Efficient Crossover Designs For Comparing Test Treatments With a Control Treatment

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Abstract

Within a large family of crossover designs this paper characterizes the mathematical structures of A-optimal and A-efficient crossover designs for the purpose of statistical comparison between t experimental treatments with a control (standard) treatment. It further guides the user how to go about the construction of these designs and if needed doing the last minute modifications. To demonstrate the ideas some very interesting optimal and efficient small designs are constructed. The mathematical and statistical tools developed here could be very useful in other areas of design of experiments. Many interesting and not yet solved design problems for further research are implicitly stated throughout the paper.

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

1 Introduction

Crossover designs, where experimental subjects are used in two or more (p) periods for the purpose of evaluating and studying two or more (t) treatments have proven to be widely effective in a variety of fields, especially in phase I and phase II pharmaceutical clinical trials. In comparing treatments there are generally two situations which experimenters are interested in. One is that all treatments comparisons are equivalently important and the other is comparing new treatments with an established standard or a control treatment. Many published articles on crossover designs have addressed the statistical/mathematical

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issues related to the first situation. The reader is referred to the selected key articles in the bibliography. As for the second situation the list of unsolved problems is very vast and less than a dozen of articles have dealt with the related mission. Some selected recent references include Pigeon and D. Raghavarao [1], Jacroux [2], Jaggi, Gupta, and Parsad [3], Mandal, Shah, and Sinha [4], Solorzano and Spurrier [5], Ting [6], and Hedayat and Yang [7]. In this paper, we will concentrate on the second situation.

Let T be a set of $t+1$ elements denoted by 0, 1, ..., t. A p-sequence on T is an ordered column vector of size p with entries from T. By a crossover design with parameters $t+1$, n, and p we mean any collection of n p-sequences on T with the condition that each element of T is used in at least one p-sequence. We can compactly represent any such design by a $p \times n$ array in which columns are the p-sequences. For example, if $t = 3$, $p = 3$, and $n = 8$ the following is a crossover design with parameters 4, 8, and 3.

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

The class of all such crossover designs will be denoted by $\Omega(t+1, n, p)$. A crossover design looks like a proper block design except that the elements in each block are now ordered and they are no longer subsets of T.

In practice crossover designs can be used for many experimentations. For example, if we want to test and compare t drugs each being tested in a patient for say 3 months, then to minimize patient to patient variability and if under certain medical conditions each patient can participate in more than one period then we can test and collect multiple data on each patient by allowing him/her to go through a sequence of treatment testing. Thus for example, if we want to compare 3 doses of a newly developed drug with a placebo utilizing 100 patients, then if each patient is available for 9-month medical test, then each patient can be given a 3-sequence treatments. Which design in $\Omega(3+1, 100, 3)$ should be recommended to the experimenters? From a statistical point of view this depends on the model of observations and the statistical criteria we hope to achieve. Next section provides a model and the criteria which we shall use for our design selection.

2 Model for the Observations and the Optimality Criteria

The model we consider here is the most frequently used model in crossover design literature. It is called the traditional homoscedastic, additive, and fixed effects model formally introduced by Hedayat and Afsarinejad [8], namely

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

where Y_{dks} denotes the response from subject s in period k to which treatment $d(k, s)$ was assigned. In this model 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 errors 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 $p-1$ 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 sequences, the total replications of treatment i limited to the first $p-1$ periods of the sequences, and total replications of control treatment 0 limited to the last $p-1$ periods respectively. Let $z_d = \sum_{s=1}^{n}\sum_{i=1}^{t}(n_{dis}-1)^+$. Here, m^+ is m when $m > 0$ or 0 when $m \leq 0$.

In matrix notation we can write model (2.1) for the $n \times p$ observations as

$$Y_d = \mu 1 + P\alpha + U\beta + T_d\tau_d + F_d\rho_d + e. \tag{2.2}$$

where $Y_d = (Y_{d11}, Y_{d21}, \ldots, Y_{dpn})'$, $\alpha = (\alpha_1, \ldots, \alpha_p)'$, $\beta = (\beta_1, \ldots, \beta_n)'$, $\tau_d = (\tau_0, \ldots, \tau_t)'$, $\rho_d = (\rho_0, \ldots, \rho_t)'$, $e = (e_{11}, e_{21}, \ldots, e_{pn})'$, $P = 1_n \otimes I_p$, $U = I_n \otimes 1_p$, $T_d = (T'_{d1}, \ldots, T'_{dn})'$, and $F_d = (F'_{d1}, \ldots, F'_{dn})'$. Here T_{ds} stands for the $p \times (t+1)$ period-treatment incidence matrix for subject s under design d and $F_{ds} = LT_{ds}$ with the $p \times p$ matrix L defined as

$$\begin{pmatrix} 0_{1\times(p-1)} & 0 \\ I_{(p-1)\times(p-1)} & 0_{(p-1)\times 1} \end{pmatrix}.$$

The information matrix for direct effects, C_d, can now be expressed as

$$C_d = T'_d pr^{\perp}([P|U|F_d])T_d,$$

where, $pr^{\perp}(X) = I - X(X'X)^{-}X'$. When the experimenters are interested in the comparisons between t experimental test treatments and an established standard or a control treatment, i.e., $\hat{\tau}_i - \hat{\tau}_0 (1 \leq i \leq t)$, the corresponding information matrix M_d can be obtained from C_d by deleting the first row and the first column of C_d by Lemma 1 of Hedayat and Yang [7].

For comparing test treatments with a control, the most frequently used optimality criterion is A-optimality. An A-optimal design minimizes $\sum_{i=1}^{t} Var_d(\widehat{\tau}_i - \widehat{\tau}_0)$, which is equivalent to minimizing $Tr(M_d^{-1})$. Another optimality criterion, which is associated with A-optimality, is MV-optimality. An MV-optimal design minimizes $Max_{i=1,\ldots,t} Var_d(\widehat{\tau}_i - \widehat{\tau}_0)$. If a design d is A-optimal and its information matrix M_d is completely symmetric, it is also MV-optimal.

3 Optimal and Efficient Crossover Designs

Majumdar [9] considered A-optimal and MV-optimal crossover designs for comparing several test treatments with a control treatment and established that some known strongly balanced crossover designs can be modified to obtain optimal designs for this problem, but this result is limited to the situation where $t = w^2$, $p = m(w^2 + w)$, and $m \geq 2$. The first nontrivial case will be $t = 4$ and $p = 12$. In many cases, the experimenter is interested in designs in which the number of periods are less than or equal to the number of total treatments, i.e. $p \leq t + 1$.

When $p = 2$, Hedayat and Zhao [10] (Theorem 5.1) studied this problem and established that A-optimal and MV-optimal designs can be obtained from some corresponding one-way block designs.

When $p \leq t + 1$, Hedayat and Yang [7] characterized a class of designs which are A-optimal for comparing several treatments with a control in $\Lambda_{t+1,n,p}$, the class of designs d in $\Omega_{t+1,n,p}$ in which no treatment is allowed to follow immediately by itself and the control treatment is uniform in periods. The A-optimality or A-efficiency of their designs in the entire class of designs $\Omega_{t+1,n,p}$ remains open. Thus a natural question which can be posed here is this: How good an A-optimal design in $\Lambda_{t+1,n,p}$ will be if the class of competing designs is expanded from $\Lambda_{t+1,n,p}$ to $\Omega_{t+1,n,p}$? While this is a difficult question to answer we know that there are A-better designs outside of $\Lambda_{t+1,n,p}$. For example, the following design

$$d_2 : \begin{array}{cccccccccccc} 0 & 0 & 0 & 0 & 3 & 1 & 4 & 2 & 4 & 3 & 2 & 1 \\ 2 & 4 & 1 & 3 & 0 & 0 & 0 & 0 & 3 & 1 & 4 & 2 \\ 3 & 1 & 4 & 2 & 0 & 0 & 0 & 0 & 2 & 4 & 1 & 3 \\ 4 & 3 & 2 & 1 & 2 & 4 & 1 & 3 & 0 & 0 & 0 & 0. \end{array}$$

in which there are sequences with control treatment being immediately followed by itself has $Tr(M_{d_2}^{-1})$ of 0.8733. This design which is not a member of $\Lambda_{4+1,12,4}$ is A-better than the A-optimal design in $\Lambda_{4+1,12,4}$ since by Lemma 5 of Hedayat and Yang [7] along with a simple computer search indicates that $Tr(M_d^{-1}) \geq 0.8879$ for any design $d \in \Lambda_{4+1,12,4}$. It is natural to postulate that we may even find a better design than d_2 in the entire class of designs. The design questions are: What is the characterization of an optimal/efficient design in $\Omega_{t+1,n,p}$? For an optimal/efficient design in $\Lambda_{t+1,n,p}$, how efficient it is in $\Omega_{t+1,n,p}$? Do we sacrifice a lot in efficiency if we use the optimal/efficient design in $\Lambda_{t+1,n,p}$?

In this paper we investigate the structure of an A-optimal crossover design over the class of designs d in $\Omega_{t+1,n,p}$ in which the control treatment is uniform in all periods. The collection of such designs is denoted by $\Omega^1_{t+1,n,p}$. For some parameters t and p, we obtain a new lower bound for $Tr(M_d^{-1})$, and give the characterization of efficient designs in $\Omega^1_{t+1,n,p}$. We also construct some interesting efficient designs based on our characterization. Further, we obtain the efficiency of the design proposed by Hedayat and Yang [7] and show that they are highly efficient in $\Omega^1_{t+1,n,p}$ even in $\Omega_{t+1,n,p}$. Note that $\Omega^1_{t+1,n,p}$ is much less restricted than the subclass of designs considered by Hedayat and Yang [7]. It does not have the restriction that no treatment is allowed to follow immediately by itself. Throughout this article, unless otherwise specified, we always assume $p \geq 4$.

4 Main result

To find an A-optimal design, we need to find a design that minimizes $Tr(M_d^{-1})$ over the class of competing designs. One way to achieve this is first to find the $min_{d\in\Omega_{t+1,n,p}} Tr(M_d^{-1})$ and then characterize the design that achieves this minimum value. Although for general design d, it is difficult to write down the expression of $Tr(M_d^{-1})$, we can use Lemma 4 in Hedayat and Yang [7] and provide an achievable lower bound for $Tr(M_d^{-1})$.

Lemma 1. *(Lemma 4 of Hedayat and Yang [7]) For any design d, in which* $0 < \widetilde{r}_{d0} < n(p-1)$*, we have*

$$Tr(M_d^{-1}) \geq \frac{t-1}{x_0} + \frac{1}{y_0},$$

where

$$\begin{aligned} x_0 &= \frac{t(np - r_{d0} - \frac{1}{p}\sum_{s=1}^n \sum_{i=1}^t n_{dis}^2) - (r_{d0} - \frac{1}{p}\sum_{s=1}^n n_{d0s}^2)}{t(t-1)} - \\ &\quad \frac{tp\left(\sum_{i=1}^t (m_{dii} - \frac{1}{p}\sum_{s=1}^n n_{dis}\widetilde{n}_{dis}) + \frac{1}{t}(\widehat{r}_{d0} - \frac{p-1}{p} r_{d0} - m_{d00} + \frac{1}{p}\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s})\right)^2}{(t-1)[n(p-1)(pt-t-1) - (pt-t+p-2)\widetilde{r}_{d0} + \sum_{s=1}^n \widetilde{n}_{d0s}^2]} \\ y_0 &= \frac{1}{t}(r_{d0} - \frac{1}{p}\sum_{s=1}^n n_{d0s}^2) - \\ &\quad \frac{p[n(p-1) - \widetilde{r}_{d0}](m_{d00} - \frac{1}{p}\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s})^2 + p\widetilde{r}_{d0}(\widehat{r}_{d0} - \frac{p-1}{p} r_{d0} - m_{d00} + \frac{1}{p}\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s})^2}{t[np(p-1)\widetilde{r}_{d0} - \widetilde{r}_{d0}^2 - n(p-1)\sum_{s=1}^n \widetilde{n}_{d0s}^2]}. \end{aligned}$$

Further, $Tr(M_d^{-1}) = \frac{t-1}{x_0} + \frac{1}{y_0}$ *will hold when the following conditions are satisfied.*

(i) $l_{dik} = r_{di}/p, i = 0, \ldots, t.$*,*

(ii) $T_d' pr^\perp(U) T_d$, $T_d' pr^\perp(U) F_d$, *and* $F_d' pr^\perp(U) F_d$ *are invariant under any permutation of test treatments.*

(iii) Each test treatment appears at most once in the first $p-1$ *periods.*

Although the preceding Lemma provides a lower bound of $Tr(M_d^{-1})$, it is very difficult to find the minimum value of the above lower bound for given t, n, and p since there are 10 variables in the lower bound and these are related to each other. So we will consider the A-optimality of a crossover design d in $\Omega^1_{t+1,n,p}$, in which the control treatment is uniform in all periods. Then immediately from the preceding Lemma, we have $Tr(M_d^{-1}) \geq \theta(d)$ for any $d \in \Omega^1_{t+1,n,p}$. Here,

$$\theta(d) = \frac{t-1}{x_d} + \frac{1}{y_d}, \tag{4.1}$$

where

$$\begin{aligned} x_d &= \frac{t(np - r_{d0} - \frac{1}{p}\sum_{s=1}^n \sum_{i=1}^t n_{dis}^2) - (r_{d0} - \frac{1}{p}\sum_{s=1}^n n_{d0s}^2)}{t(t-1)} \\ &\quad - \frac{tp\left(\sum_{i=1}^t (\frac{1}{p}\sum_{s=1}^n n_{dis}\widetilde{n}_{dis} - m_{dii}) - \frac{1}{t}(\frac{1}{p}\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s} - m_{d00})\right)^2}{(t-1)[n(p-1)(pt-t-1) - (pt-t+p-2)\widetilde{r}_{d0} + \sum_{s=1}^n \widetilde{n}_{d0s}^2]} \qquad (4.2) \\ y_d &= \frac{1}{t}(r_{d0} - \frac{1}{p}\sum_{s=1}^n n_{d0s}^2) - \frac{np(p-1)(\frac{1}{p}\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s} - m_{d00})^2}{t[np(p-1)\widetilde{r}_{d0} - \widetilde{r}_{d0}^2 - n(p-1)\sum_{s=1}^n \widetilde{n}_{d0s}^2]}. \qquad (4.3) \end{aligned}$$

$\theta(d)$ provides an achievable lower bound of $Tr(M_d^{-1})$ as the function of variables r_{d0}, $\sum_{u=1}^n \sum_{i=1}^t n_{dis}^2$, $\sum_{s=1}^n n_{d0s}^2$, $\sum_{i=1}^t \sum_{u=1}^n n_{dis}\widetilde{n}_{dis}$, $\sum_{i=1}^t m_{dii}$, $\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s}$, m_{d00}, $\widetilde{r}_{d0}$, and $\sum_{s=1}^n \widetilde{n}_{d0s}^2$.

Let $A(t,n,p) = Min_{d \in \Omega^1_{t+1,n,p}} \theta(d)$. If we can find a design $d^* \in \Omega^1_{t+1,n,p}$ such that $Tr(M_{d^*}^{-1}) = A(t,n,p)$, then d^* is an A-optimal design for comparing t test treatments with a control. Further, if M_{d^*} is also completely symmetric, then d^* is also MV-optimal. If we cannot find such a design, we can use $A(t,n,p)$ as a criterion to evaluate the efficiency of a design d by defining the efficiency ratio as $\frac{A(t,n,p)}{Tr(M_d^{-1})}$. For given t, n, and p, we may directly use computer to search for the minimum value of $\theta(d)$. But these problems need to be dealt with: (i) The number of all possible combinations of above variables is extremely large and a desktop computer may not be able to handle it; (ii) The variables are related to each other; (iii) Even though we find the values that minimize $\theta(d)$, these values may not be admissible for constructing the related design.

Since the variables in the expression of $\theta(d)$ are related to each other, it is difficult to characterize $\theta(d)$ of an efficient design if we consider all designs $d \in \Omega^1_{t+1,n,p}$. Our main purpose is to characterize a design whose $\theta(d)$ is small. Thus, it is not necessary to study designs whose $\theta(d)$'s are large. Therefore, our main strategy is to set up a cutoff point $\theta(d_0)$ (Lemma 2) and only study the subclass of designs for which $\theta(d)$ is less than $\theta(d_0)$. If we can characterize $\theta(d)$ for all the designs in that subclass, then it is equivalent to the characterization of $\theta(d)$ for efficient designs in $\Omega^1_{t+1,n,p}$.

Lemma 2. *Suppose $p \geq 4$ and $t \geq (p-3)(p-2)+2$, then $A(t,n,p) < \theta(d_0)$. Here,*

$$\theta(d_0) < \frac{tp}{n(p-1)} \frac{p^2-p-1}{p^2-p-2} \frac{t^2+tp-3t}{tp-t-1}.$$

Proof. See the Appendix. □

The proof of Lemma 2 needs the assumption that n is a multiple of p. However, this assumption is no longer required in the rest of paper. Note that the goal of Lemma 2 is to show that $A(t,n,p) < \theta(d_0)$ and thus, for the situation that n is not a multiple of p, if we can find a design d such that $\theta(d)$ is less than the cutoff point $\theta(d_0)$, then we can still use the subsequent results of the paper. In the Example section, we shall exhibit a design of this type.

Since the variables related to the test treatments are involved with x_d only, $\theta(d)$ will be minimized when x_d is maximized while the variables related to the control treatment are kept fixed. Answers to the following three problems can help us to achieve our goal: (i) Is $\sum_{i=1}^{t}(\frac{1}{p}\sum_{s=1}^{n} n_{dis}\widetilde{n}_{dis} - m_{dii}) - \frac{1}{t}(\frac{1}{p}\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - m_{d00})$ positive or negative for efficient designs? (ii) If r_{d0} and z_d are fixed, what are the values for $\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2$ and $\sum_{i=1}^{t}(\frac{1}{p}\sum_{s=1}^{n} n_{dis}\widetilde{n}_{dis} - m_{dii})$ in term of r_{d0} and z_d so that x_d is maximized for efficient designs? (iii) 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? Solutions to Problem (i) and (ii) can help us to characterize the positions of test treatments for efficient designs. And a solution to Problem (iii) can help us to characterize the positions of the control treatment for efficient designs. The next three Lemmas answer these questions. To make our notation simple, we define the following expression:

$$\begin{aligned}
\Delta_1 &= t(p-1)(np-r_{d0}) - 2tz_d - p(r_{d0} - \frac{1}{p}\sum_{s=1}^{n} n_{d0s}^2) \\
&\quad - \frac{[t(p-1)(n-z_d) - t\widetilde{r}_{d0} - (\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - pm_{d00})]^2}{n(p-1)(pt-t-1) - (pt-t+p-2)\widetilde{r}_{d0} + \sum_{s=1}^{n}\widetilde{n}_{d0s}^2}; \qquad (4.4)
\end{aligned}$$

$$\Delta_2 = p(r_{d0} - \frac{1}{p}\sum_{s=1}^{n} n_{d0s}^2) - \frac{n(p-1)(\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - pm_{d00})^2}{np(p-1)\widetilde{r}_{d0} - \widetilde{r}_{d0}^2 - n(p-1)\sum_{s=1}^{n}\widetilde{n}_{d0s}^2}; \qquad (4.5)$$

$$S_1 = \frac{t(p-1)(n-z_d) - t\widetilde{r}_{d0} - (\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - pm_{d00})}{n(p-1)(pt-t-1) - (pt-t+p-2)\widetilde{r}_{d0} + \sum_{s=1}^{n}\widetilde{n}_{d0s}^2}; \qquad (4.6)$$

$$S_2 = \frac{n(p-1)(\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - pm_{d00})}{np(p-1)\widetilde{r}_{d0} - \widetilde{r}_{d0}^2 - n(p-1)\sum_{s=1}^{n}\widetilde{n}_{d0s}^2}. \qquad (4.7)$$

Lemma 3. *Suppose $p \geq 4$ and $(p-3)(p-2)+2 \leq t \leq (p-2)(p-1)+1$. For any design $d \in \Omega_{t+1,n,p}^1$,*

$$\sum_{i=1}^{t}(\frac{1}{p}\sum_{s=1}^{n} n_{dis}\widetilde{n}_{dis} - m_{dii}) \geq \frac{1}{t}(\frac{1}{p}\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - m_{d00}) \qquad (4.8)$$

if $\theta(d) < \theta(d_0)$.

Proof. See the Appendix. □

Lemma 4. *Suppose* $(p-3)(p-2)+2 \leq t \leq (p-2)(p-1)+1$. *For any design* $d \in \Omega^1_{t+1,n,p}$,

$$\theta(d) \geq \frac{t(t-1)^2 p}{\Delta_1} + \frac{tp}{\Delta_2} \tag{4.9}$$

if $\theta(d) < \theta(d_0)$. *The equality in Inequality (4.9) holds when the following conditions are satisfied: (i) Each test treatment appears at most once in the first* $p-1$ *periods and (ii) There are* z_d *sequences in which each test treatment appears in both the pth and* $(p-1)$*th periods.*

Proof. See the Appendix. □

Lemma 5. *Suppose* $(p-3)(p-2)+2 \leq t \leq (p-2)(p-1)+1$ *and* $n \geq p(p-1)/2$. *For any design* $d \in \Omega^1_{t+1,n,p}$, *we have* $1+S_2 > 0$ *and*

$$\frac{1+S_2}{1+S_1} \geq \frac{(t-1)\Delta_2}{\Delta_1} \tag{4.10}$$

if $\theta(d) < \theta(d_0)$ *and* $\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s} - pm_{d00} > -\frac{p}{2}$.

Proof. See the Appendix. □

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

$$\begin{aligned}\sum_{s=1}^n n^2_{d0s} &= \sum_{s\in\Gamma_d} n^2_{d0s} + \sum_{s\overline{\in}\Gamma_d} n^2_{d0s} \\ &= \sum_{s\in\Gamma_d} (\widetilde{n}_{d0s}+1)^2 + \sum_{s\overline{\in}\Gamma_d} \widetilde{n}^2_{d0s} \\ &= \sum_{s=1}^n \widetilde{n}^2_{d0s} + 2\Psi_d + \frac{r_{d0}}{p}. \end{aligned} \tag{4.11}$$

Similarly, we have

$$\sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s} = \sum_{s=1}^n \widetilde{n}^2_{d0s} + \Psi_d. \tag{4.12}$$

The first theorem shows that the lower bound value for $\theta(d)$ is a function of variables r_{d0}, z_d, and Ψ_d and provides a characterization of efficient designs. Notice that those variables are independent of each other. The second theorem provides sufficient conditions for A-optimal and MV-optimal designs. These conditions can guide us to construct A-efficient and MV-efficient designs.

Theorem 1. *Suppose* $(p-3)(p-2)+2 \le t \le (p-2)(p-1)+1$ *and* $n \ge p(p-1)/2$. *For any design* $d \in \Omega^1_{t+1,n,p}$ *with fixed* r_{d0}, z_d, *and* Ψ_d, *we have*

$$\theta(d) \ge \min_{m_{d00}} \left(\frac{t(t-1)^2 p}{\overline{\Delta}_1} + \frac{tp}{\overline{\Delta}_2} \right) \tag{4.13}$$

if $\theta(d) < \theta(d_0)$. *Here,*

$$\begin{aligned} \overline{\Delta}_1 &= t(p-1)(np - r_{d0}) - 2tz_d - p(r_{d0} - \frac{1}{p}\min\sum_{s=1}^{n} n^2_{d0s}) \\ &\quad - \frac{[t(p-1)(n-z_d) - t\widetilde{r}_{d0} - (\min\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - pm_{d00})]^2}{n(p-1)(pt-t-1) - (pt-t+p-2)\widetilde{r}_{d0} + \min\sum_{s=1}^{n}\widetilde{n}^2_{d0s}} \end{aligned}$$

and

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

The equality in (4.13) will hold when the following conditions are simultaneously satisfied:
(i) Each test treatment appears at most once in the first $p-1$ *periods;*
(ii) There are z_d *sequences in which each test treatment appears in both the pth and* $(p-1)$*th periods;*
(iii) $\sum_{s=1}^{n} n^2_{d0s}$, $\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s}$, *and* $\sum_{s=1}^{n}\widetilde{n}^2_{d0s}$ *are minimized for given* Ψ_d;
(iv) m_{d00} *is the integer which minimizes* $\frac{t(t-1)^2p}{\overline{\Delta}_1} + \frac{tp}{\overline{\Delta}_2}$.

Proof. See the Appendix. □

Theorem 1 established a lower bound for $\theta(d)$ and provided sufficient conditions for those cases that $\theta(d) < \theta(d_0)$. Since d_0 is a design in $\Omega^1_{t+1,n,p}$ (Lemma 2), we therefore do not need to consider those designs with $\theta(d) \ge \theta(d_0)$ when we are looking for the lower bound of $\theta(d)$. We have the following theorem.

Theorem 2. *Suppose* $(p-3)(p-2)+2 \le t \le (p-2)(p-1)+1$ *and* $n \ge p(p-1)/2$. *We have*

$$A(t,n,p) = \min_{r_{d0}, z_d, \Psi_d, m_{d00}} \left(\frac{t(t-1)^2 p}{\overline{\Delta}_1} + \frac{tp}{\overline{\Delta}_2} \right). \tag{4.14}$$

Here, $\overline{\Delta}_1$ *and* $\overline{\Delta}_2$ *are those in Theorem 1. The sufficient conditions on design* d^* *such that* $\theta(d^*) = A(t,n,p)$ *are*
(i) r_{d^*0}, m_{d^*00}, Ψ_{d^*}, *and* z_{d^*} *are the integers which minimizes* $\frac{t(t-1)^2p}{\overline{\Delta}_1} + \frac{tp}{\overline{\Delta}_2}$;
(ii) Each test treatment appears at most once in the first $p-1$ *periods;*
(iii) There are z_{d^*} *sequences in which each test treatment appears in both the pth and*

$(p-1)$th period;
(iv) For the given Ψ_{d^*}, $\sum_{s=1}^{n} n_{d^*0u}^2$, $\sum_{s=1}^{n} n_{d^*0u}\widetilde{n}_{d^*0u}$, and $\sum_{s=1}^{n} \widetilde{n}_{d^*0u}^2$ are minimized.
If $Tr(M_{d^*}^{-1}) = A(t,n,p)$, then d^* is an A-optimal design in $\Omega_{t+1,n,p}^1$; if M_{d^*} is also completely symmetric, then d^* is also an MV-optimal design in $\Omega_{t+1,n,p}^1$. In addition to the four conditions stated above, the sufficient conditions that d^* is both A-optimal and MV-optimal design are
(v) $l_{d^*ik} = r_{d^*i}/p, i = 0,\ldots,t.$;
(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.

Proof. By Theorem 1 and the definition of $A(t,n,p)$, we can easily establish (4.14) and the corresponding sufficient conditions.

In addition to Conditions (i) to (iv), from Lemma 1, we can see that Conditions (v) and (vi) are sufficient conditions for d^* to be A-optimal and MV-optimal design. □

Theorem 2 guides us in finding a lower bound of $\theta(d)$ and provides a characterization of the designs which can achieve this lower bound. Although we need computer to search for the values of variables r_{d0}, z_d, Ψ_d, and m_{d00} such that the minimum value of $\theta(d)$ can be achieved. It is very easy to write such a computer program that can easily identify the corresponding values. It could be difficult to construct a design which enjoys the exact characterization. However, the characterization can guide us to construct efficient designs. We will give some examples in Section 5.

5 Examples and Discussions

In this section, we shall construct some small size efficient designs based on our results. The procedure consists of these steps: 1. We search for the value $A(t,n,p)$, and those values which are closed to it, as well as their corresponding parameters r_{d0}, Ψ_d, m_{d00}, and z_d based on (4.14); 2. We then evaluate the possibility of constructing a design based on the parameters we found, and choose those parameters for which the construction is not difficult and $\theta(d)$ is closed to $A(t,n,p)$; 3. We then construct a design based on the selected parameters and force it to satisfy as closely as possible the conditions stated in Theorem 2.

Example 1. Let $t = 4$, $n = 12$, and $p = 4$. Notice that, by Lemma 5 of Hedayat and Yang [7] and a simple computer search, we can find that the lower bound of $Tr(M_d^{-1})$ is 0.8879 for any design $d \in \Lambda_{4+1,12,4}$. For the designs in $\Omega_{4+1,12,4}^1$, a computer search showed that $A(t,n,p) = 0.8683$, and the corresponding parameters r_{d^*0}, Ψ_{d^*}, m_{d^*00}, and z_{d^*} are 16, 2, 4, and 1 respectively. It seems that it is not easy to construct a design which satisfies such parameters and the conditions stated in Theorem 2. So we choose $r_{d^*0} = 16$, $\Psi_{d^*} = 0$, $m_{d^*00} = 4$, and $z_{d^*} = 0$. The corresponding value of $\theta_{d^*} = 0.87149$, which is very closed to the minimum value 0.8683. We make a design as balanced as possible based on the selected parameters. The constructed design is design d_2 in Section 3. It can be checked that its $Tr(M_{d_2}^{-1})$ is 0.8733, which is at least 99.4% efficient compared to the lower bound 0.8683.

Example 2. Let $t = 4$, $n = 17$, and $p = 4$. By Lemma 5 of Hedayat and Yang [7] and a simple computer search, we can find that the lower bound of $Tr(M_d^{-1})$ is 0.6409 for any design $d \in \Lambda_{4+1,17,4}$. For the designs in $\Omega^1_{4+1,17,4}$, a computer search showed that $A(t,n,p) = 0.6072$. Although $n = 17$ is not a multiple of $p = 4$, we may still use Theorem 2 to guide us to find an efficient design, say d_3. If $Tr(M_{d_3}^{-1}) < \theta(d_0) = 0.62677$, then this reaffirms that the subclass of designs in which $\theta(d)$ is less than $\theta(d_0)$ is not empty. So our result can be applied in this case.

When $A(t,n,p) = 0.6072$, the corresponding parameters r_{d^*0}, Ψ_{d^*}, m_{d^*00}, and z_{d^*} are 20, 3, 3, and 1 respectively. Again it is not easy to construct a design which satisfies such parameters and the conditions stated in Theorem 2, so we replace $z_{d^*} = 1$ by $z_{d^*} = 0$ and keep the other parameters unchanged. The corresponding value of $\theta_{d^*} = 0.6077$, which is very closed to the minimum value 0.6072. We make the design as balanced as possible based on the selected parameters. It can be checked that its $Tr(M_{d_3}^{-1})$ is 0.6200, which is less than the cutoff point $\theta(d_0) = 0.62677$ and at least 97.9% efficient compared to the lower bound 0.6072.

$$d_3: \begin{array}{ccccccccccccccccc} 0 & 0 & 0 & 0 & 3 & 1 & 4 & 2 & 4 & 1 & 2 & 3 & 4 & 3 & 2 & 1 & 0 \\ 2 & 4 & 1 & 3 & 0 & 0 & 0 & 0 & 3 & 2 & 4 & 1 & 3 & 1 & 4 & 0 & 2 \\ 3 & 1 & 4 & 2 & 4 & 3 & 2 & 1 & 0 & 0 & 0 & 0 & 2 & 4 & 0 & 3 & 1 \\ 4 & 3 & 2 & 1 & 2 & 4 & 1 & 3 & 1 & 4 & 0 & 0 & 0 & 0 & 0 & 2 & 3 \end{array}$$

Example 3. Let $t = 7$, $n = 28$, and $p = 4$. According to Example 5 in Hedayat and Yang [7], the following design d_4 is the optimal design in $\Lambda_{7+1,28,4}$ and its $Tr(M_{d_4}^{-1}) = 1.02327$.

$$d_4: \begin{array}{cccccccccccccccccccccccccccc} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 3 & 4 & 5 & 6 & 7 & 1 & 2 & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 4 & 5 & 6 & 7 & 1 & 2 & 3 \\ 1 & 2 & 3 & 4 & 5 & 6 & 7 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 4 & 5 & 6 & 7 & 1 & 2 & 3 & 3 & 4 & 5 & 6 & 7 & 1 & 2 \\ 3 & 4 & 5 & 6 & 7 & 1 & 2 & 4 & 5 & 6 & 7 & 1 & 2 & 3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 2 & 3 & 4 & 5 & 6 & 7 \\ 4 & 5 & 6 & 7 & 1 & 2 & 3 & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 3 & 4 & 5 & 6 & 7 & 1 & 2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{array}$$

For designs in $\Omega^1_{7+1,28,4}$, a computer search showed that $A(t,n,p) = 1.02252$. So the efficiency of Design d_4 is at least 99.9%. In this case, the optimal design in $\Lambda_{7+1,28,4}$ is highly efficient in $\Omega^1_{7+1,28,4}$.

Although our conclusion is limited to $p \geq 4$ and $(p-3)(p-2)+2 \leq t \leq (p-2)(p-1)+1$, we believe that Theorem 2 remains true for any $t \geq p$. The proof could be similar, but we have to choose a different cutoff point. Once we chose the proper cutoff point, we can then use the same strategy and show that those designs whose $\theta(d)$ is less than that cutoff point will have similar properties. Of course the proof will be involved and requires very complicated algebra. As for $p = 3$, although we may have a similar conclusion as that in Theorem 2, the method used in this paper is not helpful. We have to seek for a new method to solve this problem.

Appendix

We only outline the proofs here. For the detail of the proofs, please refer to the technical report Hedayat and Yang [11].

Proof of Lemma 2. Since $p \geq 4$ and $t \geq (p-3)(p-2)+2$, thus $p < t+1$, and we can construct a design $d_0 \in \Omega^1_{t+1,n,p}$ with the following properties: (i) $r_{d_0 0} = n$; (ii) Every treatment appears at most once in any sequence; (iii) No treatment can immediately follow by itself in any sequence. By direct calculations and the definition of $A(t,n,p)$, the conclusion follows (Lemma 2 of Hedayat and Yang [11]). □

Proof of Lemma 3. Since $\theta(d) < \theta(d_0)$, it can be proved that $z_d < (np - r_{d0})/2$ and $\frac{n}{2} < r_{d0} < 2n$ (Lemmas 3 and 4 of Hedayat and Yang [11]). Using the fact that $z_d < (np - r_{d0})/2$, $r_{d0} < 2n$ and $\theta(d) < \theta(d_0)$, we can further prove that (Excluding the case $t = p = 4$) $z_d < n - \frac{r_{d0}}{p} - \frac{n}{p(p-1)}$ (Lemma 5 of Hedayat and Yang [11]). When $n - \frac{r_{d0}}{p} - \frac{n}{p-1} \leq z_d < n - \frac{r_{d0}}{p} - \frac{n}{p(p-1)}$, using the fact $r_{d0} < 2n$ and $\theta(d) < \theta(d_0)$, it can be shown that (Lemma 7 of Hedayat and Yang [11])

$$\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - pm_{d00} < t[(p-1)(n-z_d) - \widetilde{r}_{d0}]. \tag{5.1}$$

When $z_d < n - \frac{r_{d0}}{p} - \frac{n}{p-1}$, Inequality (5.1) still holds (Lemma 8 of Hedayat and Yang [11]). For the case $t = p = 4$, we can have the same conclusion (Lemma 6 of Hedayat and Yang [11]).

Since $(p-3)(p-2)+2 \leq t \leq (p-2)(p-1)+1$ for $p \geq 4$, we have $t \geq p$. Thus, by Proposition 9 of Hedayat and Yang [11], we have

$$\begin{aligned} \frac{1}{p}\sum_{i=1}^{t}\sum_{s=1}^{n} n_{dis}\widetilde{n}_{dis} - \sum_{i=1}^{t}\sum_{s=1}^{n} m_{dii} &\geq \frac{1}{p}\sum_{i=1}^{t}\sum_{s=1}^{n} n_{dis}\widetilde{n}_{dis} - z_d \\ &\geq \frac{1}{p}[(p-1)(n-z_d) - \widetilde{r}_{d0}] \\ &\geq \frac{1}{t}(\frac{1}{p}\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - m_{d00}). \end{aligned}$$

The conclusion follows. □

Proof of Lemma 4. By the definition of y_d in (4.3), we have $\Delta_2 = tpy_d$. By the definition of $\theta(d)$ in (4.1), we have the result if we can show that $\Delta_1 \geq t(t-1)px_d$.

By definition of z_d and noticing that $\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis} = np - r_{d0}$, it is easy to verify that

$$\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2 \geq np - r_{d0} + 2z_d. \tag{5.2}$$

By the definition of x_d in Equation (4.2), inequalities (4.8) in Lemma 2, and inequalities (5.2) we have

$$\Delta_1 \geq t(t-1)px_d. \tag{5.3}$$

The equality in Inequality (5.3) holds when (i) Each test treatment appears at most once in the first $p-1$ periods and (ii) There are z_d sequences in which each test treatment appears in both the pth and $(p-1)$th periods. □

Proof of Lemma 5. (Lemma 10 of Hedayat and Yang [11] provides the details) First, by Lemma 4, we have Inequality (4.9). Combining Inequality (4.9) and Lemma 2, we have

$$\frac{t(t-1)^2p}{\Delta_1} + \frac{tp}{\Delta_2} < \frac{tp}{n(p-1)}\frac{p^2-p-1}{p^2-p-2}\frac{t^2+tp-3t}{tp-t-1}.$$

From the preceding Inequality, we can obtain that

$$\frac{(t-1)\Delta_2}{\Delta_1} < \frac{\Delta_2}{n(p-1)(t-1)}\frac{p^2-p-1}{p^2-p-2}\frac{t^2+tp-3t}{tp-t-1} - \frac{1}{t-1}. \tag{5.4}$$

Second, we can prove the following inequality

$$S_1 \quad < \quad \frac{t(p-2)}{t(p-2)(p-1)-3p+4}. \tag{5.5}$$

Third, it is clear that $\sum_{s=1}^{n}\widetilde{n}_{d0s}^2 \leq \sum_{s=1}^{n} n_{d0s}^2 - l_{d0p}$, where l_{d0p} is the number of times the control treatment appears in period p. Since $\sum_{s=1}^{n} n_{d0s}^2 < (2+\frac{1}{p})r_{d0}$ (Lemma 4 of Hedayat and Yang [11]) and $l_{d0p} = r_{d0}/p$, we have

$$np(p-1)\widetilde{r}_{d0} - \widetilde{r}_{d0}^2 - n(p-1)\sum_{s=1}^{n}\widetilde{n}_{d0s}^2 > n(p-1)(p-3)r_{d0} - \frac{(p-1)^2r_{d0}^2}{p^2}. \tag{5.6}$$

Next, we will prove our conclusion in two cases: (i) $p \geq 5$ and (ii) $p = 4$.

Case (i): By Inequality (5.5), we can verify that $S_1 \leq \frac{1}{3}$. Since $\theta(d) < \theta(d_0)$, we have $\frac{n}{2} < r_{d0} < 2n$ (Lemma 4 of Hedayat and Yang [11]). Combing this fact with Inequality (5.6), we have

$$np(p-1)\widetilde{r}_{d0} - \widetilde{r}_{d0}^2 - n(p-1)\sum_{s=1}^{n}\widetilde{n}_{d0s}^2 > n^2[\frac{(p-1)(p-3)}{2} - \frac{(p-1)^2}{4p^2}].$$

Then by the preceding Inequality and the condition $\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - pm_{d00} > -\frac{p}{2}$, we have

$$
\begin{aligned}
S_2 &> -\frac{2p^3}{n(2p^3-6p^2-p+1)} \\
&> -\frac{4p^2}{(p-1)(2p^3-6p^2-p+1)}.
\end{aligned} \tag{5.7}
$$

On the other hand, since $r_{d0} < 2n$,

$$
\begin{aligned}
\Delta_2 &\leq pr_{d0} - \frac{r_{d0}^2}{n} \\
&\leq 2np - 4n = 2(p-2)n.
\end{aligned} \tag{5.8}
$$

By the inequality $S_1 \leq \frac{1}{3}$, Inequalities (5.7), (5.4), and (5.8), to reach our conclusion it is enough if we can show

$$
\begin{aligned}
1 - \frac{4p^2}{(p-1)(2p^3-6p^2-p+1)} &> \\
&\frac{4}{3}\left(\frac{2(p-2)}{(p-1)(t-1)}\frac{p^2-p-1}{p^2-p-2}\frac{t^2+tp-3t}{tp-t-1} - \frac{1}{t-1}\right).
\end{aligned} \tag{5.9}
$$

We can verify this directly for $p = 5$. When $p \geq 6$, we can easily verify that $\frac{4p^2}{(p-1)(2p^3-6p^2-p+1)} < \frac{1}{p-1}$ and $\frac{p-2}{p-1}\frac{p^2-p-1}{p^2-p-2} < 1$, and thus by Inequality (5.9) it is sufficient to show

$$
\frac{p-2}{p-1} > \frac{8t^2+4tp-20t+4}{3(t-1)(tp-t-1)},
$$

which is equivalent to

$$
t^2(3p^2-17p+14) - t(11p^2-38p+24) + 3p - 6 > 0.
$$

The preceding inequality holds if $t \geq \frac{11p^2-38p+24}{3p^2-17p+14}$, which can be easily verified when $t \geq 14$ and $p \geq 6$. Since $(p-3)(p-2)+2 \leq t \leq (p-2)(p-1)+1$, our conclusion follows.

Case (ii): By Lemma 4 of Hedayat and Yang [11], we have $\frac{2n}{3} < r_{d0} < \frac{11n}{6}$. Applying the condition $\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - pm_{d00} > -\frac{p}{2} = -2$, i.e., $\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - pm_{d00} \geq -1$, and Inequality (5.6), we have

$$
S_2 \geq \begin{cases} -\frac{3n}{3nr_{d0}-\frac{9nr_{d0}}{16}} = -\frac{16}{13r_{d0}}, & \text{when } \frac{2n}{3} < r_{d0} < n; \\ -\frac{3n}{3nr_{d0}-\frac{11n}{6}\frac{9r_{d0}}{16}} = -\frac{32}{21r_{d0}}, & \text{when } n \leq r_{d0} < \frac{11n}{6}. \end{cases} \tag{5.10}
$$

Since $n \geq p(p-1)/2 = 6$, we can further have

$$
S_2 \geq \begin{cases} -\frac{16}{13\frac{2n}{3}} \geq -\frac{4}{13}, & \text{when } \frac{2n}{3} < r_{d0} < n; \\ -\frac{32}{21n} \geq -\frac{16}{63}, & \text{when } n \leq r_{d0} < \frac{11n}{6}. \end{cases} \tag{5.11}
$$

Thus, $1 + S_2 > 0$ follows. On the other hand, we have

$$\Delta_2 \leq \begin{cases} 3r_{d0} < 3n, & \text{when } \frac{2n}{3} < r_{d0} < n; \\ r_{d0} + 2n < \frac{23n}{6}, & \text{when } n \leq r_{d0} < \frac{11n}{6}. \end{cases} \tag{5.12}$$

When $\frac{2n}{3} < r_{d0} < n$ by Inequalities (5.4), (5.5), (5.11), and (5.12), to reach our conclusion it is sufficient to show

$$\frac{9}{13} \geq (1 + \frac{t(p-2)}{t(p-2)(p-1) - 3p + 4})(\frac{3}{(p-1)(t-1)} \frac{p^2 - p - 1}{p^2 - p - 2} \frac{t^2 + tp - 3t}{tp - t - 1} - \frac{1}{t-1}),$$

which can be verified directly.

When $n \leq r_{d0} < \frac{11n}{6}$, by Inequalities (5.4), (5.5), (5.11), and (5.12), to reach our conclusion it is sufficient to show

$$\frac{47}{63} \geq (1 + \frac{t(p-2)}{t(p-2)(p-1) - 3p + 4})(\frac{23}{6(p-1)(t-1)} \frac{p^2 - p - 1}{p^2 - p - 2} \frac{t^2 + tp - 3t}{tp - t - 1} - \frac{1}{t-1}),$$

which can be verified directly except for $t = 4$. Under the special situation that $p = 4$ and $t = 4$, $S_1 \leq \frac{1}{2}$ by Inequality (5.5); $S_2 \geq -\frac{32}{21r_{d0}}$ by Inequality (5.10); $\frac{(t-1)\Delta_2}{\Delta_1} < \frac{2(r_{d0}+2n)}{9n} - \frac{1}{3}$ by Inequalities (5.4) and (5.12). Thus our conclusion follows if the following inequality holds:

$$1 - \frac{32}{21r_{d0}} \geq \frac{3}{2}(\frac{2(r_{d0} + 2n)}{9n} - \frac{1}{3}),$$

which is equivalent to

$$14r_{d0}^2 - 35r_{d0}n + 64n < 0.$$

The preceding inequality is true since $n \leq r_{d0} < \frac{11n}{6}$ and $n \geq 6$. □

Proof of Theorem 1. By Lemma 4, we have Inequality (4.9).

Let m_{ds00} be the number of times that control treatment is immediately followed by itself in subject s. For any subject s, if $n_{d0s}\widetilde{n}_{d0s} - pm_{ds00} < 0$, we can always reshuffle the treatment sequence in this subject, such that (i) n_{d0s} and $\widetilde{n}_{d0s}$ are the same; (ii) m_{ds00} is one less than before reshuffling. Now, suppose $\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - pm_{d00} \leq -\frac{p}{2}$, then there exist some subjects in which $n_{d0s}\widetilde{n}_{d0s} - pm_{ds00} < 0$. Thus, we can reshuffle treatment sequences within some subjects, such that

$$-\frac{p}{2} < \sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - pm_{d00} \leq \frac{p}{2}.$$

By Inequality (5.1), we have

$$t(p-1)(n - z_d) - t\widetilde{r}_{d0} - (\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s} - pm_{d00}) > 0. \tag{5.13}$$

By (5.13) and the definition of Δ_1, we can see that Δ_1 is larger after the reshuffling. We can also see that Δ_2 will at least be the same after the reshuffling. Thus, the value of $\frac{t(t-1)^2p}{\Delta_1}+\frac{tp}{\Delta_2}$ will be smaller after the reshuffling. So the integer m_{d00}, which minimizes $\frac{t(t-1)^2p}{\Delta_1}+\frac{tp}{\Delta_2}$, will satisfy $\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s}-pm_{d00}>-\frac{p}{2}$.

For the given $\sum_{s=1}^{n}\widetilde{n}_{d0s}^2$, r_{d0}, and Ψ_d, using (4.11) and (4.12), we can rephrase $\frac{t(t-1)^2p}{\Delta_1}+\frac{tp}{\Delta_2}$ as a function of r_{d0}, z_d, $\sum_{s=1}^{n}\widetilde{n}_{d0s}^2$, Ψ_d, and m_{d00}, say

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

By a simple calculation, we can see that

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

The preceding inequality is due to Lemma 5. Thus, for fixed r_{d0}, z_d, Ψ_d, and m_{d00}, $\frac{t(t-1)^2p}{\Delta_1}+\frac{tp}{\Delta_2}$ 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

$$\theta(d)\geq\frac{t(t-1)^2p}{\overline{\Delta}_1}+\frac{tp}{\overline{\Delta}_2}. \tag{5.14}$$

The equality in (5.14) holds when for fixed Ψ_d, $\sum_{s=1}^{n} n_{d0s}^2$, $\sum_{s=1}^{n} n_{d0s}\widetilde{n}_{d0s}$, and $\sum_{s=1}^{n}\widetilde{n}_{d0s}^2$ are minimized. By (5.14), we can easily establish (4.13) and the corresponding conditions in the theorem. □

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References

[1] J. G. Pigeon and D. Raghavarao, Crossover designs for comparing treatments with a control, Biometrika 74 (1987), no. 2, 321–328.

[2] M. Jacroux, The *A*-optimality of block designs for comparing test treatments with a control, J. Amer. Statist. Assoc. 84 (1989), no. 405, 310–317.

[3] S. Jaggi, V. K. Gupta, and R. Parsad, *A*-efficient block designs for comparing two disjoint sets of treatments, Comm. Statist. Theory Methods 25 (1996), no. 5, 967–983.

[4] N. K. Mandal, K. R. Shah, and B. K. Sinha, Comparison of test vs. control treatments using distance optimality criterion, Metrika 52 (2000), no. 2, 147–162.

[5] E. Solorzano and J. D. Spurrier, Comparing more than one treatment to more than one control in incomplete blocks, J. Statist. Plann. Inference 97 (2001), no. 2, 385–398.

[6] Chao-Ping Ting, Optimal and efficient repeated measurements designs for comparing test treatments with a control, Metrika 56 (2002), no. 3, 229–238.

[7] A. S. Hedayat and M. Yang, Optimal crossover designs for comparing test treatments with a control treatment, Ann. Statist. 33 (2005), no. 2, 915–943.

[8] A. S. Hedayat and K. Afsarinejad, Repeated Measurements Designs, I, A survey of statistical design and linear models, (J. N. Srivastava, ed.) (1975), 229–242, North-Holland, Amsterdam.

[9] D. Majumdar, Optimal repeated measurements designs for comparing test treatments with a control, Comm. Statist. Theory Methods 17 (1988), no. 11, 3687–3703.

[10] A. S. Hedayat and W. Zhao, Optimal two-period repeated measurements designs, Ann. Statist. 18 (1990), no. 4, 1805–1816. Corrigendum, 20 (1992), 619.

[11] A. S. Hedayat and M. Yang, Efficient Crossover Designs For Comparing Test Treatments With a Control Treatment, techincal report, Department of mathematics, statistics, and computer science, University of Illinois-Chicago.