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MULTIPLE-OBJECTIVE DESIGNS IN A DOSE-RESPONSE EXPERIMENT

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The toxicity/efficacy of a potential drug must be examined before it can be approved for general use. Quantal dose-response experiments are conducted in both preclinical and clinical trials for this purpose. A usual practice in the design of a dose-response experiment is to divide the dosage interval evenly and allocate equal number of subjects to each of the dosage levels. It is shown here that this scheme may not be efficient. We propose multiple-objective optimal designs, including sequential designs, as a practical alternative.

1. Introduction. The study of drug toxicity and efficacy is a crucial part of the drug development process. Quantal dose-response experiments are routinely conducted in preclinical and phase I, II clinical trials for this purpose. Due to the multiple-objective nature of the experiment and the lack of well-established allocation rules, researchers often use the uniform equal allocation scheme in the hope that it will be an efficient design for their purposes. This rule allocates equal number of subjects to a selected set of equally spaced dosage levels. However, we show here that this rule can be inefficient for estimating parameters in the model. The efficiencies of the equal allocation schemes vary according to different levels of prior knowledge on the "median lethal/effective dose" level — the dosage level at which the probability of being poisoned/cured is 50%. As an alternative, we propose multiple-objective Bayesian optimal designs and compare their performance to the uniform equal allocation rules. For the cases considered here, the results suggest a two-stage Bayesian design can be potentially useful when there is little prior information for the parameters.

One common model assumed in a quantal dose-response experiment is the simple logit model

$$\log \frac{\pi(x)}{1-\pi(x)} = \beta(x-\alpha), \tag{1.1}$$

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where $\pi(x) = 1/(1+\exp(-\beta(x-\alpha)))$ is the probability of a response at dosage x, and $x \in \chi$, where χ is an interval containing the dosage levels of interest. The parameter β is the slope in the logit scale. The location parameter α is the value of x at which the probability of being poisoned/cured is 0.5. It is the median in the logit scale and is oftentimes referred to as the median lethal dose or the median effective dose. In this paper, we will denote this quantity by LD50. More generally, we use LD100π to denote the dose level x_0 at which the probability of being poisoned is π. From (1.1), we have

$$\pi(x_0) = 1/(1+\exp(-\beta(x_0-\alpha))),$$

and it follows that

$$LD100\pi = x_0 = \alpha + \frac{\gamma}{\beta}, \tag{1.2}$$

where $\gamma = \log \pi/(1-\pi)$.

There are usually several objectives in a dose-response experiment. Two common objectives are the estimation of the model parameters α and β. The LD50 (α) is often used as an indicator of the experiment outcome. For instance, scientific investigators often try to characterize a pharmacological agent by determining its LD50. In this work, it will be assumed that it is reasonable to impose a certain precision threshold on the estimation of α. On the other hand, in order to study the overall shape of the logit curve, we need to estimate the slope β as precisely as possible, subject to the constraint on α. The optimal design satisfying several objectives (of various importance) simultaneously is called a multiple-objective optimal design. Here we have a two-objective optimal design problem with the primary objective of estimating α, and the secondary objective of estimating β or vice versa. Examples of quantal dose-response experiments can be found in Duggleby (1979) and Kalish (1990), where both noted that the parameters in the model can have unequal importance to the researcher and it is useful to include this information when designing the study. Specifically, Duggleby (1979) studied the widely used Michaelis-Menten model in biological sciences given by

$$Ey = ax/(b+x), \; x > 0$$

and noted that the Michaelis constant b is oftentimes more interesting than the parameter a. Likewise, Kalish (1990) noted that efficient designs for estimating α in the logistic model may not perform well for estimating β. Duggleby (1979) realized that the standard 'equal-interest' D-optimal design did not reflect accurately the practical needs of the researcher but he did not provide an alternative design. Kalish (1990) considered a class of models, which includes the logistic model as a special case, and proposed a sequential approach for estimating the parameters.

The optimal designs developed in this paper for the simple logit model are more flexible than the traditional single-objective designs. Unlike Duggleby (1979) and Kalish (1980), our designs do allow and require prior information of the parameters to be incorporated at the design stage and additionally, require the researcher to specify in advance the level of efficiency desired for estimating selected parameters. The method

employed here for constructing these optimal designs is a general one [Cook and Wong (1994)] but in what is to follow, we will focus on the design problem for estimating parameters in the simple logit model as an illustrative example.

2. Background.

2.1. *The frequentist's approach.* Let the response data be denoted by $y^T = (y_1, \cdots, y_N)$, where $y_i = 1$ or 0 depending on whether there is a response from the ith subject or not. The contribution to the likelihood of a single observation at the design point x_i is $\pi(y_i \mid x_i, \theta)$, where $\pi(1 \mid x_i, \theta) = \pi(x_i)$ and $\pi(0 \mid x_i, \theta) = 1 - \pi(x_i)$, where $\theta^T = (\alpha, \beta)$. Following convention, we measure the worth of a design by its Fisher information matrix. The (i,j)th element of the standardized observed Fisher information matrix for a design ξ is given by

$$[M(\theta, \xi)]_{ij} = -\int \frac{\partial^2}{\partial\theta_i \partial\theta_j} \log(\pi(y \mid x, \theta))\, \xi(dx). \tag{2.1}$$

Many popular design criteria are expressed in terms of the information matrix. For instance, the D-optimality criterion seeks to minimize the volume of the confidence ellipsoid for the parameters of interest, α and β by design. The D-optimal design for the logit model (1.1) allocates half the subjects to each of the doses LD82.4 and LD17.6 [White (1975); Kalish and Rosenberger (1978)]. It can be shown easily that the LD50 optimal design is a one-point design at the LD50, and the Slope optimal design is a two-point design equally supported at the LD8.3 and the LD91.7.

The frequentists' optimal designs depend on the dosage level LD100π, which is unknown. One solution is to guess the values of the unknown parameters and construct a locally optimal design. Therefore the LD50 and the Slope optimal designs given above are often termed the local LD50 and the local Slope optimal designs respectively. Abdelbasit and Plackett (1983) proposed a sequential approach and found D-optimal designs for estimating α and β using the Fiducial method. They pointed out that higher-stage designs are more efficient for poor initial estimates, but not for good ones. Minkin (1987) strengthened their results by proposing a two-stage procedure, assuming the availability of good initial parameter estimates, and the adequacy of the quadratic approximation to the log-likelihood function.

2.2. *The Bayesian approach.* The uncertainty of the accuracy of the initial estimation can be addressed in a Bayesian framework. This assumes a prior distribution for the unknown parameters is available, either from previous studies or by elicitation. Chaloner and Larntz (1989) considered Bayesian optimal designs which are found by minimizing criteria of the form $\Phi(\xi) = E_\theta \Upsilon(M(\theta, \xi))$, where Υ is some convex functional and the expectation is taken with respect to the prior distribution on θ.

Chaloner and Larntz (1989) proposed two optimality criteria analogous to the frequentists' version, namely, the Bayesian $D-$optimality given by

$$\Phi(\xi) = -E_\theta \log\det M(\theta, \xi),$$

and the Bayesian A-optimality given by $\Phi(\xi) = E_\theta[trA(\theta) M(\theta, \xi)^{-1}]$. In the latter case, $A(\theta)$ is some user selected nonnegative definite matrix. For example, if we are

interested in estimating a given function of θ, say $c(\theta)$, we set $A(\theta) = \nabla c(\theta) (\nabla c(\theta))^T$, where $\nabla c(\theta)$ is the vector of partial derivatives of $c(\theta)$. In this case, the A-optimality reduces to c-optimality. Since α and β are each a function of $\theta^T = (\alpha, \beta)$, we will concentrate on the c-optimality criterion from now on.

The design efficiency of an arbitrary nonsingular design ξ relative to the $c-$ optimal design ξ^* is defined as

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

It can be viewed as the ratio of the expected variances for the estimated $c(\theta)$ given by the two designs. Note that the design efficiency is invariant to the sample size and that the expected variances of the estimated model parameters are inversely proportional to the sample size. Therefore, to achieve the same variance for estimating $c(\theta)$, a design with efficiency 0.5 would require twice the sample size needed by the optimal design. In this paper, we will assume that the sample size is already determined by some other considerations such as cost constraints on the study.

3. Multiple-Objective Optimal Designs.

3.1. *Overview.* Two approaches have been suggested for constructing a multiple-objective optimal design. One way is to find a compound optimal design [Cook and Wong (1994)] and the other is to find a constrained optimal design [Lee (1987)]. For simplicity, suppose there are two distinct objectives as implemented by the convex functions Φ_1 and Φ_2. We assume Φ_1 and Φ_2 are the primary and the secondary criteria respectively, and $\Psi_i(\xi)$ is Φ_i divided by its minimal value attained at ξ^i, the Φ_i-optimal design, $i = 1, 2$. The compound optimal design ξ_λ is the design which minimizes the weighted average of the functional Ψ_1 and Ψ_2,

$$\Phi(\xi \mid \lambda) = \lambda \Psi_1(\xi) + (1 - \lambda) \Psi_2(\xi), \tag{3.1}$$

where $0 \leq \lambda \leq 1$ is a user-selected constant. Let $E_i(\xi)$ denote the design efficiency of ξ relative to ξ^i, $i = 1, 2$. The constrained optimal design ξ_{e_1} is the design which maximizes $E_2(\xi)$ subject to the constraint that $E_1(\xi) \geq e_1$, where e_1 is a user defined constant between 0 and 1.

There are algorithms for finding compound optimal designs but the designs are harder to interpret. The opposite is true for constrained optimal designs [Lee (1987)], especially when we have more than two objectives. Before the establishment of equivalence between these two approaches (i.e. every compound optimal design is a constrained optimal design and vice versa) by Cook and Wong (1994) and Clyde and Chaloner (1996), it was difficult to find useful constrained optimal designs. With the help of the equivalence theorem, however, we can now find the constrained optimal design indirectly from compound optimal designs. This approach is particularly straightforward to implement when we have two-objective design problems; the designs sought can be found graphically from the efficiency plot [Cook and Wong (1994)].

3.2. *Compound/Constrained optimal designs for the LD50 and the slope.* The results of quantal dose-response experiments are often summarized by an estimate of the LD50 (α), along with an estimate of the slope β. The importance of these two estimates

might differ, but the researcher usually has an idea about their relative importance in the study. This can be formulated as a two-objective constrained optimization problem. The desired constrained optimal design is found graphically from an efficiency plot of Bayesian compound optimal designs generated from the Logit-Design program from Chaloner and Larntz (1989), after some modifications.

For the logit model (1.1), assume the design region χ is closed and bounded. Consider a design ξ on χ with weight p_i at design points x_i, $i = 1, \cdots, K$, and $\sum p_i = 1$. Define

$$\begin{aligned} w_i &= \pi(x_i)(1 - \pi(x_i)), \quad t = \sum_{i=1}^{K} p_i w_i, \\ \overline{x} &= t^{-1} \sum_{i=1}^{K} p_i w_i x_i \text{ and } s = \sum_{i=1}^{K} p_i w_i (x_i - \overline{x})^2. \end{aligned}$$

The inverse of the Fisher information matrix given in (2.1) can be shown to be

$$M(\theta, \xi)^{-1} = \beta^{-2} \begin{bmatrix} 1/t + (\overline{x} - \alpha)^2 / s & \beta(\overline{x} - \alpha)/s \\ \beta(\overline{x} - \alpha)/s & \beta^2/s \end{bmatrix}. \tag{3.2}$$

When prior information is used to design the study, the LD50 and the Slope optimal designs are Bayesian $c-$optimal designs, with $c(\theta) = \alpha$ and $c(\theta) = \beta$ respectively. The design criteria are

$$\Phi_\alpha(\xi) = E_\theta\left\{\beta^{-2}\left[1/t + (\overline{x} - \alpha)^2/s\right]\right\}, \text{ and } \Phi_\beta(\xi) = E_\theta(1/s).$$

Let ξ^i, $i = 1, 2$ be the LD50 and the Slope optimal designs for the given priors respectively. By the definition of the compound optimal designs, the design criterion for estimating the LD50 and the slope is to minimize, for each λ,

$$\Phi(\theta, \xi \mid \lambda) = \lambda \Phi_\alpha(\xi)/\Phi_\alpha\left(\xi^1\right) + (1 - \lambda)\Phi_\beta(\xi)/\Phi_\beta\left(\xi^2\right).$$

Zhu and Wong (1997) considered four combinations of independent uniform priors which were used by Chaloner and Larntz (1989). These priors are $\alpha \sim U[-0.1, 0.1]$, $\beta \sim U[6.9, 7.1]$; $\alpha \sim U[-0.1, 0.1]$, $\beta \sim U[6, 8]$; $\alpha \sim U[-1, 1]$, $\beta \sim U[6.9, 7.1]$; and $\alpha \sim U[-1, 1]$, $\beta \sim U[6, 8]$. The priors $U[-1, 1]$ and $U[6, 8]$ have relatively large support sets implying more uncertainty in the unknown parameters than the priors $U[-0.1, 0.1]$ and $U[6.9, 7.1]$. Our results agree with Chaloner and Larntz (1989) in that the compound optimal designs appear to be much more sensitive to the prior distribution on α than on β, and in general, as the uncertainty in the prior distribution on α increases so does the number of design support points.

For the same prior on β, the compound optimal designs under the two priors on α, namely, $\alpha \sim U[-0.1, 0.1]$ and $\alpha \sim U[-1, 1]$, are very different. The former one with a more informative prior has two support points while the latter has six. Moreover, the two objectives are very competitive under the informative prior $\alpha \sim U[-0.1, 0.1]$, while all compound optimal designs are more than 90% efficient for both objectives under the non-informative prior $\alpha \sim U[-1, 1]$. Tables 1 and 2 list some of these designs.

For the same prior on α, the compound optimal designs under the two priors on β, namely, $\beta \sim U[6.9, 7.1]$ and $\beta \sim U[6, 8]$, are very similar. They have the same number of support points with about the same values and the same design weights. Their design efficiencies for the same objective are also very similar. For $\alpha \sim U[-0.1, 0.1]$, one can observe this striking similarity directly from Table 1. For $\alpha \sim U[-1, 1]$, we have a similar conclusion. For example, when $\beta \sim U[6.9, 7.1]$,

$$\xi_{\lambda=0.8} = \left\{ \begin{array}{cccccc} -.971 & -.560 & -.186 & .185 & .559 & .971 \\ .164 & .170 & .166 & .166 & .170 & .164 \end{array} \right\}$$

with the two efficiencies equal to 0.996 and 0.950 respectively.

TABLE 1

Selected Compound Optimal Designs: $\alpha \sim U[-0.1, 0.1]$, $\beta \sim U[6.9, 7.1]$ *(*) and* $\alpha \sim U[-0.1, 0.1]$, $\beta \sim U[6, 8]$ *(**)*

λ	x_1*	x_2*	$E_1(\xi_\lambda)$*	$E_2(\xi_\lambda)$*	x_1**	x_2**	$E_1(\xi_\lambda)$**	$E_2(\xi_\lambda)$**
1.0	-0.127	0.127	1.00	0.379	-0.128	0.128	1.00	0.388
0.80	-0.176	0.176	0.925	0.612	-0.176	0.176	0.928	0.620
0.60	-0.208	0.208	0.831	0.747	-0.207	0.207	0.8351	0.755
0.52	-0.219	0.219	0.792	0.792	-0.218	0.218	0.798	0.798
0.40	-0.238	0.238	0.731	0.852	-0.237	0.237	0.737	0.859
0.20	-0.274	0.274	0.612	0.941	-0.273	0.273	0.621	0.945
0.00	-0.340	0.340	0.425	1.00	-0.335	0.335	0.441	1.00

TABLE 2

Selected Compound Optimal Designs: $\alpha \sim U[-1, 1]$, $\beta \sim U[6, 8]$

λ	ξ_λ						$E_1(\xi_\lambda)$	$E_2(\xi_\lambda)$
1.0	−0.942	−0.527	−0.165	0.179	0.535	0.944	1.00	0.919
	0.182	0.166	0.155	0.153	0.162	0.181		
0.80	−0.973	−0.565	−0.188	0.188	0.564	0.973	0.996	0.952
	0.163	0.169	0.168	0.167	0.169	0.163		
0.49	−1.01	−0.583	−0.196	0.196	0.583	1.01	0.980	0.980
	0.150	0.171	0.179	0.179	0.171	0.150		
0.20	−1.05	−0.586	−0.196	0.198	0.587	1.05	0.951	0.995
	0.144	0.165	0.192	0.191	0.164	0.144		
0.00	−1.08	−0.582	−0.193	0.193	0.582	1.08	0.910	1.00
	0.140	0.155	0.205	0.205	0.155	0.140		

Zhu and Wong (1997) showed that as long as the prior on α is symmetric about 0, the compound optimal design will be approximately symmetrical about 0; i.e., the

design will have symmetrical support points and the design weights associated with each pair of symmetrical support points are about the same. For the prior $\alpha \sim U[-0.1, 0.1]$, every compound optimal design is symmetrically supported at two points (Table 1).

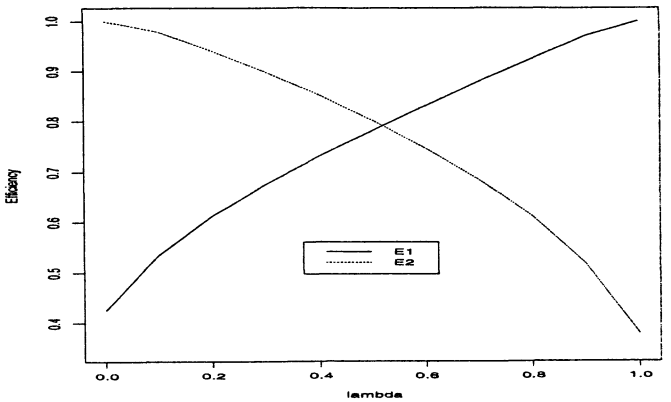

FIG. 1. *Efficiency plot of compound optimal designs for the estimation of the LD50 and the slope when* $\alpha \sim U[-0.1, 0.1]$ *and* $\beta \sim U[6.9, 7.1]$.

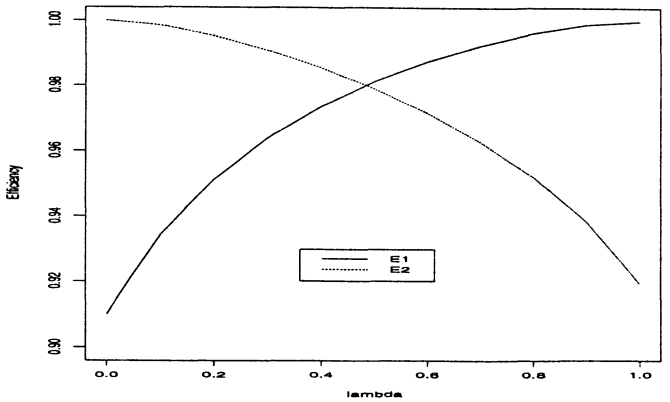

FIG. 2. *Efficiency plot of compound optimal designs for the estimation of the LD50 and the slope when* $\alpha \sim U[-1, 1]$ *and* $\beta \sim U[6, 8]$.

The desired constrained optimal design can be found directly from the efficiency plot which is a plot of the design efficiencies of ξ_λ under the two objectives versus λ. Because the efficiency plots under the same prior on α are similar, only two such plots are provided (Figures 1 and 2). Since a constrained optimal design ξ_{e_1} maximizes $E_2(\xi)$ subject to $E_1(\xi) \geq e_1$, the value of λ for the corresponding compound optimal design ξ_λ is given at the intersection of the horizontal line passing through $E_1(\xi_\lambda) = e_1$ and the efficiency curve. The cross point of the two efficiency curves corresponds to the design which has the same efficiency for both objectives. For example, if the prior for α is $U[-0.1, 0.1]$, Figure 1 shows the cross point is 0.52. For this value of λ, the corresponding compound Bayesian optimal design is

$$\xi_{\lambda \approx 0.52} \approx \left\{ \begin{array}{cc} -0.22 & 0.22 \\ 0.5 & 0.5 \end{array} \right\}.$$

From Figure 1, we see that this design is about 80% efficient for both objectives. As mentioned earlier, the same result is obtained when the other β prior is used. Interestingly, this design is also the locally D-optimal design with the best guess of (α, β) as $(0, 7)$. When the prior for α is $\sim U[-1, 1]$, Figure 2 shows that the cross point is about 0.49. The corresponding compound Bayesian optimal design is

$$\xi_{\lambda \approx 0.49} \approx \left\{ \begin{array}{cccccc} -1 & -0.58 & -0.20 & 0.20 & 0.58 & 1 \\ 0.15 & 0.17 & 0.18 & 0.18 & 0.17 & 0.15 \end{array} \right\}$$

and the plot shows this design has about 98% efficiency for both objectives. Again, a similar conclusion is reached if the other β prior is used.

4. Efficiencies of the Uniform Equal Allocation Schemes. One simple dosage allocation scheme is to divide the dosage range evenly into several intervals and allocate equal number of subjects to each dosage level. Three types of uniform equal allocation schemes are considered in this section. Without loss of generality, we will denote the dosage interval as $[-1, 1]$. The type 1 scheme is to divide the whole interval uniformly and assign equal numbers of subjects to each division point, including the two end points. Type 2 is the same as type 1 except that the two end points are excluded. The type 3 scheme is motivated by ethical issues and subjects are assigned to dose levels below the expected LD50, 0 in this case. The interval $[-1, 0]$ is divided uniformly and subjects are assigned equally to each division point including -1 and 0.

Since it is unlikely that researchers would want a design with more than nine points, eight type 1 designs were considered with two to nine support points. They are {-1, 1}, {-1, 0, 1}, {-1, -1/3, 1/3, 1}, etc.. Six type 2 designs were obtained by deleting the end points of the type 1 designs with four through nine support points. They are {-1/3, 1/3}, {-0.5, 0, 0.5}, {-0.6, -0.2, 0.2, 0.6}, etc. In addition, five type 3 designs, {-1, 0}, {-1, -0.5, 0}, {-1, -2/3, -1/3, 0}, {-1, -0.75, -0.5, -0.25, 0} and {-1, -0.8, -0.6, -0.4, -0.2, 0} were studied.

The efficiencies of these designs under each of the two objectives are displayed in Table 3. The results are dominated by the priors on α. For the non-informative prior

$\alpha \sim U[-1,1]$, the six-point type 1 design is highly efficient (≈ 0.986 for α and ≥ 0.957 for β). However, under the informative prior $\alpha \sim U[-0.1,0.1]$, none of the uniform equal allocation scheme is efficient for estimating α and β. This echoes the observation of Abdelbasit and Plackett (1983) in that a blind procedure without utilizing the abundant information is unlikely to be efficient.

TABLE 3

Efficiencies of Uniform Equal Allocation Rules

	$\alpha \sim U[-1,1]$				$\alpha \sim U[-.1,.1]$			
	$\beta \sim U[6.9,7.1]$		$\beta \sim U[6,8]$		$\beta \sim U[6.9,7.1]$		$\beta \sim U[6,8]$	
Type 1	E_1	E_2	E_1	E_2	E_1	E_2	E_1	E_2
2-point	0.005	0.003	0.004	0.002	0.005	0.100	0.004	0.086
3-point	0.412	0.345	0.408	0.311	0.324	0.078	0.317	0.068
4-point	0.849	0.808	0.842	0.786	0.224	0.555	0.226	0.555
5-point	0.959	0.945	0.960	0.940	0.282	0.398	0.328	0.390
6-point	0.986	0.957	0.986	0.959	0.324	0.488	0.319	0.489
7-point	0.991	0.948	0.992	0.952	0.332	0.477	0.338	0.486
8-point	0.992	0.937	0.993	0.942	0.336	0.496	0.342	0.505
9-point	0.990	0.929	0.991	0.933	0.342	0.500	0.346	0.499
Type 2								
2-point	0.008	0.040	0.007	0.032	0.444	0.999	0.446	0.999
3-point	0.057	0.162	0.054	0.145	0.537	0.588	0.541	0.579
4-point	0.168	0.317	0.164	0.300	0.470	0.676	0.475	0.679
5-point	0.302	0.446	0.300	0.433	0.463	0.624	0.472	0.635
6-point	0.420	0.537	0.420	0.528	0.446	0.625	0.454	0.637
7-point	0.507	0.597	0.506	0.592	0.438	0.611	0.443	0.610
Type 3								
2-point	0.000	0.002	0.000	0.001	0.321	0.050	0.308	0.043
3-point	0.001	0.010	0.001	0.008	0.383	0.267	0.384	0.260
4-point	0.001	0.013	0.001	0.011	0.306	0.295	0.308	0.294
5-point	0.001	0.014	0.001	0.011	0.262	0.285	0.263	0.285
6-point	0.001	0.014	0.001	0.011	0.235	0.274	0.236	0.274

Numerical results in Table 3 suggest that the following two-stage Bayesian sequential design for estimating α and β is highly efficient for either of the priors on α. A theoretical justification for this strategy is not available at this time.

Stage 1. Adopt the type 1 six-point uniform design, allocate 1/6 of subjects to each of the six dosage levels $\{-1, -0.6, -0.2, 0.2, 0.6, 1\}$. This design is highly efficient (≈ 0.986 for α and ≥ 0.957 for β) under the non-informative prior $\alpha \sim U[-1,1]$. If the number of subjects is limited, a four- or five-point type 1 design may also be used.

Stage 2. Estimate the model parameters using the results from stage 1. A maximum likelihood estimator might be the easiest to calculate. Recenter the dosage interval around the estimator $\widehat{\alpha}$, and assume a new informative prior $\alpha \sim U[-0.1,0.1]$. Implement the design

$$\xi_{\lambda \approx .52} \approx \left\{ \begin{array}{cc} -0.22 & 0.22 \\ 0.5 & 0.5 \end{array} \right\}$$

which gives us about equal efficiencies (0.8) for the estimation of α and β. Note that this design coincides with the locally D-optimal design with degenerate priors $\alpha \approx 0$ and $\beta \approx 7$. Therefore, in general, we can use the locally D-optimal design

$$\xi_D^* = \left\{ \begin{array}{cc} LD17.6 & LD82.4 \\ 0.5 & 0.5 \end{array} \right\}$$

as the second stage design with the plug-in maximum likelihood estimates of α and β obtained from stage 1. Alternatively, one may use the posterior from stage 1 as the new prior and proceed with the construction of the stage 2 optimal design.

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