Geometric construction of optimal designs for dose-response models with two parameters

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Abstract

In dose-response studies, the dose range is often restricted due to concerns over drug toxicity and/or efficacy. We derive optimal designs for estimating the underlying dose-response curve for a restricted or unrestricted dose range with respect to a broad class of optimality criteria. The underlying curve belongs to a diversified set of link functions suitable for the dose response studies and having a common canonical form. These include the fundamental binary response models – the logit and the probit as well as the skewed versions of these models. Our methodology is based on a new geometric interpretation of optimal designs with respect to Kiefer's Φ_p-criteria in regression models with two parameters, which is of independent interest. It provides an intuitive illustration of the number and locations of the support points of Φ_p-optimal designs. Moreover, the geometric results generalize the classical characterization of D-optimal designs by the minimum covering ellipsoid [see Silvey (1972) or Sibson (1972)] to the class of Kiefer's Φ_p-criteria. The results are illustrated through the re-design of a dose ranging trial.

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1 Introduction

The motivation for preparing this article arose from a commonly observed design problem in dose-response experiments which are routinely conducted in preclinical and Phase I and II clinical trials to study the relationship between the dose level of a drug and the probability of a response, be it "cured" or "poisoned". For decades, statisticians have been searching and advocating the adoption of optimal designs in clinical trials. However, computer algorithms for generating theoretical optimal designs usually assume an unrestricted dosage range; see for example, Chaloner and Larntz (1989), Zhu and Wong (2001). The issue of a restricted dose range is especially pertinent to studies done with human subjects. In clinical trials it was often noted (Gart et al., 1986) that "for many agents, the response rate at the high dose in the optimal design may exceed that found at the maximum tolerated dose". We recently encountered such an example. Prior to a dose ranging trial on a new rheumatoid arthritis drug at the Merck Research Laboratories, a pilot study was done where 120 patients were equally randomized into a placebo (dose 0) and a high dose (dose 50) group for a 6-week trial. According to this pilot study, the dose-response relationship with the original doses was found to be logistic (Zeng, Zhu and Wong (2000)) and as a consequence the original dose level was used in the dose-response function instead of the log dose level. The observed response rates were 35% at the placebo and 65% at the high dose. Based on these parameter estimates it follows from Ford, Torsney and Wu (1992), Table 4, that the locally optimal design for estimating the shape (slope) of the underlying dose-response curve (logit) would allocate half of the subjects to dose -71 and the other half to dose 121. It is impossible to implement such a design because the higher dose (121) exceeds the safety limit, and the lower dose (-71) has less drug content than the placebo. It is also hard to justify the role of this optimal design as a 'gold standard' in gauging other competing designs.

Little work has been done on the construction of optimal designs for dose response studies with a restricted dose interval. Extensive literature search yielded three related papers one by Ford, Torsney and Wu (1992), who derived locally c- and D-optimal designs on restricted and unrestricted design spaces, one by Mats, Rosenberger and Flournoy (1998) where they derived the locally c- and D-optimal designs for estimating the maximum tolerated dose in a Phase I clinical trial on a restricted design space, and one by Haines, Perevozskaya and Rosenberger (2003) where they extended the latter approach to Bayesian c- and D-optimal designs. For the Merck dose ranging trial, the goal was indeed to estimate the shape of the logit curve as precisely as possible subject to the constraint that the median effective dose, which is often regarded as the key index of a dose-response study, will be estimated with a certain precision. Such an optimal design is called a constrained optimal design (Lee, 1987). The constrained optimal designs are often hard to derive and little progress was made until Cook and Wong (1994) showed that there is a 1-1 correspondence between the constrained and the compound optimal designs. The compound optimal design would minimize a convex combination of the individual design criteria (in our example two variances) and is in general easier to solve for than its constrained counterpart. The implication is that we can now construct the entire class of compound optimal designs first and then search among them for the desired constrained optimal design using such straightforward tool as the efficiency plot proposed in Cook and Wong (1994).

For the Merck dose ranging trial, the locally compound optimal designs with unrestricted design interval carry the same undesirable feature as the slope optimal design. Therefore in this paper, we will focus on the derivation of restricted optimal designs for estimating the location and slope parameters of a binary response model, where the probability of a response at dose level x is given in a common canonical form for the usual class of dose-response models; see Wu (1988) and Mats, Rosenberger and Flournoy (1998) among many others. Our results, however, apply to the case of an unrestricted design interval as well. In Section 2 of this article, we put this design problem into a much more general framework. Following Chernoff (1953), we consider "locally optimal" design problems depending on a "best guess" for the unknown model parameters. In the ensuing discussion we will omit the word "locally" for simplicity. We will also suppress dependence on the nonlinear parameters in the notation which follows. Section 3 contains the main theoretical results of this paper. We present a new geometric interpretation of optimal design problems with respect to Kiefer's Φ_p-criteria in regression models with two parameters, which is of its own interest independent to the dose-response scenario. Roughly speaking, the Φ_p-optimal design problem is equivalent to the problem of finding the ellipse, which covers the induced design space and has minimal content relative to an ℓ_{2q}-norm of the lengths of the maximal and minimal diameter of the ellipse (where $1/p + 1/q = 1$). This optimal ellipse essentially determines the support points but not necessarily the weights; see Example 1 in Section 3. For the D-optimality criterion our result simplifies to the famous minimum covering ellipsoid problem studied by many authors [see, e.g., Silvey (1972), Sibson (1972), Silvey and Sibson (1973) and Haines (1993) among many others], but the geometric characterization of the optimal designs with respect to the other optimality criteria is novel, and provides a better understanding of the structure of Φ_p-optimal designs. In Section 4, we use this new geometric interpretation to study the properties of optimal designs in binary response models for a broad class of link functions with respect to all Φ_p-optimality criteria. In particular, we deal with the problem of restricted design spaces, which includes restrictions with respect to one as well as the two boundaries of the design interval. Moreover, we utilize the results of Pukelsheim and Torsney (1991) to derive formulas for the weights of the optimal designs. To illustrate the application of this new approach, we apply our results in Section 5 to re-design the dose ranging trial conducted at the Merck Research Laboratories (XXX, 1997). Some conclusions are given in Section 6, while the proofs of our results are deferred to an appendix.

Works most similar in spirit to the present paper are the publications of Ford, Torsney and Wu (1992) and Haines (1993). Ford, Torsney and Wu (1992) restricted themselves to the D- and c-optimality criteria. They used Elfving's (1952) and Sibson's (1972) classical geometric characterization of D- and c-optimality to determine optimal designs for regression models with two parameters. In some models only minimally supported D-optimal designs are determined. Haines (1993) also considered the D-optimality criterion and minimally supported designs. In the present paper we present a new geometric interpretation of Φ_p-optimal designs, which is of independent interest and generalizes the classical results of Silvey (1972) and Sibson (1972). We use these arguments to derive sufficient conditions for the two-parameter binary dose-response link functions such that the corresponding Φ_p-optimal designs are supported at exactly two points. Our conditions are satisfied within a broad class of binary response models on restricted or unrestricted dose ranges, and the theoretical results are applicable to ALL Φ_p-optimality criteria.

2 Optimal designs for binary response experiments

In a dose-response experiment, suppose we have n subjects and a proportion of ω_i subjects are allocated to dose $x_i,\ i = 1, 2, \ldots, k$. The corresponding design is usually denoted by

$$\xi = \left\{ \begin{array}{cccc} x_1 & x_2 & \cdots & x_k \\ \omega_1 & \omega_2 & \cdots & \omega_k \end{array} \right\}.$$

Let $\pi(x)$ represent the probability of success at a given dose level x, $H : [0,1] \to \mathbb{R}$ denotes a given distribution function (assumed to be almost surely continuously differentiable) and $h^2(z)$ is defined by

$$h^2(z) = \frac{(H')^2}{H(1-H)}(z). \tag{1}$$

The Fisher information matrix under the model $\pi(x) = H(\beta(x-\alpha))$ is given by

$$M(\xi) = \sum_{i=1}^{k} n\omega_i h^2(\beta(x_i - \alpha)) \begin{pmatrix} \beta^2 & -\beta(x_i-\alpha) \\ -\beta(x_i-\alpha) & (x_i-\alpha)^2 \end{pmatrix}.$$

For convenience, we will consider only approximate designs in the following, i.e. designs where $n\omega_i,\ i = 1, \ldots, k$, are not necessarily integers. For practical applications, some rounding procedure (see, e.g., Pukelsheim and Rieder (1992)) must be applied to the optimal approximate design before use.

For moderate sample sizes, the covariance of the maximum likelihood estimator for the parameter $K^T\theta = K^T(\alpha,\beta)^T$ is approximately proportional to the matrix $K^T M^{-1}(\xi) K$. An optimal design maximizes an appropriate function of the information matrix

$$C(\xi) = (K^T M^{-1}(\xi) K)^{-1}, \tag{2}$$

where the 2×2 matrix K used in this paper is defined by $K = \mathrm{diag}(\sqrt{\lambda}, \sqrt{1-\lambda})$ for some value $\lambda \in (0,1)$, reflecting different emphasis on the precision of the estimation of the respective parameters α and β. For the choice $\lambda = 1/2$, K is proportional to the identity matrix, yielding the corresponding design problem for estimating the parameter $(\alpha,\beta)^T$. Since we deal with optimal designs for estimating two model parameters, the support of such a design contains at least two different points, therefore we obtain a non-singular Fisher information matrix $M(\xi)$. That is the inverse $M^{-1}(\xi)$ used in the formulas above exists. In this work, we consider the well-known Φ_p-criteria,

$$\Phi_p(C) = (\frac{1}{2}\mathrm{tr}\, C^p)^{1/p} \ \text{ with } p \in (-\infty, 1], \quad \Phi_{-\infty}(\xi) = \lambda_{\min}(C), \tag{3}$$

where $\lambda_{\min}(C)$ denotes the minimum eigenvalue of the matrix C; see Kiefer (1974) or Pukelsheim (1993). A design ξ^* is called Φ_p-optimal for estimating the vector of weighted parameters $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$ if ξ^* maximizes the function $\Phi_p(C(\xi))$. The most widely used criteria are the well known A-, D- and E-optimality criterion, where $p = -1,\ 0,\ -\infty$, respectively. We further note that the matrix $C(\xi)$ is also proportional to the Fisher information matrix for the parameter $(\tau_1, \tau_2)^T$ in the linear regression model

$$y = \phi_1(z)\tau_1 + \phi_2(z)\tau_2 + \eta,\ z \in \mathcal{Z} \tag{4}$$

where $z = \beta(x-\alpha)$, $\phi_1(z) = -\beta h(z)/\sqrt{\lambda}$, $\phi_2(z) = z \cdot h(z)/(\beta\sqrt{1-\lambda})$, τ_1 and τ_2 are model parameters and η is a normal distributed error with mean 0 and variance σ^2. In (4) the design space $\mathcal{Z}$ is obtained from the original dose range by the transformation $z = \beta(x-\alpha)$. Note that if the original dose range in the binary response model is given by $\mathbb{R}$ we have $\mathcal{Z} = \mathbb{R}$ and we call this an unrestricted design space. Similarly, if the dose range is of the form $[x_{\min}, \infty)$ or $(-\infty, x_{\max}]$ the set $\mathcal{Z}$ is of the form $[A, \infty)$ or $(-\infty, B]$, which is denoted as one-sided or one-sided restricted design space. Finally two restrictions on the dose range, i.e. $x \in [x_{\min}, x_{\max}]$, yield a two-sided or two-sided restricted design space, say $\mathcal{Z} = [A, B]$. Thus, the Φ_p-optimal design problem for estimating the weighted parameter vector $(\sqrt{\lambda}\ \alpha, \sqrt{1-\lambda}\ \beta)$ in the binary response model coincides with a Φ_p-optimal design problem for the linear model (4). We finally note that Φ_p-optimal designs for different values of the location parameter, say μ_1, μ_2, are related by the transformation $x \to x + (\mu_1 - \mu_2)$. A similar statement, however, is not true for the scaling parameter, because the regression functions ϕ_1 and ϕ_2 in the equivalent linear model (4) depend on the parameter β.

3 A geometric interpretation of Φ_p-optimal designs in models with two parameters

The geometric interpretation of optimal design problems has a long history. Elfving (1952) characterized c-optimal designs, Silvey (1972), Sibson (1972) and Silvey and Titterington (1973) studied the geometric properties of D-optimal designs. Haines (1993) provided an alternative proof of this result and also considered minimally supported D-optimal designs. A geometric characterization of E-optimal designs can be found in Dette and Haines (1994), Dette and Studden (1993a, b), while more general versions of Elfving's work (for D-optimality and Bayesian optimality criteria) can be found in Dette (1993) and Dette (1996). Ford, Torsney and Wu (1992) used Elfving's (1952), Silvey's (1972) and Sibson's (1972) geometric characterizations to derive c-optimal and D-optimal designs for nonlinear regression models with two parameters (for the D-optimality criterion only minimally supported designs are determined by these authors). The same methods were used by Mats, Rosenberger and Flournoy (1998) to find c- and two-point D-optimal designs for binary response models. In this section, we derive a new interpretation of Φ_p-optimal designs, which generalizes the classical interpretation of Silvey (1972) and Sibson (1972) for the D-optimality criterion to all Φ_p-criteria. In the subsequent sections, we will use these geometric results to study the properties of Φ_p-optimal designs in binary response models with a restricted or unrestricted dose range.
As pointed out in the previous section, the optimal design problem for the binary response model is equivalent to an optimal design problem in the two-dimensional linear regression model (4). In the following, we consider the problem of maximizing $\Phi_p(C(\xi))$ where ξ is a design on $\mathcal{Z}$, and $C(\xi)$ denotes the information matrix in model (4). In order to guarantee the existence of a Φ_p-optimal design we assume that the induced design space

$$\mathcal{G} = \{(\phi_1(z), \phi_2(z))^T \mid z \in \mathcal{Z}\} \tag{5}$$

is compact. Define $\phi(z) = (\phi_1(z), \phi_2(z))^T$ as the design locus [see Haines (1993)] and for a nonnegative definite matrix $N \in \mathbb{R}^{2\times 2}$ the ellipse

$$E_N = \{u \in \mathbb{R}^2 \mid u^T N u \leq 1\}. \tag{6}$$

Let $q \in [-\infty, 1]$ denote the conjugate of $p \in [-\infty, 1]$, that is $p + q = pq$, and for a vector $x = (x_1, x_2)^T \in \mathbb{R}^2$ its ℓ_{2q}-mean or norm by

$$\ell_{2q}(x) = \Big[\frac{1}{2}\Big(|x_1|^{2q} + |x_2|^{2q}\Big)\Big]^{1/2q}. \tag{7}$$

It is easy to see that $2q \geq 1$ if and only if $p \in [-\infty, -1]$, and consequently for "most" of the Φ_p-criteria the formula (7) defines actually a norm on $\mathbb{R}^2$. For an ellipse E_N of the form (6) let $\ell_{2q}(E_N)$ denote the ℓ_{2q}-mean of the lengths of its major and minor diameter and define $\mathrm{Vol}(E_N)$ as its volume. Note that for a 2×2 matrix N with eigenvalues λ_i $(i = 1, 2)$ it follows that $\mathrm{Vol}(E_N) = \pi/\sqrt{\lambda_1\lambda_2}$ and $\ell_{2q}(E_N) = [(|2/\sqrt{\lambda_1}|^{2q} + |2/\sqrt{\lambda_2}|^{2q})/2]^{1/2q}$. The following result states that the problem of finding an ellipse of the form (6) covering $\mathcal{G}$ with minimal v_{2q}-content

$$v_{2q}(E_N) = \frac{\mathrm{Vol}(E_N)}{\ell_{2q}(E_N)} \tag{8}$$

is the dual of the Φ_p-optimal design problem in the linear regression model (4).

Theorem 1 *If the assumptions stated at the beginning of this section are satisfied, the Φ_p-optimal design problem in the linear regression model (4) is the dual of the problem of finding a centered ellipse which covers the induced design space $\mathcal{G}$ defined in (5) and has minimal v_{2q}-content, i.e.*

$$\max_{\xi} \Phi_p(C(\xi)) = 2\pi^{-2} \cdot \min_{\mathcal{G} \subset E_N} v_{2q}^2(E_N) = 2\pi^{-2} \cdot \min_{\mathcal{G} \subset E_N} \Big\{\frac{\mathrm{Vol}(E_N)}{\ell_{2q}(E_N)}\Big\}^2. \tag{9}$$

Moreover, the ellipse with minimal v_{2q}-content touches the induced design space $\mathcal{G}$ at the points $\phi(z_i^*)$, where z_i^* are the support points of any Φ_p-optimal design in the linear regression model (4).

Remark 1 Note that in the case $p = 0$ we have $q = 0$ which means

$$\ell_{2q}(E_N) = \Big(\frac{4}{\sqrt{\lambda_1\lambda_2}}\Big)^{1/2} = 2\sqrt{\mathrm{Vol}(E_N)/\pi},$$

where λ_1, λ_2 are the eigenvalues of the matrix N corresponding to the ellipse E_N. Therefore the duality in (9) reduces to the well known geometric interpretation of the D-optimal design problem [see Silvey (1972) or Sibson (1972)].

There are some other cases of particular interest. For example, if $p = -\infty$ (corresponding to the E-criterion) we have $q = 1$ and

$$v_2(E_N) = \frac{\mathrm{Vol}(E_N)}{\ell_2(E_N)}$$

gives the ratio of the volume and an ℓ_2-norm of the length of the maximal and minimal diameter of the ellipse. Similarly, the important case of A-optimality $(p = -1, q = 1/2)$ corresponds to an ℓ_1-norm, i.e.

$$v_1(E_N) = \frac{\mathrm{Vol}(E_N)}{\ell_1(E_N)}.$$

Example 1 Note that the ellipse which covers $\mathcal{G}$ with minimal v_{2q}-volume determines the support $supp(\xi^*)$ of a Φ_p-optimal design ξ^* in the sense that each point $z_i^* \in supp(\xi^*)$ corresponds to a point $\phi(z_i^*) = (\phi_1(z_i^*), \phi_2(z_i^*))^T \in \mathcal{G}$, where the minimum ellipse touches the induced design space. It might be tempting to derive a similar geometric characterization for the weights of the Φ_p-optimal design. However, the following example shows that this is not possible in general. Consider the linear regression model

$$y = \tau_1 z_1 + \tau_2 z_2 + \eta, \quad (z_1, z_2)^T \in [0,1]^2. \tag{10}$$

Then the induced design space is the unit square, i.e. $\mathcal{G} = [0,1]^2$, and the Φ_p-optimal design has masses $\omega,\ (1-\omega)/2,\ (1-\omega)/2$ at the points $\binom{1}{1}, \binom{1}{0}, \binom{0}{1}$, respectively, where

$$\omega = 1 - \frac{4}{3 + 3^{1/(1-p)}} \tag{11}$$

[see Pukelsheim (1993)]. The corresponding information matrix is given by

$$C(\xi^*) = \frac{1}{2} \begin{pmatrix} 1+\omega & 2\omega \\ 2\omega & 1+\omega \end{pmatrix}$$

and has eigenvalues $\frac{1}{2}(1+3\omega)$ and $\frac{1}{2}(1-\omega)$, which yields

$$\Phi_p(C(\xi^*)) = \frac{1}{2}\Big\{\frac{1}{2}\Big[(1+3\omega)^p + (1-\omega)^p\Big]\Big\}^{\frac{1}{p}} = \frac{2}{6^{1/p}}\Big(3 + 3^{1/(1-p)}\Big)^{(1-p)/p}, \tag{12}$$

where we used (11) in the last step. On the other hand the ellipse

$$E_{N^*} = \Big\{\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} \mid x_1^2 - x_1 x_2 + x_2^2 \le 1\Big\} \tag{13}$$

obviously contains the induced design space $\mathcal{G} = [0,1]^2$ and touches $\mathcal{G}$ at the points $\binom{1}{1}, \binom{0}{1}, \binom{1}{0}$ [see Figure 1]. A straightforward calculation using the relation $\frac{1}{p} + \frac{1}{q} = 1$ shows that

$$v_{2q}^2(E_{N^*}) = \Big(\frac{\mathrm{Vol}(E_{N^*})}{\ell_{2q}(E_{N^*})}\Big)^2 = \frac{\pi^2}{2}\Big\{\frac{1}{2}(1+3^q)\Big\}^{-\frac{1}{q}} = \frac{\pi^2}{6^{1/p}}(3 + 3^{1/(1-p)})^{(1-p)/p},$$

and a comparison with (12) shows that E_{N^*} is in fact the covering centered ellipse with minimal v_{2q}-content [see also Figure 1].
Therefore for any $p \in [-\infty, 1]$ the minimal ellipse is given by E_{N^*}, which does not depend on p, whereas the weights of the Φ_p-optimal design depend on the parameter p in a nontrivial way by (11). This example demonstrates that in general the weights of optimal designs cannot be obtained from the optimal ellipse E_{N^*}. In paragraph 4.5 of the following section, we will present an explicit method for determining the weights of the Φ_p-optimal design if the support points have been found by the geometric arguments presented in Theorem 1.

4 Φ_p-optimal designs for binary response models

In the situation considered in Section 2 we obtain for the design locus

$$\phi(z) = (\phi_1(z), \phi_2(z))^T = (-\beta\, h(z)/\sqrt{\lambda}, zh(z)/(\beta\sqrt{1-\lambda}))^T,$$

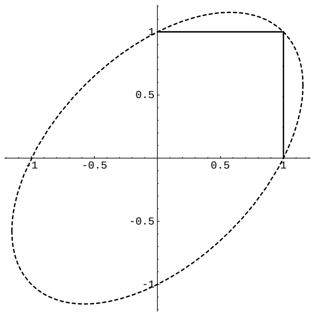

Figure 1: *The induced design space $\mathcal{G} = [0,1]^2$ (solid line) in model (10) and the covering centered ellipse E_{N^*} with minimal v_{2q}-content (dotted line), which is the same for all $p = 1 - 1/q \in [-\infty, 1]$.*

and the induced design space defined by (5) is given by

$$\mathcal{G} = \left\{ (-\beta\, h(z)/\sqrt{\lambda}, zh(z)/(\beta\sqrt{1-\lambda}))^T \mid z \in \mathcal{Z} \right\} \tag{14}$$

(note that $\mathcal{Z}$ is obtained from the original dose range by the transformation $z = \beta(x - \alpha)$ and therefore depends on α and β). By the assumption $\lambda \in (0,1)$ the Φ_p-optimal design ξ^* must have a non-singular information matrix $C(\xi^*)$ and therefore at least two support points. On the other hand it follows from Caratheodory's theorem [see Silvey (1980)] that there exists a Φ_p-optimal design with at most three support points.
We will now use the geometric intepretation in Theorem 1 to derive a suffient condition such that Φ_p-optimal designs in particular binary response models are minimally supported for all $p \in [-\infty, 1]$. Following the discussion in Section 3, we have to find an ellipse, say E_{N^*}, with minimal v_{2q}-volume defined by (8), which covers the induced design space $\mathcal{G}$. In Figure 2, we illustrate the induced design space for the logistic, complementary log-log (left part) and the double exponential and reciprocal model (right part) in the case $\lambda = 1/2$, $\beta = 1$.

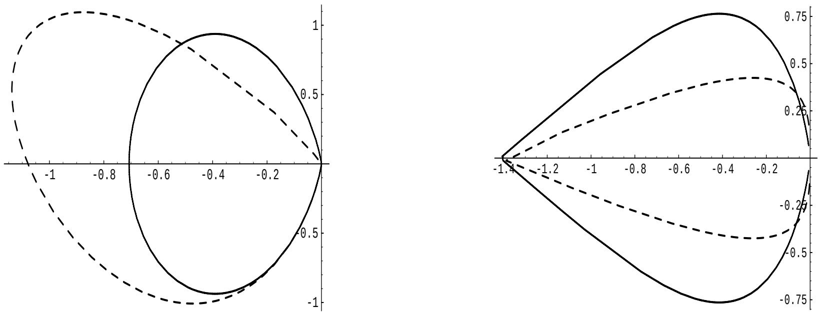

Figure 2: *The induced design space defined by (14) for $\mathcal{Z} = \mathbb{R}$, $\lambda = 1/2$, $\beta = 1$ for various binary response models. Left part: logistic model (solid) and complementary log-log model (dashed); Right part: double exponential model (solid) and double reciprocal model (dashed).*

It is apparent that a centered ellipse touching one of the induced design spaces presented in the left part at three points would have a rather large v_{2q}-volume. Therefore we expect Φ_p-optimal designs in the logistic and complementary log-log model to be supported at only two points. On the other hand, for the double exponential and reciprocal model the v_{2q}-volume of the ellipse can be diminished by using the interval $[-1, 1]$ as major diameter and consequently a centered covering ellipse with minimal v_{2q}-content would touch the induced design space at more than two points. Therefore we expect that Φ_p-optimal designs in these models have three support points. In the following we will make these heuristic arguments more rigorous. For this purpose, we state a condition on the function $h(z)$ such that the appropriate ellipse touches the induced design space at exactly two points.

Condition (I): The function $g(z) = h^{-2}(z)$ is twice differentiable on $\mathbb{R}$, and the equation $g''(z) = c$ has at most two solutions for any real constant c.

Condition (I) is satisfied by many of the commonly applied link functions, such as the logit and the probit link. A more detailed overview on the behavior of the commonly used link functions with respect to condition (I) is displayed in Table 1. Note that condition (I) is not complied with by the double exponential and the double reciprocal link functions, since the function $g(z) = h^{-2}(z)$ is not differentiable in the origin $z = 0$. The probit and logit models are the most fundamental models in dose-response studies. The logit model closely resembles the probit model and both are symmetrical around the ED50. One can easily envisage situations where the researcher would not want to impose the symmetry feature of the logit/probit link functions on their data (Stukel, 1988). The skewed logit model, also called power logit model, was first proposed by Prentice in 1976. It generalizes the logit model by adding an additional skew parameter in the form of the power of the logit function and has found applications in the biomedical field as well as other scientific research areas (e.g. Gaudard et al., 1993; Nagler, 1994; Hedayat et al., 1997; Wang and Hung,1997; Leuraud and Benichou 2001). The complementary log-log model is another asymmetrical extension of the logit/probit model especially pertinent to the toxicity studies (Kuk, 2004) and design in the time domain (Throne et al., 1995). In all these models condition (I) is satisfied.

Table 1: *Behavior of the function $h(z)$ for several common link functions $H(z)$ with respect to condition (I); ($s(z) = sign(z)$, $\Psi(z)$ the distribution function of the standard normal distribution, $\psi(z)$ the corresponding density function.)*

link function	$H(z)$	$h^2(z)$	condition (I)
Double Exponential	$\frac{1+s(z)}{2} - \frac{s(z)}{2} e^{-\lvert z\rvert}$	$\frac{1}{2e^{\lvert z\rvert}-1}$	not met
Double Reciprocal	$\frac{1+s(z)}{2} - \frac{s(z)}{2}\left(\frac{1}{1+\lvert z\rvert}\right)$	$\frac{1}{(1+\lvert z\rvert)^2(2\lvert z\rvert+1)}$	not met
Complementary Log-Log	$1 - e^{-e^z}$	$\frac{e^{2z}}{-1+e^{e^z}}$	met
Logit	$\frac{1}{(1+e^{-z})}$	$\frac{e^z}{(1+e^z)^2}$	met
Probit	$\Psi(z)$	$\frac{\psi^2(z)}{\Psi(z)(1-\Psi(z))}$	met
Skewed Logit ($m > 0$)	$\frac{1}{(1+e^{-z})^m}$	$\frac{m^2}{(1+e^z)^2(-1+(1+e^{-z})^m)}$	met

4.1 Φ_p-optimal designs on unrestricted design spaces

We now state several results about Φ_p-optimal designs in binary response models for estimating the vector of weighted parameters $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$ on the unrestricted design interval $\mathcal{Z} = \mathbb{R}$.

The proofs are given in the appendix.

Theorem 2 *Assume that condition (I) is satisfied for the binary response model under consideration.*

(a) For any $p \in [-\infty, 1]$ the Φ_p-optimal design for estimating the vector of weighted model parameters $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$ is supported at two points, which are uniquely determined.

(b) If, additionally, the function $h(z)$ is symmetric, then there exists a symmetric Φ_p-optimal design ξ on two points for estimating the vector of weighted parameters $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$, i.e. ξ is supported at points $-z_0,\ z_0$ with weights $1/2$ and $1/2$.

(c) For any $p \in (-\infty, 1)$ the Φ_p-optimal design is unique.

Note that Theorem 2 is applicable to ANY binary response model, which satisfies Condition (I). In Table 1 we have presented four examples where this condition is satisfied and as a consequence the Φ_p-optimal designs in the corresponding binary response models are supported at two points. There are many other link function, where Theorem 2 can be applied sucessfully. A typical nonstandard example is given by the Cauchy distribution function $H(z) = \frac{1}{2} + \frac{1}{\pi}\arctan(z)$, for which condition (I) can easily be checked. As a consequence all Φ_p-optimal designs for this binary response model are also supported at only two points. In the double exponential and reciprocal model condition (I) is not satisfied. This coincides with the result of Ford, Torsney and Wu (1992), who found that the D-optimal designs for these two links are supported on three points. We note that in these models the number of support points of the Φ_p-optimal designs depends on the size of the dose range and the weight λ in the optimality criterion [see our discussion in Section 4.6].

Remark 2

(a) If the function h is symmetric it follows from Theorem 2 (b) that Φ_p-optimal designs can be determined by a one-dimensional optimization problem.

(b) The results of Theorem 2 remain valid if the Φ_p-optimality criteria are replaced by general information functions in the sense of Pukelsheim (1993). This follows by a careful inspection of the corresponding proofs, where the geometric characterization of Φ_p-optimal designs has to be replaced by the general equivalence theorem in Pukelsheim (1993), sec. 7.16. A similar statement can be made for all other results presented in this paper. The geometric interpretation derived in Section 3, however, facilitates more insight and a deeper understanding of the nature of the design problem at hand, so that our results are given in terms of the geometric viewpoint, although the class of optimality criteria is thus restricted to Φ_p-criteria.

4.2 Optimal designs on restricted design spaces

To guarantee a certain level of drug efficacy due to the increasing ethics concerns, one must impose a lower bound on the design interval. Moreover, to avoid a severe side-effect or drug toxicity, one would have to impose an upper bound on the design interval. This means that the equivalent design space in the linear regression model (4) is of the form $\mathcal{Z} = [A, \infty)$, $\mathcal{Z} = (-\infty, B]$ or $[A, B]$. Note that for a restricted design space the induced design space $\mathcal{G}$ is curtailed. Consequently, if one of the support points of the unrestricted Φ_p-optimal design is not contained in the restricted design space one expects that the smallest (with respect to the v_{2q}-volume) ellipse enclosing $\mathcal{G}$ will touch $\mathcal{G}$ at one (or two) extreme point(s) corresponding to the boundary of the design space. A typical situation for the logistic regression model is depicted in Figure 3 for the case $p = -1$. For arbitrary models the situation is more complicated and an additional condition on the link function of the binary response model is required to make this geometric argument rigorous.

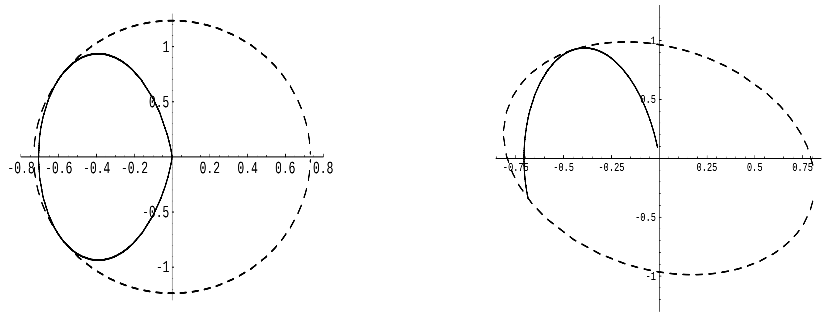

Figure 3: *The induced design space $\mathcal{G}$ defined by (14) for the logistic regression model and the covering ellipse with minimal v_1-content (corresponding to the A-criterion), where $\alpha = 0$, $\beta = 1$, $\lambda = 1/2$. The left part shows the situation for an unrestricted design space $\mathcal{Z} = \mathbb{R}$, while the case of a restricted design space $\mathcal{Z} = [-0.5, \infty)$ is illustrated in the right part of the figure.*

We will first present the left-restricted Φ_p-optimal designs for estimating the vector of weighted parameters $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$ in the binary response model with the normalized design interval in terms of $z = \beta(x - \alpha)$ being $[A, \infty)$, where $0 > A > z_L^*$, and z_L^* denotes the lower design point of the Φ_p-optimal design with the same λ on the unrestricted design interval $\mathcal{Z} = \mathbb{R}$. The derivation of optimal designs for the right-restricted design interval $(-\infty, B]$ with $B < z_U^*$, z_U^* denoting the upper design point, follows along the same lines and is thus omitted. These results will lead us to the more realistic scenario where both sides of the design interval are bounded as is true with the Merck dose ranging trial.

4.3 One-sided restricted intervals

Throughout this section, we assume that condition (I) is satisfied and denote by z_L^* and z_U^* the lower and upper support point of the unrestricted Φ_p-optimal design for estimating the vector of weighted parameters $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$. Note that in the case $z_L^* \geq A$ the Φ_p-optimal design on the unrestricted design space is obviously also Φ_p-optimal on the restricted design space $[A, \infty)$. The following two results concern the remaining case of $z_L^* < A$. We show that the left-restricted Φ_p-optimal design on $[A, \infty)$ is a two-point design, and furthermore its lower support point is always the left boundary point of the design interval. The following results hold as long as condition (I) and

Condition (II): $z \cdot h(z) \to 0$ as $z \to \pm\infty$.

are satisfied.

Lemma 1 *If condition (I) is fulfilled and $z_L^* < A$ for a given boundary value A, then the Φ_p-optimal design ξ^* for estimating the vector of weighted parameters $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$ on the interval $[A, \infty)$ is supported on exactly two different points.*

The proof of Lemma 1 follows by similar geometric considerations as given in the proof of Theorem 2 and is therefore omitted. The following theorem shows that in the case $z_L^* < A$ the point A is always a support point of the Φ_p-optimal design.

Theorem 3 *Assume that condition (I) and (II) are satisfied. If, for a given $\lambda \in (0, 1)$, the smaller support point of the Φ_p-optimal design for estimating the vector $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$ on $\mathcal{Z} = \mathbb{R}$ is not included in the interval $[A, \infty)$, then any Φ_p-optimal design for estimating the vector of weighted parameters $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$ on the interval $[A, \infty)$ has two unique support points, one of which is the boundary point A.*

It is easy to show that all link functions from Table 1 satisfy condition (II). Theorem 3 provides a sufficient condition such that Φ_p-optimal designs for estimating the vector of weighted parameters $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$ on the design space $[A, \infty)$ put masses ω_1 and $1 - \omega_1$ at the points A and z, respectively, where z denotes the upper support point of the design. A formula for the weight ω_1 is derived in paragraph 4.5, leaving only a univariate optimization problem in the variable z, which can be solved by standard numerical methods.

Remark 3 Note that Theorem 3 also applies to optimal design problems for binary response models with restricted dose ranges, where the restrictions are functions of the parameters [see e.g. Mats, Rosenberger and Flournoy (1998)]. Consider, for example, the situation where the experimenter is interested in precise estimation of the parameters α, β. Additionally no patient should be exposed to doses, where the probability of a response is less than $\pi \in (0, 1)$. In this case the dose range is $[x_{\min}, \infty)$ with $x_{\min} = \mu + H^{-1}(\pi)/\beta$, which corresponds to the design space $\mathcal{Z} = [H^{-1}(\pi), \infty)$ in the equivalent model (4).

4.4 Two-sided restricted intervals

The more realistic situation in dose-response experiments is when there exist restrictions on both the upper and the lower bound of the design interval. Furthermore, the restricted interval is not necessarily symmetrical around the location parameter α, or 0 in terms of the normalized dose level $z = \beta\,(x - \alpha)$. In the following, we assume the normalized design interval, i.e. the design interval corresponding to normalized dose levels z, to be $[A, B]$. For a given $\lambda \in (0, 1)$, we assume that the upper support point for the corresponding left-restricted Φ_p-optimal design on the design space $[A, \infty)$, say $z_{U,A}^*$, and the smaller support point for the right-restricted Φ_p-optimal design on the design space $(-\infty, B]$, say $z_{L,B}^*$, are not contained in the design interval $[A, B]$. If one of these points is in the interval $[A, B]$ the two-sided restricted Φ_p-optimal design for estimating the vector of weighted parameters $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$ coincides with the corresponding Φ_p-optimal design for the one-sided restricted design space.

Theorem 4 *Assume that conditions (I) and (II) are satisfied and $z^*_{L,B} < A < B < z^*_{U,A}$. The two-sided restricted Φ_p-optimal design $\xi^*_{A,B}$ for estimating the vector of weighted parameters $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$ on the design interval $[A,B]$ has two support points, which are given by the boundary points A and B. In particular, when the design interval and the function h are symmetric, the design which allocates equal weight to both boundary points is Φ_p-optimal for estimating the vector of weighted parameters $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$.*

4.5 A formula for the weights of optimal designs

In the cases considered in the two previous paragraphs, the optimal design problem reduces to the determination of one support point with corresponding weight in the case of a one-sided restricted design space and to the determination of the weight at one point in the case of a two-sided restricted design space. In the preceding discussion, we have provided some geometric tools for the determination of the support points of a Φ_p-optimal design. We will now derive formulas for the weights of the optimal designs using the results of Pukelsheim and Torsney (1991). For simplicity, we restrict ourselves to the case of a two-sided restricted interval $[A,B]$. The analogous results apply in the cases of unrestricted or one-sided restricted design spaces if A and B are replaced by the support points of the Φ_p-optimal design in the formulas below. Define by V the matrix $V = (XX^T)^{-1}XK$ with $X^T = (\phi(A), \phi(B)) \in \mathbb{R}^{2\times 2}$. For the given matrix K used in (2) the matrix V for a two-sided restricted Φ_p-optimal design on the design interval $[A,B]$ supported at A and B has the form

$$V = \begin{pmatrix} \frac{B\sqrt{\lambda}}{(B-A)\beta h(A)} & \frac{\beta\sqrt{1-\lambda}}{(B-A)h(A)} \\ \frac{A\sqrt{\lambda}}{(A-B)\beta h(B)} & \frac{\beta\sqrt{1-\lambda}}{(A-B)h(B)} \end{pmatrix}$$

which in turn implies that the information matrix $C = C(\xi) = (K^T M^{-1}(\xi)K)^{-1}$ of the design ξ with masses ω_1 and $1-\omega_1$ at the points A and B has the form

$$C = \begin{pmatrix} \frac{B^2\lambda}{\omega_1(B-A)^2\beta^2h^2(A)} + \frac{A^2\lambda}{(1-\omega_1)(A-B)^2\beta^2h^2(B)} & \frac{B\sqrt{1-\lambda}\sqrt{\lambda}}{\omega_1(B-A)^2h^2(A)} + \frac{A\sqrt{1-\lambda}\sqrt{\lambda}}{(1-\omega_1)(A-B)^2h^2(B)} \\ \frac{B\sqrt{1-\lambda}\sqrt{\lambda}}{\omega_1(B-A)^2h^2(A)} + \frac{A\sqrt{1-\lambda}\sqrt{\lambda}}{(1-\omega_1)(A-B)^2h^2(B)} & \frac{\beta^2(1-\lambda)}{\omega_1(B-A)^2h^2(A)} + \frac{\beta^2(1-\lambda)}{(1-\omega_1)(A-B)^2h^2(B)} \end{pmatrix}^{-1}.$$

We finally define by L the matrix $L = VC^{p+1}V^T$. In the case $p \in (-\infty, 1]$, it then follows from the results of Pukelsheim and Torsney (1991) that the weight vector $\omega = (\omega_1, 1-\omega_1)$ of a Φ_p-optimal design is given by

$$\omega_1 = \frac{\sqrt{L_{11}}}{\sum_{i=1}^2 \sqrt{L_{ii}}} \tag{15}$$

where L_{ii}, $i = 1, 2$, are the diagonal elements of the nonnegative definite 2×2 matrix L. Note that here the matrix C^{p+1} for any criterion $p \in (-\infty, 1]$ results from the eigenvalues λ_i, $i = 1, 2$, and the eigenvectors x_i, $i = 1, 2$, with $||x_i||_2 = 1$ of the matrix $C^{-1}(\xi) = K^T M^{-1}(\xi)K = V^T\Delta_\omega^{-1}V$ with $\Delta_\omega = \mathrm{diag}(\omega_1,\ 1-\omega_1)$ by the relation

$$C^{p+1} = \sum_{i=1}^{2} \lambda_i^{-p-1} x_i x_i^T.$$

The weight ω_1 can now be determined explicitly by solving the nonlinear equation (15). This problem can easily be implemented in standard software such as Mathematica or Matlab. For $p = -\infty$, i.e. the E-criterion, the $\Phi_{-\infty}$-optimal weight ω_1 corresponding to the support point A can be determined by the formula

$$\omega_1 = \sqrt{J_{11}}, \tag{16}$$

where J_{11} denotes the first diagonal element of the matrix $J = VCDCV^T$, and D is given by

$$D = \begin{cases} \dfrac{xx^T}{\lambda_{min}(C)} & \text{if } \lambda_{min}(C) \text{ is of multiplicity 1} \\ \dfrac{\gamma x_1 x_1^T + (1-\gamma) x_2 x_2^T}{\lambda_{min}(C)} & \text{if } \lambda_{min}(C) \text{ is of multiplicity 2} \end{cases};$$

see, e.g., Pukelsheim (1993). The expressions x, x_1, x_2 denote the norm 1 eigenvectors of the information matrix C corresponding to its smallest eigenvalue $\lambda_{min}(C)$, and γ is a constant from the open unit interval $(0, 1)$. The implementation of formula (16) in standard software is somewhat more complex than for the case $p \in (-\infty, 1]$ but still feasible.

Remark 4

(a) If the function h is symmetric and the design ξ has Φ_p-optimal design weights $\omega_1, 1 - \omega_1$ at the points z_1, z_2, then the Φ_p-optimal design weights of a design supported on $-z_2, -z_1$ are given by $1 - \omega_1$ and ω_1, respectively.

(b) If $\xi_A^* = \{A, z; \omega_1, 1 - \omega_1\}$ denotes a Φ_p-optimal design on the one-sided restricted interval $[A, \infty)$, then the design $\xi_{-A}^* = \{-z, -A; 1 - \omega_1, \omega_1\}$ is Φ_p-optimal on the one-sided restricted interval $(-\infty, -A]$.

(c) If $\xi_{A,B}^* = \{A, B; \omega_1, 1 - \omega_1\}$ denotes a Φ_p-optimal design on the two-sided restricted interval $[A, B]$, then the design $\xi_{-B,-A}^* = \{-B, -A; 1 - \omega_1, \omega_1\}$ is Φ_p-optimal on the two-sided restricted interval $[-B, -A]$.

Remark 4 is illustrated in Figure 4 where we display the behavior of the weight ω_1 corresponding to the smaller design support point A as a function of the value of $p \in (-\infty, 1]$ in the optimality criterion for the logit link function and on various two-sided restricted design spaces $[A, B]$ with different parameter values β and λ.
It is worthwhile to mention that the Φ_p-optimal designs highly resemble each other for $p \leq -2$. A heuristic explanation of this observation is as follows. Note that by Theorem 1 the determination of the Φ_p-optimal design requires the calculation of a covering ellipse with minimal v_{2q}-content [see the duality in (9)]. If $p \in [-\infty, -2]$ we have $2q \in [4/3, 2]$. We have depicted three unit balls with respect to the ℓ_{2q}-norm introduced in Section 3, $2q \in \{4/3, 3/2, 2\}$, in Figure 5, and the differences between these balls are not substantial. Consequently, we expect the covering ellipses with minimal ν_{2q}-content and, as a consequence, the Φ_p-optimal designs to be very similar.

Example 2 We discuss the important example of (weighted) A-optimality, which corresponds to the particular choice $p = -1$ in the Φ_p-optimality criterion. If condition (I) is satisfied the one-sided restricted Φ_{-1}-optimal design ξ_A^* on $[A, \infty)$ puts masses ω_1 and $1 - \omega_1$ at two points A and

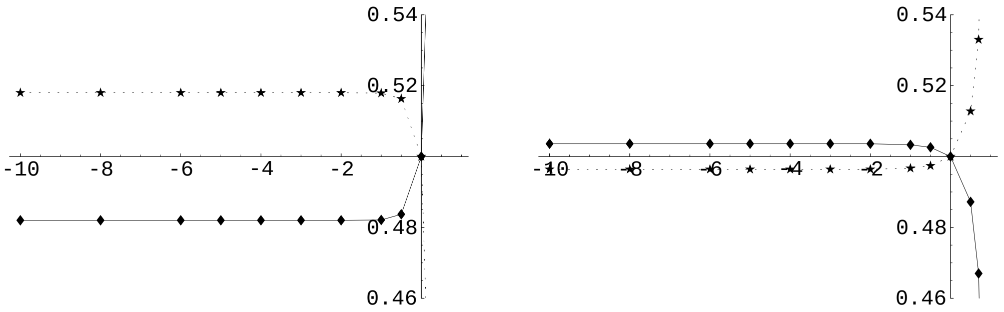

Figure 4: *The Φ_p-optimal weight ω_1 corresponding to the smaller support point A as a function of the parameter p in the Φ_p-optimality criterion. Left panel: $A = -0.4$, $B = 0.9$, $\beta = 2$, $\lambda = 0.25$ (solid line); $A = -0.9$, $B = 0.4$, $\beta = 2$, $\lambda = 0.25$ (dotted line). Right panel: $A = -0.8$, $B = 0.5$, $\beta = 2$, $\lambda = 0.75$ (solid line); $A = -0.5$, $B = 0.8$, $\beta = 2$, $\lambda = 0.75$ (dotted line).*

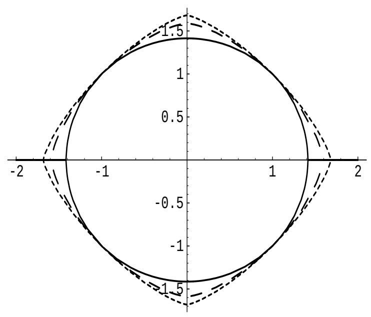

Figure 5: *The unit ball in $\mathbb{R}^2$ with respect to several ℓ_{2q}-norms. Solid line: $2q = 2$ ($p = -\infty$), dashed line: $2q = 3/2$ ($p = -3$), dotted line: $2q = 4/3$ ($p = -2$).*

z. The A-optimal design problem is now to find the support point z and the allocation proportion $\omega_1 \in [0, 1]$ such that $\text{tr}[C^{-1}(\xi)]$ is minimized. Solving equation (15) with respect to ω_1 yields

$$\omega_1 = \left[1 + \frac{h(A)}{h(z)} \sqrt{\frac{(1-\lambda)\beta^2 + \lambda A^2/\beta^2}{(1-\lambda)\beta^2 + \lambda z^2/\beta^2}}\right]^{-1}. \tag{17}$$

This weight is now used in the criterion function $\text{tr}[C^{-1}(\xi)]$ and the determination of the Φ_{-1}-optimal design becomes a univariate optimization problem for the support point z, for which standard numerical methods can be applied. In the two-sided restricted case, we obtain for ω_1 the corresponding expression with the unknown support point z replaced by the upper boundary B and the Φ_{-1}-optimal design has been found explicitly.

4.6 Binary response models with three-point optimal designs

We conclude this section with an illustration of the particular difficulties in the calculation of Φ_p-optimal designs for models, where condition (I) is not met, such as the double exponential or the double reciprocal model. In this situation, we obtain from Caratheodory's Theorem [see Silvey (1980)] that there exists a Φ_p-optimal design with at most three support points. We will

demonstrate that in this model the number of support points of the Φ_p-optimal design depends sensitively on the size of the design space and also on the parameter λ.
Again, we consider the case $p = -1$ corresponding to the A-optimality criterion, and choose the double exponential model (with $\alpha = 0$, $\beta = 1$) as an example. In Figure 6, we display the induced design space defined in (14) (solid line) and the ellipse with minimal v_1-content (dashed line) for the double exponential model, where $\lambda = 0.5$. For the set $\mathcal{Z}$ three cases are investigated: $\mathcal{Z} = \mathbb{R}$ (left panel), $\mathcal{Z} = [-0.2, \infty)$ (middle panel), and $\mathcal{Z} = [-0.2, 1]$ (right panel). If $\mathcal{Z} = \mathbb{R}$ the Φ_{-1}-optimal design allocates weights 0.3593, 0.2814 and 0.3593 to the support points -1.5936, 0 and 1.5936 (see the left panel of Figure 6). If $\mathcal{Z} = [-0.2, \infty)$ the Φ_{-1}-optimal design has also three support points -0.2, 0, 1.9056, with weights 0.3198, 0.0947, 0.5855, respectively (see the middle panel of Figure 6). The situation for the design space $\mathcal{Z} = [-0.2, 1]$ is different. Here the Φ_{-1}-optimal design has only two support points and allocates weights 0.4416 and 0.5584 to the left and right boundary of the design interval (right panel in Figure 6).

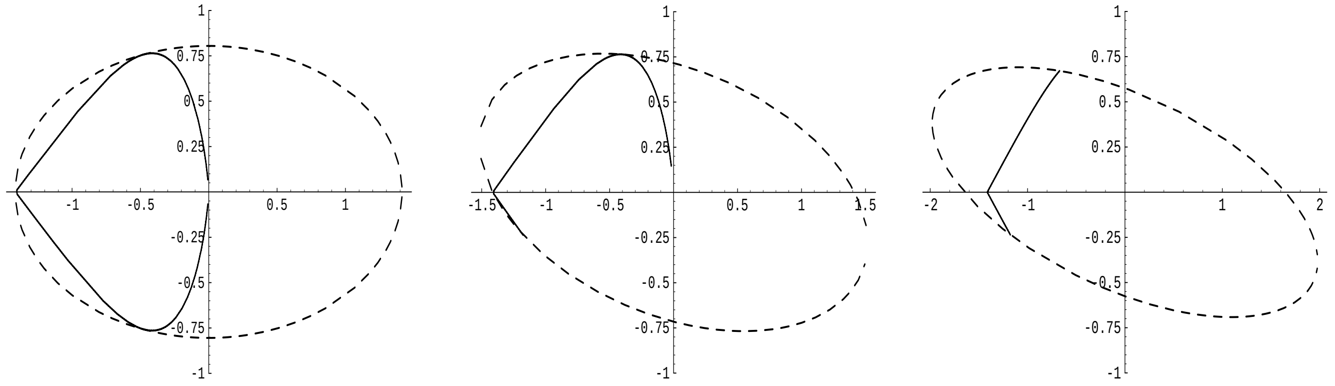

Figure 6: *The induced design space (14) with $\lambda = 0.5$ for the double exponential model (solid line) and the corresponding covering centered ellipse with minimal v_1-content (dashed line). Left panel: $\mathcal{Z} = \mathbb{R}$; Middle panel $\mathcal{Z} = [-0.2, \infty)$; Right panel: $\mathcal{Z} = [-0.2, 1]$.*

We note that the number of support points depends on the design space $\mathcal{Z}$ and a general statement regarding the number of support points of Φ_p-optimal designs will be difficult to obtain in such cases. Moreover, the picture depicted for $\lambda = 0.5$ also changes with the parameter λ. For example if $\lambda = 0.2$ only the Φ_{-1}-optimal design with $\mathcal{Z} = \mathbb{R}$ has three support points, while in the cases of $\mathcal{Z} = [-0.2, \infty)$ and $\mathcal{Z} = [-0.2, 1]$ two point designs are Φ_{-1}-optimal. On the other hand, if $\lambda = 0.8$, the Φ_{-1}-optimal design has three support points for all three scenarios. (The corresponding figures are not displayed for the sake of brevity).

5 Merck dose ranging trial revisited

In this section, we reanalyze a data example and demonstrate the practical relevance of the optimal designs derived in this work. The A-criterion discussed in Example 2 is an appropriate criterion for the given example. By this choice of optimality criterion, we obtain designs that minimize the weighted average of the variances $\lambda \mathrm{Var}(\widehat{\alpha}) + (1 - \lambda)\mathrm{Var}(\widehat{\beta})$ of the maximum likelihood estimators for the unknown model parameters α and β. This optimality criterion is also commonly referred to as compound optimality criterion in the multiple-objective optimality context.

¿From the 6-week pilot study done before the Merck dose ranging trial, the response rate at the placebo was 35% and the response rate at the high dose (dosage 50) was 65%. The logit model was fitted to these data and the maximum likelihood estimates of the model parameters were then obtained as $\widehat{\alpha} \approx 25$ and $\widehat{\beta} \approx 0.025$, which will be assumed the true values of α and β in the following. By a straightforward calculation, it follows that the variances of $\widehat{\alpha}$ and $\widehat{\beta}$ are proportional to $1/\beta^2$ and β^2, respectively, so since the value of β is very small, i.e. β^2 differs from $1/\beta^2$ considerably, we felt the necessity to use a particular standardized version of the A-optimality criterion (see, e.g., Dette (1997)), that is

$$\tilde{\lambda}\,\frac{\mathrm{Var}(\widehat{\alpha})}{v_\alpha(\xi^*_\alpha)} + (1-\tilde{\lambda})\,\frac{\mathrm{Var}(\widehat{\beta}\,)}{v_\beta(\xi^*_\beta)}, \tag{18}$$

where $v_\beta(\xi^*_\beta) = \min_\xi (0,1)M^{-1}(\xi)(0,1)^T$ corresponds to the optimal design for estimating the parameter β, $v_\alpha(\xi^*_\alpha)$ denotes the analogous expression for the parameter α, and $\tilde{\lambda} \in (0,1)$ is a preliminary weight chosen by the experimenter. In terms of the original weight λ, this approach corresponds to the choice $\lambda = (\frac{\tilde{\lambda}}{v_\alpha(\xi^*_\alpha)})/(\frac{\tilde{\lambda}}{v_\alpha(\xi^*_\alpha)} + \frac{1-\tilde{\lambda}}{v_\beta(\xi^*_\beta)})$. We derived unrestricted compound optimal designs for estimating the two model parameters α and β under the logit model. For each choice of preliminary weight $\tilde{\lambda}$, the compound optimal design is equally supported at two dose levels symmetrical to α. Selected unrestricted compound optimal designs are presented in Table 2. We found that the same negative lower dose and large higher dose pattern persists in the compound optimal designs for the Merck dose ranging trial.

To avoid the negative dose levels, we restricted the design interval to $[0,\infty)$ in terms of the original dosages where dose 0 corresponds to the placebo. This translates to a normalized dose range of $[-0.625,\infty)$. The smaller support points of the corresponding unrestricted compound optimal designs are not included in this interval. Selected left-restricted compound optimal designs in terms of the original design support points and the corresponding allocation proportions are given in Table 3. As the right support points from the left-restricted compound optimal designs appear to be high or very high, we felt it is necessary to restrict the design interval at both ends to avoid excessive toxicity and side effects, and thus use the interval $[0,60]$ in the original dose scale. The ensuing designs are supported on the two ending points with the corresponding design allocation proportions shown in Table 4.

Now that we have derived these reasonable optimal designs for the given dose ranging trial, we can gauge the efficiency of a practical design researchers wish to adopt for the upcoming trial against the optimal designs. For example, the uniform designs are popular choices for dose response studies in practice; see, e.g., Zhu, Ahn and Wong (1998). To gauge the efficiency of a 5-point equal allocation rule for estimating two logit model parameters with equal interest, we conducted the following simulation study. We assume the underlying logit model to be

$$Y_i \sim Bin(1,p_i), \quad p_i = 1/(1+e^{-\beta(x_i-\alpha)}), \tag{19}$$

where $\alpha = 25$ and $\beta = 0.025$. Two designs are compared in this study:

(1) the two-sided restricted compound optimal design ξ^*_{comp} with weight $\tilde{\lambda} = 0.5$, and

(2) the uniform design ξ^*_{uni} on the five equidistant points $0, 15, 30, 45, 60$ from the interval $[0, 60]$ including the endpoints (placebo dose and the highest dosage level allowed in the study).

Table 5 shows the simulated mean squared errors of the maximum likelihood estimates $\hat{\alpha}$, $\hat{\beta}$ for the designs defined in (1) and (2) based on data generated from model (19). The sample sizes are chosen consistently with the usual sample sizes in phase II clinical trials (for more information on sample sizes in clinical trials see, e.g., www.clinicaltrials.gov/ct/info/phase) and are given by 100, 150, 200 and 300, respectively, and 10,000 runs were carried out.
In general, the simulated mean squared errors for almost all estimates turn out to be significantly larger if the data are collected according to the uniform design ξ^*_{uni}, in particular for small to moderate sample sizes. For the large sample size of $n = 300$, the mean squared errors of the estimate $\hat{\alpha}$ become relatively close for the two designs under consideration. For the mean squared errors of $\hat{\beta}$, however, we find that for whatever sample size, the MSE of $\hat{\beta}$ based on the uniform design ξ^*_{uni} is about twice as large as the MSE of $\hat{\beta}$ when data are generated according to the two-sided restricted compound optimal design ξ^*_{comp}.
The above simulation study illustrates the importance of the compound optimal design on a restricted design interval for dose response clinical trials. In fact, virtually all dose response experiments involving human subjects have to be conducted on restricted design intervals. In the drug development process, dose-response studies are conducted mainly in the Phase I and Phase II clinical trials. The goal of the Phase I clinical trial is to determine the maximum tolerated dose (MTD). The dose response experiment is usually conducted in the interval of placebo to the larger of the dose with adverse effect and the top designed dose. In the Phase II clinical trial, the goal is to determine the dose response curve on drug efficacy. The dose response interval is between the placebo (dose 0) and the MTD (Chow, 2003). We feel that the Merck Dose Ranging study represents the typical case of a dose response study involving human subjects. It will alert statisticians and researchers to utilize optimal designs based on restricted dose intervals either directly or indirectly in their future dose-response trials.

6 Conclusions

In this paper we have presented a new geometric interpretation of Φ_p-optimal designs for regression model with two parameters, which generalizes the famous minimum ellipsoid problem for the D-optimality criterion [see Silvey (1972) or Sibson (1972)] to most of the commonly used optimality criteria. The dual problem of the Φ_p-optimal design problem is to find an centered ellipse covering the induced design space with minimal v_{2q}-content defined in (8), where q is the conjugate number of $p \in [-\infty, 1]$. This result provides some intuitive understanding of the number and location of the support points of Φ_p-optimal designs, although less can be said about the corresponding weights [see Example 1 presented in Section 3].
Our work was motivated by some optimal design problem for binary response models with restricted dose range, and we have successfully applied the above geometric characterization towards this challenge. In particular, we derived a sufficient condition on the link function such that the Φ_p-optimal design in the corresponding binary response model is minimally supported. If the dose range is restricted and the support points of the optimal designs on an unrestricted design space are not contained in the dose range under consideration we show that under a (very weak) additional

condition the boundary points of the design space always appear as support points of the optimal design. Both conditions are satisfied for most of the commonly used binary response models, but one condition is not fulfilled for the double reciprocal and the double exponential model. For the latter model, we present an example to demonstrate the difficulties in constructing Φ_p-optimal designs on restricted design spaces, if this condition is not met. In this case the answer to the question of whether the optimal design has two or three support points depends on the size of the dose range and a weight λ in the optimality criterion.
We also illustrate our methodology by re-designing an experiment conducted at the Merck Research Laboratories (XXX, 1997). We hope that our work will facilitate the utilization of optimal designs based on restricted dose intervals either directly or indirectly in the upcoming dose response trials.

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7 Appendix: Proofs

7.1 Proof of Theorem 1

Let Φ be an information function in the sense of Pukelsheim (1993), which maps the nonnegative definite 2×2 matrices on the real line. More precisely, an information function features the properties of being positively homogeneous, concave, nonnegative, non-constant and upper semicontinuous. Define

$$\Phi^\infty(D) \;=\; \inf_{A>0}\{\mathrm{tr}\,(AD)\}\ ,$$

as the polar function of an information function, where the infimum is taken over all 2×2 positive definite matrices; see Pukelsheim (1993). We use the notation $N \geq 0$ ($N > 0$) for a nonnegative (positive) definite matrix $N \in \mathbb{R}^{2\times 2}$. It follows from Pukelsheim (1993), Section 7.12, that

$$\max_{\xi} \Phi(C(\xi)) = \min_{N\in\mathcal{N}} \frac{1}{\Phi^\infty(N)} \tag{20}$$

where the maximum is taken over all designs on $\mathcal{Z}$ and

$$\mathcal{N} = \{N \geq 0 \mid u^T N u \leq 1 \quad \forall\, u \in \mathcal{G}\}. \tag{21}$$

Obviously, we have $N \in \mathcal{N}$ if and only $\mathcal{G} \subset E_N$, and it follows from (20)

$$\max_{\xi} \Phi(C(\xi)) = \min_{\mathcal{G}\subset E_N} \frac{1}{\Phi^\infty(N)}. \tag{22}$$

We now specialize this result to the case of Φ_p-optimality criteria, for which

$$\Phi_p^\infty(N) = 2\Phi_q(N) = \{(\mathrm{tr}\, N^q)/2^{1-q}\}^{1/q},$$

where $q \in [-\infty, 1]$ is the conjugate of $p \in [-\infty, 1]$. If λ_1, λ_2 denote the (positive) eigenvalues of the matrix N it follows that

$$\begin{aligned}
\Big(\frac{\mathrm{tr} N^q}{2^{1-q}}\Big)^{-\frac{1}{q}} &= \Big(\frac{1}{2^{1-q}}(\lambda_1^q + \lambda_2^q)\Big)^{-\frac{1}{q}} = \frac{\{\frac{1}{2^{1-q}}(\lambda_1^{-q} + \lambda_2^{-q})\}^{-\frac{1}{q}}}{\lambda_1 \lambda_2} \\
&= 2 \cdot \Big\{ \frac{[\frac{1}{2}\{(\frac{2}{\sqrt{\lambda_1}})^{2q} + (\frac{2}{\sqrt{\lambda_2}})^{2q}\}]^{-1/2q}}{\sqrt{\lambda_1 \lambda_2}} \Big\}^2 \\
&= 2\pi^{-2} \cdot \Big\{ \frac{\mathrm{Vol}(E_N)}{\ell_{2q}(E_N)} \Big\}^2,
\end{aligned}$$

where $\mathrm{Vol}(E_N)$ is the volume of the ellipse E_N and $\ell_{2q}(E_N)$ the ℓ_{2q}-norm defined in (7) of the lengths of its major and minor diameter. Consequently, it follows that

$$\max_{\xi} \Phi_p(C(\xi)) = 2\pi^{-2} \cdot \min_{\mathcal{G} \subset E_N} \Big\{ \frac{\mathrm{Vol}(E_N)}{\ell_{2q}(E_N)} \Big\}^2 = 2\pi^{-2} \cdot \min_{\mathcal{G} \subset E_n} v_{2q}^2(E_N), \tag{23}$$

which proves the first assertion of the theorem. Moreover, there must be equality in (23) [or equivalently in (20)] for any Φ_p-optimal design ξ^* and the centered covering ellipse E_{N^*} with minimal v_{2q}-content. Now Theorem 7.11 in Pukelsheim (1993) implies

$$1 = \mathrm{tr}(C(\xi^*)N^*) = \sum_{i=1}^{n} \omega_i^* \phi^T(z_i^*) N^* \phi(z_i^*),$$

where $\phi(z) = (\phi_1(z), \phi_2(z))^T$, and $z_1^*, \ldots, z_n^*$ denote the support points with corresponding weights $\omega_1^*, \ldots, \omega_n^*$ of the Φ_p-optimal design ξ^*. Since $\mathcal{G} \subset E_{N^*}$ it follows that the ellipse E_{N^*} with minimal v_{2q}-content touches the induced design space $\mathcal{G}$ at the suppport points of the Φ_p-optimal design ξ^*, i.e. $\phi^T(z_i^*) N^* \phi(z_i^*) = 1;\ i = 1, \ldots, n.$

□

7.2 Proof of Theorem 2

The proof of Theorem 2 is divided into two lemmata, from which the assertion of the theorem becomes obvious. The first lemma shows that a Φ_p-optimal design ξ^* for estimating the vector of weighted parameters in a binary response model will always be a two point design if condition (I) is satisfied. The second lemma deals with the symmetry of a Φ_p-optimal design.

Lemma 2 *Assume condition (I) is satisfied. Then any Φ_p-optimal design for estimating the vector of weighted parameters $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$ is supported on exactly two points.*

Proof of Lemma 2: By Theorem 1, we have to find an ellipse E_N with minimal v_{2q}-content, which covers the induced design space. Let N denote the corresponding matrix of the ellipse, then E_N contains $\mathcal{G}$ if and only if

$$\phi^T(z) N \phi(z) \leq 1 \quad \forall\, z \in \mathcal{Z}. \tag{24}$$

Moreover, the ellipse E_N touches $\mathcal{G}$ at all points $\phi(z_i)$ corresponding to the support points $z_i \in \mathcal{Z}$ of the Φ_p-optimal design, which means that there is equality in (24) for these points. A straightforward calculation shows then that the inequality in (24) is equivalent to

$$az^2 + bz + c \leq h^{-2}(z) \quad \forall\, z \in \mathcal{Z} \tag{25}$$

for some real coefficients $a,\ b,\ c$. Suppose that the Φ_p-optimal design has at least three support points $z_1 < z_2 < z_3$, i.e. we have $f(z_i) = g(z_i)$, $i = 1, 2, 3$, where $f(z)$ denotes the left hand side of the inequality (25). By the mean value theorem we obtain that there exist z_1', z_3' such that $z_1 < z_1' < z_2 < z_3' < z_3$ and $f'(z_i') = g'(z_i')$, $i = 1, 3$. Since $f(z) \le g(z)$ holds for all $z \in \mathbb{R}$, the points z_i, $i = 1, 2, 3$, are all tangent points, i.e. $f'(z_i) = g'(z_i)$. Applying the mean value theorem again to the functions $f'(z), g'(z)$, we receive points z_i'', $i = 1, \dots, 4$ such that $z_1 < z_1'' < z_1' < z_2'' < z_2 < z_3'' < z_3' < z_4'' < z_3$ and $f''(z_i'') = g''(z_i'')$, $i = 1, \dots, 4$. Since $f''(z) = 2a$ for all $z \in \mathbb{R}$, we have $g''(z_i'') = 2a$, $i = 1, \dots, 4$, which contradicts with condition (I). $\Box$

Lemma 3 *If the function h is symmetric, then there exists a symmetric Φ_p-optimal design for estimating the vector of weighted parameters $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$ on $\mathcal{Z} = \mathbb{R}$.*

Proof of Lemma 3: The existence of a Φ_p-optimal design follows from the compactness of the induced design space and the continuity of the optimality criterion. Note that the Φ_p-optimality criterion is concave and symmetric, i.e. $\Phi_p(C(\xi)) = \Phi_p(C(\xi^-))$, where ξ^- denotes the reflection of the design ξ at the origin. The existence of a symmetric Φ_p-optimal design now follows by a standard argument in decision theory. $\Box$

Proof of Theorem 2: By Lemma 2 and 3 it remains to prove the uniqueness of the support of the Φ_p-optimal design.

(a) Let ξ_1, ξ_2 be two Φ_p-optimal designs for estimating the vector $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$. ¿From Lemma 2, we conclude that they are both supported on two points. The concavity of the criterion function Φ_p implies that the design $\xi_3 = \frac{1}{2}\xi_1 + \frac{1}{2}\xi_2$ is also Φ_p-optimal. If the support of the design ξ_1 does not coincide with the support of ξ_2, the design ξ_3 is supported on more than two points, which contradicts the assertion of Lemma 2.

(b) Let ξ be a Φ_p-optimal design for estimating the vector $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$. The assumptions regarding the information function Φ_p imply that ξ^- is also Φ_p-optimal. ¿From the concavity of the criterion function we derive that $\xi_s = \frac{1}{2}\xi + \frac{1}{2}\xi^-$ is also Φ_p-optimal. If the support of ξ is not equal to the support of ξ^-, i.e. the support points of ξ are not symmetric about the origin, this is a contradiction to the assertion of Lemma 2.

(c) For $-\infty < p < 1$ the criterion function Φ_p is strictly concave, and it follows that $\xi_s = \xi$ and thus the uniqueness of the Φ_p-optimal design. $\Box$

7.3 Proof of Theorem 3

For each $\lambda \in (0, 1)$, first we notice that the Φ_p-optimal design ξ_A^* for estimating the vector of weighted parameters $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$ on the restricted design space $[A, \infty)$ satisfies condition (25) on the interval $[A, \infty)$ but not on the whole real axis. Otherwise, ξ_A^* would also be optimal in the unrestricted situation. Since we assume that the smaller support point for the unrestricted Φ_p-optimal design is not included in $[A, \infty)$, we have two designs with different support points which are both optimal in the unrestricted sense. This contradicts the uniqueness of the support of the unrestricted Φ_p-optimal design. The above reasoning implies that there exists some $z' < A$ such that $f(z')h^2(z') > 1$. Moreover, from condition (II), it follows that there exists a point $z'' < z'$ such that for $z \le z''$ the inequality $f(z)h^2(z) \le 1$ holds again. Therefore we will encounter two intersection points z_0, z_1 between the functions $f(z)$ and $h^{-2}(z)$ on the interval $(-\infty, A]$. Assume that $z_0 < z_1 < A$ and denote by z_2, z_3 the support points of the design ξ_A^*, where $A < z_2 < z_3$, i.e. $f(z_i) = g(z_i)$ for $i = 0, 1, 2, 3$. By applying the mean value theorem to f and g and bearing in mind that z_2 and z_3 are tangent points, we obtain that there exist points z_1', $z_0 < z_1' < z_1 < A$ and z_2', $z_2 < z_2' < z_3$ with $f'(z_i') = g'(z_i')$, $i = 1, 2$ and $f'(z_i) = g'(z_i)$, $i = 2, 3$. A further application of the mean value theorem yields that there exist points z_i'', $i = 1, 2, 3$, $z_1' < z_1'' < z_2 < z_2'' < z_2' < z_3'' < z_3$ where $f''(z_i'') = g''(z_i'')$, $i = 1, 2, 3$, which leads to a contradiction with the fact that the equation $g''(z) = 2a$ can have at most two different solutions. Therefore, the smaller support point for the one-sided restricted Φ_p-optimal design must be the left boundary point of the design interval.

□

7.4 Proof of Theorem 4

By the same line of argument as in the proof of Theorem 3, we can show that there exist points z', z'', $z' > B$, $z'' < A$ such that $f'(z') = g'(z')$ and $f'(z'') = g'(z'')$. Next, we will show that a Φ_p-optimal design $\xi_{A,B}^*$ for estimating the vector of weighted parameters $K^T\theta = (\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)$ on the two-sided restricted interval $[A, B]$ has only two support points by contradiction. Assume that $z_1 < z_2 < z_3$ are support points for $\xi_{A,B}^*$. The mean value theorem implies that there exist points z_1' and z_2' such that $z_1 < z_1' < z_2 < z_2' < z_3$ and $f'(z_i') = g'(z_i')$, $i = 1, 2$. Applying the mean value theorem to f' and g' again, we found three different values z_1'', z_2'', z_3'' such that $f''(z_i'') = g''(z_i'')$, $i = 1, 2, 3$. This leads to a contradiction to the fact that the equation $g''(z) = 2a$ can have at most two different solutions. Thus the Φ_p-optimal design $\xi_{A,B}^*$ has only two support points, which are given by the two boundary points A and B of the design interval $[A, B]$. If $A = -B$ and the conditions of part *(b)* of Theorem 2 are fulfilled, the optimality of the equally weighted design on $-B$, B follows along the same lines as in the proof of part *(b)* of Theorem 2. □

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Table 2: Selected unrestricted compound optimal designs for the Merck dose ranging trial in terms of the support points

$\tilde{\lambda}$	.1	.2	.3	.4	.5	.6	.7	.8	.9
x_1	-56.94	-48.94	-42.96	-37.90	-33.26	-28.73	-23.99	-18.56	-11.23
x_2	106.94	98.94	92.96	87.90	83.26	78.73	73.99	68.56	61.23

Table 3: Selected left-restricted compound optimal designs in terms of the original support points $x_1 = 0$, x_2 and the corresponding allocation proportions ω_1, ω_2

$\tilde{\lambda}$	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
x_2	129.25	124.10	119.39	114.70	109.71	104.07	97.21	88.02	73.51
ω_1	0.385	0.428	0.464	0.496	0.526	0.553	0.578	0.597	0.598
ω_2	0.615	0.572	0.536	0.504	0.474	0.447	0.422	0.403	0.402

Table 4: Selected 2-side unsymmetrically restricted compound optimal designs (supported at the boundary values $x_1 = 0$, $x_2 = 60$)

$\tilde{\lambda}$	.1	.2	.3	.4	.5	.6	.7	.8	.9
ω_1	0.492	0.495	0.499	0.503	0.509	0.516	0.524	0.535	0.550
ω_2	0.508	0.505	0.501	0.497	0.491	0.484	0.476	0.465	0.450

Table 5: Simulated mean squared errors of the maximum likelihood estimates $\hat{\alpha}$, $\hat{\beta}$ for the two-sided restricted compound optimal design ξ^*_{comp} with weight $\tilde{\lambda} = 0.5$ and the uniform design ξ^*_{uni} on five different equidistant points from the design interval $[0, 60]$ including the endpoints

	$n = 100$		$n = 150$		$n = 200$		$n = 300$	
	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\alpha}$	$\hat{\beta}$
ξ^*_{comp}	106.56	$6.10 \cdot 10^{-5}$	58.61	$3.54 \cdot 10^{-5}$	42.17	$2.72 \cdot 10^{-5}$	26.21	$1.73 \cdot 10^{-5}$
ξ^*_{uni}	176.81	$1.09 \cdot 10^{-4}$	93.67	$7.21 \cdot 10^{-5}$	57.70	$5.25 \cdot 10^{-5}$	30.05	$3.35 \cdot 10^{-5}$