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Multiple-Objective Optimal Designs for Studying the Dose Response Function and Interesting Dose Levels

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Abstract: We construct an optimal design to simultaneously estimate three common interesting features in a dose-finding trial with possibly different emphasis on each feature. These features are (1) the shape of the dose-response curve, (2) the median effective dose and (3) the minimum effective dose level. A main difficulty of this task is that an optimal design for a single objective may not perform well for other objectives. There are optimal designs for dual objectives in the literature but we were unable to find optimal designs for 3 or more objectives to date with a concrete application. A reason for this is that the approach for finding a dual-objective optimal design does not work well for a 3 or more multiple-objective design problem.

We propose a method for finding multiple-objective optimal designs that estimate the three features with user-specified higher efficiencies for the more important objectives. We use the flexible 4-parameter logistic model to illustrate the methodology but our approach is applicable to find multiple-objective optimal designs for other types of objectives and models. We also investigate robustness properties of multiple-objective optimal designs to mis-specification in the nominal parameter values and to a variation in the optimality criterion. We also provide computer code for generating tailor made multiple-objective optimal designs.

Keywords: approximate design, c-optimal design, compound optimal design, constrained optimal design, design efficiency, dose-finding study

1 Background

Experiments are increasingly expensive to conduct and it is desirable to obtain maximal information at minimal cost. Researchers now want to have several research questions answered from a single study to save cost. Designing such multi-objective experiments can be challenging because an optimal design for one objective can perform poorly under another and further, not all objectives may be equally important. Contrary to a single-objective optimal design, the sought design has to incorporate the multiple objectives at the onset and provide user-specified efficiencies for making inferences for the more important objectives.

There is some work on constructing dual-objective optimal designs but there is little in the literature on construction and properties of optimal designs for 3 or more objectives with a concrete application. Our aims in this paper are to construct 3-objective optimal designs for a pharmaceutical application, investigate effectiveness of such designs over single-objective optimal designs, and study their robustness properties under mis-specification in the nominal values of the model parameters and a change in the optimality criterion. Our focus is to estimate interesting characteristics of an agent in a dose response study where some drug characteristics may be more meaningful or important than others. Our dose response model is the flexible 4-parameter logistic model widely used in many disciplines, such as in educational research, biological sciences, pharmaceutical sciences and agronomy, to name a few. Both our application and the model are illustrative in the sense that the methodology described here also applies to other models and criteria.

Our setup assumes that we have a nonlinear regression model defined on a given compact dose interval X. The model has a known mean structure with unknown parameters and errors are assumed to be normal,

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independent and identically distributed, each with mean 0 and constant variance σ^2. The sample size n is assumed to be fixed in advance either by cost consideration or the number of subjects available for the study. Given the model and optimality criteria with possibly different degrees of importance, the research questions are (i) what is the optimal number of doses to be used in the study? (ii) what are the doses? and, (iii) what is the optimal number of subjects at each of these doses? Our focus is on approximate designs, which means that we now determine the optimal number of doses K, the location of each dose D_i and the optimal proportion w_i of subjects to assign to the dose D_i in the study, $i = 1, \ldots, K$. In practice, after the optimal approximate design is identified, we assign nw_i subjects to D_i, such that $nw_1 + nw_2 + \cdots + nw_K = n$ and each nw_i is rounded to the nearest positive integer. The advantages of this approach versus the approach of finding optimal exact designs are well documented in Kiefer [1], among others. For example, one can use convex analysis theory and construct algorithms for finding different types of optimal approximate designs. One can also assess the proximity of any design to the optimal approximate design (without knowing the optimal approximate design) by providing an efficiency lower bound for the design [2]. Equivalence Theorems are also available to confirm the optimality of an approximate design among all designs on X.

We follow convention and measure the worth of a design by its information matrix defined as the negative of the expectation of the second derivatives of the log likelihood function with respect to the model parameters. Given an approximate design ξ, this matrix is the weighted sum of information matrices over the distinct dose levels of ξ, and the weights are the proportions of subjects at the dose levels. For nonlinear models, this matrix depends on the model parameters. Because the design criteria are formulated in terms of the information matrix, the resulting optimal designs depend on the nominal values of the model parameters. These optimal designs are termed locally optimal [3] and it is well known that they can be sensitive to the choices of the nominal parameter values. This suggests that when there are conflicting nominal values for the model parameters, it is desirable to have a design that is robust to mis-specification in the nominal values. Our work also investigates whether multiple-objective optimal designs are robust to changes in the optimality criteria or changes in the degrees of interest in the objectives.

Section 2 describes the methodology for searching optimal designs when there are 3 or more objectives of varying interests. In Section 3, we discuss optimality criteria for dose response studies in the context of the popular Hill model and its relationship with the 4-parameter logistic model. In Section 4, we revisit a dose response study with 7 anti-cancer drugs from Khinkis et al. [4], report the single-objective optimal designs for estimating all parameters in the mean function, the ED_{50} and the MED, and how they compared with the multiple-objective optimal design that accounts for these objectives simultaneously at the onset. Additionally, we show how an Equivalence Theorem can be used to confirm the optimality of a multiple-objective optimal design and study sensitivities of such an optimal design to mis-specification in the nominal values, changes in the design criteria and relative interests in the multiple objectives. Our work here suggests that multiple-objective optimal designs are generally more efficient for making inferences than single-objective optimal designs and more robust to mis-specification in the nominal values of the parameters than single-objective optimal designs. We offer a conclusion in Section 5.

2 Multiple-objective optimal designs

Multiple-objective optimal designs are appealing because many scientific studies have several objectives and these objectives may vary in importance. A properly constructed design allocates resources that ensures the more important objectives are attained with user-specified efficiencies at minimum cost. Such situations arise frequently in real studies. We give three examples. In a dose response study, there is interest to infer the mean response at a specific dose and to estimate the shape of the overall dose curve accurately, and one of these objectives may be more important than the other. Another example is in estimation problems. It is often the case that some parameters are more meaningful than others and so there is greater interest in estimating selected parameters more accurately. For instance, in the 2-parameter

Michaelis-Menten model, the Michaelis-Menten constant is clearly more interesting to estimate than the other parameter because it controls the rate of an enzyme-kinetic reaction. The third example concerns model inadequacy and inference. A properly targeted multiple-objective optimal design can detect model inadequacies and provide accurate inference at the same time. For example, consider the Emax model, which is the same as the Michaelis-Menten model except that the substrate concentration variable in the model is raised to some power. With the power as the third parameter, the Emax model is more flexible and can better capture asymmetry in the mean dose response curve than the Michaelis-Menten model. Model inadequacy concern and accurate inference on the parameters for the Emax model can then be simultaneously incorporated at the design stage using a multiple-objective optimal design that requires the power parameter be estimated with a user-specified efficiency, say 90% and subject to this constraint, the design does as well as possible for estimating the other two parameters in the model.

Multiple-objective optimal designs date back to the early seventies, where the proposed methods for constructing such designs were largely either based on ad-hoc procedures or simply based on the hope that the design constructed for the most important objective will be adequate for the other objectives. Stigler [5], Lauter [6, 7] and Lee [8, 9] were early attempts to formalize the procedure. Most were concerned with polynomial regression problems. For instance, Studden [10] was concerned about model inadequacy and wanted to find a design that was robust to the degree of the assumed polynomial model. His method ensured that coefficients in the assumed model were estimated as accurately as possible, and at the same time, the design could also provide user-specified efficiencies for estimating coefficients that might be needed for a higher degree polynomial model. Subsequent work on finding dual-objectives optimal designs includes Dette [11, 12], Zhu et al. [13], Wong [14], Song and Wong [15], Tsai and Zen [16], Atkinson [17], McGree et al. [18], Tommasi [19] and, Padmanabhan and Dragalin [20]. A recent application is Zhang et al. [21] where they constructed dual-objective optimal designs for a mixture experiment.

The formulation of the multiple-objective optimal design problem invariably involves a constrained optimization problem where the goal is to find a design that simultaneously meets user-specified minimal efficiencies for the various criteria, with higher efficiencies sought for the more important criteria, and subject to these requirements, does as well as possible for the least important criterion. Of course the sought multiple-objective optimal design may not exist if the requirements are too stringent and the objectives are competitive, meaning that much efficiency of one type has to be given up for a small gain in another criterion. Ad-hoc methods generally seek to combine the multiple design criteria into a single criterion with the expectation that the resulting optimal design for the single combined criterion may be efficient for all the criteria. The common problems with such an approach include how to combine the criteria in a meaningful way and the unclear interpretation of the combined criterion.

A more formal method to search for multiple-objective optimal approximate designs when there are two objectives ϕ_1 and ϕ_2 was proposed by Cook and Wong [22]. Their method involves the following steps: (0) Decide which is the more important criterion, say ϕ_1; (1) formulate each objective as a concave function of the information matrix; (2) specify the efficiency requirement for the sought design under ϕ_1, for example, $e_1 \geq 0.9$; (3) form a compound criterion ϕ by taking a convex combination of the two objectives: $\phi = (1-\lambda)\phi_1 + \lambda\phi_2$ (which is still concave); (4) for a large number of fixed values for $\lambda \in [0, 1]$, use an algorithm to search the compound optimal design ξ_λ that maximizes the compound criterion; (5) compute the efficiencies of the compound optimal designs under the two criteria;: $e_1(\xi_\lambda)$ and $e_2(\xi_\lambda)$; (6) construct the efficiency plot by graphing both $e_1(\xi_\lambda)$ and $e_2(\xi_\lambda)$ versus values of λ over the interval $[0, 1]$; (7) on the graph, identify λ^*, the value of λ that corresponds to the intersection point where $e_1(\xi_\lambda)$ meets the horizontal line $e_1(\xi_\lambda) = e_1$ and, (8) the sought constrained optimal design is ξ_{λ^*} which is guaranteed to have at least e_1-efficiency and does as well as possible under the second criterion. Efficiency definitions are given in Section 4.2 and examples of efficiency plots to search for dual-objective optimal designs are available in Cook and Wong [22] and Wong [23].

Clyde and Chaloner [24] extended the methodology to find Bayesian multiple-objective optimal designs for nonlinear models. However, there is no work to date that focuses on constructing an optimal design for 3 or more different objectives with a concrete application. We were also unable to find work that studies robustness properties of multiple-objective optimal designs to model mis-specifications or under a change in

the optimality criterion. There are only a handful of related papers that either briefly considered finding an optimal design for a problem with 3 or more objectives or they addressed a different class of problems. For example, El-Monsef and Seyam [25] proposed optimal designs for model discrimination, parameter estimation, and estimation of a function of parameters. The paper combined the optimality criteria for the three objectives using a weighted compound criterion. However, despite the title of their paper, only the last half page outlined how one may construct a specific 3-objective optimal design. There were no practical details, examples and explanation on how to meaningfully select the weights in the combined design criterion for maximizing each efficiency. Another related work is Antognini and Zagoraiou [26], who considered a non dose-response setup and their goal was to determine an adaptive optimal allocation scheme for subjects to treatment groups under 3 criteria in a clinical trial. They wanted to balance the competing needs of ethics requirements, proper randomization and precise treatment efficacy estimation. In such problems, the number of treatment groups is fixed (i.e. the design space consists only of a few points) and so only the optimal proportion or optimal number of subjects to assign to each treatment has to be determined. Our optimization problems have a continuous dose interval and we need to determine the number of optimal dose levels, the optimal dose levels, and the optimal proportions or numbers of subjects to assign at the dose levels. Our constrained optimization problems are thus more difficult because they have more variables to optimize over a continuous multi-dimensional space. Earlier, Zhu and Wong [27] also found multiple-objective optimal designs but their setup was limiting; their interest was confined only to estimating percentiles in a two parameter logistic model and did not discuss different types of criteria, which we have here.

The dearth of work for finding an optimal design for 3 or more objectives in a dose response study with a concrete application can be partially explained by the complexity of the efficiency plot, which increases in dimension as the number of objectives increases. In a high-dimensional efficiency plot, the visual appreciation of the shapes of various efficiency plots becomes compromised and it becomes difficult to identify the correct vector λ^* to be used in the compound optimality criterion. One may resort to an exhaustive search for the sought multiple-objective optimal design by first generating a complete list of compound optimal designs and then identifying the one that meets the user-specified efficiency requirements for the constrained optimal design. This task is generally laborious and time consuming because the algorithm may require a long time to find all compound optimal designs. Huang and Wong [28] hinted that a sequential method to tackle design problems with 3 or more objectives might work. They suggested to first consider two objectives at a time and determine the dual-objective optimal design. Then sequentially pair the rest of the objectives, two at a time, and compute the dual-objective optimal designs. The multiple-objective optimal design is then determined from the collection of generated dual-objective optimal designs. However they were unclear on how to systematically pair the objectives and work with them sequentially to determine the sought multiple-objective optimal design.

This paper presents a systematic approach to construct a multiple-objective optimal design for the 3 common objectives in a dose response study and the methodology can be directly applied to find other types of multiple-objective optimal designs in other problems. We provide an efficient algorithm for searching the multiple-objective optimal design that meets different user-specified efficiencies for the objectives and for evaluating efficiency of the generated design under various criteria. We also provide a concrete application to a dose response study and study robustness properties of the multiple-objective optimal design to mis-specification in nominal values for the model parameters and under a change of criterion. Bayesian multiple-objective optimal designs can also be found using our approach and we provide an example of such an optimal design with 10 dose levels found from our algorithm.

3 Objectives, models and algorithms for finding optimal designs in dose response studies

We assume that the continuous response variable from the j^{th} subject treated at the i^{th} dose Y_{ij} can be modeled by

$$Y_{ij} = f(x_i, \Theta) + \varepsilon_{ij};\ \varepsilon_{ij} \sim \mathrm{N}(0, \sigma^2),\ j = 1, 2, \ldots, n_i,\ i = 1, 2, \ldots, K,\ n_1 + \cdots + n_K = n,$$

where $f(x_i, \Theta)$ is the mean response at dose x_i, Θ is the vector of model parameters and σ^2 is an unknown positive constant. In practice, each x_i is usually expressed as log dose and the dose is selected from a given compact dose interval X, which can be multi-dimensional. Let $\xi = \{(x_i, w_i)\}_1^K$ denote the approximate design that takes nw_i subjects at x_i.

3.1 Common objectives in dose response models

Some interesting characteristics of a drug are the shape of the dose-response, the median effective dose (ED_{50}) and the minimum effective dose level (*MED*) [29]. ED_{50} is the dose expected to produce 50% response rate when the outcome is binary. For continuous outcome, it is the dose expected to produce one-half of the anticipated difference between the maximum and the minimum expected responses. This dose is an interesting dose to estimate because it gives a reasonable expectation of the drug effect; guidelines for accurately estimating ED_{50} are given in Sebaugh [30]. Another common dose to estimate is *MED*. This dose is the expected lowest dose that produces a clinically significant effect specified by the user. Padmanabhan and Dragalin [20] defined the *MED* as the dose producing a mean response of δ units better than the minimum dose. Here δ is user-selected and represents the predetermined clinically significant effect of interest. Doses lower than the *MED* are deemed not to provide the δ clinically significant effect. When the dose-response relationship is decreasing (increasing), the value of δ is negative (positive). Our interest here is to find a tailor-made optimal design to estimate one or more such quantities as accurately as possible based on their relative importance.

A D-optimal design minimizes the volume of the ellipsoidal confidence region of the model parameters and so estimates from the D-optimal design are the most precise. When the goal is to estimate a function of the model parameters, such as the ED_{50} or the *MED*, a c-optimal design is used to minimize the asymptotic variance of the estimated function of interest. However, a single-objective optimal design usually does not perform well under other criteria and we need a model-based compromised design to balance the competing objectives and based on their importance.

3.2 A common dose response model

We now consider a versatile and popular model commonly used in dose response studies and several other disciplines. The 4-parameter Hill model has a continuous outcome and its mean response is given by

$$f(D_i, a, b, c, d) = c + \frac{(d - c)\left(\frac{D_i}{a}\right)^b}{1 + \left(\frac{D_i}{a}\right)^b}. \tag{1}$$

Here $f(D_i, a, b, c, d)$ is the mean response of a continuous outcome at dose D_i, a is the ED_{50}, the dose that produces a response mid-way between the upper limit d, and the lower limit c. The parameter b denotes the Hill constant that controls the flexibility in the slope of the response curve.

Khinkis et al. [4] conducted a cell growth inhibition study in a laboratory to investigate the effectiveness of 7 anticancer drugs to shrink the tumor using the 4-parameter Hill model. Nominal parameter values for these drugs used in the study are displayed in Table 1. Figure 1 shows the mean response shapes of (2) for the 7 different sets of values of the parameters in Khinkis et al. [4], suggesting that the characteristics of the drugs are quite different.

Let $\Theta = (\theta_1, \theta_2, \theta_3, \theta_4)$. Model (1) may be re-parameterized as

$$f(x_i, \Theta) = \frac{\theta_1}{1 + e^{\theta_2 x_i + \theta_3}} + \theta_4, \tag{2}$$

Table 1: Nominal parameter values for the 4-parameter logistic model for the 7 drugs.

Drug	Θ	Drug	Θ
TMTX	$\Theta_1 = (1.563, 1.790, 8.442, 0.137)$	AG2009	$\Theta_5 = (1.563, 1.030, -4.851, 0.137)$
MTX	$\Theta_2 = (1.563, 2.740, 10.421, 0.137)$	AG337	$\Theta_6 = (1.563, 1.540, 1.169, 0.137)$
AG2034	$\Theta_3 = (1.563, 0.825, 0.653, 0.137)$	ZD1694	$\Theta_7 = (1.563, 1.690, 5.322, 0.137)$
AG2032	$\Theta_4 = (1.563, 3.490, 8.930, 0.137)$		

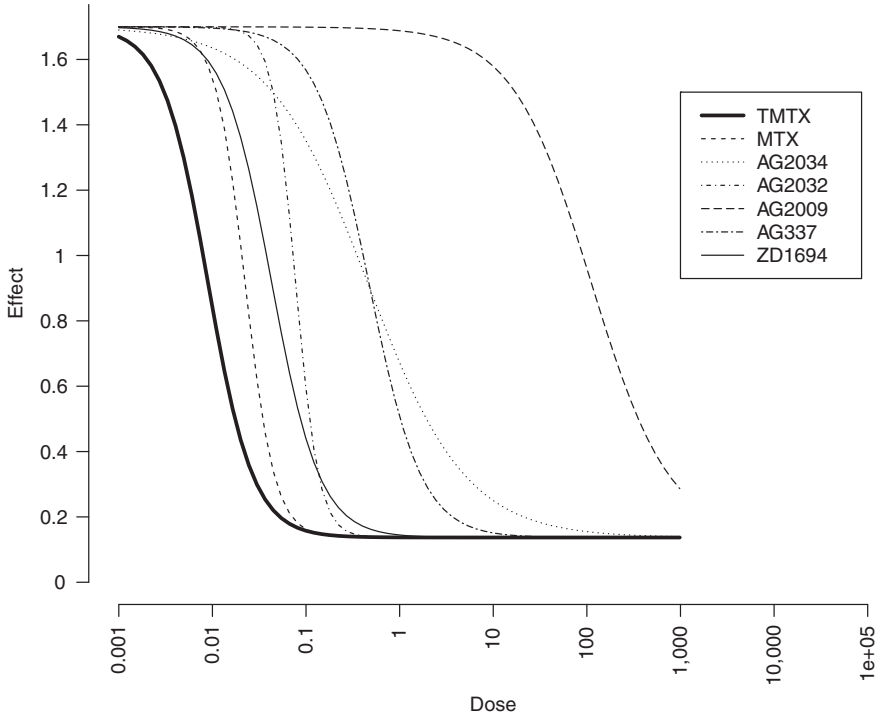

Figure 1: Expected response curves across the dose levels for the 7 drugs using nominal values of the parameters in Table 1 for Model (1).

which is sometimes referred to as the 4-parameter logistic model. This form was used in Li and Majumdar [31] and is equivalent to the above form with $\theta_1 = d - c$, $\theta_2 = -b$, $\theta_3 = b\log(a)$, $\theta_4 = c$, $\theta_1 > 0, \theta_2 \neq 0$, and $-\infty < ED_{50} < \infty$, where $x_i = \log(D_i) \in [-M, M]$ for some sufficiently large value of M. When $\theta_4 = 0$, we have the 3-parameter logistic model or hyperbolic E_{max} model. The reduced 3-parameter logistic model was used in a Phase II clinical trial for ascertaining asthma indication in Bretz et al. [32]. Fitting these curves can be accomplished using commercial software packages or more specialized software using R-codes provided by Ritz and Streibig [33]. However, in dose-response studies, fitting the curves well is harder because there are usually only a few available doses to explore. This reinforces that selecting the right doses is an important design issue.

The 4-parameter logistic model has an advantage over the Hill model in that it tends to provide more stable parameter estimates [34]. In what is to follow, we use the 4-parameter logistic model (2) and redesign the study in Khinkis et al. [4] using optimal design theory and compare benefits of our locally multiple-objective optimal designs with their locally D-optimal designs.

If the approximate design ξ takes w_i proportion of the total subjects at $x_i, i = 1, \ldots, K$, a direct calculation shows the Fisher information matrix for model (2) using ξ is

$$\mathbf{I}_{(\xi;\Theta)} = \frac{n}{\sigma^2} \sum_{i=1}^{K} w_i g(x_i)^T g(x_i), \tag{3}$$

and $g(x)$ is the gradient of the mean function $f(x, \Theta)$ evaluated at the nominal values of the parameters:

$$g(x) = \left(\frac{1}{1+e^{\theta_2 x+\theta_3}}, \frac{-\theta_1 x e^{\theta_2 x+\theta_3}}{(1+e^{\theta_2 x+\theta_3})^2}, \frac{-\theta_1 e^{\theta_2 x+\theta_3}}{(1+e^{\theta_2 x+\theta_3})^2}, 1 \right).$$

When estimates $\hat{\Theta}$ for Θ become available, the asymptotic variance of the estimated response at x is proportional to $g(x)\mathbf{I}_{(\xi,\hat{\Theta})}{}^{-1}g(x)^T$ and, as will be shown in the next section, this quantity plays an important role for finding the optimal design.

4 Dose response optimal designs

We now present single-objective optimal designs, multiple-objective optimal designs and investigate robustness properties of the latter designs to mis-specification in nominal parameter values and changes in the objectives. The nominal values in Table 1 were used to construct optimal designs on the dose interval $[\log(.001), \log(1000)] = [-6.91, 6.91]$. For model (2), Li and Majumdar [31] proved that the locally D-optimal design has 4 dose levels and the design only depends on the nominal values for the parameters θ_2 and θ_3. Yang [35] generalized these results and showed that up to 4 dose levels are required to optimize the Fisher information matrix for model (2) regardless of the values of Θ. The implication is that if the optimality criterion is a function of the Fisher information matrix, all classical optimal designs for model (2) have at most 4 dose levels. The paper also showed that all classical optimal designs for model (2) do not depend on the parameters θ_1 and θ_4. Accordingly, in what is to follow, we use the same values of θ_1 and θ_4 and different values of θ_2 and θ_3 in Table 1 to construct optimal designs.

All optimal designs in this paper were found based on the Yang-Biedermann-Tang (YBT) algorithm that has been shown to converge to an optimal design for a large class of design problems [36]. The authors also used several examples and showed that their algorithm performed faster than current algorithms for finding single-objective optimal designs, including a traditional class of algorithms such as the V-algorithm. The YBT algorithm requires that the dose range to be discretized. If there are s parameters in the mean function, the algorithm uses a starting design with $s+1$ dose levels randomly selected from the discretized set of doses in X. At each iteration, the algorithm adds the dose that maximizes the sensitivity function to the current design to form a new design. The weights for the new design are found by optimizing the design criterion over a set of known dose levels using the Newton-Raphson method. The dose levels with zero weights are removed for the next iteration.

We discovered that there was a problem in the YBT algorithm when we applied it to search for multiple-objective optimal designs. If the randomly selected $s+1$ dose levels were far from the optimal dose levels, the YBT algorithm frequently required a lot more time to find the multiple-objective optimal design and sometimes it failed to do so. We modified the YBT algorithm by having it chose better initial dose levels via the V-algorithm [37]. This modification improved the search speed and generated the multiple-objective optimal design that the original YBT algorithm could not. We offer more details with examples and software implementation in Section 4.2. Our modified algorithm includes a function called MOPT to search and verify the multiple-objective optimal designs in this paper. The function is in an R-package called **VNM** [38] and the package can be freely downloaded from the R-archive. Interested readers may also write to the first author for the codes.

4.1 Single-objective optimal designs

We recall that a D-optimal design ξ_D maximizes the determinant of the information matrix $\mathbf{I}_{(\xi;\Theta)}$ over all designs on the specified dose interval and a c-optimal design provides the most accurate estimate for a user-selected function of the model parameters. For model (2), the ED_{50} as a function of the model

parameters is given by $ED_{50} = \arg\limits_{x}\{f(x,\Theta) = \frac{1}{2}(\theta_1 + 2\theta_4)\} = -\frac{\theta_3}{\theta_2}$. Let $\widehat{ED}_{50}$ be the maximum likelihood estimate of ED_{50} and let $ED_{50}{}' = \left(0, \frac{\theta_3}{\theta_2^2}, -\frac{1}{\theta_2}, 0\right)$ be the derivative of ED_{50} with respect to Θ. The c-optimal design for estimating the ED_{50} minimizes $Var(\widehat{ED}_{50})$ and is given by

$$\xi_{ED_{50}} = \arg\min_{\xi}\ \{ED'_{50}\mathrm{I}^{-}_{(\xi;\Theta)}[ED'_{50}]^T\}, \tag{4}$$

where $\mathrm{I}^{-}_{(\xi;\Theta)}$ is a generalized inverse of $\mathrm{I}_{(\xi;\Theta)}$.

Similar to estimating the ED_{50}, the MED as a function of the model parameters in model (2) is given by $MED = \arg\limits_{x}\{f(x,\Theta) = f(x_{\min},\Theta) + \delta\} = \frac{\log\left(\frac{-\delta}{\theta_1+\delta}\right) - \theta_3}{\theta_2}$ if $\theta_2 > 0$ or $\frac{\log\left(\frac{\theta_1-\delta}{\delta}\right) - \theta_3}{\theta_2}$ if $\theta_2 < 0$. Here $x_{\min}$ is the minimum dose level and δ is a user-specified clinically significant effect, with $\delta < 0$ when $\theta_2 > 0$ or $\delta > 0$ when $\theta_2 < 0$. For the given δ, the c-optimal design for estimating the MED minimizes $Var(\widehat{MED})$ and is given by

$$\xi_{MED} = \arg\min_{\xi}\ \{MED'\mathrm{I}^{-}_{(\xi;\Theta)}[MED]^T\}, \tag{5}$$

where

$$MED' = \begin{cases} \left(\dfrac{-1}{(\theta_1+\delta)\theta_2}, \quad \dfrac{\theta_3 - \log(\frac{-\delta}{\theta_1+\delta})}{\theta_2^2}, \quad -\dfrac{1}{\theta_2}, \quad 0\right), & \text{if } \theta_2 > 0 \\ \left(\dfrac{1}{(\theta_1-\delta)\theta_2}, \quad \dfrac{\theta_3 - \log(\frac{\theta_1-\delta}{\delta})}{\theta_2^2}, \quad -\dfrac{1}{\theta_2}, \quad 0\right), & \text{if } \theta_2 < 0. \end{cases}$$

In the rest of the paper, we assume $\delta = -1$ unless we mention otherwise.

Table 2: Single-objective optimal designs for different sets of Θ.

Θ	ξ_D	$\xi_{ED_{50}}$	ξ_{MED}
Θ_1	$\begin{pmatrix} -6.91 & -5.21 & -4.08 & 6.91 \\ 0.250 & 0.250 & 0.250 & 0.250 \end{pmatrix}$	$\begin{pmatrix} -6.91 & -4.80 & 6.91 \\ 0.276 & 0.500 & 0.224 \end{pmatrix}$	$\begin{pmatrix} -6.91 & -4.61 & 6.91 \\ 0.500 & 0.454 & 0.046 \end{pmatrix}$
Θ_2	$\begin{pmatrix} -6.91 & -4.18 & -3.43 & 6.91 \\ 0.250 & 0.250 & 0.250 & 0.250 \end{pmatrix}$	$\begin{pmatrix} -6.91 & -3.80 & 6.91 \\ 0.250 & 0.500 & 0.250 \end{pmatrix}$	$\begin{pmatrix} -6.91 & -3.59 \\ 0.500 & 0.500 \end{pmatrix}$
Θ_3	$\begin{pmatrix} -6.91 & -2.00 & 0.50 & 6.91 \\ 0.250 & 0.250 & 0.250 & 0.250 \end{pmatrix}$	$\begin{pmatrix} -6.91 & -0.87 & 6.91 \\ 0.257 & 0.500 & 0.243 \end{pmatrix}$	$\begin{pmatrix} -6.91 & -0.29 & 6.91 \\ 0.500 & 0.476 & 0.024 \end{pmatrix}$
Θ_4	$\begin{pmatrix} -6.91 & -2.86 & -2.27 & 6.91 \\ 0.250 & 0.250 & 0.250 & 0.250 \end{pmatrix}$	$\begin{pmatrix} -6.91 & -2.56 & 6.91 \\ 0.250 & 0.500 & 0.250 \end{pmatrix}$	$\begin{pmatrix} -6.91 & -2.39 \\ 0.500 & 0.500 \end{pmatrix}$
Θ_5	$\begin{pmatrix} -6.91 & 3.37 & 5.22 & 6.91 \\ 0.250 & 0.250 & 0.250 & 0.250 \end{pmatrix}$	$\begin{pmatrix} 1.43 & 5.04 & 6.91 \\ 0.185 & 0.500 & 0.315 \end{pmatrix}$	$\begin{pmatrix} -1.69 & 5.27 \\ 0.500 & 0.500 \end{pmatrix}$
Θ_6	$\begin{pmatrix} -6.91 & -1.43 & -0.08 & 6.91 \\ 0.250 & 0.250 & 0.250 & 0.250 \end{pmatrix}$	$\begin{pmatrix} -6.91 & -0.75 & 6.91 \\ 0.250 & 0.500 & 0.250 \end{pmatrix}$	$\begin{pmatrix} -6.91 & -0.39 & 6.89 \\ 0.500 & 0.499 & 0.001 \end{pmatrix}$
Θ_7	$\begin{pmatrix} -6.91 & -3.75 & -2.52 & 6.91 \\ 0.250 & 0.250 & 0.250 & 0.250 \end{pmatrix}$	$\begin{pmatrix} -6.91 & -3.17 & 6.91 \\ 0.253 & 0.500 & 0.247 \end{pmatrix}$	$\begin{pmatrix} -6.91 & -2.84 & 1.49 \\ 0.500 & 0.491 & 0.009 \end{pmatrix}$

Table 2 displays the single-objective optimal designs found from our modified algorithm. All optimal designs found by the algorithm are verified by an Equivalence Theorem. This is an important tool in optimal design theory that enables one to confirm if a design is optimal among all designs on the given dose interval. It is derived from the Frechet derivative of the convex(or concave) optimality criterion, and while all the Equivalence Theorems have similar forms, each criterion has its own Equivalence Theorem. For example, for D-optimality, the Equivalence Theorem states that if we have a homoscedastic model and the mean response function has s parameters, the design ξ_D is D-optimal if and only if

$$d(x, \xi_D) = g(x)\mathrm{I}^{-1}_{(\xi_D;\Theta)}g^T(x) - s \le 0$$

for all dose levels x in the dose interval X, with equality when x is a dose level of the design ξ_D.

Equivalence Theorems for other types of optimal designs are available in design monographs, see for example, Pukelsheim [39] and Atkinson et al. [40]. For example, in order to verify if a design ξ^* is c-optimal for estimating the ED_{50} or c-optimal for estimating the MED, one checks whether one of the inequalities below is satisfied for all dose levels x in the dose interval X, with equality when x is a dose level of the design ξ^*:

$$(g(x)\mathrm{I}^-_{(\xi^*;\Theta)}[ED'_{50}]^T)^2 - ED'_{50}\mathrm{I}^-_{(\xi^*;\Theta)}[ED'_{50}]^T \le 0$$

or

$$(g(x)\mathrm{I}^-_{(\xi^*;\Theta)}[MED']^T)^2 - MED'\mathrm{I}^-_{(\xi^*;\Theta)}[MED']^T \le 0.$$

In the literature, the function on the left hand side of the inequality is sometimes refereed to as the sensitivity function. Figure 2 shows the plot of the sensitivity function for each of the single-objective optimal designs when Θ_1 is assumed as nominal values for Θ. Each plot shows the graph of the sensitivity

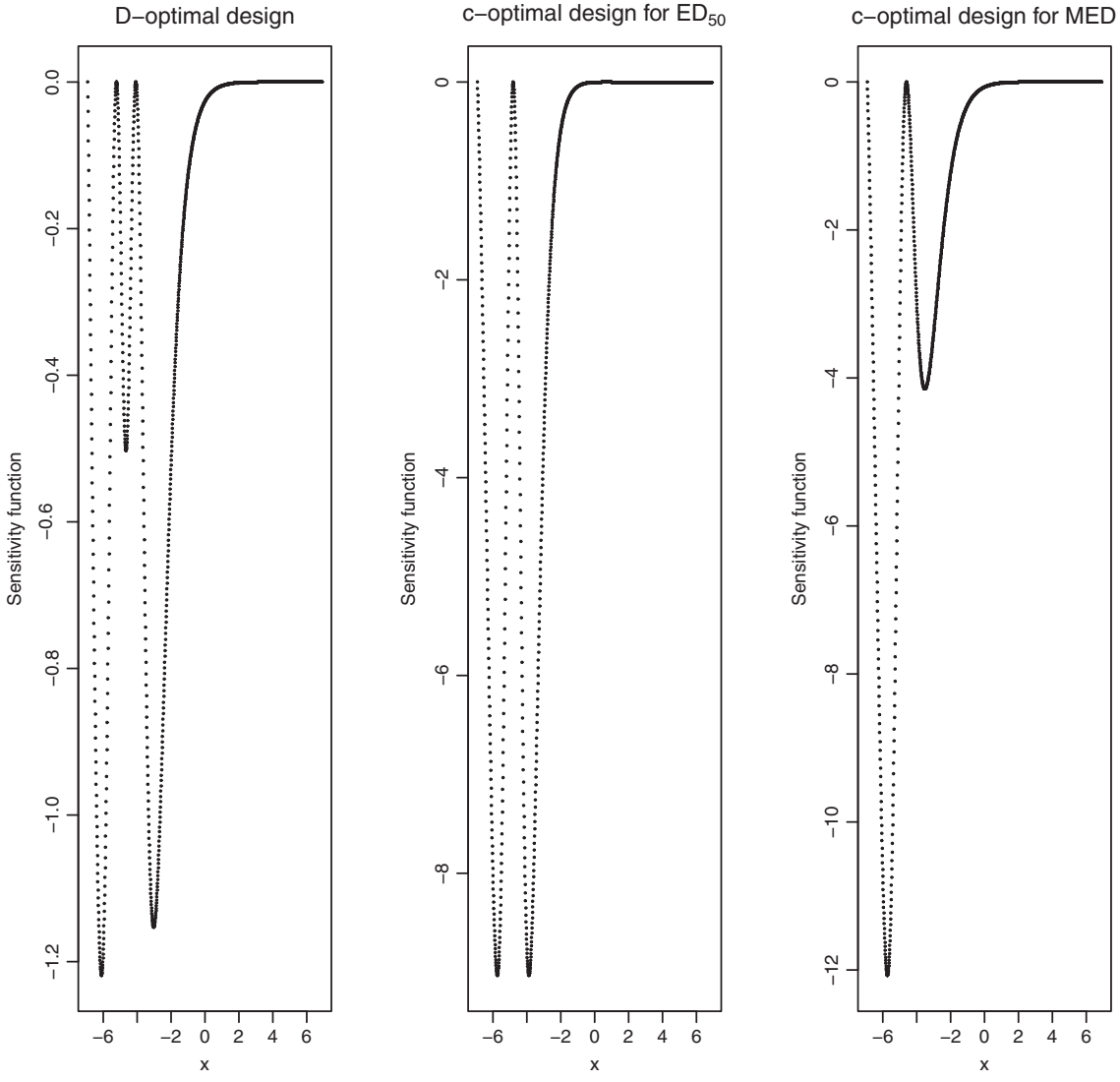

Figure 2: Plots of the sensitivity functions of the single-objective optimal designs when Θ_1 is the nominal set of values for the model parameters in Model (2).

function is bounded above by 0 with equality at the optimal dose levels and so confirms the optimality of the generated design shown in the first row of Table 2. All our optimal designs reported in this paper have been verified using an Equivalence Theorem.

Table 2 shows the optimal designs for different nominal sets for Θ and they vary depending on the nominal set of values and the study objective. For estimating Θ, the D-optimal designs are always equally supported at 4 dose levels including the lower and upper bounds of the dose interval and the middle two dose levels vary depending on Θ. Unlike the D-optimal designs, the c-optimal designs for estimating the ED_{50} may or may not include the extreme doses. Additionally, we observe that the c-optimal designs for estimating the *MED* are much more sensitive to the nominal values for the model parameters than the D-optimal designs and the c-optimal designs for estimating the ED_{50}. Depending on Θ, the c-optimal design for estimating the *MED* can have 2 or 3 dose levels with different weights. Interestingly, the smallest allowable dose is mostly included in the c-optimal designs for the sets of nominal parameter values considered here. There are two cases ($\xi_{ED_{50}}$ and ξ_{MED} for Θ_5), where the smallest allowable dose is not included in the c-optimal designs; however the lowest dose levels for these two optimal designs can be replaced with the smallest allowable dose without much loss in efficiencies. In practice, designs with more dose levels are desirable because they are likely to have non-singular information matrices and so can estimate all parameters in the model. Such optimal designs may also allow researchers to conduct a lack of fit test to assess model adequacy.

4.2 Multiple-objective optimal designs

We now apply our modified algorithm to search for multiple-objective optimal designs for estimating Θ, the ED_{50}, and the *MED* simultaneously. Because an optimal design under one objective may not perform well under another, the implemented design must be selected carefully to provide satisfactory efficiencies for the various objectives. A common approach is to use a compound design criterion that combines the 3 optimality criteria using their efficiencies and find a design that maximizes the various efficiencies at the same time. For a model with s parameters in the mean function, recall that the D-efficiency of a design ξ is

$$Eff_D(\xi) = \left(\frac{|\mathrm{I}_{(\xi;\Theta)}|}{|\mathrm{I}_{(\xi_D;\Theta)}|} \right)^{\frac{1}{s}}.$$

The efficiencies of using ξ to estimate the ED_{50} and *MED* are, respectively given by

$$Eff_{ED_{50}}(\xi) = \frac{ED'_{50}\mathrm{I}^{-}_{(\xi_{ED_{50}};\Theta)}[ED'_{50}]^T}{ED'_{50}\mathrm{I}^{-}_{(\xi;\Theta)}[ED'_{50}]^T}$$

and

$$Eff_{MED}(\xi) = \frac{MED'\mathrm{I}^{-}_{(\xi_{MED};\Theta)}[MED']^T}{MED'\mathrm{I}^{-}_{(\xi;\Theta)}[MED']^T}.$$

The above measures are all between 0 and 1 and have the following interpretation: if ξ has $Eff(\xi) = e$, then it needs $100(1/e - 1)\%$ more subjects to do as well as the optimal design. Multiple-objective optimal design for the objectives can be constructed by finding a design that maximizes the logarithm of a weighted product of the various efficiencies among all designs. Given a user-selected vector of weights $\lambda^T = (\lambda_1, \lambda_2, \lambda_3)$, the sought multiple-objective design $\xi_{M,\lambda}$ is

$$\begin{aligned}\xi_{M,\lambda} &= \arg \max_{\xi} \{\lambda_1 \log(Eff_D(\xi)) + \lambda_2 \log(Eff_{ED_{50}}(\xi)) + \lambda_3 \log(Eff_{MED}(\xi))\} \\ &= \arg \max_{\xi} \left\{ \frac{\lambda_1}{s} \log(|\mathrm{I}_{(\xi;\Theta)}|) - \lambda_2 \log(Var(\widehat{ED}_{50})) - \lambda_3 \log(Var(\widehat{MED})) \right\}.\end{aligned}$$

Here each λ_i is non-negative and $\sum_{i=1}^{3}\lambda_i = 1$. Because a convex combination of concave functionals is also concave, we may directly use directional derivative considerations and show that for a fixed λ, the sensitivity function for the locally multiple-objective criterion is

$$d(x,\xi) = \frac{\lambda_1}{s} g(x) \mathrm{I}^{-1}_{(\xi;\Theta)} g^T(x) + \lambda_2 \frac{\left(g(x)\mathrm{I}^{-}_{(\xi;\Theta)}[ED'_{50}]^T\right)^2}{ED'_{50}\mathrm{I}^{-}_{(\xi;\Theta)}[ED'_{50}]^T} + \lambda_3 \frac{\left(g(x)\mathrm{I}^{-}_{(\xi;\Theta)}[MED']^T\right)^2}{MED'\mathrm{I}^{-}_{(\xi;\Theta)}[MED']^T} - 1. \tag{6}$$

Each summand in (6) has been properly scaled, and it is easy to see that if all but one of the weights is nonzero, (6) reduces to the Equivalence Theorem for the single-objective optimal design. The Equivalence Theorem states that for a given vector λ, the design $\xi_{M,\lambda}$ is the multiple-objective optimal design if and only if for all doses x in the dose range X,

$$d(x,\xi_{M,\lambda}) \le 0,$$

with equality when x is a dose level of the design $\xi_{M,\lambda}$.

All multiple-objective optimal designs were obtained using a modified version of the YBT algorithm and confirmed using the above Equivalence Theorem in (6). As noted earlier, without the modification, we were unable to find the multiple-objective optimal designs for some cases. One reason appears to be that the YBT algorithm sometimes begins its search using poor initial dose levels that are far from the optimal dose levels. The modification we made was to first run the V-algorithm r times using the sensitivity function (6) and then select the last $s+1$ generated dose levels as the initial dose levels for the YBT algorithm. The stopping criterion we used for both algorithms was that the maximum of $|d(x,\xi^t_{M,\lambda})| < 0.001$, implying that we were willing to accept $\xi^t_{M,\lambda}$, the design generated at the t^{th} iteration as the multiple-objective optimal design if it satisfied the stopping criterion. Our experience suggests that $r = 10$ usually works for finding the multiple-objective optimal design but sometimes it may fail. This seems to happen especially when the weight for the D-optimality criterion is small. For these cases, we suggest using $r = 30$ or $r = 50$ in our modified algorithm to choose better initial dose levels to search for the multiple-objective optimal designs. We provide two examples:

Example 1: We used the set of nominal values Θ_1 in Table 1 to find the multiple-objective optimal designs using the YBT and our modified algorithms on the dose interval $[\log(.001), \log(1000)]$. The weights for the 3 criteria were $\lambda_1 = 0.05$, $\lambda_2 = 0.05$ and, $\lambda_3 = 0.90$, respectively. When the YBT algorithm was ran, it failed to find the multiple-objective optimal design. For this example, we found $|d(x,\xi^t_{M,\lambda})|$ converged to a constant (0.048) as the algorithm iterated without end. When we applied our modified algorithm with $r = 10$, the multiple-objective optimal design was found in 38 s.

Example 2: Miller et al. [29] assumed $\Theta = (16.8, -1, 4.248, 22)$, $\delta = 5$ with weights $\lambda_1 = 0.00$, $\lambda_2 = 0.10$ and, $\lambda_3 = 0.90$ to find the multiple-objective optimal designs on the dose interval $[\log(.001), log(100)]$. Again, the YBT algorithm failed to find the multiple-objective optimal design due to the same reasons as in the previous example: $|d(x,\xi^t_{M,\lambda})|$ converged to a constant (0.036). When our modified algorithm with $r = 10$ was used, the multiple-objective optimal design was found in 20 s.

Table 3 shows the multiple-objective optimal designs from the YBT algorithm and our modified algorithm for the two examples. Figures 3 and 4 confirm the optimality of the two multiple-objective optimal designs found from our modified algorithm but not the designs found from the YBT algorithm.

Table 4 shows the multiple-objective optimal designs for the different Θs found from our modified algorithm when we assumed $\lambda_1 = \lambda_2 = \lambda_3 = 1/3$. They are all supported at 4 dose levels and always include the lower and upper bound of the dose interval. The middle two dose levels and the proportions of subjects at the doses of the multiple-objective optimal designs depend on the set of nominal values for Θ. Figure 5 is the plot of the sensitivity function of the multiple-objective design shown in Table 4 when Θ_1 is assumed as the nominal values for Θ in model (2). The plot shows that the graph is bounded above by 0 with equality at the optimal dose levels and so confirms the optimality of the generated design.

Table 3: Multiple-objective optimal designs for estimating θ, ED_{50} and *MED* in Examples 1 and 2 found from the two algorithms.

	Example 1
YBT algorithm	$\begin{pmatrix} -6.91 & -4.81 & -4.54 & -4.21 & 3.45 \\ 0.481 & 0.182 & 0.221 & 0.061 & 0.055 \end{pmatrix}$
Modified algorithm	$\begin{pmatrix} -6.91 & -4.71 & -3.97 & 6.90 \\ 0.481 & 0.413 & 0.055 & 0.051 \end{pmatrix}$
	Example 2
YBT algorithm	$\begin{pmatrix} -6.91 & 2.41 & 3.47 & 4.60 \\ 0.460 & 0.084 & 0.429 & 0.027 \end{pmatrix}$
Modified algorithm	$\begin{pmatrix} -6.91 & 2.30 & 3.37 & 4.60 \\ 0.458 & 0.074 & 0.441 & 0.027 \end{pmatrix}$

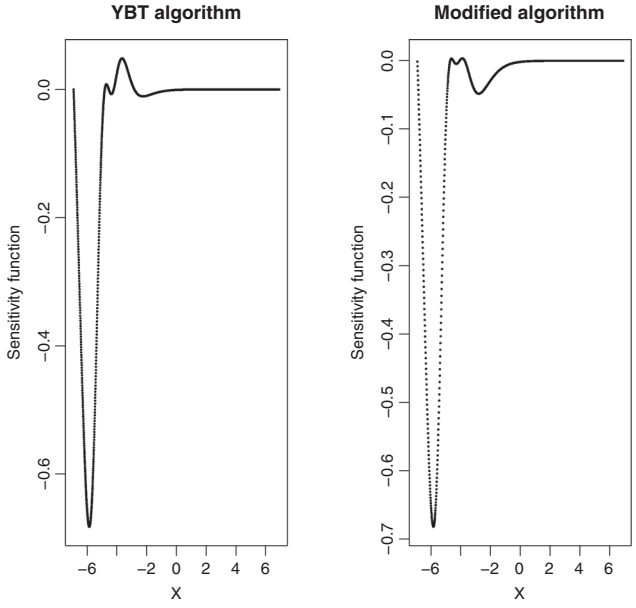

Figure 3: Plots of the sensitivity functions of the generated designs from the YBT and modified algorithms for Example 1.

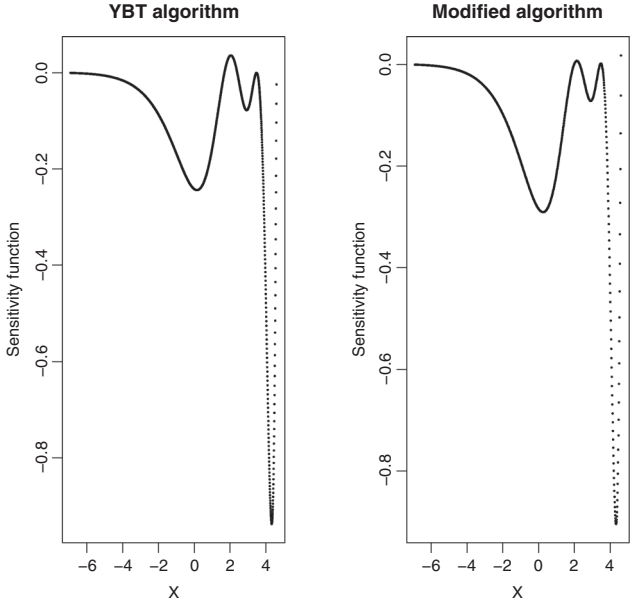

Figure 4: Plots of the sensitivity functions of the generated designs from the YBT and modified algorithms for Example 2.

Table 4: Multiple-objective optimal designs for estimating Θ, the ED_{50} and the *MED* using different sets of nominal values for Θ when $\lambda_1 = \lambda_2 = \lambda_3 = 1/3$.

Θ	$\xi_{\mathbf{M},\lambda}$	Θ	$\xi_{\mathbf{M},\lambda}$
Θ_1	$\begin{pmatrix} -6.91 & -4.89 & -4.18 & 6.91 \\ 0.344 & 0.323 & 0.162 & 0.171 \end{pmatrix}$	Θ_5	$\begin{pmatrix} -6.91 & 2.76 & 5.03 & 6.91 \\ 0.271 & 0.118 & 0.399 & 0.212 \end{pmatrix}$
Θ_2	$\begin{pmatrix} -6.91 & -4.04 & -3.57 & 6.91 \\ 0.318 & 0.187 & 0.308 & 0.187 \end{pmatrix}$	Θ_6	$\begin{pmatrix} -6.91 & -1.26 & -0.43 & 6.91 \\ 0.316 & 0.172 & 0.325 & 0.187 \end{pmatrix}$
Θ_3	$\begin{pmatrix} -6.91 & -1.52 & 0.04 & 6.91 \\ 0.329 & 0.226 & 0.262 & 0.183 \end{pmatrix}$	Θ_7	$\begin{pmatrix} -6.91 & -3.56 & -2.83 & 6.91 \\ 0.321 & 0.184 & 0.310 & 0.185 \end{pmatrix}$
Θ_4	$\begin{pmatrix} -6.91 & -2.79 & -2.38 & 6.91 \\ 0.316 & 0.183 & 0.313 & 0.188 \end{pmatrix}$		

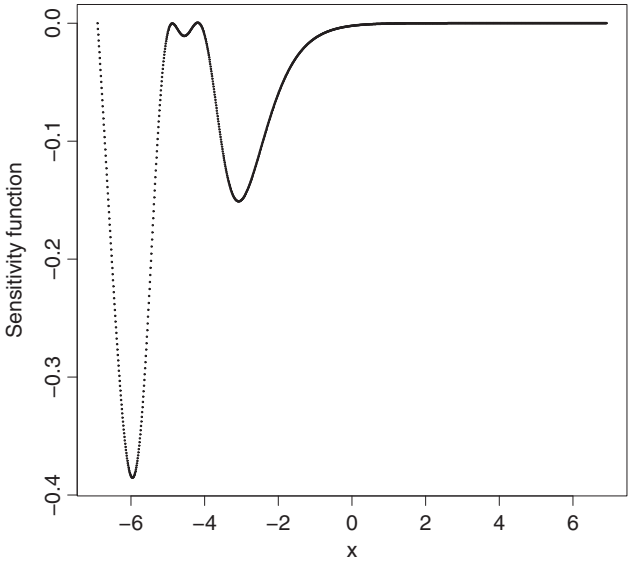

Figure 5: Plot of the sensitivity function of the multiple-objective optimal design when $\Theta = \Theta_1$ for Model (2) and $\lambda_1 = \lambda_2 = \lambda_3$.

How does a multiple-objective optimal design perform under a single-objective criterion? Table 5 displays these efficiencies and also shows how well single-objective optimal designs perform under a variation of criterion. As expected, single-objective optimal designs have efficiency 1 under their own criterion but do not perform well under different objectives. On the other hand, the multiple-objective optimal design $\xi_{M,\lambda}$ with $\lambda_1 = \lambda_2 = \lambda_3 = 1/3$, performs quite well for estimating Θ and the ED_{50} for the various sets of nominal parameter values. It provides lower efficiencies for estimating the *MED* but still clearly outperforms the other two single-objective optimal designs. We notice that the efficiencies of $\xi_{M,\lambda}$ for the 3 objectives are not equal even though we had set $\lambda_1 = \lambda_2 = \lambda_3 = 1/3$ for the 3 objectives. This is often the case suggesting that careful choice of the set for λ is important to capture the different efficiency requirements for each objective.

For multiple-objective optimal designs, the components in the weight vector λ represent the relative importance of each criterion but they can be rarely preselected to produce the targeted efficiencies, other than a sense that a larger weight for one objective should result in a higher efficiency under that objective. This means that determining in advance the correct weight vector λ to use in the compound criterion to find the multiple-objective optimal designs can be problematic. In particular, it is often difficult to predict how a change in the vector λ will translate to a change in the corresponding efficiencies, and this issue is frequently overlooked in such work. As an illustration, consider finding a dual-objective optimal design for estimating Θ and the ED_{50} in model (2) using the nominal set Θ_2. In this case, λ is a scalar and the sought dual-objective optimal design $\xi_{\lambda,dual}$ is

$$\xi_{\lambda,dual} = \arg \max_{\xi} \{\lambda \log(Eff_D(\xi)) + (1-\lambda)\log(Eff_{ED_{50}}(\xi))\}.$$

Table 5: Efficiencies of various optimal designs under different objectives and various nominal values for Θ's when $\lambda_1 = \lambda_2 = \lambda_3 = 1/3$.

Θ	Design	$Eff_D(\xi)$	$Eff_{ED_{50}}(\xi)$	$Eff_{MED}(\xi)$	Θ	Design	$Eff_D(\xi)$	$Eff_{ED_{50}}(\xi)$	$Eff_{MED}(\xi)$
Θ_1	ξ_D	1	0.599	0.511	Θ_5	ξ_D	1	0.583	0.505
	$\xi_{ED_{50}}$	·	1	0.006		$\xi_{ED_{50}}$	·	1	0
	ξ_{MED}	·	0	1		ξ_{MED}	·	0.070	1
	$\xi_{M,\lambda}$	0.866	0.815	0.746		$\xi_{M,\lambda}$	0.866	0.786	0.696
Θ_2	ξ_D	1	0.602	0.480	Θ_6	ξ_D	1	0.596	0.474
	$\xi_{ED_{50}}$	·	1	0.001		$\xi_{ED_{50}}$	·	1	0.002
	ξ_{MED}	·	0	1		ξ_{MED}	·	0	1
	$\xi_{M,\lambda}$	0.894	0.762	0.645		$\xi_{M,\lambda}$	0.895	0.761	0.642
Θ_3	ξ_D	1	0.595	0.493	Θ_7	ξ_D	1	0.595	0.470
	$\xi_{ED_{50}}$	·	1	0		$\xi_{ED_{50}}$	·	1	0.002
	ξ_{MED}	·	0.161	1		ξ_{MED}	·	0.063	1
	$\xi_{M,\lambda}$	0.880	0.782	0.694		$\xi_{M,\lambda}$	0.891	0.766	0.657
Θ_4	ξ_D	1	0.682	0.478					
	$\xi_{ED_{50}}$	·	1	0					
	ξ_{MED}	·	0.069	1					
	$\xi_{M,\lambda}$	0.895	0.761	0.650					

Notes: "·" represents undefined $Eff_D(\xi)$ due to singular $I_{(\xi_D;\Theta)}$; "0" represents $Eff_{(\cdot)}(\xi) < 0.001$.

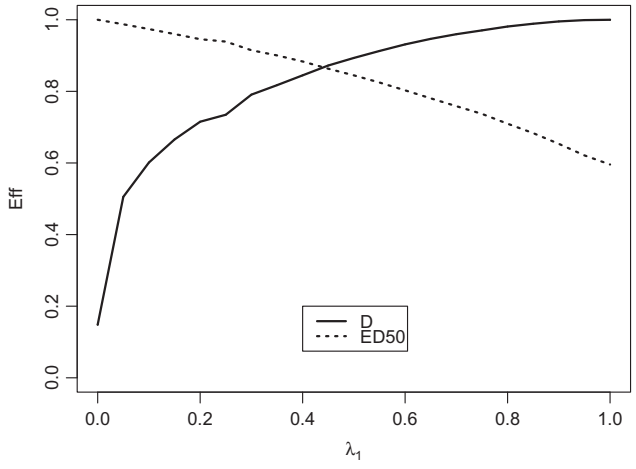

Figure 6: Efficiency plots of the dual-objective optimal designs when $\Theta = \Theta_2$ in Model (2).

Figure 6 shows the efficiency plots and visualize the effect of the choice of λ on the two efficiencies of the dual-objective optimal design. The weight λ represents the importance of estimating the model parameters relative to estimating the ED_{50}. If D-optimality is more important, λ should be large and $Eff_D(\xi_{\lambda,dual})$ should be larger than $Eff_{ED_{50}}(\xi_{\lambda,dual})$. Table 6 lists selected values of λ and shows when $\lambda = 0.55$, $Eff_D(\xi_{0.55,dual}) = 0.912$. When λ increases from 0.55 to 0.90, $Eff_D(\xi_{0.90,dual}) = 0.995$, implying that an increase of 64% in λ brings an increase of only 9% in D-efficiency. The figure also suggests that setting $\lambda = 0.45$ rather than 0.5 maximizes both efficiencies equally.

For 3 or more-objectives, it is harder to visualize the changes in the efficiencies of the generated design as the weights vary in the compound criterion from the high-dimensional efficiency plot. To this end, we generated multiple-objective optimal designs for each possible pair of values for λ_1 and λ_2 using a grid density 0.05, and evaluated the efficiencies of the resulting compound optimal designs under each of the 3 criteria. Figure 7 shows how the 3 efficiencies vary as the different values of the weights in λ change when $\Theta = \Theta_1$. The figure shows that the multiple-objective optimal design provides equal efficiencies for the 3 objectives when $\lambda_1 = 0.20, \lambda_2 = 0.35,$ and $\lambda_3 = 0.45$, and it has $Eff_D \approx Eff_{ED_{50}} \approx Eff_{MED} \approx 0.800$.

Table 6: Dual-objective optimal designs for different values of λ.

λ	ξ_{dual}				Eff_D	$Eff_{ED_{50}}$
0.55	$\begin{pmatrix} -6.91 & -4.05 & -3.59 & 6.91 \\ 0.250 & 0.247 & 0.253 & 0.250 \end{pmatrix}$				0.912	0.825
0.90	$\begin{pmatrix} -6.91 & -4.13 & -3.46 & 6.91 \\ 0.250 & 0.251 & 0.249 & 0.250 \end{pmatrix}$				0.995	0.653
0.95	$\begin{pmatrix} -6.91 & -4.15 & -3.43 & 6.91 \\ 0.250 & 0.251 & 0.249 & 0.250 \end{pmatrix}$				0.999	0.621
1.00	$\begin{pmatrix} -6.91 & -4.18 & -3.43 & 6.91 \\ 0.250 & 0.250 & 0.250 & 0.250 \end{pmatrix}$				1.000	0.596

In practice, practitioners first prioritize the importance of each objective and set efficiency requirements for each objective with higher efficiencies for the more important ones. For example, suppose Θ_1 is the set of nominal parameter values and we want to find an multiple-objective optimal design that maximizes Eff_D subject to constraints that $Eff_{ED_{50}} \geq 0.80$ and $Eff_{MED} \geq 0.70$. Figure 7 shows such an optimal design exists and is given by the plot for $\lambda_1 = 0.40$. By visual inspection, the required weights are $\lambda_1 = 0.40$, $\lambda_2 = 0.40$ and $\lambda_3 = 0.20$, and the resulting D-efficiency is $Eff_D = 0.879$ under the constraints that $Eff_{ED_{50}} = 0.838 \geq 0.80$ and $Eff_{MED} = 0.702 \geq 0.70$.

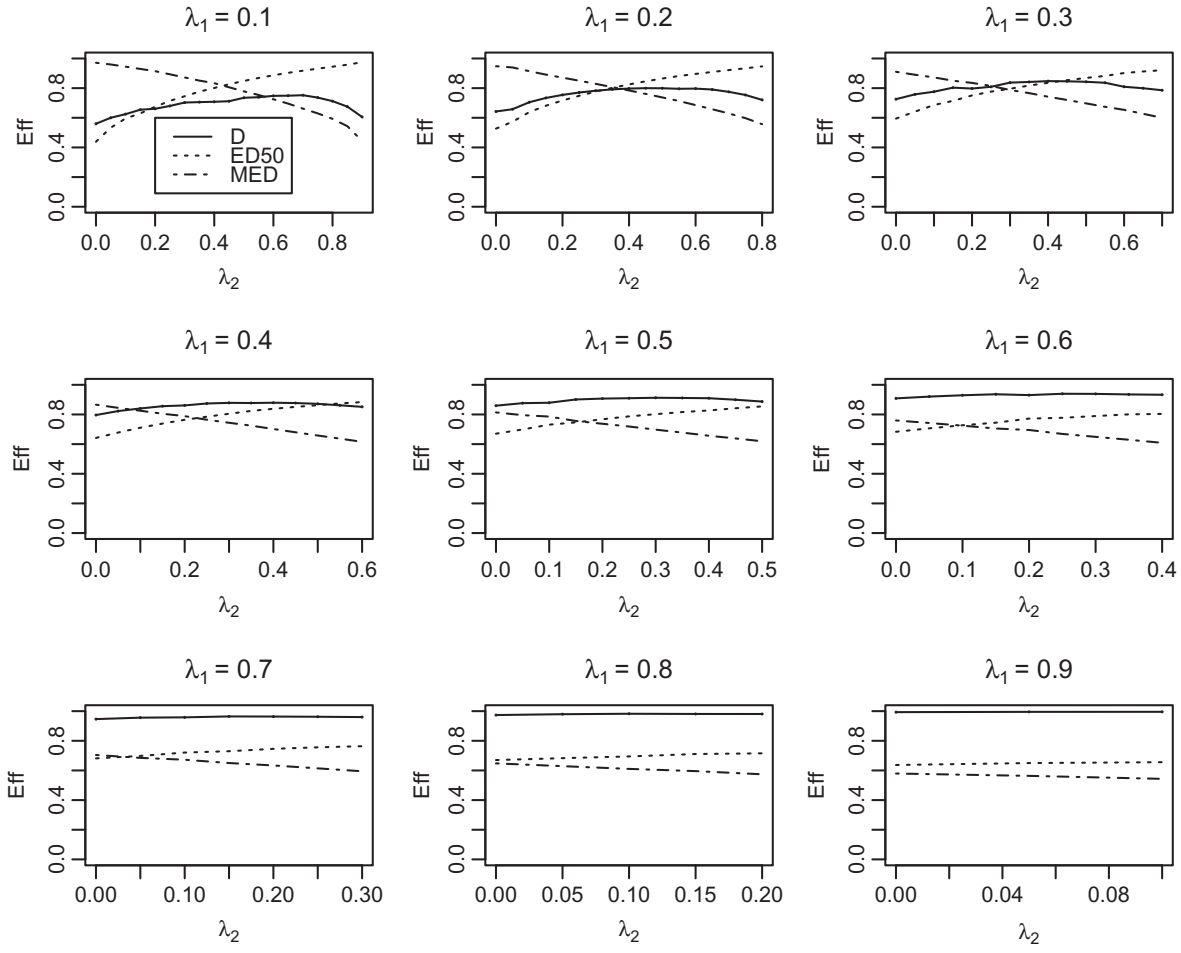

Figure 7: Efficiency plots of the multiple-objective optimal designs when $\Theta = \Theta_1$ in Model (2).

4.3 Robustness properties of multiple-objective optimal designs

This section investigates impact of uncertainty of the nominal parameter values on the multiple-objective optimal designs. This can arise when there are different single best guesses for the set of nominal values for the model parameters or there are several competing sets for the nominal values. In the latter case, one could adopt a Bayesian approach that averages the criterion over the various choices and optimize the resulting criterion. If nominal parameter values come from equally good previous studies or from equally qualified experts, one may use a uniform prior to average out the uncertainty; otherwise weights assigned to different sets of nominal parameter values may be chosen to reflect their plausibility. We now report the results from our investigation on how mis-specification in nominal values of the model parameters affect the performance of the multiple-objective optimal designs.

We first investigate whether multiple-objective optimal designs generally provide higher efficiencies for all criteria than single-objective optimal designs when there is uncertainty in the nominal parameter values. Consider the seven different sets of nominal values for Θ for the different drugs. For fixed $\lambda^T = (\lambda_1, \lambda_2, \lambda_3)$, the robust multiple-objective optimal design $\xi_{RM,\lambda}$ maximizes a weighted log product of the 3 efficiencies using a prior weight q_i for Θ_i, i.e.

$$\xi_{RM,\lambda} = \arg \max_{\xi} \left[\sum_{i=1}^{7} q_i \left\{ \frac{\lambda_1}{s} log(|\mathrm{I}_{(\xi;\Theta_i)}|) - \lambda_2 \log(Var_i(\widehat{ED}_{50})) - \lambda_3 \log(Var_i(\widehat{MED})) \right\} \right].$$

Here $Var_i(\cdot) = Var(\cdot)|_{\Theta=\Theta_i}$, $\sum_1^7 q_i = 1$ and q_i, as mentioned above, is the prior weight representing the relative plausibility of each Θ_i. If we believe that all 7 sets of the nominal values are equally likely, we may want to use a uniform prior with $q_1 = q_2 = \cdots = q_7 = 1/7$. For a user-selected λ and a given prior distribution q_i on $\Theta_i, i = 1, \ldots, 7$, a direct calculation shows the sensitivity function is:

$$d(x,\xi) = \left\{ \sum_{1}^{7} q_i \left(\frac{\lambda_1}{s} g_i(x) \mathrm{I}^{-1}_{(\xi;\Theta_i)} g_i^T(x) + \lambda_2 \frac{(g_i(x)\mathrm{I}^{-}_{(\xi;\Theta_i)}[ED'_{50i}]^T)^2}{ED'_{50i}\mathrm{I}^{-}_{(\xi;\Theta_i)}[ED'_{50i}]^T} + \lambda_3 \frac{(g_i(x)\mathrm{I}^{-}_{(\xi;\Theta_i)}[MED'_i]^T)^2}{MED'_i\mathrm{I}^{-}_{(\xi;\Theta_i)}[MED'_i]^T} \right) \right\} - 1, \tag{7}$$

where $g_i(x) = g(x)|_{\Theta=\Theta_i}$, $ED'_{50i} = ED'_{50}|_{\Theta=\Theta_i}$ and $MED'_i = MED'|_{\Theta=\Theta_i}$. For the robust multiple-objective optimal design $\xi_{RM,\lambda}$, we require that $d(x, \xi_{RM,\lambda}) \le 0$ for all doses x in the dose range X, with equality when x is a dose level in $\xi_{RM,\lambda}$. When $\lambda_1 = \lambda_2 = \lambda_3$ and $q_i = 1/7, i = 1, \ldots, 7$, the robust multiple-objective optimal design found from our modified algorithm is a 10-point design given by:

$$\xi_{RM,\lambda} = \begin{pmatrix} -6.91 & -4.89 & -3.81 & -2.87 & -2.40 & -0.75 & -0.56 & 3.19 & 5.15 & 6.91 \\ 0.168 & 0.115 & 0.150 & 0.064 & 0.130 & 0.049 & 0.126 & 0.020 & 0.121 & 0.057 \end{pmatrix}.$$

Figure 8 shows that the sensitivity function of the robust multiple-objective optimal design has a maximum value of 0 at the optimal dose levels over the dose interval and so confirms the optimality of the generated

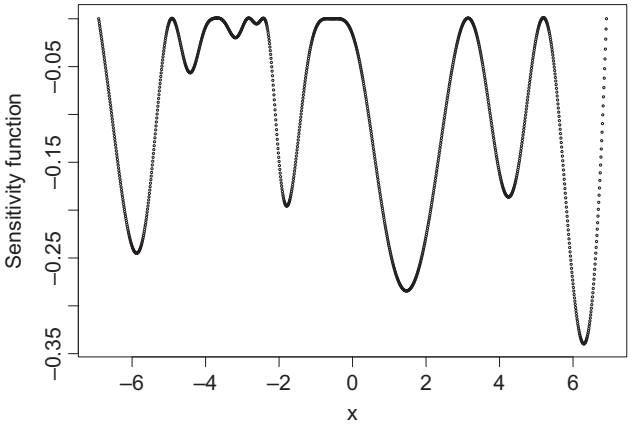

Figure 8: Plot of the sensitivity function of the robust multiple-objective optimal design $\xi_{RM,\lambda}$ from the modified algorithm when $\lambda_1 = \lambda_2 = \lambda_3$ and Model (2) is assumed.

Table 7: Efficiencies of optimal designs under various criteria for different sets of nominal values for Θ.

		Eff_D		$Eff_{ED_{50}}$		Eff_{MED}			Eff_D		$Eff_{ED_{50}}$		Eff_{MED}
Θ_1	ξ_{D_1}	1	$\xi_{ED_{50}1}$	1	ξ_{MED_1}	1	Θ_5	ξ_{D_1}	0	$\xi_{ED_{50}1}$	0	ξ_{MED_1}	0
	ξ_{D_2}	0.562	$\xi_{ED_{50}2}$	0.168	ξ_{MED_2}	0.659		ξ_{D_2}	0.001	$\xi_{ED_{50}2}$	0	ξ_{MED_2}	0
	ξ_{D_3}	0.007	$\xi_{ED_{50}3}$	0	ξ_{MED_3}	0		ξ_{D_3}	0.025	$\xi_{ED_{50}3}$	0.022	ξ_{MED_3}	0
	ξ_{D_4}	0.079	$\xi_{ED_{50}4}$	0.003	ξ_{MED_4}	0		ξ_{D_4}	0.002	$\xi_{ED_{50}4}$	0	ξ_{MED_4}	0
	ξ_{D_5}	0	$\xi_{ED_{50}5}$	0	ξ_{MED_5}	0		ξ_{D_5}	1	$\xi_{ED_{50}5}$	1	ξ_{MED_5}	1
	ξ_{D_6}	0.005	$\xi_{ED_{50}6}$	0.009	ξ_{MED_6}	0		ξ_{D_6}	0.019	$\xi_{ED_{50}6}$	0	ξ_{MED_6}	0.056
	ξ_{D_7}	0.280	$\xi_{ED_{50}7}$	0.016	ξ_{MED_7}	0		ξ_{D_7}	0.001	$\xi_{ED_{50}7}$	0	ξ_{MED_7}	0
	$\xi_{RM,\lambda}$	0.743	$\xi_{RM,\lambda}$	0.390	$\xi_{RM,\lambda}$	0.328		$\xi_{RM,\lambda}$	0.407	$\xi_{RM,\lambda}$	0.227	$\xi_{RM,\lambda}$	0.434
Θ_2	ξ_{D_1}	0.418	$\xi_{ED_{50}1}$	0.018	ξ_{MED_1}	0	Θ_6	ξ_{D_1}	0.011	$\xi_{ED_{50}1}$	0	ξ_{MED_1}	0.007
	ξ_{D_2}	1	$\xi_{ED_{50}2}$	1	ξ_{MED_2}	1		ξ_{D_2}	0.034	$\xi_{ED_{50}2}$	0	ξ_{MED_2}	0.025
	ξ_{D_3}	0.002	$\xi_{ED_{50}3}$	0	ξ_{MED_3}	0		ξ_{D_3}	0.783	$\xi_{ED_{50}3}$	0.003	ξ_{MED_3}	0.220
	ξ_{D_4}	0.140	$\xi_{ED_{50}4}$	0.006	ξ_{MED_4}	0		ξ_{D_4}	0.185	$\xi_{ED_{50}4}$	0.003	ξ_{MED_4}	0
	ξ_{D_5}	0	$\xi_{ED_{50}5}$	0	ξ_{MED_5}	0		ξ_{D_5}	0.002	$\xi_{ED_{50}5}$	0.003	ξ_{MED_5}	0
	ξ_{D_6}	0.002	$\xi_{ED_{50}6}$	0.008	ξ_{MED_6}	0		ξ_{D_6}	1	$\xi_{ED_{50}6}$	1	ξ_{MED_6}	1
	ξ_{D_7}	0.551	$\xi_{ED_{50}7}$	0.036	ξ_{MED_7}	0.780		ξ_{D_7}	0.117	$\xi_{ED_{50}7}$	0.001	ξ_{MED_7}	0.220
	$\xi_{RM,\lambda}$	0.658	$\xi_{RM,\lambda}$	0.462	$\xi_{RM,\lambda}$	0.329		$\xi_{RM,\lambda}$	0.667	$\xi_{RM,\lambda}$	0.450	$\xi_{RM,\lambda}$	0.494
Θ_3	ξ_{D_1}	0.099	$\xi_{ED_{50}1}$	0	ξ_{MED_1}	0.322	Θ_7	ξ_{D_1}	0.300	$\xi_{ED_{50}1}$	0.013	ξ_{MED_1}	0
	ξ_{D_2}	0.174	$\xi_{ED_{50}2}$	0.002	ξ_{MED_2}	0		ξ_{D_2}	0.693	$\xi_{ED_{50}2}$	0.240	ξ_{MED_2}	0.880
	ξ_{D_3}	1	$\xi_{ED_{50}3}$	1	ξ_{MED_3}	1		ξ_{D_3}	0.113	$\xi_{ED_{50}3}$	0.003	ξ_{MED_3}	0
	ξ_{D_4}	0.365	$\xi_{ED_{50}4}$	0.017	ξ_{MED_4}	0		ξ_{D_4}	0.679	$\xi_{ED_{50}4}$	0.321	ξ_{MED_4}	0.005
	ξ_{D_5}	0.050	$\xi_{ED_{50}5}$	0	ξ_{MED_5}	0		ξ_{D_5}	0	$\xi_{ED_{50}5}$	0	ξ_{MED_5}	0
	ξ_{D_6}	0.882	$\xi_{ED_{50}6}$	0.541	ξ_{MED_6}	0.030		ξ_{D_6}	0.090	$\xi_{ED_{50}6}$	0.003	ξ_{MED_6}	0
	ξ_{D_7}	0.360	$\xi_{ED_{50}7}$	0.016	ξ_{MED_7}	0		ξ_{D_7}	1	$\xi_{ED_{50}7}$	1	ξ_{MED_7}	1
	$\xi_{RM,\lambda}$	0.766	$\xi_{RM,\lambda}$	0.537	$\xi_{RM,\lambda}$	0.455		$\xi_{RM,\lambda}$	0.890	$\xi_{RM,\lambda}$	0.491	$\xi_{RM,\lambda}$	0.398
Θ_4	ξ_{D_1}	0.005	$\xi_{ED_{50}1}$	0.958	ξ_{MED_1}	0							
	ξ_{D_2}	0.071	$\xi_{ED_{50}2}$	0	ξ_{MED_2}	0.004							
	ξ_{D_3}	0.017	$\xi_{ED_{50}3}$	0	ξ_{MED_3}	0							
	ξ_{D_4}	1	$\xi_{ED_{50}4}$	1	ξ_{MED_4}	1							
	ξ_{D_5}	0	$\xi_{ED_{50}5}$	0	ξ_{MED_5}	0							
	ξ_{D_6}	0.014	$\xi_{ED_{50}6}$	0	ξ_{MED_6}	0							
	ξ_{D_7}	0.458	$\xi_{ED_{50}7}$	0.015	ξ_{MED_7}	0.829							
	$\xi_{RM,\lambda}$	0.732	$\xi_{RM,\lambda}$	0.443	$\xi_{RM,\lambda}$	0.418							

design. Table 7 displays the efficiencies of $\xi_{RM,\lambda}$ and the various single-objective optimal designs for the different Θs. In the table, ξ_{D_i}, $\xi_{ED_{50}i}$, ξ_{MED_i} are the single-objective optimal designs obtained when $\Theta = \Theta_i$, and we use 0 to represent efficiencies smaller than 0.001. We observe that the single-objective optimal designs perform very poorly on other sets of nominal parameter values. On the other hand, $\xi_{RM,\lambda}$ does not provide high efficiencies under different nominal values of Θs and under each objective due to the competitiveness of the criteria but it still clearly outperforms the single-objective optimal designs. For space consideration, we do not provide results when unequal prior weights are used to combine the 3 objectives but note that the various efficiencies also depend on the prior weights.

5 Summary

We presented a systematic method for finding multiple-objective optimal designs for the 4-parameter logistic regression model. The objectives were to estimate (1) the overall dose-response curve; (2) the ED_{50}; and (3) the *MED*. The methodology is general and can be directly applied to other models and criteria. In this paper, all objectives have the same inferential nature, but they can be more extended to balance ethical and inferential requirements in a study [41]. Our optimal designs are versatile and can be

properly tailored to provide user-specified efficiencies for the various objectives, with higher efficiencies for the more important objectives.

The YBT algorithm was recently proposed as a state-of-the-art algorithm to find single-objective optimal designs, but we found that the algorithm can sometimes fail to find multiple-objective optimal designs. We overcame the problem by modifying the YBT algorithm by ensuring it selects better initial dose levels using the traditional V-algorithm. Our modified algorithm finds tailor-made multiple-objective optimal designs and can sometimes also outperform the YBT algorithm for searching single-objective optimal designs. For instance, in Examples 1 and 2, the YBT algorithm took 7.80 and 4.91 s respectively, to find the D-optimal designs and our modified algorithm using $r = 10$ took 4.62 and 1.81 s respectively, to find the same optimal designs. We also found that our multiple-objective optimal designs obtained from our modified algorithm are more robust than single-objective optimal designs to mis-specifications in nominal values for the model parameters and to a change in the design criterion. Our software implementation can be modified to generate other types of multiple-objective designs for other models and objectives, compare them with competitive designs, and help the user make an informed decision on the design for implementation.

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