Optimal and Efficient Crossover Designs When Subject Effects Are Random

A. S. HEDAYAT, John STUFKEN, and Min YANG

Most studies on optimal crossover designs are based on models that assume subject effects to be fixed effects. In this article we identify and study optimal and efficient designs for a model with random subject effects. With the number of periods not exceeding the number of treatments, we find that totally balanced designs are universally optimal for treatment effects in a large subclass of competing designs. However, in the entire class of designs, totally balanced designs are in general not optimal, and their efficiency depends on the ratio of the subject effects variance and the error variance. We develop tools to study the efficiency of totally balanced designs and to identify designs with higher efficiency.

KEY WORDS: Fisher information matrix; Mixed-effects model; Totally balanced design; Universal optimality.

1. INTRODUCTION

In a crossover design, each subject in the study receives a treatment in each of multiple periods, typically with the primary goal of comparing the effects of the various treatments. A considerable portion of the literature on optimal and efficient crossover designs addresses the question of finding good designs for estimating treatment differences under an assumed parametric model for given numbers of treatments, periods, and subjects. An answer depends, of course, on the assumed model.

One assumption frequently made when considering this design question is that subject effects are fixed effects, even though it is often more reasonable to treat them as random effects, which is typically done in the analysis. This practice has at times been justified by a dual argument. Most of the information for treatment differences when using a crossover design is based on within-subject information, so the first part of the argument goes. Hence it is important to compare designs based on the within-subject information that they provide, which is precisely what is accomplished by treating the subject effects as fixed. Moreover, so the argument continues, a comparison of designs when subject effects are random depends in general on the unknown subject effects variance, or at least on its size relative to the error variance. Not only does this lead to more complicated expressions (possibly with limited gains), but also the size of this variance is typically unknown.

But how efficient are designs that are optimal for fixed subject effects when the subject effects are really random? Which designs are optimal when subject effects are random, and how does this change with the relative size of the subject effects variance? This article studies these questions, about which little is known.

Optimality of crossover designs when subject effects are fixed has been studied by many researchers over the last three decades, including Hedayat and Afsarinejad (1975, 1978), Cheng and Wu (1980), Kunert (1983, 1984), Hedayat and Zhao (1990), Stufken (1991), Matthews (1994), Kushner (1997, 1998), Afsarinejad and Hedayat (2002), Kunert and Stufken (2002), Hedayat and Yang (2003, 2004, 2005), and Hedayat and Stufken (2003). Additional references have been given by Stufken (1996) and Jones and Kenward (2003).

But subjects in the study may often be viewed as representing a larger population of interest from which they were more or less randomly selected. The subject effects are then more appropriately treated as random effects. There are relatively few optimality results for this problem. Mukhopadhyay and Saha (1983) showed that some of the optimality results of Hedayat and Afsarinejad (1978), Magda (1980), and Cheng and Wu (1980) for crossover designs for a model with fixed subject effects remained valid when the subject effects were assumed to be random. Jones, Kunert, and Wynn (1992) obtained additional results for the same setup. But the number of periods in these results is at least equal to the number of treatments, and moreover, some of the results are over restricted classes of designs. Laska and Meisner (1985) obtained optimal two-treatment crossover designs given arbitrary within-subject covariance. Carrière and Reinsel (1993) showed that strongly balanced two-period designs that are uniform on the periods are universally optimal for treatment effects in the entire class of designs. This also holds when subject effects are fixed (as noted in Hedayat and Zhao 1990).

As already alluded to, if the subject effects are random, then an optimal design can depend on the size of the subject effects variance relative to the error variance. Whether this is actually the case depends on the number of periods, p, and the number of treatments, t, in which we are interested, as well as on the class of competing designs. We study and identify efficient designs as a function of the ratio of the two variance components for what is arguably the most important case, namely $p \leq t$. In doing this, we model the mean response using period effects, treatment effects, and first-order carryover effects. Details about the model assumptions are given in Section 2, along with basic notation. Preliminary results appear in Section 3; main results, in Section 4. A brief discussion is provided in Section 5, and most of the technical tools for the results in Section 4 are given in the Appendix.

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The class of totally balanced designs, introduced by Kunert and Stufken (2002) for a different model, turns out to play an important role in our considerations. In a large class of competing designs, defined in Section 4, totally balanced designs turn out to be universally optimal for treatment effects, regardless of the relative size of the subject effects variance. In the entire class of designs, a totally balanced design can be optimal or highly efficient, but this depends on t and p, on the number of subjects n, and on the size of the subject effects variance relative to the error variance. Section 4 provides tools to unravel these mysteries.

2. THE RESPONSE MODEL

In a crossover design, each of n subjects is used on $p \geq 2$ occasions, called periods, for the purpose of evaluating and studying $t \geq 2$ treatments. For given t, n, and p, we denote the class of all such designs by $\Omega_{t,n,p}$. For a continuous response Y, a possible model with random subject effects can be written as

$$E(Y_{dks}) = \mu + \alpha_k + \tau_{d(k,s)} + \gamma_{d(k-1,s)},$$
$$\operatorname{var}(Y_{dks}) = \sigma_\beta^2 + \sigma^2, \tag{1}$$
$$\operatorname{cov}(Y_{dk_1s_1}, Y_{dk_2s_2}) = \begin{cases} \sigma_\beta^2 & \text{if } s_1 = s_2 \text{ and } k_1 \neq k_2 \\ 0 & \text{if } s_1 \neq s_2. \end{cases}$$

Here Y_{dks} denotes the response from subject s in period k to which treatment $d(k,s)$ was assigned by design $d \in \Omega_{t,n,p}$, $k = 1, \ldots, p$, and $s = 1, \ldots, n$. Furthermore, μ is the general mean, α_k is the kth period effect, $\tau_{d(k,s)}$ is the (direct) treatment effect of treatment $d(k,s)$, and $\gamma_{d(k-1,s)}$ is the (first-order) carryover or residual effect of treatment $d(k-1,s)$ that subject s received in the previous period (by convention $\gamma_{d(0,s)} = 0$). Finally, σ_β^2 is the subject effects variance, and σ^2 is the error variance.

Writing the $np \times 1$ response vector as $\mathbf{Y}_d = (Y_{d11}, Y_{d21}, \ldots, Y_{dpn})'$, we can write model (1) in matrix notation as

$$E(\mathbf{Y}_d) = \mathbf{1}_{np}\mu + \mathbf{P}\boldsymbol{\alpha} + \mathbf{T}_d\boldsymbol{\tau} + \mathbf{F}_d\boldsymbol{\gamma},$$
$$\operatorname{var}(\mathbf{Y}_d) = \sigma^2(\mathbf{I}_n \otimes (\mathbf{I}_p + \theta\mathbf{J}_p)), \tag{2}$$

where $\theta = \sigma_\beta^2/\sigma^2$. Here $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_p)'$, $\boldsymbol{\tau} = (\tau_1, \ldots, \tau_t)'$, $\boldsymbol{\gamma} = (\gamma_1, \ldots, \gamma_t)'$, $\mathbf{P} = \mathbf{1}_n \otimes \mathbf{I}_p$, and $\mathbf{T}_d$ and $\mathbf{F}_d$ denote the treatment and carryover incidence matrices. In presenting this model, we use $\otimes$ to denote the Kronecker product. We denote $\sigma^{-2}\operatorname{var}(\mathbf{Y}_d)$ by $\mathbf{V}$, which, from (2), depends on the unknown variance components only through θ. Thus $\operatorname{var}(\mathbf{Y}_d) = \sigma^2\mathbf{V}$, where $\mathbf{V} = \mathbf{I}_n \otimes (\mathbf{I}_p + \theta\mathbf{J}_p)$.

When using a crossover design, everything possible should be done to avoid carryover effects. But if it is not clear that this can indeed be accomplished, then the possible carryover effects should be modeled. Although the approach used here has come under some scrutiny (see, e.g., Fleiss 1989; Senn 2002), a model with first-order carryover effects is a simple, popular model. Even though hardly anyone would argue that this model is correct for any application, it is useful for many applications and is generally preferable to ignoring carryover effects when they exist. The information matrix $\mathbf{C}_d$ for $\boldsymbol{\tau}$ under model (2) can now be expressed as

$$\mathbf{C}_d = \mathbf{T}_d'\mathbf{V}^{-1/2} \times pr^\perp([\mathbf{V}^{-1/2}\mathbf{1}_{np} \mid \mathbf{V}^{-1/2}\mathbf{P} \mid \mathbf{V}^{-1/2}\mathbf{F}_d])\mathbf{V}^{-1/2}\mathbf{T}_d, \tag{3}$$

where $pr^\perp(\mathbf{X}) = \mathbf{I} - pr(\mathbf{X})$ and $pr(\mathbf{X}) = \mathbf{X}(\mathbf{X}'\mathbf{X})^-\mathbf{X}'$.

Two extreme cases are worth mentioning. The case where $\theta = 0$ corresponds to the situation of no subject effects. It is seen easily that $\lim_{\theta\to 0}\mathbf{C}_d = \mathbf{T}_d'pr^\perp([\mathbf{1}_{np}|\mathbf{P}|\mathbf{F}_d])\mathbf{T}_d$, which would indeed be precisely the information matrix for $\boldsymbol{\tau}$ if we were to ignore subject effects. Conceptually, in this case we may think of the subjects as carbon copies of each other.

The other extreme case corresponds to $\theta = \infty$. It is not hard to show that

$$\lim_{\theta\to\infty}\mathbf{C}_d = \mathbf{T}_d'pr^\perp([\mathbf{1}_{np}|\mathbf{P}|\mathbf{U}|\mathbf{F}_d])\mathbf{T}_d,$$

where $\mathbf{U} = \mathbf{I}_n \otimes \mathbf{1}_p$. This limit is precisely the information matrix that we would have obtained had we treated subject effects as fixed. In this case we can view the subjects as being so different that each subject represents its own universe rather than all subjects representing a common population. Thus letting θ vary between the two extremes spans the spectrum between ignoring subject effects and using fixed subject effects.

3. PRELIMINARY TOOLS

Using a seminal contribution by Kiefer (1975), a design d^* in $\Omega_{t,n,p}$ is universally optimal in a subclass Ω if d^* belongs to the subclass, maximizes the trace of $\mathbf{C}_d$ over Ω, and has a completely symmetric information matrix $\mathbf{C}_{d^*}$. A closed-form expression for the trace of $\mathbf{C}_d$ may not be available, however, making a direct maximization of the trace infeasible. To circumvent this problem, we use a strategy that has been proven successful elsewhere. It consists of two steps: (1) For any design d in $\Omega_{t,n,p}$ or in a subclass of interest, find a manageable upper bound for the trace of $\mathbf{C}_d$ (which may depend on d), and (2) find a design d^* in the class of interest that maximizes the upper bound, for which the upper bound coincides with the trace of $\mathbf{C}_{d^*}$ and for which $\mathbf{C}_{d^*}$ is completely symmetric. If such a design d^* exists (and there is no guarantee that it will), then it is universally optimal in the class under consideration. Even if there is no such design, just finding a design that maximizes the upper bound will help provide a lower bound for the efficiency of any existing design.

In pursuing this strategy, we start with a lemma (see the App. for a proof) that provides an upper bound for $\mathbf{C}_d$ in the Loewner ordering, which is obtained by ignoring period effects.

Lemma 1. Under model (2), for any crossover design d,

$$\mathbf{C}_d \leq \mathbf{T}_d'\mathbf{V}^{-1/2}pr^\perp(\mathbf{1}_{np} \mid \mathbf{V}^{-1/2}\mathbf{F}_d)\mathbf{V}^{-1/2}\mathbf{T}_d, \tag{4}$$

with equality if $\mathbf{T}_d'\mathbf{P} = \mathbf{T}_d'\mathbf{1}_{np}\mathbf{1}_p'/p$.

Designs that are uniform on periods, which means that all treatments are equally replicated for each period, are examples of designs that satisfy the condition $\mathbf{T}_d'\mathbf{P} = \mathbf{T}_d'\mathbf{1}_{np}\mathbf{1}_p'/p$.

Using Lemma 1, we now obtain a relatively simple and achievable upper bound for $\operatorname{Tr}(\mathbf{C}_d)$ as well as conditions that imply equality. We use the following notation:

$$q_{11}(d) = \operatorname{Tr}(\mathbf{T}_d'\mathbf{V}^{-1/2}pr^\perp(\mathbf{1}_{np})\mathbf{V}^{-1/2}\mathbf{T}_d),$$
$$q_{12}(d) = \operatorname{Tr}(\mathbf{T}_d'\mathbf{V}^{-1/2}pr^\perp(\mathbf{1}_{np})\mathbf{V}^{-1/2}\mathbf{F}_d), \tag{5}$$
$$q_{22}(d) = \operatorname{Tr}(pr^\perp(\mathbf{1}_t)\mathbf{F}_d'\mathbf{V}^{-1/2}pr^\perp(\mathbf{1}_{np})\mathbf{V}^{-1/2}\mathbf{F}_d).$$

Theorem 1. For any design $d \in \Omega_{t,n,p}$, we have that

$$\mathrm{Tr}(\mathbf{C}_d) \le q_{11}(d) - \frac{q_{12}(d)^2}{q_{22}(d)}. \qquad (6)$$

Equality holds in (6) if the following conditions are true:

(a) $\mathbf{T}_d'\mathbf{P} = \mathbf{T}_d'\mathbf{1}_{np}\mathbf{1}_p'/p$.

(b) Each of the three matrices $\mathbf{T}_d'\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{1}_{np})\mathbf{V}^{-1/2}\mathbf{T}_d$, $\mathbf{T}_d'\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{1}_{np})\mathbf{V}^{-1/2}\mathbf{F}_d$, and $\mathbf{F}_d'\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{1}_{np})\mathbf{V}^{-1/2}\mathbf{F}_d$ is completely symmetric.

Proof. With $N = t!$, let $\mathbf{S}_1 = \mathbf{I}_t, \mathbf{S}_2, \dots, \mathbf{S}_N$ denote all $t \times t$ permutation matrices. By Lemma 1 and proposition 1 of Kunert and Martin (2000a), we have that

$$\sum_{i=1}^{N}\mathbf{S}_i'\mathbf{C}_d\mathbf{S}_i \le \left(\sum_{i=1}^{N}\mathbf{S}_i'\mathbf{T}_d'\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{1}_{np})\mathbf{V}^{-1/2}\mathbf{T}_d\mathbf{S}_i\right) - \left(\sum_{i=1}^{N}\mathbf{S}_i'\mathbf{T}_d'\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{1}_{np})\mathbf{V}^{-1/2}\mathbf{F}_d\mathbf{S}_i\right) \times \left(\sum_{i=1}^{N}\mathbf{S}_i'\mathbf{F}_d'\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{1}_{np})\mathbf{V}^{-1/2}\mathbf{F}_d\mathbf{S}_i\right)^{-} \times \left(\sum_{i=1}^{N}\mathbf{S}_i'\mathbf{F}_d'\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{1}_{np})\mathbf{V}^{-1/2}\mathbf{T}_d\mathbf{S}_i\right). \qquad (7)$$

Equality in (7) holds if equality holds in our Lemma 1 and in proposition 1 of Kunert and Martin (2000a). The two conditions in the statement of Theorem 1 ensure that these equalities hold.

The four matrices in parentheses on the right side of (7) are all completely symmetric. Using the q_{ij}'s defined just before Theorem 1, it follows that

$$\sum_{i=1}^{N}\mathbf{S}_i'\mathbf{T}_d'\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{1}_{np})\mathbf{V}^{-1/2}\mathbf{T}_d\mathbf{S}_i = \frac{Nq_{11}(d)}{t-1}pr^{\perp}(\mathbf{1}_t),$$
$$\sum_{i=1}^{N}\mathbf{S}_i'\mathbf{T}_d'\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{1}_{np})\mathbf{V}^{-1/2}\mathbf{F}_d\mathbf{S}_i = \frac{Nq_{12}(d)}{t-1}pr^{\perp}(\mathbf{1}_t), \qquad (8)$$
$$\sum_{i=1}^{N}\mathbf{S}_i'\mathbf{F}_d'\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{1}_{np})\mathbf{V}^{-1/2}\mathbf{F}_d\mathbf{S}_i = \frac{Nq_{22}(d)}{t-1}pr^{\perp}(\mathbf{1}_t) + z\mathbf{J}_t$$

for some z. It now follows easily from (7) and (8) that

$$\mathrm{Tr}(\mathbf{C}_d) = \frac{1}{N}\mathrm{Tr}\left(\sum_{i=1}^{N}\mathbf{S}_i'\mathbf{C}_d\mathbf{S}_i\right) \le q_{11}(d) - \frac{q_{12}(d)^2}{q_{22}(d)}.$$

Theorem 1 requires some additional discussion. The three matrices in condition (b) in the statement of the theorem depend on the value of θ. If the complete symmetry of these matrices holds for just one particular value of θ, rather than for a range of θ-values, then the theorem will not be very useful for identifying optimal designs. We then might be able to find an optimal design for a particular value of θ, but because, in practice we will not know the value of θ, this is not very helpful. Fortunately, there are designs d for which the matrices in condition (b) of Theorem 1 are completely symmetric for *any* value of θ, while at the same time meeting the requirement in condition (a).

To see this, we note that the matrix $\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{1}_{np})\mathbf{V}^{-1/2}$, which shows up repeatedly in condition (b), can be rewritten using some algebra as

$$\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{1}_{np})\mathbf{V}^{-1/2} = \frac{1}{1+\theta p}[pr^{\perp}(\mathbf{1}_n)\otimes pr(\mathbf{1}_p)] + pr^{\perp}(\mathbf{U}), \qquad (9)$$

where, as before, $\mathbf{U} = \mathbf{I}_n \otimes \mathbf{1}_p$. Hence if $\mathbf{T}_d'\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{1}_{np}) \times \mathbf{V}^{-1/2}\mathbf{T}_d$ is completely symmetric for two values of $\theta \in [0,\infty]$, then it is completely symmetric for all values of θ in this interval. A similar statement applies with one or both matrices $\mathbf{T}_d$ replaced by $\mathbf{F}_d$. Hence, to check whether a design satisfies condition (b) in Theorem 1 for all θ, we merely need to check that it satisfies the condition for two values of θ. We select two convenient values of θ to do this:

$\theta = \infty$: $\mathbf{T}_d'pr^{\perp}(\mathbf{U})\mathbf{T}_d$, $\mathbf{T}_d'pr^{\perp}(\mathbf{U})\mathbf{F}_d$, and $\mathbf{F}_d'pr^{\perp}(\mathbf{U})\mathbf{F}_d$ must all be completely symmetric

and

$\theta = 0$: $\mathbf{T}_d'pr^{\perp}(\mathbf{1}_{np})\mathbf{T}_d$, $\mathbf{T}_d'pr^{\perp}(\mathbf{1}_{np})\mathbf{F}_d$, and $\mathbf{F}_d'pr^{\perp}(\mathbf{1}_{np})\mathbf{F}_d$ must all be completely symmetric.

Adding condition (a) of Theorem 1 to the mix, it is now not hard to see that any design with the following properties will satisfy conditions (a) and (b) in Theorem 1 for all θ:

- The design is uniform on the periods.
- Considering the design as a block design with the subjects as the blocks, the design is a balanced block design.
- After deleting the last period of the design and again considering the subjects as the blocks, the design is still a balanced block design (but now with blocks of size $p-1$).
- Throughout the design, the number of times that treatment i is immediately preceded by treatment i' in a treatment sequence is independent of the choice of i and i', $i' \neq i$.
- For any treatment i, when considering the subjects that receive this treatment in the last period, the other $t-1$ treatments must be equally replicated over these subjects.

The totally balanced designs defined by Kunert and Stufken (2002) satisfy all of these properties.

4. OPTIMAL AND EFFICIENT DESIGNS WHEN $p \le t$

For given t, n, and p, our main goal is to identify and characterize the structure of optimal and efficient designs in the entire class of designs $\Omega_{t,n,p}$. Of course, answers may depend on the value of θ, and we would also like to discover how the answer changes as θ changes.

The problem of identifying optimal designs in this entire class turns out to be more difficult than we can handle. Therefore, we adopt the strategy of identifying optimal designs in two very large subclasses and developing bounds for the efficiency of these designs in the entire class $\Omega_{t,n,p}$. The two subclasses that we study are defined as follows:

- $\Omega^1 = \Omega^1_{t,n,p}$: The subclass of $\Omega_{t,n,p}$ consisting of all designs in which each treatment is replicated n/t times in the last period.

- $\Omega^2 = \Omega^2_{t,n,p}$: The subclass of $\Omega_{t,n,p}$ consisting of all designs in which each treatment is replicated n/t times in the last period and in which no treatment is immediately preceded by itself in any of the treatment sequences of the design.

The restrictions that define these two subclasses are used solely for technical reasons, but they are very mild. It would not be at all surprising that a design that is universally optimal in Ω^1 is also universally optimal in $\Omega_{t,n,p}$. We also note that although it may seem redundant to study Ω^2 if we are able to identify optimal designs in the larger subclass Ω^1, an appealing property of Ω^2 is, as we show, that it allows designs that are universally optimal irrespective of the value of θ. In our deliberations, we pay special attention to the important case where $p = t$.

4.1 Optimal Designs in $\Omega^2_{t,n,p}$

If $p \le t$, then using a design that assigns to each subject a sequence of p distinct treatments is often appealing. Any such design in which each treatment appears equally often in the last period belongs to the class Ω^2, which also contains many designs that contain sequences that repeat treatments (just not in consecutive periods). The optimal designs identified in Theorem 2 (see the App. for the outline of a proof) do not repeat treatments for a subject and are optimal irrespective of the value of θ, including the limiting case $\theta = \infty$, which corresponds to fixed subject effects.

Theorem 2. For given t, n, and p, $p \le t$, a design d^* is universally optimal for $\boldsymbol{\tau}$ in $\Omega^2_{t,n,p}$ under model (2), irrespective of the value of θ, if d^* satisfies the two conditions stated in Theorem 1 and is equally replicated, and if each treatment appears no more than once for each subject.

A totally balanced design for $p \le t$ (Kunert and Stufken 2002) satisfies all of the conditions in Theorem 2 and is therefore universally optimal for $\boldsymbol{\tau}$ in Ω^2 for any θ. In particular, when $p = t$, we conclude that balanced uniform designs are optimal.

Example 1. When $t = 4$, $n = 12$, and $p = 3$, design d_1 is universally optimal for $\boldsymbol{\tau}$ in $\Omega^2_{4,12,3}$,

$$d_1:\quad \begin{matrix} 3\,4\,2\,4\,1\,3\,2\,4\,1\,3\,1\,2 \\ 1\,1\,1\,2\,2\,2\,3\,3\,3\,4\,4\,4 \\ 2\,3\,4\,1\,3\,4\,1\,2\,4\,1\,2\,3 \end{matrix}.$$

Example 2. When $t = 5$, $n = 20$, and $p = 3$, design d_2 is universally optimal for $\boldsymbol{\tau}$ in $\Omega^2_{5,20,3}$,

$$d_2:\quad \begin{matrix} 1\,2\,3\,4\,5\,4\,3\,2\,1\,5\,1\,3\,5\,2\,4\,2\,5\,3\,1\,4 \\ 5\,1\,2\,3\,4\,5\,4\,3\,2\,1\,4\,1\,3\,5\,2\,4\,2\,5\,3\,1 \\ 2\,3\,4\,5\,1\,3\,2\,1\,5\,4\,3\,5\,2\,4\,1\,5\,3\,1\,4\,2 \end{matrix}.$$

4.2 Optimal and Efficient Designs in $\Omega^1_{t,n,p}$ and $\Omega_{t,n,p}$

When we lift the constraint for designs in Ω^2 that a treatment sequence cannot repeat treatments in consecutive periods, totally balanced designs are generally no longer optimal. How efficient are totally balanced designs in Ω^1, and what is the structure of optimal designs in this class? How does this change when θ changes? And how efficient are these designs in the entire class $\Omega_{t,n,p}$?

Theorem 3 (see the App. for the outline of the proof) identifies the structure of optimal designs in Ω^1 for a given θ. More importantly, it provides an attainable upper bound for $\mathrm{Tr}(\mathbf{C}_d)$ for any design d in the subclass. For fixed t, n, p, and θ, we use z_1 to denote the nearest integer to $\frac{n(p-1)(\theta^2+p\theta+1)}{t(p\theta-\theta+1)^2}$.

Theorem 3. For given t, n, p, and θ, $p \le t$, design $\hat{d}$ is universally optimal for $\boldsymbol{\tau}$ in the subclass $\Omega^1_{t,n,p}$ if it satisfies the two conditions stated in Theorem 1 and is equally replicated, and if any treatment appears no more than once for any subject, except that z_1 subjects receive the same treatment in period p as in period $p-1$. Moreover, $\mathrm{Tr}(\mathbf{C}_{\hat{d}}) = f_{(t,n,p,\theta)}(z_1)$, where

$$f_{(t,n,p,\theta)}(z) = n(p-1) + \frac{n(t-p) - 2t\theta z}{t(1+p\theta)} - \frac{(n(p-1)(t\theta+1) - z(tp\theta - t\theta + t))^2}{t^2(1+p\theta)^2\left[n(p-1)\left(1 - \frac{1}{tp} - \frac{tp\theta+p-1}{tp(1+p\theta)}\right)\right]}.$$

As a function of θ, z_1 is either constant (if $p = 2$) or strictly decreasing (if $p \ge 3$). Hence z_1 will take values from its maximum of $n(p-1)/t$ when $\theta = 0$ to its minimum of $n/t(p-1)$ when $\theta = \infty$. So for $p \ge 3$, efficient designs in Ω^1 will tend to have more subjects that receive the same treatment in periods $p-1$ and p for small values of θ than for large values of θ. Because $\theta \to \infty$ corresponds to the fixed subject effects model, this implies that the optimal design when assuming fixed subject effects has the smaller number of subjects that receive the same treatment in periods $p-1$ and p.

If a design d satisfies all of the conditions in Theorem 3, except that it uses the same treatment in periods $p-1$ as p for z_d subjects, say, rather than for z_1 subjects, then design d has a completely symmetric information matrix with $\mathrm{Tr}(\mathbf{C}_d) = f_{(t,n,p,\theta)}(z_d)$. A lower bound for the efficiency of this design in Ω^1 may be computed as $f_{(t,n,p,\theta)}(z_d)/f_{(t,n,p,\theta)}(z_1)$. In particular, a totally balanced design that was seen to be universally optimal for any θ in Ω^2 has an efficiency of at least $f_{(t,n,p,\theta)}(0)/f_{(t,n,p,\theta)}(z_1)$ in Ω^1.

Identifying the structure of universally optimal designs becomes difficult when considering the entire class $\Omega_{t,n,p}$. But Theorem 4 presents an upper bound for $\mathrm{Tr}(\mathbf{C}_d)$ in this class, which can then be used to compute lower bounds for the efficiency of any design under consideration. We do not know whether this upper bound for $\mathrm{Tr}(\mathbf{C}_d)$ can actually be attained. (A proof of Thm. 4, along the lines of the proof for Thm. 3, can be found in Hedayat, Stufken, and Yang 2005.)

To formulate the result, let $\lfloor y \rfloor$ be the largest integer less than or equal to y. We define

$$\Delta(t,n,p) = \begin{cases} np\left\lfloor \dfrac{n(4p^2-4p+1-t)}{4tp} \right\rfloor, & \text{when } t \le 2p-1 \\ np\left\lfloor \dfrac{n(p-1)^2}{p(t-1)} \right\rfloor, & \text{when } t > 2p-1. \end{cases} \tag{10}$$

We also use z_0 to denote the nearest integer to $\frac{n^2p(p-1)\theta^2+[n^2p(p-1)+t(p-1)\Delta(t,n,p)]\theta+t\Delta(t,n,p)}{ntp(p\theta-\theta+1)^2}$.

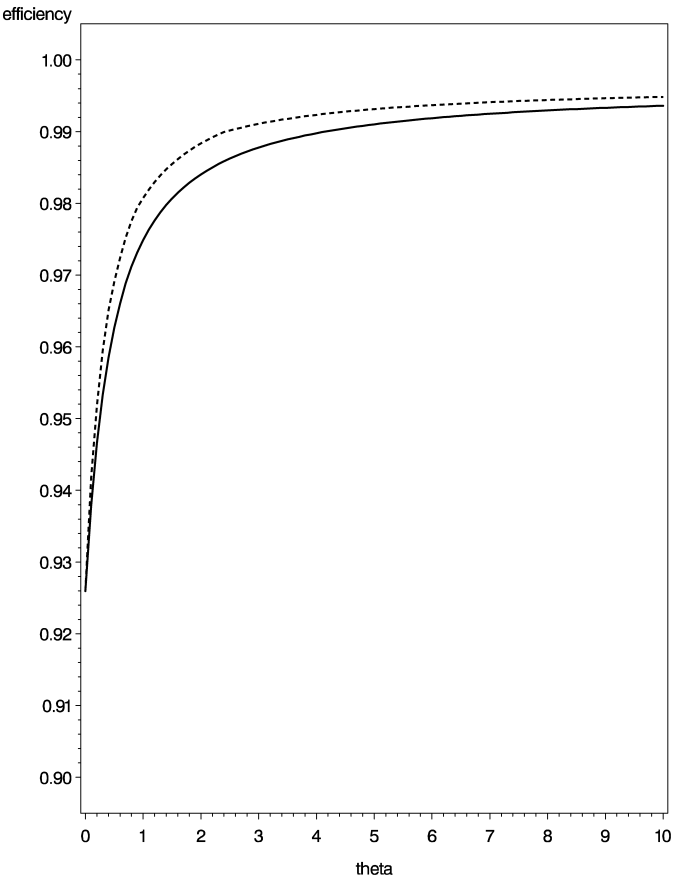

Figure 1. Efficiencies of Design d_1 in $\Omega^1_{t,n,p}$ and $\Omega_{t,n,p}$ (------ subclass; —— entire class).

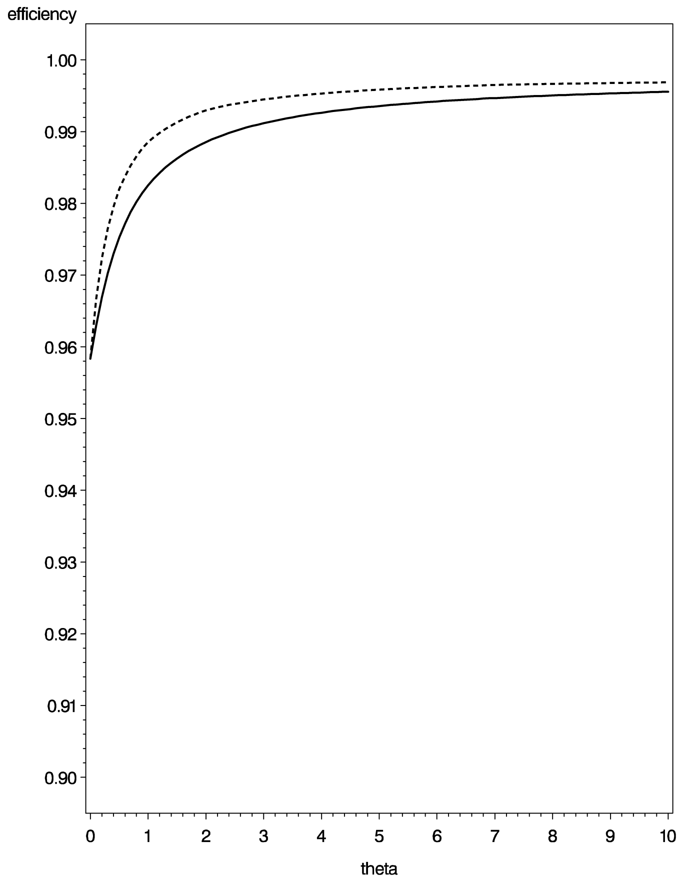

Figure 2. Efficiencies of Design d_2 in $\Omega^1_{t,n,p}$ and $\Omega_{t,n,p}$ (------ subclass; —— entire class).

Theorem 4. For given t, n, p, and θ, $p \le t$, we have that for any design $d \in \Omega_{t,n,p}$, $\mathrm{Tr}(\mathbf{C}_d) \le g_{(t,n,p,\theta)}(z_0)$, where

$$g_{(t,n,p,\theta)}(z) = n(p-1) + \frac{n(t-p) - 2t\theta z}{t(1+p\theta)} - \frac{[n^2p(p-1)\theta + \Delta(t,n,p) - np(p\theta - \theta + 1)z]^2}{n^3p^2(p-1)(1+p\theta)^2(1 - \frac{1}{tp} - \frac{tp\theta+p-1}{tp(1+p\theta)})}. \quad (11)$$

In particular, we can now conclude that a totally balanced design d^* has an efficiency of at least $f_{(t,n,p,\theta)}(0)/g_{(t,n,p,\theta)}(z_0)$ in the entire class $\Omega_{t,n,p}$.

Figures 1 and 2 show the efficiency lower bounds for the totally balanced designs d_1 (in $\Omega^1_{4,12,3}$ and $\Omega_{4,12,3}$) and d_2 (in $\Omega^1_{5,20,3}$ and $\Omega_{5,20,3}$) as functions of θ. These figures clearly show that the bounds for Ω^1 and Ω are close for these designs, which we know to be universally optimal in Ω^2. That these bounds are so close is a reflection of how close $f(z_1)$ and $g(z_0)$ are. We also see that there is more potential for finding better designs when θ is small than for large θ, which is consistent with the earlier observation concerning the monotonicity of z_1 as a function of θ. The conclusions from considering these two designs agree with those from other designs that we considered.

4.3 Efficient Designs When $p = t$

When $p = t$, optimal crossover designs have been extensively studied for the model with fixed subject effects. Balanced uniform designs (BUDs), which belong to the class of totally balanced designs when $p = t$, have played a pivotal role in some of these studies. Kunert (1984) and Hedayat and Yang (2003, 2004) showed that BUDs are universally optimal in $\Omega_{t,n,t}$ when n is not too large compared with t. But Kunert (1984) already observed that BUDs do not remain optimal if n/t is large. In that case, more efficient designs can be obtained by assigning to some subjects the same treatment in periods $t-1$ and t. Hedayat and Yang (2004) showed that designs suggested by Stufken (1991), which assign to $n/t(t-1)$ subjects the same treatment in the last two periods, are now universally optimal in the entire class $\Omega_{t,n,t}$. Nevertheless, under the fixed-effects model, BUDs remain efficient in the entire class even when they are not optimal.

Because z_1 in Theorem 3 is a decreasing function of θ if $p \ge 3$, we can expect that the efficiency of BUDs is not as good for model (2) as for the model with fixed subjects effects. The efficiency bound is a function of θ and is largest for $\theta = \infty$ (which corresponds to the fixed-effects model) and smallest for $\theta = 0$ (which assumes that subjects are carbon copies of each other). But how small can it get, and how does it change with θ? Should we consider alternative designs?

The efficiency bound for a BUD can be computed as $f_{(t,n,t,\theta)}(0)/g_{(t,n,t,\theta)}(z_0)$ in the entire class. Figure 3 provides

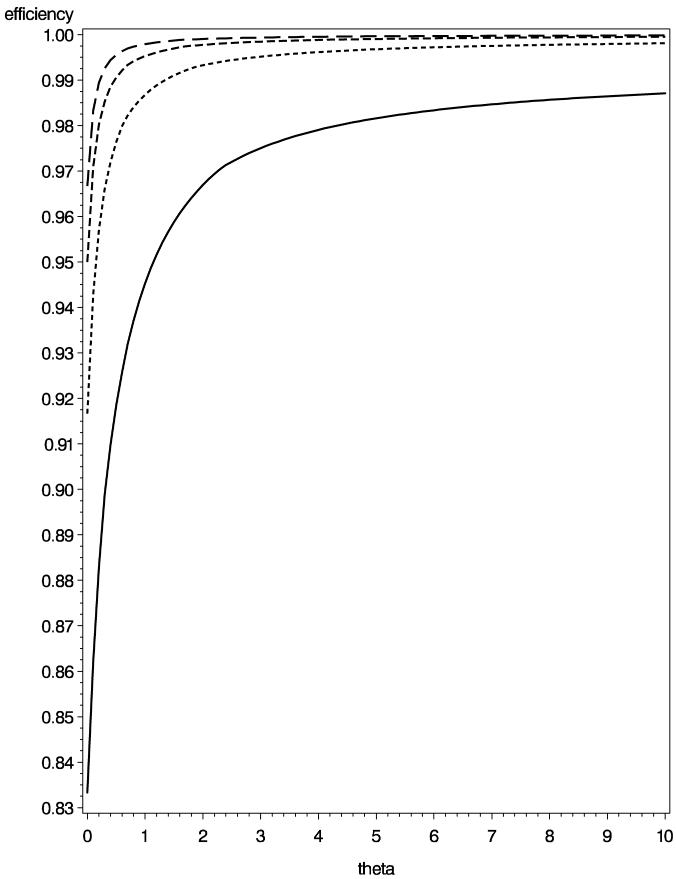

Figure 3. Efficiencies of Balanced Uniform Design in the Entire Class (—— 3; ------ 4; ---- 5; — — 6).

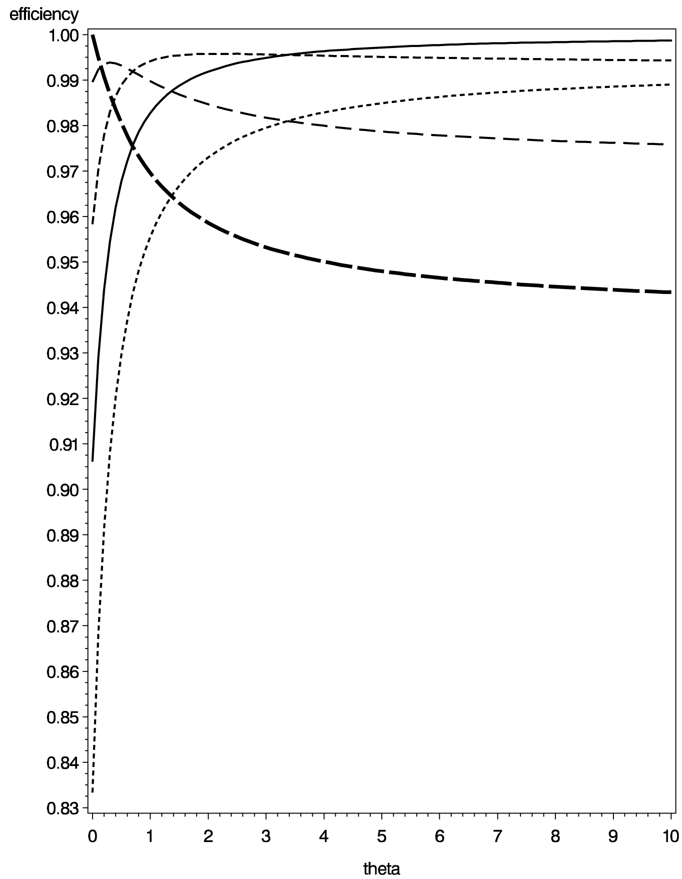

Figure 4. Efficiencies of d_3–d_7 in $\Omega_{t=3,n=36,p=3}$ (------ d_3; —— d_4; ---- d_5; — — d_6; ▬ ▬ d_7).

a graphical presentation of the results of these computations for $t = 3$ through 6 and $n = 2t$ as a function of θ. The efficiencies are not very good for θ near 0, especially for smaller t, but become quite acceptable for most purposes when θ increases. A similar graph for $n = 100t$ would look virtually the same as Figure 3.

We now take a closer look at a particular case: $t = p = 3$ and $n = 36$. Typically, we will not know θ, so that we cannot compute z_1 of Theorem 3. (We might have some idea about θ from past experience and could base our choice on that.) But, based on this theorem, we know that the value of z_1 for this particular case will be between 6 and 24. Therefore, we compare five designs, all of which use the following two smaller designs as building blocks:

$$a_1:\ \begin{matrix} 1\,2\,3\,1\,2\,3 \\ 3\,1\,2\,2\,3\,1 \\ 2\,3\,1\,3\,1\,2 \end{matrix} \quad \text{and} \quad a_2:\ \begin{matrix} 1\,2\,3\,1\,2\,3 \\ 3\,1\,2\,2\,3\,1 \\ 3\,1\,2\,2\,3\,1 \end{matrix}.$$

For $i = 3$–7, let design d_i be obtained by using each sequence in a_1 for $9 - i$ subjects and each sequence in a_2 for $i - 3$ subjects. Designs d_3–d_7, all of which belong to $\Omega_{3,36,3}$, satisfy the two conditions in Theorem 1 and have completely symmetric information matrices. They assign to 0, 6, 12, 18, and 24 subjects the same treatment in the last two periods. Design d_3 is a balanced uniform design, and design d_4 is the universally optimal design for the fixed-effects model proposed by Stufken (1991). Note that, by Theorem 3, designs d_4, d_5, d_6, and d_7 are universally optimal in $\Omega^1_{t=3,n=36,p=3}$ when $\theta \geq 23.3743$, $1.2114 \leq \theta \leq 1.5486$, $.3123 \leq \theta \leq .3982$, and $\theta \leq .0212$.

Figure 4 shows how the efficiency bounds for these five designs change with θ under the random subject effects model. As expected from the results in the previous sections, design d_3 (the BUD) is dominated by design d_4 (Stufken's design) and also by design d_5.

If θ could be small (say, <1) then design d_6 would be a good choice. It has a high efficiency for small θ, and its curve does not drop off as rapidly for larger θ as that of design d_7. If θ was expected to be larger, then designs d_4 and d_5 would be good choices.

5. DISCUSSION AND FUTURE RESEARCH

We have shown that totally balanced designs are universally optimal for treatment effects in a large class of designs, irrespective of the value of θ, the ratio of the subject effects variance and the error variance. This class, Ω^2, contains many designs that have strong practical appeal for the case $p \leq t$. Nevertheless, in the entire class of designs, or even in the subclass Ω^1, totally balanced designs are not optimal, and which design is optimal depends on the value of θ. Optimal designs in Ω^1 include some treatment sequences that use the same treatment in period $p - 1$ as in period p. For example, the designs proposed by Stufken (1991), which where shown to be universally optimal for the case of fixed subjects effects ($\theta = \infty$) by Hedayat and Yang (2004), generally outperform totally balanced designs.

Nevertheless, as shown by the tools provided in this article totally balanced designs are highly efficient in most situations. The only possible exception is for very small values of θ, when optimal designs require more treatment sequences that repeat a treatment in the last two periods than for larger values of θ. This follows from Theorem 3 and the observation that z_1 is a decreasing function of θ.

Thus an important message of this article is that designs that are "good" when subject effects are fixed are generally also good when subject effects are random. For those who have already used designs that are efficient under the fixed subjects effects model, this message has no practical consequences. Nevertheless, this article makes this message precise and provides tools for evaluating these and other designs under the random subject effects model given in (1).

There are other situations in which one could study the precise implications of treating subject effects as random. This includes models in which error terms are correlated (see, e.g., Kunert and Martin 2000b) and the problem of comparing test treatments to a control (see, e.g., Hedayat and Yang 2005). It is likely that here, too, the impact of random subject effects is limited for the design choice, but a precise analysis of this is currently not available. Other topics requiring more consideration, for both fixed and random subject effects, include identifying optimal or efficient crossover designs for categorical data and/or in the presence of covariates.

APPENDIX: PROOFS

Proof of Lemma 1

From the expression in (3), we have that

$$\begin{aligned}\mathbf{C}_d &= \mathbf{T}_d'\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{V}^{-1/2}\mathbf{1}_{np} \mid \mathbf{V}^{-1/2}\mathbf{F}_d)\mathbf{V}^{-1/2}\mathbf{T}_d \\ &\quad - \mathbf{T}_d'\mathbf{V}^{-1/2}pr\big(pr^{\perp}(\mathbf{V}^{-1/2}\mathbf{1}_{np} \mid \mathbf{V}^{-1/2}\mathbf{F}_d)\mathbf{V}^{-1/2}\mathbf{P}\big) \\ &\quad \times \mathbf{V}^{-1/2}\mathbf{T}_d. \qquad (A.1)\end{aligned}$$

Because $\mathbf{V}^{-1/2}\mathbf{1}_{np}$ is a multiple of $\mathbf{1}_{np}$, (4) follows immediately. Equality holds if and only if

$$\mathbf{T}_d'\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{V}^{-1/2}\mathbf{1}_{np} \mid \mathbf{V}^{-1/2}\mathbf{F}_d)\mathbf{V}^{-1/2}\mathbf{P} = \mathbf{0}. \qquad (A.2)$$

When $\mathbf{T}_d'\mathbf{P} = \mathbf{T}_d'\mathbf{1}_{np}\mathbf{1}_p'/p$, there are matrices $\mathbf{A}$, $\mathbf{B}$, and $\mathbf{C}$ such that $\mathbf{P} = \frac{1}{p-1}(\mathbf{A}+\mathbf{B})$, $(\mathbf{1}_{np}|\mathbf{F}_d)'\mathbf{B} = \mathbf{0}$, $\mathbf{T}_d'\mathbf{B} = \mathbf{0}$, and $(\mathbf{V}^{-1/2}\mathbf{1}_{np}|\mathbf{V}^{-1/2} \times \mathbf{F}_d)\mathbf{C} = \mathbf{V}^{-1/2}\mathbf{A}$ (see Hedayat et al. 2005 for details). This implies that

$$\begin{aligned}&\mathbf{T}_d'\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{V}^{-1/2}\mathbf{1}_{np} \mid \mathbf{V}^{-1/2}\mathbf{F}_d)\mathbf{V}^{-1/2}\mathbf{P} \\ &\quad = \frac{1}{p-1}\mathbf{T}_d'\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{V}^{-1/2}\mathbf{1}_{np} \mid \mathbf{V}^{-1/2}\mathbf{F}_d)\mathbf{V}^{-1/2}\mathbf{B} \\ &\quad = \frac{1}{p-1}\mathbf{T}_d'\mathbf{B} = \mathbf{0}. \qquad (A.3)\end{aligned}$$

For $i, j = 1, \dots, t$, $s = 1, \dots, n$, and $k = 1, \dots, p$, we use the following notation for a design $d \in \Omega_{t,n,p}$:

- n_{dis}, the number of times that d assigns treatment i to subject s
- $\tilde{n}_{dis}$, the number of times that this happens in the first $p-1$ periods
- l_{dik}, the number of times that d assigns treatment i to period k
- m_{dij}, the number of times in the treatment sequences of d that treatment i is immediately preceded by treatment j
- r_{di}, the replication of treatment i in d
- $\tilde{r}_{di}$, the replication of treatment i in the first $p-1$ periods of d.

Proposition A.1. For any design d, the quantities $q_{11}(d)$, $q_{12}(d)$, and $q_{22}(d)$ defined in (5) are equal to

$$\begin{aligned}q_{11}(d) &= np - \frac{\theta}{1+p\theta}\sum_{i=1}^{t}\sum_{s=1}^{n}n_{dis}^2 - \frac{1}{np(1+p\theta)}\sum_{i=1}^{t}r_{di}^2, \\ q_{12}(d) &= \sum_{i=1}^{t}m_{dii} - \frac{\theta}{1+p\theta}\sum_{i=1}^{t}\sum_{s=1}^{n}n_{dis}\tilde{n}_{dis} \\ &\quad - \frac{1}{np(1+p\theta)}\sum_{i=1}^{t}r_{di}\tilde{r}_{di}, \qquad (A.4) \\ q_{22}(d) &= n(p-1)(1-1/tp) - \frac{\theta}{1+p\theta}\sum_{i=1}^{t}\sum_{s=1}^{n}\tilde{n}_{dis}^2 \\ &\quad - \frac{1}{np(1+p\theta)}\sum_{i=1}^{t}\tilde{r}_{di}^2.\end{aligned}$$

Proof. Using the expressions in (5) and rewriting the expression in (9) as

$$\begin{aligned}&\mathbf{V}^{-1/2}pr^{\perp}(\mathbf{1}_{np})\mathbf{V}^{-1/2} \\ &\quad = \mathbf{I}_n \otimes \left(\mathbf{I}_p - \frac{\theta}{1+p\theta}\mathbf{J}_p\right) - \frac{1}{np(1+p\theta)}\mathbf{J}_{np}, \qquad (A.5)\end{aligned}$$

the result follows after lengthy but straightforward algebra.

Proof of Theorem 2

Let d^* be a design as in the statement of the theorem. The result follows if $\mathbf{C}_{d^*}$ is completely symmetric and its trace maximizes $\mathrm{Tr}(\mathbf{C}_d)$ over all designs in $\Omega_{t,n,p}^2$. Because d^* satisfies the two conditions in Theorem 1, by Lemma 1 and Theorem 1, $\mathbf{C}_{d^*}$ is completely symmetric, and its trace is equal to the upper bound in (6). Hence, using Proposition A.1, we merely need to show that d^* maximizes

$$\begin{aligned}&np - \frac{\theta}{1+p\theta}\sum_{i=1}^{t}\sum_{s=1}^{n}n_{dis}^2 - \frac{1}{np(1+p\theta)}\sum_{i=1}^{t}r_{di}^2 \\ &\quad - \left(\frac{\theta}{1+p\theta}\sum_{i=1}^{t}\sum_{s=1}^{n}n_{dis}\tilde{n}_{dis} + \frac{1}{np(1+p\theta)}\sum_{i=1}^{t}r_{di}\tilde{r}_{di}\right)^2 \\ &\quad \times \Bigg\{n(p-1)(1-1/tp) \\ &\qquad - \frac{\theta}{1+p\theta}\sum_{i=1}^{t}\sum_{s=1}^{n}\tilde{n}_{dis}^2 - \frac{1}{np(1+p\theta)}\sum_{i=1}^{t}\tilde{r}_{di}^2\Bigg\}^{-1} \qquad (A.6)\end{aligned}$$

over all $d \in \Omega_{t,n,p}^2$. It is clear that (A.6) is maximized if

$$\sum_{i=1}^{t}\sum_{s=1}^{n}n_{dis}^2, \quad \sum_{i=1}^{t}r_{di}^2, \quad \sum_{i=1}^{t}\sum_{s=1}^{n}\tilde{n}_{dis}^2, \quad \sum_{i=1}^{t}\tilde{r}_{di}^2,$$

$$\sum_{i=1}^{t}\sum_{s=1}^{n}n_{dis}\tilde{n}_{dis}, \quad \text{and} \quad \sum_{i=1}^{t}r_{di}\tilde{r}_{di}$$

are all minimized. It can be verified that d^* minimizes these terms; thus the conclusion follows.

Proof of Theorem 3

Let $\hat{d}$ be a design as in the statement of the theorem. That $\mathbf{C}_{\hat{d}}$ is completely symmetric and that its trace is equal to the upper bound in (6) follows as in the previous proof. Based on Proposition A.1, it remains to be shown that $\hat{d}$ maximizes

$$np - \frac{\theta}{1+p\theta}\sum_{i=1}^{t}\sum_{s=1}^{n} n_{dis}^2 - \frac{1}{np(1+p\theta)}\sum_{i=1}^{t} r_{di}^2$$
$$-\left(\sum_{i=1}^{t} m_{dii} - \frac{\theta}{1+p\theta}\sum_{i=1}^{t}\sum_{s=1}^{n} n_{dis}\widetilde{n}_{dis}\right.$$
$$\left. - \frac{1}{np(1+p\theta)}\sum_{i=1}^{t} r_{di}\widetilde{r}_{di}\right)^2$$
$$\times\left\{n(p-1)(1-1/tp) - \frac{\theta}{1+p\theta}\sum_{i=1}^{t}\sum_{s=1}^{n}\widetilde{n}_{dis}^2\right.$$
$$\left. - \frac{1}{np(1+p\theta)}\sum_{i=1}^{t}\widetilde{r}_{di}^2\right\}^{-1}$$

over $\Omega_{t,n,p}^1$. Using the definition of $\hat{d}$, it is easy to verify that $\sum_{i=1}^t \sum_{s=1}^n n_{\hat{d}is}^2 = np + 2z_1$, $\sum_{i=1}^t r_{\hat{d}i}^2 = n^2p^2/t$, $\sum_{i=1}^t m_{\hat{d}ii} = z_1$, $\sum_{i=1}^t \sum_{s=1}^n n_{\hat{d}is}\widetilde{n}_{\hat{d}is} = n(p-1) + z_1$, $\sum_{i=1}^t r_{\hat{d}i}\widetilde{r}_{\hat{d}i} = n^2p(p-1)/t$, $\sum_{i=1}^t \sum_{s=1}^n \widetilde{n}_{\hat{d}is}^2 = n(p-1)$, and $\sum_{i=1}^t \widetilde{r}_{\hat{d}i}^2 = n^2(p-1)^2/t$. By simple calculation, we can now verify that $\mathrm{Tr}(\mathbf{C}_{\hat{d}}) = f_{(t,n,p,\theta)}(z_1)$. Thus the result follows if we can show that $\mathrm{Tr}(\mathbf{C}_d) \le f_{(t,n,p,\theta)}(z_1)$ for any design $d \in \Omega_{t,n,p}^1$. This can be shown by distinguishing between the three cases $x_d \le n(p-1)/t$, $n(p-1)/t < x_d < n$, and $x_d \ge n$ (see Hedayat et al. 2005 for details).

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