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Wald-type rank tests: A GEE approach

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ABSTRACT

Factorial designs have been widely used in many scientific fields. Traditionally, such designs can be analyzed by the generalized linear mixed models (GLMMs). When making inference for the fixed effects in GLMM, however, even the robust generalized estimating equations (GEE) method may give biased results when the distributional assumption is violated. In this case, rank-based tests can be an option for inferential procedures. This paper applies the GEE technique to rank transformed data and derives a unified Wald-type rank test which can be used in any factorial design. The asymptotic properties of the proposed test are derived under the null and contiguous local alternative hypotheses. As a major contribution of this article, incorporating the rank transform statistic into the GEE framework provides a powerful tool to derive general asymptotic results of the rank-based methods and facilitates the migration of inferential procedures for GEE to rank-based methods. Small sample corrections for the proposed Wald-type rank test using GEE are also investigated. Simulation studies confirmed the validity of the proposed Wald-type rank test using GEE in large sample studies as well as that performances of the proposed small sample corrected tests are similar to the Wald-type rank test proposed in previous studies in a two-way repeated measures design. A mouse DIO study is used to illustrate the investigated methods together with SAS® code to realize select small sample corrected Wald-type rank tests using GEE supplied.

1. Introduction

Factorial designs have been widely used in medical, biological, ecological, psychological, and many other scientific fields. Under the assumption that observations from different experimental units (EUs) or subjects are independent, when each subject has just one observation, data from a factorial design can be analyzed using simple analysis of variance (ANOVA) models when the corresponding assumptions such as equal variance and normality of residuals are satisfied (Cox and Reid, 2000). When subjects may be observed repeatedly under different or under the same conditions, data from the designs can be analyzed by more complicated models which come in the framework of generalized linear mixed models (GLMMs, McCulloch and Searle, 2001). The simple ANOVA model can be viewed as a special case of the GLMM. Likelihood-based parametric methods have been thoroughly investigated for GLMMs, see, for example, Breslow and Clayton (1993), Wolfinger and O'Connell (1993), and Booth and Hobert (1999).

Because likelihood-based inference for the parameters in GLMMs heavily relies on correct specification of the model including the distribution of the observations and correlation structure for the correlated observations, with misspecified model, the inference could be biased and the bias may be serious in some cases.

When the main aim is to make inference for the fixed effects in GLMM, the generalized estimating equations (GEE, Liang and Zeger, 1986) for marginal models can partially solve this issue. Parametric inferences based on GEE are asymptotically

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consistent even with misspecified correlation structure. However, the GEE method still needs correct specification of the marginal distributions of the observations and with misspecified distributions, the inference for the fixed effects may be biased.

Another direction to solve the problem is to use nonparametric models to analyze the data. Unlike parametric models which usually use the distribution mean to make inferences and express hypotheses, nonparametric models use the whole distribution toward this goal. Nonparametric definition of the statistical inference such as treatment effects can be traced back to Hollander et al. (1974) and Govindarajulu (1975) and were extended later on and studied in more detail by Brunner and Neumann (1982), Thompson (1990, 1991), and Brunner and Denker (1994).

Regarding hypothesis testing, earlier works used the rank transform technique to conduct tests (Conover and Iman, 1981). Such technique replaces the observations by their ranks in the combined sample, and perform standard parametric procedures to the ranks to obtain inferences. Although such rank transform technique is valid in some particular simple designs to test selected hypotheses (Akritas, 1990), it is invalid in many cases (Akritas, 1991). For a review, see Brunner and Puri (2001). To obtain valid procedures for rank transformed data, a general formulation of hypotheses in nonparametric models was suggested by Akritas and Arnold (1994) who introduced the ideas of formulating the hypotheses for the marginal model in terms of the distribution functions and derived the relevant asymptotic distribution theory under the null hypothesis as well as under a sequence of nonparametric contiguous alternatives, but ties were not allowed in their work. Brunner et al. (1995) used the normalized version of the distribution function and derived the asymptotic results for two-sample rank statistics in mixed models including the case of arbitrary ties. Akritas and Brunner (1997) generalized these results to more general factorial designs with repeated measures. For more comprehensive historical review of rank methods for mixed models, we refer to Akritas and Brunner (1997).

For broader applications of the nonparametric models, unbalanced designs and inference for studies with small sample sizes have also been taken into consideration. This problem was first considered by Akritas et al. (1997) under unbalanced factorial designs with independent observations. They derived asymptotic theory for the Wald-type statistic (WTS). For small sample studies, because WTS lost control of the type I error rate, they proposed a so-called ANOVA-type statistic (ATS) employing the Box-type approximations (Brunner et al., 1997). Brunner et al. (1999) and Munzel and Brunner (2000) generalized these to multivariate factorial designs where repeated measures may occur. Their work considered unbalanced designs, derived asymptotic properties of the WTS and also inference by the ATS which applied to both small sample and large sample studies.

Besides the main and interaction effects, in practice, one-dimensional contrast effects may also be of special interest. For example, in two-way repeated measures ANOVA experiments, with two factors treatment and time and repeated measures of the subjects along different times, one-dimensional contrasts are used to compare two specific treatments instead of the overall comparison of all treatments, to compare the effects at a post-baseline time versus the baseline, and also to assess interactions of two levels of the treatment and two levels of the time factors. Subsequently, it is used in multiple testing problems to assess the three questions: 1. what is the earliest time point at which the drug shows a significant improvement w.r.t. the baseline; 2. is there a placebo effect as measured by a significant improvement w.r.t. the baseline at any time point; and 3. what is the earliest time point at which the drug shows a significantly higher improvement than the placebo w.r.t. the baseline (Munzel and Tamhane, 2002). And also, it can be used to conduct the trend test as in Konietschke et al. (2010). When testing one-dimensional contrasts, because tests based on ATS do not work sufficiently well in terms of type I error rate control, Brunner and Puri (2001) give an adjustment for the degrees of freedom of the asymptotic distribution of the WTS and such adjustment works well in small sample studies.

In this paper, we use GEE framework with an identity link function to derive the asymptotic properties of the rank transformed (RT) statistic. Incorporating the RT statistic into the GEE framework provides a powerful tool to derive general asymptotic results of the rank-based methods and has several advantages. First, it facilitates the migration of other statistical procedures for GEE Wald test such as power and sample size calculations to the Wald-type rank tests. Second, it facilitates the generalization of the rank-based methods to analysis of covariance (ANCOVA) models. Third, it allows the calculation of the inferences of the Wald-type rank tests using standard procedures for GEE that are available in common commercial statistical software such as SAS® PROC MIXED and PROC GLIMMIX. Fourth, it allows the use of GEE to solve other rank-based problems such as calculating single or simultaneous confidence intervals for the expected values of the rank means (nonparametric treatment effects) and the nonparametric Behrens–Fisher problem (Brunner and Munzel, 2000). Despite of these advantages, a major limitation of the proposed Wald-type rank tests using GEE is that in small sample studies, it may be too liberal when testing multidimensional contrasts even with the proposed small sample corrections. Therefore in small sample studies, the proposed Wald-type rank tests using GEE can only be used to test one-dimensional contrasts, which is similar to the Wald-type rank test in currently available studies (Brunner et al., 2002; Brunner and Puri, 2001).

The rest of the paper is organized as the follows. Section 2 derives the asymptotic properties of the RT statistic and also the Wald-type rank test using GEE. Section 3 derives the small sample adjustments for the proposed rank test adapting the ideas of Mancl and DeRouen (2001), Kauermann and Carroll (2001), and Fan et al. (2012). The derivations in both sections are more complicated than in the original GEE because the rank transformed data are not independent even for different subjects. Section 4 uses simulations to compare the corrected Wald-type rank tests using GEE with the corrected GEE Wald test without rank transformation and the ANOVA-type and Wald-type rank tests proposed in previous studies in two-way factorial designs with repeated measures on one factor in terms of type I error rate control and power. In Section 5, a real example is employed to illustrate the application of the methods. Conclusions and discussions are in Section 6.