Optimal Design for Quantal Bioassay via Monte Carlo Methods

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SUMMARY

In quantal bioassay, different levels of a stimulus are applied to the subjects (experimental units) to learn about the distribution of their tolerance. The response is usually assumed to be dichotomous. The design issue is to determine the levels of the stimuli and to allocate the subjects to different levels of stimuli. We adopt a nonparametric Bayesian approach and assume a Dirichlet process prior on the potency curve. The optimal design solution is derived from a preposterior analysis. When the number of stimuli increases, it becomes more and more difficult to carry out an analytic solution to the preposterior analysis. A simulation-based approach as in Müller and Parmigiani (1995) becomes quite useful. This approach replaces the exact preposterior analysis by a curve-fitting-based optimization procedure that uses Monte Carlo samples simulated from the joint parameter/sample space. We illustrate the implementation of the method by several examples.

KEYWORDS: Bayesian design; Dirichlet process prior; Stochastic optimization; Curve fitting.

1. Introduction

In the quantal bioassay problem different levels of a stimulus, such as different dosage levels of a drug, are applied to a group of subjects and the number of subjects giving a positive response at each stimulus level is recorded. The response to a given stimulus is assumed to be dichotomous: either positive or negative. A positive response is produced when the stimulus level reaches or exceeds a threshold. The threshold typically varies from one subject to another and thus is treated as a random variable with an unknown distribution F which is referred to as the potency curve or the tolerance distribution. The objective of the bioassay is to learn about the tolerance distribution.

Nonparametric Bayesian approaches to analyze bioassay data have been considered in the literature; see for example, Kuo (1983) and the references therein. Most of these approaches have used Dirichlet process priors to describe uncertainty about the tolerance distribution

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F. These earlier studies have not been successful at implementing a Bayesian analysis due to computational difficulties. But more recently a fully Bayesian approach to the bioassay problem has been developed in Gelfand and Kuo (1991) by using Markov chain Monte Carlo (MCMC) techniques.

The design problem for bioassay is concerned with specification of the number of different doses and the dose levels as well as the number of subjects to be allocated to these levels. From a Bayesian perspective the design of a bioassay is a decision problem where the dose levels and the allocation of the subjects to these levels are determined in such a way that the quality of inference about the tolerance distribution is optimized. Development of Bayesian bioassay designs has been hindered by the nonlinear nature of the design problem (see, for example, Chaloner and Verdinelli, 1996). Kuo (1983) has developed optimal designs using a Dirichlet process prior for small sample sizes, but generalization of results has been limited due to computational difficulties. The optimal design solution is derived from a preposterior analysis. When the number of stimuli increases, it becomes more and more difficult to carry out an analytic solution to the preposterior analysis.

In this paper we present a general decision theoretic setup for the design problem and develop a solution using Monte Carlo-based methods. Following Kuo (1983), to relax the restrictive assumptions on the potency curve, we adopt a nonparametric Bayesian approach and assume a Dirichlet process prior (Ferguson, 1973) with parameter αF_0 on the potency curve, where α represents our strength of prior belief and F_0 is the prior mean of the random tolerance distribution. In particular, we model the potency curve as a random discrete distribution function with random locations and random size of the jumps with the specific distribution given in Sethuraman and Tiwari (1982). The prior mean of this random distribution evaluated at t is assumed to be $F_0(t)$ and the variance of this random distribution evaluated at t is assumed to be $F_0(t)(1 - F_0(t))/(\alpha + 1)$. So α can be interpreted as the strength of prior belief or the degree of concentration of the random distribution around F_0. The larger the α is, the more concentrated F is around F_0.

In Section 2, we describe the design problem and introduce its ingredients. We present a decision theoretic setup for the design problem in Section 3 and illustrate the difficulties involved in obtaining an analytical solution to the preposterior analysis. In Section 4 we discuss how MCMC methods can be used for evaluating the posterior expected loss. We present a Monte Carlo integration technique to evaluate the preposterior expected loss and discuss the potential computational burden involved in finding the optimal design. To alleviate such computational burden, we adopt the simulation-based approach of Müller and Parmigiani (1995) where the preposterior analysis is replaced by a curve (surface)-fitting technique. This simulation-based approach has been used by Erkanli and Soyer (1997) for design of accelerated life tests and by Erkanli, Soyer, and Angold (1998) in developing two-phase designs. Other simulation based designs and computational strategies are given in Müller (1998). In Section 5, we discuss our adoption of the approach and present details regarding the evaluation of preposterior loss. We first consider a single dose design in Section 6 where all the subjects are given the same dose level and compare our results with the analytical results of Kuo (1983). We then consider generalizations to multiple dose levels and illustrate the implementation of the method by several examples.

2. Design Problem

We first assume that the number of subjects allocated to each dosage is known. Thus, we are only interested in finding the optimal dosage levels. Let $\mathbf{t} = (t_1, \ldots, t_I)$ denote the unknown dosage levels. We need the following ingredients to describe the Bayesian formulation of the design problem:

(i) A loss (utility) function that measures the cost of a specific design:

If there is no cost in sampling, the loss only consists of penalty for wrong decisions. Given that our objective is to make inferences for the entire potency curve, an integrated squared error loss function for F is considered:

$$L_1(F, \hat{F}; \mathbf{t}) = \int (F(t) - \hat{F}(t))^2 dW(t),$$

where $\hat{F}(t)$ is the estimator of $F(t)$ and $W(t)$ is a known weight function.

If there is a cost in sampling, we can incorporate the sampling cost, for example, by considering

$$L_2(F, \hat{F}; \mathbf{t}) = \int (F(t) - \hat{F}(t))^2 dW(t) + \sum_{i=1}^{I} c_i n_i$$

to reflect linear cost in sampling, where c_i is the cost for experimenting on a subject at dose t_i, where n_i denotes the total number of subjects given the dose at level t_i.

(ii) A statistical model:

The response for each subject is assumed to be dichotomous. That is, the dosage has to be stronger than the individual subject's tolerance to yield a positive response. Therefore a subject given the dosage t_i has the probability $F(t_i)$ to react positively. Furthermore, we assume that the subjects react independently and thus summarize the data by $\mathbf{x} = (x_1, \ldots, x_I)$, where x_i is the number of subjects yielding positive responses at dosage t_i. Therefore, x_i has a binomial distribution $B(n_i, F(t_i))$.

(iii) A prior distribution reflecting our quantification of the uncertainty regarding the unknown quantities:

Our object of interest is the unknown potency curve F. Therefore, a nonparametric prior on the whole space of distribution functions would be appropriate. We only consider the Dirichlet process in this paper. Other nonparametric priors would also be worthwhile pursuing. We assume F has a Dirichlet distribution with parameter αF_0, where F_0 represents the statisticians' prior belief on the shape of the tolerance distribution F, and α represents the degree of concentration of F around F_0. We use π to denote this prior. It was discussed in Kuo (1983, p.889) that it is sufficient to consider $F_0(t) = t$ for $0 < t < 1$ by choosing a suitable reparametrization of t. Therefore we will focus on this prior choice with various weight functions in this paper.

3. Decision Theoretic Approach to the Design Problem

We first assume the number of doses is known. From the decision theoretic point of view, the solution to the design problem requires a preposterior analysis. That is, for the loss L_1, we need to find $\mathbf{t}$ for a fixed I to minimize the

$$E^{\mathbf{x}|\mathbf{t}}\{E^{F|\mathbf{t},\mathbf{x}}L_1(F,\hat{F}^*)|\mathbf{t},\mathbf{x}\},$$

where $\hat{F}^*$ denotes the Bayes estimator of F for a fixed design $\mathbf{t}$ and given the sample $\mathbf{x}$.

For the L_2 loss function, the problem with sampling cost, we need to find $(\mathbf{t},\mathbf{n})$ to minimize

$$E^{\mathbf{x}|\mathbf{t},\mathbf{n}}\{E^{F|\mathbf{t},\mathbf{n},\mathbf{x}}L_2(F,\hat{F}^*)|\mathbf{t},\mathbf{n},\mathbf{x}\},$$

where $\mathbf{n}=(n_1,\ldots,n_I)$ and $\hat{F}^*$ is the Bayes estimator defined similarly with respect to the fixed design $(\mathbf{t},\mathbf{n})$.

Figure 1 represents the decision tree for the design problem. We use L_1 for illustration. The design problem for L_2 can be represented similarly with $\mathbf{t}$ replaced by $(\mathbf{t},\mathbf{n})$, and L_1 replaced by L_2. The solution to the optimal design is obtained by "folding back" the decision tree through taking expectations at random nodes and minimizing (maximizing) the expected loss (utility) at the decision nodes.

Figure 1: Decision Tree for the Design Problem

$$\begin{array}{ccccccc} D_1 & & R_1 & & D_2 & & R_2 \\ \square & \xrightarrow{\mathbf{t}} & \odot & \xrightarrow{\mathbf{x}} & \square & \xrightarrow{\hat{F}} & \odot \xrightarrow{F} \end{array}$$

The following steps describe the solution:

At R_2
Evaluate $E^{F|\mathbf{t},\mathbf{x}}[L_1(F,\hat{F})|\mathbf{t},\mathbf{x}]$.

At D_2
Choose $\hat{F}^*=\arg\min\{E^{F|\mathbf{t},\mathbf{x}}[L_1(F,\hat{F})|\mathbf{t},\mathbf{x}]\}$.
Evaluate $V^*(F|\mathbf{t},\mathbf{x})=E^{F|\mathbf{t},\mathbf{x}}[L_1(F,\hat{F}^*)|\mathbf{t},\mathbf{x}]$.

At R_1
Evaluate $V^*(F|\mathbf{t})=E^{\mathbf{x}}[V^*(F|\mathbf{t},\mathbf{x})]$.
This expectation is taken with respect to the marginal density of the data,

$$p(\mathbf{x}|\mathbf{t})=\int p(\mathbf{x}|F,\mathbf{t})\pi(dF).$$

At D_1
Choose $\mathbf{t}^*=\arg\min\{V^*(F|\mathbf{t})\}$.

The evaluation of the Bayes estimator $\hat{F}^*$ and the posterior risk $V^*(F|\mathbf{t},\mathbf{x})$ in D_2 can be done precisely for one or two dose levels. This follows straightforwardly from a beta density updating for one dose, and an updating by a mixture of Dirichlet distributions as given in Antoniak (1974) for two doses. When the number of doses increases, it is best done by the MCMC technique developed in Gelfand and Kuo (1991). The evaluation of expected preposterior loss $V^*(F|\mathbf{t})$ averaging over the sample space is done for the one dose problem in Kuo (1983). Therefore a design solution has been given precisely for the problem $I = 1$. However, the preposterior expected risk evaluation is almost infeasible for $I \geq 2$ except for a few limiting cases. We, therefore, resort to Monte Carlo methods for approximating the optimal design solution.

4. Monte Carlo Approach

4.1 Standard Monte Carlo Approach

Now, we describe the standard Monte Carlo approach to the above design problem.

Step 1: Choose a design $\mathbf{t}$.

Step 2: Generate a random F from the Dirichlet prior with parameter αF_0.

Step 3: Generate data $\mathbf{x}$ where x_i is binomial $B(n_i, F(t_i))$.

Step 4: Evaluate $V^*(F|\mathbf{t},\mathbf{x})$. This can be done by using the Gibbs sampler as in Gelfand and Kuo (1991).

Step 5: Repeat Steps 2–4 independently R times, for R large, where the generated data are denoted by $F^{(r)}$, $\mathbf{x}^{(r)}$ and $V^*(F|\mathbf{t},\mathbf{x}^{(r)})$ in the r^{th} replication. Then we can approximate $V^*(F|\mathbf{t}) \approx \sum_{r=1}^{R} V^*(F|\mathbf{t},\mathbf{x}^{(r)})/R$.

Finally, we repeat steps 1-5 to find $\mathbf{t}$ to minimize $V^*(F|\mathbf{t})$.

We note that the above approach requires an enormous computational effort. For each level of $\mathbf{t}$, R draws are required from the statistical model and we need to run a Gibbs sampler for each draw.

4.2 Monte Carlo Approach with Curve Fitting

To avoid the computation burden, we adopt the modified Monte Carlo procedure with the curve fitting idea given in Müller and Parmigiani (1995). This approach is a lot more efficient because it avoids the replication steps 2 to 4. In fact, it replaces the replication steps with a curve fitting step at the end after evaluating the posterior risks for all the chosen design points.

Step 1: Select a design $\mathbf{t}$.

Step 2: Generate a random F from the Dirichlet prior with parameter αF_0.

Step 3: Generate data $\mathbf{x}$ where x_i is binomial $B(n_i, F(t_i))$.

Step 4: Evaluate $l = V^*(F|\mathbf{t},\mathbf{x})$. This can be done by using Gibbs sampler as in Gelfand and Kuo (1991).

Step 5: Record the value $(\mathbf{t}, l)$.

Step 6: Repeat steps 1-5 independently to record the points $(\mathbf{t}^{(j)}, l^{(j)})$ for $j = 1, \ldots, J$, with J to be sufficiently large. Then we fit a curve $g(\mathbf{t})$ through the points $(\mathbf{t}^{(j)}, l^{(j)})$ and find $\mathbf{t}$ to minimize $g(\mathbf{t})$.

Note the curve fitting step in step 6 mimics the expectation step evaluated at the random node R_1. The curve fitting takes the advantage of borrowing strength from neighboring design points, (see Müller, 1998); therefore, we only need to evaluate the posterior risk once (at most a few times, if variation of the posterior risk is too big relative to the preposterior risk) instead of needing R replications. The curve fitting, therefore, allows us to save substantial time in simulation with almost no loss of accuracy.

5. Evaluation of the Preposterior Risk

Simulation from the Dirichlet process (step 2) in the above Monte Carlo procedure is difficult to carry out. It is usually carried out using the Sethuraman and Tiwari (1982) representation as described in Doss (1994). Now we will show that we can reduce the problem to generating a prior from a parametric Dirichlet distribution that is much simpler than generating a distribution function from the nonparametric prior.

The reduction follows from the observation given in Kuo (1983). Let us first note the Bayes estimator $\hat{F}^*(t)$ is the posterior mean of the F $(E(F(t)|\mathbf{x}))$ because of the integrated squared error loss. It is also straightforward to verify the interpolation formula

$$\hat{F}^*(t) = E(F(t)|\mathbf{x}) = \hat{F}^*(t_i)\frac{F_0(t_{i+1}) - F_0(t)}{F_0(t_{i+1}) - F_0(t_i)} + \hat{F}^*(t_{i+1})\frac{F_0(t) - F_0(t_i)}{F_0(t_{i+1}) - F_0(t_i)}, \tag{1}$$

for $t_i < t < t_{i+1}$. Then the preposterior risk is shown to be

$$E^{\mathbf{x}|\mathbf{t}}\{E^{F|\mathbf{t},\mathbf{x}}L_1(F, \hat{F}^*)|\mathbf{t}, \mathbf{x}\} = \int E^{\mathbf{x}}F(t)^2 dW(t) - \int E^{\mathbf{x}}\hat{F}^*(t)^2 dW(t). \tag{2}$$

Let us note that the first term in (2) is independent of the dosage levels. Therefore the design problem is to find the optimal $\mathbf{t}$ that maximize the quantity $\int E^{\mathbf{x}}\hat{F}^*(t)^2 dW(t)$.

We can evaluate $\int E^{\mathbf{x}}\hat{F}^*(t)^2 dW(t)$ using the interpolation formula in (1). Then

$$\begin{aligned}
&\int E^{\mathbf{x}}\hat{F}^*(t)^2 dW(t) = \qquad (3)\\
&\quad \sum_{i=1}^{I} E^{\mathbf{x}}\hat{F}^*(t_i)^2 \left[\int_{t_i}^{t_{i+1}} \left(\frac{F_0(t_{i+1}) - F_0(t)}{F_0(t_{i+1}) - F_0(t_i)}\right)^2 dW(t) + \int_{t_{i-1}}^{t_i} \left(\frac{F_0(t) - F_0(t_{i-1})}{F_0(t_i) - F_0(t_{i-1})}\right)^2 dW(t)\right]\\
&\quad +2\sum_{i=1}^{I} E^{\mathbf{x}}\hat{F}^*(t_i)\hat{F}^*(t_{i+1}) \left[\int_{t_i}^{t_{i+1}} \frac{(F_0(t_{i+1}) - F_0(t))(F_0(t) - F_0(t_i))}{(F_0(t_{i+1}) - F_0(t_i))^2} dW(t)\right]\\
&\quad + \int_{t_I}^{1} \left\{\left(\frac{F_0(t) - F_0(t_I)}{1 - F_0(t_I)}\right)^2 + E^{\mathbf{x}}\hat{F}^*(t_I)\frac{(1 - F_0(t))(F_0(t) - F_0(t_I))}{(1 - F_0(t_I))^2}\right\} dW(t).
\end{aligned}$$

When $F_0(t) = t$, it can be shown that

$$\int E^{\mathbf{x}}\hat{F}^*(t)^2 dW(t) = [\sum_{i=1}^{I}(t_{i+1} - t_{i-1})E^{\mathbf{x}}\hat{F}^*(t_i)^2 + \sum_{i=1}^{I-1}(t_{i+1} - t_i)E^{\mathbf{x}}\hat{F}^*(t_i)\hat{F}^*(t_{i+1}) + 1 - t_I^2]/3. \tag{4}$$

In particular, when $F_0(t) = t$ and $I = 2$, then $\int E^{\mathbf{x}}\hat{F}^*(t)^2 dW(t)$ reduces to

$$\int E^{\mathbf{x}}\hat{F}^*(t)^2 dW(t) = [t_2 E^{\mathbf{x}}\hat{F}^*(t_1)^2 + (1-t_1)E^{\mathbf{x}}\hat{F}^*(t_2)^2 + (t_2-t_1)E^{\mathbf{x}}\hat{F}^*(t_1)\hat{F}^*(t_2) + 1 - t_2^2]/3.$$

Moreover, when $I = 1$, and it reduces to

$$\int E^{\mathbf{x}}\hat{F}^*(t)^2 dW(t) = [E^{\mathbf{x}}\hat{F}^*(t_1)^2 + (1-t_1)E^{\mathbf{x}}\hat{F}^*(t_1) + 1 - t_1]/3.$$

Now we can describe our Monte Carlo method with curve fitting for the I dosage levels.

Step 1: Select a design $0 < t_1 < \cdots < t_I < 1$.

Step 2: Generate a $\mathbf{p} = (p_1, \ldots, p_I; p_{I+1})$ from the Dirichlet distribution $D(\alpha t_1, \alpha(t_2 - t_1), \ldots, \alpha(1-t_I))$.

Step 3: Generate data $\mathbf{x}$ with each x_i independent from the binomial $B(n_i, p_1 + \ldots + p_i)$, for each $i = 1, \ldots, I$.

Step 4: Evaluate the squares of the Bayes estimates evaluated at the dosage levels and the products of the two adjacent Bayes estimates. They are $\hat{F}^*(t_i)^2$, for $i = 1, \ldots, I$, and $\hat{F}^*(t_i)\hat{F}^*(t_{i+1})$ for $i = 1, \ldots, I-1$. This can be done by using the Gibbs sampler as in Gelfand and Kuo (1991).

Step 5: Evaluate $l = \sum_{i=1}^{I}(t_{i+1} - t_{i-1})\hat{F}^*(t_i)^2 + \sum_{i=1}^{I-1}(t_{i+1} - t_i)\hat{F}^*(t_i)\hat{F}^*(t_{i+1}) + 1 - t_I^2$ and record the value $(\mathbf{t}, l)$.

Step 6: Our empirical evaluation suggests that the variance of the l here for different design points is large. To reduce this variance, we suggest that we repeat steps 3 to 5 m times. We average these l's to obtain a new l called $\bar{l}$. (In our numerical examples, we find that $m = 5$ is sufficiently large.)

Step 7: Repeat steps 1-6 independently to record the points $(\mathbf{t}^{(j)}, \bar{l}^{(j)})$, for $j = 1, \ldots, J$. Then we fit a curve $g(\mathbf{t})$ through the points $(\mathbf{t}^{(j)}, \bar{l}^{(j)})$ and find $\mathbf{t}$ to minimize $g(\mathbf{t})$. Note that the curve fitting step in step 7 mimics the expectation step evaluated at the random node R_1.

6. Illustration

We have applied the methods in Section 5 to both $I = 1$ and $I = 2$ problems, where we assume $F_0(t) = t$ and $dW(t) = dt$. We use the local regression model (*loess*) to fit the curve for $I = 1$ or the surface for $I = 2$ with t_1 and t_2 as the predictors. To avoid underfitting or overfitting, we use both graphical methods for model checking and ANOVA as suggested by Cleveland, Grosse, and Shyu (1991) to experiment with specification of the surface (linear, degree=1; or quadratic, degree=2) and the neighborhood size (span). Table 1 lists the optimal design obtained by the Monte Carlo method and the choice for the *loess* fitting for the $\alpha = 1$ case. For $I = 1$, the Monte Carlo results are obtained by a fixed grid with 500 equally spaced grid points, where the corresponding utility (g) for each grid point is obtained by averaging the preposterior risks with 5 repeated samples. We have also experimented with random grids chosen from the uniform $U(0, 1)$ distribution. The results are very similar. For $I = 1$, Kuo (1983) shows that the optimal dosage level is at .5 independent of the sample size. Table 1 shows that the Monte Carlo results for the case $\alpha = 1$ (.496, for $n = 1$, and

.499 for $n = 5$) are quite good in this example. For the $I = 2$ and $n_1 = n_2 = 1$ problem, Kuo (1983) derived a precise optimal solution. It is $(t_1, t_2) = (.365, .635)$. The Monte Carlo method gives a result in the right ball park with the dosage levels pulled a little further apart.

In addition to the fixed sample size problem, we also consider the allocation problem. We assume $n_1+n_2 = 10$ for the first problem, and $n_1+n_2 = 15$ for the second problem; both with $c_1 = c_2 = .01$. The variable n_2 is treated as fixed for each problem, for example, $n_2 = 10-n_1$ for the first problem. Both results show that the optimal allocation is approximately equal sample size allocation between the two doses and the dosage levels are comparable with that of the same sample size of the dosage determination problem with known sample size.

Given that curve fitting is an extremely crucial part of our method, we also show some diagnostic plots to help us visualize the fitted curve. Figure 1 illustrates the curve fitting for the one dose problem. Although the curve is relatively flat, we are able to identify the optimal point to be around .5. Figure 2 fits the surface as a function of two dosage levels for the problem with $n_1 = n_2 = 1$.

Although our illustration is restricted to the $I = 1$ and $I = 2$ cases, our general methodology can be applied to more dosage levels (see Müller, 1998, for implementation issue). In addition to the case $dW(t) = dt$, we can also use equation (3) to study the design problem for any F_0 and W. For the problem of how many dosage levels to select, we can also compare the preposterior risks for each of the $I = 1, \ldots, n$ problems assuming a total n subjects are tested. Then we select the number of doses that minimizes the preposterior expected loss. When $\alpha \to 0$, Kuo (1983) shows that $I = n$, spreading out the dosage levels, is the optimal solution. The Monte Carlo method given here will be able to guide us for the cases with arbitrary α with an unknown number of doses.

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Table 1: Bayesian Bioassay Design by Curve Fitting of Monte Carlo Experiments

Dosage Level	Sample Size	Optimal Dosage Levels	*loess* Fitting
$I = 1$	1	.496	degree=2, span=.5
	5	.499	degree=2, span=.65
	1, 1	.32, .67	degree=1, span=.75
	2, 2	.29, .63	degree=1, span=..8
	5, 5	.34, .66	degree=1, span=.75
$I = 2$	1, 2	.42, .63	degree=1, span=.85
	2, 1	.29, .71	degree=1, span=.9
	5, 10	.35, .63	degree=1, span=.85
	10, 5	.35, .76	degree=1, span=.85
	$n_1 + n_2 = 10$	.32, .69	degree=1, span=1
$I = 2$ and		$n_1 = n_2 = 5$	
sample size allocation	$n_1 + n_2 = 15$	.43, .67	degree=1, span=.75
		$n_1 = 7$, $n_2 = 8$	

Figure 1. Curve Fitting for One-dosage Bayesian Bioassay Design

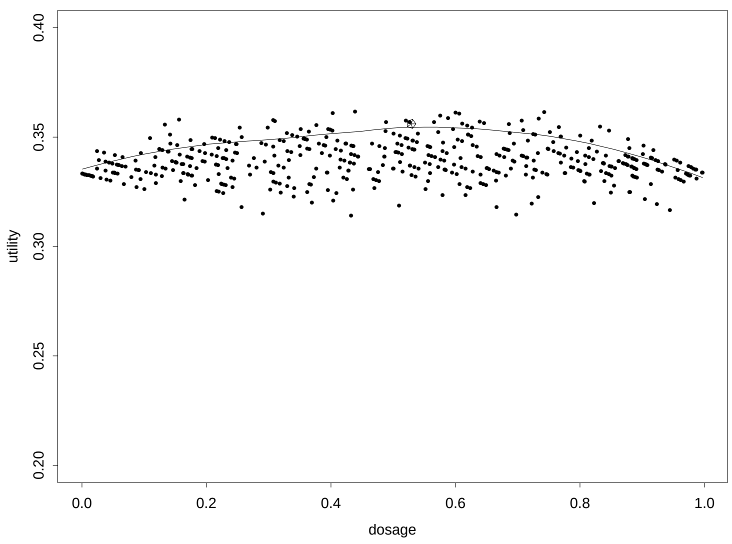

Figure 2. Fitted Surface for Two-dosage Bioassay Design (n1=n2=1)