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A Test for One-sample Repeated Measures Designs: Effect of High-dimensional Data

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Abstract: High-dimensional data, the dimension p of repeated measurements per subject larger than the number n of subjects, are increasingly encountered in various areas of modern science. A test statistic for analyzing high-dimensional one-sample repeated measure designs with no specific form of variance-covariance matrix assumed is proposed. This test statistic asymptotically follows a standard normal distribution for any high dimensional data. Monte Carlo study showed that the proposed test has good power and maintain approximately the nominal level with small n and any large p. Applying the proposed test to the data from body-weight of Wistar rats example with $n = 10$, $p = 22$ is demonstrated.

Key words: High-dimensional data, repeated measures, Monte Carlo study, nominal level, hypothesis test, type I error, power

INTRODUCTION

Repeated measures designs establish one of the most frequently used classes of designs in a many of applied fields, e.g., medical, pharmaceutical, agricultural, zoological and biological sciences (Koc, 2006; Iranparvar *et al*., 2006; Cabezas *et al*., 2007; Ghorbani *et al*., 2007; Ikem *et al*., 2007; Zakaria *et al*., 2010; Zamanian *et al*., 2010). In traditional statistical data analysis for the data from the repeated measures design, the dimension of repeated measurements p is usually smaller than the number of subjects n (Everitt, 1995; Keselman *et al*., 2001). Nowadays, it is demanded that the use of animals in scientific experiments must be adequately controlled and reduced. This proposition is enforced by ethical committees who authorize or deny permission for these kind of experiments (Lawrence *et al*., 2006; Kafas *et al*., 2007). As a consequence the statistician has to work with very small number of subjects but the large number of the dimension of repeated measurements on each subject, i.e., $n<p$, this phenomenon called high-dimensional data. Consequently, for n smaller than p, the sample variance-covariance matrix looses its full rank because of a growing number of eigenvalues become zero. Then the sample variance-covariance matrix of this kind of data becomes singular. These indicate that the available classical test statistic, such as Hotelling's T^2 test statistic, cannot apply anymore (Rencher, 2001; Schafer and Strimmer, 2005; Ahmad *et al*., 2008; Zhang and Xu, 2009).

Recently, there has been some interest in investigating the behavior of high dimensionality that can be found in the literature. In the parametric ANOVA set up when the number of factor levels is large, (Boos and Brownie, 1995; Akritas and Arnold, 2000; Bathke, 2002, 2004; Akritas and Papadatos, 2004; Wang and Akritas, 2006; Harrar and Gupta, 2007). Similarly, the analysis of nonparametric multivariate when the number of factor levels tends to infinity whereas the number of replications is small (Bathke and Harrar, 2008; Bathke *et al*., 2008; Harrar and Bathke, 2008). In an influential work, Ahmad *et al*. (2008) proposed the modified version of the ANOVA-type statistic for analysis of repeated measures designs when the data are multivariate normal and the dimension can be large compared to the sample size. It utilized a modified Box's approximation (Box, 1954) based on quadratic and bilinear forms.

The mainstream attempt in this study interests in the analysis of repeated measures designs for high-dimensional data. Therefore, developing a test statistic to analyze this kind of data from one-sample repeated measures design is interested by follow a multivariate approach to repeated measures (Rencher, 2001; Sahinler and Gorgulu, 2006; Ahmad *et al*., 2008) which no specific form of variance-covariance matrix is assumed.

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TEST STATISTICS AND ITS ASYMPTOTIC DISTRIBUTION

Let $x_k = (x_{k1}, x_{k2},..., x_{kp})^T$ be a vector of p repeated measurements taken on kth subject, where k = 1, 2, …, n. Assume that x_k is an independent, identically normal distributed with population p×1-mean vector $\mu = (\mu_1, \mu_2,..., \mu_p)^T$ and p×p-variance-covariance matrix $\Sigma = (\sigma_{ij})_{i,j=1}^{p}$ where, Σ is positive definite (Σ>0), i.e.:

$$x_k \overset{iid}{\sim} N_p(\mu,\Sigma), \Sigma > 0. \quad (1)$$

Usually, the null hypothesis to be tested is H_0: $H\mu = 0$. The matrix H can be formulated in distinctive settings depending on the objectives of the experimental research. For the simplest situation, specifically, unstructured repeated measures design, we have $H = P_p$ is called the centering matrix, where, $P_p = I_p - p^{-1} J_p$ is a projection matrix with $J_p = 1_p 1_p^T$ denoted the p×p dimensional matrix of 1s and I_p denoted the p×p dimensional identity matrix. As similar null hypothesis given by Ahmad *et al.* (2008), we can also write H_0: $G\mu = 0$ where, $G = H^T (HH^T)^- H$ is the general hypothesis matrix whereas $(HH^T)^-$ denoting a generalized inverse of HH^T and G is a projection matrix. We note that $G\mu = 0$ if and only if $H\mu = 0$, that is, the hypotheses H_0: $G\mu = 0$ and H_0: $H\mu = 0$ are equivalent. The matrix G can be formulated to test any appropriately defined general linear hypothesis, including those having to do with any factorial structure of repeated measures (Brunner *et al.*, 1997, 2002; Ahmad *et al.*, 2008; Bathke and Harrar, 2008).

Throughout this study, the notations as given in above are used for describing test statistics for classical data (n>p) situation. The modified ANOVA-type statistic for high-dimensional data (n>p) in repeated measures designs is also described and a new test statistic is presented.

The classical multivariate approach: For n>p, the data can be analyzed using the classical multivariate approach without assuming any special pattern of variance-covariance matrix Σ. There are various competing statistics to be used to test H_0, including Wald-type statistic, Hotelling's T^2 statistic and ANOVA-type statistic which are discussed in the following.

The Wald-type statistic is defined as (Rao, 1973; Brunner *et al.*, 1999, 2002):

$$W_n = n\bar{x}^T H^T \left(H\hat{\Sigma}H^T\right)^- H\bar{x} \quad (2)$$

where, $\bar{x} = (\bar{x}_1, \bar{x}_2, \ldots, \bar{x}_p)^T$ with $\bar{x}_s = \frac{1}{n}\sum_{k=1}^{n} x_{ks}$, s = 1, …, p and

$$\hat{\Sigma} = \frac{1}{n-1}\sum_{k=1}^{n}(x_k - \bar{x})(x_k - \bar{x})^T$$

are sample estimators of μ and Σ, respectively and $\left(H\hat{\Sigma}H^T\right)^-$ denotes the generalized inverse of $H\hat{\Sigma}H^T$. Under H_0, W_n has a central χ_r^2 distribution for $\hat{\Sigma} > 0$, as $n \to \infty$, where, r = rank (H) degrees of freedom and rank (.) denotes the rank of a matrix.

The Wald-type statistic can be used to define Hotelling's T^2 statistic, usually transformed to an F-statistic, as (Davis, 2002; Salawu *et al.*, 2007; Mohammadi *et al.*, 2011):

$$H_n = \frac{n-r}{(n-1)r} W_n \quad (3)$$

Under H_0, $H_n \sim F_{r,\, n-r}$ where, $F_{r,n-r}$ denotes a central F-distribution with r and n-r degrees of freedom.

The ANOVA-type statistic, T_{ATS}, as considered by Brunner *et al.* (1997, 1999) and Ahmad *et al.* (2008) is defined as:

$$T_{ATS} = n\bar{x}^T G\bar{x} \cdot tr\left(G\hat{\Sigma}\right) / tr\left(G\hat{\Sigma}\right)^2. \quad (4)$$

Further, under H_0, the T_{ATS} has approximately a central $\chi_{\hat{f}}^2$ distribution with the estimated degree of freedom:

$$\hat{f} = \left[tr\left(G\hat{\Sigma}\right)\right]^2 / tr\left(G\hat{\Sigma}\right)^2$$

where tr(.) denotes the trace of a square matrix. Ahmad *et al.* (2008) stated through their simulations that for n>p, the T_{ATS} and the H_n perform accurate but the W_n is liberal. For n≤p, the H_n totally collapses while the W_n ranges from being very liberal to very conservative and the T_{ATS} is also conservative, especially for large dimension p.

The modified ANOVA-type statistic: It is well known that the eigenvalues of the sample variance-covariance matrix $\hat{\Sigma}$ disperse from the true eigenvalues of Σ. The $\hat{\Sigma}$ defined above becomes ill-conditioned or near singular as the number of p approaches to n. When n<p, the smallest eigenvalues are zero. This indicates that the above test statistics, e.g., Hotelling's T^2 statistic and for that matter, any similarly constructed classical multivariate statistic are not powerful or fail to work when the data are high dimension, mainly because $\hat{\Sigma}$ is no longer non-singular. Therefore, Ahmad *et al.* (2008) suggested a modified version of the ANOVA-type statistic using quadratic and symmetric bilinear forms based on Box's approximation (Box, 1954) with an improved degrees of freedom to test the problem H_0: $G\mu = 0$.

When $n<p$, Ahmad *et al*. (2008) gave hints at a possibility of improving T_{ATS} for the case of high-dimensional one-sample repeated measures designs while H_n and W_n appear totally collapse for the case of $n<p$. They found that approximation of sampling distribution of the ANOVA-type statistic T_{ATS} by the scaled χ^2 distribution, using the moment estimator approach introduced by Box (1954), leads to the problem of unbiased estimation because the plug-in estimator of function tr $(G\Sigma)$ is unbiased but the estimators of the functional $[\text{tr}(G\Sigma)]^2$ and $\text{tr}(G\Sigma)^2$ are biased. These makes the estimator of the degree of freedom, f, biased and its biasness increases with increasing p. Then, when $n<p$, Ahmad *et al*. (2008) introduced the following estimators which improved the component estimators of these traces to be unbiased and that improved the performance of T_{ATS}. That is, for the model $x_k \sim N_p(\mu, \Sigma)$, $\Sigma>0$, define $Q_k = x_k^T G x_k$ and $Q_{kl} = x_k^T G x_l$, $k \neq l$ where k, l = 1, 2, ..., n, are respectively a quadratic and symmetric bilinear form. Under H_0: $G\mu = 0$, the new estimators of tr $(G\Sigma)$, $[\text{tr}(G\Sigma)]^2$ and $\text{tr}(G\Sigma)^2$ are defined as:

$$\frac{1}{n}\sum_{k=1}^{n} Q_k,\ \frac{1}{n(n-1)}\underbrace{\sum_{k=1}^{n}\sum_{l=1}^{n}}_{k\neq l} Q_k Q_l \text{ and } \frac{1}{n(n-1)}\underbrace{\sum_{k=1}^{n}\sum_{l=1}^{n}}_{k\neq l} Q_{kl}^2,$$

respectively. Under normality, the above estimators are unbiased and consistent. Therefore, a modified version of the ANOVA-type statistic, F_n, to test the problem H_0: $G\mu = 0$ used for the analysis of repeated measures design when $n<p$ is defined as:

$$F_n = \tilde{f}\cdot n\bar{x}^T G\bar{x} \Big/ \frac{1}{n}\sum_{k=1}^{n} Q_k \sim \chi^2_{\tilde{f}} \text{ as } n\to\infty, \tag{5}$$

where,

$$\tilde{f} = \underbrace{\sum_{k=1}^{n}\sum_{l=1}^{n}}_{k\neq l} Q_k Q_l \Big/ \underbrace{\sum_{k=1}^{n}\sum_{l=1}^{n}}_{k\neq l} Q_{kl}^2 \tag{6}$$

A new proposed test: As discussed above, when $n<p$, only the first n eigenvalues will be non-zero and the smallest eigenvalues will tend to zero pretty quickly as the dimensionality grows. Consequently, many of the classical techniques perform poorly because the theoretical framework for the classical approach is restricted to the case where the number of subjects grows while the dimension stays fixed. In this section, a new test statistic is introduced for analysis of repeated measures design when data are high dimension, $n<p$, under general conditions only that $\Sigma>0$.

Since, $\lambda_{max} = \max_{1\le i\le p} \lambda_i$ vary with p where, λ_i are the eigenvalues of $G\Sigma$, i = 1, 2, ..., p. Under the condition:

$$\lambda_{max} \Big/ \sqrt{\text{tr}(G\Sigma)^2} \to 0 \text{ as } p\to\infty,$$

we obtain our test statistic for the testing problem H_0: $G\mu = 0$ as:

$$Z_* = \left(2\tilde{f}\right)^{-1/2}\left\{F_n - \tilde{f}\right\} \to N(0,1) \tag{7}$$

in distribution. The proof of Eq. 7 can be found in the Appendix. The proposed test in Eq. 7 with an α level of significance rejects H_0 if $Z_*>z_\alpha$ where, z_α denotes the upper α-quantile of a standard normal variate.

SIMULATION STUDY

A study to test the normality of our test statistic is provided first. These simulations were carried out in order to assess the quality of the null distribution by asymptotically distributed as standard normal distribution. We look at the Type I error rates for normality. For comparisons, simulation study are shown aims to compare the empirical powers of the proposed test with the modified version of the ANOVA-type test statistic which proposed by Ahmad *et al*. (2008) in different situations.

Parameter selection: To evaluate the performance of the proposed one-sample test for repeated measures designs with high-dimensional data, Monte Carlo technique for 10,000 iterations is performed with setting significance level α = 0.05 at n = 10, 15, 20, 30, 50, 80 and p = cn, c = 2(1)5. For the empirical power computations, we chose G as a matrix defined above and $\mu = \eta_i u = \eta_i (u_1,...,u_p)^T$ where:

$$u_j \overset{iid}{\sim} \text{Unif}(-1/2, 1/2),$$

j = 1, 2, ..., p and η_i is the ith element of the vector of constants, η = 0 (0.1) 1.5. The empirical power of Z_* is compared with those of F_n tests under the alternative hypothesis considered (for η = 1). The multivariate normal random vectors were generated using IMSL subroutine RNMVN.

In our work presented here, the three following variance-covariance patterns were manipulated: (a) simple (SIM) pattern, (b) unstructured (UN) pattern and (c) heterogeneous compound symmetry (CSH) pattern. A simple variance-covariance pattern is defined as $\Sigma = \sigma^2 I$, where I denotes the $p\times p$ dimensional identity matrix with $\sigma^2>0$. The unstructured variance-covariance matrix refers to the SAS PROC MIXED unstructured pattern (UN). A heterogeneous compound symmetry variance-covariance pattern is defined as $\Sigma = (\sigma_{ij})^p_{i,j=1}$, where, $\sigma_{ij} = \sigma_i^2>0$ (if i = j) and $\sigma_{ij} = \sigma_i\sigma_j\rho$ (if $i \neq j$), ρ is the correlation parameter satisfying $|\rho|<1$. In present work, we select $\sigma^2 = 1$ for SIM, $\sigma_{ij} \overset{iid}{\sim} \text{Unif}(1,2)$ (if i = j) and $\rho_{ij} = (j-1)/p^2$ (if i<j) for UN and $\sigma_{ij} \overset{iid}{\sim} \text{Unif}(2,3)$ (if i = j), $\rho = 0.5$ for CSH, where, i, j = 1, 2, ..., p.

Simulation result: Table 1 provides the results for an assortment of c values for the Type I errors of our test statistic, Z_*. It is clear from this table that the Type I errors of test approximate the nominal significance level $\alpha = 0.05$ reasonably well in all cases even for n as small as 10 and p as large as 400, the estimated Type I errors are satisfactory. Therefore, we conclude that the approximation is quite accurate for all cases.

The corresponding empirical power curves of the statistic Z_* are shown in Fig. 1. We observe that the empirical power of Z_* is very high both for n is small (n = 10) and p increases (i.e., an assortment of c increases) with like the nominal significance level. Moreover, the empirical power of Z_* also increases for increasing p (i.e., increasing an assortment of c) for any n and also for increasing n against any p. In addition, the empirical power is also unaffected by changing the variance-covariance pattern. Furthermore, the performance of the statistic Z_* for n = 50 was found to be similar to the one reported above as n = 10.

Table 2 gave the empirical power of F_n compared with the Z_* tests under the alternative hypothesis with the aforementioned three variance-covariance patterns. It clearly show that our proposed test and F_n test are rather close but that of our test is always slightly higher power than F_n test for all cases considered in the simulation and both increase to 1 as n, p increases. Further, this result is not influenced by changing the variance-covariance pattern.

Table 1: Simulated Type I error of Z_* under the null hypothesis applied at nominal significance level $\alpha = 0.05$

COV pattern	p = cn	c = 2	c = 3	c = 4	c = 5
SIM	n = 10	0.051	0.046	0.045	0.045
	n = 15	0.051	0.049	0.051	0.050
	n = 20	0.057	0.055	0.055	0.053
	n = 30	0.054	0.047	0.047	0.049
	n = 50	0.053	0.052	0.051	0.053
	n = 80	0.055	0.051	0.052	0.052
UN	n = 10	0.051	0.046	0.044	0.046
	n = 15	0.052	0.052	0.050	0.051
	n = 20	0.059	0.055	0.057	0.054
	n = 30	0.055	0.049	0.047	0.049
	n = 50	0.053	0.054	0.050	0.054
	n = 80	0.055	0.053	0.053	0.051
CSH	n = 10	0.051	0.047	0.044	0.046
	n = 15	0.051	0.051	0.048	0.050
	n = 20	0.056	0.054	0.056	0.055
	n = 30	0.054	0.047	0.047	0.049
	n = 50	0.054	0.053	0.051	0.052
	n = 80	0.056	0.053	0.054	0.053

ANALYSIS OF THE BODY WEIGHT OF WISTAR RAT DATA

The data and the experimental description for a motivating example to deal with the high-dimensional data is reported by Brunner *et al.* (2002). The body-weight of male Wistar rats was observed over a period of 22 weeks to assess the toxicity of a drug. For the purpose of this paper, a group of ten animals was given a high dose of the drug (we omit the measurements taken on 10 placebo animals). The main question to be clarified is whether the body-weights of this group differ in their evolution over time. There are, therefore, a total of 22 repeated measurements taken on each of 10 subjects, i.e., high-dimensional data occur.

Table 2: Empirical power of F_n and Z_* under the alternative hypothesis applied at nominal significance $\alpha = 0.05$

		c = 2		c = 3		c = 4		c = 5	
COV	p = cn	F_n	Z_*	F_n	Z_*	F_n	Z_*	F_n	Z_*
SIM	n = 10	0.605	0.662	0.766	0.803	0.816	0.844	0.878	0.898
	n = 15	0.961	0.970	0.993	0.995	0.995	0.996	0.999	0.999
	n = 20	0.999	0.999	1.000	1.000	1.000	1.000	1.000	1.000
	n = 30	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	n = 50	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	n = 80	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
UN	n = 10	0.408	0.466	0.530	0.578	0.566	0.609	0.627	0.663
	n = 15	0.811	0.840	0.903	0.918	0.914	0.928	0.965	0.971
	n = 20	0.960	0.969	0.985	0.988	0.999	0.999	1.000	1.000
	n = 30	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	n = 50	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	n = 80	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
CSH	n = 10	0.481	0.531	0.617	0.664	0.658	0.697	0.731	0.765
	n = 15	0.878	0.901	0.949	0.958	0.958	0.965	0.984	0.987
	n = 20	0.982	0.986	0.994	0.995	1.000	1.000	1.000	1.000
	n = 30	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	n = 50	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	n = 80	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

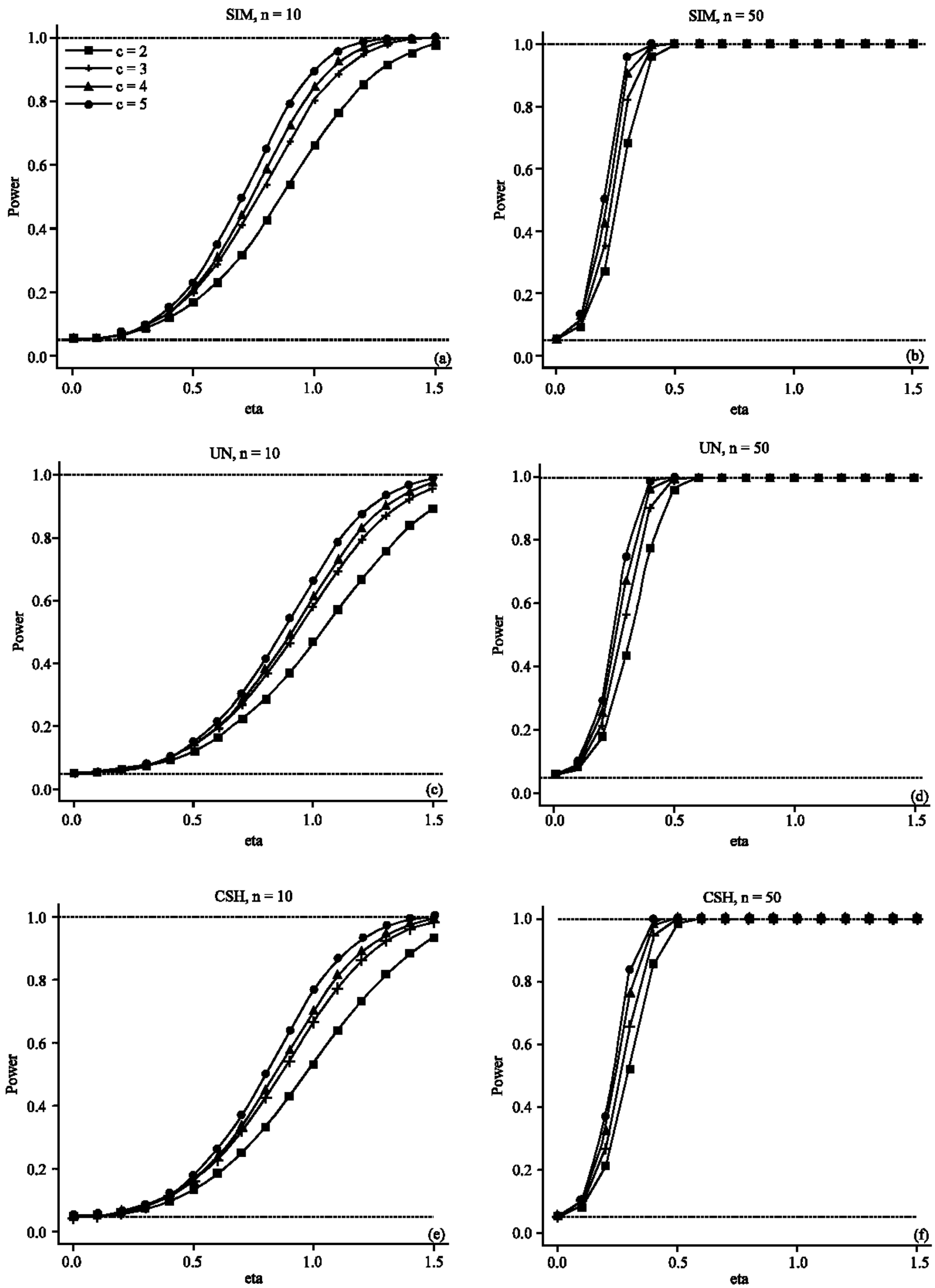

Fig. 1(a-f): Empirical power curves for Z* with p = cn

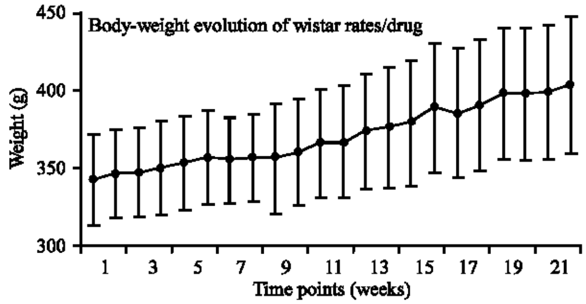

Fig. 2: Mean±SD plot for body-weights of Wistar rats (drug group)

Figure 2 gives the mean profile of the animals for times. For this data, we get test values of $Z_* = 5.7688$ with a corresponding p-value < 0.0001 and $F_n = 9.6501$ with a corresponding p-value = 0.0023 for Eq. 7 and 5 respectively. We note in each case we get a p-value rejecting the null hypothesis of no time effect.

CONCLUSION

In this study, hypothesis test for one-sample repeated measures designs when the number p of repeated observation per subject is larger than the number n of subjects with the data are multivariate normal is studied. It started by emphasizing the previous work in the literature describing test for the hypothesis H_0: $G\mu = 0$. A new proposed test statistic has an asymptotically distributed as standard normal distribution, even for moderately large n, say 10 or more. One of the main advantages of the statistic is that it can be used both for unstructured and factorially structured repeated measures designs when the underlying hypothesis matrix G is appropriately defined. The behavior of the statistic for small samples is evaluated through Monte Carlo simulation studies. However, it is demonstrated through simulations that for n as small as 10 or 15, the new test statistic very closely approximates standard normal distribution and unaffected by even for p is large for any n. Moreover, simulation studies confirm that the new proposed test, Z_*, is more powerful than the modified ANOVA type statistic, F_n, under certain alternative hypotheses while keeps a satisfactory type I error rate. The simulation results provide strong support to the proposed test. In particular, no specific form of variance-covariance matrix is assumed. The application is illustrated using the body weight of Wistar rats example with n = 10, p = 22. Furthermore, the power simulation results suggest that it may be assumed that the quality of the test statistic, Z_*, is maintained even if the dimension is in the thousands and it may also be applied for the microarray data analysis.

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APPENDIX

Technical proofs: Before proceeding to the proof of Eq. 7, we first give two useful lemmas.

Lemma 1: Srivastava (1972) [Lemma 2.1]. Let $\{a_{im}\}_{i=1}^{m}$ be a sequence of constants such that:

$$\max_{1\le i\le m} a_{im}^2 \to 0 \text{ as } m \to \infty \text{ and } \sum_{i=1}^{m} a_{im}^2 \to 1 \text{ as } m \to \infty.$$

Then for any iid random variables $x_1, x_2,..., x_m$ with mean zero and variance one:

$$\sum_{i=1}^{m} a_{im} x_i \xrightarrow{d} N(0,1), m \to \infty.$$

Lemma 2: Let $x \sim N_p(0, \Sigma)$, $\Sigma>0$ and let G be a matrix defined the same as above. Then:

$$n\bar{x}^T G\bar{x} \overset{d}{=} \sum_{i=1}^{p} \lambda_i C_i,$$

where, λ_i are the eigenvalues of $G\Sigma$ and $C_i \sim \chi^2_1$, i = 1, 2, ..., p, are independent. And note that $\overset{d}{=}$ denotes the left and right hand-side random variables have the same distribution.

Proof of Lemma 2: Under the H_0: $G\mu = 0$, notice that $\sqrt{n}G\bar{x} \sim N_p(0, G\Sigma G)$. We set $\sqrt{n}G\bar{x} \equiv Q \sim N_p(0, G\Sigma G)$. Let $v_1, v_2, ..., v_p$ and $\lambda_1, \lambda_2,..., \lambda_p$ are the corresponding orthonormal eigenvectors and eigenvalues of $G\Sigma$. It follows that $Q = \sum_{i=1}^{p} \xi_i v_i$ where, $\xi_i = Q^T v_i$, i = 1, 2, ..., p which are independent and we have E $[\xi_i] = 0$ and Var $[\xi_i] = \lambda_i >.0$ Since, Q is a normal random vector, we have $\xi_i/\sqrt{\lambda_i}$ iid $\sim N(0,1)$ for i = 1, 2, ..., p. Due to the orthonormality of the eigenvectors v_i, i = 1, 2, ..., p, then we have $Q^T Q = \sum_{i=1}^{p} \xi_i^2$. Since, $\xi_i/\sqrt{\lambda_i}$ iid $\sim N(0,1)$, then $\xi^2_i/\lambda_i \sim \chi^2_1$. Hence, $\xi_i^2 \overset{d}{=} \lambda_i C_i$, where, $C_i \sim \chi^2_1$, i = 1, 2, ..., p, are independent. It follows that $\sum_{i=1}^{p} \xi_i^2 \overset{d}{=} \sum_{i=1}^{p} \lambda_i C_i$, as desired.

Proof of Eq. 7: We first notice that:

$$\frac{1}{n}\sum_{k=1}^{n} Q_k \xrightarrow{p} tr(G\Sigma) \text{ and } \frac{1}{n(n-1)} \underbrace{\sum_{k=1}^{n}\sum_{l=1}^{n}}_{k\ne l} Q_{kl}^2 \xrightarrow{p} tr(G\Sigma)^2.$$

We can write:

$$\underbrace{\sum_{k=1}^{n}\sum_{l=1}^{n}}_{k\neq l} Q_k Q_l \approx \left(\sum_{k=1}^{n} Q_k\right)^2,$$

where, '≈' means 'approximately equal to'. Then, the statistic of interest may be written as:

$$\left(2\tilde{f}\right)^{-1/2}\left\{F_n - \tilde{f}\right\} \approx \frac{n\bar{x}^T G\bar{x} - \frac{1}{n}\sum_{k=1}^{n} Q_k}{\left(\frac{n-1}{n}\right)^{\frac{1}{2}} \cdot \sqrt{2 \cdot \frac{1}{n(n-1)} \underbrace{\sum_{k=1}^{n}\sum_{l=1}^{n}}_{k\neq l} Q_{kl}^2}} \overset{p}{=} \frac{n\bar{x}^T G\bar{x} - tr(G\Sigma)}{\sqrt{2tr(G\Sigma)^2}},$$

where, '$a \overset{p}{=} b$' denotes '$a - b \xrightarrow{p} 0$' and note that $n\text{-}1 \approx n$ for large n. Recall Lemma 2 we have $\lambda_i C_i \overset{d}{=} \lambda_i z_i^2, z_i \overset{iid}{\sim} N(0,1)$. Since, λ_i are the eigenvalues of $G\Sigma$, we usually note that $tr(G\Sigma) = \sum_{i=1}^{p}\lambda_i$ and $tr(G\Sigma)^2 = \sum_{i=1}^{p}\lambda_i^2$. And also we have:

$$z_1^2, \ldots, z_p^2 \overset{iid}{\sim} \chi_1^2$$

with $E[z_i^2] = 1$ and $Var[z_i^2] = 2$. Then from Lemma 1, under the condition:

$$\lambda_{max} \Big/ \sqrt{tr(G\Sigma)^2} \to 0$$

true, we have:

$$\frac{n\bar{x}^T G\bar{x} - tr(G\Sigma)}{\sqrt{2tr(G\Sigma)^2}} \overset{d}{=} \frac{\sum_{i=1}^{p}\lambda_i\left(z_i^2 - 1\right)}{\sqrt{2tr(G\Sigma)^2}} \xrightarrow{d} N(0,1), p \to \infty.$$

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