

# Optimal designs for discriminating between dose-response models in toxicology studies

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We consider design issues for toxicology studies when we have a continuous response and the true mean response is only known to be a member of a class of nested models. This class of non-linear models was proposed by toxicologists who were concerned only with estimation problems. We develop robust and efficient designs for model discrimination and for estimating parameters in the selected model at the same time. In particular, we propose designs that maximize the minimum of  $D$ - or  $D_1$ -efficiencies over all models in the given class. We show that our optimal designs are efficient for determining an appropriate model from the postulated class, quite efficient for estimating model parameters in the identified model and also robust with respect to model misspecification. To facilitate the use of optimal design ideas in practice, we have also constructed a website that freely enables practitioners to generate a variety of optimal designs for a range of models and also enables them to evaluate the efficiency of any design.

*Keywords:* continuous design; locally optimal design; maximin optimal design; model discrimination; robust design

## 1. Introduction

This paper addresses design issues for toxicology studies when the primary outcome is continuous and it is not known a priori which model is an appropriate one to use. Such design problems are common; see, for example, [1–3, 11, 12]. In this situation, we may consider a class of plausible models within which we believe lies an adequate model for fitting the data. The issues of interest are how to design the study to choose the most appropriate model from within the postulated class of models and, at the same time, be able to estimate the parameters of the selected model efficiently. Our design decisions include how to select the number of dose levels to observe the continuous outcome, where these levels are and how many repeated observations to take at each of these levels. This work assumes, for the sake of simplicity, that there is only one independent variable, the dose level and only non-sequential designs are considered.

When we have competing models, a design should be able to discriminate among these models and select the most appropriate ones. Dette [5–7] found optimal discrimination designs for polynomial regression models, and Dette and Roeder [9] and Dette and Haller [10] found optimal

discrimination designs for trigonometric and Fourier regression models, respectively.  $T$ -optimal designs are usually used to discriminate between homoscedastic models with normal errors [1–3,12]. For discriminating non-linear models, only numerical results are possible; Lopez-Fidalgo *et al.* [16] investigated optimal designs maximizing a weighted average of two  $T$ -criterion functions and Lopez-Fidalgo *et al.* [17] constructed  $T$ -optimal designs for Michaelis–Menten-like models. When the design problem involves model discrimination and another optimality criterion, the problem is more complicated. Hill *et al.* [12] was among the first to consider studies with two goals: model discrimination and estimation of model parameters. Dette *et al.* [8] gave a concrete example where they wanted to discriminate between the Michaelis–Menten-model and the Emax model and estimate model parameters in an enzyme-kinetic study. A key reason for there having been so little research into such design problems for non-linear models is that there are serious technical difficulties.

The motivation for this work comes from recent proposals by Piersma *et al.* [23], Slob [22], Slob and Pieters [24]) and Moerbeek *et al.* [18] to use the same class of models to study a continuous outcome in toxicological studies. Their interest was only in estimation problems and so they did not consider design issues. Our purpose here is to find an optimal design for identifying an appropriate model within the class of models and, at the same time, provide reliable parameter estimates in the selected model. To do this, we first find locally optimal designs [4]. These designs are the easiest to construct, but they can be sensitive to nominal values and the model specification. To overcome the risk of selecting an inappropriate model, we propose maximin optimal designs that appear to be robust to misspecifications in the model. These maximin optimal designs maximize the minimum efficiency, regardless of which model in the class of models is the appropriate one. As such, these optimal designs provide some global protection against selecting the wrong model from the postulated class of models. As we will show, the designs also seem quite robust to misspecification in the nominal values of the model parameters.

In Section 2, we present some background and the proposed class of models. We describe relationships between models in the class and provide locally optimal designs for discriminating between plausible models. We also show how optimal designs constructed for one set of design parameters can be used to deduce the optimal design under another set of design parameters. In Section 3, we construct maximin optimal designs for various subclasses of plausible models and in Section 4, we show that maximin optimal designs are robust to misspecification of models in the postulated class. We offer a conclusion in Section 5 and an Appendix containing technical justifications of our results.

## 2. A class of dose-response models

In a general non-linear regression model, the mean response of the outcome  $Y$  is given by  $E[Y|t] = \eta(t, \theta)$ , where we assume the unknown parameter  $\theta$  is  $m$ -dimensional. The class of models proposed by toxicologists assumes all errors are independent and normally distributed, and  $\eta(t, \theta)$  has one of the following forms defined on a user-selected interval  $[0, T]$ :

$$\eta(t, \theta) = a; \quad m = 1, \quad \theta = a > 0, \quad (2.1)$$

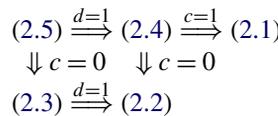
$$\eta(t, \theta) = ae^{-bt}; \quad m = 2, \quad \theta = (a, b)^T, a > 0, b > 0, \quad (2.2)$$

$$\eta(t, \theta) = ae^{-bt^d}; \quad m = 3, \quad \theta = (a, b, d)^T, a, b > 0, d \geq 1, \tag{2.3}$$

$$\eta(t, \theta) = a(c - (c - 1)e^{-bt}); \quad m = 3, \quad \theta = (a, b, c)^T, a, b > 0, c \in [0, 1], \tag{2.4}$$

$$\eta(t, \theta) = a(c - (c - 1)e^{-bt^d}); \quad m = 4, \\ \theta = (a, b, c, d)^T, a, b > 0, c \in [0, 1], d \geq 1. \tag{2.5}$$

The rationale for this class of models was given for dose-response relationships that cannot be derived from biological mechanisms. The models are nested, in the sense that the models with a smaller number of parameters can be obtained from another model by setting specific values for the parameters. For instance, model (2.5) is an extension of the models (2.4) and (2.3), model (2.3) is an extension of model (2.2) and model (2.4) is an extension of the models (2.2) and (2.1). The hierarchy of the models is illustrated in the following diagram.



We note that when  $b = 0$ , all of the models (2.2)–(2.5) reduce to the constant model (2.1), this relation not being shown in the diagram.

Following [15], we consider only continuous designs. A continuous design is simply a probability measure  $\xi$  with a finite number of support points, say  $t_1, \dots, t_n \in [0, T]$ , and corresponding weights  $\omega_1, \dots, \omega_n$  with  $\omega_i > 0$  and  $\sum_{i=1}^n \omega_i = 1$ . If we fix the number of observations  $N$  in advance, either by cost or time considerations, then, roughly,  $n_i = N\omega_i$  observations are taken at point  $t_i$ , with  $\sum_{i=1}^n n_i = N$ . For many problems, continuous designs are easier to describe and study analytically than exact designs.

Jennrich [13] showed that under regularity assumptions, the asymptotic covariance matrix of the standardized least-squares estimator  $\sqrt{N/\sigma^2} \hat{\theta}$  for the parameter  $\theta$  in the general non-linear model is given by the matrix  $M^{-1}(\xi, \theta)$ , where

$$M(\xi, \theta) = \int_0^T f(t, \theta) f^T(t, \theta) d\xi(t)$$

is the information matrix using design  $\xi$  and

$$f(t, \theta) = \frac{\partial \eta(t, \theta)}{\partial \theta} = (f_1(t, \theta), \dots, f_m(t, \theta))^T \tag{2.6}$$

is the vector of partial derivatives of the conditional expectation  $\eta(t, \theta)$  with respect to the parameter  $\theta$ . Additionally, we consider only designs with a non-singular information matrix. A sufficient condition for this property to hold is that the design has  $k$  support points, where  $k$  is greater than or equal to the number of parameters in the model.

A locally optimal design maximizes a function of the information matrix  $M(\xi, \theta)$  using nominal values of  $\theta$  [4]. There are several optimality criteria for estimating purposes and for discriminating between models [1,20]. We are interested in finding efficient designs for model selection

among models defined by (2.1)–(2.5) that also provide good and robust estimates for the parameters in the selected model. Accordingly, we construct an optimal design for pairs of competing models that fulfills at least two of three following requirements:

- (1) The design should be able to test the hypotheses for discriminating between two selected rival models. For example, the hypothesis for discriminating between the models (2.4) and (2.2) is given by

$$H_0 : c = 0 \quad \text{vs.} \quad H_1 : c \in (0, 1].$$

Van der Vaart [25] described properties of test statistics for testing such hypotheses.

- (2) The design should be able to efficiently estimate the parameters in the corresponding pair of regression models and for all models which are submodels of the model with the larger number of parameters. For example, for model (2.4), the corresponding submodels are given by (2.2) and (2.3).
- (3) The design should also be efficient for discriminating between the different submodels of the model with the larger number of parameters (which may also be nested). For example, the optimal design for discriminating between the models (2.2) and (2.4) should also be efficient for discriminating between the models (2.1)/(2.4) and (2.1)/(2.2).

To make these ideas concrete, consider the  $e_m$ -optimality criterion, where  $e_m = (0, \dots, 0, 1)^T$  and  $m$  is the larger of the number of parameters in the two models under consideration. For fixed  $\theta$ , a locally  $e_m$ -optimal design minimizes

$$e_m^T M^{-1}(\xi, \theta) e_m = \frac{\det \tilde{M}(\xi, \theta)}{\det M(\xi, \theta)}, \tag{2.7}$$

where the matrix  $M(\xi, \theta)$  is the information matrix in the model with the larger number of parameters and the matrix  $\tilde{M}(\xi, \theta)$  is obtained from  $M(\xi, \theta)$  by deleting the  $m$ th row and the  $m$ th column. A locally  $e_m$ -optimal design is just a special case of a  $c$ -optimal design used for estimating  $c^T \theta$ , where the vector  $c$  is user-specified.

The expression (2.7) is proportional to the asymptotic variance of the least-squares estimate of  $e_m^T \theta$ , which is relevant for model discrimination. In particular, minimizing the asymptotic variance (2.7) provides a design with maximal power for testing a simple hypothesis for  $e_m^T \theta$ . For example, if we want to discriminate between models (2.4) and (2.2), we have  $m = 3$  and  $e_m^T \theta = (0, 0, 1)(a, b, c)^T = c$ , and the cases  $c \neq 0$  and  $c = 0$  give the two rival models (2.4) and (2.2), respectively. Consequently, a design that minimizes the ratio in (2.7) is optimal for discriminating between the two models.

We next construct locally  $e_m$ -optimal designs for discriminating between pairs of models (2.3)–(2.5).

### 2.1. Optimal discriminating designs for the models (2.2) and (2.3)

For model (2.3) with  $\theta = (a, b, d)^T$ , the vector of partial derivatives in (2.6) is given by

$$f(t, \theta) = f(t, a, b, d) = (e^{-bt^d}, -at^d e^{-bt^d}, -abt^d \ln(t)e^{-bt^d})^T. \tag{2.8}$$

Our first result establishes basic properties of locally  $e_3$ -optimal designs for model (2.3).

**Lemma 2.1.** *The locally  $e_3$ -optimal design in model (2.3) does not depend on the parameter  $a$ . Moreover, if  $t_i(b, d, T)$  is a support point of a locally  $e_3$ -optimal design on the interval  $[0, T]$  with corresponding weight  $\omega_i(b, d, T)$ , then for any  $r > 0$  and  $d > 0$ ,*

$$\begin{aligned}
 t_i(b, d, T^{1/d}) &= t_i(b, 1, T)^{1/d}, & \omega_i(b, d, T^{1/d}) &= \omega_i(b, 1, T), \\
 t_i(rb, 1, T) &= \frac{1}{r}t_i(b, 1, rT), & \omega_i(rb, 1, T) &= \omega_i(b, 1, rT).
 \end{aligned}
 \tag{2.9}$$

To find an efficient design for discriminating between models (2.2) and (2.3), we assume that the initial parameter value of  $d$  is unity. From the lemma, it is enough to calculate locally  $e_3$ -optimal designs on a fixed design space for various values of  $b$  after the remaining parameters  $a$  and  $d$  are fixed. Locally optimal designs on a different design space or having other values of the parameters can then be calculated using the relationships given in the lemma.

To characterize locally  $e_3$ -optimal designs, we recall that a set of functions  $h_1, \dots, h_k : I \rightarrow \mathbb{R}$  is a *Chebyshev system* on the interval  $I$  if there exists an  $\varepsilon \in \{-1, 1\}$  such that the inequality

$$\varepsilon \cdot \begin{vmatrix} h_1(t_1) & \dots & h_1(t_k) \\ \vdots & \ddots & \vdots \\ h_k(t_1) & \dots & h_k(t_k) \end{vmatrix} > 0$$

holds for all  $t_1, \dots, t_k \in I$  with  $t_1 < t_2 < \dots < t_k$ . From Karlin and Studden [14], Theorem II 10.2, if  $\{h_1, \dots, h_k\}$  is a Chebyshev system, then there exists a unique function, say  $\sum_{i=1}^k c_i^* h_i(t) = c^{*T} h(t)$ , where  $h = (h_1, \dots, h_k)^T$ , with the following properties:

- (i)  $|c^{*T} h(t)| \leq 1 \forall t \in I$ ;
- (ii) there exist  $k$  points,  $t_1^* < \dots < t_k^*$ , such that  $c^{*T} h(t_i^*) = (-1)^i, i = 1, \dots, k$ .

The function  $c^{*T} h(t)$  alternates at the points  $t_1^*, \dots, t_k^*$  and is called the *Chebyshev polynomial*. The points  $t_1^*, \dots, t_k^*$  are called *Chebyshev points* and they are unique when  $1 \in \text{span}\{h_1, \dots, h_k\}$ ,  $k \geq 1$  and  $I$  is a compact interval. In this case, we have  $t_1^* = \min_{t \in I} t, t_k^* = \max_{t \in I} t$ . The following result characterizes the locally  $e_3$ -optimal design.

**Theorem 2.1.** *The components of the vector defined by (2.8) form a Chebyshev system on the interval  $[0, T]$ . The locally  $e_3$ -optimal design for model (2.3) is unique and is supported at the three uniquely determined Chebyshev points, say  $t_1^* < t_2^* < t_3^*$ . The corresponding weights  $\omega_1^*, \omega_2^*, \omega_3^*$  can be obtained explicitly as*

$$\omega^* = (\omega_1^*, \omega_2^*, \omega_3^*)^T = \frac{JF^{-1}e_3}{1_3 JF^{-1}e_3},
 \tag{2.10}$$

where the matrices  $F$  and  $J$  are defined by  $F = (f(t_1^*, \theta), f(t_2^*, \theta), f(t_3^*, \theta))$ ,  $J = \text{diag}(1, -1, 1)$ , respectively, and  $1_3 = (1, 1, 1)^T$ .

Table 1 displays selected locally  $e_3$ -optimal designs for model (2.3).

**Table 1.** Locally  $e_3$ -optimal designs for models (2.3) and (2.4) on the design space  $[0, 1]$  for various values of the parameter  $b$

$b$	Model (2.3)						Model (2.4)					
	$t_1$	$t_2$	$t_3$	$\omega_1$	$\omega_2$	$\omega_3$	$t_1$	$t_2$	$t_3$	$\omega_1$	$\omega_2$	$\omega_3$
0.1	0	0.355	1	0.311	0.500	0.189	0	0.492	1	0.242	0.500	0.259
0.5	0	0.305	1	0.294	0.493	0.213	0	0.458	1	0.212	0.492	0.296
1.0	0	0.251	1	0.276	0.473	0.251	0	0.418	1	0.180	0.469	0.351
2.0	0	0.167	1	0.241	0.403	0.356	0	0.343	1	0.127	0.384	0.490
3.0	0	0.112	0.751	0.232	0.381	0.387	0	0.281	1	0.083	0.267	0.650

### 2.2. Optimal discriminating designs for the models (2.3) and (2.4), (2.1) and (2.4)

For model (2.4), we have  $\theta = (a, b, c)^T$  and when  $c = 0$  or  $c = 1$ , model (2.4) reduces to model (2.3) or (2.1), respectively. The  $e_3$ -optimal design is optimal for discriminating between models (2.3) and (2.4) and for discriminating between models (2.1) and (2.4). The vector of partial derivatives in (2.6) is

$$f(t, \theta) = f(t, a, b, c) = (c - (c - 1)e^{-bt}, a(c - 1)te^{-bt}, a(1 - e^{-bt}))^T$$

and its components form a Chebyshev system on  $[0, T]$ . The locally  $e_3$ -optimal design is described in Theorem 2.2 and we observe that it does not depend on the parameter  $a$ . For other positive values of  $b$  and  $T$ , the support points  $t_i(b, T)$  and corresponding weights  $\omega_i(b, T)$  of the optimal design are found from  $t_i(rb, T) = \frac{1}{r}t_i(b, rT)$  and  $\omega_i(rb, T) = \omega_i(b, rT)$ .

**Theorem 2.2.** *Let  $0 \leq c < 1$ . The locally  $e_3$ -optimal design for model (2.4) on  $[0, T]$  is unique and has three points at  $t_1^* = 0$ ,  $t_3^* = T$  and (middle point)*

$$t_2^* = \frac{1}{b} + \frac{t_1^*e^{-bt_1^*} - t_3^*e^{-bt_3^*}}{e^{-bt_1^*} - e^{-bt_3^*}},$$

and the corresponding weights  $\omega_1^*$ ,  $\omega_2^*$  and  $\omega_3^*$  can be obtained explicitly from formula (2.10).

### 2.3. Optimal discrimination designs for the models (2.4) and (2.5), (2.1) and (2.5), (2.3) and (2.5)

Model (2.5) with  $\theta = (a, b, c, d)^T$  reduces to model (2.3), (2.1) or (2.4) when  $c = 0$ ,  $c = 1$  or  $d = 1$ , respectively. For testing purposes, we want an  $e_3$ -optimal design for estimating the parameter  $c$  and an  $e_4$ -optimal design for estimating the parameter  $d$ . The vector of partial derivatives of  $\eta$  for model (2.5) is

$$f(t, \theta) = (c - (c - 1)e^{-bt^d}, a(c - 1)t^d e^{-bt^d}, a(c - 1)t^d \ln(t)be^{-bt^d}, a(1 - e^{-bt^d}))^T \quad (2.11)$$

**Table 2.** Locally  $e_3$ - and  $e_4$ -optimal designs for model (2.5) on the design space  $[0, 1]$  for various values of the parameter  $b$

$b$	$t_1$	$t_2$	$t_3$	$t_4$	$e_3$ -optimal				$e_4$ -optimal			
					$\omega_1$	$\omega_2$	$\omega_3$	$\omega_4$	$\omega_1$	$\omega_2$	$\omega_3$	$\omega_4$
0.1	0	0.131	0.648	1	0.286	0.416	0.214	0.084	0.174	0.328	0.326	0.172
0.5	0	0.123	0.626	1	0.277	0.410	0.223	0.090	0.156	0.302	0.342	0.200
1.0	0	0.113	0.596	1	0.267	0.403	0.233	0.097	0.137	0.272	0.352	0.239
2.0	0	0.094	0.530	1	0.253	0.392	0.246	0.108	0.106	0.215	0.341	0.338
3.0	0	0.079	0.463	1	0.244	0.382	0.256	0.118	0.080	0.163	0.289	0.468

and its components form a Chebyshev system on the interval  $[0, T]$ . Arguments similar to those given in the proof of Lemma 2.1 show that the support points  $t_i(b, d, T)$  and weights  $\omega_i(b, d, T)$  of a locally  $e_3$ - or  $e_4$ -optimal design on the interval  $[0, T]$  satisfy relations (2.9). Moreover, the optimal designs do not depend on the parameter  $a$ . Table 2 shows some locally  $e_3$ - and  $e_4$ -optimal designs for model (2.5) obtained from Theorem 2.3 below. The proof is similar to the proof of Theorem 2.1 and is therefore omitted.

**Theorem 2.3.** *The  $e_3$ - and  $e_4$ -optimal designs for model (2.5) are uniquely supported at the four Chebyshev points, say  $t_1^* < t_2^* < t_3^* < t_4^*$ , corresponding to the Chebyshev system defined by the components in (2.11). The corresponding weights,  $\omega_1^*, \dots, \omega_4^*$ , are explicitly given by*

$$\omega^* = (\omega_1^*, \dots, \omega_4^*)^T = \frac{JF^{-1}e_k}{1_4 JF^{-1}e_k}, \quad k = 3, 4,$$

where the matrices  $F$  and  $J$  are defined by  $F = (f(t_1^*, \theta), f(t_2^*, \theta), f(t_3^*, \theta), f(t_4^*, \theta))$ ,  $J = \text{diag}(1, -1, 1, -1)$ , respectively,  $1_4 = (1, 1, 1, 1)^T$  and  $f(t, \theta)$  is given in (2.11).

### 3. Maximin optimal discriminating designs

We now wish to find an efficient design for testing several hypotheses that discriminate between models (2.3) and (2.2), (2.4) and (2.2), (2.5) and (2.3), and (2.5) and (2.4).

Let us first find an optimal design to discriminate between two models (2. $i$ ) and (2. $j$ ) and let  $\text{eff}^{(2.i)-(2.j)}(\xi, \theta)$  be the efficiency of the design  $\xi$  for discriminating between the two models. As an illustrative case, consider finding the locally optimal design for discriminating between the models (2.3) and (2.2). This optimal design minimizes  $e_3^T M_{(2.3)}^{-1}(\xi, \theta)e_3$  among all designs for which the matrix is regular (Theorem 2.1). Here, the matrix  $M_{(2.3)}(\xi, \theta)$  is the information matrix under model (2.3). If  $\xi_3^*(\theta)$  is the locally optimal design for discriminating between models (2.3) and (2.2), then the efficiency of a design  $\xi$  for discriminating between models (2.3)–(2.2) is

defined by

$$\text{eff}^{(2.3)-(2.2)}(\xi, \theta) = \frac{e_3^T M_{(2.3)}^{-1}(\xi_3^*(\theta), \theta) e_3}{e_3^T M_{(2.3)}^{-1}(\xi, \theta) e_3}.$$

This ratio is between 0 and 1; if the value is 0.5, this means that twice as many observations are required from the design  $\xi$  than the optimal design to discriminate between the two models with the same level of precision. The efficiencies of  $\xi$  for discriminating between other pairs of models are similarly defined and denoted by  $\text{eff}^{(2.4)-(2.2)}(\xi, \theta)$ ,  $\text{eff}^{(2.5)-(2.3)}(\xi, \theta)$  and  $\text{eff}^{(2.5)-(2.4)}(\xi, \theta)$ . Here, and elsewhere in our work, we remind readers that we assume  $\theta$  to be fixed throughout and so all optimal designs are only locally optimal.

Next, we use the maximin efficient approach proposed by Dette [7] and Müller [19] to find efficient designs for all four discrimination problems. For a fixed  $\theta$ , we call a design a *maximin optimal discriminating design* for models (2.1)–(2.5) if it maximizes

$$\min\{\text{eff}^{(2.3)-(2.2)}(\xi, \theta), \text{eff}^{(2.4)-(2.2)}(\xi, \theta), \text{eff}^{(2.5)-(2.3)}(\xi, \theta), \text{eff}^{(2.5)-(2.4)}(\xi, \theta)\}. \quad (3.1)$$

In practice, maximin optimal discriminating designs have to be found numerically. All computations for the optimal designs were done sequentially using the Nelder–Mead algorithm in the MATLAB package. First, maximin designs were found by maximizing the optimality criterion within the class of all 4-point designs. We started with four points because that was the number of points required for obtaining all non-zero efficiencies in (3.1). After the 4-point optimal design was found, we searched for the optimal design within the class of all 5-points designs and repeated the procedure. Each time, we increased the number of points by unity, until there was no further improvement in the criterion value. Table 3 shows maximin optimal discriminating designs and their efficiencies when  $\theta = (a, b, d, c)^T = (1, b, 1, 0)^T$  for different values of  $b$ . We observe from the rightmost columns in the table that the maximin optimal discriminating design has between 68–85% efficiency for discriminating between different pairs of rival models from the postulated class.

**Table 3.** Maximin optimal discriminating designs for the optimality criterion (3.1) on the design space  $[0, 1]$  and their efficiencies

$b$	$t_1$	$t_2$	$t_3$	$t_4$	$\omega_1$	$\omega_2$	$\omega_3$	$\omega_4$	(2.3)–(2.2)	(2.4)–(2.2)	(2.5)–(2.3)	(2.5)–(2.4)
0.1	0	0.175	0.552	1	0.236	0.255	0.322	0.187	0.724	0.724	0.724	0.786
0.5	0	0.170	0.531	1	0.220	0.260	0.308	0.212	0.719	0.719	0.719	0.787
1.0	0	0.160	0.507	1	0.200	0.265	0.287	0.249	0.714	0.714	0.714	0.793
2.0	0	0.130	0.468	1	0.161	0.250	0.249	0.340	0.705	0.702	0.702	0.848
3.0	0	0.105	0.440	1	0.141	0.233	0.199	0.427	0.705	0.682	0.682	0.871

### 4. Efficiencies of maximin optimal designs for estimating model parameters under model uncertainty

We now investigate the performance of maximin discrimination designs for estimating parameters in the different models. We first present results for estimating each parameter in the model and  $D$ -efficiencies of the maximin discrimination design for estimating all parameters in the model. We recall that  $D$ -efficiencies are computed relative to the  $D$ -optimal design for the specific model and  $D$ -optimal designs are found by maximizing the determinant of the expected information matrix over all designs on the design space.  $D$ -optimal designs are appealing because they minimize the generalized variance and thereby provide the smallest volume of the confidence ellipsoid for all parameters in the mean function.

Table 4 displays efficiencies of selected maximin optimal discriminating designs for estimating the individual parameters in the four models. The efficiencies for estimating the parameter  $a$  are consistently the lowest and efficiencies for estimating the parameters  $b, c$  and  $d$  tend to be sequentially higher for each model. It is not surprising to observe that the efficiencies are highest for estimating the particular parameter that sets the two models apart.

Table 5 shows  $D$ -efficiencies of the maximin optimal discriminating designs in Table 3. These are efficiencies relative to each of the locally  $D$ -optimal designs found for each model in the class. For the values of  $b$  in Table 5, all efficiencies are high. Recall that the optimal discriminating designs were constructed for discriminating between models (2.2) and (2.3). We observe that these efficiencies are highest for the most complicated model, (2.5), averaging 96%, while the efficiencies are about 67% for the least complicated model, (2.2). This implies that the maximin optimal designs are quite robust to misspecification of models within the class of models and also quite insensitive to small changes to the nominal values of the parameter  $b$  common to all of the models. In models (2.2) and (2.3), the  $D$ -efficiencies drop by roughly 15% when the nominal value of  $b$  is increased from 2 to 3.

**Table 4.** Efficiencies of the maximin optimal discriminating designs in Table 3 for estimating individual coefficients in models (2.2)–(2.5); the first two columns are efficiencies for estimating  $a$  and  $b$  in model (2.2), the next three columns are for estimating  $a, b$  and  $d$  in model (2.3), the next three columns are efficiencies for estimating  $a, b$  and  $c$  in model (2.4) and the last four columns are for estimating  $a, b, c$  and  $d$  in model (2.5)

$b$	Model (2.2)		Model (2.3)			Model (2.4)			Model (2.5)			
	eff <sub>1</sub>	eff <sub>2</sub>	eff <sub>1</sub>	eff <sub>2</sub>	eff <sub>3</sub>	eff <sub>1</sub>	eff <sub>2</sub>	eff <sub>3</sub>	eff <sub>1</sub>	eff <sub>2</sub>	eff <sub>3</sub>	eff <sub>4</sub>
0.1	0.42	0.495	0.26	0.495	0.724	0.30	0.726	0.724	0.24	0.784	0.724	0.786
0.5	0.37	0.501	0.25	0.490	0.719	0.27	0.725	0.719	0.22	0.773	0.719	0.787
1.0	0.32	0.545	0.22	0.495	0.714	0.25	0.716	0.714	0.20	0.760	0.714	0.793
2.0	0.24	0.609	0.17	0.325	0.705	0.21	0.661	0.702	0.16	0.759	0.702	0.849
3.0	0.20	0.429	0.15	0.514	0.705	0.18	0.560	0.682	0.14	0.708	0.682	0.871

**Table 5.**  $D$ -efficiencies of maximin designs in Table 3 under various model assumptions

$b$	$\text{eff}_D^{(2.2)}$	$\text{eff}_D^{(2.3)}$	$\text{eff}_D^{(2.4)}$	$\text{eff}_D^{(2.5)}$
0.1	0.710	0.851	0.851	0.963
0.5	0.737	0.862	0.861	0.968
1.0	0.786	0.873	0.869	0.972
2.0	0.703	0.864	0.860	0.959
3.0	0.525	0.716	0.820	0.917

## 5. Conclusions

Our work is motivated by toxicologists' recent interest in a class of non-linear nested models for studying a continuous outcome. The toxicologists were primarily interested in estimating parameters or a function of model parameters. The designs employed in their studies lacked justification. Our work addresses design issues for such a problem, where there is model uncertainty and all candidate models are non-linear models nested within one another. The proposed optimal designs are efficient for model discrimination and parameter estimation. Previous design work for discriminating between non-linear models usually focused on two rival models; our work finds efficient and analytic locally optimal discriminating designs for discriminating between pairs of models within the predetermined class.

Our proposed optimal designs were constructed using large-sample theory. The variances of the estimated parameters were obtained via the asymptotic covariance matrix that our optimal designs used to minimize the asymptotic variances. It is reasonable to ask whether the asymptotic variance is a good approximation to the actual variance of the estimated parameters encountered in practice with realistic sample size. We performed a small simulation study using the setup in [23], where rats were prenatally exposed to diethylstilbestrol and the design  $\xi_u$  had 6 animals in each of the 10 dose groups at 0, 1.0, 1.7, 2.8, 4.7, 7.8, 13, 22, 36 and 60 mg/kg body weight per day. In total, there were 60 observations from the dose interval [0, 60]. The maximin optimal design  $\xi_{mm}$  for  $b = 0.1$ ,  $d = 1$ ,  $c = 0$  requires 7 rats at the 0 dose, 12 rats at the 3.6 dose, 13 rats at the 24 dose and 28 at the 60 dose.

We simulated data with  $a = 1$ ,  $\sigma = 0.05$  and several values of the parameters  $b$ ,  $d$  and  $c$ . A total of 1000 repetitions were used in each simulation. In Table 6, we report simulated normalized variances of least-squares estimated parameters that are most important for discrimination. We see that in all of the cases we investigated, the variances using the maximin optimal design  $\xi_{mm}$  are smaller than the variances obtained from the design  $\xi_u$  of Piersma *et al.*, in many cases by a huge margin. This shows the benefits of incorporating optimal design ideas into the design of a toxicology study. The design of Piersma *et al.* was not theory-based and required more dose levels, which usually translated to higher labor, material and time costs without gain in precision for the estimates relative to the optimal design. Additional simulation results not shown here confirm that the asymptotic variances are close to the simulated variances.

Finally, we mention that, in principle, the approach presented here can be applied to discriminate between models when the difference between the dimensions of the null hypothesis and the alternative is greater than 1. For example, suppose that we wish to discriminate between

**Table 6.** Simulated normalized variances of some parameters in models (2.4)–(2.6) for several true values of parameters (left three columns)

<i>b</i>	<i>d</i>	<i>c</i>	Maximin design $\xi_{mm}$				Design $\xi_u$			
			(2.4) var( $\hat{d}$ )	(2.5) var( $\hat{c}$ )	(2.6) var( $\hat{d}$ )	(2.6) var( $\hat{c}$ )	(2.4) var( $\hat{d}$ )	(2.5) var( $\hat{c}$ )	(2.6) var( $\hat{d}$ )	(2.6) var( $\hat{c}$ )
0.10	1.0	0.0	58.85	2.02	71.07	2.48	62.73	5.53	88.42	7.81
0.10	0.8	0.0	30.38	5.39	83.93	28.91	34.93	26.72	86.34	58.80
0.10	1.0	0.2	11.86	1.96	103.40	2.79	18.43	4.83	138.97	7.77
0.10	0.8	0.2	19.39	4.21	135.00	35.91	23.57	10.88	148.29	81.56
0.06	1.0	0.0	61.67	3.91	103.78	7.17	61.62	11.35	115.70	23.33
0.08	1.0	0.1	22.58	2.47	92.44	3.68	36.83	6.48	113.39	10.80

model (2.2) and the model with mean response given by  $a + b_1e^{c_1t} + b_2t$ . In this case, the design maximizing the non-centrality parameter of the likelihood ratio test depends on the values of the parameters of the larger model. The extension of our procedure to  $D_s$ -optimal designs for minimizing the volume of the confidence ellipsoid for the parameters  $(b_1, b_2)$  would still work, but some efficiency would be lost.

To facilitate the use of optimal designs for practitioners, we have created a website that freely generates different types of tailor-made optimal designs for various popular models.

We are currently refining the computer algorithms for generating optimal designs discussed here and plan to upload them to the site at <http://optimal-design.biostat.ucla.edu/optimal>. We hope that the site will stimulate interest in design issues, inform practitioners and enable them to incorporate optimal design ideas into their work.

## Appendix: Proofs of Lemma 2.1 and Theorem 2.1

### A.1. Proof of Lemma 2.1

Let  $I(t, a, b, d) = f(t, a, b, d)f^T(t, a, b, d)$ , where  $f(t, a, b, d)$  is given in (2.8). Lemma 2.1 follows from the identities

$$\det \int_0^T I(t, a, b, d) d\xi(t) = \gamma \det \int_0^{T^d} I(t^d, 1, b, 1) d\xi(t) = \gamma \det \int_0^T I(t, 1, b, 1) d\xi(t^{1/d})$$

and

$$\det \int_0^T I(t, a, rb, 1) d\xi(t) = \gamma' \det \int_0^T I(rt, 1, b, 1) d\xi(t) = \gamma' \det \int_0^T I(t, 1, b, 1) d\xi(t/r),$$

where  $\gamma$  and  $\gamma'$  denote appropriate constants.

## A.2. Proof of Theorem 2.1

Let  $g(t) = p^T f(t)$  be an arbitrary linear combination of the functions  $e^{-bt}$ ,  $-te^{-bt}$  and  $-t \ln(t)e^{-bt}$ . One can show that  $(g(t)e^{bt})'' = c/t$  does not have any roots in the interval  $[0, T]$  and so the function  $g(t)$  has at most two roots. This proves that the system of functions  $e^{-bt}$ ,  $-te^{-bt}$ ,  $-t \ln(t)e^{-bt}$  has the Chebyshev property and this argument also shows that there exist precisely three Chebyshev points.

The proof of the remaining part now follows by a standard argument in classical optimal design theory. After showing that the functions  $e^{-bt}$ ,  $-te^{-bt}$  form a Chebyshev system on the interval  $[0, T]$ , we have

$$\begin{vmatrix} e^{-bt_1} & e^{-bt_2} & 0 \\ -t_1 e^{-bt_1} & -t_2 e^{-bt_2} & 0 \\ -t_1 \ln(t_1) e^{-bt_1} & -t_2 \ln(t_2) e^{-bt_2} & 1 \end{vmatrix} = \begin{vmatrix} e^{-bt_1} & e^{-bt_2} \\ -t_1 e^{-bt_1} & -t_2 e^{-bt_2} \end{vmatrix} \neq 0$$

for all  $0 \leq t_1 < t_2 \leq T$  and, consequently, from [14], Theorem 7.7, the locally  $e_3$ -optimal design is supported at the Chebyshev points. The assertion on the weights of the locally  $e_3$ -optimal design follows from [21].

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