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Pairwise Multiple Comparisons for Repeated Measurements

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1. Introduction

Frequently a response variable is measured to several fixed time points. We deal with the following multivariate Gauss model:

(1)
$$\mathbf{x}_j = \begin{pmatrix} x_{j1} \\ \vdots \\ x_{jk} \end{pmatrix} \sim N_k\left(\begin{pmatrix} \mu_1 \\ \vdots \\ \mu_k \end{pmatrix}, \Sigma\right)$$

for $j = 1,...,n$ independent sample vectors and $i = 1,...,k$ dependent time points. The variances σ_{ii} $(i = 1,...,k)$ will often be equal in applications.

For small *k*, usually a multivariate analysis of variance is applied, where all elements of the covariance matrix are estimated. Under the compound symmetry assumption, one can alternatively use a univariate ANOVA test (Timm,1980).

In addition to the global test of H_0: $\mu_1 = \mu_2 = ... = \mu_k$, usually orthogonal contrasts, such as Helmert contrasts or polynomial contrasts, are calculated from statistical packages as SPSS or SAS.

The so-called experimentwise error rate of a multiple comparison method is the supremum of the probability of making at least one incorrect assertion (Hsu, 1996) in all decisions of the procedure. The simplest way to ensure this experimentwise error rate is the Bonferroni adjustment, where each single test of the procedure uses the local level α/m for *m* simultaneous tests. Frequently, especially for nonlinear curves, the user wishes to carry out all pairwise comparisons and then α/m may be small.

Subsequently an alternative procedure for multiple comparisons is developed. We start with the principle of a-priori ordered hypotheses (Maurer, Hothorn and Lehmacher, 1995). Testing the hypotheses in the given a-priori order, we can use the full level α in each comparison, however, we have the stop the procedure when for the first time a hypothesis cannot be rejected. The remaining hypotheses are considered as not significant at the experimentwise level regardless of their results in the local tests.

The problem of defining a useful a-priori order of the hypothesis can be avoided by a theorem of Kropf (2000) which considers tests for the univariate hypotheses $H_i : \mu_i = 0$ (i=1,…,k) in the above Gauss model (1) (i.e., the time points are considered separately, not the differences among different points in time):

- The *k* time points are ordered for decreasing values of $\sum_{j=1}^{n} x_{ji}^2$ for $i=1,\ldots,k$.

- In this order, the usual two-tailed t tests for the hypothesis $\mu_i = 0$ are applied
- at the full level α as long as all tests are significant. The procedure stops with the first non-significant result.

This procedure keeps the experimentwise error rate α even in the case of unequal variances at different time points. However, the assumption of equal variances is necessary in order to have an indication for a convenient order of hypotheses, i.e. for the power of the multiple procedure.

The theorem is now applied to the all-pair comparisons between the different time points.

2. A New Procedure for All-Pairwise Comparisons of Dependent Samples

We consider the $p = k(k-1)/2$ pairs (1,1), (1,2),…,($k-1,k$) of different time points and calculate the corresponding differences $d_{j1},\ldots, d_{jp}$ for each sample vector $\mathbf{x}_j$ (j = 1,…, n): $d_{j1} = x_{j1} - x_{j2}, \ldots, d_{jp} = x_{j,k-1} - x_{jk}$.

For j = 1,…, n the vectors $(d_{j1},\ldots,d_{jp})'$ are independent from each other and have a multivariate normal distribution with expectation $(\theta_1,\ldots,\theta_p)'$. Under the additional compound symmetry assumption for the vectors $\mathbf{x}_j$, the p components of the vector of differences have also equal variances. Therefore the above theorem is applicable for the hypotheses $\theta_l = 0$, $l = 1,\ldots,p$, resulting in the following procedure:

- Order the $p = k(k-1)/2$ differences of time points for decreasing values of

$$\sum_{j=1}^{n} d_{jl}^2, \; l = 1,\ldots,p .$$

- In this order, carry out the usual two-tailed t tests (corresponding to the usual t test for pair differences) for the hypotheses $\theta_l = 0$, $l = 1,\ldots,p$ at the full level α as long as all tests yield significant results. Stop at the first non-significant result.

This procedure keeps the experimentwise error rate α. The resulting order of hypotheses may be useful because $\sum_{j=1}^{n} d_{jl}^2 / n = \frac{n-1}{n} s_l^2 + \bar{d}_l^2$ for each $l = 1,\ldots,p$. Therefore with equal variances for all differences, the order of hypotheses is mainly determined by the mean differences. Pairs of time points with large mean differences and hence large t values should be in the front part of the ordered sequence of pairs.

Again, if the variances or correlations in model (1) are unequal, then the procedure keeps the experimentwise error rate α nonetheless but the power of the tests may be insufficient.

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