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Optimal Designs for Carry Over Effects the Case of Two Treatment and Four Periods

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Abstract: The optimal cross-over experimental designs are derived in experiments with two treatments, four periods, and an experimental unit. The results are given for the values $n = 0 \bmod 4$, $1 \bmod 4$, $2 \bmod 4$ and $3 \bmod 4$. The criterion being the minimization of the variance of the estimated carry over effect.

Keywords: cross over designs; optimality; carry over effects

1. Introduction

The first usage of crossover experimental designs was in agriculture. In 1864 Lawes and Gilbert [1] introduced an experiment with two different treatments in the same agricultural parcel, this type of experiment has proven reliable to date. The provision of different treatments to the same experimental unit was not limited to only experiments in agriculture, it has been applied in Medicine and other scientific fields.

The majority of the experimenters search for optimal designs concerning the estimation of the parameters of a proposed model [2–10].

In crossover (or repeated measurement) designs, a sequence of treatments is applied to each experimental unit (e.u.) and one treatment is applied in each period [2]. In these designs either the estimation of the direct effect of the treatment, which is the effect of the treatment when being applied in the exam period, or the estimation of carry over, which is the effect of the treatment applied in the period before the examined one (i.e., period), can be of interest.

In the case of two treatments, A and B, the carry over δ_A and δ_B can be estimated. In this paper, the parameter of interest is the difference of carry over effects $\delta = \delta_A - \delta_B$.

In the case of optimal designs with two treatments, the model introduced by Hedayat and Afsarinejad [10] is used with slight changes and optimal designs of direct and carry over for two periods were found in [11]. Kounias and Chalikias have presented the case of three periods for direct effects and for carry over effects in [12] and for a different model with treatment period interaction for direct effect in [13]. For the case of four periods and direct effects the optimal designs are available in [14]. In our case what will specified is the case of carry over effects in two treatments A, B, and four periods.

2. Methodology

2.1. The Model

For the case of four periods there are 16 sequences of treatments

A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
A	A	B	B	A	A	B	B	A	A	B	B	A	A	B	B
A	A	A	A	B	B	B	B	A	A	A	A	B	B	B	B
A	A	A	A	A	A	A	A	B	B	B	B	B	B	B	B
u_0	u_1	u_2	u_3	u_4	u_5	u_6	u_7	u_8	u_9	u_{10}	u_{11}	u_{12}	u_{13}	u_{14}	u_{15}

where u_i , $i = 0, 1, \dots, 15$ is the number of experimental units that received the i -th sequence of treatments so $u_0 + u_1 + \dots + u_{15} = n$, and all e.u.s are n .

The model is analogous to the cases of [15,16]:

$$y_{ijk} = \mu + \tau_h + \pi_j + \delta_{i,j-1} + \gamma_i + e_{ijk} \quad (1)$$

where j corresponds to the j -th period, $j = 1, 2, 3, 4$;

i refers to the i -th sequence, $i = 0, 1, \dots, 15$;

k refers to the unit $k = 1, 2, \dots, n$;

$h = A, B$ τ_A, τ_B are direct effects of treatments A and B;

π_j : is the effect of the j -th period;

δ_A, δ_B : are the residual effects of A and B;

γ_i : is the effect of the i -th sequence; and

e_{ijk} : independent of the errors normally distributed.

The errors e_{ijk} are assumed to be independent between sequences and within sequences.

The above model (in overparameterized form) is written:

$$\mathbf{Y} = \tau_A \tau_A + \tau_B \tau_B + \delta_A \delta_A + \delta_B \delta_B + \pi_1 \pi_1 + \dots + \pi_4 \pi_4 + \gamma_0 \gamma_0 + \dots + \gamma_{15} \gamma_{15} + \mathbf{e} \quad (2)$$

and $\mathbf{Y}, \tau_A, \tau_B, \delta_A, \delta_B, \pi_1, \dots, \pi_4, \gamma_0, \dots, \gamma_{15}, \mathbf{e}$ are $1 \times 4n$ vectors; the direct effect vector is 1 if the treatment

is A, and zero if it is B. For example, for the sequence ABB... , $\tau_A = \begin{bmatrix} 1 \\ 0 \\ 0 \\ \vdots \end{bmatrix}$ is analogous to $\tau_B = \begin{bmatrix} 0 \\ 1 \\ 1 \\ \vdots \end{bmatrix}$,

$\delta_A = \begin{bmatrix} 0 \\ 1 \\ 0 \\ \vdots \end{bmatrix}$ and, in the same way, δ_B, π_i and γ_i are defined so that $\tau_A + \tau_B = \mathbf{1}_{4n}$, $\delta_A + \delta_B + \pi_1 =$

$\mathbf{1}_{4n}$, and $\pi_1 + \pi_2 + \pi_3 + \pi_4 = \mathbf{1}_{4n}$. Also, 1 when the i th unit is employed, and 0 elsewhere, so $\gamma_0 + \gamma_1 + \gamma_2 + \dots + \gamma_{15} = \mathbf{1}_{4n}$. So, in Equation (2) there are linearly dependent vectors.

In a vector form:

$$\mathbf{Y} = \mathbf{X}\mathbf{b} + \mathbf{e} \Leftrightarrow \mathbf{Y} = (\mathbf{X}_1 \mathbf{X}_2) \begin{pmatrix} \mathbf{b}_1 \\ \mathbf{b}_2 \end{pmatrix} + \mathbf{e} \quad (3)$$

where $\mathbf{Y}$ is $(4n) \times 1$, $\mathbf{b}$ is $s \times 1$, $\mathbf{X}$ is $(4n) \times s$, $\mathbf{e}$ is $(4n) \times 1$, and s is the number of unknown parameters. We write $\mathbf{b} = (\mathbf{b}_1 \mathbf{b}_2)$, where $\mathbf{b}_1$ is the vector of the r parameters of interest, and $\mathbf{b}_2$ is the vector of the $s-r$ remaining parameters.

In our case $r = 1$ and as it is referred the parameter of interest for the difference of the carry over effects, $\delta = \delta_A - \delta_B$ which is an estimable parameter as shown in the Proposition 2

Proposition 1. If $\mu, \pi_1, \pi_2, \pi_3, \pi_4, \tau_A, \tau_B, \gamma_0, \gamma_1, \dots, \gamma_{15}$ are the vectors of $\mathbf{X}_2$ which corresponds to the parameters $\mu, \pi_1, \pi_2, \pi_3, \pi_4, \tau_A, \tau_B, \gamma_0, \gamma_1, \dots, \gamma_{15}$, the vectors, $\pi_1, \pi_2, \pi_3, \tau = \tau_A - \tau_B, \gamma_0, \gamma_1, \dots, \gamma_{15}$, are a base of the linear space $R(\mathbf{X}_2)$.

Proof. If we replace δ_A, δ_B with $\delta_A + \delta_B, \delta_A - \delta_B$ the linear space $R(\mathbf{X}_2)$ not change. Moreover we observe that $1_{4n} = \boldsymbol{\mu} = \boldsymbol{\pi}_1 + \delta_A + \delta_B$, and $\gamma_0 + \gamma_1 + \dots + \gamma_{15} = 1_{4n}$, so $\boldsymbol{\mu}$ can be omitted and $\tau_A + \tau_B$ can be replaced with γ_{15} . $\square$

Corollary 1. If with $\tilde{\mathbf{X}}_2$ we note the space of $\boldsymbol{\pi}_1, \boldsymbol{\pi}_2, \boldsymbol{\pi}_3, \tau = \tau_A - \tau_B, \gamma_0, \gamma_1, \dots, \gamma_{15}$, then $R(\mathbf{X}_2) = R(\tilde{\mathbf{X}}_2)$.

$$\mathbf{X}_1 = \begin{bmatrix} \mathbf{X}_{10} u_0 \\ \mathbf{X}_{11} u_1 \\ \vdots \\ \mathbf{X}_{115} u_{15} \end{bmatrix}, \mathbf{X}_2 = \begin{bmatrix} \mathbf{X}_{20} & 1_4 & 0 & \cdots & 0 & 0 \\ \mathbf{X}_{21} & 0 & 1_4 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \cdots & \vdots & \vdots \\ \mathbf{X}_{214} & 0 & 0 & \cdots & 0 & 1_4 \\ \mathbf{X}_{215} & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

Matrixes $\mathbf{X}_{1i}, \mathbf{X}_{2i}, i = 1, 2, \dots, 15$ are available in Appendix A.

2.2. Estimation of the Carry Over Effects

Using the Best Linear Unbiased Estimators (BLUE) δ_A, δ_B [16,17] we have:

$$(\mathbf{X}_1^T \mathbf{X}_1 - \mathbf{X}_1^T \mathbf{P} \mathbf{X}_1) \begin{pmatrix} \hat{\delta}_A \\ \hat{\delta}_B \end{pmatrix} = \mathbf{X}_1^T (\mathbf{I} - \mathbf{P}) \mathbf{Y} \quad (4)$$

where $\mathbf{X}_1 = [\delta_A - \delta_B]$, $\mathbf{X}_2 = [\boldsymbol{\mu}, \boldsymbol{\pi}_1, \boldsymbol{\pi}_2, \boldsymbol{\pi}_3, \tau_A, \gamma_1, \gamma_2, \dots, \gamma_{14}]$, and $\mathbf{P} = \mathbf{X}_2 (\mathbf{X}_2^T \mathbf{X}_2)^{-1} \mathbf{X}_2^T$ is the $(4n) \times (4n)$ projection matrix in $R(\mathbf{X}_2)$.

Proposition 2. The carry over effects $\delta_A, \delta_B, \delta_A + \delta_B$ cannot be estimated, but the difference can be estimated $\delta_A - \delta_B$ with $\text{var}(\hat{\delta}_A - \hat{\delta}_B) = \sigma^2 G^{-1}$, $G = \delta_A^T (\mathbf{I} - \mathbf{P}) \delta_A = \delta_B^T (\mathbf{I} - \mathbf{P}) \delta_B = -\delta_A^T (\mathbf{I} - \mathbf{P}) \delta_B$.

Proof. We observe that $\delta_A + \delta_B + \boldsymbol{\pi}_1 = 1$, so $(\delta_A + \delta_B) \in R(\mathbf{X}_2)$ and $(\mathbf{I} - \mathbf{P})(\delta_A + \delta_B) = 0$, then $\delta_A^T (\mathbf{I} - \mathbf{P}) \delta_A = -\delta_A^T (\mathbf{I} - \mathbf{P}) \delta_B = \delta_B^T (\mathbf{I} - \mathbf{P}) \delta_B = G$.

We have,

$$\begin{bmatrix} \delta_A^T (\mathbf{I} - \mathbf{P}) \delta_A & \delta_A^T (\mathbf{I} - \mathbf{P}) \delta_B \\ \delta_B^T (\mathbf{I} - \mathbf{P}) \delta_A & \delta_B^T (\mathbf{I} - \mathbf{P}) \delta_B \end{bmatrix} \begin{bmatrix} \hat{\delta}_A \\ \hat{\delta}_B \end{bmatrix} = \begin{bmatrix} G(\hat{\delta}_A - \hat{\delta}_B) \\ -G(\hat{\delta}_A - \hat{\delta}_B) \end{bmatrix} = \begin{bmatrix} \delta_A^T (\mathbf{I} - \mathbf{P}) \mathbf{Y} \\ \delta_B^T (\mathbf{I} - \mathbf{P}) \mathbf{Y} \end{bmatrix}$$

where $\text{var}(\hat{\delta}_A - \hat{\delta}_B) = \sigma^2 G^{-1}$. So $\delta, \delta, \delta + \delta$ cannot be estimate, on the contrary $\delta - \delta$ can be estimate. $\square$

Proposition 3. $Q = \mathbf{X}_1^T (\mathbf{I}_{4n} - \mathbf{P}) \mathbf{X}_1 = \mathbf{X}_1^T (\mathbf{I}_{4n} - \tilde{\mathbf{P}}) \mathbf{X}_1$ where $\tilde{\mathbf{P}} = \tilde{\mathbf{X}}_2 (\tilde{\mathbf{X}}_2^T \tilde{\mathbf{X}}_2)^{-1} \tilde{\mathbf{X}}_2^T$.

Proof. $\mathbf{P} \mathbf{X}_1$ is the orthogonal projection of $\mathbf{X}_1$ to the linear space of $R(\mathbf{X}_2)$. Nevertheless $R(\mathbf{X}_2) = R(\tilde{\mathbf{X}}_2)$, so $\mathbf{P} \mathbf{X}_1 = \tilde{\mathbf{P}} \mathbf{X}_1$ and $\mathbf{X}_1^T (\mathbf{I}_{4n} - \mathbf{P}) \mathbf{X}_1 = \mathbf{X}_1^T (\mathbf{I}_{4n} - \tilde{\mathbf{P}}) \mathbf{X}_1$. $\square$

2.3. Calculation of $\mathbf{X}_1^T (\mathbf{I}_{4n} - \tilde{\mathbf{P}}) \mathbf{X}_1$

So we need to calculate the minimum of the $\mathbf{X}_1^T (\mathbf{I}_{4n} - \tilde{\mathbf{P}}) \mathbf{X}_1$.

Proposition 4. If $\mathbf{w} = (x_1, x_2, x_3, x_4, z_0, z_1, \dots, z_{15})^T$, then

$$\mathbf{X}_1^T (\mathbf{I}_{4n} - \tilde{\mathbf{P}}) \mathbf{X}_1 = \min_{\mathbf{w}} (\mathbf{X}_1 - \tilde{\mathbf{X}}_2 \mathbf{w})^T (\mathbf{X}_1 - \tilde{\mathbf{X}}_2 \mathbf{w}).$$

Proof. If T a point of the linear space $\mathbf{R}(\tilde{\mathbf{X}}_2)$ with $T = \tilde{\mathbf{X}}_2 \mathbf{w}$, then $(\mathbf{X}_1 - \tilde{\mathbf{X}}_2 \mathbf{w})^T (\mathbf{X}_1 - \tilde{\mathbf{X}}_2 \mathbf{w})$ is the square of the distance of T from the space $\mathbf{X}_1$, so $\mathbf{X}_1^T (\mathbf{I}_{4n} - \tilde{\mathbf{P}}) \mathbf{X}_1 = \min_w (\mathbf{X}_1 - \mathbf{X}_2 \mathbf{w})^T (\mathbf{X}_1 - \mathbf{X}_2 \mathbf{w})$. $\square$

If $F(\mathbf{x}, \mathbf{z}) = (\mathbf{X}_1 - \tilde{\mathbf{X}}_2 \mathbf{w})^T (\mathbf{X}_1 - \tilde{\mathbf{X}}_2 \mathbf{w})$, then $F(\mathbf{x}, \mathbf{z}) = \mathbf{X}_1^T \mathbf{X}_1 - 2\mathbf{X}_1^T \tilde{\mathbf{X}}_2 \mathbf{w} + \mathbf{w}^T \tilde{\mathbf{X}}_2^T \tilde{\mathbf{X}}_2 \mathbf{w}$, and

$$\begin{aligned} \mathbf{X}_1^T \mathbf{X}_1 &= u_0 \mathbf{X}_{10}^T \mathbf{X}_{10} + u_1 \mathbf{X}_{11}^T \mathbf{X}_{11} + \cdots + u_{15} \mathbf{X}_{1,15}^T \mathbf{X}_{1,15} \\ \mathbf{X}_1^T \tilde{\mathbf{X}}_2 \mathbf{w} &= u_0 \mathbf{X}_{10}^T (\tilde{\mathbf{X}}_{20} + z_0 \mathbf{1}_4) + u_1 \mathbf{X}_{11}^T (\tilde{\mathbf{X}}_{21} + z_1 \mathbf{1}_4) + \cdots \\ &\quad + u_{15} \mathbf{X}_{1,15}^T (\tilde{\mathbf{X}}_{2,15} + z_{15} \mathbf{1}_4) \\ \mathbf{w}^T \tilde{\mathbf{X}}_2 \tilde{\mathbf{X}}_2 \mathbf{w} &= \mathbf{u}_0 [\tilde{\mathbf{X}}_{20}^T \tilde{\mathbf{X}}_{20} + 2z_0 \tilde{\mathbf{X}}_{20}^T \mathbf{1}_4 + z_0^2 \mathbf{1}_4^T \mathbf{1}_4] \\ &\quad + \mathbf{u}_1 [\tilde{\mathbf{X}}_{21}^T \tilde{\mathbf{X}}_{21} + 2z_1 \tilde{\mathbf{X}}_{21}^T \mathbf{1}_4 + z_1^2 \mathbf{1}_4^T \mathbf{1}_4] + \cdots \\ &\quad + \mathbf{u}_{15} [\tilde{\mathbf{X}}_{2,15}^T \tilde{\mathbf{X}}_{2,15} + 2z_{15} \tilde{\mathbf{X}}_{2,15}^T \mathbf{1}_4 + z_{15}^2 \mathbf{1}_4^T \mathbf{1}_4] \end{aligned}$$

$$\text{where } \tilde{\mathbf{X}}_{20} = \tilde{\mathbf{X}}_{28} = \begin{bmatrix} x_1 \\ x_2 + x_4 \\ x_3 + x_4 \\ x_4 \end{bmatrix}, \tilde{\mathbf{X}}_{21} = \tilde{\mathbf{X}}_{29} = \begin{bmatrix} x_1 \\ x_2 - x_4 \\ x_3 + x_4 \\ x_4 \end{bmatrix}, \tilde{\mathbf{X}}_{22} = \tilde{\mathbf{X}}_{2,10} = \begin{bmatrix} x_1 \\ x_2 + x_4 \\ x_3 - x_4 \\ x_4 \end{bmatrix}, \tilde{\mathbf{X}}_{23} = \tilde{\mathbf{X}}_{2,11} = \begin{bmatrix} x_1 \\ x_2 - x_4 \\ x_3 - x_4 \\ x_4 \end{bmatrix}.$$

For the other vectors, $\mathbf{X}_{2,i+8} = \mathbf{X}_{2i}$, $\mathbf{X}_{2i} + \mathbf{X}_{2,15-i} = 2 \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ 0 \end{bmatrix}$, $i = 0, 1, \dots, 7$.

In order to minimize $F(x, z)$, we have, $\min_x F(x, z) = \min_x (\min_z F(x, z))$, so:

[illegible]

If we replace the solution of $z_0, z_1, \dots, z_{15}$ in $F(\mathbf{x}, \mathbf{z})$, we have:

$$F(\mathbf{x}) = u_0 \left[\mathbf{x}_{10}^T \mathbf{x}_{10} - 2\mathbf{x}_{10}^T \tilde{\mathbf{x}}_{20} + \tilde{\mathbf{x}}_{20}^T \mathbf{x}_{20} - \frac{(\mathbf{x}_{10}^T \mathbf{1}_4 - \tilde{\mathbf{x}}_{20}^T \mathbf{1}_4)^2}{4} \right] + \dots$$

$$+ u_{15} \left[\mathbf{x}_{1,15}^T \mathbf{x}_{1,15} - 2\mathbf{x}_{1,15}^T \tilde{\mathbf{x}}_{2,15} + \tilde{\mathbf{x}}_{2,15}^T \mathbf{x}_{2,15} - \frac{(\mathbf{x}_{1,15}^T \mathbf{1}_4 - \tilde{\mathbf{x}}_{2,15}^T \mathbf{1}_4)^2}{4} \right].$$

$F(\mathbf{x})$ is of the form

$$F(\mathbf{x}) = \frac{1}{4} [R - 2\tilde{\mathbf{q}}^T \mathbf{x} + \mathbf{x}^T \tilde{\mathbf{M}} \mathbf{x}] \quad (5)$$

$$\text{where } R = u_0[4\mathbf{X}_{10}^T\mathbf{X}_{10} - (\mathbf{X}_{10}^T\mathbf{1}_4)^2] + u_1[4\mathbf{X}_{11}^T\mathbf{X}_{11} - (\mathbf{X}_{11}^T\mathbf{1}_4)^2] + \dots \\ + u_{15}[4\mathbf{X}_{15}^T\mathbf{X}_{15} - (\mathbf{X}_{15}^T\mathbf{1}_4)^2]$$

$$\begin{aligned}
\tilde{\mathbf{q}}^T \mathbf{x} &= u_0[4\mathbf{X}_{10}^T \tilde{\mathbf{X}}_{20} - (\mathbf{X}_{10}^T \mathbf{1}_4)(\tilde{\mathbf{X}}_{20}^T \mathbf{1}_4)] \\
&+ u_1[4\mathbf{X}_{11}^T \tilde{\mathbf{X}}_{21} - (\mathbf{X}_{11}^T \mathbf{1}_4)(\tilde{\mathbf{X}}_{21}^T \mathbf{1}_4)] + \dots \\
&+ u_{15}[4\mathbf{X}_{1,15}^T \tilde{\mathbf{X}}_{2,15} - (\mathbf{X}_{1,15}^T \mathbf{1}_4)(\tilde{\mathbf{X}}_{2,15}^T \mathbf{1}_4)] \\
\mathbf{x}^T \tilde{\mathbf{M}} \mathbf{x} &= u_0[4\tilde{\mathbf{X}}_{20}^T \tilde{\mathbf{X}}_{20} - (\tilde{\mathbf{X}}_{20}^T \mathbf{1}_4)^2] + u_1[4\tilde{\mathbf{X}}_{21}^T \tilde{\mathbf{X}}_{21} - (\tilde{\mathbf{X}}_{21}^T \mathbf{1}_4)^2] + \dots \\
&+ u_{15}[4\tilde{\mathbf{X}}_{2,15}^T \tilde{\mathbf{X}}_{2,15} - (\tilde{\mathbf{X}}_{2,15}^T \mathbf{1}_4)^2]
\end{aligned} \tag{6}$$

Equation (5) is a quadratic form of $\mathbf{x}$ and the minimization is of the form:

$$G = \min_{\mathbf{x}} F(\mathbf{x}) = \frac{1}{4}[\mathbf{R} - \tilde{\mathbf{q}}^T \tilde{\mathbf{M}}^{-1} \tilde{\mathbf{q}}].$$

3. Results

3.1. Calculation of G in Case of four Periods and Carry Over Effects

Using the above matrixes we have

$$4G = (\boldsymbol{\delta}_A - \boldsymbol{\delta}_B)^T (\mathbf{I} - \mathbf{P})(\boldsymbol{\delta}_A - \boldsymbol{\delta}_B)$$

where $\mathbf{X}_1 = \boldsymbol{\delta}_A - \boldsymbol{\delta}_B$, then,

$$\begin{aligned}
X_{10} = X_{18} &= \begin{bmatrix} 0 \\ 1 \\ 1 \\ 1 \end{bmatrix}, X_{11} = X_{19} = \begin{bmatrix} 0 \\ -1 \\ 1 \\ 1 \end{bmatrix}, X_{12} = X_{1,10} = \begin{bmatrix} 0 \\ 1 \\ -1 \\ 1 \end{bmatrix}, \\
X_{13} = X_{1,11} &= \begin{bmatrix} 0 \\ -1 \\ -1 \\ 1 \end{bmatrix}, X_{14} = X_{1,12} = \begin{bmatrix} 0 \\ -1 \\ 1 \\ -1 \end{bmatrix}, X_{15} = X_{1,13} = \begin{bmatrix} 0 \\ -1 \\ 1 \\ -1 \end{bmatrix}, \\
X_{16} = X_{1,14} &= \begin{bmatrix} 0 \\ 1 \\ -1 \\ -1 \end{bmatrix}, X_{17} = X_{1,15} = \begin{bmatrix} 0 \\ -1 \\ -1 \\ -1 \end{bmatrix} \\
\mathbf{X}_{20} &= \begin{bmatrix} x_1 + x_4 \\ x_2 + x_4 \\ x_3 + x_4 \\ x_4 \end{bmatrix}, \mathbf{X}_{21} = \begin{bmatrix} x_1 - x_4 \\ x_2 + x_4 \\ x_3 + x_4 \\ x_4 \end{bmatrix}, \mathbf{X}_{22} = \begin{bmatrix} x_1 + x_4 \\ x_2 - x_4 \\ x_3 + x_4 \\ x_4 \end{bmatrix}, \mathbf{X}_{23} = \begin{bmatrix} x_1 - x_4 \\ x_2 - x_4 \\ x_3 + x_4 \\ x_4 \end{bmatrix}, \\
X_{2,15-i} &= 2 \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ 0 \end{bmatrix} - X_{2i}, \quad i = 0, 1, \dots, 7, \quad \mathbf{X}_{1i} \Leftrightarrow (\boldsymbol{\delta}_A - \boldsymbol{\delta}_B)_i, \quad i = 0, 1, \dots, 15.
\end{aligned}$$

Using the relations (6) we have $R = 11n - 8(u_0 + u_7 + u_8 + u_{15})$

$$q = \begin{bmatrix} q_1 \\ q_2 \\ q_3 \\ q_4 \end{bmatrix}, M = \begin{bmatrix} 3n & -n & -n & m_{14} \\ -n & 3n & -n & m_{24} \\ -n & -n & 3n & m_{34} \\ m_{14} & m_{24} & m_{34} & m_{44} \end{bmatrix} \tag{7}$$

$$\begin{aligned}
q_1 &= -3(u_0 - u_{15}) - (u_1 - u_{14}) - (u_2 - u_{13}) + (u_3 - u_{12}) - (u_4 - u_{11}) \\
&\quad + (u_5 - u_{10}) + (u_6 - u_9) + 3(u_7 - u_8) \\
q_2 &= (u_0 - u_{15}) - 5(u_1 - u_{14}) + 3(u_2 - u_{13}) - 3(u_3 - u_{12}) + 3(u_4 - u_{11}) \\
&\quad - 3(u_5 - u_{10}) + 5(u_6 - u_9) - (u_7 - u_8) \\
q_3 &= (u_0 - u_{15}) + 3(u_1 - u_{14}) - 5(u_2 - u_{13}) - 3(u_3 - u_{12}) + 3(u_4 - u_{11}) \\
&\quad + 5(u_5 - u_{10}) - 3(u_6 - u_9) - (u_7 - u_8) \\
q_4 &= 2(u_1 + u_{14}) - 6(u_2 + u_{13}) + 4(u_3 + u_{12}) - 6(u_4 + u_{11}) - 12(u_5 + u_{10}) \\
&\quad - 4(u_6 + u_9) - 2(u_7 + u_8) \\
m_{14} &= -6(u_1 - u_{14}) + 2(u_2 - u_{13}) - 4(u_3 - u_{12}) + 2(u_4 - u_{11}) - 4(u_5 - u_{10}) + 4(u_6 - u_9) \\
m_{24} &= 2(u_1 - u_{14}) - 6(u_2 - u_{13}) - 4(u_3 - u_{12}) + 2(u_4 - u_{11}) + 4(u_5 - u_{10}) - 4(u_6 - u_9) \\
m_{34} &= 2(u_1 - u_{14}) + 2(u_2 - u_{13}) + 4(u_3 - u_{12}) - 6(u_4 - u_{11}) - 4(u_5 - u_{10}) - 4(u_6 - u_9) \\
m_{44} &= 12(u_1 + u_{14}) + 12(u_2 + u_{13}) + 16(u_3 + u_{12}) + 12(u_4 + u_{11}) + 16(u_5 + u_{10}) \\
&\quad + 16(u_6 + u_9).
\end{aligned}$$

3.2. Optimal Designs for Carry Over Effects

The optimal designs minimize the variance $\text{var}(\delta_A - \delta_B) = \sigma^2 G^{-1}$ so have to maximize the quantity $R - \mathbf{q}^T \mathbf{M}^{-1} \mathbf{q}$.

Proposition 5. In the case of four periods and in order to find the optimal designs for the carry over effects two cases of n are examined:

(i) $n = 0 \bmod 2$: $G^* = \max_{u_i} G = \frac{11n}{16}$, and the solutions are, $u_0 = u_7 = u_8 = u_{15} = 0$,

$$\begin{aligned}
(u_6 - u_9) - (u_1 - u_{14}) &= 0 \\
(u_5 - u_{10}) - (u_2 - u_{13}) &= 0 \\
(u_4 - u_{11}) - (u_3 - u_{12}) &= 0 \\
(u_1 + u_{14}) - 3(u_2 + u_{13}) + 2(u_3 + u_{12}) - 3(u_4 + u_{11}) - 6(u_5 + u_{10}) - 2(u_6 + u_9) &= 0 \\
(u_1 + u_2 + u_3 + u_{11} + u_{10} + u_9) &= \frac{n}{2}
\end{aligned}$$

Some solutions which satisfy the above correlations are:

$$\begin{aligned}
(\alpha) \quad & u_1 = \frac{n}{6}, u_{14} = \frac{n}{6} + d, u_3 = u_4 = f, u_9 = d, f + d = \frac{n}{3}, n = 0 \bmod 6 \\
& u_i = 0 \quad i \neq 1, 3, 4, 9, 14 \\
(\beta) \quad & u_1 = u_{14} = \frac{3n}{8}, u_4 = u_{11} = \frac{n}{8}, n = 0 \bmod 8 \\
& u_i = 0 \quad i \neq 1, 4, 11, 14 \\
(\gamma) \quad & u_1 = u_{14} = \frac{2n}{6}, u_6 = u_9 = \frac{n}{6}, n = 0 \bmod 6 \\
& u_i = 0 \quad i \neq 1, 6, 9, 14 \\
(\delta) \quad & u_3 - 2 = u_{12} = \frac{3n}{10} - 1, u_4 - 2 = u_{11} = \frac{n}{5} - 1, n = 0 \bmod 10 \\
& u_i = 0 \quad i \neq 3, 4, 11, 12 \\
(\varepsilon) \quad & u_1 = u_{14} = n - 5\beta, u_2 = u_{13} = \beta, u_3 = u_{12} = 4\beta - \frac{n}{2}, \beta \in \left\{ \frac{n}{8}, \dots, \left\lceil \frac{n}{5} \right\rceil \right\}, n \geq 8 \\
& u_i = 0 \quad i \neq 1, 2, 3, 12, 13, 14 \\
(\sigma\tau) \quad & u_1 = u_3 = u_4 = \frac{n+2}{7}, u_9 = u_{11} = u_{12} = \frac{n-5}{7}, u_{14} = \frac{n+9}{7}, n = 12 \bmod 14 \\
& u_i = 0 \quad i \neq 1, 3, 4, 9, 11, 12, 14, \\
(\zeta) \quad & u_3 = u_{12} = \frac{n}{8}, u_5 = u_{10} = \frac{3n}{8}, n = 0 \bmod 8 \\
& u_i = 0 \quad i \neq 3, 5, 10, 12
\end{aligned}$$

$$(\eta) \quad \begin{aligned} u_3 = u_{12} = \frac{n}{8}, \quad u_5 = u_{10} = \frac{3n}{8}, \quad n = 0 \bmod 8 \\ u_i = 0 \quad i \neq 3, 5, 10, 12 \end{aligned}$$

$$(\theta) \quad \begin{aligned} u_3 = u_{12} = u_6 = u_9 = \frac{n}{4}, \quad n = 0 \bmod 4 \\ u_i = 0 \quad i \neq 3, 6, 9, 12 \end{aligned}$$

$$(\iota) \quad \begin{aligned} u_1 = u_{14} = \frac{n}{6}, \quad u_3 = u_4 = \frac{2n}{6}, \quad n = 0 \bmod 6 \\ u_i = 0 \quad i \neq 1, 3, 4, 14 \end{aligned}$$

(ii) $n = 1 \bmod 2$: $G^* = \max_{u_i} G = \frac{1}{16}(11n - \frac{3}{n})$, the solutions satisfy the relations:

$$u_0 = u_7 = u_8 = u_{15} = 0,$$

$$(u_6 - u_9) - (u_1 - u_{14}) = \pm 1$$

$$(u_5 - u_{10}) - (u_2 - u_{13}) = \pm 1$$

$$(u_4 - u_{11}) - (u_3 - u_{12}) = \mp 1$$

$$(u_1 - u_{14}) + (u_3 - u_{12}) + (u_5 - u_{10}) = \mp 1$$

$$(u_1 + u_{14}) - 3(u_2 + u_{13}) + 2(u_3 + u_{12}) - 3(u_4 + u_{11}) - 6(u_5 + u_{10}) - 2(u_6 + u_9) = 0$$

$$u_1 + u_2 + u_3 + u_9 + u_{10} + u_{11} = \frac{n \mp 1}{2}$$

Some solutions are:

$$(\alpha) \quad \begin{aligned} u_1 - 1 = u_{14} = u_3 - 2 = u_{12} - 2 = u_4 - 1 = u_{11} = \frac{n-7}{6}, \quad u_{10} = 1, \quad n = 1 \bmod 6 \\ u_i = 0 \quad i \neq 1, 3, 4, 10, 11, 12, 14, \quad n \geq 7 \end{aligned}$$

$$(\beta) \quad \begin{aligned} u_{14} = 2, \quad u_3 - 2 = u_{12} - 1 = u_6 = u_9 - 1 = u_{11} = \frac{n-7}{4}, \quad u_5 = 1, \quad n = 3 \bmod 4 \\ u_i = 0 \quad i \neq 3, 5, 6, 9, 11, 12, 14, \quad n \geq 7 \end{aligned}$$

$$(\gamma) \quad \begin{aligned} u_{14} = 2, \quad u_3 - 2 = u_{12} - 1 = u_9 - 1 = u_6 = \frac{n-7}{4}, \quad u_5 = 1, \quad n = 3 \bmod 4, \quad n \geq 7 \\ u_i = 0 \quad i \neq 3, 5, 6, 9, 12, 14 \end{aligned}$$

$$(\delta) \quad \begin{aligned} u_1 = 1, \quad u_3 - 2 = u_{12} - 2 = u_9 = u_6 = \frac{n-7}{4}, \quad u_4 = u_{10} = 1, \\ n = 3 \bmod 4, \quad n \geq 7, \quad u_i = 0 \quad i \neq 3, 5, 6, 9, 12, 14 \end{aligned}$$

$$(\varepsilon) \quad \begin{aligned} u_1 = 1, \quad u_3 - 2 = u_{12} - 2 = u_9 = u_6 = \frac{n-7}{4}, \quad u_4 = u_{10} = 1, \quad n = 3 \bmod 4, \quad n \geq 7 \\ u_i = 0 \quad i \neq 3, 5, 6, 9, 12, 14 \end{aligned}$$

$$u_1 - 1 = u_{14} - 2 = 3d, \quad u_2 = u_{13} - 1 = d, \quad u_3 - 2 = u_{12} - 1 = u_9 = u_6 = \frac{n-9}{4} - 2d,$$

$$(\sigma\tau) \quad u_4 = u_{11} = 1, \quad d \in \{0, 1, \dots, [\frac{n-9}{8}]\} \quad n = 1 \bmod 4, \quad n \geq 9$$

$$u_i = 0 \quad i \neq 1, 2, 3, 4, 6, 9, 11, 12, 13, 14$$

$$u_1 = u_{14} - 1 = 3d, \quad u_4 - 2 = u_{11} - 2 = d, \quad u_3 - 4 = u_{12} - 3 = u_9 = u_6 = \frac{n-13}{4} - 2d,$$

$$(\zeta) \quad u_{13} = 1, \quad d \in \{0, 1, \dots, [\frac{n-13}{8}]\} \quad n = 1 \bmod 4, \quad n \geq 13$$

$$u_i = 0 \quad i \neq 1, 3, 4, 6, 9, 11, 12, 13, 14$$

Proof. $n = 0 \bmod 2$: We look for the maximization of $G = \frac{1}{16}(R - q^T M^{-1} q)$, where R, q, M are of the form of (7). The maximum exists when $u_0 + u_7 + u_8 + u_{15} = 0$ and $q = 0$. We have:

$$\begin{aligned} (u_6 - u_9) - (u_1 - u_{14}) = a & \quad q_1 = 0 & \quad a + b - c = 0 & \quad a = 0 \\ (u_5 - u_{10}) - (u_2 - u_{13}) = b & \Rightarrow & \quad q_2 = 0 & \Leftrightarrow 5a - 3b + 3c = 0 & \Leftrightarrow b = 0 \\ (u_4 - u_{11}) - (u_3 - u_{12}) = c & \quad q_3 = 0 & \quad -3a + 5b + 3c = 0 & \quad c = 0 \end{aligned}$$

The solutions (α) – (ι) satisfy these necessary and sufficient conditions.

$n = 1 \bmod 2$: In that case $q_i = 1 \bmod 2$, $i = 1, 2, 3$ ex.

$$\begin{aligned}
q_1 &= -(u_1 - u_{14}) - (u_2 - u_{13}) + (u_3 - u_{12}) - (u_4 - u_{11}) + (u_5 - u_{10}) + (u_6 - u_9) = \\
&= (u_{14} + u_{13} + u_3 + u_{11} + u_5 + u_6) - (u_1 + u_2 + u_{12} + u_4 + u_{10} + u_9) \\
&= n - 2(u_1 + u_2 + u_{12} + u_4 + u_{10} + u_9) = 1 \pmod{2}
\end{aligned}$$

Moreover:

$$\mathbf{q}^T \mathbf{M}^{-1} \mathbf{q} = \frac{1}{4n} [q_1^2 + q_2^2 + q_3^2 + (q_1 + q_2 + q_3)^2] + \frac{F^2}{D}$$

$$\text{with } F = \left[q_4 - \frac{1}{4n} [q_1 m_{14} + q_2 m_{24} + q_3 m_{34} + (q_1 + q_2 + q_3)(m_{14} + m_{24} + m_{34})] \right],$$

$$D = m_{44} - \frac{1}{4n} [m_{14}^2 + m_{24}^2 + m_{34}^2 + (m_{14} + m_{24} + m_{34})^2] > 0.$$

The quantities q_i , $i = 1, 2, 3$ are odd and, $\mathbf{q}^T \mathbf{M}^{-1} \mathbf{q} \geq \frac{1}{4n} [q_1^2 + q_2^2 + q_3^2 + (q_1 + q_2 + q_3)^2] \geq \frac{3}{n}$, so for example, $|q_1| = |q_2| = |q_3| = |q_1 + q_2 + q_3| = 1$, does not give integer solutions for a, b, and c.

The solutions which minimize $q_1^2 + q_2^2 + q_3^2 + (q_1 + q_2 + q_3)^2$ are $q_1 = \pm 3$, $q_2 = \mp 1$, $q_3 = \mp 1$, then $F = q_4 \pm \frac{m_{14}}{n}$ and $q_4 = 0$, $m_{14} = 0 \Rightarrow q^T \mathbf{M}^{-1} \mathbf{q} = \frac{3}{n}$.

So the conditions of maximization of G are,

$$u_0 + u_7 + u_8 + u_{15} = 0, q_1 = \pm 3, q_2 = \mp 1, q_3 = \mp 1,$$

$$q_4 = 0, m_{14} = 0 \Rightarrow G = \frac{1}{16} (11n - \frac{3}{n}) \Rightarrow \text{var}(\delta_A - \delta_B) = \sigma^2 \frac{16n}{11n^2 - 3}.$$

The (α) – (ζ) satisfy these conditions. $\square$

4. Discussion

In the case of four periods, carry over effects optimization (in all the cases) includes the designs where $u_0 = u_7 = u_8 = u_{15} = 0$, (all the treatments are the same) as in the case of direct effects. In this case, it is obvious that there are many more solutions from the cases of two and three periods [11,13]. The cases with a greater number of periods and the examination for the case of the model with interactions periods—either for carry over effects or for direct effects—are of interest.

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Appendix A

$$\begin{aligned}
X_{10} = X_{18} &= \begin{bmatrix} 0 \\ 1 \\ 1 \\ 1 \end{bmatrix}, X_{11} = X_{19} = \begin{bmatrix} 0 \\ -1 \\ 1 \\ 1 \end{bmatrix}, X_{12} = X_{1,10} = \begin{bmatrix} 0 \\ 1 \\ -1 \\ 1 \end{bmatrix}, X_{13} = X_{1,11} = \begin{bmatrix} 0 \\ -1 \\ -1 \\ 1 \end{bmatrix}, \\
X_{14} = X_{1,12} &= \begin{bmatrix} 0 \\ -1 \\ 1 \\ -1 \end{bmatrix}, X_{15} = X_{1,13} = \begin{bmatrix} 0 \\ -1 \\ 1 \\ -1 \end{bmatrix}, X_{16} = X_{1,14} = \begin{bmatrix} 0 \\ 1 \\ -1 \\ -1 \end{bmatrix}, X_{17} = X_{1,15} = \begin{bmatrix} 0 \\ -1 \\ -1 \\ -1 \end{bmatrix}, \\
X_{20} &= \begin{matrix} \pi_1 & \pi_2 & \pi_3 & \tau \\ \begin{bmatrix} 1 & 0 & 0 & 1 \\ 0 & 1 & 0 & 1 \\ 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 1 \end{bmatrix} \end{matrix} & X_{22} = \begin{matrix} \pi_1 & \pi_2 & \pi_3 & \tau \\ \begin{bmatrix} 1 & 0 & 0 & 1 \\ 0 & 1 & 0 & -1 \\ 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 1 \end{bmatrix} \end{matrix} \\
X_{21} &= \begin{matrix} \begin{bmatrix} 1 & 0 & 0 & -1 \\ 0 & 1 & 0 & 1 \\ 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 1 \end{bmatrix} \end{matrix} & X_{23} = \begin{matrix} \begin{bmatrix} 1 & 0 & 0 & -1 \\ 0 & 1 & 0 & -1 \\ 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 1 \end{bmatrix} \end{matrix}
\end{aligned}$$

$$\begin{aligned}
X_{24} &= \begin{bmatrix} \mu & \pi_1 & \pi_2 & \pi_3 & \tau \\ 1 & 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & 1 & 1 \\ 0 & 0 & 1 & -1 & 1 \\ 0 & 0 & 0 & 1 & 1 \end{bmatrix} & X_{25} &= \begin{bmatrix} \mu & \pi_1 & \pi_2 & \pi_3 & \tau \\ 1 & 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & -1 & 1 \\ 0 & 0 & 1 & 1 & 1 \\ 0 & 0 & 0 & 1 & 1 \end{bmatrix} \\
X_{26} &= \begin{bmatrix} 1 & 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & -1 & 1 \\ 0 & 0 & 1 & -1 & 1 \\ 0 & 0 & 0 & 1 & 1 \end{bmatrix} & X_{27} &= \begin{bmatrix} 1 & 0 & 0 & -1 & 1 \\ 0 & 1 & 0 & -1 & 1 \\ 0 & 0 & 1 & -1 & 1 \\ 0 & 0 & 0 & 1 & 1 \end{bmatrix}, \\
X_{28} &= \begin{bmatrix} \pi_1 & \pi_2 & \pi_3 & \tau \\ 1 & 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 & 1 \\ 0 & 0 & 0 & -1 & 1 \end{bmatrix} & X_{29} &= \begin{bmatrix} \pi_1 & \pi_2 & \pi_3 & \tau \\ 1 & 0 & 0 & -1 & 1 \\ 0 & 1 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 & 1 \\ 0 & 0 & 0 & -1 & 1 \end{bmatrix} \\
X_{210} &= \begin{bmatrix} 1 & 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & -1 & 1 \\ 0 & 0 & 1 & 1 & 1 \\ 0 & 0 & 0 & -1 & 1 \end{bmatrix} & X_{2,11} &= \begin{bmatrix} 1 & 0 & 0 & -1 & 1 \\ 0 & 1 & 0 & -1 & 1 \\ 0 & 0 & 1 & 1 & 1 \\ 0 & 0 & 0 & -1 & 1 \end{bmatrix}, \\
X_{2,12} &= \begin{bmatrix} \pi_1 & \pi_2 & \pi_3 & \tau \\ 1 & 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & 1 & 1 \\ 0 & 0 & 1 & -1 & 1 \\ 0 & 0 & 0 & -1 & 1 \end{bmatrix} & X_{2,13} &= \begin{bmatrix} \pi_1 & \pi_2 & \pi_3 & \tau \\ 1 & 0 & 0 & -1 & 1 \\ 0 & 1 & 0 & 1 & 1 \\ 0 & 0 & 1 & -1 & 1 \\ 0 & 0 & 0 & -1 & 1 \end{bmatrix}. \\
X_{21} &= \begin{bmatrix} 1 & 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & -1 & 1 \\ 0 & 0 & 1 & -1 & 1 \\ 0 & 0 & 0 & -1 & 1 \end{bmatrix} & X_{23} &= \begin{bmatrix} 1 & 0 & 0 & -1 & 1 \\ 0 & 1 & 0 & -1 & 1 \\ 0 & 0 & 1 & -1 & 1 \\ 0 & 0 & 0 & -1 & 1 \end{bmatrix}
\end{aligned}$$

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