Optimal designs for dose finding experiments in toxicity studies

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December 10, 2007

Abstract

We construct optimal designs for estimating fetal malformation rate, prenatal death rate and an overall toxicity index in a toxicology study under a broad range of model assumptions. We use Weibull distributions to model these rates and assume that the number of implants depend on the dose level. We study properties of the optimal designs when the intra-litter correlation coefficient depends on the dose levels in different ways. Locally optimal designs are found, along with robustified versions of the designs that are less sensitive to mis-specification in the nominal values of the model parameters. We also report efficiencies of commonly used designs in toxicological experiments and efficiencies of the proposed optimal designs when the true rates have non-Weibull distributions. Optimal design strategies for finding multiple-objective designs in toxicology studies are outlined as well.

AMS Subject Classification: 62K05
Keywords and Phrases: Weibull model, dose finding experiment, locally c-optimal design, multiple-objective design, robust optimal design.

1 Introduction

Developmental toxicity studies play an important role in identifying substances that may pose a danger to developing fetuses, including prenatal death and malformation among live fetuses. Krewski and Zhu (1995) and Zhu, Krewksi and Ross (1994) demonstrate that joint dose-response models for describing prenatal death and fetal malformation in developmental toxicity experiments have a good agreement with real data. These models can be used to estimate the effective dose corresponding to a gene excess risk for both these toxicological end points, as well as for overall toxicity. It appears that toxicologists are generally less lamented and less receptive to a more rigorous treatment of design issues; see a recent article in Nature (Giles, 2006) where the author expounded on the lack of sophistication in current designs for animal experiments. Very recently there are a handful of theoretical articles that utilize statistical principles to design toxicology studies. This paper follows this trend and discusses how one may construct efficient designs for estimating malformation rate, prenatal death and overall toxicity levels under a broad range of model assumptions. A scientific sound and efficient study is crucial because toxicology studies are increasingly more expensive in terms of time and labor. An efficient design also means that potentially a lot fewer animals are required in the experiment. In what is to follow, our designs for such experiments are specified in terms of the number of doses to be used, the dose spacing, and the proportion of animals to be assigned to each dose.

Recently, Krewski, Smythe and Fung (2002) studied locally optimal designs for the estimation of the effective dose using joint Weibull dose-response models. The locally optimal designs depend on the parameters of the Weibull model and the degree of intra-litter correlation. This paper addresses several important design issues in toxicology, such as estimating benchmark doses. Estimating benchmark doses has a long history in toxicological studies and research continues to this day; some recent papers include (Woutersen, et al., 2001, Moerbeek, et al., 2004, Slob, et al., 2005). As in Krewski, Smythe and Fung (2002), we seek optimal experimental designs that minimize the variance of the estimated effective doses for prenatal death and overall toxicity given the number of implants. These are two important and common end points measuring tetratogenicity (embryotoxicity) in animal studies (Zhu, Krewski and Ross, 1994). However, in contrast to these authors, who concentrated on locally optimal designs and the numerical calculation of optimal design, we present a more sophisticated analysis of the optimal design problem for developmental toxicity experiments. First, we derive analytical properties of locally optimal designs for estimating the benchmark dose of prenatal death. In particular we prove several results on the number and levels of doses and invariance properties of the locally optimal designs. Moreover, we correct an error in the work of Krewski, Smythe and Fung (2002), who used the wrong information matrix for the construction of the optimal designs. Second, we study the robustness properties of locally optimal designs with respect to mis-specification of the initial parameters. Third, we construct locally optimal designs for estimating the effective dose of overall toxicity and investigate the performance of the locally optimal designs of prenatal death for this purpose. Fourth, we construct designs that are robust with respect to mis-specification of the initial parameters, and so mitigate a concern raised by some toxicologists. We also investigate relative efficiencies of popular designs and other designs that have been recently used in

developmental toxicity experiments.

Section 2 gives statistical background for our models, which were recently proposed in the literature for developmental toxicity studies. In Section 3 we present analytical results for locally optimal designs for estimating the effective dose of prenatal death and investigate the sensitivity of these designs with respect to mis-specification of the unknown parameters. Section 4 considers similar problems for estimating the effective dose of overall toxicity, and in Section 5 the methodology is extended to obtain robust and efficient designs by a maximin approach. Section 6 evaluates efficiencies of commonly used designs in animal studies and briefly discusses efficiencies of optimal designs when non-Weibull probability models are used. All justifications for all our results are deferred to the Appendix.

2 Background for developmental toxicity studies

In developmental toxicity experiments with laboratory animals such as rat or mice, pregnant females are usually exposed to one of several doses of the test agent (including a control group at dose zero) during a specified period in gestation. Upon examining the uterine contents of each dam, the status of each conceptus is classified and recorded. A conceptus may either be dead or alive, and a live fetus may exhibit one or more malformation.

Let m_{ij} denote the number of implants in the jth litter of the ith dose d_i, and let r_{ij} be the number of prenatal deaths, s_{ij} be the number of live fetuses, and y_{ij} be the number of fetal malformations. Summary observations from each dam yield a trinomial response $(r_{ij}, y_{ij}, s_{ij} - y_{ij})$ conditional on m_{ij} for which we have

$$m_{ij} = r_{ij} + (s_{ij} - y_{ij}) + y_{ij}.$$

The fetal malformation rate y_{ij}/s_{ij} and the prenatal death rate r_{ij}/m_{ij} are of particular interest. The joint probability of the observed outcome (y_{ij}, r_{ij}, m_{ij}) may be factored as

$$\mathrm{P}(y_{ij}, r_{ij}, m_{ij}) = \mathrm{P}(y_{ij}|s_{ij}, m_{ij})\mathrm{P}(r_{ij}|m_{ij})\mathrm{P}(m_{ij})$$

where $\mathrm{P}(m_{ij})$ is the marginal distribution of the implants number m_{ij}. Throughout, we let π_1 denote the probability of any malformation in a live fetus, let π_2 be the probability of the prenatal death, and let ϕ_i be the intra-litter correlation coefficient within ith dose group. Zhu, Krewski and Ross (1994) used generalized estimating equations in conjunction with an extended Dirichlet-multinomial covariance function, where the correlation coefficient is estimated separately. If $z_{ij} = (y_{ij}, r_{ij})^T$, the conditional covariance of the observation z_{ij} is

$$\mathrm{Cov}(z_{ij}|m_{ij}) = m_{ij}(1 + (m_{ij} - 1)\phi_i) \begin{pmatrix} \mu(1-\mu) & -\mu\pi_2 \\ -\mu\pi_2 & \pi_2(1-\pi_2) \end{pmatrix}$$

where $\mu = \pi_1(1 - \pi_2)$, $1/(1 - m_{ij}) < \phi_i < 1$.

For simplicity we assume that m_{ij} depends only on the dose level and not on the individual litter, i.e. $m_{ij} = m_i = m(d_i)$. As pointed out in Krewski, Smythe and Fung (2002) this assumption

avoids complicating the model with another level of estimation and permits the development of informative designs. Following Zhu, Krewski and Ross (1994) we use the Weibull model

$$\pi_i(d) = 1 - e^{-a_i - b_i d^{\gamma_i}}$$

to describe the probabilities π_i, where d denotes the dose level. Here a_i, $b_i > 0$ and $\gamma_i > 0$ are unknown parameters ($i = 1, 2$). We denote the parameters for the probability π_i by θ_i. Following Catalano et al. (1993) and Zhu, Krewski and Ross (1993), the *overall toxicity* is defined by

$$\pi_3(d) = 1 - (1 - \pi_1(d))(1 - \pi_2(d)) \tag{2.1}$$

of either a death or malformation occurring. The effective dose ED_α for a particular probability π_i is defined as the (unique) solution of the equation

$$\frac{\pi(ED_\alpha) - \pi(0)}{1 - \pi(0)} = \alpha$$

where $\pi(d)$ represents the probability of a response at dose d and α is a given excess risk. The excess risk represents additional risk over background among animals which would not have responded under control conditions and it is also sometimes called the benchmark dose or the virtually safe dose when α is set to be very low level, say 10^{-4} (Ryan, 1992, Al-Saidy, et al., 2003). Zhu, Krewski and Ross (1994) proposed an estimate $\hat{\theta}$ for estimating θ, the three parameters in the Weibull distribution. This estimate is based on quadratic estimating equations and has reasonable efficiencies for estimating the parameter θ. By the δ-method (Van der Vaart, 1988) the variance of the estimator $\widehat{ED}_\alpha$ for the effective dose can be approximated by

$$\mathrm{Var}(\widehat{ED}_\alpha) \approx \tilde{D}^T \mathrm{Cov}(\hat{\theta}) \tilde{D}, \tag{2.2}$$

and

$$\tilde{D} = \frac{\partial}{\partial \theta} ED_\alpha \tag{2.3}$$

is the gradient of ED_α with respect to θ. We will denote the vector of parameters in π_i by θ_i and its corresponding estimate by $\hat{\theta}_i$, i=1,2.

Throughout, a design is specified by the number of different dose levels, say k, the specific dose levels $d_1, \ldots, d_k$ and the proportion of patients, say $w_1, \ldots, w_k$ allocated at each of these dose levels. In this paper, we consider approximate designs, i.e., probability measures $\xi = \{d_i, w_i\}_{i=1}^k$ with finite support (Silvey, 1980; Pukelsheim, 1993). For a given design ξ and total sample size n, the number of observations at each dose level n_j is obtained by rounding the quantities nw_j to integers, such that $\sum_{j=1}^k n_j = n$ (Pukelsheim and Rieder, 1992). Throughout this paper we assume for the sake of simplicity that the dose range is given by the interval $[0, 1]$, but the the adaption of the methodology to other dose intervals is straightforward. In what is to follow, we will only present our design strategy and results for estimating the effective dose of prenatal death. The strategy for estimating the effective dose for a given malformation rate is completely analogous and we omit details and corresponding results for this case for space considerations.

3 Optimal designs for estimating the effective dose of prenatal death

Under the Weibull model the effective dose for prenatal death conditional number of implants equals

$$ED_\alpha = \left(-\frac{\ln(1-\alpha)}{b_2}\right)^{1/\gamma_2}.$$

Recalling that $\theta_2^T = (a_2, b_2, \gamma_2)$, the gradient (2.3) in the representation (2.2) is given by

$$\tilde{D} = \frac{\partial}{\partial\theta_2} ED_\alpha = -\frac{ED_\alpha}{\gamma_2}\begin{pmatrix} 0 \\ 1/b_2 \\ \ln(-\ln(1-\alpha)/b_2)/\gamma_2 \end{pmatrix} = -\frac{\left(-\frac{\ln(1-\alpha)}{b_2}\right)^{1/\gamma_2}}{\gamma_2}\begin{pmatrix} 0 \\ 1/b_2 \\ \frac{\ln(-\frac{\ln(1-\alpha)}{b_2})}{\gamma_2} \end{pmatrix}.$$

If $\xi = \{d_1, d_2, \ldots, d_n; w_1, w_2, \ldots, w_n\}$ denotes an approximate design and

$$D_i = \frac{\partial}{\partial\theta_2}\pi_2(d_i) = (1-\pi_2(d_i))\begin{pmatrix} 1 \\ d_i^{\gamma_2} \\ b_2 d_i^{\gamma_2}\ln(d_i) \end{pmatrix},$$

it follows that the covariance matrix of the estimate $\hat{\theta}_2$ is approximately

$$\mathrm{Cov}(\hat{\theta}_2) \approx M^{-1}(\xi, \theta_2),$$

where

$$M(\xi,\theta_2) = \sum_{i=1}^n w_i \frac{D_i D_i^T}{\mathrm{Var}(\, r_i \,|\, m_i\,)} = \sum_{i=1}^n w_i \frac{D_i D_i^T}{m_i(1+(m_i-1)\phi_i)\pi_2(d_i)(1-\pi_2(d_i))} \tag{3.1}$$

is the information matrix of the design. Note that the summands in this matrix differ by the factors m_i^2 from the corresponding terms in the information matrix derived by Krewski, Smythe and Ross (2002). Consequently we obtain from (2.2) as first order approximation for the variance of the estimate of the effective dose

$$\mathrm{Var}(\widehat{ED}_\alpha) \approx \Psi(\xi,\theta_2) = \tilde{D}^T M^{-1}(\xi,\theta_2)\tilde{D} \tag{3.2}$$

and a locally optimal design for estimating the effective dose (of prenatal death) minimizes the function Ψ among all designs for which the ED_α is estimable.

It is clear that the information matrix of the optimal design depends on the parameters of the model, and, in particular on the quantities $m_i = m(d_i)$ and $\phi_i = \phi(d_i)$. The simplest way to deal with this added complication is to use locally optimal designs proposed by Chernoff (1953). This strategy requires that a single prior guess for the unknown parameters is available. In developmental toxicity experiments such knowledge is often available from preliminary studies. The following results establish properties of locally optimal designs for estimating the effective

dose of prenatal death. In essence, it says that if the excess risk is not too extreme (i.e. near 0 or 1), the locally optimal design requires only 2 doses; otherwise the locally optimal design requires 3 doses that include the extreme levels in the dose interval. The proofs rely on the geometric characterization of c-optimal designs of Elfving (1952) and are deferred to the Appendix.

Theorem 1. *Let m and ϕ denote the functions defining $m_i = m(d_i)$ and $\phi_i = \phi(d_i)$. If the function*

$$d \longrightarrow \frac{(1-\pi_2(d))}{m(d)(1+(m(d)-1)\phi(d))\pi_2(d)} \tag{3.3}$$

is decreasing, then there exist numbers $\underline{\alpha}$ and $\bar{\alpha}$ such that the following properties hold.

(a) If $\alpha \in (0, \underline{\alpha}] \cup (\bar{\alpha}, 1)$, then the locally optimal design for estimating the effective dose of prenatal death is supported at 3-points including the boundary points $d_1^* = 0$, $d_3^* = 1$ of the design space.

(b) If $\alpha \in (\underline{\alpha}, \bar{\alpha})$, then the locally optimal design for estimating the effective dose of prenatal death is supported at 2-points.

We note that if the function ϕ is increasing, the assumption of Theorem 1 is satisfied. In particular, Bowman, Chen and George (1995) proposed a logistic-type function of the form

$$\phi(d) = \frac{2}{1+e^{u_1+u_2 d}} - 1 \tag{3.4}$$

for describing the relationship between intra-litter correlation and dose, which is widely used in practice. If $u_2 < 0$ this function satisfies the assumptions of Theorem 1. The next result tells us that we can limit our search for the optimal design to the protocol interval $[0, 1]$ and deduce the corresponding optimal design on the design interval $[0, T]$.

Theorem 2. *Assume that the quantities m_i and the function ϕ are constant. The weights of the locally optimal design for estimating the effective dose of prenatal death do not depend on the parameter γ_2. Moreover, if $d_i^*(a_2, b_2, \gamma_2)$ are the support points of the locally optimal design for estimating the effective dose of prenatal death, we have*

$$d_i^*(a_2, b_2, \gamma_2) = (d_i^*(a_2, b_2, 1))^{1/\gamma_2}.$$

Our next result shows that if the locally optimal design for estimating the prenatal death requires 3 dose levels, then the dose levels do not depend on the value of the excess risk α. It also provides a complete analytical description of the locally optimal design when it is known in advance that the locally optimal design needs only two doses, and one of which is the 0 dose.

Theorem 3. *Assume that the conditions of Theorem 1 are satisfied.*

(a) The support points of the locally optimal design for estimating the effective dose of prenatal death with 3 support points do not depend on the value of α.

(b) If the support of a 2-point locally optimal design for estimating the effective dose of prenatal death contains the point 0*, then the second support point is equal to* ED_α *and its weight at* ED_α *is equal to* $w_2 = g(0)/(g(0) + g(ED_\alpha))$ *where*

$$g(d) = \sqrt{\frac{(1-\pi_2(d))}{m(d)(1+(m(d)-1)\phi(d))\pi_2(d)}}.$$

In Table 1 we display numerical locally optimal designs for estimating the effective dose of prenatal death for various combinations of the parameters when the quantities m_i and the function ϕ are assumed to be constants. As stated in Theorem 1 the locally optimal designs are either 2-point designs or 3-point designs because the monotonicity assumption of the theorem is satisfied. In Table 2 we show some results for a non constant function ϕ of the form (3.4), which demonstrate that the assumption of monotonicity on the function (3.3) is in fact needed. For example, if $\phi(d) = 2/(1 + e^{d-1}) - 1$ the corresponding function in (3.3) is not decreasing. The locally optimal design for estimating the effective dose of prenatal death is a 3-point design, but its support dose not contain the minimal dose 0. In both Tables 1 and 2, we also display on the extreme right column the efficiency of a equally weighted design on five equally spaced points on the interval [0,1]. We denote this design by ξ_u and note that this is an example of a uniform design which is widely used in practice.The results show that in the cases considered in both tables, this particular uniform design did not perform well, averaging about 50%. This means that roughly twice as many rats will be needed in the uniform design to obtain estimates for the parameters as accurate as those provided by the locally optimal design.

In general, our numerical results show that there are four types of locally optimal designs for estimating the effective dose of prenatal death, namely:

$$\{0, d_2, 1; w_1, w_2, w_3\},\ \{0, d_2; w_1, w_2\},\ \{d_1, d_2, 1; w_1, w_2, w_3\},\ \{d_1, d_2; w_1, w_2\}.$$

Moreover, if the assumptions of Theorem 1 are satisfied there exist only two types, i.e.

$$\{0, d_2, 1; w_1, w_2, w_3\},\ \{d_1, d_2; w_1, w_2\}\ .$$

Before any design is implemented, it is useful to investigate the robustness of the locally optimal designs for estimating the effective dose with respect to mis-specification of the initial parameters. For this purpose we consider the locally optimal $\xi^*(\theta_0) = \{0, 0.686, 1; 0.396, 0.548, 0.056\}$ for the parameter $\theta_0^T = (a_2, b_2, \gamma_2) = (0.13, 0.27, 3.33)$ and calculate the efficiency

$$\text{eff}(\xi) \ = \ \frac{\tilde{D}^T M^{-1}(\xi, \theta)\tilde{D}}{\tilde{D}^T M^{-1}(\xi, \theta_0)\tilde{D}}. \tag{3.5}$$

for various values of θ. These results are listed in Table 3. We observe that locally optimal designs are not too sensitive with respect to changes of the parameter a_2, but a misspecification of the

Table 1: *Locally optimal design for estimating the effective dose of prenatal death conditional on the number of implants assuming the functions ϕ and m are constants. The table also shows the efficiency of the equidistant design $\xi_u = \{0, 1/4, 1/2, 3/4, 1; 1/5, 1/5, 1/5, 1/5, 1/5\}$ (last column).*

α	a_2	b_2	γ_2	d_1	d_2	d_3	w_1	w_2	w_3	ED	$\text{eff}(\xi_u)$
0.05	0.13	0.15	3.33	0	0.725		0.455	0.545		0.725	0.506
0.05	0.13	0.2	3.33	0	0.696	1	0.429	0.545	0.025	0.665	0.539
0.05	0.13	0.25	3.33	0	0.689	1	0.404	0.547	0.049	0.621	0.557
0.05	0.13	0.3	3.33	0	0.682	1	0.387	0.549	0.064	0.588	0.568
0.05	0.13	0.35	3.33	0	0.676	1	0.373	0.551	0.075	0.562	0.575
0.05	0.13	0.4	3.33	0	0.670	1	0.363	0.554	0.083	0.540	0.579
0.05	0.01	0.27	3.33	0	0.607		0.285	0.715		0.607	0.481
0.05	0.05	0.27	3.33	0	0.653	1	0.371	0.593	0.036	0.607	0.541
0.05	0.1	0.27	3.33	0	0.678	1	0.390	0.558	0.051	0.607	0.558
0.05	0.15	0.27	3.33	0	0.690	1	0.399	0.543	0.058	0.607	0.564
0.05	0.2	0.27	3.33	0	0.698	1	0.404	0.535	0.061	0.607	0.568
0.05	0.25	0.27	3.33	0	0.703	1	0.407	0.529	0.063	0.607	0.570
0.03	0.13	0.27	3.33	0	0.686	1	0.367	0.538	0.095	0.519	0.590
0.04	0.13	0.27	3.33	0	0.686	1	0.381	0.543	0.076	0.567	0.577
0.05	0.13	0.27	3.33	0	0.686	1	0.396	0.548	0.056	0.607	0.562
0.06	0.13	0.27	3.33	0	0.686	1	0.412	0.554	0.034	0.642	0.546
0.07	0.13	0.27	3.33	0	0.686	1	0.430	0.560	0.010	0.674	0.526
0.08	0.13	0.27	3.33	0	0.703		0.433	0.567		0.703	0.507
0.1	0.13	0.27	3.33	0	0.754		0.420	0.580		0.754	0.499

Table 2: *Locally optimal design for prenatal death conditional on the number of implants when the function m is assumed to be constant and the function ϕ modeling the correlation is given by (3.4) ($a_2 = 0.13$, $b_2 = 0.27$, $\gamma_2 = 3.33$, $\alpha = 0.05$). The table also shows the efficiency of the equidistant design $\xi_u = \{0, 1/4, 1/2, 3/4, 1; 1/5, 1/5, 1/5, 1/5, 1/5\}$ (last column).*

u_1	u_2	d_1	d_2	d_3	w_1	w_2	w_3	ED	eff(ξ_u)
0	-1	0	0.636	1	0.284	0.691	0.025	0.607	0.490
0	-2	0	0.630	1	0.242	0.737	0.021	0.607	0.472
0	-3	0	0.633	1	0.220	0.757	0.023	0.607	0.464
-1	1	0.082	0.746	1	0.447	0.482	0.071	0.607	0.588
-2	2	0.071	0.762	1	0.445	0.487	0.068	0.607	0.569
-3	3	0.052	0.767	1	0.432	0.503	0.065	0.607	0.551

parameters b_2 and γ_2 has more serious effects. The table also shows the corresponding efficiencies of the equidistant design $\xi_u = \{0, 1/4, 1/2, 3/4, 1; 1/5, 1/5, 1/5, 1/5, 1/5\}$. In most cases these are smaller than the efficiencies of the locally optimal design for estimating the effective dose. In addition, the table contains efficiencies of a maximin design ξ_{mm}, whose construction will be motivated in Section 5. This design performs substantially better than the uniform design ξ_u and achieves nearly the same efficiencies as the locally optimal design $\xi^*(\theta_0)$ in those case where $\xi^*(\theta_0)$ is very efficient.

4 Dose finding for overall toxicity conditional number of implants

If two Weibull models with parameters $\theta_1^T = (a_1, b_1, \gamma_1)$ and $\theta_2^T = (a_2, b_2, \gamma_2)$ are used for modeling the overall toxicity in (2.1), the effective dose based on $\pi_3(d)$ is defined as a solution of the equation

$$\alpha = 1 - \exp(b_1 ED_\alpha^{\gamma_1} + b_2 ED_\alpha^{\gamma_2}),$$

or, equivalently,

$$-\ln(1-\alpha) = b_1 ED_\alpha^{\gamma_1} + b_2 ED_\alpha^{\gamma_2}.$$

The approximation for the variance of the estimator based on generalized estimating equations is given by (2.2), where $\theta^T = (\theta_1, \theta_2)$ and

$$\bar{D} = \frac{\partial}{\partial \theta} ED_\alpha = \frac{-1}{b_1\gamma_1 ED_\alpha^{\gamma_1 - 1} + b_2\gamma_2 ED_\alpha^{\gamma_2 - 1}} \begin{pmatrix} 0 \\ ED_\alpha^{\gamma_1} \\ b_1 ED_\alpha^{\gamma_1} \ln(ED_\alpha) \\ 0 \\ ED_\alpha^{\gamma_2} \\ b_2 ED_\alpha^{\gamma_2} \ln(ED_\alpha) \end{pmatrix}.$$

Table 3: *Efficiency for estimating the effective dose of prenatal death. $\xi^*(\theta_0)$: locally optimal design for $\theta_0^T = (a_2, b_2, \gamma_2) = (0.13, 0.27, 3.33)$ ξ_u equidistant design with five different dose levels (including the largest and smallest dose), and design $\xi_{mm} = \{0, 0.694, 1; 0.349, 0.515, 0.136\}$ which is standardized maximin optimal for estimating the effective dose of prenatal death with respect to $\Omega = [0.05, 0.2] \times [0.2, 0.4] \times [2.5, 4.5]$.*

a_2	0.05	0.05	0.05	0.05	0.2	0.2	0.2	0.2
b_2	0.2	0.2	0.4	0.4	0.2	0.2	0.4	0.4
γ_2	2.5	4.5	2.5	4.5	2.5	4.5	2.5	4.5
$\text{eff}(\xi^*(\theta_0))$	0.802	0.766	0.526	0.967	0.944	0.695	0.749	0.862
$\text{eff}(\xi_u)$	0.522	0.475	0.563	0.521	0.550	0.496	0.588	0.544
$\text{eff}(\xi_{mm})$	0.808	0.740	0.663	0.923	0.920	0.665	0.872	0.822

If $\xi = \{d_1, d_2, \ldots, d_n; w_1, w_2, \ldots, w_n\}$ denotes an approximate design we have

$$\text{Cov}(\hat{\theta}) \approx M^{-1}(\xi, \theta),$$

where the information matrix is given by

$$M(\xi, \theta) = \begin{pmatrix} M_1(\xi, \theta) & 0 \\ 0 & M_2(\xi, \theta) \end{pmatrix}$$

and the two non-vanishing blocks are defined by

$$\begin{aligned} M_1(\xi, \theta) &= \sum_{i=1}^{n} w_i \frac{D_{(1)i} D_{(1)i}^T}{\text{Var}(\, y_i \,|\, m_i \,)} \\ &= \sum_{i=1}^{n} w_i \frac{D_{(1)i} D_{(1)i}^T}{m_i(1 + (m_i - 1)\phi_i)\pi_1(d_i)(1 - \pi_2(d_i))(1 - \pi_1(d_i)(1 - \pi_2(d_i)))}, \\ M_2(\xi, \theta) &= \sum_{i=1}^{n} w_i \frac{D_{(2)i} D_{(2)i}^T}{\text{Var}(\, r_i \,|\, m_i \,)} \\ &= \sum_{i=1}^{n} w_i \frac{D_{(2)i} D_{(2)i}^T}{m_i(1 + (m_i - 1)\phi_i)\pi_2(d_i)(1 - \pi_2(d_i))}, \end{aligned}$$

with

$$D_{(j)i} = \frac{\partial}{\partial \theta_j} \pi_j(d_i) = (1 - \pi_j(d_i)) \begin{pmatrix} 1 \\ d_i^{\gamma_j} \\ b_j d_i^{\gamma_j} \ln(d_i) \end{pmatrix}, \quad j = 1, 2.$$

Note that $M(\xi, \theta)$ is a block-diagonal matrix and as a consequence, the optimality criterion minimizing the variance of the estimate for ED_α can be interpreted as composite optimality

Table 4: *Locally optimal designs for estimating the effective dose of overall toxicity conditional on the number of implants. The function m and ϕ are constant, $\alpha = 0.05$ and ξ_u denotes the equidistant design with five different dose levels* $0, 1/4, 1/2, 3/4, 1$.

a_1	b_1	γ_1	a_2	b_2	γ_2	d_1	d_2	d_3	d_4	w_1	w_2	w_3	w_4	eff(ξ_u)
0.06	0.7	2	0.13	0.15	2	0	0.495	1		0.330	0.546	0.124		0.653
0.06	0.7	2	0.13	0.15	3.33	0	0.493	1		0.291	0.574	0.134		0.699
0.06	0.7	3.37	0.13	0.15	2	0	0.573	1		0.372	0.536	0.092		0.593
0.06	0.7	3.37	0.13	0.15	3.33	0	0.658	1		0.331	0.546	0.123		0.634
0.06	0.5	3.37	0.13	0.3	3.33	0	0.665	1		0.333	0.549	0.118		0.607
0.06	0.7	3.37	0.13	0.3	3.33	0	0.653	1		0.321	0.551	0.128		0.619
0.06	0.9	3.37	0.13	0.3	3.33	0	0.640	1		0.311	0.551	0.138		0.630
0.06	0.7	3.37	0.05	0.3	3.33	0	0.630	1		0.299	0.577	0.124		0.593
0.06	0.7	3.37	0.25	0.3	3.33	0	0.673	1		0.338	0.532	0.130		0.635
0.02	0.7	3.37	0.13	0.3	3.33	0	0.646	1		0.315	0.559	0.126		0.641
0.09	0.7	3.37	0.13	0.3	3.33	0	0.657	1		0.325	0.546	0.129		0.613
0.02	1.2	2.2	0.05	0.2	3.7	0	0.402	0.636	1	0.212	0.620	0.040	0.129	0.655
0.02	1.2	2.2	0.05	0.2	3.3	0	0.421	0.541	1	0.221	0.596	0.041	0.141	0.680
0.02	0.9	2.2	0.05	0.2	3.7	0	0.434	0.590	1	0.228	0.585	0.065	0.121	0.674
0.02	1.6	2.2	0.05	0.2	3.7	0	0.368	0.713	1	0.198	0.636	0.029	0.136	0.632

criterion in the sense of Läuter (1974), that is

$$\text{Var}(\widehat{ED}_\alpha) \approx \Phi(\xi,\theta) = \bar{D}^T M^{-1}(\xi,\theta)\bar{D} \;=\; \tilde{D}_{(1)}^T M_1^{-1}(\xi,\theta)\tilde{D}_{(1)} + \tilde{D}_{(2)}^T M_2^{-1}(\xi,\theta)\tilde{D}_{(2)}. \tag{4.1}$$

It is intuitively clear that locally optimal designs for estimating the ED_α for overall toxicity are 3-point designs if the parameters in $\pi_1(d)$ and $\pi_2(d)$ are similar. In all cases of practical interest these designs have to be calculated numerically. Some exemplary optimal designs are presented in Table 4 for constant functions m_i and ϕ_i. Table 5 presents optimal designs for the case where the correlation is of the form (3.4) and the $m_i's$ are constants. We observe that in most cases, the locally optimal designs are supported at 3-points, but there are also situations (in particular for large differences between the parameters γ_1 and γ_2), where 4 different dose levels are required for the optimal estimation of the effective dose of the overall toxicity. The results of our investigation of the robustness properties of the locally optimal designs for estimating the effective dose with respect to mis-specification of the initial parameters are summarized in Table 6.

Table 5: *Locally optimal designs for estimating the effective dose of overall toxicity conditional on the number of implants. The functions m is constant, while the correlation function ϕ is given by (3.4), $a_1 = 0.06$, $b_1 = 0.7$, $\gamma_1 = 3.37$, $a_2 = 0.13$, $b_2 = 0.3$, $\gamma_2 = 3.33$, $\alpha = 0.05$ and ξ_u denotes the equidistant design with five different dose levels* $0, 1/4, 1/2, 3/4, 1$.

u_1	u_2	d_1	d_2	d_3	w_1	w_2	w_3	$\text{eff}(\xi_u)$
0	-1	0	0.600	1	0.227	0.652	0.121	0.554
0	-2	0	0.594	1	0.192	0.690	0.118	0.538
0	-3	0	0.596	1	0.174	0.708	0.118	0.530

Table 6: *Efficiency for estimating the effective dose of overall toxicity using three designs: $\xi^*(\theta_0)$, the locally optimal design for $\theta_0^T = (a_1, b_1, \gamma_1, a_2, b_2, \gamma_2)^T = (0.06, 0.7, 3.37, 0.13, 0.27, 3.33)$, ξ_u the equidistant design with five different dose levels (including the largest and smallest dose), and the design $\xi_{mm} = \{0, 0.694, 1; 0.349, 0.515, 0.136\}$ which is standardized maximin optimal for estimating prenatal death with* $[0.05, 0.2] \times [0.2, 0.4] \times [2.5, 4.5]$.

a_1	0.03	0.03	0.03	0.03	0.09	0.09	0.09	0.09
b_1	0.4	0.4	0.9	0.9	0.4	0.4	0.9	0.9
γ_1	2.7	4.2	2.7	4.2	2.7	4.2	2.7	4.2
a_2	0.05	0.05	0.05	0.05	0.2	0.2	0.2	0.2
b_2	0.2	0.2	0.4	0.4	0.2	0.2	0.4	0.4
γ_2	2.5	4.5	2.5	4.5	2.5	4.5	2.5	4.5
$\text{eff}(\xi^*(\theta_0))$	0.875	0.873	0.681	0.982	0.981	0.705	0.880	0.882
$\text{eff}(\xi_u)$	0.588	0.566	0.594	0.584	0.606	0.574	0.619	0.614
$\text{eff}(\xi_{mm})$	0.730	0.965	0.531	0.942	0.906	0.871	0.743	0.984

Table 7: *Efficiency for estimating the effective dose of overall toxicity.* $\xi^*(\theta_0) = \{0, 0.686, 1; 0.396, 0.548, 0.056\}$*: locally optimal design for estimating the effective dose of prenatal death* ($\theta_0^T = (a_2, b_2, \gamma_2)^T = (0.13, 0.27, 3.33)$*, constant correlation);* ξ_u *equidistant design with five different dose levels* $0, 1/4, 1/2, 3/4, 1$ *and design* $\xi_{mm} = \{0, 0.694, 1; 0.349, 0.515, 0.136\}$ *which is standardized maximin optimal for estimating the effective dose of prenatal death with respect to* $\Omega = [0.05, 0.2] \times [0.2, 0.4] \times [2.5, 4.5]$.

a_1	0.02	0.02	0.02	0.02	0.1	0.1	0.1	0.1
b_1	0.3	0.3	1.1	1.1	0.3	0.3	1.1	1.1
γ_1	2.5	4.5	2.5	4.5	2.5	4.5	2.5	4.5
eff($\xi^*(\theta_0)$)	0.762	0.977	0.269	0.883	0.815	0.977	0.328	0.899
eff(ξ_u)	0.669	0.583	0.770	0.611	0.618	0.594	0.644	0.598
eff(ξ_{mm})	0.901	0.986	0.437	0.984	0.935	0.980	0.520	0.995
a_1	0.03	0.03	0.03	0.03	0.09	0.09	0.09	0.09
b_1	0.4	0.4	0.9	0.9	0.4	0.4	0.9	0.9
γ_1	2.7	4.2	2.7	4.2	2.7	4.2	2.7	4.2
eff($\xi^*(\theta_0)$)	0.754	0.959	0.443	0.885	0.796	0.965	0.491	0.899
eff(ξ_u)	0.652	0.589	0.708	0.609	0.622	0.592	0.646	0.599
eff(ξ_{mm})	0.902	0.991	0.646	0.984	0.931	0.991	0.703	0.993

We next investigate whether the locally optimal design for estimating the effective dose of prenatal death is efficient for estimating the effective dose of overall toxicity. We also compare the optimal design with the equidistant design with five different dose levels. In Tables 7 and 8, we display efficiencies of the two designs for various combinations of the parameter θ to study their robustness for estimating the effective dose of overall toxicity when the initial parameters have been misspecified and the design is optimal for estimating the effective dose of prenatal death. We observe that the performance of the locally optimal design for estimating the the effective dose of overall toxicity depends sensitively on changes of the parameters b_1 and b_2. If b_1 is very different from the parameter b_2 used in the construction of the locally optimal design for estimating the effective dose of prenatal death, this design becomes inefficient for estimating overall toxicity. In such cases even the uniform design performs better. Otherwise the locally optimal design for estimating the effective dose of prenatal death is at least as good as the uniform design (and in many cases substantially better). The table also shows efficiencies of the design ξ_{mm}, which will be constructed in the following section as a robust and efficient alternative to locally optimal designs. The design ξ_{mm} performs uniformly better than the locally optimal design $\xi^*(\theta_0)$ for estimating the effective dose of prenatal death. In many cases, it is substantially more efficient than the uniform design ξ_u and in the cases where the equal allocation rule yields the best efficiencies, the loss of efficiency obtained from ξ_{mm} is rather small.

Table 8: *Efficiency for estimating the effective dose of overall toxicity.* $\xi^*(\theta_0) = \{0, 0.686, 1; 0.396, 0.548, 0.056\}$*: locally optimal design for estimating the effective dose of prenatal death* ($\theta_0^T = (a_2, b_2, \gamma_2)^T = (0.13, 0.27, 3.33)$*, constant correlation);* ξ_u *equidistant design with five different dose levels* $0, 1/4, 1/2, 3/4, 1$ *and design* $\xi_{mm} = \{0, 0.694, 1; 0.349, 0.515, 0.136\}$ *which is standardized maximin optimal for estimating the effective dose of prenatal death with respect to* $\Omega = [0.05, 0.2] \times [0.2, 0.4] \times [2.5, 4.5]$.

a_1	0.03	0.03	0.03	0.03	0.09	0.09	0.09	0.09
b_1	0.4	0.4	0.9	0.9	0.4	0.4	0.9	0.9
γ_1	2.7	4.2	2.7	4.2	2.7	4.2	2.7	4.2
a_2	0.05	0.05	0.05	0.05	0.2	0.2	0.2	0.2
b_2	0.2	0.2	0.4	0.4	0.2	0.2	0.4	0.4
γ_2	2.5	4.5	2.5	4.5	2.5	4.5	2.5	4.5
$\text{eff}(\xi^*(\theta_0))$	0.570	0.968	0.355	0.821	0.767	0.892	0.532	0.914
$\text{eff}(\xi_u)$	0.588	0.566	0.594	0.584	0.606	0.574	0.619	0.614
$\text{eff}(\xi_{mm})$	0.730	0.965	0.531	0.942	0.906	0.871	0.743	0.984

5 Robust and efficient designs for prenatal death

As pointed out in the previous sections, locally optimal designs are not necessarily robust with respect to a mis-specification of the unknown parameters. To obtain designs that are efficient and robust over a certain range of the parameters for the Weibull model, we study a maximin approach proposed by Müller (1995) and Dette (1997), which assumes that there is prior information on the range of plausible values of unknown parameters. To be precise, we concentrate on optimal designs for estimating the effective dose of prenatal death, where the correlation function is given by the one parametric logistic family

$$\phi(d) = \frac{2}{1 + e^{-ud}} - 1. \tag{5.1}$$

We assume that the experimenter has some knowledge about the location of the parameters, i.e.

$$a_2 \in [\underline{a}, \overline{a}],\ b_2 \in [\underline{b}, \overline{b}],\ \gamma_2 \in [\underline{\gamma}, \overline{\gamma}],\ u \in [\underline{u}, \overline{u}]$$

For given $\theta^T = (a_2, b_2, \gamma_2)$ and u, define $\xi^*(\theta, u)$ as the locally optimal designs for estimating the effective dose and for a given design, define

$$\text{eff}_{\text{all}}(\xi, \theta, u) \ = \ \frac{\tilde{D}^T M^{-1}(\xi^*(\theta, u), \theta, u)\tilde{D}}{\tilde{D}^T M^{-1}(\xi, \theta, u)\tilde{D}}. \tag{5.2}$$

A design ξ_{mm} is called standardized maximin optimal for estimating the effective dose, if it maximizes the worst efficiency over some set of the parameters, i.e.

$$\xi_{mm} = \text{argmax}_\xi \min_{(\theta,u)\in\Omega} \text{eff}_{\text{all}}(\xi, \theta, u). \tag{5.3}$$

Table 9: *Standardized maximin optimal designs for estimating the effective dose of prenatal death conditional on the number of implants. The functions m and ϕ are constant, $\alpha = 0.05$ and ξ_u denotes the equidistant design with five different dose levels* $0, 1/4, 1/2, 3/4, 1$.

$\underline{a}_2$	$\overline{a}_2$	$\underline{b}_2$	$\overline{b}_2$	$\underline{\gamma}_2$	$\overline{\gamma}_2$	d_1	d_2	d_3	w_1	w_2	w_3	min eff	min eff(ξ_u)
0.1	0.12	0.25	0.3	3.1	3.5	0	0.681	1	0.387	0.551	0.063	0.976	0.549
0.1	0.15	0.25	0.3	3.1	3.5	0	0.684	1	0.389	0.546	0.065	0.972	0.549
0.1	0.17	0.22	0.3	3	3.7	0	0.696	1	0.390	0.536	0.073	0.930	0.533
0.08	0.18	0.21	0.33	2.6	4	0	0.691	1	0.371	0.524	0.105	0.809	0.514
0.07	0.19	0.2	0.34	2.5	4.1	0	0.690	1	0.366	0.519	0.115	0.757	0.502

Here the set Ω is defined by $\Omega = [\underline{a}, \overline{a}] \times [\underline{b}, \overline{b}] \times [\underline{\gamma}, \overline{\gamma}] \times [\underline{u}, \overline{u}]$ and is user-selected. Optimal designs with respect to this robust criterion have to be calculated numerically in all cases of practical interest. In Table 9 we display standardized maximin optimal designs with respect to various sets Ω assuming the quantities m_i and the correlation function (5.1) are constants, i.e. $\underline{u} = \overline{u} = 0$. We observe that in all situations the standardized maximin optimal designs are supported at 3 points and they include the largest and smallest doses. However, the results of Braess and Dette (2007) indicate that there will also exist standardized maximin optimal designs for estimating the effective dose with a larger number of support points. The table also contains the minimal efficiency of the standardized maximin optimal design for estimating the effective dose, i.e.

$$\min_{(\theta,u)\in\Omega} \text{eff}_{\text{all}}(\xi, \theta, u)$$

and the minimal efficiencies of an equidistant design with 5 different dose levels. Note that the standardized maximin optimal designs yield reasonable efficiencies over the full set Ω and that the minimal efficiency of the uniform design over this set is substantially smaller. In Table 10 we consider the case, where the correlation can be modeled by the function (5.1). We observe that the standardized maximin optimal designs are supported at 3 or 4 points and compared to Table 9 the efficiencies are smaller. This is intuitively clear, because we have incorporated more robustness with respect to the assumption of a constant correlation in the construction of efficient designs for estimating the effective dose. Again the equidistant design yields substantially smaller minimal efficiencies compared to the standardized maximin optimal design.

6 Efficiency of standard designs and concluding remarks

It is interesting to evaluate the efficiencies of commonly used designs in developmental toxicity studies. One such class is the set of uniform designs. These designs are equally spread out in the dose interval of interest and allocate equal number of animals to each dose. As such, they

Table 10: *Standardized maximin efficient optimal design for prenatal death conditional on the number of implants. The function m is constant, while the correlation function is given by (5.1) and* $\alpha = 0.05$. ξ_u *denotes the equidistant design with five different dose levels* $0, 1/4, 1/2, 3/4, 1$ *and various sets are considered in the standardized maximin optimality criterion (5.3),* $\Omega_1(\underline{u}, \overline{u}) = [0.07, 0.19] \times [0.19, 0.34] \times [2.5, 4.1] \times [\underline{u}, \overline{u}]$, $\Omega_2(\underline{u}, \overline{u}) = [0.1, 0.12] \times [0.25, 0.3] \times [3.1, 3.5] \times [\underline{u}, \overline{u}]$.

	$\underline{u}$	$\overline{u}$	d_1	d_2	d_3	d_4	w_1	w_2	w_3	w_4	$\min \text{eff}(\xi^*)$	$\min \text{eff}(\xi_u)$
$\Omega_1(\underline{u}, \overline{u})$	0	1	0	0.469	0.721	1	0.269	0.258	0.400	0.073	0.654	0.412
	0	2	0	0.460	0.722	1	0.232	0.282	0.417	0.069	0.640	0.392
	1	2	0	0.545	0.665	1	0.239	0.110	0.535	0.117	0.655	0.392
$\Omega_2(\underline{u}, \overline{u})$	0	1	0	0.653	1		0.343	0.599	0.058		0.896	0.469
	0	2	0	0.649	1		0.327	0.615	0.057		0.873	0.449
	1	2	0	0.637	1		0.254	0.700	0.046		0.946	0.449

are intuitive and easy to implement. Krewski, Smythe and Fung (2002) provided an overview of experimental designs for 11 developmental toxicity studies conducted under the US National Toxicology Program. In their Table 1, they listed the doses employed in these studies that involved either rabbits, rats or mice. The designs usually have roughly equal number of animals at each dose and some of their dose levels, after scaling to our protocol interval [0,1] are listed in our Tables 11 and 12. Following Krewski, Smythe and Fung, we call these "standard" designs.

Tables 11 and 12 display the efficiencies of "standard" designs for estimating the prenatal death rates and the overall toxicity rate. We observe that the standard design can perform poorly when model parameters are mis-specified. For instance, the efficiencies of the standard design listed in the first row can be less than 30% for estimating the prenatal death rate and the overall toxicity rate. Some standard designs have efficiencies as low as 0.22 for estimating the prenatal death rate. Interestingly, the uniform design with 5 doses has at least 50% for all cases shown in the tables. In general, it is advisable that the researcher assess the efficiencies of a design under different optimality criteria before its implementation.

In practice, there are usually several objectives in the study and these objectives may not be of equal interest to the researcher. For instance, the researcher is interested to design a study whose primary aim is to estimate the prenatal death rate, the secondary aim is to estimate the malformation rate and the tertiary aim is to estimate the overall toxicity rate as accurate as possible. To incorporate the multiple objectives in the study, one may follow the strategy laid out in Cook and Wong (1994) to find an optimal design that provides user-specified efficiency for each objective. Clearly, the optimal design sought should provide higher efficiencies for more important objectives and the user-specified efficiencies reasonable enough so that the optimal design exists. For space consideration, we do not provide multiple-objective optimal designs

Table 11: *Efficiency of "standard" designs for estimating ED_α for prenatal death with different values of parameters, $\psi(d) \equiv$ const.*

					a_2	0.13	0.05	0.13	0.13	0.05	0.13
					b_2	0.27	0.27	0.15	0.27	0.15	0.27
d_1	d_2	d_3	d_4	d_5	γ_2	3.3	3.3	3.3	2	2	1
0	0.25	0.5	1			0.28	0.31	0.23	0.53	0.46	0.75
0	0.33	0.67	0.83	1		0.61	0.55	0.57	0.53	0.48	0.52
0	0.25	0.5	0.75	1		0.56	0.54	0.51	0.57	0.51	0.62
0	0.3	0.5	0.7	1		0.54	0.54	0.46	0.62	0.54	0.65
0	0.17	0.33	0.67	1		0.49	0.47	0.44	0.50	0.45	0.63
0	0.05	0.15	0.5	1		0.28	0.31	0.24	0.49	0.43	0.51
0	0.125	0.25	0.5	1		0.26	0.29	0.22	0.46	0.40	0.64
0	0.1	0.2	0.5	1		0.27	0.30	0.23	0.46	0.40	0.58

Table 12: *Efficiency of "standard" designs for estimating ED_α for overall toxicity with different values of parameters in the Weibull model with $\psi(d) \equiv$ constant.*

					a_1	0.06	0.06	0.06	0.06	0.06	0.06	0.02
					b_1	0.7	0.7	0.7	0.7	0.7	0.2	0.7
					γ_1	3.37	3.37	3.37	3.37	1	3.37	3.37
					a_2	0.13	0.05	0.13	0.13	0.13	0.13	0.13
					b_2	0.3	0.3	0.1	0.3	0.3	0.3	0.3
d_1	d_2	d_3	d_4	d_5	γ_2	3.33	3.33	3.33	1	3.33	3.33	3.33
0	0.25	0.5	1			0.36	0.39	0.34	0.78	0.69	0.29	0.37
0	0.33	0.67	0.83	1		0.61	0.56	0.64	0.53	0.40	0.63	0.63
0	0.25	0.5	0.75	1		0.62	0.59	0.64	0.64	0.55	0.59	0.64
0	0.3	0.5	0.7	1		0.63	0.62	0.64	0.66	0.52	0.57	0.65
0	0.17	0.33	0.67	1		0.54	0.51	0.55	0.65	0.69	0.52	0.55
0	0.05	0.15	0.5	1		0.35	0.38	0.34	0.53	0.59	0.30	0.36
0	0.125	0.25	0.5	1		0.33	0.35	0.31	0.67	0.76	0.27	0.34
0	0.1	0.2	0.5	1		0.34	0.36	0.33	0.61	0.72	0.29	0.35

for simultaneously estimating the effective dose for prenatal death rate, malformation rate and overall toxicity rate, but note that the key idea for finding such a design is to first formulate each objective as a convex function of the design information matrix and then combine all the convex objectives into a single convex functional using a convex combination. As described in Cook and Wong (1994), each set of weights used in the convex combination can be judiciously chosen to satisfy the efficiency requirement for each objective. In the case of a two-objective design problem, the weights and the dual-objective optimal design can be determined graphically via efficiency plots (Imhof and Wong, 2000). Wong (1999) provided several illustrative applications of such ideas to construct multiple-objective optimal designs in several biomedical problems.

One may be rightly concerned that the optimal designs are dependent on the parametric models. This dependence is inescapable but as we have advocated all along, the user must check robustness properties of optimal designs to all assumptions before the design is implemented. We focused on the simpler situation when we were concerned about mis-specification of nominal values, but if there is concern about other aspects in the model assumptions, a similar strategy can be applied. For instance, one may question the validity of the Weibull models to describe the malformation and prenatal death rates. If scientific opinion suggests alternative models may be more appropriate, one can then construct optimal designs for different models and compare their efficiencies under the competing models. The hope is that there is a design that remains efficient under all models that experts agree on.

Here is a short illustration of the situation just discussed. Assume,as before, that both the malformation and pre-natal death rates have the same form and can be described using two plausible models :

$$\pi_2^{(2)}(d) = 1 - \frac{a_2}{1 + b_2 d^{\gamma_2}}$$

and

$$\pi_2^{(3)}(d) = 1 - \frac{a_2}{1 + e^{-b_2 + \gamma_2 d}}.$$

Suppose the sets of nominal values are $\theta_2^{(2)} = (0.88, 0.25, 2.8)$, $\theta_2^{(3)} = (0.91, 4.3, 3.5)$, $\theta_1^{(2)} = (0.94, 1.3, 5.1)$ and $\theta_1^{(3)} = (0.98, 3.5, 3.2)$. We recall that $\theta_1^{(1)} = (0.06, 0.7, 3.37)$ and $\theta_2^{(1)} = (0.13, 0.27, 3.33)$. Here the superscripts denote the three different models used to describe the probabilities rates.

Table 13 lists the locally optimal designs for $\alpha = 0.5$ and their efficiencies under different assumptions on the probability models. The robustness properties of each optimal design under each set of probability models can be compared. For this setup, the efficiency results are quite reassuring because the smallest efficiency in the table is at least 0.76. Of course, different assumptions on the sets of nominal values may not yield the same conclusions.

In summary, our proposed design strategy is quite general and possess several advantages over existing methods. Unlike uniform designs, our approach is based firmly on statistical principles and the proposed maximin optimal design provides good protection against mis-specification in

Table 13: *Various locally optimal designs (left part) and their efficiencies under different probability models for estimating of prenatal death (first 3 rows), malformation rate (middle 3 rows) and overall toxicity (last 3 rows).*

Model	x_1	x_2	x_3	w_1	w_2	w_3	$\xi^{(1)}$	$\xi^{(2)}$	$\xi^{(3)}$
weibull	0	0.686	1	0.396	0.548	0.056	1.000	0.910	0.869
model 2	0	0.624	1	0.417	0.546	0.037	0.911	1.000	0.968
model 3	0	0.630	1	0.354	0.561	0.086	0.853	0.940	1.000
weibull	0	0.616	1	0.297	0.602	0.101	1.000	0.954	0.832
model 2	0	0.662	1	0.284	0.592	0.123	0.918	1.000	0.503
model 3	0	0.535	1	0.290	0.610	0.100	0.882	0.768	1.000
weibull	0	0.654	1	0.323	0.550	0.127	1.000	0.885	0.726
model 2	0	0.581	1	0.357	0.521	0.121	0.825	1.000	0.910
model 3	0	0.544	1	0.297	0.564	0.138	0.761	0.942	1.000

the nominal values of the model parameters. The optimal design allows prior information to be included in its construction and if required, can also incorporate multiple objectives with possibly unequal interests. Consequently, the proposed optimal design is able to meet the practical needs of the researcher more adequately than current designs.

7 A. Appendix: proofs

Proof of Theorem 1. From (3.1), the information matrix for a design ξ can be represented as

$$M(\xi,\theta)=\sum_{i=1}^{k} w_i f(d_i) f^T(d_i),$$

where the vector f is defined by

$$\begin{aligned} f(d) &= \frac{D(d)}{\sqrt{m(1+(m-1)\phi(d))\pi_2(d)(1-\pi_2(d))}} \\ &= \sqrt{\frac{(1-\pi_2(d))}{m(d)(1+(m(d)-1)\phi(d))\pi_2(d)}} \begin{pmatrix} 1 \\ d^{\gamma_2} \\ b_2 d^{\gamma_2}\ln(d) \end{pmatrix}. \end{aligned}$$

We now apply Elfving's theorem [see Elfving (1952)], which gives a geometric characterization of the optimal design. More precisely, from this result it follows that a design $\xi=\{d_i,w_i\}_{i=1}^k$ is locally optimal if and only if there exist numbers $\varepsilon_1,\dots,\varepsilon_k\in\{-1,1\}$ such that for some $\nu\in\mathbb{R}$ the point

$$\nu P = \nu\left(0,1/b_2,\frac{1}{\gamma_2}\ln\Big(-\frac{\ln(1-\alpha)}{b_2}\Big)\right)^T = \sum_{j=1}^{k}\varepsilon_j w_j f(d_j) \tag{A.1}$$

is a boundary point of the Elfving set

$$\mathcal{R} = \operatorname{conv}(\{\varepsilon f(d) \mid d\in[0,1],\varepsilon\in\{-1,1\}\}). \tag{A.2}$$

A typical picture of this set is presented in Figure 1 for the case of constant functions ϕ and m. We note that the curve

$$\mathcal{X}=\{f(d),\, d\in[0,1]\}$$

is contained in subspace $\{x=(x_1,x_2,x_3)^T\in\mathbf{R}^3|\, x_1>0\}$ and the set

$$\{(1,d^{\gamma_2},b_2 d^{\gamma_2}\ln(d))|\, d\in[0,1]\}$$

defines a U-shaped curve. From the monotonicity assumption for the function (3.3), it follows that the curve $\mathcal{X}$ is also U-shaped (see also Figure 1). We denote the endpoints of this curve by A and B and recall that the first coordinate of the vector P is equal to 0 and that ν is the scaling constant such that νP touches the boundary of the Elfving set $\mathcal{R}$. Note that in the case $\alpha\to 0$ we have that

$$P\approx c\begin{pmatrix}0\\0\\1\end{pmatrix}$$

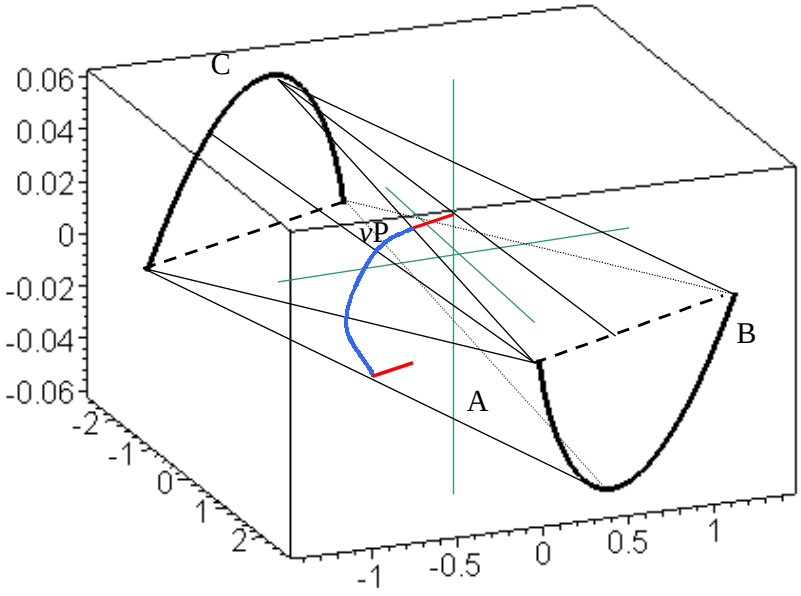

Figure 1: *The Elfving set defined in (A.2) for the parameters* $a = 0.133$, $b = 0.272$, $\gamma = 3.33$. *The points* $f(d_1)$, $-f(d_2)$, *and* $f(d_3)$ *are denoted by* A, C, *and* B, *respectively, while the point* νP *is defined in (A.1).*

for some constant c and, consequently, the vector νP touches the boundary at the plane $\mathcal{E}$ spanned by the points A, B and C, where A and B correspond to the doses 0 and 1, respectively and $-C$ corresponds to a third dose, say $d^* \in (0, 1)$. Consequently, the locally optimal design is a 3-point design with support points 0, 1 and d^*, if α is sufficiently small. In the case, where $\alpha \to 1$ the situation is exactly the same, and the locally optimal design is also supported at 3 points including the boundary points. From the geometry of the Elfving set $\mathcal{R}$ we see that there are also directions P, where the intersection with the Elfving set can represented by two points of the curves $\mathcal{X}$ and $-\mathcal{X}$. In particular this situation occurs if $\alpha \approx 1 - e^{-b}$. In this case we have

$$P \approx c \begin{pmatrix} 0 \\ 1 \\ 0 \end{pmatrix}$$

for some constant c, and the locally optimal design is supported at 2 points design. Moreover, if α moves from 0 to 1 it follows from geometry of the Elfving set that the situation is changing continously, which proves the assertion of the theorem. □

Proof of Theorem 2. From Elfving's theorem [see Elfving (1952)] it follows that a design $\{d_i; w_i\}$ is locally optimal (for the parameter $\theta = (a_2, b_2, \gamma_2)$) if and only if there exists a representation of the form

$$\text{(A.3)} \quad \nu P = \nu \begin{pmatrix} 0 \\ 1/b_2 \\ \ln(-\frac{\ln(1-\alpha)}{b_2}) \end{pmatrix} = \sum_i \varepsilon_i w_i \sqrt{\frac{(1-\pi_2(d_i))}{m(1+(m-1)\phi)\pi_2(d_i)}} \begin{pmatrix} 1 \\ d_i^{\gamma_2} \\ b_2 d_i^{\gamma_2} \ln(d_i^{\gamma_2}) \end{pmatrix}$$

for the boundary point $\nu P \in \mathcal{R}$. If $\{d_i^*(1); w_i^*\}$ denotes an optimal design for the parameter $\theta = (a_2, b_2, 1)$ it follows that equation (A.3) holds for this design with $\gamma_2 = 1$. Now it is easy to see that (A.3) is also true for the design $\{(d_i^*(1))^{1/\gamma_2}; w_i^*\}$ for the parameter $\theta = (a_2, b_2, \gamma_2)$ where $\gamma_2 > 0$ is arbitrary. □

Proof of Theorem 3. Part (a) of the Theorem follows directly from the geometry of the Elfving set. If the locally optimal design is supported at 3 points the corresponding point νP touches the Elfving set in the plane spanned by the points A, B, and C, which does not depend on the value of α. For a proof of part (b) we note that according to Elfvings theorem a locally optimal design of the form $\{0, d_2, w_1, w_2\}$ must satisfy the equation

$$\nu \begin{pmatrix} 0 \\ 1/b_2 \\ \ln(-\frac{\ln(1-\alpha)}{b_2}) \end{pmatrix} = \varepsilon w_1 g(0) \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix} - \varepsilon w_2 g(d_2) \begin{pmatrix} 1 \\ d_2^{\gamma_2} \\ b_2 d_2^{\gamma_2} \ln(d_2^{\gamma_2}) \end{pmatrix},$$

where the function g is defined by

$$g(d) = \sqrt{\frac{(1-\pi_2(d))}{m(d)(1+(m(d)-1)\phi(d))\pi_2(d)}}\,.$$

It is easy to see that this equation yields

$$\nu \begin{pmatrix} 1/b_2 \\ \ln(-\frac{\ln(1-\alpha)}{b_2}) \end{pmatrix} = -\varepsilon w_2 \sqrt{\frac{(1-\pi_2(d_2))}{m(d_2)(1+(m(d_2)-1)\phi(d_2))\pi_2(d_2)}} \begin{pmatrix} d_2^{\gamma_2} \\ b_2 d_2^{\gamma_2} \ln(d_2^{\gamma_2}) \end{pmatrix},$$

which simplifies to the equation

$$\nu \begin{pmatrix} 1 \\ \ln(ED_\alpha^{\gamma_2}) \end{pmatrix} = -\varepsilon w_2 \sqrt{\frac{(1-\pi_2(d_2))}{m(d_2)(1+(m(d_2)-1)\phi(d_2))\pi_2(d_2)}} b_2 d_2^{\gamma_2} \begin{pmatrix} 1 \\ \ln(d_2^{\gamma_2}) \end{pmatrix}.$$

It follows that $d_2 = ED_\alpha$. Since $w_1 = 1 - w_2$ from equality for first coordinate we have that $w_2 = g(0)/(g(0) + g(ED_\alpha))$.

□

Acknowledgements. The support of the Deutsche Forschungsgemeinschaft (SFB 475, "Komplexitätsreduktion in multivariaten Datenstrukturen") is gratefully acknowledged. The work of H. Dette and W.K. Wong was supported in part by a NIH grant award IR01GM072876.

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