Universal Optimality for Selected Crossover Designs

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Abstract

Hedayat and Yang (2003) 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 $n \leq t(t-1)/2$. Surprisingly, in the class of crossover designs with t treatments and $p = t$ periods a balanced uniform design may not be universally

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optimal if the number of subjects exceeds $t(t-1)/2$. This paper, among other results, shows that (i) a balanced uniform design is universally optimal in the entire class of crossover designs with $p = t$ so long as n is not greater than $t(t+2)/2$ and $3 \leq t \leq 12$; (ii) a balanced uniform design with $n = 2t$, $t \geq 3$ and $p = t$ is universally optimal in the entire class of crossover designs with $n = 2t$ and $p = t$; (iii) for the case $p \leq t$, the design suggested by Stufken (1991) is universally optimal, thus completing Kushner (1998)'s result that a Stufken design is universally optimal if n is divisible by $t(p-1)$.

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

1 Introduction

In many scientific studies, each subject is used in $p \geq 2$ occasions or periods for the purpose of evaluating and studying $t \geq 2$ treatments. In these types of studies, each subject will be exposed to a sequence of p treatments. Such a design is called a crossover design. We designate 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, the reader is referred to 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). We refer the reader to the excellent expository review paper by Stufken (1996) for additional references.

Throughout this paper, 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 further (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 $n = \lambda t$ 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 Section 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 $\Omega_{3,6,3}$. Hedayat and Yang (2003) 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 $n \leq t(t-1)/2$. They 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 the results of Kushner (1998).

For $p \leq t$ our knowledge about optimal designs for direct treatment effects in $\Omega_{t,n,p}$ was rather limited before Stufken (1991) who proved that a particular design (to be described in Section 4 and which is 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 $\Omega_{t,n,p}$. Notice that when $t=p$, the design is a balanced uniform design when $n \leq (t^2-t)/2$ while it is 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 $\Omega_{3,36,3}$ which 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 shall prove that fortunately a balanced uniform design in $\Omega_{t,n,t}$ is universally optimal so long as the number of subjects is not greater than $t(t+2)/2$ and $3 \leq t \leq 12$. 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

While several statistical models have been introduced in the literature for the purpose of modelling the data collected under crossover designs we shall use in this paper the most frequently used model in the literature, namely, the traditional homoscedastic, additive, and fixed effects model introduced formally by Hedayat and Afsarinejad (1975),

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

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 $d(k, s)$, $\rho_{d(k-1,s)}$ 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 (2.1) we have assumed that subject effects are fixed. The main reason 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 only have a small number of subjects, then the within subject information is the primary information we will get. A good family of examples will be 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 then 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 which is optimal under the fixed subject effect model will be efficient under the random subject effect model.

Throughout this paper, 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 this happens in the first $p-1$ periods, 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 replication of treatment i in its n sequences, and total replication of treatment i limited to the first $p-1$ periods, respectively. 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 (2.1) as

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

where $Y_d = (Y_{d11}, Y_{d21}, \ldots, Y_{dpn})'$, $\alpha = (\alpha_1, \ldots, \alpha_p)'$, $\beta = (\beta_1, \ldots, \beta_n)'$, $\tau_d = (\tau_1, \ldots, \tau_t)'$, $\rho_d = (\rho_1, \ldots, \rho_t)'$, $e = (e_{11}, \epsilon_{21}, \ldots, \epsilon_{pn})'$, $P = 1_n \otimes I_p$, $U = I_n \otimes 1_p$, $T_d = (T'_{d1}, \ldots, T'_{dn})'$, and $F_d = (F'_{d1}, \ldots, F'_{dn})'$. Here T_{ds} stands for the $p \times t$ 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 treatment effects, C_d, is equal to

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

where, $pr^{\perp}(U) = I - U(U'U)^{-}U'$. From the proof of Proposition 4.1 in Kunert (1984), we have

$$C_d \leq T'_d pr^{\perp}(U)T_d - T'_d pr^{\perp}(U)F_d(F'_d pr^{\perp}(U)F_d)^{-}F'_d pr^{\perp}(U)T_d. \tag{2.3}$$

In the context of matrices, if A and B are two matrices, we call $A \leq B$ if $B - A$ is a nonnegative definite matrix. The diagonal elements for $T_d' pr^{\perp}(U) T_d$, $T_d' pr^{\perp}(U) F_d$, and $F_d' pr^{\perp}(U) F_d$ 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 $\widetilde{r}_{di} - \frac{1}{p}\sum_{s=1}^{n} \widetilde{n}_{dis}^2$ respectively. The off-diagonal elements for $T_d' pr^{\perp}(U) F_d$ and $F_d' pr^{\perp}(U) F_d$ at position (i,j) are $m_{dij} - \frac{1}{p}\sum_{s=1}^{n} n_{dis}\widetilde{n}_{djs}$ and $-\frac{1}{p}\sum_{s=1}^{n} \widetilde{n}_{dis}\widetilde{n}_{djs}$ respectively.

As we shall show in Section 3, Inequality (2.3) can help us to find the achievable upper bound of $Tr(C_d)$, and as a result, we will be able to identify the universally optimal designs.

3 Optimality of balanced uniform design when $p = t$

Under Model (2.1), from Theorem 4.3 of Cheng and Wu (1980), C_{d^*} is a completely symmetric matrix. Therefore, by an optimality tool discovered by Kiefer (1975) if we can show that $Tr(C_{d^*})$ is maximized in $\Omega_{t,n,t}$, then we can conclude that design d^* is universally optimal in $\Omega_{t,n,t}$. Indeed, we will show that the trace of C_{d^*} is maximum as long as $n \leq t(t+2)/2$ and $3 \leq t \leq 12$.

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 in Kushner (1997).

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

$$Tr(C_d) \leq q_{11}(d) - \frac{q_{12}^2(d)}{q_{22}(d)}.$$

Here,

$$\begin{aligned}
q_{11}(d) &= np - \frac{1}{p}\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2, \\
q_{12}(d) &= \sum_{i=1}^{t} m_{dii} - \frac{1}{p}\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}\widetilde{n}_{dis}, \\
q_{22}(d) &= n(p-1)(1-\frac{1}{tp}) - \frac{1}{p}\sum_{s=1}^{n}\sum_{i=1}^{t} \widetilde{n}_{dis}^2.
\end{aligned}$$

Proof. Let $S_1 = I_t, S_2, \ldots, S_N$, where $N = t!$, be the set of all $t \times t$ permutation matrices representing the permutations of {1,2,...,t}. Let also $A_i = pr^{\perp}(U)T_d S_i$ and $D_i = pr^{\perp}(U)F_d S_i$, $1 \leq i \leq N$. It is easy to check that $A_i' A_i = S_i'(T_d' pr^{\perp}(U)T_d)S_i$, $A_i' D_i = S_i'(T_d' pr^{\perp}(U)F_d)S_i$, $D_i' D_i = S_i'(F_d' pr^{\perp}(U)F_d)S_i$, and $S_i' S_i = I$. Then, by Inequality (2.3) and Proposition 1 of Kunert and Martin (2000), which generalized Lemma 5.1 of Kushner (1997), we have

$$\begin{aligned}
\sum_{i=1}^{N} S_i' C_d S_i &\leq \sum_{i=1}^{N} S_i' \left(T_d' pr^{\perp}(U)T_d - T_d' pr^{\perp}(U)F_d (F_d' pr^{\perp}(U)F_d)^{-} F_d' pr^{\perp}(U)T_d \right) S_i \\
&\leq \sum_{i=1}^{N} S_i'(T_d' pr^{\perp}(U)T_d)S_i - \left(\sum_{i=1}^{N} S_i'(T_d' pr^{\perp}(U)F_d)S_i\right)\left(\sum_{i=1}^{N} S_i'(F_d' pr^{\perp}(U)F_d)S_i\right)^{-} \\
&\quad \left(\sum_{i=1}^{N} S_i'(F_d' pr^{\perp}(U)T_d)S_i\right). \qquad (3.1)
\end{aligned}$$

Therefore, by utilizing the definition of S_i, we observe that $\sum_{i=1}^{N} S_i'(T_d' pr^{\perp}(U)T_d)S_i$, $\sum_{i=1}^{N} S_i'(T_d' pr^{\perp}(U)F_d)S_i$, and $\sum_{i=1}^{N} S_i'(F_d' pr^{\perp}(U)F_d)S_i$ are completely symmetric matrices. Now, by direct calculations, we can obtain the stated result, i.e.,

$$Tr(C_d) \leq q_{11}(d) - \frac{q_{12}^2(d)}{q_{22}(d)}.$$

□

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

Lemma 2. *Suppose* $d \in \Omega_{t,n,t}$ *and* $t > 2$. *If* $Tr(C_d) > Tr(C_{d^*})$, *then* $0 < z_d < \frac{2n}{/} t(t-1)$, *where* z_d *is defined above (2.2).*

Lemma 3. *Suppose* $d \in \Omega_{t,n,t}$, $t > 2$ *and* $n \leq t(t-1)$. *If* $Tr(C_d) > Tr(C_{d^*})$, *then* d *is uniform on all subjects except on one subject, in which the treatments in the first* $p-1$ *periods are distinct and the treatments in both* $(p-1)$*th and* p*th periods are identical.*

Proof. Lemma 2 implies $z_d = 1$. Consequently, d is uniform on all subjects except on one subject, 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. (b) The treatment in the pth period is 1, but the treatment in the $(p-1)$th period is not 1.

For case (a), we have $q_{11}(d) = n(t-1) - \frac{2}{t}$, $|q_{12}(d)| \geq \frac{(n-1)(t-1)+1}{t}$, 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 noticing that $Tr(C_{d^*}) = n(t-1) - \frac{n(t-1)}{t^2-t-1}$, we have

$$\begin{aligned} Tr(C_{d^*}) - Tr(C_d) &\geq n(t-1) - \frac{n(t-1)}{t^2-t-1} - n(t-1) + \frac{2}{t} + \frac{[\frac{(n-1)(t-1)+1}{t}]^2}{n(t-1)(1-\frac{1}{t}-\frac{1}{t^2}) - \frac{2}{t}} \\ &\geq \frac{2}{t} + \frac{[(n-1)(t-1)+1]^2}{n(t-1)(t^2-t-1)} - \frac{n(t-1)}{t^2-t-1} \\ &\geq \frac{2}{t} + \frac{2(n-1)}{n(t^2-t-1)} + \frac{(n-1)^2(t-1)}{n(t^2-t-1)} - \frac{n(t-1)}{t^2-t-1} \\ &= \frac{2(n-1)(t-1)+t(t-1)-2}{nt(t^2-t-1)} \\ &> 0. \end{aligned}$$

Thus, we obtain $Tr(C_d) \leq Tr(C_{d^*})$, 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 in (a), we can again discover that $Tr(C_d) \leq Tr(C_{d^*})$, a contradiction. □

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

Proof. The t and n in the theorem satisfy the condition $n \leq t(t-1)$ in Lemma 3. Therefore, if any design d in this class satisfies $Tr(C_d) > Tr(C_{d^*})$, then d must satisfy the condition stated in Lemma 3. Without loss of generality, let treatment 1 appear in the $(p-1)$th 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 $S_1 = I_t, S_2, \ldots, S_N$, with $N = (t-1)!$, be the set of all $t \times t$ permutation matrices representing the permutations of {1,2,...,t} leaving 1 unchanged. By a similar methodology as in the proof of Lemma 1, we have the same Inequality (3.1) except the definitions of N and $S_i, i = 1, \ldots, N$ are different. Then by utilizing the definition of S_i, we observe that $\sum_{i=1}^N S_i'(T_d' pr^\perp(U)T_d)S_i$, $\sum_{i=1}^N S_i'(T_d' pr^\perp(U)F_d)S_i$, and $\sum_{i=1}^N S_i'(F_d' pr^\perp(U)F_d)S_i$ have the following form.

$$\begin{pmatrix} a & fJ_{1\times(t-1)} \\ cJ_{(t-1)\times 1} & (b-e)I_{(t-1)\times(t-1)} + eJ_{(t-1)\times(t-1)} \end{pmatrix},$$

with different values for a, b, c, e and f for these three matrices. Notice that $c = f$ for $\sum_{i=1}^N S_i'(T_d' pr^\perp(U)T_d)S_i$ and $\sum_{i=1}^N S_i'(F_d' pr^\perp(U)F_d)S_i$. It can be shown that for $\sum_{i=1}^N S_i'(T_d' pr^\perp(U)T_d)S_i$,

$$\begin{aligned} a &= N(r_{d1} - \frac{1}{p}\sum_{s=1}^n n_{d1s}^2) = N(n+1-\frac{n+3}{t}), \\ b &= \frac{N}{t-1}\sum_{i=2}^t (r_{di} - \frac{1}{p}\sum_{s=1}^n n_{dis}^2) = \frac{N}{t}(n(t-1)-1); \end{aligned}$$

for $\sum_{i=1}^N S_i'(T_d' pr^\perp(U)F_d)S_i$,

$$\begin{aligned} a &= N(m_{d11} - \frac{1}{p}\sum_{s=1}^n n_{d1s}\widetilde{n}_{d1s}) = N(1-\frac{n+1-l_1}{t}), \\ b &= \frac{N}{t-1}\sum_{i=2}^t (m_{dii} - \frac{1}{p}\sum_{s=1}^n n_{dis}\widetilde{n}_{dis}) = -\frac{N(nt-2n+l_1)}{t(t-1)}; \end{aligned}$$

and for $\sum_{i=1}^N S_i'(F_d' pr^\perp(U)F_d)S_i$,

$$\begin{aligned} a &= N(\widetilde{r}_{d1} - \frac{1}{p}\sum_{s=1}^n \widetilde{n}_{d1s}^2) = N(n-l_1)(1-\frac{1}{t}), \\ b &= \frac{N}{t-1}\sum_{i=2}^t (\widetilde{r}_{di} - \frac{1}{p}\sum_{s=1}^n \widetilde{n}_{dis}^2) = \frac{N(nt-2n+l_1)}{t-1}(1-\frac{1}{t}), \\ c &= \frac{N}{t-1}\sum_{i=2}^t (-\frac{1}{p}\sum_{s=1}^n \widetilde{n}_{d1s}\widetilde{n}_{dis}) = -\frac{N(n-l_1)(t-2)}{t(t-1)}, \\ e &= \frac{N}{(t-1)(t-2)}\sum_{i=2}^t \sum_{j\neq i, j\neq 1}^t (-\frac{1}{p}\sum_{s=1}^n \widetilde{n}_{dis}\widetilde{n}_{djs}) = -\frac{N(nt-3n+2l_1)}{t(t-1)}. \end{aligned}$$

Let 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

$$\sum_{i=1}^{N} S_i'(F_d' pr^{\perp}(U) F_d) S_i = NB - \frac{N}{t} L'L \leq NB,$$

where 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 $\sum_{i=1}^{N} S_i'(F_d' pr^{\perp}(U) F_d) S_i \leq NB$ and $1' \sum_{i=1}^{N} S_i'(T_d' pr^{\perp}(U) F_d) S_i = 0$, we shall derive the following inequality from Inequality (3.1)

$$\begin{aligned} NTr(C_d) &\leq Tr(\sum_{i=1}^{N} S_i'(T_d' pr^{\perp}(U) T_d) S_i) - Tr[\left(\sum_{i=1}^{N} S_i'(T_d' pr^{\perp}(U) F_d) S_i \right) (NB)^- \\ & \quad \left(\sum_{i=1}^{N} S_i'(F_d' pr^{\perp}(U) T_d) S_i \right)] \\ &\leq N[n(t-1) - \frac{2}{t}] - N \frac{[n(t-3)+2l_1](t-n+l_1-1)^2}{(n-l_1)[n(t^3-4t^2+3t+1)+(t^2-2)l_1]} \\ & \quad -N \frac{(nt-2n+l_1)^2}{(t-1)[n(t^2-2t-1)+(t+1)l_1]}. \end{aligned} \tag{3.2}$$

Since $0 \leq l_1 \leq n-1$, a simple counting indicates that we have 1216 different combinations for (t, n, l_1). We wrote a simple computer program to conclude that for these 1216 cases $Tr(C_d) < Tr(C_{d^*}) = n(t-1) - \frac{n(t-1)}{t^2-t-1}$. 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 Hedayat and Yang (2003) we know that a balanced uniform design in $\Omega_{t,2t,t}$ is universally optimal when $t \geq 5$, so $\Omega_{3,6,3}$ is the only class of designs among $\Omega_{t,2t,t}$ for $t \geq 3$ 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 design d in $\Omega_{3,6,3}$ satisfies $Tr(C_d) > Tr(C_{d^*})$. 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 will show that, contrary to the assumption, $Tr(C_d) < Tr(C_{d^*})$.

Note that Inequality (3.2) is still valid for the case $t = 3$ and $n = 6$. By a direct calculation, we can find that $Tr(C_d) > Tr(C_{d^*})$ implies $l_1 = 0$, where l_1 denotes the number of times which treatment 1 appears in the last period of any subject except for the first subject. We will 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 $(1,2,3)'$ appears x_1 times; $(1,3,2)'$ appears x_2 times; $(2,1,3)'$ appears x_3 times; $(3,1,2)'$ appears x_4 times with $x_1+x_2+x_3+x_4 = 5$. Using the right hand side in Inequality (2.3) and noticing that for d, $Tr(T_d' pr^{\perp}(U)T_d) = 34/3$, and

$$T_d' pr^{\perp}(U) F_d = \begin{pmatrix} -4/3 & (1 - x_1 + 2x_3)/3 & (2x_4 - x_2)/3 \\ x_1 + x_4 - 2 & -(1 + x_1 + x_3)/3 & (2x_2 - x_4)/3 \\ x_2 + x_3 - 5/3 & (2x_1 - x_3)/3 & -(x_2 + x_4)/3 \end{pmatrix},$$

and

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

we can directly calculate an upper-bound for $Tr(C_d)$ as a function of x_1, x_2, x_3 and x_4. Since $x_1 + x_2 + x_3 + x_4 = 5$, we have in all 56 combinations of (x_1, x_2, x_3, x_4) to consider. By applying Inequality (2.3) and writing a simple computer program, we can directly verify that $Tr(C_d) < Tr(C_{d^*})$ 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 which 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 (1991)'s design has trace of 58 while the balanced uniform design has 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 shall prove that the class of designs by 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) who showed that, if n is divisible by $t(p-1)$, then the design by Stufken (1991) is universally optimal in $\Omega_{t,n,p}$. We first introduce the design suggested by Stufken (1991).

Let δ^* denote the nearest integer to $\frac{n(pt-t-1)}{t(p-1)}$. The design by Stufken (1991) satisfies the following conditions:

(i)The design is uniform on the periods.

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

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

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

(v)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 by Stufken (1991).

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

Proof. From Stufken (1991), C_{d^*} is a completely symmetric matrix. Thus, we only need to show that $Tr(C_{d^*}) = Max_{d\in\Omega_{t,n,p}} Tr(C_d)$. From (4.1) in Stufken (1991),

$$\begin{aligned} Tr(C_{d^*}) &= n(p-1) - \frac{2(n-\delta^*)}{p} - \frac{t(p-1)\delta^{*2}}{np(pt-t-1)} \\ &= Max_\delta\left(n(p-1) - \frac{2(n-\delta)}{p} - \frac{t(p-1)\delta^2}{np(pt-t-1)}\right), \end{aligned} \quad (4.1)$$

where δ is a nonnegative integer. Since $\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis} = np$, at most np of 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 $a_j - 1$, thus, $-z_d$ will be the sum of all negative $a_j - 1$, which means 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

$$-(np-z_d)[\frac{np}{np-z_d}]^2 + (np+z_d)[\frac{np}{np-z_d}] + np. \quad (4.2)$$

Here, $[\frac{np}{np-z_d}]$ refers to the greatest integer which is less than or equal to $\frac{np}{np-z_d}$. When $z_d < \frac{np}{2}$, then $[\frac{np}{np-z_d}] = 1$, 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 $Tr(C_d) \leq q_{11}(d)$ for any design d. We can verify that when $z_d \geq n$, $Tr(C_d) \leq Tr(C_{d^*})$. 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 $s = 0$ in (4.1), we observe that $Tr(C_{d^*}) \geq n(p-1) - \frac{2n}{p}$, so $Tr(C_d) \leq Tr(C_{d^*})$. When $n \leq z_d < \frac{np}{2}$, $q_{11}(d) \leq n(p-1) - \frac{2z_d}{p}$, then $Tr(C_d) \leq Tr(C_{d^*})$.

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 $\sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}\widetilde{n}_{dis} = \sum_{s=1}^{n}\sum_{i=1}^{t} n_{dis}^2 - \sum_{s=1}^{n} n_d^*(s)$, where $n_d^*(s) = n_{dis}$ if treatment i is assigned to subject s in the last period. Similar to the argument 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 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 value 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 a_j's are 1 when $j = n + 1, \ldots, np - z_d$ and there exists an a_j which is not 1 or 2 when $j = 1, \ldots, n$. Then one of 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, it can be easily verified 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, $\sum_{i=1}^{t} m_{dii} \leq z_d$. So, $\frac{1}{p} \sum_{s=1}^{n} \sum_{i=1}^{t} n_{dis} \widetilde{n}_{dis} - \sum_{i=1}^{t} m_{dii} \geq (p-1)(n - z_d)/p > 0$, consequently, $q_{12}^2(d) \geq (p-1)^2 (n - z_d)^2 / p^2$.

By Lemma 1, we have

$$Tr(C_d) \leq n(p-1) - \frac{2z_d}{p} - \frac{t(p-1)(n-z_d)^2}{np(tp-t-1)}. \tag{4.3}$$

Finally, by Inequalities (4.1) and (4.3), we have $Tr(C_d) \leq Tr(C_{d^*})$. □

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 (2.1) a balanced uniform crossover design is universally optimal as long as $3 \leq t \leq 12$ and $n \leq t(t+2)/2$. In particular, this implies that a balanced uniform crossover design with $n = 2t$, $t = p \geq 3$ 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 since 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 non-existence of the Stufken design cannot be ruled out then due to heavy combinatorial demand on the Stufken design its construction is in general very difficult. For example, let us consider the case $t = p = 3$ and no more than $n = 36$ subjects. To have a balanced uniform design or the Stufken design in this range of n we may have 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 which is universally optimal based on the above result. We also know that the Stufken design with $n = 36$ exists and thus universally optimal. But, while we know that balanced uniform crossover designs for $n = 12$, 18, 24, and 30 exist; we do not know if these designs are universally optimal. Can we construct the Stufken designs for $n = 12$, 18, 24, 30?

Another issue that needs 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 (2.1). 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? Perhaps before embarking on this difficult problem 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 the latter analysis depend on the relationship between the error variance and the variance of the random subject effect.

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