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Optimal s^n factorial designs when observations within-blocks are correlated

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Abstract

In this article, we characterize D-optimal designs for s^n symmetric factorial experiments when observations within blocks are correlated. The motivation to this problem lies in a pharmaceutical experiment where the experimenter needed to develop a once-daily tablet using a factorial design. These experiments are usually conducted in healthy human volunteers and the bioavailability is estimated. Since each subject is administered more than one formulation, the observations within subjects are correlated. We provide an explicit construction of D-optimal designs for s^n factorial experiment with blocks of size s or multiples of s, where observations within blocks are correlated. We discuss in detail the construction of optimal designs for 2^n factorial experiments. We also provide an analytical proof of the D-optimality when there exist a pair of blocks of odd size and remaining blocks are of even size.

Keywords: Factorial design; Correlated data; Optimal design; Intraclass correlation

1. Introduction

The theory of optimal designs for factorial experiments usually assumes uncorrelated errors. This paper was motivated by a problem in the pharmaceutical industry where the

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experimenter needed to develop a once-daily tablet formulation that would improve patient compliance compared to the current marketed formulation administered twice daily. These experiments are usually conducted in healthy human volunteers (or subjects) who were administered several test formulations separated by drug-washout days. The bioavailability of each test formulation, as measured by area under the time-plasma concentration curve (AUC) is the response variable of interest. In general, there are several factors involved in developing these test formulations. For example, the factors may include type of polymers to prolong drug release, amount of film coat on the tablet, administration under fed or fasted state, etc. Since each subject is administered all or selected formulations, the observations from each subject are correlated. The availability of each subject for the duration of trial determines the block size. If all subjects are available for the entire duration then the block size are equal. However, a situation may arise while planning the trial where few subjects are available for couple of visits and others may be available for entire duration thereby leading to different block sizes.

The purpose of the experiment is to estimate a first-order model in the factors that explain the variation in drug bioavailability. The experimental design question in the above problem is how to allocate the levels of the factors under consideration to the subjects or blocks.

There exists numerous articles in the area of continuous optimal regression designs. In particular, Cheng (1995) and Atkins and Cheng (1995), provide approximate theory for design of blocked experiments but is of limited use when block sizes are small. Khuri (1992) discussed the analyses of response surface models with random block effects but did not consider the design aspect except for orthogonal blocking. Our work complements, Goos and Vandebroek (2001) who established connection between the design of experiments in the presence of fixed block effects and random block effects and developed an algorithm to compute D-optimal designs using computation. However, their approach was restricted to the homogeneous, orthogonally blocked designs. Street and Burgess (2004) investigated the efficiency of various small sets of choice pairs for estimation of main effects and two-factor interactions in forced choice experiments in which all attributes have 2 levels. Martin et al. (2004) consider factorial experiments where units are spatially arranged. However, they assume that there is just one block and that row and column effects are random.

In this paper, we consider a factorial design when observations within blocks are correlated. We assume throughout that interactions are negligible, so that interest is limited to precise estimation of main effects. Our theoretical background can be extended to models that include interactions. After providing preliminary introduction to the model, dependence structure and estimation in Section 2, we provide an explicit construction of D-optimal designs for s^n factorial experiment with blocks of size s or multiples of s in Section 3. We provide an analytical proof of the D-optimality which complements the proof given by Goos (2002) for equal block size. In our proof, we also consider the cases where the block are of different sizes. We provide an analytical proof of the D-optimality when there exist a pair of blocks of odd size and remaining blocks are of even size. An extension when there exist more than a pair of blocks of odd size can be obtained using the methods detailed in this paper. In general, the optimal design considered in this paper does not depend on the intra-class correlation (ρ) and can be easily constructed.

2. Notation

In this section, we introduce the notation used throughout the article. Let n be the number of factors (or covariates), s be the number of levels (or values) associated with each factor (or covariate) and s^n be the number of treatment combinations of all factors (or covariates). Let each level of the factor (or non-stochastic values of covariates) be denoted by $a_1, a_2, \ldots, a_s$ for s even or odd. For s odd the levels are symbolically denoted by $0, \pm 1, \pm 2, \ldots,$ and by $\pm 1, \pm 3, \pm 5, \ldots,$ for s even. Note that the levels for both s odd and even are equally spaced. Assume that an experiment consists of s^n experimental runs arranged in b blocks of sizes $k_1, k_2, \ldots, k_b$ such that $\sum_i k_i = s^n$. The linear model can be written as

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\theta} + \boldsymbol{\epsilon}, \tag{1}$$

where $\mathbf{Y}$ is a vector of s^n observations on the response of interest (such as AUC), the vector of $\boldsymbol{\theta}$ contains $(n+1)$ unknown fixed parameters and $\boldsymbol{\epsilon}$ is a random error.

The above model (1) can be re-written as

$$\mathbf{Y}_i = \mathbf{X}_i\boldsymbol{\theta} + \boldsymbol{\epsilon}_i, \quad i = 1, 2, \ldots, b, \tag{2}$$

where $\mathbf{Y}_i$ denotes the observations within block i and is independent of $\mathbf{Y}_j$ for all $i \neq j$, $\mathbf{X}_i$ is the design matrix for block i and $\boldsymbol{\theta} = (\mu, \boldsymbol{\beta})$, where $\boldsymbol{\beta} = (\boldsymbol{\beta}_1, \boldsymbol{\beta}_2, \ldots, \boldsymbol{\beta}_n)'$, is a vector of n linear effects of the main effects and μ is the overall mean. We assume that the observations are grouped into b blocks such that any two observations in the same block have positive correlation ρ, and any two observation from different blocks are uncorrelated. The variance–covariance matrix of the observational vector is given by $Var(\mathbf{Y}) = \sigma^2 D(\boldsymbol{\Sigma}_1, \boldsymbol{\Sigma}_2, \ldots, \boldsymbol{\Sigma}_b)$ where $\boldsymbol{\Sigma}_i = (1-\rho)\mathbf{I}_{k_i} + \rho\mathbf{J}_{k_i}$, $D(.,.,\ldots,.)$ is a diagonal matrix of its arguments, $\mathbf{J}_{k_i}$ is a $k_i \times k_i$ matrix of all ones and $\mathbf{I}_{k_i}$ is the identity matrix of order k_i. We assume that the intra-class correlation, ρ, is known. The problem of determining optimal designs for estimating the unknown parameters $\boldsymbol{\beta}_1, \boldsymbol{\beta}_2, \ldots, \boldsymbol{\beta}_n$ will be considered here. The dispersion matrix of the generalized least-squares estimators, $\hat{\mu}, \hat{\beta}_1, \ldots, \hat{\beta}_n$ is given by $\sigma^2\left[X'D\left(\boldsymbol{\Sigma}_1^{-1}, \boldsymbol{\Sigma}_2^{-1}, \ldots, \boldsymbol{\Sigma}_b^{-1}\right)X\right]^{-1}$ provided all the parameters are estimable.

Let

$$\begin{bmatrix} a_{11} & \mathbf{a}_{12}' \\ \mathbf{a}_{12} & \mathbf{A}_{22} \end{bmatrix} = X'D\left(\boldsymbol{\Sigma}_1^{-1}, \boldsymbol{\Sigma}_2^{-1}, \ldots, \boldsymbol{\Sigma}_b^{-1}\right)X. \tag{3}$$

The information matrix (Shah and Sinha, 1989) for estimating the parameter vector $\boldsymbol{\beta} = (\beta_1, \beta_2, \ldots, \beta_n)'$, is

$$A_{22.1} = A_{22} - \frac{1}{a_{11}}\mathbf{a}_{12}\mathbf{a}_{12}'.$$

The dispersion matrix of the estimated $\boldsymbol{\beta}$ is $\sigma^2 A_{22.1}^{-1}$. A design is called D-optimal if it minimizes the determinant of $A_{22.1}^{-1}$ or equivalently maximizes the determinant of $A_{22.1}$.

3. Optimal designs for s^n factorial experiments with blocks of size s or size a multiple of s

In this section, we restrict our attention to the construction of s^n factorial design with b blocks of size s or multiples of size s. Let $\mathbf{u}_i = \mathbf{X}_i'\mathbf{1} = (k_i, x_{i.1}, x_{i.2}, \ldots, x_{i.n})'$, where k_i denote the block size of the ith block and $x_{i.h}$ denote the sum of the levels for factor h in block i, for $i = 1, 2, \ldots, b$.

Theorem 1. *For a given number of blocks b of size $k_i = d_i s$, for $i = 1, 2, \ldots, b$, where d_i are non-negative integers such that $\sum_{i=1}^{b} k_i = s^n$, the design providing blocks with the sum of levels for each factor equal to 0 is D-optimal for estimating $\boldsymbol{\beta}$ parameters, i.e., if $(x_{ij1}, x_{ij2}, \ldots, x_{ijn})$ is the jth treatment combination in the ith block then $\sum_{j=1}^{k_i} x_{ijh} = 0\ \forall i, h$.*

Proof. The information matrix for the estimation of $\boldsymbol{\theta}$ given by (3) is

$$\begin{bmatrix} a_{11} & \mathbf{a}_{12}' \\ \mathbf{a}_{12} & \mathbf{A}_{22} \end{bmatrix} = \sum_{i=1}^{b} X_i' \Sigma_i^{-1} X_i$$

$$= \sum_{i=1}^{b} \frac{1}{1-\rho} X_i' X_i - \frac{\rho}{(1-\rho)(1+\rho(k_i-1))} X_i' \mathbf{1}\mathbf{1}' X_i$$

$$= \frac{1}{1-\rho} X'X - \sum_{i=1}^{b} \frac{\rho}{(1-\rho)(1+\rho(k_i-1))} \mathbf{u}_i \mathbf{u}_i'$$

$$= \frac{1}{1-\rho} \left[\begin{array}{c|c} s^n & \mathbf{0} \\ \hline \mathbf{0} & s^{n-1}\sum_{j=1}^{s} a_j^2 \mathbf{I}_n \end{array}\right] - \frac{\rho}{1-\rho} \left[\begin{array}{c|c} \sum_i c_i k_i^2 & \sum_i c_i k_i \mathbf{u}_i^{(1)\prime} \\ \hline \sum_i c_i k_i \mathbf{u}_i^{(1)} & \sum_{i=1}^{b} c_i \mathbf{u}_i^{(1)} \mathbf{u}_i^{\prime(1)} \end{array}\right],$$

where

$$\mathbf{u}_i^{\prime(1)} = (x_{i.1}, x_{i.2}, \ldots, x_{i.n}), \quad c_i = \frac{1}{1+\rho(k_i-1)},$$

$$a_{11} = \frac{1}{1-\rho}\left[s^n - \sum_{i=1}^{b} \frac{\rho}{1+\rho(k_i-1)} k_i^2\right], \quad \mathbf{a}_{12}' = -\sum_{i=1}^{b} \frac{\rho}{1+\rho(k_i-1)} k_i \mathbf{u}_i^{\prime(1)}$$

and

$$A_{22} = \frac{1}{1-\rho}\left[s^{n-1}\sum_{j=1}^{s} a_j^2 \mathbf{I}_n - \frac{\rho}{1+\rho(k_i-1)} \sum_{i=1}^{b} \mathbf{u}_i^{(1)} \mathbf{u}_i^{\prime(1)}\right]$$

Now

$$|A_{22.1}| \leqslant |A_{22}| \leqslant \left(\frac{1}{1-\rho}\right)^n \left(s^{n-1}\sum_{j=1}^{s} a_j^2\right)^n$$

The equality holds in the above equation when $\mathbf{u}_i'^{(1)} = \mathbf{0}$, or $x_{i.h} = 0\ \forall i, h$. □

The above result for equal block size is given by Goos (2002). We use the above notation for the analytical proof of 2^n case where blocks are of odd and even size.

3.1. Construction of optimal designs for s^n factorial experiment

Let us define Permutation Matrices, $P_1, P_2, P_3, \ldots, P_s$, such that $P_1 = \mathbf{I}_s$, and P_2 is formed by moving the last column of P_1 to first place and cyclically moving columns of P_1 one step to the right. Similarly, P_i $(i = 3, \ldots, s)$ are formed from P_{i-1} matrices. Now, the s^{n-1} blocks of size s can be formed by taking the rows of $[\mathbf{a}\ \ P_{i2}\mathbf{a}\ \ P_{i3}\mathbf{a}\ \ \ldots\ \ P_{in}\mathbf{a}]$, as blocks for $i_2, \ldots, i_n = \{1, 2, \ldots, s\}$.

Let us consider a 3^3 factorial experiment as an example. Here $s = 3$, $n = 3$ and the levels are -1, 0 and $+1$. The construction of optimal design with block size 3 is given below. The permutation matrix and factor levels (**a**) be defined as follows:

$$\mathbf{a} = \begin{pmatrix} -1 \\ 0 \\ +1 \end{pmatrix}, \quad P_1 = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}, \quad P_2 = \begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ 1 & 0 & 0 \end{bmatrix}, \quad P_3 = \begin{bmatrix} 0 & 0 & 1 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \end{bmatrix}.$$

The first block of size 3 (i.e., 3 experimental runs) for 3^3 factorial experiment is formed as

$$[\mathbf{a}\quad P_1\mathbf{a}\quad P_1\mathbf{a}] = \begin{bmatrix} -1 & -1 & -1 \\ 0 & 0 & 0 \\ +1 & +1 & +1 \end{bmatrix},$$

where each row in the above matrix represent an experimental run and each column represent a factor. The first experimental run is a combination of factors (x_1, x_2 and x_3) at level -1 (low). Similarly, the second and third experimental runs are combination of all three factors at levels 0 (medium) and $+1$ (high), respectively.

Now the second block of size 3 is formed as

$$[\mathbf{a}\quad P_1\mathbf{a}\quad P_2\mathbf{a}] = \begin{bmatrix} -1 & -1 & 0 \\ 0 & 0 & +1 \\ +1 & +1 & -1 \end{bmatrix}.$$

The first experimental run is a treatment combination of factors with x_1 and x_2 at level -1 (low) and x_3 at level 0 (medium). Note that for the first and second block, the sum of levels for each factor is equal to 0 $\left(\mathbf{u}_1'^{(1)} = \mathbf{u}_2'^{(1)} = \mathbf{0}\right)$. Similarly, the remaining 7 blocks of size 3 can be formed such that $\mathbf{u}_i'^{(1)} = \mathbf{0},\ i = 3, \ldots, 9$. Designs with block size a multiple of s can be constructed by combining blocks of size s such that $\mathbf{u}_i'^{(1)} = \mathbf{0},\ i = 1, 2, \ldots, b$.

4. Optimal design for 2^n factorial experiments when observations within the blocks are correlated

In this section, we will discuss in detail optimal designs for 2^n factorial experiments, when observations within blocks are correlated. The 2^n factorial designs are commonly used in all experimental settings. The D-optimal design when the block sizes are all even can be obtained by combining blocks of size 2 as outlined in the Section 3.1.

4.1. 2^n factorial experiments with blocks of odd size

First let us consider a 2^n factorial experiment where a pair of blocks is of odd size and the remaining blocks are of even size. The information matrix as defined earlier can be re-written as below

$$\mathbf{I}(\boldsymbol{\theta}) = \frac{1}{1-\rho}\begin{bmatrix} a_{11} & \mathbf{a}'_{12} \\ \mathbf{a}_{12} & \mathbf{A}_{22} \end{bmatrix},$$

where

$$a_{11} = 2^n - \sum_{i=1}^{b} \frac{\rho}{1+\rho(k_i-1)} k_i^2, \quad \mathbf{a}'_{12} = -\sum_{i=1}^{b} \frac{\rho}{1+\rho(k_i-1)} k_i \mathbf{u}_i'^{(1)}$$

and

$$\mathbf{A}_{22} = \sum_{j=1}^{2} 2^{n-1} a_j^2 \mathbf{I}_n - \sum_{i=1}^{b} \frac{\rho}{1+\rho(k_i-1)} \mathbf{u}_i^{(1)} \mathbf{u}_i'^{(1)}.$$

Without loss of generality, let us assume that the first two blocks are of odd size (k_1 and k_2) and the remaning blocks ($k_3, \ldots, k_b$) are even sized. The blocks of even size are constructed using methods described in Section 3.1. In the above $\mathbf{I}(\boldsymbol{\theta})$, note that a_{11} does not change, however, $\mathbf{a}'_{12} = -\sum_{i=1}^{2} \frac{\rho}{1+\rho(k_i-1)} k_i \mathbf{u}_i'^{(1)}$ since $x_{i.h} = 0 \ \forall i \geqslant 3$ and h.

$$\mathbf{A}_{22} = 2^{n-1} \sum_{j=1}^{2} a_j^2 \mathbf{I}_n - \left[\frac{\rho}{1+\rho(k_1-1)} \mathbf{u}_1^{(1)} \mathbf{u}_1'^{(1)} + \frac{\rho}{1+\rho(k_2-1)} \mathbf{u}_2^{(1)} \mathbf{u}_2'^{(1)}\right].$$

Since this is a complete factorial set-up, we know that $x_{1.h} + x_{2.h} = 0 \ \forall h$, which imply that $\mathbf{u}_1^{(1)} = -\mathbf{u}_2^{(1)}$.

$$\mathbf{A}_{22} = 2^n \mathbf{I}_n - \left[\frac{\rho}{1+\rho(k_1-1)} + \frac{\rho}{1+\rho(k_2-1)}\right] \mathbf{u}_1^{(1)} \mathbf{u}_1'^{(1)},$$

$$\mathbf{A}_{22.1} = A_{22} - \frac{1}{a_{11}} \mathbf{a}_{12} \mathbf{a}'_{12} \tag{4}$$

$$= A_{22} - \frac{1}{a_{11}} \left[\frac{\rho}{1+\rho(k_1-1)} k_1 - \frac{\rho}{1+\rho(k_2-1)} k_2\right]^2 \mathbf{u}_1^{(1)} \mathbf{u}_1'^{(1)}$$

$$= 2^n \mathbf{I} - c(\rho) \mathbf{u}_1^{(1)} \mathbf{u}_1'^{(1)}, \tag{5}$$

where

$$c(\rho)=\left[\sum_{i=1}^{2}\frac{\rho}{1+\rho(k_i-1)}-\frac{1}{a_{11}}\left(\frac{\rho}{1+\rho(k_1-1)}k_1-\frac{\rho}{1+\rho(k_2-1)}k_2\right)^2\right].$$

Theorem 2. *For a given number of blocks b, with block sizes multiples of 2 except for two blocks of odd size, the design is D-optimal if for those two blocks, the sum of levels for each factor is* ± 1.

Proof. Consider the determinant of (5),

$$\begin{aligned}|A_{22.1}| &= \left|2^n\mathbf{I}-c(\rho)\mathbf{u}_1^{(1)}\mathbf{u}_1^{\prime(1)}\right|\\ &\propto \left|\mathbf{I}-c^*(\rho)\mathbf{u}_1^{(1)}\mathbf{u}_1^{\prime(1)}\right|\\ &=1-c^*(\rho)\mathbf{u}_1^{\prime(1)}\mathbf{u}_1^{(1)}\\ &=1-c^*(\rho)\left(x_{1.1}^2+x_{1.2}^2+\cdots+x_{1.n}^2\right),\end{aligned}$$

where $c^*(\rho)=c(\rho)/2^n$. We note that, $x_{1.1}, x_{1.2}, \ldots, x_{1.n}$ cannot be 0 since k_1 and k_2 are odd. Therefore, $|x_{1.1}|\geqslant 1, |x_{1.2}|\geqslant 1, \ldots, |x_{1.n}|\geqslant 1$, which implies $x_{1.1}^2+x_{1.2}^2+\cdots+x_{1.n}^2\geqslant n$.

$$|A_{22.1}|\leqslant 1-nc^*(\rho).$$

The equality in the above equation holds if and only if $x_{1.1}, x_{1.2}, \ldots, x_{1.n}$ are each ± 1. □

As an extension, we considered two or more pairs of blocks of odd size and the remaining blocks are of even size. Although we did not derive the optimal designs, we can construct near optimal designs by combining runs such that the sum of levels for each factor is ± 1. It can be easily verified that when $k_1=k_2$, $k_3=k_4$ and $k_i=2d_i$, for $i=5,\ldots,b$, where d_i are positive integers such that $\sum_{i=1}^{b}k_i=2^n$, the design is D-optimal if $\mathbf{u}_1^{(1)}$ and $\mathbf{u}_3^{(1)}$ are orthogonal.

5. Concluding remarks

In this paper, we have shown optimal construction of s^n factorial experiments when observation within blocks are correlated. We provided an analytical proof of optimality for factorial experiments when block sizes are homogeneous and heterogeneous. These ideas can be extended to construction of 2^{n-p} symmetric fractional factorial experiments.

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