https://doi.org/10.56093/JISAS.V79I2.6
Available online at http://isas.org.in/isa/jisas
JOURNAL OF THE INDIAN SOCIETY OF
AGRICULTURAL STATISTICS 79(2) 2025 105–112

Studying Efficient Crossover Designs with Multiple Responses

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Received: 25 September 2025; Revised: 30 October 2025; Accepted: 10 November 2025

SUMMARY

This work on efficient multiple response crossover designs is motivated by a 3 × 3 crossover trial used to measure changes in gene expression values of multiple genes. In order to model multiple responses being measured in a crossover trial, a multivariate fixed effects model, allowing both the direct and carryover effects, is considered. The responses are assumed to have within-response correlation, with varying structures for different responses, and response-specific variances. Under this multiple response setup, a design represented as an orthogonal array of Type I and strength 2 is proved to be efficient for the direct effects over the class of binary designs with $3 \leq p \leq t$, where p and t represent the number of periods and treatments in a crossover design. A comparison of design efficiencies is evaluated for varying values of p and t.

Keywords: Binary designs, Completely symmetric, Efficient design, Orthogonal arrays

0. TRIBUTE TO DR. M.N. DAS

Dr. M.N. Das made pioneering contributions to various areas in the field of statistics, including the design and analysis of experiments. His significant contributions include the introduction of circular designs, the development of a method for the construction of rotatable designs and confounded designs (see Das 1960; Das and Narasimham 1962; Das and Rao 1967). He also investigated reinforced incomplete block designs and studied design and analysis of experiments with mixtures (see Das 1958; Murty and Das 1968). He contributed to several books as author or coauthor, including Design and Analysis of Experiments (Das and Giri 1979).

Dr. Das served as Acting Director at the Indian Agricultural Statistics Research Institute from June 1971 to October 1973. He served as the founding president of the Society of Statistics, Computer and Applications, and held the position of Vice President in the Indian Society of Agricultural Statistics. Dr. M.N. Das was the recipient of several prestigious awards, notably Professor P.V. Sukhatme National Award, conferred by Ministry of Statistics and Programme Implementation, Government of India and Sankhyiki Bhushan Award, presented by the Indian Society of Agricultural Statistics.

The pioneering work of Dr. M.N. Das continues to inspire researchers and shape the field of statistics. This section acknowledges his enduring contributions.

1. INTRODUCTION

Crossover trials trace their origins to agricultural experiments conducted as early as 1853. One of the first such studies was carried out by John Bennet Lawes at Rothamsted, England (see Jones and Kenward 2003, Section 1.4). Later, Cochran (1939) identified carryover effects in long term agricultural experiments and distinguished them from direct effects when developing suitable experimental designs. Younas *et al.* (2022) investigated the effect of three fertilizers on wheat growth using a three-period crossover design. Their analysis accounted for both direct and carryover effects. The study revealed a significant treatment effect attributable to the insecticide.

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Crossover designs were also used in various other fields, such as pharmaceutical and clinical trials, and bioequivalence and biological studies (Singh and Mukhopadhyay 2016). In crossover trials, every experimental unit receives a sequence of treatments over different time periods. However, in some biological experiments, crossover designs with g measurements, where $g > 1$, from each period may be of interest. Such crossover designs involving observations recorded on more than one response variable are termed multiple response crossover designs or multivariate crossover designs. For example, Grender and Johnson (1993) studied the effect of caffeine on the mathematical ability of boys aged 14 and 16 years in a crossover framework. In this study, diastolic and systolic blood pressure responses are recorded for each boy in each of the two periods in a crossover design setup 2×2, that is, $g = 2$. More recently, Pareek *et al.* (2023, 2025) considered multiple gene expression values measured in each period in a crossover setting.

Various researchers have studied optimal crossover designs for univariate responses in a fixed effect model setting, namely Hedayat and Afsarinejad (1975, 1978), Cheng and Wu (1980), Kunert (1983, 1984), Stufken (1991), Kushner (1997, 1998), Kunert and Martin (2000), Hedayat and Yang (2003, 2004) and Singh and Kunert (2021). For a detailed review of crossover designs, one can refer to the paper by Bose and Dey (2013), and the books by Senn (2002), Bose and Dey (2009, 2015), and Kenward and Jones (2014). However, all these works cited concentrate only on single responses measured in each period and do not discuss settings with multiple responses measured from a period.

Although these multiple response crossover studies are used in biomedical experiments, there are very few articles on optimally designing such trials (see Niphadkar and Mukhopadhyay 2024, 2025a,b). Until now, the focus has been mainly on the estimation and hypothesis testing aspects of such trials. Very recently, there have been some studies on optimal multiple response crossover designs in the statistical literature.

Niphadkar and Mukhopadhyay (2024) considered a multivariate fixed effects model. It was assumed that there are non-zero within-response correlations, while between-response correlations were taken to be zero. For the $g > 1$ case, with t treatments and p periods, for $p = t \geq 3$, the design represented by a Type I orthogonal array of strength 2 was proved to be universally optimal for the direct effects over the class of binary designs. Further, Niphadkar and Mukhopadhyay (2025b) extended the problem by considering within-response variances to be heteroscedastic in nature and within-response correlation structure to be different for various responses. Using eigenvalue analysis, an orthogonal array design of Type I and strength 2 was proved to be A-, D- and E-optimal over the class of binary designs, when $p = t \geq 3$.

Niphadkar and Mukhopadhyay (2025a) incorporated both within-response and between response correlation by considering the corresponding error dispersion matrix to be either of the proportional or the generalized Markovian type covariance structure. Under the proportional structure, for $p = t \geq 3$, an orthogonal array design of Type I and strength 2 was proved to be efficient for the direct effects over the class of binary designs. Under the Markovian covariance structure, the same design was illustrated to be highly efficient for the direct effects using a wide choice of covariance functions, namely, Mat(0.5), Mat(1.5) and Mat(∞).

In this manuscript, our main objective is to propose a new result on efficient multivariate crossover designs. We consider a multivariate fixed effects crossover model where the responses are heteroscedastic and have within-response correlation, with different structures for various responses. Along with this, we also assume that there is no correlation between responses. For the multiple response setup, by using the information matrix for the direct effects, we show that an orthogonal array design of Type I and strength 2 is efficient for the direct effets over the class of binary designs,

where $3 \leq p \leq t$.

2. MOTIVATING EXAMPLE

For motivating readers to understand the complexity involved in multivariate crossover designs we introduce them to a multiple response crossover trial with 3 treatments, 18 subjects and 3 periods considered by Leaker *et al.* (2017). The study by Leaker *et al.* (2017) is also considered as motivating example by Niphadkar and Mukhopadhyay (2024, 2025a). This experiment was ran domized, double-blind and placebo-controlled. Each of the three treatment sequences *ACB*, *BAC* and *CBA*, where *A* and *B* represent 10 mg and 25 mg of an oral dose, respectively, and *C* repre sents the placebo, was assigned to 6 subjects. The purpose of this study was to compare treatments *A* and *B*, with *C* on biomarkers of mucosal inflammation and transcriptomics. Using this 3 × 3 crossover design, changes in gene expression values after a nasal allergen challenge corresponding to 52369 probe sets, were measured. The gene profile dataset is available under the accession number *GSE*67200 at the NCBI Gene Expression Omnibus (Clough and Barrett 2016). The url for the dataset to access online is https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE67200.

Note that the design used by Leaker *et al.* (2017) is a binary and uniform design with $p = t = 3$, but not an orthogonal array of Type I and strength 2. Niphadkar and Mukhopadhyay (2024) considered 5 responses, namely, 100134584_TGI_AT, 100140918_TGI_AT, 100310234_TGI_AT, 100300789_TGI_AT and 100125346_TGI_AT, and by performing various tests observed that these responses have no significant correlation between themselves, while they have a significant within-response correlation. Figure 1 shows the binary and uniform design, when 5 responses are measured across all periods for each subject. Due to observations being recorded from five different responses, the possibility of correlation between and within responses arises as considered by Niphadkar and Mukhopadhyay (2025a). In this manuscript, however, we consider efficient designs when there is only within-response correlation.

Using this motivating example, in the following section we use a multivariate fixed effects crossover model with responses having within-response correlation without the presence of between response correlation.

3. MULTIVARIATE CROSSOVER MODEL

We consider multiple response crossover designs, i.e., $g \geq 1$ responses are measured for every subject in each period. We denote the class of all crossover designs with t treatments, n subjects and p periods by $\Omega_{t,n,p}$. We use notations similar to Niphadkar and Mukhopadhyay (2024, 2025b). For a crossover design d P $\Omega_{t,n,p}$, let Y_{dijk} be the observation measured on the k^{th} response for the j^{th} subject in the i^{th} period, where $1 \leq i \leq p$, $1 \leq j \leq n$ and $1 \leq k \leq g$. Let μ_k, $\alpha_{i,k}$, $\beta_{j,k}$, $\tau_{s,k}$ and $\rho_{s,k}$ denote the intercept, i^{th} period effect, j^{th} subject effect, direct and carryover effects due to s^{th} treatment for the k^{th} response, respectively, where $1 \leq s \leq t$. We assume that these effects are fixed and vary for each response. We consider the following multivariate fixed effects crossover model:

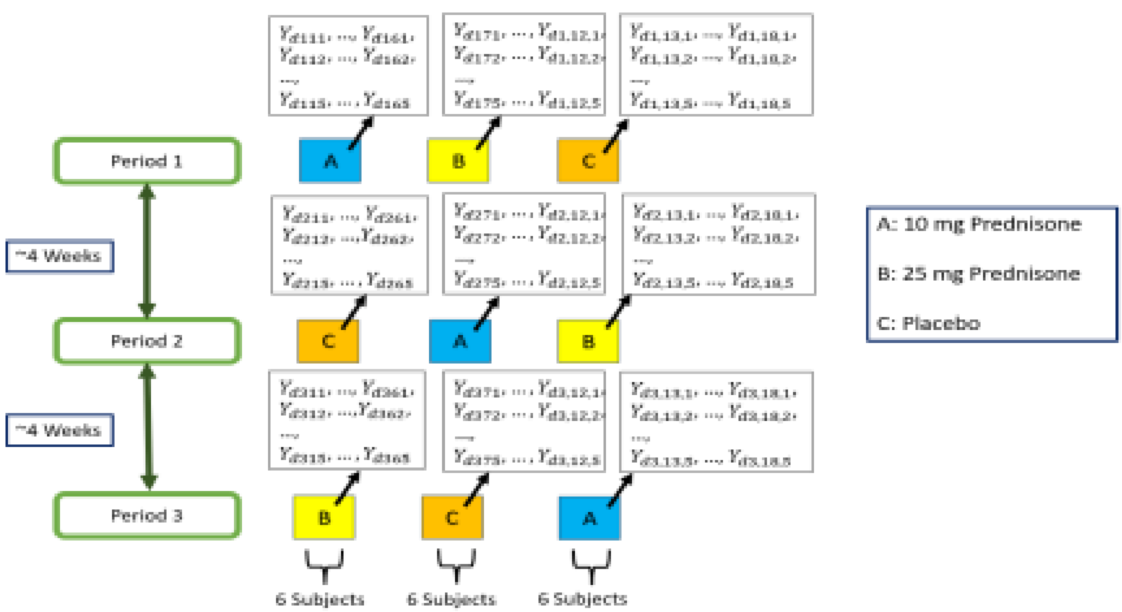

Fig. 1. 3×3 multivariate crossover design with 5 response variables. Y_{dijk} is the observation measured on the k^{th} response for the j^{th} subject in the i^{th} period, where $1 \leq i \leq 3$, $1 \leq j \leq 18$ and $1 \leq k \leq 5$.

$$Y_{dijk} = \mu_k + \alpha_{i,k} + \beta_{j,k} + \tau_{d(i,j),k} + \rho_{d(i-1,j),k} + \epsilon_{ijk}. \quad (3.1)$$

Here, ϵ_{ijk} is the corresponding error term having mean 0, and $d(i, j)$ is the treatment allocated by a design d in the i^{th} period for the j^{th} subject. We also assume that there is no carryover effect corresponding to the first period, i.e., $\rho_{d(0,j),k} = 0$. For the univariate response case, i.e., $g = 1$, this model has been discussed by Bose and Dey (2009, 2015).

Let $\boldsymbol{P} = \mathbf{1}_n \otimes \boldsymbol{I}_p$, $\boldsymbol{U} = \boldsymbol{I}_n \otimes \mathbf{1}_p$. $\boldsymbol{T}_d = [\boldsymbol{T}'_{d1} \dots \boldsymbol{T}'_{dn}]'$ be a $np \times t$ matrix such that $(i, s)^{\text{th}}$ element of $\boldsymbol{T}_{dj}$ is 1 if a design d allocates s^{th} treatment to the j^{th} subject in the i^{th} period, and 0 otherwise, and $\boldsymbol{F}_d = (\boldsymbol{I}_n \otimes \boldsymbol{\psi})\, \boldsymbol{T}_d$, where $\boldsymbol{\psi} = \begin{bmatrix} 0'_{p-1\times 1} & 0 \\ \boldsymbol{I}_{p-1} & 0_{p-1\times 1} \end{bmatrix}$. For the k^{th} response, the matrices $\boldsymbol{P}$, $\boldsymbol{U}$, $\boldsymbol{T}_d$ and $\boldsymbol{F}_d$ are the components of the design matrix that account for period, subject, direct and carryover effects. For the k^{th} response, let us denote the vector of observations, the vector of error terms and the vector of model parameters by

$\boldsymbol{Y}_{dk} = [Y_{d11k} \dots Y_{dp1k} \dots Y_{d1nk} \dots Y_{dpnk}]'$,

$\boldsymbol{\epsilon}_k = [\epsilon_{11k} \dots \epsilon_{p1k} \dots \epsilon_{1nk} \dots \epsilon_{pnk}]'$, and

$\boldsymbol{\theta}_k = [\mu_k\, \boldsymbol{\alpha}'_k\, \boldsymbol{\beta}'_k\, \boldsymbol{\tau}'_k\, \boldsymbol{\rho}'_k]'$,

respectively, where $\boldsymbol{\alpha}_k = [\alpha_{1,k} \dots \alpha_{p,k}]'$, $\boldsymbol{\beta}_k = [\beta_{1,k} \dots \beta_{n,k}]'$, $\boldsymbol{\tau}_k = [\tau_{1,k} \dots \tau_{t,k}]'$ and $\boldsymbol{\rho}_k = [\rho_{1,k} \dots \rho_{t,k}]'$ are the vectors of period, subject, direct and carryover effects, respectively. Using these notations, we write the model (3.1) in matrix form as

$$\boldsymbol{Y}_{dk} = \boldsymbol{X}_{dk}\boldsymbol{\theta}_k + \boldsymbol{\epsilon}_k, \quad (3.2)$$

where $\boldsymbol{X}_{dk} = [\mathbf{1}_{np} \;\; \boldsymbol{P} \;\; \boldsymbol{U} \;\; \boldsymbol{T}_d \;\; \boldsymbol{F}_d]$. Using the above equation, the model for g responses together is written as

$$[\boldsymbol{Y}'_{d1} \dots \boldsymbol{Y}'_{dg}]' = (\boldsymbol{I}_g \otimes \boldsymbol{X}_{d1})[\boldsymbol{\theta}'_1 \dots \boldsymbol{\theta}'_g]' + \boldsymbol{\epsilon}, \quad (3.3)$$

where $\boldsymbol{\epsilon} = [\boldsymbol{\epsilon}'_1 \dots \boldsymbol{\epsilon}'_g]'$ is the vector of all error terms.

Throughout this article, we assume that observations between different subjects are uncorrelated, i.e., $Cov\,(\epsilon_{ijk}, \epsilon_{i'j'k'}) = 0$, for $1 \le i, i' \le p$, $1 \le j \ne j' \le n$ and $1 \le k, k' \le g$. We also assume that there is no correlation between responses. But, we consider that there is presence of within-response correlation and the within-response correlation matrix for every response is different. So, $Cov\,(\epsilon_{ijk}, \epsilon_{i'j'k'}) = 0$, for $1 \le i, i' \le p$, $1 \le j, j' \le n$ and $1 \le k \ne k' \le g$, and the dispersion matrix of $\boldsymbol{\epsilon}_k$, $\mathbb{D}\,(\boldsymbol{\epsilon}_k)$, vary with k. Along with this, we consider the responses to be heteroscedastic, i.e., $Var\,(\epsilon_{ijk}) = \sigma_k^2$, where σ_k^2 is a positive unknown constant which varies with k. So, the dispersion matrix of the vector of error terms is given as

$$\mathbb{D}\,(\boldsymbol{\epsilon}) = \sigma_1^2\boldsymbol{\Sigma}_1 \oplus \dots \oplus \sigma_g^2\boldsymbol{\Sigma}_g = \oplus_{k=1}^{g}\sigma_k^2\Sigma_k, \quad (3.4)$$

where $\boldsymbol{\Sigma}_k = \boldsymbol{I}_n \otimes \boldsymbol{V}_k$, $\boldsymbol{V}_k$ is a $p \times p$ symmetric and positive definite matrix, and σ_k^2 and $\boldsymbol{V}_k$ vary with k. This multiple response fixed effects crossover model have been utilized by Niphadkar and Mukhopadhyay (2025b) to study A-, D- and E-optimal design for the direct effects.

4. EFFICIENT DESIGN

In this section, we investigate efficient designs for the direct effects under the model (3.3). According to Kiefer (1975), for $g = 1$, i.e., single response case, if a design d^* maximizes the trace of the information matrix for the direct effects over some subclass of designs and the information matrix corresponding to the design d^* is completely symmetric, then d^* is said to be a universally optimal design for the direct effects over the same subclass of designs. It may happen that one is able to find a design which maximizes the trace of the information matrix for the direct effects over some subclass of designs, but the information matrix for that design is not completely symmetric. Such a design is said to be an efficient design (see Bate and Jones 2006). The sufficient conditions by Kiefer (1975) and the concept of efficient design, both can be naturally extended for the $g > 1$ case.

For a crossover design $d \in \Omega_{t,n,p}$, let $\boldsymbol{C}_d$ be the information matrix for the direct effects. Niphadkar and Mukhopadhyay (2025b) obtained that for $g > 1$,

$$\boldsymbol{C}_d = \sigma_1^{-2}\,\boldsymbol{C}_{d(1)} \oplus \dots \oplus \sigma_g^{-2}\,\boldsymbol{C}_{d(g)}, \quad (4.1)$$

where

$$\boldsymbol{C}_{d(k)} = \boldsymbol{C}_{d(k)11} - \boldsymbol{C}_{d(k)12}\boldsymbol{C}^{-}_{d(k)22}\boldsymbol{C}_{d(k)21}. \quad (4.2)$$

Here $\boldsymbol{C}_{d(k)11} = \boldsymbol{T}'_d\boldsymbol{A}^*_k\boldsymbol{T}_d$, $\boldsymbol{C}_{d(k)12} = \boldsymbol{C}'_{d(k)21} = \boldsymbol{T}'_d\boldsymbol{A}^*_k\boldsymbol{F}_d$, $\boldsymbol{C}_{d(k)22} = \boldsymbol{F}'_d\boldsymbol{A}^*_k\boldsymbol{F}_d$, $\boldsymbol{A}^*_k = \boldsymbol{H}_n \otimes \boldsymbol{V}^*_k$, $\boldsymbol{V}^*_k = \boldsymbol{V}_k^{-1} - \delta_k\boldsymbol{V}_k^{-1}\boldsymbol{J}_{p\times p}\boldsymbol{V}_k^{-1}$, $\delta_k = (\mathbf{1}'_p\boldsymbol{V}_k^{-1}\mathbf{1}_p)^{-1}$, $\boldsymbol{J}_{p\times p} = \mathbf{1}_p\mathbf{1}'_p$, $\boldsymbol{H}_n = \boldsymbol{I}_n - \frac{1}{n}\,\mathbf{1}_n\mathbf{1}'_n$ and $\boldsymbol{C}^{-}_{d(k)22}$ is a generalized inverse of $\boldsymbol{C}_{d(k)22}$.

We consider crossover designs with $p \le t$. For the univariate response setup, i.e., $g = 1$ setup, when the response has within-response correlation, Kunert and Martin (2000) showed that an orthogonal array design of Type I and strength 2 is universally optimal for the direct effects over the class of binary designs with $3 \le p \le t$. Let d_1^* be a design represented by an orthogonal array of Type I and strength 2, which is denoted as OA_I p$n = \lambda t$p$t - 1$q, p, t, 2q, where $3 \le p \le t$ and λ is a positive integer. We denote the class of competing designs by D_1, which is given as

$D_1 = \{d \in \Omega_{t,n,p} : d \text{ is a binary design and } 3 \le p \le t\}$.

Clearly, from the definition of an orthogonal array design of Type I and strength 2 (see Bose and Dey 2009; Hedayat *et al.* 2012; Rao 1961), $d_1^* \in D_1$. Following Lemma 6 of Martin and Eccleston (1998) and Lemma 4.3 of Niphadkar and Mukhopadhyay (2025b), we get that for $g > 1$, corresponding to the design d_1^*, the information matrix for the direct effects can be expressed as

$$C_{d_1^*} = \oplus_{k=1}^{g} \sigma_k^{-2} \left(\left(t-1 \right) \det(Qk) / \left(n \times q_{(k)22} \right) \right) H_t, \tag{4.3}$$

where $\boldsymbol{Q}_k = \dfrac{n}{t-1} \begin{bmatrix} q(k)11 & q(k)12 \\ q(k)12 & q(k)22 \end{bmatrix}$, $\det(\boldsymbol{Q}_k) \neq 0$,

$q(k)_{11} = tr(Td_{_1^*1} V_k^* Td_{_1^*1})$, $\quad q(k)_{12} = tr(T'_{d_1^*1} V_k^* \psi T_{d_1^*1})$,

$q(k)_{22} = tr\left(T'_{d_1^*1} \psi' V_k^* T_{d_1^*1} \right) - \dfrac{\left(V_k^* \right)_{1,1}}{t}$, $\quad H_t = I_t - \dfrac{1}{t} 1_t 1'_t$,

$$\psi = \begin{bmatrix} 0'_{p-1\times 1} & 0 \\ I_{p-1} & 0_{p-1\times 1} \end{bmatrix},$$

$V_k^* = V_k^{-1} - \left(1'_p V_k^{-1} 1_p \right)^{-1} V_k^{-1} 1_p 1'_p V_k^{-1}$, and $\left(V_k^* \right)_{1,1}$ is the element corresponding to first row and first column of the matrix V_k^*. Further, in the Remark 4.4, Niphadkar and Mukhopadhyay (2025b) have observed that for $g > 1$, the information matrix $C_{d_1^*}$ is not completely symmetric. So for $g > 1$ setup, the sufficient conditions similar to those given by Kiefer (1975) are not applicable. Thus, we aim to determine an efficient design.

Theorem 4.1. *Let* $d_1^* \in D_1$ *be a design represented as* OA_I ($n = \lambda t$ ($t - 1$), p, t, 2)*, where* λ *is a positive integer,* $3 \le p \le t$ *and* D_1 *is a class of binary designs with* $3 \le p \le t$. *Then for the multiple response case, i.e.,* $g > 1$ *case,* d_1^* *is an efficient design for the direct effects over* D_1.

Proof. Here $d_1^* \in D_1$ is a design represented as $OA_I(n = \lambda t\ (t - 1$q, p, t, 2), where D_1 is a class of binary designs with $3 \le p \le t$ and λ is a positive integer. From Kunert and Martin (2000), we know that for the univariate response setup, i.e., $g = 1$ setup, d_1^* is universally optimal for the direct effects over D_1. So from the defintion of a universally optimal design (see Bose and Dey 2009; Kiefer 1975), we get that d_1^* maximizes tr($\boldsymbol{C}_{d(k)}$) over $d \in D_1$. Since $\sigma_k^{-2} > 0$, d_1^* maximizes $tr\left(C_d\right) = \sum_{k=1}^{g} \sigma_k^{-2} tr\left(C_{d(k)}\right)$ for $g > 1$ over $d \in D_1$. Thus for $g > 1$, d_1^* is an efficient design for the direct effects over D_1.

It should be noted that the result regarding an efficient design discussed in the above theorem does not consider any specific choice of the matrix $\boldsymbol{V}_k$. The result holds true for any symmetric and positive definite matrix $\boldsymbol{V}_k$.

5. ILLUSTRATION

In this section, we investigate the efficiency of the 3 × 3 binary crossover design used by Leaker *et al.* (2017). The efficiency of this design under various setups was also studied by Niphadkar and Mukhopadhyay (2024, 2025a,b). Along with this design, we also compare the efficiency of designs uniform on periods, uniform designs, balanced uniform designs and Patterson designs (see Patterson 1952), for various values of p and t, where $3 \le p \le t$. The efficiency is computed with respect to the orthogonal array design of Type I and strength 2, which is proved to be efficient in Theorem 4.1. For the purpose of illustration, we consider a bivariate response case, i.e., $g = 2$. Also, we consider the matrix $\boldsymbol{V}_1$ to be equicorrelated and $\boldsymbol{V}_2$ to be tridiagonal. So, for instance, when $p = 3$,

$$V_1 = \begin{bmatrix} 1 & r_{(1)} & r_{(1)} \\ r_{(1)} & 1 & r_{(1)} \\ r_{(1)} & r_{(1)} & 1 \end{bmatrix} \text{ and } V_1 = \begin{bmatrix} 1 & r_{(1)} & 0 \\ r_{(1)} & 1 & r_{(1)} \\ 0 & r_{(1)} & 1 \end{bmatrix},$$

where $-0.5 < r_{(1)} < 1/\sqrt{2}$. The constraint on the values of $r_{(1)}$ ensures that both matrices $\boldsymbol{V}_1$ and $\boldsymbol{V}_2$ are positive definite. We consider non-zero values of $r_{(1)}$, as $r_{(1)} = 0$ corresponds to the case of no correlation within response. In addition, for illustration, we consider two cases, namely, $\sigma_1^2 / \sigma_2^2 = 100$ and $\sigma_1^2 / \sigma_2^2 = 0.001$. For a binary crossover design $d^{(0)} \in D_1$, let the efficiency be given by

$$e = \frac{tr\left(C_{d(0)}\right)}{tr\left(C_{d_1^*}\right)}.$$

It should be noted that the value of e is between 0 and 1. For a given design $d^{(0)}$ and a fixed value of σ_1^2 / σ_2^2, the efficiency e depends on the values of $r_{(1)}$. So, we compute the minimum and maximum efficiency, where the minimum and maximum are computed on the values of $r_{(1)}$.

Depending on the design used by Leaker *et al.* (2017), we see that the minimum and maximum efficiency when $\sigma_1^2 / \sigma_2^2 = 100$, are 0.0737 and 0.2500, respectively. On the other hand, when $\sigma_1^2 / \sigma_2^2 = 0.001$, these values are 0.2498 and 0.2500. So, the binary crossover design utilized in the experiment by Leaker *et al.* (2017) is a highly inefficient design.

Table 1 shows the minimum and maximum efficiency of various designs for different values of p and t, for two possible values of σ_1^2 / σ_2^2. From Table 1, we see that for uniform designs in periods and uniform designs, the maximum efficiency in both cases is low, indicating that these designs are inefficient. When $\sigma_1^2 / \sigma_2^2 = 100$, for uniform balanced designs, the minimum efficiency is low but the maximum efficiency is high. This indicates that for $\sigma_1^2 = 100\sigma_2^2$, balanced uniform designs have a high efficiency for some values of $r_{(1)}$. However, for $\sigma_1^2 / \sigma_2^2 = 0.001$, both the minimum and maximum efficiency are high for a balanced uniform design, indicating that balanced uniform designs are highly efficient in this case. The minimum efficiency for Patterson designs is high in both cases, and so Patterson designs are highly efficient in both cases.

5.1 Computational Details

We have obtained the minimum and maximum efficiencies in Table 1 using R programming (R Core Team 2023) under Windows 11 (64-bit), with a 13th Gen Intel(R) Core(TM) I5-1335U processor and 8GB of RAM. The codes used to evaluate the maximum and minimum efficiency for various binary designs are available at https://github.com/rsphd/Special-Issue.

6. DISCUSSION

In this article, we considered a multivariate fixed effects crossover model having carryover effects.

Table 1. Minimum and maximum efficiency (e) for various designs.

				$\sigma_1^2 = 100\,\sigma_2^2$		$\sigma_1^2 = 0.001\,\sigma_2^2$	
p	***t***	***n***	**Design**	**Minimum *e***	**Maximum *e***	**Minimum *e***	**Maximum *e***
3	3	6	Uniform	0.0737	0.2500	0.2498	0.2500
3	4	12	Uniform on Periods	0.0781	0.2575	0.2571	0.2574
3	5	20	Uniform on Periods	0.0796	0.2586	0.2581	0.2584
3	7	42	Uniform on Periods	0.0802	0.2577	0.2572	0.2575
3	7	42	Patterson	1	1	1	1
4	4	12	Uniform	0.0586	0.2000	0.1996	0.2000
4	4	12	Balanced Uniform	0.2183	0.9999	0.9978	1
4	5	20	Uniform on Periods	0.0804	0.2082	0.2078	0.2082
4	7	42	Uniform on Periods	0.0955	0.2139	0.2134	0.2137
4	7	42	Patterson	0.9473	0.9999	0.9999	1
5	5	20	Uniform	0.1146	0.1667	0.1666	0.1667
5	5	20	Balanced Uniform	0.5914	0.9999	0.9993	1
5	7	42	Uniform on Periods	0.0921	0.1751	0.1748	0.1750
5	7	42	Patterson	0.9964	1	0.9999	1
6	7	42	Uniform on Periods	0.1129	0.1476	0.1460	0.1461
7	7	42	Uniform	0.0935	0.1250	0.1249	0.1250
7	7	42	Balanced Uniform	0.4140	0.9999	0.9984	1

We assumed that there was no correlation between responses, but within-response correlation was present. Also, the distinct responses had different variances and different within-response correla tion structures. We proved that an orthogonal array design of Type I and strength 2 is efficient for the direct effects over the class of binary designs with $3 \leq p \leq t$. A comparison of the efficiency of various designs was shown. It was observed that designs uniform on periods and uniform designs are highly inefficient, while balanced uniform designs are efficient for some values of correlation $r_{(1)}$. On the other hand, Patterson designs were observed to be highly efficient.

Although in this article, our focus was to explore efficient design for the direct effects, we may consider investigating efficient multiple response crossover designs for total effects, which is the sum of direct and carryover effects. As a future direction, we may also consider the mixed effects model with random subject effects and study efficient designs when multiple responses are observed under this setup.

ACKNOWLEDGEMENT

We thank the Editor and reviewers for their careful reading of the manuscript and for their insightful suggestions and comments, which substantially improved the manuscript.

STATEMENTS AND DECLARATIONS

- **Funding** The authors did not receive support from any organization for the submitted work. • **Competing interests** The authors declare no competing interests.
- **Ethics approval and consent to participate** This research does not involve human or animal participants.
- **Consent for publication** Not applicable.
- **Data availability** The data is available in the Gene Expression Omnibus database under accession number GSE67200 and is available at the following URL: https://www.ncbi.nlm. nih.gov/geo/query/ acc.cgi?acc=GSE67200.
- **Materials availability** Not applicable.
- **Code availability** https://github.com/rsphd/ Special-Issue contains the code used to eval uate the maximum and minimum efficiency for various designs.
- **Author contribution** All authors contributed to the study conception and design. Material preparation, analysis and investigation were performed by Shubham Niphadkar. The first draft of the manuscript was written by Shubham Niphadkar and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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