Title: Optimal Designs for a Logistic Dose-Response Model with Restricted Dose Levels

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Abstract

Dose-response studies arise in many medical applications. Although design optimality has been well studied for binary response in logistic models, little attention has been paid to the construction of optimal designs with a restricted dose-range until in recent years. The goal of this paper is to derive D- and A-optimal designs for a restricted dose-range and assess the loss-in-efficiency compared to the unrestricted case, for a commonly used parametrization of the two-parameter logistic model. We find that efficiency decreases with the increase in severity of the restrictions while two-sided restrictions result in a larger loss than a one-sided restriction.

Keywords: Restricted Dose-range; A-optimality; D-optimality; Information matrix.

1. Introduction

Consider a binary response $y_x$ resulting from a non-stochastic dose level $x$. Assuming $y_x$ takes values 0 and 1, the probability that $y_x$ takes the value 1, for a given dose level $x$, is given by

$$P(y_x = 1|x) = 1/(1 + e^{-(\alpha + \beta x)}),$$

where $\alpha$ and $\beta$ are unknown parameters with $\beta > 0$.

The optimal design problem for the estimation of $\alpha$ and $\beta$, or some function thereof, consists of optimally selecting the dose levels $x_i$ and the sample sizes $n_i$ at each level (for a given, fixed overall sample size $n$) with respect to some optimality criterion. For estimating individual parameters, the problem reduces to optimally choosing the $x_i$’s and $n_i$’s by minimizing the asymptotic variance of the maximum likelihood estimator (MLE). For the joint estimation of the parameters (or functions thereof), this amounts to minimizing some suitably scaled function of the asymptotic variance-covariance matrix of the MLEs. The D- and A-optimality criteria are well known examples. Some of the relevant references on this specific optimal design problem include Abdelbasit and Plackett (1983), Minkin (1987), Khan and Yazdi (1988), Wu (1988), Ford et. al. (1992), Sitter and Wu (1993), Hedayat et.al. (1997) and Mathew and Sinha (2001). In particular, Mathew and Sinha (henceforth referred to as MS) provided a unified approach for the derivation of D- and A-optimal designs for the estimation of a variety of functions of $\alpha$ and $\beta$ under the two-parameter logistic regression model of the form given in (1.1).

It is known that the optimum dose levels actually depend on the unknown parameters $\alpha$ and $\beta$, as is typical in non-linear settings. Hence, in order to implement the design in practice, good initial estimates of $\alpha$ and $\beta$ must be available. Many authors assume that close approximations to these parameters are known, either from previous experimentation or from pilot studies. This is generally a fair assumption in the context of medical data where most often, feasibility studies are done as an initial start to any experimentation and pilot studies are conducted to collect initial information on outcome variables of interest.

2. The Need for Restricted Design Space

Design optimality has been well studied for the logistic model with a continuous covariate. However, theoretical optimal designs usually assume an unrestricted dose range (Chaloner and Larntz 1989; Zhu and Wong 2001). The resultant optimal designs may end up with one design support point as negative, which in the context of ‘dose’, becomes meaningless. While recognizing then that the dose range should at least be positive, one also needs to pay attention to the level of drug toxicity, i.e., a threshold above which the drug is toxic. It seems clear then that the issue of a restricted dose range is extremely pertinent to studies done with human subjects. It is to be noted that if $\log(dose)$ is the covariate, then the above-described natural constraint on the dose level does not pose an issue anymore on the left limit.
While statisticians advocate the use of optimal designs in clinical trials, little work has been done on the construction of such designs for dose-response studies with a restricted dose range. The few known works in this setup include Ford et al. (1992) who derived c- and D-locally optimal designs on restricted and unrestricted design spaces, Mats et al (1998) derived locally c- and D-optimal designs for estimating the maximum tolerated dose in a Phase I clinical trial on a restricted design space and Haines et al. (2003) extended the latter approach to a Bayesian framework. In 2006, Biedermann, Dette and Zhu (henceforth referred to as BDZ) provided a first thorough consideration of a restricted dose-range and derived $\phi_o$ optimal designs (which covers D- and A-optimality criteria) for the parametrization of the form $\beta (x - \alpha)$ instead of $(\alpha + \beta x)$. In general, except for D-optimal designs, $\phi_o$ optimality is not invariant under parametrization of the model. Hence, our results for A-optimality will differ from that of BDZ.

The goal of this paper is to follow the work of BDZ and elaborate on some specific optimality criteria and assess the implications of restricted dose-ranges in a two-parameter, binary logistic regression model of the form (1.1). Resulting design support points and corresponding weights will be compared to those obtained under the unrestricted design space, as seen in MS. In section 3, we will follow BDZ to obtain the design support points and corresponding weights to achieve D-optimality for a lower-sided restricted design space. Similarly, in section 4, we will find the same for A-optimal designs and in section 5, we will have some concluding remarks.

3. The Two-Parameter Logistic Model

For a binary response $y_r$ resulting from a non-stochastic dose level $x$, the probability that $y_r$ takes the value 1, for a given dose level $x$, is given by eqn. (1.1). Following MS (eqn: 2.4), the information matrix for the joint estimation of $\alpha$ and $\beta$ is

$$I(\alpha, \beta) = \begin{pmatrix}
\sum_{i=1}^{m} \xi_i \left( \frac{e^{-a_i}}{(1+e^{-a_i})^2} \right) & \sum_{i=1}^{m} x_i \xi_i \left( \frac{e^{-a_i}}{(1+e^{-a_i})^2} \right) \\
\sum_{i=1}^{m} x_i \xi_i \left( \frac{e^{-a_i}}{(1+e^{-a_i})^2} \right) & \sum_{i=1}^{m} x_i^2 \xi_i \left( \frac{e^{-a_i}}{(1+e^{-a_i})^2} \right)
\end{pmatrix},$$

(2)

where $a_i = \alpha + \beta x_i$, $\xi_i = n_i / n$ and $\sum_{i=1}^{m} \xi_i = 1$.

**Remark 1:** It should be noted that at zero dose, the corresponding $a_i$ is equal to $\alpha$.

We need to maximize $|I(\alpha, \beta)|$ with respect to $m$, $\xi_i$’s and $x_i$’s in order to obtain the D-optimal design. Note that the determinant of $I(\alpha, \beta)$ [vide MS eqn (2.5)] is given by

$$|I(\alpha, \beta)| = \frac{1}{\beta^2} \left[ \sum_{i=1}^{m} \xi_i \left( \frac{e^{-a_i}}{(1+e^{-a_i})^2} \right)^2 - \sum_{i=1}^{m} a_i^2 \xi_i \left( \frac{e^{-a_i}}{(1+e^{-a_i})^2} \right) \right]^2,$$

(3)

In order to obtain the A-optimal design, we shall minimize $\text{Var}(\hat{\alpha}) + \text{Var}(\hat{\beta})$, where $\hat{\alpha}$ and $\hat{\beta}$ are the maximum likelihood estimators of $\alpha$ and $\beta$ and the variance being computed is the asymptotic variance. From the expression for the information matrix given in (3.1), we get [vide MS, eqn 2.8]

$$\text{Var}(\hat{\alpha}) + \text{Var}(\hat{\beta}) = \frac{\sum_{i=1}^{m} \xi_i \left( \frac{e^{-a_i}}{(1+e^{-a_i})^2} \right)^2 \sum_{i=1}^{m} (1 + x_i^2) / |I(\alpha, \beta)|}{\beta^2}.$$

(4)

4. D-Optimal Designs: Restricted versus Unrestricted Design Space

The solution to the D-optimal design problem is readily available in the literature (Minkin, 1987; Khan and Yazdi, 1988; Sitter and Wu, 1993, Mathew and Sinha, 2001). It is well-known that under a unrestricted dose-range, the D-optimal design [in the entire class of competing designs] is a two-point, point and mass symmetric design, consisting of the design support points $x_{1D}$ and $x_{2D}$ with weights 1/2 each, satisfying $\alpha + \beta x_{1D} = -c_D$ and $\alpha + \beta x_{2D} = c_D$, where $c_D = 1.5434$. 
For the solution to the D-optimal design problem in the case where the dose-range is restricted, we refer to the work of BDZ. We note that restriction on the dose-range can be of the form: $[x_{\text{min}}, \infty)$ or $(\infty, B]$; $[x_{\text{min}}, x_{\text{max}}]$ or $[A, B]$. BDZ showed that for restricted dose-range, the D-optimal design is still a two-point design, mass symmetric but not necessarily point symmetric. For ease of reference, suppose that the D-optimal solutions for both-sided restricted dose-range are given by $[z_{L}^{*}, z_{U}^{*}]$ and those for the unrestricted are given by $[z_{L}, z_{U}]$. Then, it should be noted that if both $z_{L}$ and $z_{U}$ fall within the restricted domain $[A,B]$, then the restricted and unrestricted solutions are the same i.e., $z_{L}^{*} = z_{L}$ and $z_{U}^{*} = z_{U}$. In particular, for a dose-range of the form: $(A, \infty)$, if $z_{L} > A$ then the D-optimal solution will be $[z_{L}^{*}, z_{U}]$, where $z_{U}^{*}$ is determined in the usual manner by maximizing the determinant of the information matrix. On the other hand, if $z_{L} < A$, then according to BDZ, the D-optimal solution will be $(A, z_{U}^{*})$. Similarly, for a dose-range of the form $(\infty, B]$, D-optimal solutions will be $(z_{L}^{*}, z_{U})$, if $z_{U} < B$, or $(z_{L}^{*}, B)$, if $z_{U} > B$. Likewise, for dose-range of the form $[A, B]$, the D-optimal solutions will be one of the following: $(z_{L}, z_{U})$, $(z_{L}^{*}, B)$, $(A, z_{U}^{*})$ or $(A, B)$.

Thus, referring to eqn (3.2) and a dose-range of the form $[A, \infty)$, m (optimum number of dose levels) equals 2 and we have,

$$
\beta^{2} \left| I(\alpha, \beta) \right| = \xi_{1} (1 - \xi_{1}) \frac{e^{(a_{1} + a_{2})}}{(1 + e^{-a_{1}})^{2}(1 + e^{-a_{2}})^{2}} (a_{1} + a_{2})^{2},
$$

where $\xi_{1} = n_{1}/n$, $a_{1} = \alpha + \beta x_{1}$ and $a_{2} = \alpha + \beta x_{2}$.

Remark 2: In (4.1), note that $\xi_{1}$ and $(1 - \xi_{1})$ are separable and hence always equal to 1/2 each. Thus, the weights are not susceptible to restrictions on the dose-range for D-optimal criterion. Table 1 shows the D-optimal solutions for a left-restricted dose-range. Losses in efficiency, when restriction on the dose-range is imposed, are also calculated and shown in the table. Note that the solutions for the unrestricted dose-range is always symmetric with $z_{L} = -1.5434$ and $z_{U} = 1.5434$.

Remark 3: As expected, as the left limit moves away towards zero from the unrestricted solution ($-1.54$), the solution for the right support point moves away from the upper unrestricted solution. Also, the loss in efficiency increases as the restriction becomes more severe.

5. A-Optimal Designs: Restricted versus Unrestricted Design Space

In order to obtain an A-optimal design for the restricted dose-range, we need to minimize eqn (3.3) with respect to m, $\xi_{i}$’s and $x_{i}$’s. MS derived symmetric, two-point A-optimal designs. Confining to the class of symmetric, two-point designs, they considered both the cases of mass symmetry ($\xi_{i} = 1/2$) and otherwise ($\xi_{opt}$), vide MS, Table 1. In this context, they left an open question as to the necessity of point-symmetry in A-optimal designs. Yang (2008) asserted this conjecture. In the table below, we restrict ourselves to the class of two-point designs and derive the A-optimal solutions for restricted dose-range.

Remark 4: We conjecture that the A-optimal solution with the present parametrization of the logistic model will always be a two-point design in the restricted dose-range. However, we leave that for future exploration. Table 2 shows the A-optimal solutions for a restricted dose-range of the form $(0, \infty)$ as well as the corresponding loss in efficiencies for some pairs of $(\alpha, \beta)$. Notations are explained below the table.

Remark 5: We note that when the unrestricted lower dose solution is positive, the restricted and unrestricted solutions are identical (as marked by *). When $z_{L} < 0$, $z_{L}^{*} = \alpha$, i.e., zero dose. Furthermore, for fixed $\beta$, we observe that the loss in efficiency increases for increasing $\alpha$. For fixed $\alpha$, the loss in efficiency decreases with decreasing $\beta$. Regarding the weight, we observe that for fixed $\beta$, $\xi_{1}$ decreases as $\alpha$ increases. However, when $\alpha$ is fixed, $\xi_{1}$ increases as $\beta$ decreases.

Table 3 shows the A-optimal solutions for a both-sided restricted dose-range of the form $[0, B^{*}]$ for some pairs of $(\alpha, \beta)$ where $B^{*}$ is the upper solution of the corresponding unrestricted dose-range. Similar characteristics as in table 2 are observed here.

Figure 1 shows the optimized A-optimal criterion with restrictions on both sides for $\alpha = -1.5$ and $\beta = 5$. The left restriction is fixed at $A = \alpha = -1.5$ and the right restriction is varied from 1 to 2.3. The horizontal dotted line corresponds to the optimized A-optimal criterion for the unrestricted dose-range.

Figure 2 shows the percent loss in efficiency in the A-optimal design with restrictions on both sides for $\alpha = -1.5$ and $\beta = 5$. The left restriction is fixed at $A = \alpha = -1.5$ and the right restriction is varied from 1 to 2.3.
Figure 3 shows the weight of the right support point in the A-optimal design with restrictions on both sides for $\alpha = -1.5$ and $\beta = 5$. The left restriction is fixed at $A = \alpha = -1.5$ and the right restriction is varied from 1 to 2.3. Figure 4 shows the optimized right support points for a D-optimal design with left restriction as plotted on x-axis. Figure 5 shows the loss in efficiency for a D-optimal design with left restriction as plotted on x-axis.

6. Conclusions
When conducting dose-response studies with human subjects, it is important to study design optimality in the light of restricted dose-range. An optimal dose level below zero dose is meaningless. However many works in the area provide estimated optimal solutions where the lower dose level is sometimes below zero. The work of BDZ illustrates, under general optimality criteria, that when the dose range is restricted on either or both ends, the optimal solutions are on the boundary. Furthermore, optimum allocations are not necessarily equal across doses. We derived the optimal dose levels and the corresponding weights for a restricted dose range specifically for the D- and A-optimality criteria for a two-parameter logistic dose-response model. The parametrization is slightly different from BDZ and hence not naturally extendable from their work. We also determined the loss in efficiency due to a dose-restricted range. As expected, we found that efficiency decreases with the increase in severity of the restrictions on the dose-range. Two-sided restrictions result in the larger loss in efficiency than a corresponding one-sided restriction.

References


Figure 1: Optimized A-optimal Criterion with Restrictions on Both Sides of Dose-Range for $(\alpha, \beta) = (-1.5, 5)$

Figure 2: Percent Loss in Efficiency in the A-optimal Design with Restrictions on Both Sides of Dose-Range for $(\alpha, \beta) = (-1.5, 5)$
Figure 3: Weight of the Right Support Point in the A-Optimal Design with Restrictions on Both Sides of Dose-Range for $(\alpha, \beta) = (-1.5, 5)$

Figure 4: Optimized Right Support Points for a D-optimal Design with Left Restriction on Dose-Range

Figure 5: Loss in Efficiency for a D-optimal Design with Left Restriction