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Cross-over designs for a model with self and mixed carryover effects

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Abstract. The model for cross-over designs is required to be modified for certain areas of its application, in order to incorporate the difference in assumptions regarding the nature of carryover effects. This underlines the use of model with self and mixed carryover effects for cross-over designs. Some cross-over designs that are variance balanced for the estimation of direct effects under such a model are presented and a comparison of these with the universally optimal totally balanced designs is also provided.

1. Introduction

A cross-over design is a one in which the units are used repeatedly by exposing them to a sequence of treatments over a period of time. Such designs are required in cases where the experimental units are scarce or there is a reason to believe a substantial variability amongst them.

Due to the successive application of treatments on a unit, cross-over designs are susceptible to the occurrence of carryover effects of a treatment applied in one period, in the period next to it. Carryover effect of a treatment is, in general, assumed to be same, regardless of the treatment(s) to which it is carried onto. This assumption forms the basis of the traditional model for cross-over designs, which contains a single term for carryover effects.

Applications of cross-over designs can be found in a number of areas, e. g., pharmaceutical trials, psychological studies, sensory evaluation trials, consumer research etc. In such applied fields, it would not be reasonable to assume the carryover effect of a treatment to be same, regardless of the treatment that follows it. For example, in sensory evaluation trials, the units consist of persons, and sequences of different products are presented to them for their response. In such cases, if a person strongly likes or dislikes a product, its lingering effect would show up in his evaluation of the product that follows it. So, if the same product is presented in the next period, the response wouldn't be much different. However, if a different product is presented in the following period, the response would be a greater liking for the product than usual, if the previous product was highly disliked, or else, it would be lower than the usual dislike if the previous product was strongly liked. For example, if one product is very bitter, it has been experienced that the assessors tend to rate the immediate next product with a lower than normal value of bitterness, while providing with the same rating for bitterness if the same product is presented in the immediate next

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period. Similarly, in case of pharmaceutical trials, the carryover effect of a drug in the period next to which it is applied would be different if the same drug is applied in the next period, than the carryover effect of it when the drug applied in the next period is different. This would occur due to the fact that different drugs behave differently in conjunction. The carryover effect, thus, depends on the treatment to which it is carried onto. A mathematical proof of why the carryover effect should be different if a treatment is followed by itself is given in Senn (1993). The traditional model with same carryover effect term for all cases, thus, cannot be used in such applications. This requires a model for cross-over designs that takes into account the difference in the assumptions regarding the nature of carryover effects.

A solution to this problem was provided by Sen and Mukerjee (1987) in the form of a model with interactions between direct and carryover effects, wherein each treatment has a different carryover effect for every treatment in the next period. However, this model suffers from the drawback of having too many parameters.

An alternative to this model was introduced by Afsarinejad and Hedayat (2002) wherein, they gave a model with two separate terms for carryover effects, one when the treatment carried carryover effect onto itself, called self carryover, and another when it carried onto a treatment other than itself, called mixed carryover. They studied the problem of design and analysis of cross-over designs under this model for two or more treatments and showed that the most efficient way to construct two-period cross-over designs under this model is to construct an efficient block design in a special class of block designs based on two or more treatments, utilizing a fixed total number of units. They also obtained designs that are optimal for estimating contrasts of self carryover effects only, under such a setup.

Discussion of the model with self and mixed carryover effects was carried forward by Kunert and Stufken (2002). They considered the model in the context of cases where the number of periods and number of treatments are greater than two and utilized the generalization given by Kunert and Martin (2000a), of the method introduced by Kushner (1997), to obtain conditions for designs to be optimal for estimation of direct effects. These conditions were combined to define a new class of designs, called totally balanced designs, which are optimal for estimation of direct effects under the proposed model. A salient feature of totally balanced designs is that they tend to avoid the occurrence of self carryover effects and are, hence, balanced for (mixed) carryover effects. Even if the number of periods is greater than the number of treatments, such designs do not contain consecutive identical treatment pairs. Hedayat and Yan (2008) extended this model to the case when the error terms were assumed to be correlated.

As a number of applications of cross-over designs call for the use of model with self and mixed carryover effects, it is required to obtain useful designs under such a model. Totally balanced designs, given by Kunert and Stufken (2002), though being universally optimal, do not allow for the occurrence of self carryover effects. The estimate of direct effect obtained, thus, is not needed to be adjusted for self carryover effects, although, the estimation is carried out under the model with self and mixed carryover effects. However, in certain applications of cross-over designs, for example, in pharmaceutical trials to decide upon the effect of a number of drugs when used in conjunction, the estimate of direct effects are required under the presence of both self and mixed carryovers. For example, the carryover effect of a particular medication drug on an antibiotic would be different from its carryover effect on itself, in the sense that the adverse effects (if any) of the medication drug would be somewhat subdued when followed by an antibiotic, while they may be enhanced if followed by the same medication drug. In such situations, it is required to obtain the direct effects of treatments applied on a unit in the presence of both self and mixed carryover effects. In view of this, using a method on lines of Kunert and Stufken (2002), the present work seeks to obtain some designs that are variance balanced for the estimation of direct effects of treatments, when both self and mixed carryover effects occur in the design.

The model is presented explicitly in Section 2, along with some relevant definitions. The conditions for a variance balanced cross-over design under self and mixed carryover effects model are obtained in Section 3. Section 4 gives some series of such variance balanced designs and conclusions are presented in Section 5. The notations followed are those of Kunert and Stufken (2002).

2. Model and Preliminaries

The model for self and mixed carryover effects cross-over design with ν treatments, k periods and b units, as given by Kunert and Stufken (2002), is

$$y_{ij} = \begin{cases} \alpha_i + \beta_j + \tau_{d(i,j)} + \nu_{d(i-1,j)} + \varepsilon_{ij},\ if\, d(i,j) \neq d(i-1,j) \\ \alpha_i + \beta_j + \tau_{d(i,j)} + \chi_{d(i-1,j)} + \varepsilon_{ij},\ if\, d(i,j) = d(i-1,j) \end{cases} \quad (1)$$

$1 \leq i \leq k, 1 \leq j \leq b.$

where, y_{ij} is the observed response, α_i is the effect due to i^{th} period, β_j is the effect due to j^{th} unit, $\tau_{d(i,j)}$ is the direct effect of the treatment applied in the i^{th} period to the j^{th} unit, $\nu_{d(i-1,j)}$ and $\chi_{d(i-1,j)}$are mixed and self carryover effects of the treatment applied in the $(i{-}1)^{th}$ period to the j^{th} unit, respectively, and $\varepsilon_{ij}$are random errors assumed to be independently normally distributed with zero mean and constant variance σ^2. Also, $\nu_{d(0,j)} = \chi_{d(0,j)} = 0$ for all j.

Definitions

1. *Balanced Block Design*
   A design is a balanced block design (BBD) for direct treatment effects (with units as blocks) if:
   (a) every treatment appears equally often in the design.
   (b) every treatment appears on each unit either $[k/\nu]$ or $[k/\nu] + 1$ times.
   (c) the number of units where treatments θ and ϕ both appear $[k/\nu] + 1$ times is same for every $\theta \neq \phi$, where, $[k/\nu]$ denotes the largest integer not greater that $[k/\nu]$.

   A design is said to be a BBD for carryover effects (with units as blocks) if its first $(k-1)$ periods are a BBD for the direct treatments effects.
2. *Design Uniform on Periods*
   A design is said to be uniform on periods if every treatment appears in every period exactly b/ν times.
3. *Generalized Youden Design*
   A design is called a generalized Youden design (GYD) if:
   (a) It is a BBD for direct treatment effects with units as blocks.
   (b) It is uniform on periods.

3. Main Results

Let ζbe a class of cross-over designs with ν treatments, k periods and b units for which

1. Number of periods is greater than the number of treatments, i.e., $k > \nu$.
2. Design is uniform on periods.
3. Exactly one self carryover effect occurs on each unit.
4. Self carryover effect of each treatment occurs equal number of times.
5. Mixed carryover effect of each treatment occurs equal number of times.

It is to be noted that the class is restricted to one self carryover effect per unit and an explanation for the same is provided as follows. It can be clearly visualized in Kunert and Stufken (2002) that for the lth equivalence class, the maximization of the linearized form of trace($\mathrm{B}_t\mathrm{C}_{dij}\mathrm{B}_t$), where $\mathrm{B}_t = \mathrm{I}_t = (1/t)1_t1_t'$ and $1 \leq i \leq j \leq 3$, occurs when the number of occurrences of self carryover effects on a unit are minimum possible. The minimum possible value for such an occurrence is zero, which is true for totally balanced designs. As the totally balanced designs are proven to be universally optimal under the model for self and mixed carryover effects, it is only obvious that the next best design under the same model could be one with the next possible minimum value for the number of occurrences of self carryover effects on the units. Hence, the restriction of occurrence of one self carryover effect per unit.

Define $\mathbf{U} = \mathrm{I}_b \otimes 1_k$, $\mathbf{P} = 1_b \otimes \mathrm{I}_k$, $\mathbf{T_d}$, $\mathbf{M_d}$ and $\mathbf{S_d}$ as design-matrices for units, periods, direct effects, mixed carryover effects and self carryover effects of the treatments, respectively for a given design $\boldsymbol{d}$.

Under the class of designs ζ,

$$\mathbf{T_d}\omega^{-1}([\mathbf{U}\ \mathbf{M_d}\mathbf{S_d}])\mathbf{P} = 0,$$

where, for a matrix $\mathbf{A}$,

$$\omega^{-1}(\mathbf{A}) = I - \mathbf{A}(\mathbf{A}'\mathbf{A})^{-}\mathbf{A}'.$$

This is due to the fact that in each period, all treatments occur equally often, the mixed carryover effects of all treatments occur equally often and the self carryover effects of all treatments occur equally often. Thus, from the result of Kunert (1983), the information matrix for estimation of direct effects is given as:

$$\mathbf{C_d} = \mathbf{T'_d}\omega^{-1}([\mathbf{U}\ \mathbf{M_d}\ \mathbf{S_d}])\mathbf{T_d}$$

This can be rewritten, as in Kunert and Martin (2000a), as:

$$\mathbf{C_d} = \mathbf{C_{d11}} - \mathbf{C_{d12}}\mathbf{C^{-}_{d22}}\mathbf{C'_{d12}} - (\mathbf{C_{d13}} - \mathbf{C_{d12}}\mathbf{C^{-}_{d22}}\mathbf{C_{d23}})$$
$$(\mathbf{C_{d33}} - \mathbf{C'_{d23}}\mathbf{C^{-}_{d22}}\mathbf{C_{d23}})^{-}(\mathbf{C_{d13}} - \mathbf{C_{d12}}\mathbf{C^{-}_{d22}}\mathbf{C_{d23}})'$$

where,

$$\mathbf{C_{d11}} = \mathbf{T'_d}\mathbf{T_d} - \frac{1}{k}\mathbf{T'_d}\mathbf{U}\mathbf{U'}\mathbf{T_d}$$

$$\mathbf{C_{d12}} = \mathbf{T'_d}\mathbf{M_d} - \frac{1}{k}\mathbf{T'_d}\mathbf{U}\mathbf{U'}\mathbf{M_d}$$

$$\mathbf{C_{d13}} = \mathbf{T'_d}\mathbf{S_d} - \frac{1}{k}\mathbf{T'_d}\mathbf{U}\mathbf{U'}\mathbf{S_d}$$

$$\mathbf{C_{d22}} = \mathbf{M'_d}\mathbf{M_d} - \frac{1}{k}\mathbf{M'_d}\mathbf{U}\mathbf{U'}\mathbf{M_d}$$

$$\mathbf{C_{d23}} = \mathbf{M'_d}\mathbf{S_d} - \frac{1}{k}\mathbf{M'_d}\mathbf{U}\mathbf{U'}\mathbf{S_d}$$

$$\mathbf{C_{d33}} = \mathbf{S'_d}\mathbf{S_d} - \frac{1}{k}\mathbf{S'_d}\mathbf{U}\mathbf{U'}\mathbf{S_d}$$

We wish to find a design in class ζ which is variance balanced for the estimation of direct effects in the presence of both self and mixed carryover effects. For this, our aim is to obtain a design for which the information matrix for the estimation of direct effects $\mathbf{C_d}$ is completely symmetric under model (1). Complete symmetry of matrix $\mathbf{A}$ implies that $\mathbf{A}$ can be written as $a\mathbf{I} + b\mathbf{J}, \mathbf{I}$ being the identity matrix, $\mathbf{J}$ being a matrix of all ones and, a and b are real numbers.

Define a design $\boldsymbol{d}^*$ in class ζ such that it satisfies the following conditions:

(i) $\boldsymbol{d}^*$ is a GYD.
(ii) $\boldsymbol{d}^*$ is a BBD for carryover effects.
(iii) Self carryover effects of each treatment occurs equal number of times.

(iv) Mixed carryover effects of each treatment occurs equal number of times on every other treatment.

(v) the number of units in $\boldsymbol{d}^*$ where both treatments θ and ϕ appear $[k/\nu]$ + 1 times, treatment ϕ does not appear in the last period and there is no self carryover effect of ϕ, is the same for every pair θ, ϕ, $1 \leq \theta, \phi \leq \nu$; $\theta \neq \phi$.

(vi) the number of units in $\boldsymbol{d}^*$ where both treatments θ and ϕ appear $[k/\nu]$ times and there is no self carryover effects of ϕ, is same for every pair θ, ϕ ; $1 \leq \theta, \phi \leq \nu$; $\theta \neq \phi$.

(vii) the number of units in $\boldsymbol{d}^*$ where self carryover effect of treatment ϕoccurs and treatment θoccurs $[k/\nu]$ + 1 times but not in last period, is the same for every pair θ, ϕ, $1 \leq \theta, \phi \leq \nu$; $\theta \neq \phi$.

We, now, show that $\mathbf{C_{d*ij}}$'s (i, j = 1, 2, 3) are completely symmetric under the self and mixed carryover effects model (1).

1. $\mathbf{C_{d*11}}$ is completely symmetric as $\boldsymbol{d}^*$ is BBD for direct effects.
2. $\mathbf{C_{d*22}}$ is completely symmetric in $\boldsymbol{d}^*$, as mixed carryover effects of every treatment occur with every other treatment equal number of times.
3. $\mathbf{C_{d*33}}$ is completely symmetric in $\boldsymbol{d}^*$, as self carryover effects of every treatment occur equal number of times.
4. $\mathbf{T'_{d*}M_{d*}}$ and $\mathbf{T'_{d*}S_{d*}}$ have zero diagonal elements and equal off-diagonal elements due to conditions (**iii**) and (**iv**) of $\boldsymbol{d*}$, respectively. Also, $\mathbf{M'_{d*}S_{d*}}$ is a matrix of zeroes. Hence, the three matrices are completely symmetric.
   Now, to show that $\mathbf{C_{d*12}}, \mathbf{C_{d*13}}$, and $\mathbf{C_{d*23}}$ are completely symmetric, we need to show that $\mathbf{T'_{d*}UU'M_{d*}}$, $\mathbf{T'_{d*}UU'S_{d*}}$ and $\mathbf{M'_{d*}UU'S_{d*}}$ are all completely symmetric.
5. Since $[(k-1)/\nu] = [k/\nu]$ if k is not divisible by ν, hence, carryover effect of each treatment appears in each unit either $[k/\nu]$ or $[k/\nu]$ + 1 times. This implies that a treatment does not appear for the last period of any unit where it appears only $[k/\nu]$ times.
6. For $\mathbf{T'_{d*}UU'M_{d*}}$, let x_1 = number of units in $\boldsymbol{d*}$ where θ, ϕ occur $[k/\nu]$ + 1 times, ϕ does not occur in the last period and self carryover effect of ϕ does not occur.
   x_2 = number of units in $\boldsymbol{d*}$ where θ, ϕ occur $[k/\nu]$ + 1 times, ϕoccurs in the last period and self carryover effect of ϕ occurs.
   x_3 = number of units in $\boldsymbol{d*}$ where θ occurs $[k/\nu]$ + 1 times, ϕoccurs $[k/\nu]$ times and self carryover effect of ϕ occurs.
   x_4 = number of units in $\boldsymbol{d*}$ where θ, ϕ occur $[k/\nu]$ times and self carryover effect of ϕ does not occur.
   Thus, the (i, j)th element of $\mathbf{T'_{d*}UU'M_{d*}}$ is given as:
   $x_1\{[k/\nu]+1\}^2 + (x_2 + x_3)\{[k/\nu]([k/\nu]+1)\} + x_4\{[k/\nu]\}^2 + (b - x_1 - x_2 - x_3 - x_4)\,\{[k/\nu]([k/\nu]+1)\}$
   We need to show that all the coefficient expressions are independent of θ and ϕ.
   Condition (**v**) of $\boldsymbol{d*}$ implies that x_1 is independent of θ and ϕ. Further, as $\boldsymbol{d*}$ is a BBD for direct effects, the number of units on which θ occurs $[k/\nu]$ + 1 times is independent of θ. Thus $(x_1+x_2+x_3)$ is independent of θ and consequently, (x_2+x_3) is independent of θ and ϕ. Also, condition (**vi)** implies that x_4 is independent of θ and ϕ.
   Hence, all off-diagonal elements of $\mathbf{T'_{d*}UU'M_{d*}}$ are equal. Further, for a design which has mixed carryover effects of each treatment occurring with every other treatment equal number of times, $1'\mathbf{C_{d*12}} = 0$, which, holds for $\boldsymbol{d*}$.
   $\mathbf{T'_{d*}UU'M_{d*}}$ is, thus, completely symmetric.
7. For $\mathbf{T'_{d*}UU'S_{d*}}$, let
   y_1 = number of units in $\boldsymbol{d*}$ where θ and ϕ occur $[k/\nu]$ + 1 times, ϕoccurs in the last period and self carryover effect of ϕoccurs.
   y_2 = number of units in $\boldsymbol{d*}$ where θ and ϕ occur $[k/\nu]$ + 1 times, ϕdoes not occur in the last period and self carryover effect of ϕ occurs.
   y_3 = number of units in $\boldsymbol{d*}$ where θ occurs $[k/\nu]$ + 1 times, ϕoccurs $[k/\nu]$ times and self carryover effect of ϕ does not occur.
   Thus, the (i, j)th element of $\mathbf{T'_{d*}UU'S_{d*}}$ is given as:
   $(y_1 + y_2 + y_3)\{[k/\nu] + 1\} + (b - y_1 - y_2 - y_3)\{k/\nu]\}$

We need to show that all the coefficient expressions are independent of θ and ϕ.

Condition **(v)** of $\boldsymbol{d^*}$ implies that y_2 is independent of θ and ϕ. Also, since $\boldsymbol{d^*}$ is BBD for direct treatment effects, number of units with treatment θ appearing $[k/\nu] + 1$ times is independent of θ. Thus, $(y_1+y_2+y_3)$ is independent of θ. This implies that (y_1+y_3) is independent of θ and ϕ.

Hence, all off-diagonal elements of $\mathbf{T'_{d*}UU'S_{d*}}$ are equal. Further, for a design with self carryover effects of each treatment occurring equal number of times, $1'\mathbf{C_{d*13}} = 0$, which holds in $\boldsymbol{d^*}$.

$\mathbf{T'_{d*}UU'S_{d*}}$ is, thus, completely symmetric.

8. For $\mathbf{M'_{d*}UU'S_{d*}}$, let

   z_1 = number of units in $\boldsymbol{d^*}$ where θ and ϕ occur $[k/\nu] + 1$ times, ϕoccurs in the last period and self carryover effect of ϕ occurs.

   z_2 = number of units in $\boldsymbol{d^*}$ where θ and ϕ occur $[k/\nu] + 1$ times, θ and ϕdo not occur in the last period and self carryover effect of ϕ occurs.

   z_3 = number of units in $\boldsymbol{d^*}$ where θ occurs $[k/\nu] + 1$ times, ϕoccurs $[k/\nu]$ times and θ does not occur in the last period and self carryover effect of ϕ occurs.

   Thus, the (i, j)th element of $\mathbf{T'_{d*}UU'S_{d*}}$ is given as:

   $(z_1+ z_2+ z_3)\{[k/\nu] + 1\}+ (b - z_1 - z_2 - z_3)\{k/\nu]\}$

   We need to show that all the coefficient expressions are independent of θ and ϕ.

   Condition **(vii)** of $\boldsymbol{d^*}$ implies that z_3 is independent of θ and ϕ. Also, due to condition **(v)** of $\boldsymbol{d^*}$, $(z_1+z_2+z_3)$ is independent of θ.This implies that (z_1+z_2) is independent of θ and ϕ.

   Hence, all off-diagonal elements of $\mathbf{M'_{d*}UU'S_{d*}}$ are equal. Further, diagonal elements of $\mathbf{C_{d23}}$ are all zero.

   $\mathbf{T'_{d*}UU'S_{d*}}$ is, thus, completely symmetric.

Thus, from points 1 to 8, it is proved that all $\mathbf{C_{d*ij}}$'s (i, j = 1, 2, 3) as completely symmetric, under the self and mixed carryover effects model (1). Hence, for $\boldsymbol{d^*}$, the information matrix for estimation of direct effects $\mathbf{C_{d*}}$ is completely symmetric.

This implies that within class ζ, design $\boldsymbol{d^*}$ is variance balanced for estimation of direct effects under self and mixed carryover effects model (1).

Further, such designs could be taken to be quite efficient, relative to the universally optimal totally balanced designs. This is due to the fact that they belong to the class of designs which would host the next best design under the model with self and mixed carryover effects, viz. a class of cross-over designs with self carryover effects of treatments occurring once on every unit. Hence, a comparison can be made between the new design which is variance balanced for estimation of direct treatment effects in the presence of both self and mixed carryover effects, and a known totally balanced design, to which it is the nearest, by means of obtaining D-efficiency, where,

$$\text{D-Efficiency} = \frac{Tr(\mathbf{C_{d*}})}{Tr(\mathbf{C_d})} \times 100$$

where, $Tr(\mathbf{C_{d*}})$ is the trace of the information matrix for estimating direct effects of treatments for the variance balanced design d^* and $Tr(\mathbf{C_d})$ is the same for a known totally balanced design to which d^* is nearest.

For the variance balanced designs d^*obtained here, an inherent condition is that $k = \text{p}\nu + 1$, where p is some positive integer. Thus, a known totally balanced design, to which d^* is nearest, would be one with $k = p\nu$, in the same number of treatments and units as $\boldsymbol{d^*}$. It is to be noted that totally balanced designs are proven to be universally optimal under the model for self and mixed carryover effects for $\nu \geq 3$ and $3 \leq k \leq 2\nu$. Hence, the comparison can be made for the designs $\boldsymbol{d^*}$ only when p= 1 or 2. Further, Tr $(\mathrm{C}_{\mathbf{d*}})$ would be greater than Tr (C_d) because of the fact that there is occurrence of self carryover effects of the treatments on the units of d^*, and the difference between the two designs in terms of an additional period in d^*.

4. Constructions

Methods of construction of some series of variance balanced designs for the estimation of direct effects under self and mixed carryover effects model (1), when both self and mixed carryover effects of treatments occur, are presented here. These designs are the ones which satisfy the conditions outlined for $\boldsymbol{d^*}$. A comparison of the constructed designs with known totally balanced designs, to which they are nearest, is also carried out.

Series 1

Step 1: Obtain a Williams' design [Williams' (1949)] for ν treatments.

Step 2: Replicate the design ν times and place them together.

Step 3: Repeat i^{th} treatment once on each unit of the i^{th} replication of the design; (i = 1, 2, ..., ν).

This gives two series of the required variance balanced design with parameters as follows:

Series 1A (When ν is even): $\nu, k = \nu+ 1$, $b = \nu^2$ if ν is even.

Series 1B (When ν is odd): $\nu, k = \nu+ 1$, $b = 2\nu^2$ if ν is odd.

Example 1: Let $\nu = 4$. Williams' design is, thus, given as

1 2 3 4
2 3 4 1
4 1 2 3
3 4 1 2

Replicating this design 4 times, we get

1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4
2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1
4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3
3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2

Repeating i^{th} treatment once on each unit of the i^{th} replication, we get

1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4
1 3 4 1 2 2 4 1 2 3 3 1 2 3 4 4
2 1 2 1 2 3 2 3 4 3 4 3 4 1 4 1
4 1 1 3 4 1 2 2 3 1 2 3 4 4 2 3
3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2

This is the required variance balanced design of **Series 1A** with parameters $\nu = 4$, $k = 5$, $b = 16$.

Further, D-efficiency of this design is obtained as 100.1346.

Series 2

Step 1: Consider a totally balanced design of Kunert and Stufken (2002), with ν^* treatments, $k^* = \nu^*$ periods and b^* units.

Step 2: Replicate the design ν^* times and place them together.

Step 3: Repeat i^{th} treatment once on each sequence of the i^{th} replication of the design; (i = 1, 2,..., ν^*).

This gives the required variance balanced design with parameters $\nu = \nu^*, k = \nu^*+ 1$, $b = \nu^* b^*$.

Series 3

Step 1: Obtain complete set of mutually orthogonal Latin squares (MOLS) of order ν, when ν is prime or prime power, and place them together.

Step 2: Replicate the set ν times to get $\nu \times \nu^2(\nu - 1)$ array.

Step 3: Repeat i^{th} treatment once on each sequence of the i^{th} replication of the set; (i = 1, 2,..., ν).

This gives the required variance balanced design with parameters ν, $k = \nu+ 1$, $b = \nu^2(\nu - 1)$.

Series 4

Step 1: Obtain a complete set of MOLS of order ν, when ν is prime or prime power, and place them together.

Step 2: Duplicate each sequence of the set and place them together to get a $\nu \times 2\nu(\nu - 1)$ array.

Step 3: Duplicate the array obtained in Step 2 and place it below the initial array to get a new $2\nu \times 2\nu(\nu - 1)$ array.

Step 4: Replicate this array ν times and place them together.

Step 5: Repeat i^{th} treatment once on each sequence of the i^{th} replication of the array, by repeating it at one position on one sequence and at the other position on its duplicated sequence; (i = 1, 2,. . . , ν).

This gives the required variance balanced design with parameters ν, $k = 2\nu + 1$, $b = 2\nu^2(\nu - 1)$.

Example 2: Let $\nu = 3$. Complete set of MOLS placed together is, thus, given as

1 2 3 1 2 3
2 3 1 3 1 2
3 1 2 2 3 1

Duplicating each sequence of this set, we get

1 2 3 1 2 3 1 2 3 1 2 3
2 3 1 3 1 2 2 3 1 3 1 2
3 1 2 2 3 1 3 1 2 2 3 1

Placing duplicated array one over the other, we get

1 2 3 1 2 3 1 2 3 1 2 3
2 3 1 3 1 2 2 3 1 3 1 2
3 1 2 2 3 1 3 1 2 2 3 1
1 2 3 1 2 3 1 2 3 1 2 3
2 3 1 3 1 2 2 3 1 3 1 2
3 1 2 2 3 1 3 1 2 2 3 1

Replicating this 3 times and placing together, the array obtained is

1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3
2 3 1 3 1 2 2 3 1 3 1 2 2 3 1 3 1 2 2 3 1 3 1 2 2 3 1 3 1 2 2 3 1 3 1 2
3 1 2 2 3 1 3 1 2 2 3 1 3 1 2 2 3 1 3 1 2 2 3 1 3 1 2 2 3 1 3 1 2 2 3 1
1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3
2 3 1 3 1 2 2 3 1 3 1 2 2 3 1 3 1 2 2 3 1 3 1 2 2 3 1 3 1 2 2 3 1 3 1 2
3 1 2 2 3 1 3 1 2 2 3 1 3 1 2 2 3 1 3 1 2 2 3 1 3 1 2 2 3 1 3 1 2 2 3 1

Repeating i^{th} treatment once on each sequence of the i^{th} replication of the array, by repeating it at one position on one sequence and at the other position on its duplicated sequence, we get

1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3
1 3 1 2 3 1 1 1 2 3 1 2 2 2 1 2 3 1 3 2 2 3 1 2 2 3 3 2 3 1 3 1 3 3 1 2
2 1 1 3 1 2 3 1 1 2 3 1 2 3 2 3 1 2 2 1 2 2 3 1 3 3 1 3 1 2 3 3 2 2 3 1
3 1 2 1 2 3 2 3 1 1 2 3 3 1 2 1 2 3 2 3 1 1 2 3 3 1 2 1 2 3 2 3 1 1 2 3
1 2 3 1 3 1 1 2 3 1 1 2 1 2 3 2 2 1 1 2 3 3 2 2 1 2 3 2 3 3 1 2 3 3 1 3
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This is the required variance balanced design of **Series 4** with parameters $\nu = 3$, $k = 7$, $b = 36$.

Further, D-efficiency of this design is obtained as 100.1785.

Series 5

Step 1: Consider a totally balanced design of Kunert and Stufken (2002) with ν^* treatments, $k^* = 2\nu^*$ periods and b^* units and duplicate each of its sequences to obtain a design with $2b^*$ units.

Step 2: Replicate the design obtained in Step 1 ν^* times and place them together.

Step 3: Repeat i^{th} treatment once on each unit of the i^{th} replication of the modified design, by repeating it at one position on one sequence and at the other position on its duplicated sequence; (i = 1, 2,. . . , ν^*).

This gives the required variance balanced design with parameters $\nu = \nu^*$, $k = 2\nu^* + 1$, $b = 2\nu^* b^*$.

It can be verified that the above designs are variance balanced under model (1) as they satisfy all the properties defined for $\boldsymbol{d^*}$.

5. Conclusions

It can be clearly seen that for a number of applications of cross-over designs, the traditional model, with the assumption of same carryover effects for all the treatments, irrespective of the treatment it occurs onto, cannot hold true. Hence, use of self and mixed carryover effects model is inevitable. Further, in most cases, the interest lies mainly in the estimation of direct treatment effects. It is, thus, only sensible to obtain these estimates in the presence of both self and mixed carryover effects, as we are dealing with the cases where both self and mixed carryover effects occur. This forms the basis of restricting the class ζ. Under this class, conditions are obtained for a design to be variance balanced for estimation of direct treatment effects under model (1). Any design satisfying these conditions would be a variance balanced design under the model with self and mixed carryover effects and would, thus, provide equally precise estimates of all direct treatment effects when both self and mixed carryover effects occur. Construction methods of some series of such variance balanced designs have been outlined. Also, the comparison between the obtained variance balanced designs with known totally balanced designs, to which they are nearest, shows that the constructed designs are efficient for estimation of direct effects in the presence of both self and mixed carryover effects, if only an additional period can be afforded in the design.

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