

STUDENTIZED MODIFIED MAXIMUM CONTRAST METHOD FOR UNEQUAL SAMPLE SIZES IN PHARMACOGENOMICS STUDIES

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In pharmacogenomics studies, biomedical researchers often analyze the association between genotype and pharmacokinetics (PK) parameters (i.e., AUC , C_{max} , $t_{1/2}$, and so on) using the Kruskal–Wallis test or one-way ANOVA after logarithmic transformation of the obtained data. Although the PK-related genes indicate that the monotone increasing pattern with genotype, that is, major homo, hetero and minor homo, this hypothesis testing does not consider a monotonic response pattern. In order to detect a monotonic dose-response relationship, a maximum contrast method has been proposed in clinical trials and in toxicological trials (Wakana et al., 2007). In contrast, we proposed a combination of the maximum contrast method and the modified maximum contrast method for application to the data with unequal sample sizes in pharmacogenomics studies (Sato et al., 2009). However, the distribution of the modified maximum contrast statistic depends on a nuisance parameter σ^2 , the variance. Thus, an approximate P -value was calculated by the permutation method, which requires too much computation time.

In this study, we propose a studentized modified maximum contrast statistic S_{max} that does not depend on the nuisance parameter. We derive the distribution of this statistic $S_{max} = \max_k \{ \mathbf{c}_k^t \bar{\mathbf{Y}} / \sqrt{\mathbf{V} \mathbf{c}_k^t \mathbf{c}_k} \}$, where $\bar{\mathbf{Y}}$ is group sample mean vector, V is unbiased estimator of σ^2 , and \mathbf{c}_k are contrast coefficient vectors that correspond to expected response patterns. Furthermore, we compare the performance and the computational time among these methods via simulation studies.

The simulation results showed that the studentized modified maximum contrast method was powerful for detecting the true response patterns in some conditions, and gave the lowest false positive rate. Also, it is faster and more accurate than the modified maximum contrast method. On the basis of these results, we suggest rules of thumb to select the appropriate method in a given situation. Recently, powerful array-based SNP typing platforms have heralded an era in which a genome-wide association study is a popular or standard strategy, and genotype data on 100,000–1,000,000 SNPs are increasingly available to researchers. It is virtually impossible for biomedical researchers to visually check the response patterns on such a genome scan data. Our proposed method can readily be applied to genome scans as a statistical screening method.

References

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