ADAPTIVE TWO-STAGE OPTIMAL DESIGNS FOR ESTIMATING MULTIPLE ED_pS UNDER THE 4-PARAMETER LOGISTIC MODEL

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

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ABSTRACT

In dose-finding studies, c-optimal designs provide the most efficient design to study an interesting target dose. However, there is no guarantee that a c-optimal design that works best for estimating one specific target dose still performs well for estimating other target doses. Considering the demand in estimating multiple target dose levels, the robustness of the optimal design becomes important. In this study, the 4-parameter logistic model is adopted to describe dose-response curves. Under nonlinear models, optimal design truly depends on the pre-specified nominal parameter values. If the pre-specified values of the parameters are not close to the true values, optimal designs become far from optimum. In this research, I study an optimal design that works well for estimating multiple ED_ps and for unknown parameter values. To address this parameter uncertainty, a two-stage design technique is adopted using two different approaches. One approach is to utilize a design augmentation at the second stage, the other one is to apply a Bayesian paradigm to find the optimal design at the second stage. For the Bayesian approach, one challenging task is that it requires heavy computation in the numerical calculation when searching for the Bayesian optimal design. To overcome this problem, a clustering method can be applied. These two-stage design strategies are applied to construct a robust optimal design for estimating multiple ED_ps. Through a simulation study, the proposed two-stage optimal designs are compared with the traditional uniform design and the enhanced uniform design to see how well they perform in estimating multiple ED_ps when the parameter values are mis-specified.

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DEDICATION

This dissertation is dedicated to my grandmother Yuying Ji, who encouraged me to pursue my dream and finish my dissertation.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Figure Page

1. INTRODUCTION

Experimental designs are increasingly expensive to construct in drug development. Thus, setting up an appropriate design that allows researchers to gather as much accurate information as possible at minimal cost becomes important in a dose-finding study. An optimal design can save time, cost and energy by providing the most efficient design to study the interesting objective accurately with limited resources. It identifies dose levels and the number of the subjects that assigned to each selected dose level in the most efficient way (Atikinson and Donev, 1992; Dragalin et al., 2007; Miller et al., 2007).

In general, optimal designs use different optimality criteria for studying different objectives in dose-finding trials. For instance, the c-optimal design provides the minimal variance for estimating target dose levels such as minimum effective dose (MED) and median effective dose (ED_{50}), and the D-optimal design enables the researchers to study the dose-response relationship accurately. One key objective for the dose-finding trial is to study an interesting target dose ED_p. The ED_p is the dose level that achieves $p\%$ of the maximum treatment effect within the observed dose range and p is given between 0 and 100 (Ting, 2006; Bretz et al., 2010). For example, the ED_{50} is the dose level that achieves 50% of the maximum treatment effect. C-optimal design works very well for estimating the ED_p.

The ED_{50} is a common interesting dose level since it generates a reasonable treatment effect. Other dose levels such as ED_{90} and ED_{95} are also interesting dose levels to study in practice (Kopman et al., 2000). In biological and toxicological studies, sometimes researchers want to study multiple dose levels in a single study. For instance, the dose levels ED_{40}, ED_{50}, ED_{60}, and ED_{80} are selected to study for daptomycin in infected mice (Louie et al., 2001); Another example is the dual ED_ps such as ED_{10} and ED_{50} are interesting to researchers

conducting the nefopam experiments on patients who suffer from moderate pain in the postoperative period (Beloeil et al., 2007). Considering the increasing demand in estimating multiple target dose levels from a single study, it is critical to construct an optimal design that works well for estimating multiple $\mathrm{ED}_p s$.

In this paper, I consider the flexible 4-parameter logistic (4PL) model (also called sigmoid E_{max} model) to describe the dose-response functions. The 4PL model is frequently used to study the dose-response relationship due to its sigmoid or S-shape curve in nature (MacDougall, 2006; Dragalin et al., 2007; Leonov and Miller, 2009). Zhang and Hyun (2016) stated that under the 4PL model, the c-optimal design for estimating one specific ED_p works poorly when estimating other $\mathrm{ED}_p s$. They proposed a robust c-optimal design that works well for estimating multiple $\mathrm{ED}_p s$ under the assumption that the parameter values are known. Optimal designs under nonlinear models are very sensitive to the unknown model parameter values. The nominal values of parameters need to be pre-specified in advance of implementing the optimal design. Typically, the construction of the optimal design is based on the initial guess of the parameter values. However, if the initial guess is not close to the true values, the optimal design is far from optimum (Chernoff, 1953; Wang and Yang, 2014).

To reduce the uncertainty of the parameter values, a two-stage design technique is applied based on two different approaches in this study. One approach is to adopt the design augmentation in the second stage (Dragalin et al, 2007; Padmanabhan and Dragalin, 2010). Since the optimal design obtained at the second stage takes the existing design at the first stage into account, the optimal design at the second stage is not a true optimal design but an augmented optimal design. The whole procedure has two steps which offer an efficient way to learn about

the parameters from the first stage and then the accrued data is used to determine the augmented design at the second stage. (Montepiedra and Yeh, 2004).

The other approach is applying the Bayesian paradigm to construct the Bayesian optimal design at the second stage. The Bayesian optimal design utilizes the probability distribution of the unknown parameters instead of a single set of parameters to derive a better design (Dette, 1996; Albert, 2009). Again, the two-stage procedure is performed. At the first stage, a small proportion of the subjects are assigned according to a fixed design. At the second stage, the posterior distribution of the parameters is generated based on the information learned from the first stage.

One challenging task for seeking the Bayesian optimal design is that it needs heavy computation in the numerical calculation. To overcome this problem, a clustering method can be applied. The previous research commonly used the K-means clustering method as an alternative method to the full posterior Bayesian method (Dror and Steinberg, 2006; McCallum and Bornkamp, 2015). K-means clustering reduces the computation of the high-dimensional data by partitioning N observations into k clusters by minimizing the within-cluster sum of squares (Hartigan and Wong, 1979). Various clustering methods have been developed such as Kernel K-means and Fuzzy c-means. Each of them has their own features. For instance, the kernel K-means handles the non-linear structure and the Fuzzy c-means allows a data point to belong to two or more clusters (Dhillon et al., 2004; Welling, 2013; Dunn, 1973; Bezdek, 1981). In this paper, I am also interested in comparing the performance of the three clustering methods to see if different clustering methods change the performance of the Bayesian optimal designs.

Finally, the proposed two-stage designs are compared with other traditional designs such as uniform design and D-optimal design to see how they perform for estimating multiple $ED_p s$ over a wide range of mis-specified model parameters.

Literature review on optimal designs and numerical algorithms are given in Chapter 2. Chapter 3 shows the model and robust optimal designs for estimating multiple ED_ps. In Chapter 4, two-stage optimal designs for estimating multiple $ED_p s$ which account for parameter uncertainty are proposed and their performance is studied. Several scenarios of simulations are set up to check the performance of the two-stage optimal designs compared with other designs for estimating multiple $ED_p s$ under various parameter values. Finally, the conclusion is given in Chapter 5. The flowchart of this study is also provided at the last to give some idea of constructing the optimal designs.

2. BACKGROUND

2.1. Optimal Designs

Conducting experimental designs becomes increasingly expensive and it is always desirable to obtain effective designs with minimal costs. Optimal design is an efficiency tool to reduce costs by using statistical models with fewer replications when estimating model parameters compared with standard non-optimal designs. It specifies the distribution of resources in an efficient way by providing the best dose levels to observe and the proportions of the subjects that assigned to each selected dose level.

Various optimal designs have been developed based on different research objectives. For example, c-optimal design is used for estimating a target dose level, and D-optimal design is used for estimating the dose-response relationship (Atikinson and Donev, 1992; Dragalin et al, 2007). The general design form is written as:

$$\xi = \left\{ \begin{pmatrix} x_i \\ w_i \end{pmatrix}, i = 1, 2 \dots k \right\}$$

where x_i is the i^{th} dose level, $w_i = n_i/N$ represents the proportional allocation of subjects to x_i, n_i is the number of subjects allocated to the i^{th} dose level and $N=\sum_{i=1}^{k} n_i$, which is the total number of subjects.

2.1.1. C-optimality

The c-optimal design enables researchers to study a function of model parameters by minimizing the variance of estimating the target dose level ED_p. To obtain the c-optimal design, one needs to find a design that minimizes the c-optimality criteria, Ψ_c:

$$\Psi_c = \min(\mathrm{Var}(\widehat{ED}_p))$$

2.1.2. D-optimality

When the research goal is to estimate the model parameters, the D-optimal design is applied. It minimizes the variance for model parameters by maximizing the determinant of the Fisher information matrix. The D-optimality criterion function, Ψ_D, is defined as:

$$\Psi_D = \max_{\xi} |\mathrm{M}(\xi\,;\,\Theta)|$$

2.1.3. Metropolis-Hasting (MH) Algorithm

Markov Chain Monte Carlo (MCMC) is used to simulate draws from the posterior distribution. A general way to construct a MCMC is to use a Metropolis-Hasting (MH) algorithm (Albert, 2009). The Metropolis-Hastings algorithm has the following steps:

(1) Start with an initial value θ^0.

(2) Draw a candidate θ^* from a jumping distribution $J_t(\theta^*|\theta^{t-1})$ at the t^{th} iteration.

(3) Compute the acceptance rate

$$r = \frac{p(\theta^*|y)\ /\ J_t(\theta^*|\theta^{t-1})}{p(\theta^{t-1}\,|y)\ /\ J_t(\theta^{t-1}|\theta^*)}$$

(4) Accept $\theta^* = \theta^t$ with probability $\min(r, 1)$; Otherwise, do not accept the θ^*, then set $\theta^t = \theta^{t-1}$.

(5) Repeat steps 2-4 n times to generate n draws from the $p(\theta|y)$.

2.2. K-means, Kernel K-means, and Fuzzy c-means

K-means clustering is one of the simplest clustering algorithms that reduces the dimension of huge data sets (Hartigan and Wong, 1979; Wu, 2012; Morissette and Chartier, 2013). The procedure of the k-means follows a simple way to classify the n data points into a certain number of clusters, say k clusters. It includes several steps:

(1) Place the n data points into initial k clusters.

(2) Assign each point to its closest cluster.

(3) Updates each of the k cluster centers with the centroid of the points assigned to that cluster.

(4) Finally, repeat the algorithm until all cluster centers remain unchanged.

The k-means algorithm is considered a variance minimization technique with aiming to minimize the sum of the variance within the clusters. Suppose x_{ij} is the j^{th} data point in i^{th} cluster, c_i is the center mean of the i^{th} cluster. Then k-means minimizes the objective function: $\sum_{i=1}^{k}\sum_{j=1}^{n_i}||x_{ij}-c_i||^2$, where $||x_{ij}-c_i||^2$ is the squared Euclidean distance which measures the distance between the data point $x_{ij}$and the cluster center c_i.

Kernel K-means shares the same procedure as K-means but except that it applies the kernel method to calculate the distance instead of computing the Euclidean distance (Dhillon, Guan, and Kulis, 2004; Welling, 2013). The advantage of the Kernel K-means is to classify clusters with non-linear structure. Another cluster method is Fuzzy c-means developed by Dunn in 1973. The difference of the Fuzzy c-means is that it allows one data point to belong to two or more clusters. It updates the K-means objective function by multiplying the degree of membership of data point x_i in the cluster j (Dunn, 1973; Bezdek, 1981).

2.3. General Equivalence Theorem

The General Equivalence Theorem is used to verify optimal designs (Pukelsheim, 2006; Atkinson, 2008). It can be applied to any optimal design by taking the directional derivative of the convex function with regards to the design criterion. Here, the general equivalence theorem for the c-optimal design is obtained as follows. The design ξ_c is c-optimal design if, and only if,

$$\{\mathrm{f}^T(\mathrm{x})\mathrm{M}^{-}(\xi_c;\,\Theta)\mathrm{g}'(\Theta)\}^2 \le [\mathrm{g}'(\Theta)]^T\mathrm{M}^{-}(\xi_c;\,\Theta)\mathrm{g}'(\Theta),$$

where $g'(\Theta)$ is the first derivative of g (Θ) with respect to Θ. $M^{-}(\xi_c;\ \Theta)$ is the generalized inverse of the information matrix $M(\xi_c;\ \Theta)$. Suppose $X = (x_1, \ldots, x_k)$ is the design points, and let f(X) denotes the first partial derivatives of the density function for some model of the design points with parameter vector Θ, then the information matrix is defined as M (ξ;Θ) = $\sum_{i=1}^{k} \omega_i f(X, \Theta) f(X, \Theta)^T$. The equal sign holds when x is one of the optimal design points in ξ_c. The left side of the inequality represents the standardized variance of the predicted response, while the right side is the variance of estimating g (Θ) on the c-optimal design. The maximum of the left side is always less than or equal to the right side.

2.4. V-algorithm

The V-algorithm is an iterative algorithm to search optimal designs and was established by Fedorov (1972). It starts with some initial design such as the uniform design. One restriction on the initial design is that it requires the number of the design points to be equal or greater than the number of model parameters. Otherwise, it will cause the information matrix to become singular and the algorithm cannot run. At the n^{th} iteration, this algorithm maximizes the sensitivity function d_n, denoted by:

$$d_n = \{ f^T(x)\, M_n^{-}(\xi\ ;\ \Theta) g'(\Theta)\ \}^2 - [g'(\Theta)]^T M_n^{-}(\xi\ ;\ \Theta) g'(\Theta).$$

Here, $M_n\ (\xi\ ;\ \Theta)$ is the information matrix evaluated at the n^{th} iteration. A point x^* is chosen from the design space which maximizes the d_n. The selected point x^* is then used in the next iteration to update the information matrix as below:

$$M_{n+1}\ (\xi\ ;\ \Theta) = (1 - \alpha_{n+1})\, M_n\ (\xi\ ;\ \Theta) + \alpha_{n+1} f(x^*)_{(n+1)}\ f(x^*)^{T}_{(n+1)},$$

where $\alpha_{n+1} = \frac{1}{n+1}$. The stepwise process stops when the sensitivity function reaches 0 and the c-optimal design is obtained.

2.5. YBT Algorithm

One drawback of the V-algorithm is that it focuses on searching optimal design points, so it runs large number of iterations to get the optimal weights. To address this drawback, it is useful to apply the Newton-Raphson method to find the corresponding design weights after obtaining the design points. Another drawback of the V-algorithm is that it can take a very long time to converge to an optimal design, especially for c-optimal designs. Yang et al (2013) presented the Yang-Biedermann-Tang (YBT) algorithm to find the optimal design for a single objective. They showed the YBT works better than other current algorithms, including V-algorithm (Yang et al, 2013). The YBT starts with a randomly selected initial design, and selects the design points to maximize the sensitivity function, then adds the selected design points into the previous design. Then, the optimal design weights for the updated design points are obtained by using the Newton-Raphson method.

However, the YBT algorithm needs a good guess of the initial design. When it involves a complicated optimal design problems such as multiple objective optimal designs, it might require a long time or even fail to converge to an optimal design if the selected initial design points are far from the optimum. Hyun and Wong (2015) proposed the modified YBT algorithm to update the YBT through selecting the better initial design generated by the V-algorithm. Hyun and Wong (2015) showed that the modification improves the searching speed and can generate the multiple-objective optimal design that the YBT could not.

3. OPTIMAL DESIGNS FOR ESTIMATING MULTIPLE $ED_p s$

This Chapter covers the 4-parameter logistic (4PL) model and the Fisher information matrix. Then optimal designs for estimating multiple $ED_p s$ are conducted under the model. C-optimal design works the best for estimating the ED_p because the ED_p can be expressed as a function of the model parameters under the 4PL model. In practical research, multiple $ED_p s$ might be the objective when conducting optimal design. For instance, the researchers might want to estimate the ED_{50} and ED_{80} from a single study and it is possible that they want to estimate additional $ED_p s$ from the collected data. It wastes time and resources to set up various c-optimal designs for estimating multiple $ED_p s$. To solve this problem, Zhang and Hyun (2016) presented one robust c-optimal design that works well for estimating multiple $ED_p s$. However, under nonlinear model, optimal design truly depends on the nominal values of model parameters. This might also true for the proposed robust c-optimal design by Zhang and Hyun. In this Chapter, I check how the robust c-optimal design works for estimating multiple $ED_p s$ under mis-specified model parameters.

3.1. Model and Information Matrix

It is often observed that the dose-response relationships follow a sigmoid curve. This leads us the 4PL model, which is frequently used for many toxicological and biological systems. It takes into account the minimum dose, maximum dose, ED_{50}, and the slope of the curve.

The mean response (effect) μ for the 4PL model at a given dose X_i is defined as

$$\mu(X_i,\Theta) = \theta_1+(\theta_2-\theta_1)\frac{{X_i}^{\theta_4}}{{X_i}^{\theta_4}+{\theta_3}^{\theta_4}},$$

where X_i is the i^{th} dose level. θ_1 is the minimum effect; θ_2 is the maximum effect; θ_3 is the ED_{50}, and θ_4 is the slope.

Then the continuous response Y for the i^{th} dose level and j^{th} replication is defined by

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

Here, $\Theta = (\theta_1,\ \theta_2,\ \theta_3,\ \theta_4)$, j=1,2,3,…, n_i, i=1,2,3,…, k. The variance σ^2 is assumed to be an unknown constant. Then the normalized Fisher information matrix under the 4PL model is

$$M\,(\xi;\Theta) = \frac{1}{\sigma^2} \sum_{i=1}^{k} \omega_i f(X_i, \Theta) f\,(X_i, \Theta)^T,$$

where the $f(X_i, \Theta)$ is the partial derivatives of the mean response $\mu\,(X_i,\Theta)$ with respect to model parameters Θ:

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

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

In the information equation above, we can see that the design and the model parameters are carried out by the Fisher information matrix $M\,(\xi;\Theta)$. Thus, it is an essential component in searching the c-optimal design for estimating multiple $ED_p s$. After we set up the model and the Fisher information matrix, we can search the optimal designs in the next section.

3.2. Robust Optimal Designs for Estimating Multiple $ED_p s$

To study a function of model parameters, c-optimal design can be applied. Under the 4PL model, ED_p is solved by an explicit form $p = \frac{\mu\,(X_i,\Theta) - \theta_1}{\theta_2-\theta_1}$, which leads $ED_p = \theta_3\,(\frac{p}{1-p})^{\frac{1}{\theta_4}}$, where p represents the p % of the maximum treatment response. Let $\widehat{ED_p}$ denotes the maximum likelihood estimate of the ED_p, then the variance of estimating the ED_p is defined as

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

where $[\,\mathrm{ED}_p{}']^T = \left(0,\ \ 0,\ \ \left(\frac{p}{1-p}\right)^{\frac{1}{\theta_4}}, -\left[\frac{\theta_3}{\theta_4{}^2}\left(\frac{p}{1-p}\right)^{\frac{1}{\theta_4}}\log\left(\frac{p}{1-p}\right)\right]\right)$; $\mathrm{M}(\xi;\Theta)^-$ is the generalized inverse of the Fisher information matrix mentioned earlier.

To find the c-optimal design for estimating the ED_p, one needs to find a design that minimizes $\mathrm{Var}(\widehat{\mathrm{ED}_p})$, which leads to the sensitivity function as follows:

$$\frac{\left\{\mathrm{f}^T(\mathrm{x})\mathrm{M}_n\left(\xi^*{}_{\mathrm{ED}_p};\Theta\right)^- \mathrm{g}'(\theta)\right\}^2}{[\mathrm{g}'(\theta)]^T\mathrm{M}_n\left(\xi^*{}_{\mathrm{ED}_p};\Theta\right)^- \mathrm{g}'(\theta)} \leq 1,$$

By the General Equivalence Theorem, the equality holds when x is one of the c-optimal design points.

Zhang and Hyun (2016) stated that under the 4PL model, the c-optimal design for estimating the ED_p works poorly when it is used for estimating additional $\mathrm{ED}_p s$. Thus, it is essential to seek one robust c-optimal design that performs well for estimating multiple $\mathrm{ED}_p s$. As an illustration, five $\mathrm{ED}_p s$ ($\mathrm{ED}_{10}, \mathrm{ED}_{30}, \mathrm{ED}_{50}, \mathrm{ED}_{70}, \mathrm{ED}_{90}$) are considered. The robust optimal design is obtained using the same experimental setup from Padmanabhan and Dragalin (2010): Dose range $= [0, 8]$ and $\Theta = (0, -1.7,\ 4, 5)$. In addition, another two sets of model parameters are considered to check the performance on the different parameter values. Under the 4PL model, the optimal design based on the information matrix does not depend on the parameters θ_1 and θ_2, and commonly, researchers are more interested in checking the designs with the changes in the ED_{50}, which is θ_3 (Li and Majumdar, 2008; Hyun and Wong, 2015). Thus, the three sets of the model parameters with different θ_3 are $\Theta_1 = (0, -1.7, 1, 5)$, $\Theta_2 = (0, -1.7, 4, 5)$, and $\Theta_3 = (0, -1.7, 6, 5)$. All designs are obtained by the modified YBT algorithm and verified by the General Equivalence Theorem.

Three robust c-optimal designs are obtained under the three sets of model parameters Θ_1, Θ_2 , and Θ_3, and their design efficiencies are compared. The idea of the robust c-optimal design is that it combines the c-optimality criteria for the various $\mathrm{ED}_p s$ into one compound criterion, which maximizes the weighted log product of the design efficiencies for estimating the various $\mathrm{ED}_p s$ (McGree et al., 2008). Before we can obtain the robust c-optimal designs, we need to know the definition of the design efficiency.

Design efficiency measures how a design performs with respect to some optimality criterion. Because our goal is to estimate the ED_p, we use the c-efficiency, which is the ratio of the variance of a design ξ against the c-optimal design $\xi^*_{\mathrm{ED}_p}$:

$$\mathrm{Eff}_{\mathrm{ED}_p}(\xi) = \frac{[\mathrm{ED}_p']^T \mathrm{M}\left(\xi^*_{\mathrm{ED}_p}; \Theta\right)^{-} \mathrm{ED}_p'}{[\mathrm{ED}_p']^T \mathrm{M}(\xi; \Theta)^{-} \mathrm{ED}_p'}.$$

Since the locally c-optimal design for estimating the ED_p, $\xi^*_{\mathrm{ED}_p}$provides the minimum variance, the design efficiency is always between 0 and 1. The better the design ξ performs, the closer it is to 1.

Using the design efficiency, we can obtain the robust c-optimal design for estimating the multiple $\mathrm{ED}_p s$. Let $p \in P = (10, 30, 50, 70, 90)$. Note that the five values of p are selected for an illustration purpose, and it can be extended to any other ps. The robust c-optimal design for estimating multiple $\mathrm{ED}_p s$ that maximizes the weighted log product of the relative design efficiencies is

$$\xi_{Rob} = \arg\max_{\xi} \left\{ \sum_{p \in P} \lambda_p log\left(\mathrm{Eff}_{\mathrm{ED}_p}(\xi)\right) \right\},$$

where λ_p is the pre-assigned weight, which indicates the relative importance of the corresponding ED_p, and $\sum_{p\in P}\lambda_p = 1$. By the Equivalence Theorem, ξ_{Rob} is the robust c-optimal design if, and only if,

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

Again, the equal sign holds when x is one of the design point of ξ_{Rob}. For simplicity, I consider each ED_p to be equally important, that is $\lambda_p = 0.2$. Using the five different values of ED_p, we search the robust c-optimal designs under the three sets of model parameters by the modified YBT algorithm and they are given in Table 1:

Table 1: Robust c-optimal designs for estimating multiple $\mathrm{ED}_p s$ under Θ_1, Θ_2, and Θ_3.

Θ	ξ_{Rob}
$\Theta_1 = (0, -1.7, 1, 5)$	$\begin{pmatrix} .001, .84, 1.19, 7.99 \\ 0.21, 0.29, 0.29, 0.21 \end{pmatrix}$
$\Theta_2 = (0, -1.7, 4, 5)$	$\begin{pmatrix} .001, 3.22, 4.58, 7.99 \\ 0.20, 0.27, 0.32, 0.21 \end{pmatrix}$
$\Theta_3 = (0, -1.7, 6, 5)$	$\begin{pmatrix} .001, 4.28, 6.18, 7.99 \\ 0.19, 0.27, 0.30, 0.24 \end{pmatrix}$

The robust c-optimal designs are obtained by using the five $\mathrm{ED}_p s(\mathrm{ED}_{10}, \mathrm{ED}_{30}, \mathrm{ED}_{50}, \mathrm{ED}_{70}, \mathrm{ED}_{90})$. In each design form, the first row represents the design points, and the second row represents the design weights.

The robust c-optimal design provides the design points and the proportions of the subjects that should be allocated to each design point. From Table 1, one can observe that all the robust c-optimal designs have four design points with lower bound and upper bound of the dose range included. While, the middle two design points are changed by the values of the model parameters. To interpret the designs in Table 1, here I take the robust c-optimal design under Θ_2 as an example: the robust c-optimal design assigns 20% and 21% of the subjects into the lower bound and the upper bound of the dose level respectively, then assigns 27% and 32% of the

subjects into the two middle dose levels 3.22 and 4.58 respectively. As shown in the table, the robust c-optimal designs are changed under the different sets of nominal model parameters. The General Equivalence Theorem checks the validations of the designs (see Figure 1, 2 and 3). From the three figures, we can see that all the robust c-optimal design points reach to 1.

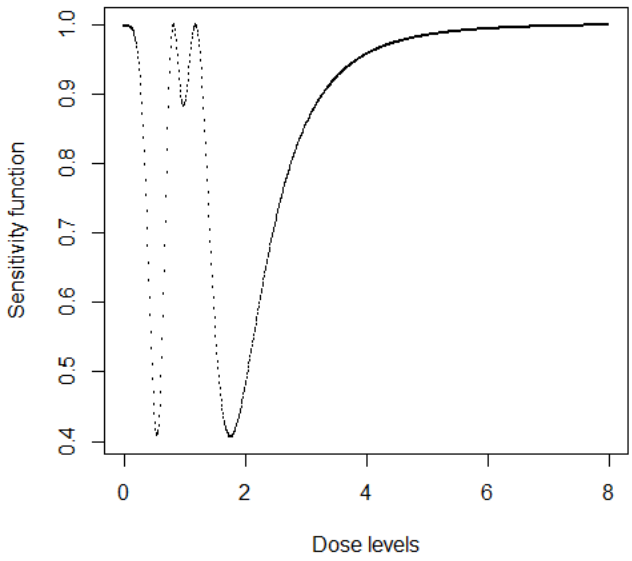

Figure 1: Plots of the sensitivity function of the robust c-optimal design for estimating multiple $ED_p s$ under $\Theta_1 = (0,\ -1.7, 1, 5)$.

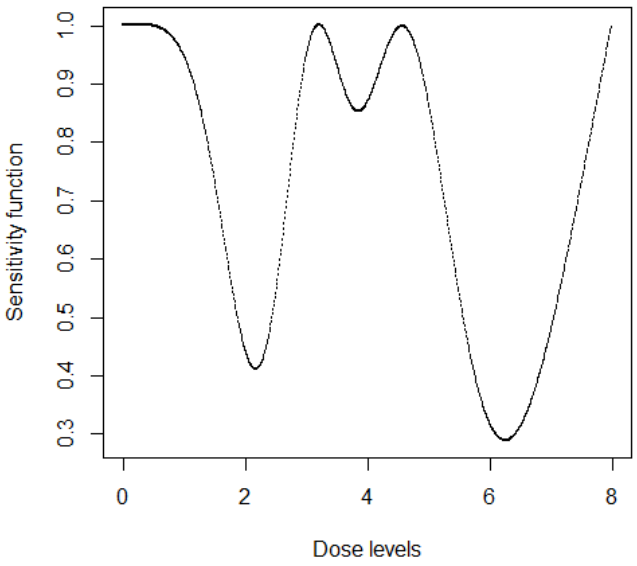

Figure 2: Plots of the sensitivity function of the robust c-optimal design for estimating multiple $ED_p s$ under $\Theta_2 = (0,\ -1.7, 4, 5)$.

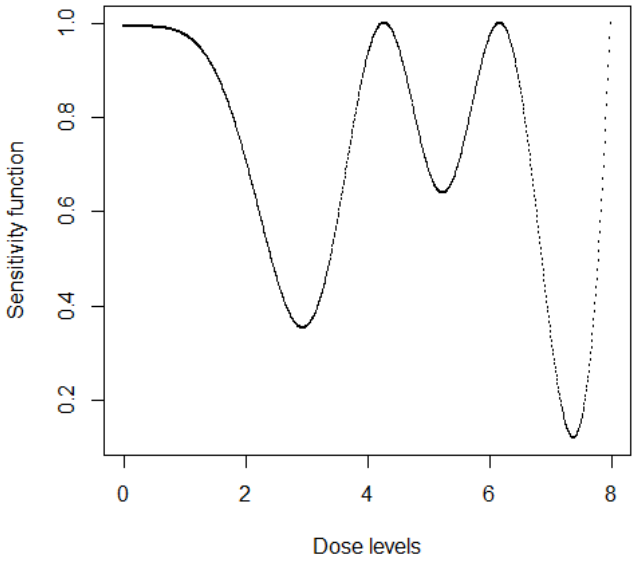

Figure 3: Plots of the sensitivity function of the robust c-optimal design for estimating multiple $ED_p s$ under $\Theta_3 = (0,\ -1.7, 6, 5)$.

Once I obtain the robust c-optimal designs, the next important procedure is to check the performances of the obtained designs for estimating the multiple $\mathrm{ED}_p s$ by design efficiencies. As a comparison, the uniform designs are used. Uniform design allocates equal subjects to fixed equally spaced doses. In this study, uniform design, ξ_{U1}, with 8 design points is selected. To enhance the performance of the uniform design, I apply the same robust design technique to find the optimal weights for the 8 points uniform design. The 8 points uniform design with optimal weights denotes as ξ_{U2}. It can be obtained by maximizing the robust c-optimal design criterion function showed earlier over the weights for the given uniform design points. ξ_{U1} and ξ_{U2} are shown as follows:

ξ_{U1} is a fixed design and it is given by:

$$\xi_{U1} = \begin{pmatrix} .001, 1.14, 2.29, 3.43, 4.57, 5.71, 6.86, 8 \\ \frac{1}{8}, \frac{1}{8}, \frac{1}{8}, \frac{1}{8}, \frac{1}{8}, \frac{1}{8}, \frac{1}{8}, \frac{1}{8} \end{pmatrix};$$

Under $\Theta_1 = (0, 1.7, 1, 5)$, ξ_{U2} is given by:

$$\xi_{U2} = \begin{pmatrix} .001, 1.14, 2.28, 3.43, 4.57, 5.71, 6.86, 7.99 \\ 0.05, 0.15, 0.42, 0.00, 0.00, 0.00, 0.00, 0.38 \end{pmatrix};$$

Under $\Theta_2 = (0, 1.7, 4, 5)$, ξ_{U2} is given by:

$$\xi_{U2} = \begin{pmatrix} .001, 1.14, 2.28, 3.43, 4.57, 5.71, 6.86, 7.99 \\ 0.00, 0.18, 0.00, 0.29, 0.36, 0.00, 0.00, 0.21 \end{pmatrix};$$

Under $\Theta_3 = (0, 1.7, 6, 5)$, ξ_{U2} is given by:

$$\xi_{U2} = \begin{pmatrix} .001, 1.14, 2.28, 3.43, 4.57, 5.71, 6.86, 7.99 \\ 0.14, 0.00, 0.00, 0.02, 0.22, 0.22, 0.18, 0.22 \end{pmatrix}.$$

I examine the design efficiencies of the robust c-optimal designs and the two uniform designs for estimating various of the $\mathrm{ED}_p s$, which are $\mathrm{ED}_{10}, \mathrm{ED}_{20}, \mathrm{ED}_{30}, \mathrm{ED}_{40}, \mathrm{ED}_{50}$, $\mathrm{ED}_{60}, \mathrm{ED}_{70}, \mathrm{ED}_{80}, \mathrm{ED}_{90}$, and ED_{99}. See Table 2 as below:

Table 2: Efficiencies of the designs for estimating multiple ED_ps under the three sets of the nominal model parameters

Θ	ξ	$Eff_{\xi_{10}}$	$Eff_{\xi_{20}}$	$Eff_{\xi_{30}}$	$Eff_{\xi_{40}}$	$Eff_{\xi_{50}}$	$Eff_{\xi_{60}}$	$Eff_{\xi_{70}}$	$Eff_{\xi_{80}}$	$Eff_{\xi_{90}}$	$Eff_{\xi_{99}}$
Θ_1	ξ_{Rob}	0.621	0.657	0.626	0.665	0.846	0.670	0.794	0.576	0.639	0.747
	ξ_{U1}	0.009	0.010	0.011	0.017	0.048	0.177	0.337	0.059	0.030	0.020
	ξ_{U2}	0.019	0.021	0.024	0.037	0.098	0.265	0.392	0.107	0.059	0.041
Θ_2	ξ_{Rob}	0.575	0.557	0.600	0.677	0.668	0.651	0.626	0.654	0.756	0.830
	ξ_{U1}	0.386	0.397	0.449	0.500	0.457	0.409	0.371	0.375	0.429	0.474
	ξ_{U2}	0.497	0.512	0.597	0.721	0.716	0.662	0.595	0.588	0.653	0.692
Θ_3	ξ_{Rob}	0.515	0.580	0.649	0.660	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}	0.516	0.623	0.593	0.532	0.542	0.601	0.635	0.675	0.667	0.687

Note: $\Theta_1 = (0, -1.7, 1, 5), : \Theta_2 = (0, -1.7, 4, 5), \text{and } \Theta_3 = (0, -1.7, 6, 5)$.

Table 2 shows that the under the nominal model parameters Θ_1 and Θ_3, the robust c-optimal design generally outperforms the two uniform designs for estimating varies of $\text{ED}_p s$ with the values of p changed from 10 to 99. Under the model parameter Θ_2, the robust c-optimal design, ξ_{Rob}, works similar with the uniform design, ξ_{U2}, when estimating the ED_{30}. For estimating the $\text{ED}_{10}, \text{ED}_{20},$ ED_{70}, ED_{80}, ED_{90}, and ED_{99}, ξ_{Rob} performs better than ξ_{U2}, while performs a little worse than ξ_{U2} when estimating the $\text{ED}_{40}, \text{ED}_{50},$ and ED_{60}; The efficiencies of the uniform design, ξ_{U1}, are relatively low for estimating the multiple $\text{ED}_p s$ compared with ξ_{U2} under the three sets of model parameters, indicating that the robust design techniques with optimal weights enhanced the design performance as expected. Overall, the robust c-optimal design provides generally constant efficiencies ranging as low as 52% to as high as 92%. However, the uniform design ranges from 1% to 54% and the uniform design with optimal weights ranges from 2% to 72%. Although I only consider five $\text{ED}_p s$ to conduct the robust c-

optimal design, it performs consistently well for estimating other $\mathrm{ED}_p s$ which are not included into the compound criterion. The corresponding efficiencies plots in Figure 4, 5 and 6 help illustrate the performance of the robust c-optimal design. It is obvious that in Figure 4 and Figure 6, the efficiency line of the robust c-optimal design is always higher than those of the uniform designs. While in Figure 5, the efficiency line of the robust c-optimal design intersects with the uniform design with optimal weights three times, but overall it works consistently and better than both uniform design.

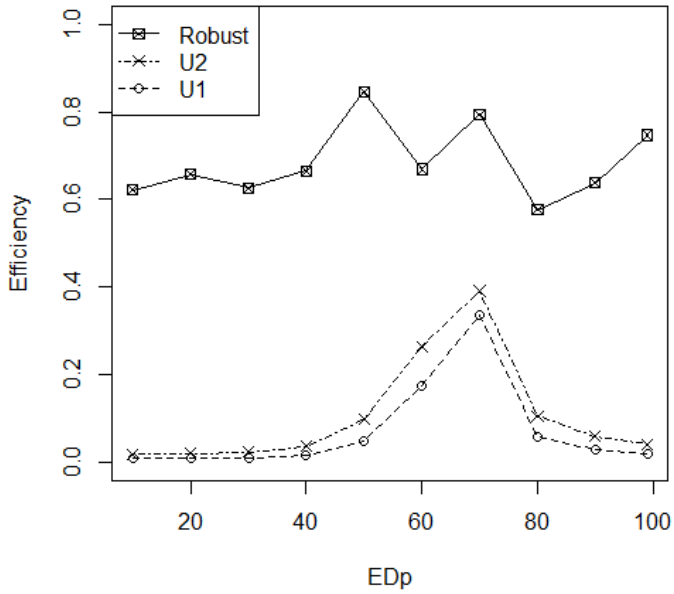

Figure 4: Design efficiencies of the robust c-optimal design and uniform designs under $\Theta_1 = (0, -1.7, 1, 5)$. In the legend of the figure, Robust represents the robust c-optimal design; U1 represents the uniform design with 8 design points; U2 represents the uniform design with 8 design points with optimal weights.

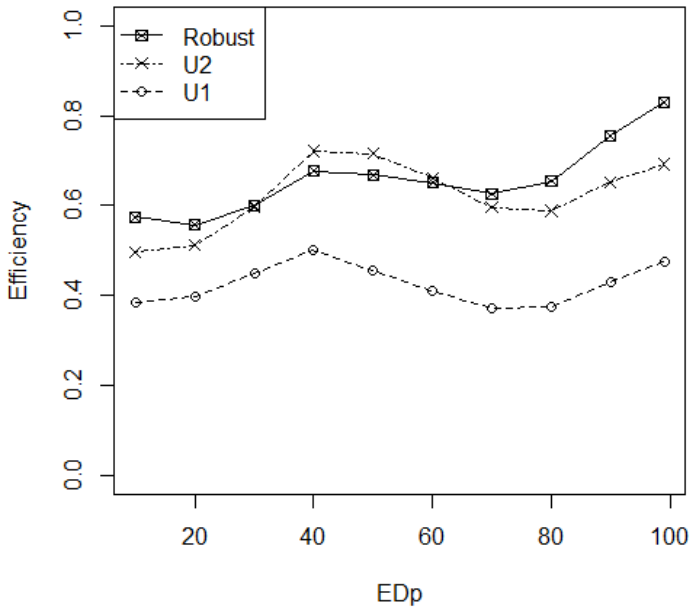

Figure 5: Design efficiencies of the robust c-optimal design and uniform designs under $\Theta_2 = (0, -1.7, 4, 5)$. In the legend of the figure, Robust represents the robust c-optimal design; U1 represents the uniform design with 8 design points; U2 represents the uniform design with 8 design points with optimal weights.

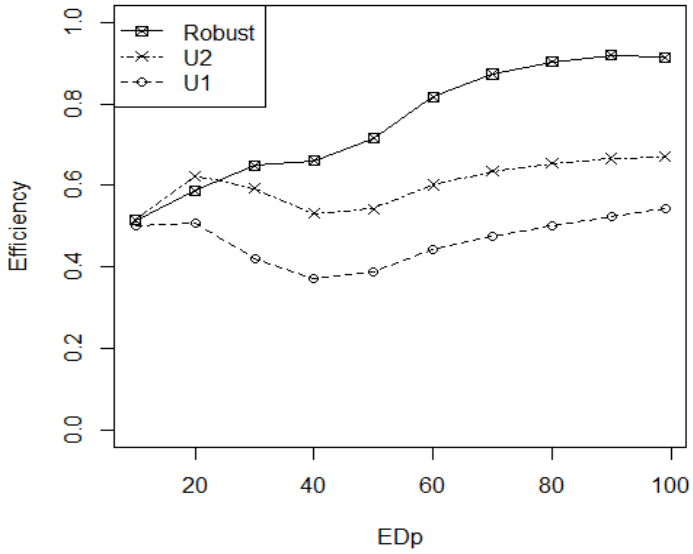

Figure 6: Design efficiencies of the robust c-optimal design and uniform designs under $\Theta_3 = (0, -1.7, 6, 5)$. In the legend of the figure, Robust represents the robust c-optimal design; U1 represents the uniform design with 8 design points; U2 represents the uniform design with 8 design points with optimal weights.

Though the obtained robust c-optimal design works well for estimating multiple $\mathrm{ED}_p s$, it might work poorly under different nominal values of parameters. In Table 3, we check the design efficiencies of the robust c-optimal design for estimating multiple $\mathrm{ED}_p s$ under the true parameter value Θ_1, ${\xi_{Rob}}^1$, when it is used for different parameter values such as Θ_2 and Θ_3. From Table 3, we can see that the design efficiencies are pretty low for the robust c-optimal design under Θ_1 when it is used for Θ_2 and Θ_3.

Table 3: Efficiencies of the robust c-optimal deigns for estimating multiple $ED_p s$ under the true value of model parameter Θ_1, ${\xi_{\mathrm{Rob}}}^1$, when the parameter values are mis-specificed to Θ_2 or Θ_3.

Θ	$Eff_{\xi_{10}}$	$Eff_{\xi_{20}}$	$Eff_{\xi_{30}}$	$Eff_{\xi_{40}}$	$Eff_{\xi_{50}}$	$Eff_{\xi_{60}}$	$Eff_{\xi_{70}}$	$Eff_{\xi_{80}}$	$Eff_{\xi_{90}}$	$Eff_{\xi_{99}}$
Θ_1 (True)	0.621	0.657	0.626	0.665	0.846	0.670	0.794	0.576	0.639	0.747
Θ_2	0.100	0.108	0.102	0.086	0.078	0.071	0.068	0.064	0.056	0.053
Θ_3	0.045	0.040	0.012	0.010	0.007	0.005	0.004	0.004	0.005	0.006

The efficiencies in the first row are the design efficiencies of the robust c-optimal design, ${\xi_{Rob}}^1$, against the c-optimal design under Θ_1; The second row are the design efficiencies of the robust c-optimal design, ${\xi_{Rob}}^1$, against the c-optimal design under Θ_2; The third row are the design efficiencies of the robust c-optimal design, ${\xi_{Rob}}^1$, against the c-optimal design under Θ_3. Here,$\Theta_1 = (0, -1.7, 1, 5)$, $\Theta_2 = (0, -1.7, 4, 5)$, and $\Theta_3 = (0, -1.7, 6, 5)$.

4. TWO-STAGE OPTIMAL DESIGNS FOR ESTIMATING MULTIPLE $ED_p s$

Optimal design under the 4PL model truly depends on the pre-specified model parameters. This is also true for the robust c-optimal design shown in the previous Chapter. To reduce the parameter dependency, the two-stage strategy is studied. One approach is to adopt the design augmentation at the second stage. The other one is to apply the Bayesian paradigm at the second stage.

4.1. Two-stage C-optimal Design for Estimating Multiple $ED_p s$

First two-stage optimal design is constructed by adopting the design augmentation at the second stage. The idea of the two-stage optimal design is as follows:

(1) 1st Stage: A small proportion of the total sample size N, say N_1, is assigned according to a fixed design, ξ_1.

(2) Fit the 4PL model to the data that collected from the first stage and uses the estimated parameters $\widehat{\Theta}$ to search the augmented optimal design ξ_2 at the second stage.

(3) 2nd Stage: Assign the rest of the sample $N_2 = N - N_1$ to the ξ_2.

For simplicity, in this study we adopt the same five $ED_p s$ ($ED_{10}, ED_{30}, ED_{50}, ED_{70}$, and ED_{90}) to conduct the two-stage c-optimal design under the same dose range and the parameters values. Let ξ_1 be a uniform design with four equally spaced dose levels used at the first stage,

$$\xi_1 = \begin{pmatrix} .001, 2.67, 5.33, 8 \\ 0.25, 0.25, 0.25, 0.25 \end{pmatrix}.$$

Let ξ_{AC} be the augmented c-optimal design at the second stage,

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

where $M^*(\xi, \widehat{\Theta}) = \alpha M(\xi_1, \widehat{\Theta}) + (1-\alpha) M(\xi, \widehat{\Theta})$, $\widehat{\Theta}$ is the maximum likelihood estimator of Θ collected from the first stage; $M(\xi_1, \widehat{\Theta})$ is the information matrix that evaluated at the first stage; and α is the proportion of the subjects allocated the first stage. Here we set $\alpha = 0.3$, which means we assign 30% of the subjects into the first stage design and the remaining 70% of the subjects are assigned to the second stage. By the General Equivalence Theorem, the sensitivity function for ξ_{AC} is:

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

Equality holds if, and only if, x is one of the dose levels in the ξ_{AC}. The augmented c-optimal design at the second stage is obtained by using the modified YBT algorithm. For illustrative purposes, it is assumed that the MLE $\widehat{\Theta}$ obtained from the first stage is Θ_1, Θ_2, and Θ_3, respectively. Now, the two-stage c-optimal design is generated based on the first stage design ξ_1 and the augmented c-optimal design at the second stage ξ_{AC} by the proportion $\alpha = 0.3$ (see Table 4). After the ξ_{AC} is searched, the two-stage c-optimal design is obtained based on: $\alpha * \xi_1 + (1-\alpha) * \xi_{AC}$. As shown in Table 4, all the two-stage c-optimal designs contain six designs points including the lower bound and upper bound dose levels.

All of the augmented c-optimal designs are verified by the Equivalence Theorem in Figure 7, 8, and 9. In Figure 10, we check the efficiencies of the two-stage c-optimal design for estimating the series of the $ED_p s$ ranging from ED_{10} to ED_{99}. One can observe that the efficiencies plots of the two-stage c-optimal design are very close to the ones of the robust c-optimal design in the previous section. After spending some portion of subjects to get information about the parameter values, the two-stage c-optimal design does not lose much efficiency for estimating various $ED_p s$. Here it is assumed that the MLE of Θ obtained from the

first stage is accurate. However, the accuracy can be changed by the sample size and the design used in the first stage. Later, using the simulation study, I study real performances of the two-stage c-optimal design under various sample sizes of the first stage.

Table 4: Two-stage c-optimal designs for estimating multiple $ED_p s$ under the three sets of the nominal model parameters Θ_1, Θ_2, and Θ_3.

Θ	ξ_{AC}	$\xi_{two-stage}$
$\Theta_1 = (0, -1.7, 1, 5)$	$\begin{pmatrix} .001, .84, 1.18, 7.99 \\ 0.16, 0.30, 0.46, 0.08 \end{pmatrix}$	$\begin{pmatrix} .001, .84, 1.18, 2.67, 5.33, 7.99 \\ 0.19, 0.20, 0.32, 0.08, 0.08, 0.13 \end{pmatrix}$
$\Theta_2 = (0, -1.7, 4, 5)$	$\begin{pmatrix} .001, 3.28, 4.53, 7.99 \\ 0.16, 0.27, 0.30, 0.27 \end{pmatrix}$	$\begin{pmatrix} .001, 2.67, 3.28, 4.53, 5.33, 7.99 \\ 0.19, 0.08, 0.19, 0.21, 0.08, 0.25 \end{pmatrix}$
$\Theta_3 = (0, -1.7, 6, 5)$	$\begin{pmatrix} .001, 4.33, 6.20, 7.99 \\ 0.10, 0.24, 0.40, 0.26 \end{pmatrix}$	$\begin{pmatrix} .001, 2.67, 4.33, 5.33, 6.20, 7.99 \\ 0.15, 0.08, 0.17, 0.08, 0.27, 0.25 \end{pmatrix}$

ξ_{AC} is the augmented c-optimal design at the second stage, $\xi_{two-stage}$ is the two-stage c-optimal design. The proportions of subjects that assigned to the first stage design and the second stage design are 0.3 and 0.7, respectively.

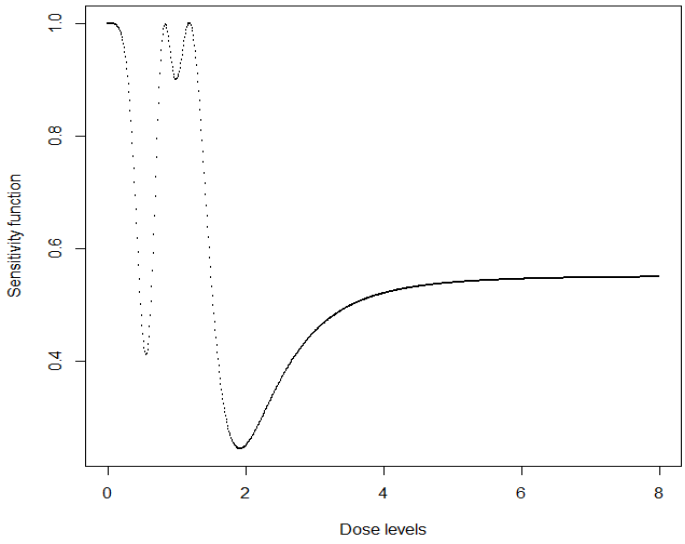

Figure 7: Plots of the sensitivity function of the augmented c-optimal design for estimating multiple $ED_p s$ under $\Theta_1 = (0,\ -1.7, 1, 5)$.

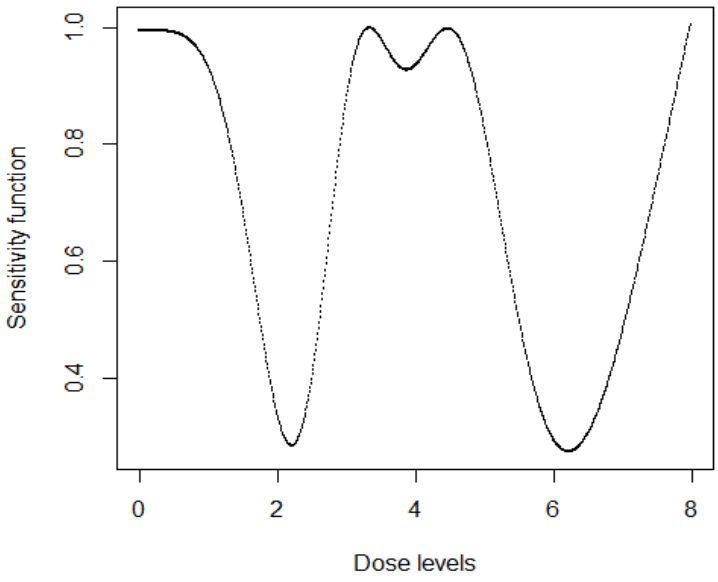

Figure 8: Plots of the sensitivity function of the augmented c-optimal design for estimating multiple $ED_p s$ under $\Theta_2 = (0,\ -1.7, 4, 5)$.

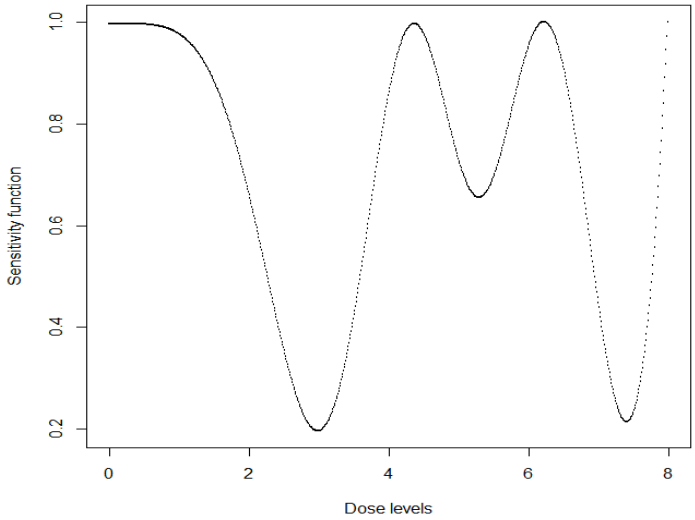

Figure 9: Plots of the sensitivity function of the augmented c-optimal design for estimating multiple $ED_p s$ under $\Theta_3 = (0,\ -1.7, 6, 5)$.

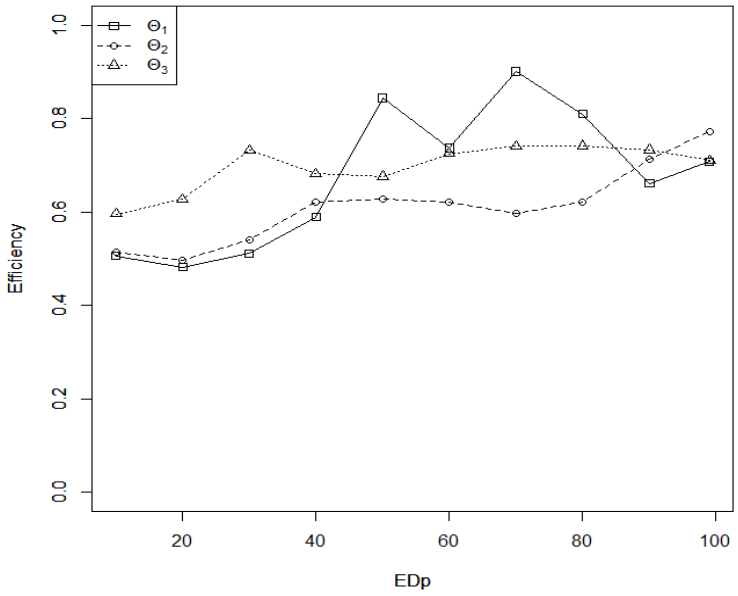

Figure 10: Efficiencies of the two-stage c-optimal design for estimating multiple ED_ps ($ED_{10}, ED_{20}, ED_{30}, ED_{40}$, ED_{50}, ED_{60}, ED_{70}, ED_{80}, ED_{90}, and ED_{99}) under $\Theta_1 = (0, -1.7, 1, 5)$, $\Theta_2 = (0, -1.7, 4, 5)$, and $\Theta_3 = (0,\ -1.7, 6, 5)$.

In order to check the performance of the two-stage c-optimal design, we run simulation 1000 times using different sample size at the first stage and the efficiencies of two-stage c-optimal design are computed under the assumption of the true parameter value $\Theta = \Theta_2 = (0, -1.7, 4, 5)$. For simplicity and consistency study, the same five values of $ED_p s$ ($\mathrm{ED}_{10}, \mathrm{ED}_{30}, \mathrm{ED}_{50}$, ED_{70}, and ED_{90}) are studied in the simulations. There are three scenarios for estimating each ED_p by changing the proportion of the first stage sample size, α. In the simulations, we set total sample size equal 300, and set α = 1/10, 1/3, and 1/2, which means the first stage simple size is 30, 100, and 150, respectively. For each simulation run, I assign the proportion α of the total 300 sample size according to the first-stage design $\xi_1 = \begin{pmatrix} .001, 2.67, 5.33, 8 \\ 0.25, 0.25, 0.25, 0.25 \end{pmatrix}$. Then I generate the response data under the continuous response model mentioned in Chapter 3, assuming that the mean response is given by 4PL model, σ =0.1, and $\Theta = \Theta_2$. Figure 11(a) and Figure 11(b) shows an example of the generated response data plot with varied of the first stage sample size N_1= 30, 100, and 150 under σ=0.1 and σ=0.5, respectively. Next, based on the generated response, $\widehat{\Theta}$ is estimated using the least squares estimate (LSE) method and used in the second stage to obtain the augmented c-optimal design at the second stage. However, the augmented c-optimal design at the second stage cannot be obtained when the parameters are not estimable from the collected data at the first stage. If the value of σ is too large, it may become harder to converge to the estimated parameter values. Thus, I compute the success rate, which is defined as the ratio of the number of the parameters that estimated successfully from the first stage over the total runs. First I run the simulation 1000 times under σ=0.1 to see the performance of the two-stage c-optimal design with varied sample sizes that assigned at the first-stage design, then I run the simulation 1000 times again by increasing the value of σ from 0.1 to 0.5 to compare the change of the success rate. In Table 5,

the success rate and summary statistics of c-efficiencies of the two-stage c-optimal design are computed when the model parameters are estimable at the first stage under σ=0.1. Additionally, it shows how the values change according to different sample sizes at the first stage N_1.

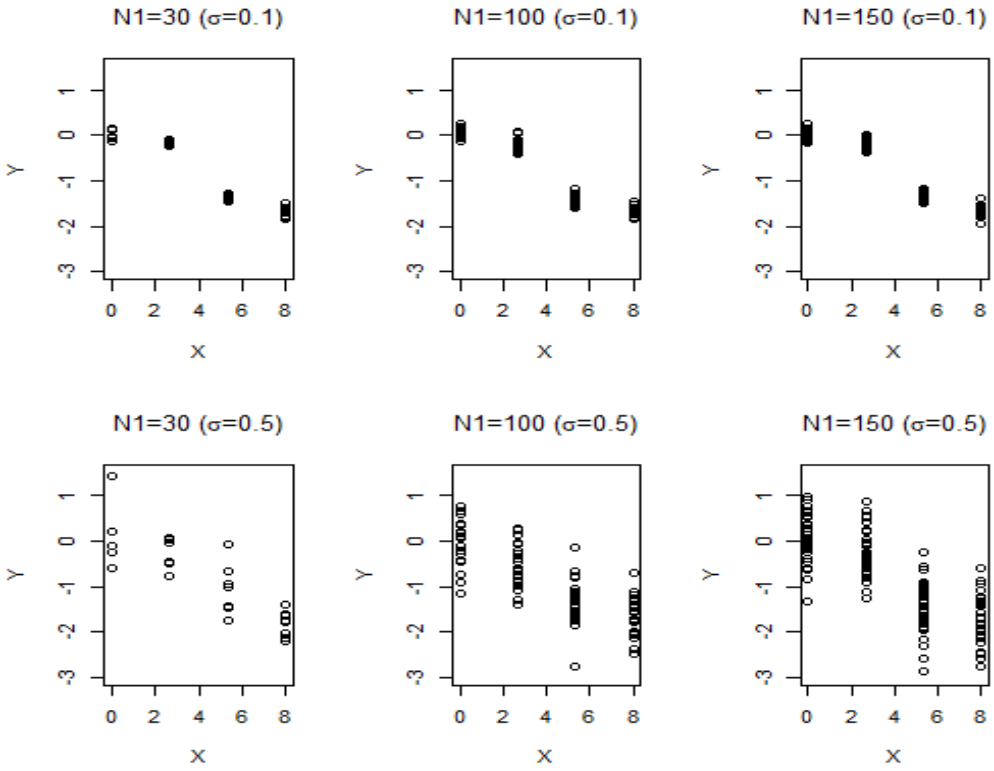

Figure 11: Generated response data from the first-stage design with varied first-stage sample size N_1=30, 100, and 150, under σ=0.1 and σ=0.5, respectively.

Table 5 demonstrates that under σ=0.1, the success rates in each scenario are 100%, which indicates all the parameters are estimable when σ is as small as 0.1. It also shows that the two-stage c-optimal design for estimating multiple $ED_p s$ performs fairly well when the parameters are estimated at the first stage. In addition, it shows that the 25% quantile has slightly increased (around 1% to 3%), while the 75% quantile has slightly decreased (around 1% to 3%) when the first sample size changed from 30 to 150. However, the median and mean does not change much, which implies that the sample size for the first stage does not impact very much on the efficiency. The mean c-efficiencies of the two-stage optimal design increase from 53% to

72% when increase the value of ED_p from ED_{10} to ED_{90}, which suggests that the two-stage c-optimal design works better to estimate higher values of $\mathrm{ED}_p s$ compared with lower $\mathrm{ED}_p s$. Figure 12, 13, 14, 15, and 16 show the histograms of c-efficiencies of the two-stage c-optimal designs for estimating multiple ED_{10}, ED_{30}, ED_{50}, ED_{70}, and ED_{90}, respectively, with changing the proportions of the first stage sample size.

Table 5: Success rate and summary statistics of c-efficiencies of the two-stage c-optimal design for estimating multiple $ED_p s$ ($\mathrm{ED}_{10}, \mathrm{ED}_{30}, \mathrm{ED}_{50}, \mathrm{ED}_{70}$, and ED_{90}) with varied values of first stage sample size (30, 100, and 150) under σ=0.1.

ED_p	N1	Success Rate	25% Quartile	Median	Mean	75% Quartile
ED_{10}	30	100%	0.5063	0.5371	0.5369	0.5670
	100	100%	0.5207	0.5341	0.5350	0.5489
	150	100%	0.523	0.5352	0.5350	0.5460
ED_{30}	30	100%	0.5342	0.5624	0.5611	0.5899
	100	100%	0.5455	0.5594	0.5596	0.5742
	150	100%	0.5495	0.5606	0.5607	0.5722
ED_{50}	30	100%	0.5918	0.6339	0.6291	0.6670
	100	100%	0.6139	0.6378	0.6346	0.6570
	150	100%	0.6191	0.6364	0.6346	0.6518
ED_{70}	30	100%	0.5541	0.5969	0.5975	0.6398
	100	100%	0.5795	0.6012	0.6010	0.6223
	150	100%	0.5807	0.5990	0.5996	0.6178
ED_{90}	30	100%	0.6657	0.7178	0.7196	0.7693
	100	100%	0.6917	0.7156	0.7177	0.7407
	150	100%	0.6984	0.7203	0.7207	0.7392

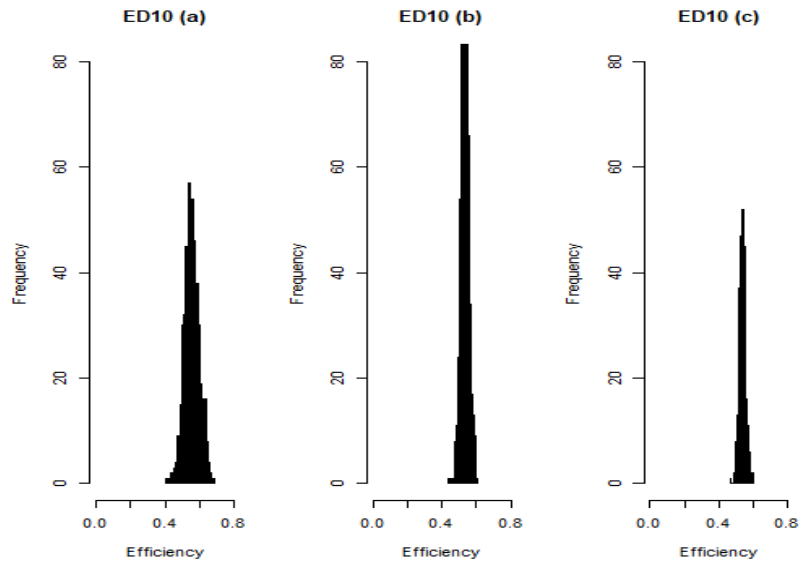

Figure 12: Histograms of c-efficiencies of the two-stage c-optimal designs for estimating the ED_{10} when the proportions of first stage sample size are varied. In the 1000 times simulations, σ=0.1, the total sample size N = 300, α represents the proportion of the first stage sample size, N_1 represents the value of the first stage sample size. (a) α=1/10, that is N_1=30; (b) α=1/3, that is N_1=100; (c) α=1/2, that is N_1=150.

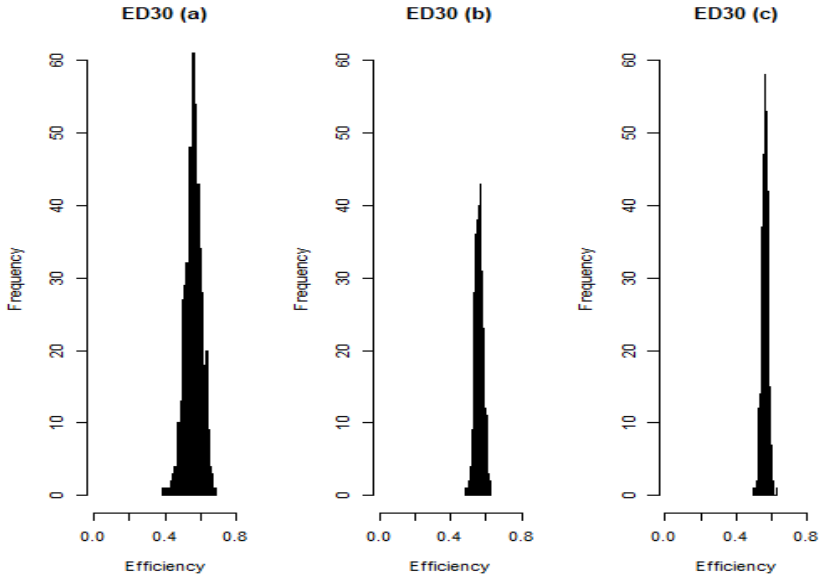

Figure 13: Histograms of c-efficiencies of the two-stage c-optimal designs for estimating the ED_{30} when the proportions of first stage sample size are varied. In the 1000 times simulations, σ=0.1, the total sample size N = 300, α represents the proportion of the first stage sample size, N_1 represents the value of the first stage sample size. (a) α=1/10, that is N_1=30; (b) α=1/3, that is N_1=100; (c) α=1/2, that is N_1=150.

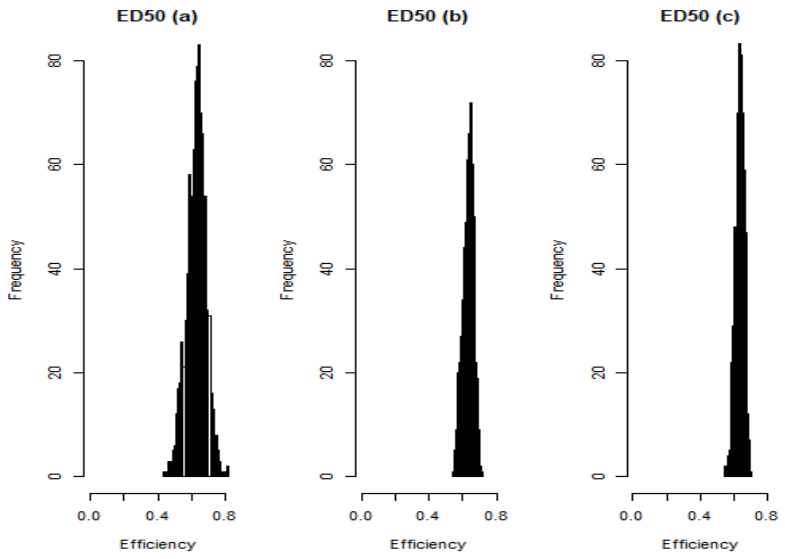

Figure 14: Histograms of c-efficiencies of the two-stage c-optimal designs for estimating the ED_{50} when the proportions of first stage sample size are varied. In the 1000 times simulations, σ=0.1, the total sample size N = 300, α represents the proportion of the first stage sample size, N1 represents the value of the first stage sample size. (a) α=1/10, that is N1=30; (b) α=1/3, that is N1=100; (c) α=1/2, that is N1=150.

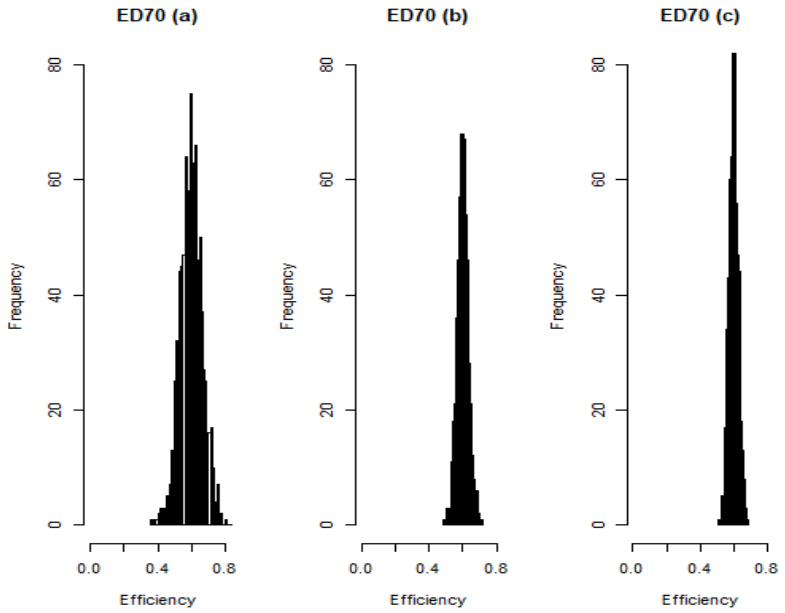

Figure 15: Histograms of c-efficiencies of the two-stage c-optimal designs for estimating the ED_{70} when the proportions of first stage sample size are varied. In the 1000 times simulations, σ=0.1, the total sample size N = 300, α represents the proportion of the first stage sample size, N1 represents the value of the first stage sample size. (a) α=1/10, that is N1=30; (b) α=1/3, that is N1=100; (c) α=1/2, that is N1=150.

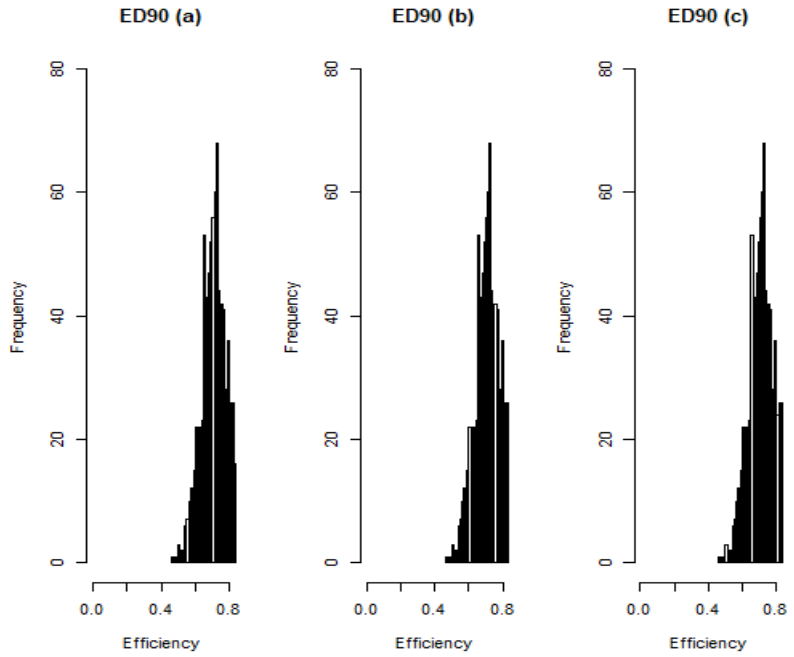

Figure 16: Histograms of c-efficiencies of the two-stage c-optimal designs for estimating the ED_{90} when the proportions of first stage sample size are varied. In the 1000 times simulations, σ=0.1, the total sample size N = 300, α represents the proportion of the first stage sample size, N_1 represents the value of the first stage sample size. (a) α=1/10, that is N_1=30; (b) α=1/3, that is N_1=100; (c) α=1/2, that is N_1=150.

Next, I run another 1000 times simulations by increasing the value of the σ to 0.5 to see how the success rate changes and how the two-stage c-optimal design performs.

Table 6 shows that after the σ value increase into 0.5, the success rates in each scenario become lower compare with full success rate when σ is 0.1. Overall, when N_1 is 30, the success rate is relatively low as 65%, when N_1 increases into 150, the success rate becomes as high as 96%. This seems reasonable because larger σ represents larger variation in the responses. When there are wider variations in the response, it is hard to estimate parameters accurately with small sample size. The success rate becomes higher by increasing N_1 but we cannot expect the same increase in the c-efficiency because the number of the subjects assigned the augmented c-optimal design at the second stage becomes smaller. Similarly, the performance of the two-stage c-optimal design remains fairly well with a slight decreases in efficiencies. Figure 17, 18, 19, 20,

and 21 show the histograms of c-efficiencies of the two-stage c-optimal designs for estimating the ED_{10}, ED_{30}, ED_{50}, ED_{70}, and ED_{90} with varied values of the proportion of the first stage sample size after set σ into 0.5. See the Table and Figures as follows:

Table 6: Success rate and summary statistics of c-efficiencies of the two-stage c-optimal design for estimating multiple $\mathrm{ED}_p s$ (ED_{10}, ED_{30}, ED_{50}, ED_{70}, and ED_{90}) with varied values of first stage sample size (30, 100, and 150) under σ=0.5.

ED_p	N1	Success Rate	25% Quartile	Median	Mean	75% Quartile
ED_{10}	30	64.80%	0.4096	0.5010	0.4604	0.5546
	100	87.90%	0.4760	0.5148	0.5046	0.5372
	150	94.90%	0.4890	0.5005	0.4952	0.5089
ED_{30}	30	64.90%	0.5778	0.5852	0.5479	0.5952
	100	90.60%	0.5479	0.5582	0.5583	0.5612
	150	94.40%	0.5180	0.5341	0.5407	0.5506
ED_{50}	30	66.60%	0.5822	0.6012	0.5904	0.6632
	100	66.60%	0.5606	0.5887	0.5777	0.6402
	150	95.50%	0.5596	0.5981	0.5844	0.6099
ED_{70}	30	66.80%	0.4398	0.5386	0.4951	0.5949
	100	90.30%	0.5422	0.5849	0.5598	0.5932
	150	95.90%	0.5467	0.5694	0.5547	0.5741
ED_{90}	30	64.80%	0.4500	0.6215	0.5654	0.6975
	100	88.70%	0.5933	0.6866	0.6406	0.7044
	150	94.50%	0.6214	0.6594	0.6410	0.6893

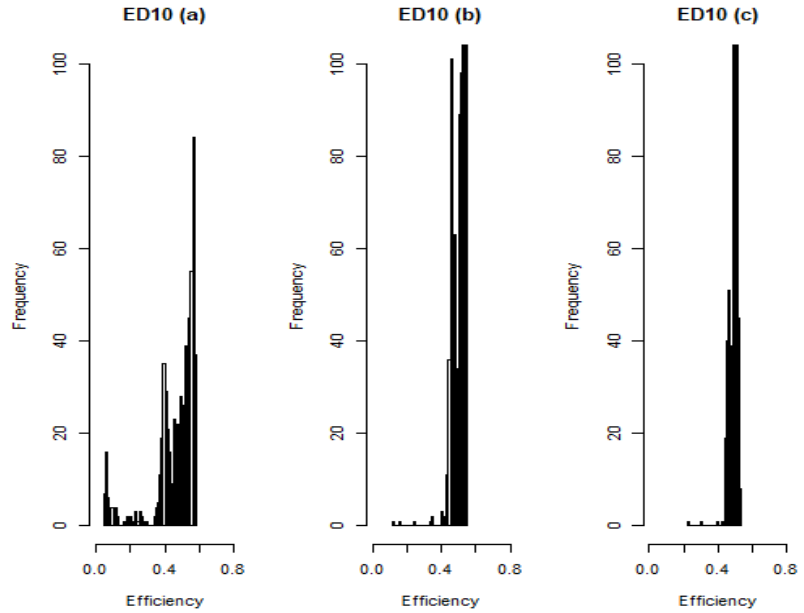

Figure 17: Histograms of c-efficiencies of the two-stage c-optimal designs for estimating the ED_{10} when the proportions of first stage sample size are varied. In the 1000 times simulations, σ=0.5, the total sample size N = 300, α represents the proportion of the first stage sample size, N_1 represents the value of the first stage sample size. (a) α=1/10, that is N1=30; (b) α=1/3, that is N_1=100; (c) α=1/2, that is N_1=150.

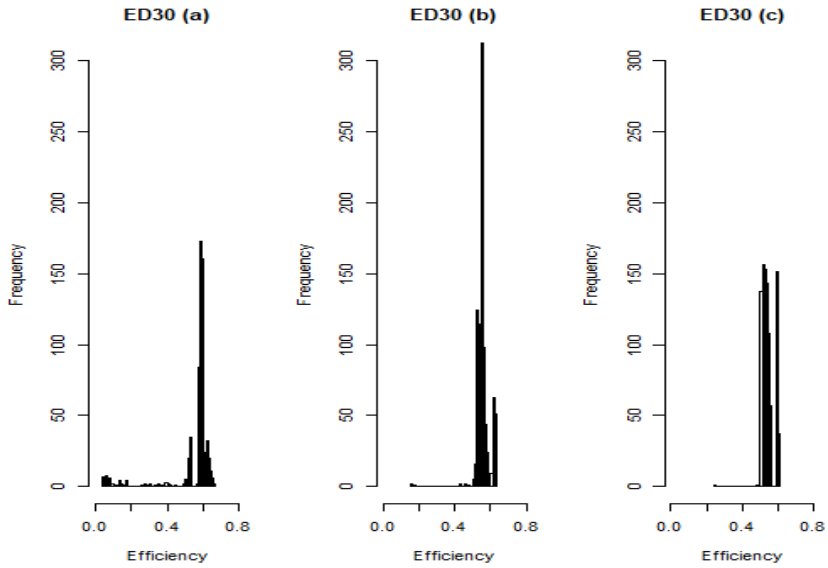

Figure 18: Histograms of c-efficiencies of the two-stage c-optimal designs for estimating the ED_{30} when the proportions of first stage sample size are varied. In the 1000 times simulations, σ=0.5, the total sample size N = 300, α represents the proportion of the first stage sample size, N_1 represents the value of the first stage sample size. (a) α=1/10, that is N_1=30; (b) α=1/3, that is N_1=100; (c) α=1/2, that is N_1=150.

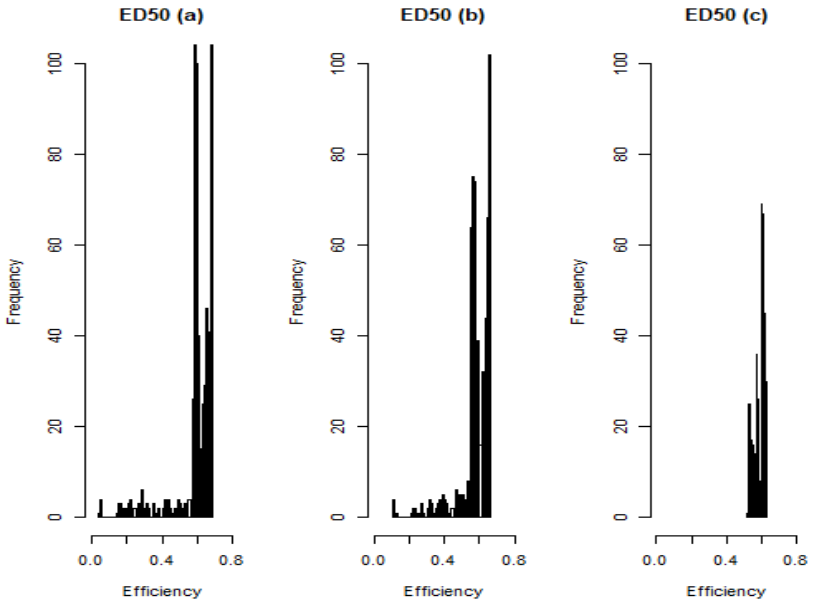

Figure 19: Histograms of c-efficiencies of the two-stage c-optimal designs for estimating the ED_{50} when the proportions of first stage sample size are varied. In the 1000 times simulations, σ=0.5, the total sample size N = 300, α represents the proportion of the first stage sample size, N_1 represents the value of the first stage sample size. (a) α=1/10, that is N_1=30; (b) α=1/3, that is N_1=100; (c) α=1/2, that is N_1=150.

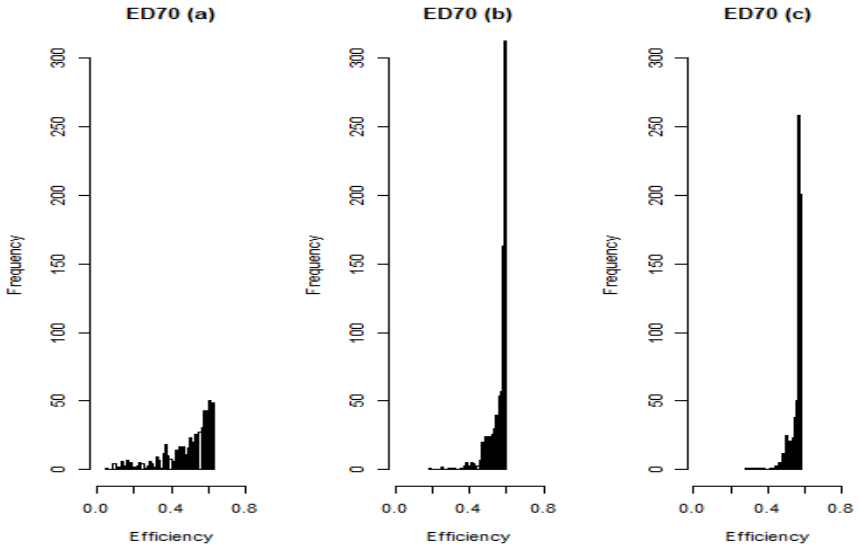

Figure 20: Histograms of c-efficiencies of the two-stage c-optimal designs for estimating the ED_{70} when the proportions of first stage sample size are varied. In the 1000 times simulations, σ=0.5, the total sample size N = 300, α represents the proportion of the first stage sample size, N_1 represents the value of the first stage sample size. (a) α=1/10, that is N_1=30; (b) α=1/3, that is N_1=100; (c) α=1/2, that is N_1=150.

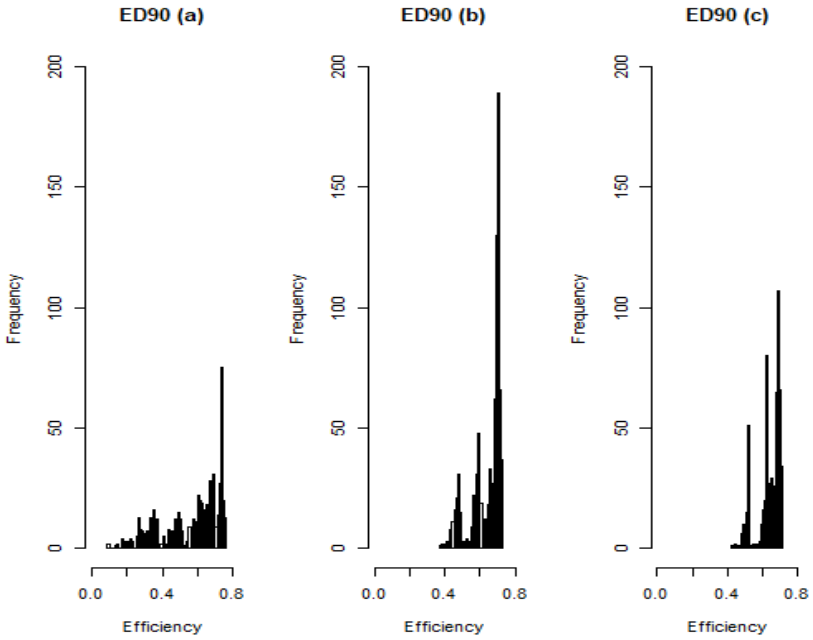

Figure 21: Histograms of c-efficiencies of the two-stage c-optimal designs for estimating the ED_{90} when the proportions of first stage sample size are varied. In the 1000 times simulations, σ=0.5, the total sample size N = 300, α represents the proportion of the first stage sample size, N_1 represents the value of the first stage sample size. (a) α=1/10, that is N_1=30; (b) α=1/3, that is N_1=100; (c) α=1/2, that is N_1=150.

4.2. Adaptive Bayesian C-optimal Design

The other two-stage optimal design to address the parameter uncertainty is applying the Bayesian paradigm at the second stage (Dette, 1996; Albert, 2009). Instead of using a single set of the parameters, the Bayesian approach considers the design incorporated with a prior probability for the parameters. In this study, since our goal is to study the target dose ED_p, we adopt the Bayesian c-optimality, which minimizes the weighted average of the variance for estimating ED_p (Atkinson and Donev, 1992):

$$\Psi_{Ba.c} = \sum_{i=1}^{m} P(\Theta_i)\mathrm{Var}(\widehat{\mathrm{ED}}_p|\Theta_i),$$

where $P(\Theta_i)$ denotes the prior probability given to Θ_i, and $\sum_{i=1}^{m} P(\Theta_i)$=1. If there is no prior knowledge of the probability $P(\Theta_i)$ and all values of the parameters are considered equally important, one can simply set $P(\Theta_i) = \frac{1}{m}$. The fact is that the Bayesian optimal design truly

depends on the prior distribution of the parameters. To reduce the prior dependency, the adaptive Bayesian optimal design is studied (McCallum and Bornkamp, 2015).

The idea of the adaptive Bayesian optimal design is similar with two-stage optimal design. In the first stage, a small proportion of the subjects is assigned to a fixed design such as uniform design. In the second stage, the posterior distribution of the model parameters is obtained based on the prior distribution and the information that is collected from the first stage. Next, the generated posterior distribution is incorporated into the Bayesian optimality.

Two challenges to construct adaptive Bayesian optimal design at the second stage are: (1) computing the undefined posterior distribution; (2) heavy numerical evaluations of the optimal criterion. In order to consider conservative performance of the adaptive Bayesian optimal design, the Jefferys prior distribution which is non-informative prior is used: $P(\Theta) = |M(\xi_1; \Theta)|^{1/2}$, where $\xi_1$is the fixed design at the first stage. Due to the Jeffreys prior distribution is used, the posteriors distribution becomes undefined. In this paper, we simulate draws by using Markov Chain Monte Carlo with M-H algorithm to generate 10,000 samples with 1000 burn-in from the posterior distribution for the parameters. In the numerical searching, the uniform design with four design points in the dose range [0,8] is used in the first stage, and a small sample size of 40 subjects are assigned into the uniform design. Under the 4PL model, let $\sigma^2 = \sqrt{2}$, and $\Theta = (0, -1.7, 4, 5)$. Since the c-optimal design under 4PL does not depend on θ_1 and θ_2, we focus on generating the posterior distributions for θ_3 and θ_4. Based on the collected information from the first stage, the sample size of 9000 for θ_3 and θ_4 are generated and their histogram and density plots are given in Figure 22. The adaptive Bayesian c-optimal designs using the sampling parameters from the posterior distribution are obtained in the following sections.

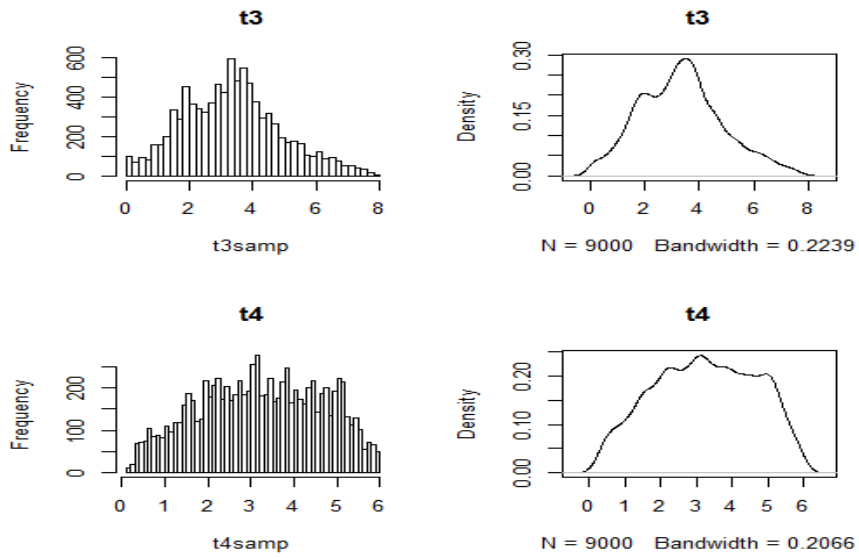

Figure 22: Histogram and density plots of the posterior distributions for θ_3 and θ_4. t3 represents the parameter θ_3 and t4 represents the parameter θ_4. Sample size of 10,000 with 1000 burn-in.

4.2.1. Bayesian C-optimal Design for Estimating ED_{50} under Full Posterior Distribution

For simplicity, in this study I start from searching an adaptive Bayesian c-optimal design for estimating the ED_{50}, which minimizes the weighted average of the variance for estimating the ED_{50}. The directional derivative of the Bayesian c-optimality criterion in equation leads to the sensitivity function as below:

$$\sum_{i=1}^{m} \lambda_i \frac{\{ f^T(x, \Theta_i) M(\xi_{Ba.c}; \Theta_i)^{-} ED'_{50}\}^2}{[ED'_{50}]^T M(\xi_{Ba.c}; \Theta_i)^{-} ED'_{50}} \leq 1$$

Where λ_i is the weight of each set of the Θ_i and is set to be $\frac{1}{m}$ with m sampling draws. Again, by the Equivalence Theorem, the equal sign holds if, and only if, x is one of the dose levels in the adaptive Bayesian c-optimal design $\xi_{Ba.c}$.

9000 parameter samples from the posterior distribution requires computation of 9000 evaluations of the Fisher information matrix to evaluate the criterion for one design. It is time-

consuming to complete the whole iterations. As an illustration study, we randomly select size of 200 samples out of the 9000 samples to obtain the adaptive Bayesian c-optimal design for estimating the ED_{50}. The Bayesian optimal design is searched by the modified YBT algorithm and verified by the Equivalence Theorem in Figure 23. The adaptive Bayesian c-optimal design for estimating the ED_{50} by using the 200 sample parameters from the posterior distribution is given by:

$$\xi_{Ba.c} = \begin{pmatrix} .0001, & .01, & .42, & 1.28, & 1.68, & 2.20, & 3.86, & 7.99 \\ 0.02, & 0.03, & 0.12, & 0.03, & 0.07, & 0.20, & 0.31, & 0.22 \end{pmatrix}.$$

One can observe that the adaptive Bayesian c-optimal design for estimating the ED_{50} contains eight design points including the lower bound and the upper bound of dose levels.

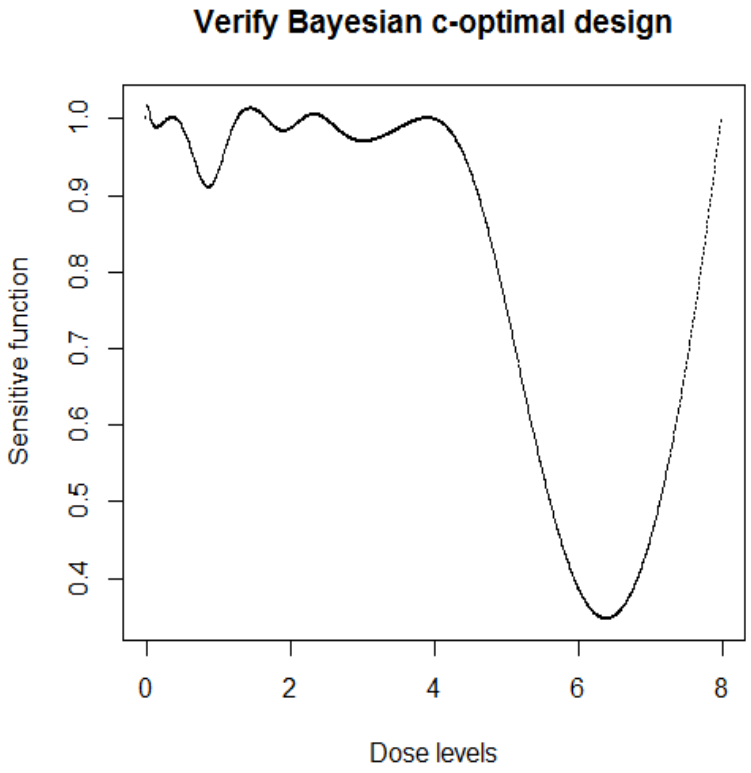

Figure 23: Plots of the sensitivity function of adaptive Bayesian c-optimal design for estimating the ED_{50} by using the sample size of 200 that randomly draw from posterior distribution.

4.2.2. K-means, Kernel K-means, and Fuzzy C-means Clustering Methods

McCallum and Bornkamp (2015) proposed an efficient alternative to reduce the laborious evaluations by adopting K-means clustering method instead of using full posterior samples and they also proved that the K-means clustering provided good theoretically approximations when number of clusters $k = 10$. In this study, we classify $m = 9000$ samples into $k = 10$ clusters using k-means clustering algorithm to conduct the adaptive Bayesian c-optimal design for estimating the ED_{50}. In this scenario, the λ_i in the Bayesian c-optimality equation becomes the weight of each clusters, which is the proportion of the samples associate with each cluster center. As a comparison, Kernel K-means and Fuzzy c-means clustering methods are also studied in searching the optimal design compare with the one based on the full posterior distribution. For simplicity, the Kernel K-means and Fuzzy c-means also use k=10 clusters. K-means, Kernel K-means, and Fuzzy c-means clustering can be easily computed by kmeans(), kkmeans() and cmeans() in R.

The adaptive Bayesian c-optimal design for estimating the ED_{50} using K-means, Kernel K-means, and Fuzzy c-means clustering methods are given in Table 7. All the optimal designs are verified by the General Equivalence Theorem. From Table 7, we can state that all the three designs contain eight design points include lower bound and upper bound of the dose level range.

Table 7: Adaptive Bayesian c-optimal designs for estimating the ED_{50} by using different clustering methods.

Clustering methods	$\xi_{Ba.c}$
K-means	$\xi_{Ba.c.K} = \begin{pmatrix} .0001, & .98, & 1.46, & 2.27, & 2.49, & 4.05, & 5.40, & 7.99 \\ 0.11, & 0.06, & 0.03, & 0.20, & 0.05, & 0.24, & 0.10, & 0.22 \end{pmatrix}$
Kernel K-means	$\xi_{Ba.c.KK} = \begin{pmatrix} .0001, & .04, & .97, & 1.64, & 2.16, & 2.61, & 4.49, & 7.99 \\ 0.9, & 0.04, & 0.02, & 0.09, & 0.07, & 0.18, & 0.28, & 0.22 \end{pmatrix}$
Fuzzy c-means	$\xi_{Ba.c.FC} = \begin{pmatrix} .0001, & .54, & 1.49, & 2.46, & 2.67, & 4.34, & 4.63, & 7.99 \\ 0.11, & 0.02, & 0.12, & 0.12, & 0.10, & 0.22, & 0.07, & 0.23 \end{pmatrix}$

$\xi_{Ba.c.K}$ represents the adaptive Bayesian c-optimal design with K-means clustering; $\xi_{Ba.c.KK}$ represents the adaptive Bayesian c-optimal design with Kernel K-means clustering; $\xi_{Ba.c.FC}$ represents the adaptive Bayesian c-optimal design with Fuzzy c-means clustering.

For further investigation of the obtained design performances, we compute the design efficiencies for the cases using the posterior, K-means, Kernel K-means, and Fuzzy c-means. I use the 9000 parameter samples and compute the design efficiencies under the selected sample parameters. Here the same dose range and the parameters values Θ_2 are used. As a comparison, the traditional designs such as uniform design and D-optimal design are studied. For illustrative purposes, I use the 8 points uniform design, U1, and the 8 points uniform design with Bayesian optimal weights, U2. Bayesian technique is adopted when search the Bayesian optimal weights to enhance the performance of the 8 points uniform design. To find the Bayesian optimal weights for the 8 points uniform design, I maximizes the Bayesian c-optimal criterion function over the weights for the given 8 design points. In addition, I am interested in checking how the two-stage c-optimal design works for various nominal parameter values, thus, the two-stage c-optimal design is included into the design comparison to see how it performs under the 9000 sampling parameters. The two-stage c-optimal design for estimating the ED_{50} is obtained under: σ=0.1, $\Theta = \Theta_2 = (0, -1.7, 4, 5)$, and the proportion of the first stage sample size α=0.3. Figure 24 and

25 show the histogram plots of the c-efficiencies for the five obtained designs and the three comparison designs. The summary statistics of 25% quartile, median, mean, and 75% quartile of the design efficiencies are provided in Table 8.

From the histogram plots and the summary statistics table, I note that there are very slight differences among the four adaptive Bayesian c-optimal designs and the uniform design with Bayesian optimal weights when estimating the ED_{50}. One potential reason that the uniform design with Bayesian optimal weights performs as well as the Bayesian optimal designs could be that it contains 8 equally spaced design points which is very close to the Bayesian optimal designs. If we reduce the 8 uniform design points to 5 or 6 design points, the uniform design with Bayesian optimal weights would perform much more poorly.

As expected, the two-stage c-optimal design for estimating the ED_{50} works worse compared with the Bayesian optimal designs and uniform design with Bayesian optimal weights. The mean efficiency of the two-stage c-optimal design is around 7% lower and its lower quartile is much lower. This implies the two-stage c-optimal design is not as robust as Bayesian c-optimal design and the uniform design with Bayesian optimal weights for mis-specified parameter values. Table 8 shows that the median and the mean design efficiencies for the Bayesian designs and uniform design with the Bayesian optimal weights are around 10% higher than the traditional uniform design, and 20% higher than the D-optimal design.

Overall, one can conclude that after reducing the parameter dependency, the adaptive Bayesian c-optimal designs still work better than the traditional uniform design and D-optimal design, as well as the two-stage c-optimal design. The table and plots are as follows:

Table 8: Summary statistics of the efficiencies of the designs for estimating the ED_{50} under the 9000 Θs.

Designs	25% quartile	Median	Mean	75% quartile
$\xi_{Ba.c}$	0.4981	0.5931	0.5763	0.6601
$\xi_{Ba.c.K}$	0.4996	0.5763	0.5596	0.6189
$\xi_{Ba.c.KK}$	0.5074	0.5704	0.5696	0.6327
$\xi_{Ba.c.FC}$	0.5062	0.5777	0.5723	0.6438
$\xi_{Two-stage}$	0.3219	0.4762	0.5022	0.6662
ξ_{U2}	0.5018	0.5800	0.5668	0.6382
ξ_{U1}	0.4481	0.4775	0.4739	0.5026
ξ_{D}	0.1388	0.3855	0.3649	0.5890

$\xi_{Ba.c}$ represents the Bayesian c-optimal design with full posterior distribution method; $\xi_{Ba.c.K}$ represents the Bayesian c-optimal design with K-means clustering method; $\xi_{Ba.c.KK}$ represents the Bayesian c-optimal design with Kernel K-means clustering method; $\xi_{Ba.c.FC}$ represents the Bayesian c-optimal design with Fuzzy c-means clustering method; $\xi_{Two-stage}$ represents the two-stage c-optimal design; ξ_{U1} represents the 8 points uniform design; ξ_{U2} represents the 8 points uniform design with Bayesian optimal weights; ξ_{D} represents the D-optimal design.

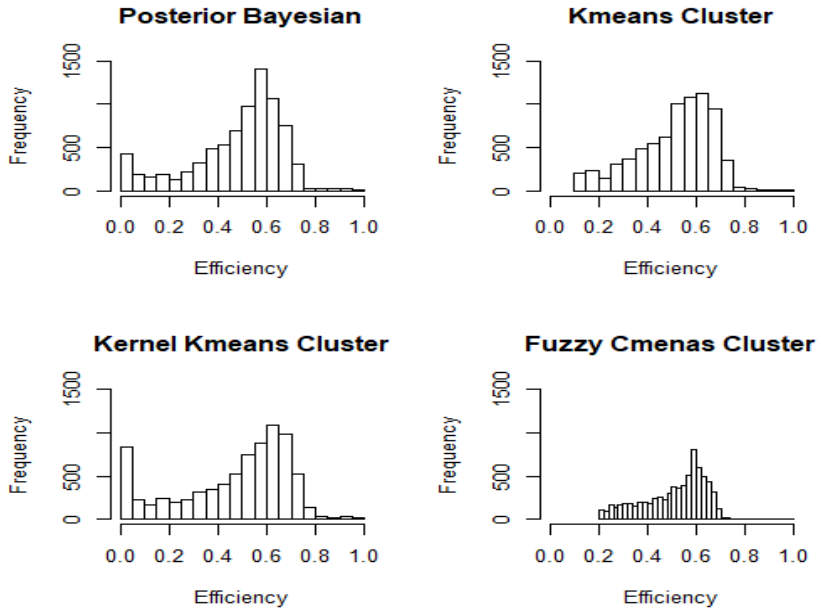

Figure 24: Histograms of c-efficiencies of the Bayesian c-optimal designs for estimating the ED_{50} using full posterior, K-means, Kernel K-means, and Fuzzy C means, under the 9000 Θs.

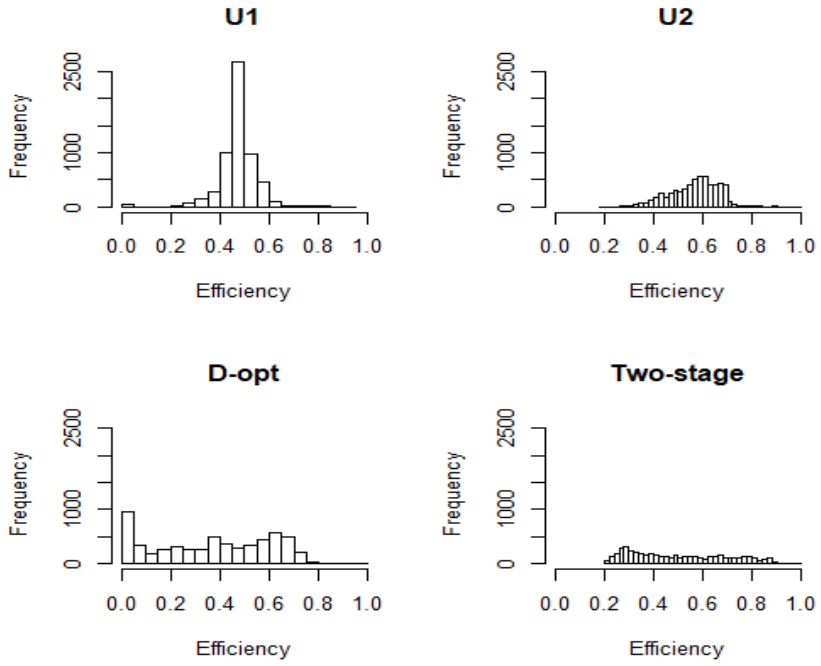

Figure 25: Histograms of c-efficiencies of the uniform designs, D-optimal design, and two-stage c-optimal design for estimating the ED_{50} under the 9000 Θs. U1 represents the 8 points the uniform design; U2 represents the 8 points uniform design with Bayesian optimal weights for estimating ED_{50}; D-opt represents the D-optimal design for estimating ED_{50}; Two-stage represents two-stage c-optimal design for estimating the ED_{50}.

4.2.3. Adaptive Bayesian C-optimal Design for Estimating Multiple $ED_p s$

From the last section, we know that K-means, Kernel K-means, and Fuzzy c-means perform similarly compared with the full posterior method. For simplicity, we use the K-means algorithm to extend the research in searching the adaptive Bayesian c-optimal design for estimating multiple $ED_p s$. The sensitivity function can be updated from the Bayesian c-optimality sensitivity equation by summarizing the multiple values of ED_p:

$$\sum_{i=1}^{k} \lambda_i \sum_{j=1}^{l} w_j \frac{\left\{ f^T(x,\Theta_i) M(\xi_{Ba.c};\Theta_i)^{-} ED'_j \right\}^2}{\left[ED'_j \right]^T M(\xi_{Ba.c};\Theta_i)^{-} ED'_j} \leq 1,$$

where l is the number of $ED_p s$, k is the number of the clusters, λ_i represents the weight of each cluster, and w_j represents the weight of each ED_p. Here we set $l = 5$ and $k = 10$.

Again, by the Equivalence Theorem, the equal sign holds if, and only if, x is one of the dose levels in the adaptive Bayesian c-optimal design, $\xi_{Ba.c}$. The modified YBT algorithm is applied to search the design for estimating multiple $\mathrm{ED}_p s$ $(\mathrm{ED}_{10}, \mathrm{ED}_{30}, \mathrm{ED}_{50}, \mathrm{ED}_{70}, \mathrm{ED}_{90})$, $\xi_{Ba.c}$ as below:

$$\xi_{Ba.c} = \begin{pmatrix} .0001, & 0.23, & 1.04, & 1.6, & 2.56, & 2.75, & 3.7, & 5.03, & 5.25, & 7.99 \\ 0.08, & 0.07, & 0.04, & 0.13, & 0.16, & 0.03, & 0.15, & 0.13, & 0.03, & 0.18 \end{pmatrix}.$$

$\xi_{Ba.c}$ is verified by General Equivalence Theorem in Figure 26.

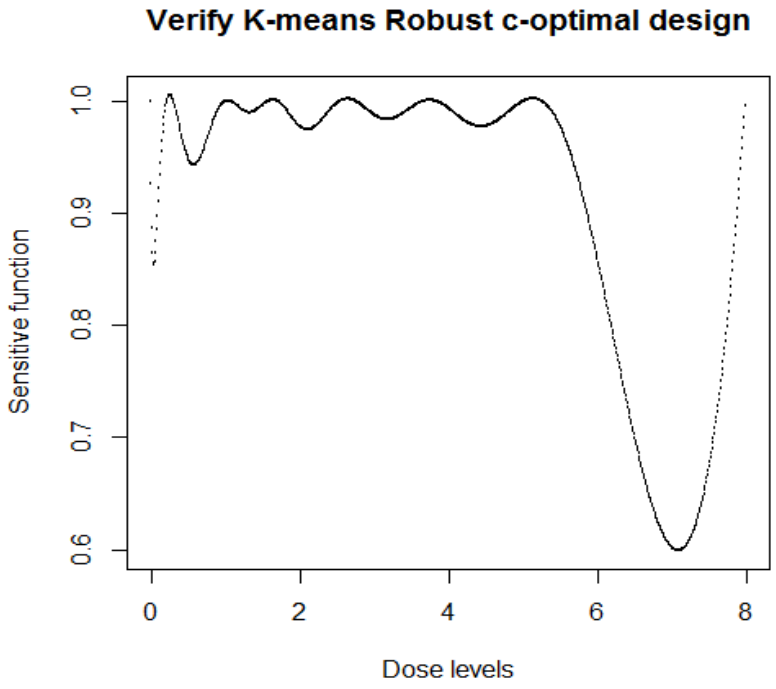

Figure 26: Plot of the sensitivity function of the adaptive Bayesian c-optimal design for estimating multiple ED_ps $(\mathrm{ED}_{10}, \mathrm{ED}_{30}, \mathrm{ED}_{50}, \mathrm{ED}_{70}, \mathrm{ED}_{90})$ using K-means clustering.

I include five ED_ps to conduct the adaptive Bayesian c-optimal design, now I am interested in investigating the performance of the design for estimating other $\mathrm{ED}_p s$. Consider covering all the possible $\mathrm{ED}_p s$, I adopt the same ten $\mathrm{ED}_p s$ $(\mathrm{ED}_{10}, \mathrm{ED}_{20}, \mathrm{ED}_{30}, \mathrm{ED}_{40}, \mathrm{ED}_{50},$

ED_{60}, ED_{70}, ED_{80}, ED_{90}, and ED_{99}) to compute the design efficiencies. Since my goal is to conduct the adaptive Bayesian c-optimal design which reduces the parameter dependency, I randomly select ten sets of model parameters from the 9000 samples and check how the adaptive Bayesian c-optimal design works to estimate the ten $ED_p s$ under the 10 randomly selected parameter values. The randomly selected ten sets of model parameters are shown in Table 9 and the design efficiency plots are given in Figure 27, 28, and 29. In the c-efficiency computation, the adaptive Bayesian c-optimal design, the two uniform designs, and the D-optimal design are fixed design. Take estimating the ED_{10} under the model parameter $\Theta_1 = (0, -1.7, 2.6, 3.6)$ as an example. First, I search the c-optimal design for estimating the ED_{10} under Θ_1, then I compute the c-efficiency by using one of the fixed designs, for example, the adaptive Bayesian c-optimal design, against the c-optimal design. All the other design c-efficiencies are computed by the same procedure.

Table 9: Ten sets of model parameters randomly selected from the 9000 Θs.

Θ	
$\Theta_1 = (0, -1.7, 2.6, 3.6)$	$\Theta_6 = (0, -1.7, 2.4, 2.8)$
$\Theta_2 = (0, -1.7, 2.9, 4.8)$	$\Theta_7 = (0, -1.7, 2.8, 4.4)$
$\Theta_3 = (0, -1.7, 2.5, 4.0)$	$\Theta_8 = (0, -1.7, 2.9, 4.5)$
$\Theta_4 = (0, -1.7, 3.5, 3.1)$	$\Theta_9 = (0, -1.7, 2.1, 4.6)$
$\Theta_5 = (0, -1.7, 2.3, 4.6)$	$\Theta_{10} = (0, -1.7, 3.6, 3.2)$

Figure 27, 28, and 29 shows that the D-optimal design works the worst for estimating various $ED_p s$ under the ten sets of the model parameters. At some point, it works better than other designs, for example, the efficiency of D-optimal design for estimating the ED_{40} is around 0.8 (see Figure 27), but overall the efficiency is low and inconsistent. The 8 points uniform

design works reasonably well, but its efficiencies are always lower than the adaptive Bayesian c-optimal design.

Compared with the 8 points uniform design and the D-optimal design, the efficiency lines of the adaptive Bayesian c-optimal design and 8 points uniform design with Bayesian optimal weights are always on the top of the plots no matter how the values of p and the parameter values change. From the efficiency plots, one can conclude that for larger ED_p (ED_{10}, ED_{20}, ED_{30}, and ED_{40}), the Bayesian c-optimal design is better than the uniform design with the Bayesian optimal weights. For higher ED_p, sometimes Bayesian c-optimal design is better and sometimes not. Thus, if researcher wants to estimate wide range of the ED_p from low p to high p, the Bayesian c-optimal design is more robust. Besides both designs utilized the Bayesian technique, another possible reason for the two designs perform similarly could be the uniform design has very close 8 design points with the Bayesian design. As discussed in the previous Section, the design efficiency would decrease if reduce the uniform design points to 5 or 6 points.

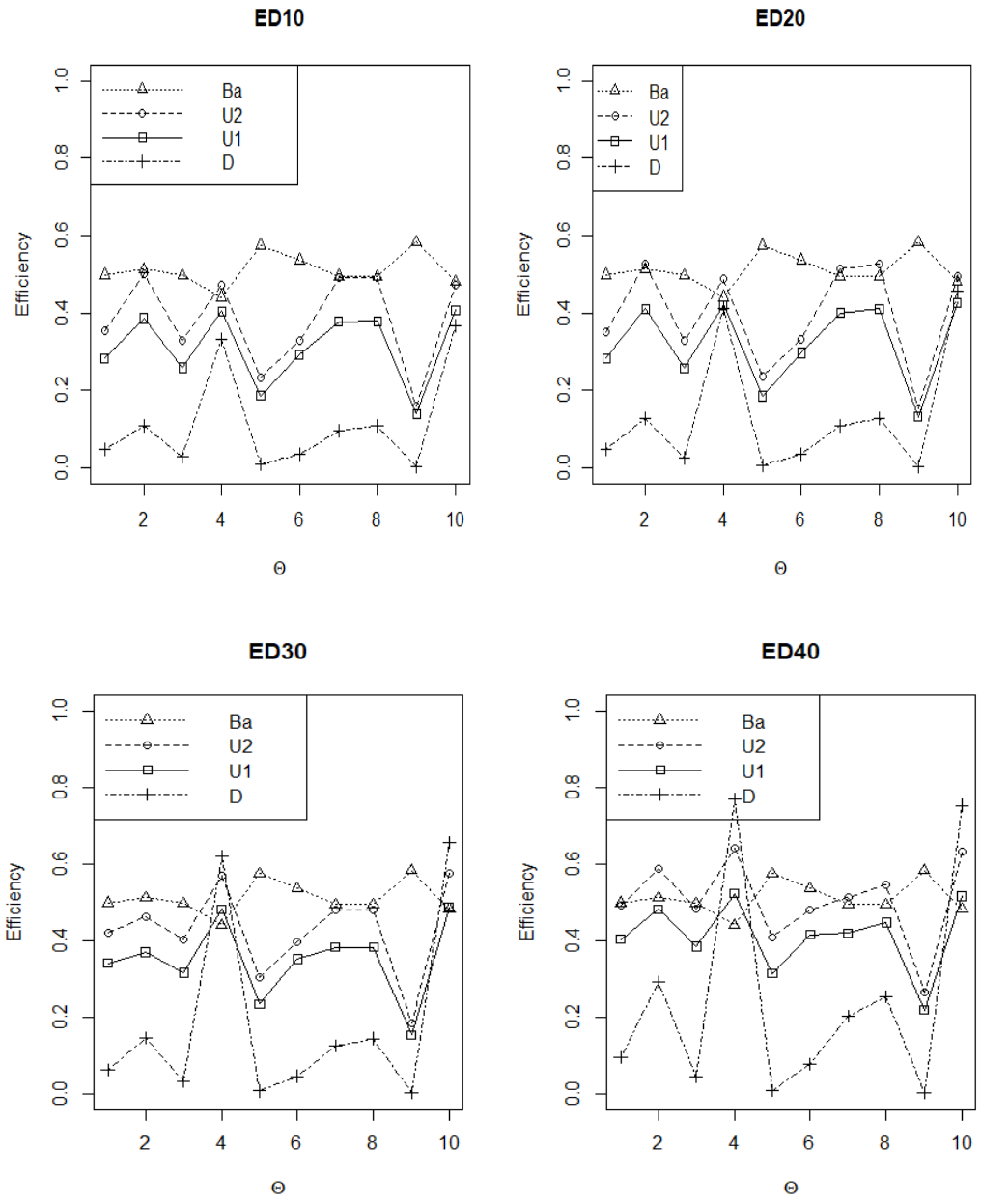

Figure 27: Efficiencies of the adaptive Bayesian c-optimal design, uniform designs and D-optimal design under ten sets of model parameters for estimating the $\mathrm{ED}_{10}, \mathrm{ED}_{20}, \mathrm{ED}_{30}$ and ED_{40} respectively. In the legend of the plots, the U1 represents the 8 points uniform design, U2 represents the 8 points uniform deign with Bayesian optimal weights, Ba represents the adaptive Bayesian c-optimal design, and D represents the D-optimal design under $\Theta = (0, -1.7, 4, 5)$.

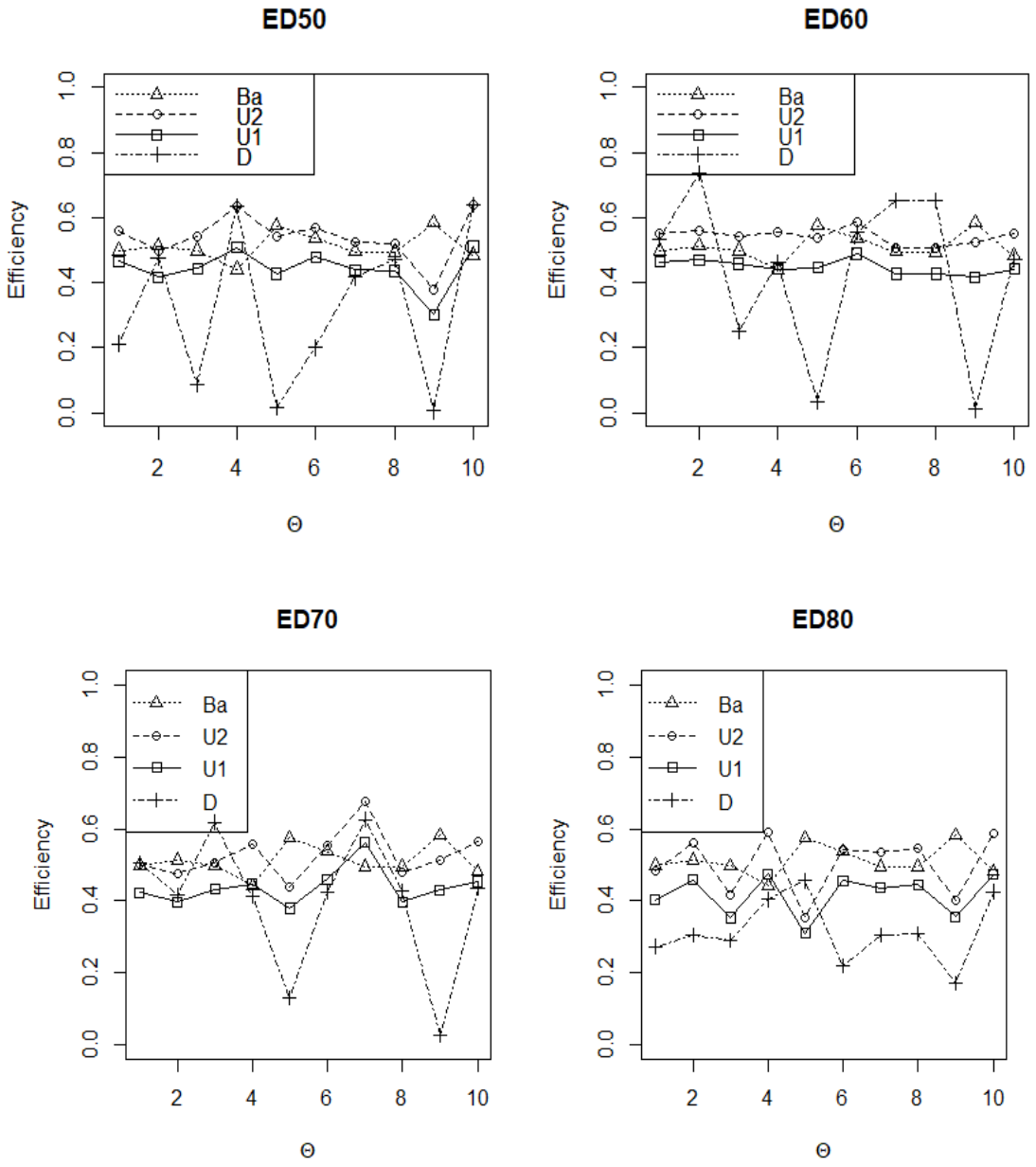

Figure 28: Efficiencies of the adaptive Bayesian c-optimal design, uniform designs and D-optimal design under ten sets of model parameters for estimating the ED_{50}, ED_{60}, ED_{70}, and ED_{80} respectively. In the legend of the plots, U1 represents the 8 points uniform design, U2 represents the 8 points uniform design with Bayesian optimal weights, Ba represents the adaptive Bayesian c-optimal design, and D represents the D-optimal design under $\Theta = (0, -1.7, 4, 5)$.

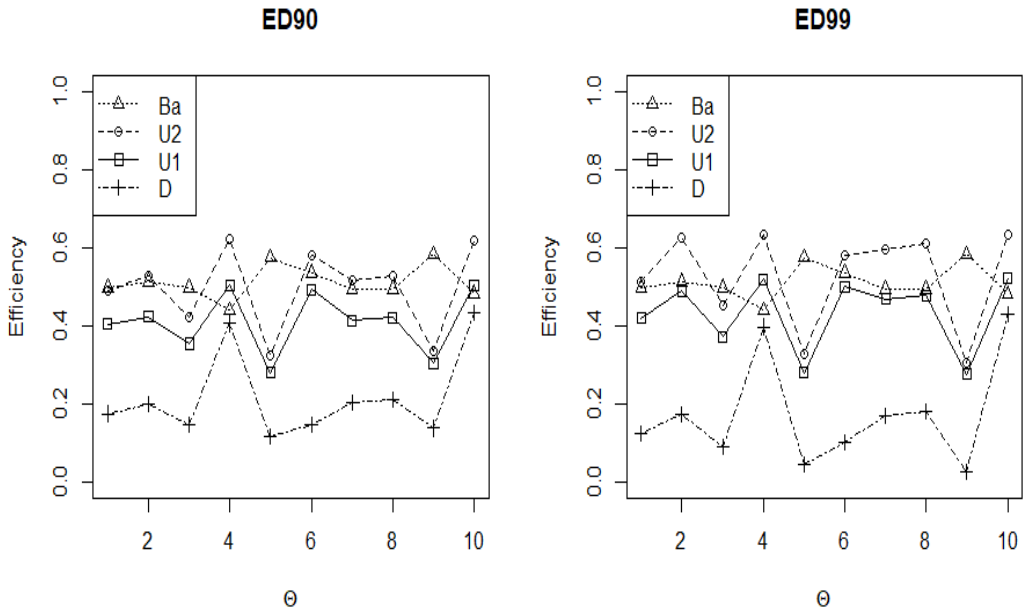

Figure 29: Efficiencies of the adaptive Bayesian c-optimal design, uniform designs and D-optimal design under ten sets of model parameters for estimating the ED_{90} and ED_{99} respectively. In the legend of the plots, U1 represents the 8 points uniform design, U2 represents the 8 points uniform deign with Bayesian optimal weights, Ba represents the adaptive Bayesian c-optimal design, and D represents the D-optimal design under $\Theta = (0, -1.7, 4, 5)$.

At this point, I compare the performance of the adaptive Bayesian c-optimal design (Ba), 8 points uniform design with Bayesian optimal weights (U2), and the two-stage c-optimal design (Two-stage) for estimating multiple $ED_p s$ under various parameter values. To see their design performance, I compute the c-efficiencies by using the 9000 sampling parameters for estimating the ED_{10}, ED_{30}, ED_{50}, ED_{70}, and ED_{90}, respectively. The two-stage c-optimal design (Two-stage) I choose to use here is the design under the set-up values: σ=0.1, $\Theta = (0, -1.7, 4, 5)$ and the proportion of the first stage sample size α=0.3. Again, as a comparison, the 8 points uniform design (U1) is included in the simulations. For each c-efficiency, I search the c-optimal design under one set of parameter value from the 9000 samples, and compute the c-efficiency of the proposed design such as the adaptive Bayesian c-optimal design against the c-optimal design.

For each design (Ba, Two-stage, U1, U2), this procedure repeats 9000 times until all the c-efficiencies are computed based on the 9000 parameter samples.

The summary statistics of 25% quartile, median, mean, and 75% quartile of the c-efficiencies are provided in Table 10. Histogram plots of the c-efficiencies of the four designs shown in Figure 30, 31, 32, 33, and 34.

Table 10: Summary statistics of c-efficiencies of the designs for estimating multiple $ED_p s$ ($ED_{10}, ED_{30}, ED_{50}, ED_{70}$, and ED_{90}) under σ=0.1.

ED_p	Designs	25% Quartile	Median	Mean	75% Quartile
ED_{10}	Ba	0.4030	0.4657	0.4656	0.5260
	Two-stage	0.3536	0.4835	0.4837	0.5817
	U2	0.3656	0.4387	0.4391	0.5111
	U1	0.3303	0.3763	0.3884	0.4654
ED_{30}	Ba	0.4715	0.5369	0.5203	0.5879
	Two-stage	0.4330	0.5579	0.5444	0.6621
	U2	0.4381	0.5349	0.5114	0.6049
	U1	0.3855	0.4671	0.4411	0.5122
ED_{50}	Ba	0.5216	0.5550	0.5526	0.5830
	Two-stage	0.4316	0.5540	0.5268	0.6511
	U2	0.5138	0.5666	0.5561	0.6074
	U1	0.4489	0.4783	0.4777	0.5032
ED_{70}	Ba	0.4916	0.5269	0.5314	0.5684
	Two-stage	0.3986	0.4907	0.4707	0.5396
	U2	0.4824	0.5375	0.5302	0.5820
	U1	0.4177	0.4534	0.4596	0.5049
ED_{90}	Ba	0.5059	0.5570	0.5553	0.6155
	Two-stage	0.2969	0.4342	0.4326	0.5489
	U2	0.4748	0.5737	0.5418	0.6204
	U1	0.4350	0.4918	0.4766	0.5469

Ba represents the adaptive Bayesian c-optimal design for estimating multiple $ED_p s$; Two-stage represents two-stage c-optimal design for estimating multiple $ED_p s$; U1 represents the 8 points uniform design; U2 represents the 8 points uniform design with Bayesian optimal weights for estimating multiple $ED_p s$.

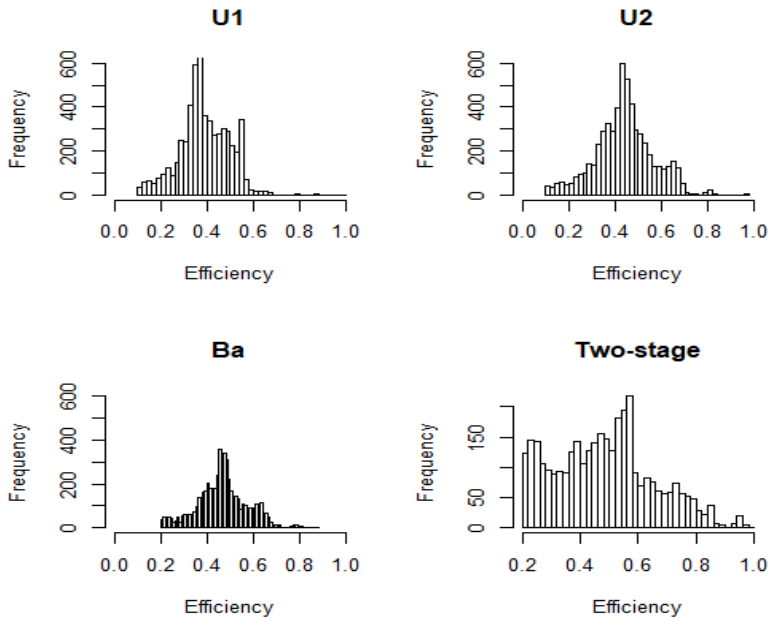

Figure 30: Histograms of c-efficiencies of the designs for estimating the ED_{10}. U1 represents the 8 points uniform design, U2 represents the 8 points uniform design with Bayesian optimal weights for estimating multiple $ED_p s$, Ba represents the adaptive Bayesian c-optimal design for estimating multiple $ED_p s$, Two-stage represents the two-stage c-optimal design for estimating multiple $ED_p s$.

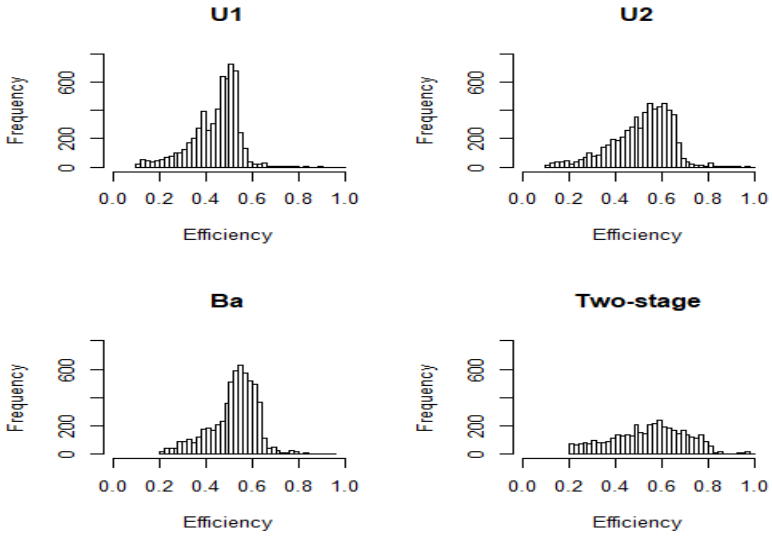

Figure 31: Histograms of c-efficiencies of the designs for estimating the ED_{30}. U1 represents the 8 points uniform design, U2 represents the 8 points uniform design with Bayesian optimal weights for estimating multiple $ED_p s$, Ba represents the adaptive Bayesian c-optimal design for estimating multiple $ED_p s$, Two-stage represents the two-stage c-optimal design for estimating multiple $ED_p s$.

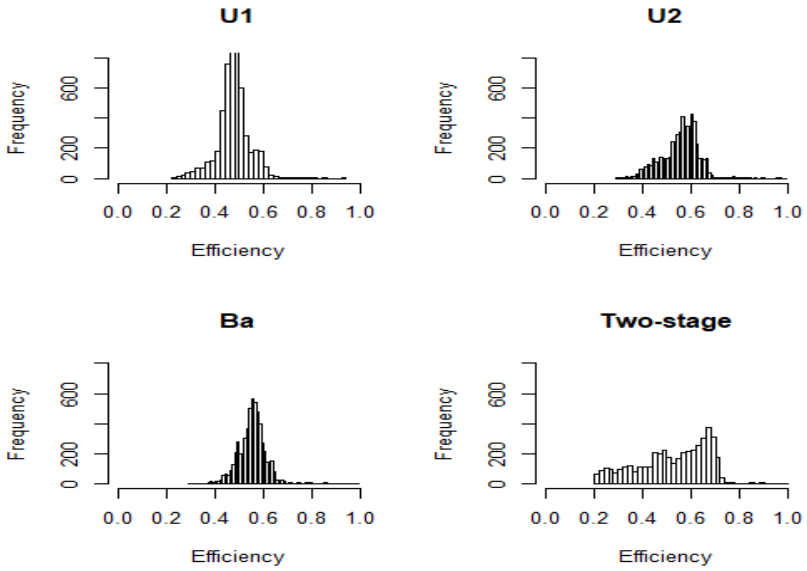

Figure 32: Histograms of c-efficiencies of the designs for estimating the ED_{50}. U1 represents the 8 points uniform design, U2 represents the 8 points uniform design with Bayesian optimal weights for estimating multiple $ED_p s$, Ba represents the adaptive Bayesian c-optimal design for estimating multiple $ED_p s$, Two-stage represents the two-stage c-optimal design for estimating multiple $ED_p s$.

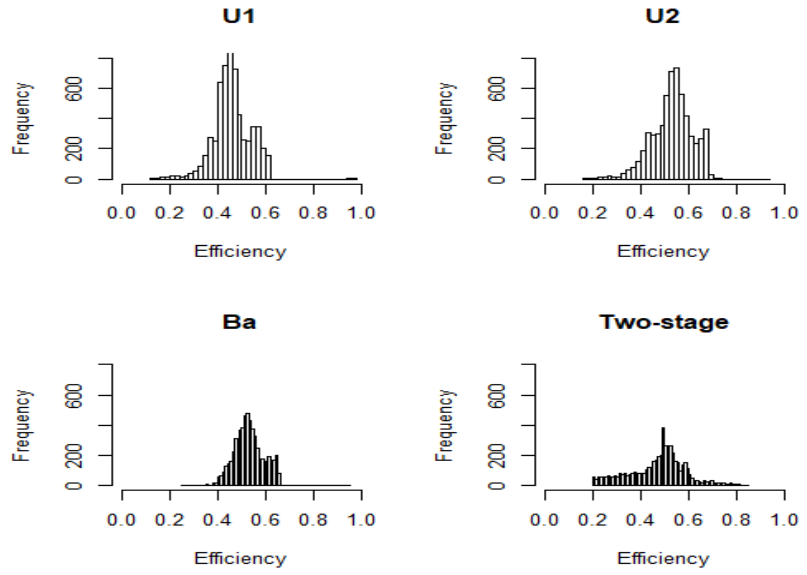

Figure 33: Histograms of c-efficiencies of the designs for estimating the ED_{70}. U1 represents the 8 points uniform design, U2 represents the 8 points uniform design with Bayesian optimal weights for estimating multiple $ED_p s$, Ba represents the adaptive Bayesian c-optimal design for estimating multiple $ED_p s$, Two-stage represents the two-stage c-optimal design for estimating multiple $ED_p s$.

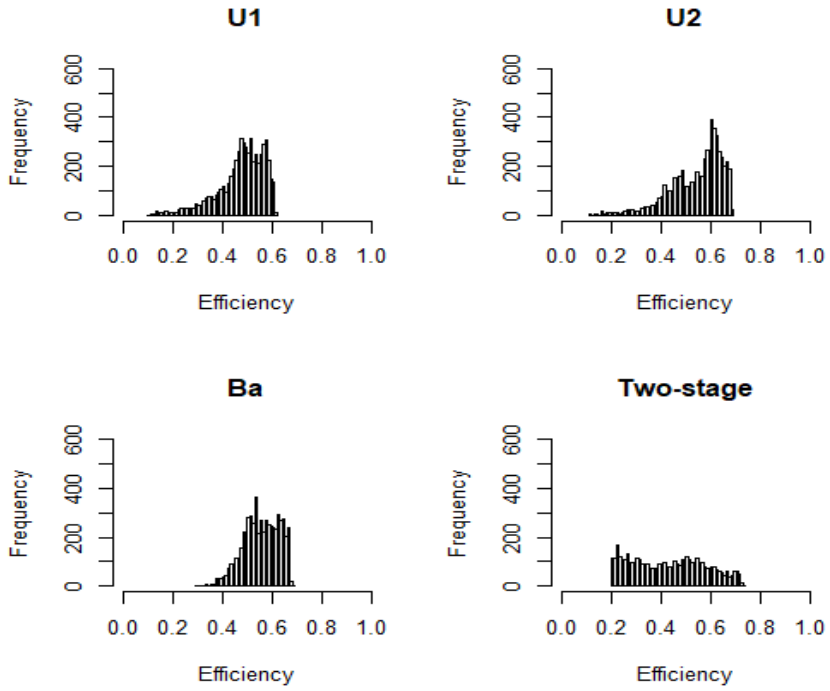

Figure 34: Histograms of c-efficiencies of the designs for estimating the ED_{90}. U1 represents the 8 points uniform design, U2 represents the 8 points uniform design with Bayesian optimal weights for estimating multiple $ED_p s$, Ba represents the adaptive Bayesian c-optimal design for estimating multiple $ED_p s$, Two-stage represents the two-stage c-optimal design for estimating multiple $ED_p s$.

Table 10 shows that when estimates of the ED_{10} and the ED_{30}, the mean efficiencies of the two-stage c-optimal design are slightly higher than the other designs in the simulation. While, for estimates of the ED_{50}, the ED_{70}, and the ED_{90}, adaptive Bayesian c-optimal design and the 8 points uniform design with Bayesian optimal weights work better than the two-stage c-optimal design. This suggests that two-stage c-optimal design sometimes works better, but sometimes not compared with the adaptive Bayesian c-optimal design. No significant difference is observed between the adaptive Bayesian c-optimal design and 8 points uniform design with Bayesian optimal weights, which further support our discussion in the previous sections. However, when we further investigate the two designs, the 25% quartile of the adaptive Bayesian c-optimal

design are always higher than the 8 points uniform design with Bayesian optimal weights. It suggests that the adaptive Bayesian c-optimal design is much safer to use when estimating wide range of the $\mathrm{ED}_p s$ since its worst case is always better than others. As expected, the traditional 8 points uniform design always works the worst with varied values of the ED_p and the mis-specified model parameters compared with the proposed optimal designs.

5. CONCLUSION

A key objective of dose-finding trials is often to study the dose-response curve or to estimate target dose levels of interest such as ED_p. In this research, the interest is in conducting the robust optimal design to estimate multiple target dose $\mathrm{ED}_p s$ and it works well for various nominal parameter values.

The robust c-optimal designs under the three sets of nominal model parameters are conducted. They work well for estimating multiple $\mathrm{ED}_p s$ under the assumed true value of parameters, however, the design performance reduces dramatically under the mis-specified values of model parameter, which indicates that the robust optimal design truly depends on the pre-specified model parameters.

To address the model parameter dependency, the adaptive optimal design for estimating multiple $\mathrm{ED}_p s$ taking into accounts the mis-specified nominal values of parameter is studied. Two types of the two-stage adaptive optimal designs are proposed to reduce the impact of parameter misspecification. One is the two-stage c-optimal design that incorporates the augmented design at the second stage; the other one is the adaptive Bayesian c-optimal design that uses the posterior distribution of the model parameter developed from the first stage.

To overcome the heavy computation issue in searching Bayesian optimal design using full posterior distribution, three clustering methods such as K-means, Kernel K-means, and Fuzzy c-means are utilized as alternative methods in constructing the Bayesian optimal design. Summary statistics of the simulation demonstrates that there is not much change observed in the Bayesian optimal design performance among the three clustering methods.

From the design efficiency plots over the varied sets of parameter values, one can observe that adaptive Bayesian c-optimal design and the uniform design with Bayesian optimal

weights work reasonable well for estimating the selected $\mathrm{ED}_p s$ compared with traditional uniform design and D-optimal design. However, a minimal difference exists between the adaptive Bayesian c-optimal design and the 8 points uniform design with Bayesian optimal weights. One potential reason as discussed earlier could be the uniform design with optimal weights has 8 equal spaced design points which are relatively close to the adaptive Bayesian c-optimal design points. Comparable results are found in the later computation of the c-efficiencies. The c-efficiency results demonstrate that the two-stage c-optimal design works slightly better when estimating lower value of ED_p (ED_{10} and ED_{30}); However, when estimating higher value of ED_p ($\mathrm{ED}_{50}, \mathrm{ED}_{70}$ and ED_{90}), Bayesian c-optimal design and uniform design with Bayesian optimal weights become better.

In summary, this research shows that both the proposed two-stage optimal designs work fairly well for estimating multiple $\mathrm{ED}_p s$ considering the model parameter uncertainty. Compare with the Bayesian c-optimal design, the two-stage c-optimal design sometimes works better, sometimes not. The Bayesian c-optimal design works similarly with the 8 points uniform design with Bayesian optimal weights, but when estimates wide range of the $\mathrm{ED}_p s$, the Bayesian c-optimal design is much safer to use because its worst case is always better than the other designs. Another result of note is that the uniform design with optimal weights employed the compounded c-optimality criteria technique and the Bayesian technique significantly enhanced the design performance compared with the traditional uniform design.

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APPENDIX. FLOWCHART FOR OPTIMAL DESIGN CONSTRUCTIONS