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CHARACTERIZATION AND CONSTRUCTION OF INCOMPLETE BLOCK DESIGNS FOR SYMMETRICAL PARALLEL LINE ASSAYS

V. K. GUPTA, A. K. NIGAM and P. D. PURI*
Indian Agricultural Statistics Research Institute, New Delhi-110012

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SUMMARY

The purpose of this article is to obtain characterization of incomplete block designs for symmetrical parallel line assays which leave important bio-assay contrasts unconfounded. For this characterization the bio-assay contrasts are basic contrasts and the loss of information on the bio-assay contrasts can be worked out from component designs only. The analysis of these designs is very elegant and simple.

Keywords : Partially efficiency balanced designs, Bio-assay contrasts.

Introduction

Incomplete block designs, although useful in bio-assays, do not find a direct application because in bio-assays the contrasts of importance are not elementary contrasts. For symmetrical parallel line (SPL) assays contrasts of preparation (L_p), combined regression (L_1) and parallelism (L') are of major importance. In a SPL assay with $v = 2m$ doses, the $v - 1$ degrees of freedom can be split into single degree of freedom contrasts L_p, L_h and L'_h, $h = 1, 2, \ldots, L_h$ and L'_h denote the sums and differences of hth power regression. It is useful to further subgroup L_h and L_h into odd and even numbered contrasts L_{2n+1}, L_{2n+2}, L'_{2n+1} and L'_{2n+2} respectively. Das and Kulkarni [2] proposed some incomplete block designs for

*H.A.U., Hissar.

SPL assays which leave L_p and L_1 unconfounded while L_1' is effected by block differences. Kulshreshtha [5] proposed designs which permit orthogonal estimation of all the three contrasts L_p, L_1 and L_1'. For a discussion of these designs and other possibilities, reference may be made to Finney [3]. Kyi Win and Dey [6] derived conditions under which L_p, L_1 and L_1' are estimated free from block effects. These conditions are used to obtain designs for SPL-assays. Nigam and Boopathy [7] obtained incomplete block designs which provide unconfounded estimates of L_p, L_{2n+1} and L_{2n+1}'. The concurrence matrix NN^T of these designs is highly structured. Some of the designs of Kyi Win and Dey could be obtained as particular cases of these designs.

This article obtains some characterizations of incomplete block designs for SPL-assays which leave L_p, L_{2n+1} and L_{2n+1}' unconfounded. The designs reported by Nigam and Boopathy essentially belong to this characterization. A large number of new designs can be constructed through this characterization.

2. Some Preliminaries

Consider an incomplete block design for a SPL-assay in $v(=2m)$ doses and b blocks such that the jth block receives $k_j(=k_{s_j}+k_{t_j})$ doses, $j=1, b$, and every dose appears in r blocks. Let $s_i(t_i)$ denote the ith dose of standard (test) preparation equi-spaced on log scale. Assuming the usual intra-block model, the information matrix pertaining to doses is

$$\mathbf{C}_d = r\,\mathbf{I}_v - \mathbf{N}\,\mathbf{K}^{-\delta}\,\mathbf{N}^T = r(\mathbf{I}-\mathbf{M}),$$

where $\mathbf{I}_v$ is an identity matrix of order v, $\mathbf{K}^{-\delta}$ is a diagonal matrix with diagonal elements $(1/k_1, 1/k_2, \ldots, 1/k_b)$ and $\mathbf{N}$ is the doses versus blocks incidence matrix. For a bio-assay design, the M-matrix is of the form

$$\mathbf{M} = \frac{1}{r}\begin{bmatrix} \mathbf{A}_{m\times m} & \mathbf{B}_{m\times m} \\ \mathbf{B}_{m\times m} & \mathbf{C}_{m\times m} \end{bmatrix}, \tag{2.1}$$

where $\mathbf{A} = \mathbf{N}_1\,\mathbf{K}^{-\delta}\,\mathbf{N}_1^T$, $\mathbf{B} = \mathbf{N}_1\,\mathbf{K}^{-\delta}\,\mathbf{N}_2^T$ and $\mathbf{C} = \mathbf{N}_2\,\mathbf{K}^{-\delta}\,\mathbf{N}_2^T$. Here $\mathbf{N}_1$ and $\mathbf{N}_2$ are $m \times b$ incidence matrices of standards versus blocks and tests versus blocks, respectively.

In a SPL assay, let e_p, e_{2n+1}, e_{2n+1}', e_{2n+2}, and e_{2n+2} denote respectively the vectors of co-efficients of the bio-assay contrasts L_p, L_{2n+1}, L_{2n+1}', L_{2n+2} and L_{2n+2}', respectively. Throughout we shall assume the doses to be arranged in the order $a_1, a_2, \ldots, a_t, a_{2t}, a_{2t-1}, \ldots, a_{t+2}, a_{t+1}$, if the number of doses is even and in the order $a_1, a_2, \ldots, a_t, a_{2t+1}, a_2, \ldots, a_{t+2}, a_{t+2}, a_{t+1}$, if the number of doses is odd. As will be seen later, such

an ordering helps in obtaining the desired structures of the designs. The coefficient vectors can be expressed as

$$\begin{aligned} e_p &= (1, -1)^T \otimes l_m \\ e_{2n+1} &= (1, 1)^T \otimes v_n \\ e'_{2n+1} &= (1, -1)^T \otimes v_n \\ e_{2n+2} &= (1, 1)^T \otimes u_n \\ e'_{2n+2} &= (1, -1)^T \otimes u_n \end{aligned} \tag{2.2}$$

where l_m is an $m \times 1$ column-vector of all elements unity and v_n and u_n are $m \times 1$ column-vectors satisfying $v_n^T\, l_m = u_n^T\, l_m = 0$. In fact v_n is an orthogonal polynomial of degree $2n + 1$, $n = 0, 1, \ldots$, and u_n is an orthogonal polynomial of degree $2n + 2$, $n = 0, 1, \ldots$.

Let $m = 2p$. Then the co-efficient vectors (2.2) can also be expressed as

$$\begin{aligned} e_p &= [(1, 1)^T \otimes l_p^T, \quad (-1, -1)^T \otimes l_p^T]^T \\ e_{2n+1} &= [(1, -1)^T \otimes x_n^T, \ (1, -1)^T \otimes x_n^T]^T \\ e'_{2n+1} &= [(1, -1)^T \otimes x_n^T, \ (-1, 1)^T \otimes x_n^T]^T \\ e_{2n+2} &= [(1, 1)^T \otimes y_n^T, \quad (1, 1)^T \otimes y_n^T]^T \\ e'_{2n+2} &= [(1, 1)^T \otimes y_n^T, \quad (-1, -1)^T \otimes y^T]^T. \end{aligned} \tag{2.3}$$

where x_n and y_n are $p \times 1$ column vectors with $y_n^T\, l_p = 0$.

Further if $m = 2p + 1$, then (2.2) can again be expressed as

$$\begin{aligned} e_p &= [1, 1)^T \otimes l_p^T, \quad 1, (-1, -1)^T \otimes l_p^T, -1]^T \\ e_{2n+1} &= [(1, -1)^T \otimes x_n^T, \ 0, (1, -1)^T \otimes x_n^T, 0]^T \\ e'_{2n+1} &= [(1, -1)^T \otimes x_n^T, \ 0, (-1, 1)^T \otimes x_n^T, 0]^T \\ e_{2n+2} &= [(1, 1)^T \otimes y_n^T, \quad 0, (1, 1)^T \otimes y_n^T, 0]^T \\ e'_{2n+2} &= [1, 1)^T \otimes y_n^T, \quad 0, (-1, -1)^T \otimes y_n^T, -0]^T. \end{aligned} \tag{2.4}$$

Here $y_n^T\, l_p \neq 0$.

3. Characterization of Bio-assay Designs

We now study some characterizations of incomplete block designs for

SPL-assays in which L_p, L_{2n+1}, and L'_{2n+1} are estimated free from block effects. Following Jones [4] and Calinski [1], L_p, L_{2n+1}, and L'_{2n+1} will be estimated orthogonally if the eo-efficient vectors (2.2) of these contrasts are eigen vectors of M-matrix (2.1) corresponding to an eigen root zero. We thus have the following theorem :

THEOREM 3.1. *For orthogonal estimation of* L_p, L_{2n+1}, *and* L'_{2n+1}, *the* M-*matrix in* (*2.1*) *should be such that*

$$\mathbf{A}\, l_m = \mathbf{B}\, l_m = \mathbf{C}\, l_m$$
$$\mathbf{A}\, y_n = \mathbf{B}\, y_n = \mathbf{C}\, y_n = 0. \tag{3.1}$$

In the sequel we shall assume $\mathbf{A} = \mathbf{C}$, because it introduces simplification in the construction of designs. We then have the following theorem :

THEOREM 3.2. *In SPL-assays with M-matrix as in* (*2.1*) *the loss of information on* L_{2n+2} *and* L'_{2n+2} *is* $2(\alpha + \beta)/r$ *and* $2(\alpha\ \beta)/r$, *respectively, if*

$$\mathbf{A}\, u_n = \alpha\, u_n \quad \text{and} \quad \mathbf{B}\, u_n = \beta\, u_n, \tag{3.2}$$

Proof. The proof follows by using (2.1), (2.2) and (3.2). Notice that e_{2n+2} and e'_{2n+2} are eigenvectors of M corresponding to eigenvalues $2(\alpha + \beta)/r$ and $2(\alpha - \beta)/r$, respectively.

Corollary. If $\alpha = \beta$ (*or* $\alpha = -\beta$), *then* L'_{2n+2} (*or* L_{2n+2}) *also becomes free from block effects and loss of information on* L_{2n+2} (*or* L'_{2n+2}) $= 4\alpha/r$, *which will also be equal to the total loss.*

From Theorem 3.2 it follows that the loss of information on L_{2n+2} and L'_{2n+2} can be worked out from component designs only.

We now study structure of A and B matrices in M such that the conditions (3.1) are satisfied. In view of the nature of co-efficient vectors of contrasts L_p, L_{2n+1} and L'_{2n+1} given in (2.3) and (2.4), it is not unrealistic to assume

$$\mathbf{A} = \mathbf{J}_2 \otimes \mathbf{A}_i, \quad \mathbf{B} = \mathbf{J}_2 \otimes \mathbf{B}_i \tag{3.3}$$

when m is even ($m = 2p$), and

$$\mathbf{A} = \begin{bmatrix} \mathbf{J}_2 \otimes \mathbf{A}_i & \underline{\delta} \\ \underline{\delta}^T & q \end{bmatrix} \tag{3.4}$$

$$\mathbf{B} = \begin{bmatrix} \mathbf{J}_2 \otimes \mathbf{B}_i & \underline{\delta} \\ \underline{\delta}^T & q \end{bmatrix}$$

when m is odd ($m = 2p + 1$). Here $\mathbf{A}_i$ and $\mathbf{B}_i$ are $p \times p$ matrices such that $\mathbf{A}_i\ l_p = \mathbf{B}_i\ l_p$, $\underline{\delta}$ is an $2p \times 1$ column vectors of non-negative real numbers and q is a positive scalar constant and is a function of design parameters, $\mathbf{J}_2$ is a square matrix of order 2 with all elements unity. It is easy to verify that the conditions (3.1) are satisfied for structures (3.3) and (3.4).

From the characterizations of Theorems 3.1 and 3.2 it follows that L_p, L_{2n+1}, L_{2n+1}, L_{2n+2}, and L'_{2n+2} are basic contrasts (Pearce, Calinski and Marshall, [8]). There are three losses of information 0.0, 2 $(\alpha + \beta)/r$ and $2(\alpha + \beta)/r$, and the design is partially efficiency balanced with three efficiency classes. In a particular situation, there are two losses of information 0, $4\alpha/r$ and the design is simple partially efficiency balanced. The analysis of these designs is very simple (Puri and Nigam, [9]).

4. Construction of Designs for SPL Assays

We now describe a general method of construction of designs for SPL assays which have the structure as described in Section 3.

Series 1. Let $v = 2m$ ($m = 2p$). Consider any conceivable connected incomplete block design (basic design) for first p doses of standard preparation in the b blocks of size $k/4$, each dose occuring in r blocks. Then to obtain the final design, include the $k/4$ doses from the remaining doses of standard preparation by replacing the ith symbol of the basic design by two doses (s_i, s_{m-i+1}) of standard preparation and two doses (t_i, t_{m-i+1}) of test preparation, $i = 1, 2, \ldots, p$. In other words, if $\{s_i\}$ is the ith block of basic design, then the ith block of the bio-assay design is $\{s_i, s_{m-i+1}, t_i, t_{m-i+1}\}$. The parameters of the resulting design are $v = 2m$, b, r, k. For this series of design the minimum block size is 8. The M-matrix of this design is

$$\mathbf{M} = \frac{1}{r}\,[\mathbf{J}_2 \otimes \mathbf{J}_2 \otimes \mathbf{A}_i],$$

where $\mathbf{A}_i = \mathbf{N}\,\mathbf{K}^{-\delta}\,\mathbf{N}^T$, and $\mathbf{N}$ is the incidence matrix of the basic design. Kulshreshtha (1971) constructed such designs when the basic design is a BIB, circular or PBIB. Further, if $\mathbf{A}\ y_n = \alpha y_n$, then L'_{2n+2} also becomes free from block effects and the loss of information on, L_{2n+2} is $4\alpha/r$.

Series 2. Let $v = 2m$ ($m = 2p + 1$). Consider the basic design in first p doses of standard preparation in b blocks of size $k/4$, as in series 1. In order to obtain the final design replace the ith symbol of basic design s_i by $(s_i, s_{m-i+1}, t_i, t_{m-i+1})$, $i = 1, 2, \ldots, p - 1$ and s_p by $(s_p, s_{p+2}, s_{p+1}, t_p, t_{p+2}, t_{p+1})$. The parameters of the resulting design are $v = 2m$, b, r, k^+

where k^+ is either k or $k + 2l$. The M-matrix of this design is

$$\mathbf{M} = \frac{1}{r}\,[I_4 \otimes \mathbf{B}_i], \quad \text{where } \mathbf{B}_i = l_2 \otimes \mathbf{A}_i \,:\, l_2 \otimes a_v],$$

$$\mathbf{A}_i = \mathbf{N}\,\mathbf{K}^{+-\delta}\,\mathbf{N}^T = [a_1 \ldots a_v]$$

and N is the incidence matrix of the basic design.

It may be mentioned here that in the designs for SPL-assays when m is odd, it is not possible to identify L_{2n+2}, L'_{2n+2} as basic contrasts. As such it is not possible to work out the loss of information on these contrasts. In a particular design, however, either L_{2n+2} or L'_{2n+2} may be a basic contrast and it would then be possible to obtain the loss of information on that contrasts.

Example 1. Lat $v = 14$ and $p = 3$. Consider the basic design N as (s_1, s_2), $(s_1\ s_3)$ and $(s_2\ s_3)$. The resulting design for SPL assay is $(s_1\ s_2\ s_6\ s_7\ t_1\ t_2\ t_6\ t_7)$, $(s_1\ s_3\ s_4\ s_5\ s_7\ t_1\ t_3\ t_4\ t_5\ t_7)$ $(s_2\ s_3\ s_4\ s_5\ s_6\ t_2\ t_3\ t_4\ t_5\ t_6)$, with parameters $v = 14$, $b = 3$, $r = 2$, $k = (8, 10, 10)'$.

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