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

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**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

**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 **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 $\lambda_1$ 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 **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 $\lambda_1$ 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 $\lambda$, taking $\lambda$ 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* **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 $\mathbf{a}^* = \left(\begin{array}{cc} \mathbf{1}'_{\frac{t+1}{2}} & -\mathbf{1}'_{\frac{t+1}{2}} \end{array}\right)'$. □

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 $\lambda$, 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 $p \le t$, 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 **W**-matrices for a Petterson design in $\Omega_{t,t(t-1),p}$ is very much dependent on the existence of the optimum **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 **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 **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 **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 **W**-matrices can be constructed for RBD($b,\ v$).

Now we consider the following theorem which gives the optimum **W**-matrices for a Patterson design.

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

**Proof:** The optimum **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 **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* **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 **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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