Efficient crossover designs for comparing test treatments with a control treatment when $p = 3$

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Abstract

Efficient crossover designs for comparing t test treatments to one control treatment with three periods is considered. Through this investigation and the characterization obtained for the A-optimal/efficient designs in the nearly entire class, the efficiency of a given design is evaluated and guidance for constructing highly efficient designs is provided.

KEY WORDS: Crossover designs; Repeated measurements; Carryover effect; Balanced designs.

1 Introduction

Crossover designs, in which t treatments are assigned to n experimental subjects in two or more (p) periods, have been widely applied in pharmaceutical clinical trials. In these designs, the subjects are used as blocks. Thus, the treatment comparisons are more precise than other designs because subject variation is removed from treatment comparisons on the same subject. The optimality of crossover designs has been studied by many authors (Hedayat and Afsarinejad (1975, 1978); Cheng and Wu (1980); Kunert (1983, 1984); Hedayat and Zhao (1990); Stufken (1991, 1996); Carrière and Reinsel (1993); Matthews (1994); Kushner (1997, 1998); Afsarinejad and Hedayat (2002); Kunert and Stufken (2002); Hedayat and Yang (2003, 2004a)). Most results are for the situation that all treatments are equally important.

However in many pharmaceutical studies, researchers are more often interested in the comparisons between t test treatments and a control treatment. How does an experimenter select an optimal/efficient design in this situation? There are relatively few results about this question. In our study we shall designate the class of all such designs based on t

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test treatments, a control treatment and n experimental subjects each used in p periods by $\Omega_{t+1,n,p}$. Pigeon and Raghavarao (1987) proposed a class of designs (control balanced residual effects design) for the purpose of comparing several test treatments to a control treatment. They studied the structure in detail, but they did not consider the optimality or efficiency of the suggested designs. Majumdar (1988) obtained some A-optimal and MV-optimal crossover designs when $t \leq p$. Later, Ting (2002) obtained additional results for the same situation. When $p = 2$, Hedayat and Zhao (1990) obtained the corresponding A-optimal and MV-optimal designs. When $p \leq t+1$, Hedayat and Yang (2005) characterized a class of designs which are A-optimal for comparing several treatments with a control in a subclass $\Lambda_{t+1,n,p}$, where the design satisfies two restrictions: (i) no treatment is allowed to follow itself and (ii) the control treatment is uniform in periods. From Lemma 3 of Hedayat and Yang (2005), an efficient design tends to have each treatment appearing the same times in each period (different treatments may have different appearances). We may expect the first one is the major restriction.

A natural question for us, then, is: if the restrictions are removed, whether the design, which is optimal/efficient in the subclass $\Lambda_{t+1,n,p}$, is still optimal/efficient? Hedayat and Yang (2004b) considered this question in a larger class $\Omega^1_{t+1,n,p}$, in which the first restriction was removed. When $p \geq 4$ and $(p-3)(p-2)+2 \leq t \leq (p-2)(p-1)+1$, they provided a way to evaluate the A-efficiency of a design and found that the optimal design in $\Lambda_{t+1,n,p}$ is no longer optimal, but it is still efficient. Notice that $\Lambda_{t+1,n,p} \subset \Omega^1_{t+1,n,p} \subset \Omega_{t+1,n,p}$.

In this paper we focus on the case $p = 3$. We investigate the A-efficiency of a crossover design $d \in \Omega^1_{t+1,n,3}$, in which the control treatment is uniform in all periods. We also give a characterization for A-optimal/efficienct designs in $\Omega^1_{t+1,n,3}$, which can guide us to construct a more efficient design than any of the designs in $\Lambda_{t+1,n,3}$. We organize this paper as follows: Section 2 introduces the model and the notations. Section 3 contains preliminary lemmas. The main result is presented in Section 4. Examples and discussion will be given in Section 5. Most of the proofs are postponed to the appendix.

2 Model of Response

The model we consider here is the traditional homoscedastic, additive, and fixed effects model introduced by Hedayat and Afsarinejad (1975), namely

$$Y_{dks} = \mu + \alpha_k + \beta_s + \tau_{d(k,s)} + \rho_{d(k-1,s)} + e_{ks}, \quad k = 1, \ldots, p; \; s = 1, \ldots, n \tag{2.1}$$

where Y_{dks} denotes the response from subject s in period k to which treatment $d(k,s)$ was assigned. Under Model (2.1), μ is the general mean, α_k is the effect due to period k, β_s is the effect due to subject s, $\tau_{d(k,s)}$ is the direct treatment effect, $\rho_{d(k-1,s)}$ is the carryover or residual effect of treatment $d(k-1,s)$ on the response observed on subject s in period

k (by convention $\rho_{d(0,s)} = 0$), and the e_{ks}'s are independently normally distributed error term with mean 0 and variance σ^2.

Hereafter we shall designate the t test treatments by 1, 2, ..., t and the control treatment by 0. Throughout this paper, for each design d, we adopt the notation n_{dis}, $\widetilde{n}_{dis}$, l_{dik}, m_{dij}, r_{di}, $\widetilde{r}_{di}$, and $\widehat{r}_{d0}$ to denote the number of times that treatment i is assigned to subject s, the number of times this happens in the first two periods associated with s, the number of times treatment i is assigned to period k, the number of times treatment i is immediately preceded by treatment j, the total replications of treatment i in its n subjects, the total replications of treatment i limited to the first two periods of the subjects, and total replications of control treatment 0 limited to the last two periods respectively. Let $z_d = \sum_{s=1}^{n}\sum_{i=1}^{t}(n_{dis}-1)^+$ and $z_0 = \sum_{s=1}^{n}(n_{d0s}-1)^+$. Here, m^+ is m when $m > 0$ and 0 when $m \leq 0$.

In the present context of control-treatment comparisons, A-optimality has an appealing interpretation, because the A-optimal design minimizes $\sum_{i=1}^{t} Var(\hat{\tau}_i - \hat{\tau}_0)$ or equivalently trM_d^{-1}. Here $\hat{\tau}_i - \hat{\tau}_0 (1 \leq i \leq t)$ is BLUE of $\tau_i - \tau_0$ and M_d is the information matrix of $\hat{\tau}_i - \hat{\tau}_0 (1 \leq i \leq t)$. For any $d \in \Omega^1_{t+1,n,3}$, define

$$\theta(d) = \frac{t-1}{x_d} + \frac{1}{y_d}, \tag{2.2}$$

where

$$\begin{aligned} x_d &= \frac{t(3n - r_{d0} - \frac{1}{3}\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2) - (r_{d0} - \frac{1}{3}\sum_{s=1}^{n} n_{d0s}^2)}{t(t-1)} \\ &\quad - \frac{3t\left(\sum_{i=1}^{t}(\frac{1}{3}\sum_{s=1}^{n} n_{dis}\widetilde{n}_{dis} - m_{dii}) - \frac{1}{t}(\frac{1}{3}\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - m_{d00})\right)^2}{(t-1)[2n(2t-1) - (2t+1)\widetilde{r}_{d0} + \sum_{s=1}^{n}\widetilde{n}_{d0s}^2]} \qquad (2.3) \\ y_d &= \frac{1}{t}(r_{d0} - \frac{1}{3}\sum_{s=1}^{n} n_{d0s}^2) - \frac{6n(\frac{1}{3}\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - m_{d00})^2}{t[6n\widetilde{r}_{d0} - \widetilde{r}_{d0}^2 - 2n\sum_{s=1}^{n}\widetilde{n}_{d0s}^2]}. \qquad (2.4) \end{aligned}$$

Note that $\widetilde{r}_{d0} = \frac{2}{3} r_{d0}$, then by Lemma 4 of Hedayat and Yang (2005), $trM_d^{-1} \geq \theta(d)$.

For a general design d, we cannot write down an expression for trM_d^{-1} because of its complicated structure. But $\theta(d)$ provides an achievable lower bound for trM_d^{-1} as a function of the variables r_{d0}, $\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2$, $\sum_{s=1}^{n} n_{d0s}^2$, $\sum_{i=1}^{t}\sum_{s=1}^{n} n_{dis}\widetilde{n}_{dis}$, $\sum_{i=1}^{t} m_{dii}$, $\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s}$, m_{d00}, $\widetilde{r}_{d0}$, and $\widetilde{n}_{d0s}^2$.

Let $A(t,n) = \min_{d\in\Omega^1_{t+1,n,3}} \theta(d)$. For $d \in \Omega^1_{t+1,n,3}$, $trM_d^{-1} \geq \theta(d) \geq A(t,n)$ and d is A-optimal in $\Omega^1_{t+1,n,3}$ when each inequality is an equality. If we can find the value of $A(t,n)$, then we can use $A(t,n)$ as a criteria to evaluate the efficiency of a design d by defining the efficiency ratio as $\frac{A(t,n)}{trM_d^{-1}}$. We may directly use a computer to search for the minimum value of $\theta(d)$ for given t and n but there are two difficulties: (i) the number of possible combinations of the above variables is extremely large, and the computer may not be able to handle it; (ii) the variables are related to each other, even though we find the values that minimize $\theta(d)$, these values may not be reasonable for constructing a design. Therefore, it is necessary to characterize optimal/efficient designs to simplify the computation and obtain an achievable value of $A(t,n)$.

3 Preliminary Lemmas

We apply the same strategy of Hedayat and Yang (2004b), i.e., a cutoff point $\frac{15t^3}{8(2t-1)n}$ is defined (the cutoff point is greater than $A(t,n)$, Lemma 1) and only those designs d whose $\theta(d)$ is less than $\frac{15t^3}{8(2t-1)n}$ are considered. As in Hedayat and Yang (2004b), the lemmas in this section help us characterize the positions of the test treatments and the control treatment for efficient designs by answering the following two questions: (i) If r_{d0} and z_d are fixed, what are $\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2$ and $\sum_{i=1}^{t}(\frac{1}{3}\sum_{s=1}^{n} n_{dis}\widetilde{n}_{dis} - m_{dii})$ in terms of r_{d0} and z_d so that x_d is maximized? and (ii) What are the relationships between related variables $\sum_{s=1}^{n} n_{d0s}^2$, $\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s}$, $\sum_{s=1}^{n} \widetilde{n}_{d0s}^2$, and m_{d00} for efficient designs?

The following lemma shows that if we choose $\frac{15t^3}{8(2t-1)n}$ as the cutoff point, the subclass of designs in which $\theta(d)$ is not larger than $\frac{15t^3}{8(2t-1)n}$ is not empty. Then the lower bound of $\theta(d)$ in this subclass is the same as $A(t,n)$.

Lemma 1. *For $p=3$ and $3 \le t \le 20$,*

$$A(t,n) < \frac{15t^3}{8(2t-1)n}.$$

Proof. See the appendix. □

The following two lemmas show that there are some restrictions for z_d and $\frac{1}{3}\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - m_{d00}$ for those designs whose $\theta(d)$ is not larger than the cutoff point.

Lemma 2. *For a design $d \in \Omega^1_{t+1,n,3}$, $3 \le t \le 20$, if $z_d \ge n - r_{d0}/3 - (n - 2r_{d0}/3)/t$, then*

$$\theta(d) > \frac{15t^3}{8(2t-1)n}.$$

Proof. See the appendix. □

Lemma 3. *For a design $d \in \Omega^1_{t+1,n,3}$, $3 \le t \le 20$, if $z_d < n - r_{d0}/3 - (n - 2r_{d0}/3)/t$ and*

$$\frac{1}{3}\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - m_{d00} > \frac{t}{3}(2n - 2z_d - \widetilde{r}_{d0}),$$

then

$$\theta(d) > \frac{15t^3}{8(2t-1)n}.$$

Proof. See the appendix. □

For those designs whose $\theta(d)$ is not larger than the cutoff point, Lemmas 2 and 3 can help us to find the values of $\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2$ and $\sum_{i=1}^{t}(\frac{1}{3}\sum_{s=1}^{n} n_{dis}\widetilde{n}_{dis} - m_{dii})$ such that x_d is maximized for fixed r_{d0} and z_d. In fact, since $\theta(d) \le \frac{15t^3}{8(2t-1)n}$, by Lemma 2, we have

$$z_d < n - r_{d0}/3 - (n - 2r_{d0}/3)/t.$$

Applying the preceding inequality and the fact $\theta(d) \le \frac{15t^3}{8(2t-1)n}$, by Lemma 3, we have

$$\frac{1}{3}\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - m_{d00} \le \frac{t}{3}(2n - 2z_d - \widetilde{r}_{d0}). \tag{3.1}$$

By the definition of z_d, we can verify that

$$\sum_{i=1}^{t}(\frac{1}{3}\sum_{s=1}^{n} n_{dis}\widetilde{n}_{dis} - m_{dii}) \ge \frac{1}{3}(2n - \widetilde{r}_{d0} - 2z_d).$$

Thus, we have

$$\begin{aligned}\sum_{i=1}^{t}\left(\frac{1}{3}\sum_{s=1}^{n} n_{dis}\widetilde{n}_{dis} - m_{dii}\right) - \frac{1}{t}\left(\frac{1}{3}\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - m_{d00}\right)& \\ \ge \frac{1}{3}(2n - \widetilde{r}_{d0} - 2z_d) - \frac{1}{t}\left(\frac{1}{3}\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - m_{d00}\right) \ge 0.&\end{aligned} \tag{3.2}$$

On the other hand, we can verify that

$$3n - r_{d0} - \frac{1}{3}\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2 \le 2n - 2r_{d0}/3 - 2z_d/3. \tag{3.3}$$

From (3.2) and (3.3), by the definition of x_d in (2.3), we can see that both $\sum_{i=1}^{t}(\frac{1}{3}\sum_{s=1}^{n} n_{dis}\widetilde{n}_{dis} - m_{dii})$ and $\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2$ should be minimized in order to maximize x_d for given z_d and the positions of the control treatment.

By some routine algebra, we obtain Lemma 4 below, which gives a new lower bound of $\theta(d)$ for those designs whose $\theta(d)$ is not larger than the cutoff point. However before we state the lemma, we introduce the following expressions to simplify our notation.

$$\begin{aligned}
\Delta_1 &= t(6n-2r_{d0}) - 2tz_d - (3r_{d0} - \sum_{s=1}^{n} n_{d0s}^2) \\
&\quad - \frac{[2t(n-z_d) - t\widetilde{r}_{d0} - (\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})]^2}{n(4t-2) - (2t+1)\widetilde{r}_{d0} + \sum_{s=1}^{n} \widetilde{n}_{d0s}^2}; \qquad (3.4)\\
\Delta_2 &= (3r_{d0} - \sum_{s=1}^{n} n_{d0s}^2) - \frac{2n(\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})^2}{6n\widetilde{r}_{d0} - \widetilde{r}_{d0}^2 - 2n\sum_{s=1}^{n} \widetilde{n}_{d0s}^2}; \qquad (3.5)\\
S_1 &= \frac{2t(n-z_d) - t\widetilde{r}_{d0} - (\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})}{n(4t-2) - (2t+1)\widetilde{r}_{d0} + \sum_{s=1}^{n} \widetilde{n}_{d0s}^2}; \qquad (3.6)\\
S_2 &= \frac{2n(\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})}{6n\widetilde{r}_{d0} - \widetilde{r}_{d0}^2 - 2n\sum_{s=1}^{n} \widetilde{n}_{d0s}^2}. \qquad (3.7)
\end{aligned}$$

Lemma 4. *For a design $d \in \Omega^1_{t+1,n,3}$, $3 \le t \le 20$, if $\theta(d) \le \frac{15t^3}{8(2t-1)n}$, then*

$$\theta(d) \ge \frac{3t(t-1)^2}{\Delta_1} + \frac{3t}{\Delta_2}. \qquad (3.8)$$

Equality in (3.8) holds when the following conditions are satisfied: (i) For each subject, each test treatment appears at most once in the first two periods and (ii) There are z_d subjects in which each test treatment is followed by itself in the last two periods.

Although the lower bound for $\theta(d)$ in Lemma 4 does not depend on $\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2$, $\sum_{i=1}^{t}\sum_{s=1}^{n} n_{dis}\widetilde{n}_{dis}$, $\sum_{i=1}^{t} m_{dii}$, it still depends on the variables z_d, r_{d0}, $\sum_{s=1}^{n} n_{d0s}^2$, $\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s}$, m_{d00}, $\widetilde{r}_{d0}$, and $\widetilde{n}_{d0s}^2$. Lemma 5, which describes the relationship among Δ_1, Δ_2, S_1, and S_2, can help us further simplify the lower bound in the main theorem.

Lemma 5. *For a design $d \in \Omega^1_{t+1,n,3}$, $3 \le t \le 20$, if $\theta(d) \le \frac{15t^3}{8(2t-1)n}$, then*

$$\frac{1+S_2}{1+S_1} \ge \frac{(t-1)\Delta_2}{\Delta_1}. \qquad (3.9)$$

Proof. See the appendix. □

4 Main Results

In this section, we study the lower bound of trM_d^{-1} for any design $d \in \Omega^1_{t+1,n,3}$, i.e, the value of $A(t,n) = \min_{d\in\Omega^1_{t+1,n,3}} \theta(d)$. Although it is difficult to find a design that achieves this lower bound, we can use the lower bound to evaluate the efficiency of a design in $\Omega^1_{t+1,n,3}$. Meanwhile, we can characterize efficient designs and use these characterization to help us construct an efficient design.

Before we state our main theorem, we will introduce some new notations. For any design d, let Γ_d be the set of subjects whose last treatment is the control treatment and $\Psi_d = \sum_{s\in\Gamma_d} \widetilde{n}_{d0s}$. Then for any design $d \in \Omega^1_{t+1,n,3}$, there are $\frac{r_{d0}}{3}$ subjects in Γ_d. Thus, we have

$$\sum_{s=1}^{n} n^2_{d0s} = \sum_{s=1}^{n} \widetilde{n}^2_{d0s} + 2\Psi_d + \frac{r_{d0}}{3} \tag{4.1}$$

and

$$\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} = \sum_{s=1}^{n} \widetilde{n}^2_{d0s} + \Psi_d. \tag{4.2}$$

Now, we are ready to present our main theorems.

Theorem 1. *For a design $d \in \Omega^1_{t+1,n,3}$, $3 \le t \le 20$, we have*

$$trM_d^{-1} \ge \theta(d) \ge A(t,n).$$

Here,

$$\begin{aligned} A(t,n) &= \min_{r_{d0},z_d,\Psi_d,m_{d00}} \left(\frac{3t(t-1)^2}{\overline{\Delta}_1} + \frac{3t}{\overline{\Delta}_2} \right), \qquad (4.3) \\ \overline{\Delta}_1 &= 2t(3n-r_{d0}) - 2tz_d - 3(r_{d0} - \frac{1}{3}\min\sum_{s=1}^{n} n^2_{d0s}) \\ &\quad - \frac{[2t(n-z_d) - t\widetilde{r}_{d0} - (\min\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})]^2}{2n(2t-1) - (2t+1)\widetilde{r}_{d0} + \min\sum_{s=1}^{n}\widetilde{n}^2_{d0s}}, \end{aligned}$$

and

$$\overline{\Delta}_2 = 3(r_{d0} - \frac{1}{3}\min\sum_{s=1}^{n} n^2_{d0s}) - \frac{2n(\min\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})^2}{6n\widetilde{r}_{d0} - \widetilde{r}^2_{d0} - 2n\min\sum_{s=1}^{n}\widetilde{n}^2_{d0s}}.$$

The sufficient conditions on d^* such that $\theta(d^*) = A(t,n)$ are
(i) r_{d^*0}, m_{d^*00}, Ψ_{d^*}, and z_{d^*} are the integers which minimize $\frac{3t(t-1)^2}{\overline{\Delta}_1} + \frac{3t}{\overline{\Delta}_2}$;
(ii) For each subject, each test treatment appears at most once in the first two periods;
(iii) There are z_{d^*} subjects in which each test treatment appears in last two periods;
(iv) For the given Ψ_{d^*}, $\sum_{s=1}^{n} n^2_{d^*0s}$, $\sum_{s=1}^{n} n_{d^*0s}\widetilde{n}_{d^*0s}$, and $\sum_{s=1}^{n}\widetilde{n}^2_{d^*0s}$ are minimized.
If $trM^{-1}_{d^*} = A(t,n)$, then d^* is an A-optimal design in $\Omega^1_{t+1,n,3}$; if M_{d^*} is also completely symmetric, then d^* is also an MV-optimal design in $\Omega^1_{t+1,n,3}$.

In addition to the four conditions stated above, the following conditions are sufficient for d^* to be both A-optimal and MV-optimal in $\Omega^1_{t+1,n,3}$,
(v) $l_{d^*ik} = r_{d^*i}/3, i = 0,\ldots,t$;
(vi) $T'_{d^*}pr^{\perp}(U)T_{d^*}$, $T'_{d^*}pr^{\perp}(U)F_{d^*}$, and $F'_{d^*}pr^{\perp}(U)F_{d^*}$ are invariant after all possible permutations on all treatments leaving the control treatment unchanged, where $pr^{\perp}(X) = I - X(X'X)^{-}X'$.

Proof. It is enough to consider designs in which $\theta(d) < \frac{15t^3}{8(2t-1)n}$ by Lemma 1.

Given $\sum_{s=1}^n \widetilde{n}_{d0s}^2$, r_{d0}, and Ψ_d, the lower bound of $\theta(d)$ in Lemma 4 can be rewritten as a function of r_{d0}, z_d, $\sum_{s=1}^n \widetilde{n}_{d0s}^2$, Ψ_d, and m_{d00}, say

$$H(r_{d0}, z_d, \sum_{s=1}^{n} \widetilde{n}_{d0s}^2, \Psi_d, m_{d00}) = \frac{3t(t-1)^2}{\Delta_1} + \frac{3t}{\Delta_2},$$

because of (4.1) and (4.2). By a simple calculation, we obtain

$$\begin{aligned} \frac{\partial H(r_{d0}, z_d, \sum_{s=1}^n \widetilde{n}_{d0s}^2, \Psi_d, m_{d00})}{\partial \sum_{s=1}^n \widetilde{n}_{d0s}^2} &= 3t(\frac{(1+S_2)^2}{\Delta_2^2} - \frac{(t-1)^2(1+S_1)^2}{\Delta_1^2}) \\ &> 0. \end{aligned}$$

The preceding inequality is due to Lemma 5 since $\theta(d) < \frac{15t^3}{8(2t-1)n}$. Thus, for fixed r_{d0}, z_d, Ψ_d, and m_{d00}, $\frac{3t(t-1)^2}{\Delta_1} + \frac{3t}{\Delta_2}$ will be minimized when $\sum_{s=1}^n \widetilde{n}_{d0s}^2$ is minimized, which also implies that $\sum_{s=1}^n n_{d0s}^2$ and $\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s}$ are minimized. Thus we have

$$\theta(d) \geq \frac{3t(t-1)^2}{\overline{\Delta}_1} + \frac{3t}{\overline{\Delta}_2}. \tag{4.4}$$

Consequently (4.3) and Conditions (i) to (iv) follow.

By Lemma 4 of Hedayat and Yang (2005), Conditions (ii), (v), and (vi) are the sufficient conditions for $trM_{d^*}^{-1} = \theta(d^*)$. Thus, Conditions (v) and (vi) follow for A-optimal and MV-optimal designs d^*. □

5 Examples and Discussion

Theorem 1 gives a lower bound for trM_d^{-1} for any $d \in \Omega_{t+1,n,3}^1$. Although the lower bound is still a function of r_{d0}, z_d, Ψ_d, and m_{d00}, they are not related to each other except on the boundary. Furthermore, a computer can handle all possible combinations of these variables. While we could construct A-optimal and MV-optimal in the $\Omega_{t+1,n,3}^1$ based on Theorem 1 for some parameters (Example 2), the most important application of this lower bound is to evaluate the efficiency of a design in the almost entire class. The conditions in Theorem 1 can be used to construct an efficient design. The following examples illustrate the use of Theorem 1.

Example 1. Consider the construction of a three period crossover design with three test treatments and one control. Fourteen subjects will be tested in this experiment. Our main interest is to compare the three test treatments with the control.

By Theorem 1 and straightforward computations we get $A(3, 14) = 0.7067$, the lower bound of trM_d^{-1} for any design $d \in \Omega_{4,14,3}^1$. The values of the corresponding parameters r_{d^*0}, Ψ_{d^*}, m_{d^*00}, and z_{d^*} are 15, 1, 1, and 1, respectively. With computer's help, a design, say d_1, is constructed based on the treatments sequences in the optimal design in $\Lambda_{t+1,n,p}$ (Example 1, Page 930, Hedayat and Yang, 2005) and a treatment sequence in which the control treatment appears in period 2 and 3. d_1 approximately satisfies the conditions in Theorem 1 with $r_{d_1} = 15$, $\Psi_{d_1} = 1$, $m_{d_1 00} = 1$, and $z_{d_1} = 0$. The corresponding value of $\theta_{d_1} = 0.7081$, which is very close to the minimum value 0.7067. For this design, we can check that $trM_{d_1}^{-1}$ is 0.7179, which is at least 98.44% efficient compared to the lower bound 0.7067. On the other hand, $trM_{d_1}^{-1}$ is smaller than the lower bound of trM_d^{-1} for any design $d \in \Lambda_{4,14,3}$, which is 0.7499. So design d_1 is at least 4.5% more efficient than any design in $\Lambda_{4,14,3}$ in terms of A-efficiency.

$$
d_1 : \begin{array}{cccccccccccccc}
0 & 2 & 3 & 1 & 0 & 3 & 0 & 1 & 2 & 0 & 1 & 2 & 0 & 3 \\
1 & 1 & 2 & 0 & 2 & 0 & 3 & 2 & 3 & 1 & 0 & 0 & 3 & 0 \\
2 & 0 & 0 & 3 & 3 & 1 & 1 & 0 & 0 & 3 & 2 & 0 & 1 & 2
\end{array}
$$

Example 2. With the same set up as Example 1, but assume we have forty two subjects.

By straightforward computations, we find $A(3,42) = 0.23557$. The values of the corresponding parameters r_{d^*0}, Ψ_{d^*}, m_{d^*00}, and z_{d^*} are 45, 3, 3, and 3, respectively. The following design satisfies the all conditions in Theorem 1, thus it is A-optimal and MV-optimal in $\Omega^1_{4,42,3}$.

$$
d_2 : \begin{array}{l}
0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;1\;1\;1\;1\;2\;2\;2\;2\;3\;3\;3\;3\;1\;1\;1\;1\;2\;2\;2\;2\;3\;3\;3\;3\;1\;2\;3 \\
1\;2\;3\;1\;1\;1\;1\;2\;2\;2\;2\;3\;3\;3\;3\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;2\;2\;3\;3\;1\;1\;3\;3\;1\;1\;2\;2\;0\;0\;0 \\
1\;2\;3\;2\;2\;3\;3\;1\;1\;3\;3\;2\;2\;1\;1\;2\;2\;3\;3\;1\;1\;3\;3\;1\;1\;2\;2\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0
\end{array}
$$

Example 3. We consider Example 9 in Hedayat and Yang (2005).

$$
d_3 : \begin{array}{l}
0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;1\;2\;3\;4\;5\;6\;7\;4\;5\;6\;7\;1\;2\;3\;4\;5\;6\;7\;1\;2\;3\;1\;2\;3\;4\;5\;6\;7\;4\;5\;6\;7\;1\;2\;3 \\
3\;4\;5\;6\;7\;1\;2\;1\;2\;3\;4\;5\;6\;7\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;1\;2\;3\;4\;5\;6\;7\;3\;4\;5\;6\;7\;1\;2\;3\;4\;5\;6\;7\;1\;2 \\
4\;5\;6\;7\;1\;2\;3\;4\;5\;6\;7\;1\;2\;3\;3\;4\;5\;6\;7\;1\;2\;3\;4\;5\;6\;7\;1\;2\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;0\;1\;2\;3\;4\;5\;6\;7
\end{array}
$$

The design is simultaneously A-optimal and MV-optimal in $\Lambda_{8,49,3}$. By applying Theorem 1, we can find the lower bound of trM_d^{-1} for any design $d \in \Omega^1_{8,49,3}$ is 0.9694. On the other hand, for design d_3, $trM_{d_3}^{-1} = 0.9712$. So design d_3 is at least 99.81% efficient in the larger class $\Omega^1_{8,49,3}$.

Theorem 1 provides a computable lower bound for designs in $\Omega^1_{t+1,n,3}$. The only difference between $\Omega_{t+1,n,p}$ and $\Omega^1_{t+1,n,p}$ is that in the latter, the control appears equally often in the periods. Since this condition is likely to hold for optimal designs, we expect that in most cases a design that is efficient in $\Omega^1_{t+1,n,p}$ will be efficient in $\Omega_{t+1,n,p}$.

6 Appendix

We only give outlines of the proofs here. Details see Yang and Park (2005).

Proof of Lemma 1. We can construct a design $d_0 \in \Omega^1_{t+1,n,p}$ with the following two properties: (i) $r_{d_0 0} = n$, thus the control treatment appears $n/3$ times in the last period and (ii) every treatment appears at most once in any subject. For such design, we could compute the values of $\sum_{s=1}^n \sum_{i=1}^t n_{d_0 is}$, $\sum_{s=1}^n \sum_{i=1}^t n_{d_0 is}\widetilde{n}_{d_0 is}$, $\sum_{s=1}^n n^2_{d_0 0s}$, $\sum_{s=1}^n n_{d_0 0s}\widetilde{n}_{d_0 0s}$, and $\sum_{s=1}^n \widetilde{n}^2_{d_0 0s}$. Then by equations (2.3) and (2.4), we have $x_d = \frac{2(2t-1)(10nt-8n)}{9t(t-1)(4t-3)}$ and $y_d = \frac{8n}{15t}$. By the definition of $A(t,n)$ and the fact that $(12t-9)(10t-8) < 5/4$, we can verify the conclusion directly. □

Proof of Lemma 2. It can be verified that

$$x_d \leq \frac{1}{3t(t-1)}\left(t[6n - 2r_{d0} - 2(n - r_{d0}/3 - (n - 2r_{d0}/3)/t)] - (3r_{d0} - \sum_{s=1}^n n^2_{d0s})\right)$$

and

$$y_d \leq \frac{1}{3t}\left(3r_{d0} - \sum_{s=1}^n n^2_{d0s}\right).$$

Thus,

$$\theta(d) \geq \frac{3t(t-1)^2}{t[6n - 2r_{d0} - 2(n - r_{d0}/3 - (n - 2r_{d0}/3)/t)] - (3r_{d0} - \sum_{s=1}^n n^2_{d0s})} + \frac{3t}{3r_{d0} - \sum_{s=1}^n n^2_{d0s}} \quad (6.1)$$

Then we could prove the lemma under the following three cases: (i) $r_{d0} > 1.5n$; (ii) $r_{d0} \leq 1.5n$ and $z_0 \geq r_{d0}/3$; and (iii) $r_{d0} \leq 1.5n$ and $z_0 < r_{d0}/3$. Here z_0 is defined as $z_0 = \sum_{s=1}^n (n_{d0s} - 1)^+$. See Yang and Park (2005) for details. □

Proof of Lemma 3. First we could verify that

$$x_d \leq \frac{1}{3t(t-1)}\left(t(6n - 2r_{d0} - 2z_d) - (3r_{d0} - \sum_{s=1}^n n^2_{d0s})\right) \quad (6.2)$$

and

$$y_d \leq \frac{1}{3t}\left(3r_{d0} - \sum_{s=1}^n n^2_{d0s} - \frac{18(\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})^2 n}{24nr_{d0} - 4r^2_{d0}}\right). \quad (6.3)$$

Define a new variable $x = n - r_{d0}/3 - z_d$. Since $0 \leq z_d < n - r_{d0}/3 - (n - 2r_{d0}/3)/t$, we have

$$(n - 2r_{d0}/3)/t \leq x < n - r_{d0}/3. \quad (6.4)$$

By the definition of x, $\widetilde{r}_{d0} = 2r_{d0}/3$, and the condition $\frac{1}{3}\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - m_{d00} > \frac{t}{3}(2n - 2z_d - \widetilde{r}_{d0})$, we have

$$\frac{1}{3}\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - m_{d00} > 2tx/3. \tag{6.5}$$

Utilizing inequalities (6.2), (6.3), (6.4), and (6.5), we could prove our conclusion in three cases: (i) $r_{d0} \geq 1.5n$, (ii) $n \leq r_{d0} < 1.5n$, and (iii) $r_{d0} < n$. See Yang and Park (2005) for details. □

Proof of Lemma 5. Since $\theta(d) \leq \frac{15t^3}{8(2t-1)n}$, by inequality (3.8) in Lemma 4, we have

$$\frac{3t(t-1)^2}{\Delta_1} + \frac{3t}{\Delta_2} \leq \frac{15t^3}{8(2t-1)n},$$

which is equivalent to

$$\frac{(t-1)\Delta_2}{\Delta_1} \leq \frac{5t^2\Delta_2}{8(t-1)(2t-1)n} - \frac{1}{t-1}. \tag{6.6}$$

On the other hand,

$$\Delta_2 \leq 3r_{d0} - \sum_{s=1}^{n} n_{d0s}^2 \leq 2n.$$

Combining the preceding two inequalities, we have

$$\frac{(t-1)\Delta_2}{\Delta_1} \leq \frac{5t^2 - 8t + 4}{4(t-1)(2t-1)}. \tag{6.7}$$

Apply $\theta(d) \leq \frac{15t^3}{8(2t-1)n}$ again, we could show that $r_{d0} < \frac{(7t+4)n}{5t}$. By this fact and $\widetilde{r}_{d0} = 2r_{d0}/3$, we have

$$6n\widetilde{r}_{d0} - \widetilde{r}_{d0}^2 - 2n\sum_{s=1}^{n}\widetilde{n}_{d0s}^2 < 4n\widetilde{r}_{d0} - \widetilde{r}_{d0}^2 < \frac{644t^2 + 256t - 64}{225t^2}n^2, \tag{6.8}$$

and

$$n(4t-2) - (2t+1)\widetilde{r}_{d0} + \sum_{s=1}^{n}\widetilde{n}_{d0s}^2 > n(4t-2) - 2t\widetilde{r}_{d0} > \frac{32t-48}{15}n. \tag{6.9}$$

Inequality (3.1) gives

$$2t(n - z_d) - t\widetilde{r}_{d0} - (\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00}) \geq 0,$$

because $\theta(d) \leq \frac{15t^3}{8(2t-1)n}$. By the preceding inequality, $z_d \geq 0$, inequality (6.9), and the definition of S_1 in (3.6), we have

$$\begin{aligned} S_1 &< \frac{2tn - t\widetilde{r}_{d0} - (\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})}{n(4t-2) - 2t\widetilde{r}_{d0}} \\ &= \frac{1}{2} + \frac{n - (\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})}{n(4t-2) - 2t\widetilde{r}_{d0}}. \end{aligned}$$

For any design $d \in \Omega^1_{t+1,n,3}$, we could show that $\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s} - 3m_{d00} \geq 0$. Utilizing this fact and inequalities (6.8) and (6.9), we further have

$$S_1 < \frac{1}{2} + \frac{n}{(32t-48)n/15} = \frac{16t-9}{32t-48} \tag{6.10}$$

and

$$S_2 \geq \frac{450t^2(\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})}{(644t^2 + 256t - 64)n} \geq 0. \tag{6.11}$$

Thus,

$$\frac{1+S_2}{1+S_1} \geq \frac{(1+S_2)(32t-48)}{48t-57} \geq \frac{32t-48}{48t-57}. \tag{6.12}$$

When $6 \leq t \leq 20$

$$\frac{32t-48}{48t-57} \geq \frac{5t^2-8t+4}{4(t-1)(2t-1)}.$$

Applying inequalities (6.7) and (6.12), inequality (3.9) holds when $6 \leq t \leq 20$.

Next, we will show inequality (3.9) is true when $t = 3$, 4, and 5. We consider two cases: (i) $4n/3 \leq r_{d0} < \frac{(7t+4)n}{5t}$ and (ii) $r_{d0} < 4n/3$.

Case (i): Let $x = S_1 - \frac{1}{2}$, then

$$x = \frac{n - 2tz_d + \widetilde{r}_{d0}/2 - \sum_{s=1}^n \widetilde{n}^2_{d0s}/2 - (\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})}{n(4t-2) - (2t+1)\widetilde{r}_{d0} + \sum_{s=1}^n \widetilde{n}^2_{d0s}}.$$

From the preceding equation, we have

$$\begin{aligned} 2tz_d = -n(4tx - 2x - 1) &+ (2tx + x + 1/2)\widetilde{r}_{d0} \\ &- (x+1/2)\sum_{s=1}^n \widetilde{n}^2_{d0s} - (\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s} - 3m_{d00}). \end{aligned} \tag{6.13}$$

By the definition of Δ_1,

$$\begin{aligned} \Delta_1 &= tn(5-2x) - tr_{d0}(5-2x)/3 - (3r_{d0} - \sum_{s=1}^n n^2_{d0s}) \\ &\quad + (x+1/2)(\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s} - 3m_{d00}) + 2tz_d(x - 1/2). \end{aligned}$$

By substituting $2tz_d$ in Δ_1 with expression (6.13),

$$\Delta_1 = n(5t - (4t-2)x^2 - 1/2) - r_{d0}(5t + 1/2 - 4tx^2 - 2x^2)/3 + (1/4 - x^2)\sum_{s=1}^{n} \widetilde{n}_{d0s}^2 + \sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00} - (3r_{d0} - \sum_{s=1}^{n} n_{d0s}^2).$$

Using $\sum_{s=1}^{n} \widetilde{n}_{d0s}^2 \le 2\widetilde{r}_{d0} = 4r_{d0}/3$, we could show that

$$\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00} > 2n + \frac{8(t-1)^2(2t-1)}{5t^2-8t+4}n - (5t-1/2)(5n/9). \tag{6.14}$$

By inequalities (6.12), (6.11), and (6.14),

$$\frac{1+S_2}{1+S_1} \ge \frac{(1+S_2)(32t-48)}{48t-57} > \frac{5t^2-8t+4}{4(t-1)(2t-1)}.$$

By inequality (6.7), our conclusion is established.

Case (ii): Since $r_{d0} < 4n/3$, we have

$$6n\widetilde{r}_{d0} - \widetilde{r}_{d0}^2 - 2n\sum_{s=1}^{n} \widetilde{n}_{d0s}^2 < 4n\widetilde{r}_{d0} - \widetilde{r}_{d0}^2 < \frac{224}{81}n^2,$$

and

$$n(4t-2) - (2t+1)\widetilde{r}_{d0} + \sum_{s=1}^{n} \widetilde{n}_{d0s}^2 > n(4t-2) - 2t\widetilde{r}_{d0} > \frac{20t-18}{9}n.$$

By arguments similar to those used to inequalities (6.10) and (6.11), we have

$$S_1 < \frac{1}{2} + \frac{n}{(20t-18)n/9} = \frac{5t}{10t-9}$$

and

$$S_2 \ge \frac{81(\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})}{112n} \ge 0.$$

Thus, we have

$$\frac{1+S_2}{1+S_1} \ge \left(1 + \frac{81(\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})}{112n}\right)\frac{10t-9}{15t-9} \ge \frac{10t-9}{15t-9}. \tag{6.15}$$

Applying the preceding inequality, we have

$$\frac{1+S_2}{1+S_1} \ge \frac{5t^2-8t+4}{4(t-1)(2t-1)}$$

if

$$\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00} \ge \frac{112n}{81}\left(\frac{(5t^2-8t+4)(15t-9)}{4(t-1)(2t-1)(10t-9)} - 1\right).$$

Thus by inequalities (6.7) and (6.12), the conclusion (3.9) holds. Now consider the case, when

$$\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00} < \frac{112n}{81}\left(\frac{(5t^2-8t+4)(15t-9)}{4(t-1)(2t-1)(10t-9)} - 1\right), \tag{6.16}$$

Inequality (3.9) still holds. We will consider two situations: $z_0 \geq r_{d0}/3$ and $z_0 < r_{d0}/3$.

When $z_0 \geq r_{d0}/3$, we have $\sum_{s=1}^{n} n_{d0s}^2 \geq r_{d0} + 2z_0 \geq \frac{5r_{d0}}{3}$. So,

$$\Delta_2 \leq 3r_{d0} - \sum_{s=1}^{n} n_{d0s}^2 \leq 4r_{d0}/3 < 16n/9.$$

By Inequality (6.6), we have

$$\frac{(t-1)\Delta_2}{\Delta_1} \leq \frac{10t^2}{9(t-1)(2t-1)} - \frac{1}{t-1}.$$

By the preceding inequality and Inequality (6.15), inequality (3.9) holds since

$$\frac{10t-9}{15t-9} > \frac{10t^2}{9(t-1)(2t-1)} - \frac{1}{t-1}.$$

When $z_0 < r_{d0}/3$, we have $2z_0 \geq 2r_{d0}/3 - (\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})$. So,

$$\sum_{s=1}^{n} n_{d0s}^2 \geq r_{d0} + 2z_0 \geq \frac{5r_{d0}}{3} - (\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00}).$$

Thus,

$$\Delta_2 \leq 3r_{d0} - \sum_{s=1}^{n} n_{d0s}^2 \leq 4r_{d0}/3 + \sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00} \leq 16n/9 + \sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00}.$$

By inequality (6.6), we have

$$\frac{(t-1)\Delta_2}{\Delta_1} \leq \frac{5t^2(16n/9 + \sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})}{8(t-1)(2t-1)n} - \frac{1}{t-1}.$$

By the preceding inequality and inequality (6.15), our conclusion holds if

$$\left(1 + \frac{81(\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})}{112n}\right)\frac{10t-9}{15t-9} \geq \frac{5t^2(16n/9 + \sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00})}{8(t-1)(2t-1)n} - \frac{1}{t-1}.$$

After simplifying, the preceding inequality is equivalent to

$$\frac{(10t^2-18t+9)(5t-3)}{3(t-1)(2t-1)(10t-9)} + \left(\frac{5t^2(15t-9)}{8(t-1)(2t-1)(10t-9)} - \frac{81}{112}\right)\frac{\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00}}{n} \leq 1.$$

By inequality (6.16) and $\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - 3m_{d00} \geq 0$, the preceding inequality is satisfied. □

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