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CROSS-OVER DESIGNS IN THE PRESENCE OF HIGHER ORDER CARRY-OVERS

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Summary

In cross-over experiments, where different treatments are applied successively to the same experimental unit over a number of time periods, it is often expected that a treatment has a carry-over effect in one or more periods following its period of application. The effect of interaction between the treatments in the successive periods may also affect the response. However, it seems that all systematic studies of the optimality properties of cross-over designs have been done under models where carry-over effects are assumed to persist for only one subsequent period. This paper proposes a model which allows for the possible presence of carry-over effects up to k subsequent periods, together with all the interactions between treatments applied at $k+1$ successive periods. This model allows the practitioner to choose k for any experiment according to the requirements of that particular experiment. Under this model, the cross-over designs are studied and the class of optimal designs is obtained. A method of constructing these optimal designs is also given.

Key words: calculus of factorial arrangements; carry-over effect of order k; cross-over designs; direct effects; interactions; strong balance of order k; universal optimality.

1. Introduction

Cross-over experiments are experiments in which various treatments are applied to each of the experimental units, successively over different time periods. The related designs are called cross-over designs. These designs are widely used in clinical trials, learning experiments, agricultural field trials and in several other areas of experimental research.

The distinctive feature of these designs is the possible presence of the 'carry-over' effects of a treatment in one or more of the subsequent periods, over and above its direct effect in the period in which it is applied. The pioneering work in this area was by Williams (1949, 1950) and now there is a vast literature on works in this area. For an excellent review of the literature we refer to Stufken (1996).

Earlier authors such as Patterson (1968, 1970, 1973), Lucas (1951, 1956, 1957), John & Quenouille (1977 pp. 196–220) studied the construction and analysis of these designs. In addition to the usual direct effect, they often considered carry-over effects which persisted beyond one period. They also included terms due to the interaction between the treatments applied in successive periods. For other interesting results in the area of cross-over designs we refer to Street & Street (1987), Street, Eccleston & Wilson (1990), Jones & Kenward (1990) and Russell & Dean (1998).

The optimality study of cross-over designs was initiated by Hedayat & Afsarinejad (1975, 1978). Cheng & Wu (1980), Magda (1980), Kunert (1984a,b, 1991), Stufken (1991) and others, studied the optimality properties of these designs under simpler additive models with carry-overs assumed to persist up to one period only and no possible interactions among the treatments applied in successive periods.

However, as remarked by John & Quenouille (1977 p. 198), the carry-over effect of any treatment may occur in any period of the experiment after the application of the treatment. Moreover, the interaction effects may also affect the response. Examples of datasets are given by John & Quenouille (1977 p. 213) and Patterson (1970) who found such effects to be statistically significant, but it seems that no systematic optimality study within sufficiently general classes is available in the literature for this general situation. In this paper, we form a general model based on the usual model for optimality studies, by incorporating the additional presence of carry-over effects up to, say, k subsequent periods, together with possible interactions among the successive treatments applied in these periods to the same subject. This general model gives the practitioner the freedom to choose a value for k depending upon the specific model requirements of the particular experiment under study.

In Section 2, we formulate the general model with carry-overs up to general order k and interactions. The developments in Sections 2 and 3 depend heavily on the Kronecker calculus for factorial arrangements.

In Section 3, we investigate optimality conditions for the separate estimation of direct effects in a very general class of designs. In Section 4, we give a method of constructing these optimal designs, with some examples. This method of construction illustrates that the conditions which are necessary for the existence of the optimal designs are also sufficient.

2. Model and analysis

Let $\Omega_{t,n,p}$ denote the class of all cross-over designs with t treatments applied to n units over p periods. Let $d(i, j)$ denote the treatment assigned by a design $d \in \Omega_{t,n,p}$ in the ith period, to the jth unit. Let Y_{ij} denote the response at the ith period from the jth subject.

Following the terminology of John & Quenouille (1977 p. 198), the carry-over effect occurring at the ith period following the period of application is called the ith order carry-over effect, $i = 1, 2, \ldots$. We introduce the following model by incorporating all carry-overs up to the kth order and all interactions among direct effects and carry-over effects of different orders and also the interaction between carry-over effects of different orders, into the usual model assumed in the literature.

The model is given by

$$\mathrm{E}(Y_{ij}) = \begin{cases} \mu + \alpha_i + \beta_j + \xi_{d(i,j),d(i-1,j),\ldots,d(i-k,j)} & (k \le i \le p-1, 1 \le j \le n), \\ \mu + \alpha_i + \beta_j + \xi_{d(i,j),d(i-1,j),\ldots,d(0,j)} & (0 \le i \le k-1,\ 1 \le j \le n), \end{cases} \quad (1)$$

where $\mu, \alpha_i, \beta_j, \xi_{h_1,h_2,\ldots,h_{k+1}}$ are respectively the general mean, the ith period effect, the jth unit effect and the effect produced when treatment h_1 is applied in the current period, h_2 in the immediately preceding period, $\ldots$, h_{k+1} in the kth preceding period ($0 \le h_1, h_2, \ldots, h_{k+1} \le t-1$). Here, $\xi_{d(i,j),d(i-1,j),\ldots,d(i-s,j)}$ stands for the sum of the direct effects of $d(i, j)$, the first order carry-over effect of $d(i-1, j), \ldots,$ the sth order carry-over effect of $d(i-s, j)$ and the interaction effects from order 2 to $s+1$ between these $s+1$ treatments.

Model (1) is a non-additive generalization of the model given in Cheng & Wu (1980), obtained by incorporating higher order carry-overs and interactions to it. This model may be useful to the practitioner who can now use an appropriate value for k to suit the experimental requirements. Similar models for the case $k = 3$ are used to analyse datasets, by John & Quenouille (1977 p. 213), Patterson (1970) and others.

Under model (1), a direct extension of the usual method of analysis and proof as given in Cheng & Wu (1980) become intractable. Instead, model (1) can be conveniently studied by first noting that cross-over designs may equivalently be looked upon as factorial experiments and then applying the calculus for factorial arrangements introduced by Kurkjian & Zelen (1962) to study these designs.

Consider $t^{k+1} = v$ treatment combinations of the form $(h_1, h_2, \ldots, h_{k+1})$, $0 \le h_1, \ldots, h_{k+1} \le t-1$, such that h_1 $(h_i, i = 2, \ldots, k+1)$ represents the treatment producing the direct effect $((i-1)$th order carry-over effect, $i = 2, \ldots, k+1)$ to an experimental unit. Thus a design in $\Omega_{t,n,p}$ can be looked upon as a symmetric t^{k+1} factorial experiment where the direct and the $(i-1)$th order carry-over effects of a treatment may be interpreted as the main effects of factors F_1 and F_i respectively, and the interactions between the treatments in the $k+1$ successive periods are given by the corresponding factorial interactions.

Noting this correspondence between cross-over designs and factorial experiments, model (1) may be written in the following equivalent form in the factorial context:

$$\mathrm{E}(Y_{ij}) = \mu + \alpha_i + \beta_j + \lambda_{ij}^{\mathsf{T}}\xi \qquad (0 \le i \le p-1,\ 1 \le j \le n), \tag{2}$$

where the $t^{k+1} \times 1$ vector

$$\xi = (\xi_{00\ldots0}, \xi_{00\ldots1}, \ldots, \xi_{00\ldots t-1}, \xi_{000\ldots010}, \xi_{00\ldots011}, \ldots, \xi_{t-1,0\ldots0}, \ldots, \xi_{t-1,t-1,\ldots,t-1})^{\mathsf{T}}$$

is the vector of the t^{k+1} treatment combinations,

$$\lambda_{ij} = e_{d(i,j)} \otimes e_{d(i-1,j)} \otimes \cdots \otimes e_{d(i-k,j)}, \qquad \text{for } k \le i \le p-1;\ 1 \le j \le n, \tag{3}$$

and for $0 \le i \le k-1,\ 1 \le j \le n$,

$$\lambda_{ij} = e_{d(i,j)} \otimes e_{d(i-1,j)} \otimes \cdots \otimes e_{d(0,j)} \otimes \{\Pi \otimes t^{-1} 1_t\}, \tag{4}$$

where $\otimes$ denotes Kronecker product, $\Pi\otimes$ denotes the Kronecker product of $(k-i)$ terms; $e_{d(i,j)}$ is a $t \times 1$ vector with 1 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

$$X^{\mathsf{T}}X = \begin{bmatrix} np & n1_p^{\mathsf{T}} & p1_n^{\mathsf{T}} & L_d^{\mathsf{T}} \\ n1_p & nI_p & 1_p1_n^{\mathsf{T}} & N_d^{\mathsf{T}} \\ p1_n & 1_n1_p^{\mathsf{T}} & pI_n & M_d^{\mathsf{T}} \\ L_d^{\mathsf{T}} & N_d & M_d & V_d \end{bmatrix}, \tag{5}$$

where

$$L_d = \sum_{i=0}^{p-1}\sum_{j=1}^{n} \lambda_{ij}, \qquad V_d = \sum_{i=0}^{p-1}\sum_{j=1}^{n} \lambda_{ij}\lambda_{ij}^{\mathsf{T}}, \tag{6}$$

$$N_d = \Big(\sum_{j=1}^{n} \lambda_{0j}, \sum_{j=1}^{n} \lambda_{1j}, \ldots, \sum_{j=1}^{n} \lambda_{p-1j}\Big), \quad M_d = \Big(\sum_{i=0}^{p-1} \lambda_{i1}, \sum_{i=0}^{p-1} \lambda_{i2}, \ldots, \sum_{i=0}^{p-1} \lambda_{in}\Big). \quad (7)$$

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^{k+1} 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

$$C_d = V_d - \frac{1}{n} N_d N_d^{\mathsf{T}} - \frac{1}{p} M_d M_d^{\mathsf{T}} + \frac{1}{np}(N_d 1_p)(N_d 1_p)^{\mathsf{T}}. \quad (8)$$

3. Optimality results

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 strongly balanced of order k if each consecutive subset of i periods in d contains each i-tuple of treatments equally often, $i = 2, \ldots, k+1$.*

Let a uniform strongly balanced design of order k in $\Omega_{t,n,p}$ be denoted by d_1.

The following two lemmas are used in the proof of the optimality result. Lemma 3.1 is from Mukerjee (1980). Lemma 3.2 follows from the condition for universal optimality in Kiefer (1975). For the definition of universal optimality we refer to Kiefer (1975).

Lemma 3.1. *In an s^m factorial experiment in a design d, the best linear unbiased estimators of contrasts belonging to a main effect $F_i, i = 1, \ldots, m$ are orthogonal to those of contrasts belonging to all other main effects and all order interactions if and only if $Z_i C_d$ can be expressed as a linear combination of Kronecker products of permutation matrices, where*

$$Z_i = \bigotimes_{a=1}^{m} U_a, \qquad U_a = \begin{cases} J_s & \text{if } a \neq i, \\ I_s & \text{if } a = i, \end{cases}$$

and $J_s = 1_s 1_s^{\mathsf{T}}$, I_s is the identity matrix of order s.

Thus, putting $i = 1$ in Lemma 3.1, one obtains the condition under which the best linear unbiased estimators of contrasts belonging to the direct effect are orthogonal to those of contrasts belonging to all order carry-over effects and interactions. Similarly, other values of i give the conditions of orthogonality of the $(i-1)$th order carry-over effect with all other effects.

For d in $\Omega_{t,n,p}$ let C_d^* be the coefficient matrix of the reduced normal equations for estimating a full set of orthonormal contrasts belonging to the direct effects. The expression of C_d^* involves a lot of notations and so is given in Lemma A.1 in the Appendix. Let tr(A) denote the trace of matrix A.

Lemma 3.2. *A design d_1 in $\Omega_{t,n,p}$ is universally optimal for the direct effects in $\Omega_{t,n,p}$ if it maximizes $\mathrm{tr}(C_d^*)$ over $\Omega_{t,n,p}$ and if $C_{d_1}^*$ is completely symmetric.*

The following theorem gives the optimality properties of d_1 under model (1).

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

Proof. By Lemma 3.1, the best linear unbiased estimators of contrasts belonging to direct effects are orthogonal to those of contrasts belonging to carry-over effects of different orders and also to interactions between direct and carry-overs and to interactions between the carry-over effects of different orders, if we can express $Z_1 C_{d_1}$ as a linear combination of Kronecker products of permutation matrices, where C_{d_1} is given by (8) and $Z_1 = (I_t \otimes J_t \otimes \cdots \otimes J_t)$.

From (7), (3) and (4),

$$N_{d_1} 1_p = \left(\sum_{j=1}^{n} \sum_{i=0}^{p-1} \lambda_{ij} \right) = \frac{np}{t^{k+1}} [1_t \otimes \cdots \otimes 1_t],$$

since d_1 is uniform. So,

$$Z_1 (N_{d_1} 1_p)(N_{d_1} 1_p)^{\top} = \frac{n^2 p^2}{t^{k+2}} (J_t \otimes \cdots \otimes J_t). \tag{9}$$

Similarly, from (3), (4) and (7), it follows after some algebra that

$$Z_1 N_{d_1} N_{d_1}^{\top} = \frac{n}{t} [1_t \otimes \cdots \otimes 1_t](N_{d_1} 1_p)^{\top} = \frac{n^2 p}{t^{k+2}} (J_t \otimes \cdots \otimes J_t), \tag{10}$$

$$Z_1 M_{d_1} M_{d_1}^{\top} = \frac{p}{t} [1_t \otimes \cdots \otimes 1_t](N_{d_1} 1_p)^{\top} = \frac{np^2}{t^{k+2}} [J_t \otimes \cdots \otimes J_t]. \tag{11}$$

Again, from (3) and (4),

$$\sum_{j=1}^{n} \lambda_{0j} \lambda_{0j}^{\top} = \frac{1}{t^{2k}} \left[\sum_{j=1}^{n} (e_{d_1(0,j)} e_{d_1(0,j)}^{\top}) \otimes J_t \otimes \cdots \otimes J_t \right] = \frac{n}{t^{2k+1}} [I_t \otimes J_t \otimes \cdots \otimes J_t],$$

since, because of uniformity on periods in d_1, each of the t treatments occurs a total of n/t times in the initial period over all the j subjects. Also, by Definition 3.2, it can be shown that

$$\begin{aligned} \sum_{j=1}^{n} \lambda_{1j} \lambda_{1j}^{\top} &= \sum_{j=1}^{n} \left[e_{d_1(1,j)} e_{d_1(1,j)}^{\top} \otimes e_{d_1(0,j)} e_{d_1(0,j)}^{\top} \otimes \frac{1_t 1_t^{\top}}{t^2} \otimes \cdots \otimes \frac{1_t 1_t^{\top}}{t^2} \right] \\ &= \frac{n}{t^{2k}} [I_t \otimes I_t \otimes J_t \otimes \cdots \otimes J_t], \end{aligned}$$

$$\sum_{j=1}^{n} \lambda_{2j} \lambda_{2j}^{\top} = \frac{n}{t^{2k-1}} [I_t \otimes I_t \otimes I_t \otimes J_t \otimes \cdots \otimes J_t],$$

$$\vdots \qquad \vdots$$

$$\sum_{j=1}^{n} \lambda_{k-1,j} \lambda_{k-1,j}^{\top} = \frac{n}{t^{k+2}} [I_t \otimes I_t \otimes \cdots \otimes I_t \otimes J_t],$$

$$\sum_{i=k}^{p-1} \sum_{j=1}^{n} \lambda_{ij} \lambda_{ij}^{\top} = \frac{n(p-k)}{t^{k+1}} [I_t \otimes \cdots \otimes I_t].$$

TABLE 1

Relative A-efficiencies of carry-over effects

Number of treatments	A-efficiency of carry-over effect of ith order relative to the direct effect			
	$i = 1, k = 2$	$i = 1, k = 3$	$i = 2, k = 2$	$i = 2, k = 3$
2	0.953	0.915	0.825	0.819
3	0.957	0.931	0.841	0.791
4	0.959	0.892	0.850	0.705

Hence, by (6), it follows that $Z_1 V_{d_1}$ is a linear combination of Kronecker products of I_t and J_t matrices. This, together with (9), (10), and (11), shows that with C_{d_1} as in (8), $Z_1 C_{d_1}$ can be expressed as a linear combination of Kronecker products of I_t and J_t matrices. This, in turn implies that $Z_1 C_{d_1}$ can be expressed as a linear combination of Kronecker products of permutation matrices. Thus, $Z_1 C_{d_1}$ satisfies the condition of Lemma 3.1. Now, by Lemma 3.1, it follows that in the design d_1, the estimates of direct effects contrasts are orthogonal to the estimates of contrasts belonging to the carry-overs and interactions.

From this, it can be shown that d_1 satisfies the conditions of Lemma 3.2. (See Lemma A.2 in the Appendix.) Hence, by Lemma 3.2, the theorem follows.

Remark 3.1. In Theorem 3.1, the optimality criterion is applied to the estimation of direct effects since, in most cross-over experiments, the primary objective is to study the direct effects of treatments, even though the models include a number of other effects which have to be taken into account when studying the direct effects. However, if one also wants to estimate the other residual and interaction effects separately, it can be shown that d_1, though optimal for the direct effects, does not remain optimal for the estimation of the carry-over or the interaction effects. This is because the condition of orthogonality, as given by Lemma 3.1, does not hold for these effects in d_1.

Remark 3.2. To evaluate the performance of d_1 for the separate estimation of residual effects, we compute the relative efficiency of estimation of the carry-over effects relative to the direct effects, based on the A-efficiency or the average variance criterion. The upper bound of these efficiencies is unity. Table 1 lists these A-efficiencies of d_1 for some values of t, k and i; it shows that the efficiency of d_1 for the estimation of carry-over effects is quite high because they are very close to unity. The efficiencies decrease as k increases and as the order of the carry-over increases. So the design d_1 is useful in the sense that, from this design, one can estimate the direct effects optimally and the residual effects with high efficiency.

Remark 3.3. The optimality result in Theorem 3.1 is quite general because the competing class is the class of all designs in $\Omega_{t,n,p}$. Moreover, as universal optimality is a very strong optimality criterion, design d_1 is also optimal under the weaker and more commonly used optimality criteria of A-, D-, E-optimality.

4. Construction of the optimal designs of order k in $\Omega_{t,n,p}$

By Definition 3.2, the conditions

$$t^{k+1} \mid n, \qquad t \mid p, \qquad p \geq (k+1)t \tag{12}$$

are necessary for the existence of the optimal design d_1 in $\Omega_{t,n,p}$. We give below a method of constructing d_1 in $\Omega_{t,t^{k+1},(k+1)t}$.

We first construct a $(k+1) \times t^k$ matrix G_{00} whose first two rows are given by

$$\begin{array}{ccccccccccccccc} 000 & \dots & 0 & 0 & 000 & \dots & 0 & 0 & \dots & 000 & \dots & 0 & 0 \\ 012 & \dots & t-2 & t-1 & 012 & \dots & t-2 & t-1 & \dots & 012 & \dots & t-2 & t-1\,. \end{array}$$

Then the other rows are filled up as follows: the t^k positions in the third row of G_{00} are grouped into t disjoint sets of t^{k-1} consecutive positions each. Let these sets be numbered $C_0, C_1, \dots, C_{t-1}$, respectively. For the third row, a symbol in any position in the set C_i is obtained by adding the symbol i, modulo t, to the element in the corresponding position in the second row of G_{00}, $i = 0, 1, \dots, t-1$.

The fourth row of G_{00} has t^k positions to be filled up. The t^{k-1} positions in the fourth row, corresponding to each of the sets C_j of the third row, are further divided into t subsets of t^{k-2} consecutive positions each, $j = 0, 1, \dots, t-1$. Let these subsets be numbered $D_{j0}, D_{j1}, \dots, D_{j,t-1}$, respectively. Then, the symbol in any position in the subset D_{ji} is obtained by adding the symbol i modulo t to the symbol in the corresponding position of C_j of the third row of G_{00}, $i = 0, 1, \dots, t-1$, $j = 0, 1, \dots, t-1$.

Continue this procedure until $(k+1)$ rows have been filled up and we get all the $(k+1)$ rows of G_{00}.

Now, let G_{i0} be the matrix obtained from G_{00} by adding the symbol i modulo t to all the symbols in the first row of G_{00}, keeping the other rows unchanged, $i = 1, \dots, t-1$.

Let $G_0 = (G_{00}, G_{10}, \dots, G_{t-1,0})$. Then $d_1 \in \Omega_{t,n,p}$ of order k is given by

$$\begin{bmatrix} G_0 \\ G_1 \\ \vdots \\ G_{t-1} \end{bmatrix},$$

where for $i = 1, \dots, t-1$, $G_i = G_0 + i 1_t 1^{\mathsf{T}}_{t^{k+1}}$, addition being done modulo t.

Remark 4.1. A design d_1 in the general class $\Omega_{t,n,p}$, where t, n, p satisfy (12), may be constructed by taking suitable copies of the design constructed above.

Remark 4.2. The above construction, together with Remark 4.1, shows that the conditions (12) are also sufficient and thus the issue of existence of d_1 is completely settled.

We illustrate the method by the following examples.

Example 1. To construct d_1 in $\Omega_{3,27,9}$ for $k = 2$:

$$G_{00} = \begin{bmatrix} 000000000 \\ 012012012 \\ 012120201 \end{bmatrix},$$

$$G_0 = \begin{bmatrix} 000 & 000 & 000 & 111 & 111 & 111 & 222 & 222 & 222 \\ 012 & 012 & 012 & 012 & 012 & 012 & 012 & 012 & 012 \\ 012 & 120 & 201 & 012 & 120 & 201 & 012 & 120 & 201 \end{bmatrix},$$

$$G_1 = \begin{bmatrix} 111 & 111 & 111 & 222 & 222 & 222 & 000 & 000 & 000 \\ 120 & 120 & 120 & 120 & 120 & 120 & 120 & 120 & 120 \\ 120 & 201 & 012 & 120 & 201 & 012 & 120 & 201 & 012 \end{bmatrix},$$

$$G_2 = \begin{bmatrix} 222 & 222 & 222 & 000 & 000 & 000 & 111 & 111 & 111 \\ 201 & 201 & 201 & 201 & 201 & 201 & 201 & 201 & 201 \\ 201 & 012 & 120 & 201 & 012 & 120 & 201 & 012 & 120 \end{bmatrix}.$$

The required design is given by

$$\begin{bmatrix} G_0 \\ G_1 \\ G_2 \end{bmatrix}.$$

Example 2. To construct d_1 in $\Omega_{2,16,8}$ for $k = 3$:

$$G_{00} = \begin{bmatrix} 00000000 \\ 01010101 \\ 01011010 \\ 01101001 \end{bmatrix}, \quad G_{10} = \begin{bmatrix} 11111111 \\ 01010101 \\ 01011010 \\ 01101001 \end{bmatrix},$$

$$G_0 = \begin{bmatrix} 0000000011111111 \\ 0101010101010101 \\ 0101101001011010 \\ 0110100101101001 \end{bmatrix}, \quad G_1 = \begin{bmatrix} 1111111100000000 \\ 1010101010101010 \\ 1010010110100101 \\ 1001011010010110 \end{bmatrix}.$$

The required design is given by

$$\begin{bmatrix} G_0 \\ G_1 \end{bmatrix}.$$

5. Concluding remarks

Using the model and the designs suggested in this paper, the experimenter can choose an appropriate value for k and thus allow for the presence of carry-overs up to the order which the experimenter believes to be suitable for the experimental conditions. The model and designs also allow for the presence of interaction terms. This is unlike previous studies in which the experimenter had to assume that the carry-over stopped after just one period and that there was no interaction between treatments.

Since the model is so general, the optimum designs under this model naturally turn out to be larger than the optimum designs under the simpler model. The actual number of units required to achieve this optimality increases with k. So, the size of the design for an experiment really depends on the number of carry-over terms which the experimenter believes to be present for that experiment. The smaller the value of k, the smaller the design.

Appendix

Lemma A.1 (Derivation of the expression of C_d^*, for a design d in $\Omega_{t,n,p}$). *Following the notation in Mukerjee (1980), let* P_t *be a* $(t-1)\times t$ *matrix such that* $(t^{-1/2}1_t, P_t^{\top})^{(t\times t)}$ *is orthogonal,* $P_t^{x_i} = t^{-1/2}1_t^{\top}$ *if* $x_i = 0$, *and* $P_t^{x_i} = P_t$ *if* $x_i = 1$. *For any vector* $x = (x_1, x_2, \ldots, x_{k+1}), x_i = 0, 1, \quad i = 1, 2, \ldots, k+1,$ *let* $P^x = P_t^{x_1} \otimes P_t^{x_2} \otimes \cdots \otimes P_t^{x_{k+1}}$. *Then* $P^{10\ldots0}\xi$ *is a full set of orthonormal contrasts belonging to the direct effects. Let* $P = \binom{P^{10\ldots0}}{P^y}$, *where* $y = (y_1, y_2, \ldots, y_{k+1}), \quad y_i = 0, 1, \ i = 1, \ldots, k+1, \ y \neq$

$(1, 0, \ldots, 0)$, $y \neq (0, 0, \ldots, 0)$. *Then, for* d *in* $\Omega_{t,n,p}$, *the coefficient matrix of the reduced normal equations for estimating* $P^{10\ldots0}\xi$ *is given by*

$$C_d^* = P^{10\ldots0}C_d(P^{10\ldots0})^\top - P^{10\ldots0}C_d(P^y)^\top [P^y C_d(P^y)^\top]^- P^y C_d(P^{10\ldots0})^\top, \qquad (A.1)$$

where C_d *is as in (8) and* $[A]^-$ *denotes the generalized inverse of a matrix* A.

Lemma A.2. *A design* d_1 *in* $\Omega_{t,n,p}$ *satisfies the conditions of Lemma 3.2.*

Proof. For the design d_1 in $\Omega_{t,n,p}$, $P^{10\ldots0}C_{d_1}(P^y)^\top = 0$ because in the proof of Theorem 3.1 it has been shown that in d_1 the estimates of direct effects contrasts are orthogonal to the estimates of contrasts belonging to carry-overs and interactions. Hence,

$$C_{d_1}^* = P^{10\ldots0}C_{d_1}(P^{10\ldots0})^\top. \qquad (A.2)$$

Note that $P^{10\ldots0}C_{d_1} = t^{-3k/2}P_t(I_t \otimes 1_t^\top \otimes \cdots \otimes 1_t^\top)Z^{10\ldots0}C_{d_1}$, and by (9), (10), (11) and the expressions for $\sum_{j=1}^n \lambda_{0j}\lambda_{0j}^\top$ derived in the proof of Theorem 3.1, it follows after some algebra that

$$Z^{10\ldots0}C_{d_1} = \frac{np}{t^{k+1}}\Big[\Big(I_t - \frac{1}{t}J_t\Big) \otimes J_t \otimes \cdots \otimes J_t\Big].$$

So, from (A.2), it follows on simplification that

$$C_{d_1}^* = \frac{np}{t^{k+1}} I_{t-1}, \qquad (A.3)$$

and hence $\mathrm{tr}(C_{d_1}^*) = np(t-1)/t^{k+1}$.

Now, from (A.1) it follows that for any d in $\Omega_{t,n,p}$, $P^{10\ldots0}C_d(P^{10\ldots0})^\top - C_d^*$ is non-negative definite. So,

$$\begin{aligned}
\mathrm{tr}(C_d^*) &\le \mathrm{tr}(P^{10\ldots0}C_d(P^{10\ldots0})^\top) \\
&\le \mathrm{tr}(P^{10\ldots0}V_d(P^{10\ldots0})^\top) \\
&= \mathrm{tr}(V_d(P^{10\ldots0})^\top P^{10\ldots0}) \\
&= \frac{1}{t^k}\,\mathrm{tr}\Big[V_d(I_t \otimes J_t \otimes \cdots \otimes J_t) - \frac{1}{t}V_d(J_t \otimes J_t \otimes \cdots \otimes J_t)\Big] \\
&= \frac{np(t-1)}{t^{k+1}}, \qquad (A.4)
\end{aligned}$$

after simplification using (3), (4) and the definition of V_d in (6).

From (A.3) and (A.4), $C_{d_1}^*$ is completely symmetric and for any d in $\Omega_{t,n,p}$, $\mathrm{tr}(C_d^*) \le \mathrm{tr}(C_{d_1}^*)$. This proves that d_1 satisfies the conditions of Lemma 3.2.

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