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Convexity issues in multivariate multiple testing of treatments vs. control

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ABSTRACT

The problem of multiple testing of each of several treatment mean vectors versus a control mean vector is considered. Both one-sided and two-sided alternatives are treated. It is shown that typical choices for marginal test procedures will lead to step-down procedures that do not have convex acceptance regions. This lack of convexity has both intuitive and theoretical disadvantages. The only exception being linear tests in the one-sided problem. Although such a procedure is atypical, it not only has convex acceptance regions but is such that critical values are obtainable so that the overall procedure can control FDR or FWER.

For both one-sided and two-sided alternatives, two other stepwise multiple testing methods are presented that do have convex acceptance regions.

1. Introduction and summary

There is, of late, considerable developing interest in treatments versus control models involving two or more co-primary endpoints with the aim of providing a comprehensive picture of the intervention's benegfits. It is often the case that a product or treatment is required to perform well in, at least, two areas. Very common occurrences involve the use of blood tests. For example, one can compare a new treatment effecting several blood analytes (perhaps cholesterol, triglycerides, etc.) with a control. In a recent clinical trials study Bliss, Balser, Horobin and Keegan [1] study aspects of mesothelioma. For another recent example see also [10] where trials concern asthma and COPD. A way to describe multiple testing in such cases is to call it multivariate multiple testing in treatment vs. control models.

This paper is concerned with multiple testing of treatments vs. control in the multivariate case. The model entails $K+1$ independent $p \times 1$ random vectors assumed to be normal with mean vectors, $\boldsymbol{\mu}_i,\ i = 1, \dots, K+1$ and known covariance matrix Σ. Population $K+1$ represents the control so that the K null hypotheses are $H_i : \boldsymbol{\mu}_i = \boldsymbol{\mu}_{K+1},\ i = 1, \dots, K$. We consider separately one-sided alternatives $K_i : \boldsymbol{\mu}_i - \boldsymbol{\mu}_{K+1} \geq \mathbf{0} \setminus H_i$ and two-sided alternatives $K_i : \boldsymbol{\mu}_i - \boldsymbol{\mu}_{K+1} \neq \mathbf{0}$.

Step-wise multiple testing procedures are valuable because they are less conservative than standard single-step procedures which often rely on Bonferroni critical values. In other words they are more powerful than their single-step counterparts. In constructing step-wise testing procedures it is common to begin with tests for the individual hypothesis testing problems that are known to have desirable properties. For example the tests may be UMPU, they may have invariance properties and would very likely have convex acceptance regions. Then a sequential component is added that ultimately tells us which hypotheses to accept or reject at each step and when to stop.

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Here, our starting point is the realization that all step-wise procedures induce new tests on the individual testing problems. Carrying out a step-wise procedure in a multiple hypothesis testing problem is equivalent to applying these induced tests separately to the individual hypotheses. Thus, if the induced individual tests can be improved, then the entire procedure is improved. Due to the sequential component, the nature of these induced tests is typically complicated and overlooked. Unfortunately they frequently do not retain all the desirable properties that the original tests possessed.

In the univariate normal case, the marginal test will always have an acceptance region that is an (possibly infinite) interval. Then the step-down multiple testing method for treatments vs. control, one-sided alternative, has two very desirable properties. Namely, the induced individual tests of each treatment vs. control has convex acceptance regions (see [3]). Secondly, results of Sarkar [14] ensure that critical values are available so that the test can control either FWER or FDR. On the other hand, for two-sided alternatives Cohen and Sackrowitz [4] have proven that the step-down method leads to induced individual tests that do not have convex acceptance regions.

In the multivariate setting there are many reasonable choices for a marginal test, all having convex acceptance regions. In this paper we focus on convexity of the induced acceptance regions. When performing tests on vector means convexity of the acceptance region is an important, intuitive, practical property. It is also an important theoretical property as tests lacking this property fall outside the complete class of tests described in [11]. One implication of this is that no Bayesian approach would lead to a procedure that lacks this convexity. Thus no prior distribution can be used to explain a lack of the convexity property. We show that for virtually all choices of marginal tests with convex acceptance regions the individual tests induced by the step-down method will NOT have convex acceptance regions. In light of the previous result mentioned concerning the univariate case this is a very surprising and important result.

The only exception to the above negative results being linear tests in the one-sided problem. Although such a procedure is atypical, it not only has convex acceptance regions but is such that critical values are obtainable so that the overall procedure can control FDR or FWER.

Methods given in [6,2] can be used to develop procedures that do have convex acceptance regions in both the one-sided and two-sided cases.

In the next section the precise models are given. Section 3 contains the basic ideas that the results are based on. It also contains the negative results regarding step-down procedures in both the one-sided and two-sided alternative situations. Section 4 is concerned with a step-down procedure for the one-sided alternative based on linear statistics. Section 5 offers procedures in the one-sided and two-sided cases that do have individual tests with convex acceptance regions.

We note that the step-down procedure in multivariate models has been used by Imada and Douke [8]. We also note that Cohen, Sackrowitz and Xu [5] have previously suggested one of the procedures in Section 5 in the multivariate case, but, had not established its convexity.

2. Models and preliminaries

Let $\mathbf{X}_1, \ldots, \mathbf{X}_{K+1}$ be independent $p \times 1$ random vectors where $\mathbf{X}$ has a $N(\boldsymbol{\mu_i}, \Sigma)$ distribution and $\boldsymbol{\mu}_i$ is unknown and Σ is a known positive definite matrix. We designate population $(K+1)$ as the control population and wish to test either a one or two sided alternative. The one sided problem tests the hypotheses $H_i : \boldsymbol{\mu}_i - \boldsymbol{\mu}_{K+1} = \mathbf{0}$ vs. $K_i : \boldsymbol{\mu}_i - \boldsymbol{\mu}_{K+1} \geq \mathbf{0} \setminus H_i$ for all $i = i, \ldots, K$. The two sided problem tests $H_i : \boldsymbol{\mu}_i - \boldsymbol{\mu}_{K+1} = \mathbf{0}$ vs. $K_i : \boldsymbol{\mu}_i - \boldsymbol{\mu}_{K+1} \neq \mathbf{0}$ for all $i = i, \ldots, K$.

We will consider vectors $\mathbf{Y}_i = \mathbf{X}_i - \mathbf{X}_{K+1}$ which are normal with mean vector $\boldsymbol{\nu}_i = \boldsymbol{\mu}_i - \boldsymbol{\mu}_{K+1}$. The $pK \times 1$ vector $\widetilde{\mathbf{Y}} = (\mathbf{Y}_1', \mathbf{Y}_2', \ldots, \mathbf{Y}_K')'$ is then normal with mean vector $\widetilde{\boldsymbol{\nu}} = (\boldsymbol{\nu}_1{}', \boldsymbol{\nu}_2{}', \ldots, \boldsymbol{\nu}_K{}')'$ and covariance matrix

$$V = \Omega \otimes \Sigma \tag{1}$$

where $\Omega = (\omega_{ij})$ with $\omega_{ii} = 2,\ i = 1, \ldots, p$ and $\omega_{ij} = 1$ for $i \neq j$.

We mention that $V^{-1} = \Omega^{-1} \otimes \Sigma^{-1}$ where Ω^{-1} has all its diagonal elements $= K/(K+1)$ and all off diagonal elements $= -1/(K+1)$.

The joint density of $\widetilde{\mathbf{Y}}$ is

$$(2\pi)^{-Kp/2}\, |V|^{1/2} \exp -1/2(\widetilde{\mathbf{y}} - \widetilde{\boldsymbol{\nu}})' V^{-1} (\widetilde{\mathbf{y}} - \widetilde{\boldsymbol{\nu}}) \tag{2}$$

which can be written as

$$(2\pi)^{-Kp/2}\, |V|^{1/2}\ \exp -(\widetilde{\mathbf{y}}' V^{-1} \widetilde{\mathbf{y}})/2\ \exp -(\widetilde{\boldsymbol{\nu}}' V^{-1} \widetilde{\boldsymbol{\nu}})/2\ \exp(\widetilde{\mathbf{y}}' V^{-1} \widetilde{\boldsymbol{\nu}}). \tag{3}$$

Since we will be concerned with each of the individual tests, without loss of generality, we focus on H_1 vs. K_1. If we let

$$\widetilde{\mathbf{U}} = V^{-1} \widetilde{\mathbf{Y}} \ \Leftrightarrow\ \widetilde{\mathbf{Y}} = V \widetilde{\mathbf{U}} \tag{4}$$

we can express (3) in exponential family form as

$$\beta(\widetilde{\boldsymbol{\nu}}) h(\widetilde{\mathbf{u}})\ \exp \widetilde{\mathbf{u}}' \widetilde{\boldsymbol{\nu}} = \beta(\widetilde{\boldsymbol{\nu}}) h(\widetilde{\mathbf{u}})\ \exp(\mathbf{u}_1' \boldsymbol{\nu}_1 + \mathbf{u}^{(1)'} \widetilde{\boldsymbol{\nu}}^{(1)}) \tag{5}$$

where $\mathbf{u}_1$ is the $p \times 1$ vector consisting of the first p components of $\widetilde{\mathbf{u}}$, $\mathbf{u}^{(1)}$ are the remaining $(K-1)p$ components of $\widetilde{\mathbf{u}}$ and $\widetilde{\boldsymbol{\nu}}^{(1)}$ consists of the last $(K-1)p$ components of $\widetilde{\boldsymbol{\nu}}$.

With this notation we can now state a result that follows from [11].