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Developments in Crossover Designs

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Abstract

Among the designs that are available for treatment comparison experiments, crossover designs occupy an important place. The application of these designs in a variety of situations has been widespread and simultaneously, many important theoretical results have been obtained. The literature is already voluminous and continues to grow. In this article, we present a review of the major results in the construction, analysis and optimality of crossover designs.

1 Introduction

1.1 Prologue

In a crossover trial, every *experimental subject* is exposed to a sequence of treatments over time, one treatment being applied to it at each time point. These subjects could be humans, animals, machines, plots of land, etc. The different time points at which the subjects are used are referred to as *periods.* Consider a crossover trial with n experimental subjects, each subject being observed for p periods, resulting in a total of np experimental *units.* We shall assume at the design stage that each such experimental unit yields a single response (which could even possibly be an average or sum over multiple observations). If such a trial aims at drawing inference on a set of t treatments, then any allocation of these t treatments to the np experimental units is called a *crossover design.* In the literature, such designs have also been referred to as *changeover or repeated measurements* designs.

Crossover designs have been extensively applied in a variety of areas including pharmaceutical studies and clinical trials, biological assays, weather modification experiments, sensory evaluation of food products, psychology, bioequivalence studies and consumer trials. Throughout this article, a crossover design with p periods, n subjects and t treatments will be displayed as a $p \times n$ array, with rows of the array representing the periods, columns representing the subjects and the numerals $1,2,\ldots,t$ denoting the treatments. The following are two examples of crossover designs.

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Example 1.
(i) $d_1 :\ t = 2 = p, n = 4$.

$$\begin{array}{cccc} 1 & 2 & 1 & 2 \\ 2 & 1 & 2 & 1 \end{array}$$

(ii) $d_2 :\ t = 3 = p, n = 6$.

$$\begin{array}{cccccc} 1 & 2 & 3 & 1 & 2 & 3 \\ 2 & 3 & 1 & 3 & 1 & 2 \\ 3 & 1 & 2 & 2 & 3 & 1 \end{array}$$

The design d_1 shown in Example 1 is a two-period two-treatment design, also called an AB/BA design, where AB stands for the treatment sequence in which treatment 1 is followed by treatment 2, BA being defined analogously. Such a design is often used in the context of clinical trials where, for example, treatment 1 could be the drug under study and 2 could be a placebo or another drug. An extensive discussion on the analysis of data from such designs is available in Jones and Kenward (2003). An application of this design in the context of pharmacokinetic studies can be found in Jones *et al.* (1999).

An advantage of a crossover design is that, for the same number of observations, this design requires a fewer number of experimental subjects compared to a traditional design where each subject gives a single observation. This is useful in situations where the subjects are scarce or expensive. However, the very feature of these designs, namely the repeated use of a subject, also brings in associated problems. For instance, a crossover design results in a longer duration of the experiment compared to a traditional design and, designs with a large number of periods may not be particularly attractive in some areas of application.

More importantly, there is a possibility that the effect of a treatment may continue to linger on in a subject beyond the period in which it is applied. For instance, in design d_2 of Example 1, in the second period, the first subject may retain some of the effect of treatment 1 applied to it in the first period and so, the response from the first subject in the second period is affected not only by the *direct* effect of treatment 2 but also possibly by the residual or, *carryover* effect of treatment 1. Similarly, the response in the third period of the first subject is influenced by the direct effect of treatment 3, the carryover effect of treatment 2 and also possibly by the effect of treatment 1 carrying over across two periods. In particular, an effect carrying over to the immediate next period is referred to as the *first order* carryover effect, and extending this idea, there may be *second order* or even higher order carryover effects in subsequent periods.

Thus, there are two types of treatment effects associated with crossover trials, the *direct effects* and the *carryover effects*, the former effects being usually of primary interest. The presence of carryover effects complicates the design and analysis of crossover trials. One option of avoiding these is to allow a larger time gap between two successive applications of treatments, with the expectation that the carryover effect, if any, would wash out during this gap. Though this strategy may help in avoiding the carryover effect, insertion of such gaps, usually called the *rest* (or *wash out*) periods, increases the total duration of the trial. Moreover, it can be difficult to determine how long a rest period should be in order to wash out the carryover effect completely. Another reason why such wash out periods may make a trial infeasible is apparent in the context of clinical trials where the subjects are patients. In such trials, adopting a wash out period is equivalent to denying a patient any treatment during this long gap, and this may be unacceptable on medical or ethical grounds. So, instead of trying to eliminate the carryover effects by inserting rest periods, if one accepts their possible presence, then the challenge is to come up with an effective design of the trial and its corresponding analysis so that the typical contrasts of interest, namely, the direct effect contrasts, can be estimated efficiently after properly adjusting for these carryover effects.

Much of the literature on crossover designs deals with solutions to this problem under different assumptions on the nature of the carryover effects. In the following sections, we provide a survey of the major results on the construction and analysis of efficient/optimal crossover designs. Throughout this paper, we assume that the responses from a crossover trial are quantitative. However, there are situations in practice when such responses may be binary or categorical in nature. We do not elaborate on the analysis of crossover trials with binary or categorical responses and refer the reader to Chapter 6 of Jones and Kenward (2003) for details and additional references.

1.2 Early history

Crossover trials have a long history and apparently, these were first applied in agriculture in 1853. We refer the reader to Jones and Kenward (2003, Section 1.4) for details of a crossover experiment in agriculture conducted by John Bennet Lawes of Rothamsted, England, in 1853. An early use of crossover trials in human nutrition was made by Simpson (1938). These trials were related to experiments on diets for children. In one such trial, four different diets were compared using 24 pairs of children, one male and one female in each pair. Each pair received one of all possible 24 permutations of four diets over 4 periods in such a way that each treatment was given equally often in each period. Simpson (1938) was aware of carryover effects and suggested the insertion of a rest (or, wash out) period between the experimental periods to remove the carryover effects. He also stated that the insertion of a wash out period to eliminate carryover effects may not always be the best strategy in all situations, especially when it may be necessary to estimate the carryover effects themselves and suggested the use of suitable designs which allow the estimation of both direct and carryover effects.

Cochran (1939) observed the existence of carryover effects in long-term agricultural experiments and was one of the first to separate out the direct and carryover effects while considering an appropriate design for experimentation. In a classic and widely cited paper, Cochran *et al.* (1941) considered a crossover trial on Holstein cows for comparing three treatments in three periods. The crossover design used was obtained by using orthogonal Latin squares, like the design d_2 of Example 1. Cochran *et al.* appear to be the first to formally describe the least squares method of estimation of direct and carryover contrasts. Another early example of an experiment indicating the presence of carryover effects was quoted by Williams (1949). In this experiment, samples of pulp suspensions were beaten in a Lampen mill to determine the effect of concentration on the properties of resulting sheets. Observations of the condition of the mill after each beating indicated that certain pulp concentrations had an effect on the mill which might affect the next beating, indicating the presence of carryover effect. A design balanced for carryover effects was therefore used.

An early use of crossover designs was made in biological assays by Fieller (1940). He used a 2-period design involving 2 treatments for comparing the effects of different doses of insulin on rabbits. Finney (1956) also described the design and analysis of several crossover designs for use in biological assay. In subsequent years, the use of these designs in many diverse areas, particularly in clinical trials and pharmaceutical studies, have been extensive. Real life examples and discussion on various aspects of crossover designs can be found in the books on this topic by Pocock (1983), Ratkowsky *et al.* (1992), Jones and Kenward (2003), Senn (2003) and Bose and Dey (2009). Over the years, several review papers have been published on these designs, including those by Hedayat and Afsarinejad (1975), Matthews (1988), Stufken (1996), Kenward and Jones (1998), Senn (2000) and Bate and Jones (2008). An early technical report due to Patterson and Lucas (1962) provides tables of useful crossover designs along with detailed steps of their analysis.

2 A model for studying crossover designs

Consider a crossover trial in which t treatments are to be compared using n experimental subjects over p time periods. As mentioned earlier, any allocation of the t treatments to the np experimental units is called a crossover design. Let $\Omega_{t,n,p}$ be the collection of all such crossover designs.

For the analysis of data arising from crossover designs, various models have been studied in the literature. We first describe a commonly used model in the following subsection. This model is henceforth called the *traditional model*.

Even though the traditional model has been widely studied, it has also been criticized for being unsuitable for some experimental situations. In order to suit different situations, the traditional model has been variously modified, for example, by making certain assumptions on the form of the carryover effect or by assuming a certain structure for the correlation of the error terms. Some of these modifications will be described in later sections.

2.1 The traditional model

The traditional model described below is an additive linear model, where the expected response from a subject at any given period is the sum of the corresponding subject and period effects, together with the direct effect of the treatment applied at that period and the carryover effect of the treatment applied in the previous period (if any). For the data from a design $d \in \Omega_{t,n,p}$, the traditional model may be expressed as

$$\begin{aligned} Y_{ij} &= \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \rho_{d(i-1,j)} + \epsilon_{ij}, \\ & \quad 1 \le i \le p, \;\; 1 \le j \le n, \end{aligned} \tag{1}$$

where Y_{ij} is the observable random variable corresponding to the observation from the jth subject in the ith period, $d(i,j)$ denotes the treatment allocated to the jth subject in the ith period according to the design d, and μ, α_i, β_j, $\tau_{d(i,j)}$ and $\rho_{d(i-1,j)}$ are, respectively, a general mean, the ith period effect, the jth subject effect, the direct effect of the treatment $d(i,j)$ and the first order carryover effect of the treatment $d(i-1,j)$, $1 \le i \le p, 1 \le j \le n$; the ϵ_{ij}'s are the error components, assumed to be uncorrelated random variables with zero means and constant variance σ^2. We define $\rho_{d(0,j)} = 0, 1 \le j \le n$, to reflect the fact that there are no carryover effects in the first period. All the parameters in (1) are considered as *fixed*, i.e., non-random. In what follows, the same notation Y_{ij} is used for the observation as well as the random variable corresponding to the observation.

2.2 Information matrices

We first express (1) in a form which is more convenient to study. Towards this end, let us write the observations from a design d as an ordered vector, where the first p entries are the p observations on subject 1, the next p are the observations on subject 2, ..., and so on. Thus, for any design $d \in \Omega_{t,n,p}$, $\boldsymbol{Y}_d = (Y_{11}, \ldots, Y_{p1}, Y_{12}, \ldots, Y_{p2}, \ldots, Y_{1n}, \ldots, Y_{pn})'$, is the $np \times 1$ vector of observations arising out of d with Y_{ij} as in (1). Here and henceforth, primes denote transposition. Let $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_p)'$, $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_n)'$ be respectively, the $p \times 1$ vector of period effects and the $n \times 1$ vector of subject effects, where α_i and β_j are as in (1). Since $d(i,j) \in \{1, 2, \ldots, t\}$, for simplicity in notation, we denote the direct (respectively, the first order carryover) effect of treatment s by τ_s (respectively, ρ_s), $1 \le s \le t$, and write $\boldsymbol{\tau} = (\tau_1, \ldots, \tau_t)'$, $\boldsymbol{\rho} = (\rho_1, \ldots, \rho_t)'$, $\boldsymbol{\epsilon} = (\epsilon_{11}, \ldots, \epsilon_{pn})'$ to denote the $t \times 1$ vector of direct effects, the $t \times 1$ vector of carryover effects and the $np \times 1$ vector of error terms, respectively, where ϵ_{ij} is as in (1). Also, let $\boldsymbol{\theta} = (\mu, \boldsymbol{\alpha}', \boldsymbol{\beta}', \boldsymbol{\tau}', \boldsymbol{\rho}')'$ with μ as in (1).

Throughout, we let $\mathbf{1}_a$ and $\mathbf{0}_a$ to denote the $a \times 1$ vectors of all ones and all zeros, respectively, and $\boldsymbol{I}_a$ to denote the identity matrix of order a, where a is a positive integer. For positive integers a and b, $\mathbf{O}_{ab}$ denotes the $a \times b$ null matrix and $\boldsymbol{J}_{ab}$, the $a \times b$ matrix of all ones; $\boldsymbol{J}_{aa}$ and $\mathbf{O}_{aa}$ will simply be written as $\boldsymbol{J}_a$ and $\mathbf{O}_a$, respectively. A square matrix $\boldsymbol{A}$ of order n is called completely symmetric if $\boldsymbol{A} = a\boldsymbol{I}_n + b\boldsymbol{J}_n$ for some scalars a, b. For a matrix $\boldsymbol{A}$, $\boldsymbol{A}^-$ denotes an arbitrary generalized inverse (g-inverse) of $\boldsymbol{A}$, i.e., $\boldsymbol{A}\boldsymbol{A}^-\boldsymbol{A} = \boldsymbol{A}$. We also define $P^{\perp}(\boldsymbol{A}) = \boldsymbol{I} - \boldsymbol{A}(\boldsymbol{A}'\boldsymbol{A})^-\boldsymbol{A}'$, where $\boldsymbol{I}$ stands for the identity matrix of appropriate order.

For a design $d \in \Omega_{t,n,p}$, let $\boldsymbol{T}_{dj}$ be a $p \times t$ matrix with its (i, s)th entry equal to 1 if subject j receives treatment s in the ith period, and zero otherwise. Similarly, let $\boldsymbol{F}_{dj}$ be a $p \times t$ matrix with its (i, s)th entry equal to 1 if subject j receives treatment s in the $(i-1)$th period, and zero otherwise. Since $\rho_{d(0,j)} = 0$ for $1 \leq j \leq n$, the first row of $\boldsymbol{F}_{dj}$ is zero and for $2 \leq i \leq p, 1 \leq j \leq n$, the ith row of $\boldsymbol{F}_{dj}$ is the $(i-1)$th row of $\boldsymbol{T}_{dj}$, i.e.,

$$\boldsymbol{F}_{dj} = \begin{pmatrix} \mathbf{0}'_{p-1} & 0 \\ \boldsymbol{I}_{p-1} & \mathbf{0}_{p-1} \end{pmatrix} \boldsymbol{T}_{dj}, \;\; 1 \leq j \leq n. \tag{2}$$

Define $\boldsymbol{T}_d = (\boldsymbol{T}'_{d1}, \ldots, \boldsymbol{T}'_{dn})'$, $\boldsymbol{F}_d = (\boldsymbol{F}'_{d1}, \ldots, \boldsymbol{F}'_{dn})'$, and let $E(\cdot)$ and $D(\cdot)$ denote the expectation and dispersion operators, respectively.

With the above notation, model (1) can equivalently be written as

$$\boldsymbol{Y}_d = \boldsymbol{X}_d\boldsymbol{\theta} + \boldsymbol{\epsilon}, \;\; E(\boldsymbol{\epsilon}) = \mathbf{0}_{np}, \;\; D(\boldsymbol{\epsilon}) = \sigma^2 \boldsymbol{I}_{np}, \tag{3}$$

where the design matrix $\boldsymbol{X}_d$ may be written in the following partitioned form:

$$\boldsymbol{X}_d = [\mathbf{1}_{np} \quad \boldsymbol{P} \quad \boldsymbol{U} \quad \boldsymbol{T}_d \quad \boldsymbol{F}_d] = [\mathbf{1}_{np} \quad \boldsymbol{X}_1 \quad \boldsymbol{X}_2], \text{ say}, \tag{4}$$

$\boldsymbol{P}, \boldsymbol{U}, \boldsymbol{T}_d$ and $\boldsymbol{F}_d$ being the parts of $\boldsymbol{X}_d$ corresponding to the period, subject, direct and carryover effects respectively, under the design d; and $\boldsymbol{X}_1 = [\boldsymbol{P} \;\; \boldsymbol{U}]$, $\boldsymbol{X}_2 = [\boldsymbol{T}_d \;\; \boldsymbol{F}_d]$. Furthermore, with the ordering of the observations as in $\boldsymbol{Y}_d$, it is clear that

$$\boldsymbol{P} = \mathbf{1}_n \otimes \boldsymbol{I}_p \quad \text{and} \quad \boldsymbol{U} = \boldsymbol{I}_n \otimes \mathbf{1}_p,$$

where $\otimes$ denotes the Kronecker (tensor) product operator. Henceforth, we will write (3) to denote the traditional model.

Then, it can be shown (see e.g., Bose and Dey (2009, Section 1.3)) that under model (3), after eliminating the nuisance parameters $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$, the information matrix for estimating $\boldsymbol{\tau}$ and $\boldsymbol{\rho}$ jointly is of the form

$$\begin{aligned} \boldsymbol{C}_d(\boldsymbol{\tau}, \boldsymbol{\rho}) &= \boldsymbol{X}'_2 P^{\perp}(\boldsymbol{X}_1)\boldsymbol{X}_2 \\ &= \boldsymbol{X}'_2\boldsymbol{X}_2 - \boldsymbol{X}'_2\boldsymbol{X}_1(\boldsymbol{X}'_1\boldsymbol{X}_1)^{-}\boldsymbol{X}'_1\boldsymbol{X}_2 \\ &= \begin{bmatrix} \boldsymbol{T}'_d\boldsymbol{A}\boldsymbol{T}_d & \boldsymbol{T}'_d\boldsymbol{A}\boldsymbol{F}_d \\ \boldsymbol{F}'_d\boldsymbol{A}\boldsymbol{T}_d & \boldsymbol{F}'_d\boldsymbol{A}\boldsymbol{F}_d \end{bmatrix}, \end{aligned}$$

with

$$\boldsymbol{A} = (\boldsymbol{I}_n - n^{-1}\boldsymbol{J}_n) \otimes (\boldsymbol{I}_p - p^{-1}\boldsymbol{J}_p). \tag{5}$$

We may rewrite $C_d(\boldsymbol{\tau}, \boldsymbol{\rho})$ as

$$\boldsymbol{C}_d(\boldsymbol{\tau}, \boldsymbol{\rho}) = \begin{bmatrix} \boldsymbol{C}_{d11} & \boldsymbol{C}_{d12} \\ \boldsymbol{C}_{d21} & \boldsymbol{C}_{d22} \end{bmatrix}, \tag{6}$$

where

$$\begin{aligned} \boldsymbol{C}_{d11} &= \boldsymbol{R}_d - n^{-1}\boldsymbol{M}_d\boldsymbol{M}'_d - p^{-1}\boldsymbol{N}_d\boldsymbol{N}'_d + (np)^{-1}\boldsymbol{r}_d\boldsymbol{r}'_d, \\ \boldsymbol{C}_{d12} &= \boldsymbol{Z}_d - n^{-1}\boldsymbol{M}_d\bar{\boldsymbol{M}}'_d - p^{-1}\boldsymbol{N}_d\bar{\boldsymbol{N}}'_d + (np)^{-1}\boldsymbol{r}_d\bar{\boldsymbol{r}}'_d = \boldsymbol{C}'_{d21}, \\ \boldsymbol{C}_{d22} &= \bar{\boldsymbol{R}}_d - n^{-1}\bar{\boldsymbol{M}}_d\bar{\boldsymbol{M}}'_d - p^{-1}\bar{\boldsymbol{N}}_d\bar{\boldsymbol{N}}'_d + (np)^{-1}\bar{\boldsymbol{r}}_d\bar{\boldsymbol{r}}'_d. \end{aligned} \tag{7}$$

Here, $\boldsymbol{r}_d$ (respectively, $\bar{\boldsymbol{r}}_d$) is the $t \times 1$ replication vector for direct (respectively, carryover) effects; $\boldsymbol{R}_d$ (respectively, $\bar{\boldsymbol{R}}_d$) is the $t \times t$ diagonal matrix with diagonal elements given by the elements of $\boldsymbol{r}_d$ (respectively, $\bar{\boldsymbol{r}}_d$); $\boldsymbol{M}_d$ (respectively, $\bar{\boldsymbol{M}}_d$) is the $t \times p$ direct (respectively, carryover) effect versus period incidence matrix; $\boldsymbol{N}_d$ (respectively, $\bar{\boldsymbol{N}}_d$) is the $t \times n$ direct (respectively, carryover) effect versus subject incidence matrix, and $\boldsymbol{Z}_d$ is the $t \times t$ direct effect versus carryover effect incidence matrix. It may be verified that these are related to the matrices $\boldsymbol{T}_d$ and $\boldsymbol{F}_d$, defined earlier as $\boldsymbol{r}_d = \boldsymbol{T}'_d \mathbf{1}_t,\ \bar{\boldsymbol{r}}_d = \boldsymbol{F}'_d \mathbf{1}_t,\ \boldsymbol{R}_d = \boldsymbol{T}'_d \boldsymbol{T}_d,\ \bar{\boldsymbol{R}}_d = \boldsymbol{F}'_d \boldsymbol{F}_d,\ \boldsymbol{Z}_d = \boldsymbol{T}'_d \boldsymbol{F}_d$.

Now, let the information matrices of the direct (respectively, carryover) effects, eliminating the carryover (respectively, direct) effects be denoted by $\boldsymbol{C}_d$ and $\bar{\boldsymbol{C}}_d$, respectively. Then, it follows from (7) that

$$\begin{array}{rcl} \boldsymbol{C}_d & = & \boldsymbol{C}_{d11} - \boldsymbol{C}_{d12} \boldsymbol{C}^{-}_{d22} \boldsymbol{C}_{d21}, \\ \bar{\boldsymbol{C}}_d & = & \boldsymbol{C}_{d22} - \boldsymbol{C}_{d21} \boldsymbol{C}^{-}_{d11} \boldsymbol{C}_{d12}. \end{array} \tag{8}$$

It can be shown that $\boldsymbol{C}_d$ and $\bar{\boldsymbol{C}}_d$ as in (8) are invariant with respect to the choice of g-inverses involved. A crossover design is said to be *connected* for direct effects if all contrasts among the direct effects are estimable, a necessary and sufficient condition for this being $\mathrm{Rank}(\boldsymbol{C}_d) = t - 1$. Connectedness for carryovers is analogously defined.

We now briefly indicate the analysis of the data arising from a crossover design under the model (3), assuming that there are no missing observations. The total sum of squares (Total SS) with $np-1$ degrees of freedom (df), can be calculated as usual on the basis of the np individual observations. The sum of squares due to periods (SSP) and that due to subjects (SSS), with $p-1$ and $n-1$ df can also be obtained routinely on the basis of the p period-wise observational totals and the n subject-wise observational totals, respectively (see e.g., Cochran and Cox (1957, Section 4.4)). Turning to the direct and carryover effects, we define the $2t \times 1$ vector of "adjusted" treatment totals as

$$\begin{array}{rcl} \boldsymbol{Q} & = & \boldsymbol{X}'_2 \boldsymbol{Y}_d - \boldsymbol{X}'_2 \boldsymbol{X}_1 (\boldsymbol{X}'_1 \boldsymbol{X}_1)^{-} \boldsymbol{X}'_1 \boldsymbol{Y}_d \\ & = & \left[\begin{array}{c} \boldsymbol{T}'_d \boldsymbol{A} \boldsymbol{Y}_d \\ \boldsymbol{F}'_d \boldsymbol{A} \boldsymbol{Y}_d \end{array} \right] \quad = \quad \left[\begin{array}{c} \boldsymbol{Q}_1 \\ \boldsymbol{Q}_2 \end{array} \right], \end{array} \tag{9}$$

where $\boldsymbol{A}$ is as in (5), $\boldsymbol{Q}_1 = \boldsymbol{T}'_d \boldsymbol{A} \boldsymbol{Y}_d$ and $\boldsymbol{Q}_2 = \boldsymbol{F}'_d \boldsymbol{A} \boldsymbol{Y}_d$. Then the sum of squares for the direct and carryover effects (jointly) after the elimination of the period and subject effects is

$$\mathrm{SS}(\boldsymbol{\tau}, \boldsymbol{\rho}) = \boldsymbol{Q}' \{\boldsymbol{C}_d(\boldsymbol{\tau}, \boldsymbol{\rho})\}^{-} \boldsymbol{Q}. \tag{10}$$

For a crossover design which is connected for both direct and carryover effects, $\mathrm{SS}(\boldsymbol{\tau}, \boldsymbol{\rho})$ has $2(t-1)$ df because $\boldsymbol{Q}'_1 \mathbf{1}_t = \boldsymbol{Q}'_2 \mathbf{1}_t = 0$. Thus the error sum of squares (SSE), with $(n-1)(p-1) - 2(t-1)$ df can be obtained as

$$\mathrm{SSE} = \text{Total SS} - \mathrm{SSP} - \mathrm{SSS} - \mathrm{SS}(\boldsymbol{\tau}, \boldsymbol{\rho}).$$

In order to test the significance of the direct effects, one requires the corresponding adjusted sum of squares as given by

$$\mathrm{SS}_{\mathrm{adj}}(\boldsymbol{\tau}) = (\boldsymbol{Q}_1 - \boldsymbol{C}_{d12}\boldsymbol{C}_{d22}^{-}\boldsymbol{Q}_2)'(\boldsymbol{C}_{d11} - \boldsymbol{C}_{d12}\boldsymbol{C}_{d22}^{-}\boldsymbol{C}_{d21})^{-}(\boldsymbol{Q}_1 - \boldsymbol{C}_{d12}\boldsymbol{C}_{d22}^{-}\boldsymbol{Q}_2),$$

with $t-1$ df, where $\boldsymbol{C}_{d11}, \boldsymbol{C}_{d12}$ and $\boldsymbol{C}_{d21}$ are as in (7). On the basis of $\mathrm{SS}_{\mathrm{adj}}(\boldsymbol{\tau})$ and SSE, the F-test can now be employed in a straightforward manner for testing the significance of direct effects. The procedure for testing the significance of carryover effects is similar.

3 Some families of crossover designs

We now introduce a few classes of crossover designs which have been widely studied in the literature. Apparently, the designs described in Definitions 1 and 2 below were first formally defined and studied by Hedayat and Afsarinejad (1978) and Cheng and Wu (1980) and systematic construction methods for these are available. However, in these designs, the numbers of periods often exceed the numbers of treatments to be compared. In some experiments, it may be difficult to accommodate a large number of periods and so one may prefer designs with $p < t$. Patterson (1952) was probably the first to give systematic methods of construction for designs with $p \leq t$. Freeman (1959), Patterson and Lucas (1962), Atkinson (1966), Hedayat and Afsarinejad (1975), Constantine and Hedayat (1982), Afsarinejad (1983, 1985) and Stufken (1991) also considered designs with $p \leq t$. Some designs with $p \leq t$ are described in Definitions 3–5. All these designs have nice combinatorial properties and, as a result, they have simple forms of the information matrix for inference on direct effects under model (3). Moreover, as will be seen later, they also enjoy excellent optimality properties.

A design is said to be *uniform on periods* if in each period, it allocates each treatment to the same number of subjects. Similarly, a design is *uniform on subjects* if for each subject, it allocates each treatment to the same number of periods. A design is simply said to be *uniform* if it is uniform on periods as well as on subjects.

The above definitions imply that for a uniform design $d \in \Omega_{t,n,p}$,

$$\boldsymbol{r}_d = \frac{np}{t}\mathbf{1}_t, \;\; \boldsymbol{R}_d = \frac{np}{t}\boldsymbol{I}_t, \;\; \boldsymbol{M}_d = \frac{n}{t}\boldsymbol{J}_{tp}, \;\; \boldsymbol{N}_d = \frac{p}{t}\boldsymbol{J}_{tn}. \qquad (11)$$

3.1 Designs with $p \geq t$

Definition 1. *A design $d \in \Omega_{t,n,p}$ is said to be balanced if in the order of application, no treatment precedes itself and each treatment is preceded by every other treatment the same number of times.*

Definition 2. *A design $d \in \Omega_{t,n,p}$ is said to be strongly balanced if in the order of application, each treatment is preceded by every treatment (including itself) the same number of times.*

Clearly, if d is either balanced or strongly balanced, we have

$$\boldsymbol{Z}_d = \boldsymbol{T}_d'\boldsymbol{F}_d \quad = \quad \frac{n(p-1)}{t(t-1)}(\boldsymbol{J}_t - \boldsymbol{I}_t), \text{ or } \boldsymbol{Z}_d = \frac{n(p-1)}{t^2}\boldsymbol{J}_t, \tag{12}$$

respectively. We now give some examples of these designs, where we define the positive integers $\lambda_1, \lambda_2, \mu_1$ and μ_2 as $\lambda_1 = n(p-1)/\{t(t-1)\}$, $\lambda_2 = n(p-1)/t^2, \mu_1 = n/t$ and $\mu_2 = p/t$. Thus, for a balanced design, $\boldsymbol{Z}_d = \lambda_1(\boldsymbol{J}_t - \boldsymbol{I}_t)$ and for a strongly balanced design, $\boldsymbol{Z}_d = \lambda_2\boldsymbol{J}_t$.

Example 2. The designs d_1 and d_2 in Example 1 are both balanced uniform designs with $\lambda_1 = 2$. Below we give two examples of strongly balanced designs with $t = 3$; the first design has $n = 9, p = 6$, and the second has $n = 6, p = 4$.

$$d_3 \equiv \begin{array}{ccccccccc} 1 & 1 & 1 & 2 & 2 & 2 & 3 & 3 & 3 \\ 1 & 2 & 3 & 1 & 2 & 3 & 1 & 2 & 3 \\ 2 & 2 & 2 & 3 & 3 & 3 & 1 & 1 & 1 \\ 2 & 3 & 1 & 2 & 3 & 1 & 2 & 3 & 1 \\ 3 & 3 & 3 & 1 & 1 & 1 & 2 & 2 & 2 \\ 3 & 1 & 2 & 3 & 1 & 2 & 3 & 1 & 2 \end{array}, \quad d_4 \equiv \begin{array}{cccccc} 1 & 2 & 3 & 3 & 1 & 2 \\ 2 & 3 & 1 & 2 & 3 & 1 \\ 3 & 1 & 2 & 1 & 2 & 3 \\ 3 & 1 & 2 & 1 & 2 & 3 \end{array}.$$

The design $d_3 \in \Omega_{3,9,6}$ is uniform, with $\mu_1 = 3, \mu_2 = 2$ and $\lambda_2 = 5$, while $d_4 \in \Omega_{3,6,4}$ is uniform only on periods with $\mu_1 = 2$ and $\lambda_2 = 2$. Note that d_4 is uniform on subjects in the first $3(= p-1)$ periods and its last period is obtained by repeating the allocation in the previous period. Patterson and Lucas (1959) named a design of the form d_4 as an extra-period design.

In view of (11) and (12) it is easy to see that the properties of uniformity and balance lead to substantial simplifications in the forms of the information matrices. Consider any two designs in $\Omega_{t,n,p}$, say, $\tilde{d}$ and d_*, which are balanced uniform and strongly balanced uniform, respectively, Then, on simplification from (7), one can show that

$$\begin{aligned} \boldsymbol{C}_{\tilde{d}11} &= \mu_1 p\boldsymbol{H}_t,\ \boldsymbol{C}_{\tilde{d}12} = -\lambda_1\boldsymbol{H}_t,\ \boldsymbol{C}_{\tilde{d}22} = \mu_1(p-1-p^{-1})\boldsymbol{H}_t, \\ \boldsymbol{C}_{d_*11} &= \mu_1 p\boldsymbol{H}_t,\ \boldsymbol{C}_{d_*12} = \mathbf{O}_t,\ \boldsymbol{C}_{d_*22} = \mu_1(p-1-p^{-1})\boldsymbol{H}_t, \end{aligned} \tag{13}$$

where for a positive integer a,

$$\boldsymbol{H}_a = \boldsymbol{I}_a - a^{-1}\boldsymbol{J}_a. \tag{14}$$

From (8), it can be verified that for a balanced uniform design $\tilde{d}$, the matrices $\boldsymbol{C}_{\tilde{d}}$ and $\bar{\boldsymbol{C}}_{\tilde{d}}$ are completely symmetric, given by

$$\boldsymbol{C}_{\tilde{d}} = \alpha_1\boldsymbol{H}_t, \qquad \bar{\boldsymbol{C}}_{\tilde{d}} = \alpha_2\boldsymbol{H}_t, \tag{15}$$

where

$$\begin{aligned} \alpha_1 &= \mu_1 p\left[1 - (p-1)^2(t-1)^{-2}(p^2-p-1)^{-1}\right], \\ \alpha_2 &= \mu_1\left[(p-1-p^{-1}) - (p-1)^2(t-1)^{-2}p^{-1}\right]. \end{aligned}$$

Since $\boldsymbol{H}_t$ is an idempotent matrix, a g-inverse of $\boldsymbol{H}_t$ is $\boldsymbol{I}_t$. Hence, one can consider g-inverses of $\boldsymbol{C}_{\tilde{d}}$ and $\bar{\boldsymbol{C}}_{\tilde{d}}$ as given respectively, by

$$(\boldsymbol{C}_{\tilde{d}})^{-} = \alpha_1^{-1}\boldsymbol{I}_t, \qquad (\bar{\boldsymbol{C}}_{\tilde{d}})^{-} = \alpha_2^{-1}\boldsymbol{I}_t. \tag{16}$$

From (16), it is thus clear that the analysis of a balanced uniform crossover design becomes extremely simple and this makes such designs attractive to users. Uniform crossover designs have been used in diverse areas of investigation and, for references to such work, we refer to Bate and Jones (2008).

From (8) and (13), it is also clear that the analysis of data from a strongly balanced uniform design d_* is further simplified owing to the fact that $\boldsymbol{C}_{d_*12} = \mathbf{O}_t$. Thus, the direct and carryover effects are orthogonally estimable under these designs and

$$\boldsymbol{C}_{d_*} = \mu_1 p \boldsymbol{H}_t, \qquad \bar{\boldsymbol{C}}_{d_*} = \mu_1(p - 1 - p^{-1})\boldsymbol{H}_t. \tag{17}$$

Such simple forms of the information matrices make it very convenient to study the statistical properties of these designs.

Again, Definitions 1 and 2 imply that the parameters t, n and p need to satisfy certain divisibility requirements for these designs to exist. For instance, a strongly balanced design exists only if t^2 divides $n(p-1)$. To overcome this problem, Kunert (1983) departed from the requirement of strong balance and introduced *nearly strongly balanced* designs where, instead of requiring that each treatment pair appear equally often in successive periods, he stipulated that each treatment pair appear in successive periods as equally often as possible. Let us write $\boldsymbol{Z}_d = (z_{dss'})$, i.e., $z_{dss'}$ is the number of times treatment s is immediately preceded by treatment s'. A design d is a nearly strongly balanced design if

(i) $z_{dss'}$ is equal to either $[n(p-1)/t^2]$ or $[n(p-1)/t^2] + 1$, for all $1 \leq s, s' \leq t$, and

(ii) $\boldsymbol{Z}_d \boldsymbol{Z}'_d$ is of the form $a\boldsymbol{I}_t + b\boldsymbol{J}_t$ for some constants a and b.

In (i) above, $[\cdot]$ is the greatest integer function. Bate and Jones (2006) introduced *nearly balanced designs* which only require condition (i) above. We give one example each of these designs; for further details including their optimality and efficiency properties, we refer to Kunert (1983) and Bate and Jones (2006).

Example 3. The design d_5 with $t = 3, n = 6 = p$, is nearly strongly balanced while d_6 with $t = 5, n = 10, p = 15$ is nearly balanced.

$$d_5 \equiv \begin{array}{cccccc} 1 & 2 & 3 & 1 & 2 & 3 \\ 2 & 3 & 1 & 1 & 2 & 3 \\ 3 & 1 & 2 & 2 & 3 & 1 \\ 3 & 1 & 2 & 3 & 1 & 2 \\ 2 & 3 & 1 & 3 & 1 & 2 \\ 1 & 2 & 3 & 2 & 3 & 1 \end{array}, \quad d_6 \equiv \begin{array}{cccccccccc} 5 & 1 & 2 & 3 & 4 & 2 & 3 & 4 & 5 & 1 \\ 2 & 3 & 4 & 5 & 1 & 1 & 2 & 3 & 4 & 5 \\ 1 & 2 & 3 & 4 & 5 & 4 & 5 & 1 & 2 & 3 \\ 4 & 5 & 1 & 2 & 3 & 3 & 4 & 5 & 1 & 2 \\ 3 & 4 & 5 & 1 & 2 & 3 & 4 & 5 & 1 & 2 \\ 3 & 4 & 5 & 1 & 2 & 4 & 5 & 1 & 2 & 3 \\ 4 & 5 & 1 & 2 & 3 & 1 & 2 & 3 & 4 & 5 \\ 1 & 2 & 3 & 4 & 5 & 2 & 3 & 4 & 5 & 1 \\ 2 & 3 & 4 & 5 & 1 & 5 & 1 & 2 & 3 & 4 \\ 5 & 1 & 2 & 3 & 4 & 5 & 1 & 2 & 3 & 4 \\ 5 & 1 & 2 & 3 & 4 & 5 & 1 & 2 & 3 & 4 \\ 1 & 2 & 3 & 4 & 5 & 4 & 5 & 1 & 2 & 3 \\ 4 & 5 & 1 & 2 & 3 & 1 & 2 & 3 & 4 & 5 \\ 2 & 3 & 4 & 5 & 1 & 3 & 4 & 5 & 1 & 2 \\ 3 & 4 & 5 & 1 & 2 & 2 & 3 & 4 & 5 & 1 \end{array}.$$

3.2 Designs with $p \leq t$

In this subsection, we consider some designs with $p \leq t$. All these designs enjoy good optimality properties and we will discuss these properties later in this paper. We begin with the definition of the class of designs considered by Patterson (1952) which we shall call *Patterson designs*. These designs are very popular among experimenters because they involve a moderate number of subjects for given t and do not involve too many periods. Several families of such designs are known.

Definition 3. *A design $d \in \Omega_{t,n,p}$ where $p \geq 3,\ t \geq 3$, will be said to be a Patterson design if the following conditions hold:*
(i) d is uniform on periods, so that $n = \mu_1 t$ for some integer $\mu_1 \geq 1$;
(ii) d is balanced, so that $n(p-1)/\{t(t-1)\} = \lambda_1$ for some integer $\lambda_1 \geq 1$;
(iii) when the subjects of d are viewed as blocks, they form the blocks of a balanced incomplete block (BIB) design with block size p ;
(iv) when d is restricted to the first $p-1$ periods, then again, the subjects of d form the blocks of a BIB design with block size $p-1$;
(v) in the set of μ_1 subjects receiving a given treatment in the last period, every other treatment is applied λ_1 times in the first $p-1$ periods.

Example 4. The design d_7 shown below is a Patterson design with $t = 4, p = 3, n = 12$.

$$d_7 \equiv \begin{array}{cccccccccccc} 1 & 2 & 3 & 4 & 1 & 2 & 3 & 4 & 1 & 2 & 3 & 4 \\ 2 & 1 & 4 & 3 & 3 & 4 & 1 & 2 & 4 & 3 & 2 & 1 \\ 3 & 4 & 1 & 2 & 4 & 3 & 2 & 1 & 2 & 1 & 4 & 3 \end{array}.$$

For a Patterson design d, it can be shown that

$$\begin{aligned} \boldsymbol{C}_{d11} &= \lambda_1 t \boldsymbol{H}_t,\ \boldsymbol{C}_{d12} = -(\lambda_1 t/p)\boldsymbol{H}_t, \\ \boldsymbol{C}_{d22} &= \{\lambda_1(pt-t-1)/p\}\boldsymbol{H}_t. \end{aligned} \tag{18}$$

So, analogously to (15), the information matrices $\boldsymbol{C}_d$ and $\bar{\boldsymbol{C}}_d$ are both constant multiples of $\boldsymbol{H}_t$, leading to considerable simplification in the analysis.

Stufken (1991) introduced a new class of designs and proved that they have good optimality properties in certain subclasses of $\Omega_{t,n,p}$. These designs, labeled as *Stufken designs*, are described below. Stronger optimality properties of these designs were established later by Hedayat and Yang (2004).

Definition 4. *A design $d \in \Omega_{t,n,p}$ will be called a Stufken design if it satisfies the following properties:*
(a) d is uniform on periods;
(b) the first $p-1$ periods of d form a BIB design with subjects as blocks;
(c) in the last period of d, θ subjects receive a treatment that was not allocated to them in any of the previous periods, while the remaining $n-\theta$ subjects receive the same treatment as in period $p-1$, where θ is the nearest integer (or one of the nearest integers) to $\dfrac{n(pt-t-1)}{(p-1)t}$;
(d) $z_{dss'} - p^{-1}\sum_{j=1}^{n} n_{dsj}\bar{n}_{ds'j}$ is independent of s and s', $s \neq s'$, where $\boldsymbol{Z}_d = (z_{dss'})$, $\boldsymbol{N}_d = (n_{dsj})$, $\bar{\boldsymbol{N}}_d = (\bar{n}_{dsj})$ are as defined earlier;
(e) $\sum_{j=1}^{n} n_{dsj}n_{ds'j}$ is independent of s and s', $s \neq s'$.
We shall describe the optimality properties of Stufken designs in Section 6.5.

Kunert and Stufken (2002) studied a general class of designs called *totally balanced* designs which satisfy more stringent combinatorial conditions and have good statistical properties. These designs are quite general in the sense that, though the number of subjects needs to be a multiple of the number of treatments, there is no restriction on the number of periods, thus allowing $p < t$, $p > t$ or $p = t$. An attractive feature of these designs is that they have good optimality properties, even under models more complicated than the one in (3). We define these designs here and will study them again later.

Definition 5. *A design $d \in \Omega_{t,n,p}$ is called totally balanced if*
(a) d is uniform on periods;
(b) each treatment is allocated as equally as possible to each subject in d, i.e., each treatment is allocated either $[p/t]$ or $[p/t]+1$ times to each subject;
(c) the number of subjects where treatments s and s' are both allocated $[p/t]+1$ times in d, is the same for every pair $s \neq s', 1 \leq s, s' \leq t$;
(d) each treatment is allocated as equally as possible to each subject in the first $p-1$ periods of d , i.e., each treatment is allocated either $[(p-1)/t]$ or $[(p-1)/t]+1$ times to each subject over periods $1,\ldots,p-1$;
(e) the number of subjects where treatments s and s' are both allocated $[(p-1)/t]+1$ times in the first $p-1$ periods of d, is the same for every pair $s \neq s', 1 \leq s, s' \leq t$;
(f) d is balanced;
(g) the number of subjects where both treatments s and s' appear $[p/t]+1$ times in d and the treatment s' does not appear in the last period is the same for every pair $s, s', 1 \leq s, s' \leq t; s \neq s'$.

Interestingly, some of the earlier designs follow as special cases of these designs; for instance, when p is a multiple of t, a totally balanced design is a balanced uniform design. The Patterson design shown in Example 4 is also a totally balanced design.

Example 5. The following is a totally balanced design with $t = 3, n = 6, p = 4$.

$$d_8 \equiv \begin{array}{cccccc} 1 & 2 & 3 & 3 & 1 & 2 \\ 2 & 3 & 1 & 2 & 3 & 1 \\ 3 & 1 & 2 & 1 & 2 & 3 \\ 1 & 2 & 3 & 3 & 1 & 2 \end{array}.$$

3.3 Two-period designs

Clearly, in a crossover design, the number of periods, p is at least two. We now review some designs with only two periods, i.e., designs with $p = 2$. These designs are of substantial interest in clinical trials and have been studied among others, by Grizzle (1965), Hills and Armitage (1979), Armitage and Hills (1982) and Willan and Pater (1986).

Hedayat and Zhao (1990) gave an interesting connection between a crossover design with two periods and a block design. We present this result below, where we write $\mathfrak{C}_d$ to denote the information matrix for treatments for an arbitrary block design d under the usual additive linear model for block designs.

Theorem 1. *Let d be a design in $\Omega_{t,n,2}$ and let there be $b \leq t$ distinct treatments in the first period of d, these treatments being labeled as $1, 2, \ldots, b$. Then there exists a block design d_0 with t treatments and b blocks of sizes $\bar{r}_{d1}, \ldots, \bar{r}_{db}$, such that the treatment versus block incidence matrix of d_0 equals $\boldsymbol{Z}_d$, and the relationship*

$$\mathfrak{C}_{d_0} = 2\boldsymbol{C}_d, \tag{19}$$

holds, where $\boldsymbol{C}_d$ is as in (6.8). Conversely, from a block design with t treatments and $b(\leq t)$ blocks one can obtain a crossover design d in $\Omega_{t,n,2}$, with n equal to the total number of experimental units in the block design, such that (19) holds.

This connection is helpful in the study of optimality of two-period crossover designs as one can invoke well known results on optimality of block designs for this purpose. The following example illustrates Theorem 1.

Example 6. Let $d \in \Omega_{3,12,2}$ be as below:

$$d \equiv \begin{array}{cccccccccccc} 1 & 2 & 3 & 1 & 2 & 3 & 1 & 2 & 3 & 2 & 3 & 1 \\ 1 & 2 & 3 & 2 & 3 & 1 & 1 & 2 & 3 & 1 & 2 & 3 \end{array}.$$

This design has $\bar{r}_{d1} = \bar{r}_{d2} = \bar{r}_{d3} = 4$. Then the corresponding block design d_0 is given by the blocks

$$d_0 \equiv \begin{array}{ll} \text{Block I:} & 1, 1, 2, 3 \\ \text{Block II:} & 1, 2, 2, 3 \\ \text{Block III:} & 1, 2, 3, 3 \end{array}.$$

Conversely, d can be obtained from d_0, and it can be verified that for these designs, (19) holds.

Again, from (19), it is clear that a design $d \in \Omega_{t,n,2}$ is connected for direct effects if and only if the corresponding block design d_0 is connected. Because of this fact, it is easy to see that the contrasts among direct effects of treatments cannot be estimated from the design d_1 in Example 1. This is because the block design d_0 corresponding to d_1 has the following two blocks:

$$\text{Block I}: \quad (2,\ 2) \quad \text{and} \quad \text{Block II}: \quad (1,\ 1).$$

The block design with the above two blocks is clearly disconnected, implying that d_1 is disconnected too. However, if d_1 is modified to include identical pairs to give a design d^* as

$$d^* \equiv \begin{matrix} 1 & 2 & 1 & 2 \\ 1 & 2 & 2 & 1 \end{matrix},$$

then the corresponding block design has blocks

$$\text{Block I}: \quad (1,\ 2) \quad \text{and} \quad \text{Block II}: \quad (2,\ 1),$$

which is connected, leading to the connectedness of d^* for direct effects.

There is another aspect of two-period designs which makes it interesting and we elaborate on this now. In the context of crossover designs, since the same subject gives multiple responses, it is sometimes reasonable to deviate from the traditional model with uncorrelated errors and instead, consider a model under which the observations from the same subject are assumed to be correlated, these correlations being the same for all subjects, while those from different subjects remain uncorrelated. Thus, for $p = 2$, the model is the same as (3) with the exception that the dispersion matrix of the errors is now $\sigma^2\boldsymbol{\Sigma}$, where $\boldsymbol{\Sigma} = \boldsymbol{I}_n \otimes \boldsymbol{V}$ and $\boldsymbol{V} = \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}$, with ρ $(-1 < \rho < 1)$ representing the correlation coefficient between the observations arising from the same subject.

An interesting aspect of 2-period crossover designs is that the properties of these designs under a model with correlated errors can be studied easily. It turns out that for a design d with $p = 2$, the information matrix for the joint estimation of direct and carryover effects under a model with correlated errors as specified above is proportional to the joint information matrix under (3); see Lemma 1.3.1 in Bose and Dey (2009). Hence, for $p = 2$, the optimality properties of a design under the uncorrelated errors model (3) remain robust even if the errors are correlated as described above.

3.4 Two-treatment designs

Experiments with only *two treatments* are often used in practice; for example, in medical experiments one treatment may be a placebo or the standard drug while the other treatment could be a newly developed drug. The literature on two-treatment designs has been enriched by various authors, including Kershner and Federer (1981), Laska and Meisner (1985), Matthews (1987, 1990), Kunert (1991), Kushner (1997a), Carriere and Reinsel (1992), Carriere and Huang (2000) and Kunert and Stufken (2008). In this context, a class of designs called *dual balanced designs* are found to have good statistical properties.

With two treatments, labeled say 1 and 2, consider a treatment sequence of length p, every element of the sequence being either 1 or 2. For any such sequence, its dual is obtained by interchanging the positions of 1 and 2. Then a dual balanced design is defined as follows.

Definition 6. *A design which assigns an equal number of subjects to any treatment sequence and its dual is called a dual balanced design.*

Example 7. The following are examples of dual balanced designs.

$$d_9 \equiv \begin{array}{cc} 1 & 2 \\ 2 & 1 \\ 1 & 2 \\ 2 & 1 \end{array}, \quad d_{10} \equiv \begin{array}{cccc} 1 & 2 & 1 & 2 \\ 1 & 2 & 2 & 1 \\ 2 & 1 & 2 & 1 \\ 2 & 1 & 1 & 2 \end{array}, \quad d_{11} \equiv \begin{array}{cc} 1 & 2 \\ 1 & 2 \\ 1 & 2 \\ 2 & 1 \end{array}.$$

Note that though these designs are called dual balanced, they need not always be balanced in the sense of Definition 1. For example, d_9 *is* balanced, while d_{10} is strongly balanced and d_{11} is neither balanced nor strongly balanced in the sense of Definitions 1 and 2.

4 Constructions of some families of designs

In this section we give methods for construction for some selected classes of designs. To see why these methods lead to the designs as claimed, we refer the reader to the related references.

4.1 Balanced uniform designs

It is clear from Definition 1 (Section 6.3.1) and the definition of uniformity (Section 6.3) that $\Omega_{t,n,p}$ can contain a balanced uniform design only if t, n and p satisfy the following three conditions:
(i) $n = \mu_1 t$, for some integer $\mu_1 \geq 1$,
(ii) $p = \mu_2 t$, for some integer $\mu_2 \geq 1$,
(iii) $n(p-1) = \lambda_1 t(t-1)$, for some integer $\lambda_1 \geq 1$.
Case 1: t even. Williams (1949) gave a method for constructing a balanced uniform design $d \in \Omega_{t,t,t}$, where t is any *even* integer. Starting with the initial $t \times 1$ vector

$$\boldsymbol{a}_0 = \left(1, t, 2, t-1, \ldots, \frac{t}{2}-1, \frac{t}{2}+2, \frac{t}{2}, \frac{t}{2}+1\right)',$$

he obtained $t-1$ other vectors as $\boldsymbol{a}_u = \boldsymbol{a}_0 + (u, u, \ldots, u)'$, $1 \leq u \leq t-1$, where all entries in $\boldsymbol{a}_u$ are reduced modulo t and, every 0 in $\boldsymbol{a}_u$ is replaced by t. Then the $t \times t$ array

$$\boldsymbol{A}_t = [\boldsymbol{a}_0, \boldsymbol{a}_1, \ldots, \boldsymbol{a}_{t-1}]$$

is a balanced uniform design in $\Omega_{t,t,t}$. As usual, rows of $\boldsymbol{A}_t$ represent the t periods and the columns represent the t subjects. The design $\boldsymbol{A}_t$ is often called a *Williams square*.

Example 8. The following are two examples of Williams squares, or balanced uniform designs, in $\Omega_{t,t,t}$, one with $t = 4$ and $\boldsymbol{a}_0 = (1, 4, 2, 3)'$ and another with $t = 6$ and $\boldsymbol{a}_0 = (1, 6, 2, 5, 3, 4).'$

$$\begin{array}{cccc} 1 & 2 & 3 & 4 \\ 4 & 1 & 2 & 3 \\ 2 & 3 & 4 & 1 \\ 3 & 4 & 1 & 2 \end{array}, \qquad \begin{array}{cccccc} 1 & 2 & 3 & 4 & 5 & 6 \\ 6 & 1 & 2 & 3 & 4 & 5 \\ 2 & 3 & 4 & 5 & 6 & 1 \\ 5 & 6 & 1 & 2 & 3 & 4 \\ 3 & 4 & 5 & 6 & 1 & 2 \\ 4 & 5 & 6 & 1 & 2 & 3 \end{array}.$$

For $n = \mu_1 t$ and $p = t$, a balanced uniform design can be obtained by juxtaposing μ_1 copies of a Williams square in $\Omega_{t,t,t}$.

Case 2: t odd. Balanced uniform designs with *odd* t in $\Omega_{t,t,t}$ are known for only a few values of t, for instance, $t = 9, 15, 21, 27, 39, 55, 57$, while they do not exist for $t = 3, 5, 7$. Higham (1998) proved that a balanced uniform design exists in $\Omega_{t,t,t}$ when t is a composite number. The design for $t = 21$ is shown in Hedayat and Afsarinejad (1975) and designs for $t = 9, 15, 27$ are given in Hedayat and Afsarinejad (1978). The above mentioned papers may be consulted for more details and references.

However, when $n = 2t$, a balanced uniform design exists in $\Omega_{t,2t,t}$ for *all odd* t. Williams (1949) gave a construction starting with *two* initial vectors. Let

$$\begin{aligned} \boldsymbol{b}_0 &= \left(1, t, 2, t-1, \ldots, \frac{t+5}{2}, \frac{t-1}{2}, \frac{t+3}{2}, \frac{t+1}{2}\right)', \\ \boldsymbol{c}_0 &= \left(\frac{t+1}{2}, \frac{t+3}{2}, \frac{t-1}{2}, \frac{t+5}{2}, \ldots, t-1, 2, t, 1\right)'. \end{aligned}$$

Note that $\boldsymbol{c}_0$ is obtained by writing the entries of $\boldsymbol{b}_0$ in the reverse order. Now, for $1 \le u \le t-1$, let $\boldsymbol{b}_u = \boldsymbol{b}_0 + (u, \ldots, u)'$ and $\boldsymbol{c}_u = \boldsymbol{c}_0 + (u, \ldots, u)'$, where the elements of $\boldsymbol{b}_u$ and $\boldsymbol{c}_u$ are reduced modulo t and, thereafter, every 0 therein is replaced by t. Then a balanced uniform design in $\Omega_{t,2t,t}$ is given by the $t \times 2t$ array

$$\boldsymbol{B}_t = [\boldsymbol{b}_0\ \boldsymbol{b}_1 \cdots\ \boldsymbol{b}_{t-1}\ \boldsymbol{c}_0\ \boldsymbol{c}_1 \cdots\ \boldsymbol{c}_{t-1}].$$

The design d_2 with $t = 3$ in Example 1 is constructed via this method. A design for $t = 5$ is shown next.

Example 9. For $t = 5$, $\boldsymbol{b}_0 = (1, 5, 2, 4, 3)'$ and $\boldsymbol{c}_0 = (3, 4, 2, 5, 1)'$ which lead to the following balanced uniform design in $\Omega_{5,10,5}$.

$$\begin{array}{ccccc|ccccc} 1 & 2 & 3 & 4 & 5 & 3 & 4 & 5 & 1 & 2 \\ 5 & 1 & 2 & 3 & 4 & 4 & 5 & 1 & 2 & 3 \\ 2 & 3 & 4 & 5 & 1 & 2 & 3 & 4 & 5 & 1 \\ 4 & 5 & 1 & 2 & 3 & 5 & 1 & 2 & 3 & 4 \\ 3 & 4 & 5 & 1 & 2 & 1 & 2 & 3 & 4 & 5 \end{array}.$$

There are several simple modifications of the Williams squares that give designs with the same balance properties. For a review of such modifications, we refer the reader to Issac *et al.* (2001).

4.2 Strongly balanced uniform designs

From the definition of uniformity (Section 6.3.1) and Definition 2 one may check that a design $\Omega_{t,n,p}$ can contain a uniform, strongly balanced design only if the following conditions hold:
(i) $n = \mu_3 t^2$, for some integer $\mu_3 \geq 1$ and,
(ii) $p = \mu_2 t$, for some integer $\mu_2 \geq 2$.

Early examples of these designs with $t = 3, n = 18, p = 6$ and $t = 4, n = 16, p = 8$ were given by Quenouille (1953). Later, Berenblut (1964) and Patterson (1973) gave general methods of their construction in $\Omega_{t,n=t^2,p=2t}$. Cheng and Wu (1980) generalized the above family to give constructions for situations where t^2 divides n and p is an *even* multiple of t. The design d_3 shown in Example 2 is one such design. Starting with designs constructed by Cheng and Wu's method, one may obtain a strongly balanced uniform design in $\Omega_{t,n=\alpha t^2,p=2\beta t}$, where α, β are integers, by juxtaposing copies of this design. Sen and Mukerjee (1987) gave a construction of strongly balanced uniform designs for cases when t^2 divides n and p is an *odd* multiple of t. This, together with the construction of Cheng and Wu (1980) shows that the necessary conditions (i) and (ii) above are sufficient as well.

Using orthogonal arrays of strength *two*, Stufken (1996) gave a unified method of construction of these designs for general μ_2, which covers both the odd and even cases. We describe this construction below.

An orthogonal array, $\mathrm{OA}(n, p, t, 2)$ of strength two is an $n \times p$ array with entries from a set of $t \geq 2$ symbols, such that any $n \times 2$ subarray contains each ordered pair of symbols equally often as a row, precisely n/t^2 times. An $\mathrm{OA}(t^2, 3, t, 2)$ exists for all $t \geq 2$, and let such an array be denoted by $\boldsymbol{A}_0$, its entries being $1, 2, \ldots, t$. Let $\boldsymbol{B}_0$ be an orthogonal array $\mathrm{OA}(t^2, 2, t, 2)$, obtained from $\boldsymbol{A}_0$ by deleting its third column. For $1 \leq u \leq t-1$, let $\boldsymbol{A}_u$ be a $t^2 \times 3$ matrix obtained by adding u to each element of $\boldsymbol{A}_0$ and similarly, let $\boldsymbol{B}_u$ be a $t^2 \times 2$ matrix obtained by adding u to each element of $\boldsymbol{B}_0$, where the elements of $\boldsymbol{A}_u$ and $\boldsymbol{B}_u$ are reduced modulo t, and then every 0 therein is replaced by t.

Finally, let $\boldsymbol{A}$ and $\boldsymbol{B}$ be the $3t \times t^2$ and $2t \times t^2$ matrices defined as

$$\boldsymbol{A} = \left[\begin{array}{cccc} \boldsymbol{A}_0 & \boldsymbol{A}_1 & \cdots & \boldsymbol{A}_{t-1} \end{array} \right]', \quad \boldsymbol{B} = \left[\begin{array}{cccc} \boldsymbol{B}_0 & \boldsymbol{B}_1 & \cdots & \boldsymbol{B}_{t-1} \end{array} \right]'.$$

Since $\mu_2 \geq 2$, let $\mu_2 = 3\alpha + 2\beta$ for some nonnegative integers α, β. It can then be verified that the $\mu_2 t \times t^2$ array

$$[\boldsymbol{A}' \cdots \boldsymbol{A}' \; \boldsymbol{B}' \cdots \boldsymbol{B}']'$$

consisting of α copies of $\boldsymbol{A}$ and β copies of $\boldsymbol{B}$ is a strongly balanced uniform design in $\Omega_{t,t^2,p=\mu_2 t}$. Now juxtaposing μ_3 copies of this design, we get a strongly balanced uniform design in $\Omega_{t,n=\mu_3 t^2,p=\mu_2 t}$.

Example 10. Let $t = 3, n = 9, p = 6$. We start with $\boldsymbol{A}_0 \equiv \text{OA}(9, 3, 3, 2)$ as shown below in transposed form.

$$\boldsymbol{A}_0' \equiv \begin{bmatrix} 1 & 1 & 1 & 2 & 2 & 2 & 3 & 3 & 3 \\ 1 & 2 & 3 & 1 & 2 & 3 & 1 & 2 & 3 \\ 1 & 2 & 3 & 2 & 3 & 1 & 3 & 1 & 2 \end{bmatrix}.$$

Here $\mu_2 = 2$ and so we take $\alpha = 0, \beta = 1$. From $\boldsymbol{A}_0$ we obtain $\boldsymbol{B}_0$ and then $\boldsymbol{B}_1$ and $\boldsymbol{B}_2$, leading to the matrix $\boldsymbol{B} = (\boldsymbol{B}_0, \boldsymbol{B}_1, \boldsymbol{B}_2)'$ as indicated above. This $\boldsymbol{B}$ will be the design d_3 displayed in Example 2.

4.3 Patterson designs

We now describe methods of construction of some families of Patterson designs (see Definition 3). Such a family exists in particular when t is a prime or a prime power. Let $u_0 = 0, u_1 = 1, u_2 = x, u_3 = x^2, \ldots, u_{t-1} = x^{t-2}$ be the elements of $GF(t)$ (a *Galois field* of order t), where x is a primitive element. Details on Galois fields may be found e.g., in Lidl and Niederreiter (1986). For $1 \le i \le t-1$, define a $t \times t$ array $\boldsymbol{L}_i$ whose (α, β)th element equals $u_i u_\alpha + u_\beta$, $0 \le \alpha, \beta \le t-1$. Then $\boldsymbol{L}_1, \ldots, \boldsymbol{L}_{t-1}$ form a complete set of $(t-1)$ mutually orthogonal Latin squares of order t. Furthermore, $\boldsymbol{L}_{i+1}$ can be obtained by cyclically permuting the last $t-1$ rows of $\boldsymbol{L}_i$, $1 \le i \le t-2$. The $t \times t(t-1)$ array $\boldsymbol{L} = [\boldsymbol{L}_1 \; \boldsymbol{L}_2 \; \ldots \; \boldsymbol{L}_{t-1}]$ is a Patterson design in $\Omega_{t,t(t-1),t}$. On deleting any $t-p$ rows of $\boldsymbol{L}$, where $t > p \ge 3$, one obtains a Patterson design in $\Omega_{t,t(t-1),p}$. The design in Example 4 is obtained by this method, after deleting the last row of the array $\boldsymbol{L}$ for $t = 4$.

Patterson (1952) obtained several families of designs which require fewer subjects than the method described above. In particular, the following families of designs were obtained by Patterson (1952):
Family I: $t = 4m + 3,\ n = t(t-1)/2,\ p = 3,\ t$ a prime or a prime power;
Family II: $t = 4u + 3,\ n = 2t,\ p = (t+1)/2,\ t$ a prime.

Example 11. The following design is a member of Family I with $t = 11, n = 55, p = 3$.

1	2	3	4	5	6	7	8	9	10	11
2	3	4	5	6	7	8	9	10	11	1
4	5	6	7	8	9	10	11	1	2	3
1	2	3	4	5	6	7	8	9	10	11
5	6	7	8	9	10	11	1	2	3	4
2	3	4	5	6	7	8	9	10	11	1
1	2	3	4	5	6	7	8	9	10	11
6	7	8	9	10	11	1	2	3	4	5 .
5	6	7	8	9	10	11	1	2	3	4
1	2	3	4	5	6	7	8	9	10	11
10	11	1	2	3	4	5	6	7	8	9
6	7	8	9	10	11	1	2	3	4	5
1	2	3	4	5	6	7	8	9	10	11
4	5	6	7	8	9	10	11	1	2	3
10	11	1	2	3	4	5	6	7	8	9

5 Optimality under the traditional model

Hedayat and Afsarinejad (1978) initiated the study of optimality of crossover designs. Subsequently, the area of optimal crossover designs has been enriched by the contributions of a number of authors. Many of these results are with respect to the universal optimality criterion of Kiefer (1975). It is well known that universal optimality implies the more common criteria like A-, D- and E-optimality in the sense that a universally optimal design is also A-, D- and E-optimal.

Let $\mathcal{D}$ be a class of competing designs in a given context and let $\boldsymbol{A}_d$ denote the information matrix for a set of relevant parametric functions (e.g., contrasts among the direct or carryover effects in the setup of this paper) under a design $d \in \mathcal{D}$ and a given model. Then, a set of sufficient conditions for a design $d^* \in \mathcal{D}$ to be universally optimal over $\mathcal{D}$ is that (i) $\boldsymbol{A}_{d^*}$ is completely symmetric and (ii) $\mathrm{trace}(\boldsymbol{A}_{d^*}) \geq \mathrm{trace}(\boldsymbol{A}_d)$ for all $d \in \mathcal{D}$. In this section, we present a selection of results on optimal crossover designs. Throughout this section, we consider the model (3).

5.1 Balanced uniform designs

It is interesting to note how the optimality results on balanced uniform designs have been successively strengthened by various authors. The first result on optimal crossover designs was obtained by Hedayat and Afsarinejad (1978) who proved that a balanced uniform design (Definition 1) in $\Omega_{t,\mu_1 t,t}$ is universally optimal for the estimation of *both direct and carryover* effects over the class of all *uniform* designs in $\Omega_{t,\mu_1 t,t}$. This result was strengthened by Cheng and Wu (1980), who removed the restriction of uniformity on the competing designs, but even then, their results are valid only in some subclasses of $\Omega_{t,n,p}$, $t \geq 3$. For instance, they proved that a balanced uniform design is universally optimal for the estimation of *carryover effects* over the class of designs in which (i) $n = \mu_1 t, p = \mu_2 t$ for some integers μ_1, μ_2, (ii) no treatment is assigned to two consecutive periods on the same subject and (iii) each treatment is equally replicated in the first $p-1$ periods. If in particular, $\mu_2 = 1$ also holds (i.e., $p = t$), then restriction (iii) is not needed. For the *direct effects*, they showed that a balanced uniform design is universally optimal for the estimation of direct effects over the class of designs which are uniform on subjects and uniform on the last period. This result on direct effects by Cheng and Wu (1980) was further extended by Kunert (1984a) who removed all restrictions on the competing class and proved that if $t = n = p > 2$, then a balanced uniform design is universally optimal for the estimation of direct effects over $\Omega_{t,t,t}$ and, if $n = 2t, p = t,\ t \geq 6$, a balanced uniform design is universally optimal for direct effects over $\Omega_{t,2t,t}$.

A more general result was obtained by Hedayat and Yang (2003) who proved that for $n = \mu_1 t,\ t = p > 2$ and $n \leq t(t-1)/2$, a balanced uniform design is universally optimal for direct effects in $\Omega_{t,n,t}$. On recalling that balanced uniform designs have completely symmetric information matrices (see (15)), the above condition $n \leq t(t-1)/2$ is crucial in their result as this is needed to establish that a balanced uniform design maximizes the trace of the information matrix for direct effects among all designs in the competing class, thereby establishing its universal optimality. It may be noted that when this condition is not satisfied, universal optimality does not hold in general, though it is indeed true for $t = p = 3, n = 6$. Earlier, Street *et al.* (1990) had shown via a computer search that a balanced uniform design in $\Omega_{3,6,3}$ is A-optimal for direct effects; Hedayat and Yang (2004) extended this result to universal optimality. For larger values of t, they also showed that if $4 \leq p = t \leq 12$ and $n \leq t(t+2)/2$, then a balanced uniform design is universally optimal for the estimation of direct effects over $\Omega_{t,n,t}$.

5.2 Stufken and Patterson designs

When we depart from balanced uniform designs, and focus on designs with uniformity on periods only, several optimality results are again available. For example, the universal optimality of Stufken designs (see Definition 4) for direct effects in certain subclasses of $\Omega_{t,n,p}$, was established by Stufken (1991). Kushner (1998) extended these results to show that if $n/\{t(p-1)\}$ is an integer, then the Stufken designs are universally optimal for direct effects in the *entire* class $\Omega_{t,n,p}$. Hedayat and Yang (2004) improved Kushner's result to prove that if a Stufken design exists in $\Omega_{t,n,p}$ then it is universally optimal for direct effects over $\Omega_{t,n,p}$ irrespective of whether or not the above divisibility condition holds. By this result, a Stufken design, which exists for $t = p = 3, n = 36$, is universally optimal in $\Omega_{3,36,3}$ and thus it dominates the balanced uniform design in this class. Note that here the condition $n \leq t(t-1)/2$ in the result of Hedayat and Yang (2003) mentioned in the earlier subsection, is violated.

The optimality properties of Patterson designs (Definition 3) were studied by Shah *et al.* (2005) who showed that these designs are universally optimal for the estimation of *both direct and carryover* effects over the subclass of all connected designs in $\Omega_{t,n,p}$ in which no treatment precedes itself.

5.3 Strongly balanced designs

We now turn to strongly balanced designs. The study of optimality aspects of such designs was initiated by Cheng and Wu (1980). They proved a very general result which shows that a strongly balanced uniform design (Definition 2) is universally optimal for the estimation of *both direct and carryover* effects over the *entire class* $\Omega_{t,n,p}$. However, since such a design exists only if $t^2|n$ and $t|p$, these designs are quite large in size. By relaxing the condition of uniformity on subjects in the class of competing designs, Cheng and Wu (1980) obtained optimal designs which are smaller in size compared to strongly balanced uniform designs. They showed that a strongly balanced design which is uniform on periods and uniform on the subjects in the first $p-1$ periods is also universally optimal for *both direct and carryover effects* over the *entire* class, $\Omega_{t,n,p}$. The fact that direct and carryover effects become orthogonally estimable in a strongly balanced design and (17) are instrumental in proving the universal optimality over the *entire* class of designs.

5.4 Two-period designs

Hedayat and Zhao (1990) used the connection established between block designs and 2-period crossover designs in Theorem 1 to obtain optimal crossover designs starting from optimal block designs. It follows from Theorem 1 that if a block design d_0 is optimal in the class of all proper (equal block size) block designs with t treatments and $b \le t$ blocks, then the 2-period crossover design corresponding to d_0 is also universally optimal for direct effects, in the class of all 2-period designs in which b treatments appear in the first period equally often. Consider for instance Example 6. There, d_0 is a balanced block design and is universally optimal over the entire class of connected block designs with $t=3$ treatments and $b=3$ blocks each of size 4. Hence it follows that the corresponding crossover design d is universally optimal for the estimation of direct effects over the subclass of $\Omega_{3,12,2}$ which are uniform on the first period.

Hedayat and Zhao (1990) also gave a set of necessary and sufficient conditions for a 2-period crossover design with t treatments and n subjects to be universally optimal in the *entire* class $\Omega_{t,n,2}$. Their result is as follows.

Theorem 2. *Let $n \equiv 0 \pmod t$. Then a 2-period, t-treatment, n-subject design d^* is universally optimal for direct effects over $\Omega_{t,n,2}$ if and only if*
(a) $f_{d^*s} \equiv 0 \pmod t$, $1 \le s \le t$, where f_{d^*s} is the number of times treatment s appears in the first period of d^*, and
(b) $z_{d^*s's} = f_{d^*s}/t$, $1 \le s' \le t$, where $z_{d^*s's}$ is the number of subjects that receive treatment s in the first period and treatment s' in the second period of d^*.

Note that the number of distinct treatments in the first period of the design d^* in Theorem 2 may be any number $\in \{1, 2, \ldots, t\}$. Condition (a) of Theorem 2 merely demands that for $1 \le s \le t$, $f_{d^*s} = \mu_s t$, where $\mu_s \ge 0$ is an integer, subject to $\sum_{s=1}^{t} f_{d^*s} = n$. In particular, one can have an optimal 2-period design as given by Theorem 2 where the same treatment is used for every subject in the first period, e.g., the design d_{12} below.

Example 12. Using Theorem 2, it is easy to see that the designs d_{12} and d_{13} below are universally optimal for direct effects over $\Omega_{3,12,2}$ and $\Omega_{6,18,2}$, respectively.

$$d_{12} \equiv \begin{array}{cccccccccccc} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ 1 & 2 & 3 & 1 & 2 & 3 & 1 & 2 & 3 & 1 & 2 & 3 \end{array},$$

$$d_{13} \equiv \begin{array}{cccccccccccccccccc} 1 & 1 & 1 & 1 & 1 & 1 & 2 & 2 & 2 & 2 & 2 & 2 & 3 & 3 & 3 & 3 & 3 & 3 \\ 1 & 2 & 3 & 4 & 5 & 6 & 1 & 2 & 3 & 4 & 5 & 6 & 1 & 2 & 3 & 4 & 5 & 6 \end{array}.$$

For the case when n is *not a multiple* of t, Hedayat and Zhao (1990) considered designs with only a single treatment in the first period and all t treatments allocated as equally as possible in the second period. Using the correspondence with block designs they showed that such crossover designs are A-optimal for direct effects over $\Omega_{t,n,2}$.

5.5 Two-treatment designs

Matthews (1990) used the approach of approximate design theory (see Kiefer, 1959) to give an easily implementable method for producing optimal dual-balanced designs (Definition 6) with two treatments. He showed that for even p, any design which is optimal for direct effects is also optimal for carryover effects, while for odd p, any design which is optimal for carryover effects is also optimal for direct effects. For example, he showed that the designs d_9 and d_{10} in Example 7 are universally optimal designs for both direct and carryover effects in $\Omega_{2,2,4}$ and $\Omega_{2,4,4}$, respectively. The designs which he obtained as optimal for *both* direct and carryover effects are identical with the strongly balanced designs, shown to be optimal by Cheng and Wu (1980) and discussed earlier in this section. However, his designs which are optimal *only* for direct effects or *only* for carryover effects need not be uniform over subjects nor uniform over subjects in the first $p-1$ periods, and so are not covered by the results of Cheng and Wu (1980).

6 Some other models and optimal designs

Now we consider some models other than the traditional one, which have been studied in the literature. Recall that the traditional model given in (3) makes some implicit assumptions about the carryover effects. For example, it assumes that only first-order carryover effects are present, the carryover effect of a treatment in a period always remains the same no matter which treatment is producing the direct effect in this period, the carryover effect of a treatment does not depend on its direct effect, and so on.

However, in practice, such assumptions need not hold in all situations and so the validity of the model (3) has been questioned, especially in medical applications; see e.g., Senn (1992) and Matthews (1994). For examples of situations in non-medical applications where the simplistic model (3) may not be appropriate, see Kempton *et al.* (2001). For such situations, it becomes necessary to model the carryover effects differently and several authors have studied the problem of finding good designs under such modified models.

Moreover, the traditional model (3) also assumes that the errors are uncorrelated, an assumption that may not be met in typical crossover trials where it might be more realistic to expect that the observations arising from the same subject over time are correlated. In view of this, models with correlated errors have been studied too. In the following subsections, we review some of these models and describe a selection of optimality results under these models.

6.1 Circular model

Recall that in (3), it was assumed that there are no carryover effects in the first period. Models with carryover effects in the first period too have been studied by some authors. For this, they proposed the inclusion of a pre-period or baseline period ('0'th period) when each subject receives the same treatment as the one allocated to it in the pth period. Even though no observation is taken during this pre-period, the treatments applied in this period cause a carryover effect to be present in the first period, thereby creating a 'circular' pattern of carryovers across the p periods. A model for studying these experiments is termed a 'circular' model, its only change from (3) being that instead of $\rho_{d(0,j)} = 0$ as in (3), it now has $\rho_{d(0,j)} = \rho_{d(p,j)}, 1 \le j \le n$. Consequently, the matrix $\boldsymbol{F}_{dj}$ defined in (2) in the context of model (3) now takes the form

$$\boldsymbol{F}_{dj} = \begin{pmatrix} \mathbf{0}'_{p-1} & 1 \\ \boldsymbol{I}_{p-1} & \mathbf{0}_{p-1} \end{pmatrix} \boldsymbol{T}_{dj}, \ \ 1 \le j \le n.$$

This leads to a considerable simplification in the analysis, but this simplicity comes at the expense of having a pre-period of experimentation. This model has been sporadically used in the literature, the traditional 'non-circular' model being far more popular. For some results on optimality under the circular model, one may refer to Magda (1980) and Kunert (1984b).

6.2 Model with self and mixed carryovers

In the models described so far, when a treatment is applied to a subject in a period, the carryover effect of this treatment in the following period is always the same, irrespective of which treatment follows it. However, in some crossover trials, for example, in medical applications, such a constant form of the carryover may not be realistic and the carryover effect of a treatment may depend on whether it is being followed by itself, or by a different treatment. For such situations, Afsarinejad and Hedayat (2002) introduced the *self and mixed carryover* model where they assumed that the carryover effect of a treatment is of two types: if a treatment is followed by itself on a subject, then the carryover effect of the former treatment is called *self* carryover effect, while if it is followed by a different treatment, then it is called *mixed* carryover effect. They studied only 2-period designs under this model while a study of designs in $\Omega_{t,n,p}$ was developed by Kunert and Stufken (2002). More recently, Kunert and Stufken (2008) studied the optimality of two-treatment designs under a model with self and mixed carryover effects. The model with self and mixed carryovers is as follows:

$$Y_{ij} \quad = \quad \begin{cases} \alpha_i + \beta_j + \tau_{d(i,j)} + \nu_{d(i-1,j)} + \epsilon_{ij}, & \text{if } d(i,j) \neq d(i-1,j), \\ \alpha_i + \beta_j + \tau_{d(i,j)} + \chi_{d(i-1,j)} + \epsilon_{ij}, & \text{if } d(i,j) = d(i-1,j), \end{cases} ,\tag{20}$$

where $\chi_{d(i-1,j)}$ is the self carryover effect and $\nu_{d(i-1,j)}$ is the mixed carryover effect of treatment $d(i-1,j)$, $\nu_{d(0,j)} = \chi_{d(0,j)} = 0$, $1 \leq i \leq p$, $1 \leq j \leq n$, and all other terms in (20) are as in (1). Analogous to (3) and remembering that $d(i,j) \in \{1, \ldots, t\}$, the model in (20) can equivalently be written as

$$\boldsymbol{Y}_d = \boldsymbol{P\alpha} + \boldsymbol{U\beta} + \boldsymbol{T}_d\boldsymbol{\tau} + \boldsymbol{G}_d\boldsymbol{\nu} + \boldsymbol{S}_d\boldsymbol{\chi} + \boldsymbol{\epsilon}, \tag{21}$$

where $\boldsymbol{\chi} = (\chi_1, \ldots, \chi_t)'$, $\boldsymbol{\nu} = (\nu_1, \ldots, \nu_t)'$, and $\boldsymbol{G}_d$ and $\boldsymbol{S}_d$ are the design matrices for the mixed carryover and self carryover effects, respectively, all other terms in (21) being as in (3). Model (20) is presented here in the same form as was considered by Hedayat and Afsarinejad (2002). This model remains unaffected if, as in (1), a general mean term is included in it. This is because the column space of $\boldsymbol{P}$ or $\boldsymbol{U}$ includes the vector $\mathbf{1}_{np}$.

For the simpler case $p = 2$, Afsarinejad and Hedayat (2002) obtained optimal 2-period designs under (21) by invoking the connection between a block design and a 2-period crossover design as given in Theorem 1. They proved that a symmetric balanced incomplete block (BIB) design with t treatments and block size k can be used to obtain a design which is optimal for direct effects under (21) over the subclass of designs in $\Omega_{t,tk,2}$ which are uniform on the first period.

The case $p > 2$ for model (21) was studied by Kunert and Stufken (2002). To identify the optimal design in this class, they first found an upper bound on the information matrix for direct effects under (21) (in the Loewner sense) and then showed that this bound is attained by a totally balanced design (see Definition 5). Next, they maximized the trace of the upper bound and showed that a totally balanced design again attains this maximum. Thus, they established the following result.

Theorem 3. *For $t \geq 3$ and $3 \leq p \leq 2t$, if a totally balanced design $d^* \in \Omega_{t,n,p}$ exists, then d^* is universally optimal for the estimation of direct effects over $\Omega_{t,n,p}$ under (21).*

By the above theorem, the design shown in Example 5 is universally optimal for direct effects over $\Omega_{3,6,4}$ under (21).

6.3 Models with direct-versus-carryover interactions

In the earlier model, the carryover effect of a treatment was only of two types, the mixed carryover effect being the same no matter which treatment followed it. One can extend this idea to postulate a model where the treatments allocated to the same subject in two successive periods may have an interaction effect, in addition to the usual direct and carryover effects. Such a model was proposed by Sen and Mukerjee (1987) and is given by

$$\begin{aligned} Y_{1j} &= \mu + \alpha_1 + \beta_j + \tau_{d(1,j)} + \epsilon_{1j},\ 1 \leq j \leq n \\ Y_{ij} &= \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \rho_{d(i-1,j)} + \gamma_{d(i,j),d(i-1,j)} + \epsilon_{ij}, \\ &\quad 2 \leq i \leq p,\ 1 \leq j \leq n, \end{aligned} \tag{22}$$

where $\gamma_{d(i,j),d(i-1,j)}$ is the interaction effect between treatments $d(i,j)$ and $d(i-1,j)$, $d(i,j) \in \{1,\ldots,t\}$, and all other terms are as in (1).

Sen and Mukerjee (1987) showed that strongly balanced uniform designs are universally optimal for *direct* effects under the non-additive model (22). However, this result does not have an exact counterpart for the estimation of carryover effects. Sen and Mukerjee (1987) proved that a strongly balanced uniform design satisfying certain extra combinatorial conditions is universally optimal for estimation of carryover effects under the model (22).

Further results on optimal crossover designs under (22) were obtained recently by Park *et al.* (2011). They considered a particular class of strongly balanced designs with $n = t^2$ units which are uniform on the periods and obtained a lower bound for the A-efficiency of the designs for estimating the direct effects. They then showed that such designs are highly efficient for any number of periods p, $2 \leq p \leq 2t$.

6.4 Model with carryover proportional to direct effect

In some crossover experiments, it is believed that the carryover effect of a treatment is proportional to its direct effect, thus requiring yet another modification of the traditional model. The constant of proportionality may be either positive or negative, but it is generally unknown. Cross (1973) gave an example of such a situation where subjects were asked to rate the loudness levels of different sound stimuli and it was found that subjects generally gave a higher rating to a stimulus when it was preceded by a loud sound and gave a lower rating to the same sound when it was preceded by a soft sound. Thus, here the constant of proportionality is positive. Schifferstein and Oudejans (1996) described another experiment where subjects were asked to rate the saltiness of several saline solutions. It was observed that the subjects rated a solution to be less salty if it was immediately preceded by a solution with high salt concentration while they rated the same solution to be more salty when preceded by one with low salt concentration. Here, the constant of proportionality is negative.

The model where carryover effects are assumed to be proportional to direct effects is given by

$$Y_{ij} = \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \gamma\tau_{d(i-1,j)} + \epsilon_{ij},\ \ 1 \leq i \leq p,\ \ 1 \leq j \leq n, \tag{23}$$

where γ is the constant of proportionality and all other terms are as in (1). We also assume that $t \geq 3$, because for $t = 2$, the model reduces to (1).

Even though this model has fewer parameters than (1), it is technically much harder to analyze as it is nonlinear in $\boldsymbol{\tau}$ and γ, both being unknown. In order to linearize (23), Kempton *et al.* (2001) used a Taylor series expansion about $\boldsymbol{\tau}_0$ and γ_0, the true values of $\boldsymbol{\tau}$ and γ, respectively. Then the information matrix for direct effects can be obtained under the linearized model. However, this information matrix now depends on the unknowns $\boldsymbol{\tau}_0$ and γ_0. Bailey and Kunert (2006) and Bose and Stufken (2007) also studied this model and we refer to them for expressions of the information matrices as obtained by them.

To overcome the aforesaid difficulty, Kempton *et al.* (2001) considered the distribution of possible vales of $\boldsymbol{\tau}_0$ and studied the performance of a design based on (a) the $\bar{A}$-criterion, which is the averaged version of the usual A-criterion, the average being taken over a multivariate normal distribution of $\boldsymbol{\tau}_0$ with zero mean vector and dispersion matrix $\boldsymbol{I}_t - t^{-1}\boldsymbol{J}_t$, and (b) the IA-criterion, where the A-criterion is averaged over both $\boldsymbol{\tau}_0$ and γ_0, with $\boldsymbol{\tau}_0$ distributed as in (a), γ_0 having the uniform distribution on [-1,1], $\boldsymbol{\tau}_0$ and γ_0 being independent. Note that the A-criterion is a local optimality criterion as it depends on γ_0. They proved the following results.
(i) Let $d \in \Omega_{t,n,p}$ where $n = \mu_1 t, \mu_1 \geq 1, p = t$, be a balanced uniform design. Then d is $\bar{A}$-optimal for the estimation of direct effects over the class of all uniform designs in $\Omega_{t,n,p}$ for all γ_0.
(ii) Let $d \in \Omega_{t,n,p}$ where $n = \mu_1 t, \mu_1 \geq 1, p = t+1$, be a strongly balanced design which is uniform on periods and uniform on subjects in the first $p-1$ periods. Then d is IA-optimal for the estimation of direct effects over $\Omega_{t,n,p}$.

Additional optimality results under (23) were obtained by Bailey and Kunert (2006). Among other things, they showed that if d^* is a totally balanced design with $t \geq p \geq 3$ or $t \geq 3, p = 2$, then for all $\gamma_0 \in [-1,1]$, d^* is $\bar{A}$-optimal for direct effects over all designs in $\Omega_{t,n,p}$ which do not assign the same treatment to successive periods in any subject.

Bose and Stufken (2007) obtained optimal designs under the model (23) when γ is *known* and not necessarily restricted to the interval $[-1,1]$. Under this assumption, the model (23) becomes linear and the more stringent universal optimality criterion can be used for obtaining optimal designs for given γ. While we refer the reader to the original source for details, we give below some examples of universally optimal designs under (23).

Example 13. Let $t = 3 = n = p$. The following designs are universally optimal for direct effects over $\Omega_{3,3,3}$ for any γ in the intervals $(0.52, 11.48)$, $(-4.73, -1.27)$ and $(-1.27, 0.52)$, respectively.

$$\begin{array}{ccc} 1 & 2 & 3 \\ 2 & 3 & 1 \\ 2 & 3 & 1 \end{array}, \quad \begin{array}{ccc} 1 & 2 & 3 \\ 2 & 3 & 1 \\ 1 & 2 & 3 \end{array}, \quad \begin{array}{ccc} 1 & 2 & 3 \\ 2 & 3 & 1 \\ 3 & 1 & 2 \end{array}.$$

6.5 Mixed effects models and models with correlated errors

Several authors considered models with random subject effects. This leads to a mixed effects version of model (1). With $p = 2$ periods, Carriere and Reinsel (1993) considered the situation where the t^2 possible treatment sequences are assigned to the subjects at random, the lth sequence being assigned to n_l subjects, $1 \leq l \leq t^2$. Accordingly, they modified model (1) to the following form:

$$Y_{ijl} = \mu + \alpha_i + \tau_{d(i,l)} + \rho_{d(i-1,l)} + \beta_{jl} + \epsilon_{ijl}, \tag{24}$$

where $d(i,l)$ is the treatment in the period i in the sequence l, Y_{ijl} is the response obtained in period i from the jth subject assigned to the sequence l, β_{jl} is the random subject effect of the jth subject assigned to sequence l, and μ, α_i, τ_s, ρ_s are as in model (1). The random subject effects and the errors ϵ_{ijl} are assumed to be mutually uncorrelated random variables with means zero and variances σ_β^2 and σ^2, respectively, $1 \leq i \leq 2,\ 1 \leq j \leq n_l,\ 1 \leq l \leq t^2$. Thus, (24) is a mixed effects model.

Then for any $d \in \Omega_{t,n,2}$, the information matrix for the direct effects, $\boldsymbol{C}_d$, under the model (24) is given by

$$\sigma^2 \boldsymbol{C}_d = (1+\nu)^{-1}\{\boldsymbol{R}_d - \nu^2 \bar{\boldsymbol{R}}_d - n^{-1}(1-\nu^2)\bar{\boldsymbol{r}}_d \bar{\boldsymbol{r}}_d' - \boldsymbol{Z}_d \bar{\boldsymbol{R}}_d^- \boldsymbol{Z}_d'\}, \tag{25}$$

where $\nu = \sigma_\beta^2/(\sigma^2 + \sigma_\beta^2)$ and $\boldsymbol{R}_d, \bar{\boldsymbol{R}}_d, \bar{\boldsymbol{r}}_d$ and $\boldsymbol{Z}_d$ are as defined in Section 6.2.2. Using (25), Carriere and Reinsel (1993) proved, among other things, that a strongly balanced 2-period design which is uniform on periods is universally optimal for direct effects over $\Omega_{t,n,2}$.

A mixed effects model for general $p(\geq 2)$ was studied by Mukhopadhyay and Saha (1983), who assumed that the β_j's in model (1) are mutually uncorrelated random variables with means zero and constant variances; these being also uncorrelated with the error variable. Under this mixed effects model, they studied the optimality of balanced and strongly balanced uniform designs, when the variances are known. This mixed effects model has been considered more recently by Hedayat *et al.* (2006) who obtained optimal and efficient crossover designs under such a model.

As has been mentioned earlier, in the context of crossover designs, the assumption of independent errors may not be realistic in some situations and a model with *correlated errors* may seem more appealing. To incorporate the correlations among observations within subjects, we may modify the traditional model (3) to

$$\boldsymbol{Y}_d = X_d\boldsymbol{\theta} + \boldsymbol{\epsilon},\ E(\boldsymbol{\epsilon}) = \boldsymbol{0},\ D(\boldsymbol{\epsilon}) = \boldsymbol{I}_n \otimes \boldsymbol{V}, \tag{26}$$

where $\boldsymbol{V}$ is a positive definite matrix of order p, representing the dispersion matrix of the errors corresponding to observations from the same subject and all other terms are as in (3). So, now the responses from different subjects are uncorrelated while those from the same subject can be correlated, these correlations being the same for all subjects. We may take various forms of $\boldsymbol{V}$ to reflect the actual error structure in different situations; for $\boldsymbol{V} = \boldsymbol{I}_p$ we are back to the traditional model. After some algebra it can be seen that the information matrix for direct effects under model (26) for a design d is given by

$$\boldsymbol{C}_d = \boldsymbol{T}_d'(\boldsymbol{I}_n \otimes \boldsymbol{V}^{-1/2})P^{\perp}\{(\boldsymbol{I}_n \otimes V^{-1/2})[\boldsymbol{P}\,\boldsymbol{U}\,\boldsymbol{F}_d]\}(\boldsymbol{I}_n \otimes \boldsymbol{V}^{-1/2})\boldsymbol{T}_d. \quad (27)$$

As in Section 3.3, for the special case $p = 2$, the problem of finding an optimal design under a correlated model with $\boldsymbol{V} = (1-\rho)\boldsymbol{I} + \rho\boldsymbol{J}$ and given ρ is equivalent to that of finding an optimal design under (3), where ρ is the correlation coefficient between a pair of observations from the same subject. For $p > 2$, finding optimal/efficient designs under the model (26) becomes simplified for the particular case $t = 2$. In this case, using the approximate theory approach, Kushner (1997a) gave a set of necessary and sufficient conditions for a dual balanced design to be universally optimal for direct effects. He also gave an expression for computing the efficiency of a dual balanced design for direct effects. Some authors have assumed that the errors within each subject follow a stationary first order autoregressive process. This reflects the belief that the correlation between the observations from different periods on the same subject diminish with time. So, $\boldsymbol{V}$ is of the form

$$\boldsymbol{V} = \begin{pmatrix} 1 & \rho & \rho^2 & \dots & \rho^{p-1} \\ \rho & 1 & \rho & \dots & \rho^{p-2} \\ \rho^2 & \rho & 1 & \dots & \rho^{p-3} \\ \dots & \dots & \dots & \dots & \dots \\ \rho^{p-1} & \dots & \rho^2 & \rho & 1 \end{pmatrix}, \quad (28)$$

or a multiple of this. For model (26) with such a $\boldsymbol{V}$, several authors (see e.g., Matthews (1987), Kunert (1991) and Kushner (1997a)) have studied the problem of obtaining efficient or optimal designs, mainly using the approximate theory.

For example, if we consider the following two pairs of dual sequences

$$\begin{array}{cccc} 1 & 2 & 1 & 2 \\ 1 & 2 & 2 & 1 \\ 2 & 1 & 2 & 1 \end{array},$$

then, a design which allocates a proportion of $\rho/(3\rho-1)$ subjects to each of the first two sequences and a proportion of $(\rho-1)/\{2(3\rho-1)\}$ to each of the last two sequences, is universally optimal for direct effects for all $\rho \in (-1, 0]$. Similarly, if we consider the following two pairs of dual sequences $(1,2,1)', (2,1,2)', (1,2,2)', (2,1,1)'$ then, a design which allocates a proportion of $\rho^2/(3+\rho)^2$ subjects to each of the first two sequences and a proportion of $(6\rho - \rho^2 + 9)/\{2(3+\rho^2)\}$ to each of the last two sequences, is optimal for direct effects for all $\rho \in (0, \rho_1)$, where $\rho_1 \approx 0.464$ (Matthews, 1987). In practice, however, ρ is unknown. Taking cognizance of this fact, Matthews (1987) showed that if we simply consider the four sequences given above and allocate each to one subject, then the resulting design in $\Omega_{2,4,3}$ has an efficiency of at least 90%

when $-0.8 \leq \rho \leq 0.8$. Thus for a large range of possible ρ values, this dual balanced design is efficient, even when errors are correlated. He also gave tables of efficiencies of several dual balanced designs with three and four periods and, for several values of ρ. These tables can be used to choose an efficient design for experimentation in situations where the parameter combinations are such that an optimal design is not available. Kunert (1991) too identified efficient designs and gave a method for constructing such efficient designs for any given value of ρ and p. Again, these efficient designs are dual balanced designs.

For arbitrary t and p, Kushner (1997b, 1998) gave a general approximate theory approach for identifying optimal designs under the model (26). Kunert (1985), Gill (1992), Donev (1998), among others, studied optimality under the exact theory approach and under various assumptions. Martin and Eccleston (1998) studied variance balanced crossover designs which allow all elementary contrasts of direct effects to be estimated with a constant variance and also ensure the same for all elementary contrasts of carryover effects under the model (26). They showed that such a design in $\Omega_{t,n,p}$ can be constructed from an orthogonal array of type I of strength two. Recall that a $u \times v$ matrix having entries from a set of $t \geq 2$ symbols is called a type I orthogonal array of strength two, if in any $2 \times v$ subarray, all $t(t-1)$ ordered 2-tuples without repetition occur equally often. A type I orthogonal array of strength two will be denoted by $OA_I(v, u, t, 2)$ and an example is given below.

Example 14. A type I orthogonal array $OA_I(6, 3, 3, 2)$ is as follows.

$$\begin{array}{cccccc} 0 & 1 & 2 & 0 & 1 & 2 \\ 1 & 2 & 0 & 2 & 0 & 1 \\ 2 & 0 & 1 & 1 & 2 & 0 \end{array}.$$

Kunert and Martin (2000) obtained a general result on the optimality of designs given by an $OA_I(n, p, t, 2)$ under model (26). Their result is as follows.

Theorem 4. *For $t \geq p > 2$, let $d^* \in \Omega_{t,n,p}$ be a crossover design given by a type I orthogonal array, $OA_I(n, p, t, 2)$, with rows of the array representing the periods and the columns representing the subjects of d^*. Then under (26) where $\boldsymbol{V}$ is any known positive definite matrix, d^* is universally optimal for the estimation of direct effects over the class of designs which are binary over subjects.*

Kunert and Martin (2000) also showed that these designs are quite efficient even over the general class. Moreover, these designs often require fewer subjects than that required by the optimum design obtained through an approximate theory approach for the same number of treatments and periods.

Hedayat and Yan (2008) extended the self and mixed carryover model (21) to one with correlated errors as in model (26). They considered two forms of $\boldsymbol{V}$, one where the errors within each subject follow a stationary first order autoregressive process, as in (28) and another, where they follow a stationary first order moving average process. In the second case,

$$\boldsymbol{V} = \boldsymbol{I}_p + \rho \boldsymbol{W}, \quad \rho \in (-1/2, 1/2), \tag{29}$$

with $\boldsymbol{W} = ((w_{ij})), w_{ij} = 1$ if $|i-j| = 1$, and $= 0$ otherwise, $1 \le i, j \le p$. They studied the performance of the designs in $\Omega_{t,n,p}$ given by an $OA_I(n, p, t, 2)$ and proved the following theorem.

Theorem 5. *For $p = 3$ and $t \ge 3$, let $d^* \in \Omega_{t,n,3}$ be a design given by a type I orthogonal array, $OA_I(n, 3, t, 2)$. Then d^* is universally optimal for direct effects over $\Omega_{t,n,3}$ under a model with self and mixed carryover effects and with dispersion structure of errors within each subject given by either*
(a) $\boldsymbol{V}$ as in (28) and any $\rho \in (-1, 1)$,or
(b) $\boldsymbol{V}$ as in (29) and any $\rho \in (-1/2, 1/2)$.

Example 15. The array given in Example 14 may be looked upon as a design in $\Omega_{3,6,3}$. By Theorem 5, this design is universally optimal for direct effects in $\Omega_{3,6,3}$ under the model (6.26) with correlated errors, the error structure being given by either (28) or (29) and the correlations as specified in (a) and (b) above.

7 Some other developments

7.1 Crossover trials for comparing treatments versus control

A problem that arises often in practice concerns the evaluation of the performance of a number of *test* treatments vis-a-vis a standard treatment, called *control*. The test treatments for instance, could be a number of new drugs, whose efficacy has to be evaluated relative to an established drug, which acts as the control treatment. For direct effects, the parametric function of interest in the present context is the contrast vector

$$\begin{pmatrix} \tau_0 - \tau_1 \\ \cdots \\ \tau_0 - \tau_t \end{pmatrix} = \begin{pmatrix} 1 & -1 & 0 & \cdots & 0 \\ 1 & 0 & -1 & \cdots & 0 \\ \vdots & & & & \\ 1 & 0 & 0 & \cdots & -1 \end{pmatrix} \boldsymbol{\tau} = \boldsymbol{B\tau} \text{ (say)},$$

where τ_0 is the direct effect of the control treatment and for $1 \le i \le t$, τ_i is the direct effect of the ith test treatment. The contrasts of interest for carryover effects can be defined similarly. Let $\Omega_{t+1,n,p}$ be the class of all crossover designs involving t test treatments and a control. For a design $d \in \Omega_{t+1,n,p}$, if $\mathfrak{I}_d$ is the information matrix for $\boldsymbol{B\tau}$ under the model (3), then it can be shown that

$$\mathfrak{I}_d = \bar{\boldsymbol{I}}' \boldsymbol{C}_d \bar{\boldsymbol{I}},$$

where $\bar{\boldsymbol{I}} = (\boldsymbol{0}_t, \boldsymbol{I}_t)'$ and $\boldsymbol{C}_d$ is as given by (8) under a design involving $t+1$ treatments.

For the test-control experiments, the A- and MV-optimality (see Chapter 3) criteria seem to be natural and are frequently used. A design $d^* \in \Omega_{t+1,n,p}$ is A-optimal for $\boldsymbol{B\tau}$ if it minimizes trace$(\mathfrak{I}_d^{-1})$ over $\Omega_{t+1,n,p}$ and, is MV-optimal if it minimizes $\{\max \mathrm{Var}(\hat{\tau}_0 - \hat{\tau}_i) : 1 \leq i \leq t\}$, where for $1 \leq i \leq t$, $\hat{\tau}_0 - \hat{\tau}_i$ is the best linear unbiased estimator of $\tau_0 - \tau_i$. The problem of finding A- and MV-optimal crossover designs has been addressed by several authors and we describe below some of their results.

Majumdar (1988) showed that if $t = c^2$ for some positive integer c and $d_0 \in \Omega_{c^2+c,n,p}$ is a strongly balanced uniform crossover design, then a design d^* obtained from d_0 by replacing each of the treatment labels $c^2+1, c^2+2, \ldots, c^2+c$, by the control treatment label 0, keeping everything else unchanged, is an A- and MV-optimal design for direct effects for comparing c^2 test treatments with a control, under the model (3). Following the approach of Majumdar (1988), Ting (2002) also obtained additional optimal/efficient crossover design for comparing several test treatments with a control. Hedayat and Zhao (1990) considered 2-period designs for the problem and starting from designs as given by Theorem 2, they obtained A- and MV-optimal designs when the number of test treatments is of the form c^2. Following Hedayat and Zhao (1990) for example, the design in Example 16 below with 4 test treatments and a control is A- and MV-optimal for direct effects over $\Omega_{4+1,18,2}$, where the control treatment is labeled 0. This design is obtained from design d_{13} in Example 12 by replacing the treatment labels 5 and 6 by the control treatment label 0, keeping everything else unchanged.

Example 16.

$$\begin{array}{cccccccccccccccccc} 1 & 1 & 1 & 1 & 1 & 1 & 2 & 2 & 2 & 2 & 2 & 2 & 3 & 3 & 3 & 3 & 3 & 3 \\ 1 & 2 & 3 & 4 & 0 & 0 & 1 & 2 & 3 & 4 & 0 & 0 & 1 & 2 & 3 & 4 & 0 & 0 \end{array}.$$

For some other results on 2-period designs for comparing test treatments with a control, see Koch *et al.* (1989) and Hedayat and Zhao (1990).

The problem of finding optimal designs when $3 \leq p \leq t + 1$, has been addressed by Hedayat and Yang (2005, 2006), Yang and Park (2007) and Yang and Stufken (2008). Hedayat and Yang (2005) defined a class of designs called *totally balanced test-control incomplete crossover designs* and showed that if such a design satisfies a certain additional condition, then it is A- and MV-optimal over the subclass of designs for which (a) the control treatment appears equally often in the p periods and (b) no treatment precedes itself. Hedayat and Yang (2005) also gave construction procedures of these optimal designs. Two such designs are given in the next example.

Example 17. Suppose $t = 4$ test treatments are to be compared with a control. Then, the following design, obtained on replacing the treatment symbol 5 by the control treatment label 0 in the uniform design shown in Example 9 is A- and MV-optimal over the subclass of $\Omega_{4+1,10,5}$ satisfying (a) and (b) above:

$$\begin{array}{cccccccccc}
1 & 2 & 3 & 4 & 0 & 3 & 4 & 0 & 1 & 2 \\
0 & 1 & 2 & 3 & 4 & 4 & 0 & 1 & 2 & 3 \\
2 & 3 & 4 & 0 & 1 & 2 & 3 & 4 & 0 & 1 \\
4 & 0 & 1 & 2 & 3 & 0 & 1 & 2 & 3 & 4 \\
3 & 4 & 0 & 1 & 2 & 1 & 2 & 3 & 4 & 0
\end{array}.$$

Example 18. Suppose $t = 3$ test treatments are to be compared with a control. Then, the following design is is A- and MV-optimal over the subclass of $\Omega_{3+1,10,5}$ satisfying (a) and (b) above:

$$\begin{array}{ccccccccc}
0 & 0 & 0 & 2 & 3 & 1 & 2 & 3 & 1 \\
1 & 2 & 3 & 0 & 0 & 0 & 1 & 2 & 3 \\
2 & 3 & 1 & 1 & 2 & 3 & 0 & 0 & 0
\end{array}$$

For some more results on optimal crossover designs for test-control comparisons, see Hedayat and Yang (2005, 2006). Yang and Park (2007) obtained designs which are optimal or efficient over a wider class of competing designs, but their results are only for 3-period designs. Yang and Stufken (2008) obtained further efficient and optimal crossover designs under a wide variety of models including (3), (20) and some variants of these. They also gave two algorithms for generating highly efficient designs under several models.

Extending the results of Hedayat and Yang (2005) to the case of random subject effects, Yan and Locke (2010) showed that under the model (3), totally balanced test-control designs with $p = 3, 4, 5$ periods are highly efficient in the class of designs in which the control treatment appears equally often in all periods and no treatment is immediately preceded by itself.

Before concluding this section, we comment on the replication numbers of the control vis-a-vis test treatments in the optimal designs studied here. Commonly, under the absence of carryover effects, optimal designs for control versus test treatments have the control replicated more often than the test treatments. However, this is not necessarily true for crossover designs. For instance, in Example 16 with only two periods, the overall replication of the control is less than that of each test treatment but in the second period the control is replicated twice as many times as each test treatment. Again, in Example 17, the control treatment is replicated as often as each test treatment while in Example 18 the control is replicated more often. This may be attributed to the versatility of the approaches underlying the identification and construction of optimal designs; see the references cited for further details.

7.2 Optimal designs when some subjects drop out

In practice, it may happen that a crossover trial cannot be performed for the initially planned p periods for all the subjects. Such a situation arises, for example, in clinical trials where certain patients drop out from the study before the entire sequence of p treatments assigned to them can be completed. When subjects drop out before the trial is completed, the final "implemented" design is a truncated version of the originally "planned" design. If these two designs are denoted by d_{imp} and d_{plan}, respectively, then d_{imp} may not remain optimal/efficient even if d_{plan} is an optimal design and in certain extreme cases, d_{imp} may not even remain connected. Therefore, while choosing d_{plan}, the possibility of subjects dropping out has to be taken into consideration.

Low *et al.* (1999, 2003) suggested a computer intensive method to ascertain the robustness of d_{plan} with $p > 2$ when the subjects drop out at random. They used the means and standard deviations of certain performance measures based on the A- and MV-optimality criteria and used these to assess the performance of d_{plan}. This line of work was further enriched by Majumdar *et al.* (2008) who started with a d_{plan} which is a balanced uniform design in $\Omega_{t,\mu_1 t,t}$ and explored the situation where all subjects remain in the experiment in the first $t-u$ periods, and then start dropping out at random, $1 \le u \le t-1$. The design consisting of the first $t-u$ periods was called by them as minimal and denoted by $d_{\min}$. They obtained a sufficient condition for $d_{\min}$, and hence d_{imp}, to remain connected, and also gave an upper bound on the maximum loss of efficiency due to subject drop outs in the last u periods when d_{plan} is a balanced uniform design in $\Omega_{t,\mu_1 t,t}$. The following example illustrates some of their findings.

Example 19. Consider the following balanced uniform designs for $t = 3, 4, 5$:

$$d_{14} \equiv \begin{array}{cccccc} 1 & 2 & 3 & 2 & 3 & 1 \\ 3 & 1 & 2 & 3 & 1 & 2 \\ 2 & 3 & 1 & 1 & 2 & 3 \end{array}, \quad d_{15} \equiv \begin{array}{cccc} 4 & 1 & 2 & 3 \\ 1 & 2 & 3 & 4 \\ 3 & 4 & 1 & 2 \\ 2 & 3 & 4 & 1 \end{array},$$

$$d_{16} \equiv \begin{array}{cccccccccc} 1 & 2 & 3 & 4 & 5 & 3 & 4 & 5 & 1 & 2 \\ 5 & 1 & 2 & 3 & 4 & 4 & 5 & 1 & 2 & 3 \\ 2 & 3 & 4 & 5 & 1 & 2 & 3 & 4 & 5 & 1 \\ 4 & 5 & 1 & 2 & 3 & 5 & 1 & 2 & 3 & 4 \\ 3 & 4 & 5 & 1 & 2 & 1 & 2 & 3 & 4 & 5 \end{array}.$$

If these designs are used as d_{plan}, then Majumdar *et al.* (2008) showed that if no observation is taken in the last period, the d_{imp} designs arising out of d_{14} and d_{16} remain connected but that arising out of d_{15} becomes disconnected. A similar observation was made by Low *et al.* (1999) too.

Bose and Bagchi (2008) studied the optimality aspects of the designs $d_{\min}$ when d_{plan} belongs to a class of designs, say $\mathcal{D}_1$, consisting of *locally balanced crossover* designs, introduced by Anderson and Preece (2002). Among other things, they showed that a design $d_{\text{plan}} \in \mathcal{D}_1$ is itself universally optimal for direct and carryover effects over the binary subclass in $\Omega_{t,n,t}$ and furthermore, $d_{\min}$ obtained from a member of $\mathcal{D}_1$ remains optimal over the binary subclass in $\Omega_{t,n,t-u}$ when $d_{\min}$ consists of $t-u \ge 3$ periods.

Example 20. For example, the design $d_{\min}$ obtained from the following design with $t = 5 = p, n = 20$ is optimal for $t - u \geq 3$:

$$\begin{array}{cccccccccccccccccccc}
1 & 2 & 3 & 4 & 5 & 2 & 3 & 4 & 5 & 1 & 1 & 2 & 3 & 4 & 5 & 2 & 3 & 4 & 5 & 1 \\
2 & 3 & 4 & 5 & 1 & 4 & 5 & 1 & 2 & 3 & 5 & 1 & 2 & 3 & 4 & 5 & 1 & 2 & 3 & 4 \\
5 & 1 & 2 & 3 & 4 & 5 & 1 & 2 & 3 & 4 & 2 & 3 & 4 & 5 & 1 & 4 & 5 & 1 & 2 & 3 \\
3 & 4 & 5 & 1 & 2 & 1 & 2 & 3 & 4 & 5 & 4 & 5 & 1 & 2 & 3 & 3 & 4 & 5 & 1 & 2 \\
4 & 5 & 1 & 2 & 3 & 3 & 4 & 5 & 1 & 2 & 3 & 4 & 5 & 1 & 2 & 1 & 2 & 3 & 4 & 5
\end{array}.$$

For some more results on efficient crossover designs when subjects drop out at random, see Zhao and Majumdar (2012). In a recent paper, Zheng (2013) obtained necessary and sufficient conditions for a crossover design to be universally optimal in approximate design theory in the presence of subject dropout. He also provided an algorithm to derive efficient exact designs.

7.3 Optimal designs via approximate theory

Most of the results on optimal crossover designs described earlier concern exact designs where each subject is allocated a sequence of treatments over the p periods and thus, the number of subjects assigned to a treatment sequence is a non-negative integer. It follows then that the proportion of subjects receiving a treatment sequence is of the form u/n where $0 \leq u \leq n$ and n is the total number of subjects. Because of the discreteness of u, this approach does not allow the use of techniques based on calculus and one has to employ combinatorial arguments to arrive at optimal designs. In contrast to the exact theory, one can often achieve considerable simplicity by allowing the above stated proportions to vary continuously over $[0, 1]$, such that the sum of these proportions over all treatment sequences is unity. As a result, one now has a continuous design framework, which allows the development of an approximate design theory and methods based on calculus can be employed to determine these in an optimal fashion.

For $t = 2$ treatments, the approximate design theory was used by Laska *et al.*(1983), Matthews (1987, 1990) and Kushner (1997a) and we have already described some of the results obtained by these authors earlier in this paper. A more detailed study of optimal crossover designs using the approximate theory was made by Kushner (1997b, 1998), who obtained optimality results for direct effects with arbitrary number of treatments under a correlated errors model as given by (26). Note that the approach of Kushner (1997b) can be employed to arrive at optimal designs under the uncorrelated errors model as well. Based on the methods of Kushner (1997b), Bose and Shah (2005) obtained optimal designs for the estimation of carryover effects under (3). A detailed exposition of these methods based on approximate theory is beyond the scope of this paper and an interested reader may refer to the above stated references or, Chapter 4 of Bose and Dey (2009) for more details.

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