Efficient crossover designs in the presence of interactions between direct and carry-over treatment effects

D.K. Park\textsuperscript{a}, Mausumi Bose\textsuperscript{b}, W.I. Notz\textsuperscript{c}, A.M. Dean\textsuperscript{c,}\textsuperscript{*}

\textsuperscript{a} Department of Information and Statistics, Yonsei University, Wonju 220-710, South Korea
\textsuperscript{b} Applied Statistics Unit, Indian Statistical Institute, 203 B. T. Road, Kolkata 700108, India
\textsuperscript{c} Department of Statistics, The Ohio State University, 1958 Neil Avenue, Columbus OH 43210, USA

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ABSTRACT

Crossover designs, or repeated measurements designs, are used for experiments in which \( t \) treatments are applied to each of \( n \) experimental units successively over \( p \) time periods. Such experiments are widely used in areas such as clinical trials, experimental psychology and agricultural field trials. In addition to the direct effect on the response of the treatment in the period of application, there is also the possible presence of a residual, or carry-over, effect of a treatment from one or more previous periods. We use a model in which the residual effect from a treatment depends upon the treatment applied in the succeeding period; that is, a model which includes interactions between the treatment direct and residual effects. We assume that residual effects do not persist further than one succeeding period.

A particular class of strongly balanced repeated measurements designs with \( n = t^2 \) units and which are uniform on the periods is examined. A lower bound for the A-efficiency of the designs for estimating the direct effects is derived and it is shown that such designs are highly efficient for any number of periods \( p = 2, \ldots, 2t \).

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1. Introduction

Crossover experiments are used in studies in which \( t \) treatments are applied to \( n \) experimental units (or subjects) successively over \( p \) time periods. Designs for such experiments are known as crossover designs or repeated measurements designs (RMD) and are widely used in research areas such as agricultural field trials, experimental psychology, clinical trials, and animal husbandry; see, for example, Kershner and Federer (1981), Ratkowski et al. (1993), Jones and Kenward (2003), and Bate and Boxall (2008). Since each experimental unit is measured over a sequence of treatments, each response can be affected not only by the “direct effect” of the treatment in the period of application, but possibly also “carry-over” or “residual” effects from treatments applied in one or more previous periods. A common assumption is that the residual effect arising from the immediately preceding treatment may be non-negligible but that residual effects from treatments in prior periods are negligibly small.

We denote the class of crossover designs with \( t \) treatments compared via \( n \) experimental units in \( p \) time periods by \( \Omega_{t,n,p} \). A crossover design is said to be strongly balanced if, in the order of application for each unit, each treatment is preceded by every treatment including itself the same number of times. A design \( d \) is said to be (i) uniform on the periods if,
in each period, the same number of units are assigned to each treatment, (ii) uniform on the units if, for each unit, each treatment appears in the same number of periods, and (iii) uniform if it is uniform both on the periods and on the units.

Optimality properties of crossover designs have been studied extensively in the literature under an additive model where the response from a unit in a given period is the sum of the unit, period, direct and residual treatment effects and a random error. (The errors may be assumed to be independent or correlated). Jones and Kenward (2003) and Stufken (1996) give reviews of these results and references. Recent work using the additive model includes results on optimal designs by Hedayat and Yang (2003, 2004, 2005), Yang and Stufken (2008), and Yang and Park (2007); results on premature stopping and dropouts by Bose and Bagchi (2008) and Majumdar et al. (2008); incorporation of correlated errors by Carriere and Huang (2000) and Williams and John (2007).

The additive model assumes that the residual effect of a treatment is the same no matter which treatment is applied in the following period. However, there are situations where the additive model does not hold. Examples are given by, for example, John and Quenouille (1977, pp. 211–214), Kunert and Stufken (2002), and Senn (1993, Chapter 10). To address this problem, Sen and Mukerjee (1987) proposed a model which incorporates interactions between direct treatment effects and residual effects, and we call this the interaction repeated measurements model. These authors extended the result of Cheng and Wu (1980) that a strongly balanced uniform crossover design is universally optimal for estimation of direct and residual treatment effects under the additive model, and showed that such a design remains universally optimal for estimation of direct treatment effects under the model with interactions. Sen and Mukerjee (1987) also gave conditions under which such designs are optimal for estimation of residual effects. Bose and Mukerjee (2000) extended the interaction repeated measurements model further to allow residual effects to persist for any number of periods, and they proved universal optimality of a class of highly balanced uniform designs for estimation of direct effects.

An alternative model with fewer parameters was proposed more recently by Afsarinejad and Hedayat (2002) where residual effects are modelled as of only two different types, depending on whether a treatment is followed in the next period by the same treatment (“self carryover” effect) or by a different treatment (“mixed carry over” effect). These authors gave methods of construction of efficient two-period crossover designs for estimation of direct effects and self and mixed carryover effects. Kunert and Stufken (2002), Hedayat and Stufken (2003), and Hedayat and Yan (2008) gave further results on optimal designs under the model with self and mixed carry over effects; the last of these papers gives results in the presence of correlated errors. Bose and Stufken (2007) studied optimal designs under a model with carryover effects proportional to direct effects. Waterhouse et al. (2006) also used proportional carryover effects, but in the context of a logistic regression model.

In this paper, we adopt the interaction repeated measurements model of Sen and Mukerjee (1987) and obtain a class of efficient designs with few periods \((p \leq 2t)\) for the estimation of direct treatment effects. The study of efficient designs under this non-additive model is made tractable by using an analogy with factorial experiments. In Section 2, we state the interaction repeated measurements model and the information matrix for estimating direct treatment effects after adjusting for units, periods, and residual effects. In Section 3, we investigate the properties of a particular class of strongly balanced designs with \(t\) treatments, \(p\) periods \((2 \leq p \leq 2t)\) and \(n=p^2\) units. These designs are obtained as a selection of \(p\) consecutive periods from the strongly balanced uniform design constructed by Berenblut (1964). In particular, we show that such designs have the adjusted orthogonality property.

For this class of designs, we prove in the on-line supplementary material that the estimates of particular sets of direct effect contrasts in the interaction repeated measurements model are identical to the estimates of the direct effects as usually calculated in the additive model. The extra benefit of the interaction model is that it also allows investigation of the interactions separately, and allows removal of the interaction effects from the estimate of error variability so as to produce more precise inferences. In Section 3, we show that the information matrix for the direct effect contrasts can be written as a sum of circulant permutation matrices. This result is used in Section 4 to obtain a lower bound for the average efficiency of the direct effects in such designs. It is shown that all such designs are highly efficient for estimating direct treatment effects for any number of periods \(p=2,\ldots,2t\). Thus, in experiments which are run period by period, such designs remain efficient if the study needs to be halted before the planned number of periods can be run. It is also shown in Section 4 that a design in this class that is \(A\)-optimal for estimation of direct effects under the traditional additive model is also \(A\)-optimal under the interaction repeated measurements model. The results in this paper can be extended in a straightforward way to designs with \(n = \mu_1 t^2\) units and \(2 \leq p \leq 2 \mu_2 t\) periods, for integers \(\mu_1 > 1, \mu_2 > 1\).

2. The interaction repeated measurements model and information matrix

Let \(d(i,j) \in \{0,1,\ldots,t-1\}\) denote the treatment assigned by design \(d \in \Omega_{n,p}\) in the \(i\)th period to the \(j\)th experimental unit \((i=1,\ldots,p; j=1,\ldots,n)\) and let \(y_{ij}\) be the corresponding response. The standard additive model for crossover designs as used, for example, by Hedayat and Afsarinejad (1978), Cheng and Wu (1980), Kunert (1984) and others, is

\[
y_{ij} = \mu_i + x_i + \beta_j + \tau_{d(i,j)} + \rho_{d(j-1),j} + \epsilon_{ij},
\]

where, for \(i=1,\ldots,p\) and \(j=1,\ldots,n\), the error variables \(\epsilon_{ij}\) are assumed to be independent and identically normally distributed with mean zero and variance \(\sigma^2\), and where \(\mu, x_i, \beta_j, \tau_{d(i,j)}, \rho_{d(j-1),j}\) are, respectively, the grand mean, the \(i\)th period effect, the \(j\)th experimental unit effect, the direct effect of treatment \(s\) and the first order residual effect of treatment \(s, s=1,\ldots,t;\)
\[ \rho_{d(i,j)} = 0 \text{ for all } j=1, \ldots, n. \]  

The modification of this model discussed by Afsarinejad and Hedayat (2002) and Kunert and Stufken (2002) replaced the carryover effect \( \rho_{d(i-1,j)} \) with a different carryover effect \( Z_{d(i-1,j)} \) whenever \( d(i-1,j) = d(j) \).

Following Sen and Mukerjee (1987), we use the interaction repeated measurements model which allows the residual effect from a treatment in a given period to depend on which treatment is applied in the following period; that is, the model allows for the possible presence of interactions between treatments applied to the same unit in two successive periods. This model is

\[ Y_{ij} = \mu + x_i + \beta_j + \tau_{d(i,j)} + \rho_{d(i-1,j)} + \gamma_{d(i,j),d(i-1,j)} + \epsilon_{ij}, \]

where \( \gamma_{s,s'} \) is the interaction effect produced when the treatment \( s \) is applied in the current period with the treatment \( s' \) being applied in the preceding period to the same unit, \( s,s' = 1, \ldots, t; \gamma_{d(i,j),d(i-1,j)} = 0 \) for \( j=1, \ldots, n \), and all other terms are as in (1).

To facilitate the study of crossover designs under this model, we view \( d \in \Omega_{t,n,p} \) as a \( p \times n \) row–column design, with two-factor treatment labels and each factor having \( t \) levels. The first factor (\( A \)) corresponds to the treatment in a given period (\( i \)) and the second factor (\( B \)) corresponds to the treatment applied in the previous period (\( i-1 \)) to the same unit. Thus, for a given unit in period \( i \), factor \( A \) produces a direct effect while factor \( B \) produces a residual effect. So a direct–residual treatment pair is equivalent to a factorial treatment combination of the form \( ab \) where \( a=d(i,j) \) and \( b=d(i-1,j) \); there being \( t^2 \) such treatment combinations in all. When \( i=1 \), there is no residual effect from a previous treatment. Thus this interaction repeated measurements model can also be written as follows:

\[ Y_{ij} = \mu + x_i + \beta_j + \lambda_{ij} + \epsilon_{ij}, \]

where, for \( i=1,\ldots,p \) and \( j=1,\ldots,n \), \( \lambda_{d(i,j),d(i-1,j)} \) is the effect of the factorial treatment combination \( d(i,j)d(i-1,j) \), and all other terms are as in (1). In this paper, we set \( \lambda_{d(i,j),d(i-1,j)} = t^{-1} \sum_{k=1}^{t} \xi_{d(i,j),d(i-1,j),k} \) for each \( j \), in keeping with the definition of factorial main effects averaged over interactions (see, for example, Dean and Voss, 1999, Chapter 7).

Model (2) may be expressed in the following form:

\[ Y_{ij} = \mu + x_i + \beta_j + \lambda_{ij} + \epsilon_{ij}, \]

for \( 1 \leq i \leq p, 1 \leq j \leq n \), where

\[ \lambda = (\xi_{00}, \xi_{01}, \ldots, \xi_{tt-1}, \xi_{tt}, \ldots, \xi_{tt-1,t-1})' \]

is the vector of the \( t^2 \) treatment combination effects. The vector \( \lambda_{ij} \) is an index vector of the form

\[ \lambda_{ij} = e_{ij} \otimes e_{i-1,j}, \]

where \( \otimes \) denotes Kronecker product, \( e_{ij} \) is a \( t \times 1 \) vector with 1 in position \( d(i,j) \) and zero elsewhere, \( i=1,\ldots,p \) and \( j=1,\ldots,n \) and \( e_{0j}=t^{-1} 1_t \), where \( 1_t \) is a \( t \times 1 \) vector with all elements unity.

For a design \( d \in \Omega_{t,n,p} \), the information matrix \( C_d \) for estimation of \( \xi \) under model (3) after eliminating the effects of periods and units is given by Sen and Mukerjee (1987) as

\[ C_d = V_d - \frac{1}{p} N_d M_d - \frac{1}{n} M_d V_d + \frac{1}{np} (M_d 1_p)(M_d 1_p)', \]

where

\[ V_d = \sum_{i=1}^{p} \sum_{j=1}^{n} \lambda_{ij} \lambda_{ij}', \]

\[ N_d = (\sum_{j=1}^{n} \lambda_{ij}, \sum_{i=1}^{p} \lambda_{ij}, \ldots, \sum_{j=1}^{n} \lambda_{ij}), \]

\[ M_d = (\sum_{j=1}^{n} \lambda_{ij}, \sum_{i=1}^{p} \lambda_{ij}, \ldots, \sum_{j=1}^{n} \lambda_{ij}). \]

Here, \( N_d \) is the \( t^2 \times n \) factorial treatment–unit incidence matrix and \( M_d \) is the \( t^2 \times p \) factorial treatment–period incidence matrix of design \( d \), and \( \lambda_{ij} \) is defined in (4).

Our interest is in estimating the direct effects after adjusting for the period, unit, residual and interaction effects under model (3). For this, we consider a set of contrasts in the effects of factor \( A \) that span the main effect space. Following John and Williams (1995, Section 8.2), we take a set of \( t \) contrasts, \( P \xi \), in the direct effects of the form \( P = P_1 \otimes t^{-1/2} 1_t \), where \( P_1 = I_{t-1} - 1'1_{t-1} \) and \( 1_t \) is the \( t \times t \) identity matrix and \( J_t = 1_1 \). Similarly, we define \( Q \xi \) and \( R \xi \) where \( Q = t^{-1/2} 1_t \otimes P_1 \), \( R = P_1 \otimes P_1 \). The elements of \( P \xi, Q \xi \) and \( R \xi \) represent complete sets of treatment contrasts belonging to the direct effects, the residual effects and the interaction effects, respectively. The choice of this set of contrasts is for ease of proving Theorem 3.1. Any set of \( (t-1) \) orthonormal direct effect contrasts \( H \xi \) satisfies \( H = KP \) where \( K \) is \( (t-1) \times t \) and \( KK' = I_{t-1} \) and \( K1_t = 0 \). Furthermore, it is shown in the on-line supplement that, for the class of designs discussed in Section 3, \( 1/\sqrt{t} P \xi = t \) where, \( \tau = (\tau_1, \ldots, \tau_t) \) is the vector of direct effects in the additive model (1). In addition, the information matrix for
\( (1/\sqrt{\pi}) P^*_\xi \) in the interaction model is identical to that of \( \tau \) in the additive model. Thus, the estimates of the direct effects are the same for the two models, but the estimate of error variability is reduced in the interaction repeated measurements model when the interaction effects are non-negligible.

Under model (3), the information matrix \( \mathbf{C}_d \) for estimating contrasts in the direct treatment effects, namely \( P^*_\xi \), after adjusting for the period, unit, residual and interaction effects can be shown to be

\[
\mathbf{C}_d = \mathbf{P}_{Cd} \mathbf{P}^* \left[ \begin{array}{cc}
\mathbf{Q}_{Cd} & \mathbf{Q}_{Cd}^R \\
\mathbf{R}_{Cd} & \mathbf{R}_{Cd}^R
\end{array} \right]^{-1} \left[ \begin{array}{cc}
\mathbf{P}_{Cd} & \mathbf{P}_{Cd}^R
\end{array} \right],
\]

where \( Z' = [Q' R'] \) and where \( \mathbf{C}_d \) is given in (5).

Similarly, under the additive model (1) with no interactions, the information matrix \( \mathbf{C}_d(\text{no int}) \) for estimating contrasts \( P^*_\xi \) in the direct treatment effects after adjusting for the period, unit and residual effects is

\[
\mathbf{C}_d(\text{no int}) = \mathbf{P}_{Cd} \mathbf{P}^* \left( \mathbf{Q}_{Cd} \mathbf{Q}_{Cd}^R \right)^{-1} \left( \mathbf{P}_{Cd} \mathbf{P}_{Cd}^R \right).
\]

It can be seen that, under the interaction repeated measurements model (3), if the information matrix \( \mathbf{C}_d \) of a design \( d \) satisfies

\[
\mathbf{P}_{Cd} \mathbf{P}^* = \mathbf{Q}_{Cd} \mathbf{R} = \mathbf{0},
\]

where \( \mathbf{0} \) is a matrix of zero elements (with size given by the context), then the expression for \( \mathbf{C}_d \) in (9) reduces to that of \( \mathbf{C}_d(\text{no int}) \) in (10). Let \( \Omega_{t,n,p} \) be the class of all designs in \( \Omega_{t,n,p} \) which satisfy condition (11). For every design in this class, the interaction effects are orthogonal to both the direct effects and the residual effects after adjusting for unit and period effects; that is, these designs have a particular form of *adjusted orthogonality* (see Eccleston and Russell, 1977).

### 3. A class of designs with adjusted orthogonality

#### 3.1. Construction and properties

Cheng and Wu (1980, Section 3) gave a method of construction of a particular class of strongly balanced uniform designs in \( \Omega_{t,n,p} \), for positive integers \( \mu_1 \) and \( \mu_2 \). The construction is an extension of that given by Berenblut (1964) for \( \mu_1 = \mu_2 = 1 \) and proceeds as follows. Denote the \( t \) treatments by the non-negative residues modulo \( t \). Assign the \( t \) treatments to the \( \mu_1 t^2 \) units in the first two periods in such a way that each treatment is applied to exactly the same number of units in each period, and each ordered pair of treatments appears \( \mu_1 \) times. The treatments in periods \( (2i+1) \) and \( (2i+2) \) are obtained by adding \( i \), modulo \( t, (1, \ldots, t-1) \) to the treatments in periods 1 and 2, respectively. This results in a \( 2t \times \mu_1 t^2 \) array and \( \mu_2 \) copies of this array taken together gives the required design in \( \Omega_{t,n,p} \). For simplicity of presentation, in this paper, we will present a study of these designs for \( \mu_1 = \mu_2 = 1 \) only. The results may be extended in a straightforward manner for \( \mu_1 > 1, \mu_2 > 1 \). An example of such a design with \( \mu_1 = \mu_2 = 1 \) is presented in Table 1, where rows correspond to periods and columns to units. Without loss of generality, the units in Table 1 have been labeled according to the lexicographical ordering of the \( t^2 \) pairs of treatments applied to the units in the first two periods. Throughout the paper, we will call such a design \( \mathbf{d}_{\text{full}}(\in \Omega_{t,n,p}) \).

For \( s=1,2,\ldots,t \), let \( j_s \) be a \( t \times 1 \) vector with \( 1 \) in the \( s \)-th position and zero elsewhere and let \( \Gamma_s \) be a \( t \times t \) circulant permutation matrix whose first row is \( j_s \). We use arithmetic modulo \( t \) and we write \( j_s = j_0 \) if \( \Gamma_s = \mathbf{I}_t \). Treatment label 0 is then regarded as synonymous with treatment label \( t \) and, for the purpose of theoretical derivation, we list the treatment labels in the order \( 1, 2, \ldots, t-1, t \) only. Then for all \( s, k=1,2,\ldots,t \),

\[
\Gamma_{1_s} = j_s, \quad \Gamma_{2_s} = 1_t, \quad \Gamma_{3_s} = \Gamma_{t+s+2} = \Gamma_{2_s}, \quad \Gamma_{4_s} = \Gamma_{s+k+1} = \Gamma_{s-k+1}, \quad j_s \Gamma_{k} = j_{s-k+1}
\]

and \( j_s \Gamma_{k} = 1 \) if \( s \neq k \) and \( j_s \Gamma_{k} = 0 \) otherwise; subscripts are reduced modulo \( t \) so that \( \Gamma_{-k} = \Gamma_{t-k} \) and \( \Gamma_{t+k} = \Gamma_k \), etc.

**Table 1**

<table>
<thead>
<tr>
<th>Periods</th>
<th>Units</th>
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<tbody>
<tr>
<td>1</td>
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<td>...</td>
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<tr>
<td>2t-1</td>
<td>t-1</td>
</tr>
<tr>
<td>2t</td>
<td>t-1</td>
</tr>
</tbody>
</table>

Strongly balanced uniform design \( d_{\text{full}} \) with \( t \) treatments on \( 2t \) periods and \( n=t^2 \) units.
Let \( D(t, t^2, p) \subset \Omega_{t, t^2, p} \) be the class of designs which consist of any set of \( p \) consecutive periods from the design \( d_{\text{full}} \) defined above. Without loss of generality, we take the first \( p(2 \leq p \leq 2t) \) periods of \( d_{\text{full}} \) and we call this resulting design \( d^p \). Let \( N^0 = [\delta_1, \ldots, \delta_{t^2}] \) be the \( t^2 \times t^2 \) treatment-unit incidence matrix for period \( i \) of a design \( d^p \in D(t, t^2, p) \), \( i = 1, 2, \ldots, p \), where the treatments are factorial pairs as described in Section 2. The treatment-unit incidence matrix for \( d^p \) is \( N_d = \sum_{i=1}^{p} N^0 \) and, from the construction above, \( d^p \) satisfies the following properties P1–P4.

P1. \( d^p \) is uniform on the periods.

P2: Each ordered pair of treatments \( (s, k) \) occurs exactly once in the pairs of periods given by \( (i, i+1) \), \( i = 1, \ldots, (p-1) \); \( a = 1, \ldots, [(p+1)-i]/2 \), \( (\lfloor \cdot \rfloor \) denotes integer part), \( s, k = 0, \ldots, t-1 \). Consequently, each ordered pair of treatments occurs exactly once in any pair of successive periods implying that \( d^p \) is a strongly balanced design.

P3. The incidence matrices \( N^0 \) for \( d^p \) have the following forms.

For \( i = 1 \),
\[
N^{(1)} = [e_{1,1}, \ldots, e_{1,t}] \otimes t^{-1} \mathbf{1}_{t} = t^{-1}[l_{t} \otimes J_{t}],
\]
\[(13)\]

For \( i = 2q, q = 1, \ldots, [p/2] \),
\[
N^{(2q)} = \left[ j_{q-1} \otimes j_{q-1} J_{q-1} \otimes j_{q-1} \cdots j_{q-2} \otimes j_{q-2} \otimes j_{q-1} \otimes j_{q-1} \cdots j_{q-2} \otimes j_{q-2} \otimes j_{q-1} \right] = \left[ \Gamma_{3-q} \otimes \Gamma_{3-q} \Gamma_{3-q} \cdots \Gamma_{3-q} \otimes \Gamma_{3-q} \right]
\]
\[(14)\]

For \( i = 2q+1, q = 1, 2, \ldots, [(p+1)/2] - 1 \),
\[
N^{(2q+1)} = \left[ j_{q-1} \otimes j_{q-1} J_{q-1} \otimes j_{q-1} \cdots j_{q-2} \otimes j_{q-2} \otimes j_{q-1} \otimes j_{q-1} \cdots j_{q-2} \otimes j_{q-2} \otimes j_{q-1} \right] = \left[ \Gamma_{3-q} \otimes \Gamma_{3-q} \right]
\]
\[(15)\]

P4: The ordered treatment pairs of the form \( (k, k+1), k = 0, \ldots, t-1 \), occur on the same unit exactly \( t \) times in the pairs of periods given by \( (i, i+2) \). So, these treatment pairs occur in periods two apart on the same unit \( t(p-2) \) times. Similarly, the ordered treatment pairs of the form \( (k, k+2), k = 0, \ldots, t-1 \), occur on the same unit exactly \( t \) times in the pairs of periods given by \( (i, i+4) \). So, these treatment pairs occur in periods four apart on the same unit \( t(p-4) \) times. Generalizing this, the treatment pairs of the form \( (k, k+h), k = 0, \ldots, t-1 \), occur in periods \( 2h \) apart on the same unit a total of \( a_h \) times, where
\[
a_h = t(p-2h) \quad \text{for} \quad h = 1, \ldots, \left[\frac{p-1}{2}\right], \quad \text{and} \quad a_0 = 0 \quad \text{otherwise}.
\]
\[(16)\]

P5: For design \( d_p \), the ordered treatment pairs of the form \( (k, k+h), k = 0, \ldots, t-1 \), occur together in the same unit a total of \( b_h \) times, where
\[
b_h = t(p-2h) \quad \text{for} \quad h = 1, \ldots, \left[\frac{p-2}{2}\right], \quad \text{and} \quad b_0 = 0 \quad \text{otherwise}.
\]
\[(17)\]

Theorem 3.1 gives the main result of this subsection and shows that a design \( d^p \), selected as \( p \) consecutive periods from \( d_{\text{full}} \), belongs to the class \( \Omega_{t, t^2, p} \) of adjusted orthogonal designs as defined in Section 2. This result is used in Section 3.2 to obtain the information matrix for estimating the direct effects in any such design \( d^p \) under the additive model (1) and the interaction repeated measurements model (3). The proof of the theorem is given in Appendix A.

**Theorem 3.1.** A design \( d^p \) has adjusted orthogonality and, consequently, belongs to \( \Omega_{t, t^2, p} \).

### 3.2. Information matrix for direct effects in design \( d^p \)

From Theorem 3.1, \( d^p \) belongs to \( \Omega_{t, t^2, p} \) and, consequently, under the repeated measurements interaction model (3), the general form of the information matrix for estimating direct effects after adjusting for unit, period, residual and interaction effects is given by (10). In Theorem 3.2, we show that this information matrix for estimating the contrasts in the direct effects, \( P^{c}_{s} \) with \( P = P_{1} \otimes t^{-1/2} \mathbf{1}_{p} \), can be expressed in a compact form as a sum of circulant matrices. This form is useful as we can exploit the properties of eigenvalues of circulant matrices to calculate the efficiency of the design (see Section 3.3.3 and Example 4.1). We first introduce some notation and some results which will be used to prove the theorem.

Let
\[
n_1 = \sum_{i=1}^{p-1} \left[ \frac{p+1-i}{2} \right], \quad n_2 = \sum_{i=1}^{p-2} \left[ \frac{p-i}{2} \right], \quad n_3 = \left[ \frac{p}{2} \right]
\]
\[(18)\]

and let
\[
c_h = t \quad \text{for} \quad h = 1, \ldots, \left[\frac{p-1}{2}\right], \quad \text{and} \quad c_0 = 0 \quad \text{otherwise}.
\]
\[(19)\]
Lemma 3.1. With $\Gamma_h$ as defined in (12), and $a_h$, $b_h$, $c_h$ as in (16), (17) and (19),

$$PC_{d^p}P' = (p-1)I_t - 2n_1p^{-1}t^{-1}J_t - p^{-1}t^{-1} \sum_{h=1}^{t-1} (a_{h} + a_{t-h})\Gamma_{h+1},$$

$$QC_{d^p}Q' = p^{-1}(p-1)^2I_t - p^{-1}t^{-1}[(p-1)(2p-1) - 2n_1]J_t - p^{-1}t^{-1} \sum_{h=1}^{t-1} (b_{h} + b_{t-h})\Gamma_{h+1},$$

$$PC_{d^p}Q' = -p^{-1}(p-1)I_t + p^{-1}t^{-1}[(p-1)(2p-1) - 2n_1]I_t - p^{-1}t^{-1} \sum_{h=1}^{t-1} (c_{t-h} + b_{h} + b_{t-h})\Gamma_{h+1}. \quad (20)$$

Proof of Lemma 3.1. The proof of the lemma is given in Appendix B. □

The following corollary, whose proof follows from Lemma 3.1, together with the facts that $J_t = \sum_{h=1}^{t} \Gamma_h$ and $I_t = \Gamma_1$, leads to the main result of this subsection, namely Theorem 3.2.

Corollary 3.1.

$$PC_{d^p}P' = \sum_{h=0}^{t-1} d_h\Gamma_{h+1}, \quad QC_{d^p}Q' = \sum_{h=0}^{t-1} f_h\Gamma_{h+1}, \quad PC_{d^p}Q' = p^{-1} \sum_{h=0}^{t-1} g_h\Gamma_{h+1} \quad (21)$$

where for $h=1, \ldots, t-1$

$$d_0 = (p-1) - p^{-1}t^{-1}2n_1, \quad f_0 = p^{-1}t^{-1}[(p-1)(tp-t-1) - 2n_2],$$

$$g_0 = -t^{-1}[(p-1)(t-p) + 2n_2 + n_3],$$

$$d_h = -p^{-1}t^{-1}[(a_h + a_{t-h}) + 2n_1], \quad f_h = -p^{-1}t^{-1}[(b_h + b_{t-h}) + (p-1) + 2n_2],$$

$$g_h = t^{-1}[(p-1) - 2n_2 - n_3 - c_{t-h} - b_h - b_{t-h}]. \quad (22)$$

Theorem 3.2. For both the interaction repeated measurements model (3) and the additive model (1), the information matrix $C_{d^p}$ for estimating the direct effect contrasts $P_{d^p}$ in $d^p$ is given by

$$C_{d^p} = \sum_{h=0}^{t-1} m_h\Gamma_{h+1}, \quad (23)$$

where

$$m_h = d_h - p^{-2} \sum_{k=0}^{t-1} \theta_k \left( \sum_{l=0}^{t-1} g_{l(k-h)} \right), \quad h = 0, \ldots, t-1, \quad (24)$$

with

$$\theta_k = t^{-1} \sum_{j=1}^{t-1} \mu_{jk}^{-1} \cos(2\pi jk/t), \quad (25)$$

and $d_0$, $g_0$ as in (22), and $\mu_0, \mu_1, \ldots, \mu_{t-1}$ being the eigenvalues of the matrix $QC_{d^p}Q'$.

Proof of Theorem 3.2. Since $\Gamma_h$ are circulant permutation matrices, it follows from John and Williams (1995, Appendix A7) that the eigenvalues of the symmetric matrix $QC_{d^p}Q'$ in (21) are $\mu_0 = 0$, $\mu_k = \sum_{h=0}^{t-1} \theta_h \cos(2\pi kh/t)$, $k=1, \ldots, t-1$, and a generalized inverse is

$$(QC_{d^p}Q')^{-1} = \left( \sum_{h=0}^{t-1} f_h\Gamma_{h+1} \right)^{-1} = \sum_{h=0}^{t-1} \theta_h\Gamma_{h+1}, \quad (26)$$

where $\theta_h$ is given in (25). From (10), (12), (21), (22), (26), and the fact that $d^p$ has adjusted orthogonality, it follows that

$$C_{d^p} = \sum_{h=0}^{t-1} d_h\Gamma_{h+1} - p^{-2} \left( \sum_{j=0}^{t-1} g_j\Gamma_{j+1} \right) \left( \sum_{k=0}^{t-1} \theta_k\Gamma_{k+1} \right) \left( \sum_{l=0}^{t-1} g_l\Gamma_{l+1} \right) \quad \text{with } i=j+k$$
and when

\[ H = K^r \]

Hence, for the model with or without interactions,\( C_p^* = C_{\text{full}} \), and trace \( K^* \) is proved.

3.3. Examples of information matrices for special cases

3.3.1. Design with \( p = 2t \)

Consider the design \( d^{2t} = d_{\text{full}} \) for any \( t \). From (18), (16), (17), we have

\[ n_1 = t^2, \quad n_2 = 2(t-1), \quad n_3 = t, \quad a_h + a_{t-h} = 2t^2, \quad b_h + b_{t-h} = 2t(t-1), \quad c_h = t. \]

Thus from (22), \( g_0 = 0, \quad d_0 = 2(t-1), \quad g_h = 0, \quad d_h = -2 \) for all \( h \neq 0 \). Consequently, from (21), \( P_{d_{\text{full}}} Q' = 0 \) and hence from (10) and (21),

\[ C_{d_{\text{full}}}^* = 2(t-1)I_1 - 2 \sum_{h=1}^{t-1} I_{h+1} = 2[(t-1)I_1 - (I_{t-1})] = 2t(I_1 - t^{-1}I_1). \]

So, for the model with or without interactions, the design \( d_{\text{full}} \) has a completely symmetric information matrix for direct effects.

3.3.2. Design with \( p = 2t - 1 \)

Consider the design \( d^{2t-1} \) with \( p = 2t - 1 \). When \( h \neq 1 \),

\[ b_h + b_{t-h} = t(p-1-2h) + t(p-1-2(t-h)) = 2t(t-2) \]

and when \( h = 1 \), \( b_1 + b_{t-1} = b_1 + 0 = 2t(t-2) \). Therefore,

\[ n_1 = (t-1), \quad n_2 = (t-1)^2, \quad n_3 = t-1, \quad a_h + a_{t-h} = 2t(t-1), \quad b_h + b_{t-h} = 2t(t-2), \quad c_h = t. \]

Now, from Corollary 3.1,

\[ g_0 = -t^{-1}(t-1), \quad g_h = t^{-1} \text{ for all } h = 1, \ldots, t-1. \]

\[ f_0 = \frac{2(t-1)(2t-3)}{2t-1}, \quad f_h = \frac{2(2t-3)}{2t-1}, \quad d_0 = \frac{4(t-1)^2}{2t-1}, \quad d_h = -\frac{4(t-1)}{2t-1}. \]

Hence, from (21)

\[ P_{d_{\text{full}}} I' = \frac{4t(t-1)}{2t-1}(I_1 - t^{-1}I_1), \quad P_{d_{\text{full}}} Q' = -\frac{1}{2t-1}(I_1 - t^{-1}I_1), \quad Q_{d_{\text{full}}} Q' = \frac{2t(2t-3)}{2t-1}(I_1 - t^{-1}I_1) \]

and, from (10), we have

\[ C_{d_{\text{full}}}^* = \frac{4t(t-1)}{2t-1}(I_1 - t^{-1}I_1) - \frac{1}{2t-1} \left[ \frac{2t(2t-3)}{2t-1} \right]^{-1} \left[ \frac{-1}{2t-1} \right](I_1 - t^{-1}I_1) = \frac{8t^2(t-1)(2t-3)-1}{2t(2t-1)(2t-3)}(I_1 - t^{-1}I_1). \]

Hence, for the model with or without interactions, \( d^{2t-1} \) has a completely symmetric information matrix for direct effects.

3.3.3. An example for design with \( p = t \)

Consider the design \( d^t \) with \( p = t = 4 \). We can easily verify that \( n_1 = 4, n_2 = 2, n_3 = 2; a_1 = 8, b_1 = 4, c_1 = 4 \). From Corollary 3.1 and Theorem 3.2, we have

\[ d_0 = t-1 - t^{-2}2n_1 = 5/2, \quad d_1 = -t^{-2}(a_1 + a_3 + 8) = -1, \quad d_2 = -1/2, \quad d_3 = -1, \quad g_0 = -t^{-1}(2n_2 + n_3) = -3/2, \quad g_1 = t^{-1}[t(t-1) - 2n_2 - n_3 - b_1 - b_3 - c_3] = 1/2, \quad g_2 = 3/2, \quad g_3 = -1/2. \]

\[ f_0 = t^{-2}[(t-1)(t^2 - t - 1) - 2n_2] = 29/16, \quad f_1 = -(b_1 + b_3 + 7)/16 = -11/16, \quad f_2 = -7/16, \quad f_3 = -11/16. \]
\[ \mu_0 = \sum_{h=0}^{3} f_h \cos(0) = 0, \quad \mu_1 = \sum_{h=0}^{3} f_h \cos(2\pi h/4) = 9/4, \]
\[ \mu_2 = \sum_{h=0}^{3} f_h \cos(\pi h) = 11/4, \quad \mu_3 = \sum_{h=0}^{3} f_h \cos(3\pi h/2) = 9/4, \]
\[ \theta_0 = 1/4 \sum_{j=1}^{3} \mu_j^{-1} = 0.31313, \quad \theta_2 = 1/4 \sum_{j=1}^{3} \mu_j^{-1} \cos(\pi j) = -0.13131, \]
\[ \theta_1 = \theta_3 = 1/4 \sum_{j=1}^{3} \mu_j^{-1} \cos(\pi j/2) = -0.0909, \]
\[ m_0 = 5/2 - \frac{2.22222}{16} = 2.36111, \quad m_1 = -16/16 - 0 = -1, \]
\[ m_2 = -1/2 - \frac{2.22222}{16} = -0.36111, \quad m_3 = -1 \]

Then, from (23), we have
\[ C_d = \begin{bmatrix} 2.36111 & -1.00000 & -0.36111 & -1.00000 \\ -1.00000 & 2.36111 & -1.00000 & -0.36111 \\ -0.36111 & -1.00000 & 2.36111 & -1.00000 \\ -1.00000 & -0.36111 & -1.00000 & 2.36111 \end{bmatrix} \]

So, for the interaction repeated measurements model, \( d^i \) does not have a completely symmetric information matrix for direct effects and the nonzero eigenvalues of\( C_d \) are \( \sum m_k \cos(\pi k/2) = 2.36115 + (-0.36115)(-1) = 2.72223 \) twice and one 4. The eigenvalues will be used in Example 4.1 to obtain the efficiency of the design \( d^i \).

### 4. Efficiency bounds for the average variance of direct effects

In this section, we develop lower bounds on the \( A \)-efficiency (average variance efficiency) of sets of contrasts in the direct effects under the interaction repeated measurements model (3). The bounds are used to show that the designs in the class under study can be highly efficient.

#### 4.1. Preliminaries

In general, let \( d \) be a crossover design in \( \Omega_{t,n,p} \) and let \( A \) be the set of all \( t! \) permutations of treatments \( 0, \ldots, t-1 \). Let \( \sigma d \), \( \sigma \in A \), be the design resulting from \( d \) by the permutation \( \sigma \) of the treatments in \( d \). We define
\[ \bar{C}_d = \sum_{\sigma \in A} C_{\sigma d}/t!, \quad \bar{C}^\circ_d = \sum_{\sigma \in A} C^\circ_{\sigma d}/t!, \quad \bar{N}_d = \sum_{\sigma \in A} N_{\sigma d}/t!, \quad \bar{V}_d = \sum_{\sigma \in A} V_{\sigma d}/t. \]

Thus, for a design \( d \in \Omega_{t,n,p} \), from Eqs. (9) and (10), we have
\[ \bar{C}_d = \bar{P} \bar{C}_d \bar{P} - \sum_{\sigma \in A} (PC_{\sigma d}Z)(ZC_{\sigma d}Z)^\circ (PC_{\sigma d}Z)^\circ/t! \]

and
\[ \bar{C}^\circ_d (no \ int) = \bar{P} \bar{C}^\circ_d \bar{P} - \sum_{\sigma \in A} (PC_{\sigma d}Q)(QC_{\sigma d}Q)^\circ (PC_{\sigma d}Q)^\circ/t!. \]

We write \( M \succ N \) if \( M - N \) is a positive semi-definite matrix. From Majumdar and Notz (1983), we know that \( \phi(C_d) \leq \phi(C^\circ_d) \), for any \( \phi \) that is (i) a convex real-valued nonincreasing (with respect to \( \succ \) ) possibly infinite function on the set of all \( t \times t \) non-negative definite matrices and (ii) invariant under permutations. For the expressions for \( \bar{C}_d \) and \( \bar{C}^\circ_d (no \ int) \) given above, \( C_{\sigma d} \) is a positive semi-definite matrix and the terms in the sum are symmetric. Hence, we have \( \bar{C}_d \preceq \bar{P} \bar{C}_d \bar{P} \) and \( \bar{C}^\circ_d (no \ int) \preceq \bar{P} \bar{C}^\circ_d \bar{P} \) and
\[ \phi(\bar{P} \bar{C}_d \bar{P}) \preceq \phi(\bar{C}_d) \leq \phi(\bar{C}^\circ_d) \]
and
\[ \phi(\bar{P} \bar{C}^\circ_d \bar{P}) \preceq \phi(\bar{C}^\circ_d (no \ int)) \]

Since model (1) has fewer terms than model (3), the following lemma is natural and we give a formal proof below.
Lemma 4.1. For \( d \in \Omega_{t,n,p}, C_d \preceq C_d^*(\text{no int}), \) with equality if and only if \( d \) has adjusted orthogonality.

**Proof of Lemma 4.1.** Define \( S = (QC_d Q^\top)^{-1} O C_d R^\top \) and \( H = R C_d R^\top - R C_d Q S, \) Then from (9) and (10), we have

\[
C_d = P C_d P^\top - [P C_d Q^\top C_d R^\top] \begin{bmatrix} (QC_d Q^\top)^{-1} + SH'S' & -SH' \\ -H'S' & H' \end{bmatrix} \begin{bmatrix} QC_d P \\ R C_d P \end{bmatrix}
\]

\[
= P C_d P^\top - [P C_d Q^\top C_d R^\top] \begin{bmatrix} (QC_d Q^\top)^{-1} \\ 0 \end{bmatrix} [-PC_d Q^\top C_d R^\top] \begin{bmatrix} SH'S' & -SH' \\ -H'S' & H' \end{bmatrix} \begin{bmatrix} QC_d P \\ R C_d P \end{bmatrix}
\]

\[
= C_d^*(\text{no int}) - [P C_d Q^\top C_d R^\top] \begin{bmatrix} [-S \\ I] H' [-S' \\ I] \end{bmatrix} \begin{bmatrix} QC_d P \\ R C_d P \end{bmatrix}.
\]

Since \( H \) is a positive semi-definite matrix and the second term on the right hand side is symmetric, the lemma follows. \( \square \)

From (29) and Lemma 4.1, we have

\[
\phi (P C_d P^\top) \leq \phi (C_d^*(\text{no int})) \leq \phi (C_d^*).
\]

(30)

For the \( A \)-criterion, \( \phi (C_d^*) = \text{trace}((C_d^*)^{-1}), \) which is a convex non-increasing function and invariant under treatment permutations. The \( A \)-efficiency of the direct effects for a design \( d_0 \in \Omega_{t,n,p} \) is defined as

\[
E_{A,d_0} = \frac{\min_{d \in \Omega_{t,n,p}} \phi (C_d^*)}{\phi (C_{d_0})} = \frac{\min_{d \in \Omega_{t,n,p}} \text{trace}((C_d^*)^{-1})}{\phi (C_{d_0})} = \frac{\min_{d \in \Omega_{t,n,p}} \phi (C_d^*)}{\phi (C_{d_0})}.
\]

(31)

Using the Eqs. (30) and (31) the following inequality holds for \( d_0 \in \Omega_{t,n,p}. \)

\[
\frac{\min_{d \in \Omega_{t,n,p}} \phi (P C_d P^\top)}{\phi (C_{d_0})} \leq \frac{\min_{d \in \Omega_{t,n,p}} \phi (C_d^*(\text{no int}))}{\phi (C_{d_0})} \leq \frac{\min_{d \in \Omega_{t,n,p}} \phi (C_d^*)}{\phi (C_{d_0})} = E_{A,d_0}.
\]

Notice that, as expected, these inequalities imply that a design that is \( A \)-optimal for the model with no interactions is \( A \)-optimal for the model with interactions if \( C_d = C_d^*(\text{no int}); \) that is, for designs in \( \Omega_{t,n,p}. \) The above inequalities will next be used to develop lower bounds on the \( A \)-efficiencies of certain designs.

### 4.2. \( A \)-efficiency bounds for the average variance of direct effects for a crossover design which is uniform on periods

For a design \( d \in \Omega_{t,n,p}, \) for \( s,k = 0,\ldots,t-1, \) define

- \( r_s = \text{number of appearances of treatment } s \) in the design,
- \( \bar{r}_s = \text{number of appearances of treatment } s \) in the first \( p-1 \) periods of the design,
- \( q_{sk} = \text{number of appearances of treatment pairs } (s,k) \) on the same unit not necessarily in consecutive periods,
- \( \bar{q}_{sk} = \text{number of appearances of treatment pairs } (s,k) \) on the same unit in the first \( p-1 \) periods, not necessarily in consecutive periods,
- \( z_{sk} = \text{number of appearances of treatment pairs } (s,k) \) on the same unit where treatment \( s \) comes in period \( p \) and treatment \( k \) in period \( i, (i = 1,\ldots,p-1), \)
- \( m_{sk} = \text{number of appearances of treatments } s \) and \( k \) in consecutive periods on the same unit with \( s \) being preceded by \( k. \)

After averaging over all \( t! \) permutations of the \( t \) treatments it is not hard to show that the averaged values of the design parameters listed above are as follows:

- \( \bar{r}_s = tp, \quad \bar{r}_s = t(p-1), \quad (s = 0,\ldots,t-1), \)
- \( \bar{m}_{ss} = \alpha_1, \quad \bar{m}_{sk} = \beta_1, \quad (s \neq k; \ s,k = 0,\ldots,t-1), \)
- \( q_{ss} = \alpha_2, \quad \bar{q}_{sk} = \beta_2, \quad (s \neq k; \ s,k = 0,\ldots,t-1), \)
- \( q_{sk} = \alpha_3, \quad \bar{q}_{sk} = \beta_3, \quad (s \neq k; \ s,k = 0,\ldots,t-1), \)
- \( z_{ss} = \alpha_4, \quad z_{sk} = \beta_4, \quad (s \neq k; \ s,k = 0,\ldots,t-1), \)
Hence since note that \(d \) has units. After computing \(\nabla_{d_1} \) from (6), we get

\[
\nabla_{d_1} = t^{-1}(I_t \otimes J_t) + \text{diag}(\overline{m}_{00}, \overline{m}_{01}, \ldots, \overline{m}_{t-1,t-1}) = t^{-1}(I_t \otimes J_t) + \beta_1(I_t \otimes I_t) + (x_1 - \beta_1) \sum_{h=0}^{t-1} j_h j_h = \frac{(t-1)p}{\beta_2} \equiv L_{\beta_2}. 
\]

Then,

\[
P\nabla_{d_1} = t^{-1}(P_1 \otimes t^{-1/2} 1, P_2 \otimes t^{-1/2} 1) + \beta_1 P_1 P_1 + (x_1 - \beta_1) \sum_{s=1}^n (P_1 \otimes t^{-1/2} 1)(1, 1, 1, \ldots, 1) = t^{-1}[P_1 P_1 + \beta_1 P_1 P_1 + (x_1 - \beta_1) \sum_{h=0}^{t-1} j_h j_h] = \beta_1 (I_t - t^{-1} I_t)
\]

Again, from the form of \(P N_{d_1} P \) in the proof of Lemma 3.1, we have

\[
P N_{d_1} P = t^{-1}[P_1 ((p + 2)x_2) I_t + \beta_2 (I_t - I_t)] P_1 = t^{-1}[p + 2x_2 - \beta_2] (I_t - t^{-1} I_t) = (\beta_2 - \beta_2) (I_t - t^{-1} I_t)
\]

on simplification using (32). Hence

\[
P\nabla_{d_1} = t^{-1} P N_{d_1} P = t^{-1} \beta_2 (I_t - t^{-1} I_t).
\]

Therefore

\[
\text{trace}(t^{-1} P N_{d_1} P) = \frac{(t-1)\beta_2}{p}.
\]

Now noting that

\[
\text{trace}(t^{-1} P N_{d_1} P) = \frac{(t-1)^2 \beta_2}{p}
\]

the proof is complete.

In \(L_{\beta_2} \equiv (t-1)p/\beta_2 \) the value of \(\beta_2 \) depends on the design. We now propose two lower bounds for \(L_{\beta_2} \) based on upper bounds for \(\beta_2 \).

Firstly, for any arbitrary design \(d \in \Omega_{t,P,p} \), \(x_2 \geq 0 \) and so from (32), we get \(\beta_2 \leq \frac{tp(t-1)}{t-2} \). Thus,

\[
L_{\beta_2} \geq \frac{(t-1)^2}{(t-2)} = L_1.
\]

Then, from (34), \(L_1 \) is a lower bound for \(\min_{d \in \Omega_{t,P,p}} \text{trace}(C_n) \).

Next, suppose that \( t < p \). Recall that we have \(p \leq 2t \). Then, in every unit at most \(p-t \) treatments appear more than once. It is not hard to show that for each unit \(\sum_{s=1}^n q_{ss} \geq p-t \) so that with \(n = t^2 \), \(x_2 \geq \frac{t^2(p-t)}{t} \). Hence \(\beta_2 \leq \frac{t^4(p-t)}{(t-2)(t-1)} \) and
Thus the design

\[ L_p \geq \frac{(t-1)^2 p}{t(p-1) - 2(p-t)} \equiv L_2 \]

is a lower bound for \( \min_{d \in \Omega_{k,p}} \text{trace}(C_d^{-1}) \) when \( p > t \).

**Remark.** It may be noted that \( L_1 \) is a general bound, but when \( p > t \), then \( L_2 \) is tighter and becomes the general bound. These bounds obtained above for the particular case \( n=t^2 \) may be easily extended for the general case where \( n = \mu_1 t^2 \) for integer \( \mu_1 \geq 1 \).

**Example 4.1** (\( d^4 \) and \( d^5 \)). Consider the design \( d^4 \in \Omega_{4,16,4} \) which was studied in Section 3.3.3. Note that \( C_{d^4} = C_{d^4}(\text{no int}) \). Here \( p=t \) so we use the lower bound \( L_1 \). The nonzero eigenvalues of \( C_{d^4} \) are 4, 2.72, 2.72. Here \( L_1 = 0.75 \) and so \( E_{A,d^4} \) is bounded below by \( 0.75/(1/4 + 2/2.72) = 0.76 \). Thus the design \( d^4 \) has at least 0.76 efficiency.

Next, consider the design \( d^5 \in \Omega_{4,16,5} \). Here \( p > t \) so we will use the lower bound \( L_2 \).

Note that \( C_{d^5} = C_{d^5}(\text{no int}) \). The nonzero eigenvalues of \( C_{d^5} \) are 4.8, 4.275, and 4.275. Here \( L_2 = 5/8 \) and so \( E_{A,d^5} = 0.92 \). Thus the design \( d^5 \) is efficient with at least 0.92 efficiency.

**Example 4.2.** Consider the design \( d_{full} \in \Omega_{t^2,2t,t} \) which was considered in Section 3.3.1. Here \( p > t \) so we use bound \( L_2 \). Note that \( C_{d_{full}} = 2t(i_1-j_1)/t \), which has \( t-1 \) nonzero eigenvalues all equal to \( 2t \). Here \( L_2 = (t-1)/2t \), and so \( E_{A,d_{full}} \) is equal to 1. Thus for \( d_{full} \), the lower bound is attained. This result is well known; see Bose and Mukherjee (2003).

In general, a design is better for the model without interactions is not necessarily better for the model with interactions. This is illustrated in the following example.

**Example 4.3.** Consider the design \( d^4 \) in Example 4.1 and \( d_a \) (which is not a strongly balanced design) shown below

\[
\begin{align*}
    d_a : & 0 0 0 0 1 1 1 1 2 2 2 3 3 3 \\
        & 0 1 2 3 1 2 3 0 2 3 0 1 3 0 1 2 \\
        & 1 2 3 1 0 3 0 2 0 1 3 3 1 2 2 0 \\
        & 2 3 1 2 3 0 2 3 0 1 0 2 1 0 1
\end{align*}
\]

The eigenvalues of \( C_{d^4} = C_p(\text{no int}), C_{d^4}(\text{no int}) \) and \( C_{d_a} \) are, respectively,

\[
\{4.2, 7.2, 2.72\}, \{3.77, 3.37, 2.84\}, \{2.48, 2.25, 1.93\}.
\]

We see that \( d_a \) is more efficient than \( d^4 \) for the model without interactions, whereas \( d^4 \) is better than \( d_a \) for the model with interactions.

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**Appendix A. Proof of Theorem 3.1**

Here \( n = t^2 \). Property P2 implies that \( \sum_{i=1}^{n} \lambda_i = 1 \) for each \( i = 1, \ldots, p \) and from (8) it follows that \( M_{d^p} = J_{t^2,p} \). So, \( (1/n)M_{d^p} M_{d^p} = (p/n)J_{2t} = (1/np)(M_{d^p} 1_p)(M_{d^p} 1_p)' \). So, from (5), \( C_{d^p} \) is given by

\[
C_{d^p} = V_{d^p} = \frac{1}{p} N_{d^p} N_{d^p}'.
\]

By definition \( d^p \) belongs to the class \( \Omega_{t^2,n} \) if (11) holds. So, from (35) it is enough to show that

\[
(a) \quad PV_{d^p} R = QV_{d^p} R = 0 \quad \text{and} \quad (b) \quad PN_{d^p} N_{d^p} R = QN_{d^p} N_{d^p} R = 0,
\]

where \( P = P_1 \otimes t^{-1/2} 1_t \), \( Q = t^{-1/2} 1_t \otimes P_1 \) and \( R = P_1 \otimes P_1 \) and where \( P_1 = (I_t - t^{-1} J_t) \).

From (6),

\[
V_{d^p} = \sum_{i=1}^{p} \sum_{j=1}^{n} (e_{ij} \otimes e_{i-1,j})(e_{ji} \otimes e_{i-1,j})
\]

\[
= \sum_{j=1}^{n} e_{i,j} e_{i,j}^* \otimes e_{0,j} e_{0,j}^* + \sum_{i=2}^{p} \sum_{j=1}^{n} e_{ij} e_{ij}^* \otimes e_{i-1,j} e_{i-1,j}^*
\]

\[
= t^{-2} \sum_{j=1}^{n} e_{i,j} e_{i,j}^* \otimes J_t + \sum_{i=2}^{p} \left[ \sum_{j=1}^{n} e_{ij} e_{ij}^* \otimes (e_{i-1,j} e_{i-1,j}^*) \right]
\]

\[
= t^{-1}[I_t \otimes J_t] + (p-1)J_t.
\]
by properties P1 and P2. Since $P_i$ is a symmetric contrast matrix, and $\mathbf{1}_i P_1 = \mathbf{0}$ and $PR = QR = \mathbf{0}$, it follows that

$$PV_{12} R = t^{-1}(P_1 \otimes t^{1/2} \mathbf{1}_i)(P_1 \otimes P_1) + (p-1)PR = \mathbf{0},$$

(37)

$$QV_{12} R = t^{-1}(t^{-1/2} \mathbf{1}_i \otimes P_1)(P_1 \otimes P_1) + (p-1)QR = \mathbf{0}.$$

(38)

Thus, (36a) is proved. Now, $N_{12} = \sum_{i=1}^p N^{(i)}$, and so $N_{12} N_{12} = \sum_{i=1}^p \sum_{j=1}^p N^{(i)} N^{(j)}$. Hence, in order to prove (36b), it is enough to show that

$$PN^{(i)} N^{(i)'} R = \mathbf{0}, \quad QN^{(i)} N^{(i)'} R = \mathbf{0} \quad \text{for all } i,i' = 1,2,\ldots,p.$$

(39)

First set $i' = 1$. Then from (13) and the fact that $P_1 \mathbf{1}_1 = \mathbf{0}$, we have $N^{(1)} R = \mathbf{0}$ and $QN^{(1)} = \mathbf{0}$, and so

$$PN^{(i)} N^{(1)'} R = QN^{(i)} N^{(1)'} R = QN^{(i)} N^{(1)} R = \mathbf{0} \quad \text{for all } i = 1,2,\ldots,p.$$

(40)

From (13)–(15),

$$N^{(1)} N^{(2q+1)} R = t^{-1}(I_t \otimes J_t)(I_{q} \otimes I_{q-1}) R = t^{-1}(I_{q} \otimes J_t)(P_1 \otimes P_1) = \mathbf{0}$$

and

$$RN^{(2q)} N^{(1)} [P_1 I_{3-q} P_1 J_{q-1} P_1 I_{3-q} P_1 J_q \ldots P_1 I_{3-q} P_1 J_{q-2}] \times t^{-1}[I_t \otimes (J_t \otimes 1)] = \mathbf{0}.$$

Consequently,

$$PN^{(1)} N^{(0)'} R = \mathbf{0} \quad \text{for all } i = 1,\ldots,p.$$

(41)

Now let $i$ and $i'$ both be even integers or both be odd integers ($> 1$). From (14),

$$N^{(2q)} N^{(2q)} = \sum_{i=0}^{i=q} \sum_{j=0}^{j=q} \Gamma_{3-q} \Gamma_{3-q} \otimes \mathbf{J}_q \mathbf{J}_q \ldots \mathbf{J}_q \mathbf{J}_q = \Gamma_{3-q} \Gamma_{3-q} \otimes \mathbf{I}_{3-q} \mathbf{I}_{3-q}.$$

(42)

Similarly,

$$N^{2q+1} N^{2q+1} = (\Gamma_{2-q} \otimes \Gamma_{2-q}) (\Gamma_{3-q} \otimes \Gamma_{3-q}) = \Gamma_{3-q} \Gamma_{3-q} \otimes \Gamma_{3-q} \Gamma_{3-q}.$$

So,

$$PN^{(2q)} N^{(2q)} R = PN^{(2q+1)} N^{(2q+1)} R = (P_1 \Gamma_{s-q+1} \otimes t^{-1/2} \mathbf{1}_i)(P_1 \otimes P_1) = \mathbf{0}$$

and

$$QN^{(2q)} N^{(2q)} R = QN^{(2q+1)} N^{(2q+1)} R = \left(t^{-1/2} \mathbf{1}_i \otimes P_1 \Gamma_{s-q+1}\right) (P_1 \otimes P_1) = \mathbf{0}.$$

Hence

$$PN^{(i)} N^{(i)'} R = QN^{(i)} N^{(i)'} R = \mathbf{0} \quad \text{for all even } i,i' \text{ or odd } i,i'.$$

(42)

Now, let $i$ even and $i'$ be odd. From (14) and (15), we have

$$PN^{(2q)} N^{(2q+1)} R = t^{-1/2} [P_1 \Gamma_{3-q} P_1 \Gamma_{3-q} \ldots P_1 \Gamma_{3-q}][G^{(2q+1)} R]$$

$$= t^{-1/2} [\mathbf{1}_i \otimes P_1 \Gamma_{3-q}][G_{\Gamma_3} \otimes G_{\Gamma_3} R]$$

$$= t^{-1/2} [\mathbf{1}_i \otimes P_1 \Gamma_{3-q} \Gamma_{3-q}](P_1 \otimes P_1) = \mathbf{0}. $$

(43)

Also, $QN^{(2q)} = t^{-1/2} [\mathbf{1}_i \otimes P_1 J_{q-1} \mathbf{1}_i \otimes P_1 J_q \ldots \mathbf{1}_i \otimes P_1 J_{q-2}].$ Since, for any $t \times 1$ vector $a$, the identity $\mathbf{1}_i \otimes a = a \otimes \mathbf{1}_i$ holds, we have

$$QN^{(2q)} N^{(2q+1)} R = (P_1 J_{q-1} P_1 J_q \ldots P_1 J_{q-2}) \otimes \mathbf{1}_i (\Gamma_{3-q} P_1 \otimes \Gamma_{3-q} P_1) = \mathbf{0}. $$

(44)

Now, let $i$ be odd and $i'$ be even, and write $P_1 = [p_1 p_2 \ldots p_l]$, where $p_j$ is the $j$th column of $P_1$. Then,

$$PN^{(2q+1)} = (p_1 p_2 \ldots p_l) \otimes t^{-1/2} \mathbf{1}_i (\Gamma_{3-q} \otimes \Gamma_{3-q})$$

$$= t^{-1/2} [p_1 p_{q+1} \ldots p_{q-1}] \otimes \mathbf{1}_i$$

$$= t^{-1/2} [p_1 \mathbf{1}_i p_{q+1} \mathbf{1}_i \ldots p_{q-1} \mathbf{1}_i].$$
Again using the identity $1_i \otimes a = a \otimes 1_i$, for a $t \times 1$ vector $a$, we have

$$P^{N^{(2i+1)}} \Gamma^{(2i)} \Gamma^{(2i+1)} = t^{-1/2} \left[ 1_i \otimes p_{s+1} 1_i \otimes p_{s+2} \ldots 1_i \otimes p_{s+1} \right] \Gamma_{3-s} \otimes j_{q-1}$$

$$= t^{-1/2} \left[ 1_i \otimes p_{s+1} 1_i \otimes p_{s+2} \ldots 1_i \otimes p_{s+1} \right] R^*$$

$$= t^{-1/2} \left[ 1_i \otimes p_{s+1} 1_i \otimes p_{s+2} \ldots 1_i \otimes p_{s+1} \right] (P_1 \otimes P_1) = 0.$$

(45)

Also,

$$Q^{N^{(2i+1)}} = \left[ e^{\Gamma_{3-s} \otimes [p_1 p_2 \ldots p_s]} \right] \Gamma_{3-s} = t^{-1/2} \left[ 1_i \otimes p_{s+1} 1_i \otimes p_{s+2} \ldots 1_i \otimes p_{s+1} \right]$$

$$= t^{-1/2} \left[ p_{s+1} p_{s+2} \ldots p_{s+1} \ldots p_{s+1} \right] \Gamma_{3-s} = t^{-1/2} \left[ p_{s+1} p_{s+2} \ldots p_{s+1} \right] \Gamma_{3-s} = 0.$$  

Then,

$$Q^{N^{(2i+1)}} N^{2q} = t^{-1/2} \sum_{k=1}^{t} [p_{s+q+2} \ldots p_{s+q}] \otimes j_{q-2+k}$$

$$= t^{-1/2} \left[ 1_i \otimes \sum_{k=1}^{t} j_{q-2+k} \right] \Gamma_{3-s} = t^{-1/2} \left[ 1_i \otimes \sum_{k=1}^{t} j_{q-2+k} \right] \Gamma_{3-s} = 0.$$  

and so $Q^{N^{(2i+1)}} N^{2q} \Gamma = 0$. Taking this result together with (40)–(45), proves (39) and, together with (37) and (38) shows that (36) is satisfied and hence the theorem is proved.

**Appendix B. Proof of Lemma 3.1**

In the following, $n_1$, $n_2$, $n_3$ are as defined in (18) and other parameters as in Section 4.2. From property P1, we have for any design $d^p$,

$$r = t (p-1) \quad \text{for all } s = 0, 1, \ldots, t-1.$$

(46)

From property P2, it can be seen that the total number of appearances of treatment pair $(s, s)$ on the same unit in $d^p$ in any pair of periods (not necessarily consecutive) is given by

$$q_{ss} = n_1.$$

(47)

Again, from P2 and P4, for $s \neq k$ with $a_k$ as in (16)

$$q_{sk} = 2n_1 + a_h + a_{t-h}, \quad \text{for } k = s + h,$$

(48)

and similarly, with $b_h$ as in (17),

$$q_{sk} = 2n_2 + b_h + b_{t-h}, \quad \text{for } k = s + h.$$  

(49)

From P2, it is then clear that with $c_h$ as in (19),

$$z_{ss} = n_3 \quad \text{and } z_{sk} = n_3 + c_{t-h}, \quad \text{for } k = s + h.$$  

(50)

It can be verified after some algebra that the various quantities defined above satisfy the following relations

$$\left( \frac{p}{2} \right) = t^{-1} \sum_{h=1}^{t-1} a_h + n_1, \quad \left( \frac{p-1}{2} \right) = t^{-1} \sum_{h=1}^{t-1} b_h + n_2, \quad p-1 = t^{-1} \sum_{h=1}^{t-1} c_h + n_3.$$  

(51)

From (7)

$$PN_d = P \left( \sum_{i=1}^{p} \xi_{i1}, \sum_{i=1}^{p} \xi_{i2}, \ldots, \sum_{i=1}^{p} \xi_{in} \right)$$

$$= (P_1 \otimes t^{-1/2} 1_i) \left( e_{i1} \otimes t^{-1} 1_i + \sum_{i=2}^{p} e_{i1} \otimes e_{i-1,1} \right), \ldots, \left( e_{in} \otimes t^{-1} 1_i + \sum_{i=2}^{p} e_{in} \otimes e_{i-1,n} \right)$$

$$= t^{-1/2} \left( P_1 e_{i1} + P_1 \sum_{i=2}^{p} e_{i1} \right), \ldots, \left( P_1 e_{in} + P_1 \sum_{i=2}^{p} e_{in} \right)$$

$$= t^{-1/2} P_1 \left( \sum_{i=1}^{p} e_{i1}, \ldots, \sum_{i=1}^{p} e_{in} \right)$$

(52)
Similarly, from (53), (46), (47), (48) and (51) and noting that $P_i\Gamma_h P_i = \Gamma_{h-t^{-1}J_i}$, we have

$$Q_{N_d}^d = \left( t^{-1/2} V_1 \otimes P_1 \right) \left[ \begin{array}{c} e_{11} \otimes t^{-1} I_1 + \sum_{i=2}^{p} e_{1i} \otimes e_{i-1,1} \\ \vdots \\ e_{1n} \otimes t^{-1} I_1 + \sum_{i=2}^{p} e_{1n} \otimes e_{i-1,n} \end{array} \right] = t^{-1/2} \left[ \begin{array}{c} t^{-1} P_1 I_1 + \sum_{i=2}^{p} P_1 e_{i-1,1} \\ \vdots \\ t^{-1} P_1 I_1 + \sum_{i=2}^{p} P_1 e_{i-1,n} \end{array} \right] = t^{-1/2} P_1 \left( \sum_{i=1}^{q-1} e_{i1}, \ldots, \sum_{i=1}^{q-1} e_{in} \right)$$

(53)

Thus, from (52), (46), (47), (48) and (51) and noting that $P_i\Gamma_h P_i = \Gamma_{h-t^{-1}J_i}$, we have

$$PN_d Q^d = t^{-1} P_1 \left( \sum_{i=1}^{n} \sum_{j=1}^{p} \sum_{i=1}^{p} e_{ij} e_{ij} \right) P_1$$

$$t^{-1} P_1 \left[ \sum_{j} e_{ij} e_{jj} + \sum_{j} e_{ij} e_{jj} P_1 \right] = t^{-1} P_1 \left[ \begin{array}{c} r_{0} + 2q_{00} \quad q_{01} \quad \cdots \quad q_{0t-1} \\ q_{10} \quad r_{1} + 2q_{11} \quad \cdots \quad q_{1t-1} \\ \vdots \quad \vdots \quad \vdots \\ q_{t-1,0} \quad q_{t-1,1} \quad \cdots \quad r_{t-1} + 2q_{t-1,t-1} \end{array} \right] P_1$$

$$= t^{-1} P_1 \left[ t p l_1 + 2 n_1 J_t + \sum_{h=1}^{t-1} (a_h + a_{t-h}) \Gamma_{h+1} \right] P_1$$

$$= t^{-1} P_1 \left[ t p l_1 + 2 n_1 J_t + \sum_{h=1}^{t-1} a_h (\Gamma_{h+1} + \Gamma_{t+1-h}) \right] P_1$$

$$= p p l_1 + t \sum_{h=1}^{t-1} a_h [\Gamma_{h+1} + \Gamma_{t+1-h}] - 2 J_t \sum_{h=1}^{t-1} a_h$$

$$= p l_1 - (p^2 - 2 n_1) t^{-1} J_t + t^{-1} \sum_{h=1}^{t-1} [a_h + a_{t-h}] \Gamma_{h+1}$$

(54)

Similarly, from (53), (46), (49) and (51)

$$Q_{N_d}^d Q' = t^{-1} P_1 \left( \sum_{i=1}^{n} \sum_{j=1}^{p} \sum_{i=1}^{p} e_{ij} e_{ij} \right) P_1$$

$$t^{-1} P_1 \left[ \begin{array}{c} \tilde{r}_0 + 2\tilde{q}_{00} \quad \tilde{q}_{01} \quad \cdots \quad \tilde{q}_{0t-1} \\ \tilde{q}_{10} \quad \tilde{r}_1 + 2\tilde{q}_{11} \quad \cdots \quad \tilde{q}_{1t-1} \\ \vdots \quad \vdots \quad \vdots \\ \tilde{q}_{t-1,0} \quad \tilde{q}_{t-1,1} \quad \cdots \quad \tilde{r}_{t-1} + 2\tilde{q}_{t-1,t-1} \end{array} \right] P_1$$

$$= t^{-1} P_1 \left[ \begin{array}{c} t(p-1) l_1 + 2 n_2 J_t + \sum_{h=1}^{t-1} (b_h + b_{t-h}) \Gamma_{h+1} \end{array} \right] P_1$$

$$= (p-1) l_1 - [(p-1)^2 - 2 n_2] t^{-1} J_t + t^{-1} \sum_{h=1}^{t-1} [b_h + b_{t-h}] \Gamma_{h+1}$$

(55)

Again, from (52), (53), (55), (50) and (51)

$$PN_d Q^d Q' = t^{-1} P_1 \left( \sum_{i=1}^{n} \sum_{j=1}^{p} \sum_{i=1}^{p} e_{ij} e_{ij} \right) P_1 + t^{-1} P_1 \left( \sum_{i=1}^{n} \sum_{j=1}^{p} \sum_{i=1}^{p} e_{ij} e_{ij} \right) P_1$$

$$= Q_{N_d}^d Q' + t^{-1} P_1 \left( \sum_{i=1}^{n} \sum_{j=1}^{p} \sum_{i=1}^{p} e_{ij} e_{ij} \right) P_1$$

$$= Q_{N_d}^d Q' + t^{-1} P_1 \left( \begin{array}{c} Z_{00} \quad Z_{01} \quad \cdots \quad Z_{0t-1} \\ Z_{1,0} \quad Z_{11} \quad \cdots \quad Z_{1t-1} \\ \vdots \quad \vdots \quad \vdots \\ Z_{t-1,0} \quad Z_{t-1,1} \quad \cdots \quad Z_{t-1,t-1} \end{array} \right) P_1.$$
Also, from (6) it can be shown that
\[
P_{v\varphi}P' = t^{-1}(P_1 \otimes t^{-1/2}1_t)(t^{-1/2}1_t)(P_1 \otimes t^{-1/2}1_t) + (p-1)(P_1 \otimes t^{-1/2}1_t)x(P_1 \otimes t^{-1/2}1_t) = pt^{-1}J_t.
\]
\[
Q_{v\varphi}Q' = (p-1)(t^{-1}J_t), \quad P_{v\varphi}Q' = 0.
\]
Hence the lemma follows from (35).

Appendix C. Supplementary material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jspi.2010.08.005.

References