EFFICIENT GEOMETRIC AND UNIFORM DESIGN STRATEGIES FOR SIGMOIDAL REGRESSION MODELS

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Key words: Bioassay; curvature; D-efficiency; goodness of fit; lack of fit; logistic model; nonlinear regression; optimal design; rules of thumb.

Summary: This paper provides practical guidelines for choosing efficient geometric and uniform designs for the logistic class of dose-response bioassay model functions in both the homoskedastic Gaussian and Binomial settings. The efficiencies of the designs provided here are typically above 90%, and since the number of design support points generally exceeds the number of parameters, these designs provide a useful and efficient means to confirm the assumed model. Extensions of our basic strategy include a Bayesian maxi-min design approach to reflect a range of values of the initial parameter estimates, as well as geometric/uniform design analogues when uncertainty exists as to the correct scale or to take account of curvature.

AMS: 62K05

1. Introduction

In many applied branches of study, nonlinear regression models are more accurate and reasonable for modelling various biological and chemical processes than are linear ones since they tend to fit the data well and since these models and model parameters are more scientifically meaningful. As a result, applied statisticians are often required to provide optimal or near-optimal designs for a given nonlinear model. As noted in O'Brien (1996) and Atkinson *et al.* (2007), however, a common shortcoming of optimal designs for nonlinear models used in practical settings is that these designs typically have only as many support points as the number of unknown model parameters. Although such designs may present no problem when the model function can be assumed to be known with complete certainty and when all other model assumptions are met, in practice researchers typically desire designs that are near-optimal but which contain 'extra' design points which can be used to test for model adequacy. Design strategy references include Silvey (1980), Seber and Wild (1989), Pukelsheim (1993), Dette and O'Brien (1999), O'Brien and Funk (2003), and the reference provided therein. Robust design strategies are given in Sitter (1992), Dette (1993), Pukelsheim and Rosenberger (1993), Zen and Tsai (2004), Dette *et al.* (2005), and Bischoff and Miller (2006), and applications of uniform designs are provided in Hedayat *et al.* (1997, 2002) and Mathew and Sinha (2001).

Since sigmoidal models are used extensively in practice, this paper focuses on the logistic class of model functions; this is a rich class of models since it also includes the log-logistic and the Michaelis-Menten models. The geometric designs considered here have design points of the form $x_1 = a,\ \ x_2 = ab,\ \ x_3 = ab^2 ... x_{K+1} = ab^K,$ and their use is pervasive in biomedical and applied research. Arbitrary choices of a, b and K in these designs can lead to experiments which are at best inefficient and at worst useless to estimate the model parameters and test for model adequacy. In the context of homoskedastic Gaussian and the Binomial distributions, geometric designs are discussed and illustrated for the log-logistic family of models, both using the original (e.g. dose) scale and using the log-dose scale. We also examine optimal uniform designs, or designs with support points of the form $x_1 = A,\ x_2 = A + B,\ x_3 = A + 2^*B, ...x_{K+1} = A + K^*B,$ providing the means for the optimal choice of *A* and *B*, as well as an indication of whether to use a geometric or a uniform design. In general, the geometric and uniform designs herein have at least 90% D-efficiency and provide a useful and important means to test for goodness of fit of the assumed model.

In the next section, we provide notation and background details. In Section 3, an overview of examples using geometric and uniform designs in practice is given. Our general design methodologies are given and illustrated in Section 4 for the homoskedastic Gaussian dose-response model and in Section 5 for the Binary Logistic case. Finally, important extensions are discussed and contrasted in Section 6.

2. Background in design and nonlinear models

Choosing an optimal design for parameter estimation for a given nonlinear model is challenging for several reasons, most notably since the optimality criterion must be chosen from amongst several and since the chosen design depends upon the unknown model parameters. Equally important is the assessment of the validity of the assumed model after the data has been observed. Since most optimal designs only have as many support points as model parameters, these minimal-support designs cannot in general be used to evaluate lack of fit. Practitioners therefore seek instead near-optimal so-called 'robust' designs – such as the geometric and uniform designs provided here.

An n-point design is denoted here as ξ and written

$$\xi = \left\{ \begin{array}{c} x_1,\ x_2,\ ...,\ x_n \\ \omega_1,\ \omega_2,\ ...,\ \omega_n \end{array} \right\}.$$

In this expression, the ω_k are non-negative weights that sum to one, and the x_k (which may be vectors) belong to the design space and are not necessarily distinct. Also, in the usual homoskedastic Gaussian setting for the model function $\eta\,(x,\ \theta)$, the $n \times p$ Jacobian matrix is written $\mathbf{V} = \partial\eta/\partial\theta$ and the $p \times p$ Fisher information matrix is given by $\mathbf{M}(\xi,\ \theta) = \mathbf{V^T\Omega V}$, where $\mathbf{\Omega}$ is the diagonal matrix with diagonal elements $\omega_1,\ \omega_2,\ ...,\ \omega_n$. Then, the first-order (and asymptotic) variance of the least-squares estimator of the p-vector θ is proportional to $\mathbf{M}^{-1}$, so designs are often chosen to minimize some convex function of $\mathbf{M}^{-1}$. For example, designs which minimize its determinant (or equivalently those which maximize the determinant of $\mathbf{M}$) are called D-optimal, and those that minimize its trace are called A-optimal. Since for nonlinear models, $\mathbf{V}$ depends upon θ, a Bayesian strategy is sometimes used; see Atkinson *et al.* (2007) and Section 6 below. Whenever the sample size (n) is a multiple of $(K+1)$, the designs considered here are exact designs, so that D-optimal designs maximize the determinant of $\mathbf{V}^T\mathbf{V}$; in all other cases, we consider the approximate designs as given in the above expression.

The A-optimality criterion is generally used in "block design" situations (including cyclic-, row-, column- and alpha-designs) since it focuses on minimizing the average variance of the parameters (or contrasts of parameters). In contrast, D-optimality is preferred for regression models since this criterion (but neither A- nor E-optimality) is invariant to a linear or nonlinear change in scale; see Silvey (1980) and O'Brien and Funk (2003). Since we consider here only (nonlinear) regression models, we therefore use the D-optimality criterion.

For a given model, when one wants to compare an arbitrary design ξ with the D-optimal design, ξ_D, a useful measure of the loss of information is the D-efficiency,

$$D_{EFF} = \left[\frac{\det\left(M\left(\xi\right)\right)}{\det\left(M\left(\xi_D\right)\right)}\right]^{1/p}. \tag{1}$$

The D-efficiency measure is used here to compare to the D-optimal design a $(K+1)$-point geometric design with support points of the form $x_1 = a,\ x_2 = a^*b,\ x_3 = a^*b^2,\ ..,\ .x_{K+1} = a^*b^K$ and a $(K+1)$-point uniform design with support points of the form $x_1 = A,\ x_2 = A+B,\ x_3 = A+2^*B,\ ...,\ x_{K+1} = A+K^*B.$

Nonlinear models and Binary Logistic models – including the Sigmoidal growth and decay models considered here – are examined in Ratkowsky (1983,1990), Bates and Watts (1988), Seber and Wild (1989), Huet *et al.* (1996), Agresti (2002, 2007), and Collett (2003); additional theoretical results are given in Gallant (1987) and McCullagh and Nelder (1989).

Due to its widespread popularity, our focus here is the two-parameter log-logistic (LL2) model function,

$$\eta\left(x,\ \theta\right) = \frac{1}{1+t} = \frac{1}{1+\left(x/\theta_2\right)^{\theta_3}}. \tag{2}$$

In this expression, $t = \left(x/\theta_2\right)^{\theta_3}$.

A related model function is the two-parameter logistic (LOG2) model function, given by the equation

$$\eta\left(x,\ \theta\right) = \frac{1}{1+u} = \frac{1}{1+e^{\theta_3(x-\theta_2)}}. \tag{3}$$

Here, $u = e^{\theta_3(x-\theta_2)}$. In both of these expressions, the parameter θ_2 is the so-called LD_{50} (also called ED_{50} or LC_{50}), and is the value of x such that $\eta = \frac{1}{2}$. When the slope parameter θ_3 in the LL2 model function is positive, the associated graph is down-sloping from an "upper asymptote" of unity (for $x = 0$) to a lower asymptote of zero (for very large values of x); similar results hold for the LOG2 model function but with the upper asymptote occurring at very large negative values of x. Graphs of these two model functions for the LD_{50} = 5 and various choices of the slope parameter are given in Figure 1.

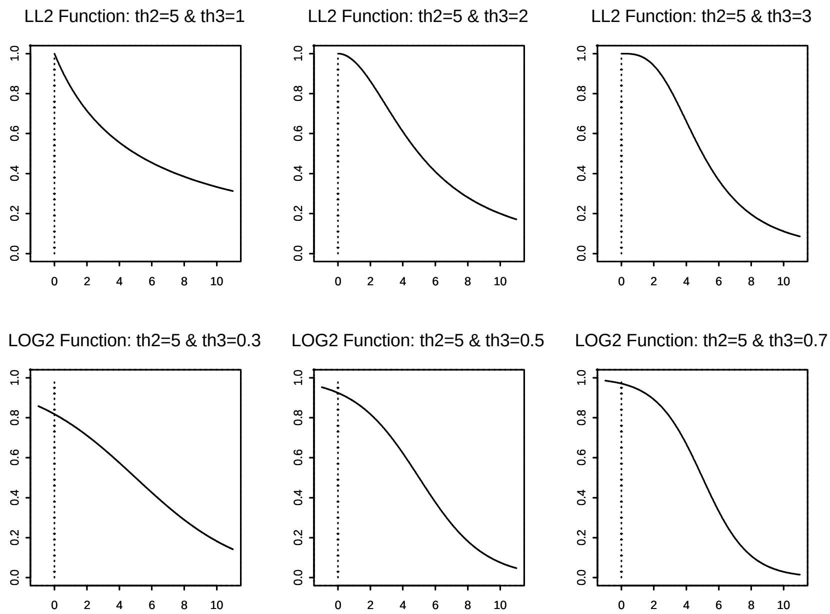

Figure 1 Graphs of LL2 model function (top row) and LOG2 model function (bottom row) for $th2 = \theta_2 = LD_{50} = 5$ and various slopes $(th3 = \theta_3)$ indicated above each plot. For both these functions, θ_2 controls the left or right shift (held constant here) and θ_3 controls the slope or steepness of decline of the curve

In settings where the upper and lower asymptotes in the LL2 setting are not 1 and 0, but need to be estimated, this model is easily extended to the four-parameter log-logistic (LL4) model function,

$$\eta\,(x,\ \theta) = \theta_4 + \frac{\theta_1 - \theta_4}{1 + (x/\theta_2)^{\theta_3}}. \tag{4}$$

When the slope parameter in this expression is positive, θ_1 is the "upper asymptote" (at $x = 0$) and θ_4 is the lower asymptote (for large x). This LL4 model function has been extensively applied in applications as diverse as nutrition (Morgan *et al.*, 1975), bioassay (O'Connell *et al.*, 1993), weed science (Seefeldt *et al.*, 1995), and pharmaceutical science (Fedorov *et al.*, 2007). Here, we focus on designs for the LL2 and LOG2 models; additional results related to the three- and four-parameter logistic models are given in Li and Majumdar (2008).

To connect the LL2 and LOG2 model functions, we now define the three-parameter scaled logistic (SL3) model function,

$$\eta\,(x,\ \theta) = \frac{1}{1+v} = \frac{1}{1 + e^{\theta_3[z(x)-z(\theta_2)]}}. \tag{5}$$

In this expression, $v = e^{\theta_3(z(x)-z(\theta_2))}$ and we use the Box-Cox transformation for both x and θ_2,

$$z\,(x) = \frac{x^\gamma - 1}{\gamma}. \tag{6}$$

Clearly the LOG2 model function is a special case of the scaled logistic function when γ is chosen to equal 1, and the LL2 model function corresponds to $\gamma \to 0$. This scaled logistic model is important both to connect these two model functions under one generalized model "umbrella" and since the LOG2 model results in this model when the dose scale is used whereas the LL2 model function results when the log-dose scale is used.

Since in practice one can only rarely be certain which scale should be used, O'Brien *et al.* (2007) demonstrate fitting the scaled logistic model so as to first determine the appropriate scale. When this is not done, errors can easily result. For example, practitioners and students are easily left confused when Example 4.1 in Myers *et al.* (2002) fits the Binary Logistic model to a set of data on both the concentration and the log-concentration scale but provides no indication of which scale is preferred and why. Similarly, the wrong scale is used for Example 13.1 in Montgomery *et al.* (2001) in fitting the Binary Logistic model; this is clearly indicated when one first fits the scaled logistic model. Indeed, an important ramification of this error is that the LD_{50} and other model parameters are often estimated incorrectly and inefficiently. We return to issues of the proper scale in Section 6.2.

3. Some representative applications of geometric and uniform designs

In this section, we briefly highlight the widespread usage of the geometric and uniform designs by providing some representative illustrations. As specified above, $(K+1)$-point geometric design support points are of the form $x_1 = a,\ x_2 = a^*b,\ x_3 = a^*b^2,\ ...,\ x_{K+1} = a^*b^K,$ with the (*a, b, K*) terms specified by the researcher; similarly, $(K+1)$-point uniform design support points can be written $x_1 = A,\ x_2 = A+B,\ x_3 = A+2^*B,\ ...,\ x_{K+1} = A+K^*B,$ so that the (*A, B, K*) terms need to be chosen. The illustrations given here exemplify the ubiquitous nature of geometric and uniform designs in the applied literature and provide useful contexts for the guidelines given in the next sections.

Illustrations include:

- In the Binomial Logistic setting, Collett (2003) provides data wherein the chosen design is of the above geometric structure with $a = 1,\ b = 2$ and $K = 5$.
- Variations on this "halving dilution" $(b = 2)$ design approach are used in Finney (1976), Price *et al.* (1987), Giltinan *et al.* (1988), Gouws (1995), and Zocchi and Demétrio (2000).

- ELISA data are provided in Huet *et al.* (1996) wherein the response is optical density and the independent variable is of the form $x = log10(1/d)$ and $1/d$ is reciprocal dilution. The chosen design for the reciprocal dilutions are essentially of the geometric structure with $a = 30, b = 3$, and $K = 7$. Myers *et al.* (2002) provides a similar (essentially) geometric illustration with $a = 0.10$, $b = 1.45$, and $K = 6$.
- A (near) uniform design is used in Bailer and Piegorsch (2000), for which $x = 0, 80, 160, 235$ and 310.
- Seefeldt *et al.* (1995) report data in which the explanatory variable is the dose of an herbicide, and a reasonable model function for these data is the LL4 model function given in Equation (4). For this study, the authors used the design points $x = 0, 0.066, 0.198, 0.660, 1.98$ and 6.60. Thus, in addition to the zero point, this design combines two geometric designs both with $b = 10$ – the first one uses $a_1 = 0.066$ and the second with $a_2 = 0.198 = 3^* a_1$. Stokes *et al.* (2000) provide a similar illustration but with $a_1 = 0.01$, $a_2 = 0.03 = 3^* a_1$, $b = 10$, and $K = 3$.

With these examples in mind, it is important to distinguish between the geometric designs considered here and the serial dilution design strategy explored in Chase and Hoel (1975) and illustrated in Verkooyen *et al.* (1996) and Sigurdsson *et al.* (2002). In the later instances, a researcher is unable to count, for example, the number of viruses in a medium and then serially dilute (for example using a dilution factor of 10) the medium until a count is indeed possible; this resulting count is then used to estimate the original number. On the other hand, although geometric designs may indeed be obtained by a "dilution," the goal here is to assess, for example, the toxicity of a chemical using the dose-response regression models given above.

4. Efficient designs in the homoskedastic Gaussian case

When it is reasonable to assume that the response variable follows the constant-variance Gaussian distribution with mean given by the LL2 model function and design region $[0, \infty)$, for a chosen value of K we obtain a $(K+1)$-point geometric design with support points $x = a,\ a^{*}b,\ a^{*}b^{2},\ \ldots,\ a^{*}b^{K}$ by first choosing the corresponding value of 'm' from the following table.

Table 1 Optimal values of *m* and D-efficiencies (D-EFF) for various choices of *K* for the Gaussian LL2 and LOG2 models. Values of *m* and *K* are then used to obtain values of *a* and *b* or *A* and *B* to be used to obtain experimental designs

K	1	2	3	4	5	6
m	8.0627	3.4025	2.4845	2.0598	1.8215	1.6698
D-EFF (%)	100.0	92.21	91.40	91.03	90.85	90.74
K	7	8	9	10	11	19
m	1.5650	1.4884	1.4299	1.3839	1.3468	1.1952
D-EFF (%)	90.67	90.62	90.59	90.56	90.55	90.48

Next, *a priori* estimates of the model parameters θ_2 and θ_3 are used to obtain the values

$$b = m^{1/\theta_3} \text{ and } a = \theta_2 / b^{K/2}. \tag{7}$$

These values are then used to generate the desired geometric design. The optimal values of *m* for given choices of K provided in Table 1 have been obtained using computer programs in which geometric designs are provided that minimize the D-optimality criterion given in Section 2. Sample SAS® and GAUSS® computer code to obtain these designs is available from the authors. D-efficiencies are also calculated and given in the table so as to convey the degree of the loss of information in using a geometric design instead of the two-point D-optimal design.

Example 5. To illustrate, if we desire a 7-point geometric design $(K = 6)$, and we feel that reasonable parameter choices are $\theta_2 = 5$ and $\theta_3 = 2$, then we obtain from Table 1, $m = 1.6698$ with associated D-efficiency = 90.74%, and by calculation $b = 1.2922$ and $a = 2.3172$. The optimal geometric design therefore has support points $x = 2.317, 2.994, 3.869, 5.000, 6.460, 8.349$ and 10.788. The value $b = 1.2922$ here means that this design uses a dilution of $1/b = 0.77$ or approximately $\frac{3}{4}$; thus, for every three parts of the active substance, the researcher would then add four parts of water or similar inert substance. That is, in many settings this is not impractical so that choosing a value of *b* other than an integer is indeed often viable. ■

Several points are worth noting when examining the values given in Table 1 and the methodology given here to obtain *a* and *b* using equation (7). First, even for the very large 20-point geometric design $(K = 19)$, the information loss is not too great – only 9.5% for this model. This implies that in some sense these optimal geometric designs are 'close' to the D-optimal design, where 'closeness' is defined in terms of the determinant of the Fisher information matrix. Indeed, in many practical settings, our experience shows that researchers are willing to sacrifice such a small amount of parameter-estimate efficiency in order to obtain a robust near-optimal design which can be used to test for model mis-specification. This willingness to sacrifice some efficiency to validate the model as well as the ease to implement geometric designs in practice is perhaps best evidenced by the extensive list of examples given in the previous section.

Second, the case $K = 1$ corresponds to the two-point (local) D-optimal design. For *t* defined by the expression $t = (x/\theta_2)^{\theta_3}$ so that the LL2 model function in equation (2) is written $\eta = 1/(1 + t) -$ we point out that the reciprocal values of *t* in the D-optimal design solve the expression

$$(1+t)+2\,(1-t)\log(t)=0. \tag{8}$$

These values are $t_1 = 0.352175$ and $t_2 = 2.839497$, and are such that the expected responses are $\eta_1 = 0.739549$ and $\eta_2 = 0.260451$, so that the D-optimal design support points correspond to the expected responses being symmetric around $\frac{1}{2}$. Of course, this is no coincidence for the LL2 model function since for reciprocal values t_1 and $t_2 = 1/t_1$, we have $\eta_1 = 1 - \eta_2$. Symmetries associated with minimal-support optimal designs for logistic models are highlighted in Mathew and Sinha (2001).

We observe similar reciprocal patterns for all other choices of *K*. To illustrate, for Example 5 above, the optimal values are $t = 0.2148,\ 0.3586,\ 0.5989,\ 1.0000,\ 1.6698,\ 2.7883$ and 4.6560 (so the first and last are reciprocals, as are the second and penultimate, etc.), and the corresponding expected response values are $\eta = 0.8232,\ 0.7360,\ 0.6254,\ 0.5000,\ 0.3746,\ 0.2640$ and 0.1768; these values are repeated in the first row of Table 3 to facilitate comparisons. Also, we point out that in general the optimal values of *t* are of the form $t = m^r$, with *m* chosen from Table 1 for the corresponding value of K and with $r = -K/2, -(K-2)/2, -(K-4)/2,\ \ldots,\ (K-2)/2$, and $K/2$. Interestingly, this means that the optimal choices of *t* do not depend upon the *a priori* guesses of the model parameter $(\theta_2$ and $\theta_3)$ since *m* in Table 1 does not depend upon these values. That said, these assumed parameter values are very important in choosing the corresponding design support points since here $x = \theta_2 t^{1/\theta_3}$.

Third, although we return to the issue of incorrectly specifying θ_2 and/or θ_3 in greater detail in Section 6, we point out how important it is to understand the roles of these model parameters in the LL2 model function given in equation (2). As such, we find it very useful to discuss graphs such as those in Figure 1 with practitioners seeking experimental designs for this model. Since θ_2 is the model LD_{50} parameter, it can usually be quite accurately approximated. In contrast, practitioners often find the analogous parameter in the Weibull and Richards models considered in Dette and Pepelyshev (2008) harder to interpret and to approximate. The plots on the top of Figure 1 are helpful to understand the role of the slope parameter in the LL2 model function. Often, researchers can only give a range for these parameter values, and in Section 6 we return to the impact this uncertainty has on our recommendations for optimal geometric designs.

Furthermore, we have observed that when seeking optimal geometric designs for the two-parameter Gaussian logistic (LOG2) model function given in equation (3) and with design region $(-\infty,\ \infty)$, none of these geometric designs fared as well as *uniform* designs – i.e. those with support points of the form $x = A, A + B, A + 2^{*}B,\ \ldots,\ A + K^{*}B$. Interestingly, but perhaps not unexpectedly, the corresponding optimal values of *m* for these designs are exactly those given in Table 1 (and with the same D-efficiencies), and with the new relations,

$$B = \log(m)/\theta_3 \text{ and } A = \theta_2 - K^{*}B/2. \tag{9}$$

The connection between equations (7) and (9) is therefore obvious and underscores the fact that $u = exp\{\theta_3(x - \theta_2)\}$ in the LOG2 function simply takes the role of t in the LL2 model function. Thus the D-optimal design for the LOG2 model solves equation (8) with t replaced by u; see the first two rows of Table 4 to visualize these designs and appreciate the difference between the support points of the above geometric design for the Gaussian LL2 model and the uniform design for the Gaussian LOG2 model. We return to the issue of discriminating between the LL2 and the LOG2 model functions in Section 6.2.

5. Efficient designs in the binary logistic case

As we noted in Section 3, it sometimes is appropriate to use either of the LL2 or LOG2 model functions with the Bernoulli or Binomial distribution – the so-called Binary Logistic model. That is, for a given value of x, one assumes for this model that each of n experiments results in one of two independent Bernoulli outcomes with success probability π; of course, n here may depend upon x. Counterparts of the LL2 and LOG2 model functions given above in equations (2) and (3) are

$$\pi = \frac{1}{1+t} = \frac{1}{1+(x/\theta_2)^{\theta_3}} \tag{10}$$

and

$$\pi = \frac{1}{1+u} = \frac{1}{1+e^{\theta_3(x-\theta_2)}} \tag{11}$$

respectively; the respective design regions are $[0,\ \infty)$, and $(-\infty,\ \infty)$. This latter equation can be written in the familiar form,

$$\log\left(\frac{\pi}{1-\pi}\right) = -\theta_3\left(x-\theta_2\right). \tag{12}$$

The negative sign on the right-hand side of equation (12) is necessary for $\theta_3 > 0$ when the (decay) curves are down sloping as in Figure 1; it is removed in the case of growth curves. Also, since the parameters enter into these expressions in a nonlinear manner, these models now fall under the rubric of generalized nonlinear models; this results since the LD50 parameter is explicitly made one of the model parameters. For the LL2 model, the corresponding right-hand side in equation (12) is $-\theta_3\left\{\log\left(x\right)-\log\left(\theta_2\right)\right\}$. Similarly, the Binary counterpart of the SL3 model in equation (5) can also be written as in equation (12) but with right-hand side equal to the expression $-\theta_3\left\{z\left(x\right)-z\left(\theta_2\right)\right\}$, where $z(x)$ is the Box-Cox function defined in equation (6).

Our approach and findings here are analogous to those given in the previous section but with two important distinctions. First, whereas in the Gaussian case we use the identity link and so the exact-design Fisher information matrix is proportional to $\mathbf{V^T V}$, here the corresponding Fisher information matrix is of the form $\mathbf{V^T W V}$ since we are using the logit link. As shown in Atkinson *et al.* (2007), $\mathbf{W}$ is a diagonal matrix with typical diagonal element equal to $\pi\,(1-\pi)$ for π given in equation (10) for the Binary LL2 model and in equation (11) for the Binary LOG2 model. Thus, geometric and uniform designs are chosen in the Binary case considered here to maximize the determinant of $\mathbf{V^T W V}$. Important references wherein minimal-support optimal designs are provided and studied in this setting are provided in Atkinson *et al.* (2007); our focus here is on geometric and uniform designs.

Second, for the Binary LL2 model with success probability given in equation (10), the values of t in the D-optimal design solve the equation

$$(1+t)+(1-t)\log(t)=0. \tag{13}$$

This expression is analogous to Equation (8) which applies to the LL2 model in the Gaussian case; the reciprocal values that solve equation (13) are $t_1 = 0.213652$ and $t_2 = 4.680499$, and are such that the expected proportions are $\pi_1 = 0.823959$ and $\pi_2 = 0.176041$ and again the D-optimal design support points are such that the expected responses are symmetric around $\frac{1}{2}$. However, in contrast with the expected responses in the Gaussian LL2 setting (viz, $\eta_1 = 0.739549$ and $\eta_2 = 0.260451$), note that here the D-optimal design points have shifted so that the expected responses are further away from the centre $(\pi = \frac{1}{2})$. This is indeed reasonable since for this Binary model the variability, which is proportional to $\pi(1-\pi)$, decreases as we move away from $\pi = \frac{1}{2}$; the variability in the Gaussian case, on the other hand, is assumed to be constant (σ^2) over the range of the curve.

These differences notwithstanding, our approach to finding optimal geometric (for the LL2 model) and optimal uniform (for the LOG2 model) designs in the Binary Logistic case is analogous to the Gaussian case given in the last section, but with different values of m. These new m values and the D-efficiencies are given in Table 2 for the corresponding choices of K.

Table 2 Optimal values of m and D-efficiencies (D-EFF) for various choices of K for the Binary LL2 and LOG2 models. Values of m and K are then used to obtain values of a and b or A and B to be used to obtain experimental designs

K	1	2	3	4	5	6
m	21.9071	6.3606	4.0053	3.0099	2.4966	2.1868
D-EFF (%)	100.0	92.94	92.45	92.15	91.99	91.90
K	7	8	9	10	11	19
m	1.9811	1.8350	1.7262	1.6422	1.5754	1.3130
D-EFF (%)	91.85	91.81	91.78	91.76	91.74	91.69

The values of a and b are then again obtained using Equation (7) for the Binary LL2 model, and the values of A and B are obtained using Equation (9) for the Binary LOG2 model. Similarly, the values of t and u are again given by the relations $t = m^r$ for the LL2 model and $u = m^r$ for the LOG2 model with the powers $r = -K/2,\ -(K-2)/2,\ -(K-4)/2,\ \ldots,\ (K-2)/2$ and $K/2$.

To illustrate, consider again Example 5 discussed in the last section but now with the assumed distribution being the Binomial one. In this case, the optimal value of m is 2.1868 and since the D-efficiency is 91.90% the information loss here is only 8.1%. When the Binary LL2 model in equation (10) is assumed, we obtain $a = 1.5442$ and $b = 1.4788$; when the Binary LOG2 model in equation (11) is used, the relevant values are $A = 0.3053$ and $B = 1.5649$. To compare these results and the corresponding values of t for the LL2 model and u for the LOG2 model with the Gaussian case, these values are listed in Table 3. This table again shows that the design points become more dispersed for the Binomial distribution when compared with the Gaussian case.

Table 3 Optimal values for Example 5 under Gaussian and Binomial settings for LL2 model function (with $\theta_2 = 5,\ \theta_3 = 2$) and the LOG2 model function (with $\theta_2 = 5,\ \theta_3 = 0.5$)

Distribution	m	D-eff.	LL2 values	LOG2 values	t or u (expected responses)
Gaussian	1.6698	90.74%	$a = 2.317$	$A = 1.924$	$0.2148\ (0.8232)$
			$b = 1.292$	$B = 1.025$	$0.3586\ (0.7360)$
					$0.5989\ (0.6254)$
					$1.0000\ (0.5000)$
					$1.6698\ (0.3746)$
					$2.7883\ (0.2640)$
					$4.6560\ (0.1768)$
Binomial	2.1868	91.90%	$a = 1.544$	$A = 0.305$	$0.0956\ (0.9127)$
			$b = 1.479$	$B = 1.565$	$0.2091\ (0.8271)$
					$0.4573\ (0.6862)$
					$1.0000\ (0.5000)$
					$2.1868\ (0.3138)$
					$4.7821\ (0.1729)$
					$10.4576\ (0.0873)$

Finally, in order to highlight the impact on the final design support points for this example, these support points are given under the four settings considered here and above in the first four rows of Table 4. Note that the first and third designs are geometric and the second and fourth are uniform, and each contains the LD_{50} as a support point (this occurs only when K is even).

Table 4 Optimal design support points for Example $5(K = 6)$ under Gaussian and Binomial settings for LL2 and LOG2 model functions. Starred designs (8 and 9) use the second-order volume criterion with $\sigma = 0.25$ (see text)

Design	Model (chosen parameter values)	Design support points (x)						
1	Gaussian LL2 $(\theta_2$=5, θ_3=2$)$	2.32	2.99	3.87	5.00	6.46	8.35	10.79
2	Gaussian LOG2 $(\theta_2$=5, θ_3=0.5$)$	1.92	2.95	3.98	5.00	6.03	7.05	8.08
3	Binary LL2 $(\theta_2$=5, θ_3=2$)$	1.55	2.29	3.38	5.00	7.39	10.93	16.17
4	Binary LOG2 $(\theta_2$=5, θ_3=0.5$)$	0.31	1.87	3.44	5.00	6.57	8.13	9.70
5	Gaussian LL2 $(\theta$-robust$)$	1.75	2.36	3.18	4.29	5.78	7.80	10.51
6	Gaussian SL3 $\gamma \to 0(\theta_2$=5, θ_3=2$)$	1.50	2.24	3.35	5.00	7.47	11.17	16.69
7	Binary SL3 $\gamma \to 0(\theta_2$=5, θ_3=2$)$	0.67	1.31	2.56	5.00	9.77	19.07	37.25
8	Gaussian LL2 $(\theta_2$=5, θ_3=2$)^*$	2.93	3.65	4.55	5.66	7.05	8.78	10.93
9	Gaussian LOG2 $(\theta_2$=5, θ_3=0.5$)^*$	2.39	3.30	4.20	5.11	6.01	6.92	7.82

Note too that the given parameter values were chosen since the corresponding curves are very similar (see Figure 1). We return to the issue of wrongly specifying the *a priori* estimates of the parameter values in the next section. We also address there the issue of whether the LL2 or the LOG2 model should be chosen, and how to choose robust designs where there is uncertainty as to which is the better choice. Before doing so, we again underscore the over-riding point: using Tables 1 and 2, geometric and uniform designs can easily be chosen so that the information loss is modest (i.e. less than 10%), yet these designs provide us with the important ability to test model goodness of fit.

6. Further robustness concerns

Efficient geometric and uniform designs are very useful since they are often practical to implement and since they allow for a check of model fit. However, the methods to obtain these designs given above hinge upon several crucial assumptions or requirements including: (a) the parameter values be known with certainty, (b) the scale in our Logistic model be known (so we can choose either the LL2 or the LOG2 model function) with certainty, and (c) the first-order variance estimate is acceptable and therefore D-optimality is the appropriate design criterion. We address each of these issues in turn and modify the above rules-of-thumb accordingly in situations where these conditions are not met.

6.1 Incorporating uncertainty of model parameters

As noted in Section 2, choosing an optimal design for a nonlinear model is often complicated by the fact that one must first have an accurate idea of the values of the model parameters before the design can be obtained; indeed, a 'point estimate' of the parameter vector is used above in the information matrix in order to generate the local optimal designs. Some authors have thus taken a Bayesian approach wherein a prior distribution is substituted in place of this parameter vector choice and designs are obtained to maximize expected information instead; details can be found in Chaloner and Larntz (1989) and Atkinson *et al.* (2007). We use a similar approach here – the so-called maximin approach – so as to modify the methods given in the previous sections to obtain geometric and uniform designs and to address situations in which there is uncertainty in the values of the model parameters; references for the maximin design methodology are given in Atkinson *et al.* (2007). Our findings and conclusions are well appreciated in the context of the following illustration.

Example 6 In the context of the homoskedastic Gaussian LL2 model given in equation (2), we consider here the performance of the optimal geometric design for $K = 4$ using the initial parameter estimates $\theta_2 = 5$ and $\theta_3 = 2$. Thus, from Table 1, we obtain $m = 2.0598$ and by calculation $a = 2.4274$ and $b = 1.4352$. This model function is graphed in each of the panels of Figure 2 (solid curve) as are the optimal geometric design support points (filled circles) – obtained by intersecting the LL2 function with the cut-lines $\eta = 0.81,\ 0.67,\ 0.50,\ 0.33,\ 0.19$ (horizontal dotted lines).

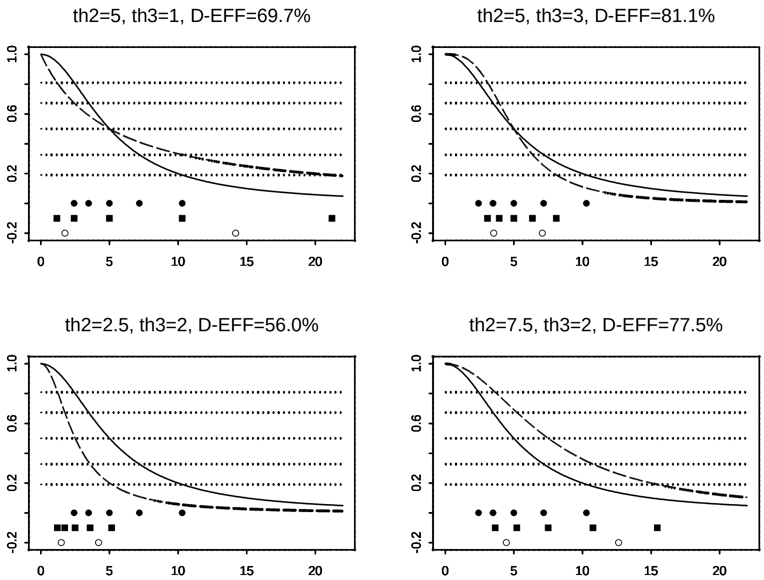

Figure 2 Graphs of LL2 model function for $\theta_2 = 5$ and $\theta_3 = 2$ (solid curve) and other parameter choices given at top of individual panels. Filled circles correspond to optimal geometric design points for $K = 4,\ \theta_2 = 5,\ \theta_3 = 2$ case. Filled squares correspond to optimal geometric design points and open circles to D-optimal design points for indicated parameter values in respective graphs. Dotted horizontal lines indicate how optimal geometric designs are obtained by intersection with the respective LL2 curves (both solid and dashed curves)

We next consider in turn subtracting and adding a 50% adjustment to each of the initial parameter values, so the additional LL2 functions plotted in this Figure (dashed curves) correspond to $\theta_2 = 5$ and $\theta_3 = 1$ (top left panel), $\theta_2 = 5$ and $\theta_3 = 3$ (top right), $\theta_2 = 2.5$ and $\theta_3 = 2$ (bottom left), and $\theta_2 = 7.5$ and $\theta_3 = 2$ (bottom right). Also plotted in each of these panels are the optimal geometric design points (solid squares) and the two-point D-optimal design points (open circles) for the respective parameter choices given at the top of each of the four panels. The reported D-efficiency values in each panel correspond to the comparison of the optimal geometric design for the choice $\theta_2 = 5$ and $\theta_3 = 2$ with the actual two-point D-optimal design for the parameter choices in the respective cases. It is indeed striking how the D-optimal design support points change for the various parameter choices. It is also striking that the D-efficiencies of the original optimal geometric design range between 45.45% and 91.03% over the grid of values $(2.5 \leq \theta_2 \leq 7.5) \times (1 \leq \theta_3 \leq 3)$.■

Since the D-efficiency of the original geometric design can be quite low (e.g. as low as 45% in the previous example), we now seek another practical manner of finding optimal geometric designs in situations where there is uncertainty about the model parameters. Specifically, based on the LL2 model function graphs given in the top panels of Figure 1, we take a discretized uniform prior over the grid of parameter values, $(2.5 \leq \theta_2 \leq 7.5) \times (1 \leq \theta_3 \leq 3)$. For computational purposes, in our analysis this grid comprised 441 points with θ_2 ranging from 2.5 to 7.5 by steps of 0.25 and θ_3 taken from 1 to 3 by steps of 0.10. Using the above Example 6 as a starting point, we then searched for efficient geometric designs so that the worst case D-efficiency over this grid was as high as possible – that is, we searched for a 'maxi-min' geometric design. Specifically, we sought to find geometric designs for various choices of K by choosing the a and b to maximize the minimum D-efficiency over this uniform grid of parameter values. For each choice of K and m from Table 1 and the maxi-min values of a and b, we then sought the corresponding values of θ_2 and θ_3 from equation (7). Our empirical results for numerous choices of K have led us to deduce the following refinement of our rule of thumb given in section 2 for optimal geometric designs for the Gaussian LL2 model when uncertainty exists about the initial parameter values of the manner examined here:

The 6/7 Rule: In the calculation of a and b in Equation (7),

- $\theta_2^* = (6/7)^* \, \theta_2$ should be used in place of θ_2, and
- $\theta_3^* = (6/7)^* \, \theta_3$ should be used in place of θ_3

Thus, for example for the set up in Example 6 with $K = 4$ and uniform initial parameter estimates over the above uniform grid, we now use $\theta_2{*} = 4.286$ and $\theta_3^* = 1.714$, and we obtain $m = 2.0598$, $a = 1.8446, b = 1.5243$. In this case, the 'θ-robust' geometric design support points are $x = 1.8446$, $2.8116, 4.2857, 6.5326$, and 9.9575. For purposes of comparison, the 'local' geometric design support points are $x = 2.4274,\ 3.4838,\ 5.00,\ 7.1760$ and 10.2989 when the initial parameter estimates are assumed known precisely (i.e. $\theta_2 = 5$ and $\theta_3 = 2$). In both cases, the (reciprocal) t values are $t = 0.2357,\ 0.4855,\ 1.00,\ 2.0597$ and 4.2427, with expected responses $\eta = 0.8093,\ 0.6732,\ 0.5000,\ 0.3268$ and 0.1907; the different design support points given here result from the different parameter choices in the calculations using the relation $x = \theta_2 t^{1/\theta_3}$. Most notably, whereas the minimum D-efficiency of the local geometric design over the uniform grid is 45.45%, this minimum value increases to 59.68% for the θ-robust geometric design. In addition, the D-efficiency at the centre point $(\theta_2 = 5,\ \theta_3 = 2)$ drops from 91.03% for the local design to just 87.99% for the θ-robust geometric design. We are thus led to prefer the θ-robust geometric design obtained using the "6/7 Rule" when parameter uncertainty exists of the nature described here.

Our findings also show that the above results carry over to efficient uniform designs for the LOG2 model and to situations involving the Binomial distribution instead of the constant-variance Gaussian distribution. The "6/7 Rule" also applies for the other values of K given in Tables 1 and 2; the support points for the Gaussian LL2 model in Example 5 $(K = 6)$, given in the fifth row of Table 4, show the same downward shift as in the above example with $K = 4$. Of course, it is important to point out that this rule has been developed using the $(2.5 \leq \theta_2 \leq 7.5) \times (1 \leq \theta_3 \leq 3)$ uniform grid; quite expectedly, as this grid is shrunken closer and closer to the central point $\theta_2 = 5$ and $\theta_3 = 2$, the "6/7" fraction approaches one. Further, instead of using the 'maxi-min' approach in which we have sought geometric designs which maximize the minimum D-efficiency over a given prior distribution of the parameter values, we could have easily chosen some other measure such as the average D-efficiency over the region. Clearly, the specific choice of the parameter-robust design criterion as well as the prior distribution of parameter values will need to be determined on an *ad hoc* basis and attempts to address each specific contingency is not possible in general.

Our point here is to demonstrate that with only minor modification, our above methodology for finding efficient geometric and uniform designs is easily extended to cover various patterns of uncertainty of the initial parameter values. Also, given the graphs in Figure 1, the grid of parameter values used here are indeed reasonable in many realistic situations, and so the "6/7 rule" recommended and implemented here is of important practical consequence.

6.2 Incorporating uncertainty regarding the appropriate scale

As pointed out in Section 2 and examples contained therein, researchers are sometimes unsure as to whether the Logistic model should be fitted on the original scale or the log-scale. This uncertainty is easily incorporated into the above geometric/uniform design methodology. Specifically, we consider here settings in which a researcher feels that either the Gaussian or Binary LL2 model function in Equations (2) or (10) is appropriate but is not completely certain that the log-scale is correct. Noting that the LL2 model function is equivalent to the scaled Logistic (SL3) model with γ approximately zero, our goal here is to seek efficient geometric designs for the SL3 model taking $\gamma \to 0$. This approach is similar to the nesting strategies examined in O'Brien (1994) and O'Brien (1996) but here we consider only geometric designs. Our findings here are indeed analogous to those given in Sections 4 and 5.

In the case of the Gaussian LL2 model but with some uncertainty as to the proper scale – that is, for the Gaussian SL3 $(\gamma \to 0)$ model so v in Equation (5) approaches t in Equation (2) – efficient $(K+1)$-point geometric designs of the form $x = a,\ a^*b,\ a^*b^2.,\ ..,\ a^*b^K$ are obtained by first choosing the value m from the following table.

Table 5 Optimal values of m and D-efficiencies (D-EFF) for various choices of K for the Gaussian SL3 model with $\gamma \to 0$. Values of m and K are then used to obtain values of a and b or A and B to be used to obtain experimental designs

K	2	3	4	5	6	7
m	7.2453	4.0495	3.1117	2.5589	2.2331	2.0172
D-EFF (%)	100.0	93.37	93.46	93.17	93.03	92.94
K	8	9	10	11	12	19
m	1.8645	1.7510	1.6635	1.5941	1.5377	1.3222
D-EFF (%)	92.88	92.84	92.81	92.78	92.77	92.71

As above, we then again use the value of m and Equation (7) to find the optimal values of a and b and thus the design support points.

When we choose $K = 2$, the local D-optimal design has three support points. Interestingly, these D-optimal support points are such that $t_2 = 1$ (so that $x_2 = \theta_2$), and the reciprocal values t_1 and $t_3 = 1/t_1$ solve the equation

$$(1 + t) + \tfrac{2}{3}\,(1 - t)\log(t) = 0. \tag{14}$$

This equation, which is the Gaussian SL3 $(\gamma \to 0)$ model analogue of equation (8) for the Gaussian LL2 and LOG2 models, has solutions $t_1 = 0.138020$ and $t_3 = 7.245338$. Thus, the local D-optimal design again has t values and expected response values $(\eta = 0.8787,\ \frac{1}{2},\ 0.1213)$ that do not depend on the initial parameter estimates, and again η_1 and η_3 are again symmetric around $\eta = \frac{1}{2}$.

In comparing equations (8) and (13), it is not surprising that for the Binary SL3 $(\gamma \to 0)$ model, in addition to $t_2 = 1$, the reciprocal values t_1 and $t_3 = 1/t_1$ solve the equation

$$(1 + t) + \tfrac{1}{3}\,(1 - t)\log(t) = 0 \tag{15}$$

and are thus $t_1 = 0.039022$ and $t_3 = 25.626771$. With the expected proportions here of $\pi = 0.9624,\ \frac{1}{2},\ 0.0376$, we again see the expected responses moving away from the centre $(\pi = \frac{1}{2})$ in the Binomial case when compared with the Gaussian case. In the case of the Binary SL3 $(\gamma \to 0)$ model, efficient $(K+1)$-point geometric designs are obtained by choosing the value m from the Table 6 and again using Equation (7) to calculate the values of a and b and whence to obtain the design support points.

Table 6 Optimal values of m and D-efficiencies (D-EFF) for various choices of K for the Binary SL3 model with $\gamma \to 0$. Values of m and K are then used to obtain values of a and b to be used to obtain experimental designs

K	2	3	4	5	6	7
m	25.627	9.9635	6.7177	4.7724	3.8145	3.2185
D-EFF (%)	100.0	93.09	94.22	93.80	93.74	93.67
K	8	9	10	11	12	19
m	2.8230	2.5426	2.3345	2.1744	2.0477	1.5924
D-EFF (%)	93.63	93.61	93.59	93.57	93.56	93.52

To illustrate these methods, consider again the setup in Example 5 where we desire an efficient 7-point geometric design $(K = 6)$ but now for the Gaussian SL3 $(\gamma \to 0)$ model; that is, we now envisage a situation in which the Gaussian LL2 model fits our data but are uncertain as to the assumed log-dose scale. In this case, from Table 5, we obtain $m = 2.2331$, $a = 1.4984$ and $b = 1.4943$. Here, the optimal values of t are $t = 0.0898,\ 0.2005,\ 0.4478,\ 1.00,\ 2.2331,\ 4.9866,$ and 11.1356, and the optimal expected responses are $\eta = 0.9176,\ 0.8330,\ 0.6907,\ \frac{1}{2},\ 0.3093,\ 0.1670,$ and 0.0824. Thus, again t_1 and t_7 are reciprocals and so on, and the corresponding expected responses sum to one. The geometric design points for the SL3 $(\gamma \to 0)$ model for the Gaussian and Binomial cases are given as designs 6 and 7 in Table 4; in comparing these designs with the respective LL2 model counterparts (designs 1 and 3 in the same table), we see how uncertainty of the scale increases the dispersion of the design support points.

Thus again with only minor modification, the methods given here provide researchers with the means to obtain efficient geometric designs for the Gaussian and Binary LL2 model when some uncertainty exists as to the assumed log-dose scale.

6.3 Second-order design criterion

D-optimal designs for Gaussian nonlinear models may ignore important second-order 'curvature' terms. As a result, Hamilton and Watts (1985) proposed a design criterion based on a second-order volume approximation related to the generalized variance. This design criterion, herein called Q-optimality, requires parameter estimates for the model parameters (θ) as well as for σ; details of the criterion are given in Hamilton and Watts (1985) and an extension is given in O'Brien (1992). Here, we extend the rules of thumb given above in Section 4 for obtaining efficient D-optimal geometric designs for the Gaussian LL2 model and uniform designs for the LOG2 model so as to incorporate the Q-optimality design criterion.

For the Q-optimality criterion, as σ gets nearer and nearer to zero, Q-optimal designs approach the corresponding D-optimal design. It follows that the values of m given in Table 1 correspond to the Q-optimal case with $\sigma = 0$. As noted in Section 4, for the D-criteria considered above, the values of m (and thus of t, u, and η) do not depend upon the initial parameter estimates (θ). This is no longer the case for the Q-optimality criterion with $\sigma \neq 0$. Thus, we direct our search here for the optimal values a and b for geometric designs and A and B for uniform designs. The following table provides these values for up to 7-point designs for the local LL2 and LOG2 models and parameter values considered above.

Table 7 Optimal values of a and b for the Gaussian LL2 model and of A and B for the Gaussian LOG2 model obtained using the Q-optimal design criterion

	LL2$(\theta_2 = 5,\ \theta_3 = 2)$ model			LOG2$(\theta_2 = 5,\ \theta_3 = 0.50)$ model		
K	σ = 0	σ = 0.10	σ = 0.25	σ = 0	σ = 0.10	σ = 0.25
1	a = 2.967 b = 2.840	a = 3.208 b = 2.643	a = 3.406 b = 2.485	A = 2.913 B = 4.175	A = 3.013 B = 3.975	A = 3.092 B = 3.817
2	a = 2.711 b = 1.845	a = 2.781 b = 1.770	a = 3.083 b = 1.676	A = 2.551 B = 2.449	A = 2.341 B = 2.343	A = 2.429 B = 2.230
3	a = 2.527 b = 1.576	a = 2.719 b = 1.553	a = 3.022 b = 1.492	A = 2.270 B = 1.820	A = 2.529 B = 1.784	A = 2.598 B = 1.731
4	a = 2.427 b = 1.435	a = 2.771 b = 1.404	a = 3.118 b = 1.363	A = 2.110 B = 1.445	A = 2.450 B = 1.371	A = 2.660 B = 1.283
5	a = 2.363 b = 1.350	a = 2.661 b = 1.324	a = 3.024 b = 1.292	A = 2.002 B = 1.199	A = 2.300 B = 1.134	A = 2.524 B = 1.057
6	a = 2.317 b = 1.292	a = 2.565 b = 1.273	a = 2.934 b = 1.245	A = 1.924 B = 1.025	A = 2.165 B = 0.973	A = 2.393 B = 0.905

For these models, $\sigma = 0.25$ corresponds to a rather high value since for the model considered here it corresponds to a coefficient of variation of 25% at the highest expected response. Thus we note that as σ increases, both geometric and uniform designs are shifted to the right and the range of the design support points is reduced. The corresponding Q-optimal design points for the $K = 6$ scenario considered in Example 5 are given in Table 4 (designs 8 and 9) to facilitate comparisons with the other designs considered above; indeed the 'centre' of the geometric design is shifted from 5.00 to 5.66 and the range drops from 8.47 to 8.00.

7. Discussion

Noteworthy algebraic results related to optimal design points for the Gaussian and Binary LL2, LOG2 and SL3 ($\gamma \to 0$) models are given in Equations (8), (13), (14) and (15), and these results are useful in helping practitioners find local D-optimal designs for these models. These results notwithstanding, the key results given in this paper provide researchers with the means to choose 'robust' experimental designs that are both highly efficient and easy to implement. As underscored in Govaerts (1996), optimal designs with only p support points are rarely or never used in practice as they cannot be used to test lack of fit of the assumed model. On the other hand, the geometric and uniform designs provided by our methodologies are both easy to implement and very useful to test for any potential model inadequacies. In light of the often appropriate adage that 'all models are wrong some models are useful' (Box, 1979), these characteristics are indeed notable and paramount.

Inherent in our above rules of thumb is the requirement that the logistic class is the appropriate one. Clearly, the log-logistic and logistic model functions are very popular in applied research (see references given in Sections 2 and 3 above as well as Seber and Wild, 1989, and Ratkowsky, 1983, 1990) perhaps due to the ease of interpreting the parameter values. Indeed even the Michaelis-Menten model examined in Dette *et al.* (2005) is simply a special case of the LL3 model considered here. As pointed out above, interpreting the model parameters in the Weibull and Richards model functions considered in Dette and Pepelyshev (2008) is not nearly as clear-cut.

Inherent in the use of geometric and uniform designs with 'extra' support points is the reasonable contention that these robust designs can be used to test for mis-specification – of the model function, of the chosen scale for the independent variable, or of the initial parameter estimates. Although we have directly considered the latter two concerns here, we have not addressed the issue of wrongly choosing the model function. This is a relatively simple task in the case of linear models; see Dette (1993), Pukelsheim and Rosenberger (1993), Zen and Tsai (2004), and Bischoff and Miller (2006). This is not the case for nonlinear models, and one reasonable approach is the nesting approach introduced and applied in Atkinson (1972) and O'Brien (1994, 1996). Atkinson (1972) shows that the nesting criterion is related to the power of the lack-of-fit test. Indeed, current research is ongoing related to geometric and uniform designs related to model nesting for nonlinear sigmoidal models; as this is outside the realm of the current research it is not discussed further here.

As noted in Section 3, geometric designs are used extensively in applications. Left to their own means, and based on the examples given in Section 3, practitioners choose values of b (reciprocal dilution values) as low as 1.45, although integer values of 2, 3, 5 and 10 are more common. Clearly one of the potential problems with choosing a value as large as $b = 5$ – and one we have unfortunately witnessed in our own consulting sessions – is that the subsequent values of the response variable are then seen to be near the maximum value for low values of x (e.g. for $x = 5$ and $x = 25$) and near the minimum value for large values of x (e.g. for $x = 125$ and $x = 625$). In these situations, only the upper and lower asymptotes in Equation (4) can be estimated, and the model cannot be fitted to the data since no information can be gleaned relating to either the LD50 or slope parameters. Thus, at a minimum, our methods given here provide researchers with reasonable benchmarks for their dilution factors obtained using either Table 1 or 2. At the other end of the spectrum, practitioners concerned with uncertainty of the initial parameter values, the appropriate scale, and ignoring curvature should follow the suggestions given above in Section 6.

Acknowledgements

T.E. O'Brien gratefully acknowledges the kind hospitality and support of the Department of Statistics, Faculty of Science, Chiang Mai University, which hosted him during his Fulbright Scholar visit in 2006–7, as well as the generous financial support of the United States Department of State, the J. William Fulbright Foreign Scholarship Program, and the Thailand – United States Educational Foundation. N. Homkham expresses thanks to her M.Sc. advisors S. Chooprateep, K. Nimitkiatklai, and T.E. O'Brien for their valuable guidance. The authors are also grateful for the comments of the reviewers, which have resulted in important improvements to the original manuscript.

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Manuscript received, 2008.04.10, revised, 2008.10.07, accepted, 2008.12.19.