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Abstract

For a general cross-over design, combined intra-inter unit reduced normal equations for estimating linear functions of direct and residual effects are obtained under a mixed effects, non-additive model. The unit effects are considered as random and the model allows for possible interactions among treatments applied at successive periods. Several existing families of designs which are optimal under a fixed effects model are shown to be so under the considered mixed model as well.

Keywords : Mixed effects model; Calculus for factorial arrangements; Direct effects; Carry-over effects; Interactions; Balance; Universal optimality.

1 Introduction

Cross-over designs (also known as change over or, repeated measurements designs) are used for experiments in which each of the experimental subjects or, units receive different treatments successively over a number of time periods. These designs are widely used in several areas, viz., clinical trials, learning experiments, animal feeding experiments and agricultural field trials. 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 (or, residual) effect complicates the designing and analysis of such experiments. Considerable literature on the design and analysis of cross-over experiments is already available and for an excellent review of the literature, a reference may be made to Stufken (1996). Optimality aspects of cross-over designs under fixed effects additive models, with no possible interactions among the treatments applied in successive periods have been studied, among others, by Hedayat and Afsarinejad (1978), Cheng and Wu (1980), Kunert (1984), Stufken (1991) and Hedayat and Zhao (1990).

In this paper, we consider a mixed effects model with unit effects being treated as random. Consideration of such a model is motivated by the fact that in many practical situations, it is more reasonable to hypothesize that the units are a random sample from a population of units. For instance, in clinical trials, it is realistic to assume that the patients (subjects) are a random sample from a large population of patients and thus, it is reasonable to assume that patient effects are indeed random rather than fixed. Apart from the direct and first order residual effects, we also include in the model, the interaction between the treatments producing the direct and first order residual effects. A non-additive model is also motivated from practical considerations as in many experimental situations, the interaction effects may also affect the response. Data sets given in e.g., John and Quenouille (1977, p. 213) and Patterson (1970), show the presence of such interaction effects and, in such situations, a non-additive model seems more appropriate. Under such a mixed effects non-additive model, combined intra-inter unit reduced normal equations for estimating linear functions of direct and residual effects are obtained.

From the general expressions obtained in this paper, one can check the optimality of a given design under the considered mixed effects model. This verification becomes particularly simple for designs that are known to be universally optimal under a fixed effects model. Throughout, we consider only the first order residual effects (i.e., where the residual effect carries over only to the next succeeding period) and, 'optimality' means the universal optimality criterion of Kiefer (1975). It is shown that many of the existing results on optimal cross-over designs under a fixed effects, additive model as well as under a non-additive model, continue to hold under the mixed effects model also. In proving the results, we make use of the Kronecker calculus, introduced by Kurkjian and Zelen (1962). For a review of the calculus in the context of complete and fractional factorials, see Gupta and Mukerjee (1989) and Dey and Mukerjee (1999) respectively.

2 Model and combined analysis

Consider a cross-over experiment in which t treatments are compared via n experimental units over p time periods. An allocation of the t treatments to the np experimental positions is called a cross-over design. Let $\Omega_{t,n,p}$ be the class of all such cross-over designs. For a typical design $d \in \Omega_{t,n,p}$, let $d(i,j)$ denote the treatment applied to the jth unit at the ith period according to the design d, $i = 0, 1, \ldots, p-1;\ j = 1, 2 \ldots, n$. We postulate the following model :

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

and

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

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 first order residual or, carry-over effect due to treatment $d(i-1,j)$ and the interaction effect between $d(i,j)$ and $d(i-1,j)$, $i = 0, 1, \ldots, p-1,\ j = 1, 2, \ldots, n$, where we define $\rho_{d(0,j)} = \gamma_{d(1,j),d(0,j)} = 0$. It is further assumed that the vector of subject effects $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_n)'$ has the normal distribution

$N(\mathbf{0},\sigma_1^2 I)$, the error vector has the normal distribution $N(\mathbf{0},\sigma^2 I)$, and $\boldsymbol{\beta}$ is independent of the error terms. Here and in the rest of the paper, $\mathbf{0}$ denotes a null vector (or, a null matrix) and I_s, an identity matrix of order s. We shall drop the subscript s when the order is clear from the context. Also, A^- denotes an arbitrary generalized inverse of a matrix A.

Cross-over experiments can be conveniently studied by noting that these 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) given below, by applying the calculus for factorial arrangements introduced by Kurkjian and Zelen (1962).

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

$$E(Y_{ij}) = \mu + \alpha_i + \beta_j + \boldsymbol{\lambda}'_{ij}\boldsymbol{\xi}, \quad 0 \le i \le p-1, \quad 1 \le j \le n, \tag{2}$$

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

$$\boldsymbol{\lambda}_{ij} = \boldsymbol{e}_{d(i,j)} \otimes \boldsymbol{e}_{d(i-1,j)}, \quad 1 \le i \le p-1; \ 1 \le j \le n, \tag{3}$$

$$\boldsymbol{\lambda}_{0j} = \boldsymbol{e}_{d(0,j)} \otimes t^{-1}\mathbf{1}_t, \quad 1 \le j \le n, \tag{4}$$

where for a pair of matrices A, B, $A \otimes B$ denotes their Kronecker (tensor) product; $\boldsymbol{e}_{d(i,j)}$ is a $t \times 1$ vector with 1 in the position corresponding to the treatment $d(i,j)$ and zero elsewhere and for positive integral s, $\mathbf{1}_s$ is an $s \times 1$ vector with all elements unity.

For presenting the main result of this section, we need to introduce some notation. For a design $d \in \Omega_{t,n,p}$, define

$$V_d = \sum_{i=0}^{p-1}\sum_{j=1}^{n} \boldsymbol{\lambda}_{ij}\boldsymbol{\lambda}'_{ij}, \ V_d^* = \sum\sum \boldsymbol{\lambda}_{ij}Y_{ij}, \ N_d = (\sum_{j=1}^{n}\boldsymbol{\lambda}_{0j}, \sum_{j=1}^{n}\boldsymbol{\lambda}_{1j}, \ldots, \sum_{j=1}^{n}\boldsymbol{\lambda}_{p-1,j}) \tag{5}$$

$$N_d^* = (\sum_j Y_{0j}, \ldots, \sum_j Y_{p-1,j}), \ M_d = (\sum_{i=0}^{p-1}\boldsymbol{\lambda}_{i1}, \sum_{i=0}^{p-1}\boldsymbol{\lambda}_{i2}, \ldots, \sum_{i=0}^{p-1}\boldsymbol{\lambda}_{in}), \ M_d^* = (\sum_i Y_{i1}, \ldots, \sum_i Y_{in}). \tag{6}$$

Note that the matrices N_d and M_d above are the treatment versus period and the treatment versus unit incidence matrices respectively, where the treatments are actually the t^2 treatment combinations in $\boldsymbol{\xi}$. Also, let

$$C_d = V_d - n^{-1}N_dN_d' - p^{-1}M_dM_d' + (np)^{-1}(N_d\mathbf{1}_p)(N_d\mathbf{1}_p)'. \tag{7}$$

It can be verified that the matrix C_d in (7) is the coefficient matrix of the reduced normal equations for estimating linear functions of $\boldsymbol{\xi}$ under a design $d \in \Omega_{t,n,p}$ when the model is the usual fixed effects model. Furthermore, let $\omega_1 = \sigma^{-2}$ and $\omega_2 = (p(\sigma^2 + p\sigma_1^2))^{-1}$. Finally, let P_t be a $(t-1) \times t$ matrix such that $(t^{-\frac{1}{2}}\mathbf{1}_t, P_t')$ is orthogonal. Define

$$P^{01} = (t^{-\frac{1}{2}}\mathbf{1}_t') \otimes P_t, P^{10} = P_t \otimes (t^{-\frac{1}{2}}\mathbf{1}_t'), P^{11} = P_t \otimes P_t. \tag{8}$$

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

Under the stated assumptions on the vector $\boldsymbol{\beta}$ and the error terms, we now have the following result, a proof of which appears in the Appendix.

Theorem 1. *The combined intra-inter unit reduced normal equations for estimating linear functions of the elements of* $\boldsymbol{\xi}$*, using a design* $d \in \Omega_{t,n,p}$ *are given by*

$$(\omega_1 C_d + \omega_2 C_d^*)\boldsymbol{\xi} = (\omega_1 \boldsymbol{Q}_d + \omega_2 \boldsymbol{Q}_d^*), \tag{9a}$$

where

$$C_d^* = M_d M_d' - n^{-1}(M_d \mathbf{1})(M_d \mathbf{1})', \tag{9b}$$

$$Q_d = V_d^* - n^{-1} N_d N_d^{*\prime} - p^{-1} M_d M_d^{*\prime} + (np)^{-1}(M_d \mathbf{1}_n)(M_d^* \mathbf{1}_n)',$$

and

$$Q_d^* = M_d M_d^{*\prime} - n^{-1}(M_d \mathbf{1}_n)(M_d^* \mathbf{1}_n)'.$$

3 Optimal designs under the mixed model

Writing $C_{md} = (\omega_1 C_d + \omega_2 C_d^*)$, it is clear from (9a) that C_{md} is the mixed model analogue of the information matrix C_d as given by (7) for the fixed effects model. For determining optimal designs under the considered mixed model, we assume ω_1 and ω_2 to be known and, under this assumption, the optimality results of this section are valid for *all* $\omega_1,\ \omega_2$.

When the model is as in (1), i.e., when the interactions are included in the model, together with the direct and first order residual effects, then starting from the matrix

$$\begin{pmatrix} P^{10} \\ P^{01} \\ P^{11} \end{pmatrix} \quad C_{md} \quad ((P^{10})', (P^{01})', (P^{11})'),$$

the information matrices for estimating complete sets of orthonormal contrasts belonging to direct and residual effects are respectively given by

$$\begin{aligned} C_{d(\mathrm{dir})} \quad &= \quad P^{10} C_{md} (P^{10})' - \\ &[P^{10} C_{md} (P^{01})' \;\; P^{10} C_{md} (P^{11})'] \begin{bmatrix} P^{01} C_{md} (P^{01})' & P^{01} C_{md} (P^{11})' \\ P^{11} C_{md} (P^{01})' & P^{11} C_{md} (P^{11})' \end{bmatrix}^{-} \begin{bmatrix} P^{01} C_{md} (P^{10})' \\ P^{11} C_{md} (P^{10})' \end{bmatrix}, \end{aligned} \tag{10}$$

and

$$
\begin{aligned}
C_{d(\mathrm{res})} &= P^{01}C_{md}(P^{01})' - \\
&\quad [P^{01}C_{md}(P^{10})' \;\; P^{01}C_{md}(P^{11})'] \begin{bmatrix} P^{10}C_{md}(P^{10})' & P^{10}C_{md}(P^{11})' \\ P^{11}C_{md}(P^{10})' & P^{11}C_{md}(P^{11})' \end{bmatrix}^{-} \begin{bmatrix} P^{10}C_{md}(P^{01})' \\ P^{11}C_{md}(P^{01})' \end{bmatrix}.
\end{aligned}
\tag{11}
$$

In order to verify if a given design d_0 is universally optimal for direct effects (residual effects) in the sense of Kiefer (1975) in a certain class of competing designs $\mathcal{D}$, one has to check the conditions of complete symmetry and maximum trace of $C_{d(\mathrm{dir})}(C_{d(\mathrm{res})})$ in $\mathcal{D}$. Such a verification becomes considerably simple if it is known that the design $d_0 \in \mathcal{D}$ is universally optimal under a fixed effects model over $\mathcal{D}$. In that case, using the results under a fixed effects model based on C_{d_0}, the information matrix of d_0, and noting that C_{md_0} is a linear combination of C_{d_0} and $C^*_{d_0}$, it can often be checked after some simple algebra whether the optimal properties of d_0 remain robust under the corresponding mixed effects model. In what follows, we illustrate this discussion via some examples. To make the presentation self-contained, we recall some definitions.

Definition 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 2. *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.*

Definition 3. *A design d in $\Omega_{t,n,p}$ is called strongly balanced if, in the order of application, each treatment is preceded by itself and all other treatments equally often.*

We also let $\Lambda_{t,n,p}$ to denote the subclass of $\Omega_{t,n,p}$ containing all designs in which no treatment is preceded by itself.

Most of the known optimality results on cross-over designs are based on an additive model with no direct versus residual interactions. The corresponding mixed model is an additive version of the model (1) containing no interactions, which we shall denote by model (1$'$). Under (1$'$), it is clear that the information matrices for direct and residual effects are respectively given by the simplified versions of (10) and (11) respectively, with the terms involving P^{11} omitted. For example, under (1$'$), we have

$$
\begin{aligned}
C_{d(\mathrm{dir})} &= \omega_1 P^{10}C_d(P^{10})' + \omega_2 P^{10}C^*_d(P^{10})' \\
&- [\omega_1 P^{10}C_d(P^{01})' + \omega_2 P^{10}C^*_d(P^{01})'] \times \\
&\quad [\omega_1 P^{01}C_d(P^{01})' + \omega_2 P^{01}C^*_d(P^{01})']^{-}[\omega_1 P^{10}C_d(P^{10})' + \omega_2 P^{10}C^*_d(P^{10})'].
\end{aligned}
\tag{12}
$$

A similar expression can also be obtained for $C_{d(\mathrm{res})}$ under the stated model (1$'$).

In the following theorems, we show that many of available results on optimality of a cross-over design under a *fixed* effects model remain robust under a corresponding *mixed* effects model. The appropriate references for the fixed-effects results under a additive model corresponding to each of the theorems is given in the parentheses.

Theorem 2 (Cheng and Wu, 1980; Theorem 3.1). *For $n = \lambda_1 t^2, p = \lambda_2 t, \lambda_1 \geq 1, \lambda_2 \geq 2$, let d_0 be a strongly balanced uniform design in $\Omega_{t,n,p}$. Then, under model* (1)*, d_0 is universally optimal for the estimation of complete sets of orthonormal contrasts belonging to direct effects over $\Omega_{t,n,p}$. Furthermore, in the absence of interactions, i.e., under the model* (1′)*, d_0 is universally optimal for the estimation of complete sets of orthonormal contrasts belonging to direct as well as residual effects over $\Omega_{t,n,p}$.*

Proof. It has been shown in the proof of the optimality result in the fixed effects, additive case, that under d_0, the direct effects are estimable orthogonally to the residual effects. In the notation of this paper, this is equivalent to $P^{10}C_{d_0}(P^{01})' = \mathbf{0}$. Also, it can be shown after some algebra that under d_0, direct effects are estimable orthogonally to interaction effects, i.e., $P^{10}C_{d_0}(P^{11})' = \mathbf{0}$. Hence, from (10) and (9b), for a design $d \in \Omega_{t,n,p}$, under (1),

$$\begin{aligned} C_{d(\text{dir})} &\leq \omega_1 P^{10}C_d(P^{10})' + \omega_2 P^{10}C_d^*(P^{10})' \\ &- [\omega_2 P^{10}C_d^*(P^{01})', \omega_2 P^{10}C_d^*(P^{11})'] \begin{bmatrix} R & S \\ S' & T \end{bmatrix}^- \begin{bmatrix} \omega_2 P^{01}C_d^*(P^{10})' \\ \omega_2 P^{11}C_d^*(P^{10})' \end{bmatrix}, \end{aligned}$$

where, $R = \omega_1 P^{01}C_d(P^{01})' + \omega_2 P^{01}C_d^*(P^{01})', S = \omega_1 P^{01}C_d(P^{11})' + \omega_2 P^{01}C_d^*(P^{11})'$, $T = \omega_1 P^{11}C_d(P^{11})' + \omega_2 P^{11}C_d^*(P^{11})'$ and, for a pair of nonnegative definite matrices A, B, $A \leq B$ means $B - A$ is nonnegative definite. Note that equality above is attained when $d \equiv d_0$. It follows then that

$$\text{tr}(C_{d(\text{dir})}) \leq \text{tr}(C_{d_0(\text{dir})}), \qquad \text{for all } d \in \Omega_{t,n,p}, \tag{13}$$

where $\text{tr}(\cdot)$ denotes the trace of a square matrix. Using the fact that d_0 is uniform and strongly balanced, it can be shown that

$$P^{10}C_{d_0}^*(P^{01})' = \mathbf{0} \text{ and } P^{10}C_{d_0}^*(P^{11})' = \mathbf{0}$$

and this leads to

$$C_{d_0(\text{dir})} = \text{constant. } I_t. \tag{14}$$

From the sufficient conditions for universal optimality, as in Kiefer(1975), the universal optimality of d_0 for direct effects follows from (13) and (14). The optimality of d_0 for direct and residual effects under (1′) can be proved similarly.

Theorem 3 (Cheng and Wu, 1980; Theorem 3.3). *For $n = \lambda_1 t^2, p = \lambda_2 t + 1, \lambda_1, \lambda_2 \geq 1$, let d_0 be a strongly balanced design in $\Omega_{t,n,p}$ which is uniform on the periods and uniform on the units in the first $(p-1)$ periods. Then, under the model* (1)*, d_0 is universally optimal for the estimation of complete sets of orthonormal contrasts belonging to residual effects over $\Omega_{t,n,p}$.*

Also, under model $(1')$, d_0 *is universally optimal for complete sets of orthonormal contrasts belonging to direct as well as residual effects over* $\Omega_{t,n,p}$.

Proof. As shown by Cheng and Wu (1980), under a fixed effects additive model, direct effects are estimable orthogonally to the residual effects. Additionally, under d_0, the residual effects are orthogonally estimable to the interaction effects, i.e., $P^{01}C_{d_0(\text{res})}(P^{11})' = \mathbf{0}$. Using these facts, coupled with arguments similar to the ones used in the proof of Theorem 2 to show that d_0 maximixes the trace of $C_{d_0(\text{res})}$, one can show the claimed optimality of d_0 under (1). Similarly, under $(1')$, using the stated properties of d_0, the proof follows after noting that $P^{01}C_{d_0}(P^{10})' = \mathbf{0}$ and that $C_{d_0(\text{dir})}$ and $C_{d_0(\text{res})}$ are completely symmetric.

Theorem 4 (Cheng and Wu, 1980; Theorem 4.3). *Let* d_0 *be a balanced uniform design in* $\Lambda_{t,\lambda_1 t,\lambda_2 t}$. *Then, under the model* $(1')$, d_0 *is universally optimal for the estimation of complete sets of orthonormal contrasts belonging to direct effects over the class of designs in* $\Lambda_{t,\lambda_1 t,\lambda_2 t}$ *which are uniform on each unit and the last period.*

Proof. First observe that unlike Theorems 2 and 3, the design d_0 is *not* strongly balanced and thus, in general, $P^{10}C_{d_0}(P^{01})' \neq \mathbf{0}$.

Instead, since d_0 is uniform, it can be shown that $P^{10}C^*_{d_0}(P^{01})' = \mathbf{0}$. Let $\bar{\Lambda}_{t,\lambda_1 t,\lambda_2 t}$ denote a subclass of $\Lambda_{t,\lambda_1 t,\lambda_2 t}$ consisting of designs which are uniform on each unit and the last period. Then, for a design $d \in \bar{\Lambda}_{t,\lambda_1 t,\lambda_2 t}$, from (8) and (6), we have

$$\begin{aligned} P^{01}M_d &= t^{-\frac{1}{2}}P_t(\mathbf{1}' \otimes I)(\cdots,\ \sum_{i=1}^{p-1}\boldsymbol{e}_{d(i,j)} \otimes \boldsymbol{e}_{d(i-1,j)} + t^{-1}\boldsymbol{e}_{d(0,j)} \otimes \mathbf{1}_t,\ \cdots)_{j=1,\ldots,n} \\ &= t^{-\frac{1}{2}}P_t(\cdots,\ \sum_{i=0}^{p-2}\boldsymbol{e}_{d(i,j)},\ \cdots)_{j=1,\ldots,n} \qquad (15) \end{aligned}$$

on simplification.

Since d is uniform over the last period, without loss of generality, we can rearrange the units in d such that the last period has treatments in the order : $1,\ldots,1,2,\ldots,2$ $,\ldots,t,\ldots,t$, each treatment appearing exactly λ_1 times. Then, $(\cdots,\ \sum_{i=0}^{p-2}\boldsymbol{e}_{d(i,j)},\ \cdots)$ is of the form

$$(\mathbf{1}_t + \boldsymbol{\alpha}_1, \ldots, \mathbf{1}_t + \boldsymbol{\alpha}_1, \ldots, \mathbf{1}_t + \boldsymbol{\alpha}_t, \ldots, \mathbf{1}_t + \boldsymbol{\alpha}_t)$$

where for each $i = 1,\ldots t$, the term $\mathbf{1}_t + \boldsymbol{\alpha}_i$ appears in the above expression precisely λ_1 times and $\boldsymbol{\alpha}_u$ is a $t \times 1$ vector with -1 in the uth position and zeros elsewhere, $1 \leq u \leq t$. Hence, from (15),

$$P^{01}M_d = t^{-\frac{1}{2}}P_t(\boldsymbol{\alpha}_1, \ldots, \boldsymbol{\alpha}_1, \ldots, \boldsymbol{\alpha}_t, \ldots, \boldsymbol{\alpha}_t). \qquad (16)$$

It follows then that $P^{01}M_d\mathbf{1} = \mathbf{0}$. Again, from (16), it follows after simplification that $P^{01}M_dM_d'(P^{01})' = t^{-1}\lambda_1 I_{t-1}$ and thus, $P^{01}C^*_d(P^{01})' = t^{-1}\lambda_1 I_{t-1}$ for all $d \in \bar{\Lambda}_{t,\lambda_1 t,\lambda_2 t}$.

On similar lines, one can show that for a $d \in \bar{\Lambda}_{t,\lambda_1 t,\lambda_2 t}$,

$$P^{10}C^*_d(P^{10})' = P^{10}C^*_d(P^{01})' = \mathbf{0}.$$

Hence, under ($1'$), for a design $d \in \bar{\Lambda}_{t,\lambda_1 t,\lambda_2 t}$, from (10), $C_{d(\mathrm{dir})}$ reduces to

$$\begin{aligned} C_{d(\mathrm{dir})} &= \omega_1 P^{10} C_d (P^{10})' - (\omega_1 P^{10} C_d (P^{01})')(\omega_1 P^{01} C_d (P^{01})' + \lambda_1 \omega_2 t^{-1} I_{t-1})^{-} \times \\ & (\omega_1 P^{01} C_d (P^{10})'), \end{aligned}$$

which, except for the term $\lambda_1 \omega_2 t^{-1} I_{t-1}$, is identical with the corresponding information matrix for direct effects under the fixed effects model. Hence, the claimed optimality of the design d_0 in $\bar{\Lambda}_{t,\lambda_1 t,\lambda_2 t}$ under the mixed effects model ($1'$) follows.

Theorem 5 (Kunert, 1984). *For $n = \lambda_1 t, p = t$, let d_0 be a uniform balanced cross-over design in $\Omega_{t,n,p}$. Then, under the model ($1'$), d_0 is universally optimal for the estimation of complete sets of orthonormal contrasts belonging to direct effects over $\Omega_{t,n,p}$ if (i) $\lambda_1 = 1$ and $t \geq 3$ or, (ii) $\lambda_1 = 2$ and $t \geq 6$.*

Proof. As in Theorem 4, the design d_0 is *not* strongly balanced and thus, in general, $P^{10} C_{d_0} (P^{01})' \neq \mathbf{0}$. However, $P^{10} C^*_{d_0} (P^{01})' = \mathbf{0}$, since d_0 is uniform. Thus, from (12),

$$\begin{aligned} C_{d(\mathrm{dir})} &\leq \omega_1 P^{10} C_d (P^{10})' + \omega_2 P^{10} C^*_d (P^{10})' \\ &- [\omega_1 P^{10} C_d (P^{01})'][\omega_1 P^{01} C^*_d (P^{01})' + P^{01} C^*_d (P^{01})']^{-}[\omega_1 P^{01} C_d (P^{10})'], \end{aligned}$$

with equality holding for $d \equiv d_0$. Thus,

$$\mathrm{tr}(C_{d_0(\mathrm{dir})}) \geq \mathrm{tr}(C_{d(\mathrm{dir})}), \text{ for all } d \in \Omega_{t,n,p}.$$

Now, for $d = d_0$, we get after simplification,

$$P^{01} C^*_{d_0} (P^{01})' = t^{-1} P^{01} \sum_{j=1}^{n} (\sum_{i=0}^{p-2} \boldsymbol{e}_{d_0(i,j)})(\sum_{i=0}^{p-2} \boldsymbol{e}'_{d_0(i,j)})(P^{01})'.$$

Since d_0 is uniform over periods, it is also uniform over the last period. We can therefore rearrange the units such that the last period is of the form $1, 2, \ldots, t, \ldots, 1, 2, \ldots, t$, where each treatment symbol is repeated λ_1 times. Recalling that $p = t$ and d_0 is uniform over units, it follows then that

$$\sum_{j=1}^{n} (\sum_{i=0}^{p-2} \boldsymbol{e}_{d_0(i,j)})(\sum_{i=0}^{p-2} \boldsymbol{e}'_{d_0(i,j)}) = \lambda_1 I_t + \lambda_1 (t-2) J_t,$$

where J_t is a $t \times t$ matrix of all ones. We can now show that

$$C_{d_0(\mathrm{dir})} = \omega_1 P^{10} C_{d_0} (P^{10})' - (\omega_1 P^{10} C_{d_0} (P^{01})')(\omega_1 P^{01} C_{d_0} (P^{01})' + \omega_2 t^{-1} \lambda_1 I)^{-}(\omega_1 P^{01} C_{d_0} (P^{10})'). \tag{17}$$

All the terms in the right hand side of (17) are terms for the fixed effects model and thus, complete symmetry of $C_{d_0(\mathrm{dir})}$ follows from the results under a fixed effects model. This completes the proof.

On similar lines, one can also prove the following result about the optimality of a subclass of designs considered by Hedayat and Zhao (1990).

Theorem 6 (Hedayat and Zhao, 1990). *For* $p = 2, n = t^2$*, let* d_0 *be a design in* $\Omega_{t,n,p}$*, given by an orthogonal array* $OA(n, 2, t, 2)$*, where the columns of the orthogonal array represent the units and rows, the periods. Then, under the model* $(1')$*,* d_0 *is universally optimal for the estimation of complete sets of orthonormal contrasts belonging to direct effects over* $\Omega_{t,n,p}$*.*

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Appendix

Proof of Theorem 1. The model (1) (or, equivalently, (2)) can be written as

$$E(\boldsymbol{y}) = X\boldsymbol{\theta},\ D(\boldsymbol{y}) = V, \tag{A.1}$$

where $\boldsymbol{y}$ is the observation vector, $\boldsymbol{\theta}$ represents the vector of all parameters in the model, $E(\cdot), D(\cdot)$ respectively stand for the expectation and dispersion (variance-covariance) matrix and the design matrix X is given by

$$X = \begin{bmatrix} & & \boldsymbol{\lambda}'_{01} \\ \mathbf{1}_p & I_p & \vdots \\ & & \boldsymbol{\lambda}'_{p-1,1} \\ \cdots & \cdots & \cdots \\ & & \boldsymbol{\lambda}'_{0n} \\ \mathbf{1}_p & I_p & \vdots \\ & & \boldsymbol{\lambda}'_{p-1,n} \end{bmatrix}. \tag{A.2}$$

Also, it is not hard to see that the dispersion matrix V is given by

$$V = I_n \otimes A, \tag{A.3}$$

where the $p \times p$ matrix A is

$$A = \begin{bmatrix} \sigma^2 + \sigma_1^2 & \sigma_1^2 & \cdots & \sigma_1^2 \\ \sigma_1^2 & \sigma^2 + \sigma_1^2 & \cdots & \sigma_1^2 \\ \vdots & & & \\ \sigma_1^2 & \sigma_1^2 & \cdots & \sigma^2 + \sigma_1^2 \end{bmatrix}. \tag{A.4}$$

Under the model (A.1), the normal equations for $\boldsymbol{\theta}$ are

$$(X'V^{-1}X)\boldsymbol{\theta} = X'V^{-1}\boldsymbol{y}. \tag{A.5}$$

After some routine but lengthy algebra, one can show that (A.5) can be simplified to

$$\begin{bmatrix} \frac{np}{\sigma^2+p\sigma_1^2} & \frac{n}{\sigma^2+p\sigma_1^2}\mathbf{1}'_p & \mathbf{1}'_pA^{-1}(\sum_j \boldsymbol{\lambda}'_j) \\ \frac{n}{\sigma^2+p\sigma_1^2}\mathbf{1}_p & nA^{-1} & A^{-1}(\sum_j \boldsymbol{\lambda}'_j) \\ (\sum_j \boldsymbol{\lambda}_j)A^{-1}\mathbf{1}_p & (\boldsymbol{\lambda}_j)A^{-1} & \sum_j \boldsymbol{\lambda}_j A^{-1}\boldsymbol{\lambda}'_j \end{bmatrix} \begin{pmatrix} \mu \\ \boldsymbol{\alpha} \\ \boldsymbol{\xi} \end{pmatrix} = \begin{bmatrix} \mathbf{1}'_pA^{-1}\sum_j \boldsymbol{y}_j \\ A^{-1}\sum_j \boldsymbol{y}_j \\ A^{-1}\sum_j \boldsymbol{\lambda}_j A^{-1}\boldsymbol{y}_j \end{bmatrix}, \tag{A.6}$$

where for $1 \le j \le n$,

$$\boldsymbol{\lambda}'_j = \begin{pmatrix} \boldsymbol{\lambda}'_{0j} \\ \vdots \\ \boldsymbol{\lambda}'_{p-1,j} \end{pmatrix},$$

$\boldsymbol{y}_j = (Y_{0j}, Y_{1j}, \ldots, Y_{p-1,j})'$ and $\boldsymbol{\alpha}$ is the vector of period effects.

It is easy to see that the rank of the matrix on the left hand side of (A.6) is equal to the rank of the matrix

$$\begin{bmatrix} nA^{-1} & A^{-1}(\sum_j \boldsymbol{\lambda}_j') \\ (\sum_j \boldsymbol{\lambda}_j)A^{-1} & \sum_j \boldsymbol{\lambda}_j A^{-1}\boldsymbol{\lambda}_j' \end{bmatrix}.$$

Premultiplying both sides of (A.6) by

$$\begin{bmatrix} I_{p+1} & O \\ -\boldsymbol{b}B_1^- & I_{t^2} \end{bmatrix},$$

where

$$\boldsymbol{b}' = \begin{pmatrix} \mathbf{1}_p' A^{-1} \sum_j \boldsymbol{\lambda}_j' \\ A^{-1} \sum_j \boldsymbol{\lambda}_j' \end{pmatrix},$$

$$B_1 = \begin{pmatrix} n\mathbf{1}_p' A^{-1}\mathbf{1}_p & n\mathbf{1}_p' A^{-1} \\ nA^{-1}\mathbf{1}_p & nA^{-1} \end{pmatrix},$$

and simplifying, we get the reduced normal equations for estimating linear functions of $\boldsymbol{\xi}$ as

$$(B_2 - \boldsymbol{b}B_1^-\boldsymbol{b}')\boldsymbol{\xi} = \boldsymbol{d}_2 - \boldsymbol{b}B_1^-\boldsymbol{d}_1, \tag{A.7}$$

where $B_2 = \sum_j \boldsymbol{\lambda}_j A^{-1}\boldsymbol{\lambda}_j'$, $\boldsymbol{d}_2 = A^{-1}\sum_j \boldsymbol{\lambda}_j \boldsymbol{y}_j'$ and

$$\boldsymbol{d}_1 = \begin{pmatrix} \mathbf{1}_p' A^{-1} \sum_j \boldsymbol{y}_j' \\ A^{-1} \sum_j \boldsymbol{y}_j' \end{pmatrix}.$$

Since the rankB_1 = rank$(nA^{-1}) = p$, a choice of a generalized inverse of B_1 is $B_1^- = n^{-1}A$. Using this fact and after some lengthy but routine algebra, we obtain the required reduced combined intra-inter unit normal equations in the required form.