Optimal crossover designs under a general model

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Abstract: Some assumptions are implicit in the traditional model used for studying the optimality properties of cross-over designs. Many of these assumptions might not be satisfied in experimental situations where these designs are to be applied. In this paper, we modify the model by relaxing these assumptions and show a class of designs to be universally optimal under the modified model.

Key words and phrases : Direct effects, carry-over effects of k-th order, interactions, random subject-effect, calculus for factorial arrangements, universal optimality.

1. Introduction

In cross-over designs, a number of experimental subjects are exposed to the treatments under study applied sequentially over some time periods, and in addition to the direct effect of a treatment in the period of application, there is also the possible presence of the carry-over effect(s) of a treatment in one (or more) subsequent periods. These designs are widely used in clinical trials and also in agricultural field trials, dairy experiments and in many other areas of experimental research.

The optimality properties of these designs have been extensively studied in the literature. We refer to Stufken(1996) for a review of these results. Most of the available optimality results are based on the following model of Cheng and Wu(1980).

$$Y_{ij} = \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \rho_{d(i-1,j)} + e_{ij}; \quad i = 1 \ldots, p; \quad j = 1, \ldots, n; \;\; \rho_{d(0,j)} = 0 \qquad (1)$$

where μ, α_i and β_j represent the general mean, the i-th period effect and the jth subject effect; $d(i,j)$ denotes the treatment assigned to the j-th subject in the i-th period, Y_{ij} is the response under $d(ij)$, τ_h and ρ_h are the direct effect and first-order carry-over effect of treatment h respectively and e_{ij} is the error.

Model(1) makes the following four main assumptions:

1. Carry-over effects stop after the first period.
2. There is no interaction between the treatments applied in successive periods to the same subject.
3. The subject effects are fixed effects.
4. The errors are independent with mean zero and constant variance.

Clearly, in situations where these designs are used, specially in the recent applications of these designs, one or more of these assumptions are likely to be violated. The first assumption is untenable

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in situations where the effect of a treatment does not die out abruptly after one period, which is often the case when the interval between successive time periods is small. Regarding assumption 2, it is known that in many situations the successive treatments do interact and possibly the earliest data set reflecting this is in John and Quenouille (1977, pp 211-213). In experiments where the subjects are a random sample of possible subjects, assumption 3 will be invalid. Finally, since the same subject is giving rise to a set of observations over time, it is unlikely that all these observations will be uncorrelated.

It seems that no study is available in the literature under a model where all the above 4 assumptions are *simultaneously* relaxed. In this paper, we first propose a modified version of model (1) for which *all* the above assumptions are removed. Then, under this modified model, a class of designs is shown to be universally optimal for direct effects in the class of all cross-over designs with the same set of parameters.

2. Modified model and optimality

The proposed modified model is:

$$Y_{ij} = \mu + \alpha_i + \beta_j + \eta_{d(i,j)d(i-1,j),\ldots,d(i-k,j)} + e_{ij}, \quad k \le i \le p-1, 1 \le j \le n;$$

$$Y_{ij} = \mu + \alpha_i + \beta_j + \eta_{d(i,j)d(i-1,j),\ldots,d(0,j)} + e_{ij}, \quad 0 \le i \le k-1, \ 1 \le j \le n, \tag{2}$$

where μ, α_i are as in (1), β_j is the random subject effect. We assume that the carry-over effect of a treatment can persist for upto $k \ge 1$ periods, say, and there can be possible interaction among succssive treatments for upto k periods. For simplicity of notation, we use one term, viz, $\eta_{d(i,j),\ldots,d(i-k,j)}$ to denote the sum of the direct effect of treatment $d(i,j)$, the first order carry-over effect of $d(i-1,j),\ldots$, the k-th order carry-over effect of $d(i-k,j)$ and all the interaction effects between the treatments $d(i,j),\ldots,d(i-k,j)$.

We assume that $\beta = (\beta_1,\ldots,\beta_n)'$ and $e = (\ldots,e_{ij},\ldots)'$ are independently distributed with variance matrices $\sigma^2_\beta I_n$ and $\sigma^2_e I_n$, respectively, where I_a is the $a \times a$ identity matrix. This gives a resultant error structure where observations from the same subject are correlated while observations from different subjects are uncorrelated. This seems a more reasonable error structure for these designs than that of independent errors as in model (1.1).

Clearly, model given by (2) relaxes all the assumptions 1, 2, 3 and 4 of model (1).

Remark 2.1 With model(2), the practitioner now has the freedom to choose k according to the experimental conditions. If we put $k = 1$, ignore the interactions, take β to be fixed effects and assume independent and homoscedastic errors, model(2) reduces to the standard model (1).

Let $\Omega_{t,n,p}$ be the class of all cross-over designs with t treatments, n experimental subjects and p time periods. Following Bose and Mukherjee(2000), a design in $\Omega_{t,n,p}$ is studied as a t^{k+1} factorial arrangement in a $p \times n$ array where the direct and the $(i-1)$-th order carry-over effects are interpreted as the main effect of factor F_1 and F_i respectively, and their different interactions are interpreted as the factorial interactions between the factors $F_1, F_2, \ldots, F_{k+1}$. While initially our formulation of the problem is influenced by that of Bose and Mukherjee(2000), considerable additional work is needed to incorporate the present setting. For example, model(2) is different from that in Bose and Mukherjee(2000) and so expressions like (3),(4),(5) do not arise in their set-up and as a consequence, the subsequent development in this paper is different from theirs. Model(2) is rewritten as follows in a form suitable for factorial treatments so that the Kronecker Calculus for factorial arrangements, as introduced by Kurkjian and Zelen (1962), may be used.

$$E(Y) = X\theta, \quad D(Y) = \sum \tag{3}$$

where $Y = (Y_{01}, Y_{11}, \ldots, Y_{p-11}, Y_{02}, \ldots, Y_{p-12}, \ldots, Y_{0n}, \ldots Y_{p-1n})$, X is the design matrix, $\theta = (\mu, \alpha_0, \ldots, \alpha_{p-1}, \eta_{00\ldots0}, \eta_{00\ldots1}, \ldots, \eta_{t-1,t-1,\ldots,t-1})'$, $\sum = diag(A, \ldots, A)$, $A = \sigma_e^2 I_p + \sigma_\beta^2 1_p 1_p'$ and 1_p is the $p \times 1$ unit vector. In (3), $E(.)$ stands for the expectation operator and $D(.)$ for the dispersion matrix.

After considerable algebra using properties of Kronecker product of matrices, it may be shown that under model (2), for a design $d\epsilon\Omega_{t,n,p}$, the coefficient matrix C_d of the reduced normal equations for η is given by

$$\begin{aligned} C_d \;=\; & \frac{1}{\sigma_e^2}\sum_{i=0}^{p-1}\sum_{j=1}^{n}\lambda_{ij}\lambda_{ij}' - a\sum_{j=1}^{n}(\sum_{i=0}^{p-1}\lambda_{ij})(\sum_{i=0}^{p-1}\lambda_{ij}') \\ & -\frac{1}{n\sigma_e^2}N_dN_d' - \frac{a^2\sigma_\beta^2}{n}G_d1_p1_p'G_d' - \frac{a^2\sigma_e^2}{n}G_dG_d' \\ & -\frac{\sigma_\beta^2}{n\sigma_e^4}N_d1_p1_p'N_d' + \frac{\sigma_\beta^2}{n\sigma_e^2}aN_d1_p1_p'G_d' \\ & +\frac{a}{n}N_dG_d' + \frac{\sigma_\beta^2}{n\sigma_e^2}aG_d1_p1_p'N_d' + \frac{a}{n}G_dN_d', \end{aligned} \tag{4}$$

where $a = \sigma_e^2\sigma_\beta^{-1}(\sigma_e^2 + p\sigma_\beta^2)^{-1}$,

$$\begin{aligned} \lambda_{ij} \;&=\; \nu_{d(i,j)} \otimes \nu_{d(i-1,j)} \otimes \ldots \otimes \nu_{d(i-k,j)}, k \le i \le p-1, 1 \le j \le n, \\ &=\; \nu_{d(i,j)} \otimes \nu_{d(i-1,j)} \otimes \ldots \otimes \nu_{d(0,j)} \otimes \left\{\Pi \otimes t^{-1}1_t\right\},\; 0 \le i \le k-1, 1 \le j \le n, \end{aligned}$$

$$G_d = (\sum_{i=0}^{p-1}\sum_{j=1}^{n}\lambda_{ij}, \ldots, \sum_{i=0}^{p-1}\sum_{j=1}^{n}\lambda_{ij}), \tag{5}$$

$$N_d = (\sum_{j=1}^{n}\lambda_{0j}, \ldots, \sum_{j=1}^{n}\lambda_{p-1,j}). \tag{6}$$

and $\Pi\otimes$ denotes the Kronecker product of $(k-i)$ terms, ν_m is a $t \times 1$ vector with 1 in the m-th position and zero elsewhere.

Let d_1 be a design in $\Omega_{t,n,p}$ in which each treatment is applied equally often to a subject and equally often in a period and in which each subset of $2, 3, \ldots, k+1$ consecutive periods contains each 2-plet, 3-plet, $\ldots, (k+1)$-plet of treatments equally often. Theorem 2.1 establishes the universal optimality of d_1 under model (2). For the definition of universal optimality we refer to Kiefer (1975).

Theorem 3.1 Under the model(2), d_1 is universally optimal for the separate estimation of full sets of orthonormal contrasts of direct effects, over $\Omega_{t,n,p}$.

Proof : It is enough to show that the factorial experiment corresponding to d_1 is universally optimal for estimating full sets of orthonormal contrasts of main effect F_1. By a result in Mukerjee(1980), in d_1, the contrasts belonging to main effect F_1 will be estimable orthogonally to those belonging to all other main effects and interaction effects if $Z_1 C_{d_1}$ is symmetric, where Z_1 is the Kronecker product of $k+1$ matrices given by $Z_1 = E_t \otimes I_t \otimes I_t \ldots \otimes I_t,\ E_t = 1_t 1_t,\ I_t$ is the identity matrix of order t.

On simplification, using (5),(6) and the definition of d_1, we can show that for the design d_1,

$$\begin{aligned} Z_1 \sum_{i=0}^{p-1} \sum_{j=1}^{n} \lambda_{ij} \lambda'_{ij} &= Z_1 (\frac{n}{t^{2k+1}} [I_t \otimes E_t \otimes \ldots \otimes E_t] \\ &+ \frac{n}{t^{2k}} [I_t \otimes I_t \otimes E_t \otimes \ldots \otimes E_t] + \ldots \\ &+ \frac{n}{t^{k+2}} [I_t \otimes I_t \otimes \ldots \otimes I_t \otimes E_t] + \frac{n(p-k)}{t^{k+1}} [I_t \otimes \ldots \otimes I_t]) \\ &= \tfrac{np}{t^{k+1}} (I_t \otimes E_t \otimes \ldots \otimes E_t) \end{aligned} \qquad (7).$$

$$\begin{aligned} Z_1 \sum_{j=1}^{n} (\sum_{i=0}^{p-1} \lambda_{ij})(\sum_{i=0}^{p-1} \lambda'_{ij}) &= \sum_{j=1}^{n} \frac{p}{t} (1_t \otimes \ldots \otimes 1_t)(\sum_{i=0}^{p-1} \lambda'_{ij}) \\ &= \frac{np^2}{t^{k+2}} (E_t \otimes E_t \otimes \ldots \otimes E_t) \end{aligned} \qquad (8)$$

$$\begin{aligned} &Z_1 N_{d_1} N'_{d_1} = \frac{n^2 p}{t^{k+2}} (E_t \otimes \ldots \otimes E_t),\ Z_1 N_{d_1} G'_{d_1} = \frac{n^2 p^2}{t^{k+2}} (E_t \otimes \ldots \otimes E_t) \\ &G_{d_1} G'_{d_1} = \frac{n^2 p^3}{t^{2k+2}} (E_t \otimes E_t \otimes \ldots \otimes E_t),\ N_{d_1} E_p N'_{d_1} = \frac{n^2 p^2}{t^{2k+2}} (E_t \otimes E_t \otimes \ldots \otimes E_t) \\ &G_{d_1} E_p G'_{d_1} = \frac{n^2 p^4}{t^{2k+2}} (E_t \otimes \ldots \otimes E_t),\ N_{d_1} E_p G'_{d_1} = \frac{n^2 p^3}{t^{2k+2}} (E_t \otimes \ldots \otimes E_t) \end{aligned} \qquad (9).$$

From (4), (7), (8) and (9), it follows that $Z_1 C_{d_1}$ is symmetric and so, in d_1, direct effect contrasts are estimable orthogonally to contrasts belonging to all other effects. Hence, using standard notations it follows that

$$C_{d_1(direct)} = P^{10\ldots0} C_{d_1} (P^{10\ldots0})',\ C_{d(direct)} \leq P^{10\ldots0} C_d (P^{10\ldots0})' \qquad (10)$$

for all $d \epsilon \Omega_{t,n,p}$, where the coefficient matrix of the reduced normal equations for the full set of orthonormal contrasts belonging to direct effects in a design $d \epsilon \Omega_{t,n,p}$ is denoted by $C_{d(direct)}$, and $P^{10\ldots0} = P \otimes \frac{1'_t}{\sqrt{t}} \otimes \ldots \otimes \frac{1'_t}{\sqrt{t}}$, where P is such that $(\frac{1_t}{\sqrt{t}}, P')'$ is orthogonal.

Again, using (7),(8) and (9), $C_{d_1(direct)}$ as in (10) simplifies to the form

$$C_{d_1(direct)} = \alpha [I_t \otimes \ldots \otimes I_t], \qquad (11)$$

where α is a constant, being a function of n, p, t and k. Thus, $C_{d_1(direct)}$ is completely symmetric.

From (4), (7), (10) and (11) it follows after considerable algebra that d_1 maximizes $trace(C_{d(direct)})$ over $d \epsilon \Omega_{t,n,p}$.

Hence, d_1 satisfies the sufficient conditions for universal optimality as given in Kiefer (1975) and the theorem is proved.

Remark 3.2. Theorem 3.1 is quite general in the sense that the class of competing designs include all designs in $\Omega_{t,n,p}$. The size of d_1 naturally becomes larger than that required for optimality under the model (1), because the simplifying assumptions of (1) are removed and d_1 is optimal under more general conditions. The actual size of d_1 depends on the value of k to be used in the model. The higher the order of carry-over effects present in the experiment, the larger will be the design. It is expected that in most experiments k will be moderate and so the design will not be very large.

The following is an example of a design $d_1 \epsilon \Omega_{2,8,6}$ with $k = 2$. The design is written with periods as rows and subjects as columns.

0 0 0 0 1 1 1 1
0 1 0 1 0 1 0 1
0 1 1 0 0 1 1 0
1 1 1 1 0 0 0 0
1 0 1 0 1 0 1 0
1 0 0 1 1 0 0 1

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