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Robust C-optimal Design For Estimating Multiple ED_p Under The 4-parameter Logistic Model

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Abstract The four-parameter logistic model is often used to describe dose-response functions in many toxicological studies. In this study, under the four-parameter logistic model, optimal designs to estimate the ED_p are studied. The ED_p is the dose achieving $p\%$ of the expected difference between the maximum and the minimum responses. C-optimal design works the best for estimating the ED_p, but the best performance is only guaranteed when the goal is for estimating a single ED_p. If the c-optimal design for studying a specific ED_p is used for studying different ED_p values, it may work poorly. This paper shows that the c-optimal design for estimating the ED_p truly depends on the value of p under the 4-parameter logistic model. We present a robust c-optimal design that works well for the change in the value of p, so that the design can be used effectively for studying multiple ED_p values. In addition, this paper presents a two-stage robust c-optimal design for estimating multiple ED_p that is not substantially affected by the mis-specified nominal parameter values.

Keywords Dose-response Study, Compound Optimal Design, Robust Design, Equivalence Theorem

AMS 2010 subject classifications 62K05

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1. Introduction

A dose-finding trial is a fundamental part in clinical trials. One common objective of a dose-finding trial is to study a target dose level such as ED_p [4, 13]. The ED_p is the dose level that achieves $p\%$ of the anticipated difference between the maximum and the minimum expected response within the observed dose range[16]. In this paper, we study optimal designs for estimating the various ED_ps accurately.

An optimal design provides the most efficient design to study an interesting objective accurately with limited resources. It identifies dose levels to be tested and how to allocate subjects to the selected doses in the most efficient manner [2, 4, 7]. Different types of optimal designs are used for different purposes. For instance, D-optimal design enables researchers to estimate the shape of dose-response accurately, and c-optimal design allows researchers to precisely estimate an interesting target dose level. In this paper, we study c-optimal designs for estimating the ED_p. The ED_{50} is a common interesting dose level because it provides a reasonable expectation of the drug effect. Other dose levels such as ED_{10} or ED_{90} are also interesting dose levels sometimes.

In general, multiple doses levels are used to conduct experimental designs in biological and toxicological studies. For example, researchers choose doses ED_{40}, ED_{50}, ED_{60}, and ED_{80} to establish dose-range studies for daptomycin in infected mice [11]. Another example is the effective doses ED_{50} and ED_{80} were used to perform nefopam experiments on patients who suffering from moderate pain in the postoperative period [5]. These multiple doses need to be accurately estimated in early phase toxicology trials, and sometimes the objective is in estimating

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dual ED_ps such as ED_{10} and ED_{50} rather than estimating one specific ED_p [17]. Then the question is how can we construct an optimal design to estimate multiple ED_ps effectively?

C-optimal design minimizes an asymptotic variance of estimating the ED_p, where the value of p is predetermined at the beginning of the study. In general, optimal design works very well for studying a single objective but works poorly for studying different objectives. Thus, c-optimal design for estimating the ED_p performs well for estimating a single specified ED_p but there is no guarantee that the c-optimal design still performs well for estimating other ED_ps. In this paper, we study the sensitivity of the c-optimal design for estimating the ED_p on the values of p, and we present a robust c-optimal design for estimating the ED_p that works fairly well for the change in the value of p. We employ several sets of model parameters and check the performance of the robust c-optimal design. Another challenge in optimal designs for nonlinear models is that the optimal designs depend on model parameter values [13]. To reduce this dependence problem, we present two-stage robust c-optimal design for estimating the ED_p as well.

We consider a flexible four-parameter logistic model to describe dose-response relationships [7]. The four-parameter logistic model is a frequently used non-linear model in many dose response studies. In this paper, all optimal designs are obtained under the four-parameter logistic model.

In Section 2, the dose-response model and the Fisher information matrix under the model is presented. In Section 3, c-optimal designs for estimating the ED_p, the robust c-optimal design for estimating the ED_p for the changes in the value of p, and the two-stage robust c-optimal design are studied. Finally, brief summary is given in Section 4.

2. Model

he mean response for the four-parameter logistic model at a given dose x_i is

$$\mu(x_i, \Theta) = \theta_1 + (\theta_2 - \theta_1)\left(\frac{{x_i}^{\theta_4}}{{x_i}^{\theta_4} + {\theta_3}^{\theta_4}}\right) \tag{1}$$

where x_i is the i^{th} dose; θ_1 is the mean response at the minimum dose; θ_2 is the mean response at the maximum dose; θ_3 is the dose corresponding to the mean response that is halfway between the minimum and the maximum expected responses (we also call it ED_{50}); θ_4 is the slope parameter that controls the steepness of the curve.

To perform our study, we assume that the dose response Y is a continuous response and is modeled by

$$Y_{ij} = \mu(x_i, \Theta) + \varepsilon_{ij}, \varepsilon \sim N(0, \sigma^2),$$

where $\mu(x_i, \Theta)$ is given by the four-parameter logistic model (1); $\Theta = (\theta_1, \theta_2, \theta_3, \theta_4); j = 1, 2, \cdots, n_i; i = 1, 2, \cdots, k$; and $n_1 + n_2 + \cdots + n_k = n$. Here n_i is the number of subjects assigned at x_i and n is the total number of subjects. We assume that the variance σ^2 is an unknown constant. Let $\xi = \{(x_i, w_i)\}_1^k$ denote an approximate design. The approximate design tells the number of doses k, the location of each dose x_i, and the proportional allocation w_i of subjects at each dose x_i. In practice, the closest integer of nw_i becomes n_i. Under this model setup, the normalized Fisher information matrix for Θ is obtained below

$$M(\xi, \Theta) = \frac{1}{\sigma^2} \sum_{i=1}^{n} \omega_i f(x_i, \Theta) f(x_i, \Theta)^T \tag{2}$$

where,

$$f(x_i, \Theta) = \left(\frac{\partial \mu(x_i, \Theta)}{\partial \theta_1}, \frac{\partial \mu(x_i, \Theta)}{\partial \theta_2}, \frac{\partial \mu(x_i, \Theta)}{\partial \theta_3}, \frac{\partial \mu(x_i, \Theta)}{\partial \theta_4}\right)^T =$$

$$\left(\frac{{\theta_3}^{\theta_4}}{{x_i}^{\theta_4} + {\theta_3}^{\theta_4}}, \frac{{x_i}^{\theta_4}}{{x_i}^{\theta_4} + {\theta_3}^{\theta_4}}, \frac{\theta_4(\theta_1 - \theta_2){\theta_3}^{(\theta_4 - 1)}{x_i}^{\theta_4}}{({x_i}^{\theta_4} + {\theta_3}^{\theta_4})^2}, \frac{\theta_4(\theta_2 - \theta_1){\theta_3}^{\theta_4}{x_i}^{\theta_4} \ln \frac{x_i}{\theta_3}}{({x_i}^{\theta_4} + {\theta_3}^{\theta_4})^2}\right)^T$$

This Fisher information matrix plays a very important role to search c-optimal designs for estimating the ED_p in next section.

3. Designs

We find c-optimal designs for estimating the ED_p under the four-parameter logistic model. V-algorithm is a common numerical algorithm to obtain locally optimal designs and was developed by Fedorov in 1972 [8, 9]. The algorithm selects one dose that maximizes the sensitive function which is derived from the directional derivative of the optimal criterion at each iteration and stops once the design satisfies the Equivalence Theorem [1, 2, 14]. The problem for V-algorithm is that sometime it takes very long time to converge to the locally optimal designs. [19] proposed a state-of-the art algorithm(YBT algorithm) to find locally optimal designs for a single objective and showed that it outperformed to other current algorithms including V-algorithm. Starting from a randomly selected initial design, the YBT algorithm selects the dose that maximizes the sensitivity function and adds to the previously selected designs. At the same time, their optimal weights are obtained directly using the Newton-Raphson method[15]. However, the problem in YBT is that if the selected initial design points far from the optimal design points, then the YBT requires a lot more time to converge to an optimal design and sometimes it failed to do so. In this paper, the modified YBT algorithm [10] was employed to obtain the c-optimal designs. [10] modified the procedure by selecting better starting design points via the V-algorithm, and this improved the search speed to obtain the optimal designs. The modified algorithm performs greatly to obtain all the optimal designs in this paper.

To illustrate the c-optimal designs, we adopt the experimental setup in [13]. The dose range is from 0 to 8, and three sets of nominal model parameter values are considered using different θ_3 values: Θ_1=(0, -1.7, 1, 5); Θ_2=(0, -1.7, 4, 5); Θ_3=(0, -1.7, 6, 5). Under the four-parameter logistic model, it is known that the optimal designs that minimize(maximize) a convex-concave function of Fisher information matrix do not depend on the parameters θ_1 and θ_4 [18], and researchers often want to see how the designs are changed by the value of θ_3. All the obtained optimal designs are verified by the General Equivalence Theorem.

3.1. C-optimal designs to estimate the ED_p

In this section, we present c-optimal designs for estimating the ED_p under the four-parameter logistic model. The ED_p is the solution of x_i in the following equation [13]:

$$p = \frac{f(x_i, \Theta) - \theta_1}{\theta_2 - \theta_1},$$

where p represents $p\%$ of the difference between the maximum and the minimum expected responses; $f(x_i, \Theta)$ is the mean response at x_i; Under the four-parameter logistic model, the ED_p is expressed in explicit form:

$$ED_p = \theta_3 \left(\frac{p}{1-p} \right)^{\frac{1}{\theta_4}}.$$

Let $\widehat{ED_p}$ denotes the maximum likelihood estimate of ED_p, then the asymptotic variance of estimating the ED_p is,

$$Var(\widehat{ED_p}) = [ED_p']^T M(\xi, \Theta)^- ED_P',$$

where $M(\xi, \Theta)^-$ is a generalized inverse of $M(\xi, \Theta)$ in equation (2) and

$$ED_p' = \left(\frac{\partial ED_p}{\partial \theta_1}, \frac{\partial ED_p}{\partial \theta_2}, \frac{\partial ED_p}{\partial \theta_3}, \frac{\partial ED_p}{\partial \theta_4} \right)^T \tag{3}$$

$$= \left(0, 0, \left(\frac{p}{1-p} \right)^{\frac{1}{\theta_4}}, - \left[\frac{\theta_3}{{\theta_4}^2} \left(\frac{p}{1-p} \right)^{\frac{1}{\theta_4}} \ln \left(\frac{p}{1-p} \right) \right] \right)^T.$$

The c-optimal design for estimating the ED_p, ξ_{ED_P} minimizes the asymptotic variance of estimating the ED_p. According to the Equivalence Theorem, the design ξ_{ED_p} is the c-optimal design if and only if

$$\left\{ f^T(x,\Theta) M\left(\xi_{ED_p},\Theta\right)^{-} ED_p' \right\}^2 - [ED_p']^T M\left(\xi_{ED_p},\Theta\right)^{-} ED_p' \leq 0, \tag{4}$$

where the equality holds if x is the dose level in the c-optimal design. The left side of (4) is the sensitivity function and it is used to select the optimal dose levels in the modified algorithm. In order to illustrate the c-optimal designs for estimating the ED_p, we consider five different values of p = (10, 30, 50, 70, 90), see Table 1.

Table I. C-optimal designs for estimating the ED_p under Θ_1, Θ_2, and Θ_3. Each row gives three c-optimal designs for the ED_p based on the different parameter sets.

ξ_{ED_P}	Θ_1=(0, -1.7, 1, 5)	Θ_2=(0, -1.7, 4, 5)	Θ_3=(0, -1.7, 6, 5)
$\xi_{ED_{10}}$	$\begin{pmatrix} .0001 & .77 & 1.31 \\ .36 & .50 & .14 \end{pmatrix}$	$\begin{pmatrix} .001 & 3.11 & 5.22 \\ .36 & .50 & .14 \end{pmatrix}$	$\begin{pmatrix} .0001 & 4.67 & 7.85 \\ .36 & .50 & .14 \end{pmatrix}$
$\xi_{ED_{30}}$	$\begin{pmatrix} .0001 & .88 & 1.57 \\ .32 & 0.50 & .18 \end{pmatrix}$	$\begin{pmatrix} .001 & 3.51 & 7.99 \\ .32 & .50 & .18 \end{pmatrix}$	$\begin{pmatrix} 2.43 & 5.93 & 7.99 \\ .20 & .50 & .30 \end{pmatrix}$
$\xi_{ED_{50}}$	$\begin{pmatrix} .0001 & .99 & 7.99 \\ 0.25 & .50 & 0.25 \end{pmatrix}$	$\begin{pmatrix} .99 & 4.18 & 7.99 \\ .21 & .50 & .29 \end{pmatrix}$	$\begin{pmatrix} 4.12 & 6.35 & 7.99 \\ .18 & .50 & .32 \end{pmatrix}$
$\xi_{ED_{70}}$	$\begin{pmatrix} .50 & 1.13 & 7.99 \\ .18 & .50 & .32 \end{pmatrix}$	$\begin{pmatrix} 2.46 & 4.60 & 7.99 \\ .17 & .50 & .33 \end{pmatrix}$	$\begin{pmatrix} .0001 & 4.18 & 6.35 & 7.99 \\ 0.8 & .25 & .42 & .25 \end{pmatrix}$
$\xi_{ED_{90}}$	$\begin{pmatrix} .77 & 1.28 & 7.99 \\ .14 & .50 & .36 \end{pmatrix}$	$\begin{pmatrix} .001 & 3.02 & 4.90 & 7.99 \\ .05 & .20 & .45 & .30 \end{pmatrix}$	$\begin{pmatrix} .0001 & 4.17 & 6.39 & 7.99 \\ .14 & .29 & .36 & .21 \end{pmatrix}$

Table I displays the c-optimal designs for the three different nominal sets of Θ, and we can see that they are changed depending on the different θ_3 values. Each paharenthesis represents the sought c-optimal design. In the paharenthesis, the first line represents the sought optimal dose levels and the second line represents the optimal allocation of subject to the corresponding dose levels. For example, under Θ_2, the c-optimal design for estimating the ED_{50}, $\xi_{ED_{50}}$ allocates 21% of the subjects to .99, 50% of the subjects to 4.18, and 29% of the subjects to 7.99. Except few cases, the c-optimal designs have three dose levels and about 50% of the subjects are assigned at the middle dose levels. Figure 1 shows the verification of the c-optimal design for estimating the ED_{50} under Θ_2 based on the Equivalence Theorem (4). The plot shows that the sensitivity function is bounded above by 0 with the equality at the optimal dose levels. All other c-optimal designs are also verified by the Equivalence Theorem.

3.2. Efficiency

A design efficiency shows how a design performs with respect to some optimality criterion[6]. $Eff_{ED_p}(\xi)$ measures the efficiency of a design ξ for estimating the ED_p against ξ_{ED_p} and it is obtained as,

$$Eff_{ED_p}(\xi) = \frac{[ED_p']^T M\left(\xi_{ED_p};\Theta\right)^{-1} ED_p'}{[ED_p']^T M\left(\xi;\Theta\right)^{-1} ED_p'}. \tag{5}$$

Since ξ_{ED_p} provides the minimum variance of estimating the ED_p, the $Eff_{ED_p}(\xi)$ is between 0 and 1. When the efficiency of a design ξ is q, it implies that the design ξ needs $100(1/q-1)\%$ more subjects to provide the same accuracy for estimating the ED_p as the c-optimal design provides. For example, $Eff_{ED_p}(\xi) = .5$ implies that $100(1/.5-1)\% = 100\%$ more subjects are needed for the design ξ to estimate the ED_p with the same accuracy as

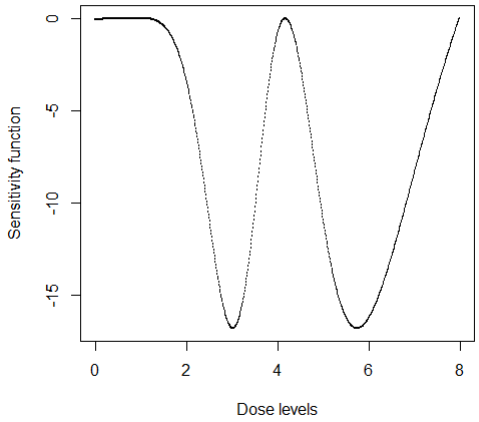

Figure 1. Verification of the c-optimal design for estimating the ED_{50} under Θ_2.

the c-optimal design provides. If a design ξ works very close to the c-optimal design for estimating the ED_p, then $Eff_{ED_p}(\xi) \approx 1$. Otherwise, $Eff_{ED_p}(\xi)$ becomes far from 1.

It was showed that the c-optimal designs are changed by different p values in the previous section. Using the efficiency, we want to see how the c-optimal designs perform when they are used for estimating different ED_ps. For simplicity, we use the same five different values of p in the previous section and compute their efficiencies in Table II.

Table II. Efficiencies of the c-optimal designs for estimating various ED_ps.

Θ	Design	$Eff_{\xi_{10}}$	$Eff_{\xi_{30}}$	$Eff_{\xi_{50}}$	$Eff_{\xi_{70}}$	$Eff_{\xi_{90}}$	Θ	Design	$Eff_{\xi_{10}}$	$Eff_{\xi_{30}}$	$Eff_{\xi_{50}}$	$Eff_{\xi_{70}}$	$Eff_{\xi_{90}}$
Θ_1	$\xi_{ED_{10}}$	1	0	0	0	0	Θ_3	$\xi_{ED_{10}}$	1	0	0	0	0
	$\xi_{ED_{30}}$	0.003	1	0	0	0.001		$\xi_{ED_{30}}$	0	1	0	0	0
	$\xi_{ED_{50}}$	0.001	0.002	1	0.003	0.002		$\xi_{ED_{50}}$	0	0	1	0	0
	$\xi_{ED_{70}}$	0	0	0.001	1	0.004		$\xi_{ED_{70}}$	0.28	0.56	0.87	1	0.93
	$\xi_{ED_{90}}$	0	0	0	0	1		$\xi_{ED_{90}}$	0.41	0.57	0.75	0.96	1
Θ_2	$\xi_{ED_{10}}$	1	0	0	0	0							
	$\xi_{ED_{30}}$	0	1	0	0	0							
	$\xi_{ED_{50}}$	0.001	0.003	1	0.005	0.002							
	$\xi_{ED_{70}}$	0	0	0	1	0.002							
	$\xi_{ED_{90}}$	0.22	0.20	0.34	0.71	1							

Notes: '0' represents $Eff_\xi < 0.001$.

Table II shows that the c-optimal design for estimating one specified ED_p works really poorly for estimating other ED_ps and their changes are very dramatic. For example, under Θ_1, the c-optimal design $\xi_{ED_{50}}$ has efficiency 1 when it is used for estimating the ED_{50}, however the efficiency becomes less than 0.01 when it is used

for estimating other ED_ps. Under Θ_3, sometimes the c-optimal designs for estimating ED_{70} or ED_{90} provide reasonable efficiencies for estimating higher ED_p values like ED_{50}, ED_{70}, or ED_{90}, but they still provide considerably low efficiencies when they are used for estimating other ED_p values.

3.3. Robust c-optimal design to estimate various ED_ps

In practice, researchers may want to study several different ED_ps at a single study to save cost. For example, they want to estimate the ED_{10}, ED_{50}, and ED_{90} effectively from a single study and it is also possible they want to estimate other ED_ps additionally from the collected data. As shown in the previous section, the c-optimal design works the best for estimating a single ED_p but the c-optimal design for estimating the ED_p is changed by different values of p, and it performs poorly when the targeted ED_p is changed to other values. In this section, we present a robust c-optimal design for estimating the ED_p that works well under the changes in the value of p. For illustration, we consider the five different values of p to obtain the robust c-optimal design, but this can be extended to any other values of p. The robust c-optimal design combines the five c-optimality criteria into one optimality criterion using the idea of compound design [3, 12]. The robust c-optimal design maximizes the weighted log product of the 5 efficiencies for estimating the five different ED_ps. Let $p \in P = (10, 30, 50, 70, 90)$. The robust c-optimal design for estimating the ED_p, ξ_{Rob} is,

$$\xi_{Rob} = \arg\max_{\xi}\{\sum_{p\in P} \lambda_p \log(Eff_{ED_p}(\xi))\},$$

where $\sum_{p\in P} \lambda_p = 1$ and λ_p is a prespecified weight that represents the relative importance of corresponding ED_p in the set of P. Based on the Equivalence Theorem, ξ_{Rob} is the robust c-optimal design if and only if,

$$\sum_{p\in P} \lambda_p \frac{(f^T(x,\Theta)M(\xi_{Rob};\theta)^- ED_p')^2}{[ED_p']^T M(\xi_{Rob};\theta)^- ED_p'} \leq 1,$$

where the equality holds when x is a dose level in the design ξ_{Rob}. We assume that the five different ED_ps are equally important, and so $\lambda_p = .2$. Using the modified algorithm, the robust c-optimal designs for estimating the five different ED_ps is presented in Table III.

Table III. Robust c-optimal designs for estimating the ED_p under Θ_1, Θ_2, and Θ_3.

Θ	ξ_{Rob}			
Θ_1	$\begin{pmatrix} .001 \\ .21 \end{pmatrix}$	$\begin{matrix} .84 \\ .29 \end{matrix}$	$\begin{matrix} 1.19 \\ .29 \end{matrix}$	$\begin{matrix} 7.99 \\ .21 \end{matrix}$
Θ_2	$\begin{pmatrix} .001 \\ .20 \end{pmatrix}$	$\begin{matrix} 3.22 \\ .27 \end{matrix}$	$\begin{matrix} 4.58 \\ .32 \end{matrix}$	$\begin{matrix} 7.99 \\ .21 \end{matrix}$
Θ_3	$\begin{pmatrix} .001 \\ .19 \end{pmatrix}$	$\begin{matrix} 4.28 \\ .27 \end{matrix}$	$\begin{matrix} 6.18 \\ .30 \end{matrix}$	$\begin{matrix} 7.99 \\ .24 \end{matrix}$

The robust c-optimal designs have four dose levels and include the lower and upper bounds of the dose range. The middle two dose levels and the optimal weights are changed by the parameter values. Take Θ_2 as an example: The robust c-optimal design allocates 20% of the subjects to the lower bound in the design space, 27% and 32% of the subjects to the middle two dose levels respectively, and 21% of the subjects to the upper bound in the design space. All the optimal designs in Table III are verified by the Equivalence Theorem and Figure 2 shows the verification plot of the robust c-optimal design under Θ_2.

In order to check the performance of the robust c-optimal design, we check its efficiencies for estimating various ED_ps and compare with the ones of uniform designs. A uniform design is commonly used in practice because of its

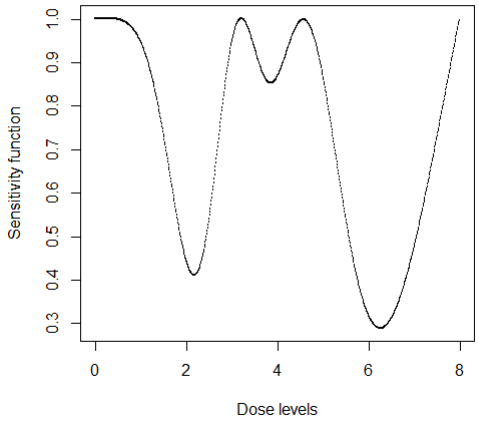

Figure 2. Verification of the robust c-optimal design under Θ_2.

simplicity. For the comparisons, two different uniform designs are considered: ξ_{U1} and ξ_{U2} represent the uniform designs with 8 and 11 equally spaced dose levels with equal weights, respectively.

Table IV. Efficiencies of the designs for estimating various ED_ps.

Θ	Design	$Eff_{\xi_{10}}$	$Eff_{\xi_{20}}$	$Eff_{\xi_{30}}$	$Eff_{\xi_{40}}$	$Eff_{\xi_{50}}$	$Eff_{\xi_{60}}$	$Eff_{\xi_{70}}$	$Eff_{\xi_{80}}$	$Eff_{\xi_{90}}$	$Eff_{\xi_{99}}$
Θ_1	ξ_{Rob}	0.621	0.657	0.626	0.665	0.846	0.67	0.794	0.576	0.639	0.747
	ξ_{U1}	0.009	0.01	0.011	0.017	0.048	0.177	0.337	0.059	0.030	0.02
	ξ_{U2}	0.256	0.249	0.197	0.165	0.170	0.122	0.145	0.114	0.142	0.2
Θ_2	ξ_{Rob}	0.575	0.557	0.6	0.677	0.668	0.651	0.626	0.654	0.756	0.83
	ξ_{U1}	0.386	0.397	0.449	0.5	0.457	0.409	0.371	0.375	0.429	0.474
	ξ_{U2}	0.388	0.401	0.451	0.5	0.455	0.406	0.368	0.373	0.427	0.473
Θ_3	ξ_{Rob}	0.515	0.58	0.649	0.66	0.715	0.816	0.873	0.903	0.919	0.914
	ξ_{U1}	0.503	0.508	0.421	0.373	0.389	0.442	0.477	0.502	0.523	0.544
	ξ_{U2}	0.510	0.48	0.382	0.338	0.354	0.406	0.442	0.468	0.492	0.518

Figure 3, 4, and 5 display their relative efficiencies for estimating the ED_p under the tree nominal sets of model parameter values when the p is changed from 0.1 to 0.99. All the three figures show that the robust c-optimal designs outperform the uniform designs for estimating all different ED_ps. The efficiencies of uniform designs are pretty low and it is not guaranteed that the uniform design with more design points provides higher efficiency for estimating various ED_ps. The robust c-optimal designs provide the efficiency as low as 52% and as high as 92% for estimating various ED_ps. Although only five different ED_ps were considered to construct the robust c-optimal designs, they work quite well for estimating other ED_ps that were not considered. The efficiencies corresponding to the Figure 3, 4, and 5 are listed in Table IV as well.

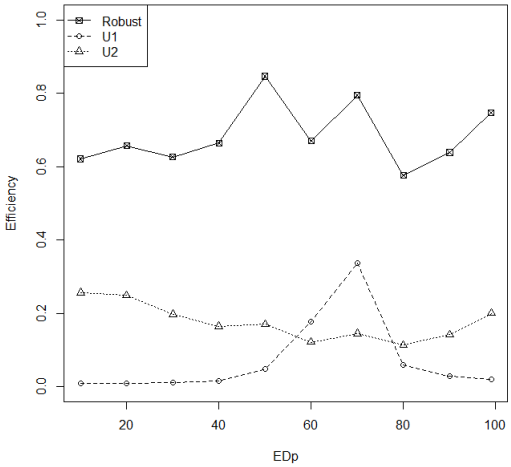

Figure 3. Efficiencies of the designs for estimating ED_ps under Θ_1.

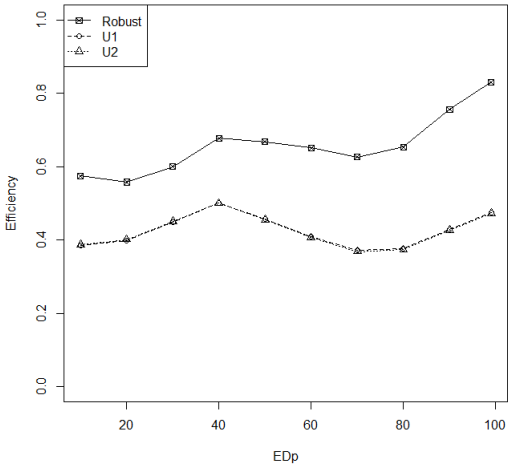

Figure 4. Efficiencies of the designs for estimating ED_ps under Θ_2.

3.4. Two-stage robust c-optimal design

The optimal designs under nonlinear model truly depend on the nominal parameter values and the robust c-optimal design in the previous section has the same problem. The best performance of the robust c-optimal design for estimating various ED_ps may not be guaranteed when the predetermined nominal parameter values are not close to their true values. In order to overcome this dependence problem, a two-stage design approach is used. Two-stage robust c-optimal design for estimating various ED_ps assigns half of the subjects according to a uniform design at the first stage, and then assigns the other half of the subjects according to the augmented robust c-optimal design at the second stage. The augmented robust c-optimal design is the robust c-optimal design taking into account the uniform design at the first stage and is obtained based on the model parameter values estimated from the first stage.

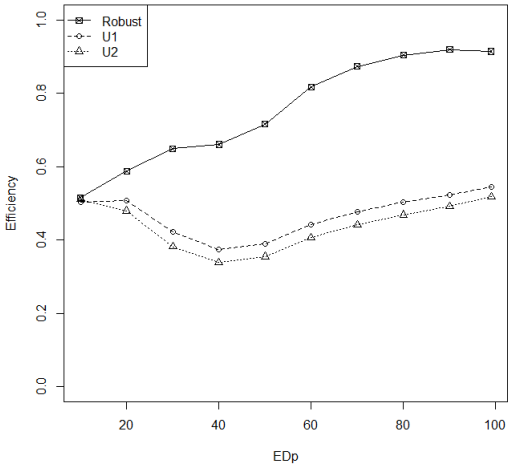

Figure 5. Efficiencies of the designs for estimating ED_ps under Θ_3.

Let ξ_1 denote a uniform design used at the first stage. For the uniform design, four equally spaced dose levels in the dose interval with equal weights are used:

$$\xi_1 = \left\{ \begin{array}{cccc} .001 & 2.67 & 5.33 & 8 \\ .25 & .25 & .25 & .25 \end{array} \right\}$$

Then the augmented robust c-optimal design ξ_{AC} at the second stage is given by:

$$\xi_{AC} = \arg\min_{\xi} \left\{ \sum_{p \in P} \lambda_p log([ED'_p]^T M^*(\xi, \hat{\Theta}) ED'_p) \right\},$$

where $M^*(\xi, \hat{\Theta}) = \alpha M(\xi_1, \hat{\Theta}) + (1-\alpha) M(\xi, \hat{\Theta})$ and $\hat{\Theta}$ is the maximum likelihood estimate of Θ obtained from the first stage. Here $M(\xi_1, \hat{\Theta})$ is the information matrix evaluated at ξ_1; α is the proportion of subjects assigned to the first stage. The Equivalence Theorem demonstrates that ξ_{AC} is the true augmented robust c-optimal design if and only if:

$$\sum_{p \in P} \lambda_p \frac{\left\{ f(x)^T M^*(\xi_{AC}, \Theta)^- ED'_p \right\}^2}{[ED'_p]^T M^*(\xi_{AC}, \Theta)^- M(\xi_{AC}, \Theta) M^*(\xi_{AC}, \Theta)^- ED'_p} \leq 1,$$

For simplicity, we assign 30% of subjects to the first stage and 70% of subjects to the second stage , then $\alpha = .3$. This proportion can be changed based on the researcher's set-up for the experiment. For example, if researcher wants to put more number of subjects, say half of the subjects to the first stage and the other half to the second stage, we can set $\alpha = .5$. For illustration purpose, it is assumed that earlier three parameter sets are the estimated parameter values from the first stage, and the previously used five different ED_ps with the same values of λs are used to search the augmented robust c-optimal design. Using the modified algorithm, the augmented robust c-optimal designs are obtained in Table V. Again, the augmented robust c-optimal designs are verified by the Equivalence Theorem. As an example, the verification plot for Θ_2 is given in Figure 6.

The two-stage robust c-optimal design $\xi_{two-stage}$ assigns $100\alpha\%$ of the subjects according to ξ_1 and $100(1-\alpha)\%$ of the subjects according to ξ_{AC}. Under Θ_2, for example, $\xi_{two-stage}$ is:

$$\xi_{two-stage} = \left\{ \begin{array}{cccccc} .001 & 2.67 & 3.28 & 4.53 & 5.33 & 8 \\ .19 & .08 & .19 & .21 & .08 & .25 \end{array} \right\}$$

Table V. Augmented robust c-optimal designs at the second stage under Θ_1, Θ_2, and Θ_3.

Θ	ξ_{AC}			
Θ_1	.001	.84	1.18	7.99
	.16	.30	.46	.08
Θ_2	.001	3.28	4.53	7.99
	.16	.27	.30	.27
Θ_3	.001	4.33	6.20	7.99
	.10	.24	.40	.26

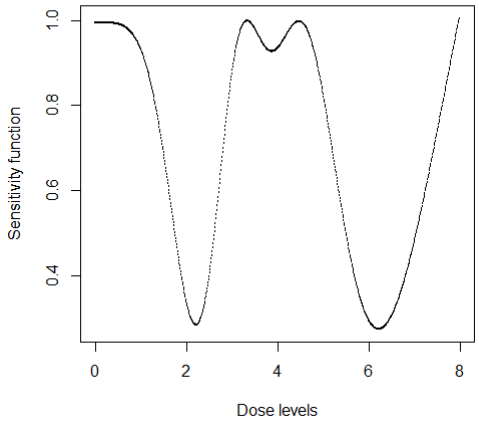

Figure 6. Verification of the augmented robust c-optimal design at the second stage for Θ_2.

Based on the efficiencies for estimating the ED_p, the performances of the two-stage robust c-optimal designs for estimating various ED_ps under Θ_1, Θ_2, and Θ_3 are shown in Figure 7. The three efficiency plots under the three sets of parameter values are very similar to the ones for the previous robust c-optimal designs. The two-stage design uses 30% of the subject at the first stage to estimate the model parameter values and uses the other 70% of the subjects to estimate the ED_ps, but it does not lose much efficiency for estimating various ED_ps.

4. Conclusion

Optimal design plays an important role in designing experiments efficiently. It specifies how to use resources in the most efficient way. Different types of optimal designs have different goals. In this paper, we study c-optimal designs for estimating the ED_p. We found that the c-optimal design for estimating the ED_p is changed by the value of p under the four-parameter logistic model, and the c-optimal design performs very poorly when the value of p is changed. In order to reduce this dependence on the value of p, we present the robust c-optimal design for estimating various ED_ps, and it works fairly well for estimating various ED_ps. Another common problem of optimal designs under non-linear models is that it truly depends on the nominal parameter values. In order to avoid this dependence problem, the two-stage robust c-optimal designs for estimating ED_ps are presented. The two-stage robust c-optimal design can reduce the risk of using mis-specified parameter values, and at the same time, it works fairly well as the robust c-optimal design for estimating various ED_ps.

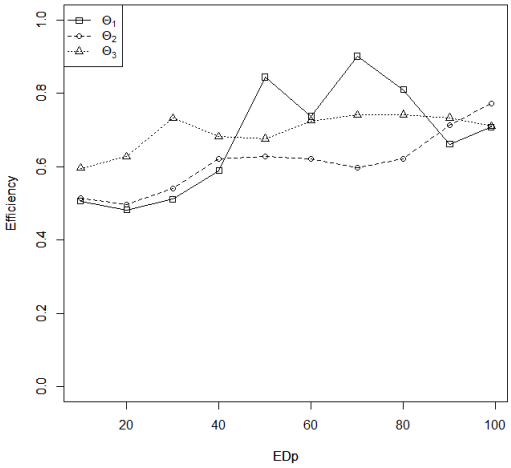

Figure 7. Efficiencies of the two-stage robust c-optimal designs for estimating various ED_ps under Θ_1, Θ_2, and Θ_3.

In this paper, the modified YBT algorithm was used to search all the optimal designs. When multiple criteria are combined into one criterion like our case, the modified YBT algorithm works very greatly. This algorithm can be applied to any other types of optimal designs as long as its criterion is a convex (or concave) function of the information matrix. Interested readers may also write to the first author for the codes.

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