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*Zofia Hanusz**

MULTIVARIATE BIASSAY IN A TWO-WAY ELIMINATION OF HETEROGENEITY DESIGN

Abstract. Estimation of the constant potency of a test preparation relative to a standard preparation in multivariate parallel-line assays is discussed. The case when doses of both preparations are administered to experimental units forming a two-way elimination of heterogeneity design is considered. For such a design, a multivariate linear model of observations is described and test functions for the hypotheses about parallelism and relative potency of the preparations are presented.

Key words: relative potency, parallel-line assay, multivariate observations, a two-way elimination of heterogeneity design.

I. INTRODUCTION

One of the fields of the biometric research is comparison of the influence of a test preparation on multivariate observations to that of a standard preparation. One of the methods of such comparison is to provide estimation of potency of a test preparation relative to a standard preparation. In the case when doses of the preparations are administered to experimental units characterised by two-directional changeability, a two-way elimination of the heterogeneity design should be applied. In the paper of Hanusz (1995, 1999) such designs are considered in the case when the standard and test preparations are administered in separate designs. In practice, however, the case when both preparations are administered in the same design could also occur. Such designs allow for elimination of two sets of nuisance parameters, which form row effects and column effects.

* Dr., Department of Applied Mathematics, Agricultural University of Lublin.

In the paper, we consider the so called parallel-line designs with multivariate variables having the multivariate normal distribution with the same covariance matrix. We also assume that variables are mutually independent.

II. NOTATIONS AND GENERAL LINEAR MODEL

Let S denote the standard preparation which is known and T – the test preparation, which is unknown. Suppose that the preparations are applied in v_S and v_T doses denoted by: $u_{S1}, u_{S2}, ..., u_{Sv_S}$ for the standard preparation and $u_{T1}, u_{T2}, ..., u_{Tv_T}$ for the test preparation. Let us consider an experiment in which doses of both preparations are allocated to experimental units arranged in b_1 rows and b_2 columns. With respect to preparations, such an experiment is uniquely characterized by three types of incidence matrices: $\mathbf{N}_{1i}$ – dose and row, $\mathbf{N}_{2i}$ – dose and column and $\mathbf{N}_{3i}$ – row and column, where $i = S, T$ denotes an index for a respective preparation. For the standard and the test preparations taken together, the appropriate incidence matrices are equal to: $\mathbf{N}_1 = \begin{bmatrix} \mathbf{N}_{1S} \\ \mathbf{N}_{1T} \end{bmatrix}$, $\mathbf{N}_2 = \begin{bmatrix} \mathbf{N}_{2S} \\ \mathbf{N}_{2T} \end{bmatrix}$, $\mathbf{N}_3 = \mathbf{N}_{3S} + \mathbf{N}_{3T}$. Moreover, for $v = v_S + v_T$, the following relations hold: $\mathbf{N}'_1 \mathbf{1}_v = \mathbf{N}_3 \mathbf{1}_{b_2} = \mathbf{k}_1$, $\mathbf{N}'_2 \mathbf{1}_v = \mathbf{N}_3 \mathbf{1}_{b_1} = \mathbf{k}_2$ and $\mathbf{k}_1$, $\mathbf{k}_2$ are vectors of row and column sizes.

By way of illustration, let us consider an experimental plan with three doses of the standard preparation and two doses of the test preparation applied in the following way:

	Column 1	Column 2	Column 3
Row 1	u_{S1} u_{S2} u_{S3} u_{T1} u_{T2}	u_{S1} u_{S3} u_{T1}	u_{S2} u_{S3} u_{T2}
Row 2	u_{S1} u_{S2} u_{T1} u_{T2}	u_{S1} u_{S2} u_{S3} u_{T1} u_{T2}	u_{S1} u_{S2} u_{S3} u_{T2}

This plan is characterized by the following incidence matrices for preparations:

$$\mathbf{N}_{1S} = \begin{bmatrix} 2 & 3 \\ 2 & 3 \\ 3 & 2 \end{bmatrix}, \mathbf{N}_{1T} = \begin{bmatrix} 2 & 2 \\ 2 & 3 \end{bmatrix}, \mathbf{N}_{2S} = \begin{bmatrix} 2 & 2 & 1 \\ 2 & 1 & 2 \\ 1 & 2 & 2 \end{bmatrix}, \mathbf{N}_{2T} = \begin{bmatrix} 2 & 2 & 0 \\ 2 & 1 & 2 \end{bmatrix},$$

$$\mathbf{N}_{3S} = \begin{bmatrix} 3 & 2 & 2 \\ 2 & 3 & 3 \end{bmatrix}, \mathbf{N}_{3T} = \begin{bmatrix} 2 & 1 & 1 \\ 2 & 2 & 1 \end{bmatrix},$$

which yield the incidence matrices for the entire plan:

$$\mathbf{N}_1 = \left[\begin{array}{ccc|cc} 2 & 2 & 3 & 2 & 2 \\ 3 & 3 & 2 & 2 & 3 \end{array}\right]', \mathbf{N}_2 = \left[\begin{array}{ccc|cc} 2 & 2 & 1 & 2 & 2 \\ 2 & 1 & 2 & 2 & 1 \\ 1 & 2 & 2 & 0 & 2 \end{array}\right]', \mathbf{N}_3 = \begin{bmatrix} 5 & 3 & 3 \\ 4 & 5 & 4 \end{bmatrix}$$

Let us assume that the influence of the preparations on the experimental units is measured by the number of p different traits, forming a p-variate vector of observations. Each p-variate observation is then determined by the dose of the preparation and also by $(p \times 1)$ vectors of row effects, column effects and random errors. As far as the relative potency of the preparations is concerned, the row and column effects have to be treated as nuisance parameters.

A general linear model for observations in the experiment may be written as follows:

$$\mathbf{Y} = \mathbf{XB} + \mathbf{E} \tag{1}$$

where

$$\mathbf{Y} = \begin{bmatrix} \mathbf{Y}_S \\ \mathbf{Y}_T \end{bmatrix}, \mathbf{X} = [\mathbf{D} \vdots \Delta], \mathbf{D} = \left[\begin{array}{c|c} \mathbf{D}_{1S} & \mathbf{D}_{2S} \\ \hline \mathbf{D}_{1T} & \mathbf{D}_{2T} \end{array}\right], = [\mathbf{D}_1 \ \ \mathbf{D}_2],$$

$$\Delta = \left[\begin{array}{cc|cc} \mathbf{1}_{n_S} & \mathbf{0} & \mathbf{x}_S & \mathbf{0} \\ \hline \mathbf{0} & \mathbf{1}_{n_T} & \mathbf{0} & \mathbf{x}_T \end{array}\right],$$

$$\mathbf{B} = \begin{bmatrix} \mathbf{B}_1 \\ \mathbf{B}_2 \end{bmatrix}, \mathbf{B}_1 = \begin{bmatrix} \boldsymbol{\omega} \\ \boldsymbol{\kappa} \end{bmatrix}, \mathbf{B}'_2 = [\boldsymbol{\alpha}_S, \boldsymbol{\alpha}_T, \boldsymbol{\beta}_S, \boldsymbol{\beta}_T], \mathbf{E} = \begin{bmatrix} \mathbf{E}_S \\ \mathbf{E}_T \end{bmatrix},$$

and $\mathbf{Y}$ is a $(n \times p)$ matrix whose rows are p-variate observations, $\mathbf{D}$ is a $(n \times (b_1 + b_2))$ binary matrix, whose submatrices $\mathbf{D}_{ij}$ $(i = 1, 2; j = S, T)$ are related to rows and columns effects for the standard and the test preparations, respectively, $\mathbf{1}_k$ denotes a vector of k units, $\mathbf{x}_S$ and $\mathbf{x}_T$ are vectors of the logarithms to base 10 of all applied doses of the preparations S and T arranged in the same order as the observations in $\mathbf{Y}$, $n = n_S + n_T$

and n_S, n_T are the numbers of experimental units where standard and test preparations are applied. Moreover, matrix $\mathbf{B}$ of unknown parameters consists of the matrices of row and column effects (nuisance effects), denoted by $\mathbf{B}_1$, and the matrix of intercept vectors and slope vectors for the standard and the test preparations. The rows of the matrix of errors – $\mathbf{E}$ are assumed to be independently and identically distributed as N_p ($\mathbf{0}'$, Σ), with Σ – a ($p \times p$) unknown covariance matrix.

III. HYPOTHESIS ABOUT PARALLELISM

Test preparation can be compared to the standard preparation by means of the relative potency when both have a similar impact on the experimental units. Such similarity occurs in the so called parallel-line assays (Finney (1952)). For such assays, in the model (1), the vectors of slopes have to be equal. This equality of the slopes vectors can be formulated as the following hypothesis of parallelism:

$$H_\beta^0 : \mathbf{C}'\mathbf{B} = \mathbf{0}' \text{ versus } H_\beta^1 : \mathbf{C}'\mathbf{B} \neq \mathbf{0}' \tag{2}$$

where $\mathbf{C}' = [\mathbf{0}'_{b_1+b_2}, \mathbf{c}']$, $\mathbf{c}' = [0, 0, 1, -1]$.

To test H_β^0 we can use *lambda Wilks'* statistic which takes a form:

$$\Lambda = \frac{|\mathbf{S}_E|}{|\mathbf{S}_E + \mathbf{S}_H|} \tag{3}$$

where $\mathbf{S}_E = (\mathbf{Y} - \mathbf{X}\tilde{\mathbf{B}})'(\mathbf{Y} - \mathbf{X}\tilde{\mathbf{B}})$, $\mathbf{S}_H = (\mathbf{C}'\tilde{\mathbf{B}})'(\mathbf{C}'(\mathbf{X}'\mathbf{X})^-\mathbf{C})^{-1}(\mathbf{C}'\tilde{\mathbf{B}})$, $\tilde{\mathbf{B}} = (\mathbf{X}'\mathbf{X})^-\mathbf{X}'\mathbf{Y}$.

By analogy, as in Hanusz (1995), instead of the form given in (3) we use a transformed form:

$$\Lambda = \left(1 + \frac{(\mathbf{C}'\tilde{\mathbf{B}})\mathbf{S}_E^{-1}(\mathbf{C}'\tilde{\mathbf{B}})'}{\mathbf{C}'(\mathbf{X}'\mathbf{X})^-\mathbf{C}}\right)^{-1} \tag{4}$$

Since *rank* $(\mathbf{C}') = 1$, $\dfrac{n\text{-}rank\ (\mathbf{X}) - p + 1}{p} \cdot \dfrac{1 - \Lambda}{\Lambda}$ has the F distribution with (p, n-*rank* $(\mathbf{X}) - p + 1$) degrees of freedom.

To calculate the test function in (4) and to prove testability of the hypothesis H_β^0 in (2) we give the general inverse to the matrix $\mathbf{X}'\mathbf{X}$. Note that $\mathbf{X}'\mathbf{X} = \left[\begin{array}{c|c} \mathbf{D}'\mathbf{D} & \mathbf{D}'\Delta \\ \hline \Delta'\mathbf{D} & \Delta'\Delta \end{array}\right]$ and $\mathbf{D}'\mathbf{D} = \left[\begin{array}{c|c} \mathbf{k}_1^\delta & \mathbf{N}_3 \\ \hline \mathbf{N}_3' & \mathbf{k}_2^\delta \end{array}\right]$, where $\mathbf{k}_1^\delta = \mathbf{D}_1'\mathbf{D}_1$ and

$\mathbf{k}_2^\delta = \mathbf{D}_2'\mathbf{D}_2$ are diagonal matrices having entries equal to row and column sizes, respectively, $\mathbf{N}_3$ is the incidence matrix defined in the previous section. It can be proved that the general inverse to $\mathbf{X}'\mathbf{X}$, satisfying the condition: $\mathbf{X}'\mathbf{X}(\mathbf{X}'\mathbf{X})^-\mathbf{X}'\mathbf{X} = \mathbf{X}'\mathbf{X}$, is a matrix of the following form:

$$(\mathbf{X}'\mathbf{X})^- = \left[\begin{array}{c|c} \mathbf{A}^- + \mathbf{A}^-\mathbf{D}'\Delta\mathbf{H}^-\Delta'\mathbf{D}\mathbf{A}^- & -\mathbf{A}^-\mathbf{D}'\Delta\mathbf{H}^- \\ \hline -\mathbf{H}^-\Delta'\mathbf{D}\mathbf{A}^- & \mathbf{H}^- \end{array}\right] \tag{5}$$

where $\mathbf{A}^- = (\mathbf{D}'\mathbf{D})^- = \left[\begin{array}{c|c} \mathbf{k}_1^{-\delta}(\mathbf{I}_{b_1} + \mathbf{N}_3\mathbf{C}^-\mathbf{N}_3'\mathbf{k}_1^{-\delta}) & -\mathbf{k}_1^{-\delta}\mathbf{N}_3\mathbf{C}^- \\ \hline -\mathbf{C}^-\mathbf{N}_3'\mathbf{k}_1^{-\delta} & \mathbf{C}^- \end{array}\right]$,

$\mathbf{C} = \mathbf{k}_2^\delta - \mathbf{N}_3'\mathbf{k}_1^{-\delta}\mathbf{N}_3$, $\mathbf{H} = \Delta'\Phi\Delta$, $\Phi = \mathbf{I}_n - \mathbf{D}\mathbf{A}^-\mathbf{D}' = \mathbf{I}_n - \mathbf{D}_1\mathbf{k}_1^{-\delta}\mathbf{D}_1' -$ $+ (\mathbf{D}_2 - \mathbf{D}_1\mathbf{k}_1^{-\delta}\mathbf{N}_3)\mathbf{C}^-(\mathbf{D}_2 - \mathbf{D}_1\mathbf{k}_1^{-\delta}\mathbf{N}_3)'$, $\mathbf{D}_1 = \begin{bmatrix}\mathbf{D}_{1S}\\ \mathbf{D}_{1T}\end{bmatrix}$, $\mathbf{D}_2 = \begin{bmatrix}\mathbf{D}_{2S}\\ \mathbf{D}_{2T}\end{bmatrix}$, $\mathbf{k}_1^{-\delta}$ denotes the inverse of $\mathbf{k}_1^\delta$, $\mathbf{C}^-$ and $\mathbf{H}^-$ – the general inverse to $\mathbf{C}$ and $\mathbf{H}$, respectively.

Using the general inverse in (5), testability of the hypothesis H_β^0 could be proved. First we prove a useful lemma.

Lemma 1. *The matrix* Φ *fulfils*: (i) $\Phi\mathbf{D} = \mathbf{0}$, (ii) $\Phi\mathbf{1}_n = \mathbf{0}$, (iii) $\Phi' = \Phi$, (iv) $\Phi\Phi = \Phi$.

Proof. Let us notice that

(i) $$\Phi\mathbf{D}_1 = \mathbf{D}_1 - \mathbf{D}_1\mathbf{k}_1^{-\delta}\underbrace{\mathbf{D}_1'\mathbf{D}_1}_{\mathbf{k}_1^\delta} - (\mathbf{D}_2 - \mathbf{D}_1\mathbf{k}_1^{-\delta}\mathbf{N}_3)\mathbf{C}^-(\underbrace{\mathbf{D}_2'\mathbf{D}_1}_{\mathbf{N}_3'} - \mathbf{N}_3'\mathbf{k}_1^{-\delta}\underbrace{\mathbf{D}_1'\mathbf{D}_1}_{\mathbf{k}_1^\delta}) = \mathbf{0}$$

$$\Phi\mathbf{D}_2 = \mathbf{D}_2 - \mathbf{D}_1\mathbf{k}_1^{-\delta}\underbrace{\mathbf{D}_1'\mathbf{D}_2}_{\mathbf{N}_3} - (\mathbf{D}_2 - \mathbf{D}_1\mathbf{k}_1^{-\delta}\mathbf{N}_3)\mathbf{C}^-(\underbrace{\mathbf{D}_2'\mathbf{D}_2}_{\mathbf{k}_2^\delta} - \mathbf{N}_3'\mathbf{k}_1^{-\delta}\underbrace{\mathbf{D}_1'\mathbf{D}_2}_{\mathbf{N}_3}) =$$

$$= \mathbf{D}_2 - \mathbf{D}_1\mathbf{k}_1^{-\delta}\mathbf{N}_3 - (\mathbf{D}_2 - \mathbf{D}_1\mathbf{k}_1^{-\delta}\mathbf{N}_3)\mathbf{C}^-\mathbf{C} = \mathbf{0}$$

and finally we get $\Phi\mathbf{D} = [\Phi\mathbf{D}_1, \Phi\mathbf{D}_2] = [\mathbf{0}, \mathbf{0}] = \mathbf{0}$.

In the second equality we used the fact that $(\mathbf{D}_2 - \mathbf{D}_1\mathbf{k}_1^{-\delta}\mathbf{N}_3)\ \mathbf{C}^-\mathbf{C} = \mathbf{D}_2 - \mathbf{D}_1\mathbf{k}_1^{-\delta}\mathbf{N}_3)$. It is proved in Lemma 2.1 of Przybyłowski and Walkowiak (1981).

(ii) $$\Phi\mathbf{1}_n = \mathbf{1}_n - \mathbf{D}_1\mathbf{k}_1^{-\delta}\underbrace{\mathbf{D}_1'\mathbf{1}_n}_{\mathbf{k}_1} - (\mathbf{D}_2 - \mathbf{D}_1\mathbf{k}_1^{-\delta}\mathbf{N}_3)\mathbf{C}^-(\underbrace{\mathbf{D}_2'\mathbf{1}_n}_{\mathbf{k}_2} - \mathbf{N}_3'\mathbf{k}_1^{-\delta}\underbrace{\mathbf{D}_1'\mathbf{1}_n}_{\mathbf{k}_3})$$

$$= \mathbf{1}_n - \mathbf{1}_n - (\mathbf{D}_2 - \mathbf{D}_1\mathbf{k}_1^{-\delta}\mathbf{N}_3)\mathbf{C}^-(\mathbf{k}_2 - \mathbf{k}_2) = \mathbf{0}_n$$

(iii) This equality holds since $\mathbf{I}_n - \mathbf{D}_1\mathbf{k}_1^{-\delta}\mathbf{D}_1)$ is symmetric and $(\mathbf{D}_2 - \mathbf{D}_1\mathbf{k}_1^{-\delta}\mathbf{N}_3)\ \mathbf{C}^-(\mathbf{D}_2' - \mathbf{N}_3'\mathbf{k}_1^{-\delta}\mathbf{D}_1')$ is invariant on the choice of general inverse to $\mathbf{C}$ (see Lemma 2.2 of Przybyłowski and Walkowiak (1981)). As $\mathbf{C}\mathbf{C}^{-}\mathbf{C} = \mathbf{C}$ so $\mathbf{C}'(\mathbf{C}^{-})'\mathbf{C}' = \mathbf{C}'$ and $\mathbf{C}' = \mathbf{C}$ so $\mathbf{C}(\mathbf{C}^{-})'\mathbf{C} = \mathbf{C}$ hence $(\mathbf{C}^{-})'$ is the general inverse to $\mathbf{C}$.

$$\text{(iv)}\ \Phi\Phi = \Phi - \mathbf{D}_1\mathbf{k}_1^{-\delta}\underbrace{\mathbf{D}_1'\Phi}_{0} - (\mathbf{D}_2 - \mathbf{D}_1\mathbf{k}_1^{-\delta}\mathbf{N}_3)\mathbf{C}^{-}(\underbrace{\mathbf{D}_2'\Phi}_{0} - \mathbf{N}_3'\mathbf{k}_1^{-\delta}\underbrace{\mathbf{D}_1'\Phi}_{0}) = \Phi$$

Theorem 1. *The hypothesis* $H_\beta^0 : \mathbf{C}'\mathbf{B} = \mathbf{0}'$ *is testable in the model* (1).

Proof. We prove that $\mathbf{C}'(\mathbf{X}'\mathbf{X})^{-}(\mathbf{X}'\mathbf{X}) = \mathbf{C}'$, the necessary and sufficient condition for testability of the hypothesis given by Rao (1965, § 4.1.2.), is fulfilled. Multiplying the general inverse given in (5) by $\mathbf{X}'\mathbf{X}$ in (1) and using the equality from Lemma 1, we obtain:

$$(\mathbf{X}'\mathbf{X})^{-}(\mathbf{X}'\mathbf{X}) = \left[\begin{array}{c|c} \mathbf{A}^{-}\mathbf{A} & \mathbf{A}^{-}\mathbf{D}'\Delta(\mathbf{I}_4 - \mathbf{H}^{-}\mathbf{H}) \\ \hline \mathbf{0} & \mathbf{H}^{-}\mathbf{H} \end{array}\right]$$

$$\mathbf{C}'(\mathbf{X}'\mathbf{X})^{-}(\mathbf{X}'\mathbf{X}) = [\mathbf{0}',\ \mathbf{c}'\mathbf{H}^{-}\mathbf{H}]$$

Now we have to show that $\mathbf{c}'\mathbf{H}^{-}\mathbf{H} = \mathbf{c}'$. From Lemma 2.2.4 (i) of Rao and Mitra (1971) this equality holds if and only if the space spanned by $\mathbf{c}'$ is included in the space spanned by the rows of matrix $\mathbf{H}$. It can be shown that rows of $\mathbf{H}$ are orthogonal to a vector $\mathbf{w} = [1, 1, 0, 0]'$ corresponding to only one zero eigenvalue of $\mathbf{H}$. Namely, $\Delta\mathbf{w} = \mathbf{1}_n$ and from (ii) of Lemma 1 we have $\mathbf{H}\mathbf{w} = \Delta'\Phi\Delta\mathbf{w} = \Delta'\Phi\Delta\mathbf{1}_n = \mathbf{0}'$ what denotes that the space spanned by $\mathbf{w}$ is an orthogonal complement to the space spanned the rows of $\mathbf{H}$. Moreover $\mathbf{c}'$ is also orthogonal to $\mathbf{w}$, therefore $\mathbf{c}'$ has to be included in the space spanned by the rows of $\mathbf{H}$. ▪

Using the general inverse in (5) lambda Wilks' statistic in (4) could be described in the following form:

$$\Lambda = \left(1 + \frac{(\mathbf{c}'\mathbf{H}^{-}\Delta'\Phi\mathbf{Y})\,\mathbf{S}_E^{-1}\,(\mathbf{c}'\mathbf{H}^{-}\Delta'\Phi\mathbf{Y})'}{\mathbf{c}'\mathbf{H}^{-}\mathbf{c}}\right)^{-1}$$

Actually, under the truthfulness of H_β^0, the value of test function F^0 is equal to:

$$F^0 = \frac{n - b_1 - b_2 - p - 2}{p} \cdot \frac{(\mathbf{c}'\mathbf{H}^{-}\Delta'\Phi\mathbf{Y})\,\mathbf{S}_E^{-1}\,(\mathbf{c}'\mathbf{H}^{-}\Delta'\Phi\mathbf{Y})'}{\mathbf{c}'\mathbf{H}^{-}\mathbf{c}}$$

IV. HYPOTHESIS ABOUT CONSTANT RELATIVE POTENCY

Let us assume that the hypothesis H^0_β in (2) is not rejected on a given significant level α. In further considerations we could take the same vector of slopes for both preparations and transform the general model (1) to the following form:

$$\mathbf{Y} = \tilde{\mathbf{X}}\mathbf{B} + \mathbf{E} \tag{6}$$

where

$$\tilde{\mathbf{X}} = \begin{bmatrix} \mathbf{D}_{1S} & \mathbf{D}_{2S} & \vdots & \mathbf{1}_{n_S} & \mathbf{0} & \vdots & \tilde{\mathbf{x}}_S \\ \mathbf{D}_{1T} & \mathbf{D}_{2T} & \vdots & \mathbf{0} & \mathbf{1}_{n_T} & \vdots & \tilde{\mathbf{x}}_T \end{bmatrix}, \quad \mathbf{B} = [\boldsymbol{\omega}' \ \boldsymbol{\kappa}' \quad \boldsymbol{\alpha}_S \, \boldsymbol{\alpha}_T \ \vdots \ \boldsymbol{\beta}]', \quad \mathbf{E} = \begin{bmatrix} \mathbf{E}_S \\ \mathbf{E}_T \end{bmatrix}$$

The hypothesis about the constant logarithm of the relative potency of preparations is of the following form:

$$H^0_\mu : \mathbf{C}'_\mu \mathbf{B} = \mathbf{0}' \text{ versus } H^1_\mu : \mathbf{C}'_\mu \mathbf{B} \neq \mathbf{0}' \tag{7}$$

where $\mathbf{C}'_\mu = [\mathbf{0}'_{b_1+b_2}, \mathbf{c}'_\mu]$, $\mathbf{c}'_\mu = [1, -1, -\mu]$

To test the hypothesis H^0_μ in (7) we use lambda-Wilks' statistic of the form given in (4), putting $\mathbf{C}'_\mu$ and $(\tilde{\mathbf{X}}'\tilde{\mathbf{X}})^-$ instead of $\mathbf{C}'$ and $(\mathbf{X}'\mathbf{X})^-$, respectively. The general inverse $(\tilde{\mathbf{X}}'\tilde{\mathbf{X}})^-$ could be obtained from the form given in (5) replacing Δ by $\tilde{\Delta} = \begin{bmatrix} \mathbf{1}_{n_S} & \mathbf{0} & \vdots & \mathbf{x}_S \\ \mathbf{0} & \mathbf{1}_{n_T} & \vdots & \mathbf{x}_T \end{bmatrix}$ and $\mathbf{H}$ by $\tilde{\mathbf{H}} = \tilde{\Delta}'\Phi\tilde{\Delta}$.

Theorem 2. The hypothesis $H^0_\mu : \mathbf{C}'_\mu \mathbf{B} = \mathbf{0}'$ is testable in the model (6).

Proof. As in Theorem 1 we show that the condition of testability $\mathbf{C}'_\mu(\tilde{\mathbf{X}}'\tilde{\mathbf{X}})^-(\tilde{\mathbf{X}}'\tilde{\mathbf{X}}) = \mathbf{C}'_\mu$ is fulfilled in the model (6). In this model we have:

$$(\mathbf{X}'\mathbf{X})^-(\mathbf{X}'\mathbf{X}) = \left[\begin{array}{c|c} \mathbf{A}^-\mathbf{A} & \mathbf{A}^-\mathbf{D}'\tilde{\Delta}(\mathbf{I}_3 - \tilde{\mathbf{H}}^-\tilde{\mathbf{H}}) \\ \hline \mathbf{0} & \tilde{\mathbf{H}}^-\tilde{\mathbf{H}} \end{array}\right]$$

$$\mathbf{C}'_\mu(\tilde{\mathbf{X}}'\tilde{\mathbf{X}})^-(\tilde{\mathbf{X}}'\tilde{\mathbf{X}}) = [\mathbf{0}', \ \mathbf{c}'_\mu\tilde{\mathbf{H}}^-\tilde{\mathbf{H}}]$$

As in the previous theorem, we will show that $\mathbf{c}'_\mu\tilde{\mathbf{H}}^-\tilde{\mathbf{H}} = \mathbf{c}'_\mu$. It can be proved that the rows of $\tilde{\mathbf{H}}$ as well as $\mathbf{c}_\mu$ are orthogonal to the same vector $\tilde{\mathbf{w}} = [1, \ 1, \ 0]$, which is the eigenvector corresponding to the only zero eigenvalue of $\tilde{\mathbf{H}}$. So the space spanned on $\mathbf{c}'_\mu$ is included in the space spanned on the columns of $\tilde{\mathbf{H}}$?

The test function for the hypothesis H^0_μ depends on μ and takes the following form:

$$\Lambda(\mu) = \left(1 + \frac{(\mathbf{C}'_\mu \tilde{\mathbf{B}}) \mathbf{S}_E^{-1} (\mathbf{C}'_\mu \tilde{\mathbf{B}})'}{\mathbf{C}'_\mu (\mathbf{X}'\mathbf{X})^- \mathbf{C}_\mu}\right)^{-1} = \left(1 + \frac{(\mathbf{c}'_\mu \tilde{\mathbf{H}}^- \tilde{\Delta}' \Phi \mathbf{Y}) \mathbf{S}_E^{-1} (\mathbf{c}'_\mu \tilde{\mathbf{H}}^- \tilde{\Delta}' \Phi \mathbf{Y})'}{\mathbf{c}'_\mu \mathbf{H}^- \mathbf{c}_\mu}\right)^{-1}$$

When the hypothesis H^0_μ is true then $-\left(n - r(\mathbf{X}) - \frac{p-1}{2} + \frac{1}{\min \Lambda(\mu)}\right) \cdot$ $\cdot\, ln\,(\Lambda(\mu))$ has the χ^2 distribution with (p-1) degrees of freedom (Williams (1988)). If for some value of $\hat{\mu}$ $\Lambda(\hat{\mu})$ reaches the maximum and $-\left(n - r(\mathbf{X}) - \right.$ $\left. + \frac{p-1}{2} + \frac{1}{\min \Lambda(\mu)}\right) \cdot ln\,(\Lambda(\hat{\mu}))$ does not exceed the critical value $\chi^2_{p-1}(a)$ on the significant level a, then we adopt $\hat{\mu}$ as the estimator of the logarithm of the relative potency.

V. CONCLUSIONS

Comparing the results obtained in the present paper to those given in Hanusz (1995, 1999) we can say that the hypothesis about parallelism is testable in both considered experiments with a two-way elimination of heterogeneity designs. The hypothesis about the relative potency is testable in the case when both preparations are administered jointly to experimental units, forming a two-way elimination of heterogeneity designs. The same hypothesis is not testable in the case when each preparation is applied in a different two-way elimination of heterogeneity design. In the latter case, to test the hypothesis we need to put a restriction on nuisance parameters.

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Zofia Hanusz

WIELOCECHOWE DOŚWIADCZENIA BIOLOGICZNE W UKŁADZIE Z DWUKIERUNKOWĄ ELIMINACJĄ NIEJEDNORODNOŚCI

(Streszczenie)

W pracy rozważa się problem testowalności dwóch hipotez związanych z estymacją względnej mocy dwóch preparatów stosowanych we wspólnym układzie z dwukierunkową eliminacją niejednorodności jednostek eksperymentalnych. Dla takiego układu przedstawia się model liniowy wielowymiarowych obserwacji, hipotezy związane z estymacją względnej mocy preparatów oraz funkcje testowe do weryfikacji hipotez zerowych. Dowodzi się, że obydwie hipotezy dla rozważanego układu doświadczalnego są testowalne.