Universal Optimality for Selected Crossover Designs

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Hedayat and Yang earlier proved that balanced uniform designs in the entire class of crossover designs based on t treatments, n subjects, and $p = t$ periods are universally optimal when $n \le t(t-1)/2$. Surprisingly, in the class of crossover designs with t treatments and $p = t$ periods, a balanced uniform design may not be universally optimal if the number of subjects exceeds $t(t-1)/2$. This article, among other results, shows that (a) a balanced uniform design is universally optimal in the entire class of crossover designs with $p = t$ as long as n is not greater than $t(t+2)/2$ and $3 \le t \le 12$; (b) a balanced uniform design with $n = 2t$, $t \ge 3$, and $p = t$ is universally optimal in the entire class of crossover designs with $n = 2t$ and $p = t$; and (c) for the case where $p \le t$, the design suggested by Stufken is universally optimal, thus completing Kushner's result that a Stufken design is universally optimal if n is divisible by $t(p-1)$.

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

1. INTRODUCTION

In many scientific studies, each subject is used in $p \ge 2$ occasions or periods for the purpose of evaluating and studying $t \ge 2$ treatments. In these types of studies, each subject is exposed to a sequence of p treatments. Such a design is called a *crossover design*. We denote the class of all such designs based on t treatments and n subjects each used in p periods by $\Omega_{t,n,p}$. The study of optimality and efficiency of these designs has a history of at least 27 years; for a sample of results in this area, see the works by Hedayat and Afsarinejad (1975, 1978), Cheng and Wu (1980), Kunert (1983, 1984), Jones and Kenward (1989), Stufken (1991), Hedayat and Zhao (1990), Carrière and Reinsel (1993), Matthews (1994), Kushner (1998), Afsarinejad and Hedayat (2002), Kunert and Stufken (2002), Hedayat and Yang (2003), and Hedayat and Stufken (2003). See the excellent expository review article by Stufken (1996) for additional references. Throughout this article, a design is called "universally optimal" if it is universally optimal for estimating contrasts in direct treatment effects.

A design $d \in \Omega_{t,n,p}$ is said to be a balanced uniform design if in its n sequences (1) no treatment is immediately preceded by itself, and each treatment is immediately followed by each other treatment equally often; (2) each treatment appears equally often for each subject; and (3) each treatment appears equally often in each period. A necessary condition for the existence of a balanced uniform design in $\Omega_{t,n,t}$ is that $n = \lambda t$ for some positive integer λ. According to Higham (1998), the class $\Omega_{t,n,t}$ contains a balanced uniform design when either n is an even multiple of t or t can be written as a product of two positive integers each larger than 1. Under the traditional model (see Sec. 2), Street, Eccleston, and Wilson (1990) showed by a computer search that a balanced uniform design in $\Omega_{3,6,3}$ is A-optimal for estimating direct treatment effects. However, until now it was unknown whether a balanced uniform design is universally optimal in $\Omega_{3,6,3}$. In earlier work (Hedayat and Yang 2003) we generalized a result of Kunert (1984) and proved that when $p = t$, a balanced uniform design is universally optimal in $\Omega_{t,n,p}$ when $n \le t(t-1)/2$. We also observed that the preceding result is of no help in identifying a universally optimal design in $\Omega_{3,6,3}$, $\Omega_{4,8,4}$, and $\Omega_{4,12,4}$, although balanced uniform designs exist in those classes.

Kushner (1998) provided necessary and sufficient conditions for a universally optimal design under approximate theory, and showed that some of those universally optimal deigns under approximate theory are also universally optimal under exact theory. But balanced uniform designs are not covered by Kushner's results.

For $p \le t$, our knowledge about optimal designs for direct treatment effects in $\Omega_{t,n,p}$ was rather limited before Stufken (1991) proved that a particular design (described in Sec. 4) not necessarily a balanced uniform design, is universally optimal for direct treatment effects within the subset of designs in $\Omega_{t,n,p}$, whose first $p-1$ periods form a balanced incomplete blocks (BIB) design with block size $p-1$. Later, Kushner (1998) proved that when n is divisible by $t(p-1)$, a Stufken design is universally optimal in the entire class $\Omega_{t,n,p}$. Note that when $t = p$, the design is a balanced uniform design when $n \le (t^2 - t)/2$, but not when $n > (t^2 - t)/2$.

Unfortunately, a balanced uniform design with $p = t$ may not be universally optimal in $\Omega_{t,n,p}$ when $n > t(t-1)/2$. As an example, there is a balanced uniform design in $\Omega_{3,36,3}$ that is not universally optimal. Therefore, it is of both theoretical and practical interest to find out the universal optimality status of a balanced uniform design when the number of subjects is larger than $t(t-1)/2$. We prove that, fortunately, a balanced uniform design in $\Omega_{t,n,t}$ is universally optimal as long as the number of subjects is not greater than $t(t+2)/2$ and $3 \le t \le 12$. Thus, for example, a balanced uniform design in $\Omega_{4,12,4}$ is universally optimal. We also show that the design by Stufken (1991), when it exists, is universally optimal in the entire class $\Omega_{t,n,p}$.

2. RESPONSE MODEL

Although several statistical models have been introduced in the literature for the purpose of modeling the data collected

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under crossover designs, in this article we use the most frequently used model in the literature, namely the traditional homoscedastic, additive, fixed-effects model introduced formally by Hedayat and Afsarinejad (1975),

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

where Y_{dks} denotes the response variable observed on subject s in period k to which treatment $d(k,s)$ was assigned by design d. In this model μ is an overall 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 effect for treatment $d(k,s)$, and $\rho_{d(k-1,s)}$ is the carryover or residual effect of treatment $d(k-1,s)$ on the response observed on subject s in period k. We take $\rho_{d(0,s)} = 0$, meaning that there is no carryover effect for a response in the first period, and the e_{ks}'s are uncorrelated normally distributed error variables with mean 0 and common variance σ^2.

In model (1) we assume that the subject effects are fixed. The main reason for this is that at the design stage we want a design that provides optimal within-subject information. If there is relatively large variability between subjects and we have only a small number of subjects, then the within-subject information is the primary information that we will get. A good family of examples is phase II clinical trials for studying pharmacokinetic parameters. However, we should mention that when the subjects are randomly selected from a large population of interest, it is common to consider subject effects as random instead of fixed when analyzing the data. Under these circumstances, it is then natural to explore the optimality and the efficiency status of the optimal crossover designs under random effects for the subjects in the model. Clearly, the relative advantages of the latter analysis depend on the relationship between the error variance and the variance of random subject effects. We conjecture that the design that is optimal under the fixed subject effect model will be efficient under the random subject effect model.

Throughout the article, for each design d we adopt the notation n_{dis}, $\widetilde{n}_{dis}$, l_{dik}, m_{dij}, r_{di}, and $\widetilde{r}_{di}$ to denote the number of times that treatment i is assigned to subject s, the number of times that this happens in the first $p-1$ periods, the number of times that treatment i is assigned to period k, the number of times that treatment i is immediately preceded by treatment j, the total replication of treatment i in its n sequences, and the total replication of treatment i limited to the first $p-1$ periods. We further define z_d to be the sum over all i and s of all positive $x_{dis} = n_{dis} - 1$.

In matrix notation, we can write model (1) as

$$\mathbf{Y}_d = \mu\mathbf{1} + \mathbf{P}\boldsymbol{\alpha} + \mathbf{U}\boldsymbol{\beta} + \mathbf{T}_d\boldsymbol{\tau}_d + \mathbf{F}_d\boldsymbol{\rho}_d + \mathbf{e}, \quad (2)$$

where $\mathbf{Y}_d = (Y_{d11}, Y_{d21}, \dots, Y_{dpn})'$, $\boldsymbol{\alpha} = (\alpha_1, \dots, \alpha_p)'$, $\boldsymbol{\beta} = (\beta_1, \dots, \beta_n)'$, $\boldsymbol{\tau}_d = (\tau_1, \dots, \tau_t)'$, $\boldsymbol{\rho}_d = (\rho_1, \dots, \rho_t)'$, $\mathbf{e} = (e_{11}, \epsilon_{21}, \dots, \epsilon_{pn})'$, $\mathbf{P} = \mathbf{1}_n \otimes \mathbf{I}_p$, $\mathbf{U} = \mathbf{I}_n \otimes \mathbf{1}_p$, $\mathbf{T}_d = (\mathbf{T}'_{d1}, \dots, \mathbf{T}'_{dn})'$, and $\mathbf{F}_d = (\mathbf{F}'_{d1}, \dots, \mathbf{F}'_{dn})'$. Here $\mathbf{T}_{ds}$ denotes for the $p \times t$ period-treatment incidence matrix for subject s under design d and $\mathbf{F}_{ds} = \mathbf{L}\mathbf{T}_{ds}$ with the $p \times p$ matrix $\mathbf{L}$ defined as

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

The information matrix for direct treatment effects, $\mathbf{C}_d$, is equal to

$$\mathbf{C}_d = \mathbf{T}'_d \operatorname{pr}^{\perp}([\mathbf{P}|\mathbf{U}|\mathbf{F}_d])\mathbf{T}_d,$$

where $\operatorname{pr}^{\perp}(\mathbf{X}) = \mathbf{I} - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-}\mathbf{X}'$. From the proof of proposition 4.1 of Kunert (1984), we have

$$\mathbf{C}_d \le \mathbf{T}'_d \operatorname{pr}^{\perp}(\mathbf{U})\mathbf{T}_d - \mathbf{T}'_d \operatorname{pr}^{\perp}(\mathbf{U})\mathbf{F}_d \times \left(\mathbf{F}'_d \operatorname{pr}^{\perp}(\mathbf{U})\mathbf{F}_d\right)^{-}\mathbf{F}'_d \operatorname{pr}^{\perp}(\mathbf{U})\mathbf{T}_d. \quad (3)$$

In the context of matrices, if $\mathbf{A}$ and $\mathbf{B}$ are two matrices, we say that $\mathbf{A} \le \mathbf{B}$ if $\mathbf{B} - \mathbf{A}$ is a nonnegative definite matrix. The diagonal elements for $\mathbf{T}'_d \operatorname{pr}^{\perp}(\mathbf{U})\mathbf{T}_d$, $\mathbf{T}'_d \operatorname{pr}^{\perp}(\mathbf{U})\mathbf{F}_d$, and $\mathbf{F}'_d \operatorname{pr}^{\perp}(\mathbf{U})\mathbf{F}_d$ at position (i,i) are $r_{di} - \frac{1}{p}\sum_{s=1}^n n_{dis}^2$, $m_{dii} - \frac{1}{p}\sum_{s=1}^n n_{dis}\widetilde{n}_{dis}$, and $\widetilde{r}_{di} - \frac{1}{p}\sum_{s=1}^n \widetilde{n}_{dis}^2$. The off-diagonal elements for $\mathbf{T}'_d \operatorname{pr}^{\perp}(\mathbf{U})\mathbf{F}_d$ and $\mathbf{F}'_d \operatorname{pr}^{\perp}(\mathbf{U})\mathbf{F}_d$ at position (i,j) are $m_{dij} - \frac{1}{p}\sum_{s=1}^n n_{dis}\widetilde{n}_{djs}$ and $-\frac{1}{p}\sum_{s=1}^n \widetilde{n}_{dis}\widetilde{n}_{djs}$.

As we show in Section 3, inequality (3) can help us find the achievable upper bound of $\operatorname{Tr}(\mathbf{C}_d)$. As a result, we will be able to identify the universally optimal designs.

3. OPTIMALITY OF BALANCED UNIFORM DESIGN WHEN $p = t$

Let d^* be a balanced uniform design in $\Omega_{t,n,t}$. Under model (1), from theorem 4.3 of Cheng and Wu (1980), $\mathbf{C}_{d^*}$ is a completely symmetric matrix. Therefore, by an optimality tool discovered by Kiefer (1975), if we can show that $\operatorname{Tr}(\mathbf{C}_{d^*})$ is maximized in $\Omega_{t,n,t}$, then we can conclude that design d^* is universally optimal in $\Omega_{t,n,t}$. Indeed, we can show that the trace of $\mathbf{C}_{d^*}$ is maximum as long as $n \le t(t+2)/2$ and $3 \le t \le 12$.

Before presenting our results, we need the following useful lemmas. The first lemma can be derived by using a similar methodology as in lemma 5.1 of Kushner (1997).

Lemma 1. For any design $d \in \Omega_{t,n,p}$, we have the inequality:

$$\operatorname{Tr}(\mathbf{C}_d) \le q_{11}(d) - \frac{q_{12}^2(d)}{q_{22}(d)}.$$

Here,

$$q_{11}(d) = np - \frac{1}{p}\sum_{s=1}^n \sum_{i=1}^t n_{dis}^2,$$

$$q_{12}(d) = \sum_{i=1}^t m_{dii} - \frac{1}{p}\sum_{s=1}^n \sum_{i=1}^t n_{dis}\widetilde{n}_{dis},$$

and

$$q_{22}(d) = n(p-1)\left(1 - \frac{1}{tp}\right) - \frac{1}{p}\sum_{s=1}^n \sum_{i=1}^t \widetilde{n}_{dis}^2.$$

Proof. Let $\mathbf{S}_1 = \mathbf{I}_t, \mathbf{S}_2, \dots, \mathbf{S}_N$, where $N = t!$, is the set of all $t \times t$ permutation matrices representing the permutations of $\{1, 2, \dots, t\}$. Also let $\mathbf{A}_i = \operatorname{pr}^{\perp}(\mathbf{U})\mathbf{T}_d\mathbf{S}_i$ and $\mathbf{D}_i = \operatorname{pr}^{\perp}(\mathbf{U})\mathbf{F}_d\mathbf{S}_i$, $1 \le i \le N$. It is easy to check that $\mathbf{A}'_i\mathbf{A}_i = \mathbf{S}'_i(\mathbf{T}'_d \operatorname{pr}^{\perp}(\mathbf{U})\mathbf{T}_d)\mathbf{S}_i$, $\mathbf{A}'_i\mathbf{D}_i = \mathbf{S}'_i(\mathbf{T}'_d \operatorname{pr}^{\perp}(\mathbf{U})\mathbf{F}_d)\mathbf{S}_i$, $\mathbf{D}'_i\mathbf{D}_i = \mathbf{S}'_i(\mathbf{F}'_d \operatorname{pr}^{\perp}(\mathbf{U})\mathbf{F}_d)\mathbf{S}_i$, and $\mathbf{S}'_i\mathbf{S}_i = \mathbf{I}$. Then, by inequality (3) and proposition 1 of Kunert and Martin (2000), which generalized lemma 5.1 of Kushner (1997), we have

$$\sum_{i=1}^{N}\mathbf{S}_i'\mathbf{C}_d\mathbf{S}_i \le \sum_{i=1}^{N}\mathbf{S}_i'\big(\mathbf{T}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})\mathbf{T}_d - \mathbf{T}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})\mathbf{F}_d \times \big(\mathbf{F}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})\mathbf{F}_d\big)^{-}\mathbf{F}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})\mathbf{T}_d\big)\mathbf{S}_i$$

$$\le \sum_{i=1}^{N}\mathbf{S}_i'\big(\mathbf{T}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})\mathbf{T}_d\big)\mathbf{S}_i - \left(\sum_{i=1}^{N}\mathbf{S}_i'\big(\mathbf{T}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})\mathbf{F}_d\big)\mathbf{S}_i\right) \times \left(\sum_{i=1}^{N}\mathbf{S}_i'\big(\mathbf{F}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})\mathbf{F}_d\big)\mathbf{S}_i\right)^{-} \times \left(\sum_{i=1}^{N}\mathbf{S}_i'\big(\mathbf{F}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})\mathbf{T}_d\big)\mathbf{S}_i\right). \tag{4}$$

Therefore, using the definition of $\mathbf{S}_i$, we observe that

$$\sum_{i=1}^{N}\mathbf{S}_i'\big(\mathbf{T}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})T_d\big)\mathbf{S}_i, \qquad \sum_{i=1}^{N}\mathbf{S}_i'\big(\mathbf{T}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})\mathbf{F}_d\big)\mathbf{S}_i,$$

and

$$\sum_{i=1}^{N}\mathbf{S}_i'\big(\mathbf{F}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})\mathbf{F}_d\big)\mathbf{S}_i$$

are completely symmetric matrices. Now, by direct calculations, we can obtain the stated result,that is,

$$\mathrm{Tr}(\mathbf{C}_d) \le q_{11}(d) - \frac{q_{12}^2(d)}{q_{22}(d)}.$$

The following lemma follows directly from the proof of theorem 1 of Hedayat and Yang (2003).

Lemma 2. Suppose that $d \in \Omega_{t,n,t}$ and $t > 2$. If $\mathrm{Tr}(\mathbf{C}_d) > \mathrm{Tr}(\mathbf{C}_{d^*})$, then $0 < z_d < \frac{2n}{t(t-1)}$, where z_d is defined above (2).

Lemma 3. Suppose that $d \in \Omega_{t,n,t}$, $t > 2$ and $n \le t(t-1)$. If $\mathrm{Tr}(\mathbf{C}_d) > \mathrm{Tr}(\mathbf{C}_{d^*})$, then d is uniform on all subjects except one in which the treatments in the first $p-1$ periods are distinct and the treatments in both the $(p-1)$st and pth periods are identical.

Proof. Lemma 2 implies that $z_d = 1$. Consequently,d is uniform on all subjects except one, in which only one treatment, say 1, appears twice and the remaining treatments appear at most once. Suppose that the last two periods of that subject do not both contain treatment 1; then two possibilities can occur for the subject in which treatment 1 appears twice: (a) the treatment in the pth period is not 1, or (b) the treatment in the pth period is 1, but the treatment in the $(p-1)$st period is not 1.

For case (a), we have $q_{11}(d) = n(t-1) - \frac{2}{t}$, $|q_{12}(d)| \ge \frac{(n-1)(t-1)+1}{t}$, and $q_{22}(d) = n(t-1)(1 - \frac{1}{t} - \frac{1}{t^2}) - \frac{2}{t}$, where $q_{11}(d)$, $q_{12}(d)$, and $q_{22}(d)$ are as defined in Lemma 1. Applying Lemma 1 and noting that $\mathrm{Tr}(\mathbf{C}_{d^*}) = n(t-1) - \frac{n(t-1)}{t^2-t-1}$, we have

$$\begin{aligned}
&\mathrm{Tr}(\mathbf{C}_{d^*}) - \mathrm{Tr}(\mathbf{C}_d)\\
&\quad\ge n(t-1) - \frac{n(t-1)}{t^2-t-1} - n(t-1)\\
&\qquad + \frac{2}{t} + \frac{[((n-1)(t-1)+1)/t]^2}{n(t-1)(1-1/t-1/t^2) - 2/t}\\
&\quad\ge \frac{2}{t} + \frac{[(n-1)(t-1)+1]^2}{n(t-1)(t^2-t-1)} - \frac{n(t-1)}{t^2-t-1}\\
&\quad\ge \frac{2}{t} + \frac{2(n-1)}{n(t^2-t-1)} + \frac{(n-1)^2(t-1)}{n(t^2-t-1)} - \frac{n(t-1)}{t^2-t-1}\\
&\quad= \frac{2(n-1)(t-1) + t(t-1) - 2}{nt(t^2-t-1)}\\
&\quad> 0.
\end{aligned}$$

Thus we obtain $\mathrm{Tr}(\mathbf{C}_d) \le \mathrm{Tr}(\mathbf{C}_{d^*})$, a contradiction.

For case (b), we have $q_{11}(d) = n(t-1) - \frac{2}{t}$, $|q_{12}(d)| = \frac{n(t-1)+1}{t}$, and $q_{22}(d) = n(t-1)(1 - \frac{1}{t} - \frac{1}{t^2})$. By a similar strategy as for (a), we can again discover that $\mathrm{Tr}(\mathbf{C}_d) \le \mathrm{Tr}(\mathbf{C}_{d^*})$, a contradiction.

Theorem 1. A balanced uniform design in $\Omega_{t,n,t}$ is universally optimal for any $4 \le t \le 12$ when $n \le t(t+2)/2$.

Proof. The t and n in the theorem satisfy the condition $n \le t(t-1)$ in Lemma 3. Therefore, if any design d in this class satisfies $\mathrm{Tr}(\mathbf{C}_d) > \mathrm{Tr}(\mathbf{C}_{d^*})$, then d must satisfy the condition stated in Lemma 3. Without loss of generality, let treatment 1 appear in the $(p-1)$st and pth periods for the first subject in d. Let l_i denote the number of times that treatment $i, i = 1, \ldots, t$, appears in the last period of any subject except for the first subject. Thus, $\sum_{i=1}^{t} l_i = n-1$.

Let $\mathbf{S}_1 = \mathbf{I}_t, \mathbf{S}_2, \ldots, \mathbf{S}_N$, with $N = (t-1)!$, be the set of all $t \times t$ permutation matrices representing the permutations of $\{1, 2, \ldots, t\}$ leaving 1 unchanged. By a similar methodology as in the proof of Lemma 1, we have the same inequality (4), except the definitions of N and $\mathbf{S}_i, i = 1, \ldots, N$, are different. Then, by utilizing the definition of $\mathbf{S}_i$, we observe that $\sum_{i=1}^{N}\mathbf{S}_i'(\mathbf{T}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})\mathbf{T}_d)\mathbf{S}_i$, $\sum_{i=1}^{N}\mathbf{S}_i'(\mathbf{T}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})\mathbf{F}_d)\mathbf{S}_i$, and $\sum_{i=1}^{N}\mathbf{S}_i'(\mathbf{F}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})\mathbf{F}_d)\mathbf{S}_i$ have the following form:

$$\begin{pmatrix} a & f\mathbf{J}_{1\times(t-1)} \\ c\mathbf{J}_{(t-1)\times 1} & (b-e)\mathbf{I}_{(t-1)\times(t-1)} + e\mathbf{J}_{(t-1)\times(t-1)} \end{pmatrix},$$

with different values for a, b, c, e, and f for these three matrices. Note that $c = f$ for $\sum_{i=1}^{N}\mathbf{S}_i'(\mathbf{T}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})\mathbf{T}_d)\mathbf{S}_i$ and $\sum_{i=1}^{N}\mathbf{S}_i'(\mathbf{F}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})\mathbf{F}_d)\mathbf{S}_i$. It can be shown that for $\sum_{i=1}^{N}\mathbf{S}_i'(\mathbf{T}_d'\,\mathrm{pr}^{\perp}(\mathbf{U})\mathbf{T}_d)\mathbf{S}_i$,

$$a = N\left(r_{d1} - \frac{1}{p}\sum_{s=1}^{n} n_{d1s}^2\right) = N\left(n + 1 - \frac{n+3}{t}\right)$$

and

$$b = \frac{N}{t-1}\sum_{i=2}^{t}\left(r_{di} - \frac{1}{p}\sum_{s=1}^{n} n_{dis}^2\right) = \frac{N}{t}\big(n(t-1) - 1\big);$$

for $\sum_{i=1}^N \mathbf{S}_i'(\mathbf{T}_d' \,\mathrm{pr}^\perp(\mathbf{U})\mathbf{F}_d)\mathbf{S}_i$,

$$a = N\left(m_{d11} - \frac{1}{p}\sum_{s=1}^n n_{d1s}\widetilde{n}_{d1s}\right) = N\left(1 - \frac{n+1-l_1}{t}\right)$$

and

$$b = \frac{N}{t-1}\sum_{i=2}^t\left(m_{dii} - \frac{1}{p}\sum_{s=1}^n n_{dis}\widetilde{n}_{dis}\right) = -\frac{N(nt-2n+l_1)}{t(t-1)};$$

and for $\sum_{i=1}^N \mathbf{S}_i'(\mathbf{F}_d' \,\mathrm{pr}^\perp(\mathbf{U})\mathbf{F}_d)\mathbf{S}_i$,

$$a = N\left(\widetilde{r}_{d1} - \frac{1}{p}\sum_{s=1}^n \widetilde{n}_{d1s}^2\right) = N(n-l_1)\left(1-\frac{1}{t}\right),$$

$$b = \frac{N}{t-1}\sum_{i=2}^t\left(\widetilde{r}_{di} - \frac{1}{p}\sum_{s=1}^n \widetilde{n}_{dis}^2\right) = \frac{N(nt-2n+l_1)}{t-1}\left(1-\frac{1}{t}\right),$$

$$c = \frac{N}{t-1}\sum_{i=2}^t\left(-\frac{1}{p}\sum_{s=1}^n \widetilde{n}_{d1s}\widetilde{n}_{dis}\right) = -\frac{N(n-l_1)(t-2)}{t(t-1)},$$

and

$$e = \frac{N}{(t-1)(t-2)}\sum_{i=2}^t\sum_{j\neq i, j\neq 1}^t\left(-\frac{1}{p}\sum_{s=1}^n \widetilde{n}_{dis}\widetilde{n}_{djs}\right) = -\frac{N(nt-3n+2l_1)}{t(t-1)}.$$

Let $\mathbf{L}$ be the following $1\times t$ vector:

$$\left(\frac{(n-l_1)(t-2)}{\sqrt{(t-1)(n(t-3)+2l_1)}}, \sqrt{\frac{n(t-3)+2l_1}{t-1}}, \ldots, \sqrt{\frac{n(t-3)+2l_1}{t-1}}\right).$$

Then we have

$$\sum_{i=1}^N \mathbf{S}_i'\big(\mathbf{F}_d' \,\mathrm{pr}^\perp(\mathbf{U})\mathbf{F}_d\big)\mathbf{S}_i = N\mathbf{B} - \frac{N}{t}\mathbf{L}'\mathbf{L} \le N\mathbf{B},$$

where $\mathbf{B}$ is a $t\times t$ diagonal matrix with diagonal elements

$$(n-l_1)\frac{n(t^3-4t^2+3t+1)+(t^2-2)l_1}{t(t-1)[n(t-3)+2l_1]}, \frac{n(t^2-2t-1)+(t+1)l_1}{t(t-1)}, \ldots, \frac{n(t^2-2t-1)+(t+1)l_1}{t(t-1)}.$$

By the facts that $\sum_{i=1}^N \mathbf{S}_i'(\mathbf{F}_d' \,\mathrm{pr}^\perp(\mathbf{U})\mathbf{F}_d)\mathbf{S}_i \le N\mathbf{B}$ and $\mathbf{1}'\sum_{i=1}^N \mathbf{S}_i'(\mathbf{T}_d' \,\mathrm{pr}^\perp(\mathbf{U})\mathbf{F}_d)\mathbf{S}_i = 0$, we derive the following inequality from inequality (4):

$$\begin{aligned} N\,\mathrm{Tr}(\mathbf{C}_d) &\le \mathrm{Tr}\left(\sum_{i=1}^N \mathbf{S}_i'\big(\mathbf{T}_d' \,\mathrm{pr}^\perp(\mathbf{U})\mathbf{T}_d\big)\mathbf{S}_i\right) \\ &\quad - \mathrm{Tr}\left[\left(\sum_{i=1}^N \mathbf{S}_i'\big(\mathbf{T}_d' \,\mathrm{pr}^\perp(\mathbf{U})\mathbf{F}_d\big)\mathbf{S}_i\right)(N\mathbf{B})^- \left(\sum_{i=1}^N \mathbf{S}_i'\big(\mathbf{F}_d' \,\mathrm{pr}^\perp(\mathbf{U})\mathbf{T}_d\big)\mathbf{S}_i\right)\right] \\ &\le N\left[n(t-1) - \frac{2}{t}\right] \\ &\quad - N\frac{[n(t-3)+2l_1](t-n+l_1-1)^2}{(n-l_1)[n(t^3-4t^2+3t+1)+(t^2-2)l_1]} \\ &\quad - N\frac{(nt-2n+l_1)^2}{(t-1)[n(t^2-2t-1)+(t+1)l_1]}. \end{aligned} \qquad (5)$$

Because $0\le l_1\le n-1$, simple counting indicates that we have 1,216 different combinations for (t,n,l_1). We wrote a simple computer program to conclude that for these 1,216 cases, $\mathrm{Tr}(\mathbf{C}_d) < \mathrm{Tr}(\mathbf{C}_{d^*}) = n(t-1) - \frac{n(t-1)}{t^2-t-1}$. Now we can use the tool discovered by Kiefer (1975) and reach the conclusion.

From Theorem 1, we know that a balanced uniform design in $\Omega_{4,8,4}$ is universally optimal. And from our earlier work (Hedayat and Yang 2003), we know that a balanced uniform design in $\Omega_{t,2t,t}$ is universally optimal when $t\ge 5$, so $\Omega_{3,6,3}$ is the only class of designs among $\Omega_{t,2t,t}$ for $t\ge 3$ for which we do not know whether a balanced uniform design is universally optimal. The following theorem will settle this question.

Theorem 2. A balanced uniform design, d^*, in $\Omega_{3,6,3}$ is universally optimal.

Proof. Suppose that design d in $\Omega_{3,6,3}$ satisfies $\mathrm{Tr}(\mathbf{C}_d) > \mathrm{Tr}(\mathbf{C}_{d^*})$. By Lemma 3, d must be uniform on all subjects except one, say the first subject, in which the two treatments in the first two periods are distinct and the treatment in the third period is identical to the treatment in the second period. Without loss of generality, let the sequence of treatments in the first subject be $(2,1,1)'$. We show that, contrary to the assumption, $\mathrm{Tr}(\mathbf{C}_d) < \mathrm{Tr}(\mathbf{C}_{d^*})$.

Note that inequality (5) is still valid for the case where $t=3$ and $n=6$. By a direct calculation, we can find that $\mathrm{Tr}(\mathbf{C}_d) > \mathrm{Tr}(\mathbf{C}_{d^*})$ implies $l_1 = 0$, where l_1 denotes the number of times in which treatment 1 appears in the last period of any subject except the first subject. We now consider the structure of the sequences in d. The sequence $(2,1,1)'$ appears only once in d, and no other sequence in d can terminate with treatment 1. For the remaining four sequences in d, suppose that $(1,2,3)'$ appears x_1 times, $(1,3,2)'$ appears x_2 times, $(2,1,3)'$ appears x_3 times and $(3,1,2)'$ appears x_4 times with $x_1+x_2+x_3+x_4 = 5$. Using the right-hand side in inequality (3) and noting that for d, $\mathrm{Tr}(\mathbf{T}_d' \,\mathrm{pr}^\perp(\mathbf{U})\mathbf{T}_d) = 34/3$,

$$\mathbf{T}_d' \,\mathrm{pr}^\perp(\mathbf{U})\mathbf{F}_d = \begin{pmatrix} -\frac{4}{3} & \frac{1-x_1+2x_3}{3} & \frac{2x_4-x_2}{3} \\ x_1+x_4-2 & -\frac{1+x_1+x_3}{3} & \frac{2x_2-x_4}{3} \\ x_2+x_3-\frac{5}{3} & \frac{2x_1-x_3}{3} & -\frac{x_2+x_4}{3} \end{pmatrix},$$

and

$$\mathbf{F}_d' \,\mathrm{pr}^\perp(\mathbf{U})\mathbf{F}_d = \begin{pmatrix} 4 & -\frac{1+x_1+x_3}{3} & -\frac{x_2+x_4}{3} \\ -\frac{1+x_1+x_3}{3} & \frac{2(1+x_1+x_3)}{3} & 0 \\ -\frac{x_2+x_4}{3} & 0 & \frac{2(x_2+x_4)}{3} \end{pmatrix},$$

we can directly calculate an upper bound for $\mathrm{Tr}(\mathbf{C}_d)$ as a function of x_1, x_2, x_3, and x_4. Because $x_1+x_2+x_3+x_4=5$, we have in a total of 56 combinations of (x_1,x_2,x_3,x_4) to consider. By applying inequality (3) and writing a simple computer program, we can directly verify that $\mathrm{Tr}(\mathbf{C}_d) < \mathrm{Tr}(\mathbf{C}_{d^*})$ for all these 56 combinations, a contradiction.

4. UNIVERSAL OPTIMALITY WHEN THE NUMBER OF PERIODS IS NO MORE THAN THE NUMBER OF TREATMENTS

Unfortunately, not all balanced uniform designs are universally optimal. For example, Kunert (1984) showed that if t is fixed and n is allowed to increase, then some balanced uniform designs are not universally optimal in $\Omega_{t,n,t}$. To cite one such example, consider the designs in $\Omega_{3,36,3}$. This class contains a balanced uniform design that is not universally optimal. Instead, Kushner (1998) has shown that the design by Stufken (1991) is universally optimal in this class. Although both designs have completely symmetric information matrices, Stufken's (1991) design has a trace of 58, whereas the balanced uniform design has a trace of 57.6. Therefore, an important question in this area is what design, if any, is universally optimal if a balanced uniform design is not optimal or does not exist. In this section we prove that the class of designs of Stufken (1991), which are not balanced, are universally optimal in $\Omega_{t,n,p}$. Our result extends a result of Stufken (1991), who proved the universal optimality of his designs in a subclass of designs whose first $p-1$ periods form BIB designs with block size $p-1$. Our result also extends a result of Kushner (1998) showing that if n is divisible by $t(p-1)$, then the design of Stufken is universally optimal in $\Omega_{t,n,p}$. We first introduce the design suggested by Stufken.

Let δ^* denote the nearest integer to $\frac{n(pt-t-1)}{t(p-1)}$. The design of Stufken satisfies the following conditions:

a. The design is uniform on the periods.

b. When restricted to the first $p-1$ periods, the collection of truncated sequences form a BIB design with block size $p-1$.

c. In the last period, δ^* subjects receive a treatment that was not assigned to them in any of the previous periods, whereas other subjects receive the same treatment as in period $p-1$.

d. For $i \neq j$, $m_{ij} - \sum_{s=1}^{n} n_{dis}\widetilde{n}_{djs}/p$ is independent of i and j.

e. For $i \neq j$, $\sum_{s=1}^{n} n_{dis}n_{djs}$ is independent of i and j.

Now we are ready to present our result concerning the design of Stufken.

Theorem 3. The design of Stufken (1991), when it exists, is universally optimal in $\Omega_{t,n,p}$.

Proof. Let d^* be the design of Stufken. From Stufken (1991), $\mathbf{C}_{d^*}$ is a completely symmetric matrix. Thus we need only show that $\mathrm{Tr}(\mathbf{C}_{d^*}) = \max_{d\in\Omega_{t,n,p}} \mathrm{Tr}(\mathbf{C}_d)$. From (4.1) in Stufken (1991),

$$\begin{aligned}\mathrm{Tr}(\mathbf{C}_{d^*})& \\ &= n(p-1) - \frac{2(n-\delta^*)}{p} - \frac{t(p-1)\delta^{*2}}{np(pt-t-1)} \\ &= \max_{\delta}\left(n(p-1) - \frac{2(n-\delta)}{p} - \frac{t(p-1)\delta^2}{np(pt-t-1)}\right), \qquad (6)\end{aligned}$$

where δ is a nonnegative integer. Because $\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis} = np$, at most np of the n_{dis}'s are greater than 0 and others are 0. Without loss of generality, we can rename these np possible positive n_{dis}'s as $a_1, \ldots, a_{np}$. Then, we have $\sum_{j=1}^{np} a_j = np$ and $\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2 = \sum_{j=1}^{np} a_j^2$. Therefore, z_d will be the sum of all positive $a_j - 1$, and thus $-z_d$ will be the sum of all negative $a_j - 1$, which means that z_d of a_j's are 0 among $a_1, \ldots, a_{np}$ and the others must be greater than 0. Thus we can assume that $\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2 = \sum_{j=1}^{np-z_d} a_j^2$ subject to $\sum_{j=1}^{np-z_d} a_j = np$, where $a_j \geq 1$. It can be verified that the minimum value of $\sum_{j=1}^{np-z_d} a_j^2$ is

$$-(np-z_d)\left[\frac{np}{np-z_d}\right]^2 + (np+z_d)\left[\frac{np}{np-z_d}\right] + np. \qquad (7)$$

Here $[\frac{np}{np-z_d}]$ refers to the greatest integer that is less than or equal to $\frac{np}{np-z_d}$. When $z_d < \frac{np}{2}$, we have $[\frac{np}{np-z_d}] = 1$, and therefore $\min \sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2 = np + 2z_d$. When $z_d \geq \frac{np}{2}$, notice that $(np-z_d)[\frac{np}{np-z_d}] \leq np$ and $[\frac{np}{np-z_d}] \geq 2$, and thus $\min \sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2 \geq 2np$.

By Lemma 1, we have $\mathrm{Tr}(\mathbf{C}_d) \leq q_{11}(d)$ for any design d. We can verify that when $z_d \geq n$, $\mathrm{Tr}(\mathbf{C}_d) \leq \mathrm{Tr}(\mathbf{C}_{d^*})$. In fact, when $z_d \geq \frac{np}{2}$, $q_{11}(d) = np - \frac{1}{p}\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2 \leq np - 2n$. On the other hand, by letting $\delta = 0$ in (6), we observe that $\mathrm{Tr}(\mathbf{C}_{d^*}) \geq n(p-1) - \frac{2n}{p}$, so $\mathrm{Tr}(\mathbf{C}_d) \leq \mathrm{Tr}(\mathbf{C}_{d^*})$. When $n \leq z_d < \frac{np}{2}$, $q_{11}(d) \leq n(p-1) - \frac{2z_d}{p}$, and then $\mathrm{Tr}(\mathbf{C}_d) \leq \mathrm{Tr}(\mathbf{C}_{d^*})$.

Now we assume that $z_d < n$. We have $q_{11}(d) \leq n(p-1) - \frac{2z_d}{p}$, and it is easy to verify that maximum value of $q_{22}(d)$ is $n(p-1)\frac{tp-t-1}{tp}$. For $q_{12}^2(d)$, we notice that $\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis} \times \widetilde{n}_{dis} = \sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2 - \sum_{s=1}^{n} n_d^*(s)$, where $n_d^*(s) = n_{dis}$ if treatment i is assigned to subject s in the last period. Similar to the argument that we made in the previous two paragraphs, there are only $np - z_d$ of n_{dis}'s that are positive, and we can rename these $np - z_d$ positive n_{dis}'s as $a_1, \ldots, a_{np-z_d}$. Therefore, $\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2 - \sum_{s=1}^{n} n_d^*(s)$ is equivalent to $\sum_{j=1}^{np-z_d} a_j^2 - \sum_{j=1}^{n} a_j$ subject to $\sum_{j=1}^{np-z_d} a_j = np$, where $a_j \geq 1$ is an integer, $j = 1, \ldots, np - z_d$. We claim that the minimum value of $\sum_{j=1}^{np-z_d} a_j^2 - \sum_{j=1}^{n} a_j$ is reached when a_j is either 1 or 2, $j = 1, \ldots, n$ and the remaining a_j's are all 1. Otherwise, there are only two competing alternatives:

1. Suppose some of a_j's are not 1 when $j = n+1, \ldots, np - z_d$, say, $a_{n+1} > 1$. Then one or more of the a_j's must be 1 when $j = 1, \ldots, n$, say, $a_1 = 1$, because $\sum_{j=1}^{np-z_d} a_j = np$. By exchanging the values of a_{n+1} and a_1 and keeping the others unchanged, we can obtain a smaller value for $\sum_{j=1}^{np-z_d} a_j^2 - \sum_{j=1}^{n} a_j$.
2. Suppose that all of the a_j's are 1 when $j = n+1, \ldots, np - z_d$ and that there exists an a_j that is not 1 or 2 when $j = 1, \ldots, n$. Then one of the a_j's ($j = 1, \ldots, n$) must be 1, because $\sum_{j=1}^{np-z_d} a_j = np$. Without loss of generality, we assume that $a_1 = 1$ and $a_2 = \kappa > 2$. By changing a_1 to 2 and a_2 to $\kappa - 1$ and keeping the remaining a_i's unchanged, we can easily verify that the latter case produces a smaller value for $\sum_{j=1}^{np-z_d} a_j^2 - \sum_{j=1}^{n} a_j$.

So the minimum value of $\sum_{j=1}^{np-z_d} a_j^2 - \sum_{j=1}^{n} a_j$ is $np - n + z_d$. On the other hand, $\sum_{i=1}^{t} m_{dii} \leq z_d$, and thus $\frac{1}{p}\sum_{s=1}^{n} \times \sum_{i=1}^{t} n_{dis}\widetilde{n}_{dis} - \sum_{i=1}^{t} m_{dii} \geq (p-1)(n-z_d)/p > 0$. Consequently, $q_{12}^2(d) \geq (p-1)^2(n-z_d)^2/p^2$.

By Lemma 1, we have

$$\mathrm{Tr}(\mathbf{C}_d) \leq n(p-1) - \frac{2z_d}{p} - \frac{t(p-1)(n-z_d)^2}{np(tp-t-1)}. \qquad (8)$$

Finally, by inequalities (6) and (8), we have $\mathrm{Tr}(\mathbf{C}_d) \leq \mathrm{Tr}(\mathbf{C}_{d^*})$.

5. DISCUSSION AND FUTURE RESEARCH

The combination of results established in Theorems 1 and 2 tells us that if we want to test t treatments based on a crossover design with n subjects each to be exposed to a sequence of $p(=t)$ treatments, then under model (1), a balanced uniform crossover design is universally optimal as long as $3 \le t \le 12$ and $n \le t(t+2)/2$. In particular, this implies that a balanced uniform crossover design with $n = 2t$, $t = p \ge 3$ is universally optimal. In practical applications, it would be highly desirable if we could remove the upper bound on n and keep the universal optimality of a balanced crossover design. Unfortunately, this is not the case. Indeed, we know that a balanced uniform design may lose its universal optimality as n gets large—a very surprising result by itself. A possible remedy for such cases is to search for the corresponding Stufken design, because we know that the Stufken design will be universally optimal regardless of the size of n. But there are two problems here. First, the Stufken design may not exist for the given t and n. Second, if the nonexistence of the Stufken design cannot be ruled out, then, due to heavy combinatorial demand on the Stufken design, its construction is generally very difficult. For example, consider the case where $t = p = 3$ and there are no more than $n = 36$ subjects. To have a balanced uniform design or the Stufken design in this range of n, we may need to limit n to be 6, 12, 18, 24, 30, or 36. For these values of n, we know that a balanced uniform crossover design with $n = 6$ exists that is universally optimal based on the foregoing result. We also know that the Stufken design with $n = 36$ exists and thus is universally optimal. But although we know that balanced uniform crossover designs for $n = 12$, 18, 24, and 30 exist, we do not know whether these designs are universally optimal. Can we construct the Stufken designs for $n = 12, 18, 24, 30$?

Another issue meriting attention and research concerning crossover designs is deciding whether the subject effects should be fixed or random. We gave an argument in support of fixed subject effects after we introduced model (1). If we are not sure about the fixed or random nature of the subject effect, then can we construct a model robust crossover design for our problem? Before tackling this difficult problem, perhaps we should see how efficient optimal crossover designs under fixed effects will be if we analyze the data under the random subject model. Clearly, the relative advantages of such an analysis depend on the relationship between the error variance and the variance of the random subject effect.

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REFERENCES

Afsarinejad, K., and Hedayat, A. S. (2002), "Repeated Measurements Designs for Model With Self and Mixed Carryover Effects," *Journal of Statistical Planning and Inference*, 106, 449–459.

Carrière, K. C., and Reinsel, G. C. (1993), "Optimal Two-Period Repeated Measurement Designs With Two or More Treatments," *Biometrika*, 80, 924–929.

Cheng, C. S., and Wu, C.-F. (1980), "Balanced Repeated Measurements Designs," *The Annals of Statistics*, 8, 1272–1283; corr. (1983), 11, 349.

Hedayat, A. S., and Afsarinejad, K. (1975), "Repeated Measurements Designs, I," in *A Survey of Statistical Design and Linear Models*, ed. J. N. Srivastava, Amsterdam: North-Holland, pp. 229–242.

——— (1978), "Repeated Measurements Designs, II," *The Annals of Statistics*, 6, 619–628.

Hedayat, A. S., and Stufken, J. (2003), "Optimal and Efficient Crossover Designs Under Different Assumptions About the Carryover Effect," *Journal of Biopharmaceutical Statistics*, 13, 519–528.

Hedayat, A. S., and Yang, M. (2003), "Universal Optimality of Balanced Uniform Crossover Designs," *The Annals of Statistics*, 31, 978–983.

Hedayat, A. S., and Zhao, W. (1990), "Optimal Two-Period Repeated Measurements Designs," *The Annals of Statistics*, 18, 1805–1816; corr. (1992), 20, 619.

Higham, J. (1998), "Row-Complete Latin Squares of Every Composite Order Exist," *Journal of Combinatorial Designs*, 6, 63–77.

Jones, B., and Kenward, M. G. (1989), *Design and Analysis of Cross-Over Trials*, New York: Chapman & Hall.

Kiefer, J. (1975), "Construction and Optimality of Generalized Youden Designs," in *A Survey of Statistical Design and Linear Models*, ed. J. N. Srivastava, Amsterdam: North-Holland, pp. 333–353.

Kunert, J. (1983), "Optimal Design and Refinement of the Linear Model With Applications to Repeated Measurements Designs," *The Annals of Statistics*, 11, 247–257.

——— (1984), "Optimality of Balanced Uniform Repeated Measurements Designs," *The Annals of Statistics*, 12, 1006–1017.

Kunert, J., and Martin, R. J. (2000), "On the Determination of Optimal Designs for an Interference Model," *The Annals of Statistics*, 28, 1728–1742.

Kunert, J., and Stufken, J. (2002), "Optimal Crossover Designs in a Model With Self and Mixed Carryover Effects," *Journal of the American Statistical Association*, 97, 898–906.

Kushner, H. B. (1997), "Optimal Repeated Measurements Designs: The Linear Optimality Equations," *The Annals of Statistics*, 25, 2328–2344.

——— (1998), "Optimal and Efficient Repeated-Measurements Designs for Uncorrelated Observations," *Journal of the American Statistical Association*, 93, 1176–1187.

Matthews, J. N. S. (1994), "Modeling and Optimality in the Design of Crossover Studies for Medical Applications," *Journal of Statistical Planning and Inference*, 42, 89–108.

Street, D. J., Eccleston, J. A., and Wilson, W. H. (1990), "Tables of Small Optimal Repeated Measurements Designs," *Australian Journal of Statistics*, 32, 345–359.

Stufken, J. (1991), "Some Families of Optimal and Efficient Repeated Measurements Designs," *Journal of Statistical Planning and Inference*, 27, 75–83.

——— (1996), "Optimal Crossover Designs," in *Handbook of Statistics*, Vol. 13, eds. S. Ghosh and C. R. Rao, Amsterdam: North-Holland, pp. 63–90.