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Optimal cross-over designs for total effects under a model with self and mixed carryover effects

Pierre Druilhet [a,*], Walter Tinsson [b]

[a] Laboratoire de Mathématiques, UMR CNRS 6620, Clermont Université, Université Blaise Pascal, BP 80026, 63177 Aubiere Cedex, France

[b] Laboratoire de Mathématiques Appliquées, UMR CNRS 5142, Université de Pau, BP 1155, 64013 Pau Cedex, France

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ABSTRACT

We consider cross-over designs for a model that includes specific carryover effects when a treatment is preceded by itself. When the parameters of interest are total effects, i.e. the sum of direct effects of treatment and self-carryover effects, we show that optimal designs are a compromise between designs balanced on subjects such as balanced binary block designs and designs with subjects having a single treatment. We also propose universally optimal designs with a reduced number of subjects.

1. Introduction

In cross-over designs, it is often assumed that the response on a given period depends on both the treatment applied to that period (direct treatment effect) and the treatment applied to the previous period (carryover effect). The optimal designs depend on the way the interference between these two effects is modelized (see Bose and Dey, 2009, for a recent review of optimal cross-over designs). The simpler way to modelize this interference is to assume that carryover and direct treatment effects are additive, which means that the carryover effect of a treatment is the same no matter the treatment applied to the following period is. For example Kunert (1984), Kushner (1998), and Bailey and Druilhet (2004) obtained optimal or efficient designs for this model, Zheng (2013) considers optimal designs in the presence of drop out subjects. The additive model is often too coarse. To enrich the model, Kempton et al. (2001) proposed a model where carryover effects are proportional to direct effects and Bailey and Kunert (2006) obtained optimal designs for that model. Sen and Mukerjee (1987) proposed a model with interaction between carryover and direct treatment effect. Park et al. (2011) obtained efficient cross-over designs under that model. As a compromise between additive and full interaction models, Afsarinejad and Hedayat (2002) proposed a model with two different kinds of carryover effects for a treatment: a self-carryover when the following treatment is the same one and a mixed carryover effect when the following treatment is a different one. This is equivalent to assume a partial interaction between treatment and carryover effects. Kunert and Stufken (2002) obtained optimal designs for the estimation of direct treatment effects under this model. For designs with pre-periods and circularity conditions, Druilhet and Tinsson (2009) obtained efficient designs when the parameters of interest are total effects, i.e. the effects of treatments preceded by themselves.

In this paper we consider designs without pre-period and therefore without circularity condition for the model with self- and mixed carryover effects. We obtain optimal designs for total effects based on the construction of optimal sequences

* Corresponding author. Tel.: +33 4 73 40 76 93.
E-mail address: pierre.druilhet@math.univ-bpclermont.fr (P. Druilhet).

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initially proposed by Kushner (1997). Then, we propose a method to derive universally optimal designs with a limited number of subjects.

2. Models with self- and mixed carryover effects

Let b be the number of subjects, k the number of periods, t the number of treatments and $n=bk$ the total number of observations. For $1\le u\le b$ and $1\le j\le k$, denote by $d(u,j)$ the treatment assigned to subject u in period j. As in Afsarinejad and Hedayat (2002), we assume that the response y_{uj} is

$$y_{uj}=\beta_u+\tau_{d(u,j)}+\lambda_{d(u,j-1)}+\chi_{d(u,j-1)d(u,j)}+\varepsilon_{uj}, \tag{1}$$

where β_u is the effect of subject u, τ_i is the effect of treatment i, λ_i is the general carryover effect of treatment i, $\chi_{ii'}$ is the additional specific carryover effect when treatment i is followed by itself, with $\chi_{ii'}=0$ if $i\neq i'$, and ε_{uj} are independent identically distributed errors with expectation 0 and variance σ^2. In vector notation, we have

$$Y=B\beta+T_d\tau+L_d\lambda+S_d\chi+\varepsilon \tag{2}$$

where Y is the n-vector of responses, β the b-vector of subject effects, τ the t-vector of treatment effects, λ the t-vector of carryover effects and χ the t-vector of self-carryover effects whose entries are χ_{ii}, $1\le i\le t$. The matrices B, T_d, L_d and S_d are the design matrices of subjects, direct treatments, carryover and specific self-carryover effects, respectively. Note that $\mathrm{var}(\varepsilon)=\sigma^2 I_{bk}$. We define the vector ϕ of total effects by $\phi=\tau+\lambda+\chi$, which corresponds to the direct effect of a treatment in addition to that treatment's carryover effect when preceded by itself. If $\theta'=(\tau',\lambda',\chi')$ and $K'=(I_t|I_t|I_t)$, then

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

The model we have described does not include period effects. However, it will be seen in Section 3.3 that the optimal designs obtained for this model are also optimal when period effects are present. We denote by $\Omega_{t,b,k}$ the set of all cross-over designs with t treatments, b subjects and k periods. We also denote respectively by I_n, J_n and $\mathbb{1}_n$ the $n\times n$ identity matrix, the $n\times n$ matrix of ones and the n-vector of ones.

3. Information matrix, symmetric designs and linearization of the problem

3.1. Information matrices and symmetric designs

There are two equivalent ways to define the information matrix for the parameter ϕ (see Pukelsheim, 1993, Chapter 3). The first one is to consider a linear reparameterize of the model by $\theta\mapsto\eta=(\phi',\psi')'$, then calculate the partitioned information matrix $C_d(\eta)$ of η and derive the information matrix $C_d(\phi)$ for ϕ by taking the Schur-complement in $C_d(\eta)$. This approach allows one to compute the information matrix for a given design, but may lead to untractable formulae to derive optimal designs. In order to adapt Kushner's (1997) methods to our case, it is preferable to use a definition of $C_d(\phi)$ through an extremal representation which allows linearization techniques. This approach is presented below.

The information matrix for the whole parameter $\theta'=(\tau',\lambda',\chi')$ is given by

$$C_d(\theta)=(T_d|L_d|S_d)'\omega_B^{\perp}(T_d|L_d|S_d)$$

denoting $\omega_B=B(B'B)^{-1}B'=(1/k)BB'$ the projection matrix onto the column span of B and $\omega_B^{\perp}=I_n-\omega_B$. So

$$C_d(\theta)=\begin{pmatrix} T'_d\omega_B^{\perp}T_d & T'_d\omega_B^{\perp}L_d & T'_d\omega_B^{\perp}S_d\\ L'_d\omega_B^{\perp}T_d & L'_d\omega_B^{\perp}L_d & L'_d\omega_B^{\perp}S_d\\ S'_d\omega_B^{\perp}T_d & S'_d\omega_B^{\perp}L_d & S'_d\omega_B^{\perp}S_d\end{pmatrix}=\begin{pmatrix} C_{d11} & C_{d12} & C_{d13}\\ C'_{d12} & C_{d22} & C_{d23}\\ C'_{d13} & C'_{d23} & C_{d33}\end{pmatrix}. \tag{3}$$

The information matrix for the total effects ϕ may be obtained from $C_d(\theta)$ by the following extremal representation proposed by Gaffke (1987):

$$C_d(\phi)=\min_{L\in\mathbb{R}^{3t\times t}:L'K=I_t} L'C_d(\theta)L, \tag{4}$$

where the minimum, which exists and is unique, is taken relative to the Loewner ordering. We recall that, for two $t\times t$ symmetric matrices M and N, $M\le N$ relative to the Loewner ordering means that $u'Mu\le u'Nu$ for any t-vector u.

Lemma 1. *The row and column sums of $C_d(\phi)$ are zero, i.e. $C_d(\phi)\mathbb{1}_t=0$.*

Proof. It is equivalent to prove that $\mathbb{1}_t'C_d(\phi)\mathbb{1}_t=0$. Since $T_d\mathbb{1}_t=\mathbb{1}_n$ and $\omega_B^{\perp}\mathbb{1}_n=0$, we have $\mathbb{1}_t'C_{d11}\mathbb{1}_t=0$. Consider $L_1=(I_t|0_t|0_t)'$ where 0_t is the $t\times t$ zero matrix. L_1 satisfies the constraint $L'_1K=I_t$. Therefore, from (4), $\mathbb{1}_t'C_d(\phi)\mathbb{1}_t\le\mathbb{1}_t'L'_1C_d(\theta)L_1\mathbb{1}_t=\mathbb{1}_t'C_{d11}\mathbb{1}_t=0$. □

The definition of $C_d(\phi)$ given by (4) does not provide an explicit expression. Especially, the matrix L^* that achieves the minimum has usually an untractable form (see Pukelsheim, 1993, Chapter 3).

A design d is said to be *symmetric* if all its matrices C_{dij} are completely symmetric, i.e. if $C_{dij}=(a_{ij}I_t+b_{ij}J_t)$ for some scalars a_{ij} and b_{ij}. Note that this definition of symmetric design is more general than Kushner' (1997) one which requires invariances