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Abstract

We discuss design issues for pharmacokinetic and pharmacodynamic (PK/PD) models and provide closed form descriptions for locally optimal designs for estimating individual parameter in two frequently used models. We propose standardized maximin optimal designs that remove dependence on the particular parameter of interest by maximizing the minimal efficiency across all parameters. Further, robust designs are proposed to overcome the dependence on the parameters of interest and the nominal values of the parameters. We compare performance of these optimal designs with designs used in four real studies from the pharmacokinetic/pharmacodynamic literature and show that our proposed designs provide definite advantages over those used in practice.

Keywords: Pharmacokinetic/dynamic experiments, approximate design, D-optimal design, equivalence theorem, maximin optimal design, nominal value, robust design.

1 Introduction

Pharmacokinetic-pharmacodynamic modeling is a recognized tool in drug development. The pharmacokinetic (PK) model describes the relationship between systematic drug concentration and time. The pharmacodynamic (PD) model describes the relationship between effect and systematic drug concentration. There is increasing interest to study pharmacokinetic and pharmacodynamic of a drug by combining the PK and PD models and estimate model parameters simultaneously.Current research in this area focuses on model formulation and estimating issues for a PK/PD model and only a couple of papers discussed design issues for such models. One example is Fang and Hedayat (2008) where they studied locally D-optimal design for PK/PD models from a theoretical viewpoint. Others compared several designs strategies via simulation.

A motivation for our paper is that research work in the pharmaceutical literature do not usually justify or discuss the choice of the study design; see examples in Section 6. In subsequent analysis, the researchers estimated model parameters and specific functions of the parameters. The research question is whether the sampling time points employed in the design affected the precision of the estimates and whether one could have used a more efficient design. Efficiency here could mean requiring fewer time points and/or fewer subjects for the same precision of the estimates at lower cost.

In this paper we study design issues for two commonly used PK/PD models: the Emax/mono- and the Emax/effect-compartment models. We construct three types of optimal designs for these models: locally optimal designs, standardized maximin optimal designs and robust optimal designs. The latter two types of designs are new and therefore have not found their way into the pharmaceutical literature. Our aim is to introduce them for application to PK/PD models, show how they are constructed using two exemplary models and compare their performance with designs used in practice. Our results suggest that the proposed maximin optimal designs and robust designs can serve as compelling alternatives and complementary designs in drug studies.

When a model has been specified, locally optimal designs are the oldest and the simplest to determine. They were proposed by Chernoff (1953). When the model is nonlinear, as it is the case here, these designs require nominal values for the parameters be available before they can be implemented. Nominal values typically come from pilot studies, experts' opinion or related studies from the literature. Locally optimal designs usually represent an intermediate step in a sequential experimentation and they frequently are used as tools to build more complex designs, as we exemplify in Section 3. A locally optimal design can be verified to be optimal using an equivalence theorem. Equivalence theorems are available when the design criterion is a convex of the information matrix (Pukelsheim, 1993) and allows one to easily verify a design optimality by plotting the directional derivative of the criterion evaluated at that design over the design interval. Huang and Wong (1998), and Zhu, Zeng and Wong (2000) gave illustrative examples with such plots in bio-pharmaceutical studies.

It is well known that locally optimal designs can depend on the nominal values sensitively. This means that small mis-specification in the nominal values can result in very different optimal designs. Consequently, a locally optimal design constructed under one set of nominal values can become inefficient when another set of nominal values is assumed. Standardized maximin optimal designs were introduced by Dette (1995) and Müller and Pázman (1997) as another way to avoid the dependence on the nominal values. In the simplest case, they maximize the minimum of efficiencies that may arise from mis-specification of the nominal values. Equivalently, minimax optimal designs seek to minimize the worst possible loss from mis-specification of the nominal values. In either the minimax or maximin approach, we need to specify a plausible region for all possible values of the model parameters so that we may optimize within this region. This is usually accomplished by specifying a plausible interval for each parameter. Our experience is that this is easier for practitioners to do than having them specify a single best guess or a prior distribution for the values of the parameters of interest. Consequently, maximin or minimax optimal designs can be appealing in practice. However, the construction of minimax or maximin optimal design for nonlinear models is notoriously difficult and they defy analytical description, except for the simplest problems. Wong (1992) provided an overview of theoretical design issues for minimax optimality criteria and Dette (1995) provided yet another compelling rationale for use of such optimal designs in practice.

The paper is organized as follows. In Section 2 we discuss two popular PK/PD models and in Section 3, we formally define our two maximin design criteria. The first maximin approach begins by assigning an index to each model parameter of interest to form an index set, say J. Ordinarily, $J = \{1, 2, 3, \ldots, k\}$ if all the k model parameters are of interest. For a given set of nominal values, we define a standardized maximin optimal design as one that maximizes the minimum of efficiencies over the index set J. In practice, for a given set of parameters of interest, we first determine the locally optimal design for estimating each of the parameters in the index set J and the variances of all these parameter estimators. The standardized maximin optimal design sought is the one that provides the maximal minimum of efficiencies among a class of all designs on the design interval.

In many experiments, we may be constrained to use only a fixed maximal number of time points. This may arise because it is impractical to sample at a new time point or simply because of budget limits. This means that if we are only allowed s time points, then we must search within the class of designs with s points. We call the resulting design a s-point standardized maximin optimal design. Such designs are typically easier to find numerically than standardized maximin optimal designs.

The standardized maximin optimal design still depends on the nominal values. One may extend the above optimization by specifying a plausible interval for each parameter. This is our second maximin approach and is a clear natural extension of the first. The plausible region now comprises (i) the set J and (ii) the plausible interval for each parameter. The resulting optimal design is called a robust design because the design maximizes the minimum of the set of efficiencies of estimated parameters in the set J and, for each parameter, over each of its possible values in the plausible interval.

We consider the Emax/mono-compartment model in Section 4 and present locally optimal designs for estimating each parameter in the model, standardized maximin optimal designs and robust designs. We also report efficiencies of the commonly used locally D-optimal design relative to our proposed designs. Section 5 presents corresponding optimal designs for the Emax/effect-compartmental model. In Section 6, we evaluate the efficiencies of some designs used in practice relative to the designs proposed in this paper. Conclusions are offered in Section 7 and technical justifications for our results are given in the Appendix.

2 PK/PD Models

We consider the common nonlinear regression model given by

$$y_{i,j} = \eta(t_{i,j}, \theta) + \varepsilon_{i,j}, \; i = 1, \ldots, n, \; j = 1, \ldots, n_i \tag{1}$$

where $y_{i,j}$ is an observation from the ith subject at time $t_{i,j} \in [0, T]$, errors $\varepsilon_{i,j}$ are independent and identically distributed random variable with zero mean and variance $\sigma^2 > 0$ and $N = \sum_i n_i$ denotes the total sample size. In the present paper we study the fixed-effect model. Design issues for some nonlinear random-effect models can be found in Mentre et al. (1997), Dette et al. (2009) among others. The last named authors also discuss designs for correlated errors.

A PK/PD model is obtained by composing a PK-model and a PD model, that is

$$\eta(t, \theta) = \eta_{\mathrm{PD}}(\eta_{\mathrm{PK}}(t, \theta^{\mathrm{PK}}), \theta^{\mathrm{PD}}) \, ,$$

where the vector of model parameters is given by $\theta = (\theta^{\mathrm{PD}}, \theta^{\mathrm{PK}})$. For the PD model $\eta_{\mathrm{PD}}(C, \theta^{\mathrm{PD}})$ the traditional model choice is the Emax model

$$\eta_{\mathrm{PD}}(C, \theta^{\mathrm{PD}}) = \theta_0^{\mathrm{PD}} + \frac{\theta_1^{\mathrm{PD}} C}{\theta_2^{\mathrm{PD}} + C}$$

where $\theta^{\mathrm{PD}} = (\theta_0^{\mathrm{PD}}, \theta_1^{\mathrm{PD}}, \theta_2^{\mathrm{PD}})^T$, θ_0^{PD} is the baseline effect (placebo), θ_1^{PD} is the maximal effect related to the drug, θ_2^{PD} is the plasma concentration producing 50% of the maximal effect, and C is a concentration (Ritschel, 1992). The PD relationship may be described by the Hill model or the Emax model, see Toutain (2002) among others.

The choice of PK model depends on the particular application at hand. We consider two widely used models in the present paper.

(1) The first is a mono-exponential model or a single compartment model given by

$$\eta_{\mathrm{PK}}(t,\theta^{\mathrm{PK}}) = D_1 e^{-t\,\theta_1^{\mathrm{PK}}},$$

where θ_1^{PK} is the plasma clearance (or the total elimination rate).

(2) The second model is an effect compartment model given by

$$\eta_{\mathrm{PK}}(t,\theta^{\mathrm{PK}}) = D_1 \frac{\theta_2^{\mathrm{PK}}}{\theta_2^{\mathrm{PK}} - \theta_1^{\mathrm{PK}}} \left(e^{-t\,\theta_1^{\mathrm{PK}}} - e^{-t\,\theta_2^{\mathrm{PK}}} \right),$$

where D_1 is the administered dose in the unit of drug amount per unit body weight, θ_2^{PK} is the absorbtion rate and θ_1^{PK} is the total elimination rate. The actual dose for each subject is $D_1 V$ where V is a volume/mass of the subject/animal.

More details for these models an other choices for a PK model can be found in El-Masri and Portier (1998), Schaedeli el at. (2002), for example, and in textbooks such as Shargel and Yu (1985) and, Rowland and Tozer (1995).

3 Optimality criterion

Throughout we assume that a fixed total sample size N for the study is pre-determined either from cost or other physical constraints. The design problem is how to obtain the N observations in some optimal fashion. Following convention, we formulate our optimality criterion in terms of the Fisher information matrix. The Fisher information matrix for the general nonlinear model defined in (1) is

$$M(\xi_N,\theta) = \sum_{i=1}^{n}\sum_{j=1}^{n_i} f(t_{i,j}) f^T(t_{i,j}), \quad f(t) = f(t,\theta) = \frac{\partial \eta(t,\theta)}{\partial \theta},$$

and the inverse of $M(\xi_N)$ is asymptotically proportional to the covariance matrix of the nonlinear least squares estimator of the parameter θ. An optimal design minimizes or maximizes a statistically meaningful function of the information matrix.

To simplify the design problem, we work with approximate designs that are essentially discrete probability measures defined on the design interval. We denote such a design with r design points $t_1, t_2, \dots, t_r$ and corresponding weights $w_1, w_2, \dots, w_r$ by $\xi =$

$\{t_1, t_2, \ldots, t_r; w_1, w_2, \ldots, w_r\}$. The Fisher information matrix of design ξ is defined by

$$M(\xi, \theta) = \sum_{j=1}^{r} w_j f(t_j) f^T(t_j),$$

see Pukelsheim (1993). In practice, for a given statistical model and a design criterion, the design problem consists of selecting the optimal number r of design points, the optimal time points $t_1, \ldots, t_r$ and corresponding optimal proportions $w_1, \ldots, w_r$ of observations to allocate at these points. The exact design is implemented by assigning approximately Nw_i observations at t_i, $i = 1, \ldots, r$ subject to $Nw_1 + \cdots + Nw_r = N$. Approximate designs are much easier to find and study than exact optimal designs and they perform just as well as exact optimal designs when we have moderate sample sizes (Pukelsheim and Rieder, 1992). More importantly, when the design criterion is convex over the space of information matrices, computer algorithms are available for generating many types of optimal approximate designs for many types of problems.

In what is to follow, we focus on design criteria that estimate selected parameters in the model. For estimating a single parameter, we want to construct a design that accurately estimates $c^T\theta$, where $c = e_j$ and e_j is the zero vector with the i^{th} entry equals to one. Such an optimal design minimizes the variance of the estimated jth parameter among all designs on the design interval. When all the parameters of interest are represented in the set J, we want a design that maximizes the minimal efficiency for estimating the selected parameters. This means that we want to find a design that maximizes

$$\min_{j \in J} \{\text{eff}_j(\xi)\}, \tag{2}$$

where

$$\text{eff}_j(\xi) = \text{eff}_j(\xi, \theta) = \frac{e_j^T M^-(\xi_{e_j}^*, \theta) e_j}{e_j^T M^-(\xi, \theta) e_j}\,; \quad j \in J\,,$$

and $\xi_{e_j}^*$ is the locally e_j-optimal design for estimating the jth parameter, i.e. $\xi_{e_j}^*$ is the design that minimizes

$$e_j^T M^-(\xi, \theta) e_j \tag{3}$$

over all designs ξ such that $e_j \in \text{range}\, M(\xi, \theta)$. Note that we have used $M^-(\xi, \theta)$ to denote a generalized inverse of the Fisher information matrix because the information matrix of an optimal design may be singular.

Following Dette (1995) or Müller and Pázman (1998) we call a design maximizing the criterion (2) standardized maximin optimal design. Clearly, these optimal designs still depend on the model parameters that we try to estimate and so they are locally optimal. To remove the dependence on the nominal values, we introduce a concept of robust optimality criterion and define a robust design as the design that maximizes

$$\min_{j \in J} \min_{\theta \in \Omega} \{\text{eff}_j(\xi, \theta)\} \tag{4}$$

for a user-selected plausible set Ω for the unknown model parameters. In practice, the set Ω is a cartesian product of the intervals specified for each parameter.

We compute standardized maximin and robust designs, first, by maximizing the optimality criterion within the class of all k-point designs on the given design space. Here k is typically the minimal number of points required for estimation of all parameters in the model. We employ the Nelder-Mead algorithm in the MATLAB package for optimization. After the optimal k-point standardized maximin design is found, we consider the class of all $k+1$-points designs and find an optimal design within this class and repeat the procedure. At each iteration, we increase the number of points by one, until no reduction in the criterion value is observed. The value of k for our two models was $k = 4$.

4 Emax/mono-compartment model

4.1 Locally optimal design

The Emax/mono-compartment model is given by

$$\eta(t, \theta) = \theta_0 + \frac{\theta_1}{\theta_2/D_1 e^{\theta_3 t} + 1} \tag{5}$$

where $\theta = (\theta_0, \theta_1, \theta_2, \theta_3)^T$ and the explanatory variable t varies in the interval $[0, T]$. Without loss of generality we put $D_1 = 1$ (this is valid due to substitution $\theta_2/D_1 \to \tilde{\theta}_2$). A direct calculation shows the gradient of the mean function in model (5) is

$$f(t) = f(t, \theta_1, \theta_2, \theta_3) = \left(1, \frac{1}{\theta_2 e^{\theta_3 t} + 1}, \frac{-\theta_1 e^{\theta_3 t}}{(\theta_2 e^{\theta_3 t} + 1)^2}, \frac{-\theta_1 \theta_2 t e^{\theta_3 t}}{(\theta_2 e^{\theta_3 t} + 1)^2}\right)^T. \tag{6}$$

We now construct and study properties of the locally e_k-optimal designs. Justifications for our procedure and claims are provided in the appendix as Lemma 1. The technical result also tells us how the optimal design changes when the design interval changes.

It can be argued that the components $\{f_1(t), f_2(t), f_3(t), f_4(t)\}$ of the gradient defined in (6) form a Chebyshev system on the interval $[0, T]$ and that the left hand side of equation (8) is proportional to the corresponding Chebyshev polynomial. It follows that the solution of (8) is unique even though there are 4 equations and 8 variables in the system of equations; see Karlin and Studden (1966) and the Appendix for more details.

Table 1 displays the locally e_k-optimal designs for various parameter combinations of (θ_2, θ_3) for the design space $[0, T] = [0, 120]$, where we have used the same values for the parameters as Fang and Hedayat (2008) for the sake of comparison. These authors determined locally D-optimal designs in this context. Note that the locally optimal design for

Table 1: *The locally e_k-optimal designs $\{t_1^*, t_2^*, t_3^*, t_4^*; w_1, w_2, w_3, w_4\}$ for the Emax/mono-compartment model* (5) *with $t_1^* = 0$, $t_4^* = T = 120$.*

				e_1-optimal				e_2-optimal			
θ_2	θ_3	t_2^*	t_3^*	w_1	w_2	w_3	w_4	w_1	w_2	w_3	w_4
0.2	0.10	12.117	33.502	0	0	0	1	0.308	0.279	0.192	0.221
0.1	0.10	16.031	38.673	0	0	0	1	0.354	0.226	0.146	0.274
0.4	0.10	9.163	29.157	0	0	0	1	0.264	0.315	0.236	0.185
0.2	0.05	23.335	63.612	0.039	0.086	0.166	0.708	0.291	0.284	0.209	0.216
0.2	0.20	6.060	16.756	0	0	0	1	0.309	0.279	0.191	0.221
				e_3-optimal				e_4-optimal			
0.2	0.10	12.117	33.502	0.232	0.391	0.268	0.109	0.127	0.270	0.373	0.230
0.1	0.10	16.031	38.673	0.244	0.398	0.256	0.102	0.140	0.284	0.360	0.216
0.4	0.10	9.163	29.157	0.217	0.378	0.283	0.122	0.114	0.255	0.386	0.245
0.2	0.05	23.335	63.612	0.239	0.399	0.261	0.101	0.137	0.286	0.363	0.214
0.2	0.20	6.060	16.756	0.232	0.391	0.268	0.109	0.127	0.270	0.373	0.230

estimating the baseline effect θ_0 advises the experimenter to run most of the experiments under the maximal condition $t = T$. A heuristic explanation of this observation is given by the fact that for the Emax/mono-compartment model (5) we have $\lim_{t\to\infty} \eta(t, \theta) = \theta_0$. In other words: the best identification of the baseline effect is obtained for large values of the explanatory variable.

It might also be of interest to investigate the efficiency of the locally D-optimal designs derived in Fang and Hedayat (2008) for the estimation of the individual parameters. These efficiencies are listed in Table 2, and it can be observed that the locally D-optimal designs minimizing the volume of the ellipsoid of concentration yield rather low efficiencies for estimating the baseline effect. The efficiencies for estimating the parameters θ_2 and θ_3 are approximately 80%, while high efficiencies are only obtained for estimating the maximal effect related to the drug.

Table 2: *The locally D-optimal designs $\{t_1^{*D}, t_2^{*D}, t_3^{*D}, t_4^{*D}; w_1, w_2, w_3, w_4\}$ for the Emax/mono-compartment model* (5) *and their e_k-efficiencies with $t_1^{*D} = 0$, $t_4^{*D} = T = 120$, $w_i = 1/4, i = 1, 2, 3, 4$.*

θ_2	θ_3	t_2^{*D}	t_3^{*D}	eff_1	eff_2	eff_3	eff_4
0.2	0.10	13.479	31.616	0.251	0.951	0.810	0.836
0.1	0.10	17.645	36.667	0.252	0.917	0.799	0.842
0.4	0.10	10.278	27.386	0.251	0.932	0.824	0.827
0.2	0.05	25.860	60.310	0.471	0.957	0.802	0.844
0.2	0.20	6.741	15.812	0.250	0.951	0.810	0.836

4.2 Standardized maximin optimal and robust design

We now discuss standardized maximin optimal and robust designs. The primary goal of standardized maximin optimal designs is to provide efficient estimates for several individual parameters of interest. The robust designs provide additional level of protection against mis-specification of the unknown model parameters in a practical way. This is important because it is well documented in the literature that locally optimal designs can depend sensitively on the nominal values of the model parameters. Both types of designs achieve their aims by maximizing over a certain region of plausible values for the parameters.

Standardized maximin optimal designs are a subset of the class of minimax or maximin designs and it is well known such optimal designs are notoriously difficult to construct. Except for the simplest models with a single or two optimality criteria, these optimal designs have to be determined numerically and in a computationally burdensome manner. Fortunately, the standardized maximin optimal designs for the Emax/mono-compartment model and Emax/effect-compartment model do not depend on θ_0 and θ_1. This simplifies the calculation for standardized maximin optimal designs considerably and the justifications for our assertion can be deduced from Lemma 1 or Lemma 3 in the appendix.

Table 3 displays standardized maximin optimal designs for selected values of the parameters. The first part of the table shows the different designs and efficiencies when the minimum in the criterion (2) is taken over all parameters, i.e. $J = \{1, 2, 3, 4\}$. In this case the standardized maximin optimal design yields efficiencies between 56% and 85%, because it is a compromise between two very different types of designs: the locally optimal design for estimating the baseline effect θ_0, which puts most of its weight at the right boundary of the design interval and the locally optimal designs for estimating the remaining parameters $\theta_1, \theta_2, \theta_3$, which use less observations at the point T. On the other hand, if estimation of the baseline is not the primary goal, one could use the set $J = \{2, 3, 4\}$ in the criterion (2) and the standardized maximin optimal designs are extremely efficient; see the second part of Table 3. A similar result as Lemma 1 shows that the robust designs also do not depend on intervals specified for θ_0 and θ_1. Some robust designs are given in Table 4. Note that the robust designs have 6 support points and can also be used for model checking. The right column of Table 4 contains the minimum efficiency, where the minimum is taken over the set J (of parameters of interest) and the set Ω [see equation (4)]. Note that this value corresponds to the worst case in $J \times \Omega$, and for most values (j, θ) the efficiencies of the robust design are substantially higher.

Table 3: *Standardized maximin optimal designs* $\{t_1^*, t_2^*, t_3^*, t_4^*; w_1, w_2, w_3, w_4\}$ *for the Emax/mono-compartment model* (5) *with* $t_1^* = 0$, $t_4^* = T$.

criterion (2) with $J = \{1,2,3,4\}$											
θ_2	θ_3	t_2^*	t_3^*	w_1	w_2	w_3	w_4	eff$_1$	eff$_2$	eff$_3$	eff$_4$
0.2	0.10	12.916	36.811	0.104	0.179	0.154	0.564	0.567	0.627	0.567	0.610
0.1	0.10	17.001	42.077	0.108	0.183	0.150	0.559	0.564	0.611	0.564	0.607
0.4	0.10	9.797	32.326	0.097	0.173	0.160	0.570	0.572	0.620	0.572	0.616
0.2	0.05	24.552	65.193	0.139	0.242	0.198	0.421	0.715	0.804	0.715	0.793
0.2	0.20	6.462	18.430	0.103	0.178	0.154	0.565	0.565	0.625	0.565	0.609
criterion (2) with $J = \{2,3,4\}$											
θ_2	θ_3	t_2^*	t_3^*	w_1	w_2	w_3	w_4		eff$_2$	eff$_3$	eff$_4$
0.2	0.10	12.167	33.275	0.220	0.298	0.287	0.195		0.933	0.933	0.933
0.1	0.10	16.025	38.701	0.260	0.282	0.247	0.212		0.904	0.904	0.904
0.4	0.10	9.261	28.892	0.183	0.303	0.320	0.194		0.945	0.945	0.945
0.2	0.05	23.491	63.381	0.215	0.319	0.287	0.179		0.944	0.944	0.944
0.2	0.20	6.085	16.643	0.220	0.298	0.287	0.195		0.933	0.933	0.933

Table 4: *Robust standardized maximin optimal designs for the Emax/mono-compartment model* (5). *The set* Ω *in the criterion* (4) *is given by* $\Omega = \{\theta : 0.1 \le \theta_2 \le 0.4, 0.05 \le \theta_3 \le 0.2\}$. *The right part of the table shows the minimal efficiencies calculated over the set* Ω *and the class* J *of parameters included in the optimality criterion.*

5-point robust design for criterion (4) with $J = \{1,2,3,4\}$						
t_1^* 0	t_2^* 8.355	t_3^* 20.986	t_4^* 51.299	t_5^* 120		
w_1 0.164	w_2 0.221	w_3 0.254	w_4 0.114	w_5 0.247		min eff 0.265
6-point robust design for criterion (4) with $J = \{1,2,3,4\}$						
t_1^* 0	t_2^* 7.178	t_3^* 16.665	t_4^* 30.966	t_5^* 60.097	t_6^* 120	
w_1 0.121	w_2 0.139	w_3 0.157	w_4 0.125	w_5 0.108	w_6 0.349	min eff 0.386
5-point robust design for criterion (4) with $J = \{2,3,4\}$						
t_1^* 0	t_2^* 8.622	t_3^* 20.521	t_4^* 50.073	t_5^* 120		
w_1 0.176	w_2 0.252	w_3 0.308	w_4 0.140	w_5 0.124		min eff 0.280
6-point robust design for criterion (4) with $J = \{2,3,4\}$						
t_1^* 0	t_2^* 7.041	t_3^* 16.702	t_4^* 30.803	t_5^* 57.507	t_6^* 120	
w_1 0.171	w_2 0.166	w_3 0.198	w_4 0.166	w_5 0.176	w_6 0.123	min eff 0.472

5 Emax/effect-compartment model

5.1 Locally optimal design

The Emax/effect-compartment model is given by

$$\eta(t,\theta) = \theta_0 + \frac{\theta_1(e^{-\theta_3 t} - e^{-\theta_4 t})}{\theta_2(1-\theta_3/\theta_4)/D_1 + (e^{-\theta_3 t} - e^{-\theta_4 t})} \tag{7}$$

where $\theta = (\theta_0, \theta_1, \theta_2, \theta_3, \theta_4)^T$. Without loss of generality we put $D_1 = 1$. The corresponding vector of regression function for model (7) is given by

$$f(t) = f(t,\theta_1,\theta_2,\theta_3,\theta_4) = \Bigg(1, \frac{\left(e^{-\theta_3 t}-e^{-\theta_4 t}\right)\theta_4}{\theta_2(\theta_4-\theta_3)+\theta_4(e^{-\theta_3 t}-e^{-\theta_4 t})}, \frac{-\theta_1\left(e^{-\theta_3 t}-e^{-\theta_4 t}\right)\theta_4(\theta_4-\theta_3)}{\left(\theta_2(\theta_4-\theta_3)+\theta_4(e^{-\theta_3 t}-e^{-\theta_4 t})\right)^2},$$
$$-\frac{\theta_1\theta_4\theta_2\left(te^{-\theta_3 t}(\theta_4-\theta_3)-e^{-\theta_3 t}+e^{-\theta_4 t}\right)}{\left(\theta_2(\theta_4-\theta_3)+\theta_4(e^{-\theta_3 t}-e^{-\theta_4 t})\right)^2}, \frac{\theta_1\theta_2\left(\theta_4 te^{-\theta_4 t}(\theta_4-\theta_3)-e^{-\theta_3 t}\theta_3+e^{-\theta_4 t}\theta_3\right)}{\left(\theta_2(\theta_4-\theta_3)+\theta_4(e^{-\theta_3 t}-e^{-\theta_4 t})\right)^2}\Bigg)^T.$$

The construction of the e_k-optimal designs for this model is similar to the method for the Emax/mono-compartment model and is fully described in the appendix as Lemma 3. This result greatly simplifies the numerical construction of such optimal designs and enables us to study properties of the designs. The last part of Lemma 3 tells us how the optimal design changes when the design interval changes.

Table 5 presents locally optimal designs for selected nominal values of the parameters. We observe that in all cases these designs are supported at only four points although model (7) has five parameters. Because locally D-optimal designs are commonly used, we also listed them and their efficiencies for estimating the individual parameters in Table 6. We observe that the locally D-optimal designs yield rather low efficiencies for estimating the individual parameters.

5.2 Standardized maximin optimal and robust design

We pointed out earlier on that standardized maximin designs are not dependent on the nominal values of θ_0 and θ_1 and this observation is important because we can now find these designs using numerical methods substantially faster. Standardized maximin optimal designs for the Emax/effect-compartment model for selected values of the model parameters are given in Table 7 and some robust designs are presented in Table 8. Similarly to the situation discussed in Section 4, the inclusion of baseline effect in the optimality criterion (2), i.e. $1 \in J$, reduces the minimal efficiency of the standardized maximin optimal design; see the first part of Table 7. On the other hand, if $J = \{2,3,4,5\}$ the standardized maximin optimal designs have remarkable good efficiencies for estimating

Table 5: *Locally e_k-optimal designs $\{t_1^*, t_2^*, t_3^*, t_4^*, t_5^*; w_1, w_2, w_3, w_4, w_5\}$ for the Emax/effect-compartment model* (7) *with $t_1^* = 0$.*

			e_2-optimal								
θ_2	θ_3	θ_4	t_2^*	t_3^*	t_4^*	t_5^*	w_1	w_2	w_3	w_4	w_5
0.2	0.10	0.5	0.085	2.331	14.223	35.800	0	0.325	0.407	0.175	0.093
0.1	0.10	0.5	0.025	2.032	17.512	40.465	0	0.364	0.432	0.136	0.068
0.4	0.10	0.5	0.219	2.717	12.415	33.462	0	0.297	0.366	0.202	0.134
0.2	0.05	0.5	0.073	2.436	23.994	68.486	0	0.309	0.399	0.191	0.101
0.2	0.20	0.5	0.096	2.108	9.706	20.553	0	0.344	0.402	0.156	0.097
0.2	0.10	0.3	0.155	3.641	17.801	39.117	0	0.339	0.404	0.161	0.096
0.2	0.10	0.9	0.042	1.347	12.160	34.386	0	0.311	0.401	0.189	0.099
			e_3-optimal								
0.2	0.10	0.5	0.149	2.583	14.947	37.915	0	0.185	0.269	0.315	0.231
0.1	0.10	0.5	0.073	2.302	18.210	42.029	0	0.152	0.277	0.348	0.223
0.4	0.10	0.5	0.255	2.816	12.742	34.733	0	0.219	0.259	0.281	0.241
0.2	0.05	0.5	0.131	2.694	25.382	71.467	0	0.161	0.278	0.339	0.221
0.2	0.20	0.5	0.128	2.205	9.862	21.037	0	0.210	0.238	0.290	0.262
0.2	0.10	0.3	0.234	3.898	18.284	40.642	0	0.205	0.248	0.295	0.252
0.2	0.10	0.9	0.075	1.488	12.883	35.993	0	0.164	0.279	0.336	0.221
			e_4-optimal								
0.2	0.10	0.5	0.031	2.152	13.867	35.059	0	0.255	0.150	0.245	0.350
0.1	0.10	0.5	0.013	1.962	17.409	40.303	0	0.231	0.162	0.268	0.338
0.4	0.10	0.5	0.059	2.319	11.536	30.803	0	0.279	0.137	0.221	0.363
0.2	0.05	0.5	0.032	2.272	23.304	67.423	0	0.250	0.161	0.250	0.339
0.2	0.20	0.5	0.016	1.878	9.470	20.017	0	0.261	0.126	0.238	0.374
0.2	0.10	0.3	0.035	3.315	17.383	38.173	0	0.261	0.131	0.239	0.369
0.2	0.10	0.9	0.018	1.252	11.806	33.815	0	0.250	0.161	0.250	0.339
			e_5-optimal								
0.2	0.10	0.5		1.449	13.019	34.306	0.114	0	0.296	0.386	0.204
0.1	0.10	0.5		0.989	16.327	39.611	0.105	0	0.309	0.395	0.191
0.4	0.10	0.5		1.897	11.013	30.156	0.130	0	0.271	0.370	0.229
0.2	0.05	0.5		1.589	21.174	65.989	0.103	0	0.318	0.397	0.182
0.2	0.20	0.5		1.129	9.042	19.731	0.154	0	0.241	0.346	0.259
0.2	0.10	0.3		2.025	16.528	37.522	0.140	0	0.257	0.360	0.243
0.2	0.10	0.9		0.883	10.766	33.101	0.103	0	0.318	0.397	0.182

the parameters $\theta_1, \theta_2, \theta_3, \theta_4$ in the Emax/effect-compartment model (see the second part of Table 7).

Table 8 shows the robust designs and their corresponding minimal efficiencies calculated over the set $J \times \Omega$. Because the set Ω used in the optimality criterion is rather large, the resulting minimal efficiencies are small. However, it should be noted again that these values represent the minimal efficiencies over the set Ω, and at most points in this set, the efficiencies are substantially larger. On the other hand, the minimal efficiency of the

Table 6: *The locally D-optimal designs* $\{t_1^{*D}, t_2^{*D}, t_3^{*D}, t_4^{*D}, t_5^{*D}; w_1, w_2, w_3, w_4, w_5\}$ *for the Emax/effect-compartment model* (7) *and their* e_k*-efficiencies with* $t_5^{*D} = T = 120$, $w_i = 1/5, i = 1, 2, 3, 4, 5$.

θ_2	θ_3	θ_4	t_1^{*D}	t_2^{*D}	t_3^{*D}	t_4^{*D}	eff_1	eff_2	eff_3	eff_4	eff_5
0.2	0.10	0.5	0.280	2.947	14.694	32.650	0.200	0.622	0.643	0.704	0.605
0.1	0.10	0.5	0.165	2.812	18.655	37.883	0.201	0.613	0.635	0.701	0.616
0.4	0.10	0.5	0.428	3.083	12.105	28.503	0.200	0.615	0.648	0.696	0.611
0.2	0.05	0.5	0.293	3.347	25.578	62.389	0.200	0.638	0.619	0.691	0.576
0.2	0.20	0.5	0.264	2.560	10.020	19.031	0.200	0.616	0.681	0.678	0.645
0.2	0.10	0.3	0.448	4.464	18.368	36.119	0.200	0.617	0.673	0.689	0.637
0.2	0.10	0.9	0.162	1.819	12.875	31.270	0.200	0.635	0.621	0.695	0.578

robust design is close to the minimal efficiency of standardized maximin optimal design if the set Ω is small.

Table 7: *Standardized maximin optimal designs* $\{t_1^*, t_2^*, t_3^*, t_4^*, t_5^*; w_1, w_2, w_3, w_4, w_5\}$ *for the Emax/effect-compartment model* (7) *with* $t_1^* = 0$.

criterion (2) with $J = \{1, 2, 3, 4, 5\}$																
θ_2	θ_3	θ_4	t_2^*	t_3^*	t_4^*	t_5^*	w_1	w_2	w_3	w_4	w_5	eff_1	eff_2	eff_3	eff_4	eff_5
0.2	0.10	0.5	0.215	2.49	13.88	37.6	0.490	0.083	0.171	0.156	0.100	0.490	0.490	0.493	0.493	0.490
0.1	0.10	0.5	0.133	2.28	18.12	43.6	0.505	0.065	0.150	0.166	0.114	0.505	0.505	0.505	0.531	0.505
0.4	0.10	0.5	0.310	2.77	11.91	33.5	0.478	0.104	0.162	0.147	0.108	0.478	0.478	0.509	0.489	0.478
0.2	0.05	0.5	0.224	2.53	23.96	73.2	0.497	0.072	0.160	0.166	0.105	0.498	0.498	0.498	0.512	0.498
0.2	0.20	0.5	0.190	2.36	9.60	21.2	0.485	0.100	0.168	0.133	0.115	0.486	0.486	0.506	0.501	0.486
0.2	0.10	0.3	0.336	4.03	17.46	40.6	0.486	0.094	0.171	0.140	0.110	0.487	0.487	0.501	0.498	0.487
0.2	0.10	0.9	0.131	1.46	12.03	36.8	0.496	0.070	0.162	0.170	0.102	0.496	0.496	0.496	0.502	0.496
criterion (2) with $J = \{2, 3, 4, 5\}$																
θ_2	θ_3	θ_4	t_2^*	t_3^*	t_4^*	t_5^*	w_1	w_2	w_3	w_4	w_5		eff_2	eff_3	eff_4	eff_5
0.2	0.10	0.5	0.174	2.22	13.02	34.0	0.106	0.153	0.301	0.276	0.164		0.752	0.764	0.752	0.752
0.1	0.10	0.5	0.094	1.92	16.17	39.9	0.149	0.124	0.315	0.267	0.145		0.754	0.760	0.754	0.754
0.4	0.10	0.5	0.306	2.59	11.21	30.0	0.103	0.171	0.273	0.266	0.186		0.733	0.776	0.733	0.733
0.2	0.05	0.5	0.175	2.28	21.34	65.7	0.105	0.142	0.304	0.288	0.161		0.773	0.773	0.773	0.773
0.2	0.20	0.5	0.183	2.11	9.08	19.6	0.129	0.162	0.277	0.244	0.187		0.718	0.804	0.718	0.718
0.2	0.10	0.3	0.304	3.60	16.57	37.3	0.121	0.161	0.283	0.256	0.180		0.727	0.791	0.727	0.727
0.2	0.10	0.9	0.096	1.26	10.96	32.8	0.104	0.142	0.306	0.288	0.160		0.771	0.771	0.771	0.771

6 Comparison with designs used in practice

We now compare performance of the robust designs and commonly used designs when we analyze data with the Emax/mono-compartment model or the Emax/effect-compartment model. We provide three comparisons for the former model and one for the latter model.

Table 8: *Robust standardized maximin optimal designs for the Emax/effect-compartment-model* (7). *The set* Ω *in the criterion* (4) *is given by* $\Omega = \{\theta : 0.1 \leq \theta_2 \leq 0.4, 0.05 \leq \theta_3 \leq 0.2, 0.3 \leq \theta_4 \leq 0.9\}$. *The numbers on the extreme right of the table show the minimal efficiency calculated over the set of* Ω *and the set* J *of parameters included in the criterion.*

6-point robust design for criterion (4) with $J = \{1, 2, 3, 4, 5\}$							
t_1^*	t_2^*	t_3^*	t_4^*	t_5^*	t_6^*		
0	0.372	2.663	9.700	21.765	52.112		
w_1	w_2	w_3	w_4	w_5	w_6		min eff
0.206	0.080	0.178	0.159	0.253	0.125		0.206
7-point robust design for criterion (4) with $J = \{1, 2, 3, 4, 5\}$							
t_1^*	t_2^*	t_3^*	t_4^*	t_5^*	t_6^*	t_7^*	
0	0.210	1.863	5.619	13.690	26.264	55.369	
w_1	w_2	w_3	w_4	w_5	w_6	w_7	min eff
0.262	0.098	0.126	0.110	0.107	0.173	0.125	0.262
6-point robust design for criterion (4) with $J = \{2, 3, 4, 5\}$							
t_1^*	t_2^*	t_3^*	t_4^*	t_5^*	t_6^*		
0	0.308	2.557	9.581	21.245	51.054		
w_1	w_2	w_3	w_4	w_5	w_6		min eff
0.086	0.104	0.191	0.187	0.267	0.165		0.218
7-point robust design for criterion (4) with $J = \{2, 3, 4, 5\}$							
t_1^*	t_2^*	t_3^*	t_4^*	t_5^*	t_6^*	t_7^*	
0	0.181	1.809	5.904	13.990	26.894	53.788	
w_1	w_2	w_3	w_4	w_5	w_6	w_7	min eff
0.106	0.115	0.145	0.129	0.118	0.212	0.175	0.296

The purpose of the comparisons is to evaluate the suitability of robust designs for practical applications in terms of efficiencies gained or loss because of its added flexibility. The first three studies uses the Emax/mono-compartment model for data analysis and the fourth uses the Emax/effect-compartment model.

(1) Rosarior et al. (2006) used a viral dynamics model to compare the effectiveness of in vivo viral inhibition of several doses of maraviroc and used a modeling approach to support design considerations for a monotherapy using different dose regimens of maraviroc. We focus on the sampling time scheme on the last day of treatment where plasma samples were taken at 0, 1, 2, 4, 6, 8, 24, 48, 72 and 120h postdose for PK measurements. Subjects were asymptomatic HIV-1 infected patients.

(2) Agoram et al. (2006) describe an experiment where PK samples were collected at 0, 0.5, 6, 24, 48, 72, 96, and 120 hours for studying chemotherapy-induced anemia. Subjects were given Darbepoetin Alfa and the aim was to develop and evaluate a population pharmacokinetic-pharmacodynamic model.

(3) Danhof et al. (1998) used an integrated pharmacokinetic-pharmacodynamic approach to optimize R-apomorphine delivery in patients with idiopathic Parkinsons disease. The sampling scheme was to use equidistant time points in the study.

(4) Magee et al. (2002) conducted a study to assess lymphocyte responsiveness to immunosuppressive therapy using a three-component complex model to characterize effects of prednisoloone. Blood samples were drawn at 0, 1, 2, 4, 6, 8, 12, 18, 24 and 32 hours from healthy volunteers who received a single total body weight-based oral dose of prednisone.

There was no justification for the sampling scheme used in each study. For easy reference, we denote these designs respectively by

$$\begin{aligned}\xi_1 &= \{0, 1, 2, 4, 6, 8, 24, 48, 72, 120\},\\ \xi_2 &= \{0, 0.5, 6, 24, 48, 72, 96, 120\},\\ \xi_3 &= \{0, 12, 24, 48, 60, 72, 84, 96, 108, 120\},\\ \xi_4 &= \{0, 1, 2, 4, 6, 8, 12, 18, 24, 32\}.\end{aligned}$$

We now evaluate the efficiencies of these designs relative to the robust designs. For space considerations, we compare the first three designs using the Emax/mono-compartment model and the fourth design using the Emax/effect-compartment model. The ratio

$$\mathrm{C}_k(\xi_r, \xi_j, \theta) = \frac{e_k^T M^-(\xi_j, \theta) e_k}{e_k^T M^-(\xi_r, \theta) e_k}$$

measures the efficiency of the design ξ_j for estimating the k^{th} parameter in the model relative to the robust design ξ_r in the j^{th} study.

Figures 1 – 4 display the function $\mathrm{C}_k(\xi_r, \xi_j, \theta)$ for various values of the parameter θ. We observe that the optimal designs and each quantity C_k does not depend on the parameters θ_0 and θ_1. The value C_k can be interpreted as follows. If θ is the "true" set of parameter values for the model, the robust design has C_k times smaller variance for the estimated kth parameter compared with the design ξ_j. This implies if $C_k > 1$ the robust design ξ_r should be preferred; otherwise if $C_k < 1$, the design ξ_j has a smaller variance for the estimated k^{th} parameter and so it is preferred. In most cases the robust designs yield substantially smaller variances than the designs ξ_1, ξ_2, ξ_3 and ξ_4 used in practice.

Figures 1 and 2 show that the variances of the estimated parameters $\theta_0, \theta_1, \theta_2, \theta_3$ obtained from the robust design are on average 1.2-1.4 times smaller than the corresponding variances for the design ξ_1, ξ_2. In terms of confidence interval, the lengths of the confidence intervals for these parameters are shorter using our proposed robust designs. The improvement can be substantial. For example, if the "true" parameters are $\theta_2 = \theta_3 = 0.3$, the variance for the baseline effect θ_0 in the Emax/mono-compartment model obtained by the robust design ξ_r, is approximately 1.7 times smaller than the variance obtained from the commonly used design ξ_1 (see the upper left panel in Figure 1).

In Figure 3 we show the corresponding results for the design ξ_3, which has more points than the robust design ξ_r and the designs ξ_1 and ξ_2. The variances for the estimated parameters $\theta_1, \theta_2, \theta_3$ obtained from the robust design are in average 1.6 times smaller than the corresponding variances obtained from the design ξ_3. On the other hand, the commonly used design ξ_3 yields up to 0.75 times smaller variances for the parameter θ_0 in the Emax/mono-compartment model if $\theta_3 > 0.08$ and up to 1.6 times larger variances if $\theta_3 < 0.08$.

Finally, some results for the Emax/effect-compartment model are shown in Figure 4. Here the variances for the estimated parameters $\theta_1, \theta_2, \theta_3$ obtained from the robust design are in average 1.8 times smaller than the corresponding variances obtained from the design ξ_4. On the other hand, the variance for the parameter θ_5, obtained by the commonly used design ξ_4, are up to 0.6 times smaller than the variance obtained by the robust design if $\theta_3 > 0.08$. However, if $\theta_3 < 0.08$, the advantages of the robust design ξ_r are obvious. The variances obtained from this design are up to 4 times smaller than those obtained from the commonly used design.

7 Conclusion

Optimal designs for estimating individual parameters or some of the parameters in a linear model are relatively straightforward, but the task is much harder for nonlinear models. We provided new and fairly closed analytical description for locally optimal designs for estimating individual model parameter in two popular models in PK/PD studies – the Emax/mono-compartment and Emax/effect-compartment model. These designs do not require iterative methods for construction and so this facilitates studying their properties. These designs were then used to construct designs that are efficient for estimating several parameters of the model and at the same time, they are less sensitive to the nominal values of the model parameters.

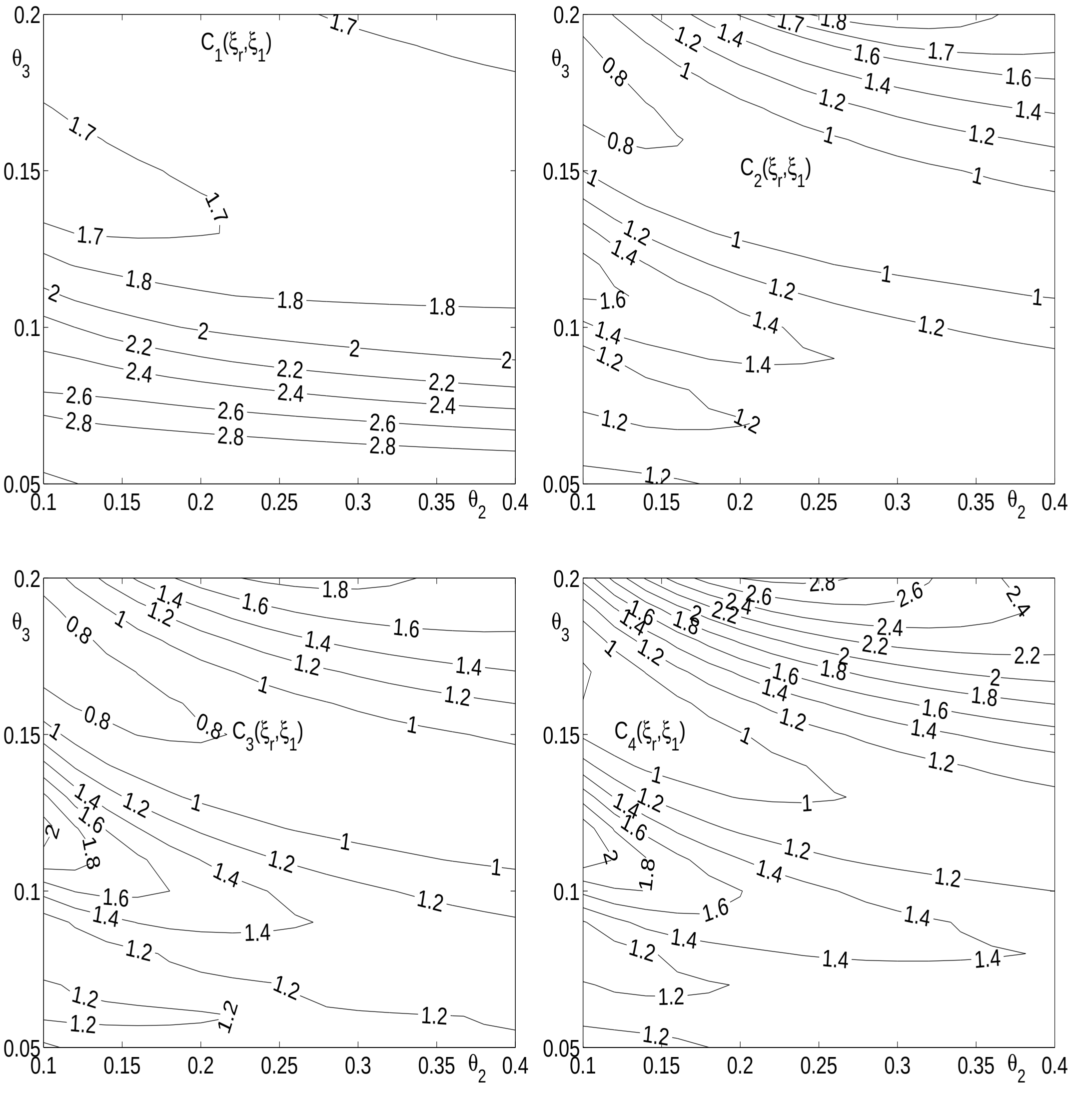

Figure 1: *Comparisons of the design* $\xi_1 = \{0, 1, 2, 4, 6, 8, 24, 48, 72, 120\}$ *and the robust design* $\xi_r = \{0, 7.2, 16.7, 31.0, 60.1, 120; 0.121, 0.139, 0.157, 0.125, 0.108, 0.349\}$ *for estimating the parameters in the Emax/mono-compartment model* (5).

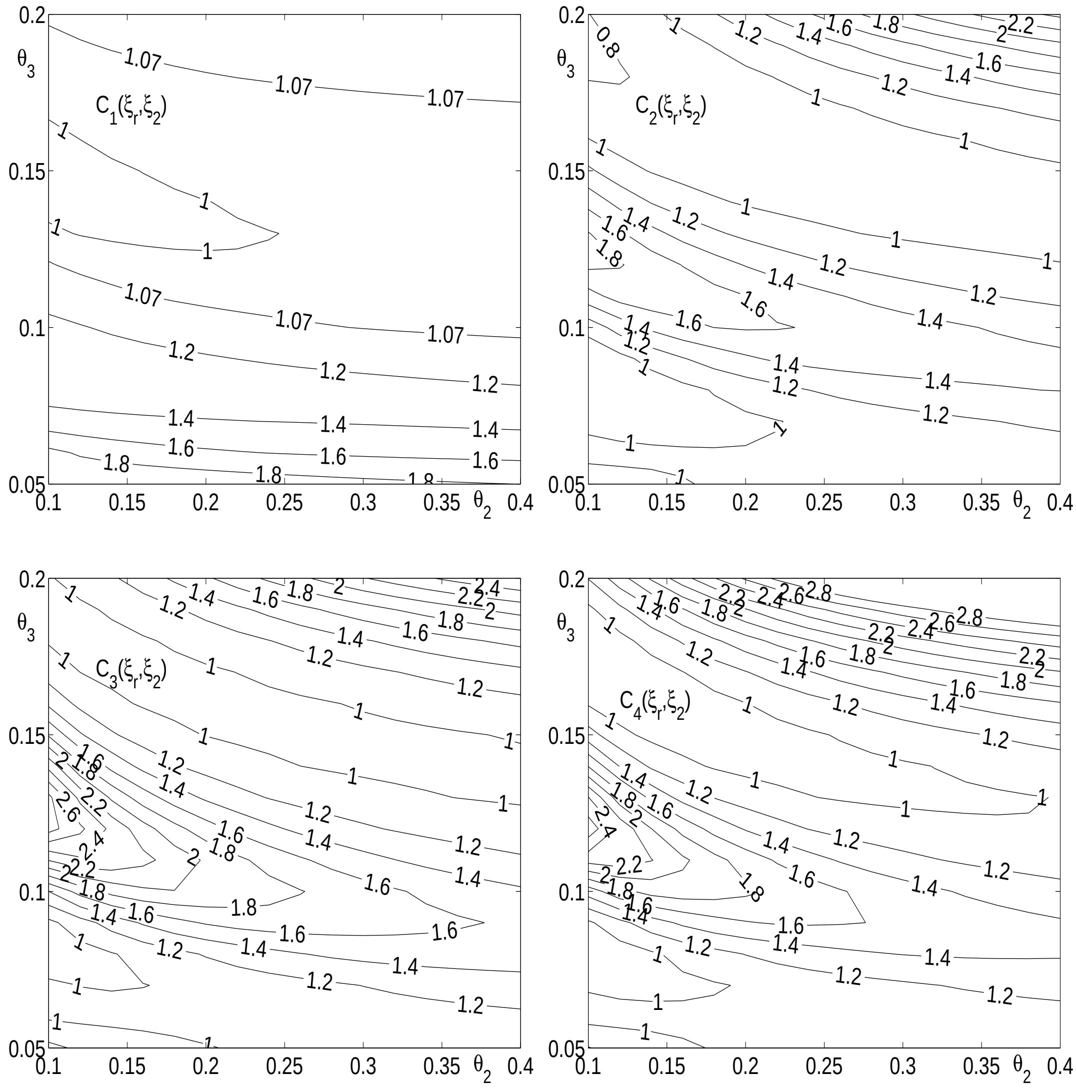

Figure 2: *Comparisons of the design* $\xi_2 = \{0, 0.5, 6, 24, 48, 72, 96, 120\}$ *and the robust design* $\xi_r = \{0, 7.2, 16.7, 31.0, 60.1, 120; 0.121, 0.139, 0.157, 0.125, 0.108, 0.349\}$ *for estimating the parameters in the Emax/mono-compartment model* (5).

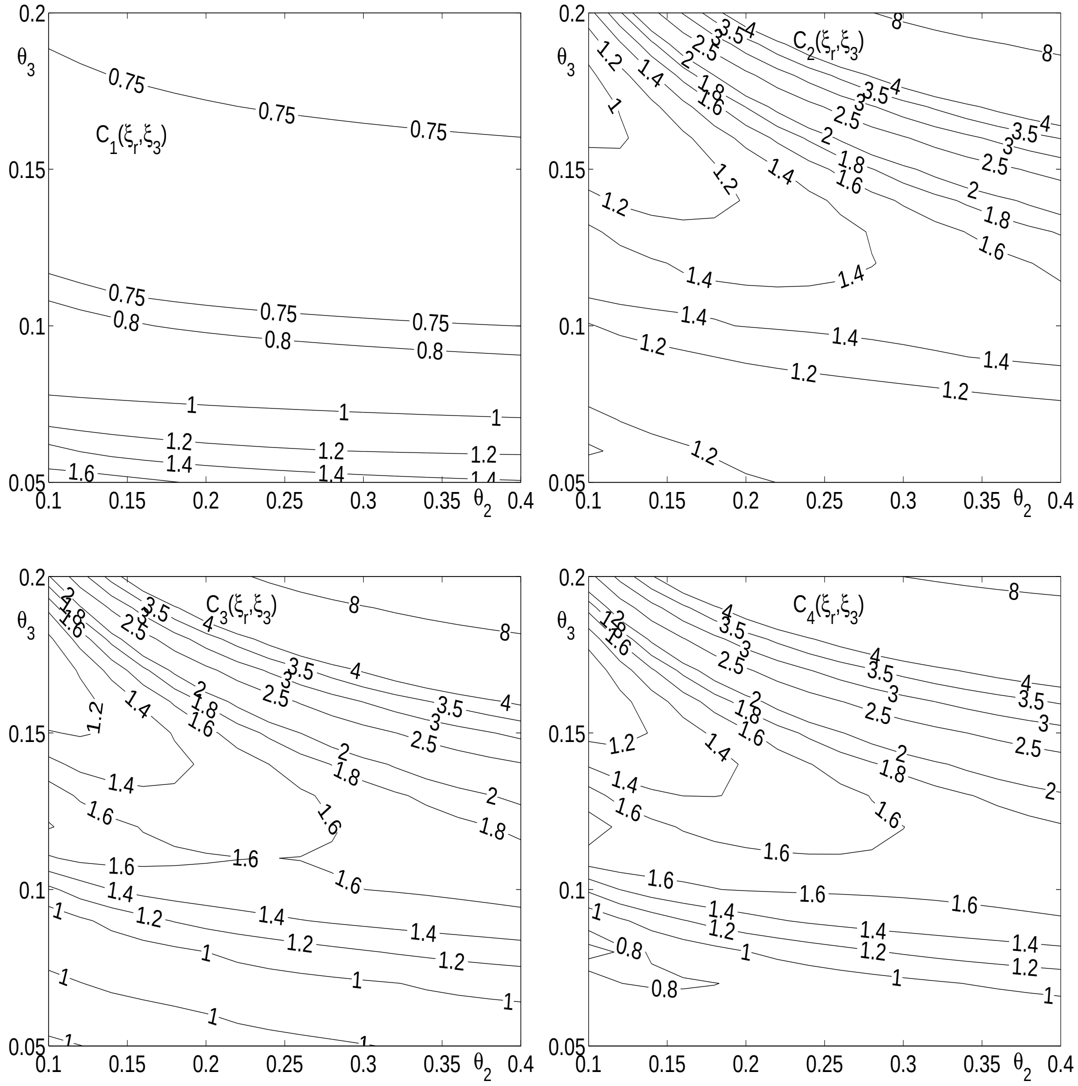

Figure 3: *Comparisons of the design* $\xi_3 = \{0, 12, 24, 48, 60, 72, 84, 96, 108, 120\}$ *and the robust design* $\xi_r = \{0, 7.2, 16.7, 31.0, 60.1, 120; 0.121, 0.139, 0.157, 0.125, 0.108, 0.349\}$ *for estimating the parameters in the Emax/mono-compartment model* (5).

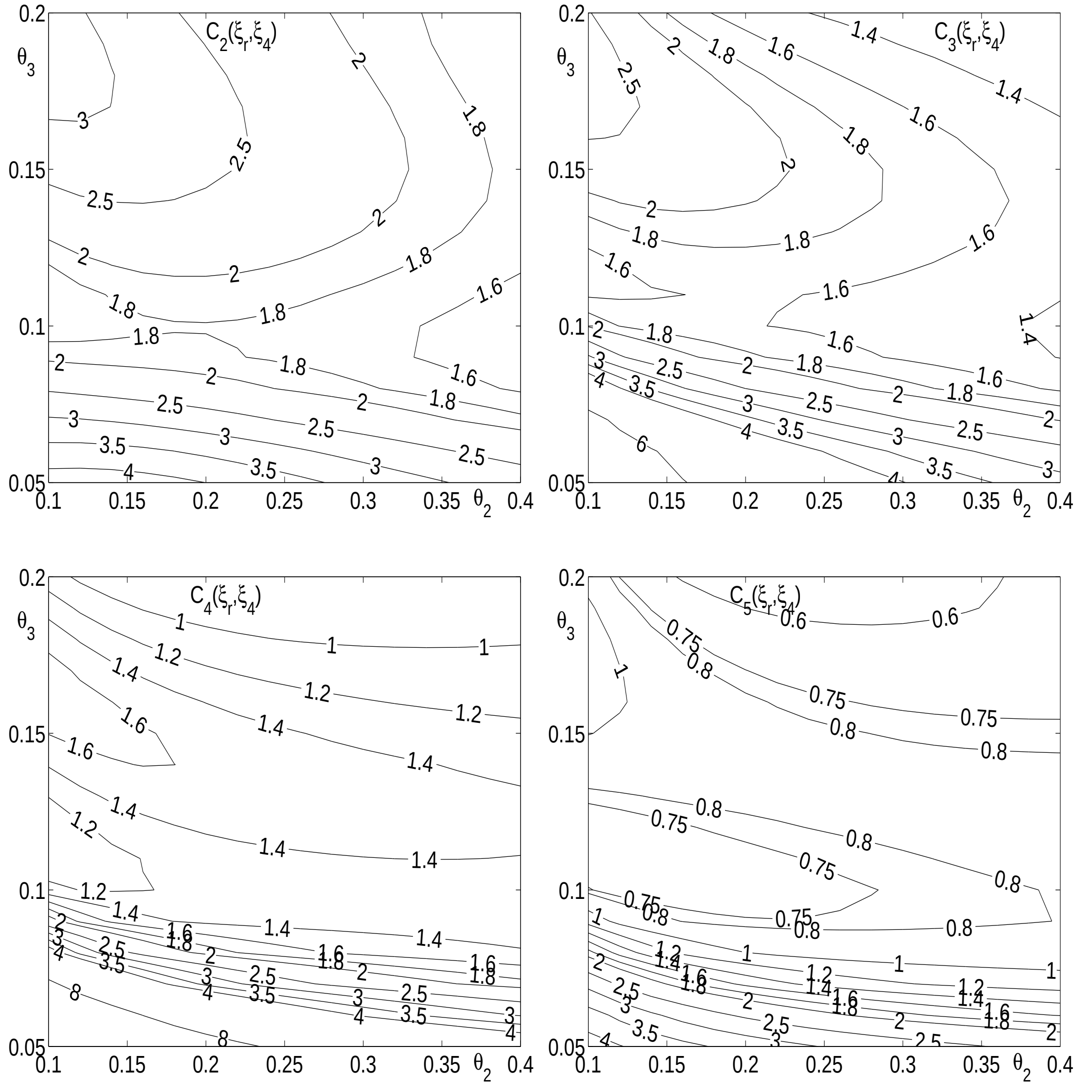

Figure 4: *Comparisons of the design* $\xi_4 = \{0, 1, 2, 4, 6, 8, 12, 18, 24, 32\}$ *and the robust design* $\xi_r = \{0, 0.18, 1.81, 5.9, 14.0, 26.9, 53.8; 0.106, 0.115, 0.145, 0.129, 0.118, 0.212, 0.175\}$ *for estimating the parameters in the Emax/effect-compartment model* (7) *with* $\theta_4 = 0.5$.

We proposed standardized maximin and robust optimal designs for the Emax/mono-compartment and Emax/effect-compartment models and showed that robust designs offered certain advantages over commonly used designs. First, they do not require only a single best guess for the model parameters, which can sometimes be difficult to accommodate in practice. This happens, for example, when there are conflicting opinions for the single best guess. Our approach allows robust designs to incorporate additional flexibility by allowing the researcher to specify an interval containing plausible values for each model parameter of interest. Second, we showed robust designs can outperform these commonly used designs frequently and sometimes substantially in terms of providing more precise estimates for the parameters of interest.

A limitation of our approach is that we assume errors are independently distributed. This assumption may not be applicable for some studies because responses within patient over a short period of time are likely to be correlated. However, we view our proposed design strategy as an intermediary step to building more efficient and practical designs. Our future research will be to improve the current work by constructing optimal designs that account for the correlated responses over time.

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8 Appendix: Justifications

We first state an auxiliary result for finding locally optimal designs for the two models. The Lemma is a reformulation of the equivalence theorem for e_k-optimality and very useful in the present context. Details are in Pukelsheim (1993).

Lemma A. *Let $f(t) = (f_1(t), \ldots, f_m(t))^T$ and assume the components are linearly independent continuous functions on the interval $[0, T]$. The design $\xi = \{t_1, t_2, \ldots, t_r; w_1, w_2, \ldots, w_r\}$ is e_k-optimal for estimating the k^{th} parameter if and only if there exists a vector $q \in \mathbb{R}^m$, such that $q_k \neq 0$ and the generalized polynomial $q^T f(t)$ satisfies the following conditions*

(i) $q^T f(t_i) = (-1)^i \qquad i = 1, \ldots, m$

(ii) $|q^T f(t)| \leq 1 \qquad$ *for all* $\quad d \in [0, T]$

(iii) $Fw = \nu e_k$

for some $\nu > 0$*, where* $F = ((-1)^j f_i(t_j))_{i,j=1}^{m,r}$ *and* $w^T = (w_1, \ldots, w_r)$*. Moreover,* $e_k^T M^-(\xi) e_k = 1/\nu^2$*.*

Here are 2 technical lemmas for the construction of the proposed optimal designs.

Lemma 1. *For the Emax/mono-compartment model* (5)

1. *The locally* e_k*-optimal designs do not depend on the parameters* θ_0 *and* θ_1*.*

2. *The locally* e_3*- and* e_4*-optimal designs are supported at four well defined points, say* $t_1^*, t_2^*, t_3^*, t_4^*$*, which are determined as the unique solution of the system of nonlinear equations*

$$q_1 + q_2 \frac{1}{\theta_2 e^{\theta_3 t_i} + 1} + q_3 \frac{-\theta_1 e^{\theta_3 t_i}}{(\theta_2 e^{\theta_3 t_i} + 1)^2} + q_4 \frac{-\theta_1 \theta_2 t e^{\theta_3 t_i}}{(\theta_2 e^{\theta_3 t_i} + 1)^2} = (-1)^{i-1}, \quad i = 1, \ldots, 4 \quad (8)$$

   with respect to scalar numbers $q_1, \ldots, q_4$ *and points* $t_1, \ldots, t_4$ *subject to the condition* $|(q_1, \ldots, q_4)^T f(t)| \leq 1$ *for all* $t \in [0, T]$*. The corresponding weights are given by*

$$w^* = \frac{F^{-1} e_k}{\mathbf{1}^T F^{-1} e_k},$$

   where $\mathbf{1} = (1, \ldots, 1)^T$*,* $F = (f(t_1^*), -f(t_2^*), f(t_3^*), -f(t_4^*))$*. Moreover,* $t_1^* = 0$ *and* $t_4^* = T$*.*

3. *Let* $t_j(\theta_2, \theta_3, T)$ *be a point with corresponding weight* $w_j(\theta_2, \theta_3, T)$ *of the locally* e_k*-optimal design on the interval* $[0, T]$*. Then for any* $\gamma > 0$ *we have*

$$\gamma t_j(\theta_2, \theta_3, T) = t_j(\theta_2, \theta_3/\gamma, \gamma T), \quad w_j(\theta_2, \theta_3, T) = w_j(\theta_2, \theta_3/\gamma, \gamma T).$$

8.1 Proof of Lemma 1.

Since $f(t, \theta) = \mathrm{diag}(1, 1, \theta_1, \theta_1) \tilde{f}(t, \theta_2, \theta_3)$ where

$$\tilde{f}(t, \theta_2, \theta_3) = \left(1, \frac{1}{\theta_2 e^{\theta_3 t} + 1}, \frac{-e^{\theta_3 t}}{(\theta_2 e^{\theta_3 t} + 1)^2}, \frac{-\theta_2 t e^{\theta_3 t}}{(\theta_2 e^{\theta_3 t} + 1)^2}\right)^T,$$

the optimality criterion (3) is a product of two functions. The first function depends on the parameter θ_1 but not on the design, while the second function depends on the design but does not depend on the parameters θ_0 and θ_1. Consequently, we obtain the first statement of the Lemma.

By standard arguments it can be shown that functions $\{f_1(t), f_2(t), f_3(t), f_4(t)\}$ form a Chebyshev system on the interval $[0, T]$ and each of the systems $\{f_1(t), f_2(t), f_3(t)\}$ and $\{f_1(t), f_2(t), f_4(t)\}$ is also a Chebyshev system. Therefore, it follows that the optimal designs for estimating the parameters θ_3 and θ_4 are supported at the Chebyshev points defined by equation (8) [see e.g. Karlin and Studden (1966)]. The weights can then determined using results of Pukelsheim and Torsney (1991) and this proves the second part of the Lemma. The third part of the lemma follows from the fact that

$$f(\gamma t, \theta_1, \theta_2, \theta_3) = \mathrm{diag}(1, 1, 1, \gamma) f(t, \theta_1, \theta_2, \gamma\theta_3).$$

$\square$

Lemma 2. *For the Emax/effect-compartment model* (7)

1. *The locally* e_k*-optimal designs do not depend on the parameters* θ_0 *and* θ_1*.*
2. *The locally* e_1*-optimal design is a one-point design supported at the point 0.*
3. *Let* $t_j(\theta_2, \theta_3, T)$ *be a point with corresponding weight* $w_j(\theta_2, \theta_3, \theta_4, T)$ *of a locally* e_k*-optimal design on the interval* $[0, T]$*. Then for any* $\gamma > 0$ *we have*

$$w_j(\theta_2, \theta_3, \theta_4, T) = w_j(\theta_2, \theta_3/\gamma, \theta_4/\gamma, \gamma T), \quad \gamma t_j(\theta_2, \theta_3, \theta_4, T) = t_j(\theta_2, \theta_3/\gamma, \theta_4/\gamma, \gamma T).$$

8.2 Proof of Lemma 2.

The first part is obtained using similar arguments in the proof of Lemma 1. The second part directly follows from Lemma A with $q = e_1$. The third part follows from the identity

$$f(\gamma t, \theta_1, \theta_2, \theta_3, \theta_4) = f(t, \theta_1, \theta_2, \gamma\theta_3, \gamma\theta_4).$$

$\square$

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