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Row-column and Cross-over Designs for Comparing Dual with Single Treatments

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ABSTRACT

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The study concerns the design of experiments whose purpose is to compare the joint effects of two drugs A and B, at n and m levels respectively, with the effect of each individual drug. The treatment containing both drugs at the zero level is excluded from the experiment on ethical grounds. The aim of this investigation is to identify efficient row-column and cross-over designs for estimating the dual versus single treatment contrasts, in the sense of having small total variance for the contrast estimators.

Initially, attention is restricted to row-column designs, that is designs for two orthogonal blocking factors. The criterion used for design selection is the A-criterion. Lower bounds on the total variance of the estimators of the contrasts of interest are developed and used to assess the performance of row-column designs obtained by amalgamating two single blocking factor designs which are part-balanced for the dual versus single contrasts. A subclass of part-balanced row-column designs, with the property that treatments are orthogonal to row blocks, is identified. A method of finding efficient designs for estimating any specific given set of treatment contrasts is also described.

In the latter part of this thesis, designs are identified for cross-over experiments where each subject is given a sequence of two or more distinct treatments. For such studies, it is necessary to consider the possibility that the effect of a particular treatment may persist beyond the period of application. Designs are considered for the cases where treatment effects persist for one and for two periods and simple additive models including first- and second-order carryover effects are assumed. Designs are obtained by rearranging an efficient row-column design within columns and selecting the arrangement which has the smallest total variance for the estimators of the dual versus single contrasts under the carryover model. Finally, an investigation of the robustness of designs to the assumption of non-negligible second-order carryover effects is presented.

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Chapter 1

Introduction

1.1 Description of the Problem

The problem considered concerns the selection of efficient designs for a factorial experiment with one treatment combination excluded. This issue is of particular importance in clinical trials and can be illustrated by means of the following practical example.

Suppose there are two drugs, A and B, both known from previous studies to be individually effective in the treatment of a medical condition. Drug B is to be investigated at m different doses, labelled 0, 1, ..., $m-1$ and drug A at n doses, labelled 0, 1, ..., $n-1$. Thus there are $n \times m$ distinct treatment combinations denoted by ij where i and j are the doses of A and B respectively. The aim of the experiment is to determine whether a combination of these two drugs, both at non-zero doses, is more effective than either of the drugs administered individually, that is to estimate the dual versus single contrasts $\tau_{ij} - \tau_{i0}$, $\tau_{ij} - \tau_{0j}$ ($1 \leq i \leq n-1$, $1 \leq j \leq m-1$; $i = j = 0$ excluded), where τ_{ij} denotes the effect of treatment combination ij. Throughout this thesis, a treatment τ_{ij} which contains both drugs at a non-zero level is referred to as a dual treatment, and a treatment which has either of the drugs at the zero level is referred to as a single treatment.

A key feature of the study is that one of the treatment combinations, labelled 00, is the double placebo, that is it represents no active treatment. There are many medical situations in which it would be highly unethical to deny a patient

treatment and such a trial would not be authorised by the appropriate ethical committees monitoring drug research and administration. Thus, there is a need to find an efficient design for an $n \times m$ factorial experiment with the double placebo treatment excluded. Efficient designs for estimating the dual versus single treatment contrasts in the presence of a single blocking factor were constructed by Gerami and Lewis (1992). These designs are appropriate for a situation where the subjects are grouped on the basis of a single characteristic, such as age. An aim of this thesis is to construct row-column designs for the same treatment structure and contrasts. An example of their application is experiments where subjects are grouped according to two characteristics, for example age and sex.

In order to assess the performance of row-column designs, lower bounds on the total variance of the estimated treatment contrasts of interest are developed and discussed in Chapter 2. The performance of these bounds is investigated by comparison with the results obtained from an optimal design search algorithm. The bounds are then used to assess the performance of row-column designs, constructed by amalgamating two suitable block designs, which are listed in Chapter 3. Row and column component designs from the family of reinforced group divisible designs are considered, in addition to the PBDS block designs identified by Gerami, Lewis, Majumdar & Notz (1993). In Chapter 4, designs with the additional property that row blocks are orthogonal to treatments are investigated. The variances of the estimators of the treatment contrasts for these designs are unaffected by adjustment for the effects of the row blocks.

A further example of the application of row-column designs is in cross-over experiments, that is experiments in which each of a number of subjects receives a sequence of treatments throughout the duration of the study. In some cross-over experiments it can be assumed that the effects of a treatment do not persist beyond the period of application. This may be due to the nature of the treatment or the use of washout periods; the latter are relatively short intervals of time interspersed between two consecutive treatment periods during which a subject receives no treatment. For this type of cross-over experiment a row-column design may be employed where row blocks correspond to periods and column blocks to subjects.

The second part of this thesis addresses the problem of finding efficient designs for cross-over studies when it is thought that the effects of a treatment may persist after the period of application. Hence measurements taken in the second and

subsequent periods are not necessarily solely affected by the current treatment but may also include a residual or carryover effect from the treatment given in the previous period, see Jones & Kenward (1989, p 4). In recent years, this area has stimulated much interest and controversy. The advantages and disadvantages of using a cross-over design in a medical study are discussed in greater depth in Chapter 6. A review of the carryover models given in the literature is presented and criticisms of this type of study are discussed.

In order to distinguish between the two types of treatment effects, a direct treatment effect is defined to be the effect observed in the current period which is attributable solely to the treatment given in that period, whereas any treatment effects observed in the current period but attributable to the treatment given in the immediately preceding period are called *first-order carryover* or *residual effects*. It is usually assumed that the effects of treatments applied in earlier periods are negligible. In Chapter 7, designs are found under a model for the observations which assumes simple additive first-order carryover effects. The search is extended to find designs under a model which also allows for carryover effects which persist for two periods. The designs found under the second model are evaluated under the model for first-order carryover effects to assess how much precision has been sacrificed by allowing for non-negligible second-order carryover effects.

In this thesis, the estimation of the direct treatment effects is considered to be of primary importance and carryover effects are regarded as a nuisance factor which may or may not be present. In this type of situation, experimenters may prefer the protection of using designs which allow for the estimation of the contrasts of interest in the presence of carryover effects. This implies a need to identify designs which perform well both in the presence and in the absence of such effects. Investigations into this area have already been conducted. Some interest has been centred on cases with a single unstructured set of treatments and pairwise comparison of these treatments, see Kunert (1984, 1985) and Matthews (1987). Attention has also been given to the estimation of factorial contrasts in cross-over designs with a factorial treatment structure, see Fletcher & John (1985) and Lewis, Fletcher & Matthews (1988).

In addition, in Chapter 5 the general problem of designing experiments to estimate specific treatment contrasts is considered and results on the general form of the information matrix for theoretical A-optimal designs is given.

In the remainder of this introductory chapter, the aims of the thesis are presented before discussing some basic concepts and definitions commonly used in the design and analysis of experiments. In the next section, a simple additive model is defined under which efficient row-column designs are found and an outline of the analysis of these designs is given. The concept of efficiency factors is introduced to aid discussion of optimality criteria which enable the comparison of designs with respect to a particular aspect of design performance. For example, an A-optimal design minimises the total variance of the estimators of the contrasts of interest. This leads to the following criterion for design choice.

Definition 1.1 *Design d_1 is a* better *choice than design d_2, for estimating a specific set of treatment contrasts* under the A-criterion, *if d_1 has a smaller total variance for the estimators of the contrasts than d_2.*

The relationship between the efficiency factors of the row-column design and its row and column component designs is presented in Section 1.3, followed by a review of the design characteristics associated with the dual versus single treatment structure.

The aims of this thesis are, for two treatment factors and one excluded treatment combination,

1. to find efficient row-column designs for estimating the dual versus single treatment contrasts under an additive model with no carryover effects.
2. to obtain lower bounds on the total variance of the estimated dual versus single treatment contrasts to enable the performance of row-column designs in estimating these contrasts to be assessed.
3. to obtain efficient cross-over designs for estimating the same contrasts when three or four periods and four or more subject groups are used and a model is adopted in which simple additive first-order carryover effects are included.
4. to obtain cross-over designs for estimating the same contrasts under the assumption of a model which includes parameters for both first- and second-order carryover effects, and hence to examine the robustness of design choice to the assumption of negligible second-order carryover effects.

1.2 Model, analysis and methods of assessing row-column designs

In this section, a model and some methods of analysis are briefly outlined for reference in the later chapters of this thesis. Consider an experiment having $t = mn - 1$ treatments and two blocking factors denoted by rows and columns. Each experimental unit is classified according to the two blocking factors. Let R denote the number of rows and C denote the number of columns. Attention is not restricted to equi-replicate designs and the treatment replications are stored in a $t \times 1$ vector r. A simple additive model is assumed, as follows

$$y_{ijk} = \mu + \alpha_i + \beta_j + \tau_k + \varepsilon_{ijk} \; (i = 1, \ldots, R;\; j = 1, \ldots, C;\; k = 1, \ldots, t), \quad (1.1)$$

where y_{ijk} is the response obtained when the kth treatment is applied to the unit in row i and column j, μ is the overall mean, α_i is the ith row effect, β_j is the jth column effect, τ_k is the kth treatment effect and the ε_{ijk} are random errors which are assumed to be independent, identically distributed N(0,σ^2) random variables.

The model can be more conveniently expressed in matrix notation as:

$$Y = 1_n\mu + X_\alpha\alpha + X_\beta\beta + X_\tau\tau + \varepsilon, \quad (1.2)$$

or alternatively as:

$$Y = Xa + \varepsilon, \quad (1.3)$$

where $X = \begin{pmatrix} 1_n & X_\alpha & X_\beta & X_\tau \end{pmatrix}$, $a' = \begin{pmatrix} \mu & \alpha' & \beta' & \tau' \end{pmatrix}$, α, β and τ are the vectors of row, column and treatment effects respectively and 1_n is an $n \times 1$ vector with every element unity.

The least squares estimator of the parameter vector a, obtained by minimising the error sum of squares $\varepsilon'\varepsilon$ with respect to a, is found by solving the normal equations:

$$(X'X)\hat{a} = X'Y.$$

In terms of (1.3) the normal equations are:

$$\begin{aligned} n\hat{\mu} + C1'_R\hat{\alpha} + R1'_C\hat{\beta} + r'\hat{\tau} &= G \\ C1_R\hat{\mu} + CI_R\hat{\alpha} + J_{R,C}\hat{\beta} + N'_R\hat{\tau} &= R_{TOT} \\ R1_C\hat{\mu} + J_{C,R}\hat{\alpha} + RI_C\hat{\beta} + N'_C\hat{\tau} &= C_{TOT} \\ r\hat{\mu} + N_R\hat{\alpha} + N_C\hat{\beta} + r^\delta\hat{\tau} &= T_{TOT} \end{aligned}$$

where N_R is the $t \times R$ incidence matrix of the row component design, N_C is the $t \times C$ incidence matrix of the column component design, r^δ is a diagonal matrix with the elements of r on the diagonal, $J_{u,v}$ is a $u \times v$ matrix with every element unity, $G = 1_n' Y$ is the overall total, $R_{TOT} = X_\alpha' Y$ is the $R \times 1$ vector of row totals, $C_{TOT} = X_\beta' Y$ is the $C \times 1$ vector of column totals and $T_{TOT} = X_\tau' Y$ is the $t \times 1$ vector of treatment totals.

By eliminating both the row and column effects from these equations, the reduced normal equations are obtained as

$$A_{RC}\hat{\tau} = Q \tag{1.4}$$

where

$$A_{RC} = r^\delta - \frac{1}{C} N_R N_R' - \frac{1}{R} N_C N_C' + \frac{rr'}{RC}$$

and

$$Q = T_{TOT} - \frac{1}{C} N_R R_{TOT} - \frac{1}{R} N_C C_{TOT} + \frac{rG}{RC}.$$

A_{RC} is known as the *intra-block information matrix of the row-column design* and Q is the *vector of treatment totals adjusted for the row and column effects.* A solution to (1.4) is given by

$$\hat{\tau} = \Omega_{RC} Q, \tag{1.5}$$

where Ω_{RC} is a generalised inverse of A_{RC}. It is not possible to find a unique inverse since $A_{RC} 1_t = 0$ hence $rank(A_{RC}) \leq t-1$. However, apart from Chapter 5, attention is restricted to connected designs, that is designs for which $rank(A_{RC}) = t - 1$.

Experiments are considered whose purpose is to estimate a set of treatment comparisons or contrasts. Let C_t denote a matrix containing contrasts in the t treatments. It is known that the least squares estimator of $C_t\tau$ is given by $C_t\hat{\tau}$. Suppose A_d is the information matrix for a design d, satisfying $A_d 1_t = 0$, then $C_t\tau$ is estimable if and only if $C_t\Omega_d A_d = C_t$. If d is connected then any contrast in the treatment effects will be estimable, see John (1987, p 19). An *estimable* set of contrasts C_t has the property that $E(C_t\hat{\tau}) = C_t\tau$,

$$V(C_t\hat{\tau}) = C_t\Omega_d C_t'\sigma^2 \tag{1.6}$$

and the sum of squares due to testing $H_0 : C_t\tau = \alpha$, for some given vector α, is

$$SS(C_t\hat{\tau}) = (C_t\hat{\tau} - \alpha)'(C_t\Omega_d C_t')^{-1}(C_t\hat{\tau} - \alpha)$$

with degrees of freedom equal to $rank(A_d) = t - 1$.

Many criteria for choosing efficient designs are based on $C_t \Omega_d C_t'$. For example, in Definition 1.1 it was stated that the A-criterion seeks to minimise the total variance of the estimators of the contrasts of interest. This is equivalent to minimising the trace of (1.6).

In the remaining part of this section, some common assessments of performance of designs for estimating the pairwise treatment comparisons are considered, before discussing the appropriate measures of design performance for estimating contrasts in three or more treatments. The relevance of these measures for assessing the row-column designs of Chapters 3 and 4 is also addressed.

A convenient measure of the difference in the precision of the estimation of the pairwise treatment contrasts in two designs is provided by the efficiency factors. A *pairwise* efficiency factor of a design d, with equal treatment replication r_e, for estimating the difference between two treatment effects, τ_i and τ_j, is a comparison of the variance of the estimated contrast in d with the variance of the estimated contrast in a randomised block design, where it is assumed that the error variance is the same for the two designs. This can be written more concisely as

$$E_{ij} = \frac{2\sigma^2/r_e}{V(\hat{\tau}_i - \hat{\tau}_j)\sigma^2} = \frac{2/r_e}{V(\hat{\tau}_i - \hat{\tau}_j)}.$$

A convenient summary of the efficiency factors is provided by the average efficiency factor, E, defined by $E = 2\sigma^2/r_e\bar{v}$, where $\bar{v}$ is the average variance over all pairwise treatment comparisons. This measure is not used to assess the designs listed in this thesis since, for the dual versus single treatments problem, interest is not centred on the full set of pairwise treatment comparisons. Note that minimising E is equivalent to minimising the average variance of all the estimated pairwise treatment comparisons, see John (1987, p 28).

So far, discussion has been limited to the pairwise contrasts of interest. However, it is often desirable to make comparisons which involve more than two treatment effects. For example, it may be necessary to compare one treatment effect with the average of the effects of the remaining $t - 1$ treatments. In general, a linear expression $L = \sum_{i=1}^{t} \alpha_i \tau_i$ is a *contrast* in the treatment effects if the α_i's are constant and $\sum_{i=1}^{t} \alpha_i = 0$. The contrast is said to be normalised if $\sum_{i=1}^{t} \alpha_i^2 = 1$. The performance of a design for estimating a contrast L can be

assessed through the efficiency factor for L, that is

$$E_L = \frac{2\sigma^2/r_e}{V(L)}.$$

When examining several treatment contrasts simultaneously, the analysis and interpretation of the results are simplified if the contrasts are orthogonal, where two contrasts $L_1 = \sum_{i=1}^{t} \alpha_i \tau_i$ and $L_2 = \sum_{i=1}^{t} \alpha_i' \tau_i$ are orthogonal if and only if $\sum_{i=1}^{t} \alpha_i \alpha_i' = 0$.

In order to obtain an overall assessment of the *efficiency* of a block or row-column design for estimating a set of $t-1$ orthogonal contrasts, the following contrasts are used.

Definition 1.2 *A set of basic contrasts for a block or row-column design with information matrix A_d is*

$$\xi_i' \tau \ (i = 1, \ldots, t-1),$$

where ξ_i is an eigenvector corresponding to λ_i, a non-zero eigenvalue of A_d, and

$$\xi_i' \xi_j = \begin{cases} 1 & \text{if } i = j \\ 0 & \text{if } i \neq j \end{cases}.$$

The basic contrasts are, by definition, both normalised and orthogonal and lead to another measure of design performance, known as the canonical efficiency factors of a design. For a design with equal treatment replications r_e, a canonical efficiency factor is the efficiency factor for a basic contrast $\xi_i \tau$ and can be shown to be $e_i = \lambda_i / r_e$, where λ_i is the eigenvalue of A_d corresponding to the eigenvector ξ_i. Two important properties of canonical efficiency factors should be noted. The first is that they are related to the average variance over all pairwise differences by the following

$$\bar{v} = \frac{2\sigma^2}{r_e E},$$

where E is the average efficiency factor. The second property states that the largest and smallest canonical efficiency factors place upper and lower bounds on the efficiency factor of *any* treatment contrast, see John (1987, p 27).

When designs with unequal treatment replication are employed there are two approaches to defining efficiency factors, see John (1987, p 35). The approach

used in this thesis is to assume that the treatment replications are fixed, the efficiency factors can then be defined as follows

Definition 1.3 *The canonical efficiency factors (for fixed treatment replications) for a connected block or row-column design d, having replication matrix r^δ and information matrix A_d, are the eigenvalues of $r^{-\delta/2}A_d r^{-\delta/2}$ except for the zero eigenvalue which corresponds to the eigenvector $r^{\delta/2}1_t$.*

There are various criteria available which allow different designs to be compared, these can be expressed as functions of the canonical efficiency factors. The A-criterion can be considered to maximise the harmonic mean of the canonical efficiency factors. Another commonly used criterion is the E-criterion which maximises the minimum canonical efficiency factor of any treatment contrast. The D-criterion seeks to minimise the determinant of the variance-covariance matrix of the estimated contrasts of interest but can also be considered to maximise the geometric mean of the canonical efficiency factors. The (M, S)-criterion is evaluated in two stages. The first step is to locate a class of designs which maximises the mean of the canonical efficiency factors, this class then has M-optimality. The next task is to identify the designs within this class which minimise the variance of the canonical efficiency factors which gives S-optimality.

In general, an optimality criterion is a function $\Phi : \beta_{t,0} \rightarrow (-\infty, \infty]$ where $\beta_{t,0}$ is the collection of $t \times t$ nonnegative definite matrices with zero row and column sums. A design d is called Φ-optimal if it minimises $\Phi(A_d)$ over the set of competing designs. The set of competing designs is determined by the effects which are of interest in the comparisons to be estimated. Note that $A_d \in \beta_{t,0}$ in this setting.

The following definition of universal optimality is due to Kiefer (1975).

Definition 1.4 *A design d^* will be termed universally optimal in the class $\mathcal{D}$ of competing designs if d^* minimises $\Phi(A_d)$ for every Φ satisfying:*

(i) Φ *is convex,*

(ii) $\Phi(bA_d)$ *is non-increasing in the scalar* $b \geq 0$,

(iii) Φ *is invariant under each simultaneous permutation of rows and columns,*

where A_d is the information matrix for the contrasts of interest corresponding to the design d.

A design which is universally optimal is also A-, D- and E-optimal. It should be noted that a design which is optimal under one of the latter criteria is not necessarily optimal under any of the other criteria. However, various studies have indicated that a design which performs well under one criterion tends to perform well under the others.

The canonical efficiency factors can be used as a crude assessment of design performance in estimating the dual versus single treatment contrasts, since they enable upper and lower bounds to be specified for the variances of the estimators of these contrasts. However, a more accurate assessment can be made by considering the individual variances of the specific contrasts, or more easily, the total variance of the contrast estimators. It has already been stated that, when interest is focused on the pairwise treatment contrasts, assessments of a design d are made by comparing the variance of the estimator of a particular pairwise contrast under design d with the variance of the corresponding contrast under the known universally optimal design for estimating the contrast. For the pairwise treatment comparisons, the class of universally optimal designs is randomised block designs. Since there are no results for universally optimal row-column designs for estimating the dual versus single treatment contrasts, lower bounds on the total variance of the estimators of these contrasts developed in Chapter 2 are used as a basis for comparison.

1.3 Row-column designs as amalgamations of two block component designs

In this thesis, row-column designs found by amalgamating two block designs are considered. In this section, a relationship between the row-column design and the row and column component designs is defined. The row component design has the rows as blocks and ignores the column blocking factor. The column component design has the columns as blocks and ignores the row blocking factor. Example 3.1 shows how a row-column design for treatments with levels $m = 2$ and $n = 3$ arranged in three rows and six columns can be obtained by combining

two block designs with $m = 2$ and $n = 3$, one consisting of three blocks of size six and the other consisting of six blocks of size three.

The information matrices for the row and column component designs respectively are $A_R = r^{\delta} - \frac{1}{C}N_R N_R'$, where $A_R 1_t = 0$, and $A_C = r^{\delta} - \frac{1}{R}N_C N_C'$, where $A_C 1_t = 0$. From Cheng (1978), the relationship between the information matrices of the three designs can be expressed as

$$A_{RC} = A_R + A_C - r^{\delta} + \frac{rr'}{RC}. \tag{1.7}$$

Several authors, such as Shah (1977) and Raghavarao & Shah (1980), have considered row-column designs which have a common set of basic contrasts ξ_i, $(i = 1, \ldots, t)$ for A_{RC}, A_R and A_C when seeking efficient designs for pairwise treatment comparisons. Equation (1.7) can then be written

$$A_{RC}\xi_i = A_R\xi_i + A_C\xi_i - (r^{\delta} - \frac{rr'}{RC})\xi_i.$$

The advantage of this property is that it ensures that *efficient* row-column designs are achieved when *efficient* row and column component designs are amalgamated. For Definition 1.3, the efficiency factors of the row-column design and the row and column component designs are linked as follows.

Since, in the case of unequal treatment replications, the elements of the vector r are regarded as fixed, the terms of (1.7) can be pre-multiplied by $r^{-\delta/2}$ and post-multiplied by $r^{-\delta/2}\xi_i$ to give

$$r^{-\delta/2}A_{RC}r^{-\delta/2}\xi_i = r^{-\delta/2}A_R r^{-\delta/2}\xi_i + r^{-\delta/2}A_C r^{-\delta/2}\xi_i - (I_t - \frac{1}{t}r^{\delta/2}J_t r^{\delta/2})\xi_i \tag{1.8}$$

where J_t is a $t \times t$ matrix with every element equal to unity. Using the fact that $r^{-\delta/2}A_{RC}r^{-\delta/2}\xi_i = e_{RC_i}\xi_i$, it follows that

$$r^{\delta/2}\xi_i = \frac{A_{RC}r^{-\delta/2}\xi_i}{e_{RC_i}}$$

where e_{RC_i}, $(i = 1, \ldots, t-1)$, are the non-zero eigenvalues of $r^{-\delta/2}A_{RC}r^{-\delta/2}$. Substituting into (1.8)

$$r^{-\delta/2}A_{RC}r^{-\delta/2}\xi_i = r^{-\delta/2}A_R r^{-\delta/2}\xi_i + r^{-\delta/2}A_C r^{-\delta/2}\xi_i - I_t\xi_i + \frac{1}{t}r^{\delta/2}J_t\frac{A_{RC}r^{-\delta/2}\xi_i}{e_{RCi}}.$$

Since $J_t A_{RC} = 0$, by definition of A_{RC}, it follows that

$$r^{-\delta/2}A_{RC}r^{-\delta/2}\xi_i = r^{-\delta/2}A_R r^{-\delta/2}\xi_i + r^{-\delta/2}A_C r^{-\delta/2}\xi_i - \xi_i$$

which can be expressed as

$$e_{RC_i}\xi_i = e_{R_i}\xi_i + e_{C_i}\xi_i - \xi_i,$$

where e_{R_i}, e_{C_i} and e_{RC_i} $(i = 1, \ldots, t-1)$, are the non-zero eigenvalues of $r^{-\delta/2}A_R r^{-\delta/2}$, $r^{-\delta/2}A_C r^{-\delta/2}$ and $r^{-\delta/2}A_{RC} r^{-\delta/2}$ respectively. The final efficiency relationship is

$$e_{RC_i} = e_{R_i} + e_{C_i} - 1. \tag{1.9}$$

Equation (1.9) has limited application to the dual versus single treatments problem since the row-column designs of Chapter 3 rarely have an information matrix with a set of basic contrasts which is also common to the information matrices of the component designs. This point is discussed further in Section 3.6. However, the efficiency relationship (1.9) applies to the row-orthogonal designs of Chapter 4 where it is used to show that the efficiency of the row-orthogonal design is equal to the efficiency of the column component design.

1.4 Design characteristics and contrasts of interest for the problem

In Section 1.1, it was stated that efficient designs were required which would enable an investigator to determine whether a combination of two drugs, both having non-zero levels, is more effective than either of the drugs administered individually. The contrasts of interest involve comparing dual treatments with single treatments. For the $n \times m$ experiment, these contrasts can be split into two groups

1. the dual versus A contrasts

$$\tau_{ij} - \tau_{i0} \; (i = 1, \ldots, n-1; \; j = 1, \ldots, m-1) \tag{1.10}$$

2. the dual versus B contrasts

$$\tau_{ij} - \tau_{0j} \; (i = 1, \ldots, n-1; \; j = 1, \ldots, m-1). \tag{1.11}$$

It is assumed that the estimation of each of these contrasts has equal importance, that is higher precision on certain comparisons is not required. The natural choice

of criteria for design selection in this situation is the A-criterion which seeks to minimise the sum of the variances of the estimators of the treatment contrasts of interest.

Throughout this thesis, the treatment effects in the vector τ will be ordered as $(\tau_{01}, \ldots, \tau_{0q}, \tau_{10}, \ldots, \tau_{p0}, \tau_{11}, \ldots, \tau_{1q}, \tau_{21}, \ldots, \tau_{2q}, \ldots, \tau_{p1}, \ldots, \tau_{pq})$, where $p = n-1$ and $q = m-1$, following Gerami & Lewis (1992). Then (1.10) and (1.11) can be written as $H\tau$ where

$$H = \begin{pmatrix} -I_q \otimes 1_p & O_{l,p} & E \\ O_{l,q} & -I_p \otimes 1_q & I_l \end{pmatrix} \tag{1.12}$$

and $O_{u,v}$ is a $u \times v$ matrix with every element zero, $\otimes$ denotes Kronecker product, $l = pq$ and $E = (E_{ij})$ is an $l \times l$ matrix in which submatrix E_{ij} has size $p \times q$, with entry 1 in the $(j,i)th$ position and zero elsewhere $(i = 1, \ldots, q;\ j = 1, \ldots, p)$.

Gerami & Lewis (1992) found that the class of block designs having the property of part-balance for estimating the dual versus single contrasts contained many highly efficient designs for estimating (1.10) and (1.11).

Definition 1.5 *Designs for an $n \times m$ experiment with part-balance for the dual versus single treatment comparisons (PBDS) satisfy the following conditions*

$$V(\hat{\tau}_{ij} - \hat{\tau}_{i0}) = v_A \ (i = 1, \ldots, n-1;\ j = 1, \ldots, m-1)$$

and

$$V(\hat{\tau}_{ij} - \hat{\tau}_{0j}) = v_B \ (i = 1, \ldots, n-1;\ j = 1, \ldots, m-1).$$

Note that the part-balance property includes total balance for estimating (1.10) and (1.11) as a special case. For a single blocking factor, designs having total balance were found to be too large for most practical cases, see Gerami (1991).

From Definition 1.5, a PBDS design d has variance-covariance matrix

$$H\Omega_d H' = \begin{pmatrix} (\alpha_1 - \beta_1)I_p + \beta_1 J_p & (\delta - \phi)I_p + \phi J_p \\ (\delta - \phi)I_p + \phi J_p & (\alpha_2 - \beta_2)I_p + \beta_2 J_p \end{pmatrix} \tag{1.13}$$

where $\alpha_i \neq \beta_i$ $(i = 1, 2)$, δ and ϕ are constants, and an information matrix, A_d, whose form is given by the following theorem.

Theorem 1.1 (Gerami and Lewis, 1992) *A necessary and sufficient condition for a design d for an $n \times m$ experiment with b blocks of size k to have part-balance for estimating the dual versus single treatment comparisons is that the intra-block information matrix has the form:*

$$A_d = \begin{pmatrix} a_1 & a_2 1_p' & a_3 1_p' \\ a_2 1_p & a_4 I_p + a_5 J_p & a_6 I_p + a_7 J_p \\ a_3 1_p & a_6 I_p + a_7 J_p & a_8 I_p + a_9 J_p \end{pmatrix} \tag{1.14}$$

where a_i $(i = 1, \ldots, 9)$ are constants.

Note that this result applies to the information matrix of any design with orthogonal blocks.

Theorem 1.1 enables types of designs possessing part-balance for estimating the dual versus single treatment contrasts to be easily identified by examining the form of the information matrix. The family of reinforced group divisible designs discussed in Chapter 3 was found in this way.

Chapter 2

Lower bounds on the total variance

2.1 Introduction

In order to assess how well a design can estimate particular treatment contrasts, it is useful to have a lower bound on the total variance of the estimators of the contrasts of interest for the design, since this gives an indication of the scope for possible improvement. The purpose of this chapter is to develop bounds for row-column designs for estimating the dual versus single treatment contrasts defined in (1.10) and (1.11). The chapter includes a brief review of bounds in the literature for incomplete block designs and row-column designs.

Most work in the literature concentrates on bounds for the average variance of all pairwise treatment comparisons in designs with a *single* blocking factor and equal treatment replication. These are commonly formulated as upper bounds on the average efficiency factor E (defined in Section 1.2) and are briefly reviewed in Section 2.2. Lower bounds on E for row-column layouts are reviewed in Section 2.3. A further important area where lower bounds on the average variance have been developed is the test treatment versus control treatment problem which is outlined in Section 2.2. In Section 2.4, lower bounds available for the dual versus single treatments problem with a single blocking factor are reviewed.

The remainder of the chapter describes new work on lower bounds for the total variance of the dual versus single treatment comparisons when a row-column

design is employed. The first bound, B_F, is already available in the literature. In Section 2.5, two further bounds, $B_1(H)$ and $B_2(H)$, are derived. Bound $B_2(H)$ is shown to be tighter than B_F for certain experiment sizes. The bounds are critically compared in Section 2.6 and recommendations on their use are given. The bounds are used in Chapter 3 to assess the efficiency of new designs.

2.2 Upper bounds for the average efficiency factor in single blocking factor designs

One of the simplest upper bounds on the average efficiency factor, which is applicable only to connected binary designs with equal block sizes k, is

$$U_0 = \frac{t(k-1)}{(t-1)k}.$$

This bound uses the fact that the harmonic mean of the canonical efficiency factors cannot be greater than the arithmetic mean and has been cited by many authors including Williams & Patterson (1977) and Jarrett (1977). U_0 was extended by Williams, Patterson & John (1976) to the bound U_1 which covers non-binary designs and is given by

$$U_1 = 1 - \frac{k'(t-k')}{k^2(t-1)},$$

where $k' \equiv k \ (mod\ t)$. A tighter bound than U_0 and U_1 is that given by Jarrett (1977) which depends on the sum of squares of the canonical efficiency factors and their average and can be written

$$U_2 = U_0 - \frac{(t-2)S^2}{U_0 + (t-3)S}, \tag{2.1}$$

where $(t-1)(t-2)S^2 = S_2 = \sum_{i=1}^{t-1}(e_i - \bar{e})^2$ and $\bar{e} = (\sum_{i=1}^{t-1} e_i)/(t-1)$. It should be noted that, in general, $U_0 \neq \bar{e}$ unless the canonical efficiency factors of the design are all equal. The most useful bounds are design independent, that is they can be expressed in terms of the design parameters, r, t and k since they allow the comparison of several candidate designs for one experimental situation. Jarrett shows that bound U_2 can be written in such a form by finding a lower bound for S_2, but it then only applies to equi-replicate and equal block size binary designs.

The bound U_2 improves upon U_0 and U_1 by including the information available on the number of circuits of length 2 in the treatment concurrence graph of the design. A treatment concurrence graph allows information on the design's blocking structure to be represented in a diagrammatic form. Such a graph is constructed by letting the vertices of the graph represent the treatments, lines are then drawn between two vertices if the corresponding treatments occur together in a block. The number of lines joining any two vertices is given by the appropriate element in the treatment concurrence matrix NN'. A *circuit* is defined as a *path* which joins a vertex to itself and a *path* joining two vertices i and j is a route from i to j using a sequence of distinct lines in the treatment concurrence graph, see Wilson (1979) for further information on graph theory. Jarrett (1983) develops an even tighter bound, U_3, by also including information on the number of circuits of length 3 to give

$$U_3 = U_0 - \frac{S_2^2}{(t-1)(S_3 + U_0 S_2)}, \tag{2.2}$$

where $S_3 = \sum_{i=1}^{t-1}(e_i - \bar{e})^3$. U_3 can also be expressed in a design independent form, but is then limited in application to 2-concurrence designs, that is designs for which the off-diagonal elements of the concurrence matrix take one of two possible values. In the literature, interest is concentrated on the special case of regular graph designs where the off-diagonal elements of NN' differ by at most one since many designs of this type are known to be highly efficient, see John & Mitchell (1977). For example, Jacroux and Seely (1980) showed that sufficient conditions for (M, S)-optimality (defined in Section 1.2) of binary designs are that the off-diagonal elements of the concurrence matrix, NN', differ by at most one and the off-diagonal elements of the block characteristic matrix, $N'N$, differ by at most one. Williams & Patterson (1977) give a bound constrained by this condition and Jarrett (1983) develops a further bound for equi-replicate designs where $r = r_e 1_t$, also satisfying this condition on the concurrence matrix, by substituting lower bounds for S_2 and S_3 in equation (2.2) to obtain

$$U_4 = U_0 - \frac{t\alpha(1-\alpha)}{r_e k\{r_e k U_0 + z - (t+1)\alpha\}},$$

where α equals the fractional part of $r_e(k-1)/(t-1)$ and

$$z = \begin{cases} t & \text{if } 2(t-1)\alpha \geq t \\ (t-2)\alpha/(1-\alpha) & \text{if } 2(t-1)\alpha < t \end{cases}.$$

Jarrett (1983) conjectures that this bound holds for *any* equi-replicate binary design.

All the bounds mentioned so far are best used when $t \leq b$. When $t > b$, tighter bounds can be obtained by considering the relationship between a design and its dual, see John (1987, p 37).

The bounds U_2, U_3 and U_4 can all have a different formulation in the special case where the design has equal e_i's ($i = 1, \ldots, t-1$) giving $U_0 = \bar{e}$. Tjur (1990) interprets the second form of U_4 as a lower bound for the harmonic mean of the canonical efficiency factors in terms of the first three moments of a random variable which takes the values $e_1, \ldots, e_{t-1}$ with equal probabilities. Tjur gives a further bound based on the first and second moments of this random variable

$$U_5 = \frac{\bar{e}(1-\bar{e}) - V}{1 - \bar{e} - V}$$

where $V = t\alpha(1-\alpha)/(k^2 r_e^2)$. U_5 is not uniformly better than U_4, but it is tighter in a large number of individual cases.

A further case for which bounds on the average variance of a different set of contrasts of interest is useful is the test treatments versus control treatment problem, see Hedayat, Jacroux & Majumdar (1988). A review of the literature reveals the following bounds for the average variance of the contrasts of interest for designs with $t-1$ test treatments and one control treatment, arranged in b blocks each of size k.

Stufken (1988) gives a bound for the trace of the inverse of the information matrix of the contrasts of interest,

$$\tau_i - \tau_0, \tag{2.3}$$

where τ_0 denotes the effect of the control treatment and τ_i denotes the effect of the ith test treatment ($i = 1, \ldots, t-1$), for augmented balanced incomplete block designs.

Gupta (1989) constructs a lower bound on the average variance of the contrasts (2.3) for non-orthogonal binary S-type designs. An S-type design is defined as a design in which the number of concurrences of the control treatment with each test treatment takes a common value, λ_C say, and the number of concurrences of each pair of test treatments takes a common value, λ_T say, for all $t-1$ test treatments. An extension of this type of design, appropriate for the dual versus single treatments case, is discussed in Section 3.5. In Gupta's investigation of binary S-type designs, as in Stufken's work, interest is centred on M_d^{-1},

the inverse of the information matrix of the contrasts (2.3). The bound, U_6, is developed using certain combinatorial properties of binary S-type designs in conjunction with the fact that the harmonic mean of the diagonal elements of M_d^{-1} will not exceed the arithmetic mean of the diagonal elements of M_d^{-1} and has the form

$$U_6 = \frac{(t-1)(2+t^{\frac{1}{2}})^2}{b(k-1)(1+t^{\frac{1}{2}})^2}.$$

The bound, U_6, is generally not an achievable bound. It can be applied to any proper block designs but may be loose for non-binary designs since these designs are not as efficient as binary designs for estimation of the pairwise treatment comparisons.

2.3 Bounds on the average efficiency factor for row-column designs

Most interest in the field of row-column designs has been focused on finding specific groups of row-column designs which are optimal with respect to some predefined criterion. Consequently, far fewer bounds have been published for the average efficiency factor of an $R \times C$ row-column design for t treatments each replicated r_e times, compared with the single blocking factor case. Some of these results are discussed below.

Raghavarao & Shah (1980) develop an upper bound on the average efficiency factor for connected binary designs given by

$$U_{RC1} = \frac{t(R-1)(C-1)+RC-t}{RC(t-1)}.$$

This bound is derived using the fact that the harmonic mean of the canonical efficiency factors is not greater than the arithmetic mean and is analogous to U_0 in Section 2.2. They specify a further upper bound

$$U_{RC2} = \frac{2(R-1)^2-1}{(R-1)(2R-1)},$$

which has a limited application, since it is valid only for designs which satisfy the parameter relationships $t = 2R$, $r = R-1$ and $C = 2(R-1)$.

Eccleston & McGilchrist (1985) derive an upper bound, U_{RC3}, on the average efficiency factor of a row-column design in terms of the average efficiency factors

of the row and column component designs where the component designs share a common set of eigenvectors. This bound can be written as

$$U_{RC3}^{-1} = E_R^{-1} + E_C^{-1} - 1,$$

where E_R and E_C are the average efficiency factors of the row and column component designs respectively. The bound U_{RC3} has been found particularly useful in assessing row-column designs constructed by the method of amalgamation of component designs. This bound performs well since it uses the actual average efficiencies of the components, however, it has the disadvantage of being dependent on the chosen components.

Eccleston & McGilchrist found a design independent bound, U_{RC4}, by substituting bounds for E_R and E_C which are expressed in terms of the design parameters. If the bounds on E_R and E_C are denoted by E_1 and E_2 with $E_R < E_1$ and $E_C < E_2$ then

$$U_{RC4}^{-1} = E_1^{-1} + E_2^{-1} - 1.$$

The performance of bound U_{RC4} is variable since it is dependent on the performance of bounds E_1 and E_2.

John & Eccleston (1986) give upper bounds for the harmonic mean of the canonical efficiency factors for the restricted class of row-column α-designs. The simplest upper bound, U_{RC0}, obtained when all the canonical efficiency factors are equal, is

$$U_{RC0} = \frac{t(RC - R - C + r_e)}{RC(t-1)}$$

which is an alternative formulation of U_{RC1}. However, a tighter bound is obtained by using Jarrett's result (2.1) with U_0 replaced by U_{RC0}. As in the analogous result for block designs, the bound can be expressed in a design independent form by using a lower bound for S^2, namely

$$S^2 \geq \frac{t\alpha(1-\alpha)}{(t-2)r_e^2R^2C^2},$$

where α is the fractional part of $r_e(RC - R - C + r_e)/(t-1)$. The bound U_{RC0} is used to show that row-column α-designs can be very efficient.

John & Street (1992) develop an upper bound, U_{RC5}, by taking the approach of John & Eccleston (1986). In this case the lower bound on S^2 is found by minimising $\sum_{i=1}^{t} e_i^2$ subject to constraints on the number of distinct concurrences

in the row and column component designs. This bound is not simply expressed in closed form and is not stated here. The performance of bound U_{RC5} was examined for parameter values $3 \leq R \leq 10$, $C \leq R$, $2 \leq r_e < C$ and improved on bound U_{RC3} in 20% of cases. An upper bound for the restricted class of resolvable row-column designs, derived by the same approach, is also given which, when evaluated for parameters $3 \leq R \leq 10$, $C \leq R$, $2 \leq r_e \leq 10$, improved on bound U_{RC3} in a large number of cases.

2.4 Lower bounds on the total variance of the dual versus single contrasts for designs with a single blocking factor

In this section, two bounds found to be appropriate for the total variance of the dual versus single contrasts in the single blocking factor case are considered. The first bound B_F, is the minimum value of a function of the allocation of experimental units to the sets of particular types of treatment combinations, defined as follows:

Definition 2.1 *The sets of* A-alone, B-alone *and* dual treatment combinations *are* $\{i0; i = 1, \ldots, p\}$, $\{0j; j = 1, \ldots, q\}$ *and* $\{ij; i = 1, \ldots, p; j = 1, \ldots, q\}$ *respectively, where* $p = n - 1$ *and* $q = m - 1$.

Definition 2.2 *Let* $D^*(n,m,b,k)$ *be the class of all connected designs for an* $n \times m$ *experiment with 00 excluded, arranged in b blocks with equal block size k.*

For $d \in D^*$, the total number of units which are allocated to the sets of A-alone, B-alone and dual treatments are denoted by T_A, T_B and T_D.

Theorem 2.1 (Gerami & Lewis, 1992, Theorem 2) *For a design* $d \in D^*$, *let* T_A *and* T_B *be fixed and such that* $T_A \geq p$, $T_B \geq q$ *and* $T_A + T_B \leq bk - pq$. *Also let* $\bar{r}_A = [T_A/p]$, $\bar{r}_B = [T_B/q]$ *and* $\bar{r}_D = [T_D/pq]$. *Then* $tr(Hr^{-\delta}H') \geq F(T_A, T_B)$, *where* r^δ *is the diagonal matrix of treatment replications and*

$$F(T_A, T_B) = q\left\{\frac{2p\bar{r}_A + p - T_A}{\bar{r}_A(\bar{r}_A + 1)}\right\} + p\left\{\frac{2q\bar{r}_B + q - T_B}{\bar{r}_B(\bar{r}_B + 1)}\right\} + 2\left\{\frac{2pq\bar{r}_D + pq - T_D}{\bar{r}_D(\bar{r}_D + 1)}\right\}.$$

Corollary 2.1 (Gerami & Lewis, 1992, Corollary 3) *Let the bound* $B_F = min\{F(t_A, t_B);\ (t_A, t_B) \in T\}$, *where* $T = \{(t_A, t_B);\ t_A \geq p,\ t_B \geq q;\ t_A + t_B \leq bk - pq,\ t_A, t_B \in N^+\}$, *for* N^+ *the set of positive integers. Then* B_F *is a lower bound on* $tr(H\Omega_d H')$ *for all* $d \in D^*$.

The second bound, for the single blocking factor case, is based on a function of the eigenvalues of both the information and $C_t'C_t$ matrices, where C_t is any contrast matrix for t treatments.

Theorem 2.2 (Gerami & Lewis, 1992, Theorem 1) *Let* D *be a class of designs having one or more blocking factors and* t *treatments. For any* $d \in D$ *let* $C_t\tau$ *contain* $L \geq t-1$ *contrasts of interest, where* $rank(C_t) = t-1$. *If* $\theta_1 \geq \theta_2 \geq \ldots \geq \theta_{t-1} > \theta_t = 0$ *and* $\lambda_1 \geq \lambda_2 \geq \ldots \geq \lambda_{t-1} > \lambda_t = 0$ *are the respective eigenvalues of* $C_t'C_t$ *and* A_d, *the intra-block information matrix, then*

$$tr(C_t\Omega_d C_t') \geq \sum_{i=1}^{t-1} \theta_i/\lambda_i.$$

Remark: Let $B(C_t)$ denote the lower bound on $tr(C_t\Omega_d C_t')$, then $B(H)$ is the lower bound on $tr(H\Omega_d H')$. Gerami & Lewis (1992) perform a numerical assessment of the bounds B_F and $B(H)$ for the parameter values $2 \leq n, m \leq 10$, $b \leq 30$ and $2 \leq k \leq 15$ and conclude that $B_F > B(H)$ for $t < k$. Outside these ranges, neither of the two bounds is uniformly greater. Hence the lower bound is taken to be $max\{B_F, B(H)\}$.

2.5 Lower bounds on the total variance of the dual versus single contrasts for row-column designs

The aim of this section is to develop lower bounds on the total variance of the dual versus single contrasts in row-column designs.

2.5.1 Bound B_F

Bound B_F of Corollary 2.1 can be applied directly to the row-column case without any adaptation since the development of this bound is not dependent on the

assumption of a particular blocking structure.

It has been found that this bound can be loose, particularly when both R and C are less than t. In order to gain a more accurate assessment of designs, a second bound is derived in the following subsection.

2.5.2 Bound $B_1(H)$

The approach taken to obtain bound $B_1(H)$ is to develop, from the design-dependent bound in Theorem 2.2, a bound which has only one value for a given experiment size. This involves an examination of the information matrix, A_{RC}, of the row-column design and its eigenvalues. The strategy adopted is to find an upper bound on $tr(A_{RC})$ and then to apply the following result.

Corollary 2.2 (Gerami & Lewis, 1992, Corollary 2 to Theorem 1) *Let* $B(C_t) = (\sum_{i=1}^{t-1} \theta_i^{1/2})^2/c_{max}$, *where* $c_{max} = max\{tr(A_d);\ d \in D\}$, *then* $B(C_t)$ *is a lower bound on* $tr(C_t\Omega_d C_t')$, *for all* $d \in D$.

The following lemma is given by Kiefer (1958, p 689). The lemma is restated and a proof given.

Lemma 2.1 *The minimum value of* $S = \sum_{j=1}^{k} m_j^2$, *subject to the constraints* $\sum_{j=1}^{k} m_j = q$ *and* m_j $(j = 1, \ldots, k)$ *is integer, is*

$$q + (2q - k)[q/k] - k[q/k]^2,$$

where $[x]$ *denotes the largest integer* $\leq x$.

Proof: Let λ be a Lagrange multiplier and $T = \sum_{j=1}^{k} m_j^2 + \lambda(\sum_{j=1}^{k} m_j - q)$. Regarding T as a continuous function of real numbers m_j, $(j = 1, \ldots, k)$,

$$\frac{\partial T}{\partial m_j} = 2m_j + \lambda$$

which has zero value when $\lambda = -2m_j$ or $m_j = -\lambda/2$, $(j = 1, \ldots, k)$. Since $\partial^2 T/\partial m_j^2 = 2 > 0$ for $j = 1, \ldots, k$, it follows that S is minimised when $m_j = -\lambda/2$ $(j = 1, \ldots, k)$. Now $\sum_{j=1}^{k} m_j = q$ which implies that $\lambda = -2q/k$. Hence for minimum S :

$$m_j = q/k \ (j = 1, \ldots, k).$$

Therefore

$$min_{\mathcal{M}}\, S = q^2/k, \tag{2.4}$$

where $\mathcal{M} = \{(m_1,\ldots,m_k); m_j \in R^+, j = 1,\ldots,k, \sum_{j=1}^{k} m_j = q\}$. It is also necessary to consider the further constraint that m_j $(j = 1,\ldots,k)$ must be integer. Since S is a continuous function, its minimum value occurs when each m_j $(j = 1,\ldots,k)$ takes the nearest integer value $[q/k]$ or $[q/k]+1$. Suppose α of the m_j's are each $[q/k]$ and the remaining $k-\alpha$ values are each $[q/k]+1$. Then

$$\sum_{j=1}^{k} m_j = \alpha[q/k] + (k-\alpha)([q/k]+1) = q.$$

Hence $\alpha = k([q/k]+1) - q$ and $(k-\alpha) = q - k[q/k]$. Then the minimum value of S is $\alpha[q/k]^2 + (k-\alpha)([q/k]+1)^2$ which, after manipulation, can be written as $S = q + (2q-k)[q/k] - k[q/k]^2$.

The following theorem establishes a bound on $tr(A_{RC})$.

Theorem 2.3 *Any connected row-column design d, having t treatments arranged in an $R \times C$ array and information matrix A_{RC} has*

$$tr(A_{RC}) \leq RC - R - (R/C)(2C-t)[C/t] + (Rt/C)[C/t]^2.$$

Proof: From (1.7)

$$tr(A_{RC}) = tr(A_R) + tr(A_C) - RC + \frac{1}{RC}\sum_{i=1}^{t} r_i^2.$$

Since $tr(A_k) = RC - (1/k')\sum_{i=1}^{t}\sum_{j=1}^{k} n_{kij}^2$ for $k' \neq k = R, C$, where n_{kij} denotes the replication of treatment i in block j for design component k for $i = 1,\ldots,t$; $j = 1,\ldots,k$ and $k = R, C$, $tr(A_{RC})$ can be expressed as

$$tr(A_{RC}) = RC - \frac{1}{C}\sum_{i=1}^{t}\sum_{j=1}^{R} n_{Rij}^2 - \frac{1}{R}\sum_{i=1}^{t}\sum_{j=1}^{C} n_{Cij}^2 + \frac{1}{RC}\sum_{i=1}^{t} r_i^2. \tag{2.5}$$

Putting $k = C$, $m_j = n_{Cij}$ and $q = r_i$ in (2.4),

$$\sum_{j=1}^{C} n_{Cij}^2 \geq \frac{r_i^2}{C}\ (i = 1,\ldots,t).$$

It follows that

$$\frac{1}{R}\sum_{i=1}^{t}\left(\sum_{j=1}^{C} n_{Cij}^2 - \frac{r_i^2}{C}\right) \geq 0 \tag{2.6}$$

and from (2.5),

$$tr(A_{RC}) \leq RC - \frac{1}{C}\sum_{i=1}^{t}\sum_{j=1}^{R} n_{Rij}^2. \tag{2.7}$$

The RHS of (2.7) has its maximum value when $\sum_{i=1}^{t}\sum_{j=1}^{R} n_{Rij}^2$ is minimised subject to the constraints that $\sum_{i=1}^{t}\sum_{j=1}^{R} n_{Rij} = RC$ and n_{Rij} $(i = 1,\ldots,t; j = 1,\ldots,R)$ are integer. The result follows from applying Lemma 2.1.

A lower bound, $B_1(H)$, can now be established on the total variance of the contrasts of interest, using Corollary 2.2 with c_{max} taking the value of the upper bound on $tr(A_{RC})$ of Theorem 2.3. It should be noted that the upper bound on $tr(A_{RC})$ is not symmetrical in R and C and this generates two values for the bound on the total variance of the contrast estimators for each array size. This difficulty is resolved by taking the bound $B_1(H)$ to be the larger of the two possible values.

Definition 2.3 *$B_1(H)$ is a lower bound on the total variance of the dual versus single treatment contrasts, given by*

$$B_1(H) = max\left(\frac{(\sum_{i=1}^{t-1}\theta_i^{1/2})^2}{f(t,R,C)}, \frac{(\sum_{i=1}^{t-1}\theta_i^{1/2})^2}{f(t,C,R)}\right)$$

where $f(t,b,k) = bk - b - (b/k)(2k-t)[k/t] + (bt/k)[k/t]^2$ and θ_i, $i = 1,\ldots,t-1$, are the non-zero eigenvalues of the $H'H$ matrix for H given in (1.12).

The following two examples show the advantage of having a choice of bounds instead of restricting attention to one bound which may perform poorly for certain parameter values.

Example 2.1 *For $m = n = C = 3$ and $R = 8$, the bound $B_1(H) = 6.3185$ and the bound $B_F = 5.3333$. $B_1(H)$ is the tighter bound in this case and improves upon the value of B_F by 18.5%.*

Example 2.2 *For $m = 2$, $n = 4$, $R = C = 4$, $B_1(H)$ has the value 5.1122 and $B_F = 5.1667$. In this case B_F is the tighter bound since it improves on the value of $B_1(H)$ by 1.1%.*

The performance of the bound $B_1(H)$ is discussed in Section 2.6.

2.5.3 Bound $B_2(H)$

Although one bound has been developed for use in conjunction with the bound B_F, an inspection of (2.6) indicates that it may be possible to tighten the bound by leaving $\sum_{i=1}^{t}\sum_{j=1}^{C} n_{Cij}^2$ and $\sum_{i=1}^{t} r_i^2$ as separate terms and then minimising $tr(A_{RC})$ directly with respect to n_{kij} $(i = 1,\ldots,t; j = 1,\ldots,k; k = R, C)$. In the remaining part of this chapter it is shown how to achieve this. The key step is maximising $\sum_{i=1}^{t} r_i^2$ for which it is necessary to consider the different ways of choosing t integers, not necessarily distinct, from the set $\{a, a+1,\ldots,a+m\}$ so that the sum of the selected integers has a fixed value, q, say. The ultimate objective is to identify the choice of integers which has the maximum (uncorrected) sum of squares and to use that choice in calculating $\sum_{i=1}^{t} r_i^2$ in (2.5) to find a bound. This is done in Theorem 2.5 for which the following definitions and results are needed.

Notation: Let n_i $(1 \leq n_i \leq t)$ denote the number of integers allocated the value i $(a \leq i \leq a+m)$.

The first step is to devise a method of generating all permissible choices of t integers via the following definitions and lemma.

Definition 2.4 *For any allocation of integers $n_a, n_{a+1},\ldots,n_{a+m}$ such that $n_{b_i} \neq 0$ $(i = 1,2)$ where $a \leq b_1 \leq b_2 - 2 \leq a+m-2$, the operation which forms a new allocation by subtracting 1 from n_{b_i} $(i = 1,2)$ and adding 1 to each of n_{b_1+h} and n_{b_2-h}, for $1 \leq h \leq [(b_2-b_1)/2]$, is called an* internal reallocation from b_1 and b_2 via h *and is denoted by $I(b_1, b_2; h)$.*

Remark: The term *internal* is used since $b_1 < b_1 + h \leq b_2 - h < b_2$.

Definition 2.5 *For any allocation of integers $n_a, n_{a+1},\ldots,n_{a+m}$ such that $n_{b_i} \neq 0$ $(i = 1,2)$ where $a < b_1 \leq b_2 < a+m$, the operation which forms a new allocation by subtracting 1 from n_{b_i} $(i = 1,2)$ and adding 1 to each of n_{b_1-h} and n_{b_2+h}, for $1 \leq h \leq min(b_1 - a, a+m-b_2)$, is called an* external reallocation from b_1 and b_2 via h *and is denoted by $E(b_1, b_2; h)$.*

Remark: The term *external* is used since $b_1 - h < b_1 \leq b_2 < b_2 + h$.

Definition 2.6 *The* maximising allocation $A_0(t, a, m, q)$ *has $n_a^0, n_{a+1}^0,\ldots,n_{a+m}^0$, where $n_{a+m}^0 = [(q-at)/m]$ and*

(i) if $q - at \equiv 0 \ (mod\ m)$, *then* $n_a^0 = t - [(q - at)/m]$, $n_i^0 = 0$ *for* $a < i < a + m$,

(ii) if $q - at \equiv k \ (mod\ m)$ *where* $k \neq 0$, *then* $n_a^0 = t - 1 - [(q - at)/m]$, $n_{a+k}^0 = 1$, $n_i^0 = 0$ *for* $a < i < a + m \ (i \neq a + k)$.

Lemma 2.2 *Any allocation* $n_a, n_{a+1}, \ldots, n_{a+m}$, *which satisfies* $\sum_{i=a}^{a+m} n_i = t$ *and* $\sum_{i=a}^{a+m} in_i = q$, *for integers* a, m *and* n_i $(i = a, a + 1, \ldots, a + m)$, *can be reached from* $A_0(t, a, m, q)$ *by a sequence of 1-step internal reallocations.*

Proof: Let $\mathcal{A}_g$ denote the set of allocations formed by applying all possible internal reallocations $I(b_1, b_2; h)$, for all $1 \leq h \leq [(b_2 - b_1)/2]$, to the members of $\mathcal{A}_{g-1}$ $(g = 1, 2, \ldots)$ where $\mathcal{A}_0 = \{A_0\}$. Assume the elements of $\mathcal{A}_g$ are (partially) ordered by the value of h.

The sequence of enumerations is finite since at some stage, $G - 1$ say, $\mathcal{A}_{G-1}$ will consist solely of allocations with the property that $n_u = t - \beta$, $n_{u+1} = \beta$ and $n_i = 0$ for $0 \leq \beta \leq t$, $a \leq i \leq a + m$ and $a \leq u \leq a + m - 1$ such that $un_u + (u + 1)n_{u+1} = q$ $(i \neq u, u + 1)$. From Definition 2.4, there are no possible internal reallocations $I(u, u + 1; h)$, and $\mathcal{A}_G = \phi$. Hence, by starting at A_0 and progressively reallocating internally, all possible allocations must be considered.

Remark: This result is reinforced by showing that external reallocations will not yield any new allocations. There are no feasible external reallocations from $A_0 \in \mathcal{A}_0$ since $E(a, a + m; h)$ does not exist. Now consider $\mathcal{A}_1$. From Definitions 2.4 and 2.5, it is clear that any $E(b_1, b_2; h)$ will yield an allocation which is already a member of $\mathcal{A}_1$ or $\mathcal{A}_0$. Now assume $\mathcal{A}_0$,$\mathcal{A}_1$, ..., $\mathcal{A}_{g-1}$ have already been enumerated, then by definition $\mathcal{A}_g$ is generated from $\mathcal{A}_{g-1}$ by internal reallocations. Any external reallocation operating on $\mathcal{A}_{g-1}$ gives a member of $\bigcup_{i=1}^{g-1} \mathcal{A}_i$. Hence, if all possible internal reallocations of $\mathcal{A}_0$, $\mathcal{A}_1, \ldots$ are enumerated until $\mathcal{A}_G = \phi$, all possible allocations satisfying the required conditions must have been considered.

The following theorem establishes that the *maximising allocation* A_0 maximises $tr(A_{RC})$; the subsequent corollary gives an explicit closed form for the maximum value of $\sum_{i=1}^{t} r_i^2$.

Theorem 2.4 *For integers* a, m $(a, m > 0)$ *and* n_i $(i = a, \ldots, a + m)$ *such that* $\sum_{i=a}^{a+m} n_i = t$ *and* $\sum_{i=a}^{a+m} in_i = q$, *the function* $S = \sum_{i=a}^{a+m} i^2 n_i$ *is maximised by the allocation* $A_0(t, a, m, q)$.

Proof: The approach taken is to show that any changes to the allocation A_0 result in a reduction in S. From Lemma 2.2, all permissible allocations can be generated by starting at allocation A_0 and performing all possible $I(b_1, b_2; h)$ on each set of allocations. A general set of allocations $\mathcal{A}_g$ will be examined. The set $\mathcal{A}_{g+1}$ is generated by applying each $I(b_1, b_2; h)$, for $h = 1, \ldots, [(b_2 - b_1)/2]$, to the members of $\mathcal{A}_g$.

Consider a particular member of $\mathcal{A}_g$, having $n_i = n_i^g$ for $i = a, \ldots, a+m$, and apply a particular $I(b_1, b_2; h_0)$, where $1 \leq h_0 \leq [(b_2 - b_1)/2]$. Then, by Definition 2.4, the members of $\mathcal{A}_{g+1}$ are obtained which have $n_{b_1}^{g+1} = n_{b_1}^g - 1$, $n_{b_1+h_0}^{g+1} = n_{b_1+h_0}^g + 1$, $n_{b_2-h_0}^{g+1} = n_{b_2-h_0}^g + 1$, $n_{b_2}^{g+1} = n_{b_2}^g - 1$ and $n_i^{g+1} = n_i^g$ for $i = a, \ldots, a+m$ such that $i \neq b_1, b_1 + h_0, b_2 - h_0, b_2$. Hence, the contributions to S from the particular allocation in $\mathcal{A}_g$ and the new allocation in $\mathcal{A}_{g+1}$ differ by

$$\begin{aligned} S_g - S_{g+1} &= b_1^2 - (b_1 + h_0)^2 - (b_2 - h_0)^2 + b_2^2 \\ &= 2h_0(b_2 - b_1 - h_0). \end{aligned}$$

Since $1 \leq h_0 \leq [(b_2 - b_1)/2]$, it follows that $b_2 - b_1 - h_0 > 0$. Hence $S_g - S_{g+1} > 0$.

This shows that any allocation in $\mathcal{A}_{g+1}$ will always make a smaller contribution to S than its *parent* allocation in set $\mathcal{A}_g$ which must, in turn, make a smaller contribution to S than its *parent* allocation in set $\mathcal{A}_{g-1}$. Hence, by iteration, the theorem is proved.

The following corollary establishes the maximum value of S.

Corollary 2.3 *For integers a, m $(a, m > 0)$ and n_i $(i = a, \ldots, a+m)$ such that $\sum_{i=a}^{a+m} n_i = t$ and $\sum_{i=a}^{a+m} i n_i = q$, the maximum value of $S = \sum_{i=a}^{a+m} i^2 n_i$ is*

$$\begin{cases} (m + 2a)(q - at) + a^2 t & \text{if } q - at \equiv 0 \ (mod\ m) \\ (a+m)^2 \left[\frac{q-at}{m}\right] + (a+k)^2 + a^2 \left(t - 1 - \left[\frac{q-at}{m}\right]\right) & \text{otherwise.} \end{cases}$$

Proof:
Case I: When $q - at \equiv 0 \ (mod\ m)$ then, from Theorem 2.4, $n_{a+m} = (q - at)/m$, $n_a = t - (q - at)/m$ and $n_i = 0$, $i = a+1, \ldots, a+m-1$, will give the maximum value of S, namely

$$\begin{aligned} max\ S &= (a+m)^2(q - at)/m + a^2(t - (q - at)/m) \\ &= (2a + m)(q - at) + a^2 t. \end{aligned}$$

Case II: When $q - at \equiv k \ (mod\ m)$, $k \neq 0$, then again using Theorem 2.4, $n_{a+m} = [(q-at)/m]$, $n_{a+k} = 1$, $n_a = t - 1 - [(q-at)/m]$ and $n_i = 0$ for $i = a+1, \ldots, a+m-1$, $i \neq a+k$,

$$max\ S = (a+m)^2 \left[\frac{q-at}{m}\right] + (a+k)^2 + a^2 \left(t - 1 - \left[\frac{q-at}{m}\right]\right).$$

The following theorem establishes a second upper bound on $tr(A_{RC})$.

Theorem 2.5 *Any connected row-column design d, having t treatments arranged in R rows and C columns and information matrix A_{RC} has*

$$\begin{aligned} tr(A_{RC}) \leq\ & RC - \frac{1}{C}\{RC + R(2C-t)[C/t] - Rt[C/t]^2\} \\ & - \frac{1}{R}\{RC + C(2R-t)[R/t] - Ct[R/t]^2\} + max\left\{\sum_{i=1}^{t} r_i^2\right\}/(RC), \end{aligned}$$

where $max\{\sum_{i=1}^{t} r_i^2\}$ is as in Corollary 2.3 with $a = r_l = max(C[R/t], R[C/t], 1)$, $a+m = r_h = min(C[R/t]+C, R[C/t]+R)$, $q = RC$ and $RC - r_l t \equiv k \ (mod\ r_h - r_l)$.

Proof: By (2.5), maximising $tr(A_{RC})$ is equivalent to minimising

$$L = \frac{1}{C}\sum_{i=1}^{t}\sum_{j=1}^{R} n_{Rij}^2 + \frac{1}{R}\sum_{i=1}^{t}\sum_{j=1}^{C} n_{Cij}^2 - \frac{1}{RC}\sum_{i=1}^{t} r_i^2,$$

subject to the constraints

$$\sum_{i=1}^{t}\sum_{j=1}^{k} n_{kij} = RC \ (k = R, C). \tag{2.8}$$

Expressing L as a function symmetrical in the n_{Rij}'s and n_{Cij}'s,

$$L = \frac{1}{C}\sum_{i=1}^{t}\sum_{j=1}^{R} n_{Rij}^2 + \frac{1}{R}\sum_{i=1}^{t}\sum_{j=1}^{C} n_{Cij}^2 - \frac{1}{4RC}\sum_{i=1}^{t}\left(\sum_{j=1}^{C} n_{Cij} + \sum_{j=1}^{R} n_{Rij}\right)^2.$$

To apply the method of Lagrange multipliers let

$$\begin{aligned} L^* =\ & \frac{1}{C}\sum_{i=1}^{t}\sum_{j=1}^{R} n_{Rij}^2 + \frac{1}{R}\sum_{i=1}^{t}\sum_{j=1}^{C} n_{Cij}^2 - \frac{1}{4RC}\sum_{i=1}^{t}\left(\sum_{j=1}^{C} n_{Cij} + \sum_{j=1}^{R} n_{Rij}\right)^2 \\ & + \lambda_1\Big(\sum_{i=1}^{t}\sum_{j=1}^{R} n_{Rij} - RC\Big) + \lambda_2\Big(\sum_{i=1}^{t}\sum_{j=1}^{C} n_{Cij} - RC\Big), \end{aligned}$$

where λ_1 and λ_2 are Lagrange multipliers. Then

$$\frac{\partial L^*}{\partial n_{Rij}} = \frac{2}{C} n_{Rij} - \frac{1}{2RC} \sum_{i=1}^{t} \left(\sum_{j=1}^{C} n_{Cij} + \sum_{j=1}^{R} n_{Rij} \right) + \lambda_1.$$

Setting this expression equal to 0 and using (2.8), λ_1 can be evaluated in terms of t, R and C and gives $n_{Rij} = C/t$. This is a minimum point of the function L since

$$\frac{\partial^2 L^*}{\partial n_{Rij}^2} = \frac{2}{C} - \frac{1}{2RC} > 0.$$

Since L is symmetrical, $n_{Cij} = R/t$ also gives a minimum point.

However, the n_{Rij}'s and n_{Cij}'s are required to be integers, and since L is a continuous function the solution is taken which has the n_{kij}'s ($i = 1, \ldots, t$; $j = 1, \ldots, k$; $k = R, C$) as equal as possible subject to this constraint. This occurs when the n_{Rij}'s are equal to $[C/t]$ or $[C/t] + 1$ and the n_{Cij}'s are equal to $[R/t]$ or $[R/t] + 1$. It is easily verified that $C(t[R/t] + t - R)$ of the n_{Cij}'s should be set equal to $[R/t]$ and the remaining $C(R - t[R/t])$ set equal to $[R/t] + 1$, and $R(t[C/t] + t - C)$ of the n_{Rij}'s should be set equal to $[C/t]$ and the remaining $R(C - t[C/t])$ set equal to ([C/t]+1). Then

$$\begin{aligned} min\ L \;=\; & \frac{1}{C}\{RC + R(2C - t)[C/t] - Rt[C/t]^2\} && (2.9) \\ & + \frac{1}{R}\{RC + C(2R - t)[R/t] - Ct[R/t]^2\} && (2.10) \\ & - \frac{1}{4RC} \sum_{i=1}^{t} \left(\sum_{j=1}^{R} n_{Rij} + \sum_{j=1}^{C} n_{Cij} \right)^2 . && (2.11) \end{aligned}$$

Note that the terms (2.9) and (2.10) are the same as those obtained by applying Lemma 2.1 separately to $\sum_{i=1}^{t} \sum_{j=1}^{k} n_{kij}^2$, $k = R, C$. Since $\sum_{j=1}^{C} n_{Cij} = r_i = \sum_{j=1}^{R} n_{Rij}$ ($i = 1, \ldots, t$), the term (2.11) can be shown to equal $(\sum_{i=1}^{t} r_i^2)/RC$ and bounds r_l and r_h on the range of possible values for r_i ($i = 1, \ldots, t$) can be developed. These are

$$max(C[R/t], R[C/t], 1) \leq r_i \leq min(C[R/t] + C, R[C/t] + R).$$

Using Corollary 2.3, with $a = r_l$, $a + m = r_h$, $q = RC$ and $RC - r_l t \equiv k\ (mod\ r_h - r_l)$, the maximum value of $\sum_{i=1}^{t} r_i^2$ can be calculated directly. It then follows that the maximum value of $tr(A_{RC})$ is $RC - min\ L$, as in the statement of the theorem.

Remark: Several different formulations of L were minimised which, when tested, all gave the same numerical values of the bound. The above formulation was chosen because it produced a symmetrical bound and the restricted range for the feasible replications enabled the maximum value of $S = \sum_{i=1}^{t} r_i^2$ to be expressed in closed form.

A further bound on the total variance is now obtained by using Corollary 2.2 with c_{max} equal to the upper bound on $tr(A_{RC})$ of Theorem 2.5.

Definition 2.7 *Let the lower bound $B_2(H)$ on the total variance of the dual versus single treatments contrasts be*

$$B_2(H) = (\sum_{i=1}^{t-1} \theta_i^{1/2})^2 / max\{tr(A_{RC})\}$$

where θ_i, $i = 1, \ldots, t-1$, are the non-zero eigenvalues of the $H'H$ matrix for H given in (1.12) and $max\{tr(A_{RC})\}$ is the upper bound of Theorem 2.5.

Examples 2.1 and 2.2 are now reconsidered to see whether $B_2(H)$ improves upon $B_1(H)$ in these two cases.

Example 2.3 *For $n = m = C = 3$ and $R = 8$, $B_2(H) = B_1(H) = B(H) = 6.3185$ and since $B_F = 5.3333$, $B(H)$ remains the tighter of the two bounds.*

Example 2.4 *For $m = 2$, $n = 4$, $R = C = 4$, $B_2(H)$ takes the value 5.4530 which improves upon $B_1(H) = 5.1122$ by 6.6% and since $B_F = 5.1667$, $B_2(H)$ is the tighter bound and has an improvement of 5.5% on the value of B_F.*

2.6 Assessing the accuracy of the bounds

In order to test the accuracy of the bounds of the previous section, a program written by Jones & Eccleston (1980) was used. This program will be referred to as *JE* in this thesis. The algorithm allows two user-given components or computer-generated components to be almagamated in order to obtain a row-column design. In both cases, the algorithm then uses exchange and interchange procedures on the initial row-column design in an attempt to find the A-optimal row-column design for the specified experiment size. The program has parameter

limits of fifteen on each of the number of treatments, rows and columns and tends to become slow when processing large designs. However, it has been very useful in assessing both design and bound performance and a comparison with *JE* has been included in all the design assessments given in Chapter 3.

Definition 2.8 *The* discrepancy *of a design d compared with a value Q for the estimation of* $H\tau$ *is*

$$\frac{tr(H\Omega_d H') - Q}{Q} \times 100.$$

For the purposes of this thesis the value Q will either represent a lower bound on the total variance of our contrasts of interest or $min\{tr(H\Omega_d H')\}$ found by *JE*.

A numerical assessment of the bounds $B_1(H)$, $B_2(H)$ and B_F was performed for the parameter values $2 \leq m \leq 5$, $3 \leq n \leq 5$, $2 \leq R, C \leq 15$. This revealed that $B_1(H)$ only improved upon B_F when R was small in comparison with the number of treatments. This is illustrated in Example 2.1 where $B_1(H)$ is greater than B_F and has a discrepancy of 6.9% with $tr(H\Omega_{RC}H')$ of the design found by *JE* with the smallest total variance of the estimators of the dual versus single contrasts. Hence $B_1(H)$ is an acceptable bound in this case. In Example 2.2, B_F is the tighter of the two bounds, yet it has a discrepancy of 34.1% with the total variance of the contrasts of interest of the most A-efficient design found by *JE*, so neither bound performs well in this particular case. The proportion of cases in the numerical study for which $B_1(H) > B_F$ for each value of t depends on t; an exact relationship has not been formulated. For the experiment sizes used in the assessment, the proportion of cases for which $B_1(H) > B_F$ ranges from 25% to 50% for $5 \leq t \leq 24$.

The performance of the bound $B_2(H)$ is now considered. The same numerical study showed that $B_2(H) \geq B_1(H)$ for the entire range of parameter values. Hence the bound $B_1(H)$ is not used in any further work. The largest improvements occur when R is small compared with the size of t and C. These conclusions are reinforced by considering Examples 2.3 and 2.4. In the latter, $B_2(H)$ is the tighter bound and has a discrepancy of 27.1% with $tr(H\Omega_{RC}H')$ of the most A-efficient design found by *JE*. Although this is a poor performance it is better than the 34.1% discrepancy between B_F and the results of *JE*. In the first example which has $t - 1 = R > C$, it is seen that $B_2(H)$ does not improve upon $B_1(H)$.

It is also interesting to consider for which parameter values the bound $B_2(H)$ improves upon B_F. The numerical comparison revealed that $B_2(H)$ is greater than B_F when R is small in comparison with t which is also when $B_1(H)$ tends to improve upon B_F. It was noted that although $B_2(H)$ is always greater than or equal to $B_1(H)$, the improvement gained through using $B_2(H)$ is often to no avail because B_F remains the tighter bound. There were some cases where $B_2(H)$ improved on both $B_1(H)$ and B_F to overtake B_F as the tighter bound but these were relatively few. The proportion of cases in the numerical study for which $B_2(H) > B_F$ ranges from 0% to 15% for $5 \leq t \leq 24$.

The following two examples serve to further emphasize the points made above. In Example 2.5, t is less than both R and C and B_F is seen to be the tighter bound whereas Example 2.6 shows that $B_2(H)$ is tighter for small R and C.

Example 2.5 *For* $m = 2$, $n = 3$ *and* $R = C = 14$, $B_2(H) = 0.1810$, $B_F = 0.1989$ *and for these parameter values the most efficient row-column design, under the A-criterion, found by* JE *has* $tr(H\Omega_{RC}H') = 0.2008$. *The discrepancies of bounds* $B_2(H)$ *and* B_F *with the result of* JE *are 10.9% and 0.9% respectively, indicating that, although* $B_2(H)$ *is acceptable for this experiment size,* B_F *is much tighter.*

Example 2.6 *For* $m = 2$, $n = 3$, $R = 5$ *and* $C = 2$, $B_2(H) = 5.6472$, $B_F = 4.0$ *and the best row-column design, under the A-criterion, generated by* JE *has* $tr(H\Omega_{RC}H') = 6.4$. *The discrepancies of* $B_2(H)$ *and* B_F *with the result of* JE *are 13.3% and 60% respectively, indicating that* $B_2(H)$ *is an acceptable bound for these parameter values while* B_F *has a very poor performance.*

2.6.1 Recommended bound

Since it has not been possible to determine conditions under which one bound is uniformly tighter than the other, the recommended overall bound B is

$$B = max\{B_F, B_2(H)\}. \tag{2.12}$$

A further assessment of bound performance will be made in Chapter 3 by comparing the shortfall between the bound of (2.12) and the total variance of the best design, under the A-criterion, found by *JE*.

Chapter 3

Row-column Designs with part-balance for the dual versus single treatment comparisons

3.1 Introduction

The purpose of this chapter is to investigate row-column designs which have both component designs part-balanced with respect to the dual versus single treatments contrasts.

Balanced row-column designs with t treatments, each replicated r_e times and arranged in R blocks of size C, have the property that all pairwise treatment comparisons are estimated with the same accuracy under model (1.1). However, these designs only exist for limited combinations of t, R and C, and generally require an infeasibly large value of r_e. Part-balanced row-column designs are a compromise between total balance and the absence of balance. The advantage of using part-balanced designs for estimating the dual versus single treatments comparisons is that all the *dual versus A* comparisons are estimated with a common variance, v_A say, and all the *dual versus B* comparisons are estimated with a common variance v_B.

In this chapter, several types of row-column designs are examined. The family of reinforced group divisible row-column designs is defined in Section 3.3 and necessary conditions for the existence of the designs are established. Properties

of the designs are investigated in Section 3.4. In Section 3.5, efficient row and column component designs selected from the classes of R-type and S-type part-balanced designs are identified. The construction of row-column designs using these components is discussed in Section 3.6. For both these families of designs, tables are given listing the most A-efficient PBDS row-column designs found which also include a critical assessment of design performance against the bounds of Chapter 2 and against the most A-efficient design found by *JE*.

3.2 PBDS Row-Column Designs

From Theorem 1.1, a row-column design has part-balance with respect to the dual versus single treatment contrasts if and only if its information matrix, A_{RC}, has structure (1.14).

Definition 3.1 *Let $D^*_{RC}(n, m, R, C)$ be the class of all connected row-column designs for an $n \times m$ experiment with 00 excluded, arranged in R rows and C columns.*

Designs in D^*_{RC} can be obtained by amalgamating row and column PBDS designs, as in the following example.

Example 3.1 *For m=2, n=3, R=3 and C=6 and using designs tabulated by Gerami (1991) let the row component be*

Block 1	*01*	*10*	*20*	*11*	*11*	*21*
Block 2	*01*	*10*	*20*	*11*	*21*	*21*
Block 3	*01*	*01*	*10*	*20*	*11*	*21*

and the column component be

Block 1	*01*	*10*	*11*
Block 2	*01*	*20*	*21*
Block 3	*01*	*10*	*11*
Block 4	*01*	*20*	*21*
Block 5	*10*	*11*	*21*
Block 6	*20*	*11*	*21.*

On amalgamation, the following row-column design is obtained

$$\begin{array}{cccccc} 01 & 20 & 10 & 21 & 11 & 11 \\ 10 & 01 & 11 & 20 & 21 & 21 \\ 11 & 21 & 01 & 01 & 10 & 20. \end{array}$$

The following theorem shows that any row-column design constructed in this way has part-balance.

Theorem 3.1 *Let $d \in D^*_{RC}(n, 2, R, C)$ have PBDS row and column component designs, then d has part-balance for the dual versus single treatment comparisons.*

Proof: From (1.7), the structure of A_{RC} depends on the structure of A_R, A_C and r and from (1.14), A_R and A_C have the form

$$A_j = \begin{pmatrix} a_{j1} & a_{j2}1'_p & a_{j3}1'_p \\ a_{j2}1_p & a_{j4}I_p + a_{j5}J_p & a_{j6}I_p + a_{j7}J_p \\ a_{j3}1_p & a_{j6}I_p + a_{j7}J_p & a_{j8}I_p + a_{j9}J_p \end{pmatrix}, \tag{3.1}$$

where $j = R$ or C respectively. Then, putting $b_i = a_{Ri} + a_{Ci}$ $(i = 1, \ldots, 9)$,

$$A_R + A_C = \begin{pmatrix} b_1 & b_2 1'_p & b_3 1'_p \\ b_2 1_p & b_4 I_p + b_5 J_p & b_6 I_p + b_7 J_p \\ b_3 1_p & b_6 I_p + b_7 J_p & b_8 I_p + b_9 J_p \end{pmatrix}.$$

Let r have ith entry r_i $(i = 1, \ldots, 2n-1)$. Then

$$\frac{rr'}{RC} - r^{\delta} = \frac{1}{RC} \begin{pmatrix} r_1(r_1 - RC) & r_1 r_2 & \cdots & r_1 r_{2n-1} \\ r_1 r_2 & r_2(r_2 - RC) & \cdots & r_2 r_{2n-1} \\ \vdots & \vdots & \ddots & \vdots \\ r_1 r_{2n-1} & r_2 r_{2n-1} & \cdots & r_{2n-1}(r_{2n-1} - RC) \end{pmatrix}.$$

Since PBDS designs have a treatment replication vector of the form

$$\begin{pmatrix} r_B & r_A 1'_{n-1} & r_D 1'_{n-1} \end{pmatrix}', \tag{3.2}$$

it follows that A_{RC} has structure (1.14).

Corollary 3.1 *The information matrix for a row-column design* $d \in D^*_{RC}(n, 2, R, C)$ *with part-balanced row and column component designs has structure (3.1) with* $j = RC$, *and*

$$\begin{aligned}
a_{RC1} &= a_{R1} + a_{C1} - r_B + r_B^2/RC \\
a_{RC2} &= a_{R2} + a_{C2} + r_B r_A/RC \\
a_{RC3} &= a_{R3} + a_{C3} + r_B r_D/RC \\
a_{RC4} &= a_{R4} + a_{C4} - r_A \\
a_{RC5} &= a_{R5} + a_{C5} + r_A^2/RC \\
a_{RC6} &= a_{R6} + a_{C6} \\
a_{RC7} &= a_{R7} + a_{C7} + r_A r_D/RC \\
a_{RC8} &= a_{R8} + a_{C8} - r_D \\
a_{RC9} &= a_{R9} + a_{C9} + r_D^2/RC.
\end{aligned}$$

In this thesis, attention is restricted to connected row-column designs, that is designs for which A_{RC} has only one zero eigenvalue. The following lemma characterises connected designs in the PBDS class.

Lemma 3.1 *Let* d *be a PBDS block or row-column design with information matrix (1.14), then* d *is disconnected if and only if* $a_6^2 = a_4 a_8$ *or* $(a_6 + pa_7)^2 = (a_4 + pa_5)(a_8 + pa_9)$, *where* a_i $(i = 4, \ldots, 9)$ *denote* a_{RCi}, a_{Ri} *or* a_{Ci}, *the parameters of the information matrices of the row-column design, row and column component designs respectively.*

Proof: If design d is disconnected then at least one of the eigenvalues, denoted by λ_i $(i = 1, \ldots, t-1)$, of the information matrix A_d must be zero. From Table 3.1, $\lambda_1 = 0$ implies $\gamma \leq 0$ and $(a_6 + pa_7)^2 = (a_4 + pa_5)(a_8 + pa_9)$ and $\lambda_2 = 0$ implies $\gamma \geq 0$ and $(a_6 + pa_7)^2 = (a_4 + pa_5)(a_8 + pa_9)$. Hence, if λ_1 or λ_2 is equal to zero then $(a_6 + pa_7)^2 = (a_4 + pa_5)(a_8 + pa_9)$. Similarly, $\lambda_3 = 0$ implies $a_4 + a_8 \leq 0$ and $a_6^2 = a_4 a_8$ and $\lambda_4 = 0$ implies $a_4 + a_8 \geq 0$ and $a_6^2 = a_4 a_8$. Hence, if λ_3 or λ_4 equal to zero then $a_6^2 = a_4 a_8$.

Conversely if $(a_6 + pa_7)^2 = (a_4 + pa_5)(a_8 + pa_9)$ then

$$\lambda_1 = \begin{cases} 0 & \text{if } \gamma \leq 0 \\ \gamma & \text{otherwise} \end{cases}$$

Table 3.1: Eigenvalues of the intra-block information matrix of a PBDS design; γ denotes $(p+1)(a_4+pa_5+a_8+pa_9)+2p(a_6+pa_7)$, $p=n-1$ and $a_4,\ldots,a_9$ denote the parameters of the information matrix of the design, see equation (1.14).

Eigenvalues	Multiplicity
$\lambda_1 = \frac{\gamma+\sqrt{\gamma^2+4(2p+1)[(a_6+pa_7)^2-(a_4+pa_5)(a_8+pa_9)]}}{2}$	1
$\lambda_2 = \frac{\gamma-\sqrt{\gamma^2+4(2p+1)[(a_6+pa_7)^2-(a_4+pa_5)(a_8+pa_9)]}}{2}$	1
$\lambda_3 = \frac{a_4+a_8+\sqrt{(a_4+a_8)^2+4(a_6^2-a_4a_8)}}{2}$	$p-1$
$\lambda_4 = \frac{a_4+a_8-\sqrt{(a_4+a_8)^2+4(a_6^2-a_4a_8)}}{2}$	$p-1$
$\lambda_5 = 0$	1

and

$$\lambda_2 = \begin{cases} -\gamma & \text{if } \gamma \leq 0 \\ 0 & \text{otherwise} \end{cases},$$

where γ is given in Table 3.1. Hence either λ_1 or λ_2 must be zero for all a_i $(i=4,\ldots,9)$. If $a_6^2 = a_4a_8$ then

$$\lambda_3 = \begin{cases} 0 & \text{if } a_4+a_8 \leq 0 \\ a_4+a_8 & \text{otherwise} \end{cases}$$

and

$$\lambda_4 = \begin{cases} -(a_4+a_8) & \text{if } a_4+a_8 \leq 0 \\ 0 & \text{otherwise} \end{cases}.$$

Hence either λ_3 or λ_4 must be zero for all a_i $(i=4,\ldots,9)$.

3.3 Reinforced Group Divisible Designs

The purpose of this section is to examine necessary conditions for a row-column PBDS design to be constructed from row and column components which are

both reinforced group divisible designs. Firstly, consider the definition and some properties of group divisible (GD) designs.

Let $t_1 = m_1 m_2$ treatments be arranged in m_1 groups each of m_2 treatments, where treatments in the same group are called first associates and those in different groups are called second associates. A GD design with parameters $(b, k, r_e, \lambda_1, \lambda_2)$ has b blocks of size k, equal treatment replication r_e and each treatment appearing λ_1 times with each of its first associates and λ_2 times with each of its second associates.

All GD designs have parameter values which satisfy certain conditions, see John (1980, Chapter 5). In particular,

$$r_e t_1 = bk \tag{3.3}$$

$$r_e(k-1) = \lambda_1(m_2 - 1) + \lambda_2 m_2(m_1 - 1) \tag{3.4}$$

$$r_e k \geq 0 \tag{3.5}$$

$$\lambda_2 \leq r_e k / t_1 \tag{3.6}$$

$$\lambda_1 \leq r_e. \tag{3.7}$$

The following definition of a reinforced group divisible design (RGDD) for an $n \times 2$ experiment with b blocks of size k, where $2 < k < t = 2n - 1$, is due to Gerami & Lewis (1992).

Definition 3.2 *Let d_1 be a group divisible design with $m_1 m_2$ treatments, where $m_1 = n - 1 \geq 2$ and $m_2 = 2$, replication r_e, b blocks of size $k_1 = k - 1 \geq 2$ and jth associates occurring in λ_j blocks $(j = 1, 2)$. Map the treatment labels in d_1 to $i0$, $i1$ $(i = 1, \ldots, n-1)$ so that $i0$, $i1$ $(i = 1, \ldots, n-1)$ form the pairs of first associates. A reinforced group divisible design is then formed by reinforcing each block by the inclusion of treatment* 01.

It follows from Definition 3.2 that an RGDD has part-balance for the dual versus single contrasts and will always have a replication vector of the form $r' = \begin{pmatrix} b & r_e 1'_{n-1} & r_e 1'_{n-1} \end{pmatrix}'$. Hence, from Theorem 3.1, any row-column design having RGDD components has part-balance. This suggests that RGDDs may make suitable components for row-column designs.

Definition 3.3 *A reinforced group divisible row-column (RGDRC) design is a design having row and column components which are both reinforced group divisible designs.*

The following example shows that such row-column designs exist.

Example 3.2 *Suppose* $m = 2$, $n = 3$ *and* $R = C = 4$ *and identical row and column RGDD components are used:*

Block 1	*01*	*10*	*11*	*21*
Block 2	*01*	*20*	*11*	*21*
Block 3	*01*	*10*	*11*	*21*
Block 4	*01*	*20*	*11*	*21,*

which amalgamate to the RGDRC design

01	*11*	*10*	*21*
11	*01*	*21*	*20*
10	*21*	*01*	*11*
21	*20*	*11*	*01.*

Note that the above example has an equal number of rows and columns. The following result shows that reinforced group divisible row-column designs exist only when the numbers of rows and columns are equal.

Theorem 3.2 *A necessary condition for the existence of a reinforced group divisible row-column design in an* $R \times C$ *array is that* $R = C$.

Proof: The parameters of the row-column design are subject to the conditions imposed by the group divisible construction of the component designs. Let the row component design have R blocks of size C and arise by reinforcing a group divisible design with parameters $(R, C-1, r_e, \lambda_1^R, \lambda_2^R)$. Then from (3.3), (3.4), (3.6) and (3.7),

$$2r_e(n-1) = R(C-1) \tag{3.8}$$

$$r_e(C-2) = \lambda_1^R + 2(n-2)\lambda_2^R \tag{3.9}$$

$$\lambda_2^R \leq \frac{r_e(C-1)}{2(n-1)} \tag{3.10}$$

$$\lambda_1^R \leq r_e. \tag{3.11}$$

Similarly, the column component design is formed from a GD design with parameters $(C, R-1, r_e, \lambda_1^C, \lambda_2^C)$ and hence

$$2r_e(n-1) = C(R-1) \tag{3.12}$$

$$r_e(R-2) = \lambda_1^C + 2(n-2)\lambda_2^C \tag{3.13}$$

$$\lambda_2^C \leq \frac{r_e(R-1)}{2(n-1)} \tag{3.14}$$

$$\lambda_1^C \leq r_e. \tag{3.15}$$

Equating (3.8) and (3.12) gives $2r_e(n-1) = R(C-1) = C(R-1)$ and the result follows.

A further necessary condition is identified in Theorem 3.3 for which the following two lemmas are needed. The first lemma investigates conditions on the parameters λ_1 and λ_2 of the component designs.

Lemma 3.2 *A necessary condition for a row-column design to be obtained from two component reinforced group divisible designs with respective parameters* $(R, R-1, r_e, \lambda_1^R, \lambda_2^R)$ *and* $(R, R-1, r_e, \lambda_1^C, \lambda_2^C)$*, for the row and column component designs, where* $\lambda_i^R \neq \lambda_i^C$ *for at least one of* $i = R, C$*, is*

$$|\lambda_1^R - \lambda_1^C| \geq 2(n-2).$$

Proof: Using Theorem 3.2, equations (3.9) and (3.13) can be rewritten as

$$r_e(R-2) = \lambda_1^R + 2(n-2)\lambda_2^R$$

and

$$r_e(R-2) = \lambda_1^C + 2(n-2)\lambda_2^C$$

respectively. Hence

$$\lambda_1^R - \lambda_1^C = 2(n-2)(\lambda_2^C - \lambda_2^R). \tag{3.16}$$

Since $n \geq 3$ by Definition 3.2, from (3.16) and the fact that $\lambda_i^R \neq \lambda_i^C$ for at least one of $i = R, C$, it follows that both $\lambda_1^R \neq \lambda_1^C$ and $\lambda_2^R \neq \lambda_2^C$. Without loss of generality let $\lambda_1^R > \lambda_1^C$ then, from (3.16), $\lambda_2^C > \lambda_2^R$. Since λ_2^j $(j = R, C)$ are integers, by definition, $\lambda_2^C - \lambda_2^R \geq 1$. Hence $\lambda_1^R - \lambda_1^C \geq 2(n-2)$.

Lemma 3.3 *For any two reinforced group divisible component designs in the class $D^*(n,2,R,R)$, of Definition 2.2, with the property that $\lambda_i^R \neq \lambda_i^C$ $(i=1,2)$,*

$$|\lambda_1^R - \lambda_1^C| \leq M_n(R) = \frac{R(R-1)(2n-R-1)}{2(n-1)^2}.$$

Proof: The first step is to establish a lower bound on λ_1^j $(j = R, C)$. Using (3.9) and Theorem 3.2, λ_2^R can be expressed in the form

$$\lambda_2^R = \frac{r_e(R-2) - \lambda_1^R}{2(n-2)},$$

and hence, by (3.10),

$$\frac{r_e(R-2) - \lambda_1^R}{2(n-2)} \leq \frac{r_e(R-1)}{2(n-1)}.$$

It follows, after some manipulation, that

$$\frac{r_e(R-n)}{n-1} \leq \lambda_1^R.$$

Hence, using (3.11),

$$\frac{r_e(R-n)}{n-1} \leq \lambda_1^R \leq r_e.$$

A similar argument, using equations (3.13), (3.14) and (3.15) shows that

$$\frac{r_e(R-n)}{n-1} \leq \lambda_1^C \leq r_e.$$

Now, assuming again without loss of generality, that $\lambda_1^R > \lambda_1^C$,

$$\begin{aligned} M_n(R) &= max(\lambda_1^R) - min(\lambda_1^C) \\ &= r_e - \frac{r_e(R-n)}{n-1} \\ &= \frac{r_e(2n-R-1)}{n-1}. \end{aligned}$$

But $r_e = R(R-1)/\{2(n-1)\}$ from (3.8) with $R = C$. Hence

$$M_n(R) = \frac{R(R-1)(2n-R-1)}{2(n-1)^2}.$$

Theorem 3.3 *A necessary condition for the existence of a reinforced group divisible row-column design, with component parameters* $(R, R-1, r_e, \lambda_1^R, \lambda_2^R)$ *and* $(R, R-1, r_e, \lambda_1^C, \lambda_2^C)$, *is that* $\lambda_i^R = \lambda_i^C$ $(i = 1, 2)$.

Proof: Suppose that $\lambda_i^R \neq \lambda_i^C$ for at least one of $i = 1, 2$. Then, from (3.16), $\lambda_i^R \neq \lambda_i^C$ $(i = 1, 2)$. From Lemmas 3.2 and 3.3, it follows that a necessary condition for an RGDRC design to be obtained from two component designs with different association parameters is

$$M_n(R) \geq |\lambda_1^R - \lambda_1^C| \geq 2(n-2). \tag{3.17}$$

To investigate whether this inequality can be satisfied, the maximum value of $M_n(R)$ for fixed n is evaluated by setting the derivative of $M_n(R)$ with respect to R equal to zero. This gives the equation

$$3R^2 - 4nR + (2n-1) = 0$$

which has roots

$$R = \frac{2n \pm \sqrt{4n^2 - 6n + 3}}{3}.$$

The root with the negative sign is infeasible since

$$4n^2 - 6n + 3 = (2n - 3/2)^2 + 3/4.$$

Hence,

$$\sqrt{4n^2 - 6n + 3} > 2n - 3/2,$$

and on substituting for R,

$$R = \frac{2n - \sqrt{4n^2 - 6n + 3}}{3} < \frac{2n - (2n - 3/2)}{3} = \frac{1}{2}.$$

Since $R \geq 2$, it follows that $R = (2n + \sqrt{4n^2 - 6n + 3})/3$ is the only feasible solution. This value of R is easily shown to maximise $M_n(R)$ for fixed n by evaluating its second derivative.

Evaluating $M_n(R)$ at $R = (2n + \sqrt{4n^2 - 6n + 3})/3$ gives

$$max_R \{M_n(R)\} = \frac{(8n^3 - 18n^2 + 9n + (4n^2 - 6n + 3)^{3/2})}{27(n-1)^2}.$$

Therefore

$$max_R \{M_n(R)\} - 2(n-2) = \frac{-46n^3 + 198n^2 - 261n + 108 + (4n^2 - 6n + 3)^{3/2}}{27(n-1)^2} \tag{3.18}$$

which is dependent on n only. It is easily shown that $-46n^3+198n^2-261n+108 < 0$ for $n \geq 3$ and that $(4n^2-6n+3)^{3/2} > 0$ for all n. From (3.18) and the fact that $\sqrt{4n^2-6n+3} < 2n-1$ for $n \geq 2$, it follows that

$$max_R\{M_n(R)\} - 2(n-2) < \frac{-38n^2+148n-107}{27(n-1)}.$$

Therefore $max_R\{M_n(R)\} - 2(n-2) < 0$ for $n \geq 3$ and $R \geq 3$. Hence (3.17) can never be satisfied and the theorem is proved by contradiction.

Corollary 3.2 *A necessary condition for the existence of a reinforced group divisible row-column design is that* $A_R = A_C$.

Proof: Using Theorem 3.2, the information matrices for the RGD component designs can be written in the form

$$A_j = \frac{1}{R}\begin{pmatrix} R(R-1) & -r_e 1_p' & -r_e 1_p' \\ -r_e 1_p & [r_e(R-1)+\lambda_2^j]I_p - \lambda_2^j J_p & -(\lambda_1^j-\lambda_2^j)I_p - \lambda_2^j J_p \\ -r_e 1_p & -(\lambda_1^j-\lambda_2^j)I_p - \lambda_2^j J_p & [r_e(R-1)+\lambda_2^j]I_p - \lambda_2^j J_p \end{pmatrix} \tag{3.19}$$

for $j = R, C$. Then the result follows directly from Theorem 3.3.

3.4 Properties of RGD row-column designs

A useful feature of row-column designs constructed from RGD components is that the variances of the dual versus single treatment comparisons can be expressed in terms of the parameters of the information matrix of the repeated component design.

Theorem 3.4 *The variance-covariance matrix of a reinforced group divisible row-column design is* $H\Omega_{RC}H'\sigma^2$ *where*

$$H\Omega_{RC}H' = \begin{pmatrix} x_1 I_p + y J_p & (x_1-x_2)I_p \\ (x_1-x_2)I_p & 2(x_1-x_2)I_p \end{pmatrix},$$

H is given in (1.12), $x_1 = a_{RC4}/(s_1 s_2)$, $x_2 = -a_{RC6}/(s_1 s_2)$, $y = -a_{RC5}/\{s_2(s_2+2pa_{RC5})\}$, $s_1 = a_{RC4} - a_{RC6}$ *and* $s_2 = a_{RC4} + a_{RC6}$.

Proof: The information matrix of an RGDD for a single blocking factor is of the form (3.1) with

$$a_{j1} = R - 1, \tag{3.20}$$

$$a_{j2} = a_{j3} = -r_e/R, \tag{3.21}$$

$$a_{j4} = a_{j8} = [r_e(R-1) + \lambda_2]/R, \tag{3.22}$$

$$a_{j5} = a_{j7} = a_{j9} = -\lambda_2/R, \tag{3.23}$$

$$a_{j6} = -(\lambda_1 - \lambda_2)/R. \tag{3.24}$$

From Theorem 3.3, an RGDRC design has the same parameters for the row and column components. From Corollary 3.1, it follows that the information matrix for the row-column design will be of the same form as the information matrices for the components but with corresponding entries $a_{RC1} = R-1$, $a_{RC2} = -r_e/R$, $a_{RC4} = [r_e(R-2)+2\lambda_2]/R$, $a_{RC5} = -(2R\lambda_2 - r_e^2)/R^2$ and $a_{RC6} = -2(\lambda_1 - \lambda_2)/R$. In order to find a generalised inverse of the row-column information matrix, A_{RC} is expressed in the form

$$A_{RC} = \begin{pmatrix} a_{RC1} & a_{RC2}1'_{2p} \\ a_{RC2}1_{2p} & F \end{pmatrix},$$

where $F = [\{(a_{RC4} - a_{RC6})I_2 + a_{RC6}J_2\} \otimes I_p + a_{RC5}J_2 \otimes J_p]$. Then, from Searle (1971, p2), a generalised inverse Ω_{RC} of A_{RC} is F^{-1} augmented by a first row and first column with every entry zero. F^{-1} is found by applying the following result

$$(X \otimes I_p + Y \otimes J_p)^{-1} = X^{-1} \otimes I_p - \{(X + pY)^{-1}YX^{-1}\} \otimes J_p,$$

which holds for any square matrices X and Y for which all the inverses exist. In this particular application $X = (a_{RC4} - a_{RC6})I_2 + a_{RC6}J_2$ and $Y = a_{RC5}J_2$. Using the result

$$(aI_t + bJ_t)^{-1} = \frac{1}{a}I_t - \frac{b}{a(a+tb)}J_t, \tag{3.25}$$

the inverse of X can be written as

$$X^{-1} = \frac{1}{a_{RC4} - a_{RC6}}I_2 - \frac{a_{RC6}}{(a_{RC4} - a_{RC6})(a_{RC4} + a_{RC6})}J_2.$$

Since $(X + pY) = (a_{RC4} - a_{RC6})I_2 + (pa_{RC5} + a_{RC6})J_2$, a further application of (3.25) gives

$$(X + pY)^{-1} = \frac{1}{a_{RC4} - a_{RC6}}I_2 - \frac{(pa_{RC5} + a_{RC6})}{(a_{RC4} - a_{RC6})(a_{RC4} + a_{RC6} + 2pa_{RC5})}J_2.$$

Hence

$$\begin{aligned}(X+pY)^{-1}Y &= \frac{a_{RC5}}{a_{RC4}-a_{RC6}}J_2 - \frac{2a_{RC5}(pa_{RC5}+a_{RC6})}{(a_{RC4}-a_{RC6})(a_{RC4}+a_{RC6}+2pa_{RC5})}J_2 \\ &= \frac{a_{RC5}}{a_{RC4}+a_{RC6}+2pa_{RC5}}J_2,\end{aligned}$$

and

$$(X+pY)^{-1}YX^{-1} = \frac{a_{RC5}}{(a_{RC4}+a_{RC6}+2pa_{RC5})(a_{RC4}+a_{RC6})}J_2.$$

It follows that

$$F^{-1} = [(x_1-x_2)I_2 + x_2J_2] \otimes I_p + yJ_2 \otimes J_p,$$

where $x_1 = a_{RC4}/(s_1s_2)$, $x_2 = -a_{RC6}/(s_1s_2)$, $y = -a_{RC5}/[s_2(s_2+2pa_{RC5})]$, $s_1 = a_{RC4}-a_{RC6}$ and $s_2 = a_{RC4}+a_{RC6}$.

The generalised inverse can be written as

$$\Omega_{RC} = \begin{pmatrix} O & O_p' & O_p' \\ O_p & x_1I_p+yJ_p & x_2I_p+yJ_p \\ O_p & x_2I_p+yJ_p & x_1I_p+yJ_p \end{pmatrix}.$$

Note that it can be verified that $A_{RC}\Omega_{RC}A_{RC} = A_{RC}$.

For an $n \times 2$ experiment, the contrast matrix (1.12) is

$$H = \begin{pmatrix} -1_p & O_{p,p} & I_p \\ O_p & -I_p & I_p \end{pmatrix}.$$

Hence

$$H\Omega_{RC}H' = \begin{pmatrix} x_1I_p+yJ_p & (x_1-x_2)I_p \\ (x_1-x_2)I_p & 2(x_1-x_2)I_p \end{pmatrix}. \tag{3.26}$$

Note that the variance-covariance matrices for the single blocking factor components are of the form (3.26) with the same expressions for x_1, x_2, y, s_1 and s_2, given in terms of the a_{kj} for $j = 1,\ldots,9$ and $k = R, C$.

The dual versus single contrast variances can now be expressed in terms of the parameters of the component designs.

Theorem 3.5 *A reinforced group divisible row-column design has*

$$v_{RCA} = var(\hat{\tau}_{i1} - \hat{\tau}_{i0}) = \frac{2\sigma^2}{2f_1 - r_e}$$

and

$$\begin{aligned} v_{RCB} &= var(\hat{\tau}_{i1} - \hat{\tau}_{01}) \\ &= \left[\frac{2a_4 - r_e}{(2f_1 - r_e)(2f_2 - r_e)} - \frac{2a_5 + r_e^2/R^2}{(2f_2 - r_e)(2f_2 - r_e + 2p[2a_5 + r_e^2/R^2])}\right]\sigma^2 \end{aligned}$$

for $i = 1, \ldots, p$, *where* $f_1 = a_4 - a_6$, $f_2 = a_4 + a_6$ *and the* a_j $(j = 1, \ldots, 9)$ *are the parameters of the row component design.*

Proof: From Theorem 3.4,

$$v_{RCA} = 2(x_1 - x_2)\sigma^2 = \frac{2}{s_1}\sigma^2$$

and

$$v_{RCB} = (x_1 + y)\sigma^2 = \left(\frac{a_{RC4}}{s_1 s_2} - \frac{a_{RC5}}{s_2(s_2 + 2pa_{RC5})}\right)\sigma^2.$$

From Corollary 3.1, the a_{RCj}'s can be written in terms of the a_{Rj}'s and a_{Cj}'s $(j = 1, \ldots, 9)$ and, from Corollary 3.2, $a_{Rj} = a_{Cj}$ for $j = 1, \ldots, 9$. Let a_j $(j = 1, \ldots, 9)$ denote the parameters of the component design then the result follows after some algebraic manipulation.

This section concludes with a table listing the RGDRC designs. The component designs were identified by examining the group divisible designs tabulated by Clatworthy (1973), Freeman (1976) and John & Turner (1977) for suitable candidates for amalgamation. In general, the tabulated row-column design is not unique. It is the solution obtained by using the algorithm *JE* to amalgamate two component designs, see Jones & Eccleston (1980). For the smaller designs, amalgamation by hand is possible.

Some of the designs can be obtained by manipulating sets of mutually orthogonal Latin squares (MOLS), see the first entry of Table 3.2. This design has 3×2 treatments arranged in a 4×4 array and the group divisible part of the component design is an unreduced balanced incomplete block design with $t = 2n - 2$ treatment labels in an $R \times (C - 1)$ array. This design can be transformed to a Latin square by reinforcing each block with its previously missing A-alone or dual treatment. The Latin square can then be rearranged to have t distinct elements on the diagonal, provided that a set of MOLS exists for that order. The RGDRC design can be found by replacing each of the diagonal elements by the B-alone treatment, 01. The third entry in Table 3.2 which has seven treatments in a 6×6

array also has an unreduced balanced incomplete block design as its group divisible part of the component design. Unfortunately, the row-column design cannot be constructed using the above method since a set of MOLS does not exist for order six.

The small number of designs in this family, due to the restrictions on compatible designs given in Section 3.3, has made it difficult to identify similarities in the arrangements of the treatments in the row-column designs.

The figures in the column headed *% Disc* in Table 3.2 are the percentage discrepancies for the row-column design, the row component and the column component, each compared with an appropriate bound. The fourth figure represents the discrepancy between the listed row-column design and the most efficient design, under the A-criterion, found by *JE*.

It can be seen that the designs for $n = 4$ in a 6×6 array and $n = 8$ in a 7×7 array perform well since they both have a discrepancy of less than 10% with bound B of (2.12) and very small discrepancies with the total variance of the contrast estimators of the most A-efficient design found by *JE*. The design for $n = 3$ in a 4×4 array performs well in comparison with the most A-efficient design found by *JE* but has a discrepancy of 14.7% with the bound. However, it was remarked at the end of Chapter 2 that neither of the bounds $B_2(H)$ and B_F perform particularly well for the case where both R and C are less than t. It should be noted that this PBDS row-column design has a smaller total variance for the estimators of the contrasts of interest than any other PBDS row-column design found for parameters $n = 3$ and $R = C = 4$ and hence also appears in Table 3.5 at the end of the chapter. The design for $n = 4$ in a 4×4 array performs poorly compared with bound B of (2.12) and with the most A-efficient result found by running *JE*. However, it is a considerable improvement on the PBDS row-column design with S-type components which is listed in Table 3.10.

This section has shown that reinforced group divisible row-column designs can be as efficient or more efficient than some other PBDS designs and are a useful, but limited, source of designs. In the remaining sections of this chapter different types of PBDS component designs are investigated.

Table 3.2: Reinforced group divisible row-column designs for $m = 2$

n	R	C	Row-column design	% Disc R-C	Row	Col	JE
3	4	4	01 20 11 10 10 01 20 21 11 21 01 20 21 11 10 01	14.7	6.6	6.6	0.6
			Most A-efficient design found in the study for this expt size				
4	4	4	01 10 20 30 10 01 31 21 20 31 01 11 30 21 11 01	65.0	24.3	24.3	31.1
			More A-efficient than R-C design of Table 3.10				
	6	6	01 10 20 30 21 11 10 01 11 21 20 31 20 11 01 10 31 30 30 21 31 11 10 01 21 31 10 01 30 20 11 20 30 31 01 21	7.8	5.1	5.1	3.0
			PBDS R-C design in Table 3.12 has smaller total variance				
8	7	7	01 20 40 41 10 21 11 20 21 30 50 51 01 31 40 31 41 01 60 61 30 41 51 01 40 50 70 71 10 50 61 51 11 60 01 21 01 60 71 61 20 70 11 30 31 70 01 71 10	7.7	2.8	2.8	0
	8	8	01 10 20 40 30 50 60 70 10 01 41 21 51 30 71 60 20 41 01 10 61 71 31 50 40 21 10 01 70 61 51 31 30 51 61 70 01 11 20 41 50 30 71 61 11 01 40 21 60 71 31 51 20 40 01 11 70 60 50 31 41 21 11 01	26.2	12.2	12.2	17.2

3.5 PBDS row-column designs using R- and S-type block components

In this section, a special class of component designs is discussed. The class is a subclass of PBDS designs for a single blocking factor, arranged in b blocks each of size k. The section briefly outlines the subclass of C-designs and shows the structure of three distinct types. In Section 3.6, a method of obtaining row-column designs by amalgamating pairs of tabulated C-designs is described.

C-designs are defined and obtained by Gerami, Lewis, Majumdar & Notz (1993). The approach followed is to establish a design dependent bound on the trace of the inverse of the information matrix of the contrasts of interest, M^{-1}, using permutation matrices in a similar way to that of Kiefer (1975). The lower bound for any connected design d is given by

$$tr(M_d^{-1}) \geq tr(\bar{M}_d^{-1}), \tag{3.27}$$

where $\bar{M}_d$ is the average of M_d over all possible permutations in $\Pi = \{\pi : \pi = I_2 \otimes p_i\}$ and p_i, for $i = 1, \ldots, (n-1)!$, is the full set of permutation matrices each having order $n-1$.

An upper bound on $tr(\bar{M}_d^{-1})$ is developed which can be expressed in terms of combinatorial features of the design using the following notation:

Let n_{Bj}, n_{Aij} and n_{Dij} denote the replications within the jth block ($j = 1, \ldots, b$) of the treatment combinations 01, $i0$ and $i1$ belonging to treatment sets $B = \{01\}$, $A = \{i0;\ i = 1, \ldots, p\}$ and $D = \{i1;\ i = 1, \ldots, p\}$ where $p = n-1$. The following quantities can then be defined:

$$T_{Bj} = n_{Bj},\ T_{Aj} = \sum_{i=1}^{p} n_{Aij},\ T_{Dj} = \sum_{i=1}^{p} n_{Dij},$$

which denote the total number of units assigned to treatment combinations belonging to sets B, A and D respectively in block j, and

$$T_B = \sum_{j=1}^{b} T_{Bj},\ T_A = \sum_{j=1}^{b} T_{Aj},\ T_D = \sum_{j=1}^{b} T_{Dj}$$

denote the total number of units assigned to treatment combinations in sets B, A and D, as stated in Section 2.4.

The upper bound can now be expressed as

$$tr(\bar{M}_d^{-1}) \geq \frac{(n-1)}{T_B} + \frac{(n-1)^2}{T_A} + \frac{2(n-1)^2}{T_D}. \tag{3.28}$$

The authors define a class of desirable designs referred to as the U-class. A design is said to belong to the U-class if $M_d = \bar{M}_d$ and

$$n_{Yij} = [T_{Yj}/p] \text{ or } [T_{Yj}/p] + 1, \text{ for } Y = A, D$$

and

$$T_{Yj} = [T_Y/b] \text{ or } [T_Y/b] + 1, \text{ for } Y = A, B.$$

An improved upper bound on $tr(\bar{M}_d^{-1})$ is obtained for designs in the U-class which can be used to evaluate the performance of any design. It is desirable to find designs which achieve this upper bound. An algorithm has been developed to find the values of T_Y, T_{Yj} and n_{Yij} $(Y = A, B, D)$ which minimise $tr(\bar{M}_d^{-1})$ given in (3.28) subject to various combinatorial constraints. Let this set of parameters be denoted by $C^* = \{T_B^*, T_A^*, T_D^*, T_{Bj}^*, T_{Aj}^*, T_{Dj}^*, n_{Bij}^*, n_{Aij}^*, n_{Dij}^*\}$.

Definition 3.4 *A C-design is a design which belongs to the U-class and has parameters given by* C^*.

Once the set of parameters C^* has been obtained, the next stage is to construct the corresponding C-design. The design will have one of the following layouts, where u_i denotes the integer part of T_i/b for $i = B, A, D$.

R-type: If $u_i = T_i/b$ for $i = B, A, D$ are all integer then the design is said to be R-type and the layout of the design is shown in Figure 3.1.

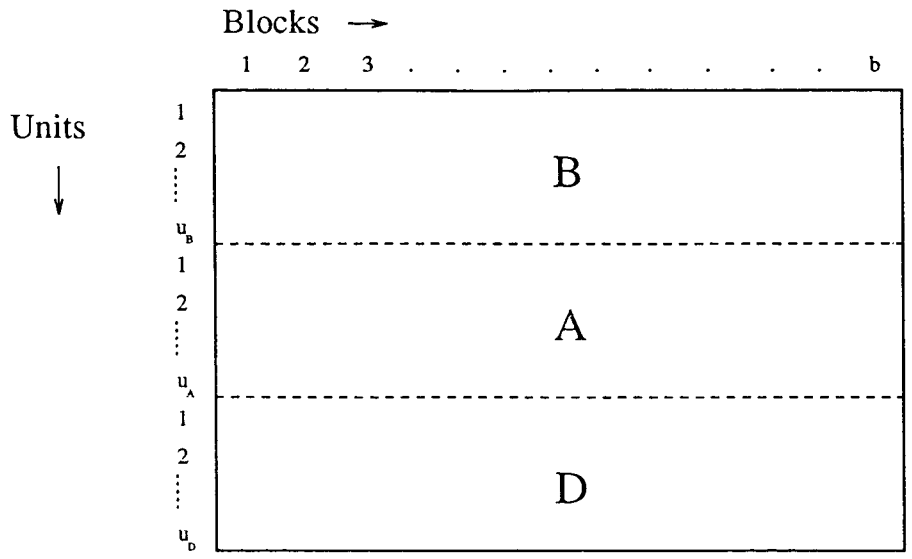

Figure 3.1: An R-type design; where $u_i = T_i/b$ is integer for $i = A, B, D$.

(R,S)-type: here 3 cases need to be considered.

1. R-type in terms of the B-alone treatment and S-type for the other two treatment sets. This will occur when T_B/b is integer and T_A/b and T_D/b are not integers. See Figure 3.2 for the layout of the design.

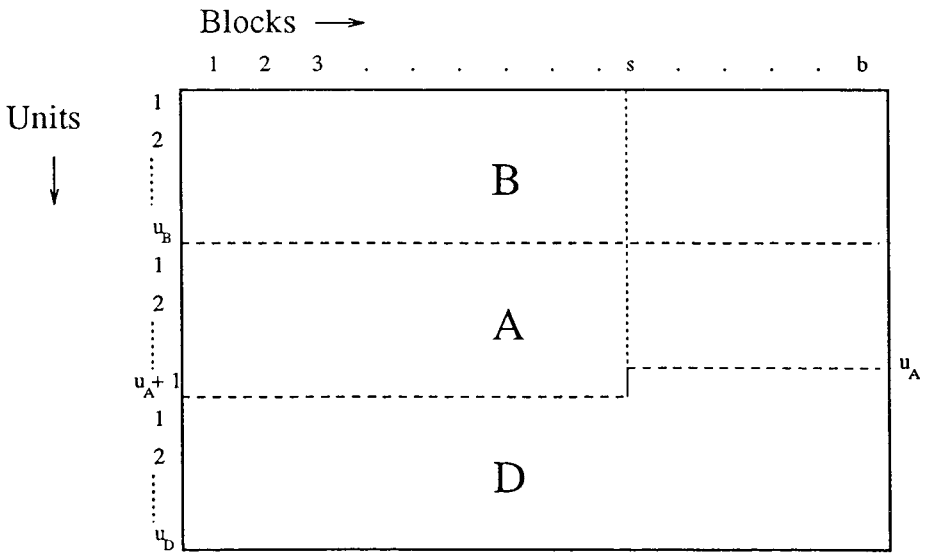

Figure 3.2: An (R,S)-type design, when T_A/b is not an integer and $s = T_A - bu_A$.

2. R-type in terms of the A-alone treatments and S-type in terms of the other two sets. This is the case when T_A/b is integer and T_B/b and T_D/b are not integers. Figure 3.3 shows the layout of the design.

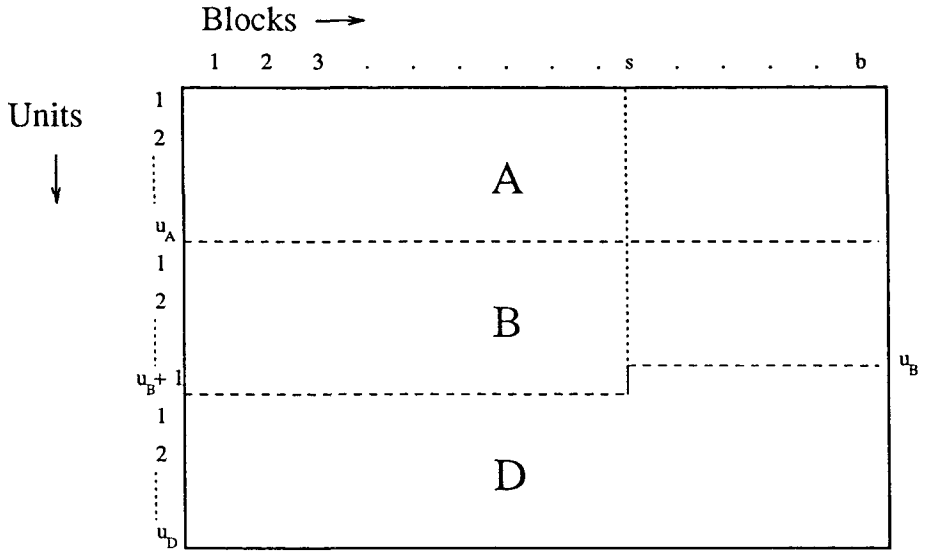

Figure 3.3: An (R,S)-type design, when T_B/b is not an integer and $s = T_B - bu_B$.

3. R-type in terms of the dual treatments and S-type in terms of the other two sets. This is the case when T_D/b is an integer and T_A/b and T_B/b are not integers. The layout of the design is shown in Figure 3.4.

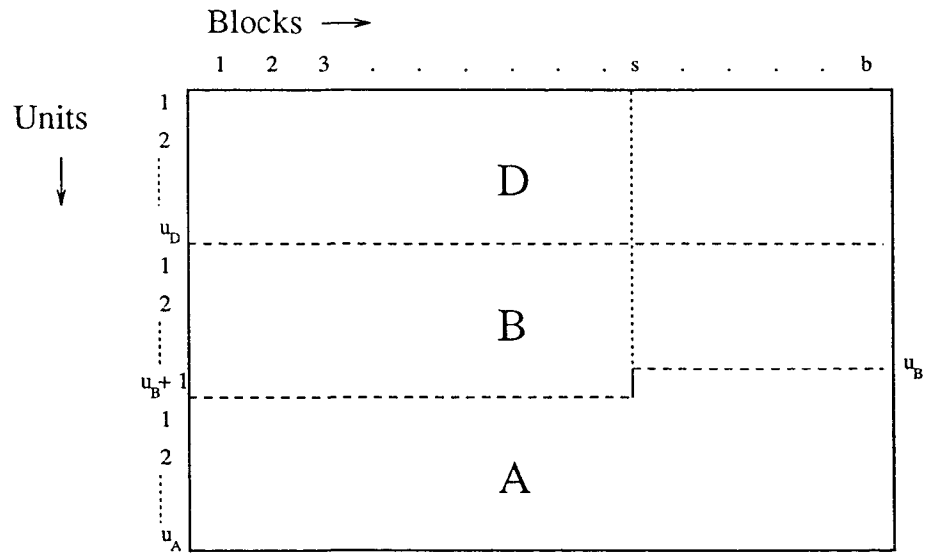

Figure 3.4: An (R,S)-type design, when T_B/b is not an integer and $s = T_B - bu_B$.

S-type: If none of the quantities T_A/b, T_B/b and T_D/b is integer then the design is said to be S-type and the layout of the design is given in Figure 3.5.

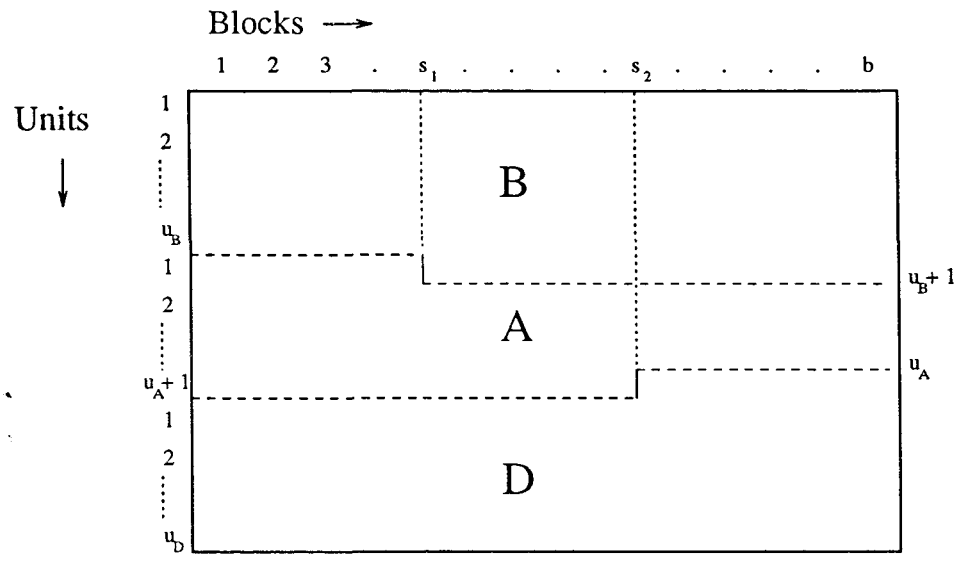

Figure 3.5: An S-type design, when $s_1 < s_2$, $s_1 = b - T_B + bu_B$ and $s_2 = T_A + b - bu_A - s_1$.

In the following section, pairs of C-designs found by the method outlined above are amalgamated to obtain efficient PBDS row-column designs.

3.6 Construction of row-column designs

This section begins by stating a simple necessary condition for the amalgamation of two designs for a single blocking factor. It then describes how two component C-designs, see Section 3.5, are selected for amalgamation.

Lemma 3.4 *A necessary condition for a row-column design having t treatments, R rows and C columns to be constructed by amalgamating two block designs for t treatments, one with R blocks of size C and the other with C blocks of size R is that the two block designs possess a common vector of treatment replications.*

Proof: In order to construct a row-column design by the amalgamation of two component designs, it is necessary to rearrange the treatments within blocks for one of the designs in such a way that the remaining block design is obtained

by taking blocks in the other direction. Since none of the treatments is removed or replaced, it is clear that two compatible block designs must have the same number of experimental units and equal treatment replication vectors.

The following method was used to obtain the row-column designs which are listed in the table at the end of this chapter. The initial step was to generate lists of efficient PBDS block designs for t treatments, arranged in b blocks each of size k, by the method of the search algorithm developed by Gerami, Lewis, Majumdar & Notz (1993) which is described in the previous section. A Fortran coding of the algorithm, written by Gerami (1991), which also checks for the existence of a PBDS design with the values of T_i^*, $i = A, B, D$, was used. Since it was considered desirable to look at a range of efficient PBDS designs and not just the best that could be found for each set of parameter values, the program was adapted to enable the generation of a maximum of twenty block designs in ascending order of the value of $tr(C_t \Omega_d C_t')$. The list of designs for t treatments in R blocks of size C was then compared with the list of designs for C blocks of size R and amalgamation was attempted for designs with the same values of T_i^* $(i = A, B, D)$ using the algorithm of Jones & Eccleston (1980).

It was found, by considering examples, that component designs which satisfy the condition of Lemma 3.4 usually could be combined. However, the following example demonstrates that the condition of Lemma 3.4 is not sufficient for amalgamation of components.

Example 3.3 *For $m = 2$, $n = 4$, and $R = C = 3$, let both the row and column components be the following design:*

Block 1	*01*	*10*	*11*
Block 2	*01*	*20*	*21*
Block 3	*01*	*30*	*31.*

Then Lemma 3.4 is satisfied with replication vector $r' = \begin{pmatrix} 3 & 1_3' & 1_3' \end{pmatrix}$.

The repeated component design is connected and an examination of the information matrix for the row-column design, A_{RC}, reveals that the row-column design would be connected if it were possible to construct it. However, it is impossible to rewrite the above block design in a form which has both a row block and a column block containing the treatments $i0$ and $i1$, for $i = 1, 2, 3$, since these treatments appear only once in the design.

There are some gaps in the row-column catalogue of Section 3.7 since it is not combinatorially possible to find compatible PBDS component designs for the entire range of values for n, b and k. Other gaps are due to the fact that some of the row-column designs with small numbers of experimental units are disconnected, although both the row and column component designs are connected. An examination of the elements of the row-column information matrix, A_{RC}, showed that these designs satisfy the conditions for disconnectedness given in Lemma 3.1.

Example 3.4 *For $m = 2$, $n = 3$, $R = 2$ and $C = 4$, let the row component be*

Block 1	*01*	*10*	*11*	*21*
Block 2	*01*	*20*	*11*	*21*

and the column component be

Block 1	*01*	*11*
Block 2	*01*	*21*
Block 3	*10*	*11*
Block 4	*20*	*21.*

The row-column design obtained by amalgamation of these components is

11	*01*	*10*	*21*
01	*21*	*11*	*20.*

This design has parameters $a_{RC4} = 0.25$, $a_{RC5} = 0.125$, $a_{RC6} = 0.5$, $a_{RC7} = a_{RC9} = 0$ and $a_{RC8} = 1$, which satisfy the condition for disconectedness, $a_{RC6}^2 = a_{RC4}a_{RC8}$, of Lemma 3.1.

A further complication of small R and C is illustrated by the design with $n = 3$, $m = 2$ and $R = C = 3$ in Table 3.4. The column component design is fairly efficient since the total variance of the contrasts of interest has a discrepancy of 13.3% when compared with the appropriate bound of Section 2.4. However, Gerami & Lewis (1992) state that these bounds are loose for block sizes $k = 2$ and $k = 3$. This conclusion is reinforced by using the Jones & Eccleston algorithm to find the most A-efficient block design for the above parameter values, the column component design has a discrepancy of 0.1% with the result of the algorithm. This row-column design is unusual, it is arranged in a square array but does

not have identical row and column component designs. It was combinatorially impossible to combine two copies of the A-best PBDS block design for these parameter values. However, the A-best block design was used as the column component design. In order to leave the treatment group totals of the design, T_B, T_A and T_D, unchanged, it was necessary to consider a design with less efficient blocks for the row component. In this case, efficiency was sacrificed in order to obtain component designs compatible for amalgamation, although it should be noted that JE was unable to improve upon this row-column design.

The study revealed that amalgamating the PBDS block design, with the smallest trace of the variance-covariance matrix, for t treatments in an $R \times C$ array with the PBDS block design with the smallest trace for t treatments in a $C \times R$ array does not necessarily yield the most A-efficient row-column design. This is demonstrated in the following example.

Example 3.5 *For $m = 2$, $n = 3$ and $R = C = 6$, the most A-efficient PBDS design for a single blocking factor consists of two copies of the blocks:*

Block 1	*01*	*01*	*10*	*20*	*11*	*21*
Block 2	*01*	*10*	*20*	*11*	*11*	*21*
Block 3	*01*	*10*	*20*	*11*	*21*	*21.*

This design has $tr(H\Omega_d H') = 1.1123$ and, when used for both the row and column component designs, generates a row-column design with $tr(H\Omega_{RC}H') = 1.1439$. As an alternative, consider the block design composed of three copies of the following two blocks

Block 1	*01*	*10*	*20*	*11*	*11*	*21*
Block 2	*01*	*10*	*20*	*11*	*21*	*21*

This design has $tr(H\Omega_d H') = 1.1241$ which is larger than the value for the previous block design. However, taking this design as both the row and column component design, a more efficient row-column design is obtained, having $tr(H\Omega_{RC}H') = 1.1389$.

A further example is the most A-efficient PBDS row-column design for five treatments in a 5×5 array. The most A-efficient PBDS design for a single blocking factor has $T_A = 8$, $T_B = 5$, $T_D = 12$ and $tr(H\Omega_d H') = 1.5997$. Taking

this design as both the row and column component design yields a row-column design with $tr(H\Omega_{RC}H') = 1.6370$. However, the Latin square of order five has $tr(H\Omega_{RC}H') = 1.6$ so, by using the less efficient randomised block design for the row and column component designs, a more efficient row-column design has been found.

The row-column designs found by amalgamating the two most A-efficient component designs, which have a slightly larger total variance for the estimators of the contrasts of interest than the alternative designs given in Tables 3.3–3.15, are presented in Table 3.16.

In order to discover how to select the component designs to reduce the variance of the estimators of the contrasts of interest in the row-column design, an investigation into the relationship between the row-column design and the row and column component designs was conducted. Such relationships are straightforward to establish if the contrasts of interest correspond to a set of basic contrasts for the design, see Section 1.3 for a discussion and equation (1.9) for the relationship. Unfortunately, this is not true for the dual versus single treatments problem. An outline of the approach followed is given below. Full details of the algebra are not presented, since it was not possible to see how the parameters of the information matrices for the component designs should be manipulated in order to reduce the variances.

Firstly, a general set of orthonormalised eigenvectors, ξ_i^* $(i = 1, \ldots, t)$, of the replications-adjusted information matrix, $A_d^* = r^{-\delta/2} A_d r^{-\delta/2}$, was found using the symbolic algebra package MAPLE (1991). This set of eigenvectors was expressed in terms of the parameters a_{di}^* $(i = 1, \ldots, 9)$ of A_d^* but existence of the set was subject to the validity of various parameter constraints. Using an approach given by Shah & Sinha (1989, p 78), the variances of the contrasts of interest were expressed in terms of the elements of ξ_i^* by writing the basic contrasts and the contrasts of interest in terms of linear combinations of ξ_i^* for $i = 1, \ldots, t$. Corresponding expressions for the variances, in terms of the parameters a_{di}^*, were obtained by substitution. However, the formulae consisted of very complicated expressions for the variances of the estimators of the contrasts of interest which did not indicate how the values of r_j $(j = B, A, D)$ and a_{di}^* should be altered to achieve smaller variances.

Since the above approach was unsuccessful, a different method of linking the parameters of the component designs to the variances of the row-column design

was adopted. Using an analogous approach to that employed in Section 3.4 to find the variances of the contrasts of interest for an RGDRC design, the variances of the contrasts for any connected PBDS block or row-column design were expressed in terms of the parameters of the information matrix of that design. This approach improved upon the previous method since the expressions for the variances were valid for all PBDS designs and involved no parameter restrictions. The variances of the row-column design were then expressed in terms of the parameters of the information matrices of the row and column component designs using Corollary 3.1. Since the expressions for the contrast variances of the row-column design in terms of a_{RCi} $(i = 4, \ldots, 9)$ were very complicated, the substitution of a_{Ri} and a_{Ci} from Corollary 3.1 only served to confuse the issue further.

The above discussion indicates that it is very difficult to establish a relationship between the variances of the row-column design and the variances of the two component designs for the dual versus single treatments problem. It has not been possible to formulate an explicit relationship by the methods described in this chapter. This is an area for future research.

3.7 Catalogue of PBDS row-column designs

This chapter concludes with a catalogue of designs obtained by amalgamating PBDS block designs. The design found is a solution given by JE and is not necessarily unique. Each entry in the catalogue is the most A-efficient PBDS row-column design that could be found for the particular values of n, R and C, unless otherwise indicated in the table.

An examination of the figures in the four columns headed *% Disc* confirms the conclusions of Section 2.6: when R or C is less than the number of treatments t, discrepancies are observed between the variance of the contrast estimators for the row-column design and the bound which are in excess of 10%. However, it can be seen from the column subheaded *JE* that, for $n = 3$, the design search algorithm rarely improves upon the listed design. This reinforces the opinion that bound B of (2.12) must be loose under these conditions. The bound is much tighter for large R and C.

The results for $n = 4$ and $n = 5$ are not quite so impressive. Again, large

row-column discrepancies can be seen for small R and C but JE is able to improve upon the listed design in twenty-one out of a total of twenty-eight cases, although the improvement is less than 5% in twelve of these cases. The designs for $n = 4$ and $R = 4$ perform poorly when compared to both the bound and the results of JE, but it can be seen that the column component performs substantially worse than the row component in all these cases. A similar, but less severe, situation is observed for the row-column designs with $n = 3$, $R = 3$. A possible explanation is that C-designs for $t = 2n - 1$ treatments in b blocks of size n tend to be inefficient.

The designs for $n = 5$ also perform quite poorly when R or $C < t - 1$. This is not due to the poor performance of the bounds but to poor performance of the component designs. In order to find PBDS block designs which are compatible for amalgamation, it is necessary to sacrifice some efficiency. The performance of designs for this value of n is better for larger values of R and C.

Note that designs in the catalogue marked with † have the property that each treatment combination occurs once within every row block. Designs having this property are investigated further in Chapter 4 and are called *row-orthogonal designs.*

The catalogue establishes that PBDS row-column designs generated by amalgamating a pair of compatible component C-designs can be highly efficient.

Catalogue of PBDS row-column designs

For $2 \leq R, C \leq 9$, $3 \leq n \leq 5$ and $m = 2$, the following tables list the connected row-column designs obtained by amalgamating two compatible PBDS block designs. The figures in the column headed *% Disc* are the percentage discrepancies for estimating the dual versus single contrasts in the row-column design, the row component and the column component, each compared with an appropriate bound (see Chapter 2). The fourth figure represents the percentage discrepancy between the row-column design and the best design found by *JE*. Throughout these tables, † denotes a row-orthogonal design.

Table 3.3: PBDS row-column designs for $n = 3$, $R = 2$ and $5 \leq C \leq 9$

n	R	C	Row-column design	% Disc			
				R-C	Row	Col	JE
3	2	5	01 21 11 20 10 11 01 10 21 20	13.3 †	0	13.3	0
	2	6	01 01 11 21 10 20 11 21 10 20 01 01	13.3	5.0	13.3	0
	2	7	01 01 11 21 10 20 11 11 21 10 20 01 01 21	10.2	1.2	8.6	0
	2	8	01 01 11 21 10 20 11 21 11 21 01 01 11 21 10 20	13.3	0	13.3	2.7
	2	9	01 01 10 11 21 21 10 20 11 11 21 11 10 20 20 01 01 21	6.0	0.6	4.3	0

Table 3.4: PBDS row-column designs for $n = 3$, $R = 3$ and $3 \leq C \leq 9$

n	R	C	Row-column design	% Disc R-C	Row	Col	JE
3	3	3	01 11 21 21 10 01 11 01 20	51.1	41.7	13.3	0
	3	4	01 21 10 11 11 01 21 20 10 20 11 21	15.4	5.7	11.2	0.1
	3	5	01 20 11 10 21 10 01 21 11 20 11 21 01 20 10	8.2 †	0	8.2	0
	3	6	01 20 10 21 11 11 10 01 11 20 21 21 11 21 01 01 10 20	8.1	2.7	4.7	0
	3	7	01 01 10 20 11 11 21 10 20 01 01 21 21 11 11 21 11 21 01 10 20	7.1	1.7	5.1	0
	3	8	01 01 10 20 21 21 11 11 10 11 11 01 01 20 10 21 11 10 01 21 20 01 21 20	6.0	1.0	4.0	0.1
	3	9	01 01 10 20 20 21 11 11 21 10 10 11 01 01 20 21 21 11 11 11 01 21 21 01 10 20 01	5.3	1.0	4.1	0

Table 3.5: PBDS row-column designs for $n = 3$, $R = 4$ and $4 \leq C \leq 9$

n	R	C	Row-column design	% Disc R-C	Row	Col	JE
3	4	4	01 11 10 21 11 21 01 20 10 20 11 01 21 01 20 10	14.7	6.6	6.6	0.6
				This is an RGDRC design			
	4	5	01 20 10 11 21 10 01 11 21 20 11 11 21 01 10 21 21 01 20 11	8.1	2.4	5.4	0
	4	6	01 20 11 11 10 21 10 01 21 21 11 20 11 21 01 01 20 10 21 11 10 20 01 01	8.9	2.6	6.1	0.5
	4	7	01 01 10 20 11 21 21 10 11 01 01 21 20 11 11 10 21 21 01 11 20 21 21 11 11 20 01 10	7.7	2.1	5.9	0
	4	8	01 01 10 20 11 21 11 21 10 11 01 21 21 11 01 20 11 10 21 11 01 01 20 10 21 21 11 01 20 20 10 01	7.2	1.0	5.9	0.1
	4	9	01 01 10 20 11 11 10 21 21 10 10 01 01 21 21 11 20 11 11 11 21 21 01 01 20 10 20 21 21 11 11 20 20 01 01 10	6.5	0.6	5.7	0

Table 3.6: PBDS row-column designs for $n = 3$, $R = 5$ and $5 \leq C \leq 9$

n	R	C	Row-column design	% Disc R-C	Row	Col	JE
3	5	5	01 10 20 11 21 10 01 11 21 20 20 11 01 10 21 11 21 10 01 11 21 20 21 11 01	4.5	2.1	2.1	2.3
				An improved design is the Latin square, see Table 4.2			
	5	6	01 10 20 11 11 21 10 01 11 20 21 21 20 11 01 21 10 11 11 21 21 10 01 20 21 20 10 01 11 01	4.3	2.4	1.9	0
	5	7	01 01 10 20 11 11 21 10 20 01 01 21 11 21 20 10 11 10 01 21 11 11 21 20 21 10 01 20 21 11 21 11 20 10 01	3.9	2.2	1.9	0.1
	5	8	01 01 10 10 20 11 11 21 10 10 01 01 11 20 21 11 20 20 11 21 01 21 10 01 11 21 20 20 21 10 01 01 21 11 21 11 10 01 01 20	3.3	1.9	2.4	0
	5	9	01 01 10 10 20 11 11 21 21 10 20 01 01 10 21 21 11 11 11 11 20 21 21 01 01 10 20 11 21 21 20 11 10 20 01 01 21 21 11 11 01 20 10 20 10	2.7	1.3	1.9	0

Table 3.7: PBDS row-column designs for $n = 3$, $R = 6$ and $6 \leq C \leq 9$

n	R	C	Row-column design	% Disc			
				R-C	Row	Col	JE
3	6	6	11 01 10 20 11 21 01 10 20 11 21 11 10 20 11 21 21 01 11 21 01 21 10 20 21 11 21 01 20 10 20 11 21 10 01 11	5.1	3.8	3.8	0
	6	7	01 01 10 20 11 11 21 10 20 01 11 21 21 01 20 10 11 21 01 01 11 11 21 20 21 01 01 10 11 11 21 01 10 10 20 21 21 11 10 20 20 01	4.4	1.6	2.7	0
	6	8	01 01 10 20 11 11 21 21 01 01 11 11 10 20 21 21 10 20 01 01 21 21 11 11 20 10 21 21 11 11 01 01 11 11 01 21 01 10 10 20 21 21 11 01 20 01 20 10	3.8	1.2	2.9	0
	6	9	01 01 10 10 20 11 11 21 21 10 20 01 01 11 21 21 20 11 20 10 11 21 01 21 01 11 10 11 11 20 21 21 01 01 10 20 11 21 21 20 11 10 10 01 01 21 21 11 11 10 20 20 01 01	3.3	0.6	2.7	0

Table 3.8: PBDS row-column designs for $n = 3$, $R = 7$ and $7 \leq C \leq 9$

n	R	C	Row-column design	% Disc			
				R-C	Row	Col	JE
3	7	7	01 01 10 20 11 11 21 01 01 20 10 11 21 21 10 20 01 01 21 11 11 20 10 11 21 21 01 01 11 11 21 21 01 10 20 11 21 01 11 10 10 20 21 21 11 01 20 20 10	3.9	1.9	1.9	0
	7	8	01 01 10 20 11 11 21 21 01 01 20 10 11 21 11 21 10 20 01 11 21 21 01 11 20 10 11 21 01 01 11 10 11 11 01 21 01 10 10 20 11 21 21 01 10 01 20 20 21 21 11 01 20 20 10 01	2.9	1.2	1.8	0
	7	9	01 01 10 10 20 11 11 21 21 01 01 20 11 10 10 21 11 21 10 10 01 01 11 21 21 11 20 20 20 01 01 21 21 11 10 11 11 11 21 21 01 01 10 20 20 11 21 11 21 01 20 20 01 10 21 21 11 20 11 01 01 10 01	2.6	0.8	1.8	0

Table 3.9: PBDS row-column designs for $n = 3$ and $8 \leq R, C \leq 9$

n	R	C	Row-column design	% Disc			
				R-C	Row	Col	JE
3	8	8	01 01 10 10 20 11 11 21 01 01 20 20 10 11 21 21 10 20 01 01 11 21 21 11 10 20 01 01 21 21 11 11 20 11 11 21 21 01 01 10 11 10 21 21 11 01 01 20 11 21 21 11 01 10 20 01 21 21 11 11 01 20 10 01	2.1	1.4	1.4	0
	8	9	01 01 10 10 20 11 11 21 21 01 01 10 20 10 11 11 21 21 10 10 01 01 11 21 21 20 11 10 20 01 01 11 21 21 10 11 20 20 11 21 21 01 01 11 10 11 11 20 21 21 01 01 10 20 11 21 21 20 01 10 20 11 01 21 21 11 11 01 20 10 01 20	2.0	0.6	1.3	0
	9	9	01 01 10 10 20 11 11 21 21 01 01 10 10 20 11 21 11 21 10 10 01 01 11 20 21 21 11 10 10 01 01 21 21 20 11 11 20 20 11 11 21 21 01 10 01 11 11 21 21 01 01 10 20 20 11 11 21 21 01 01 20 20 10 21 21 20 20 11 10 11 01 01 21 21 11 11 10 20 01 01 01	1.5	0.7	0.7	0.2

Table 3.10: PBDS row-column designs for $n = 4$, $R = 2$, $C = 9$, $R = 3, 5 \leq C \leq 9$ and $R = C = 4$

n	R	C	Row-column design	% Disc R-C	Row	Col	JE
4	2	9	01 01 01 11 21 31 10 20 30 11 21 31 10 20 30 01 01 01	17.4	11.1	17.3	1.3
	3	5	10 21 01 11 20 11 01 30 31 10 01 20 31 21 30	18.5	2.3	18.2	0
	3	6	01 20 31 10 11 21 10 01 30 21 31 11 11 21 01 31 20 30	15.2	2.0	13.2	6.4
	3	7	01 20 01 10 21 31 11 10 01 31 11 01 30 21 11 21 30 01 20 01 31	11.8	4.1	8.4	2.1
	3	8	01 01 30 10 21 31 11 20 10 20 31 11 01 01 21 30 11 21 01 01 20 30 31 10	11.3	2.4	11.3	2.5
	3	9	01 01 30 11 20 31 10 11 21 10 20 01 01 21 30 21 31 11 11 21 31 10 01 01 31 20 30	8.4	1.0	7.1	3.0
	4	4	01 11 31 21 11 21 10 20 31 10 11 30 21 20 30 31	84.7	43.6	43.6	45.4 RGDRC design is better, see Table 3.2

Table 3.11: PBDS row-column designs for $n = 4$, $R = 4$, $C = 6, 8, 9$ and $R = 5$, $5 \leq C \leq 6$

n	R	C	Row-column design	% Disc			
				R-C	Row	Col	JE
4	4	6	01 11 11 10 31 21 21 01 31 21 11 20 31 21 01 11 30 31 11 31 21 20 10 30	33.0	12.7	23.3	20.2
	4	8	01 01 11 11 21 21 31 31 11 11 01 21 31 20 10 21 21 31 31 01 11 10 11 30 31 21 21 31 01 11 30 20	44.3	20.4	35.3	31.8
	4	9	01 11 11 10 20 30 31 21 21 11 01 21 20 10 11 30 31 31 21 31 01 11 21 31 10 20 30 31 21 31 21 11 10 11 30 20	32.3	16.8	29.6	22.0
	5	5	01 10 20 11 21 10 01 30 31 11 20 30 01 21 31 11 31 21 01 01 21 11 31 01 01	23.6	12.7	12.7	13.1
	5	6	01 10 20 11 21 31 10 01 30 21 31 11 20 30 01 31 11 21 11 31 21 10 30 20 21 11 31 20 10 30	21.8	12.9	17.2	12.8

Table 3.12: PBDS row-column designs for $n = 4$, $R = 5$, $C = 7$ and $R = 6$, $6 \leq C \leq 9$

n	R	C	Row-column design	% Disc R-C	% Disc Row	% Disc Col	% Disc JE
4	5	7	01 10 20 11 31 30 21 10 01 30 20 11 21 31 20 11 21 10 01 31 01 11 30 31 21 10 01 01 21 31 01 01 30 20 11	5.2	1.9	4.1	0.6
	6	6	01 10 20 11 21 31 10 01 30 21 31 11 20 30 01 31 11 21 11 21 31 01 10 20 21 31 11 10 01 30 31 11 21 20 30 01	4.7	2.2	2.2	0
	6	7	01 10 20 30 11 31 21 10 01 30 20 21 11 31 20 11 21 31 01 10 30 11 30 31 21 10 01 20 21 31 01 11 20 30 10 31 21 11 10 30 20 01	6.7 †	3.8	6.7	2.7
	6	8	01 10 20 30 11 11 21 31 10 01 30 20 21 21 31 11 20 30 01 10 31 31 11 21 11 11 21 31 01 10 20 30 21 21 31 11 10 01 30 20 31 31 11 21 20 30 01 10	7.5	4.9	6.6	3.1
	6	9	01 01 20 10 30 11 11 21 31 10 30 01 01 11 20 21 31 21 20 10 30 11 21 31 31 01 01 11 11 21 20 31 21 01 10 30 21 31 11 31 01 30 10 11 20 31 21 31 21 10 01 20 30 11	4.0	1.9	2.4	0

Table 3.13: PBDS row-column designs for $n = 4$, $R = 7$, $7 \leq C \leq 9$ and $R = C = 8$

n	R	C	Row-column design	% Disc R-C	% Disc Row	% Disc Col	% Disc JE
4	7	7	01 10 20 30 11 21 31 10 01 30 11 20 31 21 20 30 01 21 31 10 11 30 20 10 31 21 11 01 11 21 31 01 10 01 20 21 31 11 10 01 01 30 31 11 21 20 01 30 01	2.7	1.5	1.5	0
	7	8	01 01 10 20 30 11 21 31 10 20 01 01 11 21 31 30 20 10 30 11 01 31 01 21 30 11 20 21 31 01 10 01 11 30 11 31 21 10 01 20 21 21 31 10 20 01 30 11 31 31 21 30 10 20 11 01	3.3	2.3	1.8	0
	7	9	01 01 01 10 30 20 11 21 31 01 01 20 11 10 30 21 31 11 10 30 01 01 11 21 31 20 21 20 10 30 21 31 31 01 11 01 11 11 21 31 01 01 10 30 20 21 21 31 01 01 11 20 10 30 31 31 11 20 21 01 30 01 10	3.9	2.5	2.7	0.8
	8	8	01 01 10 20 30 11 21 31 01 01 20 10 11 30 21 31 10 20 01 01 21 11 31 30 20 10 01 01 31 21 30 11 30 11 21 31 01 01 10 20 11 30 11 21 01 31 20 10 21 21 31 30 10 20 11 01 31 31 30 11 20 10 01 21	3.8	2.4	2.4	0.3

Table 3.14: PBDS row-column designs for $n = 4$, $8 \leq R \leq 9$, $C = 9$ and $n = 5$, $R = C = 6$, $R = 7$, $C = 8$

n	R	C	Row-column design	% Disc			
				R-C	Row	Col	JE
4	8	9	01 01 01 10 20 30 11 21 31 01 01 01 20 10 11 30 31 21 10 20 30 01 01 21 31 11 11 20 10 11 01 21 31 21 01 30 30 11 21 31 31 01 01 10 20 11 30 31 21 01 01 10 20 10 21 31 10 30 11 20 20 01 01 31 21 20 11 30 10 01 30 01	5.5	5.5	4.2	1.9
	9	9	01 01 10 20 30 11 11 21 31 01 01 20 10 11 30 21 21 31 10 20 01 01 21 31 30 31 11 20 10 01 01 21 31 11 11 30 30 11 21 21 01 01 31 10 20 11 30 31 31 01 01 10 20 21 11 21 30 11 31 10 20 01 01 21 21 31 11 10 20 01 30 01 31 31 11 30 20 21 01 01 10	2.5	1.5	1.5	0
5	6	6	01 10 11 20 21 01 10 11 01 31 01 30 11 01 10 01 41 40 20 30 01 21 01 31 21 01 40 01 20 41 01 31 41 30 40 01	24.6	17.8	17.8	15.8
	7	8	01 10 30 20 11 21 31 41 10 01 40 21 20 11 41 31 30 40 01 31 10 41 11 21 20 11 31 01 41 30 21 40 11 20 10 41 21 31 40 30 21 41 11 30 31 40 10 20 31 21 41 40 30 10 20 11	23.8	18.2	20.5	19.2

Table 3.15: PBDS row-column designs for $n = 5$, $8 \leq R, C \leq 9$

n	R	C	Row-column design	% Disc R-C	Row	Col	JE
5	8	8	01 10 30 20 11 21 31 41 10 01 40 11 20 31 41 21 30 40 01 21 10 41 11 31 20 11 21 31 41 01 30 40 11 20 31 41 01 10 21 30 21 41 10 01 31 20 40 11 31 21 41 40 30 11 10 01 41 31 11 30 21 40 01 20	3.8	2.7	2.7	0
	8	9	01 10 30 20 40 11 21 31 41 10 01 40 30 20 21 11 41 31 20 40 01 11 10 31 41 30 21 30 20 21 31 41 01 10 11 40 11 21 10 41 31 20 01 40 30 21 31 41 01 11 30 40 10 20 31 41 11 40 21 10 30 20 01 41 11 31 21 30 40 20 01 10	7.6 †	5.9	7.6	4.1
	9	9	01 01 10 20 30 11 21 31 41 01 01 40 11 10 20 31 41 21 10 40 01 01 11 30 41 21 31 20 11 01 21 31 41 01 30 40 30 10 11 31 41 21 20 40 01 11 20 30 41 21 31 40 01 10 21 31 41 01 20 40 10 11 30 31 41 21 30 40 01 11 10 20 41 21 31 40 01 10 30 20 11	2.5	1.8	1.8	0.1

Table 3.16: Table of alternative PBDS row-column designs obtained by amalgamating the two most A-efficient component designs, the most A-efficient row-column designs are given in the tables indicated below

n	R	C	Row-column design	% Disc			
				R-C	Row	Col	JE
3	6	6	01 01 10 20 11 21 01 10 20 11 11 21 10 20 01 21 21 11 20 11 21 01 01 10 11 11 21 01 10 20 21 21 11 10 20 01	5.6	2.7	2.7	0.4
				See Table 3.7			
	8	8	01 01 10 10 20 11 11 21 01 01 10 20 11 20 21 21 10 10 01 01 11 11 21 20 10 20 01 01 21 21 20 11 20 11 11 21 01 21 01 10 11 20 11 21 21 01 10 01 11 21 21 20 01 10 01 11 21 21 20 11 10 01 11 01	2.2	1.2	1.2	0.1
				See Table 3.9			
5	8	8	01 01 10 20 30 11 21 31 01 01 40 21 10 20 11 41 10 40 01 01 11 31 41 30 20 21 01 01 31 41 30 40 30 10 11 31 41 21 01 20 11 20 31 41 01 10 40 21 31 11 41 30 21 40 10 01 21 41 30 40 20 01 31 11	4.0	2.2	2.2	0.2
				See Table 3.15			

Chapter 4

Row-orthogonal PBDS designs

4.1 Introduction

The purpose of this chapter is to consider the class of row-column designs which are obtained by amalgamating a randomised block design with an appropriate PBDS design. This class of designs is useful because, since treatments are orthogonal to blocks in one direction with respect to the model (1.1), the estimates of the treatment parameters are the same as those yielded by the model from which the particular block effects have been deleted. An example of this is the *clinical trial* where it is often useful to have treatments orthogonal to periods so that treatments appear exactly once in each period, giving estimates of the treatment parameters which do not involve adjustment for period effects.

In this chapter, an investigation is made of the groups of candidate PBDS component designs discussed in Chapter 3 and those designs which are compatible with a randomised block design are identified. A necessary and sufficient condition is given for a PBDS design to amalgamate with a randomised block design. Tables are presented of PBDS row-column designs formed in this way which have total variance for the dual versus single contrasts within 17% of the lower bound of (2.12).

4.2 Existence of row-orthogonal PBDS designs

Definition 4.1 *A row-orthogonal design under model (1.1) has a randomised*

block design as the row component and any block design as the column component.

Definition 4.2 *A row-orthogonal PBDS design under model (1.1) has a randomised block design for the row component and a PBDS block design as the column component.*

To find component PBDS designs which amalgamate with randomised block designs, only equi-replicate designs need to be considered, since the treatment replications must be identical in the two components from Lemma 3.4. Therefore, throughout this chapter, equi-replicate designs will be considered in which each treatment is replicated r_e times, that is $r = r_e 1_t$. In order to establish conditions on the parameters for which a row-orthogonal PBDS design exists the following lemma is applied.

Lemma 4.1 (Smith & Hartley, 1948) *Given any set of bk elements made up of b varieties of objects each repeated k times, suppose that the set is arbitrarily arranged in a two-way classification of k rows and b columns. Then, it is always possible to rearrange the elements in each column so that each row will contain one and only one element of each variety.*

Theorem 4.1 *Necessary and sufficient conditions for the existence of a row-orthogonal PBDS design for t treatments, each replicated r_e times, and arranged in an $R \times C$ array are*

(i) the PBDS design has $C = t$ blocks of size $R = r_e$

(ii) the randomised block design has t treatments and R blocks of size C.

Proof: From the properties of a randomised block design, each treatment must occur exactly once in each block, hence $C = t$ and $r_e = R$. It follows from Lemma 4.1 with $b = C$ and $k = R$ that it will always be possible to construct a row-orthogonal design by rearranging the elements within column blocks so that each treatment appears exactly once in each row.

Remark: This argument is valid for all possible block sizes in the column component; the blocks in the row component are all of size t by definition.

The following example illustrates how these designs compare with row-column designs which have two PBDS component designs.

Example 4.1 *For $m = 2$, $n = 3$, $R = 6$ and $C = 5$, the row-orthogonal design listed in Table 4.2 is obtained with $tr(H\Omega_{RC}H') = 1.3714$. The PBDS row-column design for five treatments in a 5×6 array, given in Table 3.6, which does not possess row-orthogonality has $tr(H\Omega_{RC}H') = 1.3610$. The discrepancy between the total variances of these two designs is 0.8% and they have discrepancies of 5.1% and 4.3% respectively with the bound of (2.12) which has the value $B = 1.3047$ in this case. The additional constraint of row-orthogonality has resulted in a very small loss of precision, demonstrating that it is possible to have efficient row-orthogonal PBDS designs.*

In order to simplify the search for row-orthogonal PBDS designs, the implications of Theorem 4.1 for each of the designs defined in Chapter 3, Sections 3.3 and 3.5 are now investigated to establish if they are suitable for amalgamating with randomised block designs.

Case I : RGDD component

The following result states the condition for the existence of a row-orthogonal PBDS design with an RGDD column component.

Theorem 4.2 *Any row-orthogonal reinforced group divisible design is a Latin square.*

Proof: From the properties of a randomised block design it is known that $r_e = R$ and $C = t = 2n - 1$. On substituting for r_e and $2(n-1)$ in (3.12), the relationship $R(C-1) = C(R-1)$ is obtained and this is satisfied when $R = C$. It follows that the conditions for the existence of group divisible designs (3.13), (3.14) and (3.15) can be rewritten as

$$R(R-2) = \lambda_1^C + (R-3)\lambda_2^C \tag{4.1}$$

$$\lambda_2^C \leq R \tag{4.2}$$

$$\lambda_1^C \leq R. \tag{4.3}$$

The next step is to find lower limits on the λ_i $(i = 1, 2)$. Since (4.1) can be expressed as $\lambda_1^C = R(R-2) - (R-3)\lambda_2^C$, it follows from (4.3) that λ_2^C must satisfy the constraint

$$R(R-2) - (R-3)\lambda_2^C \leq R.$$

If $R \neq 3$, this expression can be rearranged to give $\lambda_2^C \geq R$ which, when combined with (4.2), requires λ_2^C to be equal to R. Similarly, (4.1) can be expressed as $\lambda_2^C = [R(R-2) - \lambda_1^C]/(R-3)$ and, using (4.2), λ_1^C is required to satisfy

$$\frac{R(R-2) - \lambda_1^C}{R-3} \leq R.$$

It follows, using (4.3), that $\lambda_1^C = R$. Hence the design parameters R, C, t, r, λ_1 and λ_2 are required to be equal for $R > 3$. To satisfy this condition, each treatment must occur with each of the other $t-1$ treatments equally frequently in every block, that is the component design must be a randomised block design.

If $R = 3$, a degenerate reinforced group divisible design is obtained, having the treatments 01, 10 and 11 occurring in each block, which is a randomised block design. The second associates are no longer defined in this case. Hence, the value of λ_2^C cannot be determined. It follows that a reinforced group divisible row-orthogonal design must be a Latin Square.

The following example shows that row-orthogonal PBDS designs with an RGDD column component can be efficient.

Example 4.2 *For $m = 2$, $n = 4$ and $R = C = 7$, the row-orthogonal PBDS design with an RGDD column component given in Table 4.3 has $tr(H\Omega_{RC}H') =$ 1.7143. The discrepancy between the total variance of the design and the bound B of (2.12) is* 3.9%.

Corollary 4.1 *A row-orthogonal reinforced group divisible design has $v_{RCA} = v_{RCB}$, where $v_{RCA} = var(\hat{\tau}_{i1} - \hat{\tau}_{i0})$ and $v_{RCB} = var(\hat{\tau}_{i1} - \hat{\tau}_{01})$ for $i = 1, \ldots, p$.*

Proof: This result follows directly from Theorem 4.2 since all pairwise comparisons have equal variances for a Latin square design.

Note that the corollary can also be derived by expressing the component design parameters, given by (3.20) to (3.24), in terms of R and substituting the new a_j $(j = 1, \ldots, 9)$ in v_{RCA} and v_{RCB} of Theorem 3.5.

Case II : R-type component

The following result shows that R-type designs can be used only for certain values of R and C.

Theorem 4.3 *A necessary condition for the existence of an $n \times 2$ row-orthogonal PBDS design with R rows and C columns and having an R-type column component is that $C = 2n - 1$ is a divisor of R.*

Proof: The randomised block row component design forces $r_e = R$ and $t = C$. Hence the total allocation to the B-alone treatments must be $T_B = R$, and the total allocations to the A-alone and dual treatment groups must be $T_A = T_D = (n-1)R$. A necessary condition for the existence of an R-type design is that T_i $(i = B, A, D)$ is divisible by C. Hence both R and $(n-1)R$ are required to be divisible by C.

It follows from the above result that, if an R-type design is used for the column component, then larger row-orthogonal designs can be constructed by joining together copies of a randomised block design, as illustrated by the following example.

Example 4.3 *A row-orthogonal PBDS design for $m = 2$, $n = 3$, $R = 5$ and $C = 10$ has a row component which consists of two copies of the randomised block design for five blocks each of size five arranged in a 5×10 array and the column component again has two copies of this randomised block design arranged in a 10×5 array. The components amalgamate to yield a 5×10 array containing two copies of the 5×5 Latin square which has $tr(H\Omega_{RC}H') = 0.8$ and a discrepancy of 2.5% with the bound B of (2.12).*

Case III : (R,S)-type component

It is shown below that (R,S)-type designs are not suitable for amalgamation with a randomised block design.

Theorem 4.4 *Row-orthogonal PBDS designs with an (R,S)-type column component do not exist.*

Proof: Since the design must have $r_e = R$ and $t = C$ the total allocations to the groups of B-alone, A-alone and dual treatments are $T_B = R$, $T_A = (n-1)R$ and $T_D = (n-1)R$ respectively. Without loss of generality, the (R,S)-type design is taken to be R-type in the A-alone treatments, then $(n-1)R$ must be divisible

by C. Consequently, the design must also be R-type in the dual treatments. Since it is impossible to have a design which is R-type in two sets of treatments and S-type in the third, it is necessary to also have R divisible by C. It follows that if the column component of a row-orthogonal design is R-type in any one treatment then it must be R-type in all three of them due to the equal treatment replication. Hence row-orthogonal designs with an (R,S)-type column component do not exist.

Case IV : S-type component

The remaining type of possible column components is the class of S-type PBDS designs which exist when C is not a divisor of R. This is the largest set of PBDS column components compatible with a randomised block design. Eleven of the fourteen designs listed in the table at the end of this chapter were derived from an S-type component.

Example 4.4 *The row-orthogonal design for* $m = 2$, $n = 5$, $R = 8$ *and* $C = 9$ *is given in Table 4.4 and has* $tr(H\Omega_{RC}H') = 2.0317$ *with a discrepancy of* 7.6% *with the bound* $B = 1.8889$.

4.3 Analysis and properties of row-orthogonal PBDS designs

In this section, results applicable to row-orthogonal designs and row-orthogonal PBDS designs are established. Some of the results are related and hence there may be several different ways of deriving a particular property. The following theorem gives a relationship between the variances of a contrast estimator in the components and in the row-column design.

Theorem 4.5 *For any row-orthogonal design, having* t *treatments arranged in an* $R \times C$ *array, the variance of the least squares estimator for any estimable treatment contrast is the same in the row-column design and the column component design.*

Proof: Using (1.7) with $A_k = r^{\delta} - (1/k')N_k N_k'$ for $k' \neq k = R, C$ and the fact that a randomised block design has equal replications $r_e = R$, block size $C = t$ and

incidence matrix $N_R = J_{t,R}$, the information matrix for the row-column design can be written as

$$A_{RC} = r_e I_t - \frac{1}{C} J_{t,R} J_{R,t} - \frac{1}{R} N_C N_C' + \frac{r_e^2}{RC} J_t. \tag{4.4}$$

Now $J_{t,R} J_{R,t} = R J_t$, hence (4.4) can be expressed as

$$A_{RC} = r_e I_t - \frac{1}{R} N_C N_C'$$

which is identical to A_C.

Hence, the information matrix of the row column design is the same as that of the column component. Therefore $\Omega_{RC} = \Omega_C$ and $V(C_t \Omega_{RC} C_t') = V(C_t \Omega_C C_t')$, for any contrast matrix C_t.

The following results give some further useful properties of row-orthogonal designs.

Lemma 4.2 *For any row-orthogonal design, the information matrices for the separate row and column component designs commute.*

Proof: Taking the randomised block design as the row component, $A_R = R I_t - (R/C) J_t$ since $r_e = R$ and $N_R = J_{t,R}$ by definition. Then, since the rows and columns of an information matrix always sum to zero, that is $J_t A_C = 0$ and $A_C J_t = 0$, it follows that

$$A_R A_C = R A_C - \frac{R}{C} J_t A_C = R A_C$$

and

$$A_C A_R = R A_C - \frac{R}{C} A_C J_t = R A_C.$$

Hence the information matrices commute.

Corollary 4.2 *All row-orthogonal designs possess a common set of orthonormal eigenvectors.*

Proof: The result follows directly from Lemma 4.2 and a result due to Graybill (1983, Theorem 12.2.12) which states that a pair of commuting matrices will always have a common set of orthonormal eigenvectors.

Alternative Proof: From the proof of Theorem 4.5, $A_{RC} = A_C$ for a roww-orthogonal design and hence the eigenvectors of A_{RC} and A_C will be the same. Any set of orthonormal eigenvectors will be eigenvectors of a randomised block design due to the fact that the information matrix of the randomised block design has one non-zero eigenvalue with multiplicity $t-1$. Hence A_R, A_C and A_{RC} must have a common set of eigenvectors.

Remark: The above corollary is particularly useful in the case where the contrasts of interest are orthogonal, since the canonical efficiency factors of the row-column design can be expressed in terms of the efficiency factors of the two component designs, see (1.9). When the contrasts of interest are the non-orthogonal dual versus single comparisons, the corollary can be used to show that the variances of the comparisons are the same for the row-orthogonal design and for the column component design. Since it is known that the efficiency factors for a randomised block design are all equal to one, (1.9) can be expressed as

$$e_{RCi} = e_{Ci}. \tag{4.5}$$

Let l_i, for $i = 1, \ldots t-1$, denote a set of common basic contrasts for the row-column design and the column component. Then the variance of a contrast estimator, $u\hat{\tau}$, where $u = \sum_{i=1}^{t-1} \gamma_i l_i$, can be written as

$$V_{RC}(u'\hat{\tau}) = \sum_{i=1}^{t-1} \frac{\gamma_i^2 \sigma^2}{e_{RCi}}. \tag{4.6}$$

However, substituting (4.5) into (4.6) gives $V_{RC}(u'\hat{\tau}) = \sum_{i=1}^{t-1}(\gamma_i^2/e_{Ci})\sigma^2$. This is the expression for the variance of the contrast estimator, $u\hat{\tau}$, estimated using the column component design. This result also follows from the fact that no adjustment is required for the row blocks.

The properties of row-orthogonal designs result in some simplifications in the analysis of variance. The sum of squares for treatments for the model (1.1), after adjusting for both rows and columns, is given by

$$\hat{\tau}'Q = \hat{\tau}'(T_{TOT} - \frac{1}{R} N_C C_{TOT}),$$

where Q denotes the vector of treatment totals adjusted for the row and column effects, T_{TOT} is the unadjusted vector of treatment totals, N_C is the incidence matrix of the column component design and C_{TOT} is the vector of column totals of

the design. This sum of squares is the same as the treatment sum of squares after adjusting for columns alone for a design with a single blocking factor, columns. Hence the advantage of using designs with this property is that no account need be taken of the differences between rows.

4.4 Tables of designs and conclusions

This chapter concludes with Tables 4.1–4.4 which contain fourteen efficient row-orthogonal PBDS designs. In this section the performance of the designs is discussed. The designs were obtained by amalgamating a randomised block design for t treatments arranged in R blocks each of size C with a PBDS block design for t treatments arranged in C blocks of size R. The listed row-column designs are a solution provided by *JE* and are not necessarily unique. In most cases, the row-orthogonal design is less efficient than the row-column design of Chapter 3 due to the constraint of equal treatment replication which forces the selection of less efficient component designs for amalgamation.

Example 4.5 *For $n = 3$, $m = 2$, $R = 9$ and $C = 5$, the total variance of the estimators of the contrasts of interest for the row-orthogonal design of Table 4.3 has a discrepancy of 3.7% with the bound of (2.12) and a discrepancy of 1.0% with the total variance of the contrast estimators for the most A-efficient design found by* JE. *The row-column design for the above parameters in Table 3.6 has corresponding discrepancies of 2.7% and 0%. An examination of the performance of the component designs reveals that in the row-orthogonal case the component designs have discrepancies of 2.5% and 3.7% for the block designs in nine blocks of size five and five blocks of size nine respectively. The row-column design has component designs with corresponding discrepancies of 1.9% and 1.3%.*

Note that the majority of designs listed in the tables are either Latin squares, Youden Squares or generalised Youden designs according to whether the column component is a randomised block design, a balanced incomplete block design, or a balanced block design. From Theorem 4.5 and using the fact that all these row-column designs have an information matrix of the form $A_{RC} = aI_t + bJ_t$, the designs have variance balance for the dual versus single contrasts, that is the dual versus A contrasts and the dual versus B contrasts are all estimated with a

common variance. The remaining row-orthogonal designs, for parameters $n = 3$, $R = 2, 3, 7, 8$ and $C = 5$, have PBDS column components with equal treatment replications. These designs also have variance balance for the dual versus single treatment contrasts.

It can be shown, using the conditions given by Ash (1981), that generalised Youden designs for t treatments, arranged in an $(mt + c_t) \times t$ array do not exist for $t = 5$ with $c_t = 2, 3$, $t = 7$ with $c_t = 2, 4, 5$ and $t = 9$ with $c_t = 2, 3, 4, 5, 6, 7$. This explains why the collection of efficient row-orthogonal designs is small. It could be extended by considering cases with $R > 9$, but such designs have an unnecessarily large treatment replication and are unlikely to be of practical use.

An examination of Tables 4.1–4.4 reveals that the row-orthogonal designs perform well when compared with the bound of Chapter 2. Out of a total of fourteen designs, only two have a discrepancy between the total variance of the estimators of the dual versus single contrasts and the bound which exceeds 10%. These two cases both have a small value of R and the numerical assessment of the bounds performed in Chapter 2 suggests that both bound $B_2(H)$ and bound B_F are loose for small block sizes. The possibility of using the extra information available on the incidence structure of a row-orthogonal design to improve upon the upper bound on $tr(A_{RC})$ of Theorem 2.5 was investigated. However, the resulting bound was found to be identical to the bound $B_2(H)$ of (2.12).

The row-orthogonal designs also compare well with the best design found by *JE*. The case $n = 3$ yields the best results, since the discrepancy between the total variance of the dual versus single contrasts and the best design found by *JE* does not exceed 1%. The designs for $n = 4$ and 5 have discrepancies with *JE* of less than 5%, with the single exception of the design for 7 treatments in a 3×7 array which has a discrepancy of 7.2%.

The tables serve to reinforce the fact that introducing the additional constraint of row-orthogonality does not necessarily imply that a great deal of precision is lost. They provide efficient designs with the row-orthogonal property which might be preferred to those in Tables 3.3–3.15 due to the simplification in the analysis (see Section 4.3) and in the interpretation of the results. Note that in some cases, see Example 4.5, the larger percentage discrepancy of the row-orthogonal design compared with the alternative in Tables 3.3–3.15, may make the row-orthogonal design the second choice.

Tables of row-orthogonal PBDS designs

For $3 \leq n \leq 5$, $m = 2$, $2 \leq R \leq 9$ and $C = 2n - 1$, the following tables list the connected row-orthogonal designs obtained by amalgamating a randomised block design with R blocks each of size C with a PBDS block design which has C blocks of size R and the same replication vector as the randomised block design. The figures in the column headed *% Disc* are the percentage discrepancies for estimating the dual versus single contrasts in the row-orthogonal design, the randomised block component and the PBDS component each compared with an appropriate bound (see Chapter 2). The fourth figure represents the percentage discrepancy between the row-column design and the best design found, under the A-criterion, by *JE*.
In the following tables, ♣ denotes the most A-efficient PBDS row-column design found in the studies of Chapters 3 and 4.

Table 4.1: Row-orthogonal PBDS designs for $n = 3$, $2 \leq R \leq 4$ and $C = 5$

n	R	C	Row-orthogonal design	% Disc			
				R-C	RB	PBDS	JE
3	2	5	01 21 11 20 10 11 01 10 21 20	13.3 ♣	0	13.3	0
	3	5	01 20 11 10 21 10 01 21 11 20 11 21 01 20 10	8.2 ♣	0	8.2	0
	4	5	01 10 11 20 21 10 01 21 11 20 20 21 10 01 11 11 20 01 21 10	8.5	1.7	8.5	0.3

Table 4.2: Row-orthogonal PBDS designs for $n = 3$, $5 \leq R \leq 8$ and $C = 5$

n	R	C	Row-orthogonal design	% Disc R-C	RB	PBDS	JE
3	5	5	01 10 20 11 21 10 01 11 21 20 20 11 21 01 10 11 21 10 20 01 21 20 01 10 11	2.1	2.1	2.1	0
	6	5	01 10 20 11 21 01 20 10 21 11 10 01 11 21 20 20 11 21 01 10 11 21 10 20 01 21 20 01 10 11	5.1	2.2	5.1	0.8
	7	5	01 10 20 11 21 01 20 10 21 11 10 01 21 11 20 20 11 21 01 10 11 21 01 10 20 21 01 11 20 10 21 11 20 10 01	4.5	2.3	4.5	0.7
	8	5	01 10 20 11 21 10 01 11 20 21 10 20 01 21 11 20 10 01 21 11 20 11 21 01 10 11 21 10 01 20 11 21 10 20 01 21 20 11 10 01	4.1	2.4	4.1	0.8

Table 4.3: Row-orthogonal PBDS designs for $n = 3$, $R = 9$, $C = 5$ and $n = 4$, $R = 3, 6, 7$ and $C = 7$

n	R	C	Row-orthogonal design	% Disc R-C	RB	PBDS	JE
3	9	5	01 10 20 11 21 01 10 20 11 21 10 01 11 21 20 10 01 11 21 20 20 11 21 01 10 20 11 21 01 10 11 21 10 20 01 21 20 01 10 11 21 20 01 10 11	3.7	2.5	3.7	1.0
4	3	7	01 20 30 31 10 11 21 10 01 31 20 21 30 11 11 21 01 10 30 20 31	17.4	2.1	17.4	7.2
	6	7	01 10 20 30 11 21 31 10 01 30 20 21 31 11 20 30 01 11 31 10 21 30 20 21 31 01 11 10 21 31 11 01 10 20 30 31 11 10 21 30 01 20	6.7	3.8	6.7	2.7
	7	7	01 10 20 30 11 21 31 10 01 30 20 21 31 11 20 30 01 10 31 11 21 30 11 21 31 01 10 20 11 20 31 21 10 01 30 21 31 10 11 20 30 01 31 21 11 01 30 20 10	3.9	3.9	3.9	1.2

Table 4.4: Row-orthogonal PBDS designs for $n = 4$, $R = 8$, $C = 7$ and $n = 5$, $R = 8, 9$ and $C = 9$

n	R	C	Row-orthogonal design	% Disc			
				R-C	RB	PBDS	JE
4	8	7	01 10 20 30 11 21 31 01 20 10 11 30 31 21 10 01 20 21 31 30 11 20 30 01 10 31 21 11 30 11 21 31 01 10 20 11 30 31 01 21 20 10 21 31 30 10 20 11 01 31 21 11 20 10 01 30	5.9	4.2	5.9	2.5
5	8	9	01 10 20 30 40 11 21 31 41 10 01 30 20 11 40 31 41 21 20 30 01 10 21 31 41 11 40 30 20 10 01 31 41 40 21 11 40 11 21 31 41 01 10 20 30 21 40 41 11 01 10 20 30 31 31 41 40 21 20 30 11 01 10 41 31 11 40 30 21 01 10 20	7.6	5.9	7.6	4.1
	9	9	01 10 20 30 40 11 21 31 41 10 01 30 20 11 40 31 41 21 20 30 01 10 21 31 41 40 11 30 20 10 01 31 41 11 21 40 40 11 21 31 41 01 10 20 30 11 40 31 41 01 21 20 30 10 21 31 41 40 10 20 30 11 01 31 41 11 21 30 10 40 01 20 41 21 40 11 20 30 01 10 31	5.9	5.9	5.9	3.3

Chapter 5

Finding efficient designs for estimating specific treatment contrasts

5.1 Introduction

Experience gained through investigating efficient designs for the dual versus single treatments contrast problem has led to the consideration of finding efficient designs for any specified contrasts of interest. The strategy employed for finding efficient row-column designs in the dual versus single treatments case was to find a class of designs which contains efficient and A-optimal members and then locate the best designs in this class. The search for these designs was simplified owing to the characteristic structure (1.14) of the information matrix of designs in this class. This strategy has also been used by Kiefer (1958) to find single blocking factor and row-column designs for estimating sets of orthogonal contrasts. The same approach enabled A-optimal block designs to be found for comparing test treatments with a control (Majumdar, 1986) and for comparing dual with single treatments (Gerami & Lewis, 1992).

The more general problem of finding efficient block designs for any set of specific treatment contrasts has already been addressed by Lewis & Gerami (1993). The authors identify a class of *aligned designs* which can contain highly efficient block designs; this class is discussed in Section 5.2. In this chapter, an A-optimal

information matrix is identified for estimating a particular set of treatment contrasts from an experiment, assuming an additive model for either one or two blocking factors. It is shown in Subsection 5.2.1 that, if a design having this information matrix exists, then the design is A-optimal over the class of incomplete block designs (or row-column designs) for the experiment size. Subsection 5.2.2 shows that, for example, the A-optimality of balanced incomplete block designs and balanced block designs can be established by checking that their information matrices have this A-optimal form. However, designs with information matrices corresponding to this particular information matrix do not necessarily exist. For this reason, the term *approximate information matrix* is used in this chapter to refer to any $t \times t$, symmetric, non-negative definite matrix, A, having $rank \geq 1$ and zero row and column sums, regardless of whether a design actually exists having information matrix A. In Section 5.3, some methods of finding designs which have information matrices close to the approximate information matrix are discussed. Finally, Section 5.4 describes applications of the results of this chapter to two sets of contrasts of interest in certain pharmaceutical experiments.

5.2 Aligned designs

5.2.1 General results

Connected designs with t treatments, arranged under blocking structure B, are considered for estimating a pre-specified set of L treatment contrasts, denoted by $C_L\tau$, where τ is the vector of treatment effects and C_L is an $L \times t$ matrix of contrasts with $rank(C_L) = n$, for $1 \leq n \leq t-1$. The class of such designs is denoted by $D(t, C_L, B)$. The following definition identifies the subclass of aligned designs $D_a(t, C_L, B)$.

Definition 5.1 (Lewis & Gerami, 1993) *A connected design, d, involving one or more blocking factors is* aligned *with contrast matrix C_L if A_d and $C_L'C_L$ have a complete set of orthogonal eigenvectors in common.*

In this chapter, a set of orthonormalised eigenvectors common to both A_d and $C_L'C_L$, where $d \in D_a(t, C_L, B)$, is denoted by ξ_i $(i = 1, \ldots, t)$ with $\xi_t = t^{-1/2}1_t$. Using the spectral decomposition of a matrix, the intra-block information matrix

can be written as $A_d = \sum_{i=1}^{t-1} \lambda_i \xi_i \xi_i'$. Similarly, the Moore-Penrose generalised inverse can be expressed as $\Omega_d = \sum_{i=1}^{t-1} \lambda_i^{-1} \xi_i \xi_i'$.

An aligned design has the property that the total variance of the least squares estimators of the contrasts of interest achieves the design dependent lower bound of Gerami & Lewis (1992), see Theorem 2.2. This result is stated in the following lemma.

Lemma 5.1 (Lewis & Gerami, 1993, Theorem 1) *For C_L a contrast matrix of rank $t-1$ and $d \in D_a(t, C_L, B)$*

$$tr(C_L \Omega_d C_L') = \sum_{i=1}^{t-1} \frac{\theta_i}{\lambda_i^d}$$

where $\theta_1 \geq \ldots \geq \theta_{t-1} > \theta_t = 0$ and $\lambda_1^d \geq \ldots \geq \lambda_{t-1}^d > \lambda_t^d = 0$ are the eigenvalues of $C_L' C_L$ and A_d respectively and Ω_d is a generalised inverse of A_d.

Note that Lemma 5.1 holds when C_L is a matrix of rank n where $1 \leq n \leq t-1$. In this case, the eigenvalues of $C_L' C_L$ are $\theta_1 \geq \ldots \geq \theta_n > \theta_{n+1} = \ldots = \theta_t = 0$.

Lewis & Gerami show that if a design $d^* \in D_a(t, C_L, B)$ is such that $\sum_{i=1}^{t-1} \theta_i / \lambda_i^{d^*}$ attains a minimum value over all designs in $D(t, C_L, B)$ then d^* is A-optimal in D.

A subclass of the aligned designs is considered in order to further reduce the search for efficient designs.

Definition 5.2 (Lewis & Gerami, 1993) *A design $d \in D_a(t, C_L, B)$ is* strongly aligned *with a set of contrasts $C_L\tau$ provided $\lambda_i^d = \lambda_j^d$ if and only if $\theta_i = \theta_j$, where λ_i^d and θ_i are the non-zero eigenvalues of A_d and $C_L' C_L$ respectively corresponding to the common eigenvector ξ_i $(i = 1, \ldots, t-1)$.*

Provided d is a strongly aligned design, knowledge of a set of eigenvectors and the multiplicities of the corresponding eigenvalues defines the structure of A_d via the spectral decomposition.

The authors show that, when $C_L\tau$ holds any set of orthogonal contrasts, the class of strongly aligned designs $D_s(t, C_L, B)$ is the class of balanced block designs, that is designs in which each pair of treatments occur together equally frequently in a block. They also show that, when $C_L\tau$ holds the test treatments

versus one control treatment contrasts, $D_s(t, C_L, B)$ consists of the classes of balanced treatment incomplete block designs, see Bechhofer & Tamhane (1981), and balanced treatment block designs of Ting & Notz (1988).

As an extension of the above work, the following result examines designs in D_a and shows that if the design with a variance-covariance matrix having trace which achieves the design independent bound $B(C_L)$ of Corollary 2.2 is in this class, then it must be in D_s. The practical use of the result is that, rather than searching D_a for a design achieving $B(C_L)$, attention can be restricted to D_s.

Theorem 5.1 *A design $d \in D_a(t, C_L, B)$ achieves bound $B(C_L)$ of Corollary 2.2 for estimating a specific set of treatment contrasts $C_L\tau$ if $d = d^*$, where $d^* \in D_s(t, C_L, B)$ with $\lambda_i^{d^*} = c_{max}\sqrt{\theta_i}/(\sum_{j=1}^{t-1}\sqrt{\theta_j})$, C_L is an $L \times t$ contrast matrix with rank n $(1 \leq n \leq t-1)$, τ is a vector of treatment parameters, $\lambda_i^{d^*}$ and θ_i $(i = 1, \ldots, t-1)$ are the non-zero eigenvalues of A_{d^*} and $C_L'C_L$ respectively, and $c_{max} = max_{d \in D}\, tr(A_d)$.*

Proof: From Lemma 5.1, a design $d \in D_a$ has the property that $tr(C_L\Omega_d C_L') = \sum_{i=1}^{t-1}\theta_i/\lambda_i^d$. Hence it is necessary to establish the conditions under which $S = \sum_{i=1}^{t-1}\theta_i/\lambda_i^d$ is minimised. This is carried out in two stages.

Firstly, attention is restricted to the class of designs $D_c = \{d \in D_a;\ tr(A_d) = \sum_{i=1}^{t-1}\lambda_i^d = c\}$ and S is minimised within this class. Let

$$S^* = \sum_{i=1}^{t-1}\frac{\theta_i}{\lambda_i^d} + \alpha(\sum_{i=1}^{t-1}\lambda_i^d - c),$$

then

$$\frac{\partial S^*}{\partial \lambda_i^d} = \frac{-\theta_i}{(\lambda_i^d)^2} + \alpha,$$

for $i = 1, \ldots, t-1$. Setting the derivative equal to zero, gives $\lambda_i^d = \sqrt{(\theta_i/\alpha)}$, for $i = 1, \ldots, t-1$. Using the constraint $\sum_{i=1}^{t-1}\lambda_i^d = c$, it can be shown that $\lambda_i^d = c\sqrt{\theta_i}/(\sum_{j=1}^{t-1}\sqrt{\theta_j})$. Now since $\partial^2 S^*/\partial(\lambda_i^d)^2 > 0$, it follows that $min_{d \in D_c} S$ is obtained when λ_i^d is proportional to $\sqrt{\theta_i}$, for $i = 1, \ldots, t-1$. Since $d \in D_a$, it follows from Definition 5.2 that d must be a strongly aligned design.

Let $M_c = min_{d \in D_c} S = (\sum_{i=1}^{t-1}\sqrt{\theta_i})^2/c$ then, in order to find $min_{d \in D} S$, M_c must be minimised by allowing c to take all possible values. Since θ_i $(i = 1, \ldots, t-1)$ is fixed, this problem is equivalent to maximising $c = tr(A_d)$.

Let $c_{max} = max_{d \in D}\, tr(A_d)$ then it can be shown, using Lemma 2.1, that

$$c_{max} = \begin{cases} bk - f(t,b,k), & \text{for block designs,} \\ RC - f(t,R,C) - f(t,C,R) & \\ +\frac{1}{RC} max(\sum_{i=1}^{t} r_i^2), & \text{for row-column designs,} \end{cases}$$

where $f(p,q,s) = (q/s)\{s + (2s-p)[s/p] - p[s/p]^2\}$
and $max(\sum_{i=1}^{t} r_i^2)$ is as stated in Corollary 2.3,
with $a = r_l = max(C[R/t], R[C/t], 1)$,
$a + m = r_h = min(C[R/t] + C, R[C/t] + R)$, $q = RC$
and $RC - r_l t \equiv k \; mod(r_h - r_l)$.
Note that, on substituting for $f(t,b,k)$, the block design formula for c_{max} reduces to $b(k-1) - (b/k)[k/t](2k - t - t[k/t])$.

It follows that M_c is minimised when $c = c_{max}$ and $\lambda_i^d = c_{max}\sqrt{\theta_i}/(\sum_{j=1}^{t-1} \sqrt{\theta_j})$.

The theorem suggests a form for an approximate information matrix A_{d^*}, derived by substituting $\lambda_i^{d^*} = c_{max}\sqrt{\theta_i}/(\sum_{j=1}^{t-1} \sqrt{\theta_j})$ into the spectral decomposition of the information matrix.

Corollary 5.1 *The approximate information matrix for estimating a set of treatment contrasts, $C_L\tau$, given by*

$$A_{d^*} = \frac{c_{max}}{\sum_{j=1}^{t-1} \sqrt{\theta_j}} \sum_{i=1}^{t-1} \sqrt{\theta_i}\xi_i\xi_i', \tag{5.1}$$

where ξ_i $(i = 1, \ldots, t-1)$ are the eigenvectors corresponding to the non-zero eigenvalues of $C_L'C_L$, has trace achieving bound $B(C_L)$ of Corollary 2.2.

Proof: This result follows directly from Theorem 5.1.

Note: For any design $d \in D(t, C_L, B)$, $tr(A_d) \leq c_{max} = tr(A_{d^*})$, from (5.1). Hence A_{d^*} will be called the *A-optimal approximate information matrix* throughout this chapter.

Corollary 5.1 shows that if a design d^* exists, with an information matrix equal to A_{d^*}, then d^* is A-optimal over the class $D(t, C_L, B)$. In practice, a design with information matrix A_{d^*} rarely exists for specified contrasts $C_L\tau$. However, for the following class of problems, A-optimal designs are established directly from Corollary 5.1.

5.2.2 Estimating a full set of orthogonal contrasts

When the specified contrasts are a set of $t-1$ orthogonal contrasts in the treatment effects, Theorem 5.1 can be used to derive the well known results for A-optimality of balanced incomplete block designs and Youden squares, discussed in this subsection. In order to do this, the following lemma is required.

Lemma 5.2 *Suppose $x_1, \ldots, x_{t-1}$ is a set of $t \times 1$ orthonormalised vectors such that $x_i' 1_t = 0$, $i = 1, \ldots, t-1$, where 1_t is a $t \times 1$ vector of ones, then $\sum_{i=1}^{t-1} x_i x_i' = I_t - (1/t)J_t$ where $J_t = 1_t 1_t'$ and I_t is the $t \times t$ identity matrix.*

The optimality result can be shown in the following way. From Lemma 5.2, any set of orthogonal contrasts $C_O\tau$ in t treatments has $C_O'C_O = I_t - (1/t)J_t$. It is easily verified that the eigenvalues of $C_O'C_O$ are $\theta_i = 1$ for $i = 1, \ldots, t-1$. From Theorem 5.1, the eigenvalues of the information matrix A_{d^*} are

$$\lambda_i^{d^*} = \lambda^{d^*} = \frac{c_{max}}{t-1}, \; i = 1, \ldots, t-1, \tag{5.2}$$

where c_{max} is the maximum trace of A_{d^*} which equals $b(k-1)$ for binary designs.

The A-optimal approximate information matrix is calculated using the spectral decomposition $A_{d^*} = \sum_{i=1}^{t-1} \lambda_i^{d^*} \xi_i \xi_i'$ which, after substituting for $\sum_{i=1}^{t-1} \xi_i \xi_i'$ from Lemma 5.2 and for $\lambda_i^{d^*}$ from equation (5.2), simplifies to

$$A_{d^*} = \frac{b(k-1)}{t-1}(I_t - \frac{1}{t}J_t).$$

A balanced incomplete block design is known to have $A_d = rE(I_t - (1/t)J_t)$, with $E = \lambda_b t/(rk)$, where λ_b denotes the number of blocks in which each pair of treatments occurs. Using the necessary conditions for the existence of a balanced incomplete block design, that $bk = tr$ and $r(k-1) = \lambda_b(t-1)$, it follows that $rE = \lambda_b t/k$ can be expressed as $b(k-1)/(t-1)$. Hence

$$A_d = \frac{b(k-1)}{t-1}(I_t - \frac{1}{t}J_t) = A_{d^*}.$$

A similar argument can be used to show that Youden squares are A-optimal row-column designs. Since a Youden square has row and column component designs consisting of a randomised block design and a balanced incomplete block design respectively, $A_{RC} = A_C$, see the proof of Theorem 4.5. Hence $A_{RC^*} = A_{d^*}$

and the above argument for the A-optimality of balanced incomplete block designs also establishes the A-optimality of Youden squares.

Theorem 5.1 provides a sufficient condition for the A-optimality of a strongly aligned design. It is extremely difficult to establish necessary conditions for a design to be A-optimal over D, owing to the problem of design existence. In the discussion of the methods of finding designs, given in Section 5.3, it is noted that designs with information matrices corresponding to the approximate information matrix rarely exist. However, designs with an information matrix close, in some sense, to the approximate information matrix are highly efficient. This is illustrated in Section 5.4, in which some examples for several different sets of practical treatment contrasts are discussed.

5.3 Applications to finding efficient designs

In this section, possible methods of finding designs with information matrices corresponding to the A-optimal approximate information matrices of Corollary 5.1 are discussed. The search for efficient designs must be undertaken by separate consideration of the specific contrasts of interest, $C_L\tau$, since the eigenvalues of $C_L'C_L$ are used to determine the design independent bound of Corollary 2.2.

There are several possible approaches to finding block designs using Corollary 5.1. The first approach is to try to construct a design from the information matrix produced by the corollary. The second approach is to search, within the class of aligned designs, for designs with information matrices close to A_{d^*}. A further approach is appropriate when the nature of the treatment contrasts makes the class of efficient aligned designs very small. This approach involves searching for efficient designs with the same information matrix structure as A_{d^*}.

The first approach is composed of two stages. First, it is necessary to consider the possible treatment replication structure of the design, for which the following lemma is needed.

Lemma 5.3 *A design d, for t treatments arranged in b blocks each of size k, with an information matrix A_d which achieves $max_{d\in D}\, tr(A_d)$ must have treatment replications r_i $(i = 1, \ldots, t)$ in the range*

$$max(1, b[k/t]) \leq r_i \leq b[k/t] + b.$$

Proof: The value of $max_{d \in D}\, tr(A_d)$ is calculated assuming that the elements of the incidence matrix N_d are as equal as possible subject to the constraints that $\sum_{i=1}^{t} n_{ij} = k$ $(j = 1, \ldots, b)$ and $\sum_{j=1}^{b} n_{ij} = r_i$ $(i = 1, \ldots, t)$. Hence, the elements of N_d take one of two integer values, either $n_{ij} = [k/t]$ or $[k/t] + 1$. The result is obtained by considering the maximum and minimum values of $\sum_{j=1}^{b} n_{ij}$; see the proof of Theorem 2.5 for use of a similar argument.

The above lemma generates many possible treatment replications, each of which requires investigation to see whether a corresponding design exists as described below. Alternatively, a single allocation of replications to treatments can be obtained using the formula of Jones (1976), that is $r_i = (\sum_{j=1}^{L} w_j c_{ij}^2)^{1/2}$ where c_{ij} is the element of the jth contrast vector corresponding to the ith treatment, all contrasts having been scaled so that $\sum_{i=1}^{t} c_{ij}^2 = 1$, and w_j is the weight assigned to that contrast $(i = 1, \ldots, t;\ j = 1, \ldots, L)$.

The next step is to calculate, for each treatment replication possibility, a concurrence matrix using $N_{d^*} N'_{d^*} = kr^{\delta} - kA_{d^*}$. The existence of a design with concurrence matrix $N_{d^*} N'_{d^*}$ can be investigated using an algorithm similar to the one developed by Taylor & John (1983) to construct a binary design from a given concurrence matrix. Examination of a range of examples for different sets of treatment contrasts has revealed that designs corresponding to the information matrix A_{d^*} rarely exist since $N_{d^*} N'_{d^*}$ rarely has integer elements. A possible way forward is to round the entries of the concurrence matrix but this rounding is somewhat artificial since it has to be performed subject to satisfying the existing constraints on $N_d N'_d$. For non-binary designs, $kr_i = \sum_{l=1}^{t} \sum_{j=1}^{b} n_{ij} n_{lj}$ $(i = 1, \ldots, t)$ must be satisfied. Binary designs have the additional constraint that $\sum_{j=1}^{b} n_{ij}^2 = r_i \leq b$ for $i = 1, \ldots, t$. Hence, it may be necessary to consider all concurrence matrices which have some integer elements similar in magnitude to the corresponding elements of $N_{d^*} N'_{d^*}$ and also satisfy the design constraints.

There are a number of disadvantages to this approach. Firstly, there is no guarantee that any of the resulting concurrence matrices will correspond to an existing design. In addition, the approach will not easily extend to designs for two orthogonal blocking factors, since it is extremely difficult to determine the incidence matrices for the row and column component designs for a given A_{RC^*} and replication vector r. Since the effort required to find efficient designs via this approach is considerable, it seems more appropriate to use *JE*.

The second approach to finding designs is to restrict attention to the class of aligned designs and locate highly efficient and A-optimal designs within this class. This approach is demonstrated in Subsection 5.4.1, where examples are given of efficient block and row-column designs which are aligned with the particular contrasts of interest and have information matrices with entries close to A_{d^*}.

The third approach focuses attention on finding designs which have the same pattern to the entries of their information matrix as the A-optimal approximate information matrix. This method is illustrated by the examples of Subsection 5.4.2.

5.4 Application to further contrasts from the pharmaceutical industry

Within the pharmaceutical industry, interest is often focused on non-orthogonal treatment comparisons in two or more treatments. The previous chapters of this thesis are concerned with finding efficient designs which are part-balanced with respect to one such set of contrasts, namely, the dual versus single treatment contrasts. This case is discussed further in Subsection 5.4.2. Another set of non-orthogonal pairwise contrasts is considered in the following subsection.

5.4.1 A reduced set of contrasts for a large number of pairwise treatment comparisons

Consider an experiment for t treatments, labelled $1, \ldots, t$ and arranged in b blocks each of size k, for which the set of all pairwise treatment comparisons is of interest. If t is very large, an infeasibly large number of comparisons may need to be estimated and interpreted. In this type of situation, it may be possible to use prior knowledge of the treatments to provide an initial ranking of the treatment effects. For the case considered in this subsection, the following contrasts are of primary interest:

$$\tau_i - \tau_{i+j} \text{ for } i = 1, \ldots, t;\ j = 1, \ldots, p, \tag{5.3}$$

where $p \leq t - 1$ and $i + j$ is evaluated as $i + j - t$ when $i + j > t$.

Let C_C denote the contrast matrix for (5.3) then the matrix $C_C'C_C$ is circulant with initial row $\{\ 2p\ \ -1_p'\ \ 0\ \ -1_p'\ \}$. Hence, from Definition 5.1 and the fact that all circulant matrices of the same size have a common set of eigenvectors (Davis, 1979, p 73), the class of aligned designs contains all designs with circulant information matrices and in particular the A-optimal approximate information matrix A_{d^*} (see Corollary 5.1) is circulant.

For this specific set of contrasts, attention is restricted to equi-replicate designs where $r = r_e 1_t$. This is a reasonable assumption since the diagonal elements of A_{d^*} are all equal and the design is constrained to have equal block sizes. A further justification is that, in this particular set of contrasts, each treatment effect occurs the same number of times with the same coefficients, and such balance is likely to require an equi-replicate design. The following example demonstrates how efficient equi-replicate designs may be found.

Example 5.1 *Suppose an investigator is interested in comparing six treatments, arranged in twelve blocks each of size three. Prior knowledge of the treatments suggests that* $p = 2$ *and the resulting* $C_C'C_C$ *matrix is circulant with intial row* $\{\ 4\ \ -1\ \ -1\ \ 0\ \ -1\ \ -1\ \}$. *From Corollary 5.1, with* $c_{max} = 24$, *the A-optimal approximate information matrix is given by the initial row*

$$\{\ 4.0000\ \ -0.8990\ \ -0.8990\ \ -0.4041\ \ -0.8990\ \ -0.8990\ \}.$$

For cyclic designs, the diagonal elements of the information matrices are easily shown to be $k^{-1}r_e(k-1)$. *Since* $k = 3$ *and* $A_{dii} = 4$ $(i = 1, \ldots, t)$, r_e *is taken as six in this case. A design with this information matrix does not exist, however, since the concurrence matrix is given by the initial row*

$$\{\ 6.0000\ \ 2.6969\ \ 2.6969\ \ 1.2122\ \ 2.6969\ \ 2.6969\ \},$$

which does not have integer elements.

The next stage is to consider various roundings of the elements of $N_{d^*}N_{d^*}'$ *which satisfy the design restrictions concerning treatment replications and block sizes. The circulant matrices generated by the following initial rows are considered:*

(i) (6 3 3 0 3 3),
(ii) (6 3 2 2 2 3),
(iii) (6 2 3 2 3 2).

A cyclic design exists with concurrence matrix given by (ii). This design is generated by cycling on the initial blocks (1 2 3) and (1 2 4). It should be noted that this design is not unique. The following block design also has its concurrence matrix given by (ii)

Block 1	*1*	*2*	*3*	*Block 7*	*2*	*3*	*4*
Block 2	*1*	*2*	*6*	*Block 8*	*2*	*3*	*5*
Block 3	*1*	*2*	*6*	*Block 9*	*2*	*4*	*5*
Block 4	*1*	*3*	*4*	*Block 10*	*3*	*4*	*6*
Block 5	*1*	*4*	*5*	*Block 11*	*3*	*5*	*6*
Block 6	*1*	*5*	*6*	*Block 12*	*4*	*5*	*6.*

Note that the designs are not isomorphic since the second design has a repeated block, whereas the first design does not. Both these designs have $tr(C_C\Omega_d C_C') = 4.9962$ *and an efficiency of 99.1% when compared with the design independent bound of Corollary 2.2.*

Group divisible designs with concurrence matrices given by (i) and (iii) also exist. The design with $N_d N_d'$ *corresponding to (i) has association scheme (1 4), (2 5), (3 6) and* $\lambda_1 = 0$, $\lambda_2 = 3$. *The design with* $N_d N_d'$ *given by (iii) has association scheme (1 3 5), (2 4 6) and* $\lambda_1 = 3$, $\lambda_2 = 2$. *Both these designs have* $tr(C_C\Omega_d C_C') = 5.0$ *and a corresponding efficiency of 99% when compared with the design independent bound of Corollary 2.2. Hence, by confining attention to the class of aligned designs, highly efficient designs have been identified.*

Note that, for these examples, row-column designs for estimating $C_C\tau$ can be obtained by amalgamating the incomplete block design with a complete block design. From Lemma 4.1, row-column designs can always be constructed in this way when the component designs have equal treatment replications and compatible dimensions. The resulting designs will be row-orthogonal with the same total variances and efficiencies as their respective incomplete block component designs.

5.4.2 The dual versus single treatments problem

When the approach of the previous section is applied to the dual versus single treatments case, it is found that the class of aligned designs contains highly efficient designs for only a small number of parameter values. Therefore, in this

section, the third approach to seeking efficient designs with the same information matrix structure as the A-optimal approximate information matrix is adopted.

The contrasts for this particular problem are given by $H\tau$, where the contrast matrix H is defined in equation (1.12). An examination of a selection of examples has indicated that the bound of Corollary 2.2 may be loose for this particular set of contrasts under certain parameter values. The following examples illustrate this point, in addition to showing that efficient PBDS block and row-column designs are not necessarily aligned with H although their information matrices have structure (1.14).

Example 5.2 *Suppose an experiment has parameters* $m = 2$, $n = 3$, $b = 4$ *and* $k = 9$, *the corresponding value of* $c_{max} = max_{d \in D}\, tr(A_d)$ *is 28.4444. The A-optimal approximate block information matrix given by Corollary 5.1 is*

$$A_{d^*} = \begin{pmatrix} 6.5899 & -0.7778\,1_2' & -2.5171\,1_2' \\ -0.7778\,1_2 & 4.7878I_2 - 0.3575J_2 & -2.3939I_2 - 0.4505J_2 \\ -2.5171\,1_2 & -2.3939I_2 - 0.4505J_2 & 7.1818I_2 - 0.6849J_2 \end{pmatrix}$$

with $tr(H\Omega_{d^*}H') = 0.9927$. *The most A-efficient PBDS block design, with information matrix structure (1.14), found by Gerami, Lewis, Majumdar & Notz (1993) has*

$$A_d = \begin{pmatrix} 6.2222 & -1.3333\,1_2' & -1.7778\,1_2' \\ -1.3333\,1_2 & 5.7778I_2 - 0.8889J_2 & -1.3333J_2 \\ -1.7778\,1_2 & -1.3333J_2 & 8I_2 - 1.7778J_2 \end{pmatrix}$$

with $tr(H\Omega_d H') = 1.0898$. *The efficiency of the PBDS design d found by comparing* $tr(H\Omega_{d^*}H')$ *with* $tr(H\Omega_d H')$ *is 91.1%. However, bound* B_F *of Chapter 2 has a value of 1.0833 and hence is tighter than the bound of Corollary 2.2 in this case. Design d has an efficiency of 99.4% when compared with bound* B_F.

Note that design d is not aligned with the contrast matrix H which may explain its low efficiency when compared with the bound $B(H)$ of Corollary 2.2.

Example 5.3 *Consider an experiment with* $m = 2$, $n = 3$, $R = 6$ *and* $C = 7$. *From Theorem 5.1,* c_{max} *takes the value 32.0952 and the A-optimal approximate row-column information matrix is*

$$A_{RC^*} = \begin{pmatrix} 7.4357 & -0.8777\,1_2' & -2.8402\,1_2' \\ -0.8777\,1_2 & 5.4024I_2 - 0.4034J_2 & -2.7012I_2 - 0.5083J_2 \\ -2.8402\,1_2 & -2.7012I_2 - 0.5083J_2 & 8.1035I_2 - 0.7727J_2 \end{pmatrix}$$

which has $tr(H\Omega_{RC^*}H') = 0.8798$. *The most A-efficient PBDS row-column design for these parameter values, given in Table 3.7, has*

$$A_{RC} = \begin{pmatrix} 7.1429 & -1.5714\,1_2' & -2\,1_2' \\ -1.5714\,1_2 & 6.8572I_2 - 1.1429J_2 & -0.1428I_2 - 1.4286J_2 \\ -2\,1_2 & -0.1428I_2 - 1.4286J_2 & 8.2380I_2 - 1.6190J_2 \end{pmatrix}$$

with $tr(H\Omega_{RC}H') = 0.9713$. *The PBDS row-column design has an efficiency of 90.6% when compared with the design independent bound of Corollary 2.2. However, this bound is not recommended for use in this case since bound* B_F *has a value of 0.9302. The PBDS row-column design has an efficiency of 95.8% when compared with bound* B_F. *It should be noted that the row-column design and the row and column component designs are not aligned with* H.

5.5 Conclusions

In this chapter, a method of identifying classes of designs which can contain highly efficient designs for estimating a specific set of treatment contrasts is described. A specification for the information matrix of a design, sufficient for its trace to achieve the design independent bound $B(C_L)$ of Corollary 2.2, is given and applications to methods of finding efficient designs are described. Illustrations for two different sets of contrasts from the pharmaceutical industry are discussed. Further recent work undertaken jointly with S.M. Lewis, L.-J. Kao & A.M. Dean (Ohio State University) has established the necessity of the form of the A-optimal approximate information matrix, A_{d^*}, given in Corollary 5.1 for achieving bound $B(C_L)$. The work in this chapter, together with the additional recent result, has been written up and submitted for publication.

Chapter 6

Models for cross-over studies

6.1 Introduction

In the remaining chapters of this thesis, efficient designs for cross-over trials constructed from the efficient PBDS row-column designs of Chapters 3 and 4 are considered. The first issue to address is what constitutes a suitable model for a cross-over trial. Several different model formulations have been used in the past, some of which have received criticism in the more recent literature, see Fleiss (1989) and Senn (1992). In this chapter, models used in the literature for planning trials are reviewed and some controversial issues are discussed.

A popular study design for a medical experiment is the parallel group study in which patients are randomly assigned to treatment groups and receive doses of one treatment throughout the duration of the experiment. A cross-over study is more complicated in design, but has the advantage that resources are conserved by repeatedly treating each experimental unit. In such a study, each subject is given a series of treatments over a sequence of time periods and the response of each subject is measured at the end of every period. This enables treatment comparisons to be made *within-subject* and, since in medical trials it is usually true that within-subject variability is much smaller than between-subject variability, important contrasts can be estimated much more efficiently. Trials are considered for t treatments allocated to s subjects over p periods, with periods and subjects represented by the rows and columns respectively of the design. The treatment sequence for a given subject may consist entirely of distinct treatments or may involve repetitions.

Designs which have been developed for use in this type of study are known as cross-over or change-over designs. They may also be referred to as repeated measurements designs, although this term includes situations where each patient is repeatedly observed while receiving only one treatment throughout the duration of the experiment, as well as those where the patient receives a sequence of different treatments.

A disadvantage of using a cross-over study is the need to allow for the possibility of a carryover effect of the treatment administered in period i into subsequent periods, since it is often unrealistic to assume that a treatment effect disappears as soon as the treatment is stopped. This problem is often reduced by employing a *washout* period. This is a time interval inserted between each pair of treatment periods, during which the patient receives no treatment. Hence any residual treatment effects will have lessened or may have disappeared completely before the next course of treatment commences. This approach serves to reduce pharmacological carryover effects but may be of little help in reducing carryover effects of a psychological nature.

The study of psychological effects in medical experiments has been aided by the development of the placebo. This is an inactive substance which is usually matched to the shape, taste and colour of the treatment under investigation so that the patient is unaware that a dummy treatment is being administered, thus enabling the true effect of the active treatment to be observed. This is known as a blind trial. A double blind trial is one in which neither the patient nor the clinician observing patient response knows which treatment is being administered in each period. Studies which reveal a placebo effect are recorded in the literature, not only for psychological experiments involving illnesses which may have a psychosomatic cause such as anxiety and stress, but also for conditions such as vomiting and post-operative pain. Beecher (1955) reviews fifteen studies from the medical literature, involving more than 1,000 patients, for a range of conditions including severe post-operative pain, cough, pain from angina, anxiety and tension and headache. The results indicate that approximately 35% of the patients received relief from a placebo.

Since it is widely accepted that the power of suggestion may have a significant effect on a patient's condition, there is no reason to assume that this type of effect does not carryover into the next treatment period. Although the use of a washout period may ensure that all pharmacological traces of the drug have

been eliminated from the patient before the next treatment period begins, it is not necessarily true that the patient is no longer affected by the treatment of the previous period. Willan & Pater (1986) discuss psychological carryover, sometimes referred to as negative carryover, in their paper which defends the use of cross-over trials in the presence of carryover effects. They describe psychological carryover as the patients' change in attitude as they enter the second period as a result of their experiences in the first period. For example, a patient receiving little relief from a placebo in the first period may not be happy about continuing the trial. Such reservations may alter the patient's evaluation of the performance of the active treatment administered in the second period. Jones & Kenward (1989, p 42) also mention this issue. Willan & Pater discuss a specific example to illustrate this point. They cite a double blind 2×2 cross-over trial designed to compare the efficacy of two drugs in controlling nausea and vomiting caused by cancer chemotherapy. Patients were randomised to receive either drug A or B for their first course of chemotherapy and then crossed over to receive the other drug for their second course. The response measured was the degree of nausea, rated on a linear analog scale, experienced in four six-hour intervals following chemotherapy. Estimates of direct treatment and carryover effects, assuming a model for additive first-order carryover effects and random subject effects (see Section 6.5), are presented separately for each interval and reveal significant carryover effects in the second and third intervals. These effects are thought to have a psychological cause since a patient who experiences nausea in the first interval after chemotherapy may expect to experience it in the second period and consequently is more likely to experience it.

A further example of a possible psychological carryover effect is a recent study by Dunn (1993) concerning the effectiveness of quinine in relieving night cramps. Twenty-eight patients were allocated quinine or placebo for thirty days and then crossed over to receive the alternative treatment for thirty days after a washout period of three days. The proportion of nights in which a patient experienced night cramps was the observed response. A carryover effect was found to be significant at the 5% level using a Mann-Whitney test. This is surprising because there is usually low power to test for this type of effect, an issue discussed by Hills & Armitage (1979). The latter authors also stress the fact that the estimates of direct treatment effects for a 2×2 cross-over trial, such as the Dunn (1993) study, will be biased if the assumption of negligible carryover effects is not valid. In this case, the use of estimates of treatment effects based solely on the data

from the first period is advocated. The authors outline a test for the assumption of negligible carryover effects but point out that it has low statistical power and hence will only detect very large effects. In order to achieve sufficient power to test for carryover, it would be necessary to employ as many subjects as for a parallel group study thus removing one of the advantages of a cross-over study. Grizzle (1965) and Brown (1980) also address this issue, see Section 6.5. Willan & Pater (1986) disagree with the view that a parallel group study should be used whenever carryover effects are suspected of being present. The authors demonstrate, by means of an example, that even in the presence of significant carryover effects the cross-over analysis, which estimates the direct treatment effects using data from both periods, can provide a more powerful test of treatment effect than the estimates based on first period data only. Jones & Kenward (1989, p 85) agree that the power of the preliminary test for the presence of carryover effects in the 2×2 trial is inadequate, but show how the power of the test may be increased by including baseline measurements or covariates in the analysis.

A review of the literature reveals some controversy, outlined in this section, over the use of cross-over trials. However, there is sufficient evidence from past studies to indicate that the assumption of negligible carryover effects may not always be appropriate.

The designs described in Chapter 7 are obtained mainly under the assumption of first-order carryover effects, where the effect of a treatment may be present in the period immediately following the period in which that treatment was administered, but will be assumed negligible in any of the subsequent periods. The aim is to find designs which perform well both in the presence and absence of first-order carryover effects, since designs are sought for trials involving treatments with short term effects which make it very difficult to predict, at the planning stage, if carryover effects will be present. The approach followed takes an efficient row-column design under model (1.1) and rearranges it to find a layout which achieves minimum variance for the contrasts of interest under a model including additive first-order carryover effects. The same approach is used to find designs for situations when carryover effects are thought to persist for two periods. An investigation of the robustness of the designs to the presence and persistence of carryover effects is presented in Subsection 7.6.2.

The estimation of direct treatment effects is considered of primary importance since this is most commonly the case in practice. The carryover effects, if found to

be present, are regarded as a nuisance factor. In order to decide whether carryover effects are present, a significance test applied at some specified significance level is used. It is common practice to remove carryover effects from the model unless they are found to be significantly different from zero. A problem associated with this technique occurs if the carryover effects actually exist but are found to be non-significant. If the carryover effects are then dropped from the model, the resulting estimates of the treatment effects, $\tilde{\tau}$, are biased. Conversely, if the carryover effects are very small but accounted for in the model, then the estimated treatment effects adjusted for carryover effects, denoted by $\hat{\tau}$, are unbiased but will usually have larger variance due to the inclusion of extra parameters in the model and the fact that a substantial decrease in the mean square error is not achieved by including the carryover terms.

Abeyasekera & Curnow (1984) consider this issue and suggest that when the estimation of direct treatment effects is of primary interest, it may be more appropriate to base the decision of whether or not to adjust for carryover effects on procedures which lead to estimators with smallest mean square errors (MSEs) rather than on significance tests. The authors choose to estimate treatment differences by:

$$\tau^* = \begin{cases} \hat{\tau} & \text{if } |\hat{b}| > T \\ \tilde{\tau} & \text{if } |\hat{b}| < T, \end{cases} \tag{6.1}$$

where $\hat{b}$ is an unbiased estimator of the bias b in the estimator $\hat{\tau}$ which is unadjusted for carryover effects. Three examples are considered for a range of parameter values and the maximum percentage increase in root mean square error (RMSE) when τ^* results in the wrong decision is computed. The findings suggest that the decision not to adjust when the adjusted estimator would have been preferable does not lead to substantially less accurate estimators. However, if the adjusted estimator is used when the unadjusted estimator would have been preferable, increases in RMSE are as high as 10% in some cases. The increase in RMSE is also considered for the situation when the adjusted estimator is always used, and the resulting figures are of similar magnitude to those obtained by using the adjusted estimator when the unadjusted estimator would have been a better choice. It is noted that these errors, resulting from always using the adjusted estimator, will only occur if the true difference between carryover effects is quite small. Hence, the authors conclude that the best approach is to always use the adjusted estimators. However, in the dual versus single treatments case, designs

are considered for situations in which carryover effects are expected to be small if not entirely negligible. Therefore, it may not be advisable to always adopt the estimators adjusted for carryover effects.

In the following sections, a review of the carryover models which have appeared in the literature is presented. In Section 6.3, models for additive carryover effects are discussed. A brief description of some models with a factorial treatment structure is given in Section 6.4, followed by a discussion of models for random subject effects, see Section 6.5. The possibility of interactions between effects is considered in Section 6.6 and autoregressive models are discussed in Section 6.7. In the next section, the validity of the assumption of independent errors, when the same individuals are measured repeatedly, is considered.

6.2 Models with correlated error structures

In this section, it is assumed that carryover effects are negligible and an additive model for two blocking factors, given as equation (1.1) in Chapter 1, is adopted. For a trial with p periods and s subjects the model can be written as

$$y_{ij} = \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \varepsilon_{ij} \quad (i = 1, \ldots, p;\ j = 1, \ldots, s), \tag{6.2}$$

where y_{ij} denotes the response obtained from the jth subject in the ith period, μ is the overall mean, α_i is the ith period effect, β_j is the jth subject effect, $\tau_{d(i,j)}$ is the direct effect of the treatment given to subject j in period i and ε_{ij} are correlated random variables with mean 0 and variance σ^2. Correlated error structures can be thought of as an alternative way of modelling the relationship between measurements on the same unit in a cross-over situation. However, they should not be regarded as a replacement for carryover effects since there is no formal link between the two; correlated errors being a function of time only and carryover effects a function of treatment only. There are many possible forms of error structure which might be appropriate for this type of situation but much of the literature devotes attention to the following two cases.

Case I ***Errors follow a stationary first-order autoregressive process.*** *Under this process, the errors for subject j $(j = 1, \ldots, s)$ take the form*

$$\varepsilon_{ij} = \begin{cases} \eta_{ij} & \text{for } i=1 \\ \lambda\varepsilon_{i-1,j} + \eta_{ij} & \text{for } i=2,\ldots,p, \end{cases} \tag{6.3}$$

where η_{ij} are independent identically distributed random variables with mean 0 and variance σ_e^2 and λ is the parameter of the autoregression. This results in a variance-covariance matrix $V = (v_{ij})$ which has elements

$$v_{ij} = \frac{\lambda^{|i-j|}}{1-\lambda^2}\sigma_e^2 \ (i = 1, \ldots, p;\ j = 1, \ldots, s),$$

where $-1 < \lambda < 1$.

Under model (6.2), optimal designs for a particular experiment size are likely to depend on the value of λ. This is illustrated by the results of Kunert (1985) in his search for optimal cross-over designs, in the sense of minimum variance of the Best Linear Unbiased Estimate of treatment effects. Kunert shows that a Williams design with balanced end pairs, that is with the same number of units receiving treatments i and j in the first and last periods $(i, j = 1, \ldots, t)$, is universally optimal (see Definition 1.4) for the estimation of treatment effects over the class of all repeated measurements designs for t treatments, s subjects and $p = t$ periods when $\lambda \geq \lambda^*(t)$ where

$$\lambda^*(t) = \begin{cases} -1 & \text{if } t = 3 \\ \frac{-1/2\{t-2-(t^2-8)^{1/2}\}}{t-3} & \text{if } t \geq 4 \end{cases}.$$

Kunert claims that an error structure with correlation decreasing over time is a sensible approximation to reality. However, some of the model's popularity is probably due to its mathematical tractability. A drawback of this model is that λ is usually assumed to be known, and although it may be possible to obtain information about λ from previous similar experiments, this is unlikely to provide more than a rough approximation to the parameter's true value. Street (1989) also uses this model in her discussion of possible construction methods for the optimal designs of Kunert (1985).

Case II ***Errors follow a stationary first-order moving average process.*** *The errors for subject j $(j = 1, \ldots, s)$ can be written as*

$$\varepsilon_{ij} = \begin{cases} \eta_{ij} & \text{for } i=1 \\ \eta_{ij} - \lambda\eta_{i-1,j} & \text{for } i=2,\ldots,p, \end{cases} \tag{6.4}$$

where the η_{ij} are as for Case I and λ is the parameter of the process. This process produces a variance-covariance matrix which has elements

$$v_{ij} = \begin{cases} \lambda^{|i-j|}\sigma_e^2 & \text{if } |i-j| \leq 1 \\ 0 & \text{otherwise,} \end{cases} \tag{6.5}$$

where $-1/2 \leq \lambda \leq 1/2$.

The model with additive effects for treatments and blocking factors and Case II type error structure has received much less attention in the literature. Matthews (1990) considers this type of error structure in his review of the efficiency of ordinary least squares analysis of cross-over designs. A more general mixed autoregressive-moving average process, with parameters p and q, is considered by Rochon & Helms (1989) in their work on maximum likelihood estimation for incomplete repeated measurements designs. An advantage of this type of error model is that it can provide for a wide variety of structures in the covariance matrix of the observations while requiring only a small number of parameters to be estimated, but the authors give little discussion of where this structure might occur in practice.

It is an advantage to be able to provide optimal or at least efficient designs under different error structures if it is known in which type of practical situations these forms of error are likely to arise. Williams (1952) designs one-dimensional treatment sequences under a Case I type error structure and, using some data on wheat yields from different plots of land, shows that this type of error structure may be appropriate for agricultural data. However, at the planning stage of an experiment, it is very difficult to determine which type of error structure may be applicable. It is therefore necessary to consider how the reliability of the study conclusions is affected if the experiment is designed or analysed under a model with an inappropriate error structure.

Ideally, a design should be employed which is *robust* over several plausible error models, that is information on the parameters of interest can be extracted efficiently irrespective of the assumptions about error. The question of interest is whether such designs exist. Behrenblut & Webb (1974) consider this problem and show that the minimum variance unbiased estimates of treatment effects for Williams Latin Squares have optimum properties under a model with independent, identically distributed errors and also under a model with errors following a first-order autoregressive process for both positive and negative λ.

The consequence of the assumption of an inappropriate error structure is to incorrectly estimate the variance of the parameter of interest. Kunert (1987) addresses this type of problem by finding an upper bound on X, the quantity by which the estimate of the parameter variance needs to be multiplied in order

to make it unbiased. A limitation of this work is that the calculated bound does not relate to the true amount of underestimation but is a bound for the worse possible scenario. The value of the bound is that it may help to determine whether the conclusions of an experiment conducted under the assumption of independent, identically distributed errors would be worthless under a general covariance structure for error. In a sense, the bound gives some indication of the robustness of conclusions to different error models.

Matthews (1990) addresses the related problem of efficiency of analysis under Ordinary Least Squares (OLS) if the errors are correlated. For simplicity, the covariance matrix of the errors is assumed to be dependent on a single parameter λ. Two alternative forms of analysis are considered for the case where $\lambda \neq 0$, namely Generalised Least Squares (GLS), which is based on the assumed dispersion matrix $V(\lambda)$ but has the disadvantage that λ is required to be known, and an empirical form of generalised least squares (EGLS) which is also based on the assumed dispersion matrix, this time evaluated at $\hat{\lambda}$ which is estimated from the data. However, EGLS will often be less efficient than OLS due to a poor estimate of λ resulting from sampling variation.

Matthews defines two quantities which enable the performance of OLS analysis to be assessed. These are denoted by R_1 and R_2 and are calculated as

$$R_1 = 1 - \frac{\text{root mean estimated variance using OLS}}{\text{actual standard error using OLS}}$$

and

$$R_2 = \frac{\text{actual standard error using GLS}}{\text{actual standard error using OLS}},$$

where the standard error is that of the direct treatment effect. The efficiency of OLS analysis is measured using R_2.

The efficiency of the analysis of a design using OLS, relative to that obtained using GLS, can be calculated if a value for λ is assumed, but the performance of the OLS analysis is dependent on the particular value assumed. The approach taken is to see whether the OLS analysis achieves some specified level of efficiency (to be fixed by the experimenter or statistician) for all plausible values of λ. If this level is sufficiently high then the design may be considered robust to errors to some extent. However, since the estimate of the parameter variance using OLS is not unbiased for the true variance under OLS, the size of the bias should also be considered when making decisions about robustness. Summary measures of

these two factors, R_2 and R_1 given above, are calculated under the asumption of Case I and Case II type error structures for a range of possible values for λ. The results, which are restricted to the case where $t = 2$, suggest that the summary measures vary according to design, error process and the true value of λ. Hence it is difficult to recommend designs. It should be noted that designs which are efficient under OLS analysis are not always efficient designs under the model of interest. Therefore design selection which is based solely on performance of designs under OLS analysis may result in the selection of a poor design for the particular experiment.

In practice, there are many factors which need to be taken into consideration when selecting an experimental design, not all of which are statistical. The above discussion indicates that there are both advantages and disadvantages of assuming correlated errors. The assumption of independent errors is very common in practice, since it is very difficult to determine at the outset of an experiment which type of error structure may be applicable and there are technical difficulties associated with estimating the parameters of the error processes as discussed in this section. Owing to these types of problems, models with correlated error structures are not used for the dual versus single treatment problem in this thesis.

6.3 Models with additive carryover effects

In this section several different types of model are described and their suitability for application to the dual versus single treatment contrast problem is considered. The discussion begins with the most popular model which has been discussed and used by many authors.

6.3.1 Additive first-order carryover effects

The model for this case is similar to (6.2) and y_{ij} is written as

$$y_{ij} = \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \rho_{d(i-1,j)} + \varepsilon_{ij} \quad (i = 1, \ldots, p;\ j = 1, \ldots, s), \tag{6.6}$$

where $\rho_{d(i-1,j)}$ is the carryover effect, observed in period i, of the treatment administered in the $(i-1)th$ period to the jth subject and $\rho_{d(0,j)} = 0$ for $j = 1, \ldots, s$. All other effects in (6.6) are as for (6.2).

Consider equation (6.6) with the assumption of independent, normal errors. Many authors have used this model, including Williams (1949) who found experimental designs combinatorially balanced for the estimation of carryover effects under this assumption, in the sense of having each of the t treatments preceded equally frequently by every other treatment. A consequence, under equation (6.6), is that the estimators of all pairwise comparisons have equal variances. Pigeon & Raghavarao (1987) assume this model and find cross-over designs which are balanced for the estimation of carryover effects for the test treatment versus control treatment contrasts, in the sense of having each contrast estimated with equal precision.

The model is also adopted by Russell (1991) in his search for good cross-over designs for situations where there are fewer subjects than treatments. This type of design is useful in product testing experiments, for example wine tasting, where there are more products to be tested by each judge than there are judges available. Russell found that near A-optimal designs for an even number of treatments t can be obtained by selecting a set of s columns, which gives a design connected in the direct treatment effects with the smallest average variance for the elementary treatment contrasts, from the t possible columns of a Williams Square.

Equation (6.6) expresses the carryover effect in its simplest possible form and hence it is sometimes referred to as the *simple carryover model.* This lack of complexity accounts for much of its popularity in the statistical journals. However, as already discussed, the assumption of independent errors may not be valid and models of the form of (6.6) with the correlated error structures of Cases I or II of Section 6.2 have also been considered. Matthews (1987) obtains cross-over designs for two treatments which minimise the variance of the estimated direct treatment and carryover effects under a Case I type error structure with λ known.

Models based on equation (6.6) have received some criticism in recent years since they involve some assumptions which are not satisfied in many practical experiments. These criticisms, which are in the context of pharmacological measurements, are briefly mentioned here for completeness but are discussed in greater detail in Section 6.8. Fleiss (1986, 1989) discusses the assumption, implicit in equation (6.6), that the carryover effect of a treatment A onto a second treatment B, will be the same as the carryover effect of A onto itself. He argues that such an assumption is unlikely to hold in most practical settings. The assumption does appear unrealistic since most drugs have a *maximum effect* level and once

this level has been attained no further increase in treatment effect can be gained by continuing the treatment for a longer period. Matthews (1993) also discusses this problem and formulates an alternative model for two treatments, which can be extended to apply to t treatments to give:

$$\begin{aligned} y_{ij} &= \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \rho_{d(i-1,j)}\{1-\phi\} + \varepsilon_{ij} \\ &\quad (i = 1, \ldots, p;\ j = 1, \ldots, s), \end{aligned} \tag{6.7}$$

where

$$\phi = \begin{cases} 1 & \text{if } d(i-1,j) = d(i,j) \\ 0 & \text{otherwise} \end{cases} . \tag{6.8}$$

Note that, if $t > 2$, it is possible that the design has no treatment sequences in which the same treatment appears in two successive periods. If so, then the problem does not arise. In particular, treatment sequences containing the same treatment in consecutive periods will not occur in designs which are binary with respect to the subject blocking factor, since $t > p$ and the incidence matrix for subjects will not contain any elements with a value greater than unity. This problem does not arise in the dual versus single treatments case since the cross-over designs given in Chapter 7 usually have a small number of periods and hence a non-binary design for the subjects would result in poor within-subject estimation of the contrasts of interest.

Fleiss (1989) also questions the assumption that carryover effects persist for only one period. Senn (1992) discusses the existence of higher order carryover effects in multiperiod designs and concludes that there is no adequate reason to exclude them if first-order carryover effects are included. Models for this situation are considered in Subsection 6.3.3. In the light of these criticisms it is clear that models based on (6.6) cannot be used indiscriminately. However, this type of carryover structure is considered by many to serve a useful purpose in trials with relatively short treatment periods, where prior medical knowledge suggests that the treatments may have short term carryover effects of a psychological or pharmacological nature, and it cannot be certain that the allowable washout is adequate.

A variation on the model consisting of (6.6) together with the assumption of independent, normal errors is the circular model, see Magda (1980) and Hedayat (1981), which has the form of equation (6.6) but includes a preperiod in the experiment, labelled $i = 0$, where each subject receives the treatment that he or

she will also receive in the final period. Hence $\rho_{d(0,j)} = \rho_{d(p,j)}$ for $j = 1, \ldots, s$. Although this model has mathematical advantages, it would be difficult to justify to clinicians why the extra period has been used when the data is not included in the analysis. In many medical contexts the ethics of such a trial would be in doubt. Hence, this model is not considered in this thesis.

6.3.2 Carryover effects proportional to direct effects

Consider a special case of equation (6.6) in which the carryover effect $\rho_{d(i-1,j)}$ is now modelled as a fraction of the direct effect from the previous treatment administered to subject j, resulting in the model

$$\begin{aligned} y_{ij} &= \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \lambda\tau_{d(i-1,j)} + \varepsilon_{ij} \\ &\quad (i = 1, \ldots, p;\ j = 1, \ldots, s), \end{aligned} \tag{6.9}$$

where $\tau_{d(0,j)} = 0$ and λ is a constant of proportionality with $0 \leq \lambda < 1$.

The model consisting of (6.9) together with the assumption of independent, identically distributed errors is considered by Patterson & Lucas (1962) in their catalogue of changeover designs. Sen & Sinha (1986) use the same model in their analysis of serially balanced sequences. Two cases of the model are considered, namely λ known and λ unknown. The latter authors propose an alternative model in which the constant of proportionality is treatment dependent, so that treatment i has corresponding constant λ_i $(i = 1, \ldots, t)$. This is merely a reparameterisation of the model based on (6.6) with $\rho_{d(i-1,j)} = \lambda_{d(i-1,j)}\tau_{d(i-1,j)}$.

Senn (1992) adopts a form of the model based on (6.9) in his discussion of an example of a dose finding cross-over trial. However, it should be noted that Senn is considering the physical carryover of the treatment substance to be modelled in this way and ignores the possibility of psychological carryover effects, whereas equation (6.9) refers to the carryover effect of the treatment which may be psychological or pharmacological.

A model based on (6.9) is intuitively attractive since this type of relationship between the direct and carryover effects is quite likely to occur in biological or clinical contexts. Yet this model has not received much attention in the literature. Since equation (6.9) is a special case of equation (6.6), it is not used explicitly in this thesis. However, efficient designs under (6.6) with independent, identically distributed errors are identified in Chapter 7.

6.3.3 Higher order carryover effects

In multiperiod studies, it is possible that carryover effects may persist for more than one period. If each kth-order carryover effect persists up to and including the kth time period after the application of the treatment, then $\rho^{(k)}_{d(i-k,j)}$ can be incorporated into (6.6) giving

$$\begin{aligned} y_{ij} &= \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \rho^{(1)}_{d(i-1,j)} + \rho^{(2)}_{d(i-2,j)} + \ldots + \rho^{(k)}_{d(i-k,j)} \\ &\quad + \varepsilon_{ij} \ (i = 1, \ldots, p;\ j = 1, \ldots, s), \end{aligned} \tag{6.10}$$

where $\rho^{(h)}_{d(i-h,j)} = 0$ for $i \leq h$ where $h = 1, \ldots, k$.

Similarly, (6.9) could be generalised to give

$$\begin{aligned} y_{ij} &= \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \lambda\tau_{d(i-1,j)} + \lambda^2\tau_{d(i-2,j)} + \ldots + \lambda^k\tau_{d(i-k,j)} \\ &\quad + \varepsilon_{ij} \ (i = 1, \ldots, p;\ j = 1, \ldots, s), \end{aligned} \tag{6.11}$$

or

$$\begin{aligned} y_{ij} &= \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \lambda_{d(i-1,j)}\tau_{d(i-1,j)} + \lambda_{d(i-2,j)}\tau_{d(i-2,j)} + \ldots \\ &\quad + \lambda_{d(i-k,j)}\tau_{d(i-k,j)} + \varepsilon_{ij} \ (i = 1, \ldots, p;\ j = 1, \ldots, s), \end{aligned} \tag{6.12}$$

where $\lambda_{d(i-h,j)}$ is a constant and $\tau_{d(i-h,j)} = 0$ for $i \leq h$ where $h = 1, \ldots, k$; see Finney (1956) for use of models consisting of (6.11), with independent, normal errors and also with correlated errors, in bioassay.

For higher order carryover effects, most attention in the literature has been focused on the case where both first- and second-order carryover effects need to be considered. Williams (1949,1950) considers designs balanced for both first- and second-order carryover effects, firstly when the interaction between first- and second-order carryover effects is ignored and secondly when such an interaction is accounted for in the model. In the former case, any set of $(t-1)$ mutually orthogonal Latin Squares gives a design combinatorially balanced for the effects of $k-1 < t$ preceding treatments, in the sense that each treatment in the kth period is preceded equally frequently by every treatment in the ith period ($i = 1, \ldots, k-1$), provided that the initial column of each square has the treatments arranged in the same order. Nair (1967) considers the design and analysis of one-dimensional sequences combinatorially balanced for both first- and second-order carryover effects. The possibility of interactions between the carryover effects is not discussed. Patterson & Lucas (1962) consider the design and analysis

of experiments involving multiple carryover effects in their review of changeover designs.

However, the criticisms of the simple additive model for first-order carryover effects are, in general, also true of a model including both first- and second-order carryover effects. A design found under the latter model may require more subjects than a design under the simple model due to the increased number of parameters to be estimated. Designs for the dual versus single treatment contrast problem under a model including first- and second-order carryover effects are given in Chapter 7.

Discussion The models discussed in this section are appropriate for the dual versus single treatment contrasts problem, provided their assumptions are reasonable in the particular practical setting. The models based on (6.10) with $h = 2$ and (6.6), together with the assumption of independent, normal errors, are used to identify good cross-over designs in Chapter 7. The latter model has simple assumptions regarding carryover structure which limit the extent of its practical use. It is mathematically tractable and has widespread use both in the statistical and medical journals, although it does possess disadvantages. Models based on (6.10) have similar advantages and disadvantages, with the additional problem that their use is limited to larger experiments which have sufficient subjects to allow for the increased parameter estimation.

6.4 Models with factorial treatment effects

Berenblut (1967) considers a design for testing a quantitative factor at four equally spaced levels. The case in which both the direct treatment and first-order carryover effects have a linear, quadratic and cubic component is examined and the analysis is conducted under the following model:

$$\begin{aligned} y_{ij} &= \mu + \alpha_i + \beta_j + t_L\xi_1 + t_Q\xi_2 + t_C\xi_3 + r_L\eta_1 + r_Q\eta_2 + r_C\eta_3 + \varepsilon_{ij} \quad (6.13) \\ &\quad (i = 1, \ldots, p,\ j = 1, \ldots, s), \end{aligned}$$

where t_L, t_Q, t_C, r_L, r_Q and r_C are the linear, quadratic and cubic components of the direct treatment and carryover effects respectively and ξ_i and η_i $(i = 1, 2, 3)$ are the orthogonal polynomials for four treatments. The design under discussion is arranged in such a way that the three degrees of freedom for direct

treatment effects are mutually orthogonal to the degrees of freedom for the linear and cubic components of the carryover effects and has the special feature that, if the quadratic and cubic components of the carryover effects are negligible, then the variances of the estimates of the direct treatment parameters are minimised. Berenblut (1968) extends his previous work to find designs for a quantitative treatment at any number of equally spaced levels. On this occasion, a slightly different model is adopted in which both the direct treatment and first-order carryover effects are assumed to be predominantly linear, with carryover effects small by comparison with direct effects and proportional to them. A term for the *linear direct treatment* × *linear carryover* interaction is included in the model.

Patterson (1970) also considers designing for a quantitative treatment factor at four equally spaced levels. Attention is concentrated on those designs which are efficient for the estimation of the linear direct treatment × linear carryover interaction. Models with interaction terms are discussed more fully in Section 6.6.

6.5 Models with random subject effects

It is considered by some authors that the assumption of fixed subject effects is unrealistic since subjects are frequently selected from the population and assigned to treatments at random. Hence a model for random subject effects may be considered more appropriate for certain stages of the study. Experiments designed under the assumption of fixed subject effects may be analysed under a random subjects effects model and vice versa. In this section, three types of model having random subject effects are briefly discussed. The effect of the jth subject ($j = 1, \ldots, s$) within the kth treatment sequence ($k = 1, \ldots, g$), denoted by β_{jk}, is now considered to be an independent, identically distributed normal random variable with mean 0 and variance σ_s^2.

The first model is written as

$$\begin{aligned} y_{ijk} &= \mu + \alpha_i + \beta_{jk} + \tau_{d(i,j,k)} + \varepsilon_{ijk} \\ &\qquad (i = 1, \ldots, p;\ j = 1, \ldots, s;\ k = 1, \ldots, g), \end{aligned} \tag{6.14}$$

where $\tau_{d(i,j,k)}$ is the treatment administered to the jth subject within the kth sequence in the ith period and the errors ε_{ijk} are assumed to be identically distributed random variables, with mean 0 and variance σ_e^2, independent of each

β_{jk} and of each other. It can be shown that the covariance between two observations y_{ijk} and $y_{i'jk}$ is σ_s^2. Cornell (1991) uses a similar model, with different distributional assumptions on the random effects, to develop tests of differences of dispersion for the comparison of two treatments. In Cornell's model, the subject effects are no longer required to have a normal distribution and the errors are assumed to have distributions of the same form except that they may have different variances under the two treatments.

The next model differs from (6.14) in that it includes a term, $\rho_{d(i-1,j,k)}$, for the carryover effect from period $i-1$ to period i. This extended model has received much attention in the literature. Grizzle (1965) uses it to develop a test for the validity of the assumption of equal carryover effects for the 2×2 cross-over trial. Brown (1980) adopts Grizzle's extended model to investigate the advantages of the 2×2 cross-over trial relative to other simple designs and concludes that such cross-over trials are only beneficial if the carryover effects are negligible. Brown also argues that Grizzle's test for the assumption of equal carryover effects under this model is not sufficiently powerful to give a reliable result and hence there is no adequate way to test the assumption from the data.

Although most of the occurrences in the literature of model (6.14), with the inclusion of a first-order carryover effect, have been in the context of experiments for two treatments and two periods, there is no reason why the model cannot be extended for use in higher order experiments. Jones, Kunert & Wynn (1992) briefly consider a carryover model with random subject effects and independent errors in their investigation of the structure of information matrices for mixed effects models.

Attention is often concentrated on the 2×2 case because of its practical importance in medical trials. The cross-over design most widely used in drug testing experiments is the simplest 2×2 design consisting of the treatment sequences AB and BA. However, the analysis of such a design is complicated by the problem of confounding between sets of parameters. The AB/BA design does not allow separate estimation of the difference between sequence groups, the difference between carryover effects and the treatment $\times$ period interaction. Different approaches and forms of analysis have been developed to take account of this problem including Bayesian analysis, see Grieve (1985).

The second variation on (6.14) retains the term for the carryover effect but also includes a fixed sequence effect, δ_k. Laska, Meisner & Kushner (1983) con-

sider this model, as well as the corresponding model with fixed subject effects, in their search for good designs for two treatments. It is shown, under the assumption of either model, that a universally optimal design with an even number of periods greater than two yields the best obtainable efficiency per observation. This result is independent of the use of baseline information and assumptions about carryover. The situation is much more complicated when the experiment is restricted to two periods. Elswick & Uthoff (1989) develop a non-parametric analysis of the two treatment, two period, four sequence cross-over design under the extended model which includes sequence effects, although this model could be applied in situations where more than two treatments are to be compared.

Matthews (1993) discusses the possibility of assuming subject effects to be independent random variables with mean β and variance $\theta\sigma_\epsilon^2$ which are also independent of the ε_{ij}. Matthews notes that although optimality of designs is not affected by the assumptions concerning subject effects, the efficiencies of non-optimal designs may be dependent on the value of θ. Hence, in the dual versus single treatments problem, there is a need to be wary of searching for efficient designs under a model with random subject effects, since the efficiencies of these designs, where sub-optimal, may be altered by changes to the size of the subject variances.

6.6 Models containing interaction terms

In this section, models which allow for interaction between certain parameters are considered, starting with those which include the *treatment* $\times$ *period* interaction since this has received much attention in the literature.

6.6.1 The direct treatment $\times$ period interaction

The presence of a treatment $\times$ period interaction indicates that the direct treatment effect differs according to the period in which the treatment is administered. This causes a problem with interpretation since it is then difficult to draw conclusions about the efficacy of the drug when it is not administered in a cross-over situation and there is no longer a period effect. This model can be written as:

$$y_{ij} = \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \delta_{d(i,j),i} + \varepsilon_{ij} \ (i = 1, \ldots, p;\ j = 1, \ldots, s) \qquad (6.15)$$

where $\delta_{d(i,j),i}$ denotes the treatment $\times$ period interaction and ε_{ij} are assumed to be independent, identically distributed random variables with mean 0 and variance σ^2.

Most of the evidence in the literature for the presence of a direct treatment $\times$ period interaction is found in the context of 2×2 cross-over trials, where this type of interaction is confounded with carryover effects, see Jones & Kenward (1989, p 42). Some authors use the terms carryover and treatment $\times$ period interaction interchangeably when discussing the 2×2 experiment since the two terms cannot be estimated separately. However, this is not advisable since the two terms may have different interpretations. Hills & Armitage (1979) and Armitage & Hills (1982) consider model (6.15) when discussing the merits of the 2×2 cross-over trial. In their opinion the two terms are distinguishable since the interaction may be completely unrelated to carryover effects and hence may exist in the absence of any carryover effects of either a pharmacological or psychological nature. For example, there may be a substantial period effect due to changing environmental circumstances, or a *practice effect* in the first period when patients are adjusting to the trial. The treatment effect may vary in magnitude with the response causing an interaction. It should be noted that it is often difficult to make a priori assumptions about the presence of carryover. The authors conclude that in the presence of a significant carryover effect or interaction term, the analysis should be limited to the data from the first period. An illustration of the interpretation of the treatment $\times$ period interaction is given by Poloniecki & Daniel (1981) who reanalyse some data from Hills & Armitage's study on treatments for enuresis.

Balaam (1968) uses a model including a treatment $\times$ period interaction and excluding all carryover effects. He finds two period designs for t^2 experimental units for the comparison of t treatments which are efficient and allow for the presence of an interaction term. Laserre (1991) uses model (6.15), with the additional assumption of random subject effects, to find efficient designs for cross-over trials to compare two treatments.

6.6.2 The direct treatment $\times$ first-order carryover interaction

Another important term which may be included in the model is the *direct treatment $\times$ first-order carryover* interaction. The presence of this interaction in-

dicates differential carryover effects which occur when the carryover effect of a particular treatment observed in period i for subject j varies according to which treatment is currently being administered to subject j in period i. A model, with a factorial treatment structure, which included this term is given by Berenblut (1968) and is discussed in Section 6.4. Patterson (1970) considers designs for testing a single quantitative factor at four equally spaced levels which provide efficient estimates of the linear direct $\times$ linear first-order carryover interaction. It is shown that designs which are suitable for the estimation of direct treatment and first-order carryover effects are not necessarily the best designs for estimating the interaction term.

Kôk & Patterson (1976) employ a model with a direct treatment $\times$ first-order carryover interaction when they define the class of serial factorial designs in which direct effects are orthogonal to first-order carryover effects. A subclass of this family of designs, called R-orthogonal designs, is found whose members have the additional property that the first-order carryover effects are orthogonal to the direct treatment $\times$ first-order carryover interaction. This property enables efficient estimation of carryover effects.

6.6.3 The direct treatment $\times$ subject interaction

Another potentially important interaction is the direct treatment $\times$ subject interaction. This area has received little attention in the literature; it is briefly mentioned by Senn (1993, p 41). A possible explanation is that this type of interaction does not affect the validity of the analysis but adds to the general variability of the experiment. Cox (1984) discusses this issue in his review of some aspects of interaction. The 2×2 cross-over trial is considered in detail and it is argued that, under an additive fixed effects model for direct treatments, first-order carryover, periods and subjects, interaction terms involving subjects may be regarded as error since it is possible to conduct two independent analyses, one using within-subject measurements and the second using the subject totals.

Another problem associated with this type of interaction is that of interpretation. If a significant treatment $\times$ subject interaction is observed, it implies that the benefit of the drug varies with each patient which makes it very difficult to gauge the efficacy of the drug for a particular patient before administration.

A disadvantage common to all the models discussed in this section is that

they all require many more parameters to be estimated, resulting in increases in the number of subjects required for the experiment. This fact, coupled with the problem of interpretation of the interactions, may explain why many authors ignore the possibility of interaction effects in cross-over models.

6.7 Autoregressive models

In this section, the relationship between successive responses is modelled by an entirely different technique. The response observed for subject j in period i now depends on the response observed for subject j in period $i-1$ in addition to the fixed effects for treatments, subjects and periods. The response observed for subject j in period i can be written as

$$\begin{aligned} y_{ij} &= \theta y_{(i-1)j} + \tau_{d(i,j)} + \alpha_i + \beta_j + \varepsilon_{ij} \\ &\quad (i = 1, \ldots, p;\ j = 1, \ldots, s), \end{aligned} \tag{6.16}$$

where θ is the parameter of the autoregression and $\tau_{d(i,j)}$, α_i and β_j are the effects for treatment $d(i,j)$, period i and subject j respectively. Equation (6.16) is similar to equation (6.11) in which carryover effects of all orders are assumed proportional to the direct treatment effect of the previous period. Equation (6.16) differs in that carryover effects are considered proportional to the sum of all the effects from the previous period. As the trial progresses, the response of subject j depends on the entire previous history of that subject.

Finney (1956) considers a model based on (6.16) with independent errors in his discussion of cross-over models for biological assay. It is noted that autoregressive models are often unsuitable in this context since the parameter estimation generally requires long sequences of observations which are not available in bioassay. This argument also renders such models unsuitable for cross-over trials. Gill & Shukla (1987) consider a model of the form of (6.16), together with within-subject errors following a first-order autoregressive process as in Case I of Section 6.2. Assuming the parameters, θ and λ, of the two autoregressive processes are known, results are established for universally optimal and near-optimal designs under models for both fixed and random subject effects. Again, as discussed in Section 6.2, there are technical problems associated with estimating these parameters in practice.

Taka & Armitage (1983) adopt a further variation on (6.16) to illustrate a problem already discussed in Section 6.2, namely that design choice for a particular experiment is dependent on the assumptions regarding the covariance structure of the errors. Taka & Armitage do not provide any solid evidence for the use of this model although the plausibility of a model with two autoregressive components is mentioned. The authors note that further data analysis is required to determine the importance of both autoregressive components in practice.

This type of model is not used for the dual versus single treatments problem due to the difficulty of estimating the parameters of the autoregression within relatively short treatment sequences.

In the following section, some of the arguments which have been used against the simple model, based on equation (6.6), are considered in more detail.

6.8 Problems associated with using the simple carryover model

Although several authors have drawn attention to the deficiencies of models based on (6.6), see Fleiss (1986, 1989) and Matthews (1993), one of the most detailed discussions of the disadvantages of adopting a model of this form has been given by Senn (1993), in which he addresses five main points. Attention is restricted entirely to pharmacological effects, such as the presence of a drug in the blood, and the discussion concerns multiple dose studies. An important concept in this type of study, and one to which Senn makes frequent reference, is that of the *steady state* response, that is the maximum response obtained by consecutive doses of a particular treatment. In this section, each of the arguments put forward by Senn is reviewed in a separate subsection and their application to the dual versus single treatments problem is considered.

Note that the model referred to, following Senn, as *the simple model* is the model consisting of equation (6.6) together with the assumption of independent, normal errors.

6.8.1 If carryover applies, the investigator can design a trial which eliminates it

The argument focuses on the design given in the following example.

Example 6.1 *A design for 2 treatments, 2 treatment sequences and 4 periods is*

Sequence	*1*	*2*
Period 1	*A*	*B*
2	*A(a)*	*B(b)*
3	*B(a)*	*A(b)*
4	*B(b)*	*A(a)*

where the first-order carryover effects are given in brackets.

Senn discusses how this design is equivalent to the 2-treatment, 2-period cross-over design with sequences AB and BA and measurements taken halfway through the treatment period as well as at the end. He argues that if the investigator is interested in a comparison between the steady state effects of the two treatments then he or she will need to use the responses A(a) and B(b) since these are more likely to represent the steady state than A and B alone. The former responses are the measurements observed in periods 2 and 4 of the design and Senn concludes that, if the estimates of effects are restricted to measurements from these two periods, the results are equivalent to those that would be obtained from the 2-period design.

The points made are valid although attention has been restricted to a limited area of the subject. Situations where there are more than two treatments under investigation are not mentioned. The argument is not extended to consider *mixed* treatment sequences in which a treatment never follows itself. Several authors have considered the implausibility of the assumption that the carryover of a treatment onto itself is the same as the carryover of that treatment onto any other treatment in the experiment, see Fleiss (1989) and Matthews (1993).

In conclusion, it may not always be possible to be sure that a study has been designed which will eliminate carryover. A washout period may help to reduce pharmacological carryover, but its maximum length is determined by ethical considerations for the patient's safety and hence may not be sufficient to eliminate

the carryover effects completely. The study by Dunn (1993) to investigate the effectiveness of quinine in reducing night cramps applied a washout period and yet a significant carryover effect or treatment × period interaction was observed. In these circumstances employing a design which is efficient under the simple model may be of value as it enables, at least, a diagnostic check on the assumption of no carryover effects.

6.8.2 The simple model is implausible given elementary pharmacokinetic and pharmacodynamic theory

Senn's argument is again presented in the context of an experiment for two treatments, one of which is active and the other is a placebo. Under a model for a pharmacological response, it is shown that the carryover from active treatment A onto the placebo P is not the same as the carryover from the active treatment onto itself. This directly contradicts the usual assumption of the carryover model which was discussed in the previous subsection. In defence of the simple model, the direct use of this assumption can be avoided by ensuring that a particular treatment does not occupy two consecutive positions in any treatment sequence. Hence for studies involving $t > 2$ treatments, a slightly weaker assumption is employed which requires the carryover effect of treatment i onto treatment j $(j \neq i = 1, \ldots, t)$ to be same as the carryover effect of treatment i onto treatment k for $k \neq i$, $k \neq j$, $1 \leq k \leq t$. It is possible that this assumption may also be shown to be invalid under pharmacological theory, although Senn does not address this point specifically.

Senn shows by means of an example that under the assumption of a particular pharmacokinetic model, that is a model for the handling of a drug within the body including its absorption, distribution and excretion, the carryover of an active treatment A onto a placebo P is the same as the carryover of A onto itself. However, the carryover of two consecutive applications of A onto the placebo treatment is not the same as the carryover of one application of treatment A onto itself. Senn concludes that carryover depends on the total previous history of treatment administration and not just the preceding period.

The pharmacological and pharmacokinetic arguments against the simple carryover model, described in this subsection, may hold for studies involving more than two treatments. However, the simple model may still be of value when it

is necessary to consider the possibility of psychological carryover which has been acknowledged as an important factor in drug trials, see Willan & Pater (1986).

6.8.3 The models which incorporate simple carryover are self-contradicting

Senn puts forward this criticism of the simple model in the context of a factorial treatment structure. His case is that in this type of situation potentially important interactions between direct treatments and carryover effects may not be considered while less important interactions between pairs of carryover effects can be allowed for in the model. The possibility of such interactions being important will depend upon the nature of the treatments involved and the length of the washout.

In defence of the model, work on designing factorial carryover trials has, to date, focused on the simple case where direct treatment $\times$ subject and direct treatment $\times$ carryover interactions are assumed negligible, see Fletcher & John (1985). Designs efficient for estimating the direct main effects of each factor, carryover main effects of each factor and interactions between direct treatment effects have been found for the simple case, see Lewis, Fletcher & Matthews (1988) and Fletcher, Lewis & Matthews (1990). However, similiar work seeking efficient designs capable of estimating further interactions is possible. Generalised cyclic factorial designs have the property that carryover $\times$ carryover interactions can be estimated, if desired. If these effects are not of interest, because they are likely to be negligible, they do not need to be included in the model or they may be included and used as a diagnostic check for validity of model assumptions.

6.8.4 The estimators based on the simple model are inefficient

Senn outlines an analysis of the design of Example 6.1 which shows that the estimates of the treatment effects, adjusted for simple additive carryover effects, will have larger variance and larger bias than the unadjusted estimates. This is undeniably true for the example given and, in general, adjusting the estimates of treatment effects for carryover will increase their variance and may increase their bias. However, Senn has made various pharmacokinetic and pharmacodynamic

assumptions in the calculations. For example, drug disposition is assumed to be modelled by a particular pharmacokinetic model, called the one-compartment model, and the model for pharmacological response is assumed to be given by a specific equation, see Hill (1910). The result may also be altered by the inclusion of psychological carryover effects.

Senn's conclusion that adjusting for carryover effects increases the variance and bias of the estimated treatment effects is in direct opposition to the view of Abeyasekera & Curnow (1984). The latter authors recommend that the wisest approach is to always adjust for carryover, since ignoring small carryover effects can cause bias in the estimation of direct treatment effects.

In experimental design, blocking factors are introduced into a model to reduce systematic variation and subsequently the residual sum of squares. Similarly, if carryover effects are included in the model and found to be substantial then the corresponding reduction in residual sum of squares would compensate for the loss of degrees of freedom through fitting the extra parameters. If carryover effects are found to be insignificant then the reduction in degrees of freedom can be regarded as the price of checking the negligibility of carryover effects.

6.8.5 The designs associated with the simple model are not necessarily better than others

The key issue here appears to be that different assumptions about carryover effects render different designs optimal. This is an important consideration when planning a study and the investigator needs to be fully aware of any assumptions which are implicit in the chosen model.

Senn's most general criticism of the simple model is that it encourages the belief that the validity of the estimates obtained does not depend upon adequate washout having taken place. Clearly, it is advantageous if washout periods are of sufficient duration to eliminate the possibility of carryover effects. However, it is extremely difficult to determine the required length of time which obviously varies according to the nature of the drug. This approach may also cause an ethical problem, since the patient's health may be endangered by relatively long periods of time without treatment.

The conclusions from considering Senn's criticisms are that indiscriminate use

of the simple model is unwise, since the model has disadvantages and involves assumptions which are unrealistic in some practical settings. However, there are experimental situations where it may not be appropriate to ignore the possible presence of carryover effects at the planning stage and, in the absence of any carryover model which provides a more useful approximation to reality, the simple model seems to be an acceptable starting point. Ideally, one would hope to find no evidence of carryover effects indicating that a successful washout has been applied since, if significant carryover effects are shown to be present, the interpretation of the analysis may be very difficult.

6.9 Conclusion

In this chapter, models suitable for designing and analysing cross-over trials have been reviewed. A study of the literature has revealed that authors do not place much emphasis on the practical applications of their results and that one of the main criteria for model selection appears often to be mathematical tractability. Correlated error structures are considered desirable because they dispense with the unrealistic assumption of independence of measurements taken on a particular individual. However, assuming the wrong type of error structure for the data may have worse consequences than the assumption of independent errors.

It is difficult to recommend one particular model, since all the models discussed have their own advantages and disadvantages and may also have specific areas of application. This suggests that an important area for future research is designs which are robust to different structures of treatment carryover and within-subject errors. There are relatively few investigations involving comparisons of design performance under different models in the literature.

The next chapter presents designs for cross-over trials for the dual versus single treatment problem under the model with structure (6.6) and independent, normal errors and also under the extension of this model which allows for both first- and second-order carryover effects. The results of an investigation of the robustness of the designs is also given.

Chapter 7

Cross-over designs under additive carryover models

7.1 Introduction

The aim of the work in this chapter is to identify efficient designs for cross-over studies. Experimental situations involving short term effects and a correspondingly low probability of the presence of carryover effects are considered. In this type of study, it is extremely difficult to predict at the planning stage whether carryover effects need to be accounted for in the model.

Suppose an investigator makes an assumption about the presence or absence of carryover effects. If this assumption is later shown to be incorrect then one possibility is that the analysis may ignore the presence of potentially important effects so that the original model may be retained. This may result in dubious study conclusions. Alternatively, a new model may be used at the analysis stage which includes parameters for the carryover effects. However, the design used in the study may perform badly under the extended model, since it was originally selected for its performance under a row-column model. As design optimality is model dependent, little reliability can then be attached to the conclusions of the trial.

One solution to this problem is to select a design which performs well both in the presence and absence of carryover effects. In other words, a design is required which is efficient under both the row-column model of equation (1.1) and an

appropriate carryover model. The additive carryover models considered in this chapter include terms for first- and for first- and second-order carryover effects and consist of equation (6.6) and equation (6.10) with $h = 2$, respectively, together with the assumption of independent normal errors. A feasible approach to finding designs is to consider all possible rearrangements of an efficient row-column design and then to select the arrangement which has the minimum total variance for the least squares estimators of the contrasts of interest, in the direct treatment effects, under the appropriate carryover model after adjusting for carryover effects. In the remainder of this chapter, this approach is used employing the catalogue of efficient row-column designs for estimating the dual versus single treatment comparisons, presented in Tables 3.3–3.15 at the end of Chapter 3. This approach can also be adopted when the main purpose of the investigation is to estimate the carryover effects. However, this type of study is usually of secondary interest in the type of experiment described in this thesis.

In the following section, an outline of the ordinary least squares estimation of direct treatment effects is presented and some measures of cross-over design performance are introduced. In Section 7.3, a method of obtaining cross-over designs is discussed and an algorithm for finding designs using this approach is given. The results are presented in Section 7.4. Cross-over designs for larger experiment sizes are considered in Section 7.5. In Section 7.6, designs under an additive model including both first- and second-order carryover effects are considered. An outline of parameter estimation under this model is given, together with tables of designs and their efficiencies.

7.2 Parameter estimation and assessment of design performance under a model including first-order carryover effects

In order to estimate the direct treatment or carryover effects, it is necessary to express the model based on equation (6.6) in matrix form:

$$Y = 1_n\mu + P\alpha + U\beta + D\tau + R\rho + \varepsilon \tag{7.1}$$

or alternatively as

$$Y = Xa + \varepsilon$$

where $X = \begin{pmatrix} 1_n & P & U & D & R \end{pmatrix}$, $a' = \begin{pmatrix} \mu & \alpha' & \beta' & \tau' & \rho' \end{pmatrix}$, P, U, D and R are the design matrices for periods, subjects, direct treatments and first-order carryover treatments respectively, α, β, τ and ρ are the vectors of period, subject, direct treatment and first-order carryover effects respectively, 1_n is an $n \times 1$ vector with every element equal to one and ε denotes the vector of independent, normal errors.

The least squares estimator of the parameter vector a is found by solving the normal equations:

$$(X'X)\hat{a} = X'Y.$$

These can be written in terms of the parameters of (7.1):

$$n\hat{\mu} + s1'_p\hat{\alpha} + p1'_s\hat{\beta} + r'\hat{\tau} + \tilde{r}'\hat{\rho} = G \tag{7.2}$$

$$s1_p\hat{\mu} + sI_p\hat{\alpha} + J_{p,s}\hat{\beta} + N'_p\hat{\tau} + \tilde{N}'_p\hat{\rho} = P_{TOT} \tag{7.3}$$

$$p1_s\hat{\mu} + J_{s,p}\hat{\alpha} + pI_s\hat{\beta} + N'_s\hat{\tau} + \tilde{N}'_s\hat{\rho} = S_{TOT} \tag{7.4}$$

$$r\hat{\mu} + N_p\hat{\alpha} + N_s\hat{\beta} + r^\delta\hat{\tau} + L\hat{\rho} = T_{TOT} \tag{7.5}$$

$$\tilde{r}\hat{\mu} + \tilde{N}_p\hat{\alpha} + \tilde{N}_s\hat{\beta} + L'\hat{\tau} + \tilde{r}^\delta\hat{\rho} = R_{TOT} \tag{7.6}$$

where r and $\tilde{r}$ are the replication vectors for direct and carryover treatments, r^δ and $\tilde{r}^\delta$ are the diagonal matrices having the elements of r and $\tilde{r}$ respectively on the diagonal, N_p and $\tilde{N}_p$ are the $t \times p$ period incidence matrices for direct and carryover treatments, N_s and $\tilde{N}_s$ are the $t \times s$ subject incidence matrices for direct and carryover treatments, L is a $t \times t$ matrix with l_{ij} denoting the number of times treatment i is preceded by treatment j, G is the overall experiment total and P_{TOT}, S_{TOT}, T_{TOT} and R_{TOT} are the vectors of unadjusted period totals, subject totals, direct treatment and carryover treatment totals respectively.

The reduced normal equations can be derived by eliminating the period and subject effects from equations (7.2) to (7.6). They can now be expressed in the form:

$$A_{11}\hat{\tau} + A_{12}\hat{\rho} = q_1 \tag{7.7}$$

$$A'_{12}\hat{\tau} + A_{22}\hat{\rho} = q_2 \tag{7.8}$$

where

$$A_{11} = r^\delta - \frac{1}{s}N_pN'_p - \frac{1}{p}N_sN'_s + \frac{1}{ps}N_pJ_{p,s}N'_s, \tag{7.9}$$

$$A_{12} = L - \frac{1}{s}N_p\tilde{N}_p' - \frac{1}{p}N_s\tilde{N}_s' + \frac{1}{ps}N_pJ_{p,s}\tilde{N}_s', \quad (7.10)$$

$$A_{22} = \tilde{r}^{\delta} - \frac{1}{s}\tilde{N}_p\tilde{N}_p' - \frac{1}{p}\tilde{N}_s\tilde{N}_s' + \frac{1}{ps}\tilde{N}_pJ_{p,s}\tilde{N}_s' \quad (7.11)$$

and

$$q_1 = T_{TOT} - \frac{1}{s}N_pP_{TOT} - \frac{1}{p}N_sS_{TOT} + \frac{1}{ps}N_pJ_{p,s}S_{TOT},$$

$$q_2 = R_{TOT} - \frac{1}{s}\tilde{N}_pP_{TOT} - \frac{1}{p}\tilde{N}_sS_{TOT} + \frac{1}{ps}\tilde{N}_pJ_{p,s}S_{TOT}.$$

From equations (7.7) and (7.8), the direct treatment effects can be estimated using

$$\hat{\tau} = \Omega_{CO_\tau}(q_1 - A_{12}A_{22}^{-}q_2)$$

where Ω_{CO_τ} is a generalised inverse of $A_{11} - A_{12}A_{22}^{-}A_{12}'$ and A_{22}^{-} is a generalised inverse of A_{22}.

Similarly, the residual treatment effects can be estimated using

$$\hat{\rho} = \Omega_{CO_\rho}(q_2 - A_{12}'A_{11}^{-}q_1)$$

where Ω_{CO_ρ} is a generalised inverse of $A_{22} - A_{12}'A_{11}^{-}A_{12}$.

A design's performance for estimating the treatment contrasts of interest, C_t, can be evaluated by calculating the variance-covariance matrix of the contrasts

$$V(C_t\hat{k}) = C_t\Omega_{CO_k}C_t'\sigma^2 \quad (7.12)$$

for $k = \tau, \rho$. The condition for the estimability of a set of treatment contrasts is given in Section 1.2. As before, estimability of all treatment contrasts is guaranteed if attention is restricted to connected designs.

In this chapter, interest is focused on finding designs which estimate the dual versus single contrasts, H, in the direct treatment effects after elimination of the carryover effects.

Before considering a method of obtaining cross-over designs, some measures of the efficiency of such designs are briefly discussed. Efficiency factors of block designs were introduced in Section 1.2. Similar quantities can be defined in the cross-over situation. Jones & Kenward (1989, p 194) define the efficiency with which a design estimates the pairwise contrast, $\tau_i - \tau_j$, as

$$E_t = \frac{2\sigma^2/r}{V(\hat{\tau}_i - \hat{\tau}_j)} \times 100,$$

with the subscript t denoting that the treatments have not been adjusted for carryover effects. Efficiency in the presence of carryover effects can be defined in the same way, with $V(\hat{\tau}_i - \hat{\tau}_j)$ now denoting the variance of the contrast for the direct treatment effects, under model (7.1), after adjusting for carryover effects. Average efficiency factors for the two cases can be obtained by replacing $V(\hat{\tau}_i - \hat{\tau}_j)$ by the average variance over all contrasts.

The above measures can be used to assess the performance of designs for estimating the set of all standard pairwise treatment comparisons but are not appropriate for the dual versus single treatments problem. The following quantity is used to assess the performance of designs, found under model (7.1), for estimating the dual versus single treatments contrasts. The measure of efficiency, denoted by E_{CO}, for a particular cross-over design d is found by taking the total variance of the dual versus single treatment contrasts, H, of the most A-efficient row-column design d_1 for the specified experiment size, found by the method of Section 3.6, as a fraction of the total variance of the same contrasts in the direct treatment effects, estimated from design d under the carryover model (7.1), after adjustment for first-order carryover effects. This can be expressed as

$$E_{CO} = \frac{tr(H\Omega_{RC}H')_{d_1}}{tr(H\Omega_{CO_\tau}H')_d}, \tag{7.13}$$

where H is given in equation 1.12 and Ω_{RC} and Ω_{CO_τ} are the generalised inverses of the information matrices for the direct treatment effects under models (1.1) and (7.1) respectively.

In the following section, an approach to finding designs which perform well both in the presence and absence of carryover effects is discussed.

7.3 A method of finding cross-over designs

As already discussed in Section 7.1, it is extremely difficult to predict at the outset of an experiment whether carryover effects will be present. This is an important issue since it determines the choice of model which in turn determines the selection of a design. One way of reducing this problem is to use a design which performs acceptably both in the presence and absence of carryover effects, since this will give the study results some protection against the invalidity of assumptions regarding the presence of additive carryover effects. The investigator

is free to choose the more appropriate of the two models for use at the analysis stage. In this section, attention is restricted to first-order carryover effects.

The following approach for finding designs is used. Firstly, an efficient row-column design for a particular experiment size is selected from the catalogues of designs given in Chapters 3 and 4. All possible rearrangements of this design, obtained by interchanging elements within the subject blocks, which do not increase the total variance under the row-column model (1.1) are considered. The design which has the smallest total variance for estimating the contrasts of interest in the direct treatment effects, under model (7.1), after adjusting for first-order carryover effects is selected.

The following example provides an illustration of the approach to finding designs.

Example 7.1 *Consider a* 3×2 *experiment for six subjects in three periods. An efficient part-balanced design under the row-column model (1.1) is given in Table 3.4 and has a total variance for the dual versus single treatment contrasts of 2.5432. The corresponding variances under the simple carryover model (7.1) have a total of 28.4970. Hence, the total variance has been substantially increased by including the first-order carryover effects.*

By examining all the valid connected rearrangements of the original row-column design, the arrangement under model (7.1) which achieves minimum total variance of the contrasts in the direct treatment effects, after adjustment for first-order carryover effects, is:

11	*21*	*01*	*21*	*10*	*20*
10	*01*	*11*	*20*	*11*	*21*
01	*20*	*10*	*01*	*21*	*11.*

This connected design has a reduced total variance of 5.0502 while the total variance under the row-column model has remained unchanged.

Example 7.1 indicates that if an investigator uses the second design, he or she will be in a better position to analyse the experiment under the simple carryover model if it should prove necessary. The efficiency, E_{CO}, of the second design is 0.50 which is low. However, it should be noted that the use of model (7.1) requires the estimation of more parameters due to the inclusion of first-order carryover effects.

In the design shown in Example 7.1, there are only three periods hence only a small number of treatment comparisons can be estimated using measurements taken on the same subjects. This is one of the causes of the large size of the total variance.

The effect of introducing another set of parameters into the model may be to reduce the systematic variation in the experiment and hence reduce the residual sum of squares. This is the principle which motivates the use of blocking factors in experimental design. However, this is unlikely to be the case in the above example since the carryover effects are expected to be small if not entirely negligible. In this situation, the increase in total variance can be regarded as the price of checking the assumption of the presence of first-order carryover effects.

Before discussing the search algorithm which was developed to find the best arrangement of a row-column design, the issue of connectivity is addressed.

7.3.1 Connectivity of cross-over designs

The property of connectivity is discussed in Section 1.2. It is an essential property since if a design is connected for a set of effects under a particular model then all possible contrasts in those effects are estimable, see John (1987, p 19). All the designs considered in this chapter are connected under model (1.1) since all the row-column designs of Chapters 3 and 4 possess this property. However, it is possible that some of the rearrangements of these designs may be disconnected under model (7.1) as the following example demonstrates.

Example 7.2 *Consider a* 3×2 *experiment for five subjects and three periods. An efficient part-balanced design under model (1.1) is given in Table 3.4 and has a total variance for the estimators of the dual versus single treatment contrasts of 3.0545. This particular design is disconnected under model (7.1) since the information matrix for the direct treatment and first-order carryover effects is of insufficient rank. The connected rearrangement of this design which achieves the smallest total variance under model (7.1) is given in Table 7.1.*

A check for the connectivity of cross-designs under model (7.1) is incorporated into the algorithm for finding designs which is discussed in the following subsection.

7.3.2 Algorithm for identifying efficient designs

In this subsection, an outline of the search algorithm is first given. This is followed by further detail and justification of aspects of the algorithm.

The design search was carried out in the following steps:

1. Given an initial row-column design for t treatments in R rows and C columns, all possible permutations of the elements of this array are found by a recursive process which combines each of the $R!$ possible arrangements of the first column with each of the $R!$ possible arrangements of the second and subsequent columns in the design. In total, $(R!)^C$ permutations are generated for each design.

2. A check is performed to ensure that only permutations which are valid rearrangements of the original row-column design are considered for variance estimation. A valid rearrangement is defined to be a design which has the same single blocking factor component designs as the original row-column design. This condition ensures that, whichever arrangement is chosen under model (7.1), the total variance of the contrasts of interest under model (1.1) remains unchanged. Since the rearrangements are performed within-subject, a check on the block design for periods is sufficient to determine design validity.

3. The variances of the dual versus single treatment contrasts in the direct treatment effects are calculated using equation (7.12) with $k = \tau$. A NAG routine is used to find a suitable generalised inverse, Ω_{CO_τ}.

4. A storage list capable of holding thirty designs and their corresponding variance-covariance matrices is maintained. A new design is admitted to the list if its total variance for the contrasts of interest is less than or equal to any of the designs present in the existing store.

Medical trials commonly have four or fewer periods due to the increased chance of subjects dropping out of studies of long duration. Hence, the algorithm allows designs with a maximum of four treatment periods to be considered. For more than four periods the large increase in the number of permutations of the original design would make the search impractically long at present. Some reduction in search time could be achieved by identifying and removing isomorphic designs.

The maximum number of subject groups, or distinct treatment sequences, is currently set at nine. This figure was partly determined by the requirement of limiting the design search to a manageable length and by the maximum dimensions of the initial row-column designs. However, cross-over trials generally have a relatively small number of subject groups since designs involving large numbers of distinct treatment sequences are difficult to implement in practice. The size of the experiment can be increased by allocating more than one subject to each treatment sequence. Checks on the validity of the input data are performed to ensure that the designs considered do not have period and subject parameters which exceed the specified limits. A further check is conducted to ensure that sufficient degrees of freedom are available for the estimation of all the parameters.

The algorithm also includes a check for the design property of connectivity, see Section 1.2 and Subsection 7.3.1. Example 7.2 illustrated that the search algorithm may yield designs which are disconnected under model (7.1). A method of checking for this problem is to calculate the rank of the information matrix A_{CO}, where

$$A_{CO} = \begin{pmatrix} A_{11} & A_{12} \\ A_{12}' & A_{22} \end{pmatrix} \tag{7.14}$$

and A_{11}, A_{12} and A_{22} are given in equations (7.9) to (7.11). A design which is connected for both direct treatment and first-order carryover effects should have $rank(A_{CO}) = 2t - 2$. Any design which is found to have insufficient rank is discarded.

A Pascal coding of the algorithm is given in Appendix A.

7.4 Tables of results and discussion

In this section, the designs found under model (7.1) with the smallest total variance for the contrasts of interest in the direct treatment effects, after adjustment for first-order carryover effects, are presented in Tables 7.1–7.3. A discussion of the performance of the designs is also given.

Results are obtained for parameters $3 \leq p \leq 4$, $4 \leq s \leq 9$, $3 \leq n \leq 4$ and $m = 2$, by rearranging the PBDS row-column and PBDS row-orthogonal designs, listed in Tables 3.4, 3.5, 3.10, 3.11, 4.1 and 4.3. The individual variances of the contrasts when model (7.1) is used are given in Tables 7.1–7.3, together with

the total variances calculated under this model, denoted by (C-O), and under model (1.1), denoted by (R-C). The efficiency factor E_{CO}, see equation (7.13), is also listed as a measure of the cost of including the first-order carryover effects.

It is clear that the cross-over designs perform very poorly when the experiment involves a small number of subjects or periods. Note that the designs for $p = 3$ and $s = 5, 6$ in Table 7.1 have values of E_{CO} in the range 40–50% whereas the designs for $p = 4$ and $s = 5, 6$ in Table 7.2 have values of E_{CO} of at least 85%. The following example of a two-period study further illustrates this point.

Example 7.3 *Consider a 3×2 experiment for two periods and nine subjects. The most A-efficient PBDS design found in the study under model (1.1) is given in Table 3.3 and has $tr(H\Omega_{RC}H') = 3.3258$. The rearrangement of this design which achieves the minimum total variance of the contrasts in the direct treatment effects under model (7.1), after adjustment for first-order carryover effects, is*

$$\begin{array}{ccccccccc} 01 & 21 & 10 & 11 & 21 & 20 & 01 & 20 & 11 \\ 11 & 01 & 11 & 10 & 20 & 21 & 10 & 01 & 21. \end{array}$$

This rearrangement has $tr(H\Omega_{CO_\tau}H') = 28$. Hence the total variance of the design has been greatly increased by including first-order carryover effects in the model.

The design in Example 7.3 has other disadvantages besides its large total variance. As a result of limiting the study to two periods, the *direct treatment* $\times$ *period* interaction is aliased with first-order carryover effects, preventing separate estimation of both sets of effects. A further drawback is that designs for two periods require a large number of subjects in order to gain sufficient degrees of freedom for the estimation of parameters. Hence, designs for two periods are not considered further in this work.

One of the advantages of using a cross-over study is that comparisons are made *within subject*. One of the causes of the inefficiency of designs with a small number of periods is that few comparisons can be made using measurements on the same subject, hence comparisons are made *between subjects* which increases the total variance. Another cause of the inefficiency may be attributable to the structure of the precedence matrix, L, whose elements l_{ij} $(i, j = 1, \ldots, t)$ denote the number of times treatment i is preceded by treatment j in the design. When

Table 7.1: Table of cross-over designs for $n = 3$, $p = 3$ and $5 \leq s \leq 9$, found under model (7.1) which includes first-order carryover effects. Variances of the individual contrasts are calculated using this model.

p	s	Design	$V(\hat{\tau}_{i1} - \hat{\tau}_{01})$ $i = 1, 2$	$V(\hat{\tau}_{i1} - \hat{\tau}_{i0})$ $i = 1, 2$	tot var C-O	totvar R-C	E_{CO}
3	5	11 20 01 10 21 01 21 11 20 10 10 01 21 11 20 (Row-orthogonal)	1.7333 1.6000	1.0667 2.9333	7.3333	3.0545	0.42
3	6	11 21 01 21 10 20 10 01 11 20 11 21 01 20 10 01 21 11	1.1068 1.5492	1.3161 1.0782	5.0502	2.5432	0.50
3	7	10 20 01 01 21 11 11 01 01 10 20 11 21 21 11 21 11 21 01 10 20	0.7135 0.5739	0.8087 0.9065	3.0026	2.1595	0.72
3	8	10 11 01 01 20 21 21 11 01 01 10 20 21 20 11 21 11 10 11 21 01 01 10 20	0.5662 0.5647	0.6206 0.7773	2.5288	1.8698	0.74
3	9	10 11 01 01 21 20 11 21 01 11 10 11 20 01 01 21 20 21 01 01 10 21 20 21 10 11 11	0.4400 0.5099	0.6063 0.5558	2.1120	1.6524	0.78

Table 7.2: Table of cross-over designs for $n = 3$, $p = 4$ and $4 \leq s \leq 6$, found under model (7.1) which includes first-order carryover effects. Variances of the individual contrasts are calculated under this model.

p	s	Design	$V(\hat{\tau}_{i1} - \hat{\tau}_{01})$ $i = 1, 2$	$V(\hat{\tau}_{i1} - \hat{\tau}_{i0})$ $i = 1, 2$	tot var C-O	totvar R-C	E_{CO}
4	4	01 20 11 21 10 11 20 01 21 01 10 20 11 21 01 10	1.1492 0.7694	1.3140 0.9139	4.1465	2.8667	0.69
4	5	01 10 21 20 11 10 21 11 01 20 20 01 10 11 21 11 20 01 21 10 (Row-orthogonal)	0.6085 0.6085	0.6085 0.6085	2.4341	2.1333	0.88
4	5	01 20 21 11 10 11 21 01 20 21 21 11 10 01 20 10 01 11 21 11	0.5513 0.5407	0.6658 0.7358	2.4936	2.1259	0.85
4	6	01 20 11 01 10 21 11 11 21 20 01 10 10 01 01 21 11 20 21 21 10 11 20 01	0.4579 0.4287	0.5424 0.5347	1.9636	1.7787	0.91

Table 7.3: Table of cross-over designs for $n = 4$, $p = 3$, $7 \leq s \leq 9$ and $p = 4$, $s = 6$, found under model (7.1) which includes first-order carryover effects. Variances of the individual contrasts are calculated using this model.

p	s	Design	$V(\hat{\tau}_{i1} - \hat{\tau}_{01})$ $i = 1, 2, 3$	$V(\hat{\tau}_{i1} - \hat{\tau}_{i0})$ $i = 1, 2, 3$	tot var C-O	totvar R-C	E_{CO}
3	7	11 21 01 20 10 30 31	1.8571	2.4286	13.1429	5.1429	0.39
		01 20 31 10 30 11 21	2.4286	1.8571			
		10 01 30 31 21 20 11	1.8571	2.7143			
		(Row-orthogonal)					
3	7	01 21 31 01 20 30 11	3.8333	4.0000	19.1667	4.8980	0.26
		11 20 01 10 21 01 31	1.2500	1.3333			
		10 01 30 11 01 31 21	7.7500	1.0000			
3	8	10 20 31 11 01 01 21 30	1.0438	1.1753	11.4525	4.2667	0.37
		11 01 01 10 21 30 31 20	2.0809	2.5457			
		01 21 30 01 20 31 11 10	2.0611	2.5457			
3	9	10 20 01 11 21 01 21 31 30	1.8081	0.8760	7.2236	3.6961	0.51
		01 21 30 01 20 31 10 11 11	0.8954	1.0957			
		11 01 31 10 01 30 31 20 21	0.8956	1.6528			
4	6	01 11 21 11 10 31	0.8616	2.1734	9.5118	4.5958	0.48
		11 31 01 21 31 30	1.1100	2.7848			
		21 01 31 20 11 21	1.0339	1.5481			
		31 21 11 10 30 20					

all the pairwise treatment contrasts are of interest, highly efficient cross-over designs under model (7.1) have been found which have the off-diagonal elements of L as equal as possible, such as Williams Latin squares, see Williams (1949, 1950). In the dual versus single treatments case, it is difficult to make analogous statements concerning a desirable structure for L since the contrasts do not form an orthogonal set. This topic is an area for further work.

It is clear from Tables 7.1–7.3 that the efficiencies of designs for three and four periods improve as more subjects are included. This is due to the fact that the increased number of distinct treatment sequences allows more *direct treatment, carryover* combinations to be included in the design.

An examination of Tables 7.1–7.3 reveals that the cross-over designs with the smallest total variance are generally not part-balanced under model (7.1) with respect to the dual versus single treatment contrasts. An exception is the row-orthogonal design for $p = 4$ and $s = 5$ in Table 7.2 which is also variance-balanced, that is, the contrasts in both the dual versus A and dual versus B groups are estimated with the same variance. However, further designs which are part-balanced for the contrasts of interest under model (7.1) may exist for the experiment sizes considered in this chapter. The algorithm used to find the rearrangements of the row-column array currently stores thirty design arrays in ascending value of total variance. Part-balanced designs may be present in this list, although if the design has a large total variance the advantage of using a design with part-balance is unlikely to compensate for the loss in precision. The following example illustrates this point.

Example 7.4 *A part-balanced cross-over design for a* 3×2 *experiment for three periods and five subjects is:*

$$\begin{array}{ccccc} 01 & 20 & 21 & 11 & 10 \\ 11 & 21 & 01 & 10 & 20 \\ 10 & 01 & 11 & 20 & 21. \end{array}$$

This design has $tr(H\Omega_{CO_\tau}H') = 14.4$ *which is considerably larger than the total variance of the alternative design in Table 7.1. The non-PBDS cross-over design would be the recommended design in this case.*

Further PBDS rearrangements may exist with a total variance which is sufficiently large to prevent entry to the design list. However, such designs are not of

practical interest. Note that row-orthogonal designs are a fruitful source of PBDS rearrangements since these designs have replication vectors for both direct and carryover treatment effects of the PBDS form, that is the A-alone treatments are each replicated r_A times and the dual treatments are each replicated r_D times, see equation (3.2). The replication vector of carryover effects in designs without row-orthogonality rarely takes this form since there are no carryover effects for the final period.

For some experiment sizes, there is a choice of cross-over designs. For example, if an investigator wishes to conduct a study for a 3×2 experiment with four periods and five subjects either of the two efficient designs in Table 7.2 may be used. The row-orthogonal design which has higher efficiency than the alternative design also has the additional property of variance-balance for the dual versus single contrasts. This may make the row-orthogonal design the preferred choice. For a 4×2 experiment with three periods and seven subjects, see Table 7.3, the row-orthogonal design with $E_{CO} = 0.39$ is again preferable to the alternative design which has $E_{CO} = 0.26$. Neither of the designs has part-balance for the dual versus single contrasts under model (7.1).

In conclusion, the designs in Tables 7.1–7.3 demonstrate that cross-over designs which perform acceptably in the presence and absence of additive first-order carryover effects can be obtained by rearranging efficient row-column designs. The use of these designs will afford some protection against the assumption of non-negligible first-order carryover effects.

7.5 Obtaining larger designs

In the previous section, it was noted that the smaller designs found by the method of exhaustive search are not highly efficient. One way of improving the efficiency of studies with a small number of subjects is to increase the number of subjects. Since it is not practical to use the search algorithm of Subsection 7.3.2 to find larger designs, a second approach is now developed. This involves building designs by combining copies of the designs in Tables 7.1–7.3 and is referred to as the *building brick* method, using the terminology of Pearce (1983, p 126). In this section, the method is applied to finding designs for two specimen cases.

Example 7.5 *Consider a* 3×2 *experiment for three periods and ten subjects. The most A-efficient PBDS row-column design, found in the study by the method of Section 3.6 under model (1.1), is*

$$\begin{array}{cccccccccc} 01 & 01 & 01 & 20 & 10 & 21 & 10 & 21 & 11 & 11 \\ 10 & 20 & 11 & 01 & 01 & 01 & 11 & 20 & 21 & 21 \\ 11 & 21 & 10 & 21 & 11 & 20 & 01 & 01 & 10 & 20. \end{array}$$

This design has $tr(H\Omega_{RC}H') = 1.4837$ *which has a discrepancy of 5.1% with the bound of (2.12). The row and column component designs have discrepancies of 1.5% and 4.3% respectively with the appropriate bound of Section 2.4. An obvious choice for the building bricks of the cross-over design in a* 3×10 *array is two copies of the cross-over design in a* 3×5 *array, see Table 7.1. The resulting design has a total variance of* 3.6667 *and* $E_{CO} = 0.40$.

The efficiency of the cross-over design relative to the A-best row-column design found by the method of Section 3.6 for $t = 5$, $p = 3$ and $s = 10$, given in Example 7.5, is much lower than the corresponding efficiency for the cross-over design for $t = 5$, $p = 3$ and $s = 9$ listed in Table 7.1. This is not surprising since the number of distinct treatment sequences in the larger design has not been increased, instead two subjects have been allocated to each of the five distinct sequences. Consequently, the structure of the precedence matrix, L, has not changed. However, the size of the non-zero elements has been doubled, increasing the disparity between them.

In order to reinforce this point, a second example is considered.

Example 7.6 *Suppose a design is required for a* 3×2 *experiment with three periods and twelve subjects. The most A-efficient PBDS design found under model (1.1) using the method of Section 3.6 has* $tr(H\Omega_{RC}H') = 1.2343$. *The discrepancies of the total variances of the row-column design, compared with the bound of (2.12), and the row and column component designs, each compared with the appropriate bound of Section 2.4, are 4.9%, 0.6% and 4.2% respectively. The following cross-over design can be obtained by using two copies of the design for* $t = 5$, $p = 3$ *and* $s = 6$*:*

$$\begin{array}{cccccccccccc} 11 & 21 & 01 & 21 & 10 & 20 & 11 & 21 & 01 & 21 & 10 & 20 \\ 10 & 01 & 11 & 20 & 11 & 21 & 10 & 01 & 11 & 20 & 11 & 21 \\ 01 & 20 & 10 & 01 & 21 & 11 & 01 & 20 & 10 & 01 & 21 & 11, \end{array}$$

which has $tr(H\Omega_{CO_r}H') = 2.5251$ *and* $E_{CO} = 0.49$. *An alternative design is obtained by taking one copy of each of the designs for* $t = 5$, $p = 3$, $s = 5$ *and* $t = 5$, $p = 3$, $s = 7$ *as shown below,*

11	*20*	*01*	*10*	*21*	*10*	*20*	*01*	*01*	*21*	*11*	*11*
01	*21*	*11*	*20*	*10*	*01*	*01*	*10*	*20*	*11*	*21*	*21*
10	*01*	*21*	*11*	*20*	*11*	*21*	*11*	*21*	*01*	*10*	*20.*

This design has a total variance of 1.7001 *and* $E_{CO} = 0.73$.

The difference in the performance of the two cross-over designs of Example 7.6 is due to the fact that the second design has twelve distinct treatment sequences, allowing more combinations of direct treatment and carryover effects.

The exhaustive search algorithm which produced the designs of Tables 7.1–7.3 generates a list of thirty cross-over designs stored in ascending value of total variance. The list does not contain any designs with a common variance-covariance matrix but may contain designs which have a common set of contrast variances arranged in a different order on the leading diagonal of the variance-covariance matrix. It was noted that, if the variances in the dual versus B and dual versus A contrast sets are distinct, groups containing a maximum of $(n-1)!$ designs each with a common total variance are obtained. An obvious area of further investigation is to see whether combining two distinct designs with the same total variance yields an improved design.

Example 7.5 for a 3×2 experiment in a 3×10 array is now reconsidered to see whether an improved design can be obtained using the above approach.

Example 7.7 *For* $n = 3$, *pairs of designs with a common total variance are obtained. Taking the two distinct designs for* $t = 5$, $p = 3$ *and* $s = 5$, *both with a total variance of* 7.3333 *as the building bricks, the following design is obtained*

11	*20*	*01*	*10*	*21*	*10*	*21*	*01*	*11*	*20*
01	*21*	*11*	*20*	*10*	*11*	*01*	*21*	*20*	*10*
10	*01*	*21*	*11*	*20*	*01*	*20*	*11*	*10*	*21.*

This design has a total variance of 2.1483 *and an efficiency relative to the A-best row-column design of* 0.69. *It also has the property of part-balance for the dual versus single treatment contrasts.*

Extending this idea, further designs for a 3×10 *array can be obtained by considering more than one pair of designs from the list generated by the search algorithm. For the investigation of this example, attention was restricted to the first three pairs on the design list which have total variances of* 7.3333, 9.7333 *and* 12.0 *respectively. The best combination of designs is*

11	*20*	*01*	*10*	*21*	*10*	*01*	*21*	*11*	*20*
01	*21*	*11*	*20*	*10*	*11*	*21*	*01*	*20*	*10*
10	*01*	*21*	*11*	*20*	*01*	*20*	*11*	*10*	*21*

with $tr(H\Omega_{CO_\tau}H') = 2.0904$ *and* $E_{CO} = 0.71$. *This combined design is not PBDS.*

A further design for $t = 5$, $p = 3$ and $s = 10$, without the property of part-balance, can be obtained by the exhaustive search method of Subsection 7.3.2 and has $tr(H\Omega_{CO_\tau}H') = 1.9217$ and $E_{CO} = 0.77$. This design is not a marked improvement on the design with the smallest total variance, obtained by the building brick method, given in Example 7.7.

A similar procedure was followed for the second example for a 3×2 experiment with $t = 5$, $p = 3$ and $s = 12$.

Example 7.8 *Three pairs of designs for* $t = 5$, $p = 3$ *and* $s = 6$, *having total variances of* 5.0502, 5.1250 *and* 5.4265 *respectively, are considered for construction. The A-best design found by the building brick approach for five treatments in a* 3×12 *array is obtained by combining the two distinct designs, both with a total variance of* 5.1250, *to give*

10	*21*	*01*	*21*	*11*	*20*	*11*	*01*	*11*	*20*	*01*	*21*
11	*01*	*11*	*20*	*10*	*21*	*10*	*21*	*01*	*21*	*11*	*20*
01	*20*	*10*	*01*	*21*	*11*	*01*	*20*	*10*	*01*	*21*	*11.*

This design has $tr(H\Omega_{CO_\tau}H') = 1.5604$, $E_{CO} = 0.79$ *and is part-balanced.*

It was noted that, for the examples considered in this section, combining two distinct designs with the same total variance produces a cross-over design which is part-balanced for the dual versus single treatment contrasts under model (7.1).

The same method can be used to find designs for a 3×2 experiment in a 3×12 array using building bricks of sizes 3×5 and 3×7. The A-best design, found

by considering all possible combinations of the six designs having the smallest total variance for three periods and five subjects with the six designs having the smallest total variance for three periods and seven subjects, has a total variance of 1.6070 and $E_{CO} = 0.77$. This is not an improvement on the best design found in Example 7.8.

In this section, a method for constructing efficient cross-over designs for large numbers of subjects has been discussed. It has been shown, by means of examples, that more efficient designs can be obtained by combining pairs of distinct designs which do not necessarily have the same number of subjects rather than using two copies of the same design. The designs found in the two specimen cases were constructed manually and then input to a program for variance calculations. The whole process could easily be carried out by one computer algorithm. This would allow more building bricks to be considered and would reduce the possibility of input errors. The development and coding of such an algorithm is an area for further work.

7.6 Cross-over designs under a model for both first- and second-order carryover effects

In the remaining part of this chapter, efficient cross-over designs found under the assumption of an additive model including both first- and second-order carryover effects are considered. An analogous approach to that outlined in Section 7.3 is used. The search algorithm remains unchanged; the necessary alterations occur in the modules concerned with parameter estimation. The method of estimation is outlined below.

7.6.1 Ordinary least squares estimation of direct treatment effects, after adjusting for first- and second-order residual effects

The additive model assumed in this section has the following matrix form:

$$Y = 1_n\mu + P\alpha + U\beta + D\tau + R\rho + R2\pi + \varepsilon \qquad (7.15)$$

or

$$Y = Xa + \varepsilon$$

where $X = \begin{pmatrix} 1_n & P & U & D & R & R2 \end{pmatrix}$, $a' = \begin{pmatrix} \mu & \alpha' & \beta' & \tau' & \rho' & \pi' \end{pmatrix}$, 1_n, P, U, D, R, α, β, τ, ρ and ε are as given in Section 7.2, $R2$ is the design matrix for second-order carryover effects and π is the vector of second-order carryover effects.

The normal equations, $(X'X)\hat{a} = X'Y$, can be expressed in terms of the parameters of model (7.15), to obtain:

$$\begin{aligned}
n\hat{\mu} + s1'_p\hat{\alpha} + p1'_s\hat{\beta} + r'\hat{\tau} + \tilde{r}'\hat{\rho} + \tilde{r}'_2\hat{\pi} &= G && (7.16)\\
s1_p\hat{\mu} + sI_p\hat{\alpha} + J_{p,s}\hat{\beta} + N'_p\hat{\tau} + \tilde{N}'_p\hat{\rho} + \tilde{N}'_{p2}\hat{\pi} &= P_{TOT} && (7.17)\\
p1_s\hat{\mu} + J_{s,p}\hat{\alpha} + pI_s\hat{\beta} + N'_s\hat{\tau} + \tilde{N}'_s\hat{\rho} + \tilde{N}'_{s2}\hat{\pi} &= S_{TOT} && (7.18)\\
r\hat{\mu} + N_p\hat{\alpha} + N_s\hat{\beta} + r^\delta\hat{\tau} + L\hat{\rho} + L_2\hat{\pi} &= T_{TOT} && (7.19)\\
\tilde{r}\hat{\mu} + \tilde{N}_p\hat{\alpha} + \tilde{N}_s\hat{\beta} + L'\hat{\tau} + \tilde{r}^\delta\hat{\rho} + L_c\hat{\pi} &= R_{TOT} && (7.20)\\
\tilde{r}_2\hat{\mu} + \tilde{N}_{p2}\hat{\alpha} + \tilde{N}_{s2}\hat{\beta} + L'_2\hat{\tau} + L'_c\hat{\rho} + \tilde{r}_2^\delta\hat{\pi} &= R2_{TOT} && (7.21)
\end{aligned}$$

where r, $\tilde{r}$, N_p, $\tilde{N}_p$, N_s, $\tilde{N}_s$, L, G, P_{TOT}, S_{TOT}, T_{TOT} and R_{TOT} are as defined in Section 7.2. The new notation is defined in a similar way where $\tilde{r}_2$ is the replication vector for second-order carryover effects, $\tilde{N}_{p2}$ and $\tilde{N}_{s2}$ are the $t \times p$ and $t \times s$ incidence matrices for periods and subjects, respectively, with second-order carryover effects, $L_c = (l_{cij})$ denotes the number of times treatment i is preceded by treatment j in the first $p-1$ periods, $L_2 = (l_{2ij})$ denotes the number of times treatment i is administered to a subject in period k when treatment j was administered to the same subject in period $k-2$ and, finally, $R2_{TOT}$ is the vector of unadjusted second-order carryover treatment totals.

After eliminating period and subject effects, equations (7.16) to (7.21) can be expressed as

$$\begin{aligned}
A_{11}\hat{\tau} + A_{12}\hat{\rho} + A_{13}\hat{\pi} &= q_1 && (7.22)\\
A'_{12}\hat{\tau} + A_{22}\hat{\rho} + A_{23}\hat{\pi} &= q_2 && (7.23)\\
A'_{13}\hat{\tau} + A'_{23}\hat{\rho} + A_{33}\hat{\pi} &= q_3 && (7.24)
\end{aligned}$$

where

$$A_{11} = r^\delta - \frac{1}{s}N_pN'_p - \frac{1}{p}N_sN'_s + \frac{1}{ps}N_pJ_{p,s}N'_s,$$

$$
\begin{aligned}
A_{12} &= L - \frac{1}{s}N_p\tilde{N}'_p - \frac{1}{p}N_s\tilde{N}'_s + \frac{1}{ps}N_pJ_{p,s}\tilde{N}'_s,\\
A_{13} &= L_2 + \frac{1}{s}N_p\tilde{N}'_{p2} - \frac{1}{p}N_s\tilde{N}'_{s2} + \frac{1}{ps}N_pJ_{p,s}\tilde{N}'_{s2},\\
A_{22} &= \tilde{r}^{\delta} - \frac{1}{s}\tilde{N}_p\tilde{N}'_p - \frac{1}{p}\tilde{N}_s\tilde{N}'_s + \frac{1}{ps}\tilde{N}_pJ_{p,s}\tilde{N}'_s,\\
A_{23} &= L_c - \frac{1}{s}\tilde{N}_p\tilde{N}'_{p2} - \frac{1}{p}\tilde{N}_s\tilde{N}'_{s2} + \frac{1}{ps}\tilde{N}_pJ_{p,s}\tilde{N}'_{s2},\\
A_{33} &= \tilde{r}_2^{\delta} - \frac{1}{s}\tilde{N}_{p2}\tilde{N}'_{p2} - \frac{1}{p}\tilde{N}_{s2}\tilde{N}'_{s2} + \frac{1}{ps}\tilde{N}_{p2}J_{p,s}\tilde{N}'_{s2}
\end{aligned}
$$

and

$$
\begin{aligned}
q_1 &= T_{TOT} - \frac{1}{s}N_pP_{TOT} - \frac{1}{p}N_sS_{TOT} + \frac{1}{ps}N_pJ_{p,s}S_{TOT},\\
q_2 &= R_{TOT} - \frac{1}{s}\tilde{N}_pP_{TOT} - \frac{1}{p}\tilde{N}_sS_{TOT} + \frac{1}{ps}\tilde{N}_pJ_{p,s}S_{TOT},\\
q_3 &= R2_{TOT} - \frac{1}{s}\tilde{N}_{p2}P_{TOT} - \frac{1}{p}\tilde{N}_{s2}S_{TOT} + \frac{1}{ps}\tilde{N}_{p2}J_{p,s}S_{TOT}.
\end{aligned}
$$

After further eliminating first- and second-order carryover effects from equations (7.22) to (7.24), the reduced normal equations can be written as:

$$A_{CO2}\hat{\tau} = Q$$

where $A_{CO2} = M_{11} - M_{12}M_{22}^{-}M'_{12}$ and $Q = q_1 - A_{13}A_{33}^{-}q_3 - M_{12}M_{22}^{-}(q_2 - A_{23}A_{33}^{-}q_3)$, with $M_{ij} = A_{ij} - A_{i3}A_{33}^{-}A'_{j3}$, $(i,j = 1,2)$.

The direct treatment effects can now be estimated by

$$\hat{\tau} = \Omega_{CO2_\tau}Q,$$

where Ω_{CO2_τ} is a generalised inverse of A_{CO2}. The total variance of a set of contrasts, C_t, in the direct treatment effects is given by

$$tr(C_t\Omega_{CO2_\tau}C'_t\sigma^2). \tag{7.25}$$

7.6.2 Tables of designs found under a model for first- and second-order carryover effects

In this section, cross-over designs which estimate the dual versus single treatment contrasts in the direct treatment effects, under model (7.15) after elimination of the carryover effects, are presented.

Table 7.4: Table of cross-over designs for $n = 3$, $p = 3$, $7 \leq s \leq 9$, found under model (7.15) which includes first- and second-order carryover effects. Variances of the individual contrasts are also calculated under this model.

p	s	Design	$V(\hat{\tau}_{i1} - \hat{\tau}_{01})$ $i = 1, 2$	$V(\hat{\tau}_{i1} - \hat{\tau}_{i0})$ $i = 1, 2$	tot var C-O2	E_{CO2}	E_{CCO}
3	7	11 20 01 21 01 10 21 01 21 10 20 11 21 11 10 01 11 01 21 11 20	3.5556 2.2222	4.0000 6.2222	16.0000	0.13	0.89
3	8	10 11 01 01 20 21 21 20 01 01 10 21 21 20 11 11 11 10 11 20 01 01 10 21	1.5429 2.1714	4.6857 4.8000	13.2000	0.14	0.98
3	9	10 11 01 01 01 21 21 20 11 01 01 11 20 21 20 10 11 21 11 10 10 21 20 01 11 21 01	1.5792 1.7971	2.3589 2.2797	8.0149	0.21	0.86

For $m = 2$, $n = 3$, $p = 3$, $7 \leq s \leq 9$ and $p = 4$, $5 \leq s \leq 6$, designs are obtained using the algorithm described in Subsection 7.3.2 with the following modifications. In Step 3, the variances of the dual versus single contrasts are calculated using equation 7.25. The connectivity condition now examines each design information matrix for direct treatment and first- and second-order carryover effects to check that it has a rank of $3t - 3$.

The total variance of the least squares estimators of the contrasts of interest found under model (7.15), denoted by *tot var C-O2*, is given for each design in Tables 7.4 and 7.5.

Note that designs for $n = 3$, $p = 3$ and $s < 7$ could not be obtained since there are insufficient degrees of freedom available for the estimation of parameters in these cases.

In order to evaluate the performance of the designs, the relative efficiency of

Table 7.5: Table of cross-over designs for $n = 3$, $p = 4$, $5 \leq s \leq 6$, found under model (7.15) which includes first- and second-order carryover effects. Variances of the individual contrasts are also calculated under this model.

p	s	Design	$V(\hat{\tau}_{i1} - \hat{\tau}_{01})$ $i = 1, 2$	$V(\hat{\tau}_{i1} - \hat{\tau}_{i0})$ $i = 1, 2$	tot var C-O2	E_{CO2}	E_{CCO}
4	5	01 10 21 20 11 10 21 11 01 20 20 01 10 11 21 11 20 01 21 10 (Row-orthogonal)	0.9352 0.9352	0.9352 0.9352	3.7408	0.57	1.0
4	5	10 01 21 11 20 11 21 10 01 11 21 11 01 20 21 01 20 11 21 10	0.8722 0.9264	1.0521 1.4316	4.2822	0.50	0.92
4	6	01 20 10 01 11 21 11 01 11 21 20 10 10 11 21 20 01 01 21 21 01 11 10 20	0.5899 0.7348	0.7899 0.7770	2.8917	0.62	0.88

the cross-over design found under model (7.15) compared to the most A-efficient PBDS row-column design found in the study is used. This is denoted by E_{CO2} and is calculated by taking the total variance, corresponding to the most A-efficient PBDS row-column design listed in the catalogues of Chapters 3 and 4, as a fraction of the total variance of the design found under model (7.15), that is

$$E_{CO2} = \frac{tr(H\Omega_{RC}H')}{tr(H\Omega_{CO2_\tau}H')}, \tag{7.26}$$

where H is given in (1.12) and Ω_{CO2_τ} is a generalised inverse of A_{CO2}, see Subsection 7.6.1.

This measure indicates that the three-period designs of this section perform badly whereas the values of E_{CO2} improve substantially when the experiment extends over four periods. It is probable that a further similar improvement would occur if designs for $p = 5$ were obtained. The explanation for this phenomenon has already been discussed in Section 7.4. An experiment having a small number of periods does not provide sufficient *within subject* measurements for the efficient estimation of carryover effects.

The designs listed in Tables 7.4 and 7.5 are not, in general, part-balanced with respect to the dual versus single treatment contrasts. The exception is the row-orthogonal design for $n = 3$, $p = 4$ and $s = 5$, which is not only part-balanced but is variance-balanced under model (7.15) for these contrasts. Further cross-over designs which are part-balanced under model (7.15) may be obtained by considering less efficient designs (see Section 7.4). However, these designs are unlikely to be of practical use.

A further measure, E_{CCO}, has been included in Tables 7.4 and 7.5. This provides a measure of how much precision has been sacrificed by including a second set of carryover effects in the model. It involves a comparison of the total variances, under model (7.1), of the A-best designs d_1 and d_2 found under models (7.1) and (7.15), respectively, by the method of Subsection 7.3.2, and is defined as

$$E_{CCO} = \frac{tr(H\Omega_{CO_\tau}H')_{d_1}}{tr(H\Omega_{CO_\tau}H')_{d_2}}. \tag{7.27}$$

Hence, it is possible to estimate how much efficiency has been lost in order to gain the ability to investigate the size of second-order carryover effects.

An inspection of the values of E_{CCO} in Tables 7.4 and 7.5 reveals that the loss in efficiency ranges from 0%–12%. Note that the row-orthogonal design for

$n = 3$, $p = 4$ and $s = 5$ is the best rearrangement of the A-best PBDS row-column design under model (7.15) and model (7.1). The values of E_{CCO} in Tables 7.4 and 7.5 are much higher than the values of E_{CO} in Tables 7.1–7.3. This indicates that the effect on the design efficiency of including a second set of carryover effects in the simple carryover model (7.1) is much less marked than the effect of including the first set of carryover effects in the row-column model (1.1). Hence, by using a design from Tables 7.4 and 7.5, an investigator can gain some protection against the assumption of non-negligible second-order carryover effects.

7.7 Conclusions and Further Research

In this final section, there are two issues to be addressed. Firstly, what conclusions can be drawn from the research in this thesis and, secondly, directions for future research.

7.7.1 Conclusions

The work presented in this thesis concerned the design of investigations of two drugs A and B, available at n and m prespecified dose levels respectively, in order to determine whether a combination of the drugs is more beneficial than either of the drugs administered singly. It was not advisable to consider existing designs for a factorial treatment structure due to the additional constraint that the treatment consisting of both drugs at the zero level is excluded on ethical grounds.

One main aim of the work was to find efficient designs with two orthogonal blocking factors, for estimating the particular contrasts of interest, by amalgamating two designs for a single blocking factor.

A further aim was to construct designs for cross-over trials under the assumption of simple additive models for carryover effects. Designs were required which perform well both in the presence and absence of carryover effects in order to achieve some protection against the validity of assumptions regarding the presence of carryover effects.

In Chapter 1, the problem was described and the direction of the research was outlined. A brief review of parameter estimation under a linear additive

model and methods of assessing the performance of designs for estimating the pairwise treatment comparisons was given. The implications of obtaining row-column designs by amalgamating two designs for a single blocking factor were discussed, in addition to the properties of designs which are part-balanced for the dual versus single treatment contrasts.

Chapter 2 was concerned with lower bounds on the total variance of the contrasts of interest. A review of some of the bounds given in the literature for single blocking factor and row-column designs was presented. Several design independent bounds, appropriate for use with the dual versus single treatment contrasts, were developed. Since it was not possible to establish conditions under which any one bound was uniformly better than the alternatives, the overall bound was taken to be the bound which achieved the maximum value for a particular set of design parameters.

In Chapter 3, some properties of connected row-column designs found by the method of amalgamation were given. The class of reinforced group divisible designs was investigated as a source of component designs and some necessary conditions for the existence of row-column designs obtained from these components were given. The class of C-designs, constructed by R- and S-type blocks, was also considered. Tables of efficient row-column designs, under the A-criterion, found by amalgamating components from these two classes were presented, together with an assessment of design performance using the bounds of Chapter 2.

The class of row-orthogonal designs was the subject of Chapter 4. These designs are characterised by having row blocks orthogonal to treatments, that is each treatment occurs exactly once in each row block. Necessary conditions were given for obtaining such designs by amalgamating a randomised block design with a suitable block design from the classes discussed in Chapter 3. Tables of designs were presented and it was noted that it is not necessary to sacrifice a great deal of precision in order to gain the property of row-orthogonality.

In Chapter 5, the problem of finding efficient designs for estimating any set of specific treatment contrasts was discussed. A method of identifying a class of designs likely to contain highly efficient and A-optimal members for the particular contrasts of interest was outlined. Several approaches to finding designs within such a class were discussed in the context of some practical examples.

The discussion of cross-over experiments was the primary function of Chap-

ter 6. This type of experimental situation was described and a review of the models presented in the literature was given. This subject has caused some controversy in recent years; the reasons for this were examined and the criticisms of some of the models which have been used in the past were presented.

In the previous sections of this chapter, cross-over designs were found under the assumption of simple additive models for first-order and first- and second-order carryover effects. The method followed was to rearrange the row-column designs of Chapters 3 and 4 within columns and select the arrangement with the minimum total variance under the appropriate carryover model. A study of design robustness to the assumption of non-negligible second-order carryover effects was also given.

7.7.2 Topics for further research

The following areas require further investigation.

1. The extension of bound $B_2(H)$ of Chapter 2 so that it can be used for the assessment of multi-dimensional designs.

2. Some simple necessary conditions for the amalgamation of two block designs were given in Chapter 3. It would be useful to establish some sufficient conditions for amalgamation.

3. In Section 3.6, the relationship between the variances of the least squares estimators of the dual versus single treatment contrasts for a row-column design and the parameters of the information matrices of its component designs was investigated. This is an area of further work.

4. The development of bounds on the total variance of the contrasts of interest for cross-over designs is a challenging area of research.

5. The development of an algorithm for obtaining larger cross-over designs by using the cross-over designs of Tables 7.1–7.5 as building bricks, see Section 7.5.

6. Following the discussion of carryover models in Chapter 6, it would be useful to perform studies of design robustness to different assumptions for error structures, and for the persistence and structure of carryover effects.

Appendix A

Computer Algorithm to find cross-over designs under a model for additive first-order carryover effects

```
program carryover (input, output);
{ program takes an efficient row-column design and rearranges it within sub-
ject blocks in order to find the best layout under the simple additive model for
first-order carryover effects. This version includes checks on the validity of the
rearranged design to ensure that the total variance under the row-column model
has not increased and that the design is connected under the carryover model. }
label 100;
const
maxd = 9;
maxr = 4;
maxdes = 30;
maxt = 5;
mult = 10;
tol = 0.00000001;
acc = 0.000001;
type
dmatrix = array[1..maxr, 1..maxd] of integer;
inmatrix = array[1..maxt, 1..maxd] of integer;
```

```
trinmat = array[1..maxd, 1..maxt] of integer;
sqinmat = array[1..maxt, 1..maxt] of integer;
invec = array[1..maxt] of integer;
rmatrix = array[1..maxt, 1..maxt] of real;
rvec = array[1..maxt] of real;
svec = array[1..maxdes] of real;
svmat = array[1..maxdes] of rmatrix;
sdmat = array[1..maxdes] of dmatrix;
var
i, j, nc, R, C, t : integer;
des : dmatrix;
N1 : inmatrix;
ct : rmatrix;
trace : svec;
svcv : svmat;
sdes : sdmat;

procedure initialise ( R, C : integer; var mat : dmatrix );
{ sets every element of design matrix equal to zero }
var
i, j : integer;
begin {initialise}
for i := 1 to R do
for j := 1 to C do
mat[i, j] := 0;
end {initialise};

procedure rinitialise ( R, C : integer; var mat : rmatrix );
{ sets every element of a square real matrix equal to zero }
var
i, j : integer;
begin {initialise}
for i := 1 to R do
for j := 1 to C do
mat[i, j] := 0;
end {initialise};
```

```
procedure iswap ( var a, b : integer);
{ swaps 2 integer elements of a vector }
var
temp : integer;
begin {iswap}
temp := a;
a := b;
b := temp;
end {iswap};

procedure rswap ( var a, b : real );
{ swaps 2 real elements of a vector }
var
temp : real;
begin {rswap}
temp := a;
a := b;
b := temp;
end {rswap};

procedure iaswap ( var a, b : dmatrix);
{ swaps 2 design matrices in a vector }
var
temp : dmatrix;
begin {iaswap}
temp := a;
a := b;
b := temp;
end {iaswap};

procedure raswap ( var a, b : rmatrix );
{ swaps 2 real matrices in a vector }
var
temp : rmatrix;
begin {raswap}
```

```
temp := a;
a := b;
b := temp;
end {raswap};

procedure printdm ( grid : dmatrix; R, C : integer );
{ prints out a design matrix }
var
i, j : integer;
begin {printdm}
for i := 1 to R do
begin
for j := 1 to C do
write( output, grid[i, j]:3 );
writeln(output);
end;
writeln(output);
end {printdm};

procedure printrm ( mat : rmatrix; R, C : integer );
{ prints out a real matrix }
var
i, j : integer;
begin {printrm}
for i := 1 to R do
begin
for j := 1 to C do
write( output, mat[i, j]:9:4 );
writeln(output);
end;
writeln(output);
end {printrm};

procedure incidence ( grid : dmatrix; R, C, t : integer;
                      var NP, NS, NPC, NSC : inmatrix );
{ calculates the period and subject (direct and residual) incidence matrices }
```

```
var
i, j : integer;
begin {incidence}
for i := 1 to t do
begin {i}
for j := 1 to R do
begin {j}
NP[i, j] := 0;
NPC[i, j] := 0;
end {j};
for j := 1 to C do
begin j
NS[i, j] := 0;
NSC[i, j] := 0;
end {j};
end {i};
for i := 1 to R do
for j := 1 to C do
begin {j}
NP[grid[i, j], i] := NP[grid[i, j], i] + 1;
NS[grid[i, j], j] := NS[grid[i, j], j] + 1;
end {j};
for j := 1 to C do
for i := 1 to R-1 do
begin {i}
NPC[grid[i, j], i+1] := NPC[grid[i, j], i+1] + 1;
NSC[grid[i, j], j] := NSC[grid[i, j], j] + 1;
end {i};
end {incidence};

procedure rincidence ( grid : dmatrix; var N : inmatrix;
                       R, C, t : integer );
{ finds the direct incidence of the row component }
var
i, j : integer;
begin {rincidence}
```

```
for i := 1 to t do
for j := 1 to R do
N[i, j] := 0;
for i := 1 to R do
for j := 1 to C do
N[grid[i, j], i] := N[grid[i, j], i] + 1;
end {rincidence};

procedure calcreps ( N : inmatrix; t, b : integer; var reps : sqinmat );
{ calculates treatment reps by summing the row elements of incidence mat }
var
i, j : integer;
begin {calcreps}
for i := 1 to t do
for j := 1 to t do
reps[i, j] := 0;
for i := 1 to t do
for j := 1 to b do
reps[i, i] := reps[i, i] + N[i, j];
end {calcreps};

procedure precedence ( grid : dmatrix; R, C, t : integer; var L : sqinmat );
{ calculates the precedence relationship of a design, element (i,j) is number of
times treatment i is preceded by treatment j }

var
i, j : integer;
begin {precedence}
for i := 1 to t do
for j := 1 to t do
L[i,j] := 0;
for j := 1 to C do
for i := 1 to R-1 do
L[grid[i+1, j], grid[i, j]] := L[grid[i+1, j], grid[i, j]] + 1;
end {precedence};
```

```
procedure itranspose ( R, C : integer; A : inmatrix; var B : trinmat );
{ transposes an integer incidence matrix }
var
i, j : integer;
begin {itranspose}
for i := 1 to R do
for j := 1 to C do
B[j, i] := A[i, j];
end {itranspose};

procedure rtranspose ( R, C : integer; A : rmatrix; var B : rmatrix );
{ transposes a square real matrix }
var
i, j : integer;
begin {rtranspose} for i := 1 to R do
for j := 1 to C do
B[j,i] := A[i,j];
end {rtranspose};

procedure intmult ( m, n, p : integer; A : inmatrix; B : trinmat;
                    var C : sqinmat );
{ multiplies a t x d integer matrix with a d x t integer matrix }
var
i, j, k : integer;
begin {intmult}
for i := 1 to m do
for j := 1 to p do
C[i, j] := 0;
for i := 1 to m do
for j := 1 to p do
for k := 1 to n do
C[i, j] := C[i, j] + A[i, k]*B[k, j];
end {intmult};

procedure intmult2 ( m, n, p : integer; A : inmatrix; B : dmatrix;
                     var C : inmatrix );
```

```
multiplies a t x d integer matrix with a d x d integer matrix
var
i, j, k : integer;
begin {intmult2}
for i := 1 to m do
for j := 1 to p do
C[i, j] := 0;
for i := 1 to m do
for j := 1 to p do
for k := 1 to n do
C[i, j] := C[i, j] + A[i, k]*B[k, j];
end {intmult2};

procedure rmult ( m, n, p : integer; A, B : rmatrix; var C : rmatrix );
{ multiplies 2 t x t real matrices }
var
i, j, k : integer;
begin {rmult} for i := 1 to m do
for j := 1 to p do
C[i, j] := 0;
for i := 1 to m do
for j := 1 to p do
for k := 1 to n do
C[i, j] := C[i, j] + A[i, k]*B[k, j];
end {rmult};

function check ( grid : dmatrix; N : inmatrix; R, C, t : integer ) : boolean;
{ checks the validity of an arrangement by checking that the new concurrence
matrix is the same as the original concurrence matrix }
var
i, j : integer;
NT : trinmat;
N2 : inmatrix;
NNT, N2N2T : sqinmat;
indic : boolean;
```

```
begin {check}
indic := true;
itranspose( t, R, N, NT );
intmult( t, R, t, N, NT, NNT );
rincidence( grid, N2, R, C, t );
itranspose( t, R, N2, NT );
intmult( t, R, t, N2, NT, N2N2T );
for i := 1 to t do
for j := 1 to t do
if ( NNT[i, j] <> N2N2T[i, j] ) then
indic := false;
check := indic;
end {check};

function samemat ( A, B : rmatrix; m, n : integer ) : boolean;
{ checks whether 2 real matrices are the same }
var
i, j : integer;
indic : boolean;
begin {samemat}
indic := true;
for i := 1 to m do
for j := 1 to n do
if ( abs( A[i, j] - B[i, j] ) ≥ acc ) then
indic := false;
samemat := indic;
end {samemat};

function present ( store : svmat; A : rmatrix; num, n, m : integer) : boolean;
{ ckecks through the store to see if A matches any element }
var
i : integer;
begin {present}
present := false;
for i := 1 to num do
if samemat( store[i], A, n, m ) then
```

```
present := true;
end {present};

procedure addmat ( f, g, h : integer; A, B, C, D : sqinmat;
                   var sum : rmatrix );
{ finds the sum of a linear combination of t x t integer matrices }
var
i, j : integer;
a, b, c, d : real;
begin {addmat} a := 1.0;
b := -1/h;
c := -1/g;
d := 1/(g*h);
for i := 1 to f do
for j := 1 to f do
sum[i,j] := a*A[i, j] + b*B[i, j] + c*C[i, j] + d*D[i, j];
end {addmat};

procedure f01blf ( m, n : integer; tol : real; var a : rmatrix;
                   ia : integer; var aijmax : rvec; var irank : integer;
                   var inc : invec; var d : rvec; var u : rmatrix;
                   iu : integer; var du : rvec; var ifail : integer );
                   external fortran;
{ nag routine to find the g-inverse of an information matrix }

function goodrank ( m : integer; A11, A12, A21, A22 : rmatrix ) : boolean;
{ checks to ensure that the full information matrix for both direct and residual
effects has sufficient rank }
const
alpha = 2;
type
intvec = array[1..mult] of integer;
realvec = array[1..mult] of real;
realmat = array[1..mult, 1..mult] of real;
var
i, j, newm, indic, rank : integer;
```

```
vec1, vec3, vec4 : realvec;
vec2 : intvec;
A, mtmp : realmat;
check : boolean;
procedure f01blf ( m, n : integer; tol : real; var a : realmat;
                   ia : integer; var aijmax : realvec;
                   var irank : integer; var inc : intvec;
                   var d : realvec; var u : realmat; iu : integer;
                   var du : realvec; var ifail : integer );
                   external fortran;
begin {goodrank} check := false;
newm := alpha*m;
for i := 1 to m do
for j := 1 to m do
begin {j}
A[i, j] := A11[i, j];
A[i, m+j] := A12[i, j];
A[m+i, j] := A21[i, j];
A[m+i, m+j] := A22[i, j];
end {j};
indic := 0;
f01blf(newm,newm,tol,A,newm,vec1,rank,vec2,vec3,mtmp,newm,vec4,indic);
if ( rank = (2*m - 2) ) then check := true;
goodrank := check;
end {goodrank};

procedure infomat ( grid : dmatrix; p, s, t : integer;
                    var A : rmatrix; var rankOK : boolean );
{ finds the overall information matrix A by calculating the 4 sub-matrices, ac-
cording to the standard theory }
var
indic, i, j, rank : integer;
J : dmatrix;
NP, NS, NPC, NSC, prod3 : inmatrix;
NT : trinmat;
Dr, L, Cr, prod1, prod2, prod4 : sqinmat;
```

```
vec2 : invec;
A11, A12, A21, A22, mtmp, mtmp2 : rmatrix;
vec1, vec3, vec4 : rvec;
begin {infomat} for i := 1 to p do
for j := 1 to s do
J[i, j] := 1;                          { initialises J to 1 }
incidence( grid, p, s, t, NP, NS, NPC, NSC );
calcreps( NP, t, p, Dr );
itranspose( t, p, NP, NT );
intmult( t, p, t, NP, NT, prod1 );
itranspose( t, s, NS, NT );
intmult( t, s, t, NS, NT, prod2 );
intmult2( t, p, s, NP, J, prod3 );
intmult( t, s, t, prod3, NT, prod4 );
addmat( t, p, s, Dr, prod1, prod2, prod4, A11 );
{ calculates A11 }
precedence( grid, p, s, t, L );
itranspose( t, p, NPC, NT );
intmult( t, p, t, NP, NT, prod1 );
itranspose( t, s, NSC, NT );
intmult( t, s, t, NS, NT, prod2 );
intmult( t, s, t, prod3, NT, prod4 );
addmat( t, p, s, L, prod1, prod2, prod4, A12 );
{ calculates A12 }
rtranspose( t, t, A12, A21 );
{ calculates A21 }
calcreps( NPC, t, p, Cr );
itranspose( t, p, NPC, NT );
intmult( t, p, t, NPC, NT, prod1 );
itranspose( t, s, NSC, NT );
intmult( t, s, t, NSC, NT, prod2 );
intmult2( t, p, s, NPC, J, prod3 );
intmult( t, s, t, prod3, NT, prod4 );
addmat( t, p, s, Cr, prod1, prod2, prod4, A22);
{ calculates A22 }
rankOK := goodrank( t, A11, A12, A21, A22 );
```

```
if rankOK then
begin {if}
indic := 0;
f01blf(t,t,tol,A22,t,vec1,rank,vec2,vec3,mtmp,t,vec4,indic);
{ calls nag routine to find g-inverse of A22 }
rmult( t, t, t, A12, A22, mtmp );
rmult( t, t, t, mtmp, A21, mtmp2 );
for i := 1 to t do
for j := 1 to t do
A[i, j] := A11[i, j] - mtmp2[i, j];
end {if}
else rinitialise( t, t, A );
end {infomat};

procedure variance ( grid : dmatrix; p, s, t, nc : integer; cont : rmatrix;
                     var vcv : rmatrix; var trace : real );
{ finds the variance-covariance matrix of a design under the additive model and
the total variance }
var
indic, i, rank : integer;
vec2 : invec;
A, mtmp, contt : rmatrix;
vec1, vec3, vec4 : rvec;
rankchk : boolean;
begin {variance}
indic := 0;
infomat( grid, p, s, t, A, rankchk );
if rankchk then
begin {if}
f01blf(t,t,tol,A,t,vec1,rank,vec2,vec3,mtmp,t,vec4,indic);
rmult( nc, t, t, cont, A, mtmp );
rtranspose( nc, t, cont, contt );
rmult( nc, t, nc, mtmp, contt, vcv );
trace := 0;
for i := 1 to nc do
trace := trace + vcv[i, i];
```

```
end {if}
else
begin {else}
trace := 9999999.0;
rinitialise( nc, nc, vcv );
end {else};
end {variance};

procedure sort ( var avec : svec; var avcv : svmat; var ades : sdmat );
{ sorts the elements of a real vector into ascending order and carries the associated
design and vcv matrices }
var
count, i : integer;
begin {sort}
for count := 1 to (maxdes-1) do
for i := 1 to (maxdes-1) do
if ( avec[i] > avec[i+1] ) then
begin
rswap( avec[i], avec[i+1] );
raswap( avcv[i], avcv[i+1] );
iaswap( ades[i], ades[i+1] );
end
end {sort};

procedure arrange ( grid : dmatrix; R, C, t, nc, PC : integer;
                    cont : rmatrix; N : inmatrix; var trace : svec;
                    var svcv : svmat; var sdes : sdmat );
{ finds all the possible permutations of a design, checks that a rearrangement is
a valid design, calculates the vcv, holds the best 30 designs i.e. the designs with
the smallest total variance }
label 10;
var
lp1, lp2, lp3, lp4 : integer;
vcv : rmatrix;
totvar : real;
begin {arrange}
```

```
PC := PC + 1;
if ( PC > C ) then goto 10;
case R of
2 :
begin {case 2}
for lp1 := 1 to 2 do
begin {lp1}
iswap( grid[1, PC], grid[lp1, PC] );
arrange( grid, R, C, t, nc, PC, cont, N, trace, svcv, sdes );
if ( PC = C ) and ( check( grid, N, R, C, t ) ) then
begin
variance( grid, R, C, t, nc, cont, vcv, totvar );
if ( trace[maxdes] > totvar ) and
not present( svcv, vcv, maxdes, nc, nc ) then
begin {if2} trace[maxdes] := totvar;
svcv[maxdes] := vcv;
sdes[maxdes] := grid;
sort( trace, svcv, sdes );
end {if2};
end;
end {lp1};
end {case 2};
3 :
begin {case 3}
for lp1 := 1 to 3 do
begin {lp1}
iswap( grid[1, PC], grid[2, PC] );
for lp2 := 2 to 3 do
begin {lp2} iswap( grid[2, PC], grid[lp2, PC] );
arrange( grid, R, C, t, nc, PC, cont, N, trace, svcv, sdes );
if ( PC = C ) and ( check( grid, N, R, C, t ) ) then
begin {if} variance( grid, R, C, t, nc, cont, vcv, totvar );
if ( trace[maxdes] > totvar ) and
not present( svcv, vcv, maxdes, nc, nc ) then
begin {if2} trace[maxdes] := totvar;
svcv[maxdes] := vcv;
```

```
sdes[maxdes] := grid;
sort( trace, svcv, sdes );
end {if2};
end {if};
end {lp2};
end {lp1};
end {case 3};
4 :
begin {case 4}
for lp1 := 1 to 4 do
begin {lp1}
iswap( grid[1, PC], grid[lp1, PC] );
for lp2 := 2 to 4 do
begin {lp2}
iswap( grid[2, PC], grid[3, PC] );
for lp3 := 3 to 4 do
begin {lp3}
iswap( grid[3, PC], grid[lp3, PC] );
arrange( grid, R, C, t, nc, PC, cont, N, trace, svcv, sdes );
if ( PC = C ) and ( check( grid, N, R, C, t ) ) then
begin
variance( grid, R, C, t, nc, cont, vcv, totvar );
if ( trace[maxdes] > totvar ) and
not present( svcv, vcv, maxdes, nc, nc ) then
begin {if2}
trace[maxdes] := totvar;
svcv[maxdes] := vcv;
sdes[maxdes] := grid;
sort( trace, svcv, sdes );
end {if2};
end {if};
end {lp3};
end {lp2};
end {lp1};
end {case 4};
end;
```

```
10:end {arrange};

begin {carryover}
writeln(output);
readln( t, R, C );
write( output, ' Crossover designs for ', t:1, ' treatments, ', R:1 );
writeln( output, ' periods and ', C:1, ' subjects.');
writeln( output );
{ checks for wrong parameters }
if ( R > maxr ) or ( C > maxd ) then
begin
writeln( output, ' Design is too large.');
goto 100;
end;
if ( R*C - 2*t - R - C + 4 ≤ 0 ) then
begin
writeln(output,' Insufficient observations to estimate all parameters.');
goto 100;
end;
{ reads in contrasts }
readln( nc );
for i := 1 to nc do
begin
for j := 1 to t do
read( ct[i, j] );
readln;
end;
writeln( output, ' Matrix of contrasts of interest is :-' );
printrm( ct, nc, t );
{ reads in starting design }
for i := 1 to R do
begin
for j := 1 to C do
read( des[i, j] );
readln;
end;
```

```
writeln( output, ' Starting design is :- ');
printdm( des, R, C );
writeln( output, ' Possible rearrangements are :- ');
{ initialises the storage arrays for total variance, designs and vcvs }
for i := 1 to maxdes do
begin {i}
trace[i] := 9999999.0;
rinitialise( nc, nc, svcv[i] );
initialise( R, C, sdes[i] );
end {i};
rincidence( des, N1, R, C, t );
arrange( des, R, C, t, nc, 0, ct, N1, trace, svcv, sdes );
{ prints out the storage arrays for total variance, designs and vcvs }
for i := 1 to maxdes do
begin {i}
printdm( sdes[i], R, C );
printrm( svcv[i], nc, nc );
writeln( output, ' Total variance = ', trace[i]:10:6 );
writeln( output );
end {i};
100:end{carryover}.
```

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