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Optimal repeated measurement designs for a model with partial interactions

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Abstract

We consider circular crossover designs for models with partial interactions: we assume that the carryover effect of a treatment on itself is different from the carryover effect on other treatments. We generalize Kushner (1997) and Kunert and Martin (2000) methods to find optimal designs when the parameters of interest are total effects, which corresponds to the use of a single treatment, once selected. We give a lower bound of Φ_p criteria and propose efficient designs of small sizes.

AMS 2000 *subject classifications*. Primary 62K05, 62K10.

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1 Introduction

In traditional crossover designs, the statistical model considers that each treatment has a carryover effect, which, for parsimony, is assumed not interacting with direct treatment effects. To enrich this model, Hedayat and Afsarinejad (2002) propose a model with partial interactions: the carryover effect of a treatment is different if the treatment is preceded by itself. For such model, Kunert and Stufken (2002) find that universally optimal designs for direct treatment effects have no consecutive pairs of identical treatments. This feature is mainly due to the fact that partial interactions between carryover and direct treatment effects are considered as nuisance parameter. However, the aim of an experiment is to select a single treatment which will be used alone and then will be preceded by itself. In that case, the parameter of interest, called total effects, is the sum of direct treatments and self carryover effects. Bailey and Druilhet (2004) give a review of situations where total effects are considered in the literature. They show that neighbour balanced designs having no treatment preceded by itself are efficient when the number of periods is small. However, for models with partial interactions, such designs are inefficient because total effects are not estimable.

In this paper, we propose a general method to construct optimal circular

crossover designs for total effects under models with partial interactions. Upper bounds of the information matrix are obtained by a new method that generalizes the approaches of Kushner (1997), Kunert and Martin (2000) and Druilhet and Bailey (2004). Then we show that, in most cases, optimal designs are generated by one sequence or a mixture of two sequences that belongs to a set of $k - 1$ possible sequences, where k is the number of periods. Finally, we give some examples of optimal designs for several values of k . We also propose efficient designs generated by only one sequence of treatments. To simplify our presentation, we first construct optimal design for a model without period effects. Then we obtain optimal designs for a model with period effects by generalizing Kunert (1983) results on orthogonal effects.

2 The designs and the models

Let $d(i, j) \in \{1, \dots, t\}$ be the treatment assigned to subject i in period j , $1 \leq i \leq b$, $1 \leq j \leq k$. We assume that the response y_{ij} follows the model:

$$y_{ij} = \beta_i + \tau_{d(i,j)} + \lambda_{d(i,j-1)} + \chi_{d(i,j-1)d(i,j)} + \varepsilon_{ij} \quad (1)$$

where β_i is the effect of subject i , τ_i is the effect of treatment i , λ_i is the general carryover effect of treatment i and χ_{ij} is the additional specific carryover effect when treatment i is followed by itself ($\chi_{ij} = 0$ if $i \neq j$). The

errors ε_{ij} are assumed i.i.d. with expectation 0 and variance σ^2 . The model with period effects is considered in Section 5. In vector notation, we have:

$$Y = B\beta + T_d\tau + L_d\lambda + S_d\chi + \varepsilon \quad (2)$$

where B , T_d , L_d and S_d are incidence matrices of subjects, direct treatments, carryover and specific self-carryover effects. Note that the parametrization, although equivalent, is slightly different from that of Hedayat and Afsarinejad (2002) or Kunert and Stufken (2002): in our model, the self carryover effect is equal to $\rho_{d(i,j-1)} + \chi_{d(i,j-1)d(i,j)}$. We define the vector ϕ of *total effects* by $\phi = \tau + \lambda + \chi$. It corresponds to the effect of a treatment when it is preceded by itself. Note that if $\theta' = (\tau', \lambda', \chi')$ and $K' = (I_t | I_t | I_t)$, then

$$\phi = K'\theta.$$

Because the effect of having no treatment differs from the carryover effect of any treatment, we consider only designs with pre-periods, i.e. designs with one period, called pre-period, added at the beginning. On this preperiod, each subject receive a treatment but the response is not used in the analysis. We assume that the designs are circular, i.e. the treatment assigned to a subject in the pre-period is the same as the treatment assigned in the last period. The circularity condition may be written $d(i, 0) = d(i, k)$. We denote

by $\Omega_{t,b,k}$ the set of all circular designs with t treatments, b subjects and k periods.

3 Some technical tools

In this section, we present a general method to derive optimal crossover designs. We generalize and unify the techniques developed by Kushner (1997), Kunert and Martin (2000) and Bailey and Druilhet (2004).

Let denote by $\mathbf{1}_k$, I_k and J_k respectively the vector of ones of length k , the (k, k) identity matrix and the (k, k) matrix of ones. For any matrix A , denote by A^+ the Moore-Penrose inverse of A . The projection matrix onto the column span of matrix A is denoted by $\text{pr}_{(A)} = A(A'A)^+A'$. We denote $\text{pr}_{(A)}^\perp = I - \text{pr}_{(A)}$ and $Q_k = \text{pr}_{(\mathbf{1}_k)}^\perp = I_k - k^{-1}J_k$. For a square matrix A , we denote by $\text{tr}(A)$ the trace of A . For two symmetric matrices M and N , $M \leq N$ means that $N - M$ is a nonnegative definite matrix (Loewner ordering). A matrix M is *completely symmetric* if $M = aI + bJ$ for some scalars a and b .

3.1 Information matrices and its extremal representation

Consider a generic partitioned linear model:

$$Y = A\alpha + B\beta + \varepsilon \quad \text{with} \quad \mathbb{E}(\varepsilon) = 0 \quad \text{and} \quad \text{Var}(\varepsilon) = \sigma^2 I,$$

where α is a vector of length q . It is well known (see e.g. Kunert, 1983) that the information matrix $C[\alpha]$ of the parameter α is

$$C[\alpha] = A' \text{pr}_{(B)}^\perp A. \quad (3)$$

Consider now a subsystem $K'\alpha$ where K is a (q, s) matrix. The information matrix $C[K'\alpha]$ of $K'\alpha$ may be defined by the extremal representation (Gaffke, 1987 or Pukelsheim, 1993):

$$C[K'\alpha] = \min_{L \in \mathbb{R}^{q \times s}; L'K = I_s} L' C[\alpha] L. \quad (4)$$

where the minimum, taken relative to the Loewner ordering, exists and is unique. If L^* is a (q, s) matrix that minimizes $L' C[\alpha] L$ under the constraint $L'K = I_s$, then

$$C[K'\alpha] = L^{*'} C[\alpha] L^*. \quad (5)$$

Formula (5) will be central in the following mainly because it provides a linear relationship between $C[\alpha]$ and $C[K'\alpha]$.

The main issue to construct optimal designs will be to find L^* for designs candidate to optimality. Because a global minimum in (4) exists, L^* minimizes $L' C[\alpha] L$ iff L^* minimizes $\text{tr}(L' C[\alpha] L)$. So, we have

$$\text{tr}(C[K'\alpha]) = \text{tr}(L^{*'}C[\alpha]L^*) = \min_{L \in \mathbb{R}^{q \times s}: L'K = I_s} \text{tr}(L'C[\alpha]L). \quad (6)$$

In our problem, the matrix $C[\alpha]$ will have a natural block structure with completely symmetric blocks. In that case, the following results show that the matrices L^* have also completely symmetric blocks.

Proposition 1 *Let $C[\alpha] = ((C_{ij}))_{i,j=1,\dots,q}$ be a block matrix, where the blocks C_{ij} are (t, t) completely symmetric matrices for $i = 1, \dots, q$ and $j = 1, \dots, q$. Let $K' = (K'_1, \dots, K'_q)$ where for all i , K_i are (t, t) completely symmetric matrices. Then $C[K'\alpha]$ is completely symmetric. Moreover, if $L^{*'} = (L_1^{*'}, \dots, L_q^{*'})$ satisfies both Eq. (5) and the constraint $L^{*'}K = I_t$, then L_i^* , $i = 1, \dots, q$, can be chosen completely symmetric.*

Proof: The proof is given in Appendix A. □

The interest of this result is that $L_i^* = a_i^*I_t + b_i^*J_t$ can be found out by minimizing $q(a_1^*, b_1^*, \dots, a_q^*, b_q^*) = \text{tr}(L^{*'}C[\alpha]L^*)$ which is a polynomial of second degree in $a_1^*, b_1^*, \dots, a_q^*, b_q^*$.

Corollary 2 *Under the notations and assumptions of Proposition 1, if moreover $C_{ij}\mathbb{1}_t = 0$ for $i = 1, \dots, q$ and $j = 1, \dots, q$, then L_i^* can be chosen equal to $a_i^*I_t$ for some scalar a_i^* .*

Proof : By Proposition 1, L_i^* can be chosen equal to $a_i^* I_t + b_i^* J_t$. Since, $\mathcal{C}_{ij} J_t = J_t \mathcal{C}_{ij} = 0$, $L_i' \mathcal{C}_{ij} L_j = a_i^* a_j^* \mathcal{C}_{ij}$ does not depends on b_i^* and b_j^* and the result follows. $\square$

The following lemma, although straightforward, is useful to calculate explicitly L^* .

Lemma 3 *Let C be a nonnegative (u, u) matrix, γ be a k -vector, and $\gamma \mapsto L_\gamma$ be a linear mapping with L_γ a (u, v) matrix. Then, $q(\gamma) = \text{tr}(L_\gamma' C L_\gamma)$ is a multivariate convex quadratic polynomial in $\gamma_1, \dots, \gamma_k$. Moreover, $q(\gamma^*)$ is a minimum of $q(\gamma)$ if and only if $\frac{\partial q}{\partial \gamma}(\gamma^*) = 0$.*

3.2 Some examples

Under the notations and assumptions of Proposition 1 and Corollary 2, i.e. assuming that $\mathcal{C}_{ij}$ are completely symmetric and that $\mathcal{C}_{ij} \mathbb{1}_t = 0$, we show in some cases how the matrices L^* can be obtained. The three first examples give new presentations of known results. The last one will be used in this paper. We denote $c_{ij} = \text{tr}(\mathcal{C}_{ij})$.

Example 1 : let $q = 2$ and $K' = (I_t | 0)$. By Corollary 2 and because $L^{*'} K = I_t$, $L^{*'}$ can be chosen to be equal to $(I_t | x^* I_t)$ for some $x^* \in \mathbb{R}$. By

Eq. (6), x^* can be found out by minimizing

$$q(x) = \text{tr}(L'C[\alpha]L) = c_{11} + 2x c_{12} + x^2 c_{22}.$$

This quadratic function was used by Kushner (1997, Eq. 4.1). The minimum is obtained for $x^* = \frac{c_{12}}{c_{22}}$ and we found $C[K'\alpha] = \mathcal{C}_{11} - \mathcal{C}_{12}\mathcal{C}_{22}^+\mathcal{C}_{21}$, the Schur-complement of $\mathcal{C}_{22}$.

Example 2: let $q = 3$ and $K' = (I_t|0|0)$. As in example 1, $L^{*'}$ can be chosen equal to $(I_t|x^*I_t|y^*I_t)$, where x^* and y^* minimize the quadratic function

$$q(x, y) = \text{tr}(L'C[\alpha]L) = c_{11} + x^2 c_{22} + y^2 c_{33} + 2x c_{12} + 2y c_{13} + 2xy c_{23}.$$

This quadratic function was used by Kunert and Martin (2000, Proposition 3).

Example 3: let $q = 2$ and $K' = (I_t|I_t)$. We have $L^{*'} = (x^* I_t|(1 - x^*) I_t)$, where x^* minimizes

$$q(x) = x^2 c_{11} + (1 - x)^2 c_{22} + 2x(1 - x) c_{12}.$$

If $\mathcal{C}_{11} = \mathcal{C}_{22}$, then $x^* = \frac{1}{2}$ and $L^* = \frac{1}{2}K$. Therefore, $C[K'\alpha] = \frac{1}{4}K'C[\alpha]K$.

This equation was obtained in a different way by Bailey and Druilhet (2004) in order to construct optimal designs for total effects under models without interaction.

Example 4: let $q = 3$ and $K' = (I_t | I_t | I_t)$. We assume that $\mathcal{C}_{11} = \mathcal{C}_{22}$ and that $\mathcal{C}_{13} = \mathcal{C}_{23}$. We no longer assume that $\mathcal{C}_{33}\mathbb{1}_t = 0$. We have $L^{*'} = (x_1^* I_t | x_2^* I_t | (1 - x_1^* - x_2^*)I_t + y^* J_t)$, where x_1^* , x_2^* and y^* minimize

$$\begin{aligned} q(x_1, x_2, y) = & (x_1^2 + x_2^2)c_{11} + 2(x_1 + x_2)c_{11} - (x_1 + x_2)^2(2c_{13} + c_{33}) \\ & + 2(x_1 + x_2)(c_{13} - c_{33} - \tilde{c}_{33}) \\ & + 2y\tilde{c}_{33} + ty^2\tilde{c}_{33} + c_{33} \end{aligned} \quad (7)$$

with $\tilde{c}_{33} = \text{tr}(J_t \mathcal{C}_{33}) = t^{-1} \text{tr}(J_t \mathcal{C}_{33} J_t)$. Note that L^* does not satisfy $L^{*'}K = I_t$. This is in fact a simplified form of

$$\tilde{L}^{*'} = (x_1^* I_t + u^* J_t | x_2^* I_t - (u^* + v^*)J_t | (1 - x_1^* - x_2^*)I_t + y^* J_t),$$

noting that the terms $u^* J_t$ and $(u^* + v^*)J_t$ vanish in the expression of $\tilde{L}^{*'} C[\alpha] \tilde{L}^*$. By lemma 3 and by symmetry of $q(x_1, x_2, y)$ in x_1, x_2 , it is easy to see that x_1^* and x_2^* can be chosen equal. Denote $x^* = x_1^* = x_2^*$. From Eq. (7), x^* and y^* can be found out by minimizing

$$\begin{aligned} q(x, y) = & c_{33} + 4(c_{13} - c_{33})x + 2\tilde{c}_{33}y + 2(c_{11} + c_{12} - 4c_{13} + 2c_{33})x^2 \\ & + t\tilde{c}_{33}y^2 - 4\tilde{c}_{33}xy, \end{aligned} \quad (8)$$

and the minimum $q(x^*, y^*)$ is equal to $\text{tr}(C[K'\alpha])$.

4 Optimal circular crossover designs for total effects

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 in $\Omega_{t,b,k}$ is universally optimal. In this section, we propose a method to construct universal optimal design for total effects.

4.1 Upper bound of $\text{tr } C_d[\phi]$

For a design d , the information matrix for the whole parameter $\theta' = (\tau', \lambda', \chi')$ in Model (1) is:

$$C_d[\theta] = \begin{pmatrix} T_d' \text{pr}_{(B)}^\perp T_d & T_d' \text{pr}_{(B)}^\perp L_d & T_d' \text{pr}_{(B)}^\perp S_d \\ L_d' \text{pr}_{(B)}^\perp T_d & L_d' \text{pr}_{(B)}^\perp L_d & L_d' \text{pr}_{(B)}^\perp S_d \\ S_d' \text{pr}_{(B)}^\perp T_d & S_d' \text{pr}_{(B)}^\perp L_d & S_d' \text{pr}_{(B)}^\perp S_d \end{pmatrix} = \begin{pmatrix} \mathcal{C}_{d11} & \mathcal{C}_{d12} & \mathcal{C}_{d13} \\ \mathcal{C}_{d12}' & \mathcal{C}_{d22} & \mathcal{C}_{d23} \\ \mathcal{C}_{d13}' & \mathcal{C}_{d23}' & \mathcal{C}_{d33} \end{pmatrix}.$$

By circularity of the designs, $B'T_d = B'L_d$, $T_d'T_d = L_d'L_d$ and $T_d'S_d = L_d'S_d = S_d'S_d = S_d'L_d = S_d'T_d$ and therefore $\mathcal{C}_{d22} = \mathcal{C}_{d11}$ and $\mathcal{C}_{d23} = \mathcal{C}_{d13}$. As in Section 3.2, we define $c_{dij} = \text{tr}(\mathcal{C}_{dij})$ and $\tilde{c}_{dij} = \text{tr}(J\mathcal{C}_{dij})$.

A design is said to be *symmetric* if all the blocks C_{dij} are completely symmetric, or equivalently, if $C_d[\theta]$ is invariant by any permutations of the treatment labels.

Proposition 4 *For any design d , the information matrix for total effects ϕ satisfies:*

$$\text{tr } C_d[\phi] \leq \min_{x,y} q_d(x, y)$$

where $q_d(x, y)$ is defined by (8). Equality holds if $C_{dij}[\theta]$ are completely symmetric for $1 \leq i \leq 3$ and $1 \leq j \leq 3$.

Proof: For a design d , we denote $\overline{C}_d[\theta] = \frac{1}{t!} \sum_{\sigma \in \mathcal{S}_t} (I_3 \otimes P_\sigma) C_d[\theta] (I_3 \otimes P'_\sigma)$ the symmetrized information matrix for θ . By construction, $\overline{C}_{dij}$ are completely symmetric for all i and j . Moreover, $c_{dij} = \text{tr}(C_{dij}) = \text{tr}(\overline{C}_{dij})$ and $\tilde{c}_{dij} = \text{tr}(J_t C_{d33}) = \text{tr}(J_t \overline{C}_{d33})$. Denote by $\overline{C}_d[\phi]$ the information matrix of ϕ associated to $\overline{C}_d[\theta]$. By concavity of $C_d[\phi]$ w.r.t. $C_d[\theta]$, (see Pukelsheim, 1993 p. 77), $C_d[\phi] \leq \overline{C}_d[\phi]$ and $\text{tr } C_d[\phi] \leq \min_{x,y} q_d(x, y)$. $\square$

A design is called degenerate if $\tilde{c}_{d33} = \text{tr}(J_t C_{d33}[\theta]) = 0$ or equivalently if each block either contains only one treatment or has no treatment preceded by itself. Note that the information matrix of a degenerate design is null and therefore such a design is not considered. The following lemma shows that the minimization of $q_d(x, y)$ may be reduce to the minimization of a one variable quadratic function.

Lemma 5 *Let d be a non-degenerate design. The values x^* and y^* that*

minimize $q_d(x, y)$ satisfy $2x^* - ty^* - 1 = 0$. Moreover, x^* minimizes $q_d(x)$,

where

$$q_d(x) = c_{d33} - \frac{1}{t}\tilde{c}_{d33} + 4(c_{d13} - c_{d33} + \frac{1}{t}\tilde{c}_{d33})x + 2(c_{d11} + c_{d12} - 4c_{d13} + 2c_{d33} - \frac{2}{t}\tilde{c}_{d33})x^2, \quad (9)$$

and $q_d(x^*, y^*) = q_d(x^*)$.

Proof: by lemma 3, $\frac{\partial q_d}{\partial y}(x^*, y^*) = 0$ at the minimum. For a non-degenerate design, this is equivalent to $2x^* - ty^* - 1 = 0$. Replacing y by $2(x - 1)/t$, we found $q_d(x, y) = q_d(x)$. Therefore, x^* necessarily minimizes $q_d(x)$. $\square$

4.2 Decomposition over the blocks

It is well known that $C_d[\theta]$ is the sum of the information matrices C_{du} corresponding to Block u . Denote by T_{du} , L_{du} and S_{du} the incidence matrices for Block u . Thus, $T'_d = (T'_{d1} \mid \dots \mid T'_{db})$, $L'_d = (L'_{d1} \mid \dots \mid L'_{db})$, $S'_d = (S'_{d1} \mid \dots \mid S'_{db})$ and:

$$C_d[\theta] = \sum_{u=1}^b C_{du}[\theta] = \sum_{u=1}^b \begin{pmatrix} T'_{du} Q_k T_{du} & T'_{du} Q_k L_{du} & T'_{du} Q_k S_{du} \\ L'_{du} Q_k T_{du} & L'_{du} Q_k L_{du} & L'_{du} Q_k S_{du} \\ S'_{du} Q_k T_{du} & S'_{du} Q_k L_{du} & S'_{du} Q_k S_{du} \end{pmatrix}$$

We decompose in the same way $\text{tr}(\mathcal{C}_{dij})$ and $\text{tr}(\mathcal{C}_{dij}J_t)$:

$$c_{dij} = \text{tr}(\mathcal{C}_{dij}) = \sum_{u=1}^b c_{dij}^{(u)} \text{ and } \tilde{c}_{dij} = \text{tr}(\mathcal{C}_{dij}J_t) = \sum_{u=1}^b \tilde{c}_{dij}^{(u)}$$

denoting by $c_{dij}^{(u)}$ and by $\tilde{c}_{dij}^{(u)}$ the contributions of Block u . For example, for

$i = j = 1$ we have:

$$c_{d11} = \text{tr}(\mathcal{C}_{d11}) = \text{tr}\left(\sum_{u=1}^b T'_{du} Q_k T_{du}\right) = \sum_{u=1}^b c_{d11}^{(u)} \text{ with } c_{d11}^{(u)} = \text{tr}(T'_{du} Q_k T_{du}).$$

Simplifications of these forms give:

$$c_{d11}^{(u)} = k - \frac{n_u^s}{k}, c_{d12}^{(u)} = m_u - \frac{n_u^s}{k}, c_{d13}^{(u)} = m_u - \frac{l_u}{k}, c_{d33}^{(u)} = m_u - \frac{m_u^s}{k}, \tilde{c}_{d33}^{(u)} = m_u - \frac{m_u^2}{k},$$

with $n_u^s = \sum_{i=1}^t n_{ui}^2$, $m_u = \sum_{i=1}^t m_{ui}$, $m_u^s = \sum_{i=1}^t m_{ui}^2$, $l_u = \sum_{i=1}^t n_{ui} m_{ui}$,

denoting by n_{ui} the number of plots in Block u which receive Treatment i

and by m_{ui} the number of times Treatment i is preceded by itself in the

Block u . It follows that:

$$q_d(x) = \sum_{u=1}^b h_d^{(u)}(x)$$

where

$$h_d^{(u)}(x) = c_{d33}^{(u)} - \frac{1}{t} \tilde{c}_{d33}^{(u)} + 4(c_{d13}^{(u)} - c_{d33}^{(u)} + \frac{1}{t} \tilde{c}_{d33}^{(u)})x + 2(c_{d11}^{(u)} + c_{d12}^{(u)} - 4c_{d13}^{(u)} + 2c_{d33}^{(u)} - \frac{2}{t} \tilde{c}_{d33}^{(u)})x^2.$$

Two sequences of treatments in two blocks u_1 and u_2 are said to be *equiv-*

alent if $(n_{u_1}^s, m_{u_1}, m_{u_1}^s, l_{u_1}) = (n_{u_2}^s, m_{u_2}, m_{u_2}^s, l_{u_2})$, which is the case if one

sequence is obtained from the other one by relabelling the treatments. So, for given k and t , we can divide the set of all possible treatment sequences into K equivalence classes of treatments. Since n_u^s , m_u , m_u^s , l_u and $c_{dij}^{(u)}$ are the same for all u from one equivalent class ℓ , we change the notation and write n_ℓ^s , m_ℓ , m_ℓ^s , l_ℓ and $c_{dij}(\ell)$ instead. We define:

$$h_\ell(x) = \left(m_\ell - \frac{m_\ell^s}{k} - \frac{\delta_\ell}{t}\right) + \frac{4}{k} \left(m_\ell^s - l_\ell + \frac{k\delta_\ell}{t}\right) x + 2 \left[(k - m_\ell) + \frac{2}{k} (2l_\ell - n_\ell^s - m_\ell^s) - \frac{2\delta_\ell}{t}\right] x^2$$

where $\delta_\ell = m_\ell(1 - m_\ell/k)$. For a design d , we denote by $\pi_{d\ell}$ the proportion of blocks assigned to the class ℓ ($1 \leq \ell \leq K$). So, we have:

$$q_d(x) = b \sum_{\ell=1}^K \pi_{d\ell} h_\ell(x). \quad (10)$$

4.3 Optimality conditions

Our goal, in order to find an optimal configuration d^* , is to obtain a value x^* and proportions $\pi'_{d^*} = (\pi_{d^*1}, \dots, \pi_{d^*K})$ such that:

$$q_{d^*}(x^*) = \max_{\pi_d} q_d^* \text{ with } q_d^* = \min_x q_d(x).$$

The following propositions characterizes universally optimal designs.

Proposition 6 (Kunert and Martin, 2000) *Consider a symmetric design $d^* \in \Omega_{t,b,k}$ and a point x^* such that the first derivative of q_{d^*} is zero.*

If we have also:

$$\forall \ell = 1, \dots, K, \quad bh_\ell(x^*) \leq q_{d^*}^*,$$

then d^* is universally optimal over $\Omega_{t,b,k}$.

The following proposition reduce to $k-1$ the number of equivalent classes that possibly appear in an optimal design. We denote by $\lfloor x \rfloor$ the integer part of x .

Proposition 7 *If a symmetric design $d^* \in \Omega_{t,b,k}$ is universally optimal, then the treatment sequences present in the design necessarily satisfies:*

1. *all the periods receiving the same treatment are side by side in the sequence.*
2. *each treatment present in the sequence occurs $\lfloor k/v \rfloor$ or $\lfloor k/v \rfloor + 1$ times, where v is the number of different treatments present in the sequence.*
The number of treatments that occur $\lfloor k/v \rfloor + 1$ times is $k - v\lfloor k/v \rfloor$ and the number of treatments that occurs $\lfloor k/v \rfloor$ times is $v(\lfloor k/v \rfloor + 1) - k$.

Proof : The proof is given in Appendix B. □

It is worth noting that for each value of v , there is only one equivalent class of treatment sequences that may appear in the optimal design.

4.4 Construction of optimal designs

Consider a sequence ℓ present in an optimal design. From Proposition 7, a treatment i in ℓ satisfies $m_{\ell i} = n_{\ell i} - 1$. Moreover we have $v_\ell = k - m_\ell$. So

$n_\ell^s = m_\ell^s + m_\ell + k$, $l_\ell = m_\ell^s + m_\ell$ and then:

$$h_\ell(x) = \left(m_\ell - \frac{m_\ell^s}{k} - \frac{\delta_\ell}{t}\right) + \frac{4}{k} \left(\frac{k\delta_\ell}{t} - m_\ell\right)x + 2 \left[(k - m_\ell) \left(\frac{k-2}{k}\right) - \frac{2\delta_\ell}{t}\right]x^2,$$

with $\delta_\ell = m_\ell(1 - m_\ell/k)$.

Therefore an optimal design for this one-dimensional problem is obtained using one class or a mixture of two different classes (see Kushner (1997)).

The following method (for given k and t) can be used in order to prove that a design d^* is optimal.

- If the optimal design d^* is constituted by one sequence of treatment

ℓ_1 (i.e. $q_{d^*}(x) = bh_{\ell_1}(x)$):

- find x^* that minimize h_{ℓ_1} and then the minimum $q_{d^*}^*$ of q_{d^*} ,

- check that: $\forall \ell = 1, \dots, K$, $bh_\ell(x^*) \leq q_{d^*}^*$ (cf. Prop. 6).

- If the design d^* is constituted by two different classes of treatments ℓ_1

and ℓ_2 (i.e. $q_{d^*}(x) = b(\pi_{d^*\ell_1}h_{\ell_1}(x) + \pi_{d^*\ell_2}h_{\ell_2}(x))$):

- find an admissible intersection point x^* according to the definition

of Kushner (1997), i.e. $h_{\ell_1}(x^*) = h_{\ell_2}(x^*)$ and $\frac{\partial h_{\ell_1}}{\partial x}(x^*) \frac{\partial h_{\ell_2}}{\partial x}(x^*) \leq 0$,

- find the proportions $\pi_{d^*\ell_1}^*$ and $\pi_{d^*\ell_2}^*$ in order to obtain: $\frac{\partial q_{d^*}}{\partial x}(x^*) = 0$,
- use these proportions for finding the minimum $q_{d^*}^* = q_{d^*}(x^*)$ of q_{d^*} ,
- check that: $\forall \ell = 1, \dots, K$, $bh_\ell(x^*) \leq q_{d^*}^*$ (cf. Prop. 6).

Note that the optimal proportions can be found by the following method.

$$\frac{\partial q_{d^*}}{\partial x}(x^*) = 0 \iff b \left(\pi_{d^*\ell_1}^* \frac{\partial h_{\ell_1}}{\partial x}(x^*) + \pi_{d^*\ell_2}^* \frac{\partial h_{\ell_2}}{\partial x}(x^*) \right) = 0.$$

Denote $a_i = (\partial h_{\ell_i} / \partial x)(x^*)$, $i = 1, 2$. The optimal proportions are then:

$$\pi_{d^*\ell_1}^* = \frac{a_2}{a_2 - a_1} \text{ and } \pi_{d^*\ell_2}^* = \frac{a_1}{a_1 - a_2}.$$

Now, we give optimal designs for several values of k . For $k = 3, 4$ we give explicit formulae. For $k = 5, \dots, 10$, we present numerical results.

1) *The case $k = 3$.* From proposition 7, an optimal design is constituted by one or two blocks in the following set of sequences:

<i>Sequence</i>	n_ℓ^s	m_ℓ	m_ℓ^s	l_ℓ
[1 2 3]	3	0	0	0
[1 1 2]	5	1	1	2

So the functions h_ℓ are given by (we identify each class with its value of m_ℓ):

$$h_0(x) = 2x^2 \text{ and } h_1(x) = \frac{2}{3} \left(1 - \frac{1}{t} \right) - \frac{4}{3} \left(1 - \frac{2}{t} \right) x + \frac{4}{3} \left(1 - \frac{2}{t} \right) x^2.$$

It is impossible in that case to satisfy Proposition 6 using only one of these two sequences. So, we must find an admissible intersection point x^* . Some algebra shows that:

$$x^* = \frac{\sqrt{(t-2)^2 + (t-1)(t+4)} - (t-2)}{t+4}.$$

The proportions in the optimal design d^* are then:

$$\pi_{d^*0}^* = 1 - \pi_{d^*1}^* \text{ and } \pi_{d^*1}^* = \frac{3t}{t+4} \left(1 - \frac{(t-2)}{\sqrt{t(2t-1)}} \right).$$

The following table gives the optimal proportions for several values of t .

t	3	4	5	10	20	∞
<i>Prop.</i> [1 2 3]	0.046	0.067	0.079	0.100	0.111	0.121
<i>Prop.</i> [1 1 2]	0.954	0.933	0.921	0.899	0.889	0.879

The sequence [1 1 2] is predominating in this mixture. So it can be interesting in practice to use designs generated by only this sequence. The quality of such designs can be quantified by the classical Φ_p criteria. We know (see e.g. Druilhet, 2004) that when the information matrix is completely symmetric Φ_p does not depend on p . Thus we can derive the efficiency factor of a design $d \in \Omega_{t,b,3}$ generated by one sequence ℓ :

$$\text{Eff}(d) = \frac{b h_\ell^*}{q_{d^*}(x^*)} \text{ with } h_\ell^* = \min_x h_\ell(x).$$

Numerical applications are given in the following table:

t	3	4	5	10	20	∞
<i>Eff.</i> [1 1 2]	0.989	0.985	0.982	0.976	0.974	0.971

2) *The case $k = 4$.* An optimal configuration is constituted by one or two

blocks belonging to the following set of sequences:

<i>Sequence</i>	n_ℓ^s	m_ℓ	m_ℓ^s	l_ℓ
[1 2 3 4]	4	0	0	0
[1 1 2 3]	6	1	1	2
[1 1 2 2]	8	2	2	4

The functions h_ℓ are then given by:

$$h_0(x) = 4x^2, \quad h_1(x) = \frac{3}{4} \left(1 - \frac{1}{t}\right) - \left(1 - \frac{3}{t}\right)x + 3 \left(1 - \frac{1}{t}\right)x^2,$$

$$h_2(x) = \left(\frac{3}{2} - \frac{1}{t}\right) - 2 \left(1 - \frac{2}{t}\right)x + 2 \left(1 - \frac{2}{t}\right)x^2.$$

For any t , the minimum of h_2 is obtained for $x^* = 0.5$ and satisfies the conditions of proposition 6. So the optimal design is generated by the sequence [1 1 2 2]. As an example we can consider, for $t = 4$, the optimal design such that:

$$D = \begin{bmatrix} 1 & 2 & 1 & 3 & 1 & 4 & 2 & 3 & 2 & 4 & 3 & 4 \\ 1 & 2 & 1 & 3 & 1 & 4 & 2 & 3 & 2 & 4 & 3 & 4 \\ 2 & 1 & 3 & 1 & 4 & 1 & 3 & 2 & 4 & 2 & 4 & 3 \\ 2 & 1 & 3 & 1 & 4 & 1 & 3 & 2 & 4 & 2 & 4 & 3 \end{bmatrix} \in \Omega_{4,12,4}.$$

Note that, by circularity, the design obtained by taking away one out of every two columns is universally optimal over all the designs in $\Omega_{4,6,4}$.

3) *The case $k = 5$.* The optimal design is generated by the following mixtures:

t	3	4	5	10	20	∞
<i>Prop.</i> [1 1 2 2 3]	0.167	0.250	0.300	0.400	0.450	0.500
<i>Prop.</i> [1 1 1 2 2]	0.833	0.750	0.700	0.600	0.550	0.500

The efficiencies of designs generated by only one sequence are:

t	3	4	5	10	20	∞
<i>Eff.</i> [1 1 2 2 3]	0.844	0.895	0.918	0.949	0.961	0.970
<i>Eff.</i> [1 1 1 2 2]	0.984	0.977	0.972	0.963	0.959	0.955

It can be observed that the design generated by [1 1 1 2 2] is more efficient than the one generated by [1 1 1 2 2] for $t > 18$.

4) *The case $k = 6$.* The optimal design is generated by the following mixtures:

t	3	4	5	6	7	≥ 8
<i>Prop.</i> [1 1 2 2 3 3]	0.400	0.628	0.775	0.878	0.954	1.000
<i>Prop.</i> [1 1 1 2 2 2]	0.600	0.372	0.225	0.122	0.046	

The efficiencies of designs generated by only one sequence are:

t	3	4	5	6	7	≥ 8
<i>Eff.</i> [1 1 2 2 3 3]	0.962	0.989	0.997	0.999	0.999	1.000
<i>Eff.</i> [1 1 1 2 2 2]	0.962	0.942	0.930	0.922	0.917	

We note that the sequence [1 1 2 2 3 3] is always more efficient than the sequence [1 1 1 2 2 2]. It also generates an optimal design when $t \geq 8$.

5) *The case $k = 7$.* The optimal design is generated by the following mixtures:

t	3	≥ 4
<i>Prop.</i> [1 1 1 2 2 3 3]	0.682	1.000
<i>Prop.</i> [1 1 1 1 2 2 2]	0.318	

The efficiencies of designs generated by only one sequence are:

t	3	≥ 4
<i>Eff.</i> [1 1 1 2 2 3 3]	0.994	1.000
<i>Eff.</i> [1 1 1 1 2 2 3 3]	0.938	

We note that the sequence [1 1 1 2 2 3 3] is always better than the sequence [1 1 1 1 2 2 2] and generates the optimal design when $t \geq 4$.

6) *The case $k = 8, 9, 10$.* We find that the optimal design is generated, for

every t , by only one sequence. These optimal sequences are given by:

t	8	9	10
<i>Sequence</i>	[1 1 1 2 2 2 3 3]	[1 1 1 2 2 2 3 3 3]	[1 1 1 1 2 2 2 3 3 3]

5 Models with period effects

We consider the model:

$$y_{ij} = \alpha_j + \beta_i + \tau_{d(i,j)} + \lambda_{d(i,j-1)} + \chi_{d(i,j-1)d(i,j)} + \varepsilon_{ij}, \quad (11)$$

where α_j is the effects of the period j . We denote by A the corresponding incidence matrix. A *balanced design* is a design such that all the sequences belonging to the same equivalent class appear equally often. This notion is slightly more restrictive than the notion of symmetric design defined in Section 4.1 but correspond to the design generated by one sequence or a mixture of sequences, considering all the treatment permutations.

Proposition 8 *A balanced design which is universally optimal for total effects under Model (1) is also universally optimal under Model (11).*

Proof: The proof is a direct consequence of the following lemma. □

Lemma 9 *For a balanced design, the information matrix for the total effects is the same under model (1) and (11)*

Proof: Let d be a balanced design. The difficulty is that interaction and period effects are not orthogonal. Write $\tilde{\theta}' = (\tau|\lambda|\chi|\alpha)$ and $\tilde{C}_d[\tilde{\theta}]$ the corresponding information matrix. We want to prove that $\tilde{C}_d[\tilde{K}'\tilde{\theta}] = C_d[K'\theta]$ where $\tilde{K}' = (I_t|I_t|I_t|0)$. We write:

$$\tilde{C}_d[\tilde{\theta}] = \begin{pmatrix} C_d[\theta] & C_{d12} \\ C_{d21} & C_{d22} \end{pmatrix}$$

where $C'_{d12} = (0|0|D'_d)$ with $D_d = (p_{d1}\mathbb{1}_t|p_{d2}\mathbb{1}_t|\dots|p_{db}\mathbb{1}_t)$. The real p_{dj} depends only on the number of times a treatment is preceded by itself on period j . Note that the usual orthogonality condition (see Kunert, 1983) between interaction and period effects is $D_d = 0$ which is not the case here. The key point of the proof is that

$$Q_t D_d = 0. \quad (12)$$

Denote by $\tilde{L}_d^*$ a matrix such that $\tilde{C}_d[\tilde{K}'\tilde{\theta}] = \tilde{L}_d^{*'}\tilde{C}_d[\tilde{\theta}]\tilde{L}_d^*$ and $\tilde{L}_d^{*'}\tilde{K} = I_t$. We write $\tilde{L}_d^{*'} = (M_d^{*'}|N_d^{*'})$ where M_d is a $(3t \times t)$ matrix and N_d^* is a $(b \times b)$ matrix. It is easy to see that $C_d[K'\theta]\mathbb{1}_t = 0$ and, since $\tilde{C}_d[\tilde{K}'\tilde{\theta}] \leq C_d[K'\theta]$, we have $\tilde{C}_d[\tilde{K}'\tilde{\theta}]\mathbb{1}_t = 0$. So, $C_d[\tilde{K}'\tilde{\theta}] = Q_t\tilde{C}_d[\tilde{K}'\tilde{\theta}]Q_t$. Therefore, $\tilde{L}_d^*$ can be chosen equal to $(M_d^*Q_t|N_d^*Q_t)$. For any permutation σ , we have $(I_3 \otimes P_\sigma)C_{d12} = C_{d12}$ and therefore, similarly to Proposition 1, it can be shown that the three $(t \times t)$ blocks of M_d^* can be chosen completely symmetric. So, $\tilde{L}_d^{*'}$ can be chosen equal to $(x_1^*Q_t|x_2^*Q_t|(1 - (x_1^* + x_2^*))Q_t|N^*)$. Put

$\tilde{L}' = (M'|N')$ with $M' = (x_1Q_t|x_2Q_t|(1 - (x_1 + x_2)Q_t))$. By (12), we have $M'C_{d12} = 0$ and then

$$\tilde{C}_d[\tilde{K}'\tilde{\theta}] = \min_{x_1, x_2, N} \tilde{L}'\tilde{C}[\tilde{\theta}]\tilde{L} = \min_{x_1, x_2, N} (M'C_d[\theta]M + N'C_{d12}N).$$

Since x_1, x_2 and N vary freely, N can be chosen equal to 0 and therefore, from Example 4 of Section 3.2 and the constraint on y obtained in Lemma 5, $M^*{}' \tilde{C}[\tilde{\theta}] M^* = L^*{}' C_d[\theta] L^*$. The result follows. $\square$

Appendix A

We give here the proof of Proposition 1.

Step 1: We show that the set E of matrices L that minimize $L'C[\alpha]L$ under the constraint $L'K = I_t$ is an affine subspace: consider L_a and L_b in E with $L_a \neq L_b$. It is sufficient to prove that $L_\gamma = \gamma L_a + (1 - \gamma)L_b$ belongs to E for any real γ . We have $L_\gamma'K = I_t$ and

$$L_\gamma' C[\alpha] L_\gamma = \gamma^2 L_a' C[\alpha] L_a + (1 - \gamma)^2 L_b' C[\alpha] L_b + \gamma(1 - \gamma)(L_a' C[\alpha] L_b + L_b' C[\alpha] L_a)$$

This quadratic function w.r.t. γ admits two minima relative to the Loewner ordering at $\gamma = 0$ and $\gamma = 1$ and therefore it is constant. So, L_γ minimizes $L'C[\alpha]L$ for any $\gamma \in \mathbb{R}$.

Step 2: Consider a permutation σ on $\{1, \dots, t\}$ and denote by P_σ the corresponding permutation matrix. We want to prove that if $L^* \in E$, so does $L_\sigma^* = (I_3 \otimes P'_\sigma) L^* P_\sigma$. Since C_{ij} and K_i are completely symmetric:

$$(I_3 \otimes P_\sigma)C[\alpha](I_3 \otimes P'_\sigma) = C[\alpha], \quad (13)$$

$$\text{and} \quad (I_3 \otimes P'_\sigma)K = KP_\sigma. \quad (14)$$

Moreover,

$$\begin{aligned} C[K'\alpha] &= \min_{L \in \mathbb{R}^{3t \times t}; L'K = I_t} L' C[\alpha] L, \\ &= \min_{L \in \mathbb{R}^{3t \times t}; L'K = I_t} L'(I_t \otimes P_\sigma)C[\alpha](I_t \otimes P'_\sigma)L \quad (\text{by (13)}), \\ &= P_\sigma \left(\min_{L \in \mathbb{R}^{3t \times t}; L'K = I_t} P'_\sigma L'(I_t \otimes P_\sigma)C[\alpha](I_t \otimes P'_\sigma)LP_\sigma \right) P'_\sigma. \end{aligned}$$

Put $L_\sigma = (I_3 \otimes P'_\sigma)LP_\sigma$. By (14), $L'_\sigma K = I_t$. Since, $L \leftrightarrow L_\sigma$ is a one to one mapping, we have:

$$C[K'\alpha] = P_\sigma \left(\min_{L \in \mathbb{R}^{3t \times t}; L'_\sigma K = I_t} L'_\sigma C[\alpha] L_\sigma \right) P'_\sigma = P_\sigma C[K'\alpha] P'_\sigma. \quad (15)$$

Since Eq. (15) holds for any permutation σ , $C[K'\alpha]$ is completely symmetric.

So,

$$C[K'\alpha] = \min_{L_\sigma \in \mathbb{R}^{3t \times t}; L'_\sigma K = I_t} L'_\sigma C[\alpha] L_\sigma$$

and therefore $C[K'\alpha] = L_\sigma^{*'} C[\alpha] L_\sigma^*$.

Step 3: If $L^* \in E$ then, by step 1 and 2, $\bar{L}^* = \frac{1}{t!} \sum_\sigma L_\sigma^*$ also belongs to E .

By construction, $\bar{L}_i^*$ is completely symmetric and the proof is complete.

Appendix B

We prove here Proposition 7. From Eq. (10), we have $h_\ell(x) = A_\ell + B_\ell x + C_\ell x^2$ where: $A_\ell = m_\ell - \frac{m_\ell^s}{k} - \frac{\delta_\ell}{t}$, $B_\ell = \frac{4}{k} \left(m_\ell^s - l_\ell + \frac{k\delta_\ell}{t} \right)$ and $C_\ell = 2 \left[(k - m_\ell) + \frac{2}{k} (2l_\ell - n_\ell^s - m_\ell^s) - \frac{2\delta_\ell}{t} \right]$. We denote by v_ℓ the number of treatments present in the sequence ℓ . For any treatment i in ℓ , we have:

$$n_{\ell i} \geq m_{\ell i} + 1 \quad (16)$$

with equality if and only if treatment i occurs in consecutive periods. In general, each treatment appears in the sequence ℓ in several groups of consecutive periods. The number of such groups is $\gamma_i = n_{\ell i} - m_{\ell i}$. From ℓ , we construct a new sequence $\tilde{\ell}$ as follows: in each group of consecutive periods receiving the same treatment, we replace the treatment that occurs in this group by a new treatment, such that in the new sequence $\tilde{\ell}$, each treatment have only one group. For example $\ell = (1, 1, 2, 2, 2, 1, 3, 2, 2)$ gives $\tilde{\ell} = (1, 1, 2, 2, 2, 4, 3, 5, 5)$. We have $m_{\tilde{\ell}} = m_\ell$ and $v_{\tilde{\ell}} = \gamma = k - m_\ell$, where $\gamma = \sum_i \gamma_i$ is the number of different groups in ℓ .

Lemma 10 *If d^* is optimal, then x^* that minimizes $q_{d^*}(x)$ is positive.*

Proof. From Lemma 3 we know that $h_\ell(x)$ is convex, then $C_\ell \geq 0$. So it is sufficient to show that $B_\ell \leq 0$. If $C_\ell = 0$ then $B_\ell = 0$ because we know

that $h_\ell(x)$ admits a minimum. In that case, any x is a minimum and can be chosen positive. We assume now that $C_\ell > 0$. By Eq. 16, we have $l_\ell = \sum_i m_{\ell i} n_{\ell i} \geq m_\ell + m_\ell^s$ and then

$$B_\ell \leq \frac{4}{kt} m_\ell (k - m_\ell - t)$$

with equality if and only if the occurrences of the treatments present in the sequence are placed side by side. In that case a sequence $\tilde{\ell}$ satisfies $k - m_{\tilde{\ell}} = v_{\tilde{\ell}}$ and, since $t \geq v_{\tilde{\ell}}$, $B_{\tilde{\ell}} \leq 0$. Consider now a general sequence ℓ and denote by $\tilde{\ell}$ its associated sequence with side-by-side treatments. Since $m_{\tilde{\ell}} = m_\ell$ we have also $\delta_\ell = \delta_{\tilde{\ell}}$ and then $B_\ell \leq B_{\tilde{\ell}}$ if and only if $(l_\ell - m_\ell^s) \geq (l_{\tilde{\ell}} - m_{\tilde{\ell}}^s)$. But:

$$l_\ell - m_\ell^s = \sum_{i=1}^{v_\ell} m_{\ell i} (n_{\ell i} - m_{\ell i}) \geq \sum_{i=1}^{v_\ell} m_{\ell i} = m_\ell = \sum_{i=1}^{v_{\tilde{\ell}}} m_{\tilde{\ell} i} (n_{\tilde{\ell} i} - m_{\tilde{\ell} i})$$

with equality if and only if $\ell = \tilde{\ell}$. So we have for every sequence ℓ : $B_\ell \leq B_{\tilde{\ell}} \leq 0$ $\square$

The proof of the Proposition 7 is given below.

Step 1: Let ℓ be a sequence containing v_ℓ different treatments numbered $1, \dots, v_\ell$ and $\tilde{\ell}$ the associated sequence defined above. We want to prove that $h_{\tilde{\ell}}(x) > h_\ell(x)$ for all $x \geq 0$ and $\ell \neq \tilde{\ell}$. The idea is to show that $A_\ell < A_{\tilde{\ell}}$, $B_\ell < B_{\tilde{\ell}}$ and $C_\ell < C_{\tilde{\ell}}$. Note that $m_\ell = m_{\tilde{\ell}}$ so $\delta_\ell = \delta_{\tilde{\ell}}$. Then:

- We show that $C_\ell < C_{\tilde{\ell}}$. It is equivalent to show that $(n_\ell^s - 2l_\ell + m_\ell^s) > (n_{\tilde{\ell}}^s - 2l_{\tilde{\ell}} + m_{\tilde{\ell}}^s)$. Since $n_{\tilde{\ell}i} = m_{\tilde{\ell}i} + 1$ we have:

$$n_\ell^s - 2l_\ell + m_\ell^s = \sum_{i=1}^{v_\ell} (n_{\ell i} - m_{\ell i})^2 = \sum_{i=1}^{v_\ell} \gamma_i^2 \geq \sum_{i=1}^{v_\ell} \gamma_i = k - m_\ell = \sum_{i=1}^{v_{\tilde{\ell}}} (n_{\tilde{\ell}i} - m_{\tilde{\ell}i})^2$$

with equality if and only if $\ell = \tilde{\ell}$. The result follows.

- From Lemma 10, we have $B_\ell < B_{\tilde{\ell}}$.
- We show that $A_\ell < A_{\tilde{\ell}}$. It is equivalent to show that $m_\ell^s > m_{\tilde{\ell}}^s$. This follows from the fact that $\sum_i m_{\ell i} = \sum_i m_{\tilde{\ell}i}$ and, for all i , $m_{\ell i} \geq m_{\tilde{\ell}i}$ with equality if and only if $\ell = \tilde{\ell}$.

Step 2: Consider the set $\mathcal{L}$ of sequences ℓ having the same number $v_\ell = v$ of distinct treatments and such that $\ell = \tilde{\ell}$. For a sequence $\ell \in \mathcal{L}$, $n_{\ell i} = m_{\ell i} - 1$ and $m_\ell = k - v$. So we have for every $\ell_1, \ell_2 \in \mathcal{L}$ (see Section 5.2):

$$h_{\ell_1}(x) - h_{\ell_2}(x) = \frac{1}{k} (m_{\ell_2}^s - m_{\ell_1}^s).$$

If there exists a sequence $\ell^* \in \mathcal{L}$ such that $h_{\ell^*}(x) - h_\ell(x) > 0$ (for every $\ell \neq \ell^*$) then only this sequence can belong to the optimal design. Such a sequence minimizes $m_\ell^s = \sum_{i=1}^{v_\ell} m_{\ell i}^2$ under the constraint $\sum_{i=1}^{v_\ell} m_{\ell i} = m_\ell$. So, it is well known that the m_{ℓ^*i} or equivalently the n_{ℓ^*i} ($i = 1, \dots, v_{\ell^*}$) must be as equal as possible: if k/v_{ℓ^*} is an integer, a treatment present

in ℓ^* occurs k/v_{ℓ^*} times; otherwise, a treatment present in ℓ^* occurs either $\lfloor k/v_{\ell^*} \rfloor$ or $\lfloor k/v_{\ell^*} \rfloor + 1$ times in ℓ^* $\square$

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