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RELATIVE POTENCY IN REDUCED MULTIVARIATE LINEAR MODEL. PART I – THEORY

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To the memory of Professor Wiktor Oktaba for encouraging to undertake this topic

Summary

Estimation of relative potency of several test preparations with respect to one standard preparation is considered. The hypotheses about similarity of preparations and the relative potencies for multivariate responses and proper test functions are presented. Some reduction of full linear multivariate model to chosen test preparations or to some traits in responses is proposed. For such a reduced model, some choice matrices are defined. Proper hypotheses and test functions in the reduced model are presented.

Keywords and phrases: multivariate responses, reduced model, relative potency of preparations

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1. Introduction

Estimation of a potency of test preparation relative to a standard preparation for multivariate responses has been considered in many papers (e.g. Carter and Hubert, 1985; Hanusz, 1999; Meisner et al., 1986; Rao, 1954; Vølund, 1980).

The relative potency estimates a dose of the test preparation which produces the same response as unit dose of the standard preparation. In the paper we consider estimation of the relative potency for multidimensional responses, enclosed different measurable traits affected by preparations. In multivariate setting we expect that for all traits in the responses there exists common relative potency.

In the paper we consider estimation of potencies of several test preparations with respect to one standard preparation. Moreover, we restrict our attention to so called parallel–line assays, where responses give parallel regression lines opposite to logarithm of doses of the preparations. Without lost of generality, we regard completely randomized assays, where doses of the preparations are applied to homogenous experimental units. Additionally, we assume that responses are independent and have multidimensional normal distribution with the same covariance matrix.

In the relative potency estimation two hypotheses are of the main interest. The first one checks parallelism of assays, which confirms similarity of tests and the standard preparations. The second one checks whether vector of log relative potencies satisfies equality between model parameters. In practice, however, both hypotheses are not always accepted. Then, we can conclude that we are not allowed estimating relative potencies of all test preparations for considered responses. In the paper we offer another solution. Namely, we propose farther analysis considering chosen test preparations or some traits in responses. In both cases we define proper hypotheses and test functions.

In Section 2 we define full model of preparations. In Section 3 we formulate hypotheses and test functions. In Section 4 we present model and the hypotheses in the reduced model to some test preparations. In Section 5 we restrict our attention to some chosen traits in the responses. Some conclusion remarks are formulated in Section 6. Application of the theoretical results of the paper is presented in the second part.

2. Linear model of responses for preparations

Let us consider *t* test preparations: $T_1,...,T_t$ and one standard preparation *S*. Let us assume that preparations are applied in $\nu_i \geq 2$ doses $(i = S, T_1, \ldots, T_t)$, respectively. Let us denote by u_{ij} the *j*–th dose of the *i*–th preparation $(i = S, T_1, \ldots, T_t; j = 1, \ldots, \nu_i)$, and by x_{ij} the logarithm of the dose u_{ij} ($x_{ij} = \log u_{ij}$). We assume that each dose of preparation is administered to n_{ij} homogenous experimental units. Moreover, let us assume that preparations have impact on *p* traits producing *p*–variate response $\mathbf{y}_{ijk} = [y_{ijk1}, y_{ijk2}, \ldots, y_{ijkp}]'$,

$i = S, T_1, \ldots, T_t$; $j = 1, \ldots, \nu_i$; $k = 1, \ldots, n_{ij}$. Let responses be in linear relations with logarithms of doses, namely,

$$\mathbf{y}_{ijk} = \boldsymbol{\alpha}_i + \boldsymbol{\beta}_i x_{ij} + \mathbf{e}_{ijk}, \tag{2.1}$$

where $\boldsymbol{\alpha}_i = [\alpha_{i1}, \alpha_{i2}, \ldots, \alpha_{ip}]'$ denotes vector of intercepts, $\boldsymbol{\beta}_i = [\beta_{i1}, \beta_{i2}, \ldots, \beta_{ip}]'$ – vector of slopes, $\mathbf{e}_{ijk} = [e_{ijk1}, e_{ijk2}, \ldots, e_{ijkp}]'$ – vector of errors, $i = S, T_1, \ldots, T_t$; $j = 1, \ldots, \nu_i$; $k = 1, \ldots, n_{ij}$. We assume that $\mathbf{e}_{ijk}$ are independent and normally distributed with null mean and covariance matrix $\boldsymbol{\Sigma}$ of the size $p \times p$.

To describe the total model of observations, let us denote by $\mathbf{Y}_S, \mathbf{Y}_{T_1}, \ldots, \mathbf{Y}_{T_t}$ matrices containing all responses for the standard and test preparations, respectively. Namely

$$\mathbf{Y}_i = [\underbrace{\mathbf{y}_{i11}, \ldots, \mathbf{y}_{i1n_{i1}}}_{\text{responses for the first dose}}, \ldots, \underbrace{\mathbf{y}_{i\nu_i 1}, \ldots, \mathbf{y}_{i\nu_i n_{i\nu_i}}}_{\text{responses for the last dose}}]', \quad i = S, T_1, \ldots, T_t.$$

Then, the model of all observations can be described in the form

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\Theta} + \mathbf{E}, \tag{2.2}$$

where $\mathbf{Y} = [\mathbf{Y}_S', \mathbf{Y}_{T_1}', \ldots, \mathbf{Y}_{T_t}']'$ denotes $n \times p$ matrix of all responses, $\mathbf{X} = [\boldsymbol{\Delta}_{\boldsymbol{\alpha}}, \boldsymbol{\Delta}_{\boldsymbol{\beta}}]$ is known $n \times 2(1+t)$ design matrix, where $\boldsymbol{\Delta}_{\boldsymbol{\alpha}} = diag(\mathbf{1}_{n_S}, \mathbf{1}_{n_{T_1}}, \ldots, \mathbf{1}_{n_{T_t}})$ denotes block diagonal matrix having vectors of ones on the diagonal, and $\boldsymbol{\Delta}_{\boldsymbol{\beta}} = diag(\mathbf{x}_S, \mathbf{x}_{T_1}, \ldots, \mathbf{x}_{T_t})$ is block diagonal matrix having on the diagonal vectors of log of all administered doses of preparations, and $n_i = \sum_{j=1}^{\nu_i} n_{ij}$ denotes number of experimental units where i–th preparation was administered, $n = \sum_{i=S,T_1,\ldots,T_t} n_i$ is the total number of all experimental units. Moreover, $\boldsymbol{\Theta} = [\mathbf{A}', \mathbf{B}']'$, where $\mathbf{A}' = [\boldsymbol{\alpha}_S, \boldsymbol{\alpha}_{T_1}, \ldots, \boldsymbol{\alpha}_{T_t}]$

and $\mathbf{B}' = [\boldsymbol{\beta}_S, \boldsymbol{\beta}_{T_1}, \ldots, \boldsymbol{\beta}_{T_t}]$ denote unknown $p \times (t+1)$ matrices of intercepts and slopes, respectively, $\mathbf{E} = [\mathbf{E}'_S, \mathbf{E}'_{T_1}, \ldots, \mathbf{E}'_{T_t}]'$ is $n \times p$ matrix of errors connected with the matrix **Y**.

3. Estimation of relative potencies in parallel–line assays

Test preparations $T_1, ..., T_t$ can be compared with the standard preparation *S* by their relative potency if their impact on experimental units is similar. This similarity means that slopes in the model (2.2) are equal, i.e. the same change of dose of preparations should produce the same change of responses.

3.1. Testing similarity of preparations

Similarity of test preparations and the standard one is formulated by a following hypothesis

$$H_{\boldsymbol{\beta}}^0 : \mathbf{C}\boldsymbol{\Theta} = \mathbf{0}_{t \times p}, \tag{3.1}$$

where $\mathbf{C} = [\mathbf{0}_{t \times (t+1)}, -\mathbf{1}_t, \mathbf{I}_t]$, and $\mathbf{1}_t$ denotes vector of *t* ones, $\mathbf{I}_t$ – identity matrix of the size *t*. The hypothesis $H_{\boldsymbol{\beta}}^0$ is tested against the alternative $H_{\boldsymbol{\beta}}^1 : \mathbf{C}\boldsymbol{\Theta} \neq \mathbf{0}_{t \times p}$. It is easy to notice that the hypothesis in (3.1) is equivalent to $H_{\boldsymbol{\beta}}^0 : (\boldsymbol{\beta}_{T_1} = \boldsymbol{\beta}_S) \wedge (\boldsymbol{\beta}_{T_2} = \boldsymbol{\beta}_S) \wedge \ldots \wedge (\boldsymbol{\beta}_{T_t} = \boldsymbol{\beta}_S)$. The hypothesis (3.1) can be tested using *Lambda–Wilks* test function of the form (Krzyśko, 2000; Muirhead, 1982; Rao, 1973)

$$\Lambda = \frac{|\mathbf{SSE}|}{|\mathbf{SSE} + \mathbf{SSH}|}, \tag{3.2}$$

where

$$\mathbf{SSE} = (\mathbf{Y} - \mathbf{X}\hat{\boldsymbol{\Theta}})'(\mathbf{Y} - \mathbf{X}\hat{\boldsymbol{\Theta}}),$$

$$\hat{\boldsymbol{\Theta}} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}, \ \mathbf{SSH} = (\mathbf{C}\hat{\boldsymbol{\Theta}})'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\boldsymbol{\Theta}}),$$

and $|\ |$ denotes determinant.

The test statistic (3.2) can be transformed to the form (Meisner et al., 1986)

$$\Lambda = \frac{1}{\left|\mathbf{I}_t + [\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\mathbf{\Theta}})\mathbf{SSE}^{-1}(\mathbf{C}\hat{\mathbf{\Theta}})'\right|}. \tag{3.3}$$

When (3.1) is true then $-\left(n - rank(\mathbf{X}) - \frac{p-t+1}{2}\right)\ln\Lambda$ has an asymptotic χ^2_{pt} distribution with *pt* degrees of freedom.

The hypothesis $H^0_{\boldsymbol{\beta}}$ is rejected if $-\left(n - rank(\mathbf{X}) - \frac{p-t+1}{2}\right)\ln\Lambda > \chi^2_{pt,\alpha}$, where $\chi^2_{pt,\alpha}$ is a critical value of chi–square distribution for *pt* degrees of freedom and significant level α.

3.2. Hypothesis about relative potencies of test preparations

Test preparations are similar to the standard preparation if the hypothesis (3.1) is true (is not rejected). Let us assume that the hypothesis (3.1) is not rejected. Then the model (2.2) can be transformed to the following form

$$\mathbf{Y} = \tilde{\mathbf{X}}\tilde{\mathbf{\Theta}} + \tilde{\mathbf{E}}, \tag{3.4}$$

where $\tilde{\mathbf{X}} = [\mathbf{\Delta}_{\boldsymbol{\alpha}}, \mathbf{x}]$ is a new $n \times (t+2)$ design matrix containing the only one vector $\mathbf{x} = [\mathbf{x}'_S, \mathbf{x}'_{T_1}, \ldots, \mathbf{x}'_{T_t}]'$ instead of $\mathbf{\Delta}_{\boldsymbol{\beta}}$, $\tilde{\mathbf{\Theta}} = [\mathbf{A}', \boldsymbol{\beta}]'$, where $\mathbf{B}$ in $\mathbf{\Theta}$ of (2.2) is replaced by $\boldsymbol{\beta}$, the common vector of slopes for all preparations.
In the model (3.4) we test a second hypothesis about log relative potencies of the form

$$H^0_{\boldsymbol{\mu}} : \mathbf{C}_{\boldsymbol{\mu}}\tilde{\mathbf{\Theta}} = \mathbf{0}_{t \times p}, \tag{3.5}$$

where $\mathbf{C}_{\boldsymbol{\mu}} = [-\mathbf{1}_t, \mathbf{I}_t, \boldsymbol{\mu}]$ and $\boldsymbol{\mu} = [\mu_1, \ldots, \mu_t]'$ contains log potencies of test preparations $T_1, ..., T_t$ versus the standard preparation *S*. Let us note that the hypothesis (3.5) is equivalent to the hypothesis

$$\underset{i=1,\ldots,t}{\forall} \boldsymbol{\alpha}_{T_i} - \boldsymbol{\alpha}_S + \mu_i \boldsymbol{\beta} = \mathbf{0}_p .$$

The hypothesis (3.5) is tested using *Lambda–Wilks* test function

$$\Lambda(\boldsymbol{\mu}) = \frac{|\mathbf{SSE}|}{|\mathbf{SSE} + \mathbf{SSH}(\boldsymbol{\mu})|}, \tag{3.6}$$

$$\mathbf{SSE} = (\mathbf{Y} - \tilde{\mathbf{X}}\hat{\tilde{\boldsymbol{\Theta}}})'(\mathbf{Y} - \tilde{\mathbf{X}}\hat{\tilde{\boldsymbol{\Theta}}}),\ \hat{\tilde{\boldsymbol{\Theta}}} = (\tilde{\mathbf{X}}'\tilde{\mathbf{X}})^{-1}\tilde{\mathbf{X}}'\mathbf{Y},$$

$$\mathbf{SSH}(\boldsymbol{\mu}) = (\mathbf{C}_{\boldsymbol{\mu}}\hat{\tilde{\boldsymbol{\Theta}}})'[\mathbf{C}_{\boldsymbol{\mu}}(\tilde{\mathbf{X}}'\tilde{\mathbf{X}})^{-1}\mathbf{C}_{\boldsymbol{\mu}}']^{-1}(\mathbf{C}_{\boldsymbol{\mu}}\hat{\tilde{\boldsymbol{\Theta}}}).$$

It is easy to notice that the test function $\Lambda(\boldsymbol{\mu})$ depends on unknown vector $\boldsymbol{\mu}$. Truthfulness of $H_{\boldsymbol{\mu}}^0$ in (3.5) depends on maximum likelihood estimator $\hat{\boldsymbol{\mu}}$, which maximizes the test function (3.6) (Meisner et al., 1986). If the hypothesis $H_{\boldsymbol{\mu}}^0$ for $\hat{\boldsymbol{\mu}}$ is not rejected then $\hat{\boldsymbol{\mu}}$ is considered as estimate of $\boldsymbol{\mu}$. The hypothesis $H_{\boldsymbol{\mu}}^0$ is rejected if

$$-\left(n - rank(\tilde{\mathbf{X}}) - \frac{p-t+1}{2} + \frac{\min\Lambda(\boldsymbol{\mu})}{1-\min\Lambda(\boldsymbol{\mu})}\right)\ln\Lambda(\hat{\boldsymbol{\mu}}) > \chi^2_{pt,\alpha},$$

where $\min\Lambda(\boldsymbol{\mu})$ denotes minimum of $\Lambda(\boldsymbol{\mu})$ (Williams, 1988), and $\chi^2_{pt,\alpha}$ is a critical value of chi–square distribution for *pt* degrees of freedom and significant level α.

4. Estimation of relative potencies in reduced model

In the previous section, estimation of the vector of log relative potencies $\boldsymbol{\mu}$ of *t* test preparations relative to one standard preparation for *p* dimensional responses was presented. In practice, however, both hypotheses (3.1) and (3.5) are frequently not accepted. In such cases we propose to restrict consideration to some selected test preparations or some traits in responses. In this section we present a method which reduces the model (2.2) to a model which confirms

truthfulness of both hypotheses and in the consequence allows estimating the relative potencies.

Let us assume that we would like to select t^* test preparations: $T_{i_1},\cdots,T_{i_{t^*}}$ having similar impact on experimental units, where i_j $(j=1,\ldots,t^*)$ is an index of chosen test preparations. Consequently, in the model (2.2) we have to select in **Y** the responses of t^* tests preparations and the standard one. Similarly, from the matrix **X** we have to select the corresponding rows, and from the parameter matrix $\boldsymbol{\Theta}$ – the corresponding columns. Let us define two matrices **M** and $\mathbf{M}_1$. The matrix **M** will select the rows of **Y** and **X**, but the matrix $\mathbf{M}_1$ will choose the corresponding parameters from $\boldsymbol{\Theta}$ and columns from **X**.

The matrix **M** of the size $n^* \times n$, where $n^* = \sum_{i=S,T_{i_1},\ldots,T_{i_{t^*}}} n_i$, has the following form

$$\mathbf{M} = (\boldsymbol{\delta}_{ij})_{\substack{i=S,T_{i_1},\cdots,T_{i_{t^*}} \\ j=S,T_1,\cdots,T_t}}, \quad \boldsymbol{\delta}_{ij} = \begin{cases} \mathbf{I}_{n_i} & \text{for } i = j \\ \mathbf{0}_{n_i \times n_j} & \text{elsewhere} \end{cases}.$$

The matrix $\mathbf{M}_1$ of the size $2(t^*+1)\times 2(t+1)$ has the following form

$$\mathbf{M}_1 = \mathbf{I}_2 \otimes \boldsymbol{\Delta},\ \boldsymbol{\Delta} = (\delta_{ij})_{\substack{i=S,T_{i_1},\cdots,T_{i_{t^*}} \\ j=S,T_1,\cdots,T_t}},\ \delta_{ij} = \begin{cases} 1 & \text{for } i = j \\ 0 & \text{elsewhere} \end{cases},$$

where $\otimes$ denotes Kronecker product of matrices.
We illustrate constructions of **M** and $\mathbf{M}_1$ by Example 1.

Example 1. Let us consider experiment with two test preparations T_1 and T_2 and the standard preparation *S*, influenced on *p* measurable traits. The model (2.2) of the responses takes form

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\Theta} + \mathbf{E},$$

where $\mathbf{Y} = \begin{bmatrix} \mathbf{Y}_S \\ \mathbf{Y}_{T_1} \\ \mathbf{Y}_{T_2} \end{bmatrix}$ is of the size $n \times p$, $n = n_S + n_{T_1} + n_{T_2}$, $\mathbf{X} = [\boldsymbol{\Delta}_{\boldsymbol{\alpha}}, \boldsymbol{\Delta}_{\boldsymbol{\beta}}]$ is of the size $n \times 6$, where $\boldsymbol{\Delta}_{\boldsymbol{\alpha}} = \begin{bmatrix} \mathbf{1}_{n_S} & \mathbf{0}_{n_S} & \mathbf{0}_{n_S} \\ \mathbf{0}_{n_{T_1}} & \mathbf{1}_{n_{T_1}} & \mathbf{0}_{n_{T_1}} \\ \mathbf{0}_{n_{T_2}} & \mathbf{0}_{n_{T_2}} & \mathbf{1}_{n_{T_2}} \end{bmatrix}$, $\boldsymbol{\Delta}_{\boldsymbol{\beta}} = \begin{bmatrix} \mathbf{x}_S & \mathbf{0}_{n_S} & \mathbf{0}_{n_S} \\ \mathbf{0}_{n_{T1}} & \mathbf{x}_{T_1} & \mathbf{0}_{n_{T_1}} \\ \mathbf{0}_{n_{T_2}} & \mathbf{0}_{n_{T_2}} & \mathbf{x}_{n_{T_2}} \end{bmatrix}$, $\boldsymbol{\Theta} = \begin{bmatrix} \mathbf{A} \\ \mathbf{B} \end{bmatrix}$ is $6 \times p$ matrix of parameters, $\mathbf{A} = [\boldsymbol{\alpha}_S, \boldsymbol{\alpha}_{T_1}, \boldsymbol{\alpha}_{T_2}]'$, $\mathbf{B} = [\boldsymbol{\beta}_S, \boldsymbol{\beta}_{T_1}, \boldsymbol{\beta}_{T_2}]'$.

Let us assume that we would like to select observations connected with the standard and second test preparation. The $(n_S + n_{T_2}) \times n$ matrix $\mathbf{M}$ has the form

$$\mathbf{M} = \begin{bmatrix} \mathbf{I}_{n_S} & \mathbf{0}_{n_S \times n_{T_1}} & \mathbf{0}_{n_S \times n_{T_2}} \\ \mathbf{0}_{n_{T_2} \times n_S} & \mathbf{0}_{n_{T_2} \times n_{T_1}} & \mathbf{I}_{n_{T_2}} \end{bmatrix}.$$

The matrix $\mathbf{M}_1$ is equal to $\mathbf{M}_1 = \mathbf{I}_2 \otimes \boldsymbol{\Delta}$, where $\boldsymbol{\Delta} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix}$.

It is easy to show that

$$\mathbf{MY} = \begin{bmatrix} \mathbf{Y}_S \\ \mathbf{Y}_{T_2} \end{bmatrix}, \quad \mathbf{MXM}_1' = \begin{bmatrix} \mathbf{1}_{n_S} & \mathbf{0}_{n_S} & \mathbf{x}_S & \mathbf{0}_{n_S} \\ \mathbf{0}_{n_{T_2}} & \mathbf{1}_{n_{T_2}} & \mathbf{0}_{n_{T_2}} & \mathbf{x}_{T_2} \end{bmatrix},$$

$\mathbf{M}_1\boldsymbol{\Theta} = [\boldsymbol{\alpha}_S, \boldsymbol{\alpha}_{T_2}, \boldsymbol{\beta}_S, \boldsymbol{\beta}_{T_2}]'$. ■

Using matrices $\mathbf{M}$ and $\mathbf{M}_1$ the model (2.2) takes the following form

$$\mathbf{Y}_1 = \mathbf{X}_1\boldsymbol{\Theta}_1 + \mathbf{E}_1, \tag{4.1}$$

where $\mathbf{Y}_1 = \mathbf{MY}$, $\mathbf{X}_1 = \mathbf{MXM}_1'$, $\boldsymbol{\Theta}_1 = \mathbf{M}_1\boldsymbol{\Theta}$.

Under the assumption of Section 2, observations matrix $\mathbf{Y}_1$ in (4.1) has $n^* \times p$ variate normal distribution $\mathbf{Y}_1 \sim N_{n^* \times p}(\mathbf{X}_1\mathbf{\Theta}_1, \mathbf{I}_{n^*} \otimes \mathbf{\Sigma}_1)$, where $\mathbf{\Sigma}_1$ is unknown $p \times p$ covariance matrix. Maximum likelihood estimators of $\mathbf{\Theta}_1$ and $\mathbf{\Sigma}_1$ are given by $\hat{\mathbf{\Theta}}_1 = (\mathbf{X}_1'\mathbf{X}_1)^{-1}\mathbf{X}_1'\mathbf{Y}_1$ and $\hat{\mathbf{\Sigma}}_1 = \frac{1}{n^*}(\mathbf{Y}_1 - \mathbf{X}_1\hat{\mathbf{\Theta}}_1)'(\mathbf{Y}_1 - \mathbf{X}_1\hat{\mathbf{\Theta}}_1)$.

4.1. Testing similarity of the selected test preparations

The hypothesis about equality of slopes vectors for the standard and the selected test preparations has a following form

$$H_{\boldsymbol{\beta}}^0 : \mathbf{C}\mathbf{\Theta}_1 = \mathbf{0}_{t^* \times p}, \tag{4.2}$$

where $\mathbf{C} = [\mathbf{0}_{t^* \times (t^*+1)}, -\mathbf{1}_{t^*}, \mathbf{I}_{t^*}]$.

Lambda–Wilks test statistic in (3.3) for the hypothesis (4.2) has the form

$$\Lambda = \frac{1}{\left|\mathbf{I}_{t^*} + \frac{1}{n^*}[\mathbf{C}(\mathbf{X}_1'\mathbf{X}_1)^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\mathbf{\Theta}}_1)\hat{\mathbf{\Sigma}}_1^{-1}(\mathbf{C}\hat{\mathbf{\Theta}}_1)'\right|}.$$

If the hypothesis (4.2) is true then $-\left(n^* - rank(\mathbf{X}_1) - \frac{p - t^* + 1}{2}\right)\ln\Lambda$ has asymptotical $\chi^2_{pt^*}$ central distribution with pt^* degrees of freedom. The hypothesis (4.2) is rejected to the alternative $H_{\boldsymbol{\beta}}^1 : \mathbf{C}\mathbf{\Theta}_1 \neq \mathbf{0}_{t^* \times p}$ if $-\left(n^* - rank(\mathbf{X}_1) - \frac{p - t^* + 1}{2}\right)\ln\Lambda > \chi^2_{pt^*,\alpha}$, where $\chi^2_{pt^*,\alpha}$ is a critical value of chi–square distribution for pt^* degrees of freedom and significant level α.

4.2. Potencies of the selected test preparations relative to one standard preparation

Let us assume that the hypothesis (4.2) is accepted, so we can assume that t^* test preparations have similar impact on experimental units as the standard preparation. Identically to subsection 3.2 we modify the model (4.1), taking in $\boldsymbol{\Theta}_1$ the only one $\boldsymbol{\beta}$ instead of $[\boldsymbol{\beta}_S, \boldsymbol{\beta}_{T_{i_1}}, \ldots, \boldsymbol{\beta}_{T_{i_{t^*}}}]$. Then, the model (4.2) takes a form

$$\mathbf{Y}_1 = \tilde{\mathbf{X}}_1 \tilde{\boldsymbol{\Theta}}_1 + \tilde{\mathbf{E}}_1, \tag{4.3}$$

where $\tilde{\mathbf{X}}_1 = [\mathbf{M}\boldsymbol{\Delta}_{\boldsymbol{\alpha}}\boldsymbol{\Delta}', \mathbf{M}\mathbf{x}]$ is $n^* \times (t^* + 2)$ matrix, and $\tilde{\boldsymbol{\Theta}}_1 = \begin{bmatrix} \boldsymbol{\Delta}\mathbf{A} \\ \boldsymbol{\beta}' \end{bmatrix}$ is $(t^* + 2) \times p$ matrix.

The hypothesis about potencies of selected t^* test preparations relative to the standard preparation has the form

$$H^0_{\boldsymbol{\mu}^*} : \mathbf{C}_{\boldsymbol{\mu}^*} \tilde{\boldsymbol{\Theta}}_1 = \mathbf{0}_p, \tag{4.4}$$

where $\mathbf{C}_{\boldsymbol{\mu}^*} = [-\mathbf{1}_{t^*}, \mathbf{I}_{t^*}, \boldsymbol{\mu}^*]$, $\boldsymbol{\mu}^* = [\mu_{i_1}, \ldots, \mu_{i_{t^*}}]'$.

Lambda–Wilks test statistic for the hypothesis $H^0_{\boldsymbol{\mu}^*}$ in (4.4) takes the following form

$$\Lambda(\boldsymbol{\mu}^*) = \frac{1}{\left| \mathbf{I}_{t^*} + \frac{1}{n^*} [\mathbf{C}_{\boldsymbol{\mu}^*} (\tilde{\mathbf{X}}_1' \tilde{\mathbf{X}}_1)^{-1} \mathbf{C}_{\boldsymbol{\mu}^*}']^{-1} (\mathbf{C}_{\boldsymbol{\mu}^*} \hat{\tilde{\boldsymbol{\Theta}}}_1) \hat{\tilde{\boldsymbol{\Sigma}}}_1^{-1} (\mathbf{C}_{\boldsymbol{\mu}^*} \hat{\tilde{\boldsymbol{\Theta}}}_1)' \right|},$$

where $\hat{\tilde{\boldsymbol{\Theta}}}_1 = (\tilde{\mathbf{X}}_1' \tilde{\mathbf{X}}_1)^{-1} \tilde{\mathbf{X}}_1' \mathbf{Y}_1$, $\hat{\tilde{\boldsymbol{\Sigma}}}_1 = \frac{1}{n^*} (\mathbf{Y}_1 - \tilde{\mathbf{X}}_1 \hat{\tilde{\boldsymbol{\Theta}}}_1)' (\mathbf{Y}_1 - \tilde{\mathbf{X}}_1 \hat{\tilde{\boldsymbol{\Theta}}}_1)$.

The hypothesis $H^0_{\boldsymbol{\mu}^*}$ is rejected to the alternative $H^1_{\boldsymbol{\mu}^*} : \mathbf{C}_{\boldsymbol{\mu}^*} \tilde{\boldsymbol{\Theta}}_1 \neq \mathbf{0}_p$ if

$$-\left(n^* - rank(\tilde{\mathbf{X}}_1) - \frac{p - t^* + 1}{2} + \frac{\min\Lambda(\boldsymbol{\mu}^*)}{1 - \min\Lambda(\boldsymbol{\mu}^*)}\right)\ln\Lambda(\hat{\boldsymbol{\mu}}^*) > \chi^2_{pt^*,\alpha},$$

where $\chi^2_{pt^*,\alpha}$ is critical value of chi–square distribution for pt^* degrees of freedom and significance level α.

5. Potencies of test preparations relative to the standard preparation for chosen traits

Rejection of the hypotheses $H^0_{\boldsymbol{\beta}}$ or $H^0_{\boldsymbol{\mu}}$ can be caused by a large number of traits (columns) in the responses matrix **Y** in (2.2). The experimenter could decide which traits play the most important role and restrict attention to them. In this section we present this kind of reduction of model (2.2).

5.1. Linear model for selected traits

Let *t* test preparations be compared to one standard preparation having influence on *p* measurable traits. Let us assume that the hypotheses $H^0_{\boldsymbol{\beta}}$ or $H^0_{\boldsymbol{\mu}}$ have been rejected. Next, let us assume that we decide to restrict estimation of relative potencies to chosen p^* from *p* traits $(p^* < p)$. Then, in **Y** and $\boldsymbol{\Theta}$ in model (2.2) we select columns due to p^* selected traits. Let **P** be $p \times p^*$ matrix defined as follows

$$\mathbf{P} = (\delta_{ij})_{\substack{i=1,\ldots,p \\ j=i_1,\ldots,i_{p^*}}}, \quad \delta_{ij} = \begin{cases} 1 & \text{where } i = j \\ 0 & \text{elsewhere} \end{cases}. \tag{5.1}$$

Linear model for p^* selected traits takes a form

$$\mathbf{Y}_2 = \mathbf{X}\boldsymbol{\Theta}_2 + \mathbf{E}_2. \tag{5.2}$$

New matrix of responses $\mathbf{Y}_2 = \mathbf{YP}$ has $n \times p^*$ variate normal distribution $\mathbf{YP} \sim N_{n \times p^*}(\mathbf{X}\boldsymbol{\Theta}_2, \mathbf{I}_n \otimes \boldsymbol{\Sigma}_2)$, with unknown parameter matrix $\boldsymbol{\Theta}_2 = \boldsymbol{\Theta}\mathbf{P}$ and

unknown $p^* \times p^*$ covariance matrix $\boldsymbol{\Sigma}_2$. Maximum likelihood estimators of $\boldsymbol{\Theta}_2$ and $\boldsymbol{\Sigma}_2$ are equal to $\hat{\boldsymbol{\Theta}}_2 = \hat{\boldsymbol{\Theta}}\mathbf{P}$ and $\hat{\boldsymbol{\Sigma}}_2 = \mathbf{P}'\hat{\boldsymbol{\Sigma}}\mathbf{P}$, respectively, where $\hat{\boldsymbol{\Theta}}$ and $\hat{\boldsymbol{\Sigma}} = \mathbf{SSE}/n$ are given in (3.2).
The construction of the matrix **P** we illustrate by Example 2.

Example 2. Let us consider an experiment where five traits $(p = 5)$ were measured for doses of two test preparations T_1 and T_2 and the standard preparation *S*. Responses in the experiment can be defined as follows

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\Theta} + \mathbf{E},$$

where **Y**, **X**, $\boldsymbol{\Theta}$ and **E** are the same as in Example 1 with $p = 5$. Let $\mathbf{y}_i$ $(i = 1,\ldots,5)$ be the *i*–th column of **Y**. Then $\mathbf{Y} = [\mathbf{y}_1, \mathbf{y}_2, \mathbf{y}_3, \mathbf{y}_4, \mathbf{y}_5]$. Analogously, columns of $\boldsymbol{\Theta}$ we denote by $\boldsymbol{\theta}_i$ $(i = 1,\ldots,5)$, so $\boldsymbol{\Theta} = [\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, \boldsymbol{\theta}_3, \boldsymbol{\theta}_4, \boldsymbol{\theta}_5]$. Let as assume that we select $p^* = 3$ traits, namely, second, third and fifth. Then the 5×3 matrix **P** has a form $\mathbf{P} = \begin{bmatrix} 0 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix}$.
It is easy to see that $\mathbf{Y}_2 = \mathbf{YP} = [\mathbf{y}_2, \mathbf{y}_3, \mathbf{y}_5]$, and $\boldsymbol{\Theta}_2 = \boldsymbol{\Theta}\mathbf{P} = [\boldsymbol{\theta}_2, \boldsymbol{\theta}_3, \boldsymbol{\theta}_5]$.

5.2. Testing similarity of preparations for selected traits

The similarity of test preparations with the standard one using the selected p^* traits in **Y** is expressed by the hypothesis

$$H_{\boldsymbol{\beta}}^0 : \mathbf{C}\boldsymbol{\Theta}_2 = \mathbf{0}_{t \times p^*}, \tag{5.3}$$

where $\mathbf{C} = [\mathbf{0}_{t \times (t+1)}, -\mathbf{1}_t, \mathbf{I}_t]$ is the same as in (3.1).

Lambda–Wilks test statistic for (5.3) takes the form

$$\Lambda = \frac{\left|\mathbf{P}'(\mathbf{SSE})\mathbf{P}\right|}{\left|\mathbf{P}'(\mathbf{SSE}+\mathbf{SSH})\mathbf{P}\right|},$$

where **SSE** and **SSH** are given in (3.2). This function can be also described as

$$\Lambda = \frac{1}{\left|\mathbf{I}_t + \frac{1}{n}\left[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}'\right]^{-1}(\mathbf{C}\hat{\boldsymbol{\Theta}}_2)\hat{\boldsymbol{\Sigma}}_2^{-1}(\mathbf{C}\hat{\boldsymbol{\Theta}}_2)'\right|}.$$

The hypothesis (5.3) is rejected to the alternative $H_{\boldsymbol{\beta}}^1 : \mathbf{C}\boldsymbol{\Theta}_2 \neq \mathbf{0}_{t\times p^*}$ if

$$-\left(n - rank(\mathbf{X}) - \frac{p^* - t + 1}{2}\right)\ln\Lambda > \chi^2_{p^*t,\alpha},$$

where $\chi^2_{p^*t,\alpha}$ is critical value for p^*t degrees of freedom and significance level α.

5.3. Potencies of test preparations relative to standard preparation for selected traits

If the hypothesis (5.3) is true then we conclude that test preparations are similar to standard preparation for p^* selected traits. Then, we take in model (5.2) the same vector of slopes and get the following model

$$\mathbf{Y}_2 = \tilde{\mathbf{X}}\tilde{\boldsymbol{\Theta}}_2 + \tilde{\mathbf{E}}_2, \tag{5.4}$$

where $\tilde{\boldsymbol{\Theta}}_2 = \tilde{\boldsymbol{\Theta}}\mathbf{P}$, and $\tilde{\boldsymbol{\Theta}}$, $\tilde{\mathbf{X}}$ are defined in (3.4). The $n\times p^*$ matrix $\mathbf{Y}_2 = \mathbf{YP}$ in (5.2) is normally distributed, $\mathbf{Y}_2 \sim N_{n\times p^*}(\tilde{\mathbf{X}}\tilde{\boldsymbol{\Theta}}_2, \mathbf{I}_n \otimes \tilde{\boldsymbol{\Sigma}}_2)$.

The hypothesis about relative potencies takes a form:

$$H_{\boldsymbol{\mu}}^0 : \mathbf{C}_{\boldsymbol{\mu}}\tilde{\boldsymbol{\Theta}}_2 = \mathbf{0}_{t\times p^*}, \tag{5.5}$$

where $\mathbf{C}_{\boldsymbol{\mu}} = [-\mathbf{1}_t, \mathbf{I}_t, \boldsymbol{\mu}]$, $\boldsymbol{\mu} = [\mu_1, \ldots \mu_t]'$.

Lambda–Wilks test statistic for (5.5) against the alternative $H_{\boldsymbol{\mu}}^1 : \mathbf{C}_{\boldsymbol{\mu}} \tilde{\boldsymbol{\Theta}}_2 \neq \mathbf{0}_{t \times p^*}$ takes the form

$$\Lambda(\boldsymbol{\mu}) = \frac{1}{\left| \mathbf{I}_t + \frac{1}{n} [\mathbf{C}_{\boldsymbol{\mu}} (\tilde{\mathbf{X}}' \tilde{\mathbf{X}})^{-1} \mathbf{C}_{\boldsymbol{\mu}}']^{-1} (\mathbf{C}_{\boldsymbol{\mu}} \hat{\tilde{\boldsymbol{\Theta}}}_2) \hat{\tilde{\boldsymbol{\Sigma}}}_2^{-1} (\mathbf{C}_{\boldsymbol{\mu}} \hat{\tilde{\boldsymbol{\Theta}}}_2)' \right|}, \qquad (5.6)$$

where $\hat{\tilde{\boldsymbol{\Theta}}}_2 = \hat{\tilde{\boldsymbol{\Theta}}} \mathbf{P}$ and $\hat{\tilde{\boldsymbol{\Sigma}}}_2 = \mathbf{P}' \hat{\tilde{\boldsymbol{\Sigma}}} \mathbf{P}$, and $\hat{\tilde{\boldsymbol{\Theta}}}$, $\hat{\tilde{\boldsymbol{\Sigma}}} = \mathbf{SSE}/n$ are defined in (3.6). The hypothesis (5.5) is rejected if

$$-\left(n - rank(\tilde{\mathbf{X}}) - \frac{p^* - t + 1}{2} + \frac{\min \Lambda(\boldsymbol{\mu})}{1 - \min \Lambda(\boldsymbol{\mu})} \right) \ln \Lambda(\hat{\boldsymbol{\mu}}) > \chi^2_{p^* t, \alpha},$$

where $\hat{\boldsymbol{\mu}} = [\hat{\mu}_1, \hat{\mu}_2, \ldots, \hat{\mu}_t]'$ denotes the vector maximizing $\Lambda(\boldsymbol{\mu})$. If the hypothesis (5.5) is not rejected than $\hat{\boldsymbol{\mu}}$ is taken as an estimator of $\boldsymbol{\mu} = [\mu_1, \ldots, \mu_t]'$.

6. Conclusion

In the paper the estimation of relative potencies of several test preparations with respect to one standard preparation is considered. We proposed some methods of act if the hypothesis about similarity of preparations or hypothesis about log relative potency is rejected. In the first method we proposed estimation of relative potencies of the selected test preparations. In the second method we propose to select some traits in responses. Both methods can be applied simultaneously. Application of proposed methods is presented in the second part of the paper.

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