Planning and Efficiency of Multivariate Bioassay in Block Designs

Zofia Hanusz and Joanna Olejnik
Department of Applied Mathematics
University of Agriculture
Akademicka 13
Lublin, Poland
Hanusz@ursus.ar.lublin.pl
Jolejnik@ursus.ar.lublin.pl

1. Introduction

One of the fields of statistical analysis is comparison of the influence of the test preparation on multivariate observations with that of the standard preparation. One of the methods of such comparison is to provide an estimation of potency of the test preparation relative to the standard preparation. In the case when the doses of the preparations are administered to experimental units characterised by one-directional changebility, randomized block designs should be applied. Such designs eliminate nuisance parameters connected with block effects. In the paper, the so-called parallel-line designs with multivariate responses, mutually independent, and having the multivariate normal distribution with the same covariance matrix are considered. Das and Kulgarni (1966) and Win and Dey (1980) considered incomplete block designs for parallel-line assays in the univariate case, assuming the same numbers of doses for both preparations and the doses equispaced logarithmically. With these assumptions, it is possible to construct incomplete block designs with full efficiency of some contrasts, used in the estimation of the relative potency. From the practical point of view, both the above assumptions are frequently not fulfilled. In practice, however, the number of the doses for the test preparations is generally lower than the number of the doses for the standard preparation. Moreover, the doses of both preparations do not have to be the same and they do not have to be equispaced logarithmically. The aim of this paper is to consider the efficiency of the estimation of the relative potency of experiments conducted in block designs with two groups of objects.

2. Notation and Preliminaries

Let us consider an experiment in which the doses of two preparations are administered to the experimental material allocated in b blocks. To keep the main hypothesis about log of relative potency testable, the best block designs to consider are augmented (supplemented) block designs with two classes of plots (Hanusz, 1999). Such a design allows for the appearance of both the preparations together in each block. The main problem concerning planning an experiment for bioassay is to choose a proper number of doses, the quantity of the doses and a proper design to assert the highest efficiency. Let S and T denote the standard and the test preparation respectively. Assume that ν_S doses of standard preparations, namely: $u_{S1}, u_{S2}, \ldots, u_{S\nu_S}$ are administered to the first group of experimental units and ν_T doses of test preparations: $u_{T1}, u_{T2}, \ldots, u_{T\nu_T}$ are administered to the second group of experimental units. A linear model of multivariate responses of units getting the doses of preparations can be written in the following form:

$$\mathbf{Y} = \mathbf{D}'\mathrm{t} + \mathrm{D}_1'\mathrm{a}' + \mathrm{D}_2'\mathrm{b}' + \mathbf{E} \qquad (1)$$

where $\mathbf{Y} = \begin{bmatrix} \mathbf{Y}_S \\ \mathbf{Y}_T \end{bmatrix}$ is the (nxp) matrix of all p-variate responses, t, $\mathrm{a}' = \begin{bmatrix} \mathrm{a}'_S \\ \mathrm{a}'_T \end{bmatrix}, \mathrm{b}' = \begin{bmatrix} \mathrm{b}'_S \\ \mathrm{b}'_T \end{bmatrix}$ are unknown matrices of (bxp) block effects, $(2xp)$ of intercepts and $(2xp)$ of slopes for the standard and the test, respectively, $\underset{n\times p}{\mathbf{D}'} = \begin{bmatrix} \mathbf{D}'_S \\ \mathbf{D}'_T \end{bmatrix}, \underset{n\times 2}{\mathrm{D}'_1} = \begin{bmatrix} \mathbf{1}_{n_S} & \mathbf{0}_{n_S} \\ \mathbf{0}_{n_T} & \mathbf{1}_{n_T} \end{bmatrix}, \underset{n\times 2}{\mathrm{D}'_2} = \begin{bmatrix} \mathbf{x}_S & \mathbf{0}_{n_S} \\ \mathbf{0}_{n_T} & \mathbf{x}_T \end{bmatrix}$ are known matrices of the experimental plan connected with blocks effects, intercepts and slopes of the regression lines of the responses versus the log of the doses, $\mathbf{1}_{n_i}, \mathbf{0}_{n_i}$ denote the vectors of ones and nulls of the size n_i (the numbers of all plots receiving the *i*th preparations), $\mathbf{x}_S, \mathbf{x}_T$ are vectors of log of all the applied doses in the same order as the responses in **Y,** $n = n_S + n_T$.

Let $\mathbf{k}^{-\delta} = (\mathbf{D}\mathbf{D}')^{-1}$ denote the diagonal matrix with the inverse of block sizes on the diagonal, $F_1 = \mathbf{I}_n - \mathbf{D}'\mathbf{k}^{-\delta}\mathbf{D}$, $\mathbf{C}_1 = D_1 F_1 D_1'$, $F_2 = F_1 - F_1 D_1' \mathbf{C}_1^- D_1 F_1$, $\mathbf{C}_2 = D_2 F_2 D_2'$, F_i is a projector matrix fulfilling: $F_i = F_i'$, $F_i^2 = F_i$, $F_i \mathbf{D}' = 0$, $F_i \mathbf{1}_n = 0$ for *i*=1,2, and $F_2 D_1' = 0$.

3. Estimation of two parameter functions

In the estimation of the relative potency, two hypotheses are of a major importance. The first hypothesis, $H_\beta^0 : b_S - b_T = \mathbf{0}$, asserts that the vectors of slopes in the linear regression functions of responses versus the log of doses for both preparations in model (1) are identical. The second hypothesis, $H_\mu^0 : a_S - a_T - \mu b = \mathbf{0}$, describes the relation between the log of relative potency, denoted by μ, vectors of intercepts a_S, a_T and the same vector of slopes b for both preparations (under the truthfulness of H_β^0). This hypothesis is tested in a new model with one vector of slopes for both preparations. Let us describe this model in a form:

$$\mathbf{Y} = \mathbf{D}'t + D'Q + \mathbf{E} \qquad (2)$$

and $D' = [D_1' \vdots D_2' \mathbf{1}_2]$, $\underset{3\times p}{Q} = \begin{bmatrix} a' \\ b' \end{bmatrix}$, $a' = \begin{bmatrix} a_S' \\ a_T' \end{bmatrix}$ remains the same as in model (1), b- is a vector.

Let us consider two linear functions $y_1 = \mathbf{c}'b$, $\mathbf{c}' = [1, -1]$, estimated in the model (1) and $y_2 = \mathbf{L}'Q$, $\mathbf{L}' = [-\mathbf{c}', \mu]$ estimated in model (2). It can be shown that the maximum likelihood estimators of the functions y_1 and y_2 could be written in the forms: $\tilde{y}_1 = \mathbf{c}'\tilde{b} = \mathbf{c}'\mathbf{C}_2^- D_2 F_2 \mathbf{Y}$, $\tilde{y}_2 = \mathbf{L}'\tilde{Q} = \mathbf{L}'\mathbf{C}^- D F_1 \mathbf{Y}$, where $\mathbf{C}_2^-$ denotes a general inverse of $\mathbf{C}_2$ and $\mathbf{C}^-$ is the general inverse of $\mathbf{C} = D F_1 D'$. It can be shown that $\mathbf{c}$ is an eigenvector of $\mathbf{C}_2$ corresponding to a nonzero eigenvalue and **L** can be written in a form: $\mathbf{L} = \mathbf{L}_1 + \mu \mathbf{L}_2$, where $\mathbf{L}_1'$=[-1,1,0] and $\mathbf{L}_2'$=[0,0,1] are eigenvectors of **C** corresponding to nonzero eigenvalues. In the designs considered by Das and Kulgarni (1966), Win and Dey (1980) both above estimators are unconfounded with block effects as D_2' is orthogonal to D_1' and $\mathbf{D}'$ so they are estimated with full precision. In general, this orthogonality is not fulfilled and parameters function are estimated with lower precision.

REFERENCE

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RESUME

Les formulas proposées dans la publications concernent l'estimation d'une puissance relative deux préparations par rapport au standard, appliquées dans le même expériencedans unarrangement des blocs incomplets pur le cas d'un modele linéaire-parallele avec les observations multidimensionnelles.