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Adaptive Robust Profile Analysis of a Longitudinal Data

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Abstract

This paper uses nine winsorized scores in the adaptive test of Hogg, Fisher and Randles and deals with its extension to hypothesis testing in profile analysis of a balanced longitudinal data. Simulation studies are conducted to evaluate the efficiency of the adaptive test procedure relative to the traditional ANOVA-F test for different non-normal data sets. To illustrate the feasibility of the test, we analyzed a real data set from the study of tumor sizes in mice.

Keywords: Adaptive test; longitudinal data; selector statistic; skewness; tail-weight.

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1 Introduction

Statistical test of significance concerning comparison of location of two independent samples is seen in application in many research and study domains. In the medical setting, one may wish to test whether there exist a difference in location between two populations with respect to two distinct treatment regimes. Most test for such problems, particularly the parametric ones have their own predefined assumptions. For example, the t-tests and F-tests are appropriate on the assumption that the two populations are normally distributed. However, most of these tests are not robust for size, in the sense that they do not maintain their level of significance if the normality assumption is violated. On occasions where the normality assumption is not met, the F and t-test may consequently lead to substantive misleading conclusions and inferences about the population.

Under such situations it is more appropriate to apply a nonparametric test such as Wilcoxon, or those tests which appear to be robust adaption of the t-test like the trimmed t-test and the Welch test. However, more often than not, applied researchers and data analysts have no foreknowledge regarding the underlying distribution of the data.

Most adaptive tests for the two-sample location problem are variants of the two-staged adaptive test proposed by Hogg, Fisher and Randles [1]. These adaptive tests investigates the underlying distribution of the data with respect to tailweight and skewness before a test is prescribe. A recent book by O'Gorman [2] gives detailed description of this test procedure. The test first deals with the classification of the unknown distribution underlying data with respect to tailweight and skewness under different score functions and secondly exploit a two dimensional selector statistic to select an appropriate rank score test for the classified data. Their method is confined to four scores; median scores, Wilcoxon scores, scores for right-skewed distributions and scores for light-tailed distributions.

In this paper, nine winsorized scores are considered in the adaptive test of Hogg, Fisher and Randles [1]. We then extend the adaptive two-sample location problem to longitudinal data and hence construct a statistic for testing parallelism in response profiles. In profile analysis, if the test is significant, it is reasonable to conclude that there is group and time interaction and that responses are not parallel [2]. Our interest in this problem is motivated by the fact that statistics for testing significant difference of two independent samples in longitudinal studies often utilize the parametric tests which are inefficient for non-normal distributions, hence the need for more reliable test. Moreover, we wish to inform and increase the popularity of adaptive tests among applied researchers who utilize statistical methods. In the present paper, we used data from a well known study which emphasized on different treatments for tumor in mice as a motivating example.

The remainder of the paper is organized as follows. In section 2, to present our problem, we first introduced our hypothetical data, its corresponding model and hypothesis with a data example. Adaptive tests for testing the hypothesis are discussed in section 3. In section 4 simulation studies are performed to demonstrate the practical performance of our adaptive test. Section 5 presents the analysis of the data example introduced in section 2 and sections 6 gives the outlook which concludes the paper.

2 The Problem Setting and Data Example

Consider an experiment that is performed to compare two treatments, where responses are measured in longitudinal setting. Let Y_{ijk} represents the observation of the kth subject at the jth time in the ith treatment group, where $i = 1, 2$, $j = 1, 2, ..., t$ and $k = 1, 2, ..., n_{ij}$. We assume that there are n_{ij} subjects in the ith $(i = 1, 2)$ treatment, and that $n_{1j} = n_{2j}$. We further assume that the number of subjects measured at each time point are the same for the two treatments. Thus for each time point we let $n_1 = n_2$. Table 1 gives a hypothetical description of the data in context.

Table 1. Hypothetical data for the two sample location problem in longitudinal setting

Treatment	Time			
	1	2	...	t
1	Y_{111}	Y_{121}	...	Y_{1t1}
	Y_{112}	Y_{122}	...	Y_{1t2}
	$\vdots$	$\vdots$	$\vdots$	$\vdots$
	Y_{11n}	Y_{12n}	...	Y_{1tn}
2	Y_{211}	Y_{221}	...	Y_{2t1}
	Y_{212}	Y_{222}	...	Y_{2t2}
	$\vdots$	$\vdots$	$\vdots$	$\vdots$
	Y_{21n}	Y_{22n}	...	Y_{2tn}

Let $n = \sum_{i=1}^{2} n_i$ represent the combined sample and $Y' = (Y_{1jk}, Y_{2jk})$ denote the vector of observations for the combined sample. Suppose we wish to model the response vector Y as one following two-way ANOVA model with interaction given by

$$Y_{ijk} = \mu + \alpha_i + \beta_j + \gamma_{ij} + \epsilon_{ijk} \tag{2.1}$$

where the random errors ϵ_{ijk} are uncorrelated random variables with zero mean and common variance $\sigma^2 > 0$. Here we consider the 2 treatment effects α_1, α_2 and three time effects β_j for $j = 1, ..., t$ as fixed constants. Let $Y = X\beta + \epsilon$ be a linear model, where Y is an $n \times 1$ vector of the longitudinal reponses and X an $n \times p$ design matrix consisting of 0/1 to denote treatment/placebo group. View β as the fixed effect parameter vector corresponding to X. Then if $E(\epsilon) = 0$ and $cov(\epsilon) = \sigma^2 I$, the linear model is a Gaus Markov model. In this case, Equation 2.2 is a Gauss Markov model form of Equation 2.1.

$$Y = X\beta + \epsilon \tag{2.2}$$

This is so because without loss of generality, if $n_1 = n_2 = 2$ and $t = 3$ then for Equation 2.2 we can write

$$Y = \begin{pmatrix} Y_{111} \\ Y_{112} \\ Y_{113} \\ \vdots \\ Y_{211} \\ Y_{212} \\ Y_{213} \\ \vdots \\ Y_{321} \\ Y_{322} \\ Y_{323} \end{pmatrix}, \quad X = \begin{pmatrix} 1 & 1 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix} \quad \beta = \begin{pmatrix} \mu \\ \alpha_1 \\ \alpha_2 \\ \beta_1 \\ \beta_2 \\ \beta_3 \\ \gamma_{11} \\ \gamma_{12} \\ \gamma_{13} \\ \gamma_{21} \\ \gamma_{22} \\ \gamma_{23} \end{pmatrix}$$

Note that $E(\epsilon) = 0$ and $cov(\epsilon) = \sigma^2 I$.

Given this exposition together with the hypothetical data, our interest is to test

$$H_0 : \alpha_1 = \alpha_2$$

against the two sided alternative

$$H_1 : \alpha_1 \neq \alpha_2$$

for each time point.

For now, we consider a data example for the above stated hypothesis. This data is from O'Gorman [2].

2.1 Data example

This example considers the tumor sizes of mice that were injected with mouse colon Carcinoma tumor cells. The data consists of 10 mice randomly assigned to three treatment groups. In the present paper we considered only two groups. Mice randomly assigned to Group A, that received injections of tissue culture medium around the growing tumor, and Group C mice, who received injections of normal spleen cells, immune RNA, and tumor antigen. The tumor sizes were measured on days 11, 13, 15 and 17. The data is presented in Table 2.

Table 2. Tumor Volumes (mm^3) over the course of the experiment

		Days			
Group	Mouse	11	13	15	17
A	1	157.1	217.6	379.0	556.6
	2	152.2	176.6	317.9	356.4
	3	122.4	196.1	388.9	469.3
	4	95.0	205.1	307.3	405.1
	5	168.8	196.6	340.4	507.3
	6	85.0	225.1	289.0	317.9
	7	129.8	274.7	340.3	507.2
	8	157.0	202.5	307.2	320.1
	9	129.7	205.8	419.1	421.2
	10	156.9	225.0	372.6	379.2
C	1	108.0	186.2	213.8	379.1
	2	129.6	196.6	397.1	500.0
	3	65.0	191.3	274.6	405.0
	4	52.9	129.6	303.5	415.0
	5	147.0	420.0	653.4	806.4
	6	115.2	32.0	3.2	1.4
	7	55.0	55.0	118.8	118.3
	8	156.8	84.7	291.5	400.0
	9	44.6	258.8	405.0	372.6
	10	118.3	176.4	340.2	361.0

In the present study a new data is created by removing some values from the original data and replacing them with outliers as described in the following. The tumor size of 95 mm^3 is replaced with tumor size of $1789.9mm^3$ for mouse 4 in group A on day 11. A tumor size of 258.8 mm^3 is replaced with $1550mm^3$ on day 13 for mouse 9 in group C. Mouse 2 in group A whose tumor size was $317.9mm^3$ is replaced with 1770.2 mm^3 on day 15. In group C on day 17, mouse 1 with tumor sizes $379.1mm^3$ is replaced with 1250 mm^3.

With these outliers, one should not think that the size or value of the test for H_0 for the original data will be extremely different from that of the outliers data, such that they will lead to inconsistent

decision and conclusion. We therefore need a test that is robust in the sense that the size of its actual significance level (original data) is quite close to the nominal significance level (outliers data). The test is executed in section 5.

3 Rank Based Test

3.1 Rank tests

Let Y_j represent the combined ordered sample of the two samples at the j^{th} time point in section 2 and let $f(.)$ be the probability density function of $F(.)$. Next, let R_k denote the rank of Y_{jk} $(k = 1, .., n_2)$ in the combined sample of such that $1 \leq R_k \leq n$. Let $u = \frac{R_k}{n+1}$ be $Y'_{jk}s$ rank normalized in the combined sample, where $u \in (0, 1)$. Hàjek and Šidak [3] showed that, in general, the asymptotically most powerful rank test S_u directly depends on the inverse of the cumulative distribution function(c.d.f) $F^{-1}(.)$. In that sense S_u is given by

$$S_u = \sum_{k=1}^{n} a(R_k) \tag{3.1}$$

where $a(R_k)$ is a scoring function which is defined by

$$a(R_k) = -\frac{f'[F^{-1}(u)]}{f[F^{-1}(u)]} \tag{3.2}$$

The scoring function maximizes the information in the ranks. Hence, for any distribution of interest, the most powerful rank test can be obtained by equations 3.1 and 3.2. Asymptotically, as n_1, $n_2 \to \infty$, $S_u \sim N(0, 1)$. Below are examples of rank tests for the two-sample location problem (for derivation of these examples see [4],[5],[6]).

1. The normal score test denoted S_{nor} which is considered to be the most powerful rank test when the distribution of the data is normal with the test defined by;

$$S_{nor} = \sum_{k=1}^{n_2} \Phi^{-1}\left(\frac{R_k}{n+1}\right) \tag{3.3}$$

   where Φ is the c.d.f of the standard normal distribution with mean and variance of the normal score test defined as $E(S_{nor}) = 0$ and $Var(S_{nor}) = \frac{n_2 n_1}{n(n-1)} \sum_{j=1}^{n} \left[\Phi^{-1}(\frac{j}{n+1})\right]^2$.

2. The Wilcoxon-Mann-Whitney(WMW) test is regarded the most powerful rank test once the data is known to have been drawn from a logistic distribution, with the test statistic given by;

$$S_{log} = \frac{2n_2}{n+1} \sum_{k=1}^{n_2} R_k - n_2 \tag{3.4}$$

   with the linear transformation of equation (3.4) given by $S_{WMW} = \sum_{k=1}^{n_2} R_k$. The mean and variance are respectively given as $E[S_{WMW}] = \frac{1}{2} n_2(n+1)$ and $Var[S_{WMW}] = \frac{1}{12} n_2 n_1(n+1)$.

3. The median test which is considered the most powerful test when the data is deemed to have been derived from a Laplace (double exponential) distribution, has test statistic defined as;

$$S_{lap} = \sum_{k=1}^{n_2} \text{sign}\left(R_k - \frac{k+1}{2}\right) \tag{3.5}$$

   where

$$\text{sign(x)} = \begin{cases} 1, & \text{if } x > 0 \\ 0, & \text{if } x = 0 \\ -1, & \text{if } x < 0 \end{cases}$$

Equation (3.5) is practically the same as the test that counts the number of $Y_j's$ above the median of the combined sample and increases by $\frac{1}{2}$ when the median falls in the sample of $Y_k's$ [5]. Thus

$$\begin{aligned} S_{median} &= \sum_{k=1}^{n_2} \frac{1}{2}\left[\text{sign}\left(R_k - \frac{n+1}{2}\right) + 1\right] \\ &= \frac{1}{2}S_{lap} + n_2 \end{aligned}$$

with the mean and variance of the median test given as $E[S_{median}] = \frac{n_2}{2}$ and $Var[S_{median}] = \frac{n_2 n_1}{4(n-1)}$ if n is even, and $Var[S_{median}] = \frac{n_2 n_1}{4n}$ if n is odd [5].

3.2 Adaptive test

In this paper we follow the notion of the two-sample adaptive test proposed by Hogg, Fisher and Randles (HFR) [2]. However, see [6, 7, 8, 9] for other proposals for adaptive two-sample location problem. The HFR test procedure initially classifies the unknown distribution function of the combined data from the two samples (i.e. treatment groups) under four rank scores. Secondly, a selector statistic based on measures for skewness (Q_1) and tail-weight (Q_2) is used to select the most effective rank score to execute the test. See [2] for computational details of these measures. Here, we incorporate nine winsorized scores and extend the HFR test to the context of longitudinal data.

In the following, Büning's lemma [10] is considered in the arena of longitudinal data. It is shown that the HFR test maintains its level of significance for all continuous distribution functions at each time point of the longitudinal trajectory. We state a lemma similar to (Büning, 2009)

3.3 Lemma

i Let $\mathbb{F}$ denote the class of continuous distribution functions under consideration. Suppose that each of m tests at each time point t based on the statistics $T_1, T_2, \ldots, T_m$ is distribution free over the class $\mathbb{F}$ i.e $\mathcal{P}_{H_o}(T_h \in C_h/\mathcal{F}) = \alpha$ for each $\mathcal{F} \in \mathbb{F}$.

ii Let S_j be some statistic at time t that is statistically independent of $T_1, T_2, \ldots, T_m$ under H_o; for each $\mathcal{F} \in \mathbb{F}$. Suppose that S_j is used to decide which test T_h to conduct. S_j is defined as the selector statistic at each time point t_j and Q_s denotes the set of all values of S_j with the following composition;
$Q_s = A_1 \cup A_2 \cup \ldots \cup A_m$; such that $A_h \cap A_k = \emptyset$ for all $h \neq k$, and the $A_i's$ are mutually exclusive and exhaustive.

$$\begin{aligned} \mathcal{P}_{H_o}(\text{reject} \quad H_o/\mathcal{F}) &= \mathcal{P}_{H_o}\left(\bigcup_{h=1}^{m}(S_j \in A_h \wedge T_h \in C_h/\mathcal{F})\right) \\ &= \sum_{h=1}^{m}\mathcal{P}_{H_o}(S_j \in A_h \wedge T_h \in C_h/\mathcal{F}) \\ &= \sum_{h=1}^{m}\mathcal{P}_{H_o}(S_j \in A_h/\mathcal{F}) \cdot \mathcal{P}_{H_o}(T_h \in C_h/\mathcal{F}) \\ &= \alpha \cdot \sum_{h=1}^{m}\mathcal{P}_{H_o}(S_j \in A_h/\mathcal{F}) \\ &= \alpha \cdot 1 \\ &= \alpha \end{aligned}$$

Since $\mathbb{F}$ is a class of all continuous distribution functions $\mathcal{F}$ and $T_1, T_2, \ldots, T_m$ are linear rank statistics at each of the j time points, by Basu's theorem which states that "any boundedly complete sufficient statistic is independent of an ancillary statistic". Then S_j being a function of the order statistics of the combined sample at the j^{th} time point under H_0 are the complete sufficient statistics for the common but unknown $\mathcal{F}$ and consequently independent of any statistic whose distribution is free of $\mathcal{F}$.

3.3.1 Selector statistics

The selector statics will aid in selecting a score function, $S_j = (Q_{1j}, Q_{2j})$, where Q_{1j} and Q_{2j} are the respective measures of skewness and tail weight at the j^{th} time point. Thus S_j is independent of the linear rank statistics $T_1, T_2, \ldots, T_m$ at each time point under the null hypothesis H_o. We now apply the lemma on our problem.
Let

$$w(\lambda_1, \lambda_2) = \frac{1}{l} \sum_{k=b_1+1}^{n-b_2} Y_{(k)} \tag{3.6}$$

where λ_1 and λ_2 are some fractions to be trimmed from the combined ordered data and $Y_{(k)}^{'s}$ are the ordered statistic of the combined sample at each time point of the longitudinal data. Let $b_1 = [n\lambda_1]$, $b_2 = [n\lambda_2]$, and assume $[x]$ denotes the smallest integer greater than x and $l = n - b_1 - b_2$. As a selector statistic S we choose $S_j = \{Q_{1j}^*, Q_{2j}^*\}$ such that

$$Q_{1j}^* = \frac{w(0.95, 0) - w(0.25, 0.25)}{w(0.25, 0.25) - w(0, 0.95)}$$

and

$$Q_{2j}^* = \frac{(w(0.95, 0) - w(0, 0.95))}{(w(0.5, 0) - w(0, 0.25))}$$

where Q_{1j}^* and Q_{2j}^* are measures of skewness and tail-weight respectively. Under H_0 model (2.1) becomes $Y_{ijk} = \epsilon_{ijk}$ and measures of skewness and tail weight are obtained from ϵ_{ijk} for simulations and Y_{ijk} for real life problems. At this point, two important issues arise: firstly, the cutoff values or bounds for measures of skewness and tail-weight.

Al-shomrani [11] proposed the following methods for cutoff values. These depend on the sample size n, however, as $n \to \infty$, the measures converges to those proposed by Hogg, [6]. For Q_1^*, the

$$\text{lower cutoff } = 0.36 + \frac{0.68}{n}$$

$$\text{upper cutoff } = 2.73 - \frac{3.72}{n}$$

and for Q_2^*, when the sample size is less than 25

$$\text{lower cutoff } = 2.17 - \frac{3.01}{n}$$

$$\text{upper cutoff } = 2.63 - \frac{3.94}{n}$$

however, when the sample size is at least 25, then the lower and upper cutoff are respectively defined as;

$$\text{lower cutoff } = 2.24 - \frac{4.68}{n}$$

and

$$\text{upper cutoff } = 2.63 - \frac{9.37}{n}.$$

The second issue is about the appropriate number m of categories $A_1, A_2, ..., A_m$. Four categories are common in literature, thus three for symmetric distributions (short, medium, long tails) and

one for right skewed distributions. However, for our two-sample location problem the following nine categories are utilized.

For these categories, we consider a family of Winsorized scores as the most appropriate set of rank scores for testing the hypothesis in section 2 with bench marks proposed by [11]. For these scores, as shown in Fig. 1, 1-3 represent scores for skewed Left: Light-tailed (LL), Moderate-tailed (LM) and Heavy-tailed (LH). Also, 4-6 are scores for Symmetric: SL, SM, and SH. Finally, 7-9 defines scores for skewed Right: RL, RM and RH, see [12], [13] for score functions and parameters. Figure 2 shows the adaptive scheme for the test of hypothesis formulated in section 2.

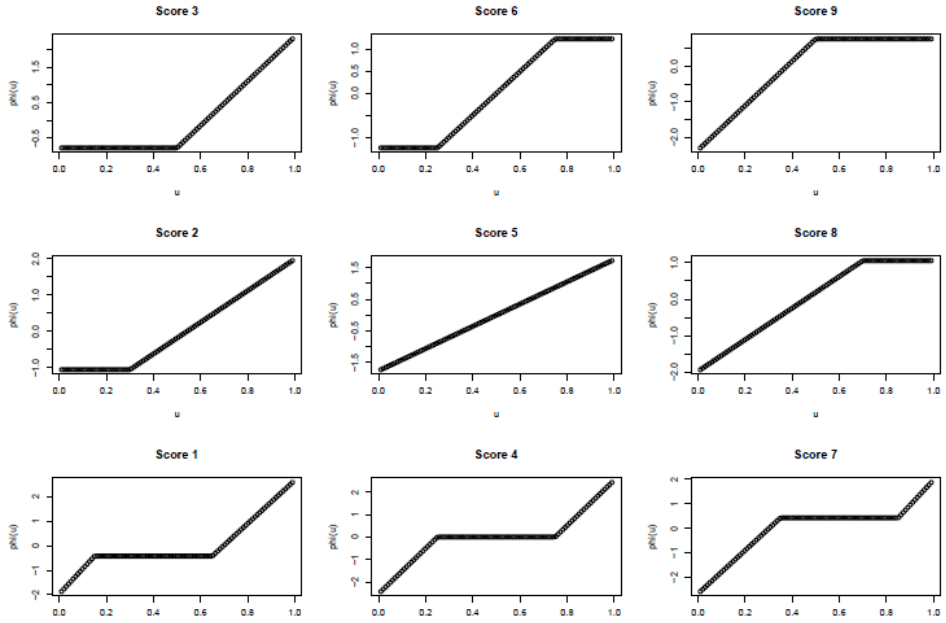

Fig. 1. Plots of the nine winsorised scores

3.3.2 Combined adaptive test

To obtain the test for the hypothesis after selecting the appropriate score, we developed the test statistic for the j time points. Under H_0, we assumed that the errors in equation 2.1 are exchangeable, thus the order statistics of the combined sample at each time point are sufficient and complete [13]. Suppose φ_{kj} is the score selected at the j^{th} time point for region h, then the test statistic for that time point is

$$S_{\varphi_{hj}} = \sum_{k=1}^{n_2} a_h(R(Y_k^{(j)})) \tag{3.7}$$

where $S_{\varphi_{kj}}$ has mean,

$$E(S_{\varphi_{hj}}) = 0$$

and variance,

$$\text{var}(S_{\varphi_{hj}}) = \frac{n_1 n_2}{n-1} \sum_{l=1}^{n} a_h^2(l)$$

see [13] for details. The test

$$Z = \frac{S_{\varphi_{hj}}}{\sqrt{\text{var}(S_{\varphi_{hj}})}} \tag{3.8}$$

is asymptotically standard normal and distribution free. We therefore pool the test statistic over time points. Thus under H_o, the overall test statistics S is;

$$S = \sum_{h=1}^{m} S_{\varphi_{hj}} = \sum_{h=1}^{m} \sum_{k=1}^{n_2} a_h(R(Y_k^{(j)})) \tag{3.9}$$

with an asymptotic distribution, $N(0, m)$. Hence for the hypothesis $H_0 : \lambda_1 = \lambda_2$ versus $H_0 : \lambda_1 \neq \lambda_2$, reject H_0 in favour of H_1 if $|S| = \left|\frac{\sum_{h=1}^{m} Z_h}{\sqrt{m}}\right| > Z_{\alpha/2}$. This overall test statistics combines all the test statistics at each of the time points. This is defined as:

$$Z = \frac{\sum_{h=1}^{m} Z_h}{\sqrt{m}}. \tag{3.10}$$

Under H_0, Z is asymptotically normal with mean 0 and variance 1, see [13]. It is worth noting that in addition to adapting on combine sample at each time point, an adaptation is done on the combined sample from all time points and results are compared with adaptation on time points.

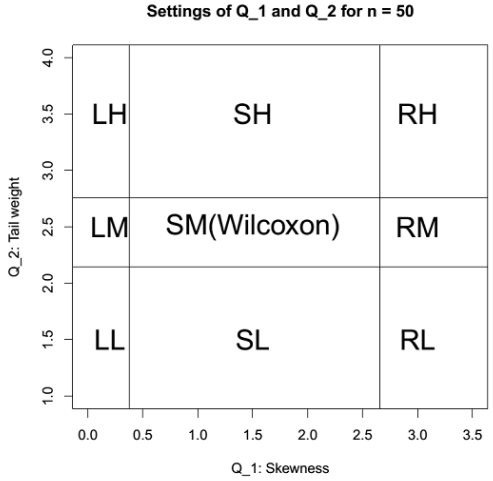

Fig. 2. Adaptive Scheme

4 Simulation Studies

In this section simulation studies are conducted for the adaptive test and the ANOVA-F test. The adaptive test is compared with the parametric ANOVA F-test under distinct scenarios. Simulation results for normal, double exponential, contaminated normal and the truncated logistic distributions for a balanced longitudinal study are considered. In the simulation of the longitudinal data, three time points with two treatment groups were considered. Equal sample sizes were generated for each treatment group at each of the time points. The intraclass correlation coefficient was however considered to be ρ =0, 0.2, 0.5 and 0.7. Under H_0, at each time point, data were generated from the model in Equation 2.1.

4.1 Simulation results for normally distributed errors

Using the normal distribution, under H_0, 10,000 simulations were carried out for sample sizes 10, 12, 15, 18 and 20 subjects each, assigned to two groups: placebo and treatment groups at each time point of the longitudinal trajectory with correlation coefficient ρ being 0, 0.2, 0.5 and 0.7.

Results from Table 3 depicts the structure of the underlying distribution at each of the time points for the various sample sizes. The values in brackets indicate the structure of the score function: see figure 1. The distributions of sample sizes 10, 15 and 20 for each group at time t_1 are symmetric and heavy-tailed whiles the distribution of sample sizes 12 and 18 are symmetric with light-tails and symmetric with moderate-tails respectively. At time point t_2, the same distributions, symmetric with moderate tails were realized for sample sizes 10, 12, 18 and 20 whiles the distribution of the sample size of 15 was symmetric and heavy-tailed. For time point t_3 however, the structure of the underlying distribution of all the sample sizes ranging from 12 to 20 were observed as being symmetric with moderate tails except for sample size 10 which was observed as belonging to class of symmetric and heavy-tailed distribution. This is an indication that as the sample size increases, the scores are classified under the class of Winsorized scores (SM(5)).

Table 3. Adaptive Test for normally distributed errors

Sample size	τ or σ			Test Statistic			Distribution(Scores)		
(n_1, n_2)	t_1	t_2	t_3	t_1	t_2	t_3	t_1	t_2	t_3
(10,10)	0.975	1.293	1.384	0.129	0.529	0.695	SH(6)	SM(5)	SH(6)
(12,12)	0.850	0.872	1.236	0.742	1.443	0.231	SL(4)	SM(5)	SM(5)
(15,15)	0.791	1.116	0.100	2.132	0.901	1.182	SH(6)	SH(6)	SM(5)
(18,18)	0.991	0.938	0.993	0.569	0.475	1.645	SM(5)	SM(5)	SM(5)
(20,20)	1.046	0.972	1.263	0.563	0.784	1.001	SH(6)	SM(5)	SM(5)

Results of the final test of the adaptive scheme is compared with the ANOVA F test for the normal distributed errors as shown in Table 4. Both tests reveals that there is no group and time interaction or that the mean profiles over time are parallel because the p-values for both test were greater than 0.05. A measure of efficiency is the efficacy or standard deviation defined as σ for the ANOVA F-test and the scale parameter (τ) for the adaptive test. As displayed in Table 4, the efficacy of the ANOVA F-test is relatively larger compared with the adaptive test for the normally distributed errors as the sample size increases. Thus based on the values obtained for the efficacy of both tests in Table 4, it is evident that the parametric ANOVA F-test is relatively more efficient than the adaptive test for normally distributed errors. Therefore the F-test is considered the optimal test when observations are drawn from a normal distribution.

4.2 Simulation results for the contaminated normal errors

This subsection contains the results of a simulation study based on contaminated normally distributed random error terms generated at each time point.

Table 5 depicts the values obtained for the scale parameter(τ or σ) and test statistic as well as the underlying distribution at each of the time points for the contaminated normal errors. As displayed in Table 5, the structure of the underlying distribution at each of the time points for the sample sizes are symmetric with heavy and moderate tails except for time points t_3 and t_2 where the structure of the underlying distribution for the data with sample sizes 12 and 15 for each treatment group revealed that the data at these time points are right skewed with heavy tails.

Table 6 also indicates that there is no group and time interaction effect. Both test fail to reject H_0 and thus conclude that the group and time interaction effect is not significant or that the test of parallelism hypothesis is reasonable. The standard deviations and the test statistic of the adaptive scheme and ANOVA F-test for each of the tests are also shown in Table 6. Based on the standard deviation(τ or σ) of the two tests ($AD(S, \varphi_k)$) and F, it is evident that the standard deviation for the adaptive test($AD(S, \varphi_k)$) are relatively smaller than that of the F-test. An indication that the adaptive test is more efficient when the error terms are drawn from the contaminated normal distribution.

Table 4. Results of Adaptive Test and F-statistic for normal distributed errors

(n_1,n_2)	Correlation	Test	Test Statistic	τ or σ	Efficacy	Interaction
(10,10)	0.0	$AD(S, \varphi_k)$	0.78	1.22	0.82	NO
		F	0.14	0.13	7.69	NO
	0.2	$AD(S, \varphi_k)$	0.96	2.13	0.47	NO
		F	0.75	1.05	0.95	NO
	0.5	$AD(S, \varphi_k)$	1.03	3.21	0.31	NO
		F	1.45	1.11	0.90	NO
	0.7	$AD(S, \varphi_k)$	0.92	2.47	0.41	NO
		F	0.79	0.99	1.01	NO
(12,12)	0.0	$AD(S, \varphi_k)$	1.40	0.99	1.01	NO
		F	0.09	0.15	6.67	NO
	0.2	$AD(S, \varphi_k)$	1.03	2.99	0.33	NO
		F	1.11	1.13	0.89	NO
	0.5	$AD(S, \varphi_k)$	1.14	3.10	0.33	NO
		F	0.85	1.26	0.79	NO
	0.7	$AD(S, \varphi_k)$	1.08	2.87	0.35	NO
		F	0.02	0.75	1.33	NO
(15,15)	0.0	$AD(S, \varphi_k)$	2.43	0.97	1.03	NO
		F	0.24	0.26	3.85	NO
	0.2	$AD(S, \varphi_k)$	0.99	2.84	0.35	NO
		F	1.67	0.95	1.05	NO
	0.5	$AD(S, \varphi_k)$	1.21	2.93	0.34	NO
		F	0.71	1.03	0.97	NO
	0.7	$AD(S, \varphi_k)$	1.06	2.13	0.47	NO
		F	0.77	1.26	0.79	NO
(18,18)	0.0	$AD(S, \varphi_k)$	1.55	0.97	1.03	NO
		F	0.31	0.29	3.45	NO
	0.2	$AD(S, \varphi_k)$	1.14	3.13	0.32	NO
		F	0.43	0.90	1.11	NO
	0.5	$AD(S, \varphi_k)$	1.07	2.94	0.34	NO
		F	1.10	0.79	1.27	NO
	0.7	$AD(S, \varphi_k)$	0.98	2.77	0.36	NO
		F	0.45	0.88	1.14	NO
(20,20)	0.0	$AD(S, \varphi_k)$	1.36	1.09	0.92	NO
		F	0.23	0.22	4.55	NO
	0.2	$AD(S, \varphi_k)$	1.32	2.11	0.47	NO
		F	0.29	1.04	0.96	NO
	0.5	$AD(S, \varphi_k)$	0.98	2.46	0.41	NO
		F	0.29	1.07	0.94	NO
	0.7	$AD(S, \varphi_k)$	1.01	2.47	0.40	NO
		F	0.08	1.01	0.99	NO

Table 5. Adaptive Test for contaminated normal errors with $\epsilon = 0.5$

Sample size	τ or σ			Test Statistic			Distribution(Scores)		
(n_1, n_2)	t_1	t_2	t_3	t_1	t_2	t_3	t_1	t_2	t_3
(10,10)	1.505	2.456	1.643	1.159	1.391	0.232	SH(6)	SH(6)	SH(6)
(12,12)	1.399	2.8032	1.356	1.168	0.989	0.207	SH(6)	SH(6)	RH(9)
(15,15)	3.957	1.850	1.552	0.643	0.130	0.973	SM(5)	RH(9)	SH(6)
(18,18)	2.597	3.814	3.197	0.011	0.190	1.008	SH(6)	SM(5)	SH(6)
(20,20)	3.418	1.703	2.374	0.657	0.216	0.379	SH(6)	SH(6)	SM(5)

Table 6. Adaptive test and F-statistic for contaminated normal errors

(n_1,n_2)	correlation	Test	Test Statistic	τ or σ	Efficacy	Interaction
(10,10)	0.0	$AD(S, \varphi_k)$	1.61	1.87	0.53	NO
		F	1.37	2.94	0.34	NO
	0.2	$AD(S, \varphi_k)$	0.92	4.13	0.24	NO
		F	1.62	7.03	0.14	NO
	0.5	$AD(S, \varphi_k)$	1.11	5.21	0.19	NO
		F	0.98	8.34	0.12	NO
	0.7	$AD(S, \varphi_k)$	0.89	3.12	0.32	NO
		F	1.22	11.21	0.09	NO
(12,12)	0.0	$AD(S, \varphi_k)$	1.37	1.85	0.54	NO
		F	1.33	3.02	0.33	NO
	0.2	$AD(S, \varphi_k)$	1.01	4.01	0.25	NO
		F	0.97	6.21	0.16	NO
	0.5	$AD(S, \varphi_k)$	1.32	5.05	0.20	NO
		F	1.03	7.96	0.13	NO
	0.7	$AD(S, \varphi_k)$	0.92	2.16	0.46	NO
		F	1.06	10.67	0.09	NO
(15,15)	0.0	$AD(S, \varphi_k)$	1.01	2.45	0.41	NO
		F	0.98	2.51	0.40	NO
	0.2	$AD(S, \varphi_k)$	1.13	3.21	0.31	NO
		F	1.11	4.32	0.23	NO
	0.5	$AD(S, \varphi_k)$	1.09	4.57	0.22	NO
		F	1.16	11.21	0.09	NO
	0.7	$AD(S, \varphi_k)$	1.26	4.32	0.23	NO
		F	2.13	15.62	0.06	NO
(18,18)	0.0	$AD(S, \varphi_k)$	0.70	2.42	0.41	NO
		F	0.44	3.26	0.31	NO
	0.2	$AD(S, \varphi_k)$	1.24	3.01	0.33	NO
		F	1.39	5.11	0.20	NO
	0.5	$AD(S, \varphi_k)$	1.16	4.42	0.23	NO
		F	0.99	9.23	0.11	NO
	0.7	$AD(S, \varphi_k)$	1.13	3.96	0.25	NO
		F	1.37	13.22	0.08	NO
(20,20)	0.0	$AD(S, \varphi_k)$	0.72	2.50	0.40	NO
		F	0.32	3.64	0.27	NO
	0.2	$AD(S, \varphi_k)$	1.09	3.21	0.31	NO
		F	1.25	8.79	0.11	NO
	0.5	$AD(S, \varphi_k)$	1.47	4.19	0.24	NO
		F	1.97	15.35	0.07	NO
	0.7	$AD(S, \varphi_k)$	0.93	3.71	0.27	NO
		F	1.05	9.39	0.11	NO

4.3 Simulation results for the Laplace Distribution

Here data was simulated from the model in equation 2.1 based on Laplace distributed errors.

From Table 7, the adaptive scheme revealed that the distribution of the data is symmetric with heavy tail weight for all the sample sizes at each of the time points except for time point t_1 with sample size 10 for both group and time point t_3 with sample size 20 for each group where the distribution of the data is left skewed with heavy tail weight and symmetric with moderate tails respectively.

Table 8 represents the overall test statistic of the adaptive and the ANOVA F-test for the error terms generated from the double exponential(Laplace) distribution. Both test indicates that there is no group and time interaction or that the mean profiles are parallel for both groups across time. The values obtained for the efficacy of the adaptive test is larger than the ANOVA F-test as shown

on Table 8. Hence the adaptive test is more efficient than the ANOVA F-test for double exponential or Laplace distributed samples.

Table 7. Adaptive Test for Laplace distribution, $\mu = 0$ and $\beta = 3$

Sample size	τ or σ			Test Statistic			Distribution(Scores)		
(n_1, n_2)	t_1	t_2	t_3	t_1	t_2	t_3	t_1	t_2	t_3
(10,10)	0.427	0.553	0.243	0.744	0.644	0.773	LH(3)	SH(6)	SH(6)
(12,12)	0.685	0.409	0.412	0.396	0.851	0.257	SH(6)	SH(6)	SH(6)
(15,15)	0.276	0.359	0.204	0.329	0.715	0.658	SH(6)	SH(6)	SH(6)
(18,18)	0.389	0.415	0.301	0.351	1.413	0.833	SH(6)	SH(6)	SH(6)
(20,20)	0.347	0.386	0.501	0.451	0.441	1.353	SH(6)	SH(6)	SM(5)

Table 8. Adaptive Test and F-statistic for the error terms generated from the Laplace distribution

(n_1,n_2)	Correlation	Test	Test Statistic	τ or σ	Efficacy	Interaction
(10,10)	0.0	$AD(S, \varphi_k)$	1.25	0.41	2.44	NO
		F	0.80	1.37	0.73	NO
	0.2	$AD(S, \varphi_k)$	1.13	7.10	0.14	NO
		F	2.10	12.87	0.08	NO
	0.5	$AD(S, \varphi_k)$	1.19	6.11	0.16	NO
		F	1.04	11.23	0.09	NO
	0.7	$AD(S, \varphi_k)$	1.11	10.12	0.10	NO
		F	1.27	17.35	0.06	NO
(12,12)	0.0	$AD(S, \varphi_k)$	0.87	0.50	2.00	NO
		F	1.06	0.91	1.10	NO
	0.2	$AD(S, \varphi_k)$	1.31	6.12	0.16	NO
		F	1.05	13.12	0.08	NO
	0.5	$AD(S, \varphi_k)$	1.02	6.98	0.14	NO
		F	1.34	12.07	0.08	NO
	0.7	$AD(S, \varphi_k)$	0.98	0.99	1.01	NO
		F	1.05	18.01	0.06	NO
(15,15)	0.0	$AD(S, \varphi_k)$	0.98	0.28	3.57	NO
		F	0.78	0.31	3.23	NO
	0.2	$AD(S, \varphi_k)$	0.99	7.06	0.14	NO
		F	1.16	10.54	0.09	NO
	0.5	$AD(S, \varphi_k)$	1.42	7.43	0.13	NO
		F	0.97	10.94	0.09	NO
	0.7	$AD(S, \varphi_k)$	1.36	11.62	0.09	NO
		F	1.45	20.23	0.05	NO
(18,18)	0.0	$AD(S, \varphi_k)$	1.50	0.37	2.70	NO
		F	1.71	1.15	0.87	NO
	0.2	$AD(S, \varphi_k)$	1.06	6.82	0.15	NO
		F	0.78	11.74	0.09	NO
	0.5	$AD(S, \varphi_k)$	1.35	6.78	0.15	NO
		F	1.33	9.97	0.10	NO
	0.7	$AD(S, \varphi_k)$	1.44	10.98	0.09	NO
		F	1.42	19.89	0.05	NO
(20,20)	0.0	$AD(S, \varphi_k)$	1.30	0.41	2.44	NO
		F	1.38	0.76	1.32	NO
	0.2	$AD(S, \varphi_k)$	1.01	7.34	0.14	NO
		F	0.94	10.57	0.09	NO
	0.5	$AD(S, \varphi_k)$	1.18	6.16	0.16	NO
		F	1.29	11.23	0.09	NO
	0.7	$AD(S, \varphi_k)$	1.01	13.45	0.07	NO
		F	1.09	24.32	0.04	NO

4.4 Simulation results for the truncated logistic distribution

The simulation results of equation 2.1 based on truncated logistic error distributions are presented.

Results for the adaptive scheme using the truncated logistic distribution as an example are displayed in Table 9. Monte Carlo simulations (10,000 simulations) were run for each sample size. From the adaptive scheme, the underlying structure of the unknown distribution at time point 1 for sample sizes 10,12 and 20 for each treatment group are right skewed with moderate tails whiles the structure of the unknown distribution at the same time point for sample sizes 15 and 18 for each of the treatment groups are skewed right but with heavy tails. At time point 2 of our longitudinal data however, for sample sizes 10,12 and 15 for each of the treatment groups, whereas the structure of the unknown distribution is right skewed with heavy tails, the underlying distribution for sample sizes 18 and 20 for each of the treatment groups are right skewed with moderate tails and symmetric with light tails respectively. Finally the structure of the unknown underlying distribution at time point 3 for sample sizes 10,15 and 18 for each of the treatment groups are right skewed with moderate tails whiles the distribution of the data with sample sizes 12 and 20 are both skewed right but with light tails and heavy tails respectively.

Table 10 compares the overall adaptive test to the ANOVA F-test for the error terms generated from the truncated logistic distribution. Table 10 indicates that the test of parallelism is reasonable for the tests since the p-values obtained for both test were greater than the α value of 0.05. However, for all the correlation values, the adaptive test has relatively larger efficacies across sample sizes than the ANOVA F-test. Hence it is statistically more efficient than the ANOVA F-test when the error terms are drawn from the truncated logistic distribution.

Table 11 summarises the asymptotic relative efficiency of the adaptive test compared to the F-test obtained for the error terms generated from the normal, contaminated normal, double exponential and truncated logistic distributions when the correlation $\rho = 0$. The simulation results for the contaminated error terms generated at each time point of the longitudinal data indicates that the adaptive test is more efficient than the ANOVA F-test. It is 102% as efficient as the ANOVA F-test for the sample size of 15 and as high as 163% efficiency for the sample size of 12. Finally results obtained for the asymptotic relative efficiency of the error terms generated from the Laplace and truncated logistic distributions gives a clear indication that the adaptive test is relatively more efficient than the ANOVA F-tests as shown in Table 11. It is about 378% efficient as the ANOVA F-test when the sample size is 18 at each time point for the error terms generated from the truncated logistic distribution.

Table 9. Adaptive Test for Truncated logistic Distribution

Sample size	τ or σ			Test Statistic			Distribution(Scores)		
(n_1, n_2)	t_1	t_2	t_3	t_1	t_2	t_3	t_1	t_2	t_3
(10,10)	1.578	0.933	0.865	0.416	1.624	3.012	RM(8)	RH(9)	RM(8)
(12,12)	0.735	0.972	1.204	0.159	1.602	1.212	RM(8)	RH(9)	RL(7)
(15,15)	0.720	0.761	1.279	0.946	0.204	2.228	RH(9)	RH(9)	RM(8)
(18,18)	0.647	0.681	1.107	0.877	1.806	0.259	RH(9)	RM(8)	RM(8)
(20,20)	1.199	1.052	1.046	1.667	0.577	1.573	RM(8)	SL(4)	RH(9)

Table 10. Adaptive Test and F-statistic for Truncated logistic distribution

(n_1,n_2)	Correlation	Test	Test Statistic	τ or σ	Efficacy	Interaction
(10,10)	0.0	$AD(S, \varphi_k)$	2.92	1.13	0.88	NO
		F	2.36	2.63	0.38	NO
	0.2	$AD(S, \varphi_k)$	1.03	3.13	0.32	NO
		F	0.99	6.56	0.15	NO
	0.5	$AD(S, \varphi_k)$	1.04	5.64	0.18	NO
		F	0.99	12.08	0.08	NO
	0.7	$AD(S, \varphi_k)$	0.89	5.12	0.20	NO
		F	1.04	12.38	0.08	NO
(12,12)	0.0	$AD(S, \varphi_k)$	1.72	0.97	1.03	NO
		F	1.24	1.73	0.58	NO
	0.2	$AD(S, \varphi_k)$	1.07	4.67	0.21	NO
		F	1.33	7.45	0.13	NO
	0.5	$AD(S, \varphi_k)$	0.98	4.98	0.20	NO
		F	1.08	9.01	0.11	NO
	0.7	$AD(S, \varphi_k)$	1.11	5.02	0.20	NO
		F	1.37	14.16	0.07	NO
(15,15)	0.0	$AD(S, \varphi_k)$	1.95	0.92	1.09	NO
		F	3.16	2.96	0.34	NO
	0.2	$AD(S, \varphi_k)$	1.00	3.98	0.25	NO
		F	0.94	8.01	0.12	NO
	0.5	$AD(S, \varphi_k)$	1.07	5.04	0.20	NO
		F	1.09	11.28	0.09	NO
	0.7	$AD(S, \varphi_k)$	0.98	4.56	0.22	NO
		F	1.53	11.67	0.09	NO
(18,18)	0.0	$AD(S, \varphi_k)$	1.70	0.81	1.23	NO
		F	2.94	3.07	0.33	NO
	0.2	$AD(S, \varphi_k)$	0.99	3.79	0.26	NO
		F	1.48	8.32	0.12	NO
	0.5	$AD(S, \varphi_k)$	0.96	5.72	0.17	NO
		F	1.09	14.32	0.07	NO
	0.7	$AD(S, \varphi_k)$	1.05	5.03	0.20	NO
		F	0.99	13.05	0.08	NO
(20,20)	0.0	$AD(S, \varphi_k)$	2.20	1.10	0.91	NO
		F	3.33	3.75	0.27	NO
	0.2	$AD(S, \varphi_k)$	0.78	4.67	0.21	NO
		F	1.02	8.88	0.11	NO
	0.5	$AD(S, \varphi_k)$	1.19	4.94	0.20	NO
		F	1.05	13.96	0.07	NO
	0.7	$AD(S, \varphi_k)$	0.79	6.45	0.16	NO
		F	0.89	14.21	0.07	NO

4.5 Asymptotic Relative Efficiency (A.R.E)

Table 11. A.R.E for the error terms based on 10,000 simulations when $\rho = 0$

		Errors		
(n_1,n_2)	Tests	CN	Laplace	Truncated Logistic
(10,10)	$AD_2(S, \varphi_k)$, F	1.5733	1.9681	2.3333
(12,12)	$AD_2(S, \varphi_k)$, F	1.6292	1.8167	1.7848
(15,15)	$AD_2(S, \varphi_k)$, F	1.0224	1.0964	3.2217
(18,18)	$AD_2(S, \varphi_k)$, F	1.3445	3.1332	3.7845
(20,20)	$AD_2(S, \varphi_k)$, F	1.4564	1.8540	3.4095

5 Analysis of data example

In section 2 data example on tumor sizes in mice was introduced. The present section presents results and analysis of the data. The question is what is the robust test for H_0 considering this data? Is it the the traditional ANOVA F test or the adaptive scheme.

Results from the adaptive scheme and ANOVA F-test for the original data and the data with outliers are displayed on Tables 12 and 13 respectively. The adaptive scheme shows that the structure of the underlying distribution for responses on day 11 is symmetric light tailed, and days 13, 15 and 17 are symmetric with heavy tail-weight. Moreover, the scheme indicates that the underlying distribution of the data with outliers is right skewed with heavy tails on days 11,13, and 15. Day 17 is symmetric and heavy tailed, and right skewed and heavy tailed for the original and outliers data respectively.

Tables 12 and 13 present the results on the test of parallelism for both the original and outliers data. The adaptive test on the original data suggests that the test is not significant (test statistic=0.0586 ; p-value= 0.4766) at 0.05 level. Similar, the F-test on the original data gives evidence of non significance (test statistic=0.0125; p-value=0.998). Thus, both tests lead to the non-rejection of H_0, meaning the mean response profiles are parallel.

The test statistic and p-value of the ANOVA F-test for the outliers data suggest that the mean response profiles are not parallel and that there is group and time interaction, contradicting the initial results. Thus there is a substantial change in the test statistic and the p-value for this test owing to the presence of outliers. The adaptive test however, irrespective of the existence of outliers changed slightly and still shows that the mean response profiles across the time points are parallel. That is using the adaptive test, the test of parallelism is still reasonable with the outliers introduced but this is not the case for the ANOVA F-test as shown in Table 1. This indicates that the adaptive test is robust for size in the presence of outliers.

Table 12. Results of the tumor size data in mice

Method	Test Statistic	τ or σ	P-value	Distribution(scores)
AD-test (time points)	0.05860	54.241	0.4766	SL(4) SH(6) SH(6)SH(6)
F-test	0.0125	112.243	0.998	Normal(not applicable)

Table 13. Results of the tumor size data in mice with outliers

Method	Test Statistic	τ or σ	P-value	Distribution(scores)
AD-test(time points)	0.0320	73.156	0.4872	RH(9) RH(9) RH(9)SH(9)
F-test	3.0328	429.3588	0.03469 *	Normal(not applicable)

6 Conclusion

In the present paper the two sample location problem has been studied and considered in the setting of longitudinal data to construct adaptive test for testing group and time interaction in profile analysis. We focused on the two dimensional selector statistic $S = \{Q_1^*, Q_2^*\}$, where Q_1^* and Q_2^* are respective measures for skewness and tail-weight of the unknown distribution function. The pioneering work of adaptive test based on only the aforementioned measures was done by Hogg, Fisher and Randles [1]. See [2] for detailed description of their method. See also [10] for a recent

proposed adaptive test for the c sample location problem based on the two dimensional selector statistic. Hogg [6] and Büning, [10] on the other hand, used a three dimensional selector statistic. Thus, they introduced a measure for peakedness in their proposed method for adaptive test. We used the two dimensional scale measure because there is no notable gain in power of the adaptive test by adding the peakedness measure, see Büning, [10]. Furthermore, we considered nine winsorized scores as the most appropriate set of rank scores for testing group and time interaction. We could have limited the number of scores to four, thus three for symmetric distributions (short, medium, long tails) and one for right skewed distributions as it appears in most studies on this subject. We however, propose to use nine scores to accommodate a wide range of distributions which are either symmetric, left-skewed or right-skewed with tail weights that vary from light-tail to heavy-tail. The adaptive test appear to be more efficient than the traditional ANOVA-F test for a class of distributions such as contaminated normal, truncated logistic and double exponential. The study has shown that the adaptive test is robust for size in data sets with outliers. Our study and that of Büning, [10] among others though consistently demonstrate the advantage of adaptive tests over the traditional parametric tests nevertheless, adaptive tests are not frequently used compared to the parametric ones. We therefore agree with Büning, [10] on the thought that adaptive procedures should be embedded in common statistical software packages.

Competing Interests

Authors have declared that no competing interests exist.

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