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Combined Intra-Inter Unit Analysis of Crossover Designs and Related Optimality Results

Mausumi Bose and Aloke Dey[1]
Indian Statistical Institute, Kolkata 700 108
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SUMMARY

For a general crossover 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. It is shown how some of the existing optimality results under a fixed effects additive model are extended or modified under the considered mixed effects, non-additive model as well.

Key words : Crossover designs, Non-additive mixed effects model.

1. INTRODUCTION

Crossover 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, e.g., clinical trials, learning experiments, animal feeding experiments and agricultural field trials. A distinctive feature of crossover 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 often complicates the designing and analysis of such experiments. Considerable literature on the design and analysis of crossover experiments is already available and for excellent reviews of the literature on crossover designs, see Matthews (1988) and Stufken (1996).

Optimality aspects of crossover 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), Hedayat and Zhao (1990) and Stufken (1991). In this paper, we consider a model in which the unit effects are treated as random while all other effects in the model are fixed. The model also allows for possible interactions among treatments applied at successive periods. Consideration of such a model is motivated by the fact that in many practical situations, it is quite 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. A non-additive model of the type considered here is also motivated from practical considerations as in many experimental situations, the interaction effects may also affect the response; see e.g., John and Quenouille (1977; p. 213) and Patterson (1970). Sen and Mukerjee (1987) considered a *fixed* effects non-additive model of the type considered in this paper and proved the optimality of certain crossover designs under this model. See also Bose and Dey (2003) in this connection.

Mixed effects, *additive* models (i.e., models with no interactions) for crossover experiments have been considered earlier by several authors. Mukhopadhyay and Saha (1983) studied crossover designs under a mixed effects additive model with unit effects random and derived the relevant information matrices under this model. By extensive algebraic computations, they showed that some of the results on optimal designs under a fixed effects (additive) model, obtained by Hedayat and Afsarinejad (1978), Cheng and Wu (1980) and Magda (1980) can be extended to their model.

Jones *et al.* (1992) considered a model in which the residual effect of each treatment is taken to be random, while other effects in the model are treated as fixed. Theorem 1 in Jones *et al.* (1992) is noteworthy as it expresses the relevant information matrix under the considered model as a linear combination of the corresponding information matrix (say, C_0) under a model ignoring the random effects and the information matrix (say, C_∞), under a model with all effects fixed. Applying this theorem, Jones *et al.* (1992) show the optimality of some classes of crossover designs under their model. A (mixed) model with unit effects random and all other effects fixed has also been considered briefly by Jones et *al.* (1992). However, as remarked by Jones *et al.*, their Theorem 1 cannot be applied in this situation directly because the relevant information matrices under this model are no longer expressible as a linear combination of C_0 and C_∞. Another relevant work in this area is due to Carriere and Reinsel (1993), who obtained universally optimal crossover designs under a mixed effects, additive model for comparing $t \geq 2$ reatments, when the number of periods is two and the number of units is either t^2 or t. For more discussion, see Stufken (1996).

As stated earlier in this section, in this paper we consider a non-additive, mixed effects model. To the best of our knowledge, optimal crossover designs under such a model has not been considered in the literature. Following Sen and Mukerjee (1987), we view a crossover experiment as a suitable factorial experiment and use the tools of Kronecker calculus for factorials, introduced by Kurkjian and Zelen (1962) to obtain the relevant information matrices leading to the study of optimal designs. For a review of this calculus, see Gupta and Mukerjee (1989). This approach greatly facilitates the study of crossover designs under a non-additive model with random unit effects. Using this approach, we obtain combined intra-inter unit reduced normal equations for estimating linear functions of direct and residual effects under the stated model. From the general expressions obtained in this paper, one can check the optimality of a given design under the considered mixed effects model. The (simpler) results under additive model and fixed effects model follow as particular cases. Moreover, by exploiting the nature of the combined intra-inter unit information matrix, establishing optimality under the considered mixed effects model becomes particularly simple for designs that are known to be optimal under a fixed effects model. To illustrate this, we demonstrate how several of the existing optimality results under a fixed effects, additive model can be extended (or, modified) under the considered mixed 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).

2. MODEL AND COMBINED ANALYSIS

Consider a crossover 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 crossover design. Let $\Omega_{t,n,p}$ be the class of all such crossover 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, . . . , p-1; j = 1, 2 . . . , n. We postulate the following model:

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

and

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

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 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 = 1, . . . , p–1; j = 1, 2, . . . , n, where we define $\rho_{d(0,j)} = \gamma_{d(1,j),d(0,j)} = 0$, j = 1, . . . , n. It is further assumed that the vector of subject effects $\beta = (\beta_1, ..., \beta_n)'$ has the normal distribution $N(0, \sigma_1^2 I)$, the error vector has the normal distribution $N(0, \sigma^2 I)$ and β is independent of the error terms. Here and in the rest of the paper, 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.

Crossover experiments may be looked upon as a t^2 factorial experiment with two factors, F_1, F_2, where the t^2 treatment combinations (u_1, u_2), $0 \le u_1, u_2 \le t-1$ are such that the first (second) member of each treatment combination represents the treatment contributing a direct (first order residual) effect to an experimental unit. The direct effects then correspond to the main effect F_1, the first order residual effects correspond to the main effect F_2 and the direct versus carry-over interaction effect is given by the usual factorial interaction, $F_1 F_2$. 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:

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

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;

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

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

where for a pair of matrices A, B, $A \otimes B$ denotes their Kronecker (tensor) product; $e_{d(i,j)}$ 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, 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 notations. For a design $d \in \Omega_{t,n,p}$, define

$$V_d = \sum_{i=0}^{p-1} \sum_{j=1}^{n} \lambda_{ij} \lambda'_{ij}, \quad V_d^* = \sum \sum \lambda_{ij} Y_{ij}$$

$$N_d = \left(\sum_{j=1}^{n} \lambda_{0j}, \sum_{j=1}^{n} \lambda_{1j}, \ldots, \sum_{j=1}^{n} \lambda_{p-1,j}\right) \tag{5}$$

$$N_d^* = \left(\sum_j Y_{0j}, \ldots, \sum_j Y_{p-1,j}\right),$$

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

$$M_d^* = \left(\sum_i Y_{i1}, \ldots, \sum_i Y_{in}\right) \tag{6}$$

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 ξ. Also, let

$$C_d = V_d - n^{-1} N_d N'_d - p^{-1} M_d M'_d + (np)^{-1} (N_d 1_p)(N_d 1_p)' \tag{7}$$

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 ξ 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 $(t^{-1/2} 1_t, P'_t)$ is orthogonal. Define

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

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

Under the stated assumptions on the vector β 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 ξ, using a design $d \in \Omega_{t,n,p}$ are given by

$$(\omega_1 C_d + \omega_2 C_d^*)\xi = (\omega_1 Q_d + \omega_2 Q_d^*) \tag{9a}$$

where

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

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

and

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

Thus, the information matrix $(\omega_1 C_d + \omega_2 C_d^*)$ is a linear combination of the information matrix under fixed effects model (C_d) and C_d^*.

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 ω_1 and ω_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

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

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

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

and

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

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 $C_{d_0(dir)}(C_{d_0(res)})$ 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 preceeded by itself and each treatment is preceeded 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 preceeded 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 preceeded by itself.

Most of the known optimality results on crossover designs are based on a fixed effects, 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 model (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 model (1′), we have

$$C_{d(dir)} = \omega_1 P^{10}C_d(P^{10})' + \omega_2 P^{10}C_d^*(P^{10})' - [\omega_1 P^{10}C_d(P^{01})' + \omega_2 P^{10}C_d^*(P^{01})'] \times [\omega_1 P^{01}C_d(P^{01})' + \omega_2 P^{01}C_d^*(P^{01})']^{-} [\omega_1 P^{10}C_d(P^{10})' + \omega_2 P^{10}C_d^*(P^{10})'] \tag{12}$$

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

In the following theorems, we show how some of the available results on optimality of a crossover design under a fixed effects model can be extended or modified under a corresponding mixed effects model. To begin with, Theorem 3.1 of Cheng and Wu (1980) under the present setup gets modified to the one in Theorem 2.

Theorem 2. 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 $P^{10}C_{d_0}(P^{01})' = 0$. Also, it can be shown after some algebra that under d_0, direct effects are estimable orthogonally to interaction effects, i.e., $P^{10}C_{d_0}(P^{11})' = 0$. Hence, from (10) and (9b), for a design $d \in \Omega_{t,n,p}$, under model (1)

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

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

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

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

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

and this leads to

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

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 model (1′) has been proved earlier by Mukhopadhyay and Saha (1983), using a different technique.

Theorem 3.3 of Cheng and Wu (1980) under the considered model gets modified to

Theorem 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., $P^{01}C_{d_0(res)}(P^{11})' = 0$. Using these facts, coupled with arguments similar to the ones used in the proof of Theorem 2 to show that d_0 maximises the trace of $C_{d_0(res)}$, one can show the claimed optimality of d_0 under model (1). Similarly, under (1′), using the stated properties of d_0, the proof follows after noting that $P^{01}C_{d_0}(P^{10})' = 0$ and that $C_{d_0(dir)}$ and $C_{d_0(res)}$ are completely symmetric. Note that the result under model (1′) was also obtained by Mukhopadhyay and Saha (1983).

Kunert (1984) proved the optimality of a certain class of uniform, balanced crossover designs. His result in the present context takes the form given in Theorem 4.

Theorem 4. For $n = \lambda_1 t, p = t$, let d_0 be a uniform balanced crossover 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. Since the design d_0 is not strongly balanced, in general, $P^{10}C_{d_0}(P^{01})' \neq 0$. However, $P^{10}C_{d_0}^*(P^{01})' = 0$, since d_0 is uniform. Thus, from (12)

$$C_{d(dir)} \le \omega_1 P^{10} C_d (P^{10})' + \omega_2 P^{10} C_d^* (P^{10})' - [\omega_1 P^{10} C_d (P^{01})'][\omega_1 P^{01} C_d^* (P^{01})' + P^{01} C_d^* (P^{01})']^{-} [\omega_1 P^{01} C_d (P^{10})']$$

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

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

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

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

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, . . . , t, . . . , 1, 2, . . . , 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

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

where J_t is a $t \times t$ matrix of all ones. We can now show that $C_{d_0(dir)}$ equals

$$\omega_1 P^{10} C_{d_0} (P^{10})' - (\omega_1 P^{10} C_{d_0} (P^{01})')(\omega_1 P^{01} C_{d_0} (P^{01})' + \omega_2 t^{-1} \lambda_1 I)^{-} \times (\omega_1 P^{01} C_{d_0} (P^{10})')$$

All the terms in the right hand side of (17) are terms for the fixed effects model and thus, complete symmetry of $C_{d_0(dir)}$ 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 5. 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, model (2)) can be written as

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

where y is the observations vector, θ 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

$$X = \begin{bmatrix} 1_p & I_p & \begin{matrix}\lambda'_{01}\\ \vdots \\ \lambda'_{p-1,1}\end{matrix} \\ \dots & \dots & \dots \\ 1_p & I_p & \begin{matrix}\lambda'_{0n}\\ \vdots \\ \lambda'_{p-1,n}\end{matrix} \end{bmatrix}$$

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 × p matrix A is

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

Under the model (A.1), the normal equations for θ are

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

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

$$F\begin{pmatrix}\mu\\ \alpha\\ \xi\end{pmatrix} = \begin{bmatrix} 1'_p A^{-1}\sum_j y_j \\ A^{-1}\sum_j y_j \\ \sum_j \lambda_j A^{-1} y_j \end{bmatrix} \tag{A.6}$$

where

$$F = \begin{bmatrix} \dfrac{np}{\sigma^2+p\sigma_1^2} & \dfrac{n}{\sigma^2+p\sigma_1^2}1'_p & 1'_pA^{-1}(\sum_j \lambda'_j) \\ \dfrac{n}{\sigma^2+p\sigma_1^2}1_p & nA^{-1} & A^{-1}(\sum_j \lambda'_j) \\ (\sum_j \lambda_j)A^{-1}1_p & (\sum_j \lambda_j)A^{-1} & \sum_j \lambda_j A^{-1}\lambda'_j \end{bmatrix}$$

$$\lambda'_j = \begin{pmatrix}\lambda'_{0j}\\ \vdots \\ \lambda_{p-1,j}\end{pmatrix},\quad 1 \le j \le n$$

$y_j = (Y_{0j}, Y_{1j}, \dots, Y_{p-1,j})'$ and α is the vector of period effects.

It is easy to see that the rank of the matrix F in (A.6) is equal to the rank of the matrix

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

Premultiplying both sides of (A.6) by

$$\begin{bmatrix} I_{p+1} & O \\ -bB_1^- & I_{t^2} \end{bmatrix}$$

where

$$b' = \begin{pmatrix} 1'_pA^{-1}\sum_j \lambda'_j \\ A^{-1}\sum_j \lambda'_j \end{pmatrix}$$

$$B_1 = \begin{pmatrix} n1'_pA^{-1}1_p & n1'_pA^{-1} \\ nA^{-1}1_p & nA^{-1} \end{pmatrix}$$

and simplifying, we get the reduced normal equations for estimating linear functions of ξ as

$$\left(B_2 - bB_1^-b'\right)\xi = d_2 - bB_1^-d_1 \tag{A.7}$$

where $B_2 = \sum_j \lambda_j A^{-1}\lambda'_j$, $d_2 = \sum_j \lambda_j A^{-1} y_j$ and

$$d_1 = \begin{pmatrix} 1'_pA^{-1}\sum_j y_j \\ A^{-1}\sum_j y_j \end{pmatrix}$$

Since rank (B_1) = rank $(nA^{-1}) = p$, a choice of a generalized inverse of B_1 is $B_1^- = \begin{pmatrix} 0 & 0 \\ 0 & n^{-1}A \end{pmatrix}$. Using this fact and after some lengthy algebra, we obtain the required reduced combined intra-inter unit normal equations in the required form.