Optimal designs for the EMAX, log-linear and exponential model

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Abstract

In this paper we derive locally D- and ED_p-optimal designs for the exponential, log-linear and three parameter EMAX-model. We show that for each model the locally D- and ED_p-optimal designs are supported at the same set of points, while the corresponding weights are different. This indicates that for a given model, D-optimal designs are efficient for estimating the smallest dose which achieves $100p\%$ of the maximum effect in the observed dose range. Conversely, ED_p-optimal designs also yield good D-efficiencies. We illustrate the results using several examples and demonstrate that locally D- and ED_p-optimal designs for the EMAX-, log-linear and exponential model are relatively robust with respect to misspecification of the model parameters.

Keywords and Phrases. Optimal design, D-optimality, ED_p-optimality, Elfving's Theorem, Chebyshev system, dose finding, dose response

AMS Subject Classification: 62K05

1 Introduction

The EMAX, log-linear and exponential models are widely used in various applications, especially in modeling the relationship between response and a given dose. These three models reflect different potential response shapes. For example, one may assume that the dose-response relationship of a drug is increasing and has a maximum effect which is achieved asymptotically at large dose levels. This is reflected by the EMAX model

$$f(x,\theta) = \theta_0 + \frac{\theta_1 x}{x+\theta_2},$$

where x denotes the dose, θ_0 the placebo effect at dose $d=0$, θ_1 the asymptotic maximum treatment benefit over placebo and θ_2 the dose that gives half of the asymptotic maximum effect. In particular, the $\mathrm{E}_{\mathrm{max}}$ can be justified on the relationship of drug-receptor interactions and therefore deduced from the chemical equilibrium equation [1].
The log-linear model describes the relationship between the dose of a drug and its effect, where the effect increases linearly in the logarithm of dose, that is

$$f(x,\theta) = \theta_0 + \theta_1 \log(x+\theta_2).$$

Here θ_0 denotes the placebo effect and θ_1 defines the increase of $\log(x+\theta_2)$, where θ_2 is an additive constant to avoid difficulties with the logarithm when the placebo response is zero. A difference between the EMAX and the log-linear model is that the latter produces an unbounded effect, as dose approaches infinity. For example, [24] used the log-linear model to relate the synthesis rate of prothrombin complex activity to the plasma concentration of warfarin; see [22] for further applications.
Relationships of dose and effect, which have a sublinear or convex structure, are described by the exponential model

$$f(x,\theta) = \theta_0 + \theta_1 \exp{(x/\theta_2)}$$

where θ_0 denotes the placebo effect, θ_1 the slope of the curve and θ_2 determines the rate of effect increase. We refer to [13] and [25] for application of this model in quantitative risk assessment and clinical dose finding studies, respectively.
Because of the broad applicability of these models, especially in the development of a new compound, such as a drug or a fertilizer, the availability of efficient experimental designs employing the EMAX, log-linear and exponential model is important. Good designs can substantially improve the efficiency of statistical analyses. Optimal designs for the EMAX model with two parameters (i.e. $E_0 = 0$) have been discussed by numerous authors [see for example Dunn (1988), Rasch (1990), Song and Wong (1998), Dette and Biedermann (2003), Dette, Melas and Pepelyshev (2003), Lopez-Fidalgo and Wong (2002) among others]. D-optimal designs for the exponential model have been discussed by Dette and Neugebauer

(1997), Han and Chaloner (2003) and Dette, Martinez Lopez, Ortiz Rodriguez and Pepelyshev (2006) among others. It appears there is scant literature on optimal designs for the log-linear model [see for example Dette, Bretz, Pepelyshev and Pinheiro (2008)]. In this paper we discuss similarities between optimal designs for these three models, when the design space is given by an interval. We consider locally optimal design problems [see Chernoff (1953)], which require initial best guesses of the unknown model parameters. Typically, optimal designs of this type are used as benchmarks in many applications. However in some cases, such as in clinical trials, relatively good initial/upfront information about the model parameter is available [see e.g. Bretz et al. (2005, 2008)]. Moreover, locally optimal designs are often needed for the construction of experimental designs with respect to more sophisticated optimality criteria, such as Bayesian or standardized maximin-optimal designs [see e.g. Chaloner and Verdinelli (1995), Dette and Neugebauer (1997), Braess and Dette (2007), Dette (1997), Müller and Pazman (1998) or Imhof (2001) among many others].

In Section 2 we motivate the methods described in this paper with an example of a clinical dose finding study. In Section 3 we briefly introduce the necessary notation. In Section 4 we determine locally D-optimal designs for the three parameter EMAX and log-linear model. For the exponential model these designs have been found in Dette and Neugebauer (1997), Han and Chaloner (2003) and Dette, Martinez Lopez, Ortiz Rodrguez and Pepelyshev (2006). In Section 5 we consider locally optimal designs for estimating the ED_p for the three models, where the ED_p is defined as the smallest dose achieving $100p\%$ of the maximum effect in the observed dose range. We demonstrate that in each of the three models the locally D- and ED_p-optimal designs are supported at the same points: the two boundary points of the design interval and one interior point depending on the model under consideration. Interestingly, the support points of locally D- and ED_p-optimal designs coincide with the interior support points of the locally optimal design for estimating the minimum effective dose (MED), if this design is supported at three points [see Dette, Bretz, Pepelyshev and Pinheiro (2008)]. This indicates that D-optimal designs are relatively efficient for estimating the MED and ED_p in the EMAX, log-linear and exponential model and vice versa. This is confirmed by several examples in Section 6. There we also demonstrate that locally optimal designs are relatively sensitive with respect to misspecification of the underlying model. On the other hand, if a given model can be justified (for example by previous trials or pharmacokinetic data) we demonstrate that locally D- and ED_p-optimal designs are robust with respect to misspecification of the model parameters.

2 A clinical dose finding study

To illustrate and motivate the methods described in this paper, we consider a clinical dose finding study for an anti-anxiety drug (Pinheiro et al., 2006). The primary endpoint is the

Table 2.1: *Dose response models with corresponding parameter values. All models are normalized such that the maximum effect is 0.4.*

Model	$f(x, \theta)$	$\theta = (\theta_0, \theta_1, \theta_2)$
EMAX	$\theta_0 + \theta_1 \frac{x}{x+\theta_2}$	(0.0, 0.467, 25)
Log-linear	$\theta_0 + \theta_1 \log(x + \theta_2)$	(0.0, 0.0797, 1)
Exp	$\theta_0 + \theta_1 \exp(x/\theta_2)$	(-0.08265, 0.08265, 85)

change from baseline in an anxiety scale score at study end. A homoscedastic normal model is assumed. Without loss of generality it is also assumed that the placebo effect is $\theta_0 = 0$ and the maximum treatment effect within the dose range $[a, b] = [0mg, 150mg]$ under investigation is 0.4. Furthermore, we assume that all dose levels within the investigated dose range are safe, so that efficacy is the primary interest. The main goal of the study is to estimate the smallest dose achieving $100p\%$ of the maximum effect in the observed dose range with $p = 0.5$. Based on discussions with the clinical team prior to the start of the study, different candidate models were identified to potentially describe the true underlying dose response profile.

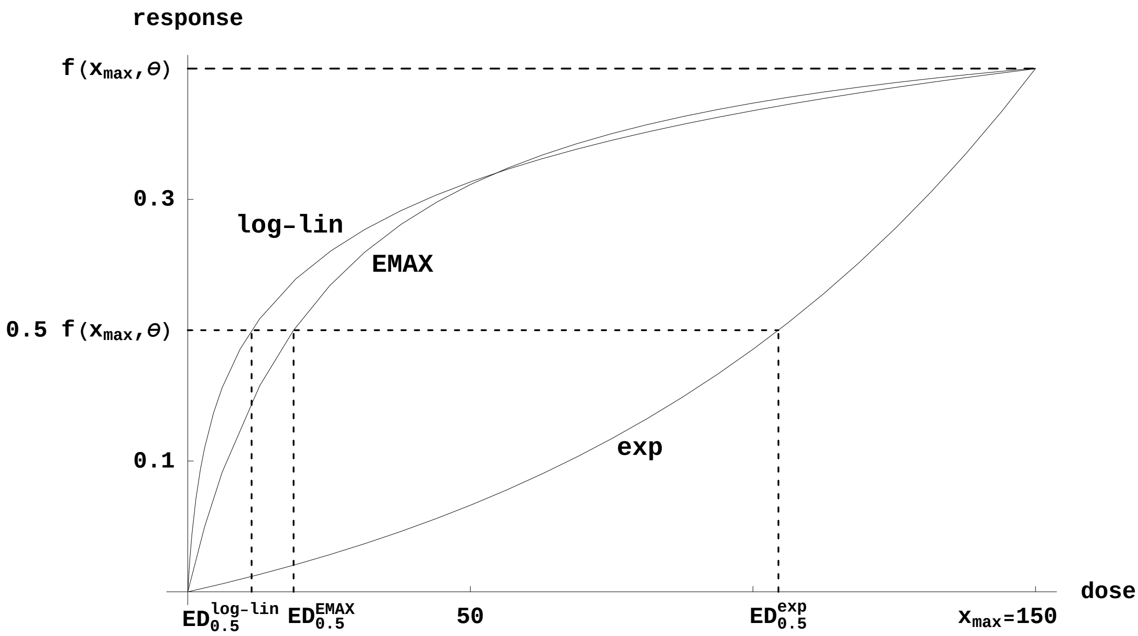

Figure 2.1: *Dose response curves corresponding to the models in Table 2.1. The ED_p for $p = 0.5$ is marked for each model.*

Table 2.1 shows these candidate models with initial parameter estimates obtained from previous studies, as described in Pinheiro et al. (2006). Note that all models are normalized such that the maximum response value is given by 0.4. The maximum effect within the dose range under investigation is attained at the maximum dose level $x_{max} = 150mg$. The corresponding curves are depicted in Figure 2.1. This Figure shows also the ED_p with $p = 0.5$ for the three models. We will use these models and corresponding parameter values to motivate and illustrate later the methodological developments of this paper.
The remaining key questions at the design stage involve the determination of the necessary number of different dose levels, the location of the dose levels within the dose range, and the proportions of patients to be allocated to each of the dose levels, such that the ED_p can be estimated efficiently for any of the candidate models. In addition, we derive D-optimal designs for each of the models from Table 2.1.
The original considerations for the example study led to a design with dose levels 0, 10, 25, 50, 100, and $150mg$ and a total sample size of 300 patients equally allocated to each of the six parallel treatment groups. This design corresponds to current pharmaceutical practice, which typically employs an equal allocation of the patients to the dose levels under investigation. The dose levels themselves are often chosen such that they are approximately equidistributed on a logarithmic scale, that is, a given dose level is approximately twice as large as the next lower dose level. Throughout this paper we call this the “standard design”. Designs of this type can be improved when using the methods proposed in this paper.

3 Notation

The three different nonlinear dose-response regression models described in the Introduction can be written in the general form

$$\mathbb{E}(Y|x) = f(x,\theta) = \theta_0 + \theta_1 f^0(x,\theta_2) \; , \tag{3.1}$$

where Y is the observation at experimental condition x, $\theta = (\theta_0, \theta_1, \theta_2)^T$ denotes the vector of unknown parameters and the expected response $\mathbb{E}(Y|x)$ is at a given x

$$f_1(x,\theta) = \theta_0 + \theta_1 x/(x+\theta_2), \tag{3.2a}$$

$$f_2(x,\theta) = \theta_0 + \theta_1 \log(x+\theta_2), \tag{3.2b}$$

$$f_3(x,\theta) = \theta_0 + \theta_1 \exp(x/\theta_2). \tag{3.2c}$$

We assume the explanatory variable x varies in the interval $\mathcal{V} = [a,b]$, where $0 \le a < b$ and normally distributed observations are available at each $x \in \mathcal{V}$ with mean $f(x,\theta)$ and variance $\sigma^2 > 0$. The non-linear regression function f is either f_1, f_2 or f_3 and the

observations are assumed to be independent.
An experimental design ξ is a probability measure with finite support defined on the set $\mathcal{V}$ [see Kiefer (1974)]. The information matrix of an experimental design ξ is defined by

$$M(\xi, \theta) = \int_{\mathcal{V}} g(x, \theta) g^T(x, \theta) d\xi(x), \tag{3.3}$$

where

$$g(x, \theta) = \frac{\partial}{\partial \theta} f(x, \theta) \tag{3.4}$$

denotes the gradient of the expected response with respect to the parameter θ. If N observations are available and the design ξ concentrates masses w_i at the points x_i, $i = 1, \ldots, n$, the quantities $w_i N$ are rounded to integers such that $\sum_{j=1}^n n_i = N$ [see Pukelsheim and Rieder (1992)], and the experimenter takes n_i observations at each point x_i, $i = 1, \ldots, n$. If the sample size N approaches infinity, then (under appropriate regularity assumptions) the covariance matrix of the maximum likelihood estimator for the parameter θ is proportional to the matrix $(\sigma^2/N) M^{-1}(\xi, \theta)$, provided that the inverse of the information matrix exists [see Jennrich (1969)]. An optimal experimental design maximizes or minimizes an appropriate functional of the information matrix or its inverse. There are numerous optimality criteria which can be used to discriminate between competing designs [see Silvey (1980) and Pukelsheim (1993)]. In this paper we investigate (i) the D-optimality criterion, which maximizes the determinant of the inverse of the information matrix with respect to the design ξ (Section 4) and (ii) the ED_p-optimality criterion, which is a special case of the c-optimality (Section 5). It is remarkable that for the three models considered here the locally D- and ED_p-optimal designs on the design space $\mathcal{V} = [a, b]$ have the same structure, that is

$$\xi^* = \begin{pmatrix} a & x^* & b \\ w_1 & w_2 & 1 - w_1 - w_2 \end{pmatrix}, \tag{3.5}$$

where the point x^* depends on the regression model but not on the optimality criterion. While the D-optimal designs are equally weighted (i.e. $w_1 = w_2 = w_3$), ED_p-optimal designs are not; their weights are given in Section 5.

4 Locally D-optimal designs

In this section we study D-optimal designs. For the non-linear regression models (3.2a), (3.2b) and (3.2c) the vectors of the partial derivatives are given by

$$
(4.1a) \qquad g_1(x,\theta) = \left(1, \frac{x}{x+\theta_2}, -\frac{\theta_1 x}{(x+\theta_2)^2}\right)^T
$$

$$
(4.1b) \qquad g_2(x,\theta) = \left(1, \log(x+\theta_2), \frac{\theta_1}{x+\theta_2}\right)^T
$$

$$
(4.1c) \qquad g_3(x,\theta) = \left(1, \exp(x/\theta_2), -\frac{\theta_1 x \exp(x/\theta_2)}{\theta_2^2}\right)^T
$$

respectively. The following result yields the general structure of the locally D-optimal designs. The explicit designs are given in Theorem 4.2.

Theorem 4.1 *The locally D-optimal design ξ_D^* on the design space $\mathcal{V} = [a,b]$ for the EMAX, log-linear and the exponential model is supported by exactly three points, where two of the support points are the boundary points of the design space.*

PROOF: We only present the proof for the case of the EMAX model, because the other cases can be treated similarly. Let $\xi_D^* = \{ {x_i^* \atop w_i} \}_{i=1}^n$ denote a locally D-optimal design for the EMAX model with design space $\mathcal{V} = [a,b]$. First, we show that $n = 3$. Next, we will show that the locally D-optimal design contains the boundary points a and b. This completes the proof.
Obviously, we have $n \geq 3$, because the information matrix $M(\xi_D^*, \theta)$ of a locally D-optimal design is nonsingular. The gradient of the regression function (3.2a) with respect to the parameter $\theta = (\theta_0, \theta_1, \theta_2)$ is given by (4.1a), which yields the variance function

$$
(4.2) \qquad d_D(x,\xi,\theta) = \left(1, \frac{x}{x+\theta_2}, -\frac{\theta_1 x}{(x+\theta_2)^2}\right) M^{-1}(\xi,\theta) \left(1, \frac{x}{x+\theta_2}, -\frac{\theta_1 x}{(x+\theta_2)^2}\right)^T,
$$

at the experimental condition $x \in \mathcal{V}$. This function has the form

$$
d_D(x,\xi,\theta) = \frac{1}{(x+\theta_2)^4} \left(\alpha_1 x^4 + \alpha_2 x^3 + \alpha_3 x^2 + \alpha_4 x + \alpha_5\right),
$$

with some coefficients $\alpha_1, \ldots, \alpha_5$. The specific relation between the coefficients α_i and the parameters is not of interest in the following discussion. Because the diagonal elements of $M^{-1}(\xi_D^*, \theta)$ are positive, the leading coefficient α_1 is also positive. Using the equivalence theorem for D-optimality [see Kiefer and Wolfowitz (1960)] it follows that a design ξ_D^* is locally D-optimal if and only if

$$d_D(x,\xi_D^*,\theta) \le 3 \text{ for all } x \in [a,b] \tag{4.3a}$$

$$d_D(x_i^*,\xi_D^*,\theta) = 3 \text{ for all } i = 1,\dots,n \text{ and } x_i^* \in [a,b]. \tag{4.3b}$$

When multiplying (4.3a) and (4.3b) by $(x+\theta_2)^4$, the required constraints on the variance function can be reformulated as

$$P_4(x) \le 0 \text{ for all } x \in [a,b] \tag{4.4a}$$

$$P_4(x_i^*) = 0 \text{ for all } i = 1,\dots,n \text{ and } x_i^* \in [a,b], \tag{4.4b}$$

where $P_4(x)$ is an appropriate polynomial of degree 4 with positive leading coefficient. Assume that $n > 3$ holds, i.e. the design has more than 3 support points on the design space $\mathcal{V} = [a,b]$. Then the polynomial $P_4(x)$ has at least 4 roots in the interval $[a,b]$. »From the characteristics of $P_4(x)$ mentioned in (4.4a) and (4.4b) and the positivity of the leading coefficient, the polynomial $P_4(x)$ has at least two zeros of order 1 and two zeros of order 2, which contradicts to the fact that the degree of $P_4(x)$ is 4.
Next we show that the locally D-optimal design contains the boundary points a and b. For this purpose we assume the contrary, i.e. a is not a support point of the design. Then the polynomial $P_4(x)$ has two roots in the interior of the interval $[a,b]$ and one root equals b or it has three roots in the interior of $[a,b]$. A polynomial with three roots satisfying the constraints (4.4a) and (4.4b) has at least two zeros of order 2 and one zero of order 1, which again leads to a contradiction. Similar arguments hold for the boundary point b. □

The following result shows that the D-optimal designs for the three models are equally weighted. In addition, we present the explicit expressions for the interior support point x^* for each of the three models.

Theorem 4.2 *The locally D-optimal design ξ_D^* on the design space $\mathcal{V} = [a,b]$ is of the form (3.5) and has equal weights on its support points. The interior support point x^* is given by*

$$x_{Emax}^* = \frac{b(a+\theta_2)+a(b+\theta_2)}{(a+\theta_2)+(b+\theta_2)} \tag{4.5}$$

for the EMAX model (3.2a),

$$x_{log-lin}^* = (b+\theta_2)(a+\theta_2)\frac{\log(b+\theta_2)-\log(a+\theta_2)}{b-a} - \theta_2 \tag{4.6}$$

for the log-linear model (3.2b) and

$$x^*_{exp} = \frac{(b-\theta_2)\exp(b/\theta_2) - (a-\theta_2)\exp(a/\theta_2)}{\exp(b/\theta_2) - \exp(a/\theta_2)} \tag{4.7}$$

for the exponential model (3.2c).

PROOF: We only present the proof for the EMAX model, because the other two cases can be treated similarly. »From Theorem 4.1 we know that a locally D-optimal design for the EMAX model is supported at three points, including the two boundary points a and b of the design space. It is easy to see that a locally D-optimal design has equal weights on its support points, i.e. $w_i = 1/3$ for $i = 1, 2, 3$ [see Silvey (1980)]. Thus, we need to prove that the interior support point has the form (4.5). Based on the definition of the information matrix (3.3) it follows

$$M(\xi, \theta) = \frac{1}{3} \sum_{j=1}^{3} g_1(x_j, \theta) g_1^T(x_j, \theta),$$

where $g_1(x, \theta)$ is given in (4.1a). Straightforward calculation yields the determinant of the information matrix

$$T(x, \theta) := |M(\xi, \theta)| = \frac{\theta_1^2 \theta_2^4 (a-x)^2 (a-b)^2 (x-b)^2}{27(a+\theta_2)^4 (x+\theta_2)^4 (b+\theta_2)^4}.$$

In order to maximize $T(x, \theta)$ we determine the roots of the derivative

$$\frac{\partial T}{\partial x}(x, \theta) = \frac{2\theta_1^2 \theta_2^4 (a-x)(a-b)^2 (x-b)(-ax + 2ab - bx + \theta_2 a - 2\theta_2 x + \theta_2 b)}{27(a+\theta_2)^4 (x+\theta_2)^5 (b+\theta_2)^4}$$

and obtain

$$x_1 = a, \qquad x_2 = \frac{b(a+\theta_2) + a(b+\theta_2)}{(a+\theta_2) + (b+\theta_2)} \qquad \text{and} \qquad x_3 = b$$

as possible extrema of the function $T(x, \theta)$. Obviously, we have $T(a, \theta) = 0$, $T(b, \theta) = 0$ and $T(x, \theta) \geq 0$ for all $x \in \mathcal{V}$. Hence, there are global minima in $x_1 = a$ and $x_3 = b$. If $p = \frac{\theta_2 + b}{2\theta_2 + a + b}$, it follows that $x_2 = ap + b(1-p)$ and $p \in [0, 1]$ and therefore $a < x_2 < b$. Furthermore, $T(x, \theta)$ is strictly increasing on the interval $[a, x_2]$ and strictly decreasing on the interval $[x_2, b]$; hence, there is a local maximum at the point x_2. $\square$

5 Locally ED_p-optimal designs

The ED_p, $0 < p < 1$, is the smallest dose achieving $100p\%$ of the maximum effect in the observed dose range $[a, b]$ (Bretz et al. (2008)). Let $h(x, \theta) = f(x, \theta) - f(a, \theta)$, where $f(x, \theta)$ is a parameterisation of the form (3.1). The ED_p can be defined as

$$ED_p = \text{argmin}_{x \in (a,b]} \{h(x, \theta)/h(x_{max}, \theta) \geq p\}. \tag{5.1}$$

Here , x_{max} denotes the dose at which the maximum expected response is observed. Because $f(x, \theta)$ is increasing for the models under consideration we have $x_{max} = b$, which does not depend on the parameters θ_0 and θ_1. Using (5.1) we can express the ED_p in terms of the underlying model parameter, that is

$$ED_p = (f^0)^{-1}(f^0(a, \theta_2) + p(f^0(b, \theta_2) - f^0(a, \theta_2))) =: \beta(\theta)$$

Evidently, if $\hat{\theta}$ denotes the maximum likelihood estimate for the parameter θ, the statistic $\beta(\hat{\theta})$ is an estimator for ED_p with asymptotic variance

$$\text{var}(\beta(\hat{\theta})) \approx \frac{1}{n} c^T(\theta) M^-(\xi, \theta) c(\theta) + \mathcal{O}(\frac{1}{n}),$$

where $c(\theta) = \frac{\partial}{\partial \theta} \beta(\theta)$ denotes the gradient of the function β with respect to θ and $M^-(\xi, \theta)$ denotes a generalized inverse of the information matrix $M(\xi, \theta)$ defined in (3.3). Hence, an appropriate choice of an optimality criterion for a precise ED_p estimation is given by

$$\Psi_{ED_p}(\xi) = c^T(\theta) M^-(\xi, \theta) c(\theta). \tag{5.2}$$

A locally ED_p-optimal design minimizes the function Ψ_{ED_p} in the class of all designs for which $c(\theta)$ is estimable, that is $c(\theta) \in \text{Range}(M(\xi, \theta))$. Note that for the three models under consideration the gradient does not depend on the parameters θ_0 and θ_1 and consequently the vector $c(\theta)$ has the form

$$c^T(\theta) = \frac{\partial}{\partial \theta} \beta(\theta)(0, 0, \gamma)$$

for some constant γ. The following results give the locally ED_p-optimal designs for three models under consideration.

Theorem 5.1 *For the EMAX, log-linear and exponential model the locally ED_p-optimal design $\xi^*_{ED_p}$ on the design space $\mathcal{V} = [a, b]$ is supported by exactly three points, where two of the support points are the boundary points of the design space.*

PROOF: We restrict the proof to the EMAX model, because the other cases can be treated similarly. The EMAX model is of the form (3.2a) and the gradient of the regression function $f(x,\theta)$ with respect to the parameter $\theta = (\theta_0, \theta_1, \theta_2)$ is given by (4.1a). In order to determine the number of support points of the locally ED_p-optimal design, we first show that the functions

$$\left\{ 1, \frac{x}{x+\theta_2}, -\frac{\theta_1 x}{(x+\theta_2)^2} \right\}$$

constitute a Chebychev-system [see Karlin and Studden (1966)]. This property holds because for all y_1, y_2, $y_3 \in \mathcal{V} = [a,b] \subseteq \mathbb{R}^{\geq 0}$ with $y_1 < y_2 < y_3$ we have

$$\begin{vmatrix} 1 & 1 & 1 \\ \frac{y_1}{y_1+\theta_2} & \frac{y_2}{y_2+\theta_2} & \frac{y_3}{y_3+\theta_2} \\ -\frac{\theta_1 y_1}{(y_1+\theta_2)^2} & -\frac{\theta_1 y_2}{(y_2+\theta_2)^2} & -\frac{\theta_1 y_3}{(y_3+\theta_2)^2} \end{vmatrix} = -\frac{\theta_1 \theta_2^2 (y_1-y_2)(y_1-y_3)(y_2-y_3)}{(y_1+\theta_2)^2(y_2+\theta_2)^2(y_3+\theta_2)^2} \neq 0.$$

Because the regression function $f(x,\theta)$ is strictly increasing, $x_{max} = b$ and the ED_p is given by

$$\begin{aligned} ED_p &= (f^0)^{-1}(f^0(a,\theta_2) + p(f^0(b,\theta_2) - f^0(a,\theta_2))) \\ &= \frac{ab + \theta_2((1-p)a + pb)}{\theta_2 + pa + (1-p)b} = \beta(\theta_2). \end{aligned}$$

Therefore, it follows that

$$c^T(\theta_2) = \frac{\partial \beta(\theta)}{\partial \theta} = \gamma(0,0,1)$$

with

$$\gamma = \frac{(1-p)p(a-b)^2}{(\theta_2 + p(a-b) + b)^2}. \tag{5.3}$$

On the other hand, we have

$$\begin{vmatrix} 1 & 1 & 0 \\ \frac{y_1}{y_1+\theta_2} & \frac{y_2}{y_2+\theta_2} & 0 \\ -\frac{\theta_1 y_1}{(y_1+\theta_2)^2} & -\frac{\theta_1 y_2}{(y_2+\theta_2)^2} & \gamma \end{vmatrix} = \gamma \frac{\theta_2(y_2-y_1)}{(y_1+\theta_2)(y_2+\theta_2)} \neq 0,$$

and it follows from Studden (1968) that the ED_p-optimal design is supported at exactly three points. Moreover, it also holds that

$$1 \in span \left\{ 1, \frac{x}{x+\theta_2}, -\frac{\theta_1 x}{(x+\theta_2)^2} \right\}.$$

Hence, based on a result from Karlin and Studden (1966), the support points are given by three points including the boundary points of the design space. □

In the following we present the explicit expressions for the interior support point x^* and the weights for each of the three models.

Theorem 5.2 *The locally ED_p-optimal design $\xi^*_{ED_p}$ on the design space $\mathcal{V} = [a, b]$ is of the form (3.5) with weight $w_2 = 1/2$. The interior support point x^* and the weight w_1 of the left boundary point of the design space are given by*

$$
\begin{aligned}
x^*_{EMAX} &= \frac{b(a+\theta_2) + a(b+\theta_2)}{(a+\theta_2)+(b+\theta_2)} \\
w_1 &= \frac{1}{4}
\end{aligned}
\tag{5.4}
$$

for the EMAX model (3.2a),

$$
\begin{aligned}
x^*_{log-lin} &= (b+\theta_2)(a+\theta_2)\frac{\log(b+\theta_2) - \log(a+\theta_2)}{b-a} - \theta_2 \\
w_1 &= \frac{\log\left(\frac{x^*_{log-lin}+\theta_2}{b+\theta_2}\right)}{2\log\left(\frac{a+\theta_2}{b+\theta_2}\right)}
\end{aligned}
\tag{5.5}
$$

for the log-linear model (3.2b) and

$$
\begin{aligned}
x^*_{exp} &= \frac{(b-\theta_2)\exp(b/\theta_2) - (a-\theta_2)\exp(a/\theta_2)}{\exp(b/\theta_2) - \exp(a/\theta_2)} \\
w_1 &= \frac{\exp(x^*_{exp}/\theta_2) - \exp(b/\theta_2))}{2(\exp(a/\theta_2) - \exp(b/\theta_2))}
\end{aligned}
\tag{5.6}
$$

for the exponential model (3.2c).

PROOF: Again, only a proof for the EMAX model is given. The corresponding results for the log-linear and exponential model are shown similarly. According to Theorem 5.1 the locally ED_p-optimal design $\xi^*_{ED_p}$ on the design space $\mathcal{V} = [a, b]$ has exactly three support points, where two of them are the boundary points a and b of the design interval.
Next, we use Elfving's theorem [see Elfving (1952)] to determine the weights w_1, w_2 and w_3 (note that the ED_p-optimality is a special case of c-optimality). For this purpose we define the Elfving set by

$$
\begin{aligned}
\mathcal{R} &= \mathrm{conv}(\{\, g_1(x,\theta) | x \in \mathcal{V} \,\} \cup \{\, -g_1(x,\theta) | x \in \mathcal{V} \,\}) \\
&= \mathrm{conv}\left(\left\{ \left(1, \frac{x}{x+\theta_2}, -\frac{\theta_1 x}{(x+\theta_2)^2}\right) | x \in \mathcal{V} \right\} \cup \left\{ \left(-1, -\frac{x}{x+\theta_2}, \frac{\theta_1 x}{(x+\theta_2)^2}\right) | x \in \mathcal{V} \right\}\right),
\end{aligned}
$$

where conv (A) denotes the convex hull of a set A. It follows from Elfving's Theorem that the design $\xi^*_{ED_p}$ is locally ED_p-optimal and minimizes $c^T(\theta)M^-(\xi,\theta)c(\theta)$, if and only if there are constants $\varepsilon_i \in \{-1, 1\}$, $i = 1, 2, 3$, and a scaling factor $\rho(c)$, such that

1. The vector $\rho(c)^{-1}c(\theta_2)$ is a boundary point of the Elfving set $\mathcal{R}$,
2. $\rho(c)^{-1}c(\theta_2) = \sum_{i=1}^{3} \varepsilon_i w_i g_1(x_i, \theta)$.

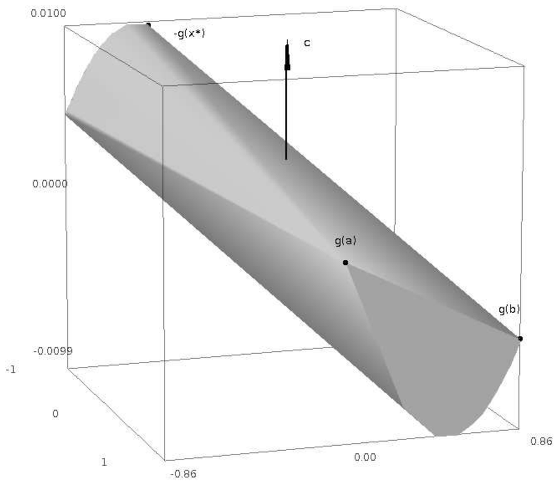

Figure 5.2: *The Elfving set for the EMAX model with parameters* $\theta_0 = 0$, $\theta_1 = 1$, $\theta_2 = 25$ *and design space* $[a, b] = [0, 150]$.

In our case $c^T(\theta_2) = (0, 0, \gamma)$, where the constant γ is defined by (5.3). A typical situation for the Elfving set is depicted in Figure 5.2 for the case $\theta_0 = 0$ $\theta_1 = 1$, $\theta_2 = 25$ and $[a, b] = [0, 150]$. Hence, the following system of equations has to be solved.

$$0 = \omega_1\varepsilon_1 + \omega_2\varepsilon_2 + \omega_3\varepsilon_3 \tag{5.7}$$

$$0 = \omega_1\varepsilon_1\frac{a}{a+\theta_2} + \omega_2\varepsilon_2\frac{x}{x+\theta_2} + \omega_3\varepsilon_3\frac{b}{b+\theta_2} \tag{5.8}$$

Choosing $\varepsilon_1 = \varepsilon_3 = 1$ and $\varepsilon_2 = -1$ and replacing w_3 by $1 - w_1 - w_2$ leads to $w_2 = 1/2$ because of (5.7). Inserting ω_2 into (5.8) results in

$$\omega_1\frac{a}{a+\theta_2} - \frac{1}{2}\frac{x}{x+\theta_2} + \left(\frac{1}{2} - \omega_1\right)\frac{b}{b+\theta_2} = 0.$$

Hence the weight ω_1 is given by

$$\omega_1 = \frac{(a+\theta_2)(b-x)}{2(b-a)(\theta_2+x)} \tag{5.9}$$

and with $\omega_3 = 1 - \omega_1 - \omega_2$ it follows that

$$\omega_3 = \frac{(b+\theta_2)(x-a)}{2(b-a)(\theta_2+x)}. \tag{5.10}$$

In order to calculate the remaining support point x^*_{EMAX}, we insert these weights in the criterion function

$$\Psi_{ED_p}(\xi) = c^T(\theta_2)M^-(\xi,\theta)c(\theta_2)$$

and minimize it. Using a straightforward calculation, this function can be simplified to

$$\Psi_{ED_p}(\xi) = c^T(\theta_2)M^{-1}(\xi,\theta)c(\theta_2) = \gamma^2\frac{4(a+\theta_2)^2(x+\theta_2)^4(b+\theta_2)^2}{\theta_1^2\theta_2^2(a-x)^2(x-b)^2}.$$

The derivative of this criterion with respect to x is given by

$$\frac{\partial}{\partial x}\Psi_{ED_p}(\xi) = \gamma^2\frac{-8(\theta_2+a)^2(\theta_2+x)^3(\theta_2+b)^2(-(ax)+2ab-xb+\theta_2(a-2x+b))}{\theta_1^2\theta_2^2(a-x)^3(x-b)^3},$$

which has the roots

$$\tilde{x} = -\theta_2,\ \bar{x} = \frac{b(a+\theta_2)+a(b+\theta_2)}{(a+\theta_2)+(b+\theta_2)}.$$

The point $\tilde{x}$ is not an element of the design space $\mathcal{V} = [a,b]$ and therefore not admissible. Hence, $\bar{x}$ is the point where Ψ_{ED_p} is minimal, because the criterion function is convex on the design space. Letting $p = \frac{\theta_2+b}{2\theta_2+a+b}$, it follows that $\bar{x} = ap + b(1-p)$ which implies that $a < \bar{x} < b$. Therefore, the remaining support point is given by $\bar{x} = x^*_{EMAX}$ and inserting $\bar{x}$ in (5.9) and (5.10) gives the corresponding weights

$$\omega_1 = \omega_3 = \frac{1}{4} \text{ and } \omega_2 = \frac{1}{2}.$$

Consequently, by Elfving's Theorem, the design with masses $w_1 = 1/4$, $w_2 = 1/2$ and $w_3 = 1/4$ at the points a, x^*_{EMAX} and b, respectively, is locally ED_p-optimal. □

6 Examples and efficiency considerations

In this section we first use the results from Sections 4 and 5 to compute D- and ED_p-optimal designs for the three models described in the example in Section 2. Then we analyse the robustness of the locally optimal designs with respect to misspecification of the model or model parameters. We further investigate the ED_p-efficiency of a locally D-optimal design and vice versa. Furthermore we compare the standard design from Section 2 with the locally optimal designs.

The D-efficiency of a design ξ is defined by

$$\text{eff}_D(\xi) = \left(\frac{|M(\xi,\theta)|}{|M(\xi_D^*,\theta)|} \right)^{1/3}, \tag{6.1}$$

where ξ_D^* denotes the locally D-optimal design. Accordingly, the ED_p-efficiency is defined by

$$\text{eff}_{ED_p}(\xi) = \frac{\Psi_{ED_p}(\xi_{ED_p}^*)}{\Psi_{ED_p}(\xi)} = \frac{c^T(\theta)M^{-1}(\xi_{ED_p}^*,\theta)c(\theta)}{c^T(\theta)M^{-1}(\xi,\theta)c(\theta)} \tag{6.2}$$

where $c^T(\theta) = \gamma(0,0,1)$ and $\xi_{ED_p}^*$ denotes the locally ED_p-optimal design (note that $\text{eff}_{ED_p}(\xi)$ does not depend on γ). In the following we investigate the D- and ED_p-efficiencies for the three dose response models from Table 2.1.

In order to investigate the loss of efficiency caused by a misspecification of the underlying model, we compare the efficiency of the locally D- and ED_p-optimal designs provided that one specific model is the "true" one. Using the results from Sections 4 and 5, the locally D- and ED_p-optimal designs with respect to the parameters specified in Table 2.1 are given by

$$\xi_{D,EMAX}^* = \begin{pmatrix} 0 & 18.75 & 150 \\ \frac{1}{3} & \frac{1}{3} & \frac{1}{3} \end{pmatrix} \quad \text{and} \quad \xi_{ED_p,Emax}^* = \begin{pmatrix} 0 & 18.75 & 150 \\ \frac{1}{4} & \frac{1}{2} & \frac{1}{4} \end{pmatrix} \tag{6.3}$$

for the EMAX-model, by

$$\xi_{D,log-lin}^* = \begin{pmatrix} 0 & 4.0507 & 150 \\ \frac{1}{3} & \frac{1}{3} & \frac{1}{3} \end{pmatrix} \quad \text{and} \quad \xi_{ED_p,log-lin}^* = \begin{pmatrix} 0 & 4.0507 & 150 \\ 0.3386 & \frac{1}{2} & 0.1614 \end{pmatrix} \tag{6.4}$$

for the log-linear model and by

$$\xi_{D,exp}^* = \begin{pmatrix} 0 & 95.9927 & 150 \\ \frac{1}{3} & \frac{1}{3} & \frac{1}{3} \end{pmatrix} \quad \text{and} \quad \xi_{ED_p,exp}^* = \begin{pmatrix} 0 & 95.9927 & 150 \\ 0.2837 & \frac{1}{2} & 0.2163 \end{pmatrix} \tag{6.5}$$

for the exponential model.

Table 6.1 shows the efficiency of the locally D-optimal designs for the three models under different "true" models. The second column shows the D-efficiency of the designs $\xi_{D,log-lin}^*$ and $\xi_{D,exp}^*$ if the EMAX model with parameters $\theta_1 = 0.467$ and $\theta_2 = 25$ is the true dose response model. For example, the D-efficiency of the locally optimal design for the log-linear model is 66.7% under a true EMAX model. The other columns in Table 6.1 are interpreted similarly. In general, we note that D-optimal designs are very sensitive with respect to the model assumptions. The efficiency is particularly poor if a locally D-optimal design for the log-linear model is used under a true exponential model. The ED_p-efficiencies

Table 6.1: *Efficiency of locally D-optimal designs for the EMAX, log-linear and exponential model with design space* $[0, 150]$ *and parameters given in Table 2.1.*

	$\text{eff}_{D,EMAX}$	$\text{eff}_{D,log-lin}$	$\text{eff}_{D,exp}$
$\xi^*_{D,EMAX}$	1	0.8220	0.4066
$\xi^*_{D,log-lin}$	0.6671	1	0.1462
$\xi^*_{D,exp}$	0.4233	0.3121	1

with respect to model misspecification are given in Table 6.2, and vary between 0.23% to

Table 6.2: *Efficiency of locally ED_p-optimal designs for the EMAX, log-linear and exponential model with design space* $[0, 150]$ *and parameters given in Table 2.1.*

	$\text{eff}_{ED_p,EMAX}$	$\text{eff}_{ED_p,log-lin}$	$\text{eff}_{ED_p,exp}$
$\xi^*_{ED_p,EMAX}$	1	0.4751	0.0521
$\xi^*_{ED_p,log-lin}$	0.2418	1	0.0023
$\xi^*_{ED_p,exp}$	0.0557	0.0170	1

47.5%. These results show that locally ED_p- and D-optimal designs are not robust with respect to model misspecification.

Beside studying the robustness properties of the derived designs with respect to model misspecification, we also investigate the relative performance of designs commonly used in practice. A common approach in practice is to approximately double the next larger dose, resulting in the standard design

$$\xi_S = \begin{pmatrix} 0 & 10 & 25 & 50 & 100 & 150 \\ \frac{1}{6} & \frac{1}{6} & \frac{1}{6} & \frac{1}{6} & \frac{1}{6} & \frac{1}{6} \end{pmatrix} \tag{6.6}$$

from Section 2. We compare this standard design with the optimal designs $\xi^*_\bullet$ for the three different models by computing their efficiencies; see Table 6.3 and 6.4 for the results under the log-linear model. As the results for the other two models are similar, they are omitted.

The last column of Table 6.3 (respectively Table 6.4) shows the efficiencies of the standard design ξ_S for different values of θ_1 and θ_2. It is remarkable that the efficiency depends only on the parameter θ_2 and varies from 66% to 72% for the D-optimality criterion and from 38% to 51% for the ED_p-optimality criterion. Because the information matrix $M(\xi, \theta)$ does not depend on θ_0, the criteria functions are linear in θ_1 and the vector $c(\theta)$ is independent of θ_0 and θ_1, and so is the efficiency independent of θ_0 and θ_1.

An additional question involves the robustness of the locally optimal designs under variation of the optimality criterion: How efficient is a locally ED_p-optimal design under

Table 6.3: *Locally D-optimal designs for the log-linear model with design space* $[0, 150]$. *The last row presents the efficiency of the standard design ξ_S defined by (6.6).*

θ_1	θ_2	x_1	x_2	x_3	$\text{eff}_D(\xi_S, \theta)$
0.0797	0.6	0	2.7285	150	0.6587
0.0797	1	0	4.0507	150	0.6984
0.0797	1.4	0	5.2180	150	0.7237
0.0997	1	0	4.0507	150	0.6986
0.0897	1	0	4.0507	150	0.6986

Table 6.4: *Locally ED_p-optimal designs for the log-linear model with design space* $[0, 150]$. *The last row presents the efficiency of the standard design ξ_S defined by (6.6).*

θ_1	θ_2	x_1	x_2	x_3	$\text{eff}_{ED_p}(\xi_S, \theta)$
0.0797	0.6	0	2.7285	150	0.3833
0.0797	1	0	4.0507	150	0.4562
0.0797	1.4	0	5.2180	150	0.5098
0.0997	1	0	4.0507	150	0.4562
0.0897	1	0	4.0507	150	0.4562

the D-optimality criterion and vice versa? In Table 6.5 the efficiencies are presented for the EMAX model; for the other two models the values are similar. We observe that the two designs are relatively robust with respect to the choice of the optimality criterion. The ED_p-efficiency of the locally D-optimal design is 89% and 95% vice versa. This is because for the models under consideration the ED_p-optimality criterion reduces to the D_1-optimality criterion (a criterion for precise estimation of θ_2), i.e.

$$\gamma^{-2}\Psi_{D_1}(\xi) = \gamma^{-2}\frac{|\tilde{M}(\xi, \theta)|}{|M(\xi, \theta)|} = \gamma^{-2}(0, 0, 1)M^{-}(\xi, \theta)(0, 0, 1)^T = \Psi_{ED_p}(\xi),$$

where $\tilde{M}(\xi, \theta)$ denotes the matrix obtained from $M(\xi, \theta)$ by deleting the last row and column. Consequently, minimizing Ψ_{ED_p} (or maximizing $|M(\xi, \theta)|$) produces large (small) values of $|M(\xi, \theta)|$ (or $\Psi_{ED_p}(\xi)$).

Finally, we investigate the robustness of locally optimal designs under parameter misspecification: How does the efficiency of a design change if the initial parameters estimates differ from the true parameter values? In Figure 6.1 a contourplot shows the efficiency of a design with parameters $\theta_1 \in [0.2, 0.7]$ and $\theta_2 \in [10, 35]$ under the assumption that the true parameters are $\theta_1 = 0.467$ and $\theta_2 = 25$. The underlying model is the EMAX-model,

Table 6.5: *ED_p-efficiency of the locally D-optimal design and D-efficiency of the locally ED_p-optimal design in the EMAX model with parameters θ_1=0.467 and θ_2=25.*

ξ^*	eff_D	eff_{ED_p}
ξ_D^*	1	0.8889
$\xi_{ED_p}^*$	0.9449	1

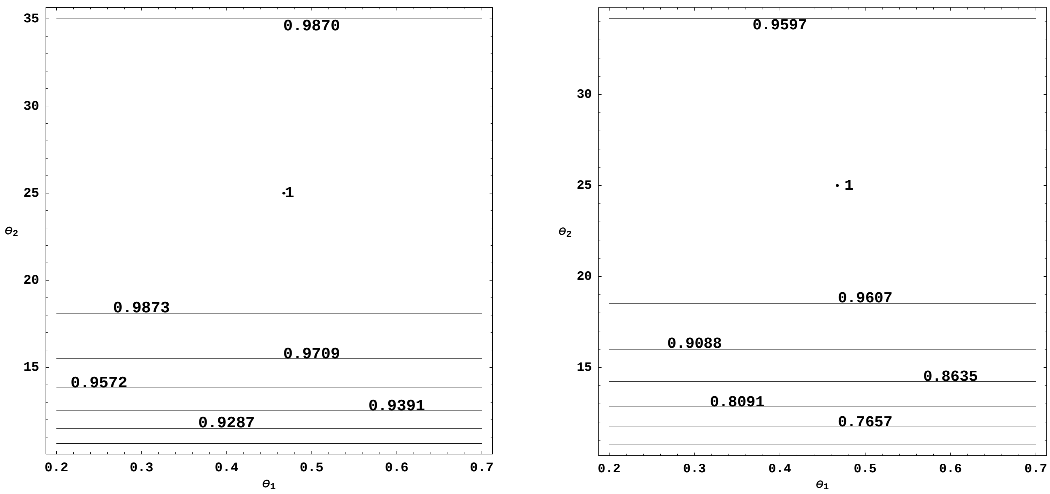

Figure 6.1: *The efficiency of the locally optimal designs in the EMAX model under misspecification of the initial parameters. Left panel: D-optimality criterion; right panel ED_p-optimality criterion.*

but the results for the two other models are similar. Remarkably, the D-efficiency does not change substantially and the ED_p-efficiency remains in a relatively wide area greater than 80%. In other words, the locally D- and ED_p-optimal designs are robust with respect to (moderate) misspecifications of the unknown parameters.

7 Conclusions

This article focused on the derivation of locally D- and ED_p-optimal designs for a class of common non-linear regression models (exponential, log-linear and three parameter EMAX-model). These models are often applied in dose finding studies conducted in the development of a new compound, such as a medicial drug or a fertilizer. We derived optimal designs, which, under a particular model, (i) minimize the asymptotic variance of the ED_p estimate or (ii) maximize the determinant of the inverse of the information matrix. We showed that for each model the locally D- and ED_p-optimal designs are supported at the

same set of points, while the corresponding weights are different.
We used a real clinical dose finding study to investigate the properties of these designs. As expected by the theoretical results, D-optimal designs are efficient for estimating the ED_p under a given model, and conversely ED_p-optimal designs also yield good D-efficiencies. We further showed that the derived designs are moderately robust with respect to an initial misspecification of the model parameters. The sensitivity of the optimality results to the prespecified dose response model is apparently more severe. If in practice the knowledge about the underlying model is limited, Bayesian or standardized maximin-optimal designs may be considered, which robustify the locally optimal designs considered here with respect to model and parameter misspecification, see Dette et al. (2008) for an application.

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