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OPTIMAL CROSS-OVER DESIGNS FOR FULL INTERACTION MODELS

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We consider repeated measurement designs when a residual or carry-over effect may be present in at most one later period. To avoid too rough a model, we assume that there are interactions between carry-over and direct treatment effects. When the aim of the experiment is to study the effects of a treatment used alone, we obtain universally optimal approximate designs. We also propose some efficient designs with a reduced number of subjects.

1. Introduction. In repeated measurement designs or crossover designs, interference is often observed between a direct treatment effect and the treatment applied in the previous period. We denote by ξ_{uv} the effect of treatment u when it is preceded by treatment v. There are several ways to model such effects. The simplest one is to assume that there is no interference. In that case, $\xi_{uv} = \tau_u$, the direct treatment effect.

For a parsimonious interference model, we may assume that the direct and the carry-over effects are additive. In that case, $\xi_{uv} = \tau_u + \lambda_v$, where τ_u is the direct effect of treatment u and λ_v is the carry-over effect due to treatment v. In practice, this model is often unrealistic.

Kempton et al. (2001) propose an interference model in which a treatment which has a large direct effect will also have a large carry-over effect. More precisely, they assume that the carry-over effect is proportional to the direct effect. Bailey and Kunert (2006) obtain optimal designs under this model.

Afsarinejad and Hedayat (2002) proposed another way to enrich the additive models: they assume that the carry-over effect of a treatment depends on whether that treatment is preceded by itself or not. In that case $\xi_{uv} = \tau_u + \lambda_v + \chi_{uv}$, where $\chi_{uv} = 0$ if $u \neq v$ and χ_{uu} represents the specific effect of treatment u preceded by itself. For that model, optimal designs are obtained by Kunert and Stufken (2002) when the parameters of interest are the direct treatment effects, and by Druilhet and Tinsson (2009) when the parameters of interest are the total effects $\tau_u + \lambda_u + \chi_{uu}$.

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The finest possible model, proposed by Sen and Mukerjee (1987), assumes full interactions between carry-over and direct treatment effects, which means that no constraints on ξ_{uv} are assumed. For a full interaction model, there is no natural way to define a direct treatment effect. For example, Park et al. (2011) obtained efficient designs when the parameters of interest are the standard least-squares means of treatments, i.e. $t^{-1}\sum_v \xi_{uv}$ for $1 \leq u \leq t$, where t is the number of treatments to be compared. Under a full interaction model, the contrasts of the least-squares means depend on all the other treatment effects through their interactions.

When the aim of the experiment is to select a single treatment which will be used alone, i.e. preceded by itself, the relevant effects to be considered are total effects $\phi_u = \xi_{uu}$ for $1 \leq u \leq t$, which correspond to the effect of a treatment preceded by itself: see Bailey and Druilhet (2004) for a review of situations where total effects have to be considered.

In this paper, we propose optimal designs for total effects under the full interaction interference model. We generalize Kushner's methods to this case, and we also propose efficient designs of reduced size.

2. The designs and the model. We consider a design d with n subjects and k periods. Let t be the number of treatments. For $1 \leq i \leq n$ and $1 \leq j \leq k$, denote by $d\,(i,j)$ the treatment assigned to subject i in period j. We assume the following full treatment $\times$ carry-over interaction model for the response y_{ij}:

$$y_{ij} = \beta_i + \xi_{d(i,j),d(i,j-1)} + \varepsilon_{ij}, \tag{1}$$

where β_i is the effect of subject i and ξ_{uv} is the effect of treatment u when preceded by treatment v. For the first period, we assume a specific carry-over effect that can be represented by a fictitious treatment labelled 0: ξ_{u0} represents the effect of treatment u with no treatment before. The residual errors ε_{ij} are assumed to be independent identically distributed with expectation 0 and variance σ^2.

In vector notation, the model can be written:

$$Y = B\beta + X_d\xi + \varepsilon,$$

where Y is the nk-vector of responses with entries y_{ij} in lexicographic order, and β is the n-vector of subject effects. The entries of the $t(t+1)$-vector ξ are denoted by ξ_{uv}, also sorted in lexicographic order. The matrices associated with these effects are respectively given by B and X_d. Note that $B = I_n \otimes \mathbb{I}_k$, where I_n denotes the identity matrix of order n, the symbol $\otimes$ denotes the

Kronecker product and $\mathbb{I}_k$ is the k-dimensional vector of ones. We have $\mathbb{E}(\varepsilon) = 0$ and $\mathrm{Var}\,(\varepsilon) = \sigma^2 I_{nk}$.

We denote by ϕ the t-vector of total effects, which corresponds to the situation where a treatment is preceded by itself. We have $\phi_u = \xi_{uu}$, for $u = 1, \ldots, t$. Denote by K the $t(t+1) \times t$ matrix with entries $K_{uv}^w = 1$ if $u = v = w$ and 0 otherwise for $u, w = 1, \ldots, t$ and $v = 0, \ldots, t$, where w is the single index for the columns and uv is the double index for the rows, similar to the index for the vector ξ_{uv}. We have

$$\phi = K'\xi. \tag{2}$$

In most applications, a period effect is included in the model. It will be seen in Section 3.3 that optimal designs found for Model (1) are also optimal for a model with a period effect.

3. Information matrices for total effects.

3.1. *Information matrix for ξ and ϕ.* Put $\omega_B = B\,(B'B)^{-1}\,B'$, which is the projection matrix onto the column space of B, and $\omega_B^\perp = I_{nk} - \omega_B = I_n \otimes Q_k$ with $Q_k = \omega_{\mathbb{I}_k}^\perp = I_k - k^{-1} J_k$, where $J_k = \mathbb{I}_k \mathbb{I}_k'$. The information matrix $C_d\,[\xi]$ for the vector ξ is given by (see e.g. Kunert, 1983):

$$C_d\,[\xi] = X_d'\,\omega_B^\perp\,X_d.$$

Denote by X_{di} the $k \times t(t+1)$ design matrix for subject i and by $C_{di}[\xi] = X_{di}'\;Q_k\;X_{di}$ the information matrix corresponding to subject i alone. We have $X_d' = (X_{d1}', \ldots, X_{dn}')$ and

$$C_d\,[\xi] = \sum_{i=1}^n C_{di}[\xi] = \sum_{i=1}^n X_{di}'\;Q_k\;X_{di}.$$

Note that X_{di} and therefore $C_{di}[\xi]$ depend only on the sequence of treatments applied to subject i. Denote by $\mathcal{S}$ the set of all sequences of k treatments. For a design d and a sequence $s \in \mathcal{S}$, denote by $\pi_d(s)$ the proportion of subjects that receive s, and denote by X_s and $C_s[\xi]$ the associated matrices. We have

$$C_d\,[\xi] = n \sum_{s\in\mathcal{S}} \pi_d(s)\;C_s[\xi] = n \sum_{s\in\mathcal{S}} \pi_d(s)\;X_s'\;Q_k\;X_s. \tag{3}$$

The information matrix for the parameter of interest $\phi = K'\xi$ may be obtained from $C_d[\xi]$ by the extremal representation (see Gaffke, 1987 or Pukelsheim, 1993):

$$C_d\,[\phi] = C_d\,[K'\xi] = \min_{L\in\mathcal{L}_K} L' C_d\,[\xi]\,L, \tag{4}$$

where $\mathcal{L}_K = \{L \in \mathbb{R}^{t(t+1)\times t} \mid L'K = I_t\}$ and the minimum is taken relative to the Loewner ordering. The minimum in (4) exists and is unique for a given design d. Put $\mathcal{E}_d = \{L \in \mathcal{L}_K \mid L'C_d[\xi]L = C_d[\phi]\}$.

In the sequel, the entries of L, or, more generally, of any matrix of size $t(t+1)\times t$, will be denoted by L^w_{uv}, for $u, w = 1, \dots, t$, and $v = 0, \dots, t$, where w is the column index and uv is the double index for the rows, similar to the vector ξ or the matrix K. The $t \times t$ matrix $L'K$ has entries $(L'K)_{uv} = L^u_{vv}$, for $u, v = 1, \dots, t$.

LEMMA 1. *For any design d, the row and column sums of $C_d[\phi]$ are zero.*

PROOF. Since $C_d[\phi]$ is symmetric, we have to prove that $\mathbb{I}'_t C_d[\phi]\mathbb{I}_t = 0$. Consider the $t(t+1)\times t$ matrix L such that L^u_{vw} is equal to 1 if $u = v$ and 0 otherwise. The matrix L satisfies $L\,\mathbb{I}_t = \mathbb{I}_{t(t+1)}$ and the constraint $L'K = I_t$. It follows from (4) that $\mathbb{I}'_t\ C_d[\phi]\ \mathbb{I}_t \le \mathbb{I}'_t\ L'\ C_d\,[\xi]\ \ L\ \mathbb{I}_t = \mathbb{I}'_{t(t+1)}\ C_d\,[\xi]\ \mathbb{I}_{t(t+1)}$. The result follows from the fact that $C_d[\xi]\mathbb{I}_{t(t+1)} = 0$. □

For a design d, denote by L^* a matrix in $\mathcal{E}_d$. Since, for any given L, $L'C_d\,[\xi]\,L$ is linear in $C_d\,[\xi]$, we have by (3):

$$C_d[\phi] = L^{*\prime}\ C_d\,[\xi]\ \ L^* = n \sum_{s\in\mathcal{S}} \pi_d(s)\ L^{*\prime}\ C_s[\xi]\ L^*. \tag{5}$$

This linearization is the basis of Kushner's methods.

3.2. *Approximate designs and symmetric designs.* An exact design is characterized, up to a subject permutation, by the proportions of sequences that appear in it. These proportions are multiples of n^{-1}. If we allow the proportions to varying continuously in $[0, 1]$ with the only restriction that the sum must be equal to 1, we obtain an approximate design. By definition, the information matrices of ξ and ϕ for an approximate designs are given by (3) and (4) as for an exact design. The second idea of Kushner's method is to find a universally optimal design in the set of approximate designs using the linearized expression (5). If the optimal approximate design is not an exact design, one can calculate a sharp lower bound for efficiency factors of competing exact designs.

We now recall the concepts of permuted sequence, symmetric design and symmetrized design as introduced by Kushner (1997). Let σ be a permutation of the treatment labels $\{1, \dots, t\}$ and s a sequence of treatments. The *permuted sequence* s_σ is obtained from s by permuting the treatment labels according to σ. Similarly, the design d_σ is the design obtained from the design d by permuting the treatment labels according to σ. A design d is said to be a *symmetric design* if, for any sequence s and any permutation σ, $\pi_d(s_\sigma) = \pi_d(s)$. For such a design, d and d_σ are identical up to a subject permutation, which may be written $d = d_\sigma$. From a design d, we define the *symmetrized design* $\bar{d}$ by

$$\pi_{\bar{d}}(s) = \frac{1}{t!} \sum_{\sigma \in S_t} \pi_d(s_\sigma), \quad \forall s \in \mathcal{S}, \tag{6}$$

where S_t is the set of all permutations of $\{1, \dots, t\}$. It is easy to see that the symmetrized design $\bar{d}$ is a symmetric design.

To a permutation σ of treatment labels, we may associate a permutation σ^* of the carry-over effect labels $\{0, 1, \dots, t\}$ where $\sigma^*(0) = 0$ and $\sigma^*(u) = \sigma(u)$ for $u = 1, \dots, t$. We also associate a permutation $\widetilde{\sigma}$ of $\{1, \dots, t\} \times \{0, \dots, t\}$ defined by $\widetilde{\sigma}(u, v) = (\sigma(u), \sigma^*(v))$. We denote by P_σ, P_{σ^*} and $P_{\widetilde{\sigma}} = P_\sigma \otimes P_{\sigma^*}$ the corresponding permutation matrices: for example, $P_\sigma(u, v) = 1$ if $\sigma(u) = v$ and $P_\sigma(u, v) = 0$ otherwise.

For $L \in \mathcal{L}_K$, put $L_\sigma = P'_{\widetilde{\sigma}} L P_\sigma$. It can be checked that $P'_{\widetilde{\sigma}} K P_\sigma = K$ (see also the definition of the matrix $L_{(1)}$ below).

LEMMA 2. *For any design d and any permutation σ in S_t, we have*

$$C_{d_\sigma}[\xi] = P_{\widetilde{\sigma}}\, C_d[\xi]\, P'_{\widetilde{\sigma}}; \tag{7}$$

$$C_{d_\sigma}[\phi] = P_\sigma\, C_d[\phi]\, P'_\sigma; \tag{8}$$

$$C_{\bar{d}}[\xi] = \frac{1}{t!} \sum_{\sigma \in S_t} P_{\widetilde{\sigma}}\, C_d[\xi]\, P'_{\widetilde{\sigma}}; \tag{9}$$

$$C_{\bar{d}}[\phi] \geq \frac{1}{t!} \sum_{\sigma \in S_t} P_\sigma\, C_d[\phi]\, P'_\sigma \quad \textit{w.r.t. the Loewner ordering}; \tag{10}$$

and $L \in \mathcal{E}_d$ if and only if $L_\sigma \in \mathcal{E}_{d_\sigma}$.

PROOF. By definition of $P_{\widetilde{\sigma}}$, $X_{d_\sigma} = X_d P'_{\widetilde{\sigma}}$, and so $C_{d_\sigma}[\xi] = X'_{d_\sigma}\, \omega_B^\perp\, X_{d_\sigma} = P_{\widetilde{\sigma}} X'_d\, \omega_B^\perp\, X_d P'_{\widetilde{\sigma}} = P_{\widetilde{\sigma}}\, C_d[\xi]\, P'_{\widetilde{\sigma}}$, which corresponds to (7). If $L \in \mathcal{L}_K$ then $L' C_{d_\sigma}[\xi] L = L' P_{\widetilde{\sigma}} C_d[\xi] P'_{\widetilde{\sigma}} L = P_\sigma L'_\sigma C_d[\xi] L_\sigma P'_\sigma$. Now $L'_\sigma K = P'_\sigma L' P_{\widetilde{\sigma}} P'_{\widetilde{\sigma}} K P_\sigma = P'_\sigma L' K P_\sigma$. If $L \in \mathcal{L}_K$ then $L'K = I_t$, so $L'_\sigma K = I_t$ and $L_\sigma \in \mathcal{L}_K$. The same argument with σ^{-1} shows that if $L_\sigma \in \mathcal{L}_K$ then $L \in \mathcal{L}_K$. The Loewner ordering is unchanged by permutations, so

$$C_{d_\sigma}[\phi] = \min_{L \in \mathcal{L}_K} (L' C_{d_\sigma}[\xi] L) = P_\sigma \left(\min_{L_\sigma \in \mathcal{L}_K} L'_\sigma C_d[\xi] L_\sigma \right) P'_\sigma = P_\sigma\, C_d[\phi]\, P'_\sigma,$$

and (8) is established. Moreover, $L \in \mathcal{E}_d$ if and only if $L_\sigma \in \mathcal{E}_{d_\sigma}$. Formula (9) follows directly from (7) and (6). Formula (10) follows from (9) and the concavity of the minimum representation (4). $\square$

We recall that a $t \times t$ matrix C is completely symmetric if $C = a\, I_t + b\; J_t$ for some scalars a and b or, equivalently, if $P_\sigma\; C\; P'_\sigma = C$ for every permutation σ in S_t.

LEMMA 3. *If d is a symmetric design then $C_d[\phi]$ is completely symmetric.*

PROOF. Since d is symmetric, $d_\sigma = d$. By (8), $C_d[\phi] = C_{d_\sigma}[\phi] = P_\sigma\; C_d[\phi]\; P'_\sigma$ for any permutation σ in S_t. Therefore $C_d[\phi]$ is completely symmetric. $\square$

The key point to obtain an optimal design is to identify the structure of the $t(t+1) \times t$ matrix L^* defined in (5), whose entries are denoted by L^{*w}_{uv}.

LEMMA 4. *If d is a symmetric design then the matrix L^* in (5) can be chosen so that it satisfies*

$$L^*_\sigma = L^*, \quad \forall \sigma \in S_t, \tag{11}$$

or, equivalently,

$$L^{*\sigma(w)}_{\sigma(u)\sigma^*(v)} = L^{*w}_{uv}, \quad \forall \sigma \in S_t. \tag{12}$$

PROOF. If $\sigma \in S_t$ then $d_\sigma = d$, so $\mathcal{E}_{d_\sigma} = \mathcal{E}_d$ and Lemma 2 shows that $L_\sigma \in \mathcal{E}$. Put $L^* = \left(\sum_{\sigma \in S_t} L_\sigma\right)/t!$, which satsifies (11). Since $\mathcal{E}$ is closed under taking averages (see Druilhet and Tinsson, 2009, proof of Lemma A1), L^* also belongs to $\mathcal{E}$. $\square$

A consequence of (12) is that the entries L^{*w}_{uv} are constant for (u, v, w) belonging to the same orbit of the permutation group $\{(\widetilde{\sigma}, \sigma)\}_{\sigma \in S_t}$ acting on $\{1, \ldots, t\} \times \{0, \ldots, t\} \times \{1, \ldots, t\}$. There are seven distinct orbits:

- $\mathcal{O}_1 = \{(u, u, u) \mid u = 1, \ldots, t\}$,
- $\mathcal{O}_2 = \{(u, v, u) \mid u, v = 1, \ldots, t,\ u \neq v\}$,
- $\mathcal{O}_3 = \{(u, v, v) \mid u, v = 1, \ldots, t,\ u \neq v\}$,
- $\mathcal{O}_4 = \{(u, v, w) \mid u, v, w = 1, \ldots, t,\ u \neq v \neq w \neq u\}$,
- $\mathcal{O}_5 = \{(u, 0, u) \mid u = 1, \ldots, t\}$,
- $\mathcal{O}_6 = \{(u, 0, w) \mid u, w = 1, \ldots, t,\ u \neq w\}$,
- $\mathcal{O}_7 = \{(u, u, w) \mid u, w = 1, \ldots, t,\ u \neq w\}$.

For $q = 1, \ldots, 7$, denote by $L_{(q)}$ the $t(t+1) \times t$ matrix with entries $L^w_{(q)uv} = 1$ if (u, v, w) belongs to the orbit $\mathcal{O}_q$ and 0 otherwise. Note that $L_{(1)} = K$.

By construction of $L_{(q)}$, we have

$$P'_{\widetilde{\sigma}}\; L_{(q)}\; P_\sigma = L_{(q)}, \quad \forall \sigma \in S_t \text{ and } q = 1, \ldots, 7. \tag{13}$$

PROPOSITION 5. *For a symmetric design d, the matrix L^* in Lemma 4 may be written as*

$$L^* = L_\gamma = L_{(1)} + \sum_{q=2}^{6} \gamma_q L_{(q)}, \tag{14}$$

where $\gamma = (\gamma_2, \dots, \gamma_7)$ is a vector of scalars.

PROOF. Since L^* satisfies (11), it is a linear combination of the matrices $L_{(q)}$: $L^* = \sum_{q=1}^{7} \gamma_q L_{(q)}$. It can be checked that $L'_{(1)} K = K'K = I_t$, $L'_{(7)} K = J_t - I_t$ and $L'_{(q)} K = 0$ for $q = 2, \dots, 6$. Consequently, the constraint $L^{*'} K = I_t$ may be written $\gamma_1 = 1$ and $\gamma_7 = 0$. $\square$

3.3. *The model with period effects.* We consider here the same model as in Section 2 with the addition of a period effect. Since a period effect is meaningless for approximate designs, we consider only exact designs. The response for subject i in period j is given by:

$$y_{ij} = \alpha_j + \beta_i + \xi_{d(i,j),d(i,j-1)} + \varepsilon_{ij}, \tag{15}$$

where α_j is the effect of period j. In vector notation, we have

$$Y = A\alpha + B\beta + X_d \xi + \varepsilon, \tag{16}$$

with $A = \mathbb{I}_n \otimes I_k$, where α is the k-vector of period effects. Denote $\theta' = (\xi', \alpha')$. The information matrix for θ is given by:

$$\widetilde{C}_d[\theta] = \begin{pmatrix} C_d[\xi] & C_{d12} \\ C_{d21} & C_{d22} \end{pmatrix} = \begin{pmatrix} X'_d \, \omega_B^\perp \, X_d & X'_d \, \omega_B^\perp \, A \\ A' \, \omega_B^\perp \, X_d & A' \, \omega_B^\perp \, A \end{pmatrix},$$

where $C_d[\xi]$ is the information matrix for ξ obtained in the model without period effects and $C_{d22} = nQ_k$.

The t-vector ϕ of total effects defined by (2) may also be seen as a subsystem of the parameter θ, because $\phi = \tilde{K}'\theta$ with $\tilde{K}' = (K', 0_{t\times k})$. The information matrix $\widetilde{C}_d[\phi]$ for ϕ under Model (15) may be obtained from $\widetilde{C}_d[\theta]$ by the extremal representation:

$$\widetilde{C}_d\,[\phi] = \min_{\widetilde{L} \in \mathcal{L}_{\widetilde{K}}} \widetilde{L}' C_d\,[\theta]\,\widetilde{L},$$

where $\mathcal{L}_{\widetilde{K}} = \{\widetilde{L} \in \mathbb{R}^{(t(t+1)+k)\times t} \mid \widetilde{L}'\widetilde{K} = I_t\}$. Partitioning $\widetilde{L}'$ as $(L' \mid N')$ with L and N of sizes $t(t+1) \times t$ and $k \times t$, we have

$$\widetilde{C}_d\,[\phi] = \min_{(L'|N')' \in \mathcal{L}_{\widetilde{K}}} \left(L' C_d\,[\xi]\,L + L' C_{d12} N + N' C_{d21} L + N' C_{d22} N\right). \tag{17}$$

Note that $(L' \mid N')' \in \mathcal{L}_{\widetilde{K}}$ is equivalent to $L \in \mathcal{L}_K$ for L and N with suitable dimensions. Choosing $N = 0$ in (17), we have $\widetilde{C}_d[\phi] \le C_d[\phi]$ with respect to the Loewner ordering, where $C_d[\phi]$ is the information matrix for ϕ under the model without period effects, as defined in (4). Therefore $\mathbb{I}_t' \widetilde{C}_d[\phi] \, \mathbb{I}_t \le \mathbb{I}_t' C_d[\phi] \, \mathbb{I}_t = 0$. Hence the row and column sums of $\widetilde{C}_d[\phi]$ are all zero, and so $Q_t \widetilde{C}_d[\phi] Q_t = \widetilde{C}_d[\phi]$.

For $\sigma \in S_t$, define the permutation $\bar{\sigma}$ of $\{1, \ldots, t\} \times \{0, \ldots t\} \times \{1, \ldots k\}$ by $\bar{\sigma}(u, v, j) = (\sigma(u), \sigma^*(v), j)$. The associated permutation matrix $P_{\bar{\sigma}}$ is the block diagonal matrix with diagonal blocks $P_{\tilde{\sigma}}$ and I_k. For $\widetilde{L}$ in $\mathcal{L}_{\widetilde{K}}$, put $\widetilde{L}_\sigma = P_{\bar{\sigma}}' \widetilde{L} P_\sigma$. If $\widetilde{L}' = (L' \mid N')$ then $\widetilde{L}_\sigma' = (L_\sigma' \mid N_\sigma')$, where $N_\sigma = N P_\sigma$.

Lemma 6. *For any design d and any permutation σ of treatment labels, we have*

$$C_{d_\sigma 12} = P_{\tilde{\sigma}} \, C_{d12}; \tag{18}$$

$$\widetilde{C}_{d_\sigma}[\phi] = P_\sigma \, \widetilde{C}_d[\phi] \, P_\sigma'. \tag{19}$$

Proof. Equation (18) follows from the fact that $X_{d_\sigma} = X_d \, P_{\tilde{\sigma}}'$. The proof of (19) is similar to the proof of (8), replacing ξ, L, $\mathcal{L}_K$ and K by θ, $\widetilde{L}$, $\mathcal{L}_{\widetilde{K}}$ and $\widetilde{K}$ respectively. □

A design is said to be *strongly balanced on the periods* if it satisfies the following conditions:

(i) for the first period, each treatment appears equally often,
(ii) for any given period, except the first one, each treatment appears preceded by itself equally often,
(iii) for any given period, except the first one, the number of times a treatment, say u, is preceded by another treatment v does not depend on u or v.

Note that a symmetric exact design is strongly balanced on the periods.

Lemma 7. *If a design d is strongly balanced on the periods and $\sigma \in S_t$ then $P_{\bar{\sigma}}' X_d' A = X_d' A$.*

Proof. The (uv, j)-entry of $X_d' A$ is equal to the number of times that treatment u occurs in period j preceded by treatment v. Strong balance implies that there is a single value for $v = 0$, another single value for $v = u$, and another single value for $v \notin \{0, u\}$. Permutation of the treatments does not change this. □

Given a design d, let G_d be the subgroup of S_t consisting of those permutations σ satisfying $d_\sigma = d$ (up to a subject permutation). Note that a symmetric design may be characterized by $G_d = S_t$. The subgroup G_d is said to be *transitive* on $\{1,\ldots,t\}$, if, given u, v in $\{1,\ldots,t\}$, there is some σ in G_d with $\sigma(u) = v$. The subgroup G_d is *doubly transitive* if, given u_1, u_2, v_1, v_2 with $u_1 \neq u_2$ and $v_1 \neq v_2$ there is some σ in G_d with $\sigma(u_1) = v_1$ and $\sigma(u_2) = v_2$.

PROPOSITION 8. *If d is an exact design with strong balance on the periods and with transitive group G_d, then the information matrix for ϕ is the same under Models (1) and (15), that is*

$$\widetilde{C}_d[\phi] = C_d[\phi].$$

In particular, this is true if d is an exact symmetric design.

PROOF. The method of proof of Lemma 4 shows that the matrix $\widetilde{L}$ used for minimizing may be chosen to satisfy $P'_{\tilde{\sigma}}\widetilde{L}P_{\sigma} = \widetilde{L}$ for all σ in G_d. This means that $L = L_\sigma$ and $N = N_\sigma = NP_\sigma$ for all σ in G_d. If $NP_\sigma = N$ for all σ in G_d and G_d is transitive then every row of N is a multiple of $\mathbb{I}'_t$.

We have $C_{d12} = X'_d\omega_B^\perp A = X'_d AQ_k$. Lemma 7 shows that if $L = L_\sigma$ then $L'C_{d12} = L'_\sigma X'_d AQ_k = L'_\sigma P'_{\tilde{\sigma}} X'_d AQ_k = P'_\sigma L'C_{d12}$. If G_d is transitive then every column of LC_{d12} is a multiple of $\mathbb{I}_t$.

Therefore, the expression in (17) is equal to $L'C_d[\xi]L + c(L,N)J_t$ for some scalar $c(L,N)$. Hence

$$\begin{aligned}
\widetilde{C}_d[\phi] = Q_t\,\widetilde{C}_d[\phi]\,Q_t &= Q_t\left(\min_{(L'|N')'\in\mathcal{L}_{\widetilde{K}}} L'C_d[\xi]L + c(L,N)J_t\right)Q_t \\
&= \min_{(L'|N')'\in\mathcal{L}_{\widetilde{K}}} (Q_tL'C_d[\xi]LQ_t) \\
&= Q_t\left(\min_{L\in\mathcal{L}_K} L'C_d[\xi]L\right)Q_t \\
&= Q_tC_d[\phi]Q_t = C_d[\phi].
\end{aligned}$$

□

For any design d whose G_d is doubly transitive, $C_d[\phi]$ is completely symmetric (replace S_t by G_d in the proof of Lemma 3). Double transitivity implies strong balance on the periods, so then $\widetilde{C}_d[\phi]$ is also completely symmetric, by Proposition 8. In Section 5.6 we give some examples that show that strong balance on the periods is not sufficient for $\widetilde{C}_d[\phi]$ to be completely symmetric.

4. Universally optimal approximate designs. From Kiefer (1975), a design d^* for which the information matrix $C_{d^*}[\phi]$ is completely symmetric and that maximizes the trace of $C_d[\phi]$ over all the designs d for t treatments using n subjects for k periods is universally optimal.

4.1. *Condition for optimal designs.* The following proposition shows that a universally optimal approximate design may be sought among symmetric designs.

PROPOSITION 9. *A symmetric design for which the trace of the information matrix is maximal among the class of symmetric designs is universally optimal among all possible approximate designs.*

PROOF. For any design d, taking the trace in (10), we have $\mathrm{tr}(C_{\bar{d}}[\phi]) \geq \mathrm{tr}(C_d[\phi])$. Since, by Lemma 3, $C_{\bar{d}}[\phi]$ is completely symmetric, $\bar{d}$ is always better than d with respect to universal optimality. If d^* maximizes the trace among the set of symmetric designs, then for any design d, $\mathrm{tr}(C_{d^*}[\phi]) \geq \mathrm{tr}(C_{\bar{d}}[\phi]) \geq \mathrm{tr}(C_d[\phi])$. Since $C_{d^*}[\phi]$ is completely symmetric and maximizes the trace, d_* is universally optimal. $\square$

For any sequence s, and $1 \leq p, q \leq 7$, put $c_{spq} = \mathrm{tr}\left(L'_{(p)}\ C_s[\xi]\ L_{(q)}\right)$. Then combining (5), (4) and (14), we have for a symmetric design,

$$\mathrm{tr}(C_d[\phi]) = \min_{\gamma_2,\ldots,\gamma_6} \sum_{s\in\mathcal{S}} n\ \pi_d(s) \sum_{p=1}^{6}\sum_{q=1}^{6} \gamma_p\gamma_q\ c_{spq} \quad \text{with } \gamma_1 = 1.$$

LEMMA 10. *For a sequence s and a permutation σ on the treatment labels, we have:*

$$c_{s_\sigma pq} = c_{spq}.$$

PROOF.

$$\begin{aligned} c_{s_\sigma pq} &= \mathrm{tr}(P'_\sigma\, L'_{(p)}\ C_{s_\sigma}[\xi]\ L_{(q)} P_\sigma), && \text{since } \mathrm{tr}(AB) = \mathrm{tr}(BA), \\ &= \mathrm{tr}(P'_\sigma\, L'_{(p)} P_{\tilde{\sigma}}\ C_s[\xi] P'_{\tilde{\sigma}}\ L_{(q)} P_\sigma), && \text{by (7)}, \\ &= \mathrm{tr}(L'_{(p)}\ C_s[\xi]\ L_{(q)}) = c_{spq}, && \text{by (13)}. \end{aligned}$$

$\square$

Two sequences are said to be *equivalent* if one can be obtained from the other one by some permutation of treatment labels. We denote by $\mathcal{C}$ the set of all possible *equivalence classes*. From Lemma 10, c_{spq} depends only on the equivalence class ℓ to which s belongs, and will be therefore denoted $c_{\ell pq}$. To each equivalence class ℓ, we may also associate the non-negative convex quadratic polynomial with five variables $\gamma = (\gamma_2, \dots, \gamma_6)$:

$$h_\ell(\gamma) = \sum_{p=1}^{6} \sum_{q=1}^{6} \gamma_p \gamma_q \, c_{\ell pq} \quad \text{where } \gamma_1 = 1.$$

For a symmetric design, we may write π_ℓ for the proportion of sequences which are in the equivalence class ℓ. Then

$$\operatorname{tr}(C_d[\phi]) = \min_\gamma \sum_{\ell \in \mathcal{C}} n \, \pi_\ell \, h_\ell(\gamma).$$

Therefore, we have the following proposition:

Proposition 11. *An approximate symmetric design d^* with proportions $\{\pi_\ell^*\}_{\ell \in \mathcal{C}}$ that achieves*

$$\max_{\{\pi_\ell\}_{\ell \in \mathcal{C}}} \; \min_\gamma \sum_{\ell \in \mathcal{C}} \pi_\ell \, h_\ell(\gamma) \tag{20}$$

is universally optimal among all possible designs.

4.2. *Determination of optimal proportions.* We propose now the following method derived from Kushner (1997). Consider

$$h^*(\gamma) = \max_{\ell \in \mathcal{C}} h_\ell(\gamma).$$

We use the following procedure:

- find γ^* that minimizes the function $h^*(\gamma)$ and denote $h^* = h(\gamma^*)$ the minimum;
- select the classes ℓ of sequences such that $h_\ell(\gamma^*) = h^*$ and denote $\mathcal{C}^*$ this set;
- solve in $\{\pi_\ell \mid \ell \in \mathcal{C}^*\}$ the linear system, $\sum_{\ell \in \mathcal{C}^*} \pi_\ell \frac{dh_\ell}{d\gamma}(\gamma^*) = 0$, for $0 < \pi_\ell < 1$ and $\sum_{\ell \in \mathcal{C}} \pi_\ell = 1$; denote $\pi^* = \{\pi_\ell^* \mid \ell \in \mathcal{C}^*\}$ the solution (not necessarily unique);
- the symmetric designs such that $\pi_\ell = \pi_\ell^*$ for $\ell \in \mathcal{C}^*$ and 0 otherwise are universally optimal.

5. Examples of optimal and efficient designs. For some values of k and t, we give optimal approximate designs. For each given k, the first table gives the optimal proportions and the second table gives the efficiency factor for a symmetric design generated by a single sequence.

Denote by $\psi(C_d[\phi])$ a real-valued criterion. The efficiency factor of a design d is defined by

$$\mathit{eff}_\psi(d) = \frac{\psi(C_d[\phi])}{\psi(C_{d^*}[\phi])}$$

where d^* is the optimal approximate design with the same values of k, n and t. The efficiency factor for a design d is defined by $\mathit{eff} = \operatorname{tr}(C_d[\phi]) / \operatorname{tr}(C_{d^*}[\phi])$.

When $C_d[\phi]$ is completely symmetric, *eff* is also the efficiency factor for the well known D-, A- and E-criteria (see Shah and Sinha, 1989 or Druilhet, 2004).

We write 0^+ or 1^- when a value is within 0.005 of 0, 1 respectively. For some values of k and t the optimal proportions have been calculated with formal calculus when tractable; all others have been obtained by numerical optimisation.

The values h^* displayed correspond to those defined in Section 4.2 for an optimal design. The information matrix for a symmetric optimal approximate design with n subjects is therefore

$$C_d[\phi] = \frac{n\,h^*}{t-1} Q_t.$$

5.1. *3 periods.* Optimal proportions for some values of t:

t	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Prop. [1 1 2]	$\frac{1}{2}$	$\frac{5}{13}$	$\frac{1}{3}$	$\frac{7}{23}$	$\frac{2}{7}$	$\frac{3}{11}$	$\frac{5}{19}$	$\frac{11}{43}$	$\frac{1}{4}$	$\frac{13}{53}$	$\frac{7}{29}$	$\frac{5}{21}$	$\frac{4}{17}$	$\frac{17}{73}$	$\frac{3}{13}$
Prop. [1 2 2]	$\frac{1}{2}$	$\frac{8}{13}$	$\frac{2}{3}$	$\frac{16}{23}$	$\frac{5}{7}$	$\frac{8}{11}$	$\frac{14}{19}$	$\frac{32}{43}$	$\frac{3}{4}$	$\frac{40}{53}$	$\frac{22}{29}$	$\frac{16}{21}$	$\frac{13}{17}$	$\frac{56}{73}$	$\frac{10}{13}$
h^*	$\frac{1}{3}$	$\frac{16}{39}$	$\frac{4}{9}$	$\frac{32}{69}$	$\frac{10}{21}$	$\frac{16}{33}$	$\frac{28}{57}$	$\frac{64}{129}$	$\frac{1}{2}$	$\frac{80}{159}$	$\frac{44}{87}$	$\frac{32}{63}$	$\frac{26}{51}$	$\frac{112}{219}$	$\frac{20}{39}$

Efficiency of symmetric designs generated by a single sequence:

t	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
eff. [1 1 2]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
eff. [1 2 2]	0	0.61	0.75	0.81	0.84	0.86	0.87	0.88	0.89	0.89	0.90	0.90	0.91	0.91	0.91

Example of universally optimal design for $t = 4$:

$$\begin{pmatrix} 1&1&1&1&1&1&2&2&2&2&2&2&3&3&3&3&3&3&4&4&4&4&4&4&1&1&1&2&2&2&3&3&3&4&4&4 \\ 2&2&3&3&4&4&1&1&3&3&4&4&1&1&2&2&4&4&1&1&2&2&3&3&1&1&1&2&2&2&3&3&3&4&4&4 \\ 2&2&3&3&4&4&1&1&3&3&4&4&1&1&2&2&4&4&1&1&2&2&3&3&2&3&4&1&3&4&1&2&4&1&2&3 \end{pmatrix}$$

5.2. *4 periods.* The optimal approximate designs are generated by the single sequence [1 1 2 2] for $2 \le t \le 30$. It is conjectured that this is true for any value of t.

5.3. *5 periods.* Optimal proportions for some values of t:

t	2	3	4	5	6	7	8	9	10	15	20	30
Prop. [1 1 2 2 2]	$\frac{1}{2}$	$\frac{7}{9}$	$\frac{17}{19}$	$\frac{47}{49}$	0.98	0.98	0.98	0.98	0.98	0.97	0.97	0.97
Prop. [1 1 1 2 2]	$\frac{1}{2}$	$\frac{2}{9}$	$\frac{2}{19}$	$\frac{2}{49}$	0	0	0	0	0	0	0	0
Prop. [1 1 2 3 3]	0	0	0	0	0.02	0.02	0.02	0.02	0.02	0.03	0.03	0.03
h^*	$\frac{7}{5}$	$\frac{68}{45}$	$\frac{148}{95}$	$\frac{388}{245}$	1.60	1.61	1.62	1.63	1.63	1.64	1.65	1.66

Efficiency of symmetric designs generated by a single sequence:

t	2	3	4	5	6	7	8	9	10	15	20	30
Eff. [1 1 2 2 2]	0.95	0.99	0.998	1^-	1^-	1^-	1^-	1^-	1^-	1^-	1^-	1^-
Eff. [1 1 1 2 2]	0.95	0.91	0.89	0.88	0.87	0.87	0.87	0.87	0.87	0.86	0.86	0.85
Eff. [1 1 2 3 3]	–	0.77	0.82	0.84	0.85	0.86	0.86	0.86	0.86	0.87	0.88	0.88

Example of universally optimal symmetric design for $t = 3$:

$$\left(\begin{array}{cccccccccccccccccccccccccccc}
1&1&1&1&1&1&1&1&1&1&1&1&1&1&2&2&2&2&2&2&2&2&2&2&2&2&2&2\\
1&1&1&1&1&1&1&1&1&1&1&1&1&1&2&2&2&2&2&2&2&2&2&2&2&2&2&2\\
1&1&1&1&1&1&1&1&1&1&1&1&1&1&2&2&2&2&2&2&2&2&2&2&2&2&2&2\\
2&2&2&2&2&2&2&3&3&3&3&3&3&3&1&1&1&1&1&1&1&3&3&3&3&3&3&3\\
2&2&2&2&2&2&2&3&3&3&3&3&3&3&1&1&1&1&1&1&1&3&3&3&3&3&3&3
\end{array}\right.$$

$$\left.\begin{array}{cccccccccccccccccccccccccc}
3&3&3&3&3&3&3&3&3&3&3&3&3&3&1&1&1&1&2&2&2&2&3&3&3&3\\
3&3&3&3&3&3&3&3&3&3&3&3&3&3&1&1&1&1&2&2&2&2&3&3&3&3\\
3&3&3&3&3&3&3&3&3&3&3&3&3&3&2&2&3&3&1&1&3&3&1&1&2&2\\
1&1&1&1&1&1&1&2&2&2&2&2&2&2&2&2&3&3&1&1&3&3&1&1&2&2\\
1&1&1&1&1&1&1&2&2&2&2&2&2&2&2&2&3&3&1&1&3&3&1&1&2&2
\end{array}\right)$$

5.4. *6 periods.* Optimal proportions for some values of t:

t	2	3	4	5	6	7	8	9	10	15	20	30
Prop. [1 1 1 2 2 2]	1	0.81	0.66	0.55	0.48	0.42	0.38	0.35	0.32	0.23	0.19	0.15
Prop. [1 1 2 2 3 3]	0	0.19	0.34	0.45	0.52	0.52	0.62	0.65	0.68	0.77	0.81	0.85
h^*	2	2.11	2.16	2.19	2.21	2.22	2.23	2.24	2.25	2.26	2.27	2.28

Efficiency of symmetric designs generated by a single sequence:

t	2	3	4	5	6	7	8	9	10	15	20	30
Eff. [1 1 1 2 2 2]	1	0.99	0.99	0.98	0.98	0.97	0.97	0.97	0.97	0.97	0.96	0.96
Eff. [1 1 2 2 3 3]	–	0.95	0.97	0.98	0.99	0.99	0.99	0.99	1^-	1^-	1^-	1^-

5.5. *7 periods.* Optimal proportions for some values of t:

t	3	4	5	6	$7 \leq t \leq 30$
Prop. [1 1 1 2 2 2 2]	0.57	0.19	0	0	0
Eff. [1 1 1 2 2 3 3]	0	0	0.09	0^+	0
Prop. [1 1 2 2 3 3 3]	0.43	0.81	0.91	1^-	1
h^*	2.60	2.70	2.76	2.80	2.82

Efficiency of symmetric designs generated by a single sequence:

t	3	4	5	6	7
Eff. [1 1 1 2 2 2 2]	0.98	0.96	0.95	0.94	0.94
Eff. [1 1 1 2 2 3 3]	0.98	0.99	0.98	0.98	0.98
Eff. [1 1 2 2 3 3 3]	0.98	1^-	1^-	1^-	1

5.6. *Efficient designs with $t(t-1)$ subjects.* For $k = 6$ or $k = 7$, we saw that efficient symmetric designs may be obtained from single sequences having three treatments by permuting all the treatment labels. Such designs require $t(t-1)(t-2)$ subjects, which may be too large. We can construct efficient designs that are strongly balanced on the periods, are generated by a single sequence, and require only $t(t-1)$ subjects, as follows.

Step 1 We start from a binary balanced incomplete-block design with block-size 3 such that for any two different periods j_1 and j_2 and any two different treatments u and v, there exists exactly one subject that receives treatment u in period j_1 and treatment v in period j_2. (This is called an orthogonal array of type I and strength two: see Rao, 1961.)

- If t is odd, use all the triplets $[u, u+v, u+2v]$ modulo t, for $u = 0, \ldots, t-1$ and $v = 1, \ldots, t-1$.
- If t is even, use the preceding construction for $t-1$ and replace each triplet of the form $[u, u+1, u+2]$ by the three sequences $[t, u+1, u+2]$, $[u, t, u+2]$ and $[u, u+1, t]$.

Step 2 Then, we construct a design with k periods by replicating the three treatments in each triplet in such a way that we obtain a sequence in the same equivalence class as the one that generates the efficient design.

For example, take $k = 7$ and $t = 5$ with generating sequence [1 1 2 2 3 3 3]. The starting design with three periods is:

$$\begin{pmatrix} 1 & 1 & 1 & 1 & 2 & 2 & 2 & 2 & 3 & 3 & 3 & 3 & 4 & 4 & 4 & 4 & 5 & 5 & 5 & 5 \\ 2 & 3 & 4 & 5 & 3 & 4 & 5 & 1 & 4 & 5 & 1 & 2 & 5 & 1 & 2 & 3 & 1 & 2 & 3 & 4 \\ 3 & 5 & 2 & 4 & 4 & 1 & 3 & 5 & 5 & 2 & 4 & 1 & 1 & 3 & 5 & 2 & 2 & 4 & 1 & 3 \end{pmatrix}$$

The resulting design with seven periods generated by [1 1 2 2 3 3 3] is

$$\begin{pmatrix}
1 & 1 & 1 & 1 & 2 & 2 & 2 & 2 & 3 & 3 & 3 & 3 & 4 & 4 & 4 & 4 & 5 & 5 & 5 & 5 \\
1 & 1 & 1 & 1 & 2 & 2 & 2 & 2 & 3 & 3 & 3 & 3 & 4 & 4 & 4 & 4 & 5 & 5 & 5 & 5 \\
2 & 3 & 4 & 5 & 3 & 4 & 5 & 1 & 4 & 5 & 1 & 2 & 5 & 1 & 2 & 3 & 1 & 2 & 3 & 4 \\
2 & 3 & 4 & 5 & 3 & 4 & 5 & 1 & 4 & 5 & 1 & 2 & 5 & 1 & 2 & 3 & 1 & 2 & 3 & 4 \\
3 & 5 & 2 & 4 & 4 & 1 & 3 & 5 & 5 & 2 & 4 & 1 & 1 & 3 & 5 & 2 & 2 & 4 & 1 & 3 \\
3 & 5 & 2 & 4 & 4 & 1 & 3 & 5 & 5 & 2 & 4 & 1 & 1 & 3 & 5 & 2 & 2 & 4 & 1 & 3 \\
3 & 5 & 2 & 4 & 4 & 1 & 3 & 5 & 5 & 2 & 4 & 1 & 1 & 3 & 5 & 2 & 2 & 4 & 1 & 3
\end{pmatrix}$$

The following table displays the A-, D-, E-efficiency factors for designs with 6 periods and $t(t-1)$ subjects generated by the sequence [1 1 2 2 3 3] using the method described above.

t	4	5	6	7	8	9	10
A-efficiency	0.951	0.977	0.973	0.978	0.974	0.970	0.968
D-efficiency	0.951	0.977	0.973	0.978	0.974	0.970	0.968
E-efficiency	0.951	0.977	0.951	0.978	0.950	0.950	0.949

We may note that this method is interesting only for $t = 7$ or $t = 8$. For the other values of t, the symmetric design with $t(t-1)$ subjects generated by the sequence [1 1 1 2 2 2] is more efficient.

The following table displays the A-, D-, E-efficiency factors for designs with 7 periods and $t(t-1)$ subjects generated by the sequence [1 1 2 2 3 3 3] using the method described above.

t	4	5	6	7	8	9	10
A-efficiency	0.974	0.990	0.982	0.983	0.978	0.973	0.971
D-efficiency	0.974	0.990	0.982	0.983	0.978	0.973	0.971
E-efficiency	0.974	0.990	0.961	0.983	0.955	0.954	0.954

For $t = 4, 5, 7$, the information matrices are completely symmetric. For $t \geq 5$ and when the number of subjects is $t(t-1)$, these designs are preferable to symmetric designs generated by the sequence [1 1 1 2 2 2 2]. This is not the case for for $t = 4$.

If $t = 4$ or t is an odd prime, this method always gives a design d for which G_d is doubly transitive and so $\widetilde{C}_d[\phi]$ is completely symmetric. If t is any prime power, there is a second method which gives a design d in $t(t-1)$ periods for which G_d is completely symmetric.

Step 1 Identify the treatments with the elements of the finite field GF(t) of order t.

Step 2 Form any triplet $[x, y, z]$ of distinct treatments.

Step 3 Use this to produce all triplets of the form $[ax + b, ay + b, az + b]$ for which a and b are in GF(t) and $a \neq 0$.

Step 4 Use these triplets to construct a design from the desired sequence just as in the previous method.

For example, when $t = 8$, one correspondence between $\{1, \dots, 8\}$ and GF(8) gives the following starting design with three periods.

$$\left(\begin{array}{cccccccccccccccccccccccccccccccc}
8&7&1&3&2&6&4&5&8&1&2&4&3&7&5&6&8&2&3&5&4&1&6&7&8&3&4&6&5&2&7&1\\
7&8&3&1&6&2&5&4&1&8&4&2&7&3&6&5&2&8&5&3&1&4&7&6&3&8&6&4&2&5&1&7\\
1&3&8&7&4&5&2&6&2&4&8&1&5&6&3&7&3&5&8&2&6&7&4&1&4&6&8&3&7&1&5&2
\end{array}\right.$$

$$\left.\begin{array}{cccccccccccccccccccccccc}
8&4&5&7&6&3&1&2&8&5&6&1&7&4&2&3&8&6&7&2&1&5&3&4\\
4&8&7&5&3&6&2&1&5&8&1&6&4&7&3&2&6&8&2&7&5&1&4&3\\
5&7&8&4&1&2&6&3&6&1&8&5&2&3&7&4&7&2&8&6&3&4&1&5
\end{array}\right)$$

The design obtained from this starting design and the generating sequence [1 1 2 2 3 3], respectively [1 1 2 2 3 3 3], has efficiency factor equal to 0.977, respectively to 0.981.

For $t = 9$, we obtain the following starting design.

$$\left(\begin{array}{cccccccccccccccccccccccccccccccccccc}
1&1&2&2&3&3&4&4&5&5&6&6&7&7&8&8&9&9&1&1&4&4&7&7&2&2&5&5&8&8&3&3&6&6&9&9\\
2&3&1&3&1&2&5&6&4&6&4&5&8&9&7&9&7&8&4&7&1&7&1&4&5&8&2&8&2&5&6&9&3&9&3&6\\
3&2&3&1&2&1&6&5&6&4&5&4&9&8&9&7&8&7&7&4&7&1&4&1&8&5&8&2&5&2&9&6&9&3&6&3
\end{array}\right.$$

$$\left.\begin{array}{cccccccccccccccccccccccccccccccccccc}
1&1&5&5&9&9&2&2&6&6&7&7&3&3&4&4&8&8&1&1&6&6&8&8&2&2&4&4&9&9&3&3&5&5&7&7\\
5&9&1&9&1&5&6&7&2&7&2&6&4&8&3&8&3&4&6&8&1&8&1&6&4&9&2&9&2&4&5&7&3&7&3&5\\
9&5&9&1&5&1&7&6&7&2&6&2&8&4&8&3&4&3&8&6&8&1&6&1&9&4&9&2&4&2&7&5&7&3&5&3
\end{array}\right)$$

The design obtained from this starting design and the generating sequence [1 1 2 2 3 3], respectively [1 1 2 2 3 3 3], has efficiency factor equal to 0.950, respectively to 0.954.

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