$\lambda = (\lambda_1 + \lambda_2)/2$			$\lambda = \lambda_2$		
λ_1	λ_2	C_1	C_2	C_3	C_1	C_2	C_3	C_1	C_2	C_3
0.6	1	0.76	0.90	0.79	0.79	0.93	0.68	0.86	0.96	0.69
0.6	1.5	0.69	0.88	0.82	0.86	0.96	0.68	1.03	0.99	0.89
0.6	2	0.75	0.88	0.89	0.87	0.93	0.92	0.90	0.91	0.96

Table 10: *Statistical analysis of the data in Ratkowsky (1983), p. 88. The table shows the parameter estimates, standard deviations, resulting t-statistic, p-value and the upper (I_U) and lower (I_L) confidence bound.*

θ	estimate	st. dev.	t	p-value	I_L	I_U
a	21.104	0.379	55.683	0.000	20.269	21.938
b	19.815	0.620	31.964	0.000	18.450	21.179
λ	0.0018	0.0010	1.771	0.104	-0.0004	0.0040
h	3.180	0.285	11.170	0.000	2.553	3.806

Table 11: *The quantities (2.20) in the Weibull regression model for the uniform design on the interval $[0.5, 14.5]$ and the standardized maximin D-optimal design in (2.19). First row: asymptotic theory; second row: simulated variances obtained from $N = 15$ observations.*

	D-maximin design				uniform design			
	D_{11}	D_{22}	D_{33}	D_{44}	D_{11}	D_{22}	D_{33}	D_{44}
asymptotic	3.47	8.11	0.000028	2.27	4.27	11.56	0.000031	2.46
finite	3.58	8.43	0.000039	2.66	4.71	11.99	0.000038	2.91

Table 12: *Some standardized maximin D-optimal designs in the Richards-regression model (1.5) on the interval $[0, 10]$ with respect to the parameter space $[b_1, b_2] \times [\lambda_1, \lambda_2]$.*

b_1	b_2	λ_1	λ_2	t_1	t_2	t_3	t_4	t_5	t_6	w_1	w_2	w_3	w_4	w_5	w_6	min eff
0.8	1.2	0.8	1.2	0	0.82	2.48	10			0.25	0.25	0.25	0.25			0.940
0.6	1.4	0.6	1.4	0	0.69	1.84	3.84	10		0.24	0.19	0.20	0.15	0.22		0.901
0.4	1.6	0.4	1.6	0	0.52	1.50	2.91	5.44	10	0.22	0.15	0.19	0.12	0.14	0.19	0.871

Table 13: *Some standardized maximin D_1-optimal designs in the Richards-regression model (1.5) on the interval $[0, 10]$ with respect to the parameter space $[b_1, b_2] \times [\lambda_1, \lambda_2]$.*

b_1	b_2	λ_1	λ_2	t_1	t_2	t_3	t_4	t_5	t_6	w_1	w_2	w_3	w_4	w_5	w_6	min eff
0.8	1.2	0.8	1.2	0	0.71	1.97	3.02	10		0.20	0.30	0.14	0.19	0.16		0.735
0.6	1.4	0.6	1.4	0	0.66	1.19	1.87	3.76	10	0.20	0.25	0.01	0.22	0.18	0.14	0.631
0.4	1.6	0.4	1.6	0	0.55	1.45	2.84	5.22	10	0.19	0.19	0.22	0.16	0.13	0.11	0.578

Table 14: *Comparison of standardized maximin D- and D_1-optimal designs in the Richards-regression model on the interval $[0, 10]$ with respect to various sets $[b_1, b_2] \times [\lambda_1, \lambda_2]$. The table shows the efficiencies $C_i = C_i(\xi^*_{D_1}, \xi^*_D, b, \lambda)$ defined by (2.18) in model (1.5).*

				$\lambda = \lambda_1,\ b = 1$				$\lambda = (\lambda_1 + \lambda_2)/2,\ b = 1$				$\lambda = \lambda_2,\ b = 1$			
b_1	b_2	λ_1	λ_2	C_1	C_2	C_3	C_4	C_1	C_2	C_3	C_4	C_1	C_2	C_3	C_4
0.8	1.2	0.8	1.2	1.55	0.89	0.92	0.90	1.48	1.00	1.08	1.02	1.38	0.98	1.05	0.99
0.7	1.3	0.7	1.3	1.51	0.92	0.93	0.93	1.43	0.91	0.97	0.93	1.28	0.91	0.98	0.92
0.6	1.4	0.6	1.4	1.50	0.95	0.95	0.96	1.40	0.90	0.95	0.91	1.24	0.90	0.97	0.91

Table 15: *Comparison of standardized maximin D- and D_1-optimal designs in the Richards-regression model on the interval $[0, 10]$ with respect to various sets $[b_1, b_2] \times [\lambda_1, \lambda_2]$. The table shows the efficiencies $C_i = C_i(\xi^*_{D_1}, \xi^*_D, b, \lambda)$ defined by (2.18) in model (1.4).*

				$\lambda = \lambda_1,\ b = 1$			$\lambda = (\lambda_1 + \lambda_2)/2,\ b = 1$			$\lambda = \lambda_2,\ b = 1$		
b_1	b_2	λ_1	λ_2	C_1	C_2	C_3	C_1	C_2	C_3	C_1	C_2	C_3
0.8	1.2	0.8	1.2	1.45	1.06	1.19	1.33	1.06	1.19	1.22	1.09	1.14
0.7	1.3	0.7	1.3	1.45	1.06	1.13	1.29	1.06	1.15	1.17	1.10	1.09
0.6	1.4	0.6	1.4	1.48	1.10	1.09	1.28	1.08	1.11	1.15	1.12	1.04