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EFFICIENT DESIGNS FOR THE ESTIMATION OF MIXED AND SELF CARRYOVER EFFECTS

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Abstract: Biosimilars are copies of biological medicines developed after the patent for the originator drug (the reference product) has expired. Extensive clinical trials are required to show the therapeutic equivalence of the biosimilar and its reference product before the biosimilar can be sold on the market. However, even after more than 10 years of experience with biosimilars, there is still uncertainty whether patients can switch between the biosimilar and its reference product without negative effects. One convenient way to assess the impact of switches is to analyze their mixed and self carryover effects: if the products are switchable, there should be no difference between the carryover effects. For $p = 3$ periods (and the number of subjects is divisible by 8) and for $p \equiv 1 \bmod 4$ periods (and the number of subjects is divisible by 4), determine a series of simple designs that efficiently compare the mixed and self carryover effects of two treatments. The proof of the efficiency is not straightforward, because the information matrices of the efficient designs are not completely symmetric.

Key words and phrases: A-optimality, biosimilars, crossover designs.

1. Introduction

After the patent for a pharmaceutical product has expired, competing companies can produce and sell a copy of the originator product (the reference product). In the context of small molecule drugs, this is already well established, and the copied products are known as generics. However, for large molecule drugs (so-called biologics), it is not possible to produce an identical chemical copy (Schellekens (2004)). Therefore, we call a copy of a biologic a biosimilar. In order to obtain market authorization for a biosimilar, a company must show that there is no clinically relevant difference between the biosimilar and the originator product (equivalence testing). This typically means observing treatment-naive patients under continuous treatment with either the reference treatment or the test treatment, and then comparing their efficacy at a predefined time point.

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There is still limited experience with biosimilars in practice. Hence, there is some uncertainty among patients, physicians, and health care providers over whether a patient on an originator product can switch to a biosimilar. There is also a debate on whether substituting the treatment at the pharmacy level is acceptable (e.g., Ebber et al. (2012)). In practice, substitution could lead to multiple switches between a biosimilar and the originator product.

In order to establish that multiple switches do affect the efficacy and safety of a treatment, a crossover study can be conducted. Here the units are observed over several periods, where the treatment can change between periods. No carryover effects are assumed in the first period. Owing to the currently used parallel groups design, in practice, only the first period is observed for a market authorization decision. Therefore, a biosimilar is accepted if the direct effects are sufficiently similar. However, later periods may include carryover effects. One way of confirming that switching does not affect the efficacy of the treatment is to analyze the carryover effects.

We consider the model introduced by Afsarinejad and Hedayat (2002), which assumes that each treatment has two carryover effects: one is present if a subject stays on the treatment (self carryover effect), and the other is present if the subject changes to a different treatment (mixed carryover effect). Kunert and Stufken (2002, 2008) determined optimal crossover designs for estimating direct effects in this model. Kunert and Stufken (2008) deal with the case of two treatments, which is relevant for our application (biosimilar and reference product). However, when examining the switchability of a biosimilar and its reference product, the direct effects are not of primary interest because their equivalence will already have been established when demonstrating biosimilarity. The effects of switching should be visible in differences between the carryover effects. Thus, to confirm switchability, we need to focus on estimating the carryover effects. Unfortunately, the literature on optimal designs for estimating carryover effects is sparse. Cheng and Wu (1980) and Kunert (1983) provide some results for carryover effects in a simpler model in which the mixed and self carryover effects are assumed identical; however, they focus on estimating direct effects. In a model with self and mixed carryover effects, Druilhet and Tinsson (2014) derived optimal designs for total effects, where the total effect of a treatment is the sum of its direct and self carryover effects. In this study, we focus on efficient designs for estimating self and mixed carryover effects.

2. The Model

We consider a model where the response $y_{u,r}$ of subject u in period r depends on a treatment effect, subject effect, period effect, and mixed or self carryover effect. We distinguish between the treatment effects of the biosimilar and the originator, even though biosimilarity has already been established. Biosimilarity only means that the direct treatment effects are similar, but not necessarily identical. Therefore, including direct effects in the model avoids bias. The model is given by

$$y_{u,r} = \begin{cases} \alpha_u + \beta_r + \tau_{d(u,r)} + \rho_{d(u,r-1)} + e_{u,r}, \text{ if } d(u,r) \neq d(u,r-1), \\ \alpha_u + \beta_r + \tau_{d(u,r)} + \chi_{d(u,r-1)} + e_{u,r}, \text{ if } d(u,r) = d(u,r-1). \end{cases}$$

Here, $d(u,r)$ is the treatment assigned to subject u in period r $(1 \leq u \leq n, 1 \leq r \leq p)$ by the design d, α_u is the effect of subject u, β_r is the effect of period r, τ_i is the direct effect of treatment i $(1 \leq i \leq t)$, and ρ_i is the mixed carryover effect and χ_i is the self carryover effect of treatment i. No carryover effect is present in the first period; that is, $\rho_{d(u,0)} = \chi_{d(u,0)} = 0$. The errors $e_{u,r}$, for $1 \leq u \leq n, 1 \leq r \leq p$, are assumed to be independent and identically distributed (i.i.d.) with expectation zero and variance $\sigma^2 > 0$. The set of all designs with t treatments, n subjects, and p periods is denoted by $\Omega_{t,n,p}$. We focus on $t = 2$, the case of two treatments (reference product R, biosimilar (test) product T). Note that, in this case, the model with self and mixed carryover effects is equivalent to the full model with interactions between the direct and carryover effects.

For a given design $d \in \Omega_{2,n,p}$, we define $\mathbf{T}_d$ as the design matrix of the direct effects, $\mathbf{S}_d$ as that of the self carryover effects, and $\mathbf{M}_d$ as that of the mixed carryover effects. We also consider the matrices $\mathbf{U} = \mathbf{I}_n \otimes \mathbf{1}_p$ and $\mathbf{P} = \mathbf{1}_n \otimes \mathbf{I}_p$, where $\otimes$ denotes the Kronecker product of matrices, $\mathbf{I}_s$ is the $(s \times s)$ identity matrix, and $\mathbf{1}_s$ is a column vector of length s with all entries equal to one. We write the vector $\mathbf{y}$ of observations as $\mathbf{y} = [y_{1,1}, \ldots, y_{1,p}, y_{2,1}, \ldots, y_{n,p}]^T$, where the superscript T denotes the transpose of a vector or a matrix. Then, $\mathbf{U}$ and $\mathbf{P}$ are the design matrices for the subject and period effects, respectively, and the model can be written in vector notation as

$$\mathbf{y} = \mathbf{T}_d\tau + \mathbf{S}_d\chi + \mathbf{M}_d\rho + \mathbf{U}\alpha + \mathbf{P}\beta + \mathbf{e},$$

where τ is a vector of direct (treatment) effects, χ is a vector of self carryover effects and ρ is a vector of mixed carryover effects. Furthermore, α, β, and $\mathbf{e}$ are vectors of subject effects, period effects, and residual errors, respectively. We are interested in estimating contrasts of the four-dimensional vector of all carryover effects,

$$\delta = \begin{bmatrix} \chi \\ \rho \end{bmatrix}.$$

For a matrix $\mathbf{A}$, we define the projection $\omega(\mathbf{A}) = \mathbf{A}(\mathbf{A}^T\mathbf{A})^+\mathbf{A}^T$, where $(\mathbf{A}^T\mathbf{A})^+$ is the Moore–Penrose generalized inverse. Setting $\omega^\perp(\mathbf{A}) = \mathbf{I}_s - \omega(\mathbf{A})$, where s is the number of rows of $\mathbf{A}$, the information matrix for the estimation of δ is given by

$$\mathbf{C}_d = [\mathbf{S}_d, \mathbf{M}_d]^T \omega^\perp([\mathbf{P}, \mathbf{U}, \mathbf{T}_d])[\mathbf{S}_d, \mathbf{M}_d];$$

see Kunert (1983, p. 248). Note that $[\mathbf{S}_d, \mathbf{M}_d]\mathbf{1}_4 = \mathbf{P}[0, 1, \ldots, 1]^T$, because each subject experiences one of the four carryover effects in all periods but the first. Therefore, because $\omega^\perp([\mathbf{P}, \mathbf{U}, \mathbf{T_d}])\mathbf{P} = \mathbf{0}$, the information matrix $\mathbf{C}_d$ has row and column sums equal to zero and only contrasts of the carryover effects are estimable.

To compare the performance of the designs, we consider the A-criterion; see, for example, Pukelsheim (1993, p. 210). We define $\lambda_i(\mathbf{A})$ as the ordered eigenvalues of a real symmetric matrix $\mathbf{A}$. Therefore, for a design $d \in \Omega_{2,n,p}$, the ordered eigenvalues of $\mathbf{C}_d$ are $\lambda_1(\mathbf{C}_d) \geq \lambda_2(\mathbf{C}_d) \geq \lambda_3(\mathbf{C}_d) \geq \lambda_4(\mathbf{C}_d)$. Note that $\lambda_4(\mathbf{C}_d) = 0$, because $\mathbf{C}_d\mathbf{1}_4 = \mathbf{0}$. We then define the A-criterion φ_A as

$$\varphi_A(d) = \begin{cases} 1/\left(\dfrac{1}{\lambda_1(\mathbf{C}_d)} + \dfrac{1}{\lambda_2(\mathbf{C}_d)} + \dfrac{1}{\lambda_3(\mathbf{C}_d)}\right), & \text{if } \lambda_3(\mathbf{C}_d) > 0, \\ 0, & \text{if } \lambda_3(\mathbf{C}_d) = 0. \end{cases}$$

An A-optimal design d^* maximizes $\varphi_A(d)$.

Ideally, to maximize $\varphi_A(d)$, we find a design with $\lambda_1(\mathbf{C}_d) = \lambda_2(\mathbf{C}_d) = \lambda_3(\mathbf{C}_d)$, where $L = \lambda_1(\mathbf{C}_d) + \lambda_2(\mathbf{C}_d) + \lambda_3(\mathbf{C}_d)$ is as large as possible. Such a design does not exist. Instead, we use a slightly smaller bound for $\varphi_A(d)$.

Proposition 1. *Assume the design $d \in \Omega_{2,n,p}$ has an information matrix with eigenvalues $\lambda_1 \geq \lambda_2 \geq \lambda_3$ and zero, with the side conditions that*

$$\lambda_1 + \lambda_2 + \lambda_3 \leq L, \text{ and } \lambda_3 \leq q,$$

where $0 < q \leq L/3$. Then, we have for the A-criterion of the design that

$$\varphi_A(d) \leq \frac{q(L-q)}{L+3q}.$$

For the proofs of all propositions presented in this paper, see the online Supplementary Material.

3. Deriving Bounds for the A-Criterion

The aim of this study is to propose efficient designs for the joint estimation of mixed and self carryover effects. The efficiency of the designs is measured by comparing their A-criteria to an upper bound for the A-criterion. To use Proposition 1, we determine an upper bound for the second-smallest eigenvalue $\lambda_3(\mathbf{C}_d)$ and an upper bound for $tr(\mathbf{C}_d)$, where $tr(\mathbf{A})$ denotes the trace of a matrix $\mathbf{A}$.

For two matrices $\mathbf{G}, \mathbf{D} \in \mathbb{R}^{s\times s}$, we write $\mathbf{G} \leq \mathbf{D}$ if $\mathbf{D} - \mathbf{G}$ is nonnegative definite. Because the information matrix $\mathbf{C_d}$ has row- and column-sums zero, we can rewrite

$$\mathbf{C}_d = \mathbf{B}_4\mathbf{C}_d\mathbf{B}_4 = \mathbf{B}_4[\mathbf{S}_d, \mathbf{M}_d]^T\omega^{\perp}([\mathbf{P}, \mathbf{U}, \mathbf{T}_d])[\mathbf{S}_d, \mathbf{M}_d]\mathbf{B}_4,$$

where $\mathbf{B}_s = \omega^{\perp}(\mathbf{1}_s) = \mathbf{I}_s - (1/s)\mathbf{1}_s\mathbf{1}_s^T$. Using this notation, we obtain an immediate upper bound for $\mathbf{C}_d$, namely,

$$\mathbf{C}_d \leq \tilde{\mathbf{C}}_d = \mathbf{B}_4[\mathbf{S}_d, \mathbf{M}_d]^T\omega^{\perp}([\mathbf{U}, \mathbf{T}_d])[\mathbf{S}_d, \mathbf{M}_d]\mathbf{B}_4; \tag{3.1}$$

see Kunert (1983, Prop. 2.3). Equality holds if and only if

$$\mathbf{B}_4[\mathbf{S}_d, \mathbf{M}_d]^T\omega^{\perp}([\mathbf{U}, \mathbf{T}_d])\mathbf{P} = 0. \tag{3.2}$$

We can write

$$\omega^{\perp}([\mathbf{U}, \mathbf{T}_d]) = \omega^{\perp}(\mathbf{U}) - \omega^{\perp}(\mathbf{U})\mathbf{T}_d(\mathbf{T}_d^T\omega^{\perp}(\mathbf{U})\mathbf{T}_d)^{+}\mathbf{T}_d^T\omega^{\perp}(\mathbf{U}),$$

see, for example, Bose and Dey (2009, Lemma 1.2.1). Hence, the matrix $\tilde{\mathbf{C}}_d$ defined in (3.1) can be split as follows:

$$\tilde{\mathbf{C}}_d = \mathbf{C}_{d11} - \mathbf{C}_{d12}\mathbf{C}_{d22}^{+}\mathbf{C}_{d12}^T,$$

where

$$\begin{aligned}
\mathbf{C}_{d11} &= \mathbf{B}_4[\mathbf{S}_d, \mathbf{M}_d]^T\omega^{\perp}(\mathbf{U})[\mathbf{S}_d, \mathbf{M}_d]\mathbf{B}_4,\\
\mathbf{C}_{d12} &= \mathbf{B}_4[\mathbf{S}_d, \mathbf{M}_d]^T\omega^{\perp}(\mathbf{U})\mathbf{T}_d,\\
\mathbf{C}_{d22} &= \mathbf{T}_d^T\omega^{\perp}(\mathbf{U})\mathbf{T}_d.
\end{aligned}$$

Note that the $\mathbf{C}_{dij}$ are not submatrices of the information matrix $\mathbf{C}_d$. Instead, they are submatrices of an information matrix used to jointly estimate the carryover effects and the direct effects; see Cheng and Wu (1980).

Equation (3.1) implies there is an upper bound for the A-criterion,

$$\varphi_A(d) \le \tilde{\varphi}_A(d),$$

where

$$\tilde{\varphi}_A(d) = \begin{cases} 1/\left(\dfrac{1}{\lambda_1(\tilde{\mathbf{C}}_d)} + \dfrac{1}{\lambda_2(\tilde{\mathbf{C}}_d)} + \dfrac{1}{\lambda_3(\tilde{\mathbf{C}}_d)}\right), & \text{if } \lambda_3(\tilde{\mathbf{C}}_d) > 0, \\ 0, & \text{if } \lambda_3(\tilde{\mathbf{C}}_d) = 0. \end{cases}$$

In what follows, we aim to identify designs that optimize $\tilde{\varphi}_A(d)$, while satisfying Equation (3.2).

Each subject receives a sequence of treatments. Define Z_p as the set of all p-dimensional vectors with entries R or T. Consider an arbitrary sequence $z \in Z_p$. For this sequence, we define

- $\mathbf{T}_z$ as the design matrix for the direct treatment effects for this sequence, that is, the design matrix for the direct effects we would get from a design consisting of one subject only, receiving sequence z;
- $\mathbf{S}_z$ as the design matrix for the self carryover effects for this sequence; and
- $\mathbf{M}_z$ as the design matrix for the mixed carryover effects for this sequence.

For a design $d \in \Omega_{2,n,p}$, define $u_d(z)$ as the number of subjects receiving sequence z, for $z \in Z_p$. Then each $u_d(z)$ is a nonnegative integer. It is convenient to consider the set $\Delta_{2,n,p}$ of *approximate designs*, where $u_d(z)$ can be any nonnegative real number, with the only restriction being that $\sum u_d(z) = n$. Obviously, $\Omega_{2,n,p} \subset \Delta_{2,n,p}$, and if a design $d \in \Omega_{2,n,p}$ is optimal over $\Delta_{2,n,p}$, it is also optimal over $\Omega_{2,n,p}$. For each $d \in \Delta_{2,n,p}$, define $\pi_d(z)$ as the proportion of subjects receiving sequence z, for $z \in Z_p$. Then, all $\pi_d(z) \ge 0$ and $\sum_{z\in Z_p} \pi_d(z) = 1$, but for an approximate design $d \in \Delta_{2,n,p}$, the $\pi_d(z)$ can be irrational numbers.

It is easy to see that $\omega^\perp(\mathbf{U}) = \mathbf{I}_n \otimes \mathbf{B}_p$. Therefore, the $\mathbf{C}_{dij}$ are linear in the sequences. More precisely, $\mathbf{C}_{dij} = n\sum_{z\in Z_p} \pi_d(z)\mathbf{C}_{ij}(z)$, where

$$\mathbf{C}_{11}(z) = \mathbf{B}_4[\mathbf{S}_z, \mathbf{M}_z]^T\mathbf{B}_p[\mathbf{S}_z, \mathbf{M}_z]\mathbf{B}_4, \tag{3.3}$$

$$\mathbf{C}_{12}(z) = \mathbf{B}_4[\mathbf{S}_z, \mathbf{M}_z]^T\mathbf{B}_p\mathbf{T}_z, \tag{3.4}$$

$$\mathbf{C}_{22}(z) = \mathbf{T}_z^T\mathbf{B}_p\mathbf{T}_z. \tag{3.5}$$

Making use of the linearity of the $\mathbf{C}_{dij}$, Kushner (1997) introduced a general method for deriving optimal crossover designs. However, Kushner (1997) considered the case where all $\mathbf{C}_{dij}$ are square matrices. In our problem, $\mathbf{C}_{d12}$ is a (4×2) matrix; therefore, we have to adapt the method to our situation.

Proposition 2. *Assume* $\mathbf{X} \in \mathbb{R}^{2\times 4}$ *is an arbitrary matrix. Then,*

$$\tilde{\mathbf{C}}_d \leq \mathbf{C}_{d11} - \mathbf{C}_{d12}\mathbf{X} - \mathbf{X}^T\mathbf{C}_{d12}^T + \mathbf{X}^T\mathbf{C}_{d22}\mathbf{X}.$$

A sufficient condition for equality is that $\mathbf{X} = \mathbf{X}_d$, *where* $\mathbf{X}_d = \mathbf{C}_{d22}^{+}\mathbf{C}_{d12}^T$.

Note that the right-hand side of the inequality in Proposition 2 is linear in the sequences; that is,

$$\begin{aligned}&\mathbf{C}_{d11} - \mathbf{C}_{d12}\mathbf{X} - \mathbf{X}^T\mathbf{C}_{d12}^T + \mathbf{X}^T\mathbf{C}_{d22}\mathbf{X}\\ &= n\sum_{z\in Z_p}\pi_d(z)\big(\mathbf{C}_{11}(z) - \mathbf{C}_{12}(z)\mathbf{X} - \mathbf{X}^T\mathbf{C}_{12}^T(z) + \mathbf{X}^T\mathbf{C}_{22}(z)\mathbf{X}\big).\end{aligned} \tag{3.6}$$

As a first step, we can use this proposition to derive an upper bound for $\lambda_3(\mathbf{C}_d)$ (see Proposition 4). Define

$$\mathbf{b}_2 = \frac{1}{\sqrt{2}}\begin{bmatrix}1\\-1\end{bmatrix}.$$

Then, $\mathbf{b}_2\mathbf{b}_2^T = \mathbf{B}_2$. Using this notation, we obtain an immediate consequence of Proposition 2.

Proposition 3. *Assume* $\mathbf{k} \in \mathbb{R}^4$ *and* $x \in \mathbb{R}$. *Then,*

$$\mathbf{k}^T\tilde{C}_d\mathbf{k} \leq \mathbf{k}^T\mathbf{C}_{d11}\mathbf{k} - 2\mathbf{k}^T\mathbf{C}_{d12}\mathbf{b}_2 x + \mathbf{b}_2^T\mathbf{C}_{d22}\mathbf{b}_2 x^2.$$

A sufficient condition for equality is that $x = \mathbf{k}^T\mathbf{C}_{d12}\mathbf{C}_{d22}^{+}\mathbf{b}_2 = x_d$, *say.*

This proposition allows us to give an upper bound for $\lambda_3(\mathbf{C}_d)$.

Proposition 4. *Consider an arbitrary design* $d \in \Delta_{2,n,p}$. *Assume that* $\mathbf{0} \neq \mathbf{k} \in \mathbb{R}^4$, *with* $\mathbf{k}^T\mathbf{1}_4 = 0$, *and that* $x \in \mathbb{R}$. *For the second-smallest eigenvalue, we then have that*

$$\lambda_3(\mathbf{C}_d) \leq n\frac{1}{\mathbf{k}^T\mathbf{k}}\max_{z\in Z_p}\{\mathbf{k}^T\mathbf{C}_{11}(z)\mathbf{k} - 2\mathbf{k}^T\mathbf{C}_{12}(z)\mathbf{b}_2 x + \mathbf{b}_2^T\mathbf{C}_{22}(z)\mathbf{b}_2 x^2\}.$$

We use another consequence of Proposition 2 to derive a bound for $tr(\tilde{\mathbf{C}}_d)$.

Proposition 5. *Consider an arbitrary design $d \in \Delta_{2,n,p}$ and any matrix $\mathbf{X} \in \mathbb{R}^{2\times 4}$. We then have*

$$tr(\mathbf{C}_d) \leq n \max_{z \in Z_p} tr\left(\mathbf{C}_{11}(z) - 2\mathbf{C}_{12}(z)\mathbf{X} + \mathbf{X}^T\mathbf{C}_{22}(z)\mathbf{X}\right).$$

Set

$$L_z(\mathbf{X}) = n\, tr\left(\mathbf{C}_{11}(z) - 2\mathbf{C}_{12}(z)\mathbf{X} + \mathbf{X}^T\mathbf{C}_{22}(z)\mathbf{X}\right).$$

Then, Proposition 5 can be written as

$$tr(\mathbf{C}_d) \leq \max_{z \in Z_p} L_z(\mathbf{X}). \tag{3.7}$$

Proposition 5 holds for any $\mathbf{X} \in \mathbb{R}^{2\times 4}$. We choose an $\mathbf{X}$ that gives a small bound. One way to find such an $\mathbf{X}$ is as follows. Assume there is a design $f \in \Omega_{2,n,p}$, for which we hope that f maximizes $tr(\mathbf{C}_d)$. Clearly, from (3.1), we have $tr(\mathbf{C}_f) \leq tr(\tilde{\mathbf{C}}_f)$. It follows from Proposition 2 that

$$\begin{aligned} tr(\tilde{\mathbf{C}}_f) &\leq tr\left(\mathbf{C}_{f11} - \mathbf{C}_{f12}\mathbf{X}_f - \mathbf{X}^T\mathbf{C}_{f12}^T + \mathbf{X}^T\mathbf{C}_{f22}\mathbf{X}\right) \\ &= \sum_{z \in Z_p} \pi_f L_z((\mathbf{X}), \end{aligned}$$

with equality for $\mathbf{X} = \mathbf{X}_f = \mathbf{C}_{f22}^{+}\mathbf{C}_{f12}$. For some $\mathbf{X} \neq \mathbf{X}_f$, this inequality can be strict. In that case, there will be at least one $z \in Z_p$, such that $L_z(\mathbf{X}) > tr(\tilde{\mathbf{C}}_f)$. However, for $\mathbf{X} = \mathbf{X}_f$, it is possible that all $L_z(\mathbf{X}_f) \leq tr(\tilde{\mathbf{C}}_f)$. If (3.2) holds for f, it is even possible that all $L_z(\mathbf{X}_f) \leq tr(\mathbf{C}_f)$. This would be sufficient for $tr(\mathbf{C}_f)$ to be maximal.

Proposition 6. *Assume $f \in \Omega_{2,n,p}$ is such that, for every sequence $z \in Z_p$, we have*

$$L_z(\mathbf{X}_f) \leq tr\left(\mathbf{C}_f\right), \text{ where } \mathbf{X}_f = \mathbf{C}_{f22}^{+}\mathbf{C}_{f12}^T,$$

as in Proposition 2. *Then,*

$$tr(\mathbf{C}_f) = \max_{d \in \Delta_{2,n,p}} tr(\mathbf{C}_d).$$

For any sequence $z \in Z_p$, there is a dual sequence $\bar{z} \in Z_p$, where each T in z is replaced by an R in $\bar{z}$, and vice versa. A design $d \in \Delta_{2,n,p}$ is called *dual balanced* if $\pi_d(z) = \pi_d(\bar{z})$ for each pair of dual sequences z and $\bar{z}$ in Z_p. The next proposition allows us to restrict our attention to dual-balanced designs in what follows.

Proposition 7. *If we allow for approximate designs, then for each design $d \in \Delta_{2,n,p}$, there is a dual-balanced design $f \in \Delta_{2,n,p}$, such that*

$$\tilde{\varphi}_A(f) \geq \tilde{\varphi}_A(d).$$

4. Efficient Dual-Balanced Designs

For a given sequence $z \in Z_p$, it is possible to give explicit entries of $\mathbf{C}_{ij}(z)$. We define n_R and n_T as the number of appearances of treatment R and T, respectively, in z. Let m_{RT} and m_{TR} be the number of appearances of the mixed carryover effects of R and T, respectively, and s_{RR} and s_{TT} be the number of appearances of the self carryover effects of R and T, respectively, in z. Then,

$$\begin{aligned}
\mathbf{S}_z^T\mathbf{B}_p\mathbf{S}_z &= \begin{bmatrix} s_{RR} & 0 \\ 0 & s_{TT} \end{bmatrix} - \frac{1}{p}\begin{bmatrix} s_{RR}^2 & s_{RR}s_{TT} \\ s_{RR}s_{TT} & s_{TT}^2 \end{bmatrix}, \\
\mathbf{S}_z^T\mathbf{B}_p\mathbf{M}_z &= -\frac{1}{p}\begin{bmatrix} m_{RT}s_{RR} & m_{RT}s_{TT} \\ m_{TR}s_{RR} & m_{TR}s_{TT} \end{bmatrix}, \\
\mathbf{S}_z^T\mathbf{B}_p\mathbf{T}_z &= \begin{bmatrix} s_{RR} & 0 \\ 0 & s_{TT} \end{bmatrix} - \frac{1}{p}\begin{bmatrix} s_{RR}n_R & s_{RR}n_T \\ s_{TT}n_R & s_{TT}n_T \end{bmatrix} \\
&= \frac{1}{p}\begin{bmatrix} s_{RR}n_T & -s_{RR}n_T \\ -s_{TT}n_R & s_{TT}n_R \end{bmatrix},
\end{aligned}$$

where we have used that $n_R + n_T = p$. Similarly,

$$\begin{aligned}
\mathbf{M}_z^T\mathbf{B}_p\mathbf{M}_z &= \begin{bmatrix} m_{RT} & 0 \\ 0 & m_{TR} \end{bmatrix} - \frac{1}{p}\begin{bmatrix} m_{RT}^2 & m_{RT}m_{TR} \\ m_{RT}m_{TR} & m_{TR}^2 \end{bmatrix}, \\
\mathbf{M}_z^T\mathbf{B}_p\mathbf{T}_z &= \begin{bmatrix} 0 & m_{RT} \\ m_{TR} & 0 \end{bmatrix} - \frac{1}{p}\begin{bmatrix} m_{RT}n_R & m_{RT}n_T \\ m_{TR}n_R & m_{TR}n_T \end{bmatrix} \\
&= \frac{1}{p}\begin{bmatrix} -m_{RT}n_R & m_{RT}n_R \\ m_{TR}n_T & -m_{TR}n_T \end{bmatrix}.
\end{aligned}$$

These (2×2) matrices can be used to determine the (4×4) matrix $\mathbf{C}_{11}(z)$ and the (4×2) matrix $\mathbf{C}_{12}(z)$. The matrix $\mathbf{C}_{22}(z)$ is given by

$$\begin{aligned}
\mathbf{C}_{22}(z) &= \mathbf{T}_z^T\mathbf{B}_p\mathbf{T}_z \\
&= \begin{bmatrix} n_R & 0 \\ 0 & n_T \end{bmatrix} - \frac{1}{p}\begin{bmatrix} n_R^2 & n_Tn_R \\ n_Tn_R & n_T^2 \end{bmatrix}
\end{aligned}$$

$$= \begin{bmatrix} n_R\left(1 - \frac{1}{p}n_R\right) & -\frac{1}{p}n_T n_R \\ -\frac{1}{p}n_T n_R & n_T\left(1 - \frac{1}{p}n_T\right) \end{bmatrix}$$
$$= \frac{1}{p}n_T n_R \begin{bmatrix} 1 & -1 \\ -1 & 1 \end{bmatrix}$$
$$= \frac{2}{p}n_T n_R \mathbf{B}_2.$$

The fact that $\mathbf{C}_{22}(z)$ is proportional to $\mathbf{B}_2$ for any z implies that, for any design d, there is a c such that $\mathbf{C}_{d22} = c\mathbf{B}_2$. Hence, one g-inverse of $\mathbf{C}_{d22}$ is given by

$$\mathbf{C}^+_{d22} = \frac{1}{c}\mathbf{B}_2.$$

4.1. Efficient designs for $\mathbf{p = 3}$

First, we consider the case $p = 3$. We try to find an approximate design d that maximizes $\tilde{\varphi}_A$. Then, there are eight possible sequences (see Table 1); and $\tilde{\varphi}_A(d)$ is uniquely determined by the eight proportions $\pi_d(z)$, for $z \in Z_3$. Note that z_1 and z_2, z_3 and z_4, z_5 and z_6, and z_7 and z_8 are pairs of dual sequences. We conclude from Proposition 7 that the best design is a dual-balanced design, that is, $\pi_d(z_1) = \pi_d(z_2) = p_1$, $\pi_d(z_3) = \pi_d(z_4) = p_3$, $\pi_d(z_5) = \pi_d(z_6) = p_5$, and $\pi_d(z_7) = \pi_d(z_8) = p_7$, say. With this restriction, we get

$$\frac{\mathbf{S}_d^T\omega^\perp(\mathbf{U})\mathbf{S}_d}{n} = \sum_z \pi_d(z)\mathbf{S}_z^T\mathbf{B}_3\mathbf{S}_z = \frac{2}{3}(p_1 + p_3 + p_7)\mathbf{I}_2,$$
$$\frac{\mathbf{S}_d^T\omega^\perp(\mathbf{U})\mathbf{M}_d}{n} = \sum_z \pi_d(z)\mathbf{S}_z^T\mathbf{B}_3\mathbf{M}_z = \begin{bmatrix} -\frac{1}{3}p_7 & -\frac{1}{3}p_3 \\ -\frac{1}{3}p_3 & -\frac{1}{3}p_7 \end{bmatrix},$$
$$\frac{\mathbf{S}_d^T\omega^\perp(\mathbf{U})\mathbf{T}_d}{n} = \sum_z \pi_d(z)\mathbf{S}_z^T\mathbf{B}_3\mathbf{T}_z = \left(\frac{2}{3}p_3 + \frac{2}{3}p_7\right)\mathbf{B}_2,$$
$$\frac{\mathbf{M}_d^T\omega^\perp(\mathbf{U})\mathbf{M}_d}{n} = \sum_z \pi_d(z)\mathbf{M}_z^T\mathbf{B}_3\mathbf{M}_z$$
$$= \begin{bmatrix} \frac{2}{3}(p_3 + p_7) + \frac{4}{3}p_5 & -\frac{2}{3}p_5 \\ -\frac{2}{3}p_5 & \frac{2}{3}(p_3 + p_7) + \frac{4}{3}p_5 \end{bmatrix},$$
$$\frac{\mathbf{M}_d^T\omega^\perp(\mathbf{U})\mathbf{T}_d}{n} = \sum_z \pi_d(z)\mathbf{M}_z^T\mathbf{B}_3\mathbf{T}_z = -\left(\frac{2}{3}p_3 + \frac{4}{3}p_7 + 2p_5\right)\mathbf{B}_2,$$

and

Table 1. Possible sequences with three periods ($p = 3$).

	Sequence	m_{TR}	m_{RT}	s_{RR}	s_{TT}	n_R	n_T
z_1	TTT	0	0	0	2	0	3
z_2	RRR	0	0	2	0	3	0
z_3	RTT	0	1	0	1	1	2
z_4	TRR	1	0	1	0	2	1
z_5	RTR	1	1	0	0	2	1
z_6	TRT	1	1	0	0	1	2
z_7	RRT	0	1	1	0	2	1
z_8	TTR	1	0	0	1	1	2

$$\frac{\mathbf{T}_d^T \omega^{\perp}(\mathbf{U})\mathbf{T}_d}{n} = \sum_z \pi_d(z)\mathbf{T}_z^T \mathbf{B}_3 \mathbf{T}_z = \frac{8}{3}\left(p_3 + p_5 + p_7\right)\mathbf{B}_2.$$

Combining these results, we have

$$\frac{1}{n}\tilde{C}_d = \mathbf{B}_4 \begin{bmatrix} a & b & e & f \\ b & a & f & e \\ e & f & c & d \\ f & e & d & c \end{bmatrix} \mathbf{B}_4,$$

where

$$\begin{aligned}
a &= \frac{2}{3}(p_1 + p_3 + p_7) - \frac{p_3^2 + p_7^2 + 2p_3p_7}{12(p_3 + p_5 + p_7)}, \\
b &= \frac{p_3^2 + p_7^2 + 2p_3p_7}{12(p_3 + p_5 + p_7)}, \\
c &= \frac{2}{3}(p_3 + p_7) + \frac{4}{3}p_5 - \frac{p_3^2 + 4p_7^2 + 9p_5^2 + 4p_3p_7 + 6p_3p_5 + 12p_7p_5}{12(p_3 + p_5 + p_7)}, \\
d &= -\frac{2}{3}p_5 + \frac{p_3^2 + 4p_7^2 + 9p_5^2 + 4p_3p_7 + 6p_3p_5 + 12p_7p_5}{12(p_3 + p_5 + p_7)}, \\
e &= -\frac{1}{3}p_7 + \frac{p_3^2 + 3p_7p_3 + 3p_3p_5 + 2p_7^2 + 3p_7p_5}{12(p_3 + p_5 + p_7)}, \\
f &= -\frac{1}{3}p_3 - \frac{p_3^2 + 3p_7p_3 + 3p_3p_5 + 2p_7^2 + 3p_7p_5}{12(p_3 + p_5 + p_7)}.
\end{aligned}$$

This matrix has eigenvalues

$$\lambda_1 = \frac{a - b + c - d}{2} + \sqrt{(e - f)^2 + \left(\frac{c - d - a + b}{2}\right)^2},$$

$$\lambda_2 = \frac{a-b+c-d}{2} - \sqrt{(e-f)^2 + \left(\frac{c-d-a+b}{2}\right)^2},$$
$$\lambda_3 = \frac{a+b+c+d}{2} - e - f,$$

and $\lambda_4 = 0$. The largest

$$\tilde{\varphi}_A(d) = \frac{1}{(1/\lambda_1 + 1/\lambda_2 + 1/\lambda_3)}$$

that we found in a numerical search was $\tilde{\varphi}_A(\tilde{d}) = 0.0636n$, attained by a design $\tilde{d}$ with proportions

$$p_{\tilde{d}}(1) = 0.0951,\ p_{\tilde{d}}(3) = 0.1033,\ p_{\tilde{d}}(5) = 0.1684, \text{ and } p_{\tilde{d}}(7) = 0.1332.$$

Unfortunately, there are two problems with $\tilde{d}$. First, it takes a large number of experimental subjects to construct an exact design with these proportions. Second, the true A-criterion of $\tilde{d}$ is less than the bound: $\varphi_A(\tilde{d}) < \tilde{\varphi}_A(\tilde{d})$. This is because $\tilde{d}$ does not satisfy (3.2).

A sufficient condition to satisfy (3.2) is as follows. Assume the design d is such that in all periods, both direct effects appear in exactly half of the subjects, and that in each of the periods $2, \ldots, p$, each of the four carryover effects appears in exactly one quarter of the subjects. This implies that

$$\sum_z \pi_d(z) \mathbf{T}_z^T = \frac{1}{2} \mathbf{1}_2 \mathbf{1}_p^T,$$

and

$$\sum_z \pi_d(z) \left[\mathbf{S}_z,\ \ \mathbf{M}_z\right]^T = \mathbf{1}_4 \left[0, \frac{1}{4}, \frac{1}{4}, \ldots, \frac{1}{4}\right].$$

Now, note that

$$\begin{aligned}
&\mathbf{B}_4[\mathbf{S}_d,\, \mathbf{M}_d]^T \omega^\perp([\mathbf{U}, \mathbf{T}_d])\mathbf{P} = \left(\mathbf{B}_4[\mathbf{S}_d,\, \mathbf{M}_d]^T - \mathbf{C}_{d12}\mathbf{C}_{d22}^+ \mathbf{T}_d^T\right)\omega^\perp(\mathbf{U})\mathbf{P} \\
&= \left(\mathbf{B}_4[\mathbf{S}_d,\, \mathbf{M}_d]^T - \mathbf{C}_{d12}\mathbf{C}_{d22}^+ \mathbf{T}_d^T\right)(\mathbf{1}_n \otimes \mathbf{B}_p) \\
&= n\left(\mathbf{B}_4 \sum_z \pi_d(z)[\mathbf{S}_z,\ \ \mathbf{M}_z]^T - \mathbf{C}_{d12}\mathbf{C}_{d22}^+ \sum_z \pi_d(z)\mathbf{T}_z^T\right)\mathbf{B}_p.
\end{aligned}$$

Thus, for our d,

$$\mathbf{B}_4[\mathbf{S}_d,\, \mathbf{M}_d]^T \omega^\perp([\mathbf{U}, \mathbf{T}_d])\mathbf{P} = 0$$

and, therefore, $\mathbf{C}_d = \tilde{\mathbf{C}}_d$.

The design $\tilde{d}$ clearly does not satisfy the sufficient condition. In periods 2 and 3, the number of subjects receiving a mixed carryover is larger than the number of subjects receiving a self carryover. The difference is larger in period 3 than in period 2. If n is divisible by eight, we can, instead of the design $\tilde{d}$, use an exact, dual-balanced design $\hat{d}_1 \in \Omega_{2,n,3}$ that allots $\pi_{\hat{d}_1}(z) = 1/8$ to all sequences in Z_3. It is easy to verify that the design $\hat{d}_1$ satisfies the sufficient conditions for (3.2). Direct computation gives $\varphi_A(\hat{d}_1) = 0.0628n$, which is very close to the numerically derived upper bound for the A-criterion ($0.0636n$). If the numerically derived bound is the true maximum, the efficiency of the design $\hat{d}_1$ is at least 0.987.

4.2. Efficient designs for $\mathbf{p \equiv 1 \bmod 4}$

We now consider the case $p = 4\ell + 1$, where ℓ is a natural number, and n is divisible by four. For this case, consider the exact design $\hat{d}_2 \in \Omega_{2,n,p}$, where each of the sequences

$$z_1 = [R\,T\,T\,R\,R \cdots T\,T\,R\,R],$$

$$z_2 = [R\,R\,T\,T\,R\,R \cdots T\,T\,R],$$

and their duals

$$\bar{z}_1 = [T\,R\,R\,T\,T \cdots R\,R\,T\,T],$$

$$\bar{z}_2 = [T\,T\,R\,R\,T\,T \cdots R\,R\,T],$$

are assigned to one quarter of the subjects.

In practice, these designs $\hat{d}_2$ are appealing, because they are not too complicated from an operational point of view, and the treatment sequence is not too obvious for the subjects, i.e., the subjects cannot easily determine when they switch.

For z_1, we get $n_R = 2\ell + 1$ and $n_T = 2\ell$, and $m_{RT} = m_{TR} = s_{RR} = s_{TT} = \ell$. This implies that

$$\mathbf{S}_{z_1}^T \mathbf{B}_p \mathbf{S}_{z_1} = \begin{bmatrix} \ell & 0 \\ 0 & \ell \end{bmatrix} - \frac{1}{p} \begin{bmatrix} \ell^2 & \ell^2 \\ \ell^2 & \ell^2 \end{bmatrix},$$

$$\mathbf{S}_{z_1}^T \mathbf{B}_p \mathbf{M}_{z_1} = -\frac{1}{p} \begin{bmatrix} \ell^2 & \ell^2 \\ \ell^2 & \ell^2 \end{bmatrix},$$

$$\mathbf{S}_{z_1}^T \mathbf{B}_p \mathbf{T}_{z_1} = \frac{1}{p} \begin{bmatrix} (2\ell+1)\ell & -(2\ell+1)\ell \\ -2\ell^2 & 2\ell^2 \end{bmatrix},$$

$$\mathbf{M}_{z_1}^T \mathbf{B}_p \mathbf{M}_{z_1} = \begin{bmatrix} \ell & 0 \\ 0 & \ell \end{bmatrix} - \frac{1}{p} \begin{bmatrix} \ell^2 & \ell^2 \\ \ell^2 & \ell^2 \end{bmatrix},$$

$$\text{and} \qquad \mathbf{M}_{z_1}^T \mathbf{B}_p \mathbf{T}_{z_1} = \frac{1}{p} \begin{bmatrix} -2\ell^2 & 2\ell^2 \\ (2\ell+1)\ell & -(2\ell+1)\ell \end{bmatrix}.$$

With straightforward algebra, we get that

$$\mathbf{C}_{11}(z_1) = \ell \mathbf{B}_4,\ \mathbf{C}_{12}(z_1) = \ell \begin{bmatrix} \mathbf{B}_2 \\ -\mathbf{B}_2 \end{bmatrix} \text{ and } \mathbf{C}_{22}(z_1) = \frac{4\ell(2\ell+1)}{p} \mathbf{B}_2.$$

Because the sequence z_2 has the same parameters, $n_R = 2\ell+1$, $n_T = 2\ell$, and $m_{RT} = m_{TR} = s_{RR} = s_{TT} = \ell$, we find that all $\mathbf{C}_{ij}(z_2) = \mathbf{C}_{ij}(z_1)$.

For the dual sequences $\bar{z}_1$ and $\bar{z}_2$, the roles of R and T are interchanged. Hence, $n_T = 2\ell+1$ and $n_R = 2\ell$, but we also have $m_{RT} = m_{TR} = s_{RR} = s_{TT} = \ell$. Thus once again, $\mathbf{C}_{11}(\bar{z}_i) = \mathbf{C}_{11}(z_1)$, $\mathbf{C}_{12}(\bar{z}_i) = \mathbf{C}_{12}(z_1)$, and $\mathbf{C}_{22}(\bar{z}_i) = \mathbf{C}_{22}(z_1)$, for $i = 1, 2$. This implies that, for the design $\hat{d}_2$,

$$\mathbf{C}_{\hat{d}_2 11} = n\ell \mathbf{B}_4,\ \mathbf{C}_{\hat{d}_2 12} = n\ell \begin{bmatrix} \mathbf{B}_2 \\ -\mathbf{B}_2 \end{bmatrix} \text{ and } \mathbf{C}_{\hat{d}_2 22} = \frac{4\ell(2\ell+1)n}{p} \mathbf{B}_2. \tag{4.1}$$

We therefore have

$$\begin{aligned} \tilde{\mathbf{C}}_{\hat{d}_2} &= n\ell \mathbf{B}_4 - \frac{n\ell p}{8(2\ell+1)} \begin{bmatrix} 1 & -1 & -1 & 1 \\ -1 & 1 & 1 & -1 \\ -1 & 1 & 1 & -1 \\ 1 & -1 & -1 & 1 \end{bmatrix} \\ &= \frac{n(p-1)}{16(p+1)} \begin{bmatrix} 2p+3 & -1 & -1 & -2p-1 \\ -1 & 2p+3 & -2p-1 & -1 \\ -1 & -2p-1 & 2p+3 & -1 \\ -2p-1 & -1 & -1 & 2p+3 \end{bmatrix}. \end{aligned}$$

To show that $\mathbf{C}_{\hat{d}_2} = \tilde{\mathbf{C}}_{\hat{d}_2}$, we verify that, in each period, the direct effect of each treatment appears in exactly two of the sequences; furthermore, in each of the periods $2, \ldots, p$, each of the four carryover effects appears in exactly one of the four sequences.

This implies that (3.2) holds and $\mathbf{C}_{\hat{d}_2} = \tilde{\mathbf{C}}_{\hat{d}_2}$. Therefore,

$$tr(\mathbf{C}_{\hat{d}_2}) = \frac{n(2p+1)(p-1)}{4(p+1)}.$$

The eigenvalues of $\mathbf{C}_{\hat{d}_2}$ are $\lambda_1(\mathbf{C}_{\hat{d}_2}) = \lambda_2(\mathbf{C}_{\hat{d}_2}) = n((p-1)/4)$, $\lambda_3(\mathbf{C}_{\hat{d}_2}) = n((p-1)/(4(p+1)))$, and zero. The eigenvector corresponding to $\lambda_3(\mathbf{C}_{\hat{d}_2})$ is $\mathbf{k}_3 = (1/2)\,[1,-1,-1,1]^T$.

Therefore, the A-criterion of the design $\hat{d}_2$ is

$$\varphi_A(\hat{d}_2) = n\frac{p-1}{4+4+4(p+1)} = n\frac{p-1}{4(p+3)}.$$

Note that this cannot be larger than $n/4$. Even if the number of periods p goes to ∞, we have $\varphi_A(\hat{d}_2) \to n/4$. This is similar to what happens for the estimation of the direct effects in the same model (see Kunert and Stufken (2008)): a large number of periods is of limited use.

In the special instance that $p = 5$, we did a numerical search to find an A-optimal design. In the best design g that we found, each of the sequences

$$[RTTRR]\,,[TRRTT]\,,[RRTTR]\,,\text{ and }[TTRRT]$$

is given to 20% of the subjects. Additionally, each of the sequences

$$[RTRRR]\,,[TRTTT]\,,[RRRTR]\,,\text{ and }[TTTRT]$$

is given to 5% of the subjects. For this design, the A-criterion is $\varphi_A(g) = n/7.9375$. This is only a small gain compared to the design $\hat{d}_2$ with $\varphi_A(\hat{d}_2) = n/8$. If g truly is the A-optimal design, then $\hat{d}_2$ has an efficiency of $7.9375/8 = 0.99$. However, the design g is more complicated from an organizational viewpoint, and it requires that the number of subjects be divisible by 20.

A practical experiment to examine switchability was carried out by Griffiths et al. (2017). They used a design h that gave each of the sequences

$$[RTRTT]\,,[TRTRR]\,,[TTTTT]\,,\text{ and }[RRRRR]$$

to 25% of the subjects. We then get $\varphi_A(h) = n/11.65$, which is clearly less than $\varphi_A(\hat{d}_2)$. However, note that Griffiths et al. (2017) did not use our model. Their analysis compared the performance of the subjects from the first two groups, with switches, to that of the subjects from the last two groups, without switches. Because every subject receives switches in design $\hat{d}_2$, the analysis of Griffiths et al. (2017). would not have been possible with $\hat{d}_2$.

Two works have derived optimal designs for our model for two treatments. Neither were interested in estimating the carryover effects. Druilhet and Tinsson (2014) derived optimal designs for the estimation of total effects. The total effect of a treatment is the sum of its direct and self carryover effects. In the case of two treatments and five periods, each subject in Druilhet and Tinsson (2014) design experiences exactly one switch: in the first two periods, the subject receives the same treatment twice, before switching to the other treatment for the last three periods. For the joint estimation of the mixed and self carryover effects, this design has an A-criterion of zero: the rank of the information matrix is only two. On the other hand, with $\hat{d}_2$, we can estiamte the total effects. However, its efficiency compared to that of the design by Druilhet and Tinsson (2014) is only 75%.

Kunert and Stufken (2008) derived optimal designs for estimating direct effects. For any given p, the set of all A-optimal designs for the estimation of direct effects is rather large. For $p \equiv 1 \bmod 4$ and n divisible by eight, it contains the designs $\hat{d}_2$. So, when estimating the direct effects, the designs $\hat{d}_2$ are, in fact, optimal.

In the next section, we derive an upper bound for the A-criterion for the estimation of the carryover effects of any design for an arbitrary p. With the help of this bound, we show that for $p \equiv 1 \bmod 4$ and $p > 5$, no other design outperforms $\hat{d}_2$.

5. An Upper Bound for the A-Criterion

In this section, for arbitrary p, we derive equation (5.2), an upper bound for the A-criterion $\varphi_A(d)$. The derivation, based on the general upper bound for $\varphi_A(d)$ given in Proposition 1, proves the upper bounds for $\lambda_3(\mathbf{C}_d)$ and $tr(\mathbf{C}_d)$ in equation (5.1) and Proposition 10, respectively. We begin with two technical lemmas.

Proposition 8. *Consider an arbitrary sequence $z \in Z_p$. Then, the design-matrices $\mathbf{T}_z$, $\mathbf{S}_z$, and $\mathbf{M}_z$ satisfy the equality*

$$\mathbf{S}_z\mathbf{b}_2 - \mathbf{M}_z\mathbf{b}_2 - \mathbf{T}_z\mathbf{b}_2 = \begin{bmatrix} a \\ 0 \\ \vdots \\ 0 \end{bmatrix},$$

where $a \in \{-1, 1\}$.

Proposition 9. *Consider an arbitrary sequence $z \in Z_p$, and choose $\mathbf{k} = (1/2)[1, -1, -1, 1]^T$. Define*

$$J_z(x) = \mathbf{k}^T\mathbf{C}_{11}(z)\mathbf{k} - 2\mathbf{k}^T\mathbf{C}_{12}(z)\mathbf{b}_2 x + \mathbf{b}_2^T\mathbf{C}_{22}(z)\mathbf{b}_2 x^2.$$

Then, for each sequence z, we get

$$J_z\left(\frac{1}{\sqrt{2}}\right) = \frac{p-1}{4p}.$$

Consider an arbitrary design $d \in \Delta_{2,n,p}$, and $\mathbf{k}$ from Proposition 9. Because $\mathbf{k}^T\mathbf{1}_4 = 0$ and $\mathbf{k}^T\mathbf{k} = 1$, it follows from Propositions 4 and 9 that

$$\lambda_3(\mathbf{C}_d) \leq n \max_{z\in Z_p} J_z\left(\frac{1}{\sqrt{2}}\right) = n\frac{p-1}{4p}. \tag{5.1}$$

Recall that $\lambda_3(\mathbf{C}_{\hat{d}_2}) = n((p-1)/(4(p+1)))$; see Section 4.2. Thus, $\lambda_3(\mathbf{C}_{\hat{d}_2})$ is slightly less than the bound in (5.1).

We now determine an upper bound for the trace of the information matrix, with the help of Proposition 5. Because we expect $\hat{d}_2$ to have a maximum trace, we choose $\mathbf{X} = \mathbf{X}_{\hat{d}_2}$.

From the equations in (4.1), we conclude that

$$\mathbf{X}_{\hat{d}_2} = \mathbf{C}^+_{\hat{d}_2 22}\mathbf{C}^T_{\hat{d}_2 12} = \frac{p}{2(p+1)}\big[\mathbf{B}_2, -\mathbf{B}_2\big].$$

Proposition 10. *Choose $\mathbf{X}^* = c\,[\mathbf{B}_2, -\mathbf{B}_2]$, where $c = p/(2(p+1))$, and consider an arbitrary sequence $z \in Z_p$. Then,*

$$L_z(\mathbf{X}^*) = n\,tr\left(\mathbf{C}_{11}(z) - 2\mathbf{C}_{12}(z)\mathbf{X}^* + \mathbf{X}^{*T}\mathbf{C}_{22}(z)\mathbf{X}^*\right) \leq n\,\frac{(2p+3)(p-1)}{4(p+1)}.$$

For $\hat{d}_2$, we showed in Section 4.2 that

$$tr(\mathbf{C}_{\hat{d}_2}) = n\frac{(2p+3)(p-1)}{4(p+1)}.$$

Therefore, it follows from Propositions 10 and 6 that $tr(\mathbf{C}_{\hat{d}_2})$ is maximal.

Even in cases where $p \equiv 1 \bmod 4$ is not satisfied, we conclude from Propositions 5 and 10 that

$$tr(\mathbf{C}_d) \leq L_z(\mathbf{X}^*) = n\frac{(2p+3)(p-1)}{4(p+1)}.$$

This inequality, together with (5.1), allows us to use Proposition 1. We therefore conclude that the A-criterion of any design d satisfies

$$\varphi_A(d) \leq \frac{q(L-q)}{L+3q},$$

with $L = n\,((2p+3)(p-1))/(4(p+1))$ and $q = n\,(p-1)/4p$. Hence, with some straightforward algebra, we have that

$$\varphi_A(d) \leq n\,\frac{(p-1)(2p^2+2p-1)}{4p(2p^2+6p+3)} = \varphi_A^*, \tag{5.2}$$

say. Recall that the A-criterion of the design $\hat{d}_2$ from Section 4.2 is $\varphi_A(\hat{d}_2) = n\,(p-1)/(4(p+3))$. This means that the efficiency of the design $\hat{d}_2$ is at least

$$\frac{\varphi_A(\hat{d}_2)}{\varphi_A^*} = \frac{2p^3+6p^2+3p}{2p^3+8p^2+5p-3},$$

which is equal to 0.88 for $p = 5$, and 0.92 for $p = 9$. The results discussed in Section 4.2 indicate that our bound seems to be not very sharp for $p = 5$. For $p \geq 9$, however, it is sharp enough to show that the designs $\hat{d}_2$ are highly efficient. If $p \to \infty$, their efficiency goes to one.

Supplementary Material

The online Supplementary Material contains detailed proofs for all propositions.

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