國立交通大學

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博 士 論 文

具異質性多變量線性模型之廣義推論

Generalized inference in heteroscedastic multivariate linear models

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摘　　　要

本論文主題在利用廣義方法處理具異質性 AR(1)共變異矩陣之迴歸模型，由 Tsui 與 Weerahandi (1989) 和 Weerahandi (1993) 提出廣義 p 值和廣義信賴區間的觀念提供不同於傳統處理異質性方法，我們把廣義 p 值和廣義信賴區間推廣到廣義多變量檢定統計量的標準化。Lin and Lee (2003)應用廣義 p 值和廣義信賴區間處理具異質性 uniform 共變異矩陣之多變量變異數分析問題，我們利用他們的程序並做適度修改來處理具異質性 AR(1)共變異矩陣之迴歸模型，所得到的涵蓋機率與預期面積是令人滿意的結果。同時我們的方法也適用於 uniform 共變異矩陣且無需限定 design matrices $\mathbf{X}_i$ 具特定形式。

關鍵詞： AR(1)、廣義信賴區、廣義 p 值、廣義檢定統計量、異質性、迴歸模型、uniform 共變異矩陣。

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ABSTRACT

Our main subject in this dissertation is applying the generalized method to deal with regression model with heteroscedastic AR(1) covariance matrices. The concepts of the generalized *p*-values and the generalized confidence intervals proposed by Tsui and Weerahandi (1989) and Weerahandi (1993), respectively, provide an alternative way to handle with heteroscedasticity. We extend these concepts to further consider the standardized expression of the generalized multivariate test variable. Lin and Lee (2003) applied the generalized method to deal with the MANOVA model with unequal uniform covariance structures among multiple groups. We utilize their process with modifications to deal with regression model with heteroscedastic serial dependence. The coverage probabilities and expected areas based on our proposed procedure display satisfactory results. Besides, we also find that our method can be applied to the uniform structures without the special design matrices $\mathbf{X}_i$ assumption.

Key words and phrases: AR(1); Generalized confidence intervals; Generalized *p*-values; Generalized test variable; Heteroscedasticity; Regression model; Uniform covariance structures.

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在本所碩士班求學期間，常常感受到指導教授李昭勝老師在教學與研究的活力和熱情，而他也會時時關注學生的課業、生活與健康。服兵役時，也不時直接或間接透過學長姐表達他對我的關懷。退伍後，在他的鼓勵下，我又回到交大統計所接受更精進細緻深入的教育與研究訓練。李老師過世之後，由他的親朋好友所透露出的點點滴滴，可知李昭勝老師在學問方面是苦學好學並勇於嘗試新的學科。執筆至此，在腦海中響起與浮現他的聲形。

論文口試時，承蒙清華大學徐南蓉教授、中央研究院黃信誠老師及本所盧鴻興教授即使準備出國參加研討會仍在暑假撥冗前來口試，對於細節與其他方向不吝指正且提供更精闢見解與寶貴意見及建議，使本論文更加完備，在此感謝每位口試委員傾囊相授。此外，再次感謝所上每位老師在我求學期間，不論是課業方面還是生涯規劃方面都適時提供幫助與建議；所上行政助理郭碧芬小姐在所務及學生事務明確告知應注意事項，使所上師生得以心無旁騖專注在課業研究。

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Chapter 1

Introduction

Our main subject in this dissertation is to find a method dealing with regression models with heteroscedastic AR(1) covariance matrices. Heteroscedasticity, the phenomenon of a set of statistical distributions with different variances, is one of the attention-getting issues for researchers. Such heteroscedasticity may be pertained to unknown variables while some heteroscedasticity may be related to variables of interest. For instance, the behavior of a chemical reaction might be affected by temperature or reaction time, the heights of children may be affected by the gender and the differences of the yields of the corn may be affected by the species of the corn, etc. Therefore, it is desirable to discuss and to find a method to handle the problem with heteroscedastic phenomena.

The Behrens-Fisher problem is the typical case where the variances of the two normal populations are not quite equal, that is, there is heteroscedasticity between two groups. Linnik (1968) has shown that the inferences about the difference of the means between two populations have no exact fixed-level tests (conventional) based on the complete sufficient statistics, that is, based on the two sample means and the two sample variances. However, exact conventional solutions based on other statistics and approximate solutions based on the complete sufficient statistics exist. For example, Scheffé (1943) gave a class of exact solutions to the Behrens-Fisher problem, but Scheffé type solutions are inefficient in the sense that they do not use all the information in the data about the true value of the parameter. The expected length of the confidence intervals given by the Scheffé solution is much larger than those given by approximate solutions. (See, Welch (1947), Lee and Gurland (1975), and Scheffé (1970), etc.) With prior distributions, the Bayesian method can make inferences about the difference of the means based on the posterior distribution, which combines the information in the prior distributions and the information in the data (the likelihood function) about the parameters. Some statisticians believe that it is not appropriate to talk about the prior distribution when it is known that the parameter is not a random variable but rather an unknown fixed number.

The concepts of the generalized p-values and the generalized confidence intervals were proposed by Tsui and Weerahandi (1989) and Weerahandi (1993), respectively. Although the generalized approach shares the same philosophy of the Bayesian approach that the inferences should be made with special regards to the data at hand, the parameters are not treated as random variables in generalized approach. Comparing to the classical tests, the generalized p-values are based on a number of test statistics whereas conventional p-values are based only on a single test statistics. The methods are exact in the sense that the tests and the confidence intervals developed are based on exact probability expressions rather than on asymptotic approximations. The method of the generalized p-values is frequently applied to deal with many practical problems concerning the situation with unequal variances or unequal covariance matrices. For example, Thursby (1992), Weerahandi (1995), Ananda and Weerahandi (1996), Chang and Huang (2000), McNally, Iyer and Mathew (2003), Krishnamoorthy and Lu (2003), Mathew and Krishnamoorthy (2003, 2004), Lee and Lin (2004), Hannig, Iyer and Patterson (2006) and many others have carried out a number of investigations and applications of generalized p-values in making inferences of the difference of two exponential means, extreme values under normality, the ratio of mean of two normal populations, some functions of the means of lognormal distribution, the Behrens-Fisher problem and the common mean of several normal populations, etc.

The generalized method is also applied to deal with the traditional multivariate statistical problems in which nuisance parameters are present and they are difficult to make inferences. Griffiths and Judge (1992), Chi and Weerahandi (1998), Gamage and Weerahandi (1998), Gamage, Mathew and Weerahandi (2004) and others presented the generalized method as an alternative way of handling multivariate statistical problems like regression models, linear models and mixed models etc., with different covariance matrices among multiple groups. However, it is desired that the generalized method in the multivariate case should be brought to more attention. We propose a new generalized test variable to make inferences on a linear combination of multivariate normal mean vectors among multiple populations. In simulation studies, when only two populations are considered, our results are equivalent to those proposed by Gamage et al. (2004) in the bivariate case which is also known as the bivariate Behrens-Fisher problem. However, in some higher dimension case, these two results are quite different. The details will be discussed later.

With the notions and concepts of generalized p-values and the generalized confidence regions, we provide the exact inferences on the multivariate analysis-of-variance model (MANOVA), including the growth curve models with the uniform covariance structures and the serial covariance structures. Lee (1988) applied the growth curve model to the multivariate linear model with two special covariance structures, that is, the uniform covariance structures and the serial covariance structures. The growth curve model was first proposed by Potthoff and Roy (1964). Lee and Geisser (1975), Lee (1988) and many others have shown that the growth curve model is one of the most useful methods for dealing with the MANOVA model with the serial covariance structures. However, the growth curve model is restricted to handling either a single group or multiple groups only under the assumption of identical error correlation among the groups. As with many traditional methods, the growth curve model has difficulty in dealing with models in which the error correlations are different among distinct groups. Hence, we will apply the generalized method to discuss the regression model with heteroscedastic AR(1) covariance matrices.

Lin and Lee (2003) showed that the generalized method provides an alternative way of dealing with the MANOVA model with unequal uniform covariance structures among multiple groups. However, the procedure was based on the assumption of the special design matrices. Thus we will extend the idea with some modifications to further consider the growth curve model with possibly unequal serial covariance matrices between different groups.

In this dissertation, we will start out with brief introduction of generalized inferences, including generalized p-values and the generalized confidence intervals in Chapter 2. We will make the generalized inferences on a linear combination of the mean vectors under the assumption of unequal covariance matrices in Chapter 3. The traditional procedure to deal with regression models when the covariance matrices are known is described in Chapter 4. The growth curve model is also described in Chapter 4. The regression models with the unequal serial covariance structures will be discussed in Chapter 5. Finally, several numerical examples and simulation studies are given to illustrate the advantages of our proposed methods in Chapter 6. The concluding remarks are also provided in Chapter 6. Based on the standardized expression of the generalized test variable (GTV), we proposed algorithms to compute the generalized p-value and the generalized confidence region in Appendix.

Chapter 2

The Theory of Generalized Inference

2.1 The theories of generalized *p*-values and generalized confidence intervals

Let $\mathbf{W}$ be a random variable whose distribution $f(\mathbf{W}\,|\,\zeta)$ depends on a vector of unknown parameter vector $\zeta = (\theta,\ \boldsymbol{\eta})$, where θ is the parameter of interest, and $\boldsymbol{\eta}$ is a vector of nuisance parameters. Suppose we are interested in testing

$$H_0 : \theta \le \theta_0 \ \text{ vs. } H_1 : \theta > \theta_0, \tag{2.1}$$

where θ_0 is a pre-specified quantity. The concepts of generalized *p*-values and generalized confidence intervals were developed by Tsui and Weerahandi (1989) and Weerahandi (1993), respectively, to deal with the statistical problems in which nuisance parameters are present such that the classical statistical methods are difficult to make inferences. We will briefly introduce these concepts as follows.

The ***generalized test variable*** (GTV) of the form $H(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta})$ with $\mathbf{w}$ being the observed value of $\mathbf{W}$ is chosen to satisfy the following requirements:

(i) For fixed $\mathbf{w}$, the distribution of $H(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta})$ is free of the vector of nuisance parameters $\boldsymbol{\eta}$.

(ii) The value of $H(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta})$ at $\mathbf{W}=\mathbf{w}$ is free of any unknown parameters.

(iii) For fixed $\mathbf{w}$ and $\boldsymbol{\eta}$, $\Pr[H(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta}) \ge h]$ is either an increasing or a decreasing function of θ for any given h. (2.2)

Under the above conditions, if $H(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta})$ is stochastically increasing in θ, then the generalized *p*-values for testing the hypothesis in (2.1) is defined as

$$p = \sup_{\theta \le \theta_0} \Pr[H(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta}) \ge h_0] = \Pr[H(\mathbf{W};\mathbf{w},\theta_0,\boldsymbol{\eta}) \ge h_0], \tag{2.3}$$

where $h_0 = H(\mathbf{w};\mathbf{w},\theta_0,\boldsymbol{\eta})$.

Under the same setup, a ***generalized pivotal quantity*** (GPQ), $D(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta})$, satisfies the following conditions:

(i) The distribution of $D(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta})$ is free of unknown parameters.

(ii) The observed value of $D(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta})$ is free of nuisance parameters $\boldsymbol{\eta}$.

Condition (i) allows us to write probability statements leading to confidence intervals that can be evaluated regardless of the values of the unknown parameters. Condition (ii) ensures that given the current sample point $D(\mathbf{w};\mathbf{w},\theta,\boldsymbol{\eta})$, we can obtain a subset of parameter space that can be computed without knowing the values of the nuisance parameters. Let c_1 and c_2 be such that

$$\Pr[c_1 \le D(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta}) \le c_2] = 1-\alpha \ , \tag{2.4}$$

then $\{\theta : c_1 \le D(\mathbf{w};\mathbf{w},\theta,\boldsymbol{\eta}) \le c_2\}$ is a $100(1-\alpha)\%$ generalized confidence interval for θ. Furthermore, if the value of $D(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta})$ at $\mathbf{W}=\mathbf{w}$ is θ, then $\{D(\mathbf{w};\alpha/2),\ D(\mathbf{w};1-\alpha/2)\}$ is a $100(1-\alpha)\%$ confidence interval for θ, where $D(\mathbf{w};\gamma)$ represents the γ^{th} quantile of $D(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta})$.

2.2 Substitution method

To get an applicable GTV or GPQ, Peterson, Berger, and Weerahandi (2003) proposed a systematic approach, that is, ***substitution method***. Let $(V_1,\ldots,V_k)$ be a set of random variables with distributions free of unknown parameters, and their joint distribution be known. Suppose that there is also a set of observable statistics $(W_1,\ldots,W_k)$, with observed values $(w_1,\ldots,w_k)$ and known distributions, such that the number of $(W_1,\ldots,W_k)$, k, is equal to that of unknown parameters of the problem, say $(\lambda_1,\ldots,\lambda_k)$. Then the substitution method is carried out in the following procedure.

1. Deposit the parameter of interest, θ, into the function of $(\lambda_1,\ldots,\lambda_k)$ or express θ in terms of $(W_1,\ldots,W_k)$ and $(V_1,\ldots,V_k)$.

2. Obtain a GTV $H(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta})$ by replacing $(W_1,\ldots,W_k)$ with $(w_1,\ldots,w_k)$ and substrate θ from step 1.

3. Check whether $H(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta})$ satisfies properties (i) and (iii) in (2.2).

4. Rewrite $(V_1,\ldots,V_k)$ terms appearing in $H(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta})$ in terms of $(W_1,\ldots,W_k)$ and $(\lambda_1,\ldots,\lambda_k)$. Then check the properties (ii) in (2.2) and show that the observed sample point on the boundary of the extreme region.

5. Calculus the generalized *p*-value based on $H(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta})$.

It should noted that to find a potential GTV or GPQ, there are various replacements of parameters by random variables and substitution of random variables by their observed values from step 1 to step 5.

2.3 Illustrative example

Weerahandi (2004) gave several examples to illustrate the substitution method and Two of them will be chosen to exhibit the substitution method for GTV and GPQ as follows.

Suppose that $X_1, X_2, \cdots, X_n$ are independent and identically distributed as $N(\mu, \sigma^2)$, with mean μ and variance σ^2. $\bar{X}$ and S^2 are sample mean and sample variance, respectively.

Example of the generalized *p*-value

Suppose $\theta = \mu + \sigma^2$ is a function of the parameters of the normal distribution. The parameter can be expressed in terms of the sufficient statistics and random variables as

$$\theta = \bar{X} - Z\,\sigma/\sqrt{n} + \sigma^2 \tag{2.5}$$

$$= \bar{X} - Z\frac{S}{\sqrt{U}} + \frac{nS^2}{U}, \tag{2.6}$$

where $Z = \dfrac{\bar{X} - \mu}{\sigma/\sqrt{n}}$ and $U = \dfrac{nS^2}{\sigma^2}$ are the independent standard normal and Chi-squared random variables. Let $\bar{x}$ and s^2 be the observed values of $\bar{X}$ and S^2, respectively, we can obtain the potential test variable as

$$\begin{aligned} H &= \bar{x} - Z\frac{s}{\sqrt{U}} + \frac{ns^2}{U} - \theta \\ &= \bar{x} - \frac{\bar{X} - \mu}{\sigma/\sqrt{n}} \frac{s\,\sigma/\sqrt{n}}{S} + \frac{s^2\sigma^2}{S^2} - \theta \\ &= \bar{x} - \frac{s(\bar{X} - \mu)}{S} + \frac{s^2\sigma^2}{S^2} - \theta. \end{aligned} \tag{2.7}$$

Having obtained the identity that relates the parameter to the sufficient statistics and random variables that are free of unknown parameters, it is clear that the observed value of H is zero and its distribution does not depend on nuisance parameters. It also follows from (2.7) that it is stochastically decreasing in the parameter of interest θ. Hence, H is indeed a test variable (GTV). So, for instance hypotheses of the form $H_0 : \theta \le \theta_0$ can be tested on the generalized *p*-value

$$p = \Pr(H \le 0 \mid \theta = \theta_0)$$

$$= \Pr(\frac{sZ}{\sqrt{U}} - \frac{ns^2}{U} \ge \bar{x} - \theta_0)\,. \tag{2.8}$$

In this example, the *p*-value can be computed by numerical integration with respect to independent *Z* and *U*. The probability of the inequality in appearing in the formula can also be evaluated by the Monte Carlo method. This is accomplished by generating a large number of random numbers from *Z* and *U*, and then finding the fraction of pairs of random numbers for which the inequality is satisfied.

Example of the generalized confidence interval

Suppose $\theta = (\mu + \sigma)/(\mu^2 + \sigma^2)$ is the parameter of interest, where μ and σ are the mean and the standard deviation of the normal distribution. Let $Z = \dfrac{\bar{X} - \mu}{\sigma/\sqrt{n}}$ and $U = \dfrac{nS^2}{\sigma^2}$ be the independent standard normal and Chi-squared random variables, then

$$\begin{aligned}\theta &= (\mu+\sigma)/(\mu^2+\sigma^2)\\ &= \frac{\bar{X} - Z\,\sigma/\sqrt{n} + \sigma}{(\bar{X} - Z\,\sigma/\sqrt{n})^2 + \sigma^2}\\ &= \frac{\bar{X} - Z\,S/\sqrt{U} + S\sqrt{n/U}}{(\bar{X} - Z\,S/\sqrt{U})^2 + nS^2/U}.\end{aligned}$$

Hence we can define two representations of the GPQ as

$$D = \frac{\bar{x} - Z\,s/\sqrt{U} + s\sqrt{n/U}}{(\bar{x} - Z\,s/\sqrt{U})^2 + ns^2/U} \tag{2.9}$$

$$= \frac{\bar{x} - s(X-\mu)/S + s\sigma/S}{(\bar{x} - s(X-\mu)/S)^2 + (s\sigma/S)^2}\,. \tag{2.10}$$

From (2.9), the distribution D is free of unknown parameters and (2.10) implies that the observed value of D is θ. Then $\{D(\mathbf{w};\alpha/2),\, D(\mathbf{w};1-\alpha/2)\}$ is a $100(1-\alpha)\%$ generalized confidence interval for θ, or with $\mathbf{w}' = (\bar{x}, s)$,

$$1-\alpha = \Pr[D(\mathbf{w};\alpha/2) \le \frac{\bar{x} - Z\,s/\sqrt{U} + s\sqrt{n/U}}{(\bar{x} - Z\,s/\sqrt{U})^2 + ns^2/U} \le D(\mathbf{w};1-\alpha/2)]\,. \tag{2.11}$$

The probability can be evaluated by numerical integration with respect to (Z,U) or by Monte Carlo integration.

Further details on the concepts of generalized *p*-values and generalized confidence intervals can be found in Weerahandi (1995, 2004). When there is more than one parameter of interest, as usually the case in linear models, the substitution method should be modified to obtain potential GTV and GPQ.

Chapter 3

Inferences on a Linear Combination of K Multivariate Normal Mean Vectors

3.1 Introduction

Suppose there exist K independent d-variate normal populations with mean vector $\boldsymbol{\mu}_i$ and covariance matrix $\boldsymbol{\Sigma}_i$, $i=1,2,\ldots,K$, where $\boldsymbol{\mu}_i$ and $\boldsymbol{\Sigma}_i$ are possibly unknown and unequal among group. We want to make inferences on a linear combination of K mean vectors. This problem arises because sometimes there is a theoretical reason for believing some characteristics of these populations to be such that their mean vectors have some relationships or practitioners want to know some characteristics of compound material. For example, in the Edgar Anderson's famous Iris data, there is a theoretical belief that the four gene structures of three species to be such that the mean vectors of the three populations, (1) iris versicolor (2) iris setosa and (3) iris virginica, are related to $3\boldsymbol{\mu}_1 = 2\boldsymbol{\mu}_2 + \boldsymbol{\mu}_3$ (Anderson, 2003).

If the difference between the covariance matrices is small and the sample sizes are large, the Hotelling's T^2-test for testing a linear combination of mean vectors has good performance. However, if the covariance matrices are quite different and/or the sample sizes are small, the nominal significance level may be distorted. Therefore, we intend to develop a procedure to provide generalized inferences for a linear combination of the mean vectors, $\boldsymbol{\theta} = \mathbf{G}\boldsymbol{\mu}$, where $\mathbf{G}$ is a designed $d \times dK$ matrix, and $\boldsymbol{\mu}$ is the dK-variate mean vector with $\boldsymbol{\mu}' = (\boldsymbol{\mu}_1', \cdots, \boldsymbol{\mu}_K')$. That is, we will provide a generalized confidence region for $\boldsymbol{\theta}$ and test the hypothesis

$$H_0 : \mathbf{G}\boldsymbol{\mu} = \boldsymbol{\theta}_0 \quad \text{vs.} \quad H_1 : \mathbf{G}\boldsymbol{\mu} \neq \boldsymbol{\theta}_0, \tag{3.1}$$

where $\boldsymbol{\theta}_0$ is a given vector. For example, in the Iris data, we can set $\mathbf{G} = (3\mathbf{I}_d, -2\mathbf{I}_d, -\mathbf{I}_d)$ and $\boldsymbol{\theta}_0 = \mathbf{0}$ to perform this hypothesis.

Suppose $\mathbf{X}_{ij}$'s are independent random vectors of sample size n_i. Define the i^{th} sample mean vector and sample covariance matrix as

$$\bar{\mathbf{X}}_i = \frac{1}{n_i}\sum_{j=1}^{n_i}\mathbf{X}_{ij} \quad \text{and} \quad \mathbf{S}_i = \frac{1}{n_i}\sum_{j=1}^{n_i}(\mathbf{X}_{ij} - \bar{\mathbf{X}}_i)(\mathbf{X}_{ij} - \bar{\mathbf{X}}_i)', \quad i = 1, \ldots, K. \tag{3.2}$$

It can be shown that

$$\bar{\mathbf{X}}_i \sim N_d(\boldsymbol{\mu}_i, \frac{\boldsymbol{\Sigma}_i}{n_i}) \quad \text{and} \quad \mathbf{A}_i = n_i \mathbf{S}_i \sim W_d(n_i - 1, \boldsymbol{\Sigma}_i), \ i = 1, \ldots, K, \tag{3.3}$$

and both of them are independently distributed, where $N_d(\boldsymbol{\pi}, \boldsymbol{\Psi})$ denotes d-variate normal distribution with mean vector $\boldsymbol{\pi}$ and $W_d(r, \boldsymbol{\Psi})$ is the d-dimensional Wishart distribution with degrees of freedom r and scale matrix $\boldsymbol{\Psi}$. Furthermore, n_i is supposed to greater than d, $n_i > d$, $i = 1, \ldots, K$, to ensure $\mathbf{S}_i^{-1}$ exists with probability one. Because the distributions of $\bar{\mathbf{X}}_i$ and $\mathbf{S}_i$ are affine invariant, and thus, we will test the problem (3.1) and construct a confidence region of $\boldsymbol{\theta}(= \mathbf{G}\boldsymbol{\mu})$ based on these judicious condensation of the data. Using the underlying distribution assumptions, our approach procedures are associated with an exact probability statement and a repeated sampling interpretation.

For K=2, $\mathbf{G} = (\mathbf{I}_d, -\mathbf{I}_d)$ and $\boldsymbol{\theta}_0 = \mathbf{0}$, (3.1) is reduced to the well-known multivariate Behrens-Fisher problem. For this topic, there are several exact as well as approximate tests are considered in the literature for the past five decades. For example, Christensen and Rencher (1997) compared seven solutions for their Type I error rates and powers and suggested that Kim's (1992) and Nel and Van der Merwe's (1986) solutions had the highest powers among solutions whose Type I error rates were not inflated. Krishnamoorthy and Yu (2004) modified the Nel and Van der Merwe's (1986) test and provided an approximate invariant solution for the problem. In addition to those approximate procedures, Bennett (1951) provided an exact solution for the generalized Behrens-Fisher problem. However, the power obtained by Bennett's method was poor under unequal sample sizes because the method was not based on sufficient statistics. Johnson and Weerahandi (1988) provided an exact Bayesian solution based on Bayesian Approach and Gamage, Mathew and Weerahandi (2004) provided the generalized p-values and generalized confidence region for the Behrens-Fisher problem.

We would like to further consider K non-homogeneous multivariate normal populations with unequal sample sizes and unequal covariance matrices, and then provide an invariant generalized test variable and construct a generalized confidence region for a linear combination of K multivariate normal mean vectors. In our proposed model, the multivariate Behrens-Fisher problem can be treated as a special case of our model. The concepts of generalized p-value and generalized confidence intervals have turned out to be extremely fruitful for obtaining tests and confidence intervals involving "non-standard" parameters. Therefore, we will use the idea to derive a new generalized pivot quantity that is simple to use for both hypothesis testing and confidence region estimation of $\mathbf{G\mu}$.

Our procedures for hypothesis testing and the generalized confidence region of $\mathbf{G\mu}$ construction are presented in Section 3.2. Several methods in the multivariate Behrens-Fisher problem are briefly introduced in Section 3.3. Results will be illustrated with real and simulated data in Chapter 6. Two simulation studies are presented in Section 6.1 to compare the type I error rates, expected areas and the coverage probabilities in different combinations of sample sizes and covariance matrices for difference procedures, and then two sets of data will be illustrated for our procedures in Section 6.2.

3.2 Hypothesis testing and confidence region estimation for $\mathbf{G\mu}$

Suppose we have K independent d-variate multivariate normal populations with mean vector $\boldsymbol{\mu}_i$ and unequal covariance matrices $\boldsymbol{\Sigma}_i$ for the ith sample. Let $\bar{\mathbf{X}}_i$ and $\mathbf{S}_i$ be the sample mean vector and sample covariance matrix for the i^{th} population, which are defined in (3.2). We will consider the problem of estimating a linear combination of K multivariate normal mean vectors, $\mathbf{G\mu}$, based on the minimal sufficient statistics $(\bar{\mathbf{X}}_1,\ldots,\bar{\mathbf{X}}_K,\ \mathbf{S}_1,\ldots,\mathbf{S}_K)$.

In this section, we will first derive the generalized p-value and construct a generalized confidence region of $\mathbf{G\mu}$ based on the generalized method and then reviewed some commonly used methods. For some special cases, especially the multivariate Behrens-Fisher problem, several methods will also be reviewed in Section 3.3.

3.2.1 Solutions based on the generalized method

It is noted that $\bar{\mathbf{X}}_i$ and $\mathbf{S}_i$ are mutually independent with $\bar{\mathbf{X}}_i \sim N_d(\boldsymbol{\mu}_i,\ \boldsymbol{\Sigma}_i/n_i)$, $\mathbf{S}_i \sim W_d(n_i-1,\dfrac{\boldsymbol{\Sigma}_i}{n_i})$ and $\mathbf{A}_i = n_i\mathbf{S}_i \sim W_d(n_i-1,\boldsymbol{\Sigma}_i)$, $i=1,\ldots,K$. Let $\bar{\mathbf{X}}' = (\bar{\mathbf{X}}_1',\ldots,\bar{\mathbf{X}}_K')$ then the MLE (maximum likelihood estimator) of $\boldsymbol{\theta}$ is

$$\hat{\boldsymbol{\theta}} = \mathbf{G}\bar{\mathbf{X}} \sim N_d(\boldsymbol{\theta},\mathbf{G\Phi G}') \quad , \tag{3.4}$$

where $\mathbf{\Phi}$ is the block diagonal matrix (Bdiag),

$$\mathbf{\Phi} = Bdiag(\frac{\mathbf{\Sigma}_1}{n_1}, \cdots, \frac{\mathbf{\Sigma}_K}{n_K}) \equiv \begin{pmatrix} n_1^{-1}\mathbf{\Sigma}_1 & & \mathbf{0} \\ & \ddots & \\ \mathbf{0} & & n_K^{-1}\mathbf{\Sigma}_K \end{pmatrix}.$$

If the covariance matrices $\mathbf{\Sigma}_i$'s are given, it is known that from (3.4) we can get

$$\left(\mathbf{G\Phi G}'\right)^{-1/2}\mathbf{G}(\bar{\mathbf{X}}-\boldsymbol{\mu}) \equiv \mathbf{Z}_d \sim N_d(\mathbf{0},\ \mathbf{I}_d). \qquad (3.5)$$

If the covariance matrix $\mathbf{\Sigma}_i$ for the i^{th} population is unknown, let $\mathbf{S} = Bdiag(\mathbf{S}_1,...,\mathbf{S}_K)$ and $\mathbf{s} = Bdiag(\mathbf{s}_1,...,\mathbf{s}_K)$ be the observed value of $\mathbf{S}$, then we can define

$$\mathbf{R} = \left[\mathbf{s}^{-1/2}\mathbf{\Phi}\mathbf{s}^{-1/2}\right]^{-1/2}\left[\mathbf{s}^{-1/2}\mathbf{S}\mathbf{s}^{-1/2}\right]\left[\mathbf{s}^{-1/2}\mathbf{\Phi}\mathbf{s}^{-1/2}\right]^{-1/2}, \qquad (3.6)$$

where $\mathbf{\Psi}^{1/2}$ means the positive definite square root of the positive definite matrix $\mathbf{\Psi}$ and $\mathbf{\Psi}^{-1/2} = (\mathbf{\Psi}^{1/2})^{-1}$. It should be noted that $\mathbf{R}$ also stands for a block diagonal matrix with $\mathbf{R} = Bdiag(\mathbf{R}_1,...,\mathbf{R}_K)$, where

$$\mathbf{R}_i = \left[\mathbf{s}_i^{-1/2}(\mathbf{\Sigma}_i / n_i)\mathbf{s}_i^{-1/2}\right]^{-1/2}\left[\mathbf{s}_i^{-1/2}\mathbf{S}_i\mathbf{s}_i^{-1/2}\right]\left[\mathbf{s}_i^{-1/2}(\mathbf{\Sigma}_i / n_i)\mathbf{s}_i^{-1/2}\right]^{-1/2}. \qquad (3.7)$$

Since $\mathbf{R}_i \sim W_d(n_i - 1,\ \mathbf{I}_d)$ is free of any unknown parameters, and for the fact that at $\mathbf{S} = \mathbf{s}$, the observed value $\mathbf{r}$ of $\mathbf{R}$ is $\left[\mathbf{s}^{-1/2}\mathbf{\Phi}\mathbf{s}^{-1/2}\right]^{-1}$, it is clear that $\mathbf{s}^{1/2}\mathbf{R}^{-1}\mathbf{s}^{1/2} = \mathbf{\Phi}$ at $\mathbf{S} = \mathbf{s}$. That means we can use the information of $\mathbf{s}$ and $\mathbf{R}$ to make inference about the nuisance parameters $\mathbf{\Phi}$. Furthermore, we will derive the generalized inferences for $\mathbf{G}\boldsymbol{\mu}$ based on $\bar{\mathbf{X}}$ and $\mathbf{R}$.

Let $\bar{\mathbf{x}}$ and $\mathbf{r}$ be the corresponding observed values of $\bar{\mathbf{X}}$ and $\mathbf{R}$, respectively, the generalized pivot quantity can be expressed as

$$\mathbf{T}(\bar{\mathbf{X}},\mathbf{R};\bar{\mathbf{x}},\mathbf{r}) = \mathbf{G}\bar{\mathbf{x}} - \left(\mathbf{G}\mathbf{s}^{1/2}\mathbf{R}^{-1}\mathbf{s}^{1/2}\mathbf{G}'\right)^{1/2}\left(\mathbf{G\Phi G}'\right)^{-1/2}\mathbf{G}(\bar{\mathbf{X}}-\boldsymbol{\mu})$$

$$= \mathbf{G}\bar{\mathbf{x}} - \left(\mathbf{G}\mathbf{s}^{1/2}\mathbf{R}^{-1}\mathbf{s}^{1/2}\mathbf{G}'\right)^{1/2}\mathbf{Z}_d. \qquad (3.8)$$

It is noted that the value of $\mathbf{T}$ in (3.8) at $(\bar{\mathbf{X}},\ \mathbf{S}) = (\bar{\mathbf{x}},\ \mathbf{s})$ is $\mathbf{G}\boldsymbol{\mu}$ which is the parameter of interest. Furthermore, given $(\bar{\mathbf{x}},\mathbf{s})$, the distribution of $\mathbf{T}$ is independent of any unknown parameters, therefore, $\mathbf{T}$ in (3.8) satisfies the two conditions in (2.4) and is truly a GPQ, which can be used to construct confidence region for $\mathbf{G}\boldsymbol{\mu}$.

The generalized *p*-value

For given $(\bar{\mathbf{x}},\ \mathbf{s})$, the distribution in (3.8) is independent of unknown parameters and hence the Monte Carlo method can be utilized to construct a confidence region of $\mathbf{G\mu}$, and test the hypothesis

$$H_0 : \mathbf{G\mu} = \boldsymbol{\theta}_0 \quad \text{vs.} \quad H_1 : \mathbf{G\mu} \neq \boldsymbol{\theta}_0, \tag{3.9}$$

where $\boldsymbol{\theta}_0$ is a given vector. Suppose $\mathbf{m_T}$ and $\mathbf{S_T}$ are the mean and covariance matrix of $\mathbf{T}$, and $\tilde{\mathbf{T}} = \mathbf{S_T}^{-1/2}(\mathbf{T} - \mathbf{m_T})$ is the standardized expression of $\mathbf{T}$, then the generalized p-value for testing (3.9) can be computed by

$$p = \Pr\{\|\tilde{\mathbf{T}}\| > \|\tilde{\boldsymbol{\theta}}_0\| \mid \bar{\mathbf{x}}, \mathbf{r}\}, \tag{3.10}$$

where $\tilde{\boldsymbol{\theta}}_0 = \mathbf{S_T}^{-1/2}(\boldsymbol{\theta}_0 - \mathbf{m_T})$, $\|\tilde{\mathbf{T}}\|$ and $\|\tilde{\boldsymbol{\theta}}_0\|$ are norms of $\tilde{\mathbf{T}}$ and $\tilde{\boldsymbol{\theta}}_0$, respectively, with $\|\tilde{\mathbf{T}}\| = \sqrt{\tilde{\mathbf{T}}'\tilde{\mathbf{T}}}$, and the null hypothesis (3.9) will be rejected whenever $p \leq \alpha$.

Furthermore, if we want to test the MANOVA problem of the form $H_0 : \boldsymbol{\mu}_1 = \ldots = \boldsymbol{\mu}_K$ which can be expressed as $H_0 : \mathbf{G}^*\boldsymbol{\mu} = \mathbf{0}$. One convenient choice for $\mathbf{G}^*$ in this particular problem is

$$\mathbf{G}^* = \begin{bmatrix} \mathbf{I}_d & -\mathbf{I}_d & \mathbf{0} & \mathbf{0} & \ldots & \mathbf{0} \\ \mathbf{I}_d & \mathbf{0} & -\mathbf{I}_d & \mathbf{0} & \ldots & \mathbf{0} \\ \vdots & & & & & \\ \mathbf{I}_d & \mathbf{0} & \mathbf{0} & \ldots & \mathbf{0} & -\mathbf{I}_d \end{bmatrix} = \begin{bmatrix} \mathbf{G}^{(2)} \\ \mathbf{G}^{(3)} \\ \vdots \\ \mathbf{G}^{(K)} \end{bmatrix},$$

where $\mathbf{G}^{(i)} = (c_1^{(i)}\mathbf{I}_d, \cdots, c_K^{(i)}\mathbf{I}_d), \quad c_j^{(i)} = \begin{cases} 1 & \text{j= 1} \\ -1 & \text{j= i} \\ 0 & \text{o.w.} \end{cases}.$

Similar to $\mathbf{T}$ in (3.8), the generalized test variable can be expressed as $\mathbf{T}^* = \mathbf{G}^*\bar{\mathbf{x}} - \left(\mathbf{G}^*\mathbf{s}^{1/2}\mathbf{R}^{-1}\mathbf{s}^{1/2}\mathbf{G}^{*\prime}\right)^{1/2}\mathbf{Z}_{d(K-1)}$. And the p-value can also be computed in the similar way as (3.10).

The generalized confidence region

If we are interested in constructing confidence interval of $\boldsymbol{\theta}$. Since $\mathbf{T}$ in (3.8) also fulfills two requirements of the generalized pivotal quantity and the observed value of $\mathbf{T}$ is $\boldsymbol{\theta}$, so it can be used to construct the confidence region of $\boldsymbol{\theta}$. Let $q_{\{\|\tilde{\mathbf{T}}\|;\ 1\text{-}\alpha\}}$ be the $100(1-\alpha)^{\text{th}}$ percentile of $\|\tilde{\mathbf{T}}\|$, such that

$$\Pr\left\{\tilde{\mathbf{T}}'\tilde{\mathbf{T}} = (\mathbf{T}-\mathbf{m_T})'\mathbf{S_T}^{-1}(\mathbf{T}-\mathbf{m_T}) \le q^2_{\{\|\tilde{\mathbf{T}}\|;\ 1\text{-}\alpha\}}\right\} = 1\text{-}\alpha\,, \tag{3.11}$$

Therefore, the $100(1-\alpha)\%$ confidence region of $\boldsymbol{\theta}$ can be solved through

$$\left\{\boldsymbol{\theta} : (\boldsymbol{\theta}-\mathbf{m_T})'\mathbf{S_T}^{-1}(\boldsymbol{\theta}-\mathbf{m_T}) \le q^2_{\{\|\tilde{\mathbf{T}}\|;\ 1\text{-}\alpha\}}\right\}. \tag{3.12}$$

Some remarks about confidence region are given in the Appendix.

3.2.2 Solutions based on the classical methods

In the classical procedure, the Hotelling's T^2 test and the Chi-square test are the commonly used methods. In Hotelling's T^2 test, we assume the population covariance matrices are the same, whereas in the classical Chi-square method, practitioners usually replace the population covariance matrices with the sample covariance matrices. We will briefly introduce these two methods to deal with our problem.

The Hotelling's T^2 test

In this method, we will assume that $\boldsymbol{\Sigma}_1 = \ldots = \boldsymbol{\Sigma}_K = \boldsymbol{\Sigma}$ and $\mathbf{G} = (c_1\mathbf{I}_d, \cdots, c_K\mathbf{I}_d)$, then the point estimator of $\boldsymbol{\theta} = \mathbf{G}\boldsymbol{\mu} = \sum_{i=1}^{K} c_i\boldsymbol{\mu}_i$ and the pool covariance matrix are

$$\hat{\boldsymbol{\mu}} = \sum_{i=1}^{K} c_i\bar{\mathbf{X}}_i$$

and

$$\mathbf{S}_H = \frac{1}{N-K}\sum_{i=1}^{K}\sum_{j=1}^{n_i}(\mathbf{X}_{ij}-\bar{\mathbf{X}}_i)(\mathbf{X}_{ij}-\bar{\mathbf{X}}_i)' = \frac{1}{N-K}\sum_{i=1}^{K} n_i\mathbf{S}_i\,, \tag{3.13}$$

respectively, where $N = \sum_{i=1}^{K} n_i$ and $\bar{\mathbf{X}}_i$ and $\mathbf{S}_i$ are defined in (3.2), respectively. The criterion is $Q^2 = (\sum_{i=1}^{K} c_i\bar{\mathbf{X}}_i - \boldsymbol{\theta})'\left[\sum_{i=1}^{K} c_i^2\mathbf{S}_H / n_i\right]^{-1}(\sum_{i=1}^{K} c_i\bar{\mathbf{X}}_i - \boldsymbol{\theta})$

$$= (\hat{\boldsymbol{\mu}}-\boldsymbol{\theta})'\left(b\mathbf{S}_H\right)^{-1}(\hat{\boldsymbol{\mu}}-\boldsymbol{\theta})\,,$$

where Q^2 has the Hotelling's T^2-distribution with $N-K$ degrees of freedom and $b = \sum_{i=1}^{K} c_i^2 / n_i$. Thus

$$\frac{Q^2}{N-K} \times \frac{N-K-d+1}{d} \sim F_{d,\,N-K-d+1}\,, \tag{3.14}$$

so the *p*-value for testing $H_0 : \sum_{i=1}^{K} c_i\boldsymbol{\mu}_i = \boldsymbol{\theta}_0$, where $\boldsymbol{\theta}_0$ is a given vector, is

$$p=\Pr\left[F_{d,\,N-K-d+1}>(\sum_{i=1}^{K}c_i\bar{\mathbf{x}}_i-\boldsymbol{\theta}_0)'\,\mathbf{S}_H^{-1}\,(\sum_{i=1}^{K}c_i\bar{\mathbf{x}}_i-\boldsymbol{\theta}_0)\cdot\frac{N-K-d+1}{bd(N-K)}\right], \tag{3.15}$$

and the $100(1-\alpha)\%$ confidence region of $\boldsymbol{\theta}$ can be solved through the inequality

$$\left\{\boldsymbol{\theta}:(\hat{\boldsymbol{\mu}}-\boldsymbol{\theta})'\mathbf{S}_H^{-1}\,(\hat{\boldsymbol{\mu}}-\boldsymbol{\theta})\le\frac{bd(N-K)}{N-K-d+1}F_{1-\alpha}(d,\,N-K-d+1)\right\}, \tag{3.16}$$

where $F_{1-\alpha}(d,\,N-K-d+1)$ is the $100(1-\alpha)^{th}$ percentile of the $F_{d,\,N-K-d+1}$ distribution.

The classical Chi-square test

The classical Chi-square method is valid when the covariance matrices are known. The statistics H_d^2, $\mathrm{H}_d^2=(\hat{\boldsymbol{\mu}}-\boldsymbol{\theta})'\left[\sum_{i=1}^{K}c_i^2\mathbf{S}_i/(n_i-1)\right]^{-1}(\hat{\boldsymbol{\mu}}-\boldsymbol{\theta})$, is distributed approximately as a Chi-square distribution with degrees of freedom *d* when the sample sizes tend to infinity, where $\hat{\boldsymbol{\mu}}=\sum_{i=1}^{K}c_i\bar{\mathbf{X}}_i$ and $\boldsymbol{\theta}=\sum_{i=1}^{K}c_i\boldsymbol{\mu}_i$. The *p*-value for testing $H_0:\sum_{i=1}^{K}c_i\boldsymbol{\mu}_i=\boldsymbol{\theta}_0$ is

$$p=\Pr\left[\chi_d^2>(\sum_{i=1}^{K}c_i\bar{\mathbf{x}}_i-\boldsymbol{\theta}_0)'\left[\sum_{i=1}^{K}c_i^2\mathbf{S}_i/(n_i-1)\right]^{-1}(\sum_{i=1}^{K}c_i\bar{\mathbf{x}}_i-\boldsymbol{\theta}_0)\right], \tag{3.17}$$

and the approximate $100(1-\alpha)\%$ confidence region of $\boldsymbol{\theta}$ may be obtained by evaluating

$$\left\{\boldsymbol{\theta}:(\hat{\boldsymbol{\mu}}-\boldsymbol{\theta})'(\sum_{i=1}^{K}c_i^2\mathbf{S}_i/(n_i-1))^{-1}\,(\hat{\boldsymbol{\mu}}-\boldsymbol{\theta})\le\chi_{1-\alpha}^2(d)\right\}, \tag{3.18}$$

where $\chi_{1-\alpha}^2(d)$ is the $100(1-\alpha)^{th}$ percentile of the χ^2 distribution with degrees of freedom *d*.

3.3 The multivariate Behrens-Fisher problem

If we are only interested in the multivariate Behrens-Fisher problem, that is, only two populations are related and $c_1=1$ and $c_2=-1$, i.e., $\mathbf{G}=(\mathbf{I}_d,-\mathbf{I}_d)$; then (3.8) for the generalized pivotal quantity becomes

$$\mathbf{T}_1(\bar{\mathbf{X}},\mathbf{S};\bar{\mathbf{x}},\mathbf{s})=(\bar{\mathbf{x}}_1-\bar{\mathbf{x}}_2)-\left(\mathbf{s}_1^{1/2}\mathbf{R}_1^{-1}\mathbf{s}_1^{1/2}+\mathbf{s}_2^{1/2}\mathbf{R}_2^{-1}\mathbf{s}_2^{1/2}\right)^{1/2}\mathbf{Z}_d\,. \tag{3.19}$$

The *p*-value for testing

$$H_0:\boldsymbol{\mu}_1=\boldsymbol{\mu}_2\quad\text{vs.}\quad H_1:\boldsymbol{\mu}_1\ne\boldsymbol{\mu}_2 \tag{3.20}$$

is similar to (3.10) by replacing $\tilde{\mathbf{T}}$ and $\tilde{\boldsymbol{\theta}}_0$ with $\tilde{\mathbf{T}}_1$ and $\tilde{\mathbf{0}}$, respectively.

Some other methods for dealing with the multivariate Behrens-Fisher problem are briefly reviewed in the follows.

Gamage, Mathew and Weerahandi (2004)

The *p*-value for testing (3.20) derived by Gamage et al. (2004) is

$$p = \Pr\left\{ \mathrm{T}_{\mathrm{Gam}} \geq (\bar{\mathbf{x}}_1 - \bar{\mathbf{x}}_2)' \left(\frac{\mathbf{s}_1}{\mathrm{n}_1 - 1} + \frac{\mathbf{s}_2}{\mathrm{n}_2 - 1} \right)^{-1} (\bar{\mathbf{x}}_1 - \bar{\mathbf{x}}_2) \mid H_0 \right\}, \tag{3.21}$$

where $\mathrm{T}_{\mathrm{Gam}}$ is defined as

$$\mathrm{T}_{\mathrm{Gam}} = \mathbf{Z}'[\mathbf{v}_1^{1/2}\mathbf{\Psi}_1^{-1}\mathbf{v}_1^{1/2} + \mathbf{v}_2^{1/2}\mathbf{\Psi}_2^{-1}\mathbf{v}_2^{1/2}]\mathbf{Z}, \tag{3.22}$$

with $\mathbf{V}_{\mathrm{i}} = \left(\frac{\mathbf{s}_1}{\mathrm{n}_1 - 1} + \frac{\mathbf{s}_2}{\mathrm{n}_2 - 1} \right)^{-1/2} \mathbf{S}_{\mathrm{i}} \left(\frac{\mathbf{s}_1}{\mathrm{n}_1 - 1} + \frac{\mathbf{s}_2}{\mathrm{n}_2 - 1} \right)^{-1/2}$, and $\mathbf{v}_i$ being the observed values of $\mathbf{V}_i$, $\mathbf{\Psi}_{\mathrm{i}} \sim \mathrm{W}_{\mathrm{d}}(\mathrm{n}_{\mathrm{i}} - 1, \mathbf{I}_{\mathrm{d}})$, $i = 1, 2$ and $\mathbf{Z} \sim N_d(\mathbf{0}, \mathbf{I}_d)$.

Furthermore, they also defined $\mathrm{T}^*_{\mathrm{Gam}}/\mathrm{t}^*_{\mathrm{Gam}}$ to test the MANOVA problem of the form $H_0 : \boldsymbol{\mu}_1 = \ldots = \boldsymbol{\mu}_K$, where $\mathrm{T}^*_{\mathrm{Gam}}(\Sigma_1,\ldots,\Sigma_K) = \sum_{\mathrm{i}=1}^{\mathrm{K}} n_i (\bar{\mathbf{X}}_{\mathrm{i}} - \hat{\boldsymbol{\mu}})' \, \Sigma_{\mathrm{i}}^{-1} (\bar{\mathbf{X}}_{\mathrm{i}} - \hat{\boldsymbol{\mu}})$, $\mathrm{t}^*_{\mathrm{Gam}}$ is the observed value of $\mathrm{T}^*_{\mathrm{Gam}}$ and $\hat{\boldsymbol{\mu}} = (\sum_{i=1}^{K} n_i \Sigma_i^{-1})^{-1} \sum_{i=1}^{K} n_i \Sigma_i^{-1} \bar{\mathbf{X}}_{\mathrm{i}}$. However, as the authors had mentioned in their paper, this new GTV $\mathrm{T}^*_{\mathrm{Gam}}/\mathrm{t}^*_{\mathrm{Gam}}$ was not invariant under non-singular transformation (Gamage et. al., 2004).

Krishnamoorthy and Yu (2004)

Krishnamoorthy and Yu (2004) modified the Nel and Van der Merwe's (1986) test and provided an approximate invariant solution for the multivariate Behrens-Fisher problem. They obtained a nonsingular invariant statistic

$$\mathrm{T}_{Kri} = \left[(\bar{\mathbf{X}}_1 - \bar{\mathbf{X}}_2) - (\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2) \right]' \left[(n_1 - 1)^{-1}\mathbf{S}_1 + (n_2 - 1)^{-1}\mathbf{S}_2 \right]^{-1} \left[(\bar{\mathbf{X}}_1 - \bar{\mathbf{X}}_2) - (\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2) \right], \tag{3.23}$$

which is approximately distributed as $\nu d F_{d,\nu-d+1}/(\nu - d + 1)$ where

$$\nu = \frac{d(d+1)}{(n_1 - 1)^{-1}\left[tr\Lambda_1^2 + (tr\Lambda_1)^2 \right] + (n_2 - 1)^{-1}\left[tr\Lambda_2^2 + (tr\Lambda_2)^2 \right]},$$

$$\Lambda_1 = \frac{\mathbf{S}_1}{n_1 - 1}\left(\frac{\mathbf{S}_1}{n_1 - 1} + \frac{\mathbf{S}_2}{n_2 - 1} \right)^{-1},$$

$$\Lambda_2 = \frac{\mathbf{S}_2}{n_2 - 1}\left(\frac{\mathbf{S}_1}{n_1 - 1} + \frac{\mathbf{S}_2}{n_2 - 1}\right)^{-1}.$$

The p-value for testing (3.20) is

$$p = \Pr\left\{ F_{d,\nu-d+1} \geq \frac{\nu - d + 1}{\nu d} \cdot (\overline{\mathbf{x}}_1 - \overline{\mathbf{x}}_2)' \left(\frac{\mathbf{s}_1}{\mathrm{n}_1 - 1} + \frac{\mathbf{s}_2}{\mathrm{n}_2 - 1} \right)^{-1} (\overline{\mathbf{x}}_1 - \overline{\mathbf{x}}_2) \mid H_0 \right\}. \tag{3.24}$$

Chapter 4

The Theories of the Regression Model and the Growth-Curve Model

In this chapter, repeated measurements with different covariance matrices among groups can be expressed by the regression model in matrix form as follows:

$$\mathbf{Y}_{ij} = \mathbf{X}_i \boldsymbol{\beta}_i + \boldsymbol{\varepsilon}_{ij}, \tag{4.1}$$

where $\mathbf{Y}_{ij} = (Y_{ij1}, \cdots, Y_{ijT})'$, Y_{ijt} are measurements at time point t for subject j in group i for $i = 1, \cdots, I$, $j = 1, \cdots, J_i$, $t = 1, \cdots, T$, and $\mathbf{X}_i$'s are the $T \times K$ design matrices with rank K, $1 \le K \le T$. Further, $\boldsymbol{\varepsilon}_{ij}$ are independent T-variate normal, with mean vector $\mathbf{0}$ and the positive definite covariance matrices $\boldsymbol{\Sigma}_i$'s. Estimating and making inferences on $\boldsymbol{\beta}_i$'s are important aspects of regression analysis. If $\boldsymbol{\Sigma}_i$'s are known, the best linear unbiased estimator (BLUE) of $\boldsymbol{\beta}_i$ can be readily obtained via standard procedures. If the error covariance matrices are not known but are assumed to be identical, maximum likelihood estimates (MLE's) via the growth-curve method is one of the approximation methods for dealing with this model when the sample size is large. However, if $\boldsymbol{\Sigma}_i$'s are unknown and distinct between different groups, the traditional methods have serious drawbacks in making inferences about $\boldsymbol{\beta}_i$'s. Even when the covariance matrices are identical among different groups, the growth-curve method can only provide an approximate result. We will briefly introduce the traditional regression model when the covariance matrices are known and the growth-curve model with two special covariance structures.

4.1 Regression model with known covariance matrices

In this section, we will briefly introduce the traditional method for making inferences on $\boldsymbol{\beta}_i$'s when the covariance matrices are known (Arnold (1981), Scheffé (1999) and Anderson(2003)). If the covariance matrices $\boldsymbol{\Sigma}_i$'s of the regression model (4.1) are known and given, we can pre-multiply $\boldsymbol{\Sigma}_i^{-1/2}$ to both sides of the regression model (4.1), where $\boldsymbol{\Sigma}_i^{-1/2}$ denotes a positive definite square root matrix of $\boldsymbol{\Sigma}_i^{-1}$, therefore we get the following standardized regression model:

$$\tilde{\mathbf{Y}}_{ij} = \tilde{\mathbf{X}}_i \boldsymbol{\beta}_i + \tilde{\boldsymbol{\varepsilon}}_{ij}, \quad j = 1, \cdots, J_i; \quad i = 1, \cdots, I, \tag{4.2}$$

where $\tilde{\boldsymbol{\varepsilon}}_{ij} \sim N_T(\mathbf{0}, \mathbf{I}_T)$, $\mathbf{I}_T$ is the T-dimension identical matrix. The best linear unbiased estimator (BLUE) of $\boldsymbol{\beta}_i$ is

$$\hat{\boldsymbol{\beta}}_i = (J_i \tilde{\mathbf{X}}_i' \tilde{\mathbf{X}}_i)^{-1} \tilde{\mathbf{X}}_i' \sum_j \tilde{\mathbf{Y}}_{ij}, \tag{4.3}$$

and $\hat{\boldsymbol{\beta}}_i \sim N_K(\boldsymbol{\beta}_i, (J_i \mathbf{X}_i' \boldsymbol{\Sigma}_i^{-1} \mathbf{X}_i)^{-1})$, $i = 1, \cdots, I$. Hence $J_i (\hat{\boldsymbol{\beta}}_i - \boldsymbol{\beta}_i)' \ \mathbf{X}_i' \boldsymbol{\Sigma}_i^{-1} \mathbf{X}_i (\hat{\boldsymbol{\beta}}_i - \boldsymbol{\beta}_i)$ are independently distributed as the χ^2-distribution with degree of freedom K for $i = 1, \cdots, I$. Researchers are interested in testing the equality of the trends with heteroscedastic phenomena, that is,

$$\mathbf{H}_0 : \boldsymbol{\beta}_1 = \cdots = \boldsymbol{\beta}_I = \boldsymbol{\beta}. \tag{4.4}$$

Under the null hypothesis (4.4), the estimator of the common $\boldsymbol{\beta}$ is

$$\hat{\boldsymbol{\beta}} = (\sum_i J_i \tilde{\mathbf{X}}_i' \tilde{\mathbf{X}}_i)^{-1} (\sum_i \sum_j \tilde{\mathbf{X}}_i' \tilde{\mathbf{Y}}_{ij}) \sim N_K(\boldsymbol{\beta}, \boldsymbol{\Psi}), \tag{4.5}$$

where $\boldsymbol{\Psi} = (\sum_i J_i \tilde{\mathbf{X}}_i' \tilde{\mathbf{X}}_i)^{-1} = (\sum_i J_i \mathbf{X}_i' \boldsymbol{\Sigma}_i^{-1} \mathbf{X}_i)^{-1}$. Let $\tilde{S}_0^2 = \sum_i \sum_j (\tilde{\mathbf{Y}}_{ij} - \tilde{\mathbf{X}}_i \hat{\boldsymbol{\beta}})' \ (\tilde{\mathbf{Y}}_{ij} - \tilde{\mathbf{X}}_i \hat{\boldsymbol{\beta}})$ be the standardized residual sum of squares under the null hypothesis and $\tilde{S}_a^2 = \sum_i \sum_j (\tilde{\mathbf{Y}}_{ij} - \tilde{\mathbf{X}}_i \hat{\boldsymbol{\beta}}_i)' \ (\tilde{\mathbf{Y}}_{ij} - \tilde{\mathbf{X}}_i \hat{\boldsymbol{\beta}}_i)$ be the standardized residual sum of squares under the alternative hypothesis. We can then obtain the F statistic with

$$F = \frac{NT - IK}{(I-1)K} \frac{\tilde{S}_0^2 - \tilde{S}_a^2}{\tilde{S}_a^2} \sim F_{((I-1)K,\, NT-IK)}, \tag{4.6}$$

where $N = \sum J_i$. The p-value for testing (4.4) can be calculated by

$$p\text{-value} = \Pr\{F_{(I-1)K, NT-IK} \geq \frac{NT - IK}{(I-1)K} \frac{\tilde{s}_0^2 - \tilde{s}_a^2}{\tilde{s}_a^2}\}, \tag{4.7}$$

where $\tilde{s}_0^2$ and $\tilde{s}_a^2$ are the observed values of $\tilde{S}_0^2$ and $\tilde{S}_a^2$, respectively, and hypothesis (4.4) is rejected if p-value $\leq \alpha$.

If the null hypothesis cannot be rejected, we may assume that the populations have the common trend $\boldsymbol{\beta}$. The estimation of $\boldsymbol{\beta}$ is then important. From (4.5), the confidence region with confidence coefficient $1-\alpha$ for the common trend $\boldsymbol{\beta}$ is

$$\{\, \boldsymbol{\beta} : (\boldsymbol{\beta} - \hat{\boldsymbol{\beta}})' \boldsymbol{\Psi}^{-1} (\boldsymbol{\beta} - \hat{\boldsymbol{\beta}}) \leq \chi_K^2 (1-\alpha) \,\}, \tag{4.8}$$

where $\boldsymbol{\Psi}^{-1} = \sum_i J_i \mathbf{X}_i' \boldsymbol{\Sigma}_i^{-1} \mathbf{X}_i$ and $\chi_K^2(1-\alpha)$ is the $100(1-\alpha)$ percent point of the

χ^2-distribution with degrees of freedom K.

4.2 The growth-curve model

Potthoff and Roy (1964) proposed the growth-curve model which is a useful generalized multivariate analysis-of-variance model especially for growth-curve problems. Rao (1967, 1975, 1977), Grizzle and Allen (1969), Geisser (1970, 1981), Fearn (1977) and others applied the growth-curve model to some biological data, the forecast of technology substitutions and Bayesian analysis. The regression model (4.1) can be expressed as a growth-curve model if the design matrices are identical. The growth-curve model can be defined as

$$\underset{T\times N}{\mathbf{Y}} = \underset{T\times K}{\mathbf{X}}\ \underset{K\times I}{\mathbf{B}}\ \underset{I\times N}{\mathbf{F}} + \underset{T\times N}{\boldsymbol{\varepsilon}}, \tag{4.9}$$

where $\mathbf{Y} = (\mathbf{Y}_{11}, \cdots, \mathbf{Y}_{IJ_I})$, $\boldsymbol{\varepsilon} = (\boldsymbol{\varepsilon}_{11}, \cdots, \boldsymbol{\varepsilon}_{IJ_I})$, $\mathbf{B} = (\boldsymbol{\beta}_1, \cdots, \boldsymbol{\beta}_I)$ and $\mathbf{F}$ is the $I \times N$ design matrix characterizing the distinct grouping of the N independent vector observations, where $N = \sum_i J_i$. Let $\mathbf{Z}$ be a known $T \times (T-K)$ matrix with rank $T-K$ such that $\mathbf{X}'\mathbf{Z} = \mathbf{0}$. We will utilize the results of the growth-curve model with two special covariance matrices proposed by Lee (1988) to make inferences on $\boldsymbol{\beta}_i$'s.

Uniform covariance structure

When the design matrix $\mathbf{X} = (\mathbf{1}_T, \mathbf{X}_2)$, $\mathbf{1}_T = (1, \ldots, 1)'$, and the covariance matrix is uniform structure, that is,

$$\boldsymbol{\Sigma} = \sigma_u^2[(1-\rho_u)\mathbf{I} + \rho_u \mathbf{1}_T \mathbf{1}_T{}'] = \sigma_u^2(1-\rho_u)\mathbf{I} + [\sigma_u^2 \rho_u]\mathbf{1}_T \mathbf{1}_T{}' \tag{4.10}$$

with $\frac{-1}{T-1} < \rho_u < 1$, then the MLE's of $\mathbf{B}$, σ_u^2 and ρ_u derived by Lee (1988) are

$$\hat{\mathbf{B}} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}\mathbf{F}'(\mathbf{F}\mathbf{F}')^{-1}, \tag{4.11}$$

$$\hat{\sigma}_u^2 = tr\mathbf{S}^* / TN,$$

$$\hat{\rho}_u = (\mathbf{1}_T{}'\mathbf{S}^*\mathbf{1}_T - tr\mathbf{S}^*) / (T-1)tr\mathbf{S}^*,$$

where $\mathbf{S}^* = \mathbf{Y}(\mathbf{I} - \mathbf{F}'(\mathbf{F}\mathbf{F}')^{-1}\mathbf{F})\mathbf{Y}' + \mathbf{Z}(\mathbf{Z}'\mathbf{Z})^{-1}\mathbf{Z}'\mathbf{Y}\mathbf{F}'(\mathbf{F}\mathbf{F}')^{-1}\mathbf{F}\mathbf{Y}'\mathbf{Z}(\mathbf{Z}'\mathbf{Z})^{-1}\mathbf{Z}'$.

Serial covariance structure

When the covariance matrix is serial structure, i.e., the AR(1) errors correlation,

$$\mathbf{\Sigma} = \sigma^2 \mathbf{C}, \tag{4.12}$$

where $\mathbf{C} = (\rho^{|m-n|})$, $1 \le m, n \le T$, $\sigma^2 > 0$, and ρ is restricted to $|\rho| < 1$, which ensures that $\mathbf{\Sigma}$ is positive definite. The MLE's of $\mathbf{B}$ and σ^2 are

$$\hat{\mathbf{B}}(\hat{\rho}) = (\mathbf{X}'\hat{\mathbf{C}}^{-1}\mathbf{X})^{-1}\ \mathbf{X}'\hat{\mathbf{C}}^{-1}\mathbf{Y}\mathbf{F}'(\mathbf{F}\mathbf{F}')^{-1} \tag{4.13}$$

and $\hat{\sigma}^2(\hat{\rho}) = \dfrac{1}{NT}\,[tr(\mathbf{X}'\hat{\mathbf{C}}^{-1}\mathbf{X})^{-1}\ \mathbf{X}'\hat{\mathbf{C}}^{-1}\ \mathbf{Y}(\mathbf{I}-\mathbf{F}'(\mathbf{F}\mathbf{F}')^{-1}\mathbf{F})\mathbf{Y}'\ \hat{\mathbf{C}}^{-1}\mathbf{X} + tr(\mathbf{Z}'\hat{\mathbf{C}}\mathbf{Z})^{-1}\mathbf{Z}'\mathbf{Y}\mathbf{Y}'\mathbf{Z}]$,

respectively, where $\hat{\mathbf{C}} = (\hat{\rho}^{|m-n|})$ and $\hat{\rho}$ is obtained by maximizing the profile likelihood function

$$L_{\max}(\rho) = (\hat{\sigma}^2(\rho))^{-NT/2}(1-\rho^2)^{-N(T-1)/2}. \tag{4.14}$$

For the single group, $\mathbf{F} = (1,\cdots,1)$, and $\mathbf{F}\mathbf{F}' = N$, $\mathbf{Y}\mathbf{F}' = \sum_i \sum_j \mathbf{Y}_{ij} = N\bar{\mathbf{Y}}$ and the MLE's of (4.13) can be written as

$$\hat{\boldsymbol{\beta}}_G(\hat{\rho}) = (\mathbf{X}'\hat{\mathbf{C}}^{-1}\mathbf{X})^{-1}\ \mathbf{X}'\hat{\mathbf{C}}^{-1}\mathbf{Y}\mathbf{F}'(\mathbf{F}\mathbf{F}')^{-1} = (\mathbf{X}'\hat{\mathbf{C}}^{-1}\mathbf{X})^{-1}\ \mathbf{X}'\hat{\mathbf{C}}^{-1}\ \bar{\mathbf{Y}}, \tag{4.15}$$

and $\hat{\sigma}^2(\hat{\rho}) = \dfrac{1}{NT}\,[tr(\mathbf{X}'\hat{\mathbf{C}}^{-1}\mathbf{X})^{-1}\ \mathbf{X}'\hat{\mathbf{C}}^{-1}\ \mathbf{Y}(\mathbf{I}-\dfrac{1}{N}\mathbf{F}'\mathbf{F})\mathbf{Y}'\ \hat{\mathbf{C}}^{-1}\mathbf{X} + tr(\mathbf{Z}'\hat{\mathbf{C}}\mathbf{Z})^{-1}\mathbf{Z}'\mathbf{Y}\mathbf{Y}'\mathbf{Z}]$,

where $\hat{\rho}$ is obtained by maximizing the profile likelihood function.

The approximate $100(1-\alpha)\%$ confidence region for $\boldsymbol{\beta}$ under (4.4) is

$$\{\, \boldsymbol{\beta} : N\hat{\sigma}^{-2}\ (\boldsymbol{\beta}-\hat{\boldsymbol{\beta}}_G)'\ (\mathbf{X}'\hat{\mathbf{C}}^{-1}\mathbf{X})\ (\boldsymbol{\beta}-\hat{\boldsymbol{\beta}}_G) \le \chi^2_K(1-\alpha)\,\}. \tag{4.16}$$

When $K = 2$, the area of the approximate $100(1-\alpha)\%$ confidence region for $\boldsymbol{\beta}$ is

$$A_G(\boldsymbol{\beta},\ 1-\alpha) = \frac{\pi}{N}\left|\hat{\sigma}^{-2}(\mathbf{X}'\hat{\mathbf{C}}^{-1}\mathbf{X})\right|^{-1/2}\ \chi^2_K(1-\alpha). \tag{4.17}$$

4.3 Growth curve models with heteroscedastic uniform covariance structure

Lin and Lee (2003) considered the unbalanced data and unequal design matrices $\mathbf{X}_i = (\mathbf{1}_T, \mathbf{X}_{i2})$ for heteroscedastic variances. The model is expressed in matrix form as follows

$$\mathbf{Y}_{ij} = \mathbf{X}_i\boldsymbol{\beta}_i + \alpha_{ij}\mathbf{1}_T + \boldsymbol{\varepsilon}_{ij}\ ,\quad j = 1,\cdots,J_i\ ,\ i = 1,\cdots,I\ , \tag{4.18}$$

where, $\boldsymbol{\varepsilon}_{ij} \sim N(\mathbf{0}, \mathbf{\Sigma}_{ei})$, the random effects $\alpha_{ij} \sim N(0,\sigma^2_\alpha)$ vary independently, and $\mathbf{\Sigma}_{ei} = \sigma_i^2[(1-\rho)\mathbf{I} + \rho\mathbf{1}_T\mathbf{1}_T{}']$ is uniform correlation structure. The covariance matrix of

$\mathbf{Y}_{ij}$ is also uniform correlation structure, that is, for $i = 1, \cdots, I$

$$Cov(\mathbf{Y}_{ij}) = \mathbf{\Sigma}_i = \sigma_\alpha^2 \mathbf{1}_T \mathbf{1}_T{}' + \mathbf{\Sigma}_{ei} = \sigma_i^2 (1-\rho)\mathbf{I} + (\rho\sigma_i^2 + \sigma_\alpha^2)\mathbf{1}_T \mathbf{1}_T{}', \tag{4.19}$$

and

$$\mathbf{\Sigma}_i^{-1} = [\sigma_i^2(1-\rho)]^{-1}[\mathbf{I} - \frac{\phi_i^2 - \sigma_i^2(1-\rho)}{T\phi_i^2}\mathbf{1}_T \mathbf{1}_T{}'], \tag{4.20}$$

with $\phi_i^2 = \sigma_i^2(1-\rho) + T(\rho\sigma_i^2 + \sigma_\alpha^2)$. The inverse of $\mathbf{\Sigma}_i$ depends on $\sigma_i^2(1-\rho)$ and ϕ_i^2, but not on by ρ itself, therefore $\mathbf{\Sigma}_i^{-1}$ can be expressed as $\mathbf{\Sigma}_i^{-1} = \mathbf{\Sigma}_i^{-1}(\sigma_i^2(1-\rho),\ \phi_i^2)$. Furthermore,

$$\hat{\boldsymbol{\beta}}_i = (\mathbf{X}_i'\mathbf{\Sigma}_i^{-1}\mathbf{X}_i)^{-1}\mathbf{X}_i'\mathbf{\Sigma}_i^{-1}\bar{\mathbf{Y}}_i = (\mathbf{X}_i'\mathbf{X}_i)^{-1}\mathbf{X}_i'\bar{\mathbf{Y}}_i \sim N(\boldsymbol{\beta}_i,\ \frac{(\mathbf{X}_i'\mathbf{\Sigma}_i^{-1}\mathbf{X}_i)^{-1}}{J_i}) \tag{4.21}$$

where $\bar{\mathbf{Y}}_i = \frac{1}{J_i}\sum_j \mathbf{Y}_{ij}$. The residual sum of squares is

$$SSE = \sum_{i=1}^{I}\sum_{j=1}^{J_i}(\mathbf{Y}_{ij} - \mathbf{X}_i\hat{\boldsymbol{\beta}}_i)'(\mathbf{Y}_{ij} - \mathbf{X}_i\hat{\boldsymbol{\beta}}_i) = \sum_{i=1}^{I} S_{W,i} + \sum_{i=1}^{I} S_{B,i}, \tag{4.22}$$

where

$S_{W,i} \equiv \sum_{j=1}^{J_i}[\mathbf{Y}_{ij} - \mathbf{X}_i\hat{\boldsymbol{\beta}}_i - (\bar{Y}_{ij.} - \bar{Y}_{i..})\mathbf{1}_T]'[\mathbf{Y}_{ij} - \mathbf{X}_i\hat{\boldsymbol{\beta}}_i - (\bar{Y}_{ij.} - \bar{Y}_{i..})\mathbf{1}_T]$ and $S_{B,i} \equiv T\sum_{j=1}^{J_i}(\bar{Y}_{ij.} - \bar{Y}_{i..})^2$

with $\mathbf{1}_T = (1,1,\cdots,1)'$, $\bar{Y}_{j.} = \frac{1}{T}\sum_t Y_{jt} = \frac{1}{T}\mathbf{1}_T'\mathbf{Y}_j$, $\bar{Y}_{..} = \frac{1}{J}\sum_j \bar{Y}_{j.} = \frac{1}{J}\sum_j \frac{1}{T}\mathbf{1}_T'\mathbf{Y}_j = \frac{1}{T}\mathbf{1}_T'\bar{\mathbf{Y}}$.

For $i = 1, \cdots, I$, $S_{W,i}$ and $S_{B,i}$ are independently distributed as

$$U_{W,i} = \frac{S_{W,i}}{\sigma_i^2(1-\rho)} \sim \chi^2_{J_i(T-1)-(K-1)} \text{ and } U_{B,i} = \frac{S_{B,i}}{\phi_i^2} \sim \chi^2_{J_i-1}, \tag{4.23}$$

respectively. Pre-multiplying $\mathbf{\Sigma}_i^{-1/2} = \mathbf{\Sigma}_i^{-1/2}(\sigma_i^2(1-\rho),\ \phi_i^2)$ to both sides of Equation (4.18), the model with identity covariance matrix can be rewritten as

$$\tilde{\mathbf{Y}}_{ij} = \tilde{\mathbf{X}}_i\boldsymbol{\beta}_i + \tilde{\boldsymbol{\varepsilon}}_{ij}, \tag{4.24}$$

where $\tilde{\boldsymbol{\varepsilon}}_{ij} \sim N_T(\mathbf{0}, \mathbf{I}_T)$, which is the same as (4.2).

Let $\tilde{S}_0^2(\sigma_1^2(1-\rho),\cdots,\sigma_I^2(1-\rho),\phi_1^2,\cdots,\phi_I^2)$ be the standardized residual sum of squares under null hypothesis (4.4) and $\tilde{S}_a^2(\sigma_1^2(1-\rho),\cdots,\sigma_I^2(1-\rho),\phi_1^2,\cdots,\phi_I^2)$ be the standardized residual sum of squares under the alternative. The generalized p-value for testing the hypothesis (4.4) $\mathbf{H}_0 : \boldsymbol{\beta}_1 = \cdots = \boldsymbol{\beta}_I = \boldsymbol{\beta}$ can be expressed as

$$p = \Pr\{\tilde{S}_0^2(\sigma_1^2(1-\rho),\cdots,\sigma_I^2(1-\rho),\phi_1^2,\cdots,\phi_I^2) > \tilde{s}_0^2(\frac{s_{w,1}}{U_{W,1}},\cdots,\frac{s_{w,I}}{U_{W,I}},\frac{s_{b,1}}{U_{B,1}},\cdots,\frac{s_{b,I}}{U_{B,I}})\}$$

$$= \Pr\{\frac{\tilde{S}_0^2 - \tilde{S}_a^2}{\tilde{S}_a^2} > \tilde{s}_0^2(\frac{s_{w,1}}{U_{W,1}/U_T},\cdots,\frac{s_{w,I}}{U_{W,I}/U_T},\frac{s_{b,1}}{U_{B,1}/U_T},\cdots,\frac{s_{b,I}}{U_{B,I}/U_T}) - 1\} \qquad (4.25)$$

$$= 1 - E_{\Delta}\{F_{\nu_1,\nu_2}[\frac{\nu_2}{\nu_1}\{\tilde{s}_0^2(\frac{s_{w,1}}{M_1M_2\cdots M_{2I}},\cdots,\frac{s_{w,I}}{(1-M_{I-1})M_I\cdots M_{2I}},\frac{s_{b,1}}{(1-M_I)M_{I+1}\cdots M_{2I}},\cdots,\frac{s_{b,I}}{(1-M_{2I-1})M_{2I}}) - 1\}]\},$$

where $\nu_1 = (I-1)K$, $\nu_2 = NT - IK$ and $U_T = \sum_{i=1}^{I}(U_{W,i} + U_{B,i}) \sim \chi^2_{\nu_2}$ with $N = \sum_{i=1}^{I} J_i$.

And E_{Δ} is the expected value with respect to the independent Beta random variables $M_r = \frac{\sum_{i=1}^{r}\lambda_i}{\sum_{i=1}^{r+1}\lambda_i} \sim Beta(\frac{\sum_{i=1}^{r} q_i}{2},\frac{q_{r+1}}{2})$, $r = 1,\cdots,(2I-1)$, with two auxiliary constants $M_0 \equiv 0$ and $M_{2I} \equiv 1$, where $(\lambda_1,\cdots,\lambda_{2I}) = (U_{W,1},\cdots,U_{W,I},U_{B,1},\cdots,U_{B,I})$, q_r is the degrees of freedom of λ_r with $q_r = \begin{cases} J_r(T-1)-(K-1), & r = 1,\cdots,I. \\ J_{r-I}-1, & r = I+1,\cdots,2I. \end{cases}$

Chapter 5

Generalized Inferences on Regression Models with Unequal AR(1) Covariance Matrices

5.1. Introduction

In many fields, such as business, engineering, medical studies, meteorology, etc., serial dependence, i.e., AR(1) errors correlation, is considered one of the most important correlation structures. In particular, a regression model with a polynomial trend (including a linear trend, especially for few measurements taken over time) and serial dependence is one of the strong candidates for analyzing the data sets collected across equally spaced time intervals. Repeated measurement with serial dependence can be expressed by the regression model in matrix form as follows:

$$\mathbf{Y}_{ij} = \mathbf{X}_i \boldsymbol{\beta}_i + \boldsymbol{\varepsilon}_{ij}, \tag{5.1}$$

where $\mathbf{Y}_{ij} = (Y_{ij1}, \cdots, Y_{ijT})'$ for $i = 1, \cdots, I$, $j = 1, \cdots, J_i$, $t = 1, \cdots, T$, and $\mathbf{X}_i$'s are design matrices. Further, $\boldsymbol{\varepsilon}_{ij}$ are independent *T*-variate normal, with mean vector **0** and the AR(1) covariance matrix $\boldsymbol{\Sigma}_i = \sigma_i^2 \mathbf{C}_i$, $\mathbf{C}_i = (\rho_i^{|m-n|})$, $1 \le m, n \le T$, $\sigma_i^2 > 0$, and ρ_i is restricted to $|\rho_i| < 1$, which ensures that $\boldsymbol{\Sigma}_i$ is positive definite.

Potthoff and Roy (1964), Lee and Geisser (1975), Lee (1988) and many others have shown that the growth-curve model is one of the most useful methods for dealing with the regression model (5.1) with AR(1) dependence. However, the growth-curve model is restricted to handling either a single group or multiple groups only under the assumption of identical error correlation among the groups. As with many traditional methods, the growth-curve model has difficulty dealing with models in which the error correlations are different among distinct groups. In this chapter, we propose a method based on the concepts of the generalized *p*-values and the generalized confidence intervals to handle the problem with heteroscedastic phenomena.

Estimating and making inferences on $\boldsymbol{\beta}_i$'s are important aspects of regression analysis. If the error covariance matrices are not known but are assumed to be identical, maximum likelihood estimates (MLE's) via the growth-curve method is one of the approximation methods for dealing with this model when the sample size is large.

However, if the nuisance parameters σ_i^2 and ρ_i are unknown and distinct between different groups, the traditional methods have serious drawbacks in making inferences about $\boldsymbol{\beta}_i$'s. Thus, an exact procedure for making inferences of the fixed effect $\boldsymbol{\beta}_i$ when the serial covariance matrices are unknown and unequal among groups needs to be explored. In Section 4.3, Lin and Lee (2003) showed that the generalized method provided an alternative way of dealing with a regression model (5.1) with unequal uniform covariance structures among multiple groups. Thus, we will extend the idea to further consider the regression model (5.1) without making the equal serial dependence assumption. We perform hypothesis testing for the equality of the fixed effects and derive the distribution of the common trend if the null hypothesis cannot be rejected.

Our procedures for dealing with a single group and multiple groups are both presented in Section 5.2. The other commonly used methods, the growth-curve model, the classical Hotelling's T^2 and the classical Chi-square method, are presented in Section 5.3. The illustrative examples of real and simulated data sets are provided in Section 6.3 for the purpose of making comparisons of the different methods with respect to their coverage probabilities, expected areas and *p*-values.

5.2 Regression model with AR(1) errors

In this section, we first introduce our method for dealing with the single group in Section 5.2.1 and then consider the multiple groups with and without the assumptions of identical AR(1) covariance matrices in Section 5.2.2. Other methods such as the ML method via growth-curve model, the classical Chi-square approximation and the Hotelling's T^2–statistic are also briefly introduced in Section 5.3.

5.2.1 Single group based on the generalized method

In the single group, the model (5.1) can be reduced to

$$\mathbf{Y}_j = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}_j, \quad j = 1, \cdots, J, \tag{5.2}$$

where $\boldsymbol{\varepsilon}_1, \cdots, \boldsymbol{\varepsilon}_J$ are identical and independent multivariate normal distributions with mean vector $\mathbf{0}$ and the AR(1) covariance matrix $\boldsymbol{\Sigma} = \sigma^2\mathbf{C}$ with $\mathbf{C} = (\rho^{|m-n|})$, $1 \le m, n \le T$.

Let $\mathbf{1}_T = (1,1,\cdots,1)'$, $\bar{Y}_{j.} = \frac{1}{T}\sum_t Y_{jt} = \frac{1}{T}\mathbf{1}_T'\mathbf{Y}_j$, $\bar{Y}_{..} = \frac{1}{J}\sum_j \bar{Y}_{j.} = \frac{1}{J}\sum_j \frac{1}{T}\mathbf{1}_T'\mathbf{Y}_j = \frac{1}{T}\mathbf{1}_T'\bar{\mathbf{Y}}$

and $\bar{\mathbf{Y}} = \frac{1}{J}\sum_j \mathbf{Y}_j$, we obtain a linear unbiased estimator $\mathbf{b} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\bar{\mathbf{Y}} = \mathbf{A}\bar{\mathbf{Y}}$ with $\mathbf{A} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'$, and $\mathbf{b}$ is distributed as $N_K(\boldsymbol{\beta}, \frac{1}{J}\sigma^2\mathbf{ACA}')$. We utilize the estimator $\mathbf{b}$ to make inferences on the unknown AR(1) covariance matrix through two independent random variables, one is the sum of square errors about $\mathbf{Xb}$ within subjects, $SSW(\mathbf{Xb}) = \sum_j [\mathbf{Y}_j - \mathbf{Xb} - (\bar{Y}_{j.} - \bar{Y}_{..})\mathbf{1}_T]'[\mathbf{Y}_j - \mathbf{Xb} - (\bar{Y}_{j.} - \bar{Y}_{..})\mathbf{1}_T]$, and the other is the sum of square errors between subjects, $SSB(\mathbf{Xb}) = T\sum_j (\bar{Y}_{j.} - \bar{Y}_{..})^2$. The sum of square errors about $\mathbf{Xb}$, $SST(\mathbf{Xb}) = \sum_j (\mathbf{Y}_j - \mathbf{Xb})'(\mathbf{Y}_j - \mathbf{Xb})$, can be expressed as the sum of $SSW(\mathbf{Xb})$ and $SSB(\mathbf{Xb})$.

Through the distributions and the expected values of $SSW(\mathbf{Xb})$ and $SSB(\mathbf{Xb})$, we can get information about $\boldsymbol{\Sigma}$. The expectations of $SST(\mathbf{Xb})$ and $SSB(\mathbf{Xb})$ are
$E(SST(\mathbf{Xb})) = E(SSW(\mathbf{Xb})) + E(SSB(\mathbf{Xb})) = \sum_j tr[Cov(\mathbf{Y}_j - \mathbf{Xb})] = \sigma^2(JT - tr(\mathbf{XAC}))$

and $E(SSB(\mathbf{Xb})) = \frac{(J-1)}{T}\sigma^2\mathbf{1}_T{}'\mathbf{C}\mathbf{1}_T$.

Let $e_b = \frac{\sigma^2}{T}\mathbf{1}_T{}'\mathbf{C}\mathbf{1}_T$ and $e_w = \frac{\sigma^2}{J(T-1)-(K-1)}(JT - tr(\mathbf{XAC}) - \frac{J-1}{T}\mathbf{1}_T{}'\mathbf{C}\mathbf{1}_T)$, then

$$U_W = \frac{SSW(\mathbf{Xb})}{e_w} \sim \chi^2_{J(T-1)-(K-1)}, \tag{5.3}$$

$$U_B = \frac{SSB(\mathbf{Xb})}{e_b} \sim \chi^2_{J-1}, \tag{5.4}$$

and U_W and U_B are independently distributed. Since the pair $\langle\sigma^2, \rho\rangle$ can be uniquely determined by the pair $\langle e_w, e_b\rangle$, we can get information about nuisance parameters σ^2 and ρ through e_w and e_b. Hence, $\boldsymbol{\Sigma}$ can be expressed as $\boldsymbol{\Sigma} \equiv \boldsymbol{\Sigma}(e_w, e_b)$. And for any positive number λ, we have $\boldsymbol{\Sigma}(\lambda e_w, \lambda e_b) = \lambda\boldsymbol{\Sigma}(e_w, e_b)$ and $\lambda\boldsymbol{\Sigma}^{-1}(\lambda e_w, \lambda e_b) = \boldsymbol{\Sigma}^{-1}(e_w, e_b)$. Thus

$$\boldsymbol{\Sigma}^{-1}(e_w\frac{ssw(\mathbf{Xb})}{SSW(\mathbf{Xb})}, e_b\frac{ssb(\mathbf{Xb})}{SSB(\mathbf{Xb})})$$

$$= \boldsymbol{\Sigma}^{-1}(\frac{ssw(\mathbf{Xb})}{U_W}, \frac{ssb(\mathbf{Xb})}{U_B})$$

$$=U_T\mathbf{\Sigma}^{-1}(U_T\frac{ssw(\mathbf{Xb})}{U_W}, U_T\frac{ssb(\mathbf{Xb})}{U_B})$$

$$=U_T\mathbf{\Sigma}^{-1}(\frac{ssw(\mathbf{Xb})}{B_{\nu_1,\nu_2}}, \frac{ssb(\mathbf{Xb})}{1-B_{\nu_1,\nu_2}}), \tag{5.5}$$

where $ssw(\mathbf{Xb})$ and $ssb(\mathbf{Xb})$ are the observed values of $SSW(\mathbf{Xb})$ and $SSB(\mathbf{Xb})$, respectively, $U_T = U_B + U_w \sim \chi^2_{JT-K}$, and B_{ν_1,ν_2} is the Beta random variable with $\nu_1 = \frac{J(T-1)-(K-1)}{2}$ and $\nu_2 = \frac{J-1}{2}$.

If e_w and e_b are known, pre-multiplying $\mathbf{\Sigma}^{-1/2}$ to both sides of Eq. (5.2), we obtain the standardized regression model with identity covariance matrix as follows.

$$\tilde{\mathbf{Y}}_j = \tilde{\mathbf{X}}\boldsymbol{\beta} + \tilde{\boldsymbol{\varepsilon}}_j,\quad j=1,\cdots,J,\ \text{where}\ \tilde{\boldsymbol{\varepsilon}}_j \sim N_T(\mathbf{0},\mathbf{I}_T), \tag{5.6}$$

which is equivalent to model (3.2). Based on (5.6), the BLUE of $\boldsymbol{\beta}$, denoted as $\hat{\boldsymbol{\beta}}_P$, $\hat{\boldsymbol{\beta}}_P = (\tilde{\mathbf{X}}'\tilde{\mathbf{X}})^{-1}\tilde{\mathbf{X}}'(\frac{1}{J}\sum_j \tilde{\mathbf{Y}}_j)$ and $\hat{\boldsymbol{\beta}}_P \sim N_K(\boldsymbol{\beta}, (J\mathbf{X}'\mathbf{\Sigma}^{-1}\mathbf{X})^{-1})$.

Since $J(\boldsymbol{\beta}-\hat{\boldsymbol{\beta}}_P)'\ \mathbf{X}'\mathbf{\Sigma}^{-1}\mathbf{X}(\boldsymbol{\beta}-\hat{\boldsymbol{\beta}}_P)$ is distributed as χ^2_K, then the random variable $\frac{J(JT-K)}{K}(\boldsymbol{\beta}-\hat{\boldsymbol{\beta}}_P)'\ \mathbf{X}'(U_T\mathbf{\Sigma})^{-1}\mathbf{X}(\boldsymbol{\beta}-\hat{\boldsymbol{\beta}}_P)$ is distributed as an *F* distribution with degrees of freedom *K* and *JT-K*. When $K=2$, the expected area of the $100(1-\alpha)\%$ coverage probability of $\boldsymbol{\beta}$ can be obtained by

$$A_P(\boldsymbol{\beta},\ 1-\alpha) = \frac{\pi K}{J(JT-K)} E_{B_{\nu_1,\nu_2}}[\left|\mathbf{X}'\mathbf{\Sigma}^{-1}(\tfrac{ssw(\mathbf{Xb})}{B_{\nu_1,\nu_2}}, \tfrac{ssb(\mathbf{Xb})}{1-B_{\nu_1,\nu_2}})\mathbf{X}\right|^{-1/2}]F_{K,JT-K}(1-\alpha), \tag{5.7}$$

where B_{ν_1,ν_2} is as defined in (5.5)

5.2.2 Multiple groups based on the generalized method

In this section, we incorporate the generalized method into the traditional regression procedure. Our proposed method will provide an alternative process for making inferences for $\boldsymbol{\beta}_i$'s of the regression model. The inferences under the assumptions of distinct AR(1) covariance matrices among groups, and the equal AR(1) covariance matrices case, are both introduced in this section.

Different covariance matrices among groups

For the situation with distinct covariance matrices among groups, we utilize similar steps as in the single group model with some modifications. First, we have to obtain the information for $\mathbf{\Sigma}_i^{-1}$ and pre-multiply $\mathbf{\Sigma}_i^{-1/2}$ to both sides of the regression model (5.1), $i = 1, \cdots, I$, then we get the standardized regression model:

$$\tilde{\mathbf{Y}}_{ij} = \tilde{\mathbf{X}}_i \boldsymbol{\beta}_i + \tilde{\boldsymbol{\varepsilon}}_{ij}, \quad j = 1, \cdots, J_i; \; i = 1, \cdots, I, \tag{5.8}$$

where $\tilde{\boldsymbol{\varepsilon}}_{ij} \sim N_T(\mathbf{0}, \mathbf{I}_T)$. In Section 5.2.1, the AR(1) covariance matrix $\mathbf{\Sigma}$ is expressed as $\mathbf{\Sigma} \equiv \mathbf{\Sigma}(e_w, e_b)$ through the generalized method. Similarly, we will obtain the AR(1) covariance matrices $\mathbf{\Sigma}_i$'s with some modification, then we can make inferences for the common trend $\boldsymbol{\beta}$ based on the standardized regression model (5.8) via the traditional regression procedure. The procedure is as follows.

Let $\bar{\mathbf{Y}}_i = \frac{1}{J_i} \sum_j \mathbf{Y}_{ij}$, $\bar{Y}_{ij.} = \frac{1}{T} \mathbf{1}_T' \mathbf{Y}_{ij}$, $\bar{Y}_{i..} = \frac{1}{T} \mathbf{1}_T' \bar{\mathbf{Y}}_i$ and $\mathbf{A}_i = (\mathbf{X}_i' \mathbf{X}_i)^{-1} \mathbf{X}_i'$, then the estimator $\mathbf{b}_i = (\mathbf{X}_i' \mathbf{X}_i)^{-1} \mathbf{X}_i' \bar{\mathbf{Y}}_i = \mathbf{A}_i \bar{\mathbf{Y}}_i$ is distributed as $N_K(\boldsymbol{\beta}_i, \frac{1}{J_i} \sigma_i^2 \mathbf{A}_i \mathbf{C}_i \mathbf{A}_i')$. The sum of square errors "within" subjects and "between" subjects are $S_{W,i} \equiv SSW(\mathbf{X}_i \mathbf{b}_i) = \sum_j [\mathbf{Y}_{ij} - \mathbf{X}_i \mathbf{b}_i - (\bar{Y}_{ij.} - \bar{Y}_{i..}) \mathbf{1}_T]' [\mathbf{Y}_{ij} - \mathbf{X}_i \mathbf{b}_i - (\bar{Y}_{ij.} - \bar{Y}_{i..}) \mathbf{1}_T]$ and $S_{B,i} \equiv SSB(\mathbf{X}_i \mathbf{b}_i) = T \sum_j (\bar{Y}_{ij.} - \bar{Y}_{i..})^2$, respectively. Let $U_{W,i} = \frac{S_{W,i}}{e_{w,i}}$ and $U_{B,i} = \frac{S_{B,i}}{e_{b,i}}$, with $e_{w,i} = \frac{\sigma_i^2}{J_i(T-1)-(K-1)} (J_i T - tr(\mathbf{X}_i \mathbf{A}_i \mathbf{C}_i) - \frac{J_i - 1}{T} \mathbf{1}_T' \mathbf{C}_i \mathbf{1}_T)$ and $e_{b,i} = \frac{\sigma_i^2}{T} \mathbf{1}_T' \mathbf{C}_i \mathbf{1}_T$, then it is known that $U_{W,i}$ and $U_{B,i}$ are independently distributed as $\chi^2_{J_i(T-1)-(K-1)}$ and $\chi^2_{J_i - 1}$, respectively. Suppose $s_{w,i}$ and $s_{b,i}$ are the observed values of $S_{W,i}$ and $S_{B,i}$, respectively, then

$$\mathbf{\Sigma}_i \left(e_{w,i} \frac{s_{w,i}}{S_{W,i}}, \; e_{b,i} \frac{s_{b,i}}{S_{B,i}}\right) = \mathbf{\Sigma}_i \left(\frac{s_{w,i}}{U_{W,i}}, \; \frac{s_{b,i}}{U_{B,i}}\right). \tag{5.9}$$

Hence we can obtain the generalized estimator $\hat{\boldsymbol{\beta}}_{P,i}$ for the individual group as $\hat{\boldsymbol{\beta}}_{P,i} = (\tilde{\mathbf{X}}_i' \tilde{\mathbf{X}}_i)^{-1} \tilde{\mathbf{X}}_i' (\frac{1}{J_i} \sum_j \tilde{\mathbf{Y}}_{ij})$.

The standardized model (5.8) can be also obtained by pre-multiplying $\mathbf{\Sigma}_i^{-1/2}$, the square root of (5.9), to both sides of the regression model (5.1), $i = 1, \cdots, I$. We are interested in testing the equality of the trends with heteroscedastic phenomena, that is,

$$\mathbf{H}_0 : \boldsymbol{\beta}_1 = \cdots = \boldsymbol{\beta}_I = \boldsymbol{\beta}\,. \tag{5.10}$$

Under the null hypothesis (5.10), the common trend estimator $\hat{\boldsymbol{\beta}}_P$ is defined as

$$\hat{\boldsymbol{\beta}}_P = (\sum_i J_i \tilde{\mathbf{X}}_i' \tilde{\mathbf{X}}_i)^{-1} (\sum_i \sum_j \tilde{\mathbf{X}}_i' \tilde{\mathbf{Y}}_{ij}) = \boldsymbol{\Psi}_P (\sum_i J_i \tilde{\mathbf{X}}_i' \tilde{\mathbf{X}}_i \hat{\boldsymbol{\beta}}_{P,i})\,, \tag{5.11}$$

which is distributed as $N_K(\boldsymbol{\beta}, \boldsymbol{\Psi}_P)$, where

$$\boldsymbol{\Psi}_P = (\sum_i J_i \tilde{\mathbf{X}}_i' \tilde{\mathbf{X}}_i)^{-1}. \tag{5.12}$$

We utilize $\tilde{S}_0^2(e_{w,1},\cdots,e_{w,I},e_{b,1},\cdots,e_{b,I}) \equiv \tilde{S}_0^2 = \sum_i \sum_j (\tilde{\mathbf{Y}}_{ij} - \tilde{\mathbf{X}}_i \hat{\boldsymbol{\beta}}_P)' \,(\tilde{\mathbf{Y}}_{ij} - \tilde{\mathbf{X}}_i \hat{\boldsymbol{\beta}}_P)$ and $\tilde{S}_a^2(e_{w,1},\cdots,e_{w,I},e_{b,1},\cdots,e_{b,I}) \equiv \tilde{S}_a^2 = \sum_i \sum_j (\tilde{\mathbf{Y}}_{ij} - \tilde{\mathbf{X}}_i \hat{\boldsymbol{\beta}}_{P,i})' \,(\tilde{\mathbf{Y}}_{ij} - \tilde{\mathbf{X}}_i \hat{\boldsymbol{\beta}}_{P,i})$ to test the null hypothesis (5.10). It is noted that $\tilde{S}_0^2$ and $\tilde{S}_a^2$ are distributed as χ^2-distribution with degrees of freedom $NT-K$ and $NT-IK$, respectively, where $N = \sum_i J_i$. Then the generalized *p*-values for testing (5.10), the hypothesis of the equality of the trends, can be calculated by

$$\begin{aligned} p &= \Pr\{\tilde{S}_0^2(e_{w,1},\cdots,e_{w,I},e_{b,1},\cdots,e_{b,I}) > \tilde{s}_0^2(\frac{s_{w,1}}{U_{W,1}},\cdots,\frac{s_{w,I}}{U_{W,I}},\frac{s_{b,1}}{U_{B,1}},\cdots,\frac{s_{b,I}}{U_{B,I}})\} \\ &= \Pr\{\frac{\tilde{S}_0^2 - \tilde{S}_a^2}{\tilde{S}_a^2} > \tilde{s}_0^2(\frac{s_{w,1}}{U_{W,1}/U_T},\cdots,\frac{s_{w,I}}{U_{W,I}/U_T},\frac{s_{b,1}}{U_{B,1}/U_T},\cdots,\frac{s_{b,I}}{U_{B,I}/U_T}) - 1\} \\ &= 1 - E_\Delta\{F_{\nu_1,\nu_2}[\frac{\nu_2}{\nu_1}\{\tilde{s}_0^2(\frac{s_{w,1}}{M_1 M_2 \cdots M_{2I}},\cdots,\frac{s_{w,I}}{(1-M_{I-1})M_I \cdots M_{2I}},\frac{s_{b,1}}{(1-M_I)M_{I+1}\cdots M_{2I}},\cdots,\frac{s_{b,I}}{(1-M_{2I-1})M_{2I}}) - 1\}]\}, \end{aligned} \tag{5.13}$$

where $U_T = \sum_i (U_{W,i} + U_{B,i}) \sim \chi^2_{NT-IK}$, F_{ν_1,ν_2} is the cumulative density function(cdf) of the F distribution with degrees of freedom $\nu_1 = (I-1)K$ and $\nu_2 = NT - IK$. And E_Δ is the expected value with respect to the independent Beta random variables $M_r = \frac{\sum_{i=1}^r \lambda_i}{\sum_{i=1}^{r+1} \lambda_i} \sim Beta(\frac{\sum_{i=1}^r q_i}{2}, \frac{q_{r+1}}{2})$, $r = 1,\cdots,(2I-1)$, with two auxiliary constants $M_0 \equiv 0$ and $M_{2I} \equiv 1$, where $(\lambda_1,\cdots,\lambda_{2I}) = (U_{W,1},\cdots,U_{W,I},U_{B,1},\cdots,U_{B,I})$, q_r is the degrees of freedom of λ_r with $q_r = \begin{cases} J_r(T-1)-(K-1), & r = 1,\cdots,I. \\ J_{r-I} - 1, & r = I+1,\cdots,2I. \end{cases}$

If the null hypothesis cannot be rejected, the common trend $\boldsymbol{\beta}$ can be estimated by $\hat{\boldsymbol{\beta}}_P$, and $(\boldsymbol{\beta} - \hat{\boldsymbol{\beta}}_P)' \boldsymbol{\Psi}_P^{-1} (\boldsymbol{\beta} - \hat{\boldsymbol{\beta}}_P)$ is distributed as χ^2_K. Hence, the random variable

$\frac{NT-IK}{K}(\boldsymbol{\beta}-\hat{\boldsymbol{\beta}}_P)'\,[U_T\boldsymbol{\Psi}_P]^{-1}(\boldsymbol{\beta}-\hat{\boldsymbol{\beta}}_P)$ is distributed as an *F* distribution with degrees of freedom *K* and *NT-IK*.

When $K=2$, the expected area, $A_P(\boldsymbol{\beta},\,1-\alpha)$, of the $100(1-\alpha)\%$ coverage probability of $\boldsymbol{\beta}$ can be obtained by

$$a_p E_\Delta\Big[\Big|\sum_i J_i\mathbf{X}_i'\boldsymbol{\Sigma}_i^{-1}\Big(\frac{s_{w,i}}{(1-M_{i-1})M_i\cdots M_{2I}},\ \frac{s_{b,i}}{(1-M_{i+I-1})M_{i+I}\cdots M_{2I}}\Big)\mathbf{X}_i\Big|^{-1/2}\Big], \tag{5.14}$$

where the constant $a_p=\frac{\pi K}{NT-IK}F_{K,NT-IK}(1-\alpha)$.

Equal covariance matrices among groups

When the AR(1) covariance matrices are equal among groups, i.e., $\sigma_1^2=\cdots=\sigma_I^2$ and $\rho_1=\cdots=\rho_I$, set $S_{cT}=\sum_i S_{T,i}$, $S_{cB}=\sum_i S_{B,i}$ and $S_{cW}=\sum_i S_{W,i}$. Let $e_{cb}=\frac{\sigma^2}{T}\mathbf{1}_T{}'\mathbf{C}\mathbf{1}_T$ and $e_{cw}=\frac{\sigma^2}{N(T-1)-I(K-1)}(NT-tr(\sum_i\mathbf{X}_i\mathbf{A}_i\mathbf{C})-\frac{N-I}{T}\mathbf{1}_T{}'\mathbf{C}\mathbf{1}_T)$, then $U_{cW}=\frac{S_{cW}}{e_{cw}}$ and $U_{cB}=\frac{S_{cB}}{e_{cb}}$ are independently distributed as $\chi^2_{N(T-1)-I(K-1)}$ and χ^2_{N-I}, respectively. The subscript *c* in these notations stands for the case of "common covariance matrix." Similar to the previous procedure, let s_{cw} and s_{cb} be the observed values of S_{cW} and S_{cB}, respectively. Then the identical covariance matrix can be expressed as

$$\boldsymbol{\Sigma}(e_{cw}\frac{s_{cw}}{S_{cW}},\ e_{cb}\frac{s_{cb}}{S_{cB}})=\boldsymbol{\Sigma}(\frac{s_{cw}}{U_{cW}},\ \frac{s_{cb}}{U_{cB}}). \tag{5.15}$$

Hence, $\hat{\boldsymbol{\beta}}_{cP}=(\sum_i J_i\tilde{\mathbf{X}}_i'\tilde{\mathbf{X}}_i)^{-1}(\sum_i\sum_j\tilde{\mathbf{X}}_i'\tilde{\mathbf{Y}}_{ij})=\boldsymbol{\Psi}_{cP}(\sum_i J_i\tilde{\mathbf{X}}_i'\tilde{\mathbf{X}}_i\hat{\boldsymbol{\beta}}_{cP,i})$, the estimator under the null hypothesis, is distributed as $N_K(\boldsymbol{\beta},\boldsymbol{\Psi}_{cP})$, where

$$\hat{\boldsymbol{\beta}}_{cP,i}=(\tilde{\mathbf{X}}_i'\tilde{\mathbf{X}}_i)^{-1}\tilde{\mathbf{X}}_i'(\frac{1}{J_i}\sum_j\tilde{\mathbf{Y}}_{ij}),$$

and $\boldsymbol{\Psi}_{cP}=(\sum_i J_i\tilde{\mathbf{X}}_i'\tilde{\mathbf{X}}_i)^{-1}$.

The generalized *p*-values for testing (5.10) can be calculated as

$$p=\Pr\{\tilde{S}_0^2(e_{cw},e_{cb})>\tilde{s}_0^2(\frac{s_{cw}}{U_{cW}},\frac{s_{cb}}{U_{cB}})\}$$

$$=\Pr\{\frac{\tilde{S}_0^2-\tilde{S}_a^2}{\tilde{S}_a^2}>\tilde{s}_0^2(\frac{s_{cw}}{U_{cW}/U_{cT}},\frac{s_{cb}}{U_{cB}/U_{cT}})-1\}$$

$$=1-E_B\{F_{\nu_1,\nu_2}[\frac{\nu_2}{\nu_1}\{\tilde{s}_0^2(\frac{s_{cw}}{B},\frac{s_{cb}}{1-B})-1\}]\},\qquad(5.16)$$

where $U_{cT}=U_{cW}+U_{cB}\sim\chi^2_{NT-IK}$, $F_{\nu_1,\nu_2}[\cdot]$ is the cdf of the F distribution with degrees of freedom $\nu_1=(I-1)K$ and $\nu_2=NT-IK$ and E_B is the expected value with respect to the Beta random variables

$$B\sim Beta(\frac{N(T-1)-I(K-1)}{2},\frac{N-I}{2}).$$

If the null hypothesis cannot be rejected, the common trend $\boldsymbol{\beta}$ is estimated by $\hat{\boldsymbol{\beta}}_{cP}$, then $\frac{NT-IK}{K}(\boldsymbol{\beta}-\hat{\boldsymbol{\beta}}_{cP})'[U_{cT}\boldsymbol{\Psi}_{cP}]^{-1}(\boldsymbol{\beta}-\hat{\boldsymbol{\beta}}_{cP})\sim F_{K,NT-IK}$. When $K=2$, the area of the $100(1-\alpha)\%$ coverage probability of $\boldsymbol{\beta}$ is

$$A_{cP}(\boldsymbol{\beta},\,1-\alpha)=\frac{\pi K}{NT-IK}E_B[\left|(\sum_i J_i\mathbf{X}_i'\boldsymbol{\Sigma}^{-1}(\frac{s_{cw}}{B},\frac{s_{cb}}{1-B})\mathbf{X}_i)\right|^{-1/2}]F_{K,NT-IK}(1-\alpha).\qquad(5.17)$$

5. 3 The other methods

The growth-curve model

The regression model (5.1) can be expressed as a growth-curve model if the design matrices are identical. The results are given in Section 4.2.

The classical Chi-square approximation

In the classical Chi-square method, researchers often substitute the unknown $\boldsymbol{\Sigma}_i$ with the sample covariance matrices $\mathbf{S}_i=\frac{1}{J_i-1}\sum_j(\mathbf{Y}_{ij}-\bar{\mathbf{Y}}_i)(\mathbf{Y}_{ij}-\bar{\mathbf{Y}}_i)'$, where $\bar{\mathbf{Y}}_i=\frac{1}{J_i}\sum_j\mathbf{Y}_{ij}$ for $i=1,\cdots,I$. Let $a_i=(J_i-T-2)/(J_i-1)$, it is then easy to show that $E(a_i\mathbf{S}_i^{-1})=\boldsymbol{\Sigma}_i^{-1}$. Under hypothesis (5.10), the estimate of the common trend $\boldsymbol{\beta}$ can be expressed as $\hat{\boldsymbol{\beta}}_{Chi}=\boldsymbol{\Psi}_{Chi}(\sum_i J_i\mathbf{X}_i'a_i\mathbf{S}_i^{-1}\mathbf{X}_i\hat{\boldsymbol{\beta}}_{(chi)i})$, where $\boldsymbol{\Psi}_{Chi}=(\sum_i J_i\mathbf{X}_i'a_i\mathbf{S}_i^{-1}\mathbf{X}_i)^{-1}$ and $\hat{\boldsymbol{\beta}}_{(chi)i}=(\mathbf{X}_i'\mathbf{S}_i^{-1}\mathbf{X}_i)^{-1}\mathbf{X}_i'\mathbf{S}_i^{-1}\bar{\mathbf{Y}}_i$.

The approximate $100(1-\alpha)\%$ confidence region for the common trend $\boldsymbol{\beta}$ is

$$\{ \boldsymbol{\beta}:\ (\boldsymbol{\beta}-\hat{\boldsymbol{\beta}}_{Chi})'\boldsymbol{\Psi}_{Chi}^{-1}\,(\boldsymbol{\beta}-\hat{\boldsymbol{\beta}}_{Chi}) \le \chi_K^2(1-\alpha) \}\ . \tag{5.18}$$

When $K=2$, the area of the approximate $100(1-\alpha)\%$ confidence region for $\boldsymbol{\beta}$ is

$$A_{Chi}(\boldsymbol{\beta},\ 1-\alpha) = \pi \left|\boldsymbol{\Psi}_{Chi}\right|^{1/2} \chi_K^2(1-\alpha)\,. \tag{5.19}$$

The Hotelling's T^2 –statistic

Assuming $\boldsymbol{\Sigma}_1 = \cdots = \boldsymbol{\Sigma}_I = \boldsymbol{\Sigma}$ and $\mathbf{X}_1 = \cdots = \mathbf{X}_I = \mathbf{X}$, pre-multiply $(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'$ to both sides of the regression model (5.1). Then the model can be transformed as $\mathbf{Y}_{ij}^* = \boldsymbol{\beta}_i + \boldsymbol{\varepsilon}_{ij}^*$, which is distributed as $N_K(\boldsymbol{\beta}_i, \boldsymbol{\Sigma}^*)$, $\boldsymbol{\Sigma}^* = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\boldsymbol{\Sigma}\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}$, for $j=1,\cdots,J_i$ and $i=1,\cdots,I$. Thus the Hotelling's T^2 –method is applicable. Under (5.10), the estimate of the common trend $\boldsymbol{\beta}$ **is** $\hat{\boldsymbol{\beta}}_H = \frac{1}{N}\sum_i J_i \bar{\mathbf{Y}}_i^*$, then the Hotelling's T^2 -statistic $T^2 = N(\hat{\boldsymbol{\beta}}_H - \boldsymbol{\beta})'\mathbf{S}_H^{*\,-1}\,(\hat{\boldsymbol{\beta}}_H - \boldsymbol{\beta})$ is distributed as $\frac{(N-I)K}{N-I-K+1}F_{K,\,N-I-K+1}$, where $\mathbf{S}_H^* = \frac{1}{N-I}\sum_i\sum_j(\mathbf{Y}_{ij}^* - \bar{\mathbf{Y}}_i^*)(\mathbf{Y}_{ij}^* - \bar{\mathbf{Y}}_i^*)'$ and $\bar{\mathbf{Y}}_i^* = \frac{1}{J_i}\sum_j \mathbf{Y}_{ij}^*$.

The $100(1-\alpha)\%$ confidence region for the common trend $\boldsymbol{\beta}$ is

$$\{ \boldsymbol{\beta}:\ (\boldsymbol{\beta}-\hat{\boldsymbol{\beta}}_H)'\mathbf{S}_H^{*\,-1}\,(\boldsymbol{\beta}-\hat{\boldsymbol{\beta}}_H) \le \frac{(N-I)K}{(N-I-K+1)N}F_{K,\,N-I-K+1}(1-\alpha) \}. \tag{5.20}$$

When $K=2$, the area of the $100(1-\alpha)\%$ confidence region for $\boldsymbol{\beta}$ is

$$A_H(\boldsymbol{\beta},\ 1-\alpha) = \frac{K(N-I)\pi}{N(N-I-K+1)}\left|\mathbf{S}_H^*\right|^{1/2} F_{K,\,N-I-K+1}(1-\alpha)\,. \tag{5.21}$$

Chapter 6

Results and Concluding Remarks

In this Chapter, two simulation studies about linear combination of mean vectors, $\mathbf{G\mu}$, discussed in Chapter 3, are presented in Section 6.1 to compare the type I error rates, expected areas and the coverage probabilities in different combinations of sample sizes and covariance matrices for difference procedures, and then two sets of data will be illustrated for our procedures in Section 6.2. The illustrative examples of real and simulated data sets with different AR(1) covariance matrices discussed in Chapter 5 are provided in Section 6.3 for the purpose of making comparisons of the different methods with respect to their coverage probabilities, expected areas and *p*-values. Finally, the concluding remarks are provided in Section 6.4.

6.1 Simulation studies about $\mathbf{G\mu}$

In this section, we first consider the multivariate Behrens-Fisher problem compared with five methods with their type I errors. Then, for the case of $K = 3\ (> 2)$, we present expected areas and coverage probabilities of three methods for various sample sizes and parameter configurations.

6.1.1 The multivariate Behrens-Fisher problem

We apply five methods to calculate the type I error probabilities of multivariate Behrens-Fisher problem under different scenarios. The results are in Table 6.1 and Table 6.2 for $d = 2$ and $d = 4$, respectively. Each combination is based on 1,000 replicates with $\alpha = 0.05$ and these comparisons presented correspond to

(1) General: The generalized method proposed in Section 3.2.1.

(2) Hote: The Classical Hotelling's method described in Section 3.2.2.

(3) Chi: Classical Chi-square test described in Section 3.2.2.

(4) Gam: Gamage, Mathew and Weerahandi described in Section 3.3. (2004)

(5) Kri: Krishnamoorthy and Yu described in Section 3.3. (2004)

The methods (1) and (4) both are based on 5,000 runs in each simulation. From Table 6.1, it is interesting to find that the results based our proposed method are very close to those proposed by Gamage et al. except only by simulated and round off errors. Both of them have the type I error probabilities close to the nominal level. The method proposed by Krishnamoorthy and Yu also has the similar results except few combinations.

Table 6.1: Type I error with 1,000 iterations $\mathbf{\Sigma}_1 = \mathbf{I}_2, \mathbf{\Sigma}_2 = a\mathbf{I}_2$

a	General	Hote	Chi	Gam	Kri
$n_1 = 10, n_2 = 15$					
9	0.045	0.032	0.080	0.045	0.054
25	0.046	0.026	0.099	0.046	0.056
100	0.045	0.023	0.104	0.044	0.044
400	0.045	0.018	0.097	0.043	0.046
$n_1 = 10, n_2 = 10$					
9	0.049	0.101	0.120	0.049	0.062
25	0.050	0.077	0.115	0.048	0.050
100	0.055	0.092	0.124	0.053	0.051
400	0.048	0.089	0.125	0.044	0.046
$n_1 = 15, n_2 = 10$					
9	0.052	0.162	0.137	0.053	0.070
25	0.055	0.161	0.124	0.054	0.056
100	0.051	0.193	0.153	0.052	0.055
400	0.053	0.178	0.128	0.052	0.051

However, in Table 6.2 with $d = 4$, except our proposed method, there are unanticipated results in the case $n_1 = 10,\ n_2 = 5$. The method proposed by Gamage et al. tends to accept the null hypothesis (3.20) since the generalized p-values calculated by their test variable do not have a uniform distribution in this case while we use the standardized GTV to calculate the generalized p-values. And the type I error probabilities of the method proposed by Krishnamoorthy and Yu range from 0.11 to 0.16. The type I error probabilities calculated based on the classical Hotelling's method are under estimated when smaller sample sizes are associated with smaller variances and over estimated when two sample sizes are equal or smaller sample sizes are associated with larger variances. Those obtained based on the classical Chi-square test are over estimated in all combinations and their performances grow worse as the degree of non-homogeneity increases. This comes to a similar conclusion with a number of other problems solved based on generalized p-values, see Thursby (1992), Zhou and Mathew (1994) and many others. They found that when the covariance matrices are quite different and the sample sizes are small, the nominal significance level obtained by the Hotelling's and the Chi-square methods may be distorted.

Although the method proposed by Krishnamoorthy and Yu is a strong candidate for the multivariate Behrens-Fisher problem, it has some weaknesses for particular combinations of sample sizes, dimensions and parameter configurations. Furthermore, it can be used only in two populations. Thus, for overall comparisons from Table 6.1 and Table 6.2, we conclude that our proposed method is useful for practical use.

Table 6.2: Type I error with 1,000 iterations $\mathbf{\Sigma}_1 = \mathbf{I}_4, \mathbf{\Sigma}_2 = a\mathbf{I}_4$

a	General	Hote	Chi	Gam	Kri
$n_1 = 10, n_2 = 5$					
9	0.036	0.467	0.578	0	0.108
25	0.042	0.525	0.647	0	0.125
100	0.052	0.650	0.684	0.001	0.161
400	0.056	0.748	0.745	0.008	0.127
$n_1 = 10, n_2 = 10$					
9	0.032	0.127	0.258	0.031	0.068
25	0.041	0.156	0.261	0.042	0.060
100	0.055	0.156	0.296	0.055	0.059
400	0.053	0.159	0.299	0.054	0.054
$n_1 = 10, n_2 = 20$					
9	0.031	0.017	0.132	0.030	0.071
25	0.043	0.013	0.138	0.039	0.057
100	0.051	0.009	0.132	0.054	0.060
400	0.048	0.010	0.125	0.047	0.050

6.1.2 The expected areas and coverage probabilities

In simulation studies, we used 1,000 iterations to calculate the expected areas of the 95% confidence regions and the corresponding coverage probabilities of $c_1\boldsymbol{\mu}_1 + c_2\boldsymbol{\mu}_2 + c_3\boldsymbol{\mu}_3$ under different scenarios. First, we chose $(c_1, c_2, c_3) = (1, -1, 0)$

which is known as the multivariate Behrens-Fisher problem, and the results compared with five methods are in Table 6.3. Next, we choose $(c_1, c_2, c_3) = (0.5, 0.5, -1)$ and the results compared with three methods are in Table 6.4.

Table 6.3: Expected areas of 95% confidence regions and coverage probabilities of $\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2$ under $\boldsymbol{\Sigma}_1 = \mathbf{I}_2$, and $\boldsymbol{\Sigma}_2 = \frac{n_2}{n_1} a\mathbf{I}_2$

a	General	Hote	Chi	Gam	Kri
$n_1 = 10, n_2 = 20$					
9	23.251(.962)	39.4807(.992)	18.228(.924)	23.267(.961)	21.639(.962)
15	36.758(.963)	65.0438(.993)	29.056(.924)	36.765(.963)	35.063(.938)
25	59.280(.958)	107.646(.994)	47.089(.922)	59.294(.960)	57.072(.957)
50	115.603(.959)	214.151(.996)	92.155(.925)	115.664(.961)	114.061(.951)
100	228.298(.959)	427.157(.996)	182.275(.926)	228.378(.960)	224.332(.953)
500	1129.820(.959)	2131.21(.997)	903.209(.929)	1129.990(.959)	1109.206(.962)
$n_1 = 20, n_2 = 10$					
9	13.705(.962)	6.563(.856)	8.556(.903)	13.713(.962)	12.796(.960)
15	22.078(.961)	9.413(.820)	13.574(.896)	22.089(.961)	21.249(.936)
25	36.033(.961)	14.124(.791)	21.928(.892)	36.061(.961)	34.617(.950)
50	70.938(.955)	25.845(.769)	42.801(.891)	70.982(.956)	69.578(.944)
100	140.755(.957)	49.233(.751)	84.539(.892)	140.829(.956)	139.740(.938)
500	699.357(.959)	236.168(.741)	418.422(.889)	699.641(.959)	693.913(.957)

From Table 6.3, we find that the coverage probabilities obtained by the Hotelling's method are over-estimated when the large sample sizes are associated with large covariance matrices and vice versa. The coverage probabilities obtained by the Chi-square method are under-estimated in all cases. On the other hand, the rest three methods have good coverage probabilities and similar expected areas in all cases. In Table 6.4, although the Hotelling's method and the Chi-square test have smaller average areas of 95% confidence regions, their confidence regions are too small to ensure their coverage probabilities are close to the nominal level 0.95. On the contrary, these simulated results support that our method not only assures the level of the test in all cases, but also has good coverage probabilities comparing to those of the classical Hotelling's method and the classical Chi-square test.

Table 6.4: Expected areas of 95% confidence regions and coverage probabilities

of $\frac{\boldsymbol{\mu}_1}{2}+\frac{\boldsymbol{\mu}_2}{2}-\boldsymbol{\mu}_3$ under $\boldsymbol{\Sigma}_1=\mathbf{I}_2, \boldsymbol{\Sigma}_2=3\mathbf{I}_2$ and $\boldsymbol{\Sigma}_3=a\mathbf{I}_2$

a	General	Hote	Chi
$(n_1\ n_2\ n_3)$= (10 8 5)			
9	118.257(.957)	18.319(.716)	29.651(.776)
25	297.648(.954)	32.708(.588)	71.844(.738)
50	614.952(.959)	56.745(.536)	145.938(.757)
100	1204.655(.941)	101.422(.486)	284.573(.750)
500	5926.295(.953)	452.362(.463)	1388.306(.756)
$(n_1\ n_2\ n_3)$= (8 10 5)			
9	110.010(.959)	18.991(.758)	27.637(.790)
25	299.104(.961)	34.243(.602)	72.169(.758)
50	616.133(.954)	58.086(.555)	145.488(.755)
100	1208.969(.953)	102.749(.507)	284.487(.770)
500	6063.718(.952)	463.086(.454)	1417.512(.759)
$(n_1\ n_2\ n_3)$= (5 10 8)			
9	42.678(.966)	20.266(.884)	20.828(.866)
25	106.023(.954)	42.525(.804)	52.563(.846)
50	207.290(.968)	77.877(.807)	103.119(.868)
100	401.150(.941)	145.413(.774)	200.280(.841)
500	2061.426(.945)	721.244(.760)	1031.064(.849)

6.2 Illustrative Examples of linear combination of mean vectors

6.2.1 Example 1

Zerbe (1979) analyzed the plasma inorganic phosphate flux data to study the association of hyperglycemia and relative hyperinsulinemia. The standard glucose tolerance tests were administered to 13 control (C) and 20 obese (O) patients on the Pediatric Clinical Research Ward of the University of Colorado Medical Center. Zerbe and Murphy (1986) divided the 20 obese patients into two subgroups; the first 12 obese patients were nonhyperinsulinemic (NO) while the latter 8 were hyperinsulinemic (HO). The sample means of plasma inorganic phosphate measurements determined from blood samples withdrawn 0, 0.5, 1, 1.5, 2, 3, 4, and 5 hours after a standard-dose oral glucose challenge are reported in Table 6.5. The researchers wanted to compare the mean curves separately over the first 3 and last 2 hours of the glucose tolerance test since the metabolic mechanism responsible for the liver changes.

Table 6.5: Sample means of plasma inorganic phosphate (mg/dl)

Group		Hours after glucose challenge							
		0	0.5	1	1.5	2	3	4	5
C		4.092	3.262	2.723	2.631	3.046	3.346	3.515	3.939
O		4.530	4.140	3.780	3.480	3.195	3.375	3.700	4.015
O	NO	4.358	4.033	3.567	3.292	3.100	3.333	3.708	4.000
	HO	4.788	4.300	4.100	3.763	3.338	3.438	3.688	4.038

We consider the multivariate Behrens-Fisher problem twice to see whether two mean vectors are equal or not. First, we want to test if the mean curves of the nonhyperinsulinemic obese group and the hyperinsulinemic obese group are the same. If we cannot reject this null hypothesis, we further discuss the equality of the mean curves of the control group and the obese group, and all results are in Table 6.6. We regard the ratio of determinants of sample covariance matrices as the crude index of the heteroscedasticity. From Table 6.6, $\mathbf{m}_T$ and $\mathbf{G}\bar{\mathbf{x}}$ are very close, and ratios don't display strong heteroscedasticity between groups. The *p*-values in Table 6.6 indicate that no significant evidence exist to reject the null hypothesis that the mean curve of the nonhyperinsulinemic obese group and that of the hyperinsulinemic obese group are equal. However, the mean curves of the control group and the obese group are the same in the 3-5 hours interval, but different in the 0-3 hours interval. Hence the metabolic mechanisms over the first 3 hours of the glucose tolerance test should be quite different from the control group to the obese group. We also run some tests with the similar conclusions as Zerbe and Murphy. It should be noted that we used $\mathbf{G}^*$ to test the equality of the mean curves of 3 groups (C, NO, HO). In the 3-5 hours interval, the ratio of determinants is (3.37, 1, 1.92) and the *p*-values by our method is 0.905 which strongly support the null hypothesis. In the 0-3 hours' interval, the ratio of determinants is (11.8, 9.88, 1) and the *p*-values is 0.035 which reject the null hypothesis.

Table 6.6: Various comparisons of mean flux curves over selected time intervals following oral glucose challenge

Groups	Interval	$\mathbf{m}_T{}'$ and $(\mathbf{G}\bar{\mathbf{x}})'$	Ratios	*p*-value		
				General	Gam	Kri
(NO, HO)	0-3 hrs	0.42, 0.26, 0.53, 0.47,0.23, 0.11 (0.43, 0.27, 0.53, 0.47, 0.24, 0.10)	(10, 1)	0.695	0.670	0.455
(NO, HO)	3-5 hrs	0.10, -0.02, 0.04 (0.10, -0.02, 0.04)	(1, 1.9)	0.869	0.897	0.880
(C, O)	0-3 hrs	0.44, 0.88, 1.06, 0.85, 0.15, 0.03 (0.44, 0.88, 1.06, 0.85, 0.15,-0.03)	(1, 1.6)	0.004	0.006	0.0001
(C, O)	3-5 hrs	0.028, 0.183, 0.078 (0.029, 0.185, 0.077)	(2.1, 1)	0.651	0.665	0.617
(C, O)	0-5 hrs	0.4, 0.9, 1.1, 0.9, 0.1, 0.03, 0.19, 0.08 (0.4, 0.9, 1.1, 0.8, 0.1, 0.03, 0.18, 0.08)	(1, 2.0)	0.036	0.050	0.001
Other comparisons						
(C, NO)	0-3 hrs	0.25, 0.76, 0.83, 0.65, 0.05, -0.02 (0.27, 0.77, 0.84, 0.66, 0.05, -0.01)	(1.2, 1)	0.021	0.023	0.007
(C, NO)	3-5 hrs	-0.015, 0.190, 0.058 (-0.013, 0.193, 0.062)	(3.4, 1)	0.642	0.642	0.579
(C, HO)	0-3 hrs	0.69, 1.04, 1.37, 1.13, 0.29, 0.09 (0.70, 1.04, 1.38, 1.13, 0.29, 0.09)	(12, 1)	0.007	0.014	0.001
(C, HO)	3-5 hrs	0.095, 0.178, 0.108 (0.091, 0.172, 0.099)	(1.8, 1)	0.899	0.923	0.902

6.2.2 Example 2

Sterczer, Vörös, and Karsai (1996) studied the effect of tap water and three kinds of cholagogues, magnesium sulphate, clanobutin and cholecystokinin, on changes in the gallbladder volume (GBV) by two-dimensional ultrasonography in six healthy dogs. In this experiment, the dogs were treated with each test substance and GBV (*ml*) was measured immediately before the administration of each test substance and at 10-minute intervals for 120 minutes thereafter. They found that the changes in the GBV treated with magnesium sulphate were very similar to those treated with clanobutin. The GBV data was available in Reiczigel (1999).

Table 6.7: Sample means of GBV and the 95% confidence region of $\mathbf{G\mu}$.

	Minutes after treatment				
	20	40	60	80	100
Tap water	12.505	14.153	15.242	16.995	18.090
Clanobutin	12.082	13.248	13.890	14.480	15.232
Cholecystokinin	16.643	16.512	16.712	16.853	16.455
$\mathbf{m_T}$	30.654	33.817	35.821	39.016	40.977
	2014.1				
	2552.8	3285.4			
$\mathbf{S_T}$	2795.0	3588.4	3940.8		
	2901.5	3751.9	4110.0	4309.2	
	2984.2	3837.7	4212.5	4402.2	4520.6

Note: From (3.12) the 95% confidence region of $\mathbf{G\mu}$ is $(\mathbf{G\mu}-\mathbf{m_T})'\mathbf{S_T^{-1}}(\mathbf{G\mu}-\mathbf{m_T}) \le 24.704$.

Studying the human medical literature about the effects exerted by tap water and clanobutin, a researcher wants to experiment with cocktail therapy, which mixing 70% tap water, 20% clanobutin and 10% cholecystokinin. The knowledge of $\mathbf{G\mu}$ can help him to prevent the patients' uncomfortableness, or the threshold value $\boldsymbol{\theta}_0$. The ratio of canine GBV to human beings is about 3:1 (50:17.4), and the ratios of one minus the maximal reductions in canine GBV to human beings are 0.75 and 0.87, with respective to tap water and clanobutin. Hence he can set $\mathbf{G\mu} = 1.575\boldsymbol{\mu}_1 + 0.522\boldsymbol{\mu}_2 + 0.3\boldsymbol{\mu}_3$ $= 3*(0.7*0.75\boldsymbol{\mu}_1 + 0.2*0.87\boldsymbol{\mu}_2 + 0.1\boldsymbol{\mu}_3)$. To ensure the inverse of the sample covariance matrix exists with probability one, the dimension of the measurements must be less than six. We take the first 5 measurements at 20-minute intervals for 100 minutes and the ratio of determinants is (1217.8, 1, 1.6). The 95% confidence region of $\mathbf{G\mu}$ from (3.12) and the summary data are in Table 6.7. The researcher can check to see if $\boldsymbol{\theta}_0$ is in the 95% confidence region with $q^2_{\{\|\tilde{\mathbf{T}}\|;\ 95\%\}}$ =24.704.

In Example 1, we not only test the multivariate Behrens-Fisher problem twice but also test the MANOVA problem. We illustrate the process to find $\mathbf{G}$ and the procedure for constructing the 95% confidence region based on our proposed method in Example 2. It should be noted that in the Edgar Anderson's Iris data, the 95% confidence region of $3\boldsymbol{\mu}_1 - 2\boldsymbol{\mu}_2 - \boldsymbol{\mu}_3$ dose not contain $\mathbf{0}$, that means that such a relationship among these three species does not exist.

According to the numerical examples, our proposed method in Chapter 3 is commended since the generalized *p*-values assure the level of the test in all simulated cases. Moreover, the coverage probabilities and the expected areas are satisfactory while the other methods become worse when the heteroscedasticities increased. The traditional methods usually are restricted to some conditions which are sometimes violated when the covariance matrices are quite different.

6.3 Illustrative examples of serial dependence

In this section we illustrate the procedures introduced in Chapter 5. First, results of a simulation study are described to make comparisons of different methods with respect to their coverage probabilities and expected areas. Next, a biological data set is utilized to compare the estimated trends via MLE method and our procedure. Finally, the generalized *p*-values to test a set of simulated data are presented.

6.3.1 Simulated studies (Comparison of coverage probabilities)

In simulation studies, we generate the data sets with the common trend of $\boldsymbol{\beta}' = (0\ 2)$, design matrices $\mathbf{X}_i' = \begin{pmatrix} 1\ 1\ 1\ 1 \\ \text{-3 -1 1 3} \end{pmatrix}$, $i = 1, 2$, and different serial covariance matrices among groups. For demonstration purposes, we compare five procedures with respect to their coverage probabilities and expected areas. These five methods are as follows:

(1) Diff: The generalized method with different covariance matrices proposed in Section 5.2.2.

(2) Equal: The generalized method with identical covariance matrix.

(3) GC: Growth-curve method described in Section 4.2.

(4) CHI: Classical Chi-square approximation described in Section 5.3.

(5) Hotell: Hotelling's T^2 –statistic described in Section 5.3.

Based on 1,000 replicates in each combination and 5,000 runs in the generalized methods (1) and (2), the coverage probabilities of the five methods under different combinations are given in Table 6.8, and the corresponding estimated expected areas of 95% confidence region are given in Table 6.9 under different scenarios.

Table 6.8: Comparison of 95% coverage probabilities of $\boldsymbol{\beta}$ under σ_1=1, ρ_1=0.1

($n_1=7$,	$n_2=15$)	Diff	Equal	GC	CHI	Hotell
σ_2	ρ_2					
1	0.1	0.952	0.957	0.931	0.882	0.953
	0.9	0.959	0.965	0.946	0.869	0.943
5	0.1	0.948	0.944	0.922	0.873	0.942
	0.9	0.960	0.964	0.948	0.876	0.951
10	0.1	0.946	0.945	0.925	0.897	0.939
	0.9	0.957	0.961	0.944	0.871	0.948
20	0.1	0.947	0.938	0.920	0.896	0.940
	0.9	0.954	0.963	0.951	0.890	0.939
($n_1=15$,	$n_2=7$)	Diff	Equal	GC	CHI	Hotell
σ_2	ρ_2					
1	0.1	0.941	0.955	0.936	0.878	0.966
	0.9	0.956	0.963	0.934	0.862	0.953
5	0.1	0.947	0.906	0.894	0.904	0.897
	0.9	0.953	0.926	0.901	0.890	0.911
10	0.1	0.948	0.907	0.905	0.908	0.871
	0.9	0.950	0.926	0.904	0.884	0.874
20	0.1	0.951	0.889	0.870	0.910	0.847
	0.9	0.950	0.935	0.914	0.901	0.876

From Table 6.8 and Table 6.9, we can see that the coverage probabilities obtained by the classical Chi-square approximation were below the nominal level 0.95 in all cases although its expected areas were small. Similarly, the coverage probabilities, obtained by methods (2), (3) and (5) with the identical covariance matrix assumption, decrease when the heteroscedasticities increase. On the other hand, the method (1), the generalized method without the equal covariance matrix assumption, had good coverage probabilities in all cases even when the heteroscedasticities among groups were large.

Table 6.9: Expected areas of 95% confidence regions of $\boldsymbol{\beta}$ under σ_1=1, ρ_1=0.1

($n_1=7$,	$n_2=15$)	Diff	Equal	GC	CHI	Hotell
σ_2	ρ_2					
1	0.1	0.112	0.118	0.097	0.138	0.123
	0.9	0.076	0.136	0.123	0.073	0.114
5	0.1	0.365	2.063	1.706	0.730	2.134
	0.9	0.326	1.603	1.665	0.484	1.289
10	0.1	0.406	8.187	6.782	0.888	8.457
	0.9	0.391	6.020	6.298	0.714	4.802
20	0.1	0.419	32.862	27.029	0.951	33.489
	0.9	0.416	23.718	24.835	0.879	19.092

$(n_1=15,\ n_2=7)$		Diff	Equal	GC	CHI	Hotell
σ_2	ρ_2					
1	0.1	0.109	0.118	0.097	0.138	0.123
	0.9	0.083	0.139	0.114	0.093	0.131
5	0.1	0.170	0.943	0.791	0.184	0.912
	0.9	0.165	0.853	0.849	0.173	0.676
10	0.1	0.170	3.434	2.955	0.182	3.286
	0.9	0.169	2.729	2.806	0.179	2.027
20	0.1	0.172	13.421	11.414	0.183	12.749
	0.9	0.172	10.381	10.759	0.182	7.571

Hence, based on the overall comparisons, the generalized method without equal covariance matrix assumption is better than the other four methods with respect to their coverage probabilities and expected areas, especially when small sample sizes are associated with large variances.

6.3.2 Example 3: the dental data

The dental data for 11 girls and 16 boys at ages 8, 10, 12 and 14 years were first considered by Potthoff and Roy (1964) and later analyzed by Lee and Geisser (1975), Lee (1988) and many others. The design matrix is set to be $\mathbf{X}' = \begin{pmatrix} 1 & 1 & 1 & 1 \\ -3 & -1 & 1 & 3 \end{pmatrix}$. From (5.13) and (5.16), the generalized *p*-values for testing the equality of the trends are about $4*10^{-7}$ and $2*10^{-8}$ for distinct covariance matrices and equal covariance matrices, respectively.

Table 6.10: Estimated trends, expected areas and hypotheses of the dental data set

	The generalized method		Growth-curve method	
Group	Estimated trend	Expected area	Estimated trend	Expected area
11 girls	$(22.638 \quad 0.485)'$	0.999	$(22.639 \quad 0.485)'$	0.924
16 boys	$(25.063 \quad 0.769)'$	1.113	$(25.027 \quad 0.773)'$	0.929
15 boys	$(25.107 \quad 0.782)'$	1.083	$(25.092 \quad 0.782)'$	0.963

Lee and Geisser had pointed out that individual 20, who is a boy, should be excluded. In this case, the generalized *p*-values are about $6*10^{-6}$ and $5*10^{-6}$ under distinct covariance matrices and equal covariance matrices, respectively. Hence we treated this dental data as arising from two different groups with distinct trends and serial covariance matrices. We used 10,000 runs to apply the generalized method to estimate trends and the expected areas of the 95% confidence region for the trends of 11 girls, 16 boys and 15 boys. The results are summarized in Table 6.10.

From Table 6.10, we can see that the estimated trends obtained by the generalized method and the growth-curve method are quite similar; however, the expected areas via the generalized method are slight larger than those via the growth-curve method. In general, the larger the expected areas, the larger the coverage probabilities. The simulation study in Section 6.3.1 also shows this phenomenon.

6.3.3 Example 4: the simulated data (Testing equality of the trends)

In order to illustrate our procedures to test the equality of the trends, five sets of data were generated assuming serial dependence regression model (5.1) with the small sample sizes $n_i = 8$, $i = 1, \cdots, 5$. The values of the parameters are $\sigma_1 = 1$, $\sigma_2 = 1.5$, $\sigma_3 = 2$, $\sigma_4 = 4$, $\sigma_5 = 20$, $\boldsymbol{\beta}_1' = \boldsymbol{\beta}_2' = \boldsymbol{\beta}_3' = (10 \;\; 2)$, $\boldsymbol{\beta}_4' = (12 \;\; 2)$, $\boldsymbol{\beta}_5' = (14 \;\; 2)$, $\rho_i = 0.3$, $i = 1, \cdots, 5$, and the design matrices are $\mathbf{X}_i' = \begin{pmatrix} 1 & 1 & 1 & 1 & 1 \\ -2 & -1 & 0 & 1 & 2 \end{pmatrix}$, $i = 1, \cdots, 5$. The generated data sets are presented in Table 6.11. The *p*-values for testing the equality of the trends are displayed in Table 6.12.

It is noted that the *p*-values in Table 6.12 are computed with 10,000 runs in each combination, p_e means the *p*-value under equal covariance matrices assumption by using formula (5.16) and p_u means the *p*-value without the assumption of equal covariance matrices by (5.13). The smaller the *p*-values, the stronger is the evidence to reject the null hypothesis. From Table 6.12, the numerical results showed that when groups are homogeneous, both p_e and p_u reached the same conclusion that there was not sufficient evidence to reject the null hypothesis. However, when heteroscedasticity is present, p_e usually fails to detect the differences between groups. On the other hand, p_u is more sensitive and is able to detect the differences between the distinct groups. Thus compared to p_e, p_u is more powerful than p_e under heteroscedasticity.

It is also noted that if we change the serial dependence into uniform covariance structure in program, the results with the procedure in Section 5.2 are very close to those proposed by Chi and Weerahandi (1998). The comparison is displayed in Table 6.13 and our results are computed with 5,000 runs in each simulated data set.

Table 6.11: The simulated data set for 5 groups

Group	t=-2	t=-1	t=0	t=1	t=2
i=1	5.317	9.454	9.192	12.461	13.720
i=1	5.809	8.271	10.402	13.639	15.084
i=1	4.225	8.239	6.988	11.676	13.713
i=1	5.515	8.044	9.359	12.326	13.002
i=1	6.209	9.348	8.789	11.061	12.339
i=1	7.268	8.806	9.038	11.525	14.740
i=1	6.950	8.159	9.876	12.741	15.100
i=1	4.751	8.423	9.788	11.517	14.328
i=2	3.479	7.283	11.478	12.476	15.240
i=2	4.768	5.964	11.269	10.437	12.298
i=2	5.684	6.795	10.870	10.457	12.453
i=2	5.597	8.183	8.025	12.269	11.619
i=2	4.656	8.680	11.735	11.069	15.841
i=2	6.705	7.992	9.593	12.772	12.005
i=2	5.375	8.474	10.931	12.306	13.233
i=2	6.648	9.760	9.541	12.024	14.737
i=3	7.792	7.853	11.848	13.339	15.404
i=3	6.704	6.747	10.522	12.626	14.499
i=3	2.623	7.420	10.141	7.929	14.943
i=3	9.040	11.211	9.210	13.447	14.008
i=3	6.226	8.143	7.233	12.126	10.774
i=3	3.188	8.114	9.059	13.483	12.891
i=3	3.303	11.286	8.380	10.021	16.122
i=3	6.784	5.921	12.561	12.478	14.418
i=4	10.047	9.090	6.987	8.703	15.811
i=4	9.890	5.362	12.305	14.816	16.782
i=4	11.747	9.269	15.375	16.333	20.243
i=4	8.576	6.958	12.237	16.103	14.539
i=4	3.357	-0.004	12.236	13.394	13.968
i=4	9.838	16.003	20.672	19.727	20.724
i=4	9.826	13.713	7.021	17.078	13.031
i=4	11.567	9.680	10.762	17.249	22.972
i=5	5.634	13.870	21.912	-4.802	22.294
i=5	2.952	21.233	-26.393	15.328	4.827
i=5	2.765	11.701	4.881	-0.456	8.499
i=5	-3.491	11.824	-1.604	42.528	20.791
i=5	11.124	30.875	38.875	16.394	34.617
i=5	37.900	-12.610	-7.722	27.170	10.618
i=5	47.762	3.990	12.793	39.530	19.299
i=5	20.352	-8.508	25.906	30.113	16.731

Table 6.12: The generalized p-values for the testing equality of the trends

Hypothesis	p_u	p_e
$H_{01}: \boldsymbol{\beta}_1 = \boldsymbol{\beta}_2 = \boldsymbol{\beta}_3$	0.083499	0.189677
$H_{02}: \boldsymbol{\beta}_1 = \boldsymbol{\beta}_2 = \boldsymbol{\beta}_4$	0.000447*	0.000001*
$H_{03}: \boldsymbol{\beta}_1 = \boldsymbol{\beta}_2 = \boldsymbol{\beta}_5$	0.047343*	0.082289
$H_{04}: \boldsymbol{\beta}_1 = \boldsymbol{\beta}_3 = \boldsymbol{\beta}_4$	0.000418*	0.000002*
$H_{05}: \boldsymbol{\beta}_1 = \boldsymbol{\beta}_3 = \boldsymbol{\beta}_5$	0.032971*	0.093071
$H_{06}: \boldsymbol{\beta}_1 = \boldsymbol{\beta}_4 = \boldsymbol{\beta}_5$	0.000187*	0.106036
$H_{07}: \boldsymbol{\beta}_2 = \boldsymbol{\beta}_4 = \boldsymbol{\beta}_5$	0.000231*	0.098681
$H_{08}: \boldsymbol{\beta}_3 = \boldsymbol{\beta}_4 = \boldsymbol{\beta}_5$	0.000398*	0.113409
$H_{09}: \boldsymbol{\beta}_2 = \boldsymbol{\beta}_3 = \boldsymbol{\beta}_4 = \boldsymbol{\beta}_5$	0.000365*	0.057247

* significance under the nominal level 0.05

Table 6.13: The generalized p-values for the testing equality of growth curves with uniform covariance matrices

Examples	Chi and Weerahandi(1998)		Section 5.2 (uniform)	
	p_u	p_e	p_u	p_e
(1) Serious heteroscedasticity	0.0236	0.0817	0.0245	0.0826
(2) Mild heteroscedasticity	0.0441	0.0113	0.0491	0.0112

We demonstrate the advantages of our proposed method when there are few subjects or few measurements taken over time in this section. The other traditional methods usually are restricted to specific conditions that are sometimes violated when the serial covariance matrices are quite different or the sample sizes are small. According to the numerical examples, our proposed method is superior since it does not require the assumption of equal covariance matrices and the generalized p-values are better able to detect the differences between the trends among the groups and for the single group case, the estimated trend is the same via the growth-curve method. Moreover, the coverage probabilities and the expected areas for this method are satisfactory while the other methods become worse when the heteroscedasticities increase.

6.4 Concluding remarks

The concepts of the generalized p-values and the generalized confidence intervals proposed by Tsui and Weerahandi (1989) and Weerahandi (1993) provide a new viewpoint of handling the problems with heteroscedastic phenomena. Although the generalized approach shares the same philosophy of the Bayesian approach that the inferences should be made with special regards to the data at hand, the parameters are not treated as random variables in generalized approach. From Section 6.1, the multivariate GTV based on the concept of the standardized expression modifies that proposed by Gamage et al.(2004) when the distribution of multivariate GTV is unknown. When the covariance matrices are quite different and the sample sizes are small, the Type I errors obtained by our proposed method are very closed to the nomial significane level while the other methods become worse when the heteroscedasticities increase or the dimension increases.

Based on the generalized approach, Lin and Lee (2003) provided an alternative way of dealing with the MANOVA model with unequal uniform covariance structures among multiple groups. However, (4.21) is true only when the covariance matrix is the uniform structure and the design matrix is the form $\mathbf{X} = (\mathbf{1}_T, \mathbf{X}_2)$. To apply the similar procedure for handling the regression model with unequal serial dependence, the procedure requires some modifications since $(\mathbf{X}'\boldsymbol{\Sigma}^{-1}\mathbf{X})^{-1}\mathbf{X}'\boldsymbol{\Sigma}^{-1}\bar{\mathbf{Y}} \neq (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\bar{\mathbf{Y}}$. Our proposed method is a strong candidate for dealing with the regression model with AR(1) dependence since it does not require the assumption of equal serial covariance matrices and the coverage probabilities obtained are close to the nominal level even when there are heteroscedasticities among groups.

From Table 6.13, the difference between the *p*-values of our proposed method, which are two simulated data sets of regression model with heteroscedastic uniform covariance matrices, and those proposed by Chi and Weerahandi (1998) is very small. Therefore, it is desirable to discuss and to find a method to handle the regression model with unequal some covariance structures $\sigma_i^2\mathbf{C}(\rho_i)$, $i = 1, \cdots, I$, where I is the number of the groups. The uniform and serial dependences are also in the consideration. Moreover, the case of the AR(p) covariance structures is also desirable to further explore.

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Appendix

The Distribution of the Multivariate GPQ

In Chapter 2, the distribution of the generalized pivotal quality (GPQ), $D(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta})$ must be free of unknown parameters. Sometimes, we express D as

$$D(\mathbf{W};\mathbf{w},\theta,\boldsymbol{\eta}) \equiv T(\mathbf{W};\mathbf{w},\boldsymbol{\eta}) - \theta\,, \tag{A.1}$$

or

$$\mathbf{D}(\mathbf{W};\mathbf{w},\boldsymbol{\theta},\boldsymbol{\eta}) \equiv \mathbf{T}(\mathbf{W};\mathbf{w},\boldsymbol{\eta}) - \boldsymbol{\theta}\,, \tag{A.2}$$

for the multivariate case.

To make inference about $\boldsymbol{\theta}$, for example, the hypothesis testing, confidence region, the expected area (volume) and the coverage probability of confidence region, the distribution of $\mathbf{D}$ plays an important part. However, the distribution of $\mathbf{D}$ usually is unknown, and the empirical cumulative distribution function is the estimated cumulative proportion of the data set that does not exceed any specified values. The distribution of $\mathbf{D}$ (or D) is free of unknown parameters while that of $\mathbf{T}$ perhaps involved with the location parameter $\boldsymbol{\theta}$ and sometimes it is more proper to apply the distribution of $\mathbf{T}$ in practice. Lin et al. (2007) proposed algorithms to compute the *p*-value and confidence region, etc.

Hypothesis testing and confidence region

Suppose that given $\mathbf{W}=\mathbf{w}$, the observed value of $\mathbf{T}$ is $\boldsymbol{\theta}$ and the distribution of $\mathbf{T}$ in (A.1) is free of nuisance parameters $\boldsymbol{\eta}$. Hence $\mathbf{T}$ can be used to construct a confidence region of $\boldsymbol{\theta}$ and test the hypothesis

$$H_0:\boldsymbol{\theta}=\boldsymbol{\theta}_0 \text{ vs. } \mathrm{H}_1:\boldsymbol{\theta}\neq\boldsymbol{\theta}_0\,, \tag{A.3}$$

where $\boldsymbol{\theta}_0$ is a pre-specified value.

Remark 1: If $\mathbf{a}$ is a $d\times 1$ column vector with elements $a_1,a_2,\ldots,a_d<\infty$, we write $\mathbf{a}=[(a_i)]$, and the *length* or *norm* of $\mathbf{a}$ is denoted by $\|\mathbf{a}\|$. Thus

$$\|\mathbf{a}\|=\sqrt{\mathbf{a}'\mathbf{a}}=(a_1^2+a_2^2+\ldots+a_d^2)^{1/2}\,.$$

Remark 2: For a vector $\mathbf{y}$, $|\mathbf{b}'\mathbf{y}|\leq c(\mathbf{b}'\mathbf{b})^{1/2}$ if and only if $\mathbf{y}'\mathbf{y}\leq c^2$, for any nonzero vector $\mathbf{b}$, which is a consequence of the *Cauchy-Schwarz inequality*.

Let $\tilde{\mathbf{T}}$ denote the standardized expression of $\mathbf{T}$ with $\tilde{\mathbf{T}}=\boldsymbol{\Sigma}_{\mathbf{T}}^{-1/2}(\mathbf{T}-\boldsymbol{\mu}_{\mathbf{T}})$, where

$\boldsymbol{\mu}_{\mathbf{T}}$ and $\boldsymbol{\Sigma}_{\mathbf{T}}$ represent the mean and covariance matrix of $\mathbf{T}$. Define $\tilde{\boldsymbol{\theta}}_0 = \boldsymbol{\Sigma}_{\mathbf{T}}^{-1/2}(\boldsymbol{\theta}_0 - \boldsymbol{\mu}_{\mathbf{T}})$, and then the generalized p-value for testing (A.3) can be given by

$$p = \Pr\{\|\tilde{\mathbf{T}}\| > \|\tilde{\boldsymbol{\theta}}_0\| \mid \mathbf{x}\}, \tag{A.4}$$

and H_0 will be rejected whenever p is less than α. Furthermore, let $q_{\{\|\tilde{\mathbf{T}}\|;\ \gamma\}}$ be the $100\gamma^{\text{th}}$ percentile of $\|\tilde{\mathbf{T}}\|$, so we have

$$\Pr\left\{\tilde{\mathbf{T}}'\tilde{\mathbf{T}} = (\mathbf{T} - \boldsymbol{\mu}_{\mathbf{T}})'\boldsymbol{\Sigma}_{\mathbf{T}}^{-1}(\mathbf{T} - \boldsymbol{\mu}_{\mathbf{T}}) \le q^2_{\{\|\tilde{\mathbf{T}}\|;\ \gamma\}}\right\} = \gamma . \tag{A.5}$$

Since the observed value of $\mathbf{T}$ is $\boldsymbol{\theta}$, the $100(1-\alpha)\%$ confidence region of $\boldsymbol{\theta}$ can be solved by the inequality

$$\left\{\boldsymbol{\theta} : (\boldsymbol{\theta} - \boldsymbol{\mu}_{\mathbf{T}})'\boldsymbol{\Sigma}_{\mathbf{T}}^{-1}(\boldsymbol{\theta} - \boldsymbol{\mu}_{\mathbf{T}}) \le q^2_{\{\|\tilde{\mathbf{T}}\|;\ 1\text{-}\alpha\}}\right\}, \tag{A.6}$$

which is equivalent to solving the inequality $\left\{\boldsymbol{\theta} : \left\|\boldsymbol{\Sigma}_{\mathbf{T}}^{-1/2}(\boldsymbol{\theta} - \boldsymbol{\mu}_{\mathbf{T}})\right\| \le q_{\{\|\tilde{\mathbf{T}}\|;\ 1\text{-}\alpha\}}\right\}$.

Simultaneous confidence intervals for the d-components of $\boldsymbol{\theta}$ can be developed from consideration of confidence intervals for $\mathbf{a}'\mathbf{T}$, where $\mathbf{a}$ is any nonzero d-variate vector.

According to Remark 2, let $\mathbf{y} = \boldsymbol{\Sigma}_{\mathbf{T}}^{-1/2}(\mathbf{T} - \boldsymbol{\mu}_{\mathbf{T}})$, $\mathbf{b} = \boldsymbol{\Sigma}_{\mathbf{T}}^{1/2}\mathbf{a}$ and $c = q_{\{\|\tilde{\mathbf{T}}\|;\ 1\text{-}\alpha\}}$, then from (A.5), we have the following:

$$(\mathbf{T} - \boldsymbol{\mu}_{\mathbf{T}})'\boldsymbol{\Sigma}_{\mathbf{T}}^{-1}(\mathbf{T} - \boldsymbol{\mu}_{\mathbf{T}}) \le q^2_{\{\|\tilde{\mathbf{T}}\|;\ 1\text{-}\alpha\}} \text{ if and only if } \left|\mathbf{a}'(\mathbf{T} - \boldsymbol{\mu}_{\mathbf{T}})\right| \le q_{\{\|\tilde{\mathbf{T}}\|;\ 1\text{-}\alpha\}} \sqrt{\mathbf{a}'\boldsymbol{\Sigma}_{\mathbf{T}}\mathbf{a}} . \tag{A.7}$$

The inequality (A.7) implies that

$$\Pr\left\{\mathbf{a}'\boldsymbol{\mu}_{\mathbf{T}} - q_{\{\|\tilde{\mathbf{T}}\|;\ 1\text{-}\alpha\}} \sqrt{\mathbf{a}'\boldsymbol{\Sigma}_{\mathbf{T}}\mathbf{a}} \le \mathbf{a}'\mathbf{T} \le \mathbf{a}'\boldsymbol{\mu}_{\mathbf{T}} + q_{\{\|\tilde{\mathbf{T}}\|;\ 1\text{-}\alpha\}} \sqrt{\mathbf{a}'\boldsymbol{\Sigma}_{\mathbf{T}}\mathbf{a}}\right\} = 1\text{-}\alpha , \tag{A.8}$$

for all nonzero vector $\mathbf{a}$. If $\mathbf{a}$ is the vector with 1 for the l^{th} element and 0 elsewhere, the simultaneous $100(1-\alpha)\%$ confidence interval for the l^{th} component of common mean vector $\boldsymbol{\theta}$, θ_l, is

$$\left(\mu_{\mathbf{T}(l)} - q_{\{\|\tilde{\mathbf{T}}\|;\ 1\text{-}\alpha\}} \sqrt{\Sigma_{\mathbf{T}}^{(l,l)}},\ \mu_{\mathbf{T}(l)} + q_{\{\|\tilde{\mathbf{T}}\|;\ 1\text{-}\alpha\}} \sqrt{\Sigma_{\mathbf{T}}^{(l,l)}}\right),\ \ l = 1, \ldots, d , \tag{A.9}$$

where $\mu_{\mathbf{T}(l)}$ is the l^{th} component of $\boldsymbol{\mu}_{\mathbf{T}}$ and $\Sigma_{\mathbf{T}}^{(l,l)}$ is the $(l,l)^{\text{th}}$ component of $\boldsymbol{\Sigma}_{\mathbf{T}}$. To take $\mathbf{T}{=}\mathbf{G}\bar{\mathbf{x}} - \left(\mathbf{G}\mathbf{s}^{1/2}\mathbf{R}^{-1}\mathbf{s}^{1/2}\mathbf{G}'\right)^{1/2}\mathbf{Z}_d$ in Chapter 3 as an example, we will use the following algorithm to compute the p-value (A.4) and confidence region of $\boldsymbol{\theta}$ (A.6).

Algorithm 1: For a given $(n_1,...,n_K)$, $(\overline{\mathbf{x}}_1,...,\overline{\mathbf{x}}_K)$, $(\mathbf{s}_1,...,\mathbf{s}_K)$ and $\mathbf{G}$:

$\overline{\mathbf{x}}' = (\overline{\mathbf{x}}_1',...,\overline{\mathbf{x}}_K')$ and $\mathbf{s} = Bdiag(\mathbf{s}_1,...,\mathbf{s}_K)$.

For $j = 1,...,m$:

Generate $\mathbf{Z}_d$ from $N_d(\mathbf{0},\ \mathbf{I}_d)$.

Generate $\mathbf{R}_i \sim W_d(n_i - 1,\ \mathbf{I}_d),\ i = 1,...,K.$

$\mathbf{R} = Bdiag(\mathbf{R}_1,...,\mathbf{R}_K)$.

Compute $\mathbf{T}_j = \mathbf{G}\overline{\mathbf{x}} - \left(\mathbf{G}\mathbf{s}^{1/2}\mathbf{R}^{-1}\mathbf{s}^{1/2}\mathbf{G}'\right)^{1/2}\mathbf{Z}_d$.

(End *j* loop)

Compute $\hat{\boldsymbol{\mu}}_{\mathbf{T}} = \frac{1}{m}\sum_{j=1}^{m}\mathbf{T}_j$ and $\hat{\boldsymbol{\Sigma}}_{\mathbf{T}} = \frac{1}{m-1}\sum_{j=1}^{m}(\mathbf{T}_j - \hat{\boldsymbol{\mu}}_{\mathbf{T}})(\mathbf{T}_j - \hat{\boldsymbol{\mu}}_{\mathbf{T}})'$.

Compute $\left\|\hat{\hat{\mathbf{T}}}_j\right\|$ and $\left\|\hat{\hat{\boldsymbol{\theta}}}_0\right\|$, where $\hat{\hat{\mathbf{T}}}_j = \hat{\boldsymbol{\Sigma}}_{\mathbf{T}}^{-1/2}(\mathbf{T}_j - \hat{\boldsymbol{\mu}}_{\mathbf{T}}),\ j = 1,...,m,$ and

$\hat{\hat{\boldsymbol{\theta}}}_0 = \hat{\boldsymbol{\Sigma}}_{\mathbf{T}}^{-1/2}(\boldsymbol{\theta}_0 - \hat{\boldsymbol{\mu}}_{\mathbf{T}})$.

Let $\tau_j = 1$ if $\left\|\hat{\hat{\mathbf{T}}}_j\right\| \geq \left\|\hat{\hat{\boldsymbol{\theta}}}_0\right\|$; else $\tau_j = 0$.

$\frac{1}{m}\sum_{j=1}^{m}\tau_j$ is a Monte Carlo estimate of the generalized *p*-value for testing (A.3).

Let $q_{\left\{\left\|\hat{\hat{\mathbf{T}}}\right\|;\ 1-\alpha\right\}}$ be the $100(1-\alpha)$th percentile of $\left\|\hat{\hat{\mathbf{T}}}_j\right\|,\ j = 1,...,m,$ then the confidence region of $\boldsymbol{\theta}$ and the simultaneous confidence interval of θ_l, $l = 1,...,d$, can be obtained through (A.6) and (A.9), respectively.

The expected area and coverage probability of the confidence region

We will compute the coverage probabilities and the expected surface areas or the expected *d*-dimensional volumes of the generalized confidence regions under $d \geq 2$.

Remark 3: Suppose we have a confidence region of $\boldsymbol{\mu}$ which satisfies the following inequality: $(\boldsymbol{\mu} - \hat{\boldsymbol{\mu}})'\mathbf{V}^{-1}(\boldsymbol{\mu} - \hat{\boldsymbol{\mu}}) \leq c^2$, where $\mathbf{V}$ is a $d \times d$ positive definite matrix. The ellipsoid center is $\hat{\boldsymbol{\mu}}$, and the axes of the ellipsoid are $\pm|c|\sqrt{e_l}$ in the direction of $\boldsymbol{\xi}_l$, where e_l's are the eigenvalues of $\mathbf{V}$ and $\boldsymbol{\xi}_l$'s are the corresponding eigenvectors, $l = 1,...,d$. Thus the expected *d*-dimensional volume of $\boldsymbol{\mu}$ can be computed by $\frac{\pi^{d/2}c^d}{\Gamma(1+d/2)}E[\sqrt{|\mathbf{V}|}]$, where $|\mathbf{V}|$ is the determinant of $\mathbf{V}$ and $\Gamma(\cdot)$ is gamma function. Specially, for $d=2$ and $d=3$, the expected area and volume can be reduced to $\pi c^2 E[\sqrt{|\mathbf{V}|}]$ and $\frac{4\pi c^3}{3}E[\sqrt{|\mathbf{V}|}]$, respectively.

According to Remark 3, the *d*-dimensional volume of the confidence region in (A.6) derived by generalized method are

$$\frac{\pi^{d/2}\cdot q^d_{\{\|\tilde{\mathbf{T}}\|;\ 1\text{-}\alpha\}}}{\Gamma(1+d/2)}E\left[\sqrt{|\boldsymbol{\Sigma}_{\mathbf{T}}|}\right]. \tag{A.10}$$

The algorithm for computing the *d*-dimensional volume as well as coverage probability is given as follows.

Algorithm 2: For a given $(n_1,\ldots,n_K),\ (\boldsymbol{\mu}_1,\ldots,\boldsymbol{\mu}_K),\ (\boldsymbol{\Sigma}_1,\ldots,\boldsymbol{\Sigma}_K)$ and $\mathbf{G}$:

For $l=1,\ldots,L$:

Generate $\bar{\mathbf{X}}_i^{(l)} \sim N_d(\boldsymbol{\mu}_i,\ \boldsymbol{\Sigma}_i/n_i),\quad i=1,\ldots,K.$

Generate $\mathbf{U}_i^{(l)} \sim W_d(n_i-1,\ \boldsymbol{\Sigma}_i/n_i),\quad i=1,\ldots,K.$

Use Algorithm 1 to compute *d*-dimensional volume H_l of the confidence region in the l^{th} iteration, $H_l = \frac{\pi^{d/2}\cdot q^{d(l)}_{\{\|\tilde{\mathbf{T}}\|;\ 1\text{-}\alpha\}}}{\Gamma(1+d/2)}\sqrt{|\hat{\boldsymbol{\Sigma}}_{\mathbf{T}}^{(l)}|}$.

Use Algorithm 1 to compute coverage probability, set $\delta_l = 1$ if

$\left\|\hat{\boldsymbol{\Sigma}}_{\mathbf{T}}^{-1/2(l)}(\boldsymbol{\theta}-\hat{\boldsymbol{\mu}}_{\mathbf{T}}^{(l)})\right\| \le q^{(l)}_{\{\|\hat{\mathbf{T}}\|;\ 1\text{-}\alpha\}}$; else $\delta_l = 0$.

(End l loop)

$\frac{1}{L}\sum_{l=1}^{L}H_l$ and $\frac{1}{L}\sum_{l=1}^{L}\delta_l$ are Monte Carlo estimates of the *d*-dimensional volume and coverage probability of the generalized confidence region, respectively.