E-optimal approximate block designs for treatment-control comparisons

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We study E-optimal block designs for comparing a set of test treatments with a control treatment. We provide the complete class of all E-optimal approximate block designs and we show that these designs are characterized by simple linear constraints. Employing the provided characterization, we obtain a class of E-optimal exact block designs with unequal block sizes for comparing test treatments with a control.

Keywords: Optimal design, Block design, Approximate design, Control treatment, E-optimality

1 Introduction

Consider a blocking experiment for comparing a set of test treatments with a control. As noted in [4], the experimental objective of comparing the test treatments with a control arises, for instance, in screening experiments or in experiments in which it is desired to assess the relative performance of new test treatments with respect to the standard treatment. Such objective is also quite natural for medical studies involving placebo (e.g., see [12], [11]).

Formally, we have

$$Y_j = \mu + \tau_{i(j)} + \theta_{k(j)} + \varepsilon_j, \quad j = 1, \dots, n,$$

where μ is the overall mean, τ_i is the effect of the i-th treatment ($0 \le i \le v$), θ_k is the effect of the k-th block ($1 \le k \le d$), and the random errors $\varepsilon_1, \dots, \varepsilon_n$ are uncorrelated, with zero mean and variance $\sigma^2 < \infty$. Treatment 0 denotes the control, and the test treatments are numbered $1, \dots, v$. By τ, we denote the vector of treatment effects and by θ the vector of block effects. The assumed objective of the experiment is to estimate the comparisons of the test treatments with the control $\tau_i - \tau_0$ ($1 \le i \le v$) or comparisons with the control in short. Let $Q := (-1_v, I_v)^T$, where 1_v is the column vector of ones of

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length v and I_v is the identity matrix. Then, the experimental objective can be expressed as the estimation of $Q^T\tau$.

There is a large amount of literature on optimal exact designs for test treatment-control comparisons, mostly considering the A- and MV-optimality criteria; for a survey, see [4] or [5]. The E-optimality criterion also received some attention; see [6], [8], [7].

In this paper, we provide the class of *all* E-optimal approximate block designs for comparisons with the control. Based on the obtained class of optimal approximate designs, we provide a class of E-optimal exact designs, which extends the known results on E-optimality to the case of unequal block sizes.

1.1 Experimental design

An *exact design* ξ_e determines in each block the numbers of trials that are performed with the various treatments. Thus, ξ_e can be expressed as a function $\xi_e : \{0,\dots,v\} \times \{1,\dots,d\} \to \{0,1,2,\dots,n\}$ such that $\sum_{i,k} \xi_e(i,k) = n$. The value $\xi_e(i,k)$ determines the number of trials performed with treatment i in block k. Suppose that the blocks $1,\dots,d$ have pre-specified non-zero sizes $m_1,\dots,m_d$. We denote the class of all block designs for $v+1$ treatments and d blocks of sizes $m = (m_1,\dots,m_d)^T$ by $D(v,d,m)$.

An *approximate design* (or simply a *design*) is a function $\xi : \{0,\dots,v\} \times \{1,\dots,d\} \to [0,1]$, such that $\sum_{i,k} \xi(i,k) = 1$. The value $\xi(i,k)$ represents the proportion of all trials that are performed with treatment i in block k. For a given design ξ, let us denote the design matrix $X(\xi) := (\xi(i,k))_{i,k}$, let $r(\xi) := X(\xi)1_d$ be the vector of total treatment proportions and let $s(\xi) := X^T(\xi)1_v$ be the vector of relative block sizes. Because we consider non-zero block sizes, we always have $s(\xi) > 0$.

The information matrix of a design ξ for estimating all pairwise comparisons of treatments is $M(\xi) := \text{diag}(r(\xi)) - X(\xi)\text{diag}^{-1}(s(\xi))X^T(\xi)$, where $\text{diag}^{-1}(s(\xi)) := \text{diag}(s_1^{-1}(\xi),\dots,s_d^{-1}(\xi))$. The parameter system $Q^T\tau$ is said to be estimable under an approximate design ξ if $\mathcal{C}(Q) \subseteq \mathcal{C}(M(\xi))$, where $\mathcal{C}$ denotes the column space. In such a case, we say that ξ is feasible and we have $\text{rank}(M(\xi)) = v$. The information matrix $N(\xi) := (Q^T M^-(\xi)Q)^{-1}$ of a feasible design ξ for estimating $Q^T\tau$ is obtained by deleting the first row and column of $M(\xi)$ (see [1], [3]). Let us partition $X(\xi)$ as $X^T(\xi) = (z(\xi), Z^T(\xi))$, where $z(\xi)$ is a $d \times 1$ vector; i.e., $Z(\xi) = (\xi(i,k))_{i>0,k}$. Then, the information matrix for comparing the test treatments with the control is

$$N(\xi) = \text{diag}(r_1(\xi),\dots,r_v(\xi)) - Z(\xi)\text{diag}^{-1}(s(\xi))Z^T(\xi). \qquad (1)$$

Note that $N(\xi)$ is proportional to the inverse of the covariance matrix of the least squares estimator of $\tau_1 - \tau_0, \ldots, \tau_v - \tau_0$. A design is said to be Ψ-optimal if it minimizes $\Psi(N(\xi))$ for some function Ψ.

We say that a design ξ that satisfies $\xi(i,k) = r_i s_k$ is a *product design* of r and s. We denote such design as $\xi = r \otimes s$.

2 E-optimality

We denote the largest (smallest) eigenvalue of a symmetric matrix A by $\lambda_{\max}(A)$ ($\lambda_{\min}(A)$). A design is E-optimal if it minimizes $\lambda_{\max}(N^{-1}(\xi))$ or, equivalently, if it maximizes $\lambda_{\min}(N(\xi))$. Such a design minimizes the maximum variance for the linear combinations $\sum_{i>0} x_i\tau_i - (\sum_{i>0} x_i)\tau_0$ over all normalized $x \in \mathbb{R}^v$. In the following theorem, we provide the complete characterization of E-optimal block designs for comparing the test treatments with the control: an approximate design ξ^* is E-optimal for the comparisons with the control if and only if

(i) in each block, ξ^* assigns one half of the trials to the control and

(ii) ξ^* is equireplicated in the test treatments.

Theorem 1. *An approximate block design ξ is E-optimal for the comparisons with the control if and only if it satisfies*

$$\xi(0,k) = \frac{s_k(\xi)}{2} \quad \text{and} \quad r_1(\xi) = \ldots = r_v(\xi) = \frac{1}{2v}. \tag{2}$$

Proof. Let ξ be E-optimal. From Theorems 1 and 6 of [10] it follows that an E-optimal design must satisfy $r_0(\xi) = 1/2$ and $r_i(\xi) = 1/(2v)$ for $i > 0$, and that the optimal value of $\lambda_{\min}(N(\xi))$ is $\lambda^*_{\min} = 1/(4v)$. Moreover,

$$\begin{aligned}
\lambda_{\min}(N(\xi)) &= \min_{x^Tx=1} x^T N(\xi) x \leq \frac{1}{v} 1_v^T N(\xi) 1_v \\
&= \frac{1}{v}\left(\sum_{i>0} r_i(\xi) - \sum_{k=1}^{d} \frac{1}{s_k(\xi)} (\sum_{i>0} \xi(i,k))^2\right) \\
&= \frac{1}{2v} - \frac{1}{v}\sum_{k=1}^{d} \frac{(q_k)^2}{s_k(\xi)},
\end{aligned}$$

where $q_k := \sum_{i>0} \xi(i,k)$ $(1 \leq k \leq d)$. Because $\sum_k \xi(0,k) = 1/2$, we have $\sum_k q_k = 1/2$. Therefore, for fixed $s(\xi)$, the following holds (which can be seen by finding the minimum of the function on the left-hand side):

$$\sum_{k=1}^{d} \frac{q_k^2}{s_k(\xi)} \geq \sum_{k=1}^{d} \frac{(s_k(\xi)/2)^2}{s_k(\xi)} = \frac{1}{4},$$

$i\backslash k$	1	2	3	4
0	1/6	1/6	1/12	1/12
1	1/6	1/12	0	0
2	0	1/12	1/12	1/12

Table 1: E-optimal approximate block design ξ for comparing two test treatments with the control in 4 blocks of relative sizes $s = (1/3, 1/3, 1/6, 1/6)^T$. The value on position (i, k) represents $\xi(i, k)$.

using the fact that $\sum_k s_k(\xi) = 1$. The inequality is attained as equality if and only if $q_k = s_k(\xi)/2$ for all $k = 1, \ldots, d$. Hence,

$$\lambda_{\min}(N(\xi)) \leq \frac{1}{2v} - \frac{1}{4v} = \frac{1}{4v} = \lambda^*_{\min}. \tag{3}$$

Since ξ is E-optimal, the inequality is attained as equality, and thus $\xi(1, k) = s_k(\xi)/2$ for all $k = 1, \ldots, d$.

For the converse part, let ξ satisfy (2). Then, ξ is connected (see [2]) and therefore feasible. Moreover, $Z^T(\xi)1_v = s(\xi)/2$ and $Z(\xi)1_d = (2v)^{-1}1_v$. Therefore,

$$N(\xi)1_v = \frac{1}{2v}1_v - \frac{1}{2}Z(\xi)\text{diag}^{-1}(s(\xi))s(\xi) = \frac{1}{2v}1_v - \frac{1}{2}Z(\xi)1_d.$$

Thus, $N(\xi)1_v = [1/(2v) - 1/(4v)]1_v = (4v)^{-1}1_v$. That is, $\lambda^* = 1/(4v)$ is an eigenvalue of $N(\xi)$ corresponding to the eigenvector 1_v. Therefore, it suffices to prove that λ^* is the smallest eigenvalue of $N(\xi)$.

Let $N(\xi) = (n_{ij})_{i,j}$. We note that $n_{ij} \leq 0$ for $i \neq j$. Using an argument similar to that in Theorem 3.1 of [6], let x be an eigenvector of $N(\xi)$. Let us denote the eigenvalue that corresponds to x as λ. By multiplying x by an appropriate constant, we obtain $\max_j |x_j| = 1$. Thus, $x_j \leq 1$ for all $1 \leq j \leq v$. Let i be the index that satisfies $|x_i| = 1$. Then, by multiplying x by ± 1, we obtain $x_i = 1$. Now, we can write

$$(N(\xi)x)_i = n_{ii}x_i + \sum_{j \neq i} n_{ij}x_j \geq n_{ii} + \sum_{j \neq i} n_{ij} = (N(\xi)1_v)_i,$$

where the inequality follows from $n_{ij} \leq 0$ for $j \neq i$, and $x_j \leq 1$ for $1 \leq j \leq v$. Because $(N(\xi)x)_i = \lambda x_i = \lambda$ and $(N(\xi)1_v)_i = \lambda^*$, we have $\lambda^* \leq \lambda$ for any eigenvalue λ. □

Table 1 gives an E-optimal block design provided by Theorem 1. Theorem 1 is a generalization of Theorems 1 and 2 of [11], where E-optimal block designs

$i \backslash k$	1	2	3
0	1	1	2
1	1	0	1
2	0	1	1

Table 2: Exact block design ξ_e for given block sizes $m = (2, 2, 4)^T$, which is E-optimal for comparing two test treatments with the control. The value on position (i, k) represents $\xi_e(i, k)$.

for comparisons with the placebo (control) for specific experimental settings are provided.

3 Exact Designs

For a strictly convex criterion, the only optimal approximate block designs are product designs with optimal treatment proportions (see [10]). For example, for given relative block sizes s, the product design $\xi^* = r^* \otimes s$, where

$$r_0^* = \frac{\sqrt{v} - 1}{v - 1}, \quad r_1^* = \ldots = r_v^* = \frac{\sqrt{v} - 1}{\sqrt{v}(v - 1)},$$

is the single A-optimal, as well as the single MV-optimal design, see [3], [10]. It is rather difficult to obtain optimal or efficient exact designs from such designs, e.g., by rounding methods (see Chapter 12 of [9]).

However, since E-optimality lacks strict convexity, the class of E-optimal designs is richer, and efficient exact designs can be obtained by the rounding methods more easily. Moreover, this allows for a simple construction of optimal exact designs for a wide range of experimental settings. We easily obtain the following theorem that provides a class of E-optimal exact designs for unequal block sizes.

Theorem 2. *If there exists an exact design $\xi_e^* \in D(v, d, m)$ that satisfies $\xi_e^*(0, k) = m_k/2$, $1 \leq k \leq d$, and ξ_e^* is equireplicated in the test treatments, then ξ_e^* is E-optimal for test treatment-control comparisons in $D(v, d, m)$.*

Proof. The approximate version ξ_e^*/n of ξ_e^* is in fact an E-optimal approximate design, because it satisfies the conditions of Theorem 1. Then, ξ_e is clearly an E-optimal exact design, because the class of approximate designs is a relaxation of the class of the "normalized" exact designs ξ_e/n. □

Theorem 2 generalizes Theorem 3.1 of [6], which provides E-optimal block designs for blocks of equal size, to blocks of unequal sizes. An E-optimal design given by Theorem 2 is provided in Table 2.

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References

[1] R. E. Bechhofer and A. C. Tamhane. Incomplete block designs for comparing treatments with a control: General theory. *Technometrics*, 23(1):45–57, 1981.

[2] J. A. Eccleston and A. Hedayat. On the theory of connected designs: characterization and optimality. *Ann. Stat.*, 2(6):1238–1255, 1974.

[3] A. Giovagnoli and H. P. Wynn. Schur-optimal continuous block designs for treatments with a control. In L. M. Le Cam and R. A. Olshen, editors, *Proceedings of the Berkeley Conference in Honor of Jerzy Neyman and Jack Kiefer*, pages 651–666, California, 1985. Wadsworth.

[4] A. S. Hedayat, M. Jacroux, and D. Majumdar. Optimal designs for comparing test treatments with controls. *Stat. Sci.*, 3(4):462–476, 1988.

[5] D. Majumdar. Optimal and efficient treatment-control designs. In S. Ghosh and C. R. Rao, editors, *Handbook of statistics 13: Design and Analysis of Experiments*, pages 1007–1053. North Holland, Amsterdam, 1996.

[6] D. Majumdar and W. I. Notz. Optimal incomplete block designs for comparing treatments with a control. *Ann. Stat.*, 11(1):258–266, 1983.

[7] J. P. Morgan and X. Wang. E-optimality in treatment versus control experiments. *J. Stat. Theory Pract.*, 5(1):99–107, 2011.

[8] W. I. Notz. Optimal designs for treatment-control comparisons in the presence of two-way heterogeneity. *J. Stat. Plan. Infer.*, 12:61–73, 1985.

[9] F. Pukelsheim. *Optimal design of experiments.* SIAM, Philadelphia, 2006.

[10] S. Rosa and R. Harman. Optimal approximate designs for estimating treatment contrasts resistant to nuisance effects. *Stat. Pap.*, 57(4):1077–1106, 2016.

[11] S. Rosa and R. Harman. Optimal approximate designs for comparison with control in dose-escalation studies. *TEST*, 2017 (to appear).

[12] S. J. Senn. *Statistical Issues in Drug Development.* Wiley, Chichester, 1997.