ROBUST c-OPTIMAL DESIGN FOR ESTIMATING THE ED_p

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ABSTRACT

Optimal design provides the most efficient design to study dose-response functions. It is common to adopt the four-parameter logistic model to describe the dose-response relationships in many dose finding trials. Under the four-parameter logistic model, optimal design to estimate the ED_p accurately is presented. The ED_p is the dose achieving $100p\%$ of the maximum treatment effect. C-optimal design works the best to estimate the ED_p, but the value of p must be predetermined in order to obtain the c-optimal design. Here we investigate the efficiency of c-optimal design to estimate the ED_p for different values of p and present robust c-optimal design that works well for the changes in the value of p. Five different values of p are considered in this study: ED_{10}, ED_{30}, ED_{50}, ED_{70}, and ED_{90}. The performance of the robust c-optimal design is obtained and compared to the c-optimal designs and traditional uniform designs.

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1. INTRODUCTION

A dose-response study is a fundamental part in clinical trials. A common objective for the dose-response study is to study dose-response relationships or to study a target dose level (such as MED and ED_p). Optimal design helps to maximize the information of such a study objective. It identities dose levels to be tested and how to allocate the subjects to the selected doses in the most efficient manner (Bretz, Dette and Pinheiro, 2010; Dragalin, Hsuan and Padmanabhan, 2007).

Optimal design is a branch of experimental designs. It provides the best design to study an interesting objective accurately with limited resources. 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 design for estimating the ED_p. Here, the ED_p is the dose level that achieves $100p\%$ of the maximum treatment effect within the observed dose range and p is given between 0 and 1 (Ting, 2006). For example, ED_{50} represents the dose level that generates 50% of the maximum response.

C-optimal design for estimating the ED_p minimizes the variance for estimating the ED_p. Here the value of p is given at the beginning of the study and it represents the target dose ED_p to be estimated. One question we have here is the performance of c-optimal design for estimating the ED_p for the changes in the value of p. For example, does the c-optimal design for estimating the ED_{50} perform well for estimating ED_{10}, ED_{30}, ED_{70} or ED_{90}? Bretz, Dette, and Pinheiro (2010) states that c-optimal design for estimating the ED_p for one specific model (E_{max} model) does not depend on the value of p. However, it might not be true for different models. In this paper, we study the sensitivity of the c-optimal design for estimating the ED_p on the value of p

under the four-parameter logistic model. Also, we present robust c-optimal design for estimating the ED_p that works well for the changes in the value of p.

We consider a flexible model to describe dose-response relationships. In this paper, the four-parameter logistic model is employed (Dragalin, Hsuan, and Padmanabhan, 2007). The four-parameter logistic model is a frequently used non-linear model in dose-response study to describe a sigmoid shaped curve. Under the four-parameter logistic model, c-optimal designs for estimating the ED_p are studied.

In Chapter 2, basic knowledge to study optimal design is described. The four-parameter logistic model and the Fisher information matrix under the model is presented in Chapter 3. In Chapter 4, c-optimal designs for estimating the ED_p and the robust c-optimal design for estimating the ED_p for the changes in the values of p are derived. Their performance are obtained and compared in Chapter 5. We discuss the conclusion in Chapter 6.

2. BACKGROUND

2.1. Optimal Design

When researchers conduct experimental designs, they are often interested in obtaining estimates of the parameters and using the fitted model for prediction. The variance of estimating parameters and predictions depend on the experimental designs, and an efficient experiment design can minimize the variance. The tool we use to minimize the variance is optimal design (Atkinson and Donev, 1992).

Optimal design specifies how to distribute resources in the most efficient way. Given a response surface, optimal design also provides the best locations to take observations. In practical situations, optimal design provides accurate statistical inferences with reduced cost. Different optimal designs have different criteria based on the goal of the experiment. To obtain the optimal design, we find a design that minimizes the optimality criteria, denoted by Ψ.

Under a given model, let Θ be the vector of model parameters, we use x_i for the i^{th} dose level, n_i represents the number of subjects allocated to the i^{th} dose level and N represents the total number of subjects, $N=\sum_{i=1}^{k} n_i$. Let $M(\xi;\ \Theta)$ denote the Fisher information matrix for Θ. $M(\xi;\ \Theta)$ only depends on design $\xi = \{(x_i, w_i),\ i=1, 2\ldots k\}$ and the parameters of Θ. Here, $w_i = n_i/N$ represents the proportional allocation of subjects to x_i. Optimal design minimizes the optimality criteria Ψ for the given Θ. Several important optimality criteria are presented below:

(1) A-optimality

A-optimality minimizes the summation of asymptotic variances of the parameter estimates. The criterion is

$$\Psi = \mathrm{tr}(M(\xi;\ \Theta)^{-1}).$$

(2) D-optimality

D-optimal design is used when we are interested in estimating parameters in the model. It minimizes the determinant of the inverse of the Fisher information matrix for Θ. The criterion is

$$\Psi = \mid M(\xi ; \Theta)^{-1} \mid.$$

(3) c-optimality

When our goal is to estimate a function of model parameters, c-optimality criteria is commonly used. It minimizes the variance of estimating the function of the model parameters, g (θ). Then the criterion is

$$\Psi = [g'(\theta)]^T M(\xi ; \Theta)^{-1} g'(\theta),$$

where $g'(\theta)$ is the first derivative of g (θ) with respect to Θ.

2.2. The General Equivalence Theorem

The General Equivalence Theorem (Kiefer, 1958; Pukelsheim, 2006) is a fundamental part to find and verify optimal designs. The General Equivalence Theorem can be applied to any optimal design that uses the function of the Fisher information matrix for the criterion. Here we present the General Equivalence Theorem for the c-optimal design. Let ξ^* denote the c-optimal design. When the interest is in estimating a function of the model parameters g (θ), the Fisher information matrix can be written as M $(\xi;\Theta) = \frac{1}{\sigma^2} \sum_{i=1}^{k} \omega_i f(X_i, \theta) f(X_i, \theta)^T$, and the General Equivalence Theorem states that

$$\{ f^T(x) M^{-1}(\xi^* ; \Theta) g'(\theta) \}^2 \leq [g'(\theta)]^T M^{-1}(\xi^* ; \Theta) g'(\theta).$$

Here $g'(\theta)$ is the first derivative of g (θ) with respect to θ, and the equality holds when x is one of the optimal design points in ξ^*.

It can be viewed as an application of the result that the derivative is zero at the minimum of the convex function. The above inequality equation is the directional derivative of the c-optimality criterion. The left side of the equation represents the standardized variance of the predicted response, and its maximum is always less than or equal to the variance of estimating g (θ) on the c-optimal design. The General Equivalence Theorem plays an important role in the V-algorithm to search the c-optimal design.

2.3. The V-algorithm

The V-algorithm is an efficient algorithm to search for optimal design. This method is established by Fedorov and Hackl (1997).

We set the values of model parameters first. In order to run the V-algorithm we need to set an initial design. Usually, a uniform design can be used for an initial design. One concern to set the initial design is that the number of initial design points must be greater than or equal to the number of model parameters. Otherwise, the information matrix based on the initial design becomes a singular matrix and the algorithm cannot be run.

The V-algorithm for searching c-optimal deign is stated here. Assume that we start with one initial design ξ with the Fisher information matrix M (ξ; Θ). Then we calculate the sensitive function in the General Equivalence Theorem at n^{th} iteration, which is denoted by d_n

$$\mathrm{d}_n = \{ \mathrm{f}^T(\mathrm{x})\, \mathrm{M}_n{}^{-1}(\xi\,;\,\Theta)\mathrm{g}'(\theta) \}^2 - [\mathrm{g}'(\theta)]^T \mathrm{M}_n{}^{-1}(\xi\,;\,\Theta)\mathrm{g}'(\theta)\ ,$$

where $\mathrm{M}_n\,(\xi\,;\,\Theta)$ is the information matrix evaluated at n^{th} iteration. And the x^* will be selected from the predetermined design space that maximizes d_n. Then the Fisher information matrix is updated as

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

where $\alpha_{n+1} = \frac{1}{n+1}$.

The stepwise process will continue until the sensitive function is very close to zero. The c-optimal design is reached when the stepwise stops (Federov and Hackl, 1997).

2.4. The Newton-Raphson Algorithm

The V-algorithm works well for finding optimal design points. However, it does not perform effectively to find optimal weights for the optimal design points. Here we use the Newton-Raphson algorithm to search optimal weights (Quinn, 2001).

For solving our problems, we rewrite this algorithm with respect to our optimality criterion Ψ and the design weights w, $w = (w_1, w_2 \dots w_{\mathrm{k}})$. The nonnegative solutions of $\frac{\partial}{\partial w}$ Ψ = 0 are the optimal weights for the given design points (Hyun, 2011). By the Newton-Raphson algorithm, w is update by

$$w_{new} = w_{old} - \left[\frac{\partial}{\partial w}\ \Psi\right] \cdot \left[\frac{\partial^2}{\partial_w}\ \Psi\right]^{-1}.$$

When | w_{new} - w_{old} | $<$ ε, where ε is a very small number, say ε=10^{-6}, the algorithm stops and w_{new} are the optimal weights for the given design points.

2.5. Carathéodory's Theorem

Carathéodory's Theorem provides an upper bound on the number of design points. By the theorem, we have no more than p(p+1)/2 +1 design points, where p is the number of parameters in the model.

3. MODEL

In this Chapter, we describe the four-parameter logistic model and present the Fisher information matrix, which plays an important role to obtain the c-optimal design.

We often observe that dose-response relationships follow a sigmoid curve. To describe such relationships, the four-parameter logistic model is frequently used. The mean response for the four-parameter logistic model at a given dose X_i is

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

where X_i is the i^{th} dose; $\theta_1$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 effects (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 effect Y is a continuous response, then the mean response at X_i is

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

Here $\mu\,(X_i,\Theta)$ is the mean dose-response from (3), $\Theta = (\theta_1,\ \theta_2,\ \theta_3,\ \theta_4)$, j = 1, 2, 3… n_i , i= 1, 2, …, k. We assume that the variance σ^2 is an unknown constant. Under this model setup, the normalized Fisher information matrix for Θ is obtained below

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

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

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

Then, we obtain the normalized Fisher information matrix as

$$\mathrm{M}\ (\xi;\theta) = \frac{1}{\sigma^2}\sum_{i=1}^{\mathrm{k}} \omega_{\mathrm{i}}$$

$$\begin{bmatrix} \frac{\theta_3{}^{2\theta_4}}{(X_i{}^{\theta_4}+\theta_3{}^{\theta_4})^2} & \frac{\theta_3{}^{\theta_4}X_i{}^{\theta_4}}{(X_i{}^{\theta_4}+\theta_3{}^{\theta_4})^2} & \frac{(\theta_1-\theta_2)\,\theta_4\theta_3{}^{(2\theta_4-1)}X_i{}^{\theta_4}}{\left(X_i{}^{\theta_4}+\theta_3{}^{\theta_4}\right)^3} & \frac{(\theta_2-\theta_1)\theta_3{}^{2\theta_4}X_i{}^{\theta_4}\,ln\frac{X_i}{\theta_3}}{\left(X_i{}^{\theta_4}+\theta_3{}^{\theta_4}\right)^3} \\ \frac{\theta_3{}^{\theta_4}X_i{}^{\theta_4}}{(X_i{}^{\theta_4}+\theta_3{}^{\theta_4})^2} & \frac{X_i{}^{2\theta_4}}{(X_i{}^{\theta_4}+\theta_3{}^{\theta_4})^2} & \frac{(\theta_1-\theta_2)\,\theta_4\theta_3{}^{(\theta_4-1)}X_i{}^{2\theta_4}}{\left(X_i{}^{\theta_4}+\theta_3{}^{\theta_4}\right)^3} & \frac{(\theta_2-\theta_1)\theta_3{}^{\theta_4}X_i{}^{2\theta_4}\,ln\frac{X_i}{\theta_3}}{\left(X_i{}^{\theta_4}+\theta_3{}^{\theta_4}\right)^3} \\ \frac{(\theta_1-\theta_2)\,\theta_4\theta_3{}^{(2\theta_4-1)}X_i{}^{\theta_4}}{\left(X_i{}^{\theta_4}+\theta_3{}^{\theta_4}\right)^3} & \frac{(\theta_1-\theta_2)\,\theta_4\theta_3{}^{(\theta_4-1)}X_i{}^{2\theta_4}}{\left(X_i{}^{\theta_4}+\theta_3{}^{\theta_4}\right)^3} & \frac{(\theta_1-\theta_2)^2\,\theta_4{}^2\theta_3{}^{2(\theta_4-1)}X_i{}^{2\theta_4}}{\left(X_i{}^{\theta_4}+\theta_3{}^{\theta_4}\right)^4} & \frac{-(\theta_1-\theta_2)^2\theta_3{}^{2\theta_4-1}\theta_4X_i{}^{2\theta_4}\,ln\frac{X_i}{\theta_3}}{\left(X_i{}^{\theta_4}+\theta_3{}^{\theta_4}\right)^4} \\ \frac{(\theta_2-\theta_1)\theta_3{}^{2\theta_4}X_i{}^{\theta_4}\,ln\frac{X_i}{\theta_3}}{\left(X_i{}^{\theta_4}+\theta_3{}^{\theta_4}\right)^3} & \frac{(\theta_2-\theta_1)\theta_3{}^{2\theta_4}X_i{}^{2\theta_4}\,ln\frac{X_i}{\theta_3}}{\left(X_i{}^{\theta_4}+\theta_3{}^{\theta_4}\right)^3} & \frac{-(\theta_1-\theta_2)^2\theta_3{}^{2\theta_4-1}\theta_4X_i{}^{2\theta_4}\,ln\frac{X_i}{\theta_3}}{\left(X_i{}^{\theta_4}+\theta_3{}^{\theta_4}\right)^4} & \frac{2(\theta_2-\theta_1)^2\theta_3{}^{2\theta_4}X_i{}^{2\theta_4}\,ln\frac{X_i}{\theta_3}}{\left(X_i{}^{\theta_4}+\theta_3{}^{\theta_4}\right)^4} \end{bmatrix}$$

This information matrix is very important to search c-optimal designs for estimating the ED_p in the next Chapter.

4. DESIGNS

In this Chapter, we discuss c-optimal designs for estimating the ED$_p$ under model (4). We employ the V-algorithm (Fedorov, 1972) to obtain the optimal design points and the Newton-Raphon algorithm to obtain the optimal weights for the selected design points. Then we verify these optimal designs by the General Equivalence Theorem. To evaluate the c-optimal designs, we adopt the experimental setup in Padmanabhan and Dragalin (2010). Let the design space be [0, 8] and the values of the model parameters Θ = (0, -1.7, 4, 5).

4.1. Uniform Design

When there is no previous knowledge, it is very common to use a uniform design in dose-response study. It allocates equal number of subjects to equally spaced dose levels. The number of design points should be greater than or equal to the number of parameters, which is 4 in our model. Also, based on the Carathéodory's Theorem, we have no more than p(p+1)/2 +1 design points, which is 11. Then the possible number of design points are between [4,11]. For our paper, we consider three different uniform designs. ξ^{U1} is a uniform design with 4 points

$$\xi^{U1} = \begin{pmatrix} .0001 & 2.67 & 5.33 & 8 \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \end{pmatrix}.$$

This uniform design allocates 25% of the subjects at each of the four design points. ξ^{U2} is a uniform design with 8 points

$$\xi^{U2} = \begin{pmatrix} .0001 & 1.14 & 2.29 & 3.43 & 4.57 & 5.71 & 6.86 & 8 \\ \frac{1}{8} & \frac{1}{8} & \frac{1}{8} & \frac{1}{8} & \frac{1}{8} & \frac{1}{8} & \frac{1}{8} & \frac{1}{8} \end{pmatrix}.$$

This one allocates 12.5% of the subjects at each of the eight design points. ξ^{U3} is a uniform design with 11 points

$$\xi^{U3} = \begin{pmatrix} .0001 & .8 & 1.6 & 2.4 & 3.2 & 4.0 & 4.8 & 5.6 & 6.4 & 7.2 & 8 \\ \frac{1}{11} & \frac{1}{11} & \frac{1}{11} & \frac{1}{11} & \frac{1}{11} & \frac{1}{11} & \frac{1}{11} & \frac{1}{11} & \frac{1}{11} & \frac{1}{11} & \frac{1}{11} \end{pmatrix}.$$

This allocates around 9% of the subjects at each of the 11 design points. These three uniform designs will be compared to our c-optimal designs for estimating the ED_p in chapter 5.

4.2. c-Optimal Design for Estimating the ED_p

In general, c-optimal design estimates a function of model parameters with a minimum variance. The c-optimal design criterion is already shown in the background. For this paper, we are interested in c-optimal design for estimating the ED_p. Under model (4), ED_p is expressed in explicit form. ED_p is the solution of the following equation,

$$p = \frac{\mu\,(X_i,\Theta) - \theta_1}{\theta_2 - \theta_1},$$

where p represents $100p\%$ of the maximum treatment effect, $\mu\,(X_i,\Theta)$ is the mean response at X_i. Then the ED_p is obtained as

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

Let $\widehat{\mathrm{ED}_p}$ denote the maximum likelihood estimate of ED_p, then the variance of estimating the ED_p is

$$\mathrm{Var}(\widehat{\mathrm{ED}_p}) = [\,\mathrm{ED}_p{}']^T \mathrm{M}(\xi;\Theta)^{-1} \mathrm{ED}_p{}',$$

where $[\,\mathrm{ED}_p{}']^T = \left(0,\ \ 0,\ \left(\frac{p}{1-p}\right)^{\frac{1}{\theta_4}}, -\left[\frac{\theta_3}{\theta_4{}^2}\left(\frac{p}{1-p}\right)^{\frac{1}{\theta_4}} \log\left(\frac{p}{1-p}\right)\right]\right)$.

C-optimal design for estimating the ED_p minimizes the variance of estimating the ED_p. We use the V-algorithm to find the c-optimal design points and the Newton-Raphson algorithm to find the optimal weights for the optimal design points. Then we use the General Equivalence Theorem to verify the design is indeed the c-optimal design. According to the General Equivalence Theorem, the design ξ^* is a c-optimal design if and only if

$$\{\, \mathrm{f}^T(\mathrm{x})\, \mathrm{M}^{-1}(\xi^*;\ \Theta) \mathrm{g}'(\theta)\,\}^2 - [\mathrm{g}'(\theta)]^T \mathrm{M}^{-1}(\xi^*;\ \Theta)\mathrm{g}'(\theta) \le 0.$$

Here the equality holds if the x is one of the c-optimal design points. To illustrate the c-optimal design for estimating the ED_p, we consider five different values of p (10, 30, 50, 70, 90).

We use the V-algorithm to find the c-optimal design points (Appendix A) and the Newton-Raphson algorithm to find the optimal weights (Appendix B). The c-optimal designs for estimating ED_{10}, ED_{30}, ED_{50}, ED_{70}, and ED_{90} are as follows:

(1) c-optimal design for estimating ED_{10} is

$$\xi_{\mathrm{ED}_{10}}=\begin{pmatrix} .001 & 3.111 & 5.221 \\ .36 & .50 & .14 \end{pmatrix}.$$

The c-optimal design for estimating ED_{10} allocates 36% of the subjects to .001, 50% of the subjects to 3.111 and 14% of the subjects to 5.221. The optimal design is verified by the General Equivalence Theorem (Figure 1). According to the General Equivalence Theorem, only when the design points are c-optimal design points, the sensitive function becomes very close to zero. Otherwise, it is always less than zero.

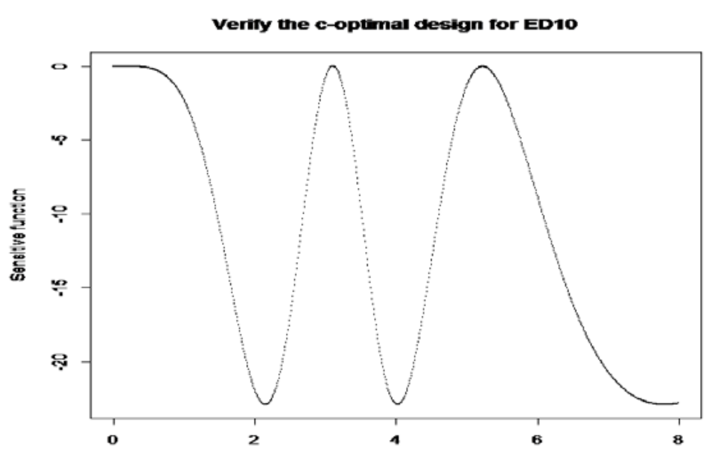

Figure 1. Plot of the sensitive function for c-optimal design for estimating ED_{10}.

(2) c-optimal design for estimating ED_{30} is

$$\xi_{\mathrm{ED}_{30}}=\begin{pmatrix} .001 & 3.511 & 7.991 \\ .323 & .500 & .176 \end{pmatrix}.$$

The c-optimal design for estimating ED_{30} allocates 32.3% of the subjects to .001, 50% of the subjects to 3.511 and 17.6% of the subjects to 7.991. The optimal design is verified by the General Equivalence Theorem (Figure 2).

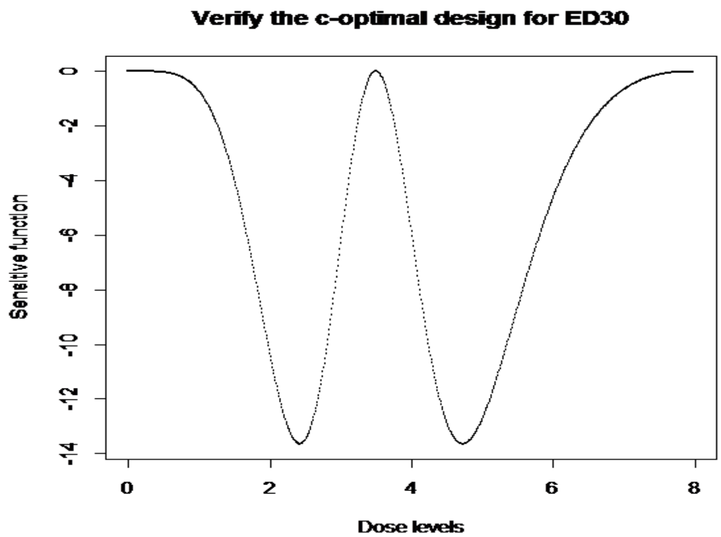

Figure 2. Plot of the sensitive function for c-optimal design for estimating ED_{30}.

(3) c-optimal design for estimating ED_{50} is

$$\xi_{\mathrm{ED}_{50}}=\begin{pmatrix} .991 & 4.181 & 7.991 \\ .214 & .500 & .286 \end{pmatrix}.$$

The c-optimal design for estimating ED_{50} allocates 21.4% of the subjects to .991, 50% of the subjects to 4.181 and 28.6% of the subjects to 7.991. The optimal design is verified by the General Equivalence Theorem (Figure 3).

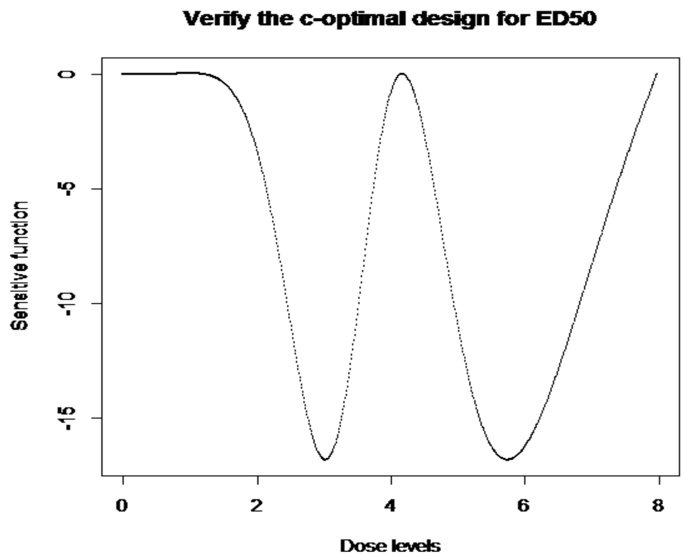

Figure 3. Plot of the sensitive function for c-optimal design for estimating ED_{50}.

(4) c-optimal design for estimating ED_{70} is

$$\xi_{\mathrm{ED}_{70}}=\begin{pmatrix} 2.461 & 4.601 & 7.991 \\ .17 & .50 & .33 \end{pmatrix}.$$

The c-optimal design for estimating ED_{70} allocates 17% of the subjects to 2.461, 50% of the subjects to 4.601 and 33% of the subjects to 7.991. The optimal design is verified by the General Equivalence Theorem (Figure 4).

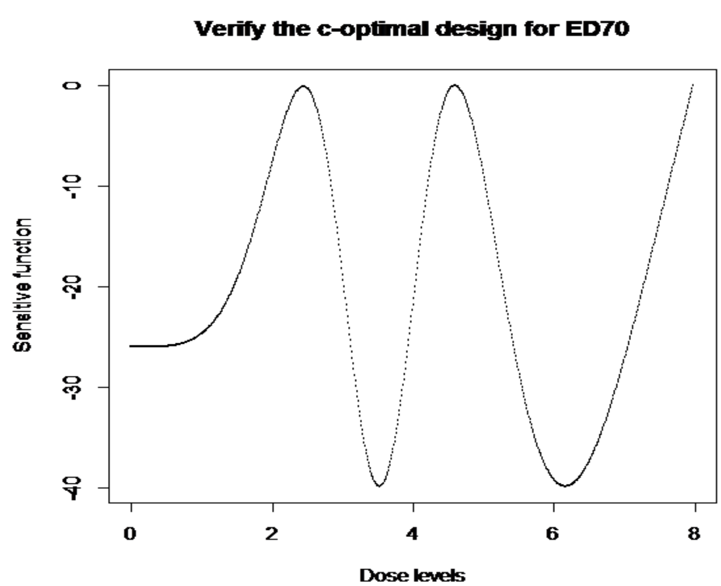

Figure 4. Plot of the sensitive function for c-optimal design for estimating ED_{70}.

(5) c-optimal design for estimating ED_{90} is

$$\xi_{\mathrm{ED}_{90}}=\begin{pmatrix} .001 & 3.021 & 4.901 & 7.991 \\ .051 & .201 & .449 & .299 \end{pmatrix}.$$

The c-optimal design for estimating ED_{90} allocates 5.1% of the subjects to .001, 20.1% of the subjects to 3.021, 44.9% of the subjects to 4.901 and 29.9% of the subjects to 7.991. The optimal design is verified by the General Equivalence Theorem (Figure 5).

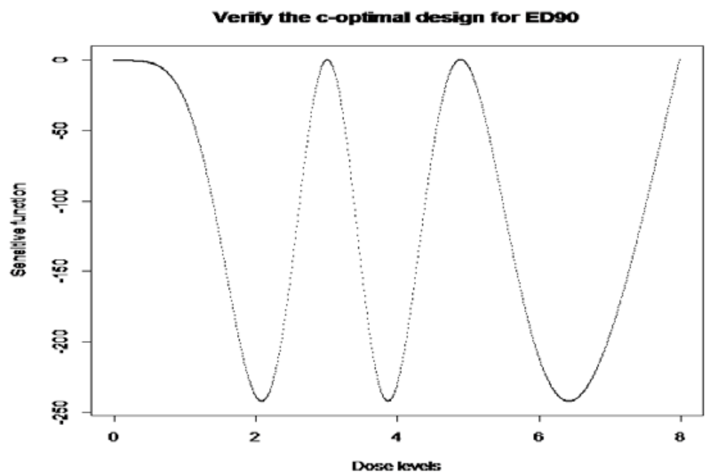

Figure 5. Plot of the sensitive function for c-optimal design for estimating ED_{90}.

Clearly, we can see that the c-optimal design for estimating the ED_p is changed by different values of p.

4.3. Robust c-Optimal Design

From previous section, we can see that for the four-parameter logistic model, the c-optimal designs for estimating the ED_p is changed by different values of p. In real studies, the researcher may want to change the values of p to study different $\mathrm{ED}_p s$ in the middle of the study. For example, they set the experiments to study the ED_{50}. Then later, they change their goal to study the ED_{30} or ED_{90}. Because c-optimal design for estimating the ED_p is changed by different values of p, it cannot be guaranteed that the c-optimal design for estimating the ED_p provides the same performance when the values of p are changed. Thus, we are interested in studying robust c-optimal design for estimating the ED_p that works well for the changes in the values of p. For illustration, we consider the five values of p to study the robust c-optimal design, but this could be extended to any values of p. The robust c-optimal design combines the five c-optimality criteria into one optimality criteria using the idea of compound design (Atkinson et al., 2007). The idea is that the robust c-optimal design maximizes the product of the five efficiencies for estimating the five different $\mathrm{ED}_p s$, so that the robust design maximizes the efficiency for estimating each ED_p.

A design efficiency shows how a design performs with respect to some criteria. $\mathrm{Eff}_{\mathrm{ED}_p}(\xi)$ measures the efficiency of a design ξ for estimating the ED_p against ξ_{ED_p} and it is obtained as

$$\mathrm{Eff}_{\mathrm{ED}_p}(\xi) = \frac{[\mathrm{ED}_p']^T \mathrm{M}\left(\xi_{\mathrm{ED}_p};\Theta\right)^{-1} \mathrm{ED}_p'}{[\mathrm{ED}_p']^T \mathrm{M}(\xi;\Theta)^{-1} \mathrm{ED}_p'}.$$

Since ξ_{ED_p} provides the minimum variance of estimating the ED_p, the $\mathrm{Eff}_{\mathrm{ED}_p}(\xi)$ is always between 0 and 1. We discuss the efficiency in the next chapter in detail.

The robust c-optimal design for estimating the ED_p is

$$\xi_{Robust} = Max\left(\mathrm{Eff}_{\mathrm{ED}_{10}}(\xi).\mathrm{Eff}_{\mathrm{ED}_{30}}(\xi).\mathrm{Eff}_{\mathrm{ED}_{50}}(\xi).\mathrm{Eff}_{\mathrm{ED}_{70}}(\xi).\mathrm{Eff}_{\mathrm{ED}_{90}}(\xi)\right) =$$

$$Max\left(\frac{Var(\mathrm{ED}_{10})_{\xi_{\mathrm{ED}_{10}}}}{Var(\mathrm{ED}_{10})_{\xi_{robust}}}\cdot\frac{Var(\mathrm{ED}_{30})_{\xi_{\mathrm{ED}_{30}}}}{Var(\mathrm{ED}_{30})_{\xi_{robust}}}\cdot\frac{Var(\mathrm{ED}_{50})_{\xi_{\mathrm{ED}_{50}}}}{Var(\mathrm{ED}_{50})_{\xi_{robust}}}\cdot\frac{Var(\mathrm{ED}_{70})_{\xi_{\mathrm{ED}_{70}}}}{Var(\mathrm{ED}_{70})_{\xi_{robust}}}\cdot\frac{Var(\mathrm{ED}_{90})_{\xi_{\mathrm{ED}_{90}}}}{Var(\mathrm{ED}_{90})_{\xi_{robust}}}\right).$$

The above equation can be rewritten as

$$\xi_{Robust} = Max(-\log(Var(\mathrm{ED}_{10})_{\xi_{robust}})-\log(Var(\mathrm{ED}_{30})_{\xi_{robust}})-\log(Var(\mathrm{ED}_{50})_{\xi_{robust}})$$

$$-\log(Var(\mathrm{ED}_{70})_{\xi_{robust}})-\log(Var(\mathrm{ED}_{90})_{\xi_{robust}})).$$

The General Equivalence Theorem states that ξ_{Robust} is the robust c-optimal design if and only if

$$\sum_{All\ p} \lambda_i \frac{(\mathrm{f(x)\ M}(\xi_{Robust}\,;\Theta)^{-1}[\,\mathrm{ED}_p'\,]^T)^2}{\mathrm{ED}_p'\ \mathrm{M}(\xi_{Robust}\,;\Theta)^{-1}[\,\mathrm{ED}_p'\,]^T} \le 1.$$

where $\sum_{All\ p} \lambda_i = 1$ and λ_i is a weight that represents the relative importance of i^{th} ED_p in the list of interesting $\mathrm{ED}_p s$. Here we assume that the five different $\mathrm{ED}_p s$ are equally important and it provides that λ_i =1/5. To find the robust c-optimal design, we again apply the V-algorithm (Appendix C). The robust c-optimal design for estimating the five different $\mathrm{ED}_p s$ is

$$\xi_{Robust} = \begin{pmatrix} .001 & 3.221 & 4.581 & 7.991 \\ .197 & .269 & .322 & .212 \end{pmatrix}.$$

The robust c-optimal design allocates 19.7% of the subjects to .001, 26.9% of the subjects to 3.221, 32.2% of the subjects to 4.581 and 21.2% of the subjects to 7.991. The optimal design is also verified by the General Equivalence Theorem (Figure 6).

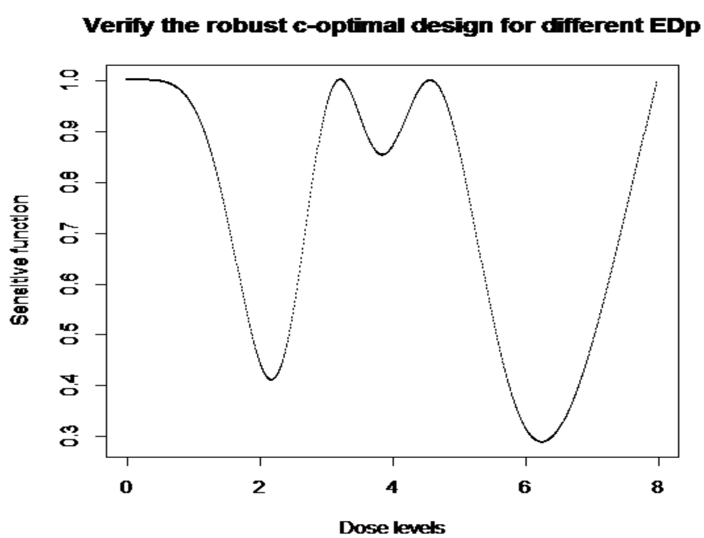

Figure 6. Plot of the sensitive function for robust c-optimal design.

Figure 6 shows that ξ_{Robust} is indeed robust c-optimal design and it maximizes the efficiencies for estimating the five different $\mathrm{ED}_p s$.

5. EFFICIENCY

In this Chapter, we compare the efficiencies of our optimal designs to see their performance. In this paper, we focus on efficiency with respect to c-optimality criterion. We compare the variance of estimating the ED_p for a given design to the variance of estimating the same ED_p under c-optimal design for the ED_p. The formula was given in the earlier chapter.

In general, if the efficiency of a design ξ is q, it implies design ξ needs 100(1/q-1)% more subjects to provide the same accuracy for estimating interesting features as the optimal design provides. So, $\mathrm{Eff}_{\mathrm{ED}_p}(\xi)$ tells us how many more samples we still need for estimating the ED_p to have the same accuracy as the c-optimal design does. If a design ξ works very close to the c-optimal design for estimating the ED_p, then $\mathrm{Eff}_{\mathrm{ED}_p}(\xi) \approx 1$. Otherwise, $\mathrm{Eff}_{\mathrm{ED}_p}(\xi)$ becomes far from 1. For example, $\mathrm{Eff}_{\xi\,\mathrm{ED}_p}$ = .5 implies 100(1/.5-1)% =100% more subjects are needed for a design ξ to estimate the ED_p with the same accuracy as the c-optimal design provides.

We compare all the designs: the c-optimal designs for estimating the ED_p , the uniform designs, and the robust c-optimal design for estimating five different $\mathrm{ED}_p s$. Again, we consider the five different values of p to demonstrate the ED_p. Their relative efficiencies are shown in Table 1. We can see that the c-optimal design for the ED_p works really poorly for different values of p and their changes are very dramatic.

The uniform designs provide efficiencies for estimating the five different $\mathrm{ED}_p s$ between 25% and 60%, regardless of the number of design points they used.

The robust c-optimal design does not provide very high efficiency for estimating the five $\mathrm{ED}_p s$. However, it outperforms compared to the other designs and provides at least 58% efficiency for estimating the five different $\mathrm{ED}_p s$ and the changes are not dramatic.

Table 1

Efficiency matrix of designs for estimating the EDp

Design	$\mathrm{Eff}_{\xi_{\mathrm{ED}_{10}}}$	$\mathrm{Eff}_{\xi_{\mathrm{ED}_{30}}}$	$\mathrm{Eff}_{\xi_{\mathrm{ED}_{50}}}$	$\mathrm{Eff}_{\xi_{\mathrm{ED}_{70}}}$	$\mathrm{Eff}_{\xi_{\mathrm{ED}_{90}}}$
$\xi_{\mathrm{ED}_{10}}$	1	0.0003042608	0.0001011274	0.000089	0.0001514567
$\xi_{\mathrm{ED}_{30}}$	0.001247212	1	0.0009560702	0.0004052225	0.0004448016
$\xi_{\mathrm{ED}_{50}}$	0.001347372	0.003143176	1	0.004628685	0.002447087
$\xi_{\mathrm{ED}_{70}}$	0.000195762	0.000218999	0.000767351	1	0.001818278
$\xi_{\mathrm{ED}_{90}}$	0.2247709	0.1990899	0.3369822	0.7059026	1
ξ^{U1}	0.3591172	0.2489504	0.2611956	0.3516158	0.6050842
ξ^{U2}	0.3888831	0.4560005	0.4627377	0.3724073	0.4291427
ξ^{U3}	0.3911447	0.4581159	0.4603254	0.369661	0.4270645
ξ_{Robust}	0.5757116	0.6056778	0.6771305	0.6325133	0.7589418

6. CONCLUSION

Optimal design plays a key role in designing experiments efficiently. It specifies how to distribute our resources over treatments in the most efficient way. Different types of optimal designs have different goals. For our 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. We checked the efficiencies and observed that the c-optimal design performs poorly when the value of p is changed. In order to avoid this problem, we present the robust c-optimal design for estimating the ED_p and it works fairly well when the values of p are changed.

The robust c-optimal design works well for the values of p that we used to construct the robust c-optimal design. In future research, we want to investigate whether the robust c-optimal design also works well for the values of p that are not used to build the robust design. For example, in our study we used ED_{10}, ED_{30}, ED_{50}, ED_{70}, and ED_{90} to construct the robust c-optimal design. However, does the robust c-optimal design still work well for estimating ED_{20}, ED_{40}, ED_{60}, and ED_{80}?

Bretz, Dette and Pinheiro (2010) states that c-optimal design for estimating the ED_p is very sensitive on the model choice. Here we used the four-parameter logistic model. We are also interested in studying the robust c-optimal design that works well for different models. In the future, we will find a robust c-optimal design that works well for both different values of p and the changes in the models.

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APPENDIX A. R CODE FOR C OPTIMAL DESIGN POINTS

```
## Generalized Inverse of a Matrix

ginv<-function(X, tol = sqrt(.Machine$double.eps))

{

  dnx <- dimnames(X)

  if(is.null(dnx)) dnx <- vector("list", 2)

  s <- svd(X)

  nz <- s$d > tol * s$d[1]

  structure(

    if(any(nz)) s$v[, nz] %*% (t(s$u[, nz])/s$d[nz]) else X,

    dimnames = dnx[2:1])

}

###c-optimality for research###

library(matrixcalc)

#Number of Parameters

k=4

#Value of Parameters

sita1=0

sita2=-1.7

sita3=4

sita4=5

#Initial value

x0=c(0.1,2.91,4.83,8)
```

```
n0=length(x0)

w=rep(1/n0,(n0-1))

D=rbind(x0,w)

#information matrix

#1.Information matrix for one design point

infor=function(x)

{f=matrix(c(sita3^sita4/(x^sita4+sita3^sita4), x^sita4/(x^sita4+sita3^sita4), (sita1-

sita2)*sita3^(sita4-1)*sita4*x^sita4/(x^sita4+sita3^sita4)^2, (sita2-

sita1)*(sita3^sita4)*x^sita4*log(x/sita3)/(x^sita4+sita3^sita4)^2),nrow=4,ncol=1,byrow=F)

f%*%t(f)}

#2.Updated information matrix

upinfor=function(W,X)

{k=length(X)

last_infor=infor(X[k])

infor=(1-sum(W))*last_infor

for (i in 1:(k-1))

{infor=infor+W[i]*infor(X[i])}

infor}

W=w[1:n0-1]

X=x0

newM=upinfor(W,X)

#initial information matrix

M0=upinfor(w,x0)
```

```
#Find dn,

f<-function(x){

matrix(c(sita3^sita4/(x^sita4+sita3^sita4), x^sita4/(x^sita4+sita3^sita4), (sita1-

sita2)*sita3^(sita4-1)*sita4*x^sita4/(x^sita4+sita3^sita4)^2, (sita2-

sita1)*(sita3^sita4)*x^sita4*log(x/sita3)/(x^sita4+sita3^sita4)^2),nrow=4,ncol=1,byrow=F)

}

phi.1 <- function(x){

	matrix(c(0, 0, (x/(1-x))^(1/sita4), -sita3/sita4^2*(x/(1-x))^(1/sita4)*log(x/(1-x))), nrow=4,

ncol=1, byrow=F)

}

p=1

t=2

while(p>.0005){

	x1=seq(0.001,8,.01)

	p1=0.1

	n1=length(x1)

	dn=rep(0,n1)

	for (j in 1:n1)

	{dn[j]=(t(f(x1[j]))%*%ginv(M0)%*%phi.1(p1))^2}

	for (j in 1:n1)

		{if(max(dn)==dn[j])x1[j]=x1[j] else x1[j]=NA}

	newX=na.omit(x1)

	newdn=max(dn)
```

```
    k=t(phi.1(p1))%*%ginv(M0)%*%phi.1(p1)
#Find alpha(n+1)
    #an=(newdn-k)/(k*(newdn-1))
    an=1/t
    #p<-abs(newdn-k)
#Get M(n+1)
    newM=c(1-an)*M0+c(an)*f(newX)%*%t(f(newX))
    M0<-newM
    p=abs((t(f(newX))%*%ginv(M0)%*%phi.1(p1))^2-
(t(phi.1(p1))%*%ginv(M0)%*%phi.1(p1)))
    newW=(1-an)*D[2,]
    W=c(newW,an)
    X=c(D[1,],newX)
    newD=rbind(X,W)
    D=newD
    print(p)
    t=t+1
}
#Summarize the result
c_optimal=by(D[2,],D[1,],FUN=sum)


#Verify c-optimal design
x0=D[1,]
```

```
n0=length(x0)

w=D[2,1:(n0-1)]

M=upinfor(w,x0)

x1=seq(0.001,8,.01)

n1=length(x1)

ds=rep(0,n1)

BB=t(phi.1(p1))%*%ginv(M)%*%phi.1(p1)

for (i in 1:n1)

{ds[i]=(t(f(x1[i]))%*%ginv(M)%*%phi.1(p1))^2-BB}

plot(x1,ds,cex=.1,main="Verify the c-optimal design for ED10",ylab="Sensitive
function",xlab="Dose levels")
```

APPENDIX B. R CODE FOR C OPTIMAL WEIGHTS

```
## Generalized Inverse of a Matrix
ginv<-function(X, tol = sqrt(.Machine$double.eps))
{
  dnx <- dimnames(X)
  if(is.null(dnx)) dnx <- vector("list", 2)
  s <- svd(X)
  nz <- s$d > tol * s$d[1]
  structure(
    if(any(nz)) s$v[, nz] %*% (t(s$u[, nz])/s$d[nz]) else X,
    dimnames = dnx[2:1])
}
#number of parameter
k=4
#design spage(log(x))
LB=log(.001)
LB=round(LB,2)
UB=log(8)
UB=round(UB,2)
x=seq(LB,UB,.01)

sita1=0
sita2=-1.7
```

```
sita3=4

sita4=5

#value of parameter

T=c(sita1,sita2,sita3,sita4)

#information matrix

#1.Information matrix for one design point

infor=function(T,X)

{f=matrix(c(T[3]^T[4]/(X^T[4]+T[3]^T[4]), X^T[4]/(X^T[4]+T[3]^T[4]), (T[1]-

T[2])*T[3]^(T[4]-1)*T[4]*X^T[4]/(X^T[4]+T[3]^T[4])^2, (T[2]-

T[1])*(T[3]^T[4])*X^T[4]*log(X/T[3])/(X^T[4]+T[3]^T[4])^2),nrow=4,ncol=1,byrow=F)

f%*%t(f)}

#2.Updated information matrix

upinfor=function(W,T,X)

{k=length(X)

last_infor=infor(T,X[k])

infor=(1-sum(W))*last_infor

for (i in 1:(k-1))

{infor=infor+W[i]*infor(T,X[i])}

infor}


#g function

g=function(X)
```

```
{matrix(c(0, 0, (X/(1-X))^(1/sita4), -sita3/sita4^2*(X/(1-X))^(1/sita4)*log(X/(1-X))), nrow=4,
ncol=1, byrow=F)}
#NW algorithm to find weight
c_weight=function(W,T,X,d,r)
{p=length(W)
k=length(X)
inv=ginv(upinfor(W,T,X))
V=g(r)%*%t(g(r))
M=upinfor(W,T,X)
f1=rep(0,p)
f2=matrix(c(rep(f1,p)),nrow=p,ncol=p,byrow=F)
for (i in 1:p)
{f1[i]=sum(diag(-inv%*%(infor(T,X[i])-infor(T,X[k]))%*%inv%*%V))}
for(i in 1:p)
{for(j in 1:p)
{f2[i,j]=(sum(diag((inv%*%(infor(T,X[j])-infor(T,X[k]))%*%inv%*%(infor(T,X[i])-
infor(T,X[k]))%*%inv+inv%*%(infor(T,X[i])-infor(T,X[k]))%*%inv%*%(infor(T,X[j])-
infor(T,X[k]))%*%inv)%*%V)))}}
newweight=W-d*(f1%*%ginv(f2))
newweight}
##NW algorithm
Search_weight=function(X,T,r)
{diff=10
```

```
k=length(X)

W=rep(1/k,k-1)

while(diff>.000000001)

{d=.2

NW=c_weight(W,T,X,d,r)

minW=min(min(NW),1-sum(NW))

while(minW<0 & d>.0001)

{d=d/2

NW=c_weight(W,T,X,d,r)

minW=min(min(NW),1-sum(NW))}

NW=c(NW,1-sum(NW))

n=length(NW)

minW=min(NW)

if (minW<0)

{for(i in 1:n)

{if (NW[i]==minW)NW[i]=0}}

diff=max(abs(W-NW[1:n-1]))

D=rbind(X,NW)

for (i in 1:n)

{if (D[2,i]==0) D[,i]=NA}

X=D[1,]

W=D[2,]

X=na.omit(X)
```

```
W=na.omit(W)

k=length(X)

W=W[1:k-1]

}

W=c(W,1-sum(W))

D=rbind(X,W)

D}

r=.9

X=c(0.001, 3.02, 4.90, 7.99)

Search_weight(X,T,r)
```

APPENDIX C. R CODE FOR ROUBST C-OPTIMAL DESIGN

```
## Generalized Inverse of a Matrix
ginv<-function(X, tol = sqrt(.Machine$double.eps))
{
  dnx <- dimnames(X)
  if(is.null(dnx)) dnx <- vector("list", 2)
  s <- svd(X)
  nz <- s$d > tol * s$d[1]
  structure(
    if(any(nz)) s$v[, nz] %*% (t(s$u[, nz])/s$d[nz]) else X,
    dimnames = dnx[2:1])
}
###c-optimality for research###
library(matrixcalc)
#Number of Parameters
k=4
#Value of Parameters
sita1=0
sita2=-1.7
sita3=4
sita4=5


#Initial value
```

```
x0=c(0.1,2.91,4.83,8)

n0=length(x0)

w=rep(1/n0,(n0-1))

D=rbind(x0,w)

#information matrix

#1.Information matrix for one design point

infor=function(x)

{f=matrix(c(sita3^sita4/(x^sita4+sita3^sita4), x^sita4/(x^sita4+sita3^sita4), (sita1-

sita2)*sita3^(sita4-1)*sita4*x^sita4/(x^sita4+sita3^sita4)^2, (sita2-

sita1)*(sita3^sita4)*x^sita4*log(x/sita3)/(x^sita4+sita3^sita4)^2),nrow=4,ncol=1,byrow=F)

f%*%t(f)}

#2.Updated information matrix

upinfor=function(W,X)

{k=length(X)

last_infor=infor(X[k])

infor=(1-sum(W))*last_infor

for (i in 1:(k-1))

{infor=infor+W[i]*infor(X[i])}

infor}

W=w[1:n0-1]

X=x0

newM=upinfor(W,X)

#initial information matrix
```

```
M0=upinfor(w,x0)
#Find dn,
f<-function(x){
matrix(c(sita3^sita4/(x^sita4+sita3^sita4), x^sita4/(x^sita4+sita3^sita4), (sita1-
sita2)*sita3^(sita4-1)*sita4*x^sita4/(x^sita4+sita3^sita4)^2, (sita2-
sita1)*(sita3^sita4)*x^sita4*log(x/sita3)/(x^sita4+sita3^sita4)^2),nrow=4,ncol=1,byrow=F)
}
phi.1 <- function(x){
        matrix(c(0, 0, (x/(1-x))^(1/sita4), -sita3/sita4^2*(x/(1-x))^(1/sita4)*log(x/(1-x))), nrow=4,
ncol=1, byrow=F)
}
p=1
t=2
ob=function(x,p)
{(((t(f(x))%*%ginv(M0)%*%phi.1(p))^2/(t(phi.1(p)))%*%ginv(M0)%*%phi.1(p)))}
while(p>.0005){
        x1=seq(0.001,8,.01)
        p1=c(.1, .3, .5, .7, .9)
    T=length(p1)
        n1=length(x1)
        dn=rep(0,n1)
        for (j in 1:n1)
```

```
	{dn[j]=.2*ob(x1[j],p1[1])+.2*ob(x1[j],p1[2])+.2*ob(x1[j],p1[3])+.2*ob(x1[j],p1[4])+.2*
ob(x1[j],p1[5])}
	for (j in 1:n1)
		{if(max(dn)==dn[j])x1[j]=x1[j] else x1[j]=NA}
	newX=na.omit(x1)
	newdn=max(dn)
	k=1
#Find alpha(n+1)
	#an=(newdn-k)/(k*(newdn-1))
	an=1/t
	#p<-abs(newdn-k)

#Get M(n+1)
	newM=c(1-an)*M0+c(an)*f(newX)%*%t(f(newX))
	M0<-newM
	p=abs(newdn-1)
	newW=(1-an)*D[2,]
	W=c(newW,an)
	X=c(D[1,],newX)
	newD=rbind(X,W)
	D=newD
	print(p)
	t=t+1
```

```
}

#Summarize the result

c_optimal=by(D[2,],D[1,],FUN=sum)

#Verify c-optimal design

x0=D[1,]

n0=length(x0)

w=D[2,1:(n0-1)]

M=upinfor(w,x0)

x1=seq(0.001,8,.01)

n1=length(x1)

ds=rep(0,n1)

#BB=t(phi.1(.1))%*%ginv(M)%*%phi.1(.1)%*%(t(phi.1(.3))%*%ginv(M)%*%phi.1(.3))%*%(t
(phi.1(.5))%*%ginv(M)%*%phi.1(.5))%*%(t(phi.1(.7))%*%ginv(M)%*%phi.1(.7))%*%(t(phi.
1(.9))%*%ginv(M)%*%phi.1(.9))

for (i in 1:n1)

{ds[i]=.2*ob(x1[i],p1[1])+.2*ob(x1[i],p1[2])+.2*ob(x1[i],p1[3])+.2*ob(x1[i],p1[4])+.2*ob(x1[i]
,p1[5])}

plot(x1,ds,cex=.1,main="Verify the robust c-optimal design for different EDp",ylab="Sensitive
function",xlab="Dose levels")
```

APPENDIX D. R CODE FOR FINDING EFFICIENCY

```
## Generalized Inverse of a Matrix
ginv<-function(X, tol = sqrt(.Machine$double.eps))
{
  dnx <- dimnames(X)
  if(is.null(dnx)) dnx <- vector("list", 2)
  s <- svd(X)
  nz <- s$d > tol * s$d[1]
  structure(
    if(any(nz)) s$v[, nz] %*% (t(s$u[, nz])/s$d[nz]) else X,
    dimnames = dnx[2:1])
}
#information matrix
#1.Information matrix for one design point
infor=function(T,X)
{f=matrix(c(T[3]^T[4]/(X^T[4]+T[3]^T[4]), X^T[4]/(X^T[4]+T[3]^T[4]), (T[1]-
T[2])*T[3]^(T[4]-1)*T[4]*X^T[4]/(X^T[4]+T[3]^T[4])^2, (T[2]-
T[1])*(T[3]^T[4])*X^T[4]*log(X/T[3])/(X^T[4]+T[3]^T[4])^2),nrow=4,ncol=1,byrow=F)
f%*%t(f)}
#2.Updated information matrix
upinfor=function(W,T,X)
{k=length(X)
last_infor=infor(T,X[k])
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```
infor=(1-sum(W))*last_infor
for (i in 1:(k-1))
{infor=infor+W[i]*infor(T,X[i])}
infor}
f<-function(x){
matrix(c(sita3^sita4/(x^sita4+sita3^sita4), x^sita4/(x^sita4+sita3^sita4), (sita1-
sita2)*sita3^(sita4-1)*sita4*x^sita4/(x^sita4+sita3^sita4)^2, (sita2-
sita1)*(sita3^sita4)*x^sita4*log(x/sita3)/(x^sita4+sita3^sita4)^2),nrow=4,ncol=1,byrow=F)
}
#g function
g=function(X)
{matrix(c(0, 0, (X/(1-X))^(1/sita4), -sita3/sita4^2*(X/(1-X))^(1/sita4)*log(X/(1-X))), nrow=4,
ncol=1, byrow=F)}
#Value of Parameters
sita1=0
sita2=-1.7
sita3=4
sita4=5
T=c(sita1,sita2,sita3,sita4)
#robust design points
X2=c(0.001,3.221,4.581,7.991)
W2=c(0.197, 0.269, 0.322)
#c-optimal design points
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X1=c(0.001,3.021,4.901,7.991)

W1=c(0.051, 0.201, 0.449)

LB=.0001

UB=8

U4=c(LB,LB+8/3,LB+2*(8/3),LB+3*(8/3))

W4=rep(1/4,3)

U8=c(LB,LB+8/7,LB+2*(8/7),LB+3*(8/7),LB+4*(8/7),LB+5*(8/7),LB+6*(8/7),LB+7*(8/7))

W8=rep(1/8,7)

U11=c(LB,LB+8/10,LB+2*(8/10),LB+3*(8/10),LB+4*(8/10),LB+5*(8/10),LB+6*(8/10),LB+7*

(8/10),LB+8*(8/10),LB+9*(8/10),LB+10*(8/10))

W11=rep(1/11,10)

##Var10

eff10=function(X2,W2)

{M10=upinfor(W1,T,X1)

M=upinfor(W2,T,X2)

p=.90

N=(t(g(p))%*%ginv(M10)%*%g(p))

DN=t(g(p))%*%ginv(M)%*%g(p)

eff=N/DN

eff}

eff10(X2,W2)

eff10(U4,W4)

eff10(U8,W8)
```

eff10(U11,W11)