Determinations of Dilution Series and Sample Sizes in Quantal Bioassay

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Abstract

In quantal bioassay, a binary response is related to different levels of a stimulus or dilution series via logit and probit models. Two common and important design issues are to determine dilution series and sample sizes given target design criteria and objectives. Based on both logit and probit models at six dilution levels, we employ locally D-optimal and A-optimal criteria along with desirable constraints (symmetry at zero on log10 scaled dilution levels or thresholds for the lowest and highest dilution levels). The design optimality and its association with constrained design space are demonstrated via efficiency measures. In addition, we demonstrate sample size calculation in terms of LD50 and potency.

Key Words: Optimal designs, quantal bioassay, LD50, potency, sample size calculation, logit and probit models

1. Introduction

Quantal bioassay studies are designed to assess quantal responses such as death or presence of a symptom of interest in a group of subjects under different dose levels. Usually several explanatory variables are present in a quantal bioassay study. For example, in a comparability study, experiments are conducted at different labs or tested drug assays come from two or more manufacture sites; a stability study involves time which may interact with dose. Without loss of generality, under assumption of one explanatory variable (dose), we tackle two primary design tasks: determinations of dilution series (or doses) and sample sizes of dose groups.

Logit (or logistic) and probit regression are often employed in quantal bioassay studies for evaluating the association of a quantal response with dose. Given the assumption of one explanatory variable, the analysis models are the 2-parameter logit and probit models including an intercept and a slope with respect to dose. Though number of dose levels has been recognized as an important design feature by Antonijevic et al. (2010) and Huang (2002), we focus on six-dose designs under consideration of experimental limitations as well as accuracy and precision of the statistical results.

Determination of dilution series was firstly motivated by providing evidence to support either wide or narrow dilution ranges tested in historical studies. And we found maximum likelihood estimation approach could fail when majority of response rates were equal to or approach 0% or 100%. When designing a quantal bioassay study, one usually starts with specification of the center and range of the doses. The center or median dose, termed as LD50, is the dose associated with 50% response rate. The LD50 can be proposed based on the median lethal doses from pilot studies or other resources if available, while the setup of the dose range also needs to incorporate regulatory recommendations on the maximum (and minimum) response rate at the lowest (and highest) doses. We adopt this common practice with addition of statistical ingredients: locally D- and A- design optimality criteria under six-dose two-parameter logit and probit models. The design constraints on the doses are formed mainly on the basis of: the constraints on the death rates at the two extreme doses, and property of equal distance between two adjacent doses as recommended by US pharmacopeia <1033>. Death rates at the two extreme doses only depend on doses after the use of parameter estimates (e.g., maximum likelihood estimates). The evenly-spaced property for doses considerably simplifies the problem and reduces the computational intensiveness.

In quantal bioassay studies, one of primary objectives is to evaluate the potency of a test assay or drug. Potency is commonly measured by LD50. For instance, smaller LD50 value generally suggests more potency of a drug. The dose levels are often reported via dilution series or factors, which can be expressed in terms of LD50 units. Specifically, if a dilution factor is 1 (or 0.8) LD50 unit, then the corresponding dose is equal to LD50 (or 80% of LD50). If proposed and actual LD50s are close to each other, dilution factors can be specified symmetric at 1. Consequently, we translate this good design feature into another constraint. For convenient implementation of the design constraints, the dilution series or factors instead of the real dose levels are regarded as the explanatory variable for derivation of constrained A- and D- optimal designs and sample size calculation.

Another key design component is calculation of sample size or number of subjects assigned to each dose group. The solution depends on design criteria. We view this task from the perspective of suitability of proposed potency, in other words, the closeness between proposed and actual potency. We measure such closeness by the ratio of the proposed potency to the actual potency. This ratio can be estimated as the LD50 (unit) through the logit and probit regression analysis. Study validation may require the equivalence between 1 and the ratio. Therefore, we propose the approaches via controlling the power of the equivalence test and 90% confidence interval for the ratio or LD50 (unit). Furthermore, it's important to attain certain accuracy and precision of actual potency, thus we also present the calculation in terms of actual potency.

2. Statistical Methodology

2.1 Logit and Probit Models

Consider m distinct dose or dilution levels in the experiment. For dose group i ($i = 1 \cdots, m$), the assay of dose x_i is administered to n experimental units (with n fixed and known) and r_i of them respond and $n - r_i$ do not response. The quantal response for the j-th experimental unit in the group i, is denoted as Y_{ij}. Thus the probability that Y_{ij} takes

the value 1 (corresponding to death or presence of the symptom) is denoted as $F(\beta_0 + \beta_1 x_i)$ and it can be expressed as follows:

$$\textbf{Logit Model: } F(a_i) = \frac{1}{1+e^{-a_i}}, \quad (1)$$

$$\textbf{Probit Model: } F(a_i) = \int_{-\infty}^{a_i} \frac{exp(-z^2)}{\sqrt{2\pi}} dz \quad (2)$$

We define

$$a_i = \beta_0 + \beta_1 * x_i, \quad (3)$$

where β_0 and β_1 ($\beta_1 > 0$) are unknown parameters and x_i is the log10-transformed dilution factor in dose group i. The optimal design problem in this context consists of optimally selecting the x_i's (in a given region), with respect to some optimality criteria, for a fixed n.

2.2 Determination of Dilution Series

We apply locally D- and A- optimal design criteria for the selection of log10-transformed dilution factors or the x_i's.

D-optimality designs seek to maximize the determinant of the Fisher information matrix with respect to the two parameters: intercept and slope (Mathew and Sinha (2001)). Because the Fisher information matrix is proportional to the inverse of the covariance matrix of the parameters, maximizing the determinant of the Fisher information matrix is equivalent to minimizing the determinant of the covariance. Thus application of a D-optimality criterion would minimize generalized variance for the intercept and the slope. The D-optimal criterion is commonly used primarily due to its computational efficiency and a particular appealing property: invariance under "re-parameterization" (i.e., linear transformation of parameters).

- **D-optimality:** seeks maximization of the determinant of the Fisher's information matrix with respect to the two parameters: intercept and slope (Mathew and Sinha (2001)): $|I(\beta_0, \beta_1)|$, where the vertical lines (|.|) indicate the determinant.

$$\text{D-Efficiency} = |I(\beta_0, \beta_1)| = \begin{vmatrix} \sum_{i=1}^{m} \xi_i \Omega(a_i) & \sum_{i=1}^{m} \xi_i x_i \Omega(a_i) \\ \sum_{i=1}^{m} \xi_i x_i \Omega(a_i) & \sum_{i=1}^{m} \xi_i x_i^2 \Omega(a_i) \end{vmatrix} \quad (4)$$

Taking the above form under both logit and probit models, the determinants depend on model parameters through $\Omega(a_i)$:

$$\Omega(a_i) = \frac{(F'(a_i))^2}{F(a_i)(1-F(a_i))} \quad (5)$$

$F(a_i)$ is given in equations (1) and (2) for the logit and probit models, $F'(a_i)$ is the first-order derivative with respect to a_i, and a_i is defined in equation (3). ξ_i is

the sample size allocation weight for dose group i. Given equal sample sizes across the groups, all of the ξ_i's are equal to $\frac{1}{m}$, with m as the number of doses.

Because the Fisher information matrix is proportional to the inverse of the covariance matrix of the parameters, maximizing the determinant of the Fisher information matrix is equivalent to minimizing the determinant of the covariance. Thus application of D-optimality criterion would minimize generalized variance for the intercept and the slope. The D-optimal criterion is commonly used primarily due to its computational efficiency and a particular appealing property: invariance under "re-parameterization" (i.e., linear transformation of parameters).

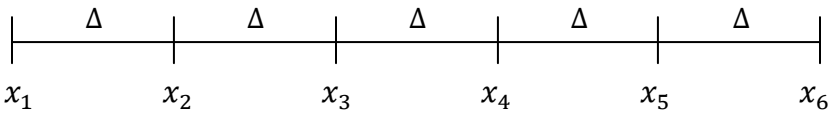
- **A-optimality:** aims at minimization of the trace of the inverse information matrix, denoted as $Trace[I(\beta_0, \beta_1)^{-1}]$, or equivalently the sum of the variances of the two parameter estimates,

$$\text{A-Efficiency} = Trace[I(\beta_0, \beta_1)^{-1}] = \frac{\sum_{i=1}^{m} \xi_i \Omega(a_i) + \sum_{i=1}^{m} \xi_i x_i^2 \Omega(a_i)}{|I(\beta_0, \beta_1)|} \qquad (6)$$

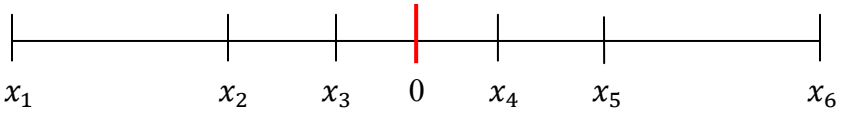
Generally the A-optimality criterion does not differ much from the D-optimality criterion except that the D-optimality criterion punishes for highly correlated estimates (Wit and McClure (2005)). In addition, as noted by Mathew and Sinha (2001), under the two-parameter logistic model, the sum is proportional to the inverse of the Fisher information matrix. This makes it harder to find a complete solution to the A-optimality problem in comparison with the D-optimal problem.

Besides locally D- and A- optimal design criteria, appropriate constraints on dilution factors are also critical to precise estimation of the shape of the dose-response curve. As stated in the introduction, we restrict our attention to the following three constraints illustrated via equations and figures:

- **Constraint 1:** Dilution factors are evenly spaced on the log10 scale: $x_i - x_j = (i - j) * \Delta,\ m \geq i, j \geq 1$, $\Delta > 0$ is the distance between two adjacent log10-scaled dilution factors x_i and x_{i+1}. The following picture demonstrates the quantitative relationship among log-scaled doses in terms of Δ:



- **Constraint 2:** Dilution factors are symmetric at 0 on the log10 scale: $x_i = -x_{7-i},\ i = 4, 5, 6$. If it is believed that the ratio of proposed potency η_P and actual potency η_A is not equal to 1, say $\eta_P/\eta_A = 1.1$, then the log10-scaled dilution factors can be specified symmetric at $log10(1.1)$.



- **Constraint 3:** Death rates at the lowest and highest doses. For example, the death rate at the lowest dose should not exceed 10% and the death rate at the highest dose should be at least 90%. This constraint should compromise feasible dilution range due to experimental limitations.

Usually constrained designs are harder to derive, in comparison of unconstrained designs. However, application of constraints 1 or 2 would reduce the number of the unknowns in the A-efficiency and D-efficiency functions, and consequently simplify the optimization. If Constraint 1 is adopted, then the A-efficiency and D-efficiency only depend on x_1 and Δ as shown below:

$$|I(\beta_0,\ \beta_1)| = \sum_{i=1}^{m}\sum_{j=1\ \&\ j\neq i}^{m}\left[\xi_i\xi_j(x_1+(j-1)\Delta)(j-i)\Delta\Omega(\omega_i)\Omega(\omega_j)\right] \quad (7)$$

$$Trace[I(\beta_0,\beta_1)^{-1}] = \frac{\left[\sum_{i=1}^{m}\xi_i\left(1+(x_1+(i-1)\Delta)^2\right)\Omega(\omega_i)\right]}{|I(\beta_0,\beta_1)|} \quad (8)$$

Where $\omega_i = \beta_0 + \beta_1(x_1 + (i-1)\Delta)$

Under Constraint 1 and Constraint 2, the A-efficiency and D-efficiency only depend on x_1 in the forms given above after with Δ replaced by $-\frac{x_1}{2.5}$.

2.3 Determination of Sample Sizes

We perform the sample size calculation via the following equivalence test:

$$H_0: \theta \leq \Delta_L \ or\ \theta \geq \Delta_U \text{ versus } H_1: \Delta_L < \theta < \Delta_U \quad (9)$$

$\Delta_L\ and\ \Delta_U$ are the equivalence margins satisfying $\Delta_L < 0 < \Delta_U$.
$\theta = log_{10}(LD50) = -\frac{\beta_0}{\beta_1}$ or $\theta = log_{10}(\eta_A) = log_{10}\left(\frac{\eta_P}{LD50}\right)$. $\eta_A\ and\ \eta_P$ denote the actual potency and proposed potency, respectively.

At a significance level α and a power of at least $1-\gamma$, dose group size (n_1; equal across groups) is the smallest positive integer satisfying, $for\ any\ \theta_0\ between\ \Delta_L\ and\ \Delta_U$,

$$\Phi\left(\frac{\Delta_U-\theta_0}{\sqrt{V\hat{A}R(\hat{\theta})}} + Z_\alpha\right) - \Phi\left(\frac{\Delta_L-\theta_0}{\sqrt{V\hat{A}R(\hat{\theta})}} + Z_{1-\alpha}\right) \geq 1-\gamma \quad (10)$$

Above inequality is derived on the normality assumption of $\hat{\theta}$. Via maximum likelihood estimation, $V\hat{A}R(\hat{\theta})$ is proportional to the reciprocal of n_1.

Another way of sample size calculation is precision-based: via controlling the width or range of the Fieller's confidence interval for θ (Fieller (1940); Buonaccorsi (1998)). The Fieller's confidence interval takes the following form:

$$\frac{1}{1-\psi}\left(\hat{\theta}-\frac{\psi\hat{v}_{12}}{\hat{v}_{22}}\pm\frac{Z_{1-\alpha/2}}{\hat{\beta}_1}\sqrt{\hat{v}_{11}-2\hat{\theta}\hat{v}_{12}+\left(\hat{\theta}\right)^2\hat{v}_{22}-\psi\left(\hat{v}_{11}-\frac{(\hat{v}_{12})^2}{\hat{v}_{22}}\right)}\right) \qquad (11)$$

where $\psi=\frac{Z_{1-\alpha/2}^2\hat{v}_{22}}{\left(\hat{\beta}_1\right)^2}$. $\hat{v}_{11}$, $\hat{v}_{22}$ and $\hat{v}_{12}$ are the estimates of the variances and covariance for the numerator and denominator of $\hat{\theta}$. Namely, given $\theta=log_{10}(LD50)=-\frac{\beta_0}{\beta_1}$, the numerator and denominator of $\hat{\theta}$ are $-\hat{\beta}_0\ and\ \hat{\beta}_1$; if $\theta=log_{10}(\eta_A)=log_{10}\left(\frac{\eta_P}{LD50}\right)$, the numerator and denominator of $\hat{\theta}$ are $\hat{\beta}_1 log_{10}(\eta_P)+\hat{\beta}_0\ and\ \hat{\beta}_1$, respectively. Depending on n_1, the variance and covariance estimates can be obtained via Delta method (Oehlert 1992).

When the Fieller's confidence interval is restricted between $C_L\ and\ C_U$, and dose group size (n_1; equal across groups) is the smallest positive integer satisfying

$$\frac{1}{1-\psi}\left(\hat{\theta}-\frac{\psi\hat{v}_{12}}{\hat{v}_{22}}\pm\frac{Z_{1-\alpha/2}}{\hat{\beta}_1}\sqrt{\hat{v}_{11}-2\hat{\theta}\hat{v}_{12}+\left(\hat{\theta}\right)^2\hat{v}_{22}-\psi\left(\hat{v}_{11}-\frac{(\hat{v}_{12})^2}{\hat{v}_{22}}\right)}\right)\in(C_L,C_U) \qquad (12)$$

3. Results

3.1 Constrained Optimal Designs

Using the model parameter estimates (i.e., -0.5093 for intercept and 25.8501 for slope under logit model) based on the data pooled from available pilot studies, we derived and compared the following evenly-spaced six-dose designs under logit model. Designs 1 to 4 were searched on log10-scaled dilution range from 0.5 to 2.0. Design 0 was solely the evenly-spaced six-dose design on the range [0.6, 1.5], without application of any constraints or design optimality criterion. Designs 1 and 2 are A- and D- optimal designs under constraints 1 & 2. Designs 3 and 4 are A- and D- optimal designs under constraints 1 & 3. Constraint 3 specifies 5% and 95% as the thresholds for the death rates at the lowest and highest doses.

Through comparisons of the A- and D-efficiency among the five designs, we can see that

- Application of constraint 2 improves both A- and D- efficiency, in comparisons of Designs 1 & 2 with Design 0;
- For evenly-spaced designs, constraint 3 (i.e., 5% and 95% death rate thresholds) tends to lead to less efficient designs with narrower dilution ranges, in comparison of constraint 2 (symmetry at 0 for log10-scaled dilutions): for example, Design 4 is less D-efficient than Design 2; Design 3 is less A-efficient than Design 3;
- Under constraints 1 & 3, A- and D- optimality lead to the identical design: Design 3 & 4.

Table 1. Evenly-Spaced Six-Dose Designs under Logit Model

ID	Design	D-Efficiency	A-Efficiency	Dilution Series on Raw Scale (Δ or distance between two adjacent dilutions on log10 scale)
0	**Under Constraint 1 on [0.6, 1.5]**	2.94E-05	2757.83	0.600, 0.721, 0.866, 1.040, 1.249, 1.500 (Δ = 0.079588)
1	**A-Optimal under Constraints 1 & 2**	5.24E-05	2302.65	0.743, 0.837, 0.942, 1.061, 1.195, 1.346 (Δ = 0.051582)
2	**D-Optimal under Constraints 1 & 2**	6.06E-05	2568.85	0.810, 0.881, 0.959, 1.043, 1.135, 1.234 (Δ = 0.03655)
3	**A-Optimal under Constraints 1 & 3**	2.69E-05	2797.99	0.638, 0.777, 0.946, 1.152, 1.403, 1.709 (Δ = 0.085576)
4	**D-Optimal under Constraints 1 & 3**	2.69E-05	2797.99	0.638, 0.777, 0.946, 1.152, 1.403, 1.709 (Δ = 0.085576)

Similarly under probit model, we generated evenly-spaced six-dose A- and D-optimal designs with or without constraints (in Table 2). Comparisons of A- and D- efficiency among the five designs suggest the same conclusion as under the logit model, except that application of constraint 3 (i.e., 5% and 95% death rate thresholds) results in more D-efficient but less A-efficient designs, in comparisons of Designs 1 & 2 with Designs 3 & 4.

Table 2. Evenly-Spaced Six-Dose Designs under Probit Model

ID	Design	D-Efficiency	A-Efficiency	Dilution Series on Raw Scale (Δ or distance between two adjacent dilutions on log10 scale)
0	**Under Constraint 1 on [0.6, 1.5]**	3.90E-05	3780.2	0.600, 0.721, 0.866, 1.040, 1.249, 1.500 (Δ = 0.079588)
1	**A-Optimal under Constraints 1 & 2**	1.87E-04	1841.62	0.828, 0.893, 0.963, 1.038, 1.120, 1.208 (Δ = 0.032775)
2	**D-Optimal under Constraints 1 & 2**	2.06E-04	1987.94	0.863, 0.916, 0.971, 1.030, 1.092, 1.158 (Δ = 0.025541)
3	**A-Optimal under Constraints 1 & 3**	2.77E-04	3356.86	0.544, 0.706, 0.916, 1.188, 1.542, 2.000 (Δ = 0.11308)
4	**D-Optimal under Constraints 1 & 3**	3.88E-04	3484.64	0.638, 0.777, 0.946, 1.152, 1.403, 1.709 (Δ = 0.085576)

Figure 1 plots the A-efficiency and D-efficiency against the lowest dose (on the raw scale) for the six-dose design with constraints 1 & 2 under the logit model. This plot shows that when the lowest dose is between 0.75 and 0.85, the designs demonstrate good A- and D- efficiency. This motivates another design criterion: simultaneous application of A- and D- optimality with appropriate weights assigned to the two criteria.

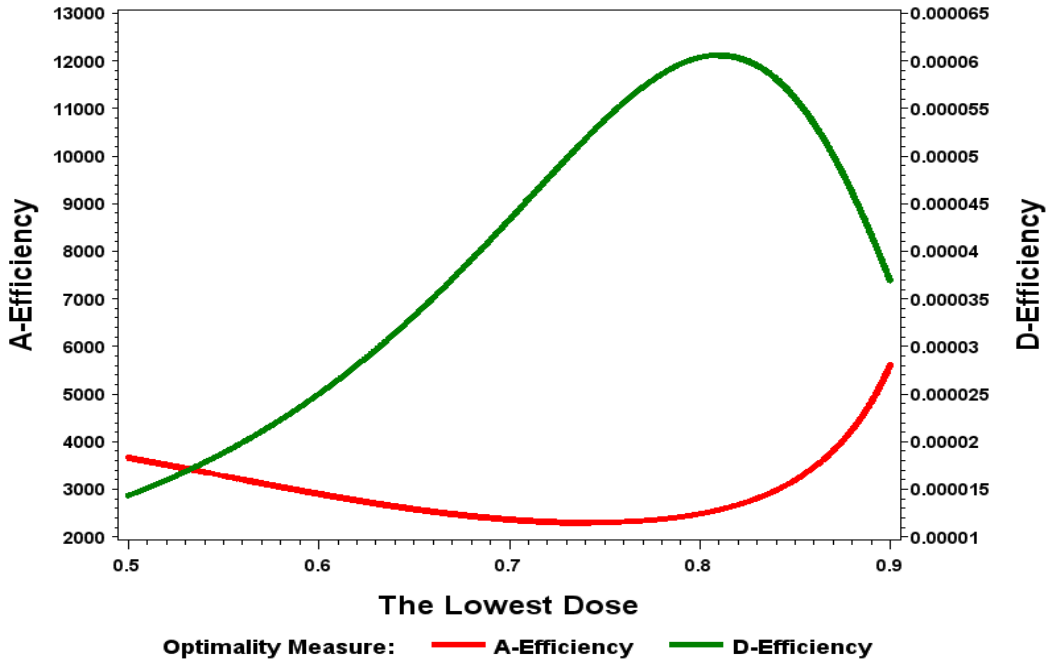


Figure 1: Overlay plot of A-efficiency and D-efficiency against the lowest dose (as LD50 unit on the raw scale)

3.2 Sample Size Calculation via Equivalence Tests

For the six-dose design under constraints 1 & 2, with the use of parameter estimates from the logit regression on the data from the pilot studies, sample sizes were obtained for the six-dose design under constraints 1 & 2. We used conventional equivalence margins $\Delta_L = log_{10}(0.8) = -0.097$ and $\Delta_U = log_{10}(1.25) = 0.097$. **Figure 2** presents sample size per dose against $\theta = \theta_0 = log_{10}(LD50)$. θ goes from -0.08 to 0.08. Each curve represents a different power. From bottom to top, the powers are 60%, 70%, 80% and 90%. Under the same settings on design and model, we can plan a new study using this figure. For instance, if the true LD50 is assumed to be 1.05 (or $log_{10}(LD50) = 0.05$), then 12 subjects per dose is required to detect the equivalence of $log_{10}(LD50)$ given 80% power.

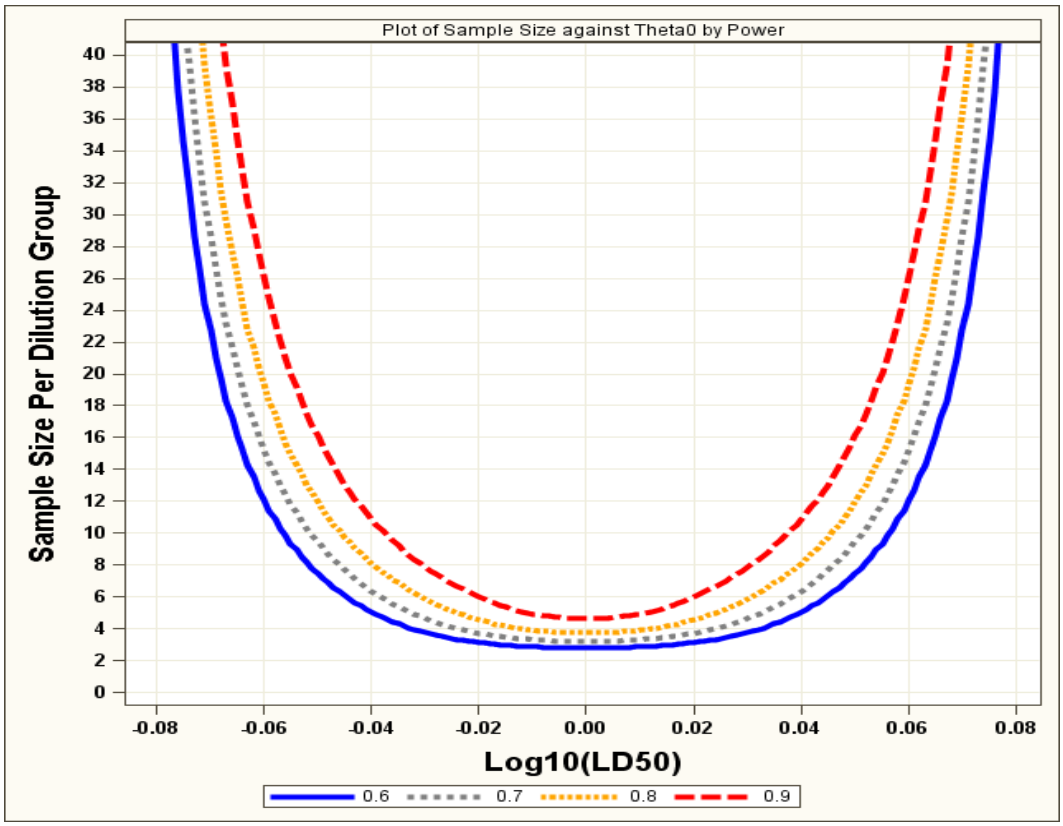


Figure 2: Plot of sample size per dose against true log10-scaled LD50 (unit)

3.2 Sample Size Calculation via Restriction on Range of Confidence Interval

Figure 3 demonstrates the relationship between sample size and the upper limit restricted on the Fieller's confidence interval for $log_{10}(LD50)$. To control the confidence interval between $C_L \; and \; C_U$, given $C_U = -C_L \;\; from \; log_{10}(1.05) \; to \; log_{10}(1.3)$, the required sample size per dose decreases from above 60 to below 4. The label "Upper Threshold" refers to C_U. If a stringent control is posted on the confidence interval, it could significantly increase the sample size and experimental cost.

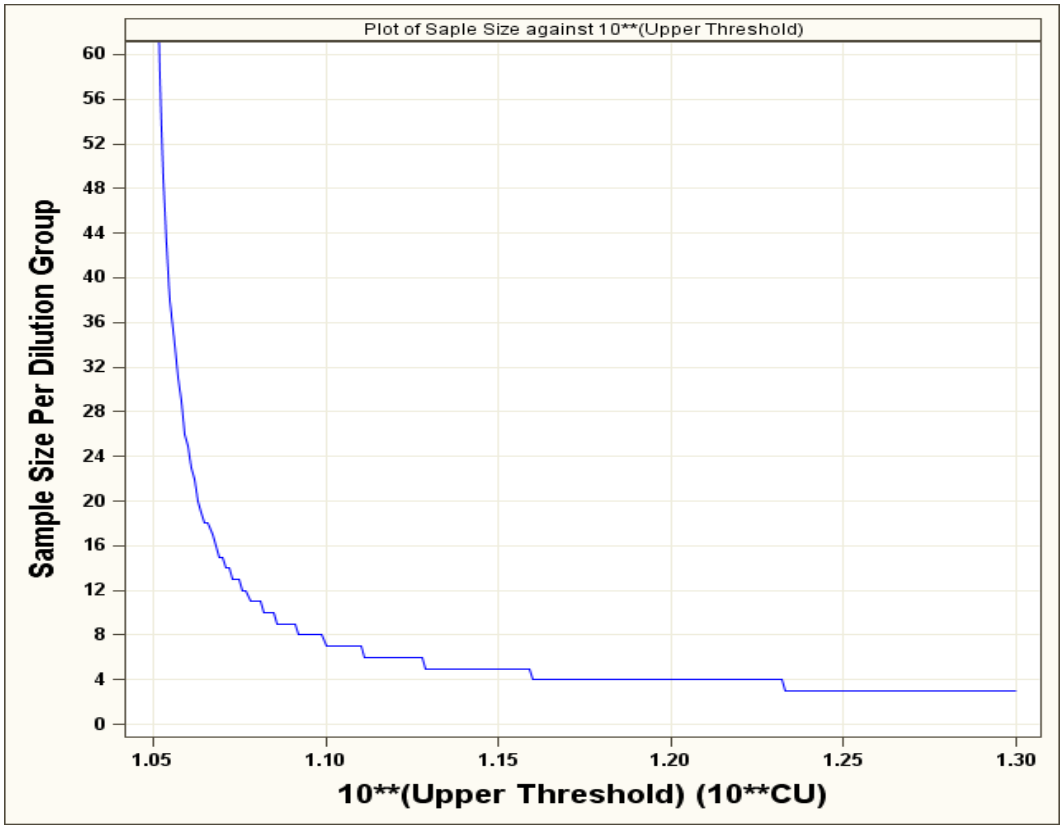


Figure 3: Plot of sample size per dose against 10^{C_U}

Discussion

Via locally D- and A- optimal design criteria, we have provided results for the determination of evenly-spaced dilution series on the log10 scale under symmetric designs and equal number of subjects per dose group. As we adopted locally A- and D-optimal design criteria not under the Bayesian framework, reliable parameter estimates from analysis of historical data are required. Therefore, we recommended conducting several pilot experiments to refine parameter estimates, dilution range and factors. Another experience we would like to share is, application of constraint 3 with more stringent thresholds for the death rates at the lowest and highest doses tends to trigger data separation issue (e.g., most of the death rates are close to either 0% or 100%). The data separation issue is usually accompanied by either non-convergence modeling issue or biased statistical results (e.g., very large standard error for the slope estimate, wide confidence interval for the LD50 and actual potency). Though Firth's approach (Firth 1993) can be adopted to deal with this issue, we emphasize the importance of having at least three or more doses having partial response rates. To achieve this goal, we consider relaxing constraint 1 by allowing the dilution series to be partially evenly-spaced. Under constraint 2, the design space with evenly-spaced dilution series is nested in the design space with partially evenly-spaced dilution series, thus the use of partially evenly-spaced zero-symmetric dilution series could not only improve A- and D- efficiency, but also increase the chance of having more partial response rates.

Because all optimal designs are model-dependent, determination of optimal dilution series in presence of random effects and/or more than one fixed effect besides dose is beyond the scope of this document. Further extensive research is required to evaluate dilution strategies in compliance with variety of experimental goals and analysis models.

We proposed methods for sample size calculation in terms of equivalence tests and confidence intervals for the LD50 and potency. Nevertheless, one often finds that sole control of the LD50 and potency may not contribute significantly to the accuracy and precision of the studies, as other variables such as administration technique, subject characteristics, and experimental conditions could impact the results to a certain degree. For example, sample size may be assessed in terms of precision of relative potency, or power of detecting parallelism. Another interesting research we've proposed is optimal allocation of unequal sample sizes to dose groups.

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