SOME SMALL AND EFFICIENT CROSS - OVER DESIGNS UNDER A NONADDITIVE MODEL

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ABSTRACT. Under a general non-circular, non-additive model which allows for the possible presence of interactions among treatments applied in successive periods, small cross-over designs are proposed. The proposed designs are shown to be optimal for the estimation of carry-over effects while being highly efficient for the direct effects under the stated model. The results are shown to be robust under a random-subject-effect model. Cheng and Wu [2] showed that these designs are optimal for both direct and carry-over effects under an additive model. Our results show that their result for carry-over effects remains robust under non-additive models and also under random-subject effects.

1. Introduction

Cross-over designs are used for experiments in which each of the experimental subjects or units receives different treatments successively over a number of time periods. These designs are widely used in clinical trials, learning experiments, animal feeding experiments, and agricultural field trials and in several other areas of experimental research.

A distinctive feature of cross-over experiments is that an observation is affected not only by the direct effect of a treatment in the period in which it is applied, but also by the effect of a treatment applied in an earlier period. That is, the effect of a treatment might also carry over to one or more of the subsequent time periods following the time of its application. The possible presence of this carry-over effect complicates the design and analysis of such experiments. An excellent review of the literature on the subject is by Stufken [20].

The study of optimality aspects of cross-over designs was initiated by Hedayat and Afsarinejad [6]. Cheng and Wu [2], Magda [13], Kunert [9,10] Stufken [19] and others studied the optimality properties of these designs

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under simple additive models, with no possible interactions among the treatments applied in successive periods.

The available cross-over designs which are optimal over a wide class of competing designs, are often quite large. However, in most experimental situations, notably in clinical trials, the number of available experimental subjects is usually quite small and the experiment cannot be continued for a large number of periods. To overcome this problem, this paper studies small efficient designs. To compare t treatments, these designs require only t subjects if t is even and t or $2t$ subjects if t is odd, and further require only $t+1$ periods. Under a model that incorporates interaction effects among direct and carry-over effects, as well as the individual direct and carry-over effects, these designs are shown to be universally optimal and hence A-, D- and E-optimal for the carry-over effects. Under the same model, these designs are highly efficient for the direct effects as well. Consideration of a non-additive model is motivated from practical considerations as, in many experimental situations, the interaction effects may also affect the response. Examples of data sets are given in John and Quenouille [7, p. 213] and Patterson [16], where such interaction effects are found to be statistically significant. In such situations, the assumption of absence of interaction may not be justified and a non-additive model seems more suitable.

The existence of these efficient designs is also discussed. Finally, we prove that all the above mentioned results are robust under a random-subject non-additive model. The proofs of the results rest heavily on the use of the Kronecker calculus, introduced by Kurkjian and Zelen [11]. For a review of the calculus in the context of complete and fractional factorials, see Gupta and Mukerjee [5] and Dey and Mukerjee [4] respectively.

Cheng and Wu [2] showed that the designs considered in this paper are universally optimal for the estimation of both direct and carry-over effects. Our results demonstrate that their result for the carry-over effects remains robust under the presence of interactions and also under random subject effects.

2. Model and Analysis

Let $\Omega_{t,n,p}$ be the class of all cross-over designs with t treatments applied to n units over p periods. We introduce the following model by incorporating interactions among direct effects and carry-over effects of the successive treatments applied to the same subject, into the usual model in the literature; see for example, Cheng and Wu [2].

Consider a cross-over experiment with t treatmnts applied to n experimental units over p time periods and let $d(i,j)$ denote the treatment applied to the jth unit at the ith period, $i = 0, 1, \ldots, p-1$; $j = 1, 2 \ldots, n$. Then the non-additive model is given by :

$$E(Y_{0j}) = \mu + \alpha_0 + \beta_j + \tau_{d(0,j)},\ j = 1, \ldots, n,$$

and for $i = 1, \ldots, p-1,\ j = 1, \ldots, n,$

$$E(Y_{ij}) = \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \rho_{d(i-1,j)} + \gamma_{d(i,j),d(i-1,j)}, \qquad (1),$$

where $\mu, \alpha_i, \beta_j, \tau_{d(i,j)}, \rho_{d(i-1,j)}, \gamma_{d(i,j),d(i-1,j)}$ are respectively the general mean, the ith period effect, the jth unit effect, the direct effect due to treatment $d(i,j)$, the carry-over effect due to treatment $d(i-1,j)$ and the interaction effect between $d(i,j)$ and $d(i-1,j)$, $i = 1, \ldots, p-1$; $j = 1, 2, \ldots, n$, where we define $\rho_{d(0,j)} = \gamma_{d(1,j),d(0,j)} = 0$.

Under model (1), a direct extension of the usual method of analysis and proof as given in Cheng and Wu [2] becomes intractable. Instead, model (2) below can be conveniently studied by noting that cross-over designs may be looked upon as a t^2 factorial experiment with two factors, F_1, F_2, where the direct effects correspond to the main effect F_1, the carry-over effects correspond to the main effect F_2 and the direct versus carry-over interaction effect corresponds to the usual factorial interaction, F_1F_2. The advantage of this formulation is that now these designs may be analysed under model (2) by applying the calculus for factorial arrangements introduced by Kurkjian and Zelen [11].

Model (1) may be rewritten in the following equivalent form:

$$E(Y_{ij}) = \mu + \alpha_i + \beta_j + \lambda_{ij}'\xi,\ i = 0, \ldots, p-1,\ j = 1, \ldots, n, \qquad (2)$$

where the $t^2 \times 1$ vector $\xi = (\xi_{00}, \xi_{01}, \ldots, \xi_{t-1,t-1})'$ is the vector of the effects of t^2 factorial treatment combinations;

$$\lambda_{ij} = e_{d(i,j)} \otimes e_{d(i-1,j)},\ i = 1, \ldots, p-1;\ j = 1, \ldots, n, \qquad (3)$$

$$\lambda_{0j} = e_{d(0,j)} \otimes t^{-1}1_t,\ j = 1, \ldots, n, \qquad (4)$$

where for a pair of matrices A and B, $A \otimes B$ denotes their Kronecker product; $e_{d(i,j)}$ is a $t \times 1$ vector with 1 in the position corresponding to the treatment $d(i,j)$ and zero elsewhere and 1_t is a $t \times 1$ vector with all elements unity.

Let X_d denote the design matrix for a design d in $\Omega_{t,n,p}$ under model (2). Then, it can be shown from model (2) that $X_d'X_d$ is given by

$$X_d'X_d = \begin{bmatrix} np & n1_p' & p1_n' & \sum_{i=0}^{p-1}\sum_{j=1}^{n}\lambda_{ij}' \\ n1_p & nI_p & 1_p1_n' & N_d' \\ p1_n & 1_n1_p' & pI_n & M_d' \\ \sum_{i=0}^{p-1}\sum_{j=1}^{n}\lambda_{ij} & N_d & M_d & V_d \end{bmatrix}, \tag{5}$$

where

$$V_d = \sum_{i=0}^{p-1}\sum_{j=1}^{n}\lambda_{ij}\lambda_{ij}', \; N_d = (\sum_{j=1}^{n}\lambda_{0j}, \sum_{j=1}^{n}\lambda_{1j}, \ldots, \sum_{j=1}^{n}\lambda_{p-1j}) \tag{6}$$

$$M_d = (\sum_{i=0}^{p-1}\lambda_{i1}, \sum_{i=0}^{p-1}\lambda_{i2}, \ldots, \sum_{i=0}^{p-1}\lambda_{in}). \tag{7}$$

The matrices N_d and M_d in (5) are the treatment versus period and the treatment versus unit incidence matrices respectively, where the treatments are actually the t^2 treatment combinations in ξ.

From (5) it follows that the coefficient matrix of the reduced normal equations for estimating ξ from a design d in $\Omega_{t,n,p}$ is given by

$$C_d = V_d - \frac{1}{n}N_dN_d' - \frac{1}{p}M_dM_d' + \frac{1}{np}(N_d1_p)(N_d1_p)'. \tag{8}$$

Let P_t be a $(t-1)\times t$ matrix such that $(t^{-\frac{1}{2}}1_t,\ P_t')$ is orthogonal. Define

$$P^{01} = (t^{-\frac{1}{2}}1_t')\otimes P_t,\; P^{10} = P_t\otimes(t^{-\frac{1}{2}}1_t'),\; P^{11} = P_t\otimes P_t. \tag{9}$$

Note that $P^{01}\xi$, $P^{10}\xi$ and $P^{11}\xi$ together represent a complete set of orthonormal treatment contrasts.

Following Mukerjee [15], it can be shown that, for a design d in $\Omega_{t,n,p}$, the coefficient matrix of the reduced normal equations for estimating the carry-over effects is given by

$$A_d = P^{01}C_d\,(P^{01})' - (P^{01}\,C_d(P^{10})',\; P^{01}C_d(P^{11})')G^{-}\begin{pmatrix} P^{10}C_d(P^{01})' \\ P^{11}C_d(P^{01})' \end{pmatrix}, \tag{10}$$

where C_d is as in (8) and G^- is a generalised inverse of G given by

$$G = \begin{bmatrix} P^{10}C_d(P^{10})' & P^{10}C_d(P^{11})' \\ P^{11}C_d(P^{10})' & P^{11}C_d(P^{11})' \end{bmatrix}.$$

3. Optimality Results

We need the following definitions in the sequel.

Definition 3.1. *A design in $\Omega_{t,n,p}$ is called uniform if the treatments occur equally often in each period and also equally often in each unit.*

Definition 3.2. *Under model* (1), *a design d in $\Omega_{t,n,p}$ is called balanced if, in the order of application, no treatment is preceded by itself and each treatment is preceded by all other treatments equally often.*

Let d_1 be a design obtained by repeating the last row of a balanced uniform design. Thus, d_1 is an extra-period balanced design as defined in Lucas [12] and Patterson and Lucas [17]. The following theorem gives the optimality properties of d_1 under model (1).

Theorem 3.1. *Under model* (1), *a design d_1 in $\Omega_{t,n,p}$ is universally optimal for the separate estimation of residual effects in the class of all designs in $\Omega_{t,n,p}$.*

Proof. The proof of the theorem rests on the following two lemmas, the proofs of which are given in the Appendix.

Lemma 3.1. *For the design d_1, the matrix A_{d_1}, given by* (10) *with d replaced by d_1, is completely symmetric.*

Lemma 3.2. *The design d_1 maximises the trace of A_d among all designs d in $\Omega_{t,n,p}$.*

From Lemmas 3.1 and 3.2, it is clear that d_1 satisfies the sufficient conditions for universal optimality of a design as given by Kiefer [8], for the estimation of complete sets of orthonormal contrasts belonging to the carry-over effects. Hence the theorem is proved.

Remark 3.1. A design that is universally optimal over a class of competing designs is also, in particular, A-, D- and E-optimal over the same class of competing designs. Thus, the design d_1 is, in particular, A-, D- and E-optimal for carry-over effects in the class $\Omega_{t,n,p}$.

Remark 3.2. Cheng and Wu [2] showed that the designs d_1 are universally optimal for both carry-over and direct effects under an additive model. Theorem 3.1 shows that their result is robust for carry-over effects under the non-additive model as well. One can show however that under model (1), though d_1 remains universally optimal for the carry-over effects, it does not necessarily remain universally optimal for the estimation of the direct or the interaction effects. It can be shown using a necessary and sufficient condition for inter-effect orthogonality in Mukerjee [15] that while, under a model with no interactions, the design d_1 permits the estimation of direct and carry-over effects orthogonally in the sense that the best linear unbiased estimator of a contrast among direct effects is uncorrelated with the best linear unbiased estimator of a contrast among carry over effects, this orthogonality does not hold under a model with interactions.

Remark 3.3. To evaluate the performance of d_1 for the separate estimation of direct effects, we compute the relative efficiency of estimation of the direct effects relative to the carry-over effects, based on the A-efficiency or the average variance criterion. Clearly, the upper bound of these efficiencies is unity. Table 1 lists the A-efficiencies of d_1 for some small values of t. From this table it is seen that the efficiency of d_1 for the estimation of direct effects is quite high. It follows then that the design d_1 is useful in the sense that, using this design, one can estimate the carry-over effects optimally and also estimate the direct effects with high efficiency, even in the presence of interactions.

Remark 3.4. The optimality result in Theorem 3.1 is quite general since the competing class, $\Omega_{t,n,p}$, is the class of all designs with t treatments, n units and p periods. As stated earlier, d_1 is also optimal under the weaker and more commonly used A-, D- and E- optimality criteria.

Table 1. *Relative A-efficiencies of direct effects*

No. of treatments	3	4	5	6
A-efficiency of direct effects	0.8136	0.9259	0.8771	0.9625

No. of treatments	7	8	9	10
A-efficiency of direct effects	0.9058	0.9783	0.9232	0.9847

4. Existence of optimal designs and some examples

For any t, the minimum values of n and p for which a design d_1 may exist are t and $t+1$ respectively. This is because, for a balanced uniform design to exist, it is necssary that

$$\text{(i) } p \equiv 0 (\text{mod } t); \text{ (ii) } n \equiv 0 (\text{mod } t) \text{ and (iii) } n(p-1) = \mu t(t-1),$$

where μ is a positive integer. The question of constructing uniform balanced designs in $\Omega_{t,t,t}$ is completely settled for t even, and is given by the $t \times t$ Williams' square [22]. Thus, repeating the last row of a Williams' square once, one can construct a design d_1 in $\Omega_{t,t,t+1}$, whenever t is an even integer.

When t is odd, no general result on the existence of a balanced uniform design in $\Omega_{t,t,t}$ is known. No such design exists for $t = 3, 5, 7$. Such designs for $t = 9, 15, 21$ and 27 were presented by Archdeacon *et al.* [1], who called these squares row complete Latin squares (now sometimes called Roman squares). Such squares can be constructed for $t = 39, 55, 57$ by methods described in Mendelsohn [14], Dénes and Keedwell [3] and Wang [21]. However, for all odd t, it has long been known that a uniform balanced design exists in $2t$ units and t periods (Williams [22]). It is now known that, for odd t, such uniform balanced designs exist in $3t$ units (and therefore in kt units for $k = 2, 3, 4, \ldots$); see Prescott [18]. It follows that, for all odd t, a design d_1 exists in $\Omega_{t,kt,t+1}$, $k = 2, 3, 4, \ldots$ and for some specific odd values of t, a design d_1 exists in $\Omega_{t,t,t+1}$. In Example 4.1, designs d_1 for some values of t are shown. The periods are given by the rows and the subjects by the columns.

Example 4.1.

$t = 3$

1	2	3	1	2	3
3	1	2	2	3	1
2	3	1	3	1	2
2	3	1	3	1	2

$t = 4$

1	2	3	4
4	1	2	3
2	3	4	1
3	4	1	2
3	4	1	2

$t = 5$

1	2	3	4	5	3	4	5	1	2
5	1	2	3	4	4	5	1	2	3
2	3	4	5	1	2	3	4	5	1
4	5	1	2	3	5	1	2	3	4
3	4	5	1	2	1	2	3	4	5
3	4	5	1	2	1	2	3	4	5

5. Robustness of the results under a random-subject-effect model

In analyzing data from cross-over experiments used in clinical trials, it is often desirable to assume the subject or patient effect to be a random variable. Under such an assumption, the non-additive random-subject-effect model is:

$$Y_{0j} = \mu + \alpha_0 + \beta_j + \tau_{d(0,j)} + \text{ error, for } j = 1, \ldots, n,$$

and for $i = 1, \ldots, p-1, j = 1, \ldots, n$

$$Y_{ij} = \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \rho_{d(i-1,j)} + \gamma_{d(i,j),d(i-1,j)} + \text{ error,} \tag{11}$$

where $\mu, \alpha_i, \beta_j, \tau_{d(i,j)}, \rho_{d(i-1,j)}, \gamma_{d(i,j),d(i-1,j)}$ are as in (1); and the vector of subject effects $\beta = (\beta_1, \beta_2, \ldots, \beta_n)'$ has the normal distribution, $N(0, \sigma_1^2 I_n)$, the error vector has the $N(0, \sigma^2 I_{np})$ distribution, β being independent of the error vector.

In consideration of Lemma 3.1, after some routine but lengthy algebra, the following result can be proved.

Lemma 5.1. *Under model* (11), *for any design* d *in* $\Omega_{t,n,p}$,

(a) *the matrix C_d is given by*

$$\begin{aligned} C_d &= \tfrac{1}{\sigma^2}V_d - \tfrac{\sigma_1^2}{n\sigma^4}N_d1_p1_p'N_d' + \tfrac{a\sigma_1^2}{n\sigma^2}N_d1_p1_p'H_d' - aM_dM_d' - \tfrac{1}{n\sigma^2}N_dN_d' \\ &+ \tfrac{a}{n}N_dH_d' + \tfrac{a\sigma_1^2}{n\sigma^2}H_d1_p1_p'N_d' - \tfrac{a^2\sigma_1^2}{n}H_d1_p1_p'H_d' + \tfrac{a}{n}H_dN_d' \\ &- \tfrac{a^2\sigma^2}{n}H_dH_d', \end{aligned} \tag{12}$$

where a is a constant involving the design parameters, σ and σ_1, $H_d = [N_d1_p, \cdots, N_d1_p\ ]$ is a $t \times p$ matrix and V_d, M_d, N_d are as in (6) *and* (7).

(b)

$$P^{01}M_{d_1}M_{d_1}' = 0,\ P^{01}N_{d_1} = 0,\ P^{01}H_{d_1} = 0.$$

It follows from (12) that $P^{01}C_{d_1} = mP^{01}V_{d_1}$ where m is a constant. Now, using steps similar to the proof of Theorem 3.1, the following result may be proved.

Theorem 5.1. *Under model* (11), *d_1 is universally optimal for the separate estimation of carry-over effects in the class of all designs in $\Omega_{t,n,p}$.*

Thus the results of Theorem 3.1 remain robust under the random-subject-effect model.

Remark 5.1. Theorems 3.1 and 5.1 show that the result of Cheng and Wu [2] mentioned in Remark 3.2 remains robust for carry-over effects under a model with random subject effects and with direct-vs-carryover interactions.

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Appendix

Proof of Lemma 3.1. From (6), (7) and Definitions 3.1 and 3.2, one can show that

$$V_{d_1} = nt^{-3}(I_t \otimes 1_t 1_t{}') + n(p-1)t^{-2} I_t \otimes I_t, \tag{A.1}$$

where for a positive integer s, I_s stands for the identity matrix of order s. Furthermore, we have

$$N_{d_1} 1_n = (npt^{-2})(1_t \otimes 1_t). \tag{A.2}$$

Recalling the definition of P^{01} from (9) and using (A.1) and (A.2), the following statements can be proved after some algebra:

$$P^{01} V_{d_1}(P^{01})' = n(p-1)t^{-2} I_{t-1}, \quad P^{01} V_{d_1}(P^{10})' = 0, \quad P^{01} V_{d_1}(P^{11})' = 0,$$

$$P^{01} N_{d_1} = 0,$$

$$P^{01}(N_{d_1} 1_n)(N_{d_1} 1_n')(P^{01})' = 0,$$

$$P^{01}(N_{d_1} 1_n)(N_{d_1} 1_n')(P^{10})' = P^{01}(N_{d_1} 1_n)(N_{d_1} 1_n')(P^{11})' = 0,$$

and

$$P^{01} M_{d_1} M_{d_1}' = 0.$$

By (10), we have $A_{d_1} = P^{01} C_{d_1}(P^{01})' = P^{01} V_{d_1}(P^{01})' = n(p-1)t^{-2} I_{t-1}$. Thus A_{d_1} is completely symmetric and the Lemma is proved.

Proof of Lemma 3.2. From (10) it is clear that $P^{01} C_d(P^{01})' - A_d$ is nonnegative definite for all d in $\Omega_{t,n,p}$. Again, as $V_d - C_d$ is nonnegative definite for all d in $\Omega_{t,n,p}$, $P^{01} V_d(P^{01})' - P^{01} C_d(P^{01})'$ is nonnegative definite for all such d. Hence,

$$\text{Trace}(A_d) \leq \text{Trace}(P^{01} V_d(P^{01})') = \text{Trace}(P^{01} C_{d_1}(P^{01})') = \text{Trace}(A_{d_1})$$

for all d in $\Omega_{t,n,p}$. This completes the proof.