Optimal crossover designs in a model with self and mixed carryover effects

by J. Kunert and J. Stufken

Universität Dortmund and Iowa State University

Abstract

We consider a variant of the usual model for crossover designs with carryover effects. Instead of assuming that the carryover effect of a treatment is the same regardless of the treatment in the next period, the model assumes that the carryover effect of a treatment on itself is different from the carryover effect on other treatments. For the traditional model optimal designs tend to have pairs of consecutive identical treatments; for the model considered here they tend to avoid such pairs. Practitioners have long expressed reservations about designs that exhibit such pairs, resulting in reservations about the traditional model. Our results provide support for these reservations if the carryover effect of a treatment depends also on the treatment in the next period.

Keywords: Balance for carryover effects; Balanced Block Design; Generalized Latin Square; Optimal Design; Universal Optimality

1 Introduction

The traditional model for crossover designs, see e.g. Hedayat and Afsarinejad (1978), assumes that each treatment has a carryover effect which does not interact with the direct effect of the treatment in the following period. This has often been criticized as a weakness of the model, see for instance Kunert (1987). To cope with this problem Sen and Mukerjee (1987) introduced a model with interactions between direct and carryover effects, such that each treatment has a different carryover effect for every treatment in the next period. However, this model contains too many parameters to be practically useful. A compromise was proposed by Hedayat and Afsarinejad (2000) who assume that each treatment A has two different carryover effects, one that is valid if treatment A is followed by A itself, and one that is valid if it is followed by any other treatment. Following their terminology, we will call these effects self and mixed carryover effects, respectively. In the case where the number of treatments equals the number of periods, we show that neighbor balanced generalized Latin squares are universally optimal in this model, even for large numbers of subjects. Note that in the traditional model, this is only true for small numbers of subjects (Kunert, 1984). If the number of periods is smaller than the number of treatments, then generalized Youden designs with neighbor balance are universally optimal over all designs. This again does not hold in the traditional model, see Stufken (1991) and Kushner (1998). Even if the number of periods gets larger than the number of treatments, the optimal designs in the model with mixed and self carryover effects do not have pairs of consecutive identical treatments. The strongly balanced generalized Latin squares introduced by Cheng and Wu (1980) are no longer optimal. This is different from the model with full interaction, see Sen and Mukerjee (1987).

The optimality proofs of this paper are done with the help of Kunert and Martin's (2000) generalization of the method introduced by Kushner (1997).

2 The model and a tool for finding optimal designs

One important application of crossover designs is in sensory trials, when assessors examine several products, one after the other. If, for instance, there is one product which is very bitter, then experience shows that assessors tend to rate the next product that they assess after the extremely bitter one with a lower than normal value of bitterness. Therefore the bitter product has a carryover effect. If, however, an assessor gets this bitter product twice in a row, then he/she usually gives about the same rating again. Thus, the carryover effect of the product is different when there is another product in the next period. A similar effect can be observed in other examples of crossover designs. A mathematical derivation which shows why the carryover effect should be different if a treatment is followed by itself can be found in section 10.3.2 of Senn (1993).

Therefore, we consider the following model. We assume that the response $y_{u,r}$ of subject u at period r, $1 \leq u \leq n$, $1 \leq r \leq p$ can be written as

$$y_{u,r} = \alpha_u + \beta_r + \tau_{d(u,r)} + \rho_{d(u,r-1)}(1 - \delta_{d(u,r),d(u,r-1)}) + \chi_{d(u,r-1)}\delta_{d(u,r),d(u,r-1)} + e_{u,r}, \qquad (1)$$

where

$d(u, r)$ is the treatment assigned to subject u in period r (with $d(u, 0) = 0$),

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,

ρ_j is the mixed carryover effect of treatment j (with $\rho_0 = 0$),

χ_j is the self carryover effect of treatment j (with $\chi_0 = 0$),

$\delta_{i,j}$ is 1 if $i = j$, and 0 if $i \neq j$

and

$e_{u,r}$, $1 \leq u \leq n$, $1 \leq r \leq p$ are independent identically distributed errors with expectation 0 and unknown variance σ^2.

The set of all designs for t treatments, n subjects and p periods is called $\Omega_{t,n,p}$. In what follows, we restrict attention to the case $p > 2$ and $t > 2$. The case $p = 2$ is studied by Hedayat and Afsarinejad (2000). The case $t = 2$ will be reported elsewhere.

We define the matrices $\mathbf{U} = \mathbf{I}_n \otimes \mathbf{1}_p$, $\mathbf{P} = \mathbf{1}_n \otimes \mathbf{I}_p$, $\mathbf{T}_d$, $\mathbf{M}_d$ and $\mathbf{S}_d$ as the design-matrices of the subject, period, direct treatment, self carryover and mixed carryover effects, respectively. Then the information matrix for the estimation of direct treatment effects can be written as

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

where for a matrix $\mathbf{F}$ the expression $\omega^{\perp}(\mathbf{F}) = \mathbf{I} - \mathbf{F}(\mathbf{F}^T\mathbf{F})^{-}\mathbf{F}^T$ is the projection on the space of all vectors which are orthogonal to $\mathbf{F}^T$, the transpose of $\mathbf{F}$.

We are interested in optimal designs for the estimation of the direct treatment effects. It follows from Kiefer's (1975) Proposition 1 that a design d^* for which the information matrix $\mathcal{C}_{d^*}$ is completely symmetric and which maximizes the trace of $\mathcal{C}_d$ over all $d \in \Omega_{t,n,p}$ is optimal under all practically useful optimality criteria - it is *universally optimal.* Complete symmetry of a matrix F means that it can be written as $\mathbf{F} = a\mathbf{I} + b\mathbf{1}\mathbf{1}^T$, where a and b are real numbers.

As in Kunert (1983) we have

$$\mathcal{C}_d \leq \mathbf{T}_d^T \omega^{\perp}([\mathbf{U}, \mathbf{M}_d, \mathbf{S}_d])\mathbf{T}_d$$

in the Loewner-sense, with equality if and only if

$$\mathbf{T}_d^T \omega^\perp([\mathbf{U}, \mathbf{M}_d, \mathbf{S}_d])\mathbf{P} = 0 \tag{2}$$

It can be shown easily that equation (2) holds if in each period (a) all treatments appear equally often, (b) the mixed carryover effects of all treatments appear equally often and (c) the self carryover effects of all treatments appear equally often.

As in Kunert and Martin (2000) we can write

$$\mathbf{T}_d^T \omega^\perp([\mathbf{U}, \mathbf{M}_d, \mathbf{S}_d])\mathbf{T}_d = \mathcal{C}_{d11} - \mathcal{C}_{d12}\mathcal{C}_{d22}^{-}\mathcal{C}_{d12}^T -$$
$$(\mathcal{C}_{d13} - \mathcal{C}_{d12}\mathcal{C}_{d22}^{-}\mathcal{C}_{d23})(\mathcal{C}_{d33} - \mathcal{C}_{d23}^T\mathcal{C}_{d22}^{-}\mathcal{C}_{d23})^{-}(\mathcal{C}_{d13} - \mathcal{C}_{d12}\mathcal{C}_{d22}^{-}\mathcal{C}_{d23})^T,$$

where

$$\mathcal{C}_{d11} = \mathbf{T}_d^T\mathbf{T}_d - \tfrac{1}{p}\mathbf{T}_d^T\mathbf{U}\mathbf{U}^T\mathbf{T}_d, \quad \mathcal{C}_{d12} = \mathbf{T}_d^T\mathbf{M}_d - \frac{1}{p}\mathbf{T}_d^T\mathbf{U}\mathbf{U}^T\mathbf{M}_d,$$
$$\mathcal{C}_{d13} = \mathbf{T}_d^T\mathbf{S}_d - \tfrac{1}{p}\mathbf{T}_d^T\mathbf{U}\mathbf{U}^T\mathbf{S}_d, \quad \mathcal{C}_{d22} = \mathbf{M}_d^T\mathbf{M}_d - \frac{1}{p}\mathbf{M}_d^T\mathbf{U}\mathbf{U}^T\mathbf{M}_d,$$
$$\mathcal{C}_{d23} = \mathbf{M}_d^T\mathbf{S}_d - \tfrac{1}{p}\mathbf{M}_d^T\mathbf{U}\mathbf{U}^T\mathbf{S}_d, \quad \text{and } \mathcal{C}_{d33} = \mathbf{S}_d^T\mathbf{S}_d - \frac{1}{p}\mathbf{S}_d^T\mathbf{U}\mathbf{U}^T\mathbf{S}_d.$$

For the standard model, where the self and mixed carryover effects are assumed identical, the following properties of designs have proved to be useful for optimality.

Definition 1

A design $d \in \Omega_{t,n,p}$ is called

(i) a *balanced block design for the direct treatment effects (with subjects as blocks)*, if every treatment appears equally often in the design, if every treatment appears for each subject either $[p/t]$ or $[p/t]+1$ times, and if the number of subjects where treatments i and j both appear $[p/t]+1$ times is the same for every $i \neq j$. Here $[p/t]$ denotes the largest integer not larger than p/t. If p/t is an integer, then for a balanced block design d each treatment must appear for each subject p/t times, and d is called *uniform on the subjects.*

(ii) a *balanced block design in the carryover effects (with subjects as blocks)*, if the first $p-1$ periods of d are a balanced block design for the direct treatments effects in $\Omega_{t,n,p-1}$.

(iii) *uniform on the periods*, if every treatment appears in every period exactly n/t times.

(iv) a *generalized Youden design*, if d is a balanced block design for the direct treatment effects with subjects as blocks and uniform on the periods. If $d \in \Omega_{t,n,p}$ is a generalized Youden design and p is divisible by t then d is called a *generalized Latin square.*

(v) *balanced for carryover effects*, if every treatment is immediately preceded by every other treatment equally often, but never by itself.

(vi) *strongly balanced for carryover effects*, if every treatment is immediately preceded by every treatment (including itself) equally often.

It is clear that if a design d is balanced for carryover effects, the self carryover effects never appear. Consequently, $\mathbf{S}_d$ is a matrix of zeroes, and our model coincides with the traditional model. For such a design we further have that

$$\mathbf{T}_d^T \mathbf{M}_d = \frac{n(p-1)}{t(t-1)} \begin{bmatrix} 0 & 1 & \cdots & 1 \\ 1 & 0 & \ddots & \vdots \\ \vdots & \ddots & \ddots & 1 \\ 1 & \cdots & 1 & 0 \end{bmatrix}. \tag{3}$$

If d is a balanced block design for the direct treatment effects, then we have that $\mathcal{C}_{d11}$ is completely symmetric. $\mathcal{C}_{d22}$ is completely symmetric if d is a balanced block design for the carryover effects that has no pairs of consecutive identical treatments. Any design that has no identical pairs of consecutive treatments has $\mathcal{C}_{d13}$, $\mathcal{C}_{d23}$ and $\mathcal{C}_{d33}$ completely symmetric, because they are matrices of zeroes.

Therefore, if a design d^* is a balanced block design for direct and carryover effects and is balanced for carryover effects, then $\mathcal{C}_{d^*11}$, $\mathcal{C}_{d^*13}$, $\mathcal{C}_{d^*22}$, $\mathcal{C}_{d^*23}$, and $\mathcal{C}_{d^*33}$ are completely symmetric. If, additionally, $\mathbf{T}_{d^*}^T\mathbf{U}\mathbf{U}^T\mathbf{M}_{d^*}$ is completely symmetric, it follows from (3) that $\mathcal{C}_{d^*12}$ is also completely symmetric.

Definition 2

A design $d^* \in \Omega_{t,n,p}$ is called *totally balanced* if

(i) d^* is a generalized Youden design,

(ii) d^* is a balanced block design for the carryover effects,

(iii) d^* is balanced for carryover effects, and

(iv) the number of subjects where both treatments i and j appear $[p/t]+1$ times and treatment j does not appear in the last period is the same for every pair $i \neq j$.

We will now argue that $\mathcal{C}_{d^*12}$ is completely symmetric for a totally balanced design d^*. If p is not divisible by t, then $[(p-1)/t] = [p/t]$. Therefore, in the totally balanced design d^* the mixed carryover effect of each treatment appears in each subject either $[p/t]$ or $[p/t]+1$ times. This implies that a treatment does not appear for the last period of any subject where it appears only $[p/t]$ times. Then the (i,j)-th element of $\mathbf{T}_{d^*}^T\mathbf{U}\mathbf{U}^T\mathbf{M}_{d^*}$, $i \neq j$ equals

$$(n - x_1 - x_2 - x_3)[p/t]^2 + (x_2 + x_3)[p/t]([p/t]+1) + x_1([p/t]+1)^2.$$

Here x_1 is the number of subjects where both treatment i and j appear $[p/t]+1$ times and treatment j does not appear in the last period, x_2 is the number of subjects where treatment i appears $[p/t]+1$ times and the mixed carryover effect of treatment j appears $[p/t]$ times, x_3 is the number of subjects where treatment i appears $[p/t]$ times and the mixed carryover effect of treatment j appears $[p/t]+1$ times.

Condition (iv) says that x_1 is the same for all $i \neq j$. For d^* the number of subjects where treatment i appears $[p/t]+1$ times does not depend on i and it equals x_1+x_2. Consequently, x_2 does also not depend on i or j. Similarly, the number of subjects where the mixed carryover effect of treatment j appears $[p/t]+1$ times does not depend on j and it equals x_1+x_3. It follows that x_3 also does not depend on i or j and all off-diagonal elements of $\mathbf{T}_{d^*}^{\mathbf{T}}\mathbf{U}\mathbf{U}^T\mathbf{M}_{d^*}$ are the same. This implies that all off-diagonal elements of $\mathcal{C}_{d^*12}$ are equal. Since $\mathbf{1}^T\mathcal{C}_{d12} = \mathbf{0}^T$ for any design d, it follows that all diagonal elements of $\mathcal{C}_{d^*12}$ are equal and that $\mathcal{C}_{d^*12}$ is completely symmetric.

If p is divisible by t, then treatment i appears p/t times for every subject and, therefore, condition (iv) trivially holds for every generalized Latin square. Further, the (i,j)-th entry of $\mathbf{T}_{d^*}^T\mathbf{U}\mathbf{U}^T\mathbf{M}_{d^*}$ equals $(n-n/t)(p/t)^2 + np(p/t-1)/t^2$, because the mixed carryover effect of treatment j appears $p/t-1$ times for those n/t subjects where treatment j appears in the last period and p/t times for all other subjects. Therefore, $\mathbf{T}_{d^*}^T\mathbf{U}\mathbf{U}^T\mathbf{M}_{d^*}$ is a multiple of $\mathbf{1}_t\mathbf{1}_t^T$ and is completely symmetric.

In all, we have for a totally balanced design d^* that all matrices $\mathcal{C}_{d^*ij}$, $1 \leq i \leq j \leq 3$, are completely symmetric.

We define $\mathbf{B}_t = \mathbf{I}_t - \frac{1}{t}\mathbf{1}_t\mathbf{1}_t^T$ and $c_{dij} = \operatorname{tr}(\mathbf{B}_t\mathcal{C}_{dij}\mathbf{B}_t)$ for $1 \leq i \leq j \leq 3$. Then we can literally translate the proof of Proposition 2 of Kunert and

Martin (2000) and for every design $d \in \Omega_{t,n,p}$ we get

$$\operatorname{tr}\left(\mathbf{T}_d^T \omega^{\perp}([\mathbf{U}, \mathbf{M}_d, \mathbf{S}_d])\mathbf{T}_d\right) \leq q_d^*, \tag{4}$$

where q_d^* is defined by the following four cases:

(i) If $c_{d22}c_{d33} - c_{d23}^2 > 0$, then

$$q_d^* = c_{d11} - \frac{c_{d12}^2 c_{d33} - 2c_{d12}c_{d13}c_{d23} + c_{d13}^2 c_{d22}}{c_{d22}c_{d33} - c_{d23}^2}.$$

(ii) If $c_{d22}c_{d33} - c_{d23}^2 = 0$ and $c_{d22} > 0$, then $q_d^* = c_{d11} - c_{d12}^2/c_{d22}$.

(iii) If $c_{d22} = 0$ and $c_{d33} > 0$, then $q_d^* = c_{d11} - c_{d13}^2/c_{d33}$.

(iv) If $c_{d22} = c_{d33} = 0$, then $q_d^* = c_{d11}$.

In equation (4) we have equality if all $\mathcal{C}_{dij}$, $1 \leq i \leq j \leq 3$, are completely symmetric.

In all, it follows that

$$\operatorname{tr} \mathcal{C}_d = q_d^*, \tag{5}$$

if equation (2) holds and if all $\mathcal{C}_{dij}$, $1 \leq i \leq j \leq 3$, are completely symmetric. Our aim is to find a design d for which (5) holds for the maximum possible value of q_{d^*}.

Let $\mathbf{T}_{du}$, $\mathbf{M}_{du}$ and $\mathbf{S}_{du}$ be the design matrix of the direct treatment effects, mixed carryover effects and self carryover effects in block u, $1 \leq u \leq n$. By writing

$c_{d11}^{(u)} = \operatorname{tr}(\mathbf{T}_{du}^T \mathbf{T}_{du} - \frac{1}{p}\mathbf{T}_{du}^T \mathbf{1}_p \mathbf{1}_p^T \mathbf{T}_{du})$,
$c_{d12}^{(u)} = \operatorname{tr}(\mathbf{T}_{du}^T \mathbf{M}_{du} - \frac{1}{p}\mathbf{T}_{du}^T \mathbf{1}_p \mathbf{1}_p^T \mathbf{M}_{du})$,
$c_{d13}^{(u)} = \operatorname{tr}(\mathbf{T}_{du}^T \mathbf{S}_{du} - \frac{1}{p}\mathbf{T}_{du}^T \mathbf{1}_p \mathbf{1}_p^T \mathbf{S}_{du})$,
$c_{d22}^{(u)} = \operatorname{tr}(\mathbf{B}_t(\mathbf{M}_{du}^T \mathbf{M}_{du} - \frac{1}{p}\mathbf{M}_{du}^T \mathbf{1}_p \mathbf{1}_p^T \mathbf{M}_{du}))$,
$c_{d23}^{(u)} = \operatorname{tr}(\mathbf{B}_t(\mathbf{M}_{du}^T \mathbf{S}_{du} - \frac{1}{p}\mathbf{M}_{du}^T \mathbf{1}_p \mathbf{1}_p^T \mathbf{S}_{du}))$,

and

$c_{d33}^{(u)} = \mathrm{tr}(\mathbf{B}_t(\mathbf{S}_{du}^T\mathbf{S}_{du} - \frac{1}{p}\mathbf{S}_{du}^T\mathbf{1}_p\mathbf{1}_p^T\mathbf{S}_{du}))$,

we get that $c_{dij} = \sum_{u=1}^{n} c_{dij}^{(u)}$, for $1 \leq i \leq j \leq 3$. The $c_{dij}^{(u)}$ are determined by the sequence of the treatments applied to subject u. We say that two sequences are equivalent, if one is derived from the other by relabelling of treatments. It is obvious that two subjects with equivalent sequences have the same $c_{dij}^{(u)}$.

Therefore we can define equivalence classes of sequences, such that $c_{dij}^{(u)}$ is the same for all u in a given class. For given p and t there are K, say, possible classes and we denote the proportion of sequences from the ℓ-th class in a given design $d \in \Omega_{t,n,p}$ by $\pi_{d\ell}$. We also define $c_{ij}(\ell) = c_{dij}^{(u_\ell)}$, where u_ℓ is any one sequence in the ℓ-th class. Then we get

$$c_{dij} = n(\sum_{\ell=1}^{K} \pi_{d\ell} c_{ij}(\ell))$$

for $1 \leq i \leq j \leq 3$. Therefore, the $\pi_{d\ell}$ determine q_d^*. However, q_d^* is a nonlinear function of the $\pi_{d\ell}$. This makes maximization of q_d^* through the determination of optimal weights $\pi_{d\ell}$ difficult. The problem is linearized by introducing the function

$$q_d(x,y) = c_{d11} + 2xc_{d12} + x^2 c_{d22} + 2yc_{d13} + y^2 c_{d33} + 2xyc_{d23}$$

Note that $q_d(x,y) \geq q_d^*$ and there is at least one point (x^*, y^*), say, such that $q_d(x^*, y^*) = q_d^*$. This follows from Proposition 3 of Kunert and Martin (2000).

For the ℓ-th equivalence class, $1 \leq \ell \leq K$, we define

$$h_\ell(x,y) = c_{11}(\ell) + 2xc_{12}(\ell) + x^2 c_{22}(\ell) + 2yc_{13}(\ell) + y^2 c_{33}(\ell) + 2xyc_{23}(\ell)$$

and get that $q_d(x,y) = n\sum_{u=1}^{K} \pi_{d\ell} h_\ell(x,y)$. Therefore, $q_d(x,y)$ is a linear combination of the $h_\ell(x,y)$.

We then can use

Proposition 1

For a design $d^* \in \Omega_{t,n,p}$ *consider a point* (x_{d^*}, y_{d^*})*, for which* $q_{d^*}(x_{d^*}, y_{d^*}) = q^*_{d^*}$*. If* $n\, h_\ell(x_{d^*}, y_{d^*}) \leq q_{d^*}(x_{d^*}, y_{d^*}) = q^*_{d^*}$ *for every* $1 \leq \ell \leq K$*, then for every* $f \in \Omega_{t,n,p}$ *we have* $\mathrm{tr}\, \mathcal{C}_f \leq q^*_{d^*}$*.*

Proof

See Kunert and Martin (2000), Proposition 4. □

We have $q_{d^*}(x_{d^*}, y_{d^*})/n = \max_\ell h_\ell(x_{d^*}, y_{d^*})$ for the design d^* of Proposition 1 and therefore

$$q_{d^*}(x_{d^*}, y_{d^*}) = \min_{x,y} q_{d^*}(x, y) = n \min_{x,y} \max_{\ell} h_\ell(x, y).$$

It follows that $n \min_{x,y} \max_\ell h_\ell(x, y)$ is an upper bound for $\mathrm{tr}\, \mathcal{C}_d$ for any $d \in \Omega_{t,n,p}$.

3 Determination of $\min_{x,y} \max_\ell h_\ell(x, y)$.

In order to calculate h_ℓ for the ℓ-th equivalence class, we have to calculate the $c_{ij}(\ell)$. Therefore, we take any sequence u_ℓ from the ℓ-th class and define the quantities

$n_j(\ell)$ is the number of appearances of treatment j in u_ℓ,

$\tilde{n}_j(\ell)$ is the number of appearances of the mixed carryover effect of j in u_ℓ, i.e. the number of appearances of treatment j followed by any other treatment,

$t_{pj}(\ell)$ is the number of appearances of treatment j in the last period of the sequence u_ℓ.

It is clear that there is exactly one j such that $t_{pj}(\ell) = 1$, all other $t_{pj}(\ell)$ are 0. Further, the number of times that treatment j is immediately followed by itself is $n_j(\ell) - \tilde{n}_j(\ell) - t_{pj}(\ell)$.

With these definitions it is easy to derive that

$$
\begin{aligned}
c_{11}(\ell) &= p - \frac{1}{p}\sum_j n_j^2(\ell) \\
c_{12}(\ell) &= -\frac{1}{p}\sum_j n_j(\ell)\tilde{n}_j(\ell) \\
c_{22}(\ell) &= \frac{t-1}{t}\sum_j \tilde{n}_j(\ell) - \frac{1}{p}\sum_j \tilde{n}_j^2(\ell) + \frac{1}{pt}(\sum_j \tilde{n}_j(\ell))^2 \\
c_{13}(\ell) &= p - 1 - \sum_j \tilde{n}_j(\ell) - \frac{1}{p}\sum_j n_j(\ell)\Big(n_j(\ell) - \tilde{n}_j(\ell) - t_{pj}(\ell)\Big) \\
c_{23}(\ell) &= -\frac{1}{p}\sum_j \tilde{n}_j(\ell)\Big(n_j(\ell) - \tilde{n}_j(\ell) - t_{pj}(\ell)\Big) \\
&\quad + \frac{1}{pt}\Big(\sum_j \tilde{n}_j(\ell)\Big)\Big(p - 1 - \sum_j \tilde{n}_j(\ell)\Big) \\
c_{33}(\ell) &= \frac{t-1}{t}\Big(p - 1 - \sum_j \tilde{n}_j(\ell)\Big) - \frac{1}{p}\sum_j \Big(n_j(\ell) - \tilde{n}_j(\ell) - t_{pj}(\ell)\Big)^2 \\
&\quad + \frac{1}{pt}\Big(p - 1 - \sum_j \tilde{n}_j(\ell)\Big)^2.
\end{aligned}
$$

Note that although the $n_j(\ell)$, $\tilde{n}_j(\ell)$ and $t_{pj}(\ell)$ depend on the choice of the representative sequence u_ℓ, the $c_{ij}(\ell)$ do not depend on u_ℓ but are the same for all u_ℓ in a given equivalence class.

Inserting this into $h_\ell(x,y)$, we find that $h_\ell(x,y)$ for $y = -1$ simplifies to

$$
\begin{aligned}
h_\ell(x,-1) &= \frac{1}{pt}\Big((p-1)(t-1) \\
&\quad + (\sum_j \tilde{n}_j(\ell))(p(t-1) + 2 - 2(p-1)x + p(t-1)x^2) \\
&\quad - (\sum_j \tilde{n}_j^2(\ell))t(1+x)^2 \\
&\quad + (\sum_j \tilde{n}_j(\ell))^2(1+x)^2 \\
&\quad - (\sum_j \tilde{n}_j(\ell)t_{pj}(\ell))2t(1+x)\Big).
\end{aligned}
\tag{6}
$$

It is interesting to note that $h_\ell(x,-1)$ does not depend on the $n_j(\ell)$.

We start with a technical proposition

Proposition 2

Restrict attention to $t \geq 3$ and $3 \leq p \leq 2t$, i.e. there are numbers $a^* \in \{0, 1\}$ and $b^* \in \{0, 1, ..., t-1\}$, such that $p - 1 = a^*t + b^*$. Further let $0 < x < 1$ and $y = -1$. Then $h_\ell(x, -1)$ is maximal if the sequence class ℓ is such that

(i) $\sum_j \tilde{n}_j(\ell) = a^*t + b^*$,

(ii) all $\tilde{n}_j(\ell) \in \{a^*, a^* + 1\}$, *and*

(iii) $\sum_j \tilde{n}_j(\ell) t_{pj}(\ell) = a^*$.

Proof

The maximization is done in two steps. Firstly, we keep $\sum_j \tilde{n}_j(\ell)$ fixed and try to maximize $h_\ell(x, -1)$ by varying $\sum_j \tilde{n}_j^2(\ell)$ and $\sum_j \tilde{n}_j(\ell) t_{pj}(\ell)$. It can be seen in (6) that $h_\ell(x, -1)$ is maximal if both $\sum_j \tilde{n}_j^2(\ell)$ and $\sum_j \tilde{n}_j(\ell) t_{pj}(\ell)$ are as small as possible.

Note that $\sum_j \tilde{n}_j(\ell) \leq p - 1 < 2t$. Therefore there are numbers $a(\ell) \in \{0, 1\}$ and $b(\ell) \in \{0, 1, ..., t-1\}$, such that $\sum_j \tilde{n}_j(\ell) = a(\ell)t + b(\ell)$. It is obvious then, that $\sum_j \tilde{n}_j^2(\ell)$ is minimal if $b(\ell)$ of the $\tilde{n}_j(\ell)$ equal $a(\ell) + 1$ and $t - b(\ell)$ of them are $a(\ell)$. Also, $\sum_j \tilde{n}_j(\ell) t_{pj}(\ell) = \tilde{n}_r(\ell)$, where r is the treatment appearing in the last period of the representative sequence u_ℓ. Clearly, this is minimized if $\tilde{n}_r(\ell) = 0$.

So simultaneous minimization of $\sum_j \tilde{n}_j^2(\ell)$ and $\sum_j \tilde{n}_j(\ell) t_{pj}(\ell)$ is not always possible. We therefore have to consider two cases.

Case 1: $\sum_j \tilde{n}_j(\ell) \leq t - 1$, i.e. $a(\ell) = 0$.

In this case we can simultaneously minimize $\sum_j \tilde{n}_j^2(\ell)$ and $\sum_j \tilde{n}_j(\ell) t_{pj}(\ell)$. We get $\sum_j \tilde{n}_j^2(\ell) \geq \sum_j \tilde{n}_j(\ell) = b(\ell)$, and $\sum_j \tilde{n}_j(\ell) t_{pj}(\ell) \geq 0$. Inserting these values we get

$$h_\ell(x, -1) \leq \frac{1}{pt}\Big((p-1)(t-1)$$

$$+b(\ell)\left(pt-p-t+2-2(p+t-1)x+(pt-p-t)x^2\right)$$
$$+b^2(\ell)(1+x)^2\Big)=\xi_1(\ell),$$

say. This bound is maximal if $b(\ell)$ is as large as possible, i.e. if $b(\ell) = \min\{p-1,\ t-1\} = q_1$, say.

To see this, we rewrite

$$\begin{aligned} pt-p-t+2 &- 2(p+t-1)x+(pt-p-t)x^2 \\ &= (pt-p-t)(1-x)^2+2+2(pt-2p-2t+1)x \\ &\geq 2+2(pt-2p-2t+1)x. \end{aligned}$$

If $p \geq 4$, then $pt-2p-2t+1 \geq 2t-7 \geq -1$ as $t \geq 3$ and therefore $2+2(pt-2p-2t+1)x \geq 2-2x \geq 0$, as $0 < x < 1$. Similarly, if $t \geq 4$, then $pt-2p-2t+1 \geq 2p-7 \geq -1$ as $p \geq 3$ and, again, $2+2(pt-2p-2t+1)x \geq 0$. For $t \geq 4$ or $p \geq 4$, it hence follows that $\xi_1(\ell)$ is increasing in $b(\ell)$.

If, however, $p = t = 3$, then

$$\xi_1(\ell) = \frac{1}{9}(4+b(\ell)(5-10x+3x^2)+b^2(\ell)(1+x)^2).$$

Some algebra shows that then $\xi_1(\ell)$ is maximal if $b(\ell) = 2 = q_1$.

Therefore, whenever $\sum_j \tilde{n}_j(\ell) \leq t-1$ we have

$$\begin{aligned} h_\ell(x,-1) &\leq \frac{1}{pt}\Big((p-1)(t-1) \\ &\quad +q_1\left(pt-p-t+2-2(p+t-1)x+(pt-p-t)x^2\right) \qquad (7)\\ &\quad +q_1^2(1+x)^2\Big) \\ &= \xi_1^*, \end{aligned}$$

say.

If $p \leq t$ the problem is solved and formula (7) gives an upper bound for $h_\ell(x,-1)$, which is attained if ℓ fulfills the conditions (i), (ii) and (iii) of the proposition.

If, however, $p > t$, then it is possible to have $\sum_j \tilde{n}_j \geq t$. Does this lead to a larger upper bound for $h_\ell(x,-1)$?

Case 2: $a(\ell) = 1$, i.e. $\sum_j \tilde{n}_j = t + b(\ell)$.

In this case the two tasks, minimizing $\sum_j \tilde{n}_j^2(\ell)$ and minimizing $\sum_j \tilde{n}_j(\ell)t_{pj}(\ell)$, are conflicting. Therefore we have two possibilities to derive an upper bound.

First possibility: Minimize $\sum_j \tilde{n}_j^2(\ell)$ by choosing $b(\ell)$ of the $\tilde{n}_j(\ell)$ equal to 2 and $t - b(\ell)$ equal to 1. It follows that $\sum_j \tilde{n}_j^2(\ell) \geq t + 3b(\ell)$ and $\sum_j \tilde{n}_j(\ell)t_{pj}(\ell) \geq 1$. Therefore,

$$\begin{aligned}
h_\ell(x,-1) \quad &\leq \quad \frac{1}{pt}\Big((p-1)(t-1) \\
&\quad +(t+b(\ell))(p(t-1)+2-2(p-1)x+p(t-1)x^2) \\
&\quad -(t+3b(\ell))t(1+x)^2 \\
&\quad +(t+b(\ell))^2(1+x)^2 \\
&\quad -2t(1+x)\Big) \\
&= \quad \xi_2(\ell),
\end{aligned}$$

say.

Second possibility: Choose one of the $\tilde{n}_j(\ell) = 0$, $b(\ell)+1$ of them equal to 2 and $t - b(\ell) - 2$ of them equal to 1. Then $\sum_j \tilde{n}_j^2(\ell) \geq t + 3b(\ell) + 2$ and $\sum_j \tilde{n}_j(\ell)t_{pj}(\ell) \geq 0$. Therefore,

$$\begin{aligned}
h_\ell(x,-1) \quad &\leq \quad \frac{1}{pt}\Big((p-1)(t-1) \\
&\quad +(t+b(\ell))(p(t-1)+2-2(p-1)x+p(t-1)x^2) \\
&\quad -(t+3b(\ell)+2)t(1+x)^2 \\
&\quad +(t+b(\ell))^2(1+x)^2\Big) \\
&= \quad \xi_3(\ell),
\end{aligned}$$

say. Since $x \geq 0$ it holds that $(1+x)^2 \geq (1+x)$ and, hence, $\xi_2(\ell) \geq \xi_3(\ell)$.

Therefore, $\xi_2(\ell)$ is an upper bound for $h_\ell(x,-1)$ for every fixed $\sum_j \tilde{n}_j(\ell) \geq t$. To continue, we rewrite

$$\begin{aligned}\xi_2(\ell) &= \frac{1}{pt}\Big((p-1)(t-1) + pt(t-1) \\ &\quad -x2tp + x^2pt(t-1) \\ &\quad +b(\ell)(pt-p-t+2-2(p+t-1)x+(pt-p-t)x^2) \\ &\quad +b^2(\ell)(1+x)^2\Big).\end{aligned}$$

Note that case 2 is possible only if $p \geq t+1 \geq 4$. We find from case 1, that $\xi_2(\ell)$ is increasing in $b(\ell)$. Therefore, $\xi_2(\ell)$ is maximal if $b(\ell)$ is as large as possible, that is if $b(\ell) = p-1-t$.

Therefore, whenever $\sum_j \tilde{n}_j \geq t$ we have

$$\begin{aligned}h_\ell(x,-1) &\leq \frac{1}{pt}\Big((p-1)(t-1) + pt(t-1) \\ &\quad -x2tp + x^2pt(t-1) \\ &\quad +(p-1-t)(pt-p-t+2-2(p+t-1)x+(pt-p-t)x^2) \\ &\quad +(p-1-t)^2(1+x)^2\Big) \\ &= \xi_2^*,\end{aligned}$$

say.

It remains to consider whether in the case $p > t$ it is best to have $\sum_j \tilde{n}_j = t-1$, or to have $\sum_j \tilde{n}_j = p-1$, that is, we have to compare ξ_1^* and ξ_2^*.

Because $q_1 = t-1$ in (7) and because $p-1-t \geq 0$, we have

$$\begin{aligned}\xi_2^* - \xi_1^* &\geq \frac{1}{pt}\Big((p-1)(t-1) + pt(t-1) \\ &\quad -x2tp + x^2pt(t-1) \\ &\quad -(p-1)(t-1) \\ &\quad -(t-1)\left(pt-p-t+2-2(p+t-1)x+(pt-p-t)x^2\right) \\ &\quad -(t-1)^2(1+x)^2\Big)\end{aligned}$$

$$
\begin{aligned}
&= \frac{1}{pt}\Big((p-1)(t-1) - 2px + (p+1)(t-1)x^2\Big) \\
&\geq \frac{1}{pt}\Big((p-1)(t-1) - 2px + 2px^2\Big) \\
&= \frac{1}{pt}\Big((p-1)(t-1) + 2p(x-\frac{1}{2})^2 - \frac{p}{2}\Big) \\
&> 0.
\end{aligned}
$$

Observe that conditions (i), (ii) and (iii) give $h_\ell(x,-1) = \xi_2^*$ if $p > t$. This completes the proof.□

The sequences that satisfy conditions (i), (ii) and (iii) of Proposition 2 are those that possess the following three properties:

(a) for any 2 treatments, the numbers of times that they appear in the sequence differ at most by 1;

(b) for any 2 consecutive periods, the treatments assigned to the periods are different; and

(c) the treatment in the last period appears the maximum number of times.

If $p \leq t$, the only sequences that satisfy these conditions are those that are equivalent to $[1,\ 2,\ ...,\ p]$. If $p > t$, there is more than one equivalence class with sequences that satisfy these conditions. For example, both $[1,\ 2,\ ...,\ t,\ 1,\ 2,\ ...,\ p-t]$ and $[1,\ 2,\ ...,\ t,\ t-1,\ t-2,\ ...,\ 2t-p]$ are fine if $p < 2t$. They are clearly not equivalent.

Proposition 3

Assume $t \geq 3$ and $3 \leq p \leq 2t$. If the ℓ^*-th sequence class is such that conditions (i), (ii) and (iii) of Proposition 2 hold, then for all x and y we have

$$h_{\ell^*}(x,y) \geq h_{\ell^*}(x^*,-1),$$

where

$$x^* = \begin{cases} \frac{t}{tp-t-1} & \text{for } p \le t \\ \frac{tp+2t(p-1-t)}{pt(t-1)+(pt-2t-1)(p-1-t)} & \text{for } p > t \end{cases}$$

Proof

Case 1: $p \le t$

As seen just before Proposition 3, ℓ^* must consist of p distinct treatments, so that $n_j(\ell^*) - \tilde{n}_j(\ell^*) - t_{pj}(\ell^*) = 0$ for all j. Hence, conditions (i), (ii) and (iii) imply that

$c_{11}(\ell^*) = p - 1$

$c_{12}(\ell^*) = -\frac{p-1}{p}$

$c_{22}(\ell^*) = \frac{(p-1)(tp-t-1)}{pt}$

and

$c_{13}(\ell^*) = c_{23}(\ell^*) = c_{33}(\ell^*) = 0.$

Therefore,

$$\begin{aligned} h_{\ell^*}(x,y) &= h_{\ell^*}(x,-1) \\ &= p - 1 - 2\frac{p-1}{p}x + \frac{(p-1)(tp-t-1)}{pt}x^2 \end{aligned}$$

and $h_{\ell^*}(x,-1)$ is minimal if $x = \frac{t}{tp-t-1} = x^*$.

Case 2: $p > t$.

Condition (i) implies that there are no pairs of consecutive identical treatments in the sequence. Hence, all but one of the $n_j(\ell^*)$ must be equal to $\tilde{n}_j(\ell^*)$. Condition (iii) implies that the one j for which $n_j(\ell^*) = \tilde{n}_j(\ell^*) + 1$ has $n_j(\ell^*) = a^* + 1 = 2$. Then, condition (ii) implies that all $n_j(\ell^*) \in \{1, 2\}$, that $\sum_j n_j^2(\ell^*) = 4(p-t) + 1(2t-p)$ and that $\sum_j n_j(\ell^*)\tilde{n}_j(\ell^*) = 4(p-1-t) + 2 + 1(2t-p)$.

Therefore

$$c_{11}(\ell^*) = p - \frac{1}{p}(4(p-t) + (2t-p))$$

$$\begin{aligned}
&= \frac{p^2-3p+2t}{p} \\
c_{12}(\ell^*) &= -\frac{1}{p}(4(p-t-1)+2+(2t-p)) \\
&= -\frac{p+2(p-1-t)}{p} \\
c_{22}(\ell^*) &= \frac{t-1}{t}(p-1)-\frac{1}{p}(4(p-1-t)+1+(2t-p))+\frac{(p-1)^2}{pt} \\
&= \frac{pt(t-1)+(pt-2t-1)(p-1-t)}{pt}
\end{aligned}$$

while

$$c_{13}(\ell^*) = c_{23}(\ell^*) = c_{33}(\ell^*) = 0.$$

It follows that

$$\begin{aligned}
h_{\ell^*}(x,y) &= h_{\ell^*}(x,-1) \\
&= \frac{p^2-3p+2t}{p} - 2\frac{p+2(p-1-t)}{p}x \\
&\quad + \frac{pt(t-1)+(pt-2t-1)(p-1-t)}{pt}x^2
\end{aligned}$$

and $h_{\ell^*}(x,-1)$ is minimal if

$$x = \frac{tp+2t(p-1-t)}{pt(t-1)+(pt-2t-1)(p-1-t)} = x^*.\square$$

Proposition 4

Assume $t \geq 3$ and $3 \leq p \leq 2t$. If the ℓ^*-th sequence class is such that conditions (i), (ii) and (iii) of Proposition 2 hold, then

$$\min_{x,y} \max_{\ell} h_\ell(x,y) = h_{\ell^*}(x^*,-1),$$

where x^* is as in Proposition 3.

Proof

Case 1: $p \leq t$

Here, $x^* = t/(tp - t - 1)$ and, therefore, $0 \leq x^* \leq 1$. From Proposition 2 it follows that

$$h_{\ell^*}(x^*, -1) = \max_{\ell} h_\ell(x^*, -1) \geq \min_{x,y} \max_{\ell} h_\ell(x, y).$$

Conversely, for all x, y we have that

$$\max_{\ell} h_\ell(x, y) \geq h_{\ell^*}(x, y) \geq h_{\ell^*}(x^*, -1),$$

where the last inequality follows from Proposition 3.

Case 2: $p > t$

Then

$$x^* = \frac{tp + 2t(p - 1 - t)}{pt(t-1) + (pt - 2t - 1)(p - 1 - t)}.$$

As $p - 1 - t \geq 0$ it follows that $x^* \geq 0$.

We also have that

$$\begin{aligned} pt(t-1) + (pt - 2t - 1)(p - 1 - t) - tp - 2t(p - 1 - t) \\ = p^2 t - 6pt - 2p + 2t^2 + 7t + 3. \end{aligned}$$

As the right hand side is increasing in p and $p \geq t$ it follows that

$$\begin{aligned} pt(t-1) &+ (pt - 2t - 1)(p - 1 - t) - tp - 2t(p - 1 - t) \\ &\geq t^3 - 6t^2 - 2t + 2t^2 + 7t + 3 \\ &= t(t-2)^2 + t + 3 > 0. \end{aligned}$$

Therefore $x^* < 1$. The rest of the proof works as in Case 1. □

4 Optimal designs

If we want to determine a universally optimal design d^*, then we have to ensure that $\mathcal{C}_{d^*}$ is completely symmetric, that d^* maximizes the upper bound

q_d^* of the trace of $\mathcal{C}_d$, and that $q_{d^*}^* = \operatorname{tr} \mathcal{C}_{d^*}$. The results of Section 3 give conditions on how to maximize q_d^*. In the following theorem we give a set of designs which also fulfill the other two conditions.

Theorem 1

For $t \geq 3$ and $3 \leq p \leq 2t$, if a totally balanced design $d^* \in \Omega_{t,n,p}$ exists, then d^* is universally optimal over $\Omega_{t,n,p}$.

Proof

For a design that is balanced for carryover effects we have that there are no pairs of consecutive identical treatments and therefore no self carryover effects in the design. Furthermore, in d^* each treatment appears exactly n/t times in each period. This implies that the direct effects of all treatments appear equally often in each period. Additionally, the mixed carryover effects of all treatments appear 0 times in period 1 and exactly n/t times in periods 2 to p. Therefore, equation (2) holds and

$$\mathcal{C}_{d^*} = T_{d^*}^T \omega^{\perp}([\mathbf{U}, \mathbf{M}_{d^*}, \mathbf{S}_{d^*}])\mathbf{T}_{d^*}.$$

To ensure that $\operatorname{tr} \mathcal{C}_{d^*} = q_{d^*}^*$, it therefore suffices to show that all $\mathcal{C}_{d^*ij}$ are completely symmetric. Following Definition 2 we have already shown that this holds for the design d^*.

The complete symmetry of all $\mathcal{C}_{d^*ij}$, $1 \leq i \leq j \leq 3$ also implies that $\mathbf{T}_{d^*}^T \omega^{\perp}([\mathbf{U}, \mathbf{M}_{d^*}, \mathbf{S}_{d^*}])\mathbf{T}_{d^*}$ is completely symmetric and, therefore, that $\mathcal{C}_{d^*}$ is completely symmetric.

To complete the proof it suffices to show that the design d^* maximizes q_d^* over $\Omega_{t,n,p}$. This, however, is done by applying Propositions 1, 3 and 4, if we note that with d^* all subjects receive a treatment sequence that is either equivalent to $[1,\ 2,\ ...,\ p]$ (if $p \leq t$), or has the same $c_{dij}^{(u)}$ as $[1,\ 2,\ ...,\ t,\ 1,\ 2,\ ...,\ p-t]$ (if $p > t$). □

Corollary 1

If $p = t$ or $p = 2t$ and a generalized Latin square d^* exists in $\Omega_{t,n,p}$ which is balanced for carryover effects, then d^* is universally optimal.

Proof

The Corollary follows from the fact that d^* is a totally balanced design. For condition (iv) of Definition 2 see the discussion after Definition 2. □

The optimal designs derived by Theorem 1 all have no pairs of consecutive identical treatments. This is a large difference to the usual model where mixed and self carryover effects are assumed to be equal. In that model, almost all optimal designs derived in the literature need pairs of consecutive identical treatments. In what follows, we give some examples of designs which are optimal for the model (1) with mixed and self carryover effects. In all examples, rows indicate periods and columns indicate subjects.

Example 1

If $t = 4$ and $p = 3$, we have a totally balanced design $d^* \in \Omega_{4,12,3}$, namely

$$d^* = \begin{bmatrix} 1 & 3 & 2 & 4 & 1 & 2 & 1 & 4 & 3 & 4 & 2 & 3 \\ 2 & 1 & 3 & 2 & 4 & 1 & 3 & 1 & 4 & 3 & 4 & 2 \\ 3 & 2 & 1 & 1 & 2 & 4 & 4 & 3 & 1 & 2 & 3 & 4 \end{bmatrix}.$$

If we have many more subjects, with n divisible by 12, an optimal design consists of multiples of d^*. It was shown by Stufken (1991) and Kushner (1998) that in the traditional model the optimal design would have some subjects receiving sequences which are equivalent to [1, 2, 2].

Example 2

If $t = 4$ and $p = 4$ we have a totally balanced design $d^* \in \Omega_{4,4,4}$, namely the carryover balanced Latin square

$$d^* = \begin{bmatrix} 1 & 2 & 3 & 4 \\ 2 & 4 & 1 & 3 \\ 3 & 1 & 4 & 2 \\ 4 & 3 & 2 & 1 \end{bmatrix}.$$

This is also optimal in the traditional model (Kunert, 1984). It was shown by Kunert (1984) that in the traditional model, if the number n of subjects gets large, the optimal design in $\Omega_{4,n,4}$ will have some subjects with a treatment sequence equivalent to [1, 2, 3, 3], while Corollary 1 shows that in the model with mixed and self carryover whenever n is divisible by 4 a design consisting of multiples of d^* is optimal.

Example 3

If $t = 3$, $p = 4$ and $n = 6$, then the so-called extra-period design

$$f = \begin{bmatrix} 1 & 2 & 3 & 3 & 1 & 2 \\ 2 & 3 & 1 & 2 & 3 & 1 \\ 3 & 1 & 2 & 1 & 2 & 3 \\ 3 & 1 & 2 & 1 & 2 & 3 \end{bmatrix}$$

is universally optimal in the traditional model (Cheng and Wu, 1980). The design f fulfills all conditions of a totally balanced design, except for the balance for carryover effects. Instead, it is strongly balanced for carryover. Therefore, in model (1) with self and mixed carryover the totally balanced design

$$d^* = \begin{bmatrix} 1 & 2 & 3 & 3 & 1 & 2 \\ 2 & 3 & 1 & 2 & 3 & 1 \\ 3 & 1 & 2 & 1 & 2 & 3 \\ 1 & 2 & 3 & 3 & 1 & 2 \end{bmatrix}$$

performs better than f and is universally optimal.

Example 4

If $t = 3$ and $p = 6$, we have a totally balanced design for $n = 6$, namely

$$d^* = \begin{bmatrix} 1 & 2 & 3 & 3 & 1 & 2 \\ 2 & 3 & 1 & 1 & 2 & 3 \\ 3 & 1 & 2 & 2 & 3 & 1 \\ 2 & 3 & 1 & 3 & 1 & 2 \\ 1 & 2 & 3 & 2 & 3 & 1 \\ 3 & 1 & 2 & 1 & 2 & 3 \end{bmatrix}.$$

This performs better than the so-called nearly strongly balanced generalized Latin square

$$f = \begin{bmatrix} 1 & 2 & 3 & 1 & 2 & 3 \\ 2 & 3 & 1 & 1 & 2 & 3 \\ 3 & 1 & 2 & 2 & 3 & 1 \\ 3 & 1 & 2 & 3 & 1 & 2 \\ 2 & 3 & 1 & 3 & 1 & 2 \\ 1 & 2 & 3 & 2 & 3 & 1 \end{bmatrix},$$

which was shown by Kunert (1983) to be universally optimal over $\Omega_{3,6,6}$ in the traditional model.

5 Discussion

The paper shows that in the model with mixed and self carryover effects the optimal designs in general do not contain pairs of consecutive identical treatments. Instead it is shown that special designs with balance for carryover effects are optimal.

This gives another theoretical justification for the use of designs that are balanced for carryover effects, which are very popular in practice. There are other theoretical arguments for the use of these designs. One example is the minimization of the bias if the carryover effect is neglected in the analysis (see Azaïs and Druilhet, 1997, and Kunert, 1998). Another example of a theoretical argument in favour of balanced designs is the possibility to get a conservative estimate of the variance, even if correlations between the errors are suspected to be present (see Kunert and Utzig, 1991).

We end the paper with two technical remarks.

Firstly, in the optimal designs derived by Theorem 1, the self carryover never appears. Therefore, it might look easier to show optimality of the design d^* in the simpler model where the self carryover effects are assumed to be zero, and then to use Kunert's (1983) strategy 1 to extend to model (1) with mixed and self carryover effects. This, however, is not possible in general. For instance, the design f from Example 3 performs better than d^* in the simpler model where self carryover effects are assumed zero. Therefore, the optimality proof for d^* has to use the two-dimensional polynomial $q_d(x, y)$.

Secondly, it should be pointed out that the optimality results of the paper could be extended to the case that $p > 2t$. This would, however, take some extra technicalities. We did not do it because the case $p > 2t$ is of less interest from a practical viewpoint.

Acknowledgement

Financial support from the Deutsche Forschungsgemeinschaft (SFB 475, "Reduction of complexity in multivariate data structures") and the National Science Foundation (DMS-9803684) is gratefully acknowledged.

References

Azaïs, J.M. and Druilhet, P. (1997), "Optimality of Neighbour Balanced Designs When Neighbour Effects Are Neglected," *Journal of Statistical Planning and Inference*, 64, 353 - 367.

Cheng, C.S. and Wu, C.F. (1980), "Balanced Repeated Measurements Designs," *Annals of Statistics*, 8, 1272 - 1283. Corr. (1983), 11, 349.

Hedayat, A. and Afsarinejad, K. (1978), "Repeated Measurements Designs II," *Annals of Statistics*, 6, 619 - 628

Hedayat, A. and Afsarinejad, K. (2000), "Repeated Measurements Designs for a Model With Self and Mixed Carryover Effects," *Journal of Statistical Planning and Inference*, (to appear).

Kiefer, J. (1975), "Construction and Optimality of Generalized Youden Designs," in *A Survey of Statistical Designs and Linear Models*, ed. J.N. Srivastava, Amsterdam: North Holland, 333 - 353.

Kunert, J. (1983), "Optimal Designs and Refinement of the Linear Model With Applications to Repeated Measurements Designs," *Annals of Statistics*, 11, 247 - 257.

Kunert, J. (1984), "Optimality of Balanced Uniform Repeated Measurements Designs," *Annals of Statistics*, 12, 1006 - 1017.

Kunert, J. (1987), "An Example of Universal Optimality in a Full-Rank Model," *Metrika*, 34, 217 - 223.

Kunert, J. (1998), "Sensory Experiments as Crossover Studies," *Food Quality and Preference*, 9, 243 - 253.

Kunert, J. and Martin, R.J. (2000), "On the Determination of Optimal Designs for an Interference Model," *Annals of Statistics*, (to appear).

Kunert, J. and Utzig, B. (1993), "Estimation of Variance in Crossover Designs," *Journal of the Royal Statistical Society B*, 55, 919 - 927.

Kushner, H. (1997), "Optimal Repeated Measurements Designs: the Linear Optimality Equations." *Annals of Statistics*, 25, 2328 - 2344.

Kushner, H. (1998), "Optimal and Efficient Repeated-Measurements Designs for Uncorrelated Observations," *Journal of the American Statistical Association*, 93, 1176 - 1187.

Sen, M. and Mukerjee, R. (1987), "Optimal Repeated Measurements Designs Under Interaction," *Journal of Statistical Planning and Inference*, 17, 81 - 91.

Senn, S. (1993), *Crossover Trials in Clinical Research*, Chichester: Wiley

Stufken, J. (1991), "Some Families of Optimal and Efficient Repeated Measurements Designs," *Journal of Statistical Planning and Inference*, 27, 75 - 83.