



## Controlled Optimal Design Program for the Logit Dose Response Model

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### Abstract

The assessment of dose-response is an integral component of the drug development process. Parallel dose-response studies are conducted, customarily, in preclinical and phase 1, 2 clinical trials for this purpose. Practical constraints on dose range, dose levels and dose proportions are intrinsic issues in the design of dose response studies because of drug toxicity, efficacy, FDA regulations, protocol requirements, clinical trial logistics, and marketing issues. We provide a free on-line software package called **Controlled Optimal Design 2.0** for generating controlled optimal designs that can incorporate prior information and multiple objectives, and meet multiple practical constraints at the same time. Researchers can either run the web-based design program or download its stand-alone version to construct the desired multiple-objective controlled Bayesian optimal designs. Because researchers often adopt ad-hoc design schemes such as the equal allocation rules without knowing how efficient such designs would be for the design problem, the program also evaluates the efficiency of user-supplied designs.

*Keywords:* Bayesian optimal design, dose response study, logit model.

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## 1. Introduction

The logit model is popular for describing the underlying dose response relationships in dose response studies (Abdelbasit and Plackett 1983; Chaloner and Larntz 1988, 1989; Kalish 1990; Carr and Portier 1993; Smith and Ridout 1998; Zhu *et al.* 1998; Zeng *et al.* 2000; Zhu and Wong 2001; Baek *et al.* 2006). Chaloner and Larntz (1989) provided a Fortran program, called **Logit Design 1.0**, for computing Bayesian single-objective optimal designs for the logit model, which

has attracted attention in the optimal design community. Later, the program was generalized in Zhu (1996) to accommodate the commonly encountered multiple-objectives scenarios in dose response studies. This **Generalized Multi-Objective Logit Design** program was applied to several dose response studies (Ahn *et al.* 1998; Zhu *et al.* 1998; Zeng *et al.* 2000; Zhu and Wong 2000a, 2001; Mugno *et al.* 2004). However, this program has drawbacks because it cannot incorporate specific constraints on the dose range, dose levels, and dose proportions for a give study, which frequently arise in practice; see for example, Kaine *et al.* (1995), Zeng and Zhu (1997), Mason *et al.* (2002), Shahinfar *et al.* (2005), and Cohen *et al.* (2007). In recent years, some progress has been made in incorporating more information and realistic constraints into the design framework. For example, Scazzero and Ord (1993) restricted the range of dose response probabilities in an industrial experiment, Mats *et al.* (1998) showed that unusual design space can arise naturally in the design of phase 1 cancer clinical trials, and Imhof *et al.* (2002, 2004) and Baek *et al.* (2006) proposed to incorporate information of potential missing observations at the design stage. However, to our best knowledge, there is no free software program that allows multiple objectives and constraints to be accounted for at the design stage.

In this paper, we proposed an optimal design software called the **Controlled Optimal Design 2.0** that integrates a modern class of optimization algorithms into a single package for practitioners in the health sciences. These optimization algorithms include both global optimizers such as the cross entropy (CE) method (Rubinstein and Kroese 2004) and local search procedures such as stochastic gradient search (Spall 1992), which are popular and standard tools for solving practical problems in the operations research community. We believe that this is the first time such techniques are applied to the optimal design literature. Our program handles different practical constraints, multiple objectives, prior information, and formulates the underlying design problem as a constrained non-linear optimization problem. The resulting optimization problem is then solved using the aforementioned built-in optimizers, leading to a feasible design we call the “controlled optimal design”. We have successfully applied this program to re-design several dose response studies. Our preliminary study indicates that the resulting controlled optimal designs can significantly outperform the designs actually implemented in the studies. The program is freely available to the public in two formats: (1) a web-based version from <http://www.optimal-design.org/>; (2) a stand-alone version that can be downloaded from the same website. It is our hope that the optimal design website will serve as a modern forum for information exchange between the users and developers of the **Controlled Optimal Design 2.0** program. Our research is still on-going, and we plan to expand the functionality of the current design software to accommodate other dose response models, design objectives, and constraints. A newer website with additional capabilities is available at <http://optimal-design.biostat.ucla.edu/optimal/>.

## 2. Logit model and optimal design terminologies

The logit dose response model

$$\ln \frac{\pi(x)}{1 - \pi(x)} = \beta(x - \alpha)$$

links the dose level  $x$  to the probability  $\pi(x)$  of observing a response (e.g., drug is effective) at the given dose. The parameter  $\beta$  is the slope in the logit scale. The parameter  $\alpha$  is the

median in the logit scale and is commonly referred to as the “median effective dose”. This parameter is sometimes denoted by ED50, where ED stands for effective dose. More generally, let  $\text{ED}100\pi$  be the dose level corresponding to a response probability  $\pi$ . It follows that

$$\text{ED}100\pi = x = \alpha + \frac{1}{\beta} \left( \ln \frac{\pi}{1 - \pi} \right).$$

A typical research goal is to estimate one or more dose levels  $\text{ED}100\pi_i$  as accurately as possible for user-selected  $\pi_i$ 's. Another goal is to estimate the underlying dose response curve (i.e. the logit model parameters) as accurately as possible. One of our main aims in this paper is to find an optimal design for estimating one or more of these parameters.

Any design  $\xi$  can be represented in the form

$$\xi = \left\{ \begin{array}{cccc} x_1 & x_2 & \cdots & x_k \\ p_1 & p_2 & \cdots & p_k \end{array} \right\},$$

where  $k$  is the number of dose levels and  $p_i$  is the proportion of subjects assigned to the dose level  $x_i$ . In this work, we follow the approximate optimal design approach (Kiefer 1974; Silvey 1980; Pukelsheim 1993). In particular, given an optimality criterion, our design problem is to find the optimal value of  $k$ , the dose levels  $x_i$ , and the proportion of subjects assigned to each of these dose levels,  $p_i$   $i = 1, 2, \dots, k$ . In practice, the total number of available subjects  $N$  is predetermined either by cost or time considerations, and our optimal design  $\xi$  assigns roughly  $Np_i$  (rounded to the nearest integer) subjects to the dose level  $x_i$ , subject to the constraint that  $\sum_i^k p_i = 1$ . Over the years, Kiefer's approach has proven to be practically useful. In particular, algorithms are available for finding a variety of optimal designs and analytical solutions become possible in many cases.

Let  $\underline{\theta}^\top = (\alpha, \beta)$ ,  $t = \sum p_j w_j$ ,  $\bar{x} = t^{-1} \sum p_j w_j x_j$ ,  $s = \sum p_j w_j (x_j - \bar{x})^2$ , and  $w_j = \pi(x_j)[1 - \pi(x_j)]$ . For the logit model, Zhu and Wong (2001) showed that the normalized observed Fisher information matrix for the design  $\xi$  is

$$M(\underline{\theta}, \xi) = \begin{pmatrix} \beta^2 t & -\beta t(\bar{x} - \alpha) \\ -\beta t(\bar{x} - \alpha) & s + t(\bar{x} - \alpha)^2 \end{pmatrix}.$$

To estimate a given function of the model parameter  $c(\underline{\theta})$ , one can use the Bayesian  $C$ -optimality criterion to minimize the estimated asymptotic variance of  $c(\underline{\theta})$ , i.e.,

$$\Phi(\xi) = E_{\underline{\theta}} \left[ \nabla c(\underline{\theta}) \right]^\top M^{-1}(\underline{\theta}, \xi) \left[ \nabla c(\underline{\theta}) \right],$$

where the expectation is taken with respect to the prior distribution of  $\underline{\theta}$ . Another important criterion is the Bayesian  $D$ -optimality criterion that estimates the logit dose response curve by minimizing the estimated volume of the joint confidence ellipsoid of the two model parameters

$$\Phi(\xi) = E_{\underline{\theta}} \left| M^{-1}(\underline{\theta}, \xi) \right|.$$

Both types of Bayesian single-objective optimality criteria were used in Chaloner and Larntz (1989). Bayesian optimal designs clearly generalize locally optimal design proposed by Chernoff (1953), because the latter designs assume a degenerate prior distribution. Both these two types of optimality criteria are convex functions of the information matrix and so results

from convex analysis can be applied to justify the optimality of the design (Silvey 1980). To evaluate the performance of an arbitrary design relative to an optimal design  $\xi^*$ , we measure its design efficiency by

$$e(\xi) = \Phi(\xi^*)/\Phi(\xi).$$

To accommodate multiple design objectives such as the estimation of certain percentiles of interest and/or the estimation of the individual parameters in the dose response curve, one may formulate the design problem as a constrained problem as follows. First, prioritize the importance of each objective; if there are  $m$  objectives, the user specifies the desired efficiency of the design for each criterion; naturally we want the design to have higher efficiencies for more important criteria or objectives. Subject to these user-specified efficiency requirements for all objectives, except for the least important criterion, the optimization problem is to maximize the design efficiency of the least important criterion within the class of designs already guaranteed to meet all other efficiency requirements. Although this formulation is both appealing and intuitive, it does not provide a clue how to determine the optimal design.

An alternative and more practical approach is to work with the compound optimality criterion proposed in Cook and Wong (1994). This approach incorporates multiple objectives into a single criterion by using a convex combination of all the objectives. Because each criterion is convex, the new criterion is also convex. Thus for each convex combination, standard algorithm can be used to generate an optimal design for the new criterion. The resulting compound optimal design is found by minimizing the new criterion, and has a nice interpretation for a given choice of the weights employed in the convex combination. Specifically, they relate to the efficiency requirements in the formulation of the constrained design problem; in particular, the sought constrained optimal design is one of the compound optimal designs and the next problem is to make the identification. Cook and Wong (1994), Clyde and Chaloner (1996), Zhu and Wong (2000a, 2001) provided details and illustrations.

As a brief illustration, suppose the individual design objective functions are  $\Phi_i$ ,  $i = 1, \dots, m$  and each is a convex function of the information matrix. The (non-standardized) compound optimality criterion is

$$\Phi(\xi|\underline{\lambda}) = \sum_{i=1}^m \lambda_i \Phi_i(\xi),$$

where  $0 \leq \lambda_i \leq 1$ ,  $\sum \lambda_i = 1$  are user selected weights. For the given set of weights, the design that minimizes this criterion is called a compound optimal design. When the magnitude of the individual design objective functions varies substantially, the standardized compound optimality criterion proposed by Dette *et al.* (2005) is preferred:

$$\Phi(\xi|\underline{\lambda}) = \sum_{i=1}^m \lambda_i \left[ \Phi_i(\xi) / \Phi_i(\xi_i^*) \right],$$

where  $\xi_i^*$  is the optimal design for objective  $i$ ,  $i = 1, \dots, m$  and the ratio represents the efficiency of the design  $\xi$  relative to the optimal design for the  $i$ th objective. In practice, for each set of weights, a compound optimal design is determined. The desired constrained optimal design is then found from within the class of compound optimal designs. When there are two objectives, the desired constrained optimal design can be determined graphically from the class of compound optimal designs using an efficiency plot; see e.g., Cook and Wong (1994).

### 3. Controlled optimal design

The traditional Bayesian multiple-objective optimal designs (Chaloner and Larntz 1988, 1989; Zhu 1996; Zhu and Wong 2000a, 2001) impose no constraint on the underlying dose range, dose levels, and dose proportions. Furthermore, they do not incorporate information on potential missing observations at different dose levels nor do they allow specific dose levels to be automatically included in the design. These drawbacks can be serious limitations for the pharmaceutical industry. For example, FDA (Food and Drug Administration) guidelines to the industry stipulate that on dose response studies, a positive dose response relationship can be demonstrated either through a positive slope or through a significantly higher proportion of responders at an active dose level in comparison to the placebo. Therefore, many parallel dose-response studies require the placebo (dose 0) to be included as one of the dose levels. However, one cannot force the placebo (or any other fixed dose level) to be a selected dose level in the traditional optimal design framework.

The controlled optimal design concept was developed over the last decade with collaborative work from colleagues in the pharmaceutical industry. The program removes several of the above limitations and provides added flexibility. In the current version of the **Controlled Optimal Design 2.0** program, we have implemented features to accommodate constraints on the following design parameters:

1. **Restricted design interval.** The traditional optimal design assumes the underlying dose range to be  $(-\infty, \infty)$ . This may result in an optimal design with the lower dose less than the placebo and/or with the upper dose level higher than the safety limit. The user can now define their own dose range based on their efficacy and toxicity considerations.
2. **Dose levels.** The user can include certain dose levels of interest such as the placebo and/or dose levels being considered for the drug label (and thus direct observation of the response rates at such dose levels would be desirable) as fixed optimal design support points. The user can also specify a range for each dose level to be used. For example, in some studies, it is desirable to include a lower dose, a medium dose, and a higher dose.
3. **Dose proportions.** For each dose level, the user define the range of its corresponding allocation proportion. In a 4-dose study, for example, we may require that at least 15% or no more than 35% of subjects are allocated at some dose levels because of trial logistics or the expected higher dropout rates at certain dose levels.
4. **Potential missing observations.** Sometimes a dose response study has lots of missing observations near the end of the trial due to subject drop-out. The reasons for drop-out typically include lack of efficiency and/or the presence of drug toxicity or simply fatigue over time especially if we have a trial that goes on for years. To capture information for the distribution of missing data at different dose levels at the design stage, we provide three potential non-missing probability functions in our package. Let  $\tau(x)$  be the percentage of subjects at dose level  $x$  that are expected to complete the study. The three available forms are the logit, exponential, and symmetric non-missing probability functions given by  $\tau(x) = [1 + \exp(ax - b)]^{-1}$ ,  $\tau(x) = 1 - a \exp(bx - c)$ , and  $\tau(x) = a(b - x)^2 + c$ , respectively. Here  $a$ ,  $b$ , and  $c$  are user selected constants that can be estimated from a pilot/previous study. Details for this methodology are given in Imhof *et al.* (2002, 2004) and Baek *et al.* (2006).

### 3.1. The optimization algorithms

We now provide a brief description of the main ideas in the **Controlled Optimal Design 2.0** program. The package consists of a global search component and a local search component. The idea is to use the global search to escape from local optima and locate promising regions of the solution space containing high quality solutions. We then use the local search to fine-tune the solutions obtained from the global search phase. Since the optimal design problem is highly constrained, multi-dimensional, and nonlinear with possibly many locally optimal solutions, a random sampling-based approach is used in our **Controlled Optimal Design 2.0** program. Compared to traditional optimization approaches such as the simplex method and the gradient-based method, our approach is more robust and is not sensitive to initial starting values/guesses.

Specifically, the global search component in our program is based on the recently proposed cross-entropy (CE) method (Rubinstein and Kroese 2004) in the operations research community. The CE method is an iterative approach that is based on random sampling from an underlying probability distribution model on the solution space, which is updated iteratively after evaluating the performance of the samples at each iteration. The essence of the method is to gradually concentrate the distribution model on promising regions of the solution space so that the probability of generating/sampling high quality solutions increases as the sampling process proceeds.

One difficulty in applying CE to the controlled design problem is how to efficiently generate feasible designs (candidate solutions) from the restricted design space. Note that the design space is characterized by the following two types of constraints: (i) the set of constraints  $g_i(\xi) \leq 0$ ,  $i = 1, \dots, m$  that form hyper-rectangles (e.g., restrictions on dose intervals, dose levels, and dose proportions), and (ii) the set of constraints  $h_j(\xi) \leq 0$ ,  $j = 1, \dots, n$  that form multi-dimensional simplexes (for example, the set of dose proportions need to satisfy the constraints  $\sum_{i=1}^k p_i = 1$ ,  $p_i \geq 0$ ). In the actual implementation of the **Controlled Optimal Design 2.0** program, an acceptance-rejection (AR) approach is used to handle the first type of constraints. The AR approach starts by generating feasible designs from the unconstrained design space, and then either accepts or rejects the generated designs by checking whether or not they fall in the regions defined by the constraints. For constraints of type (ii), a penalty function approach is used to include the constraints as parts of an unconstrained optimization problem. The optimization problem is now formulated as the weighted combination of the original objective function and a function that penalizes violation of constraints of type (ii),

$$\hat{\Phi}(\xi|\lambda) = \Phi(\xi|\lambda) + \sum_{j=1}^n c_j \max\{h_j(\xi), 0\},$$

where  $c_j > 0$  is the cost incurred by violating the  $j$ th constraint  $h_j(\xi) \leq 0$ .

Once a good design is found in the global search phase, it can be used as an initial solution in a local search method to find further improved designs. To ensure high quality solutions, the local search component of our program consists of two phases – a pure local search phase followed by a gradient-based search. A high level description of the pure local search method is as follows. Specifically, let  $\xi^t$  be the current best design found at the  $t$ th iteration of the algorithm. We start by randomly (uniformly) generating  $N$  new designs from the neighborhood of  $\xi^t$ . If a new design is found to be better than  $\xi^t$ , it replaces  $\xi^t$  as the new current best design. The above steps are performed iteratively until no further improvement

is obtained for several consecutive iterations. At the second phase, the gradient-based search takes the general recursive form

$$\xi^{t+1} = \Pi\left(\xi^t - a_t \hat{L}_t(\xi^t)\right),$$

where  $\hat{L}_t(\xi^t)$  represents an estimate of the performance gradient at the current design  $\xi^t$ ,  $a_t$  is the step size, and  $\Pi$  denotes a projection on the feasible design space characterized by the constraints. The gradient estimation can be carried out via a number of different techniques. Here we have used a two-sided simultaneous perturbation approximation approach (Spall 1992), where all elements of  $\xi^t$  are randomly perturbed to obtain two measurements of  $\Phi(\xi|\underline{\lambda})$ , and the  $j$ th directional gradient is estimated by

$$\hat{L}_{i,j} = \frac{\Phi(\xi^t + \Delta_t c_t | \underline{\lambda}) - \Phi(\xi^t - \Delta_t c_t | \underline{\lambda})}{2c_t \Delta_{t,j}},$$

where  $\Delta_t = (\Delta_{t,1}, \dots, \Delta_{t,2k})^\top$  is a random perturbation vector and  $\{c_t\}$  is a sequence of constants that gets smaller as the number of iterations  $t$  increases. For detailed implementation issues of how to choose the perturbation vector and the sequence  $\{c_t\}$ , we refer the reader to Spall (1992).

### 3.2. Controlled optimal design program 2.0, the stand-alone version

The original **Controlled Optimal Design 2.0** is written in MATLAB (The MathWorks, Inc. 2007). An executable stand-alone version of this program is provided on the optimal design website. For greater time efficiency, the user should download this program and run it on their own computers. The first-level menu of the stand-alone program is as follows:

Options:

- (1) specify the number of dose levels
- (2) calculate the optimal number of dose levels
- (0) quit the program

Once the user selects option (1) or (2), the second-level menu appears as follows.

Options:

- (1) specify the dose range
- (2) specify dose levels (e.g., placebo)
- (3) specify dose proportions
- (4) specify an initial design (optional)
- (5) specify the initial prior
- (6) select the optimality criterion
- (7) select the design criterion
- (8) specify information on potential missing observations
- (9) specify the number of iterations
- (10) calculate the optimal design
- (11) evaluate the criterion value for the current design
- (12) print out the current values
- (0) quit the program

To compute a controlled-optimal design, the user should choose options (1) through (10) in turn. Most of these options are self-explanatory except options (6) and (7). For option (6), the user chooses whether to use the non-standardized or the standardized compound optimal design criterion. We also provide the user with two approaches to estimate the model parameters. In Approach 1, we estimate each model parameter using the  $C$ -optimal design criterion and subsequently add these and other  $C$ -optimal design criteria for user-selected percentiles of interest under a unified compound  $C$ -optimal design. In Approach 2, we estimate both model parameters jointly using the  $D$ -optimal design criterion and subsequently adding this and other  $C$ -optimal design criteria for selected percentiles of interest under a unified compound  $C$ - and  $D$ -optimal design. Therefore we have 4 choices in option (6) as follows.

Available options:

- (1) standardized compound C-optimal design
- (2) standardized compound C- and D-optimal design
- (3) non-standardized compound C-optimal design
- (4) non-standardized compound C- and D-optimal design
- (5) go back to main menu

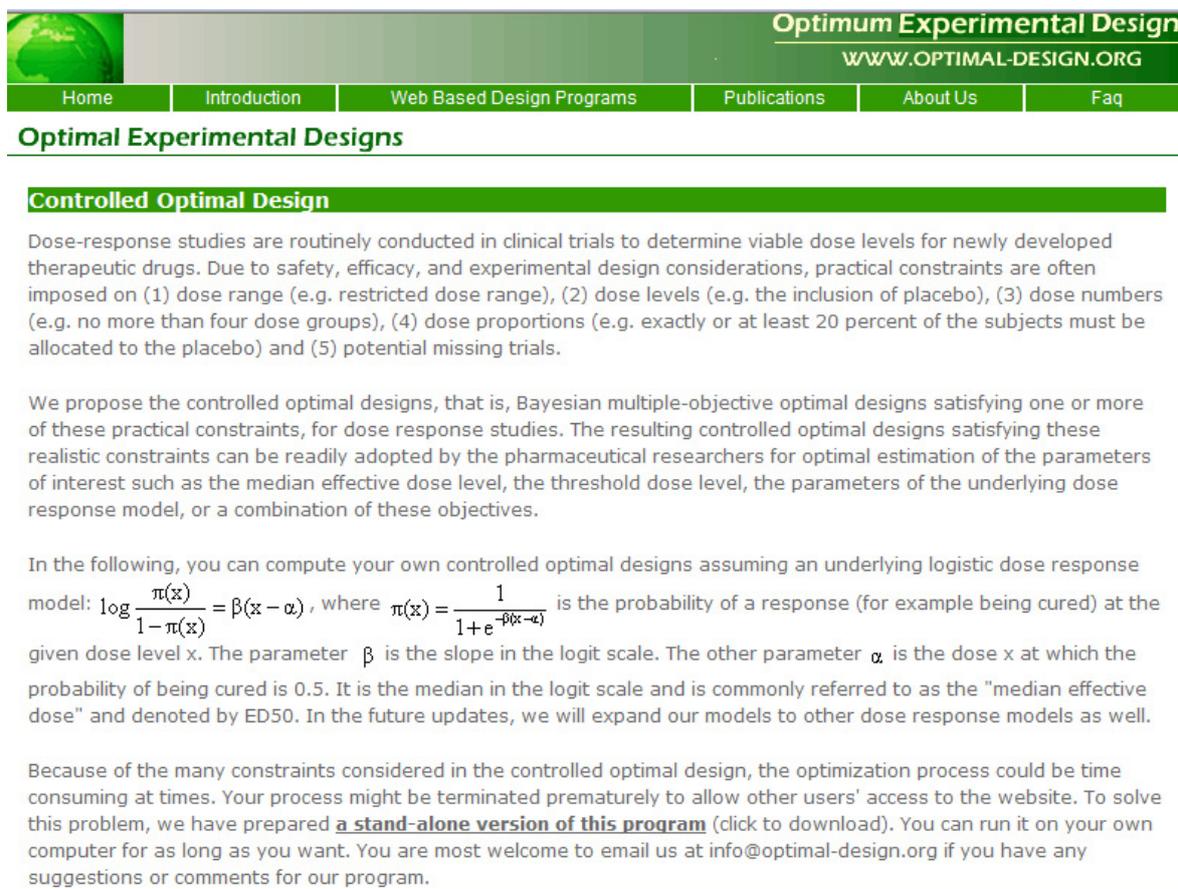
After selecting the desired approach in option (6), the user proceeds to option (7) to specify the individual objectives (percentiles etc.) and the corresponding weights ( $\lambda_i$ 's) for the chosen compound optimal design criterion. The user can print out the current values for options (1) through (9) by choosing option (12). Additionally, the user can also evaluate the design criterion value for an arbitrary design (for example, the equal allocation rule) by entering this design through option (4) and evaluating its value under the current design layout via option (11).

### 3.3. Controlled optimal design program 2.0, the web-based version

The **Controlled Optimal Design 2.0** program is available at the following website <http://www.optimal-design.org/optimal/polynomial/ControlledDesign.aspx>. A detailed introduction precedes the program and we have tried to make every option self-explanatory. For each option, every value entered by the user is stored in the memory and ready to be selected from the pull-down menu directly the next time around. The user will find the web-based program more user friendly than the stand-alone version. However, to allow greater access to other users and release computing burden on our server, the web-based program will automatically terminate a program if the running time exceeds 5 minutes. As an alternative, we provide the user with the flexibility of having a stand-alone program to run the same program on their own computers. Screen shots of portions of the web-based program are shown in Figures 1 and 2.

The web-based **Controlled Optimal Design 2.0** program adopts the client/server mode. The application consists of a web interface and a web-based MATLAB program to perform the calculation. Whenever a user submits a request through the web page, the web-based MATLAB program is invoked to run on the server end. The parameters specified on the web page are passed to the MATLAB program in the form of an HTTP request. When the calculation is complete, the results are sent back to the web page for display.

The application is developed on Windows XP and on the Microsoft Internet Information Services (IIS) web server. The web interface is essentially a web application developed using



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## Optimal Experimental Designs

### Controlled Optimal Design

Dose-response studies are routinely conducted in clinical trials to determine viable dose levels for newly developed therapeutic drugs. Due to safety, efficacy, and experimental design considerations, practical constraints are often imposed on (1) dose range (e.g. restricted dose range), (2) dose levels (e.g. the inclusion of placebo), (3) dose numbers (e.g. no more than four dose groups), (4) dose proportions (e.g. exactly or at least 20 percent of the subjects must be allocated to the placebo) and (5) potential missing trials.

We propose the controlled optimal designs, that is, Bayesian multiple-objective optimal designs satisfying one or more of these practical constraints, for dose response studies. The resulting controlled optimal designs satisfying these realistic constraints can be readily adopted by the pharmaceutical researchers for optimal estimation of the parameters of interest such as the median effective dose level, the threshold dose level, the parameters of the underlying dose response model, or a combination of these objectives.

In the following, you can compute your own controlled optimal designs assuming an underlying logistic dose response model:  $\log \frac{\pi(x)}{1-\pi(x)} = \beta(x - \alpha)$ , where  $\pi(x) = \frac{1}{1+e^{-\beta(x-\alpha)}}$  is the probability of a response (for example being cured) at the given dose level  $x$ . The parameter  $\beta$  is the slope in the logit scale. The other parameter  $\alpha$  is the dose  $x$  at which the probability of being cured is 0.5. It is the median in the logit scale and is commonly referred to as the "median effective dose" and denoted by ED50. In the future updates, we will expand our models to other dose response models as well.

Because of the many constraints considered in the controlled optimal design, the optimization process could be time consuming at times. Your process might be terminated prematurely to allow other users' access to the website. To solve this problem, we have prepared [a stand-alone version of this program](#) (click to download). You can run it on your own computer for as long as you want. You are most welcome to email us at [info@optimal-design.org](mailto:info@optimal-design.org) if you have any suggestions or comments for our program.

Figure 1: An introduction to the web-based **Controlled Optimal Design 2.0** program.

ASP.NET with C# (Microsoft Corporation 2003). The web-based MATLAB program is a modified version of the stand-alone program discussed above, with the input/output part adapted to the MATLAB web server format. The MATLAB web server is a MathWorks product that connects the web application to the web-based MATLAB program, passing data back and forth between the two.

The web interface encompasses a web page and C# code. The web page enables the user to specify the constraints and parameters for the controlled optimal design. Upon submission of the user input, the C# code is invoked to validate the input, combine it into a MATLAB structure, and then transform it into a byte array. An HTTP request is created thereafter by an ASP.NET built-in class: `HttpWebRequest`. The byte array is sent, via the HTTP request, to the MATLAB web server.

The MATLAB web server depends upon the TCP/IP networking for transmission of data between the web browser and MATLAB. It collects the input MATLAB structure from the HTTP request and passes it to an m-file (the MATLAB code file) specified in the input structure. The m-file obtains input values from the MATLAB structure and assigns them to the variables of interest. The MATLAB program then performs the computation and generates the optimal design results. Finally, the program combines the output values into a

**Parameters to be input:**Step 1: select an option.

- Design Option I - Calculate the optimal design  
 Design Option II - Evaluate the criterion value for the current design

Step 2: specify the following parameters.

Select the number of dose levels: .

**Specify the dose levels/intervals:** (e.g. If dose 1 is placebo, the lower and upper bounds would be 0 and 0. If dose 2 is to be selected in the interval [20, 50], the bounds would be 20 and 50 respectively. Please enter "inf" for positive infinity and "-inf" for negative infinity.)

Dose Level 1: Lower Bound = , Upper Bound =   
Dose Level 2: Lower Bound = , Upper Bound =   
Dose Level 3: Lower Bound = , Upper Bound =

**Specify the dose proportions:** (e.g. If one wishes to allocate exactly 20% subjects to dose 1, one would enter the bounds for dose 1 as 20% and 20%. If dose 2 would have at least 50% of the subjects, one would enter 50% and 100%.)

Dose Level 1: Lower Bound = , Upper Bound =   
Dose Level 2: Lower Bound = , Upper Bound =   
Dose Level 3: Lower Bound = , Upper Bound =

Figure 2: The input screen of the web-based **Controlled Optimal Design 2.0** program.

MATLAB output structure, and calls the function `htmlrep` to place the output structure into an HTML output document template, which is an HTML file containing the names of the output variables. The MATLAB web server then sends the data back to the web application in the form of an HTTP response. Subsequently, the C# code behind the web page receives the HTTP response via the C# built-in class `httpWebResponse`. The data passed back by the MATLAB web server are stored into a C# string. Values of the variables are obtained from the resulting string and displayed onto the web page. More technical details on the ASP.NET web application, the MATLAB web server, and web-based MATLAB programming can be found on <http://www.microsoft.com/> and <http://www.mathworks.com/>.

## 4. An example

We now demonstrate how to use the **Controlled Optimal Design 2.0** program to re-design a placebo controlled dose-finding study for greater efficiency. Various daily dosage of the drug Tacrolimus shown in Table 1 was used to treat rheumatoid arthritis (RA) patients for 24 weeks (Kondo *et al.* 2004). Prior to this trial in Japan, a dose-ranging trial on the same drug was conducted in the United States (US), Furst *et al.* (2002), and information from this

Dose levels (in mg)	0	1	3	5	Total
Number of subjects allocated to the dose level	71	69	64	64	268
Number of subjects completed the study	29	40	34	38	141
Number of subjects with improvement at the given dosage	11	20	22	32	85

Table 1: Summary of a dose ranging study on Tacrolimus reported by [Furst \*et al.\* \(2002\)](#).

trial was used in the dose response model for the Japanese study. In the US trial, 268 patients with RA who were resistant to or intolerant of methotrexate (mean dose 15.2mg/week) and had active disease for at least 6 months (mean tender joint count 28.2, mean erythrocyte sedimentation rate 46.5mm/hour) were randomized to receive treatment after discontinuation of methotrexate. Patients are judged to have benefitted from the treatment if the patient showed at least a 20% improvement in several measures. The key outcome is a composite binary outcome commonly called the ACR20. This binary outcome is a validated measure from the American College of Rheumatology and takes on the value 1 if the patient had improved and 0 otherwise. Data from the US study is summarized in Table 1.

The US study found the 5mg dose to be overly toxic and so the Japanese study was restricted to the dose interval (1mg, 3mg]. We used the SAS PROC NLMIXED procedure ([SAS Institute Inc. 2008b](#)) and determined the dose response relationship between subjects who completed the study and subjects who showed improvement in the study (rows 2 and 3 in Table 1). The fitted model was the logit model with estimated parameters  $\hat{\alpha} = 1.166$  and  $\hat{\beta} = 0.410$  with corresponding standard errors 0.495 and 0.103, respectively. We constructed the prior distributions for  $\alpha$  and  $\beta$  in the Japanese study using the 95% confidence intervals for the two parameters. The resulting prior distributions were  $\alpha \sim U[0.188, 2.143]$  and  $\beta \sim U[0.206, 0.615]$ . In **Controlled Optimal Design 2.0**, we provide more flexibility for the user to select the prior distributions. The user can select any independent beta distributions on any arbitrary intervals as their prior distributions for the two logit model parameters. This includes the uniform distribution as a special case when both beta distribution parameters are set to 1.

The data in Table 1 shows there are missing data in the trial. Our program can make use of this information to design an improved trial. We do this by estimating the form and parameters in the potential non-missing probability function discussed in [Baek \*et al.\* \(2006\)](#) and [Imhof \*et al.\* \(2002, 2004\)](#). This function estimates the probability of having an observation at dose  $x$ . In practice, it is a monotonically increasing function since we expect more dropouts as the dose levels are increased due to toxicity effects. Our analysis used subjects who entered the study and subjects who completed the study (rows 1 and 2 in Table 1). We used the SAS PROC LOGISTIC ([SAS Institute Inc. 2008a](#)) procedure and the MATLAB FIT function to determine that the best fitted potential non-missing probability function is  $\hat{\tau}(x) = 1 - \exp(-0.053x - 0.643)$ . The observed percent of patients completing the trial at the 4 doses were respectively given by 41%, 58%, 53%, and 59% versus the fitted percentages of 47%, 50%, 55%, and 60%. Our program provides three types of potential missing probability functions that we feel are likely to arise in practice. For this particular example, the exponential non-missing probability function appears to be the best model to fit the data at hand.

Now we are ready to construct the Bayesian multiple-objective controlled optimal design for

the Japanese study on Tacrolimus (Kondo *et al.* 2004). In dose response studies, the major objectives are usually the estimation of the underlying dose response curve and the estimation of key dose levels such as the threshold dose. The threshold dose is often defined as the dose that is more effective than the placebo by a certain percentage (Zeng and Zhu 1997). For the given study, we infer that the threshold dose is defined as the dose level that is 15% more efficient than the placebo. Since 11 out of the 29 patients allocated to the placebo completed the 6-month trial in the US study (Table 1), the success rate of the placebo is estimated to be  $11/29 \approx 0.38$ . Thus the placebo is estimated as ED38, and the threshold dose is estimated as ED53. We also learned that the Japanese study was designed as a 3-dose trial that required 0 and 3mg doses, with the third dose in a medium dose range somewhere between 1mg to 2mg. For better clinical trial logistics and potential missing trial considerations, it was also desired that each dose level has at least 25% of the subjects in the study.

The constraints and prior information for the Kondo *et al.* (2004) trial are summarized as follows:

1. **Number of dosages:** 3.
2. **Dose range:**  $[0, 3\text{mg}]$ .
3. **Dose levels:**
  - (a) Dose 1: placebo.
  - (b) Dose 2: in the interval of  $[1\text{mg}, 2\text{mg}]$ .
  - (c) Dose 3: 3mg.
4. **Dose proportions:**  $\geq 25\%$  at each dose level.
5. **Priors:** For the underlying logit dose response model: Independent uniform distributions (beta distribution with parameters 1 & 1) with  $\alpha \sim U[0.188, 2.143]$  and  $\beta \sim U[0.206, 0.615]$ .
6. **Potential non-missing probability function:** Exponential function with estimated parameters  $a = 1$ ,  $b = -0.053$ , and  $c = 0.643$ .

Suppose we wish to estimate the underlying logit dose response curve using the  $D$ -optimality criterion and also estimate the threshold dose (ED53) using the  $C$ -optimality criterion. Assume further that we are equally interested in both objectives. Accordingly, we set  $(\lambda_1 = \lambda_2 = 0.5)$ . To generate the controlled optimal design, we first select the *standardized compound C- and D-optimal design* option (to account for different magnitude of the individual objective functions) in **Select the optimality criterion**. In the next step – **Specify the design criteria**, we enter 53 (for ED53) for *Additional criteria other than the determinant*, and 0.5, 0.5 for *Corresponding compound optimal design weights (including the determinant)*. We ran the **Controlled Optimal Design 2.0** program and found two numerically controlled optimal designs. They are:

$$\xi^* = \left\{ \begin{array}{ccc} 0 & 1 & 3 \\ 0.33 & 0.25 & 0.42 \end{array} \right\} \quad \text{and} \quad \xi^{**} = \left\{ \begin{array}{ccc} 0 & 2 & 3 \\ 0.41 & 0.25 & 0.34 \end{array} \right\}.$$

Rounding to the nearest integer, both designs are 100% efficient for estimating the threshold dose ED53 and the dose response curve under the given constraints.

The design used by [Kondo \*et al.\* \(2004\)](#) has equal number of subjects at dosages 0, 1.5, and 3:

$$\xi^1 = \left\{ \begin{array}{ccc} 0 & 1.5 & 3 \\ 1/3 & 1/3 & 1/3 \end{array} \right\}.$$

A direct calculation shows this design is 98% efficient for estimating the threshold dose ED53 and 97% efficient for estimating the dose response curve under the given constraints.

Like many other dose response studies, [Kondo \*et al.\* \(2004\)](#) was also interested in comparing the response rates between the active dosages 1.5mg and 3mg to the placebo. The optimal design for this purpose alone allocates equal number of subjects to the active dosages and  $\sqrt{2}$  times as many subjects to the placebo ([Fleiss 1986](#); [Zhu and Wong 2000b](#)). This optimal design is

$$\xi^2 = \left\{ \begin{array}{ccc} 0 & 1.5 & 3 \\ 0.414 & 0.293 & 0.293 \end{array} \right\}$$

and can be shown to have 96% efficiency for estimating the threshold dose ED53 and 98% efficiency for estimating the dose response curve under the given constraints.

In summary, we have shown that the **Controlled Optimal Design 2.0** program is able to generate an optimal design that meets several practical constraints and the multiple goals in the study. There are two controlled optimal designs  $\xi^*$  and  $\xi^{**}$  for the problem at hand. Interestingly, both the equal allocation rule ( $\xi^1$ ) adopted by [Kondo \*et al.\* \(2004\)](#) and the best allocation scheme ( $\xi^2$ ) for simultaneous treatment-placebo comparison purposes are also highly efficient for the estimation of the threshold dose and the underlying dose response curve. In our experience, such findings are uncommon. In two other earlier dose response trials that we worked on, the original designs were significantly less efficient than the controlled optimal designs. Our hope is that the **Controlled Optimal Design 2.0** program will facilitate and enable researchers to use more efficient and realistic designs in their work using minimal resources and without sacrificing statistical efficiency.

## 5. Summary

In this paper, we introduced the **Controlled Optimal Design 2.0** program for computing multiple-objective Bayesian optimal designs in dose response studies satisfying several practical constraints on the dose range, dose levels, dose proportions, and potential missing trials simultaneously. We used an innovative optimization code in our work and are encouraged by the performance of the optimization method. Although the current program assumes an underlying logit dose response model, the code can be readily extended to accommodate other dose response models ([Smith and Ridout 1998](#); [Biedermann \*et al.\* 2006, 2007](#)).

Our design website contains not only the **Controlled Optimal Design 2.0** program but a variety of codes for generating a variety of optimal designs for several popular models in the health sciences. We hope that by providing our design programs on the website <http://www.optimal-design.org/>, we can help to bridge the gap between practice and theory, and between the pharmaceutical industry and the optimal design research community. We also hope to encourage researchers to work with web-based tools and use the internet as an efficient venue for improving design practice and as an information exchange forum.

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