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Efficient Experimental Design Strategies in Toxicology and Bioassay

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Abstract Modelling in bioassay often uses linear or nonlinear logistic regression models, and relative potency is often the focus when two or more compounds are to be compared. Estimation in these settings is typically based on likelihood methods. Here, we focus on the 3-parameter model representation given in Finney (1978) in which the relative potency is a model parameter. Using key matrix results and the general equivalence theorem of Kiefer & Wolfowitz (1960), this paper establishes key design properties of the optimal design for relative potency using this model. We also highlight aspects of subset designs for the relative potency parameter and extend geometric designs to efficient design settings of bioassay. These latter designs are thus useful for both parameter estimation and checking for goodness-of-fit. A typical yet insightful example is provided from the field of toxicology to illustrate our findings.

Keywords Goodness-of-Fit; Logistic Regression; Nonlinear Model; Optimal Design; Relative Potency; Robustness

AMS 2010 subject classifications: 62J02, 62J12, 62K05

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1. Introduction

Linear and nonlinear logistic regression modelling are amongst the most useful techniques used in bioassay to determine relationships between attributes or variables. In studying biological and toxicological assays, logistic modelling is ubiquitous and sensible since typically as concentrations of toxic substances are increased, survival percentages tend to decrease and in congruence and systematic manner. Furthermore, these curves can be combined so that compounds can be compared using the relative potency – often based on the ratio of the respective percentiles such as the corresponding LD_{50} 's. Introduction of LD_{50} 's into these models introduces nonlinearities and care is needed to obtain accurate estimates (including confidence intervals). Further, key matrices such as the Fisher information matrix, play a key role in estimation; as highlighted below, these matrices are also pivotal in choosing an efficient design since these designs are often chosen to maximize some functional of the information matrix. In this work, we focus on modelling in the setting of comparing two substances using a nonlinear logistic model adapted from Finney (1978), and we provide optimal, subset-optimal, and near-optimal geometric and uniform design strategies. Background in quantal and logistic regression modelling is given in McCullagh & Nelder (1989), Collett (2003), and Dobson & Barnett (2008). The assessment of relative potency using so-called parallel-line assays, as well as background in and discussions of the larger field of bioassay, is provided in Finney (1978). References for the overarching nonlinear modelling context include Seber & Wild (1989) and Bates & Watts (2007). Optimal design strategies are introduced and illustrated in O'Brien & Funk (2003) and Atkinson *et al* (2007), optimal design methods for relative potency are introduced in a different setting in Smith & Ridout (2003), and geometric and uniform designs are examined in O'Brien *et al* (2009).

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With an eye to typical bioassay potency data and modelling, in what follows we underscore characteristics of global and subset D-optimal designs, highlighting the benefits of derived geometric design strategies. As such, practitioners are provided with useful guidelines and rules-of-thumb.

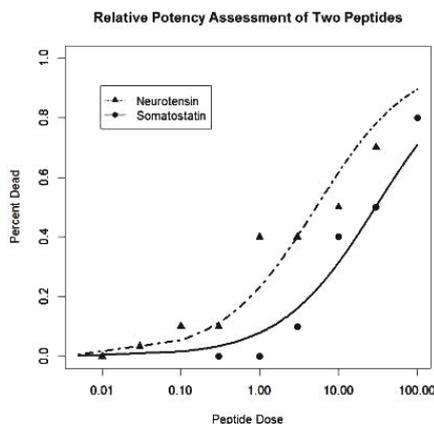
1.1. Quantal Dose-Response Modelling and Relative Potency

For the binary/binomial logistic model, the x variable corresponds to dose or concentration and the researcher selects the k dose points to run the experiment. This dose selection – as well as the number of replicates at each of these points – is the essence of the experimental design problem addressed here. This model assumes that independently n_i subjects (or experimental units) receive dose x_i , and that the number of “successes” y_i has a binomial distribution with success probability π_i . When the logit link and log-dose scale is appropriate, we obtain $\pi_i = \frac{t_i}{1+t_i}$ with $t_i = \left(\frac{x_i}{\theta_2}\right)^{\theta_3}$. In settings where two compounds are under consideration, we use this model with a modification given in Finney (1978) and elsewhere,

$$x_i = x_{1i} + \theta_4 x_{2i} \quad (1)$$

It is noted that we only consider points of the form $x_i = (x_{1i}, 0)$ or $(0, x_{2i})$ since interaction (synergy) is not considered in the potency studies here. As such, the x_1 variable corresponds to doses for the substance plotted on the horizontal axis and x_2 to the substance plotted on the vertical axis. Thus, in this model θ_2 is the LD_{50} for x_1 , θ_2/θ_4 is the LD_{50} for x_2 , θ_4 is the relative potency of horizontal substance to the vertical one; θ_3 is the associated slope parameter, and the respective curves are assumed parallel (see Smith & Ridout, 2003).

This three-parameter generalized nonlinear model can be fit using maximum likelihood estimation (MLE) methods. Since algorithms to obtain MLE's (such as the Newton-Raphson procedure discussed in Seber & Wild (1989)) often require starting values, plotting the corresponding data with percent mortality versus dose of the doses give eyeball estimates of the LD_{50} 's as well as the slope parameter, θ_3 .



To illustrate, Nemeroff *et al* (1977) and Imrey *et al* (1982) assess the relative potency of peptides neurotensin (N) and somatostatin (S); in our notation here, x_1 corresponds to somatostatin and x_2 corresponds to neurotensin. The chosen dose levels (in μg) are for N: 0.01, 0.03, 0.1, 0.3, 1, 3, 10, and 30; and for S: 0.3, 1, 3, 10, 30, and 100. In this study, 10 mice were randomized to each of the peptide-dose combinations excepting that 30 mice were randomized to each of 0.01 and 0.03 doses of N, so 180 total mice were used in this study. In addition to $\hat{\theta}_3 = 0.7234$, the corresponding MLE's of the LD'_{50} s are $\hat{\theta}_2 = 29.47(\text{S})$ and $\hat{\theta}_2/\hat{\theta}_4 = 5.20(\text{N})$, so the estimated relative potency here is $\theta_4 = 5.66$; since the LD_{50} for N is lower, it is deemed more potent/toxic. These results, as well as the original design and fitted curves are shown in the above graph.

A natural query is whether the model parameters could have been more efficiently (i.e., using a lower sample size) estimated using the corresponding optimal design, which we consider next.

2. Optimal Design Theory

An approximate design, denoted ξ , is written

$$\xi = \begin{pmatrix} \mathbf{x}_1 & \mathbf{x}_2 & \cdots & \mathbf{x}_n \\ \omega_1 & \omega_2 & \cdots & \omega_n \end{pmatrix}. \quad (2)$$

The ω_i are non-negative design weights which sum to one; the \mathbf{x}_i are design points or vectors (as in the current situation) that belong to the design space and are not necessarily distinct. Note that the model parameters are stacked into the p -vector θ . For the constant-variance normal setting with linear or nonlinear normal model function $\eta(x, \theta)$, the $n \times p$ Jacobian matrix is $V = \frac{\partial \eta}{\partial \theta}$ and with $\Omega = \text{diag}(\omega_1, \omega_2, \dots, \omega_n)$, the $p \times p$ (Fisher) information matrix is

$$\mathbf{M}(\xi, \theta) = \mathbf{V}^T \Omega \mathbf{V} \quad (3)$$

Letting LL denote the log-likelihood, the corresponding information matrix in the general case of either non-constant variance or non-normality is given by

$$\mathbf{M}(\xi, \theta) = -E \left(\frac{\partial^2 LL}{\partial \theta \partial \theta^T} \right) \quad (4)$$

As shown in Atkinson *et al* (2007) for binomial logistic models in general, the information matrix for the relative-potency logistic model considered here has the same form as in (3) with an appropriate modification of the weight matrix Ω ; specifically, Ω in this case is a diagonal matrix with i^{th} diagonal element $\omega_i \pi_i (1 - \pi_i)$, where π_i is the success probability. In many regression settings, since the (asymptotic) variance of $\hat{\theta}_{MLE}$ is proportional to $\mathbf{M}^{-1}(\xi, \theta)$, designs are often chosen to minimize some (convex) function of $\mathbf{M}^{-1}(\xi, \theta)$. For example, designs which minimize its determinant are called D-optimal. Since for nonlinear/logistic models, M depends upon θ , so-called local (or Bayesian) designs are typically obtained.

The (approximate) variance of the predicted response at the value x is

$$d(x, \xi, \theta) = \frac{\partial \eta(x, \theta)}{\partial \theta^T} \mathbf{M}^{-1}(\xi) \frac{\partial \eta(x, \theta)}{\partial \theta} = \text{tr} \{ \mathbf{M}^{-1}(\xi) \mathbf{M}(x) \} \quad (5)$$

Here, $\mathbf{M}(x) = \frac{\partial \eta(x, \theta)}{\partial \theta} \frac{\partial \eta(x, \theta)}{\partial \theta^T}$. Designs that minimize (over ξ) the maximum (over x) of $d(x, \xi, \theta)$ in (5) are called G-optimal. As noted above, since this predicted variance depends upon θ for logistic and nonlinear models, researchers often seek optimal designs either using a “best guess” for θ (called a local optimal design) or assuming a plausible prior distribution on θ (called a Bayesian optimal design).

For the relative potency model studied here, it can be shown that the (local) D-optimal design ξ_D^* comprises four support points and the four equal-weight ($\omega_i = \frac{1}{4}, i = 1, 2, 3, 4$). The support points are: $(\frac{1}{t^*}, 0), (t^*, 0), (0, \frac{1}{t^*}), (0, t^*)$ for $t^* = 3.3970$, which in turn is one of two reciprocal roots of the expression

$$(1+t) + \frac{3}{2}(1-t)\log(t) = 0 \quad (6)$$

The other root of this expression is $\frac{1}{t^*} = 0.2944$.

Since from above $t_i = \left(\frac{x_{1i} + \theta_4 x_{2i}}{\theta_2} \right)^{\theta_3}$, for the peptide example with $\hat{\theta}_2 = 29.47, \hat{\theta}_3 = 0.7234, \hat{\theta}_4 = 5.66$, we easily translate from t 's to dose levels to obtain the equal-weight 4-point design for somatostatin (S) and neurotensin (N): $(S, N) = (5.44, 0), (159.80, 0), (0, 0.96), (0, 28.21)$. The first and third of these points lie on the $\frac{1}{t^*}$ line segment, whereas the second and fourth points lie on the t^* line segment, equally spaced on a geometric (log) scale from the $t = 1$ line segment. Henceforth, we give designs in terms of the t 's mindful that these can then be converted into doses using the corresponding parameter estimates.

The General Equivalence Theorem (GET) of Kiefer and Wolfowitz (1960) establishes that D- and G-optimal designs are equivalent. This work also shows that the variance function (5) evaluated using the D-/G-optimal

design does not exceed the line $y = p$, where p is the number of model function parameters – but that it will exceed this line for all other designs. A corollary establishes that the maximum of the variance function is achieved for the D-/G-optimal design at the support points of this design; this result is quite useful for establishing optimality of a given design.

For the peptide example and using the conjectured D-optimal design with reciprocal t 's coming from (6) given above, we obtain algebraically the corresponding variance function using this optimal design (in terms of $t = \left(\frac{x}{\theta_2}\right)^{\theta_3}$),

$$d(x, \xi_D^*, \theta) = \frac{t}{t^*} \left(\frac{1+t^*}{1+t}\right)^2 \left(2 + \frac{\log^2(t)}{\log^2(t^*)}\right) \quad (7)$$

D-optimality is then proved by showing that for all values of t this expression is less than or equal to $y = 3$ and invoking the General Equivalence Theorem to establish optimality.

Mindful that for the model considered here we are more interested in efficiently estimating the relative potency parameter (θ_4) than the other parameters, we consider the partition of the Fisher information matrix as

$$\mathbf{M} = \begin{bmatrix} \mathbf{M}_{11} & \mathbf{M}_{12} \\ \mathbf{M}_{21} & \mathbf{M}_{22} \end{bmatrix}. \quad (8)$$

In this expression, each sub-matrix \mathbf{M}_{ij} is of dimension $p_i \times p_j$, for $i, j = 1, 2$ and $p_1 + p_2 = p$. We envisage the situation in which the parameter vector is similarly partitioned,

$$\theta = \begin{pmatrix} \theta_1 \\ \theta_2 \end{pmatrix}.$$

with θ_1 of dimension $p_1 \times 1$, θ_2 of dimension $p_2 \times 1$, and where θ_2 is the parameter vector of interest and θ_1 are the nuisance parameters. Also, subset D-optimal designs, as discussed in Atkinson et al (2007), maximize

$$|\mathbf{M}_{22} - \mathbf{M}_{21}\mathbf{M}_{11}^{-1}\mathbf{M}_{12}| = \frac{|\mathbf{M}|}{|\mathbf{M}_{11}|} \quad (9)$$

Noting problems associated with subset designs, O'Brien (2005) and Atkinson et al (2007) instead combine the subset and full-parameter criteria and suggest that for $\beta \in \left[\frac{p_2}{p}, 1\right]$, designs be chosen to maximize the objective function

$$\Phi_\beta(\xi, \theta) = \frac{1-\beta}{p_1} \log|M_{11}| + \frac{\beta}{p_2} \log|M_{22} - M_{21}M_{11}^{-1}M_{12}| \quad (10)$$

This objective function ranges from the D-optimal criterion for $\beta = \frac{p_2}{p}$ to the subset design criterion in (9) for $\beta = 1$. For a given choice of $\beta \in \left[\frac{p_2}{p}, 1\right]$, we call designs that maximize (10) D_β -optimal. Both the corresponding variance function associated with (10) and an extension of the General Equivalence Theorem ensure D_β -optimality by plotting this variance function.

For the relative potency model considered here, we treat the $LD_{50}(\theta_2)$ and slope parameters (θ_3) as nuisance parameters, and the relative potency parameter (θ_4) as the parameter of interest. Here, $p_1 = 2$ and $p_2 = 1$, so $\left[\frac{p_2}{p}, 1\right] = \left[\frac{1}{3}, 1\right]$. Our results show that the optimal values of $t = \left(\frac{x}{\theta_2}\right)^{\theta_3}$ for D_β -optimal designs satisfy (c.f. equation (6))

$$(1+t) + \frac{1}{1-\beta}(1-t)\log(t) = 0 \quad (11)$$

As with equation (6), the t -values which solve this expression are observed to be reciprocals. For example, for $\beta = \frac{p_2}{p} = \frac{1}{3}$, as noted, we obtain the D-criterion (and $t^* = 3.3970$). Also, as the β values approach the D-subset design (i.e., $\beta \rightarrow 1^{-1}$), the optimal (reciprocal) t -values approach 1, thereby producing a singular design. Designs of this sort are addressed in Silvey (1980).

A measure of the distance between an arbitrary design ξ and the D-optimal design ξ_D^* is the D-efficiency discussed in O'Brien & Funk (2003) and Atkinson *et al* (2007). For the peptide illustration, the D-efficiency of the chosen design (ξ_C) in Nemeroff *et al* (1977) relative to the D-optimal design is

$$\left(\frac{|\mathbf{M}(\xi_C)|}{|\mathbf{M}(\xi_D^*)|} \right)^{1/3} = 0.6803 \quad (12)$$

With a D-efficiency of 68.03%, this means that approximately 47% more (i.e., $1/0.6803$) experimental units need to be used with the chosen design ξ_C in Nemeroff *et al* (1977) to obtain the same information at the D-optimal design. This means that the same information would be achieved using the D-optimal design and only 123 mice as with the chosen design and 180 mice.

The above advantage notwithstanding, optimal designs can often only be used as starting points as they may have associated shortcomings. One such shortcoming is that in most practical situations, optimal designs for p -parameter model functions comprise only p support points (or perhaps $p + 1$). Thus, these designs provide little or no ability to test for lack of fit of the assumed model. As a result, researchers often desire near-optimal so-called "robust" designs which have extra support points that can then be used to test for model adequacy. In the next section, we give a very useful means to obtain robust optimal designs, and illustrate the associated benefits of these designs.

3. Near-Optimal Geometric and Uniform Designs

The structure of the design chosen in Nemeroff *et al* (1977) – as well as numerous examples given in O'Brien *et al* (2009) – underscores the popularity of geometric and uniform designs in practical settings. For the relative potency model considered here with $t = \left(\frac{x}{\theta_2}\right)^{\theta_3}$, $x = x_1 + \theta_4 x_2$, we now examine $(K + 1)$ -point geometric designs of the form $t = a, ab, ab^2 \dots ab^K$, with $a \geq t_{min}$ and $ab^K \leq t_{max}$. Here, K is specified by the researcher, and we provide optimal values of a and b for given values of K as well as any associated information loss (as measured by the D-efficiency). In our work, we have also sought optimal uniform designs of the form $A, A + B, A + 2B \dots A + KB$ (also with $A \geq t_{min}$ and $A + KB \leq t_{max}$), but in all cases examined, geometric designs out-performed uniform designs (higher D-efficiencies), so we limit our discussion here to our findings regarding optimal geometric designs – i.e., those maximizing $|\mathbf{M}|$.

Table 1. Values of K , optimal b^* , D-efficiencies, and t-values for optimal geometric designs for the Finney relative potency model.

K	b^*	D-efficiency	t-values
1	11.54	100%	t=0.2944, 3.3970
2	4.506	97.30%	t=0.2219, 1, 4.5061
3	3.037	96.91%	t=0.1889, 0.5738, 1.7427, 5.2928
4	2.414	96.75%	t=0.1717, 0.4143, 1, 2.4136, 5.8253
5	2.077	96.66%	t=0.1609, 0.3341, 0.6939, 1.4411, 2.9930, 6.2160

Our results demonstrate that for the optimal geometric designs with optimal b value of b^* , our optimal design algorithms yield $a^* = \frac{1}{(b^*)^{K/2}}$ and again we note that the corresponding t-values are reciprocals. Examples are given in Table 1 for $K = 1, 2, 3, 4, 5$. The case $K = 1$ corresponds to the (unconstrained) D-optimal design discussed above. For the values of K considered here (i.e., ≤ 5), it is noted that the D-efficiencies are all above 96.5%, meaning that the information loss associated with using any of these optimal geometric designs is indeed trivial.

To obtain optimal, subset and near-optimal geometric/uniform designs, we have used the "NLP" constrained nonlinear optimization procedures in SAS/IML version 9.3 (SAS Institute, Cary NC), specifically using the Newton-Raphson algorithm, "NLPNRA". Sample SAS code is given in the Appendix. This optimization algorithm requires the creation of a so-called module – such as the "CF" and "CF2" modules given in the Appendix – along with constraints and starting values. In our results, D- or subset-optimality was then established by plotting the associate variance function. Here, the "CF" module is used to obtain the (local) D-optimal design and the "CF2"

module is used to obtain the optimal geometric design with $K = 2$. In the case of geometric designs (CF2), the resulting optimal geometric design is obtained by optimizing over a and b (which are denoted “aa” and “bb” in the SAS code).

To illustrate in the context of the peptide example and using a 5-point geometric design (i.e., with $K = 4$), we obtain a 10-point design with optimal levels of the respective peptides: 2.579, 8.719, 29.47, 99.62, and 336.7 μg for somatostatin and 0.455, 1.539, 5.203, 17.59, and 59.45 μg for neurotensin. From Table 1, since the middle t -value here is 1, both of the middle values of somatostatin and neurotensin in this design correspond to the LD'_{50} s (ie, 29.47 and 5.204). Maintaining a total sample size of 180 mice, so with 18 mice at each of these 10 design points, this near-optimal geometric design represents a 42.21% improvement (i.e., reciprocal D-efficiency) over the one chosen in Nemeroff *et al* (1977). These results clearly demonstrate the advantage of taking account of optimal design strategies – yet maintaining the practical geometric structure – when choosing the experimental design for an experiment.

Of final note, in situations where there is an upper bound on the levels of the constituents (x_1 and x_2) and thus on the t -values, the methods proposed here are easily constrained, for example to settings where $ab^K \leq c$.

4. Summary

Researchers working in toxicology/bioassay require efficient design strategies for assessing relative potency of similar compounds, and local D-optimal designs clearly provide a useful starting point or benchmark. As demonstrated here, these optimal designs often lack the means to test for lack of fit of the assumed (binomial logistic) model, so we advocate instead the use of near-optimal robust designs. Additionally, since most researchers are accustomed to using geometric-type designs, the results provided here give practitioners clear suggestions as to how these should then be chosen; optimal geometric designs can be obtained using Table 1. The suggested designs are indeed very near to the optimal designs, often resulting in D-efficiencies above 95%. Clearly, an information loss of less than 5% is trivial compared with the practical nature of geometric designs and the ability to assess model goodness-of-fit.

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Appendix: SAS/IML Sample Code:

(1) SAS/IML module to obtain local D-optimal designs for the Finney relative potency model

```

start CF(des) global(th2,th3,th4);
a1=des[1]; b1=des[5];
a2=des[2]; b2=des[6];
a3=des[3]; b3=des[7];
a4=des[4]; b4=des[8];
a=a1//a2//a3//a4;
b=b1//b2//b3//b4;
w=(1/4)*j(4,1);
z=a+th4*b;
t=(z/th2)##th3;
den=1+t;
pi=t/den;
ompi=1/den;
on=j(4,1);
ww=w#pi#ompi;
v2=(th3/th2)*on;
v3=-(1/th3)*log(t);
v4=-th3*(1/z)#b;
v=v2||v3||v4;
omeg=diag(ww);
m=t(v)*omeg*v;
detm=det(m);
tomin=-detm;
return(tomin);
finish CF;

```

(2) SAS/IML module to obtain local geometric designs for the Finney relative potency model

```

start CF2(des) global(th2,th3,th4);
aa=des[1];
bb=des[2];
a1=th2*(aa**(1/th3)); b1=0;
a2=th2*((aa*bb)**(1/th3)); b2=0;
a3=th2*((aa*bb**2)**(1/th3)); b3=0;
a4=0; b4=(th2/th4)*(aa**(1/th3));
a5=0; b5=(th2/th4)*((aa*bb)**(1/th3));
a6=0; b6=(th2/th4)*((aa*bb**2)**(1/th3));
a=a1//a2//a3//a4//a5//a6;
b=b1//b2//b3//b4//b5//b6;
w=(1/6)*j(6,1);
z=a+th4*b;
t=(z/th2)##th3;
den=1+t;
pi=t/den;
ompi=1/den;

```

```
on=j(6,1);  
ww=w#pi#ompi;  
v2=(th3/th2)*on;  
v3=-(1/th3)*log(t);  
v4=-th3*(1/z)#b;  
v=v2||v3||v4;  
omeg=diag(ww);  
m=t(v)*omeg*v;  
detm=det(m);  
tomin=-detm;  
return(tomin);  
finish CF2;
```