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A-optimal completely randomized designs for incomplete factorial structures with three factors

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This paper deals with obtaining A-optimal completely randomized designs for three factors after eliminating treatments associated with triple placebo and both double and triple placebos since their administration is unethical. A number of A-optimal designs have been obtained.

1. Introduction

Factorial experiments are widely used in many research investigations to compare the effects of two or more treatment factor combinations. In factorial experiments, often it may not be possible to accommodate one or more treatment combinations in the factorial treatment structure. For example, consider a clinical trial conducted to investigate the joint effect of two drugs, each of which is either absent or is given at a number of predefined dose levels, in which it is unethical to administer a double placebo (Gerami and Lewis, 1992). So, the treatment combination related to double placebo has to be eliminated from the factorial treatment structure in the experimentation. In other words, an incomplete set from the total number of treatment combinations is to be used for experimentation. To deal with such situations, Gerami and Lewis (1992) introduced designs for comparing dual (treatment combinations having non-zero levels of both the factors) with single treatments (treatment combinations with one factor at zero level and another factor at non-zero level) in block design set up for two-factor factorial experiments. Gerami and Lewis (1994) obtained A-optimal completely randomized designs for comparing dual with single treatments for two factors after eliminating one treatment combination having zero levels of both the factors. Gerami et al. (1998) obtained efficient block designs and derived lower bound on the efficiencies of designs only for two factors. Equireplicate completely randomized designs and randomized complete block designs are considered by Gerami (2008) under incomplete factorial structure.

The aforementioned studies consider only two factors in the experimentation. However, in combination therapy of clinical trials, placebo-controlled experimentations are often conducted with three drugs, see Gilbert et al. (1998) and Shein-Chung and Jen-Pei (2004, p. 270). Since it is unethical to administer double and triple placebos, we consider designing the experiments after elimination of triple placebo and both triple and double placebos from the factorial treatment structure. In this article, we focus on zero-way elimination of heterogeneity model for obtaining A-optimal designs considering various possible comparisons of interest among different levels of treatments for three factors. We begin with preliminaries in Section 2. A-optimal designs are obtained in Sections 3 and 4 after elimination of triple placebo and both triple and double placebos, respectively.

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2. Preliminaries

Consider a factorial experiment involving three factors (A, B and C) each having levels m_1, m_2 and m_3, respectively. Levels of each factor are labelled as $0, 1, \ldots, m_h - 1$ for $h = 1, 2, 3$. We denote each treatment combination of factorial treatment structure as ijk, for $i = 0, 1, 2, \ldots, m_A, j = 0, 1, 2, \ldots, m_B$ and $k = 0, 1, 2, \ldots, m_C$, where i, j and k are the levels of the factors A, B and C, respectively and $m_A = m_1 - 1, m_B = m_2 - 1$ and $m_C = m_3 - 1$. We denote the treatment associated with the triple placebo by 000 whereas the treatments associated with double placebos by $i00$, $0j0$ and $00k$, $i = 1, 2, \ldots, m_A, j = 1, 2, \ldots, m_B$ and $k = 1, 2, \ldots, m_C$. Further, we denote a treatment combination ijk as i) a triple treatment when none of i, j and k is zero, ii) a dual treatment when any one of i, j and k is zero and other two are non-zero and iii) a single treatment when any two of i, j and k is zero and remaining one is non-zero. By above definition, a single treatment is a double placebo and vice versa.

Since administration of triple and double placebos is unethical, we consider two cases: case I which involves elimination of only triple placebo (000) and case II which involves elimination of both triple placebo (000) and double placebos ($i00$, $0j0$ and $00k$, $i = 1, 2, \ldots, m_A, j = 1, 2, \ldots, m_B$ and $k = 1, 2, \ldots, m_C$) from the factorial treatment structure. We assume zero way elimination of heterogeneity model with overall mean, the effects of treatment combinations and the homoscedastic error term and obtain A-optimal designs for both the cases.

3. A-optimal designs after elimination of triple placebo

Let $D(t_1, N)$ denote the set of all completely randomized designs for a fixed number N of experimental units and $t_1 = m_1m_2m_3 - 1$ treatment combinations after eliminating the triple placebo. The objective of the experiment is to compare triple versus dual treatments, triple versus single treatments and dual versus single treatments. Let the treatment effect due to the treatment ijk be denoted as $\tau_{ijk}(i = 0, 1, 2, \ldots, m_A; j = 0, 1, 2, \ldots, m_B; k = 0, 1, 2, \ldots, m_C)$. Then, the contrasts of triple versus dual treatments are $\tau_{ijk}-\tau_{ij0}$, $\tau_{ijk}-\tau_{i0k}$ and $\tau_{ijk}-\tau_{0jk}$, triple versus single treatments are $\tau_{ijk}-\tau_{i00}$, $\tau_{ijk}-\tau_{0j0}$, $\tau_{ijk}-\tau_{00k}$ and dual versus single treatments are $\tau_{ij0}-\tau_{i00}$, $\tau_{ij0}-\tau_{0j0}$, $\tau_{ij0}-\tau_{00k}$, $\tau_{i0k}-\tau_{i00}$, $\tau_{i0k}-\tau_{0j0}$, $\tau_{i0k}-\tau_{00k}$, $\tau_{0jk}-\tau_{i00}$, $\tau_{0jk}-\tau_{0j0}$, $\tau_{0jk}-\tau_{00k}$, respectively, with $i = 1, 2, \ldots, m_A, j = 1, 2, \ldots, m_B$ and $k = 1, 2, \ldots, m_C$. Here, the problem is to find a design $d^* \in D(t_1, N)$ which is A-optimal under zero way elimination of heterogeneity model for estimation of above mentioned contrasts. More specifically, we need to find an allocation of n_{ijk} units to treatment combinations $ijk \in U_1$ which minimizes

$$\begin{aligned}\phi_I = \sum_{i=1}^{m_A}\sum_{j=1}^{m_B}\sum_{k=1}^{m_C}\{&\mathrm{var}(\hat{\tau}_{ijk}-\hat{\tau}_{ij0})+\mathrm{var}(\hat{\tau}_{ijk}-\hat{\tau}_{i0k})+\mathrm{var}(\hat{\tau}_{ijk}-\hat{\tau}_{0jk})+\\ &\mathrm{var}(\hat{\tau}_{ijk}-\hat{\tau}_{i00})+\mathrm{var}(\hat{\tau}_{ijk}-\hat{\tau}_{0j0})+\mathrm{var}(\hat{\tau}_{ijk}-\hat{\tau}_{00k})+\mathrm{var}(\hat{\tau}_{ij0}-\hat{\tau}_{i00})+\\ &\mathrm{var}(\hat{\tau}_{ij0}-\hat{\tau}_{0j0})+\mathrm{var}(\hat{\tau}_{ij0}-\hat{\tau}_{00k})+\mathrm{var}(\hat{\tau}_{i0k}-\hat{\tau}_{i00})+\mathrm{var}(\hat{\tau}_{i0k}-\hat{\tau}_{0j0})+\\ &\mathrm{var}(\hat{\tau}_{i0k}-\hat{\tau}_{00k})+\mathrm{var}(\hat{\tau}_{0jk}-\hat{\tau}_{i00})+\mathrm{var}(\hat{\tau}_{0jk}-\hat{\tau}_{0j0})+\mathrm{var}(\hat{\tau}_{0jk}-\hat{\tau}_{00k})\}\end{aligned} \tag{1}$$

subject to $\sum_{ijk\in U_1} n_{ijk} = N$ where $U_1 = \{ijk : i = 0, 1, 2, \ldots, m_A; j = 0, 1, 2, \ldots, m_B; k = 0, 1, 2, \ldots, m_C$ with $ijk \neq 000\}$.

Often the experimenters may be interested to compare the effects among the dual treatments in addition to the comparison of triple versus dual treatments, triple versus single treatments and dual versus single treatments. Here, the aim is to find an allocation of n_{ijk} units to treatment combinations $ijk \in U_1$ which minimizes

$$\phi_{II} = \phi_I + \sum_{i=1}^{m_A}\sum_{j=1}^{m_B}\sum_{k=1}^{m_C}\{\mathrm{var}(\hat{\tau}_{ij0}-\hat{\tau}_{i0k})+\mathrm{var}(\hat{\tau}_{ij0}-\hat{\tau}_{0jk})+\mathrm{var}(\hat{\tau}_{i0k}-\hat{\tau}_{0jk})\} \tag{2}$$

subject to $\sum_{ijk\in U_1} n_{ijk} = N$.

Similarly, the experimenters may be interested to compare the effects among the single treatments in addition to the comparison of triple versus dual treatments, triple versus single treatments and dual versus single treatments. Here, the problem is to find an allocation of n_{ijk} units to treatment combinations $ijk \in U_1$ which minimizes

$$\phi_{III} = \phi_I + \sum_{i=1}^{m_A}\sum_{j=1}^{m_B}\sum_{k=1}^{m_C}\{\mathrm{var}(\hat{\tau}_{i00}-\hat{\tau}_{0j0})+\mathrm{var}(\hat{\tau}_{i00}-\hat{\tau}_{00k})+\mathrm{var}(\hat{\tau}_{0j0}-\hat{\tau}_{00k})\} \tag{3}$$

subject to $\sum_{ijk\in U_1} n_{ijk} = N$.

Finally, it may be of interest to compare the effects among dual treatments and among single treatments along with triple versus dual, triple versus single and dual versus single treatments comparisons. Here, the aim is to minimize

$$\begin{aligned}\phi_{IV} = \phi_I + \sum_{i=1}^{m_A}\sum_{j=1}^{m_B}\sum_{k=1}^{m_C}\{&\mathrm{var}(\hat{\tau}_{ij0}-\hat{\tau}_{i0k})+\mathrm{var}(\hat{\tau}_{ij0}-\hat{\tau}_{0jk})+\mathrm{var}(\hat{\tau}_{i0k}-\hat{\tau}_{0jk})+\\ &\mathrm{var}(\hat{\tau}_{i00}-\hat{\tau}_{0j0})+\mathrm{var}(\hat{\tau}_{i00}-\hat{\tau}_{00k})+\mathrm{var}(\hat{\tau}_{0j0}-\hat{\tau}_{00k})\}\end{aligned} \tag{4}$$

subject to $\sum_{ijk\in U_1} n_{ijk} = N$.

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