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ORIGINAL ARTICLE

Locally D-Optimal Designs for Binary Responses and Multiple Continuous Design Variables

Zhongshen Wang[1] · John Stufken[2]

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Abstract
We identify locally D-optimal designs for binary data when a generalized linear model with multiple continuous covariates whose values can be selected at the design stage. Yang et al. (Stat Sin 21:1415–1430, 2011) provided an explicit form for D-optimal designs when there are no interaction effects between the design variables. After providing an alternative proof of that result, we generalize the result by identifying D-optimal designs for models with interactions between the design variables that satisfy the strong effect heredity principle. We also employ orthogonal arrays to obtain more practical D-optimal designs with a smaller support size.

Keywords Locally optimal design · D-optimality · Multiple covariates · Equivalence theorem · Orthogonal arrays

JEL Classification C02 · C18 · C90

Prologue

With so many pathbreaking contributions to statistical science, Professor C.R. Rao's designation as "a living legend" is fully deserved. Any attempt to list his influential contributions and the new research areas that these have spurred would be futile. We are humbled to contribute to the celebration of Professor Rao's centennial, and are delighted that we can do so through an article that makes use of one of his ageless seminal contributions, namely orthogonal arrays.

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✉ John Stufken
jstufken@uncg.edu

Zhongshen Wang
zhongshen.wang@apellis.com

1 Apellis Pharmaceuticals, Inc., Waltham, MA 02451, USA

2 University of North Carolina at Greensboro, Greensboro, NC 27412, USA

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Introduction

Generalized linear models (GLMs) with multiple covariates have applications in many fields. While analysis of such data has received a considerable amount of attention (Agresti 2013), the optimal design of experiments literature for such problems when the covariates are design variables is rather sparse (cf. Khuri et al. 2006). Most efforts to obtain optimal designs for these types of problem are computational (cf. Lukemire et al. 2019) and are derived on a case-by-case basis for specific situations. There are some exceptions to this. For example, optimal designs for binary response experiments with two design variables are studied in Sitter and Torsney (1995b) and with more than two design variables in Sitter and Torsney (1995a) and Kabera and Haines (2012). D-optimal designs for Poisson regression models have been investigated in Russell et al. (2009). Unless the design space is restricted, information matrices for the parameters for models with two or more design variables can be made arbitrarily large (Sitter and Torsney 1995a). To avoid this, each variable could, for example, be restricted to a bounded interval. Assumptions like this are natural in many applications; for example, in a clinical study, a very high dose level may cause serious side effects, and a very low dose level may not have any effect. Therefore, we can restrict the range of dose level to a certain acceptable interval. For the main effects model, Yang et al. (2011) made such an assumption for $p-1$ of the p design variables. With that assumption, and for GLMs with the logistic or probit link function and multiple design variables, they obtained explicit formulas for a large class of optimal designs, including D-, A-, and E-optimal designs.

Using the same setup as in Yang et al. (2011), we consider the following model for subject i:

$$\begin{aligned} Prob(Y_i = 1) = P(&\beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip} \\ &+ \sum_{t=2}^{p-1} \sum_{(l_1,l_2,\cdots,l_t)\in H_t} \beta_{l_1 l_2 \cdots l_t} x_{il_1} x_{il_2} \cdots x_{il_t}) \end{aligned} \tag{1}$$

where Y_i and $(x_{i1}, x_{i2}, \dots, x_{ip})$ are the response and the p design variables, while $P(\cdot)$ is a cumulative distribution function. The first $p-1$ design variables are assumed to be bounded, with x_{ij} in the interval $[L_j, U_j]$, $1 \le j \le p-1$. The pth design variable is unrestricted. Therefore, the design space is

$$\chi = [L_1, U_1] \times \cdots \times [L_{p-1}, U_{p-1}] \times (-\infty, \infty). \tag{2}$$

Additionally, we assume that interaction terms, if any, do not include the pth design variable. The set H_t includes the subsets of size t from $\{1, \dots, p-1\}$ for which the corresponding t-way interaction is included in the model. For the main effects model, the sets H_t are empty, and the summation term in (1) would vanish.

The restrictions that one design variable is unbounded and that this variable is not involved in any interaction are purely technical.

In "Optimal designs for the main effects model" , we will provide an alternative proof of the theorem in Yang et al. (2011) which describes the structure of locally D-optimal designs for the main effects model. Using the mathematical elegance of this alternative proof, in "Optimal designs for interaction models", we obtain optimal designs for certain interaction models. Additional results for obtaining smaller D-optimal designs using orthogonal arrays are presented in "Smaller optimal designs using orthogonal arrays", followed by a brief discussion in "Summary and discussion".

Optimal Designs for the Main Effects Model

It will be convenient to make a slight change in notation. In "Introduction", for subject i, we can write the design point as $\boldsymbol{x_i} = (x_{i1}, \dots, x_{ip})$ and the row in the model matrix as $\tilde{\boldsymbol{x}}_{\boldsymbol{i}} = (1, x_{i1}, \dots, x_{i,p-1}, \dots, x_{il_1} \cdots x_{il_t}, \dots, x_{ip})^T$, where we only include interactions that are in the model. So, the subscript i stands for the ith subject. While this notation is convenient for presenting the model, in what follows, we will use i to represent the i-th distinct support point in a design. We make this change to facilitate our discussion about designs. We use n_i to denote the number of subjects assigned to the ith design point. A collection of $\boldsymbol{x_i}$'s and the corresponding n_i's, where $\sum_i n_i = n$, is called an exact design with n observations. Finding optimal exact designs (by finding the best choices for the $\boldsymbol{x_i}$'s and n_i's for a given n) is typically a difficult problem due to the discrete nature of the n_i's. As is common in the optimal design literature, we instead work with approximate designs. An exact design is converted to an approximate design by replacing each n_i by the weight $w_i = n_i/n$. In searching for optimal designs we allow the w_i's to take any non-negative values that sum to 1. Then, an approximate design can be written as $\xi = \{(\boldsymbol{x_i}, w_i), i = 1, \dots, k\}$, $w_i > 0$, $\sum_i w_i = 1$, where k is the number of support points of ξ. An optimal (approximate) design chooses values of k, the w_i's and the $\boldsymbol{x_i}$'s that optimize a specified objective function or optimality criterion.

For model (1), the parameter vector is $\boldsymbol{\beta} = (\beta_0, \beta_1, \dots, \beta_{p-1}, \dots, \beta_{l_1 \cdots l_t}, \dots, \beta_p)^T$. Define $c_i = \tilde{\boldsymbol{x}}_{\boldsymbol{i}}{}^T \boldsymbol{\beta}$ and $\tilde{\boldsymbol{c}}_{\boldsymbol{i}} = (1, x_{i1}, \dots, x_{i,p-1}, \dots, x_{il_1} \cdots x_{il_t}, \dots, c_i)^T$. Then, with the assumption that $\beta_p \neq 0$, there is a one-to-one relationship between $\tilde{\boldsymbol{x}}_{\boldsymbol{i}}$ and $\tilde{\boldsymbol{c}}_{\boldsymbol{i}}$. The approximate design $\xi = \{(\boldsymbol{x_i}, w_i), i = 1, \dots, k\}$ can also be written as $\xi = \{(\boldsymbol{c}_i, w_i), i = 1, \dots, k\}$, where $\boldsymbol{c}_i = (x_{i1}, \dots, x_{i,p-1}, c_i)$.

In this paper, we focus on D-optimality. A design ξ is called locally D-optimal for $\boldsymbol{\beta}$ if it maximizes the determinant of the information matrix,

$$I_\xi = \sum_{i=1}^{k} w_i \Psi(\tilde{\boldsymbol{x}}_{\boldsymbol{i}}{}^T \boldsymbol{\beta}) \tilde{\boldsymbol{x}}_{\boldsymbol{i}} \tilde{\boldsymbol{x}}_{\boldsymbol{i}}{}^T, \tag{3}$$

among all designs for a given $\boldsymbol{\beta}$. In the remainder of this section, we assume that model (1) only contains main effects, so that $\tilde{\boldsymbol{x}}_{\boldsymbol{i}} = (1, \boldsymbol{x}_i^T)^T$. Theorem 2 of Yang et al. (2011) provides in that case an explicit expression for locally D-optimal designs for $\boldsymbol{\beta}$. We restate their result for D-optimality in the following theorem and provide an alternative proof.

Theorem 1 (See Theorem 2 of Yang et al. 2011) *For the logistic and probit link functions, if model* (1) *only contains main effects, the design space is given by* χ *in* (2), *and* $\beta_p \neq 0$, *then a D-optimal design for* $\boldsymbol{\beta}$ *is given by*

$$\xi^* = \left\{ \left(\boldsymbol{c}_{l1}^*, \frac{1}{2^p} \right) \text{ and } \left(\boldsymbol{c}_{l2}^*, \frac{1}{2^p} \right), l = 1, \dots, 2^{p-1} \right\},$$

where $\boldsymbol{c}_{l1}^* = (h_{l1}, \dots, h_{l,p-1}, c^*)^T$ *and* $\boldsymbol{c}_{l2}^* = (h_{l1}, \dots, h_{l,p-1}, -c^*)^T$. *Here* h_{lj} *is either* L_j *or* U_j, $(h_{l1}, \dots, h_{l,p-1}), l = 1, \dots, 2^{p-1}$ *cover all possible combinations, and* c^* *maximizes* $c^2(\Psi(c))^{p+1}$ *where* Ψ *is defined as*

$$\Psi(x) = \begin{cases} \frac{e^x}{(1+e^x)^2}, & \text{for the logistic link} \\ \frac{[\Phi'(x)]^2}{\Phi(x)(1-\Phi(x))}, & \text{for the probit link} \end{cases}. \tag{4}$$

Proof Transforming to a canonical form of the original design problem (see Ford et al. 1992, Atkinson and Haines (1996) and Torsney and Gunduz (2001)), for each of the first $p-1$ design variables we define

$$v_i = \frac{x_i - (U_i + L_i)/2}{(U_i - L_i)/2}, \tag{5}$$

so that $v_i \in [-1, 1], i = 1, \dots, p-1$. For convenience, write $a_i = (U_i + L_i)/2$ and $b_i = (U_i - L_i)/2$, so that $v_i = \frac{x_i - a_i}{b_i}$. We also define $v_p = \tilde{\boldsymbol{x}}^T \boldsymbol{\beta} = c$ and write $\boldsymbol{v} = (v_1, v_2, \dots, v_p)^T$.

For an arbitrary design point $\boldsymbol{x} \in \chi$ and the corresponding model vector $\tilde{\boldsymbol{x}} = (1, \boldsymbol{x}^T)^T$, we have

$$B\tilde{\boldsymbol{x}} = \tilde{\boldsymbol{v}}, \tag{6}$$

where $\tilde{\boldsymbol{v}} = (1, \boldsymbol{v}^T)^T$ and

$$B = \begin{pmatrix} 1 & 0 & \cdots & \cdots & \cdots & 0 \\ -a_1/b_1 & 1/b_1 & 0 & \cdots & \cdots & 0 \\ -a_2/b_2 & 0 & 1/b_2 & 0 & \cdots & 0 \\ & & \vdots & & & \\ -a_{p-1}/b_{p-1} & 0 & \cdots & 0 & 1/b_{p-1} & 0 \\ \beta_0 & \beta_1 & \beta_2 & \cdots & \beta_{p-1} & \beta_p \end{pmatrix}$$

is a $(p+1) \times (p+1)$ nonsingular matrix.

The mapping from $\boldsymbol{x}$ to $\boldsymbol{v}$ induces a one-to-one mapping from a design ξ in the original variables to a design

$$\xi_v = \left\{ \begin{matrix} \boldsymbol{v_1} & \boldsymbol{v_2} & \cdots & \boldsymbol{v_k} \\ w_1 & w_2 & \cdots & w_k \end{matrix} \right\}.$$

The induced design space $\chi_v = \{\boldsymbol{v} : B\tilde{\boldsymbol{x}} = \tilde{\boldsymbol{v}}, \boldsymbol{x} \in \chi\} = [-1, 1]^{p-1} \times [-\infty, \infty]$. With $M_{\xi_v} = \sum_{i=1}^k w_i \Psi(c_i) \tilde{\boldsymbol{v}}_i \tilde{\boldsymbol{v}}_i^T$, it follows from (3) that the information matrix for $\boldsymbol{\beta}$ under design ξ is

$$\begin{aligned}
I_\xi &= \sum_{i=1}^{k} w_i \Psi(c_i) B^{-1} \tilde{\boldsymbol{v}}_i \tilde{\boldsymbol{v}}_i^T (B^{-1})^T \\
&= B^{-1} \Big[\sum_{i=1}^{k} w_i \Psi(c_i) \tilde{\boldsymbol{v}}_i \tilde{\boldsymbol{v}}_i^T \Big] (B^{-1})^T = B^{-1} M_{\xi_v} (B^{-1})^T.
\end{aligned}$$

As a result, $det(I_\xi) = det(B^{-1})^2 \cdot det(M_{\xi_v})$, meaning that maximizing $det(I_\xi)$ on χ is equivalent to maximizing $det(M_{\xi_v})$ on χ_v. Once we obtain an optimal design ξ_v^*, we may transform it back to ξ^* by mapping $\boldsymbol{v}$ back to $\boldsymbol{x}$. So from now on, we will focus only on designs ξ_v on the induced design space χ_v.

The putative optimal design ξ^* in Theorem 1 corresponds to $\xi_v^* = \{(\tilde{\boldsymbol{c}}_{l1}^*, \frac{1}{2^p}) \,\&\, (\tilde{\boldsymbol{c}}_{l2}^*, \frac{1}{2^p}), l = 1, \dots, 2^{p-1}\}$, where $\tilde{\boldsymbol{c}}_{l1}^* = (\tilde{h}_{l1}, \dots, \tilde{h}_{l,p-1}, c^*)^T$ and $\tilde{\boldsymbol{c}}_{l2}^* = (\tilde{h}_{l1}, \dots, \tilde{h}_{l,p-1}, -c^*)^T$. Here $\tilde{h}_{lj}$ is either -1 or 1 and $(\tilde{h}_{l1}, \dots, \tilde{h}_{l,p-1}), l = 1, \dots, 2^{p-1}$ cover all possible combinations.

Therfore, to show the D-optimality of ξ_v^* on χ_v, we apply the equivalence theorem (see Kiefer and Wolfowitz (1960) and Kiefer (1974)) and all we have to show is that

$$\Psi(c) \tilde{\boldsymbol{v}}^T I_{\xi_v^*}^{-1} \tilde{\boldsymbol{v}} \leq p + 1, \tag{7}$$

where the equality is attained at the support points of ξ_v^*.

Following a similar procedure as in the proof of Theorem 1 and Lemma 3 in Wang and Stufken (2020), we have

$$\begin{aligned}
\Psi(c) \tilde{\boldsymbol{v}}^T I_{\xi_v^*}^{-1} \tilde{\boldsymbol{v}} &= \frac{\Psi(c)}{\Psi(c^*)} \left\{ 1 + v_1^2 + \cdots + v_{p-1}^2 + \frac{c^2}{(c^*)^2} \right\} \\
&\leq \frac{\Psi(c)}{\Psi(c^*)} p + \frac{c^2 \Psi(c)}{(c^*)^2 \Psi(c^*)} \leq p + 1 \quad , c \in (-\infty, \infty).
\end{aligned} \tag{8}$$

Since equality holds for each design point in ξ_v^*, it follows that ξ_v^* is D-optimal on the induced space χ_v. As a result, the proposed design ξ^* is also D-optimal on the original design space χ which concludes the proof. □

The reason that we assumed x_p to be unbounded is that we do not a priori know the values of x_{p1}^* and x_{p2}^* that correspond to $-c^*$ and c^*. This depends on the value of $\boldsymbol{\beta}$, so that the smallest interval that contains x_{p1}^* and x_{p2}^* is different for locally optimal designs for different values of $\boldsymbol{\beta}$. If the design space for x_p is bounded, then the design in Theorem 1 is D-optimal provided that x_{p1}^* and x_{p2}^* are in the bounded interval for x_p. If this is not the case, then the structure of the optimal design will be different.

Optimal Designs for Interaction Models

The alternative proof of Theorem 1 in "Optimal designs for the main effects model" assists in extending the result to models with interactions. We restrict attention to models that satisfy the strong effect heridity principle. By this we mean that when a t-th order effect is included in the model, then all t'-th order effects ($t' < t$) must also be in the model. It turns out that D-optimal designs for model (1) have the same structure as in Theorem 1 under the assumption of strong effect heredity, but with a changed value of c^*. We state the main result in the next theorem.

Theorem 2 *For the logistic and probit link functions, if model (1) satisfies the strong effect heredity principle, the design space is given by χ in (2), and $\beta_p \neq 0$, then a D-optimal design for $\boldsymbol{\beta}$ is given by*

$$\xi^* = \left\{ \left(\boldsymbol{c}^*_{l1}, \frac{1}{2^p} \right) and \left(\boldsymbol{c}^*_{l2}, \frac{1}{2^p} \right), l = 1, \ldots, 2^{p-1} \right\},$$

where $\boldsymbol{c}^*_{l1} = (h_{l1}, \ldots, h_{l,p-1}, c^*)^T$ and $\boldsymbol{c}^*_{l2} = (h_{l1}, \ldots, h_{l,p-1}, -c^*)^T$. Here h_{lj} is either L_j or U_j, $(h_{l1}, \ldots, h_{l,p-1}), l = 1, \ldots, 2^{p-1}$ cover all possible combinations, and c^* maximizes $c^2(\Psi(c))^r$ where Ψ is defined in (4) and r is the length of $\boldsymbol{\beta}$.

Proof The proof mimics that of Theorem 1, except that the elements of the canonical transformation in (6) are of a higher dimension. For instance, if x_1x_2 is the only interaction effect in the model, then $\tilde{\boldsymbol{x}}$ becomes $(1, x_1, x_2, x_1x_2, x_3, \ldots, x_p)$, $\tilde{\boldsymbol{v}} = (1, v_1, v_2, v_1v_2, v_3, \ldots, v_p)$ and matrix B will have an additional row and column as follows

$$B = \begin{pmatrix} 1 & 0 & \cdots & \cdots & \cdots & \cdots & 0 \\ -a_1/b_1 & 1/b_1 & 0 & \cdots & \cdots & \cdots & 0 \\ -a_2/b_2 & 0 & 1/b_2 & 0 & \cdots & \cdots & 0 \\ a_1a_2/b_1b_2 & -a_2/b_1b_2 & -a_1/b_1b_2 & 1/b_1b_2 & 0 & \cdots & 0 \\ & & \vdots & & & & \\ -a_{p-1}/b_{p-1} & 0 & \cdots & \cdots & 0 & 1/b_{p-1} & 0 \\ \beta_0 & \beta_1 & \beta_2 & \beta_{12} & \cdots & \beta_{p-1} & \beta_p \end{pmatrix}.$$

In general, Eq. (8) becomes

$$\begin{aligned} \Psi(c)\tilde{\boldsymbol{v}}^T I^{-1}_{\xi^*_v} \tilde{\boldsymbol{v}} &= \frac{\Psi(c)}{\Psi(c^*)} \left\{ 1 + v_1^2 + \cdots + v_{p-1}^2 + \sum_{t=2}^{L} \sum_{(l_1,\cdots,l_t)\in H_t} \left(\prod_{m=1}^{t} v_{l_m}^2 \right) + \frac{c^2}{(c^*)^2} \right\} \\ &\leq \frac{\Psi(c)}{\Psi(c^*)}(r-1) + \frac{c^2\Psi(c)}{(c^*)^2\Psi(c^*)} \quad , c \in (-\infty, \infty) \end{aligned}$$

and the result follows from the equivalence theorem by using Lemma 3 in Wang and Stufken (2020). □

Note that, without loss of generality, we implicitly assume in Theorem 1 that all main effects appear in the model. If a main effect is not in the model, then, due to the strong effect heredity principle, the corresponding design variable will not appear at all in the model and can be ignored. Hence, if the only interactions in the model are interactions of two variables, then the strong effect heredity assumption is automatically satisfied. The need for the strong effect heredity assumption can be understood by considering a model with an interaction of three variables, say $x_1x_2x_3$. With the mapping in (5), when expressed in v_i's, this term becomes a linear combination of v_1, v_2, v_3, v_1v_2, v_1v_3, v_2v_3 and $v_1v_2v_3$. In other words, the model in the v_i's will need to satisfy the strong effect heredity principle. But in order for the two models to be the same, this must then also hold for the model in the x_i's.

We now illustrate Theorem 2 through the following example.

Example 1 Consider model (1) with the logistic link and $\boldsymbol{x_i}^T\boldsymbol{\beta} = c_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \beta_{12}x_{i1}x_{i2} + \beta_3 x_{i3}$. Assume that the first two design variables are restricted to [0, 2] and $[-1, 1]$, respectively, and that there is no restriction on the third design variable. Then, according to Theorem 2, a locally D-optimal design for $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2, \beta_{12}, \beta_3)^T = (1, -1, 0.5, 1, 1)^T$ is shown in Table 1. The value c^* maximizes $c^2(\Psi(c))^{4+1}$, which is approximately 0.9254.

Smaller Optimal Designs Using Orthogonal Arrays

Theorem 2 provides a nice and simple structure for locally D-optimal designs for models that satisfy the strong effect heredity principle. However, the number of support points for these designs, which is 2^p, will rapidly increase with p. For example, when p increases from 4 to 8, the support size increases from $2^4 = 16$ to $2^8 = 256$. The number of parameters to be estimated would typically be much smaller, so that designs with such large support sizes are not really necessary. Following Sitter and Torsney (1995a) and Wang and Stufken (2021), we now obtain smaller designs using orthogonal arrays (Rao 1946, 1947). An $N \times k$ array is called an orthogonal array with s levels and strength t if, for every $N \times t$ subarray, all possible combinations of t symbols occur equally often as a row (Hedayat et al. (1999)). We denote such an array as $OA(N, s^k, t)$, where "s^k" indicates that there are k factors with s levels each. We only need arrays with $s = 2$ and, without loss of generality, denote the levels by 1 and 2. Furthermore, Hedayat (1989) (see also Hedayat (1990)) introduced the concept of OAs of strength t+. An $OA(N, s^k, t+)$ is an $OA(N, s^k, t)$ that is not of strength $t + 1$, but that has one or more subarrays which form an $OA(N, s^{k'}, t + 1)$. Strength t+ arrays have also been recently employed in Wang and Stufken (2021). We now present our results for obtaining smaller D-optimal designs. Proofs are omitted because they follow

Table 1 Support points and weights for a locally D-optimal design

Support points	Weights	Support points	Weights
$(0, -1, -1.4254)$	1/8	$(2, -1, 2.5746)$	1/8
$(0, -1, 0.4254)$	1/8	$(2, -1, 4.4254)$	1/8
$(0, 1, -2.4254)$	1/8	$(2, 1, -2.4254)$	1/8
$(0, 1, -0.5746)$	1/8	$(2, 1, -0.5746)$	1/8

along similar lines as those in Wang and Stufken (2021) for a related but different problem. The assumptions in the next Theorems 3 through 6 for the design space χ and β_p are the same as in Theorem 2.

Theorem 3 *For $p \geq 3$, consider model (1) with the logistic or probit link and with only one interaction effect, say x_1x_2. Let H be the collection of rows for an $OA(N, 2^{p-1}, 2+)$ with the property that columns $(1,\ 2,\ j)$, for all $j \geq 3$, form an $OA(N, 2^3, 3)$. Define*

$$\xi_1 = \left\{ \left(\boldsymbol{c}^*_{\boldsymbol{l1}}, \frac{1}{2N} \right) \text{ and } \left(\boldsymbol{c}^*_{\boldsymbol{l2}}, \frac{1}{2N} \right), l = 1, \ldots, N \right\}$$

where $\boldsymbol{c}^*_{\boldsymbol{l1}} = (h_{l1}, \ldots, h_{l,p-1}, c^*)^T$ and $\boldsymbol{c}^*_{\boldsymbol{l2}} = (h_{l1}, \ldots, h_{l,p-1}, -c^*)^T$. Here c^* is as in Theorem 2 with $r = p + 2$, h_{lj} is either L_j or U_j, and $(h_{l1}, \ldots, h_{l,p-1})$, $l = 1, \ldots, N$ cover all rows in H. Then

$$I_{\xi_1}(\boldsymbol{\beta}) = I_{\xi^*}(\boldsymbol{\beta}),$$

so that ξ_1 is also a D-optimal design for $\boldsymbol{\beta}$.

In Theorem 3, the number of support points is reduced compared to Theorem 2 provided that $N < 2^{p-1}$, which is a choice that is typically possible. However, we still need two support points for each of the N combinations for the first $p - 1$ design variables. The next theorem shows that when the orthogonal array has an additional 2-level column, it is possible to find even smaller optimal designs.

Theorem 4 *For $p \geq 3$, consider the same model as in Theorem 3. Suppose an $OA(N, 2^p, 2+)$ exists with the property that the columns $(1,\ 2,\ j)$, for all $j \geq 3$ form an $OA(N, 2^3, 3)$, and let H again denote the collection of its rows. Partition the rows of H into two collections, H_1 and H_2, each of size $\frac{N}{2}$, depending on whether the final entry of the row is 1 or 2, respectively. Then delete that final entry from each row. Define*

$$\xi_2 = \left\{ \left(\boldsymbol{c}^*_{\boldsymbol{l1}}, \frac{1}{N} \right), l = 1, \ldots, \frac{N}{2} \right\} \cup \left\{ \left(\boldsymbol{c}^*_{\boldsymbol{l2}}, \frac{1}{N} \right), l = 1, \ldots, \frac{N}{2} \right\},$$

where $\boldsymbol{c}^*_{\boldsymbol{l1}} = (h_{l1}, \ldots, h_{l,p-1}, c^*)^T$ and $\boldsymbol{c}^*_{\boldsymbol{l2}} = (h_{l1}, \ldots, h_{l,p-1}, -c^*)^T$. Here, c^* is as in Theorem 3, h_{lj} is either L_j or U_j, and $(h_{l1}, \ldots, h_{l,p-1})$, $l = 1, \ldots, N/2$ cover all rows in H_1 and H_2 for $\boldsymbol{c}^*_{\boldsymbol{l1}}$ and $\boldsymbol{c}^*_{\boldsymbol{l2}}$, respectively. Then,

$$I_{\xi_2}(\boldsymbol{\beta}) = I_{\xi^*}(\boldsymbol{\beta}),$$

so that ξ_2 is also a D-optimal design for $\boldsymbol{\beta}$.

The next two results are for models with two 2-way interactions between design variables. Theorem 5 finds the optimal designs for a situation when there is a common design variable in these two interactions, whereas Theorem 6 does so when the four design variables in the two interactions are distinct.

Theorem 5 *For $p \geq 4$, consider model (1) with the logistic or probit link with two 2-way interaction effects that have a common design variable, say x_1x_2 and x_1x_3. Let H be the collection of rows for an orthogonal array $OA(N, 2^{p-1}, 2+)$ with the property that the columns $(1, 2, j)$ and $(1, 3, j)$, for all $j \geq 4$, form an $OA(N, 2^3, 3)$. Define*

$$\xi_3 = \left\{ \left(\boldsymbol{c}^*_{l1}, \frac{1}{2N} \right) and \left(\boldsymbol{c}^*_{l2}, \frac{1}{2N} \right), l = 1, \dots, N \right\},$$

where $\boldsymbol{c}^*_{l1} = (h_{l1}, \dots, h_{l,p-1}, c^*)^T$ and $\boldsymbol{c}^*_{l2} = (h_{l1}, \dots, h_{l,p-1}, -c^*)^T$. Here c^* is as in Theorem 2 with $r = p + 3$, h_{lj} is either L_j or U_j, and $(h_{l1}, \dots, h_{l,p-1})$, $l = 1, \dots, N$ cover all rows in H. Then

$$I_{\xi_3}(\boldsymbol{\beta}) = I_{\xi^*}(\boldsymbol{\beta}),$$

so that ξ_3 is also a D-optimal design for $\boldsymbol{\beta}$.

Moreover, suppose that an $OA(N, 2^p, 2+)$ exists with the property that the columns $(1, 2, j)$ and $(1, 3, j)$, for all $j \geq 4$ form an $OA(N, 2^3, 3)$. Form H_1 and H_2 as in Theorem 4. Define

$$\xi_4 = \left\{ \left(\boldsymbol{c}^*_{l1}, \frac{1}{N} \right), l = 1, \dots, \frac{N}{2} \right\} \cup \left\{ \left(\boldsymbol{c}^*_{l2}, \frac{1}{N} \right), l = 1, \dots, \frac{N}{2} \right\},$$

where $\boldsymbol{c}^*_{l1} = (h_{l1}, \dots, h_{l,p-1}, c^*)^T$, $\boldsymbol{c}^*_{l2} = (h_{l1}, \dots, h_{l,p-1}, -c^*)^T$, and c^* is as in the first part of this theorem. Here, h_{lj} is either L_j or U_j, and $(h_{l1}, \dots, h_{l,p-1})$, $l = 1, \dots, N/2$, cover all rows in H_1 and H_2 for $\boldsymbol{c}^*_{l1}$ and $\boldsymbol{c}^*_{l2}$, respectively. Then

$$I_{\xi_4}(\boldsymbol{\beta}) = I_{\xi^*}(\boldsymbol{\beta}),$$

so that ξ_4 is also a D-optimal design for $\boldsymbol{\beta}$.

Theorem 6 *For $p \geq 5$, consider model (1) with the logistic or probit link with two 2-way interaction effects that do not have a common design variable, say x_1x_2 and x_3x_4. Let H be the collection of rows for an orthogonal array $OA(N, 2^{p-1}, 2+)$ with the property that the columns $(1, 2, j)$ and columns $(3, 4, j)$, for all $j \geq 5$, form an $OA(N, 2^3, 3)$ and columns $(1, 2, 3, 4)$ form an $OA(N, 2^4, 4)$. Define*

$$\xi_5 = \left\{ \left(\boldsymbol{c}^*_{l1}, \frac{1}{2N} \right) and \left(\boldsymbol{c}^*_{l2}, \frac{1}{2N} \right), l = 1, \dots, N \right\},$$

where $\boldsymbol{c}^*_{l1} = (h_{l1}, \dots, h_{l,p-1}, c^*)^T$ and $\boldsymbol{c}^*_{l2} = (h_{l1}, \dots, h_{l,p-1}, -c^*)^T$. Here c^* is as in Theorem 2 with $r = p + 3$, h_{lj} is either L_j or U_j, and $(h_{l1}, \dots, h_{l,p-1})$, $l = 1, \dots, N$ cover all rows in H. Then

$$I_{\xi_5}(\boldsymbol{\beta}) = I_{\xi^*}(\boldsymbol{\beta}),$$

so that ξ_5 is also a D-optimal design for $\boldsymbol{\beta}$.

Moreover, suppose an $OA(N, 2^p, 2)$ *exists with the property that the columns* $(1,\ 2,\ j)$ *and columns* $(3,\ 4,\ j)$, *for all* $j \geq 5$, *form an* $OA(N, 2^3, 3)$ *and columns* $(1, 2, 3, 4)$ *form an* $OA(N, 2^4, 4)$. *Let* H_1 *and* H_2 *be defined as in Theorem 4. Define*

$$\xi_6 = \left\{ \left(\boldsymbol{c}^*_{l1}, \frac{1}{N} \right), l = 1, \ldots, \frac{N}{2} \right\} \cup \left\{ \left(\boldsymbol{c}^*_{l2}, \frac{1}{N} \right), l = 1, \ldots, \frac{N}{2} \right\},$$

where $\boldsymbol{c}^*_{l1} = (h_{l1}, \ldots, h_{l,p-1}, c^*)^T$, $\boldsymbol{c}^*_{l2} = (h_{l1}, \ldots, h_{l,p-1}, -c^*)^T$, *and* c^* *is as in the first part of this theorem. Here* h_{lj} *is either* L_j *or* U_j, *and* $(h_{l1}, \ldots, h_{l,p-1}), l = 1, \ldots, N/2$, *cover all rows in* H_1 *and* H_2 *for* $\boldsymbol{c}^*_{l1}$ *and* $\boldsymbol{c}^*_{l2}$, *respectively. Then*

$$I_{\xi_6}(\boldsymbol{\beta}) = I_{\xi^*}(\boldsymbol{\beta}),$$

so that ξ_6 *is also a D-optimal design for* $\boldsymbol{\beta}$.

Two other cases are worth mentioning. First, if the model has no interactions, as in Theorem 1, then any OA of strength 2 can be used to reduce the support size. Second, if all 2-way interactions among the first $p-1$ design variables are in the model, then any OA of strength 4 can be used to reduce the support size. Proofs follow along the lines of those in Wang and Stufken (2021). We now illustrate Theorem 5 through the following example.

Example 2 Consider model (1) with the logistic link and

$$\tilde{\boldsymbol{x}}_i^T \boldsymbol{\beta} = c_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \beta_3 x_{i3} + \beta_4 x_{i4} + \beta_{12} x_{i1} x_{i2} + \beta_{13} x_{i1} x_{i3} + \beta_5 x_{i5}.$$

Assume that the first four design variables are restricted to $[-1, 1]$, $[-2, 2]$, $[-1, 1]$ and $[-0.5, 0.5]$, respectively, and that there is no restriction for the last (fifth) design variable. To find locally optimal designs, we further assume that $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2, \beta_3, \beta_4, \beta_{12}, \beta_{13}, \beta_5)^T = (1, -0.5, 0.5, -1, 1, -0.5, 0.5, 1)^T$. Notice that there are two 2-way interactions in the model and that x_1 appears in both. Then, according to Theorem 5, we want to find an $OA(N, 2^4, 2+)$ so that the columns (1, 2, 4) and (1, 3, 4) both form strength 3 orthogonal arrays. Table 2 presents such an OA for $N = 8$. In fact, this is an $OA(8, 2^4, 3)$.

Based on Theorem 5, a locally D-optimal is obtained as shown in Table 3. For illustration purpose, we use lower bound L_i and upper bound U_i instead of their real values. Also we use c^* and $-c^*$ to replace the real values for the unbounded design variable x_5. In this case, the value c^* maximizes $c^2(\Psi(c))^8$, which is approximately 0.7222. Notice that the design shown in Table 3 only has 16 distinct support points compared with the 32-point design obtained from Theorem 2.

We can obtain an even smaller design by using the second part of Theorem 5 provided that there is an $OA(N, 2^5, 2+)$ so that columns (1,2,4), (1,2,5), (1,3,4) and (1,3,5) all form strength 3 orthogonal arrays. We provide such an orthogonal array in Table 4. Then, a smaller D-optimal design constructed using Theorem 5 is shown in Table 5. This design has only 8 distinct support points. With exactly 8 parameters

Table 2 An $OA(8, 2^4, 3)$

1	1	1	2
1	1	2	1
1	2	1	1
1	2	2	2
2	1	1	1
2	1	2	2
2	2	1	2
2	2	2	1

Table 3 Support points for a smaller D-optimal design based on Orthogonal Arrays for Example 2

(x_1, x_2, x_3, x_4)	x_5	(x_1, x_2, x_3, x_4)	x_5
(L_1, L_2, L_3, U_4)	$c^*; -c^*$	(U_1, L_2, L_3, L_4)	$c^*; -c^*$
(L_1, L_2, U_3, L_4)	$c^*; -c^*$	(U_1, L_2, U_3, U_4)	$c^*; -c^*$
(L_1, U_2, L_3, L_4)	$c^*; -c^*$	(U_1, U_2, L_3, U_4)	$c^*; -c^*$
(L_1, U_2, U_3, U_4)	$c^*; -c^*$	(U_1, U_2, U_3, L_4)	$c^*; -c^*$

Table 4 An $OA(8, 2^5, 2+)$ with columns (1,2,4), (1,2,5), (1,3,4) and (1,3,5) of strength 3

1	1	1	2	1
1	1	2	1	2
1	2	1	1	2
1	2	2	2	1
2	1	1	1	1
2	1	2	2	2
2	2	1	2	2
2	2	2	1	1

Table 5 Support points for a smaller D-optimal design based on orthogonal arrays for example 2

(x_1, x_2, x_3, x_4)	x_5	(x_1, x_2, x_3, x_4)	x_5
(L_1, L_2, L_3, U_4)	$-c^*$	(U_1, L_2, L_3, L_4)	$-c^*$
(L_1, L_2, U_3, L_4)	c^*	(U_1, L_2, U_3, U_4)	c^*
(L_1, U_2, L_3, L_4)	c^*	(U_1, U_2, L_3, U_4)	c^*
(L_1, U_2, U_3, U_4)	$-c^*$	(U_1, U_2, U_3, L_4)	$-c^*$

in $\boldsymbol{\beta}$ that need to be estimated, the design in Table 5 is actually a saturated D-optimal design (see Hu et al. (2015) for more details).

Summary and Discussion

Locally optimal designs for GLMs with a logistic or probit link and with multiple design variables were known when the model contains only main effects. In this paper we have extended these results to allow for the presence of interactions in models that satisfy the strong effect heredity principle. We have given explicit expressions for D-optimal designs for such models. By using orthogonal arrays, we have also shown how one might find D-optimal designs with a smaller support size.

The canonical transformation that we have used cannot be applied for models that do not satisfy the strong effect heredity principle. Whether optimal designs for such models have also a simple structure is less clear.

While we have focused attention on models with main effects and some 2-way interactions, the basic results also apply with multi-way interactions, as long as the strong effect heredity principle holds. Requirements for the orthogonal arrays become however more complicated.

The restriction that one of the design variables is unbounded is necessary for the theoretical results to make sure that, when translated to a value for x_p, the values of c^* and $-c^*$ are within the design region. If the pth design variable is also bounded and c^* and $-c^*$ in the optimality results yield values for x_p that fall within the bounds, then the designs in the theorems will still be optimal. But if the x_p values fall outside of the bounds, then optimal designs may be more complicated and use of algorithms, such as meta-heuristic algorithms (cf. Chen et al. 2015; Lukemire et al. 2019; Qiu et al. 2014) may be needed to find optimal designs.

The properties that are needed for the orthogonal arrays are fairly simple, but it may require some investigation whether a required array exists. In some cases, it will be sufficient to consider regular orthogonal arrays. When this is not the case, a repository of orthogonal arrays (e.g., http://neilsloane.com/oadir/) could be a good starting point.

Finally, while the use of orthogonal arrays, where applicable, leads to D-optimal designs with a much smaller support size, it is possible that computational methods can identify optimal designs with an even smaller support size. Such designs may or may not have an equally nice structure as the designs identified in this paper.

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Declarations

Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article.

References

Agresti, A. 2013. *Categorical data analysis*, 3rd ed. Hoboken: Wiley.

Atkinson, A.C., and L.M. Haines. 1996. Designs for nonlinear and generalized linear models. In *Handbook of statistics*, vol. 13, ed. S. Ghosh and C.R. Rao, 437–475. Amsterdam: Elsevier.

Chen, R.-B., S.-P. Chang, W. Wang, H.-C. Tung, and W.K. Wong. 2015. Minimax optimal designs via particle swarm optimization methods. *Statistics and Computing* 25: 975–988.

Ford, I., B. Torsney, and C.F.J. Wu. 1992. The use of a canonical form in the construction of locally optimal designs for non-linear problems. *Journal of the Royal Statistical Society Series B (Methodological)* 54: 569–583.

Hedayat, A.S. 1989. Orthogonal arrays of strength t+ and their statistical applications. Technical Report, Statistical Laboratory, University of Illinois, Chicago.

Hedayat, A.S. 1990. New properties of orthogonal arrays and their statistical applications. Statistical Design and Analysis of Industrial Experiments, pp. 407–422.

Hedayat, A.S., N.J.A. Sloane, and J. Stufken. 1999. *Orthogonal arrays: Theory and applications*. New York: Springer.

Hu, L., M. Yang, and J. Stufken. 2015. Saturated locally optimal designs under differentiable optimality criteria. *The Annals of Statistics* 43 (1): 30–56.

Kabera, M.G., and L.M. Haines. 2012. A note on the construction of locally D and DS-optimal designs for the binary logistic model with several explanatory variables. *Statistics Probability Letters* 82 (5): 865–870.

Khuri, A.I., B. Mukherjee, B.K. Sinha, and M. Ghosh. 2006. Design issues for generalized linear models: A review. *Statistical Science* 21: 376–399.

Kiefer, J. 1974. General equivalence theory for optimum designs (approximate theory). *The Annals of Statistics* 2: 849–879.

Kiefer, J., and J. Wolfowitz. 1960. The equivalence of two extremum problems. *Canadian Journal of Mathematics* 12: 363–365.

Lukemire, J., A. Mandal, and W.K. Wong. 2019. d-QPSO: A quantum particle swarm technique for finding D-optimal designs with mixed factors and a binary response. *Technometrics* 26: 87–105.

Qiu, J., R.-B. Chen, W. Wang, and W.K. Wong. 2014. Using animal instincts to design efficient biomedical studies via particle swarm optimization. *Swarm and Evolutionary Computation* 18: 1–10.

Rao, C.R. 1946. Hypercubes of strength "d'' leading to confounded designs in factorial experiments. *Bulletin of the Calcutta Mathematical Society* 38: 67–78.

Rao, C.R. 1947. Factorial experiments derivable from combinatorial arrangements of arrays. *Supplement to the Journal of the Royal Statistical Society* 9: 128–139.

Russell, K.G., D.C. Woods, S.M. Lewis, and J.A. Eccleston. 2009. D-optimal designs for Poisson regression models. *Statistica Sinica* 19: 721–730.

Sitter, R.R., and B. Torsney. 1995a. D-optimal designs for generalised linear models. In *Moda4—advances in model-oriented data analysis*, ed. C. Kitsos and W. Müller, 87–102. Heidelberg: Physica.

Sitter, R.R., and B. Torsney. 1995b. Optimal designs for binary response experiments with two design variables. *Statistica Sinica* 5: 405–419.

Torsney, B., and N. Gunduz. 2001. On optimal designs for high dimensional binary regression models. In *Optimum design 2000*, ed. A. Atkinson, B. Bogacka, and A. Zhigljavsky, 275–285. Boston: Springer.

Wang, Z., and J. Stufken. 2020. Locally D-optimal designs for binary responses in the presence of factorial effects. *Journal of Statistical Theory and Practice* 14: 19.

Wang, Z., and J. Stufken. 2021. Orthogonal array based locally D-optimal designs for binary responses in the presence of factorial effects. *Journal of Statistical Theory and Practice* 15: 87.

Yang, M., B. Zhang, and S. Huang. 2011. Optimal designs for generalized linear models with multiple design variables. *Statistica Sinica* 21: 1415–1430.