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Optimal choice of covariates in the set-up of crossover designs

Ganesh Dutta[1] and Rita SahaRay[2*]
[1]Basanti Devi College, Kolkata-700029, India
[2] Indian Statistical Institute, Applied Statistics Division,
Kolkata-700108, India
Email:duttaganesh78@gmail.com; rita_saharay@yahoo.com

Abstract

The use of covariates model is well accepted in practice to reduce the experimental error in order to obtain more accurate estimate of the parameters of interest. The choice of values of the controllable covariates for a given design for the estimation of covariate parameters attaining the minimum variance (global optimality) has attracted the attention of many researchers in recent times. In the present paper the problem of construction of globally optimal covariate designs have been undertaken under the set-up of strongly balanced and balanced crossover designs with as many covariates as possible in a given context. Hadamard matrices, mutually orthogonal Latin squares, orthogonal arrays and Kronecker product play the key role in this study.

Keywords: Crossover design; Covariate model; Latin square; Orthogonal array; Hadamard matrix, Kronecker product; Global optimality.

1 Introduction

The use of covariates in modeling is a well accepted practice to control the experimental error. Lopes Troya (1982a, 1982b) first studied the optimal treatments and non-stochastic controllable covariates allocation in a completely randomised design(CRD) set-up for simultaneous estimation of the (fixed) treatment effects and the covariate effects with maximum efficiency in the sense of minimum generalised variance. Later on Das et al.(2003) undertook the study of optimal choice of values of covariates in the set-ups of randomised block design(RBD) and some classes of balanced incomplete block design(BIBD) which are known to be optimal for the estimation of contrasts of treatment effects. Subsequently, many authors namely Wierich (1984), Kurotschka and Wierich (1984), Chadjiconstantinidis and Moyssiadis (1991), Chadjiconstantinidis and Chadjipadelis (1996), Liski et al. (2002), Rao et al. (2003) and Dutta and Das (2011, 2013) contributed to the development of covariate designs for the optimum estimation of the covariate effects (regression parameters) under different design set-ups. Dutta et al.(2009a) proposed optimum covariate designs in the set-ups of split-plot and strip-plot designs. Dutta (2004) and Dutta et al. (2007, 2009b, 2010a, 2010c) also considered optimal estimation of the regression coefficients under different set-ups where the ANOVA effects are not orthogonally estimable. D-optimal designs in one way classification set-up for the estimation of both the ANOVA effects and the regression parameters were considered by Dey and Mukerjee (2006) and Dutta et al.(2012). Dutta et al.(2010b) also considered D-optimal covariate designs for the estimation of regression parameters only, in an incomplete block (IB) design set-up when globally optimal design does not exist.

The problem of optimal choice of covariates in the set-up of crossover design has not been considered so far in the literature. A crossover design is used in an experiment in which a unit is exposed to various treatments over different periods. In such an experiment, t treatments are assigned to n experimental units each of which receives one treatment during each of the p periods. Such designs are very often used in many industrial, agricultural, and biological experiments. Under the traditional model, it is assumed that each treatment assigned to an experimental unit (e.u.) has a direct effect on the e.u. in the same period and also carryover effects (residual effects) in the subsequent periods. Efficient estimation and testing of the direct effects as well as residual effects are of interest to the practitioners from application point of view. The reader is referred to Stufken(1996), Hedayat and Stufken(2003) and Bose and Dey(2009) for a review on this topic. In practice, situation arises when controllable covariates are used conveniently in this set-up to control the experimental error. For example in treating arthritis pain or prevention of heart disease, the duration of daily exercise or walking plays a role besides the effects of medicines. Thus the duration of exercise or walking can be viewed as a controllable covariate when formulating an appropriate model for the study of the effects of different medicines in such cases. So the problem arises to propose appropriate designs which will allow most efficient estimation of these covariate effects on the response. The present paper aims at addressing this issue dealing with c covariates for some classes of strongly balanced and balanced crossover designs which are known to be universally optimal for the estimation of direct treatment effects and residual treatment effects in an appropriate class of competing designs. The organisation of the paper is as follows. In Section 2, some preliminary definitions and notations have been introduced. Section 3 focuses on the construction of optimum covariate designs for the series of strongly balanced and balanced crossover designs which are obtained using the methods of construction given in Stufken (1996), Williams (1949), Cheng and Wu (1980) and Patterson (1952). The concluding remarks are presented in Section 4.

2 Preliminary Definitions and Notations

We assume t treatments, denoted by $1,\ldots,t$ are to be compared using n experimental units over p periods. Let $\Omega_{t,n,p}$ denote the class of such crossover designs. A design $d \in \Omega_{t,n,p}$ is *uniform on the periods* if each treatment is assigned to equal number of subjects in each period. A design $d \in \Omega_{t,n,p}$ is *uniform on the subjects* if each treatment is assigned equally often to each subject. A design is said to be *uniform* if it is uniform on the periods and uniform on the subjects. A crossover design is said to be *balanced*, if no treatment is immediately preceded by itself and each treatment is immediately preceded by every other treatment equally often. A crossover design is called *strongly balanced* if each treatment is immediately preceded by every treatment (including itself) equally often.

In the present article, we deal with a covariate model allowing c covariates under the crossover design set-up. Let $d(i,j)$ denote the treatment assigned by $d \in \Omega_{t,n,p}$ in the i^{th} period to the j^{th} experimental unit; $i=1,\ldots,p,\ j=1,\ldots,n$. The model of response for the observation y_{ij} with $z_{ij}^{(l)}$, the value of the l^{th} covariate Z_l received in the i^{th} period on the j^{th} experimental unit is given by

$$y_{ij} = \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \rho_{d(i-1,j)} + \sum_{l=1}^{c} \gamma_l z_{ij}^{(l)} + e_{ij}, \tag{2.1}$$

where μ is the general mean, α_i is the i^{th} period effect, β_j is the j^{th} experimental unit effect, $\tau_{d(i,j)}$ is the direct effect due to treatment $d(i,j)$, $\rho_{d(i-1,j)}$ is the first order residual effect of treatment

$d(i-1,j)$ with $\rho_{d(0,j)}=0$ for all $j=1,\ldots,n$; γ_l is the regression coefficient associated with the l^{th} covariate, $l=1,\ldots,c$. As usual, the random errors $\{e_{ij}\}'s$ are assumed to be uncorrelated and homoscedastic with the common variance σ^2.

Writing the observations unit wise, in matrix notation the above model can be represented as

$$(\mathbf{Y},\ \mu\mathbf{1}_{np}+\mathbf{X}_1\boldsymbol{\alpha}+\mathbf{X}_2\boldsymbol{\beta}+\mathbf{X}_3\boldsymbol{\tau}+\mathbf{X}_4\boldsymbol{\rho}+\mathbf{Z}\boldsymbol{\gamma},\ \mathbf{I}_{np}\sigma^2) \tag{2.2}$$

where $\mathbf{Y}$ is the observation vector of order $np\times 1$, $\boldsymbol{\alpha}$, $\boldsymbol{\beta}$, $\boldsymbol{\tau}$, $\boldsymbol{\rho}$ and $\boldsymbol{\gamma}$ correspond respectively to the vectors of period effects, experimental unit effects, direct effects, first order residual effects and the covariate effects; $\mathbf{X}_1$, $\mathbf{X}_2$, $\mathbf{X}_3$,$\mathbf{X}_4$ and $\mathbf{Z}$ denote respectively the part of the design matrix corresponding to the period effects, experimental unit effects, direct effects, first order residual effects and covariate effects, $\mathbf{1}_{np}$ is a vector of all ones of order np and $\mathbf{I}_{np}$ is the identity matrix of order np.

In model (2.2) each of the covariates Z_l's, $l=1,\ldots,c$ is assumed to be a controllable non-stochastic variable. Applying a location scale transformation of the original limits of the values of the covariates, without loss of generality, it is assumed that the np values $z_{ij}^{(l)}$'s taken by the l^{th} covariate Z_l can vary within the interval [-1, 1], i.e.

$$z_{ij}^{(l)}\in[-1,1],\ i=1,\ldots,p;\ j=1,\ldots,n;\ l=1,\ldots,c. \tag{2.3}$$

With reference to model (2.2), it is evident that orthogonal estimation of the ANOVA (analysis of variance) effects and the covariate effects is possible whenever the following conditions

$$\mathbf{X}_i'\mathbf{Z}=\mathbf{0},\ \ \forall i=1,2,3,4 \tag{2.4}$$

are satisfied. Further the covariate effects are estimated with the maximum efficiency if and only if (cf. Pukelsheim (1993))

$$\mathbf{Z}'\mathbf{Z}=np\mathbf{I}_c. \tag{2.5}$$

Therefore, optimal estimation of each of the covariate effects is possible while the estimates of the ANOVA effects remain unaltered, if and only if $\mathbf{Z}$ satisfies the conditions (2.4) and (2.5) simultaneously. The design which allows such kind of estimation of the parameters is termed in the literature as *globally optimal design* (Shah and Sinha (1989)). Henceforth we shall be concerned with such optimal estimation of the regression parameters only, in a covariate model under some series of strongly balanced and balanced crossover design set-ups and by optimal covariate design, to be abbreviated as OCD hereafter, we mean only globally optimal design in the given context. The reader is referred to Hedayat, Sloane and Stufken(1999) for the definitions and discussions on Latin squares, mutually orthogonal Latin squares and Hadamard matrices which are extensively used for the construction of OCDs. In the sequel, any Hadamard matrix of order R is written as

$$\mathbf{H}_R=[\mathbf{h}_1^{(R)},\ldots,\mathbf{h}_R^{(R)}]. \tag{2.6}$$

For a Hadamard matrix in the *seminormal* form we assume, without loss of generality, $\mathbf{h}_R^{(R)}$ to be $\mathbf{1}$. We also refer to Rao(1973) for the definition of Kronecker product and Hadamard product which turn out to be useful tools in the derivation of our main results.

Note that under model (2.2) for any $d\in\Omega_{t,n,p}$, $\mathbf{X}_1=\mathbf{I}_p\otimes\mathbf{1}_n$ and $\mathbf{X}_2=\mathbf{1}_p\otimes\mathbf{I}_n$ where $\otimes$ denotes the Kronecker product. Thus for d, conditions (2.4) and (2.5) are equivalent to the following conditions:

$$\left.\begin{array}{llcl}
(i) & z_{ij}^{(l)} & = & \pm 1 \quad \forall\, i=1,\ldots,p;\ j=1,\ldots,n;\ l=1,\ldots,c,\\
(ii) & \sum\limits_{i=1}^{p} z_{ij}^{(l)} & = & 0 \quad \forall\, j=1,\ldots,n;\ l=1,\ldots,c,\\
(iii) & \sum\limits_{j=1}^{n} z_{ij}^{(l)} & = & 0 \quad \forall\, i=1,\ldots,p;\ l=1,\ldots,c,\\
(iv) & \sum\limits_{(i,j):d(i,j)=k} z_{ij}^{(l)} & = & 0 \quad \forall\, k=1,\ldots,t;\ l=1,\ldots,c,\\
(v) & \sum\limits_{(i,j):d(i-1,j)=k} z_{ij}^{(l)} & = & 0 \quad \forall\, k=1,\ldots,t;\ l=1,\ldots,c,\\
(vi) & \sum\limits_{i=1}^{p}\sum\limits_{j=1}^{n} z_{ij}^{(l)} z_{ij}^{(l')} & = & 0 \quad \forall\, l\neq l'=1,\ldots,c.
\end{array}\right\} \tag{2.7}$$

Thus to obtain an OCD for any $d \in \Omega_{t,n,p}$ it is required to construct the **Z**-matrix satisfying the conditions laid down in (2.7). In general for any arbitrary d this problem of construction is combinatorially intractable. For the rest of the paper we take up the problem of construction of an OCD i.e. optimum **Z**-matrix for strongly balanced or balanced crossover designs in $\Omega_{t,n,p}$ which are known to be universally optimal for the estimation of direct treatment effects and residual treatment effects in an appropriate class of competing designs. Thereby the resultant design will be optimal for the estimation of the ANOVA effects as well as controllable covariates' effects. We handle this issue of construction by adopting the technique used by Das et al.(2003) where *each column* of the **Z**-matrix can be recast to a **W**-matrix. Using this idea, the l^{th} column of **Z**-matrix, a vector of order $np \times 1$ is represented in the form of the matrix $\mathbf{W}^{(l)}$ of order $p \times n$, where the columns correspond to the experimental units in the order $1,\ldots,n$ and the rows correspond to the periods in the order $1,\ldots,p$. To elucidate the idea, the l^{th} column of **Z**-matrix is written as $\mathbf{W}^{(l)}$-matrix in the following way:

$$\mathbf{W}^{(l)} = \begin{pmatrix} z_{11}^{(l)} & z_{12}^{(l)} & \cdots & z_{1n}^{(l)} \\ z_{21}^{(l)} & z_{22}^{(l)} & \cdots & z_{2n}^{(l)} \\ & \vdots & & \\ z_{p1}^{(l)} & z_{p2}^{(l)} & \cdots & z_{pn}^{(l)} \end{pmatrix},\ l=1,\ldots,c. \tag{2.8}$$

The requirement of the **Z**-matrix satisfying the conditions *(ii)* and *(iii)* of (2.7) is equivalent to having zero row sums and zero column sums for each row and each column of $\mathbf{W}^{(l)}$, $l=1,\ldots,c$. To visualize the conditions *(iv)* and *(v)* of (2.7) in terms of the **W**-matrix we define two more matrices of order $p \times n$ as follows:

$$\mathbf{V}_1 = \begin{pmatrix} d(1,1) & d(1,2) & \ldots & d(1,n) \\ d(2,1) & d(2,2) & \ldots & d(2,n) \\ & \vdots & & \\ d(p,1) & d(p,2) & \ldots & d(p,n) \end{pmatrix},\ \ \mathbf{V}_2 = \begin{pmatrix} 0 & 0 & \ldots & 0 \\ d(1,1) & d(1,2) & \ldots & d(1,n) \\ & \vdots & & \\ d(p-1,1) & d(p-1,2) & \ldots & d(p-1,n) \end{pmatrix}. \tag{2.9}$$

Recalling that $d(i,j)$ denotes the treatment assigned to the j^{th} unit in the i^{th} period of $d \in \Omega_{t,n,p}$, $i=1,\ldots,p,\ j=1,\ldots,n$, it is now easy to verify that the requirement of the l^{th} column of the **Z**-matrix satisfying the conditions *(iv)* and *(v)* of (2.7) is equivalent to the requirement of the sums of $z_{ij}^{(l)}$'s corresponding to the same treatment to be equal to zero after superimposition of $\mathbf{W}^{(l)}$ on $\mathbf{V}_1$ and $\mathbf{V}_2$ respectively, $l=1,\ldots,c$.

Thus the necessary and sufficient conditions in terms of the elements of $\mathbf{W}^{(l)}$, $l = 1, \ldots, c$ for the existence of an OCD are summed up as follows:

$$\left.\begin{array}{ll}
(C_1) & \text{each of the elements of } \mathbf{W}^{(l)} \text{ is either +1 or -1;} \\
(C_2) & \mathbf{W}^{(l)}\text{-matrix has all row sums equal to zero;} \\
(C_3) & \mathbf{W}^{(l)}\text{-matrix has all column sums equal to zero;} \\
(C_4) & \text{after superimposing } \mathbf{W}^{(l)} \text{ on } \mathbf{V}_1\text{, for every treatment as specified in } \mathbf{V}_1\text{,} \\
 & \text{the sum of the elements of } \mathbf{W}^{(l)} \text{ corresponding to the same treatment} \\
 & \text{is equal to zero;} \\
(C_5) & \text{after superimposing } \mathbf{W}^{(l)} \text{ on } \mathbf{V}_2\text{, for every treatment as specified in } \mathbf{V}_2 \\
 & \text{the sum of the elements of } \mathbf{W}^{(l)} \text{ corresponding to the same treatment} \\
 & \text{is equal to zero;} \\
(C_6) & \text{the grand total of all entries in the Hadamard product of } \mathbf{W}^{(l)} \text{ and} \\
 & \mathbf{W}^{(l')} \text{ is equal to } np \text{ or zero depending on } l = l' \text{ or } l \neq l' \text{ respectively.}
\end{array}\right\} \quad (2.10)$$

It is worthwhile to note that a covariate design $\mathbf{Z}$ for c covariates is equivalent to c $\mathbf{W}$-matrices which are convenient to work with.

Definition 2.1 *With respect to model (2.2), the c $\mathbf{W}$-matrices corresponding to the c covariates are said to be optimum if they satisfy the conditions laid down in (2.10).*

Remark 2.2 *It is to be noted that if $c = 1$, only the conditions C_1-C_5 of (2.10) are to be satisfied by the $\mathbf{W}$-matrix for an OCD to exist.*

Remark 2.3 *The maximum number of covariates cannot exceed the error degrees of freedom for the ANOVA part of a given set-up.*

In the present paper we aim at constructing an OCD, in other words optimum $\mathbf{W}$-matrices, with as many $\mathbf{W}$-matrices as possible for a crossover design which is uniform strongly balanced or strongly balanced, uniform on the periods and uniform on the units in the first $p-1$ periods or uniform balanced. The construction of $\mathbf{W}$-matrices is very much dependent on the particular method of construction of the underlying basic crossover design. We will denote by c^* the maximum value of c, the number of covariates in a given context as attained by a given method of construction. In reality a limited number of covariates turn out to be useful. Thus given the choice of c^* optimum $\mathbf{W}$-matrices, the experimenter has the flexibility of selecting the optimum values of the required number of covariates from a large pool of possible options, appropriate to the experimental situation and availability of the resources.

3 Main Results

In this section the construction of $\mathbf{W}$-matrices satisfying (2.10) for different series of strongly balanced and balanced crossover designs obtained through different constructional methods are given. We briefly discuss the method of construction of the underlying basic crossover design to understand the construction of optimum $\mathbf{W}$-matrices as their interdependency has already been pointed out.

3.1 Strongly Balanced Crossover Design Set-up in $\Omega_{t,\lambda_1 t^2,\lambda_2 t}$

It has been shown in Stufken(1996) that a uniform strongly balanced crossover design d^* in $\Omega_{t,n,p}$ is universally optimal for the estimation of direct treatment effects and residual treatment effects and can always be constructed using Latin squares and orthogonal arrays whenever $n = \lambda_1 t^2$ and $p = \lambda_2 t$ for integers $\lambda_1 \geq 1$ and $\lambda_2 \geq 2$. We start with this particular method of construction of d^* assuming $\lambda_1 = 1$ and obtain an OCD. The construction of OCD with $n = \lambda_1 t^2$, $\lambda_1 > 1$ will be taken up later. Let $\mathbf{A}_t$ be an orthogonal array, denoted by OA($t^2,\ 3,\ t,\ 2$) with entries from $S = \{1,\ldots,t\}$. Such an orthogonal array can easily be obtained from a Latin square $L = ((l_{ij}))$ of order t, $t \geq 2$ as follows:

$$\mathbf{A}_t : \begin{array}{cccc} \overbrace{1\ 1\ \ldots\ 1}^{t \text{ times}} & \overbrace{2\ 2\ \ldots\ 2}^{t \text{ times}} & \ldots & \overbrace{t\ t\ \ldots\ t}^{t \text{ times}} \\ 1\ 2\ \ldots\ t & 1\ 2\ \ldots\ t & \ldots & 1\ 2\ \ldots t \\ l_{11} l_{12} \ldots l_{1t} & l_{21} l_{22} \ldots l_{2t} & \ldots & l_{t1} l_{t2} \ldots l_{tt} \end{array} . \tag{3.1}$$

Let $\mathbf{B}_t$ be an orthogonal array OA($t^2,\ 2,\ t,\ 2$), obtained from $\mathbf{A}_t$ by deleting the third row in $\mathbf{A}_t$. For $i \in \{1,\ldots,t-1\}$ let $\mathbf{A}_i = \mathbf{A}_t + i$ and $\mathbf{B}_i = \mathbf{B}_t + i$, where i is added to each element of $\mathbf{A}_t$ or $\mathbf{B}_t$, modulo t. Let the two arrays $\mathbf{A}$ and $\mathbf{B}$ of order $3t \times t^2$ and $2t \times t^2$ respectively, be defined as

$$\mathbf{A} = \begin{pmatrix} \mathbf{A}_1 \\ \mathbf{A}_2 \\ \vdots \\ \mathbf{A}_t \end{pmatrix}, \quad \mathbf{B} = \begin{pmatrix} \mathbf{B}_1 \\ \mathbf{B}_2 \\ \vdots \\ \mathbf{B}_t \end{pmatrix}. \tag{3.2}$$

With $\lambda_2 \geq 2$, writing $\lambda_2 = 3\delta_1 + 2\delta_2$ for non-negative integers δ_1 and δ_2, the $p \times t^2$ array d^* defined by

$$d^* = [\mathbf{A}',\ldots,\mathbf{A}',\ \mathbf{B}',\ldots,\mathbf{B}']' \tag{3.3}$$

consisting of δ_1 copies of $\mathbf{A}$ and δ_2 copies of $\mathbf{B}$ is a uniform strongly balanced crossover design in $\Omega_{t,n,p}$.

We now present the actual construction of OCD, in other words optimum $\mathbf{W}$-matrices for d^* in $\Omega_{t,t^2,p}$ under a variety of choices of t accommodating the maximum number of covariates as attained by the given method of construction.

Case $1 : t = 0(mod\ 4)$

The following theorem relates to an OCD for d^* in $\Omega_{t,t^2,3t}$.

Theorem 3.1 *Suppose* $\mathbf{H}_t$, $\mathbf{H}_{3t}$ *and further* $s(\geq 2)$ *mutually orthogonal Latin squares (MOLS) of order t exist. Let* d^* *in* $\Omega_{t,t^2,3t}$ *be constructed as described in (3.3). Then there exists a set of (3t-1)(t-1)(s-1) optimum* $\mathbf{W}$*-matrices* $d^* \in \Omega_{t,t^2,3t}$.

Proof: Without loss of generality we assume that $\mathbf{H}_t$ and $\mathbf{H}_{3t}$ are in the *seminormal* form. Let $L_1,\ L_2,\ldots,L_s$ be s MOLS of order t, based on the symbols $1,\ldots,t$. Suppose L_s is used for constructing $\mathbf{A}_t$ in (3.1) and $L_s^{(q)} = L_s + q$, where q is added to each element of L_s modulo t, is used to develop the third row of $\mathbf{A}_q$, $q = 1,\ldots,t-1$ in (3.2) to give rise to d^* in $\Omega_{t,t^2,3t}$ as described in (3.3). Now we proceed to construct the optimum $\mathbf{W}$-matrices for d^* in $\Omega_{t,t^2,3t}$ as follows:

In each of the L_i, $i = 1,\ldots,s-1$, replace the symbols $1,\ldots,t$ by the elements of $\mathbf{h}_j^{(t)}$ in order, for $j = 1,\ldots,t-1$. Let $\mathbf{d}_m^{ij\prime}$ denote the replaced m^{th} row of L_i, $m = 1,\ldots,t$ written with the symbols of $\mathbf{h}_j^{(t)}$. Now juxtaposing side by side these t rows, we obtain a row vector $\mathbf{D}'_{ij}$ of order t^2 given by

$$\mathbf{D}'_{ij} = \left(\mathbf{d}_1^{ij\prime} :\ \mathbf{d}_2^{ij\prime} : \ldots : \mathbf{d}_t^{ij\prime}\right). \tag{3.4}$$

Now we construct $\mathbf{W}_{ijf}$ of order $3t \times t^2$ as follows:

$$\mathbf{W}^{(l)} = \mathbf{W}_{ijf} = \mathbf{h}_f^{(3t)} \otimes \mathbf{D}'_{ij};\ \ i = 1,\ldots,s-1,\ j = 1,...,t-1,\ f = 1,...,3t-1,$$
$$l = (i-1)(t-1)(3t-1) + (j-1)(3t-1) + f. \tag{3.5}$$

Using the properties of Latin square, Hadamard matrices and the fact that $L_i,\ i = 1,\ldots,s-1$ is orthogonal with $L_s^{(q)},\ q = 1,\ldots,t-1$, defined above, it is not hard to see that $\mathbf{W}^{(l)}$'s satisfy the conditions of (2.10) and the maximum number of covariates in the given context attained by the method of construction is $c^* = (3t-1)(t-1)(s-1)$. □

An illustration of the above method of construction with $t = 4$ follows.

Example 1: $t = 4$, $d^* \in \Omega_{4,16,12}$

$$L_1 = \begin{pmatrix} 1 & 2 & 3 & 4 \\ 2 & 1 & 4 & 3 \\ 3 & 4 & 1 & 2 \\ 4 & 3 & 2 & 1 \end{pmatrix},\ L_2 = \begin{pmatrix} 1 & 2 & 3 & 4 \\ 3 & 4 & 1 & 2 \\ 4 & 3 & 2 & 1 \\ 2 & 1 & 4 & 3 \end{pmatrix},\ L_3 = \begin{pmatrix} 1 & 2 & 3 & 4 \\ 4 & 3 & 2 & 1 \\ 2 & 1 & 4 & 3 \\ 3 & 4 & 1 & 2 \end{pmatrix}$$

and

$$\mathbf{A} = \begin{pmatrix} 2 & 2 & 2 & 2 & 3 & 3 & 3 & 3 & 4 & 4 & 4 & 4 & 1 & 1 & 1 & 1 \\ 2 & 3 & 4 & 1 & 2 & 3 & 4 & 1 & 2 & 3 & 4 & 1 & 2 & 3 & 4 & 1 \\ 2 & 3 & 4 & 1 & 1 & 4 & 3 & 2 & 3 & 2 & 1 & 4 & 4 & 1 & 2 & 3 \\ 3 & 3 & 3 & 3 & 4 & 4 & 4 & 4 & 1 & 1 & 1 & 1 & 2 & 2 & 2 & 2 \\ 3 & 4 & 1 & 2 & 3 & 4 & 1 & 2 & 3 & 4 & 1 & 2 & 3 & 4 & 1 & 2 \\ 3 & 4 & 1 & 2 & 2 & 1 & 4 & 3 & 4 & 3 & 2 & 1 & 1 & 2 & 3 & 4 \\ 4 & 4 & 4 & 4 & 1 & 1 & 1 & 1 & 2 & 2 & 2 & 2 & 3 & 3 & 3 & 3 \\ 4 & 1 & 2 & 3 & 4 & 1 & 2 & 3 & 4 & 1 & 2 & 3 & 4 & 1 & 2 & 3 \\ 4 & 1 & 2 & 3 & 3 & 2 & 1 & 4 & 1 & 4 & 3 & 2 & 2 & 3 & 4 & 1 \\ 1 & 1 & 1 & 1 & 2 & 2 & 2 & 2 & 3 & 3 & 3 & 3 & 4 & 4 & 4 & 4 \\ 1 & 2 & 3 & 4 & 1 & 2 & 3 & 4 & 1 & 2 & 3 & 4 & 1 & 2 & 3 & 4 \\ 1 & 2 & 3 & 4 & 4 & 3 & 2 & 1 & 2 & 1 & 4 & 3 & 3 & 4 & 1 & 2 \end{pmatrix}.$$

The forms of $\mathbf{H}_4$ and $\mathbf{H}_{12}$ for our use are

$$\mathbf{H}_4 = \begin{pmatrix} -1 & 1 & -1 & 1 \\ 1 & -1 & -1 & 1 \\ -1 & -1 & 1 & 1 \\ 1 & 1 & 1 & 1 \end{pmatrix} \tag{3.6}$$

$$\mathbf{H}_{12} = \begin{pmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ -1 & 1 & -1 & 1 & 1 & 1 & -1 & -1 & -1 & 1 & -1 & 1 \\ -1 & -1 & 1 & -1 & 1 & 1 & 1 & -1 & -1 & -1 & 1 & 1 \\ 1 & -1 & -1 & 1 & -1 & 1 & 1 & 1 & -1 & -1 & -1 & 1 \\ -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 & 1 & -1 & -1 & 1 \\ -1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 & 1 & -1 & 1 \\ -1 & -1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 & 1 & 1 \\ 1 & -1 & -1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 & 1 \\ 1 & 1 & -1 & -1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 \\ 1 & 1 & 1 & -1 & -1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 \\ -1 & 1 & 1 & 1 & -1 & -1 & -1 & 1 & -1 & -1 & 1 & 1 \\ 1 & -1 & 1 & 1 & 1 & -1 & -1 & -1 & 1 & -1 & -1 & 1 \end{pmatrix}. \tag{3.7}$$

Now using $\mathbf{h}_1^{(4)}$, the first column of $\mathbf{H}_4$ and L_1, we construct $\mathbf{D}'_{11}$ as

$$\mathbf{D}'_{11} = \begin{pmatrix} -1 & 1 & -1 & 1: & 1 & -1 & 1 & -1: & -1 & 1 & -1 & 1: & 1 & -1 & 1 & -1 \end{pmatrix}.$$

Hence using $\mathbf{h}_1^{(12)}$, the first column of $\mathbf{H}_{12}$, $\mathbf{W}^{(1)} = \mathbf{W}_{111} = \mathbf{h}_1^{(12)} \otimes \left(\mathbf{d}_1^{11},\, \mathbf{d}_2^{11},\, \mathbf{d}_3^{11},\, \mathbf{d}_4^{11}\right)$ takes the form

$$\mathbf{W}^{(1)} = \begin{pmatrix} -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 \\ 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 \\ 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 \\ -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 \\ 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 \\ 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 \\ 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 \\ -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 \\ -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 \\ -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 \\ 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 \\ -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 \end{pmatrix}.$$

Similarly 65 more choices of the optimum $\mathbf{W}$-matrices can be constructed.

Remark 3.2 *In practice in the above situation the experimenter has the flexibility to choose the values of the required number of optimum covariates from the set of 66 possible optimum choices.*

Remark 3.3 *In particular for $t = 4$, three more optimum $\mathbf{W}^{(l)}$ for d^* in $\Omega_{4,16,12}$ can be constructed as follows:*

$$\mathbf{W}^{(67)} = \begin{pmatrix} \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \end{pmatrix}, \quad \mathbf{W}^{(68)} = \begin{pmatrix} \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \end{pmatrix},$$

$$\mathbf{W}^{(69)} = \begin{pmatrix} \mathbf{1}_4' & -\mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \end{pmatrix}.$$

Theorem 3.4 *Suppose* $\mathbf{H}_t$*, and further* $s(\geq 2)$ *mutually orthogonal Latin squares (MOLS) of order t exist. Let* d^* *in* $\Omega_{t,t^2,2t}$ *be constructed as described in (3.3). Then there exists a set of (2t-1)(t-1)s optimum* $\mathbf{W}$*-matrices* $d^* \in \Omega_{t,t^2,2t}$*.*

Proof: The proof is along the similar lines of the proof of Theorem 3.1. Note that $d^* \in \Omega_{t,t^2,2t}$ as described in (3.3) can be constructed without requiring to use L_s. So L_s can also be used to construct the row vector $\mathbf{D}_{ij}'$ (3.4) of order t^2 as before, $i = 1,\ldots,s$; $j = 1,\ldots,t-1$. Since $\mathbf{H}_t$ and hence $\mathbf{H}_{2t}$ exist, assuming both of these in the *seminormal* form, we construct $\mathbf{W}^{(l)}$ of order $2t \times t^2$ as follows

$$\mathbf{W}^{(l)} = \mathbf{W}_{ijf} = \mathbf{h}_f^{(2t)} \otimes \left(\mathbf{d}_1^{ij\prime} : \mathbf{d}_2^{ij\prime} : \ldots : \mathbf{d}_t^{ij\prime}\right); \; i = 1,\ldots,s, \; j = 1,\ldots,t-1, \; f = 1,\ldots,2t-1,$$
$$l = (i-1)(t-1)(2t-1) + (j-1)(2t-1) + f$$

with $c^* = (2t-1)(t-1)s$ in the given context. □

Remark 3.5 *For* $t = 4$*, four more optimum* $\mathbf{W}^{(l)}$ *for* d^* *in* $\Omega_{4,16,8}$ *can be constructed as described below:*

$$\mathbf{W}^{(64)} = \begin{pmatrix} \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \end{pmatrix}, \ \mathbf{W}^{(65)} = \begin{pmatrix} \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \end{pmatrix},$$

$$\mathbf{W}^{(66)} = \begin{pmatrix} \mathbf{1}_4' & -\mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \end{pmatrix}, \ \mathbf{W}^{(67)} = \begin{pmatrix} \mathbf{1}_4' & -\mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ -\mathbf{1}_4' & \mathbf{1}_4' & \mathbf{1}_4' & -\mathbf{1}_4' \\ \mathbf{1}_4' & -\mathbf{1}_4' & -\mathbf{1}_4' & \mathbf{1}_4' \end{pmatrix}.$$

Case $2 : t = 2(mod\ 4), t \neq 2, 6$

It is clear that $\mathbf{H}_t$ does not exist but if s MOLS of order t exist then $(s-1)$ optimum $\mathbf{W}$-matrices can be constructed for $d^* \in \Omega_{t,t^2,3t}$ (vide (3.3)) using the same steps followed in the proof of Theorem 3.1 and the vector $\mathbf{a}_1 = \left(\mathbf{1}'_{\frac{t}{2}}, -\mathbf{1}'_{\frac{t}{2}}\right)'$ and $\mathbf{a}_2 = \left(\mathbf{1}'_{\frac{3t}{2}}, -\mathbf{1}'_{\frac{3t}{2}}\right)'$ instead of the columns of $\mathbf{H}_t$ and $\mathbf{H}_{3t}$ respectively. Similarly if $\mathbf{H}_{2t}$ exists, $(2t-1)s$ optimum $\mathbf{W}$-matrices can be constructed for $d^* \in \Omega_{t,t^2,2t}$ (vide (3.3)) following the same steps of Theorem 3.4 using the vector $\mathbf{a}_1 = \left(\mathbf{1}'_{\frac{t}{2}}, -\mathbf{1}'_{\frac{t}{2}}\right)'$ instead of the columns of $\mathbf{H}_t$.

Case $3 : t = 2$

Since a pair of MOLS does not exist for $t = 2$, the methods discussed in earlier cases do not apply here to construct an OCD. We adopt trial and error method to construct optimum $\mathbf{W}$-matrices.

Theorem 3.6 *Let d_1^* in $\Omega_{2,4,6}$ and d_2^* in $\Omega_{2,4,4}$ be constructed as described in (3.3). Then there exist 2 optimum $\mathbf{W}$-matrices for each of d_1^* and d_2^*.*

Proof: Recalling (3.2) it is easy to see that d_1^* and d_2^* given below represent the strongly balanced design in $\Omega_{2,4,6}$ and $\Omega_{2,4,4}$ respectively.

$$d_1^* : \begin{pmatrix} 2 & 2 & 1 & 1 \\ 2 & 1 & 2 & 1 \\ 2 & 1 & 1 & 2 \\ 1 & 1 & 2 & 2 \\ 1 & 2 & 1 & 2 \\ 1 & 2 & 2 & 1 \end{pmatrix}, \ d_2^* = \begin{pmatrix} 2 & 2 & 1 & 1 \\ 2 & 1 & 2 & 1 \\ 1 & 1 & 2 & 2 \\ 1 & 2 & 1 & 2 \end{pmatrix}. \tag{3.8}$$

Optimum $\mathbf{W}$-matrices denoted by $\mathbf{W}_1^*$ and $\mathbf{W}_2^*$ for d_1^* and $\mathbf{W}_1^{**}$ and $\mathbf{W}_2^{**}$ for d_2^* respectively, can be constructed as

$$\mathbf{W}_1^* = \begin{pmatrix} 1 & 1 & -1 & -1 \\ 1 & -1 & -1 & 1 \\ -1 & 1 & 1 & -1 \\ -1 & -1 & 1 & 1 \\ -1 & 1 & 1 & -1 \\ 1 & -1 & -1 & 1 \end{pmatrix}, \quad \mathbf{W}_2^* = \begin{pmatrix} 1 & -1 & 1 & -1 \\ 1 & 1 & -1 & -1 \\ 1 & -1 & 1 & -1 \\ -1 & 1 & -1 & 1 \\ -1 & -1 & 1 & 1 \\ -1 & 1 & -1 & 1 \end{pmatrix}$$

$$\mathbf{W}_1^{**} = \begin{pmatrix} 1 & 1 & -1 & -1 \\ -1 & 1 & -1 & 1 \\ -1 & -1 & 1 & 1 \\ 1 & -1 & 1 & -1 \end{pmatrix}, \quad \mathbf{W}_2^{**} = \begin{pmatrix} 1 & -1 & -1 & 1 \\ -1 & 1 & 1 & -1 \\ 1 & -1 & -1 & 1 \\ -1 & 1 & 1 & -1 \end{pmatrix}.$$

□

Case $4 : t = 6$

It is known that for $t = 6$ a pair of MOLS does not exist and hence we take up the construction of OCD in this case separately.

We start with a uniform strongly balanced crossover design $d^* \in \Omega_{6,36,18}$ constructed (vide (3.3)) using the Latin square L (say) given by

$$L = \begin{pmatrix} 1 & 2 & 3 & 4 & 5 & 6 \\ 2 & 1 & 4 & 3 & 6 & 5 \\ 6 & 5 & 1 & 2 & 3 & 4 \\ 5 & 6 & 2 & 1 & 4 & 3 \\ 4 & 3 & 6 & 5 & 2 & 1 \\ 3 & 4 & 5 & 6 & 1 & 2 \end{pmatrix}. \tag{3.9}$$

Theorem 3.7 *Let d_1^* in $\Omega_{6,36,18}$ and d_2^* in $\Omega_{6,36,12}$ be constructed (vide (3.3)) using L of (3.9). Then there exist an optimum* **W***-matrix for d_1^* and 11 optimum* **W** *matices for d_2^*.*

Proof: Let **D** be a matrix of order 6×6 with elements ± 1 as follows:

$$\mathbf{D} = \begin{pmatrix} 1 & 1 & 1 & -1 & -1 & -1 \\ 1 & 1 & -1 & -1 & -1 & 1 \\ 1 & -1 & -1 & -1 & 1 & 1 \\ -1 & -1 & -1 & 1 & 1 & 1 \\ -1 & -1 & 1 & 1 & 1 & -1 \\ -1 & 1 & 1 & 1 & -1 & -1 \end{pmatrix} = \begin{pmatrix} \mathbf{d}_1' \\ \mathbf{d}_2' \\ \mathbf{d}_3' \\ \mathbf{d}_4' \\ \mathbf{d}_5' \\ \mathbf{d}_6' \end{pmatrix}. \tag{3.10}$$

It is to be noted that the row sums and column sums of **D** are zero. Moreover superimposing **D** on L, it can be seen that for each symbol in L, the sum of the corresponding elements of **D** is also zero. Thus an optimum **W**-matrix for d_1^* in $\Omega_{6,36,18}$ (vide (3.3)) using L of (3.9) can be formed taking $\mathbf{a}=\left(\mathbf{1}_9',\ -\mathbf{1}_9'\right)'$ and the rows of matrix **D** as

$$\mathbf{W}^{(1)} = \mathbf{a} \otimes \left(\mathbf{d}_1' : \mathbf{d}_2' :,\ \mathbf{d}_3' : \mathbf{d}_4' : \mathbf{d}_5' : \mathbf{d}_6\right).$$

But for d_2^* in $\Omega_{6,36,12}$ (vide (3.2)), 11 optimum **W**-matrices can be formed using $\mathbf{H}_{12}$ of (3.7) as follows:

$$\mathbf{W}^{(l)} = \mathbf{h}_l^{(12)} \otimes \left(\mathbf{d}_1' : \mathbf{d}_2' : \mathbf{d}_3' : \mathbf{d}_4' : \mathbf{d}_5' : \mathbf{d}_6'\right),\ l = 1, \ldots, 11.$$

□

So far we have discussed the construction of optimum **W**-matrices for uniform strongly balanced crossover design d_1^* in $\Omega_{t,t^2,3t}$ and d_2^* in $\Omega_{t,t^2,2t}$ separately. Let c_1^* and c_2^* denote the maximum number of optimum **W**-matrices for d_1^* and d_2^* respectively in the given context. Now we will consider the construction of optimum **W**-matrices for a strongly balanced crossover design d^* in $\Omega_{t,t^2,p}$ (vide (3.3)) where $p = (3\delta_1 + 2\delta_2)t$ for non-negative integers δ_1 and δ_2. Write

$$d^* = \left[\ d_1^{*\prime}, \ldots, d_1^{*\prime}, d_2^{*\prime}, \ldots, d_2^{*\prime}\ \right]' \tag{3.11}$$

taking δ_1 copies of d_1^* and δ_2 copies of d_2^*.
Define

$$\delta_0 = \min\{\delta_1,\ \delta_2\} \text{ and } c_0 = \min\{c_1^*, c_2^*\}. \tag{3.12}$$

Corollary 3.8 *Suppose $\mathbf{H}_{\delta_1}$ and $\mathbf{H}_{\delta_2}$ exist. Let d^* in $\Omega_{t,t^2,p}$ be constructed as described in (3.11) for $p = (3\delta_1 + 2\delta_2)t,\ \delta_1,\ \delta_2 \geq 0$, non-negative integers. Then there exists a set of $\delta_0 c_0$ optimum **W**-matrices for d^* where δ_0 and c_0 are defined in (3.12).*

Proof: Let the c_1^* optimum **W**-matrices for d_1^* be denoted by $\mathbf{W}_1^*, \ldots, \mathbf{W}_{c_1^*}^*$ and the c_2^* optimum **W**-matrices for d_2^* be denoted by $\mathbf{W}_1^{**}, \ldots, \mathbf{W}_{c_2^*}^{**}$. Then it can be easily seen that $\mathbf{W}^{(l)}$ defined as

$$\mathbf{W}^{(l)} = \mathbf{W}_{ij} = \begin{pmatrix} \mathbf{W}_{ij}^* \\ \mathbf{W}_{ij}^{**} \end{pmatrix};\ \text{where } \mathbf{W}_{ij}^* = \mathbf{h}_i^{(\delta_1)} \otimes \mathbf{W}_j^* \text{ and } \mathbf{W}_{ij}^{**} = \mathbf{h}_i^{(\delta_2)} \otimes \mathbf{W}_j^{**} \tag{3.13}$$

$$i = 1, \ldots, \delta_0,\ j = 1, \ldots, c_0,\ l = c_0(i-1) + j,$$

are the required **W**-matrices for d^*. □

Remark 3.9 *Note that $\mathbf{H}_{\delta_1}$ and $\mathbf{H}_{\delta_2}$ are not necessarily assumed to be in the semi-normal form. Thus $\mathbf{h}_i^{(\delta_1)}$ and $\mathbf{h}_i^{(\delta_2)}$ can as well be of the form of a vector all ones.*

Remark 3.10 *It is not hard to see that the set of $\delta_0 c_0$ **W**-matrices in Corollary 3.8 is not unique.*

Remark 3.11 *The construction of optimum **W**-matrices for a strongly balanced design d^* in $\Omega_{t,\lambda_1 t^2,p}$ for $\lambda_1 > 1$ can easily be obtained by taking the Kronecker product of the rows of $\mathbf{H}_{\lambda_1}$ and the corresponding optimum **W**-matrix of $\Omega_{t,t^2,p}$ whenever $\mathbf{H}_{\lambda_1}$ exists. In case of non-existence of $\mathbf{H}_{\lambda_1}$ for λ_1 even, the role of the rows of $\mathbf{H}_{\lambda_1}$ above can be taken by the vectors $\mathbf{1}'_{\lambda_1}$ and $(\mathbf{1}'_{\frac{\lambda_1}{2}}, -\mathbf{1}'_{\frac{\lambda_1}{2}})'$. In case of λ_1 odd, the vector of all ones serves the purpose.*

Case $5:t$ *odd*
Whenever t is odd, it is easy to verify that an OCD for a uniform strongly balanced crossover design d^* in $\Omega_{t,t^2,p}$ as described in (3.3) does not exist as Condition C_2 of (2.10) is not attainable. Let a uniform strongly balanced crossover design $d^{**} \in \Omega_{t,\lambda_1 t^2,p}$ be defined as

$$d^{**} = \mathbf{1}'_{\lambda_1} \otimes d^* \tag{3.14}$$

for some positive integer λ_1. The following theorem relates to the construction of OCD for d^{**}.

Theorem 3.12 *Suppose $\mathbf{H}_{\lambda_1 t}$, $\mathbf{H}_p$ and a pair of mutually orthogonal Latin squares of order t exist. Let d^{**} be defined as in (3.14). Then there exists a set of $(\lambda_1 t - 1)(p-1)$ optimum **W**-matrices for d^{**}.*

Proof: Suppose L_1 and L_2 are pairwise orthogonal Latin squares of order t and L_2 has been used in (3.2) and (3.3) to construct a uniform strongly balanced crossover design d^* in $\Omega_{t,t^2,p}$. Now we proceed to construct the optimum $\mathbf{W}$-matrices for d^{**}. Assuming $\mathbf{H}_{\lambda_1 t}$ and $\mathbf{H}_p$ in the *seminormal* form, for each $i = 1,\ldots,\lambda_1 t-1$, partitioning $\mathbf{h}_i^{(\lambda_1 t)}$ into λ_1 parts as

$$\mathbf{h}_i^{(\lambda_1 t)} = \left(\mathbf{h}_{i1}^{(\lambda_1 t)\prime},...,\mathbf{h}_{ij}^{(\lambda_1 t)\prime},....,\mathbf{h}_{i\lambda_1}^{(\lambda_1 t)\prime}\right)' \tag{3.15}$$

we construct a row vector $\mathbf{D}_{ij}^{*\prime}$ of order t^2 considering L_1 and $\mathbf{h}_{ij}^{(\lambda_1 t)}$, for every fixed $j \in \{1,2,\ldots,\lambda_1\}$, following the steps as described in Theorem 3.1. Thus

$$\mathbf{D}_{ij}^{*\prime} = \left(\mathbf{d}_1^{*ij\prime},\ \mathbf{d}_2^{*ij\prime},...,\mathbf{d}_t^{*ij\prime}\right). \tag{3.16}$$

Now we construct $\mathbf{W}_{if}^{(j)}$ of order $p \times t^2$ as follows:

$$\mathbf{W}_{if}^{(j)} = \mathbf{h}_f^{(p)} \otimes \left(\mathbf{d}_1^{*ij\prime},\ \mathbf{d}_2^{*ij\prime},...,\mathbf{d}_t^{*ij\prime}\right)';\ \ i = 1,\ldots,\lambda_1 t-1,\ f = 1,\ldots,p-1. \tag{3.17}$$

Finally $\mathbf{W}^{(l)}$ matrix of order $p \times \lambda_1 t^2$ is given by:

$$\mathbf{W}^{(l)} = [\mathbf{W}_{if}^{(1)},...,\mathbf{W}_{if}^{(j)},...,\mathbf{W}_{if}^{(\lambda_1)}],\ \ i = 1,\ldots,\lambda_1 t-1,\ f = 1,\ldots,p-1,\ l = (i-1)(p-1)+f.$$

It can be easily checked that these $\mathbf{W}^{(l)}$'s are the required optimum $\mathbf{W}$-matrices for d^{**} in $\Omega_{t,\lambda_1 t^2,p}$ and $c^* = (\lambda_1 t-1)(p-1)$ in this given context.

Remark 3.13 *If for p even,* $\mathbf{H}_p$ *does not exist, then* $\mathbf{a} = \left(\mathbf{1}'_{\frac{p}{2}}, -\mathbf{1}'_{\frac{p}{2}}\right)'$ *can be used instead of* $\mathbf{h}_f^{(p)}$ *in the above theorem.*

3.2 Strongly Balanced Crossover Design Set-up in $\Omega_{t,\lambda_1 t,\lambda_2 t+1}$

It has been shown in Stufken(1996) that a strongly balanced crossover design that is uniform on the periods and uniform on the units in the first $p-1$ periods is universally optimal for the estimation of direct treatment effects as well as residual treatment effects in $\Omega_{t,n,p}$. We now take up the construction of OCD for such design whenever t is odd and λ_1 is even, as otherwise an OCD fails to exist.

Whenever t is odd, a uniform balanced design d_0^* exists in $\Omega_{t,2t,t}$, which is obtained by juxtaposing two special Latin squares of order t side by side (cf. Williams (1949), Bose and Dey (2009)). A strongly balanced design $\tilde{d}^{**}$ obtained by repeating the last period of d_0^* is uniform on the periods and uniform on the units in the first t periods (cf. Cheng and Wu (1980)). Now for some positive integer λ, taking λ copies of this design let a strongly balanced design $\tilde{d}^*$ in $\Omega_{t,2\lambda t,t+1}$ be constructed as

$$\tilde{d}^* = \mathbf{1}'_\lambda \otimes \tilde{d}^{**} \tag{3.18}$$

Theorem 3.14 *Suppose* $\mathbf{H}_{2\lambda}$ *exists. Let* $\tilde{d}^*$ *be defined as in (3.18). Then there exists a set of* $2\lambda-1$ *optimum* $\mathbf{W}$*-matrices for* $\tilde{d}^*$.

Proof: Assuming $\mathbf{H}_{2\lambda}$ in the *seminormal* form, the optimum $\mathbf{W}^{(l)}$-matrix for $\tilde{d}^*$ in $\Omega_{t,2\lambda t,t+1}$ can be constructed as :

$$\mathbf{W}^{(l)} = \mathbf{a}^* \otimes \mathbf{h}_l^{(2\lambda)} \otimes \mathbf{1}'_t,\ l = 1,\ldots,2\lambda-1,$$

where $\mathbf{a}^* = \left(\ \mathbf{1}'_{\frac{t+1}{2}} \quad -\mathbf{1}'_{\frac{t+1}{2}}\ \right)'$. □

It has been shown in Stufken (1996) that the above idea of Cheng and Wu (1980) to construct a strongly balanced design from a uniform balanced design can be extended to cover $p = \lambda_2 t + 1$. The required uniform balanced design d_0^* in $\Omega_{t,\lambda_1 t,\lambda_2 t}$ is a $\lambda_2 \times \lambda_1$ array of special Latin square of order t. We refer to Stufken (1996) and Bose and Dey (2009) for the details of the construction. Now repeating the last period of this uniformly balanced design, we get a strongly balanced design $\tilde{d}^*$ in $\Omega_{t,\lambda_1 t,\lambda_2 t+1}$ which is uniform on the periods and uniform on the units in the first $p-1$ periods. The following theorem deals with the construction of OCD for this $\tilde{d}^*$.

Corollary 3.15 *Suppose $\mathbf{H}_{\lambda_2 t+1}$ and $\mathbf{H}_{\lambda_1}$ exist. Then there exists a set of $\lambda_2 t(\lambda_1 - 1)$ optimum $\mathbf{W}$-matrices for a strongly balanced $\tilde{d}^*$ in $\Omega_{t,\lambda_1 t,\lambda_2 t+1}$.*

Proof: It is readily verified that assuming $\mathbf{H}_p$ and $\mathbf{H}_{\lambda_1}$ in the *seminormal* form,

$$\mathbf{W}^{(l)} = \mathbf{W}_{ij} = \mathbf{h}_i^{(\lambda_2 t+1)} \otimes \mathbf{h}_j^{(\lambda_1)\prime} \otimes \mathbf{1}_t', \;\; i = 1,\ldots,\lambda_2 t, \; j = 1,\ldots,\lambda_1 - 1, \; l = (\lambda_1 - 1)(i-1) + j \quad (3.19)$$

are the required optimum $\mathbf{W}$-matrices. □

3.3 Balanced Crossover Design Set-up

In this section we consider the construction of OCD for Williams square and Patterson designs as the basic designs which are uniform balanced crossover design with appropriate parameters.

It is known that for all even values of t, a uniform balanced design d_0^* in $\Omega_{t,t,t}$ exists which is a balanced Latin square and is referred to as a Williams Square in the literature. There does not exist any optimum $\mathbf{W}$-matrix for d_0^* in $\Omega_{t,t,t}$ as $t-1$ being odd, Condition C_5 is not attainable. Let for some positive integer λ, a uniform balanced crossover design be constructed as

$$d_0^{**} = \mathbf{1}_\lambda' \otimes d_0^*. \quad (3.20)$$

We next deal with the construction of optimum $\mathbf{W}$-matrices for d_0^{**} in $\Omega_{t,\lambda t,t}$.

Theorem 3.16 *Suppose $\mathbf{H}_t$ and $\mathbf{H}_\lambda$ exist. Then there exist $(t-1)^2(\lambda - 1)$ optimum $\mathbf{W}$-matrices for d_0^{**} in $\Omega_{t,\lambda t,t}$ as defined in (3.20).*

Proof: Assuming $\mathbf{H}_t$ and $\mathbf{H}_\lambda$ in the *seminormal* form

$$\begin{aligned} \mathbf{W}^{(l)} = \mathbf{W}_{ijf} \;\; &= \;\; \mathbf{h}_f^{(\lambda)\prime} \otimes \mathbf{h}_i^{(t)} \otimes \mathbf{h}_j^{(t)\prime}; \;\; i,j = 1,\ldots,t-1, \; f = 1,\ldots,\lambda - 1, \\ & \qquad l = (i-1)(\lambda-1)(t-1) + (j-1)(\lambda-1) + f \end{aligned} \quad (3.21)$$

are the required optimum $\mathbf{W}$-matrices for d_0^{**} in $\Omega_{t,\lambda t,t}$.

Remark 3.17 *If $\mathbf{H}_t$ does not exist but $\mathbf{H}_\lambda$ exists then a set of $\lambda - 1$ optimum $\mathbf{W}$-matrices for d_0^* can be constructed as*

$$\mathbf{W}_l^* = \mathbf{h}_l^{(\lambda)\prime} \otimes \mathbf{a}^* \otimes \mathbf{a}^{*\prime}, \; l = 1,\ldots,\lambda$$

where $\mathbf{a}^* = \left(\mathbf{1}_{t/2}', -\mathbf{1}_{t/2}'\right)'$.

Remark 3.18 *An OCD for an uniform balanced crossover design in $\Omega_{t,t,t}$ or $\Omega_{t,2t,t}$ can not be constructed for t odd.*

A popular choice of balanced crossover design is the one given by Patterson(1952) for $p \leq t$, as this often involves moderate number of subjects while keeping the number of period small. For t a prime or prime power, consider $\{L_i\}, i = 1, \ldots, t-1$, a complete set of MOLS of order t where L_{i+1} can be obtained by cyclically permuting the last $t-1$ rows of L_i. Then the $t \times t(t-1)$ array P given by

$$P = (L_1,\ L_2, ..., L_{t-1}). \tag{3.22}$$

yields a Patterson design in $\Omega_{t,t(t-1),t}$. Now, on deleting any $t-p$ rows of P one gets a Patterson design in $\Omega_{t,t(t-1),p}$ with $p < t$ (cf. Patterson (1952) and Bose and Dey (2009)). The construction of optimum $\mathbf{W}$-matrices for a Petterson design in $\Omega_{t,t(t-1),p}$ is very much dependent on the existence of the optimum $\mathbf{W}$-matrices for a randomised block design (RBD). Hence we state some results of Das et al. (2003) and Rao et al. (2003) for the construction of $\mathbf{W}$-matrices for a given RBD with b blocks and v treatments denoted by RBD($b,\ v$) hereafter, when the observations vs. blocks and the observations vs. treatments incidence matrices are given by $\mathbf{I}_v \otimes \mathbf{1}_b$ and $\mathbf{1}_b \otimes \mathbf{I}_v$ respectively.

1. If $\mathbf{H}_b$ and $\mathbf{H}_v$ exist, then $(b-1)(v-1)$ optimum $\mathbf{W}$-matrices can be constructed for RBD($b,\ v$);
2. If $\mathbf{H}_{2b}$ and $\mathbf{H}_{v/2}$ both exist but $\mathbf{H}_b$ does not, then $(b-1)(v-1)-(b-2)$ optimum $\mathbf{W}$-matrices can be constructed for RBD($b,\ v$);
3. If $b = 2$ (mod 4) and if $b-1$ is a prime or a prime power and further if $\mathbf{H}_v$ exists, then $(b-1)(v-1)-(b-2)$ optimum $\mathbf{W}$-matrices can be constructed for RBD($b,\ v$).

Now we consider the following theorem which gives the optimum $\mathbf{W}$-matrices for a Patterson design.

Theorem 3.19 *If there exists a set of c* $\mathbf{W}$*-matrices of order* $p \times (t-1)$ *for an RBD(p, t-1), then there exists a set of c optimum* $\mathbf{W}$*-matrices for a Patterson design in* $\Omega_{t,t(t-1),p}$.

Proof: The optimum $\mathbf{W}$-matrices for the Patterson design in $\Omega_{t,t(t-1),p}$ can be obtained by replacing 1 by $\mathbf{1}'_t$ and -1 by -$\mathbf{1}'_t$ in the $\mathbf{W}$-matrices of RBD($p,(t-1)$). □

For t prime of the form $4u+3$, where u is a positive integer, a Patterson design exists in $\Omega_{t,2t,(t+1)/2}$ which is formed by juxtaposing two special RBD($(t+1)/2, t$) side by side. For details of the method of construction we refer to Patterson(1952).

Theorem 3.20 *Suppose* $\mathbf{H}_{(t+1)/2}$ *exists. Then there exists a set of* $(t-1)/2$ *optimum* $\mathbf{W}$*-matrices for a Patterson design in* $\Omega_{t,2t,(t+1)/2}$.

Proof: Assuming $\mathbf{H}_{(t+1)/2}$ in the *seminormal* form,

$$\mathbf{W}^{(l)} = \mathbf{h}_l^{(t+1)/2} \otimes (1,\ -1) \otimes \mathbf{1}'_t;\ \ l = 1, \ldots, (t-1)/2 \tag{3.23}$$

are the required optimum $\mathbf{W}$-matrices. □

4 Concluding Remarks

In this paper, we discussed the optimum choice of values for non-stochastic controllable covariates for a series of strongly balanced or a balanced crossover design which are universally optimal for the estimation of direct and residual effects in an appropriate class of competing designs. Thus the resultant design becomes optimum for the estimation of ANOVA effects as well as covariate effects. It has been observed that the construction of the optimum covariate design depends on the layout of the basic crossover design. Further research is going on to characterize a specific optimal covariate design in the crossover design set-up when the global optimal design does not exist. It is also worthwhile to identify optimal crossover designs in a covariate model when the values of the covariates are predetermined.

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