ANALYSIS OF HIGH DIMENSIONAL MULTIVARIATE REPEATED MEASUREMENTS DESIGNS

Kannigar Hirunkasi

A Dissertation Submitted in Partial
Fulfillment of the Requirements for the Degree of
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School of Applied Statistics
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ABSTRACT

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A multivariate repeated measurements design is a design applied to measurements of p response variables observed repeatedly over t times on each subject in g groups. There are two different approaches for analyzing multivariate repeated measurements, the Doubly Multivariate Model (DMM) and the Multivariate Mixed Model (MMM). These analyses are based on a classical multivariate test which requires the assumption of MANOVA in that the degrees of freedom of the sum of squares and cross product matrix (SSCP) due to error are larger than its dimension. In DMM analysis, the response matrix consists of pt response variables on each n subject whereas MMM consists of p response variables on each nt subject. Corresponding to the within subject contrast matrix of rank $u \leq t$, the test statistic of DMM analysis is based on the function of $\mathbf{S}_h\mathbf{S}_e^{-1}$ where $\mathbf{S}_e$ and $\mathbf{S}_h$ are the $pu \times pu$ SSCP matrices corresponding to error and the hypothesis and requires an assumption that $n-g > pu$. In MMM analysis, the test statistic is the function of $\mathbf{S}_h^*(\mathbf{S}_e^*)^{-1}$ where $\mathbf{S}_e^*$ and $\mathbf{S}_h^*$ are the $p \times p$ SSCP matrices and requires that $u(n-g) > p$.

In studies such as DNA microarray time course experiments, gene expressions are available on thousands of genes of an individual and can be measured several times but there are only a few individuals in the data set. Therefore classical multivariate tests of both cases are not valid to analyze these high dimensional data.

In this dissertation, multivariate tests for analyzing multivariate repeated measurements designs in a high dimensional framework are proposed. These tests are

adapted from generalizations of Dempster's test and Bai and Saranadasa's test in two approaches, DMM and MMM. In both analyses, the adapted tests from the generalization of Dempster's test, T_1 and T_1^*, have an approximate F distribution with degrees of freedom estimated by the trace function of the SSCP matrix due to error, whereas the proposed tests adapted from the generalization of Bai and Saranadasa's test, T_2 and T_2^*, are asymptotically distributed as standard normal when p and n tend to infinity.

A comparison of the performances of the proposed tests was carried out using a simulation study. The simulation results found that the attained significance levels of the T_1 and T_1^* tests from the DMM and MMM analyses on the interaction, group and time effects seemed to be similar and close to the nominal 0.05 level for all cases of n and p, whereas the attained significance levels of the T_2 and T_2^* tests are close to the nominal 0.05 level when n is large but higher than 0.05 when n is small. In tests of the interaction, group and time effects, the empirical powers of the four tests increase as p and n increase. The empirical powers of proposed tests adapted from Bai and Saranadasa's test are slightly higher than those from the Dempster's test adaptation and the empirical powers of the two proposed tests in DMM analysis are slightly higher than those in MMM analysis. In order to demonstrate a numerical example, the proposed tests were applied to the analysis of DNA time course microarray data.

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Kannigar Hirunkasi

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ABBREVIATIONS AND SYMBOLS

Abbreviations	**Equivalence**
ANOVA	Analysis of Variance
DMM	Doubly Multivariate Model
MANOVA	Multivariate Analysis of Variance
MMM	Multivariate Mixed Model
RM	Repeated Measurement
SSCP	Sum of Square and Cross Product
df	Degree of freedom of the Sum of Square and Cross Product Matrix due to Error
dim	Dimension of the Sum of Square and Cross Product Matrix due to Error
r	Ratio of Dimension and Degree of Freedom of the Sum of Square and Cross Product Matrix due to Error

SYMBOLS

$\dot{\sim}$	Approximate Distribution
$\doteq$	Approximate Equal
χ^2_v	Central Chi-Square Distribution with v_1 Degrees of Freedom
$W_m(\mathbf{\Phi}, v)$	Central Wishart Distribution with *m*-Dimensional Covariance Matrix Parameter $\mathbf{\Phi}$ and v
$\Psi_u(t)$	Characteristic Function of Random Variable u

$\rightarrow$	Converges to
$\xrightarrow{d}$	Converges in distribution to
$F(f, v_1, v_2)$	Cumulative Central F- Distribution at f with v_1 and v_2 Degrees of Freedom
$F(f, v_1, v_2, \delta)$	Cumulative Non-Central F Distribution at f with v_1 and v_2 Degrees of Freedom and Non-centrality Parameter δ
$\mathbb{N}(z)$	Cumulative Standard Normal Distribution of z
$E(X)$	Expectation of X
$\exp(x)$	Natural Exponential function of x
$\ln(x)$	Natural Logarithm function of x
$\chi^2_{v,\delta}$	Non-Central Chi-square Distribution with v_1 Degrees of Freedom and Non-centrality Parameter δ
$W_m(\mathbf{\Phi}, v, \mathbf{\Delta})$	Non-Central Wishart distribution with m-Dimensional Covariance Matrix Parameter $\mathbf{\Phi}$, v and Non-Centrality Matrix $\mathbf{\Delta}$
$\otimes$	Kronecker Product Operator
$\lfloor x \rfloor$	Largest Integer Less Than or Equal x
$N_m(\boldsymbol{\mu}, \mathbf{\Sigma})$	Multivariate Normal Distribution with mean matrix $\boldsymbol{\mu}$ and m-dimensional covariance matrix $\mathbf{\Sigma}$
T_1	Proposed Test Adapted from Generalization of Dempster Test in DMM Analysis

T_2	Proposed Test Adapted from Generalization of Bai and Saranadasa Test in DMM Analysis
T_1^*	Proposed Test Adapted from Generalization of Dempster Test in MMM Analysis
T_2^*	Proposed Test Adapted from Generalization of Bai and Saranadasa Test in MMM Analysis
$rank(\mathbf{X})$	Rank of Matrix **X**
$tr(\mathbf{X})$	Trace Operator of Matrix **X**
$T_p(\mathbf{X})$	Thompson's Generalized Trace Operator of Matrix **X**
$\mathrm{var}(X)$	Variance of X
vec(.)	Vec Operator

CHAPTER 1

INTRODUCTION

1.1 Repeated Measurements Designs

Repeated Measurements (RM) designs are one of the most frequently studied and applied designs in a variety of applied fields, such as medicine, social sciences, behavioral sciences, psychology and education. A design in which measurements on a variable are made at several occasions or under different treatment conditions on the same subject is called a *Univariate Repeated Measurement Design*. Models for the analysis of RM designs are wide-spread and varied, and have been reviewed in a number of publications, such as Hand and Taylor (1987: 56), Crowder and Hand (1990: 25), and Vonesh and Chinchilli (1997: 75).

Typically, in many researches, the set of RM data is usually taken as one response variable on n subjects forming g groups over t occasions (time points). This data is a type of split-plot design where subjects are randomly nested within a group (whole plot) factor (A), which is crossed with a time (split-plot) factor (B). The objectives of these designs are to test for the effect of the group (or treatment) factor, the effect of the time factor and the interaction effect between the group and time factors. The group factor is called as between-subject factor and the time factor is called as within-subject factor. This type of RM design can be analyzed using two models (methods of analysis): the Univariate Mixed Model and the Multivariate Linear Model. These models are briefly reviewed in the next section.

In medical science and related fields, studies are often designed to investigate changes in several variables, referred to as p variables, which are measured repeatedly over time in the participating subjects. Many statistical models have been proposed for the analysis of RM of one single outcome, although the analysis of multiple outcomes measured repeatedly often restricts the separate analysis of each response. However, the researchers' interest may be addressed in the joint testing of a treatment effect on a set of outcomes. This design requires a multivariate linear model analysis for multivariate outcomes.

When p response variables are observed repeatedly over t times on each subject in g groups, the design is called a *Multivariate Repeated Measurements Design*. Similar to the Univariate Repeated Measurements Design, there are two different models for analyzing RM of multivariate outcomes. The first model is the Doubly Multivariate Linear Model (DMM) which is a multivariate linear model of multivariate data both in the direction of distinct p responses of t repeated measurements. The second model is the Multivariate Mixed Model (MMM) which is a generalization of Scheffé's Univariate Mixed Model for the multivariate case (Boik, 1991: 1235).

1.2 Classical Analysis of Repeated Measurements Designs

1.2.1 Univariate Repeated Measurements Designs

In Univariate Repeated Measurements Designs, a response variable is repeatedly measured over t time points on n subjects in g groups. Let y_{ijk} be a response variable observed on the i^{th} subject in the j^{th} group at k^{th} time, $i = 1, 2, \ldots, n_j$, $\sum_{j=1}^{g} n_j = n$, $j = 1, 2, \ldots, g$, $k = 1, 2, \ldots, t$. The data layout of univariate repeated measurements designs is shown in Table 1.1. The sample means $\bar{y}_{.jk}$, $\bar{y}_{.j.}$, $\bar{y}_{..k}$ and overall sample mean $\bar{y}_{...}$ are defined by

$$\bar{y}_{.jk} = \frac{\sum_{i=1}^{n_j} y_{ijk}}{n_j}, \quad \bar{y}_{.j.} = \frac{\sum_{i=1}^{n_j}\sum_{t=1}^{t} y_{ijk}}{n_j t}, \tag{1.1}$$

$$\bar{y}_{..k} = \frac{\sum_{j=1}^{g}\sum_{i=1}^{n_j} y_{ijk}}{n} \quad \text{and} \quad \bar{y}_{...} = \frac{\sum_{j=1}^{g}\sum_{i=1}^{n_j}\sum_{k=1}^{t} y_{ijk}}{nt}. \tag{1.2}$$

Table 1.1 The Data Layout for Univariate Repeated Measurements Designs

Treatment Group (j)	Subject (i)	Response Vector $\boldsymbol{y}'_{11}$		Condition (Time) 1	2	$\cdots$	t	Mean over Time
1	1	$\boldsymbol{y}'_{11}$	=	$(y_{111}$	y_{112}	$\cdots$	$y_{11t})$	
	2	$\boldsymbol{y}'_{21}$	=	$(y_{211}$	y_{212}	$\cdots$	$y_{21t})$	
	$\vdots$	$\vdots$		$\vdots$	$\vdots$		$\vdots$	
	n_1	$\boldsymbol{y}'_{n_1 1}$	=	$(y_{n_1 11}$	$y_{n_1 12}$	$\cdots$	$y_{n_1 1t})$	
Mean		$\bar{\boldsymbol{y}}'_{\cdot 1}$	=	$(\bar{y}_{\cdot 11}$	$\bar{y}_{\cdot 12}$	$\cdots$	$\bar{y}_{\cdot 1t})$	$\bar{y}_{\cdot 1 \cdot}$
2	1	$\boldsymbol{y}'_{12}$	=	y_{121}	y_{122}	$\cdots$	y_{12t}	
	2	$\boldsymbol{y}'_{22}$	=	$(y_{221}$	y_{222}	$\cdots$	$y_{22t})$	
	$\vdots$	$\vdots$		$\vdots$	$\vdots$		$\vdots$	
	n_2	$\boldsymbol{y}'_{n_2 2}$	=	$(y_{n_2 21}$	$y_{n_2 22}$	$\cdots$	$y_{n_2 2t})$	
Mean		$\bar{\boldsymbol{y}}'_{\cdot 2}$	=	$(\bar{y}_{\cdot 21}$	$\bar{y}_{\cdot 22}$	$\cdots$	$\bar{y}_{\cdot 2t})$	$\bar{y}_{\cdot 2 \cdot}$
$\vdots$	$\vdots$	$\vdots$		$\vdots$	$\vdots$		$\vdots$	
g	1	$\boldsymbol{y}'_{1g}$	=	y_{1g1}	y_{1g2}	$\cdots$	y_{1gt}	
	2	$\boldsymbol{y}'_{2g}$	=	$(y_{2g1}$	y_{2g2}	$\cdots$	$y_{2gt})$	
	$\vdots$	$\vdots$		$\vdots$	$\vdots$		$\vdots$	
	n_g	$\boldsymbol{y}'_{n_g g}$	=	$(y_{n_g g1}$	$y_{n_g g2}$	$\cdots$	$y_{n_g gt})$	
Mean		$\bar{\boldsymbol{y}}'_{\cdot g}$	=	$(\bar{y}_{\cdot g1}$	$\bar{y}_{\cdot g2}$	$\cdots$	$\bar{y}_{\cdot gt})$	$\bar{y}_{\cdot g \cdot}$
Mean over Group		$\bar{\boldsymbol{y}}'_{\cdot\cdot}$	=	$(\bar{y}_{\cdot\cdot 1}$	$\bar{y}_{\cdot\cdot 2}$	$\cdots$	$\bar{y}_{\cdot\cdot t})$	$\bar{y}_{\cdot\cdot\cdot}$

The method for analysis of a univariate repeated measurements design can use either the Multivariate Linear Model or the Univariate Mixed Model.

1.2.1.1 Multivariate Linear Model Analysis

Because t repeated measurements are taken on each subject, correlated data which can be analyzed using a multivariate linear model analysis are encountered. For a multivariate linear model, the t correlated measurements $y_{ij1}, y_{ij2}, \ldots, y_{ijt}$ constitute vector $\boldsymbol{y}_{ij} = (y_{ij1}, \ldots y_{ij2}, \ldots, y_{ijt})'$. The Multivariate Linear Model of the Univariate Repeated Measurements Design is identical to the one-way Multivariate Analysis of Variance (MANOVA) model as follows:

$$\begin{aligned} \boldsymbol{y}_{ij} &= \boldsymbol{\mu} + \boldsymbol{\alpha}_j + \boldsymbol{e}_{ij}, \\ &= \boldsymbol{\mu}_j + \boldsymbol{e}_{ij} \end{aligned} \tag{1.3}$$

where $\boldsymbol{\alpha}_j$ is the $t \times 1$ vector of main effects for the group factor and $\boldsymbol{e}_{ij}$ is the $t \times 1$ random error vector on the i^{th} subject within the j^{th} group. For a full rank model, the cell means $\boldsymbol{\mu}_j = \boldsymbol{\mu} + \boldsymbol{e}_{ij}$ and $\boldsymbol{\mu}_j = (\mu_1, \mu_2, \ldots, \mu_g)'$, where $\mu_j = \mu + \alpha_j$, are used. A multivariate linear model (1.1) seems to include only group factors, but a profile analysis to test on a time factor and a group × time interaction factor can be used.

Assume that $\boldsymbol{e}_{ij}$ is identically and independently distributed (i.i.d.) according to a t-variate normal distribution with a zero mean vector and a $t \times t$ covariance matrix $\boldsymbol{\Sigma}_{t\times t}$, written as $\boldsymbol{e}_{ij} \sim N_t(\mathbf{0}, \boldsymbol{\Sigma}_{t\times t})$, for all i and j. This assumption allows t repeated measurements to be correlated in any pattern.

Putting the vector $\boldsymbol{y}_{ij} = (y_{ij1}, \cdots y_{ij2}, \cdots, y_{ijt})'$ on each row, an $n \times t$ response matrix $\mathbf{Y}_{n\times t} = (\boldsymbol{y}_{11}, \cdots \boldsymbol{y}_{n_1 1}, \cdots, \boldsymbol{y}_{1g}, \cdots \boldsymbol{y}_{n_g g})'$ in the multivariate linear model of $\mathbf{Y}_{n\times t}$ in matrix form is constructed as

$$\mathbf{Y}_{n\times t} = \mathbf{X}_{n\times g}\mathbf{B}_{g\times t} + \mathbf{E}_{n\times t}, \tag{1.4}$$

where

$$\mathbf{Y}_{n\times t} = \begin{bmatrix} \boldsymbol{y}'_{11} \\ \vdots \\ \boldsymbol{y}'_{n_1 1} \\ \hdashline \boldsymbol{y}'_{12} \\ \vdots \\ \boldsymbol{y}'_{n_2 2} \\ \hdashline \vdots \\ \hdashline \boldsymbol{y}'_{1g} \\ \vdots \\ \boldsymbol{y}'_{n_g g} \end{bmatrix} = \begin{bmatrix} y_{111} & y_{112} & \cdots & y_{11t} \\ \vdots & \vdots & \ddots & \vdots \\ y_{n_1 11} & y_{n_1 12} & \cdots & y_{n_1 1t} \\ \hdashline y_{121} & y_{122} & \cdots & y_{12t} \\ \vdots & \vdots & \ddots & \vdots \\ y_{n_2 21} & y_{n_2 22} & \cdots & y_{n_2 2t} \\ \hdashline \vdots & \vdots & \vdots & \vdots \\ \hdashline y_{1g1} & y_{1g2} & \cdots & y_{1gt} \\ \vdots & \vdots & \ddots & \vdots \\ y_{n_g g1} & y_{n_g g2} & \cdots & y_{n_g gt} \end{bmatrix}, \mathbf{E}_{n\times t} = \begin{bmatrix} \boldsymbol{e}'_{11} \\ \vdots \\ \boldsymbol{e}'_{n_1 1} \\ \hdashline \boldsymbol{e}'_{12} \\ \vdots \\ \boldsymbol{e}'_{n_2 2} \\ \hdashline \vdots \\ \hdashline \boldsymbol{e}'_{1g} \\ \vdots \\ \boldsymbol{y}'_{n_g g} \end{bmatrix} = \begin{bmatrix} e_{111} & e_{112} & \cdots & e_{11t} \\ \vdots & \vdots & \ddots & \vdots \\ e_{n_1 11} & e_{n_1 12} & \cdots & e_{n_1 1t} \\ \hdashline e_{121} & e_{122} & \cdots & e_{12t} \\ \vdots & \vdots & \ddots & \vdots \\ e_{n_2 21} & e_{n_2 22} & \cdots & e_{n_2 2t} \\ \hdashline \vdots & \vdots & \vdots & \vdots \\ \hdashline e_{1g1} & e_{1g2} & \cdots & e_{1gt} \\ \vdots & \vdots & \ddots & \vdots \\ e_{n_g g1} & e_{n_g g2} & \cdots & e_{n_g gt} \end{bmatrix},$$

$$\mathbf{X}_{n\times g} = \begin{bmatrix} \mathbf{1}_{n_1} & \mathbf{0} & \ldots & \mathbf{0} \\ \mathbf{0} & \mathbf{1}_{n_2} & \ldots & \mathbf{0} \\ \vdots & \vdots & \ddots & \vdots \\ \mathbf{0} & \mathbf{0} & \ldots & \mathbf{1}_{n_g} \end{bmatrix} \text{ and } \mathbf{B}_{g\times t} = \begin{bmatrix} \boldsymbol{\mu}'_1 \\ \boldsymbol{\mu}'_2 \\ \vdots \\ \boldsymbol{\mu}'_g \end{bmatrix} = \begin{bmatrix} \mu_{11} & \mu_{12} & \cdots & \mu_{1t} \\ \mu_{21} & \mu_{22} & \cdots & \mu_{2t} \\ \vdots & \vdots & \ddots & \vdots \\ \mu_{g1} & \mu_{g2} & \cdots & \mu_{gt} \end{bmatrix}.$$

The traditional inference of these kinds of data is as a test of the equality of the group × time interaction effect (parallelism of profile), the equality of the group effect (coincidence of profile) and the equality of the time effect (constancy of profile), which can be written as:

H_{01}: The profiles for the g groups are parallel

H_{02}: There are no differences of mean vectors among the g groups

H_{03}: There are no differences of mean vectors among the t times

With these three hypotheses described above, the Multivariate General Linear Hypothesis can be written as

$$H_0 : \mathbf{C}\mathbf{B}_{g\times t}\mathbf{A} = \mathbf{\Gamma}_{0(v_h\times u)}, \tag{1.5}$$

where $\mathbf{C}$ is a $v_h \times g$ between-subject contrast matrix, $rank(\mathbf{C}) = v_h \le g$, and $\mathbf{A}$ is a $t \times u$ within-subject contrast matrix with $rank(\mathbf{A}) = u \le t$. $\mathbf{\Gamma}_0$ is a $v_h \times u$ constant matrix which, in general, is a zero matrix.

Thus, the first hypothesis is to test whether the profiles for each group are parallel or if there is no interaction between group and time, and is stated as

$$H_{01} : \begin{bmatrix} \mu_{11} - \mu_{12} \\ \mu_{12} - \mu_{13} \\ \vdots \\ \mu_{1(t-1)} - \mu_{1t} \end{bmatrix} = \begin{bmatrix} \mu_{21} - \mu_{22} \\ \mu_{22} - \mu_{23} \\ \vdots \\ \mu_{2(t-1)} - \mu_{2t} \end{bmatrix} = \cdots = \begin{bmatrix} \mu_{g1} - \mu_{g2} \\ \mu_{g2} - \mu_{g3} \\ \vdots \\ \mu_{g(t-1)} - \mu_{gt} \end{bmatrix}. \tag{1.6}$$

Representing H_{01} in terms of the elements of $\mathbf{B}_{g\times t}$ as $H_{01} : \mathbf{C}\mathbf{B}_{g\times t}\mathbf{A} = \mathbf{\Gamma}_{0(v_h\times u)}$, the matrices $\mathbf{C}$, $\mathbf{A}$ and $\mathbf{\Gamma}_{0(v_h\times u)}$ are taken in the form

$$\mathbf{C}_{(g-1)\times g} = \left[\begin{array}{cccc:c} 1 & 0 & \dots & 0 & -1 \\ 0 & 1 & \dots & 0 & -1 \\ \vdots & \vdots & \ddots & \vdots & -1 \\ 0 & 0 & \dots & 1 & -1 \end{array}\right], \mathbf{A}_{t\times(t-1)} = \begin{bmatrix} 1 & 0 & \dots & 0 \\ -1 & 1 & \dots & 0 \\ 0 & -1 & \dots & 0 \\ \vdots & \vdots & \ddots & 0 \\ 0 & 0 & \dots & 1 \\ 0 & 0 & \dots & -1 \end{bmatrix}, \mathbf{\Gamma}_0 = [0]_{(g-1)\times(t-1)}, \tag{1.7}$$

leading to

$$H_{01}:\begin{bmatrix} (\mu_{11}-\mu_{12})-(\mu_{g1}-\mu_{g2}) & (\mu_{12}-\mu_{13})-(\mu_{g2}-\mu_{g3}) & \cdots & (\mu_{1(t-1)}-\mu_{1t})-(\mu_{g(t-1)}-\mu_{gt}) \\ (\mu_{21}-\mu_{22})-(\mu_{g1}-\mu_{g2}) & (\mu_{22}-\mu_{23})-(\mu_{g2}-\mu_{g3}) & \cdots & (\mu_{2(t-1)}-\mu_{2t})-(\mu_{g(t-1)}-\mu_{gt}) \\ \vdots & \vdots & \cdots & \vdots \\ (\mu_{(g-1)1}-\mu_{(g-1)2})-(\mu_{g1}-\mu_{g2}) & (\mu_{(g-1)2}-\mu_{(g-1)3})-(\mu_{g2}-\mu_{g3}) & \cdots & (\mu_{(g-1)(t-1)}-\mu_{(g-1)t})-(\mu_{g(t-1)}-\mu_{gt}) \end{bmatrix} = [0]_{(g-1)\times(t-1)}.$$

To test H_{02}, the differences in the group mean vectors, the hypothesis is stated as

$$H_{02}:\begin{bmatrix}\mu_{11}\\ \mu_{12}\\ \vdots\\ \mu_{1t}\end{bmatrix}=\begin{bmatrix}\mu_{21}\\ \mu_{22}\\ \vdots\\ \mu_{2t}\end{bmatrix}=\cdots=\begin{bmatrix}\mu_{g1}\\ \mu_{g2}\\ \vdots\\ \mu_{gt}\end{bmatrix}.$$

Representing the Multivariate General Linear Hypothesis, $H_{02}:\mathbf{C}\mathbf{B}_{g\times t}\mathbf{A}=\mathbf{\Gamma}_{0(v_h\times u)}$, the matrices $\mathbf{C}$, $\mathbf{A}$ and $\mathbf{\Gamma}_{0(v_h\times u)}$ are

$$\mathbf{C}_{(g-1)\times g}=\left[\begin{array}{cccc:c} 1 & 0 & \dots & 0 & -1\\ 0 & 1 & \dots & 0 & -1\\ \vdots & \vdots & \ddots & \vdots & -1\\ 0 & 0 & \dots & 1 & -1\end{array}\right],\ \text{where } \mathbf{A}=\mathbf{I}_t \quad \text{and} \quad \mathbf{\Gamma}_0=[\mathbf{0}]_{(g-1)\times t},$$

giving

$$H_{02}:\begin{bmatrix}\mu_{11}-\mu_{g1} & \mu_{12}-\mu_{g2} & \cdots & \mu_{1t}-\mu_{gt}\\ \mu_{21}-\mu_{g2} & \mu_{22}-\mu_{g2} & \cdots & \mu_{2t}-\mu_{gt}\\ \vdots & \vdots & \ddots & \vdots\\ \mu_{(g-1)1}-\mu_{gt} & \mu_{(g-1)2}-\mu_{g2} & \cdots & \mu_{(g-1)t}-\mu_{gt}\end{bmatrix}=\begin{bmatrix}0 & 0 & \dots & 0\\ 0 & 0 & \dots & 0\\ \vdots & \vdots & \ddots & \vdots\\ 0 & 0 & \dots & 0\end{bmatrix}_{(g-1)\times t}.$$

To test H_{03}, the differences in the time vectors, the hypothesis is stated as

$$H_{03}:\begin{bmatrix}\mu_{11}\\ \mu_{21}\\ \vdots\\ \mu_{g1}\end{bmatrix}=\begin{bmatrix}\mu_{12}\\ \mu_{22}\\ \vdots\\ \mu_{g2}\end{bmatrix}=\cdots=\begin{bmatrix}\mu_{1t}\\ \mu_{2t}\\ \vdots\\ \mu_{gt}\end{bmatrix}.$$

Representing $H_{03}:\mathbf{C}\mathbf{B}_{g\times t}\mathbf{A}=\mathbf{\Gamma}_{0(v_h\times u)}$, the matrices $\mathbf{C}$, $\mathbf{A}$ and $\mathbf{\Gamma}_{0(v_h\times u)}$ are

$$\mathbf{C}=\mathbf{I}_g,\quad \mathbf{A}_{t\times(t-1)}=\begin{bmatrix} 1 & 0 & \dots & 0 \\ 0 & 1 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 1 \\ \hline -1 & -1 & \dots & -1 \end{bmatrix}=\begin{bmatrix} \mathbf{I}_{(t-1)} \\ \hline -\mathbf{1}'_{1\times(t-1)} \end{bmatrix} \text{ and } \mathbf{\Gamma}_0=[\mathbf{0}]_{g\times(t-1)},$$

leading to

$$H_{03}:\begin{bmatrix} \mu_{11}-\mu_{1t} & \mu_{12}-\mu_{1t} & \cdots & \mu_{1(t-1)}-\mu_{1t} \\ \mu_{21}-\mu_{2t} & \mu_{22}-\mu_{2t} & \cdots & \mu_{2(t-1)}-\mu_{2t} \\ \vdots & \vdots & \ddots & \vdots \\ \mu_{g1}-\mu_{gt} & \mu_{g2}-\mu_{gt} & \cdots & \mu_{g(t-1)}-\mu_{gt} \end{bmatrix}=\begin{bmatrix} 0 & 0 & \dots & 0 \\ 0 & 0 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 0 \end{bmatrix}_{g\times(t-1)}.$$

For valid multivariate tests of differences in the group and time mean vector, it was not assumed that the statistic for testing the hypothesis of parallelism or the interaction effect between group and time had no significance, meaning that the tests may be confounded by the interaction. If there is no interaction effect between group and time, or if the possibility of an interaction effect between group and time is ignored, alternative tests for differences in group and time means may be of interest in the special case of the multivariate test (Timm, 1980: 52). These hypotheses, $H_{02(g)}$ and $H_{03(t)}$, are represented as follows:

$H_{02(g)}$: There are no differences in the means (averaged over time) among the g groups

$H_{03(t)}$: There are no differences in the means (averaged over group) among the t times

In terms of the parameters in the matrix $\mathbf{B}_{g\times t}$, the hypothesis $H_{02(g)}$ becomes

$$H_{02(g)}:\frac{\sum_{k=1}^{t}\mu_{1k}}{t}=\frac{\sum_{k=1}^{t}\mu_{2k}}{t}=\ldots=\frac{\sum_{k=1}^{t}\mu_{gk}}{t}. \tag{1.8}$$

The matrices $\mathbf{C}$, $\mathbf{A}$ and $\mathbf{\Gamma}_0$ represented in $H_{02(g)}:\mathbf{C}\mathbf{B}_{g\times t}\mathbf{A}=\mathbf{\Gamma}_{0(v_h\times t)}$ are

$$\mathbf{C}_{(g-1)\times g}=\left[\begin{array}{cccc:c}1&0&\dots&0&-1\\0&1&\dots&0&-1\\\vdots&\vdots&\ddots&\vdots&-1\\0&0&\dots&1&-1\end{array}\right],\ \mathbf{A}_{t\times 1}=\begin{bmatrix}1/t\\1/t\\\vdots\\1/t\end{bmatrix}\text{ and }\mathbf{\Gamma}_0=\left[0\right]_{(g-1)\times 1},\tag{1.9}$$

resulting in

$$H_{02(g)}:\frac{\sum_{k=1}^{t}\mu_{1k}-\sum_{k=1}^{t}\mu_{gk}}{t}=\frac{\sum_{k=1}^{t}\mu_{2k}-\sum_{k=1}^{t}\mu_{gk}}{t}=\dots=\frac{\sum_{k=1}^{t}\mu_{(g-1)k}-\sum_{k=1}^{t}\mu_{gk}}{t}=0.$$

Representing $H_{03(t)}$ in terms of the parameters in the matrix $\mathbf{B}_{g\times t}$, if the number of subjects in each group are equal, the hypothesis $H_{03(t)}$ is stated as

$$H_{03(t)}:\frac{\sum_{j=1}^{g}\mu_{j1}}{g}=\frac{\sum_{j=1}^{g}\mu_{j2}}{g}=\dots=\frac{\sum_{j=1}^{g}\mu_{jt}}{g}.\tag{1.10}$$

If there are unequal numbers of subjects in each group, $H_{03(t)}$ is stated as

$$H_{03(t)}:\frac{\sum_{j=1}^{g}n_j\mu_{j1}}{n}=\frac{\sum_{j=1}^{g}n_j\mu_{j2}}{n}=\dots=\frac{\sum_{j=1}^{g}n_j\mu_{jt}}{n}.\tag{1.11}$$

In the expression for the Multivariate General Linear Hypothesis, $H_{03(t)}:\mathbf{CB}_{g\times t}\mathbf{A}=\mathbf{\Gamma}_{0(v_h\times t)}$, the matrices $\mathbf{C}$ for equal numbers of subjects in each group (1.10) and unequal numbers of subjects in each group (1.11) are, respectively,

$$\mathbf{C}_{1\times g}=\left[\frac{1}{g},\frac{1}{g},\dots,\frac{1}{g}\right]\text{ and }\mathbf{C}_{1\times g}=\left[\frac{n_1}{n},\frac{n_2}{n},\dots,\frac{n_g}{n}\right],\tag{1.12}$$

$$\mathbf{A}_{t\times(t-1)}=\left[\begin{array}{cccc}1&0&\dots&0\\0&1&\dots&0\\\vdots&\vdots&\ddots&\vdots\\0&0&\dots&1\\\hdashline -1&-1&\dots&-1\end{array}\right]\text{ and }\mathbf{\Gamma}_0=\left[\mathbf{0}\right]_{1\times(t-1)}.\tag{1.13}$$

Given the matrices of $\mathbf{C}$, $\mathbf{A}$ and $\mathbf{\Gamma}_{0(v_h\times t)}$, $H_{03(t)}$ for equal numbers of subjects in each group is stated as

$$H_{03(t)}:\frac{\sum_{j=1}^{g}\mu_{j1}-\sum_{j=1}^{g}\mu_{jt}}{g}=\frac{\sum_{j=1}^{g}\mu_{j2}-\sum_{j=1}^{g}\mu_{jt}}{g}=\dots=\frac{\sum_{j=1}^{g}\mu_{j(t-1)}-\sum_{j=1}^{g}\mu_{jt}}{g}=0,$$

and $H_{03(t)}$ for unequal numbers of subjects in each group is stated as

$$H_{03(t)}: \frac{\sum_{j=1}^{g} n_j\mu_{j1} - \sum_{j=1}^{g} n_j\mu_{jt}}{n} = \frac{\sum_{j=1}^{g} n_j\mu_{j2} - \sum_{j=1}^{g} n_j\mu_{jt}}{n} = \ldots = \frac{\sum_{j=1}^{g} n_j\mu_{j(t-1)} - \sum_{j=1}^{g} n_j\mu_{jt}}{n} = 0 \; ,$$

giving the $u \times u$ sum of square (SS) matrix due to the hypothesis and due to error, denoted by $\mathbf{S}_{h(u\times u)}$ and $\mathbf{S}_{e(u\times u)}$ respectively, for each hypothesis as follows:

$$\mathbf{S}_{h(u\times u)} = (\mathbf{C}\hat{\mathbf{B}}_{g\times t}\mathbf{A})'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\mathbf{B}}_{g\times t}\mathbf{A}) \tag{1.14}$$

and $$\mathbf{S}_{e(u\times u)} = \mathbf{A}'\mathbf{Y}'_{n\times t}[\mathbf{I}_n - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}']\mathbf{Y}_{n\times t}\mathbf{A}\,, \tag{1.15}$$

where $\hat{\mathbf{B}}_{g\times t} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}_{n\times t} = \begin{bmatrix} \bar{\boldsymbol{y}}'_{.1} \\ \bar{\boldsymbol{y}}'_{.2} \\ \vdots \\ \bar{\boldsymbol{y}}'_{.g} \end{bmatrix} = \begin{bmatrix} \bar{y}_{.11} & \bar{y}_{.12} & \cdots & \bar{y}_{.1t} \\ \bar{y}_{.21} & \bar{y}_{.22} & \cdots & \bar{y}_{.2t} \\ \vdots & \vdots & \ddots & \vdots \\ \bar{y}_{.g1} & \bar{y}_{.g2} & \cdots & \bar{y}_{.gt} \end{bmatrix}$,

is the Best Linear Unbiased Estimator (BLUE) of $\mathbf{B}_{g\times t}$ (Kim and Timm, 2007: 145).

To test for the effect of the group and time factors, and the interaction effect of group$\times$ time, one can use four popular multivariate test statistics, Wilks' Lambda Criterion, the Lawley-Hotelling Trace Criterion, the Bartlett-Nanda-Pillai Trace Criterion and Roy's Largest Root Criterion. Each test of H_{01}, H_{02}, H_{03}, $H_{02(g)}$ and $H_{03(t)}$ is rejected at the significance level α (Kim and Timm, 2007: 150-151) if

(a) Wilks' Lambda Criterion

$$\Lambda = \frac{\left|\mathbf{S}_{e(u\times u)}\right|}{\left|\mathbf{S}_{e(u\times u)} + \mathbf{S}_{h(u\times u)}\right|} = \prod_{i=1}^{s}(1+\lambda_i)^{-1} < U^{\alpha}(u, v_h, v_e)$$

(b) Lawley-Hotelling Trace Criterion

$$T_0^2 = tr(\mathbf{S}_{h(u\times u)}\mathbf{S}_{e(u\times u)}^{-1}) = \sum_{i=1}^{s}\lambda_i > U_0^{\alpha}(s, M, N)$$

(c) Bartlett-Nanda-Pillai Trace Criterion

$$V = tr[\mathbf{S}_{h(u\times u)}(\mathbf{S}_{h(u\times u)} + \mathbf{S}_{e(u\times u)})^{-1}] = \sum_{i=1}^{s}\frac{\lambda_i}{1+\lambda_i} > V_0^{\alpha}(s, M, N)$$

(d) Roy's Largest Root Criterion

$$\theta = \frac{\lambda_1}{1+\lambda_1} > \theta_0^{\alpha}(s, M, N)$$

where $\lambda_1 > \lambda_2 > \ldots > \lambda_s$ are non-zero eigenvalues of $\mathbf{S}_{h(u\times u)}\mathbf{S}_{e(u\times u)}^{-1}$, $s = \min(u, v_h)$, $M = \frac{|v_h - u| - 1}{2}$, and $N = \frac{v_e - u - 1}{2}$.

The values U^{α}, U_0^{α}, V^{α} and θ^{α} correspond to tabled upper $(1-\alpha)$ 100% critical values for the four test statistics provided in Rencher (2002: 566-586). Alternatively, one may also use F approximations for these criteria (Timm, 2002: 103-104, Rencher, 2002: 161-170).

Rao's F Approximation of Wilks' Lambda Λ is given by

$$\frac{1-\Lambda^{1/a}}{\Lambda^{1/a}}\frac{v_2}{v_1} \dot{\sim} F(v_1, v_2),$$

where $v_1 = uv_h$, $v_2 = \frac{1}{a}\left[v_e - \frac{u - v_h + 1}{2}\right] - \frac{uv_h - 2}{2}$ and $a = \left[\frac{u^2 + v_h^2 - 5}{(uv_h)^2} - 4\right]^{1/2}$.

The F approximation of the Bartlett-Nanda-Pillai Trace Criterion is given by

$$\frac{(2N+s+1)}{(2M+s+1)}\frac{V}{s-V} \dot{\sim} F(v_1, v_2),$$

where $v_1 = s(2M + s + 1)$, $v_2 = s(2N + s + 1)$, $M = \frac{|v_h - u| - 1}{2}$ and $N = \frac{v_e - u - 1}{2}$.

The F approximation of the Lawley-Hotelling Trace Criterion is given by

$$\frac{2(sN+1)}{s^2(2M+s+1)}T_0^2 \dot{\sim} F(v_1, v_2),$$

where $v_1 = s(2M + s + 1)$, $v_2 = 2(sN + 1)$, $M = \frac{|v_h - u| - 1}{2}$ and $N = \frac{v_e - u - 1}{2}$.

Finally, the F approximation of Roy's Largest Root Criterion is given by

$$\frac{v_2}{v_1}\lambda_1 \dot{\sim} F(v_1, v_2),$$

where $v_1 = \max(u, v_h)$ and $v_2 = v_e - v_1 + v_h$.

1.2.1.2 Univariate Mixed Model Analysis

The Univariate Mixed Model for the Univariate Repeated Measurements Design assumes that the subjects are random and nested within the group factor which is crossed with the time factor. This design is also called a univariate split-plot design. Scheffé (1956 : 23) proposed the Univariate Mixed Model for each response y_{ijk} as

$$y_{ijk} = \mu + \alpha_j + \beta_k + (\alpha\beta)_{jk} + s_{(j)i} + e_{ijk}, \tag{1.16}$$

for $i = 1, 2, \ldots, n_j$, $\sum_{j=1}^{g} n_j = n$, $j = 1, 2, \ldots, g$, $k = 1, 2, \ldots, t$,

where μ is the overall mean, α_j is the fixed effect of the j^{th} level of the between-subject factor (or group), β_k is the fixed effect of k^{th} level of the within-subject factor (or time), $(\alpha\beta)_{jk}$ is the interaction effect between the j^{th} group and k^{th} time, $s_{(j)i}$ is the random effect of the i^{th} subject nested within the j^{th} group and e_{ijk} is the random error on the i^{th} subject within the j^{th} group at the k^{th} time. Note that the Univariate Mixed Model can be represented as the Cell Mean Model

$$y_{ijk} = \mu_{jk} + s_{(j)i} + e_{ijk}, \tag{1.17}$$

where $\mu_{jk} = \mu + \alpha_j + \beta_k + (\alpha\beta)_{jk}$.

Assume that $s_{(j)i}$ is i.i.d. normally distributed with zero mean and covariance σ_s^2, denoted by $s_{(j)i} \sim N(0, \sigma_s^2)$, e_{ijk} is i.i.d. normally distributed as $e_{ijk} \sim N(0, \sigma_e^2)$, and $s_{(j)i}$ and e_{ijk} are independent.

From the Univariate Mixed Model (1.17), let $\boldsymbol{y}_{ij} = (y_{ij1}, y_{ij2}, \ldots, y_{ijt})'$ be the $t \times 1$ vector of repeated measurements and let $\boldsymbol{\mu}_j = (\mu_{j1}, \mu_{j2}, \ldots, \mu_{jt})'$ be the $t \times 1$ vector of cell means in the j^{th} group, where $\mu_{jk} = \mu + \alpha_j + \beta_k + (\alpha\beta)_{jk}$, for $j = 1, 2, \ldots, g$, $k = 1, 2, \ldots, t$, then the Univariate Mixed Model for each vector $\boldsymbol{y}_{ij}$ is

$$\boldsymbol{y}_{ij} = \boldsymbol{\mu}_j + \mathbf{1}_t s_{j(i)} + \boldsymbol{e}_{ij}, \tag{1.18}$$

where $\mathbf{1}_t$ is a $t \times 1$ vector of ones.

Recall the assumptions that $s_{(j)i} \sim N(0, \sigma_s^2)$ and $e_{ijk} \sim N(0, \sigma_e^2)$, then the $t \times t$ covariance matrix of $\boldsymbol{y}_{ij}$ in each group is obtained as

$$\boldsymbol{\Sigma}_{ij} = \text{cov}(\boldsymbol{y}_{ij}) = \text{cov}(\mathbf{1}_t s_{i(j)} + \boldsymbol{e}_{ij})$$
$$= \sigma_s^2 \mathbf{J}_t + \sigma_e^2 \mathbf{I}_t, \tag{1.19}$$

where $\mathbf{I}_t$ is a $t \times t$ identity matrix and $\mathbf{J}_t$ is a $t \times t$ matrix of one's. The covariance matrix defined in (1.19) is called a compound symmetry structure. Thus $\boldsymbol{y}_{ij}$ is an independently and identically distributed multivariate normal distribution denoted as $\boldsymbol{y}_{ij} \sim N_t(\boldsymbol{\mu}_j, \boldsymbol{\Sigma}_{t\times t})$. The matrix form of the Univariate Mixed Model (1.18) can be defined as

$$\boldsymbol{y}_{nt\times 1} = (\mathbf{X}_{n\times g} \otimes \mathbf{I}_t)\boldsymbol{\beta}_{gt\times 1} + \boldsymbol{u}_{nt\times 1}, \tag{1.20}$$

where $\otimes$ denotes the Kronecker product operator between matrices ($\mathbf{A}\otimes\mathbf{B} = [a_{ij}\mathbf{B}]$). The layouts of vectors $\boldsymbol{y}_{nt\times 1}$, $\boldsymbol{\beta}_{gt\times 1}$, and $\boldsymbol{u}_{nt\times 1}$, and matrix $\mathbf{X}_{n\times g}$ are

$$\boldsymbol{y} = \begin{bmatrix} \boldsymbol{y}_{11} \\ \vdots \\ \boldsymbol{y}_{n_1 1} \\ \hline \boldsymbol{y}_{12} \\ \vdots \\ \boldsymbol{y}_{n_2 2} \\ \hline \vdots \\ \hline \boldsymbol{y}_{1g} \\ \\ \boldsymbol{y}_{n_g g} \end{bmatrix}, \quad \mathbf{X} = \begin{bmatrix} \mathbf{1}_{n_1} & 0 & \dots & 0 \\ 0 & \mathbf{1}_{n_2} & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & \mathbf{1}_{n_g} \end{bmatrix}, \quad \boldsymbol{\beta} = \begin{bmatrix} \boldsymbol{\mu}_1 \\ \boldsymbol{\mu}_2 \\ \vdots \\ \boldsymbol{\mu}_g \end{bmatrix} = \begin{bmatrix} \mu_{11} \\ \vdots \\ \mu_{1t} \\ \hline \mu_{21} \\ \vdots \\ \mu_{2t} \\ \hline \vdots \\ \hline \mu_{g1} \\ \vdots \\ \mu_{gt} \end{bmatrix}, \text{ and } \boldsymbol{u}_{nt\times 1} = \begin{bmatrix} \mathbf{1}_t s_{1(1)} \\ \vdots \\ \mathbf{1}_t s_{1(n_1)} \\ \hline \mathbf{1}_t s_{2(1)} \\ \vdots \\ \mathbf{1}_t s_{2(n_2)} \\ \hline \vdots \\ \hline \mathbf{1}_t s_{g(1)} \\ \vdots \\ \mathbf{1}_t s_{g(n_g)} \end{bmatrix} + \begin{bmatrix} \boldsymbol{e}_{11} \\ \vdots \\ \boldsymbol{e}_{n_1 1} \\ \hline \boldsymbol{e}_{12} \\ \vdots \\ \boldsymbol{e}_{n_2 2} \\ \hline \vdots \\ \hline \boldsymbol{e}_{1g} \\ \vdots \\ \boldsymbol{e}_{n_g g} \end{bmatrix}.$$

Note that $\text{cov}(\boldsymbol{y}) = \mathbf{I}_n \otimes \boldsymbol{\Sigma}_{t\times t}$.

In the Analysis of Variance (ANOVA) for the Univariate Mixed Model (Scheffé, 1956: 24), the validity of the exact F test is based on the assumptions of normality, independence of error variances and homogeneity of variances in each group (or treatment levels), i.e. $\text{cov}(\boldsymbol{y}_{ij}) = \boldsymbol{\Sigma}_{ij} = \boldsymbol{\Sigma}_{t\times t}$ for all *i* and *j*.

To test for differences in group × time, the hypothesis is stated as

$$H_{01} : (\alpha\beta)_{jk} - (\alpha\beta)_{j'k} - (\alpha\beta)_{jk'} + (\alpha\beta)_{j'k'} = 0, \tag{1.21}$$

or equivalently, in terms of a full rank model (1.14)

$$
\begin{aligned}
H_{01}:(\mu_{11}-\mu_{12})-(\mu_{g1}-\mu_{g2}) &= (\mu_{12}-\mu_{13})-(\mu_{g2}-\mu_{g3})=\ldots=(\mu_{1(t-1)}-\mu_{1t})-(\mu_{g(t-1)}-\mu_{gt})=0\\
(\mu_{21}-\mu_{22})-(\mu_{g1}-\mu_{g2}) &= (\mu_{22}-\mu_{23})-(\mu_{g2}-\mu_{g3})=\ldots=(\mu_{2(t-1)}-\mu_{1t})-(\mu_{2(t-1)}-\mu_{2t})=0\\
&\vdots\\
(\mu_{(g-1)1}-\mu_{(g-1)2})-(\mu_{g1}-\mu_{g2}) &= (\mu_{(g-1)2}-\mu_{(g-1)3})-(\mu_{g2}-\mu_{g3})=\ldots=(\mu_{(g-1)(t-1)}-\mu_{(g-1)t})-(\mu_{g(t-1)}-\mu_{gt})=0.
\end{aligned}
$$

To test for differences in groups, the hypothesis is stated as

$$H_{02}:\alpha_1=\alpha_2=\cdots=\alpha_g, \tag{1.22}$$

or equivalently,

$$H_{02}:\frac{\sum_{k=1}^{t}\mu_{1k}}{t}=\frac{\sum_{k=1}^{t}\mu_{2k}}{t}=\ldots=\frac{\sum_{k=1}^{t}\mu_{gk}}{t}.$$

To test for differences in time, the hypothesis has two representations because of an equal or unequal number of subjects in each group, which are respectively represented as H_{03} and $H_{03(w)}$,

$$H_{03}:\beta_1=\beta_2=\cdots=\beta_t, \tag{1.23}$$

$$H_{03(w)}:\beta_1+\sum_{j=1}^{g}\frac{n_j\alpha_j}{n}=\beta_2+\sum_{j=1}^{g}\frac{n_j\alpha_j}{n}=\cdots=\beta_k+\sum_{j=1}^{g}\frac{n_j\alpha_j}{n}. \tag{1.24}$$

or equivalently, in terms of a full rank model (1.17),

$$H_{03}:\frac{\sum_{j=1}^{g}\mu_{j1}}{g}=\frac{\sum_{j=1}^{g}\mu_{j2}}{g}=\ldots=\frac{\sum_{j=1}^{g}\mu_{jt}}{g}$$

$$H_{03(w)}:\frac{\sum_{j=1}^{g}n_j\mu_{j1}}{n}=\frac{\sum_{j=1}^{g}n_j\mu_{j2}}{n}=\ldots=\frac{\sum_{j=1}^{g}n_j\mu_{jt}}{n}.$$

Tests of the group effect, time effects and the interaction effect have been traditionally accomplished by the conventional Scheffé's Univariate F Test. The null hypotheses H_{01}, H_{02} and H_{03} respectively are rejected at significant level α if

$$F_{01}=\frac{SS_{G\times T}/(g-1)(t-1)}{SS_E/(n-g)(t-1)}>F[\alpha,(g-1)(t-1),(n-g)(t-1)],$$

$$F_{02}=\frac{SS_G/(g-1)}{SS_E/(n-g)}>F[\alpha,(g-1),(n-g)] \text{ and}$$

$$F_{03}=\frac{SS_T/(t-1)}{SS_E/(n-g)(t-1)}>F[\alpha,(t-1),(n-g)(t-1)],$$

where $SS_G = t\sum_{j=1}^{g} n_j(\bar{y}_{\cdot j\cdot} - \bar{y}_{\ldots})^2$,

$SS_T = g\sum_{k=1}^{t}(\bar{y}_{\cdot\cdot k} - \bar{y}_{\ldots})^2$,

$SS_{G\times T} = \sum_{j=1}^{g} n_j \sum_{k=1}^{t}(\bar{y}_{\cdot jk} - \bar{y}_{\cdot\cdot k} - \bar{y}_{\cdot j\cdot} + \bar{y}_{\ldots})^2$,

$SS_E = \sum_{j=1}^{g}\sum_{i=1}^{n_j}\sum_{k=1}^{t}(y_{ijk} - \bar{y}_{\cdot jk})^2$,

and $\bar{y}_{.jk}$, $\bar{y}_{.j.}$, $\bar{y}_{..k}$ and $\bar{y}_{...}$ are as defined in (1.1) and (1.2).

1.2.1.3 The Relationship between the Analyses of the Univariate Mixed Model and the Multivariate Linear Model

The Univariate Mixed Model analysis can be obtained from the analysis of the Multivariate Linear Model (1.4) by orthogonalizing the $t\times u$ matrix $\mathbf{A}$ in the Multivariate General Linear Hypothesis $H_0:\mathbf{CB}_{g\times t}\mathbf{A} = \mathbf{\Gamma}_{0(v_h\times u)}$ (Timm, 1980: 53-57). To obtain the Univariate test, the covariance matrix $\mathbf{\Sigma}$ in the Multivariate Linear Model (1.4) takes the form specified in (1.19).

The test of the group × time interaction effect in (1.21) may be recovered from the H_{01} test of parallelism stated in (1.6), where $\mathbf{C}$ and $\mathbf{\Gamma}_{0(v_h\times u)}$ are defined in (1.7), and by selecting the $t\times(t-1)$ orthogonal matrix $\mathbf{A}$, such that $\mathbf{A}'\mathbf{A} = \mathbf{I}_{(t-1)}$. In this case, the Univariate F Test is calculated using $SS_{G\times T} = tr(\mathbf{S}_{h(u\times u)})$ and $SS_E = tr(\mathbf{S}_{e(u\times u)})$, where $\mathbf{S}_{h(u\times u)}$ and $\mathbf{S}_{e(u\times u)}$ as defined by (1.14) and (1.15) are $(t-1)\times(t-1)$ sum of squares matrices. The degrees of freedom of $SS_{G\times T}$ and SS_E are obtained from $uv_h = (t-1)(g-1)$ and $uv_e = (t-1)(n-g)$, respectively.

Recall the Multivariate test $H_{02(g)}$ in (1.8) where matrices $\mathbf{C}$ and $\mathbf{\Gamma}_{0(v_h\times u)}$ are defined in (1.9). Selecting the $t\times 1$ matrix $\mathbf{A}$ that satisfies $\mathbf{A}'\mathbf{A}=1$, the Univariate F Test of the group effect H_{02} in (1.22) is identical to the multivariate test $H_{02(g)}$. In this situation, the dimension of $\mathbf{S}_{h(u\times u)}$ (1.14) and $\mathbf{S}_{e(u\times u)}$ (1.15) is 1×1, which is scalar, then $SS_G = \mathbf{S}_{h(u\times u)}$ and $SS_E = \mathbf{S}_{e(u\times u)}$. The degrees of freedom due to the hypothesis and error are $uv_h = (1)(g-1) = v_h$ and $uv_e = (1)(n-g) = v_e$.

In the absence of the interaction effect in the multivariate test, the univariate tests of differences in time, H_{03}, for equal or unequal numbers of subjects in (1.23) or (1.24) are respectively obtained from the multivariate tests $H_{03(t)}$ in (1.10) or (1.11) by using matrices $\mathbf{C}$ and $\mathbf{\Gamma}_{0(v_h \times u)}$ in (1.12) and (1.13) and providing the $t \times (t-1)$ matrix $\mathbf{A}$ satisfying $\mathbf{A}'\mathbf{A} = \mathbf{I}_{(t-1)}$. To obtain the Univariate F Test, $SS_T = tr(\mathbf{S}_{h(u \times u)})$ and $SS_E = tr(\mathbf{S}_{e(u \times u)})$, where $\mathbf{S}_{h(u \times u)}$ and $\mathbf{S}_{e(u \times u)}$ defined by (1.14) and (1.15) are $(t-1) \times (t-1)$ sum of squares matrices with $uv_h = (1)(t-1)$ and $uv_e = (t-1)(n-g)$ degrees of freedom, respectively.

Huynh and Feldt (1970: 1587) showed that a necessary and sufficient condition of the exact F test for the time factor and group × time is the assumption concerning the structure of the covariance matrix, called the sphericity condition. In the Univariate Repeated Measurement Design, the sphericity condition requires that all of the variances of the differences for all pairs of repeated measurements are equal, i.e. $\mathrm{var}(y_{ij1} - y_{ij2}) = \mathrm{var}(y_{ij1} - y_{ij3}) = \cdots = \mathrm{var}(y_{ij1} - y_{ijt}) = \mathrm{var}(y_{ij2} - y_{ij3}) = \cdots =$ $\mathrm{var}(y_{ij2} - y_{ijt}) = \cdots = \mathrm{var}(y_{ij(t-1)} - y_{ijt}) = \sigma^2$.

Specifically, there exists a $t \times (t-1)$ orthogonal contrast matrix $\mathbf{A}$ such that $\mathbf{A}'\mathbf{A} = \mathbf{I}_{t-1}$ where $\mathbf{A}'\mathbf{\Sigma}_{t \times t}\mathbf{A} = \sigma^2\mathbf{I}_{(t-1)}$, so that the covariance matrix $\mathbf{\Sigma}_{t \times t}$ satisfies the sphericity condition. A matrix which satisfies this structure is called a Type H matrix (Scheffé, 1970: 1586). Furthermore, Huynh and Feldt (1970: 1587) indicated that a sufficient but not necessary condition of the validity of the exact F test is that $\mathbf{\Sigma}_{t \times t}$ has a compound symmetry structure, $\mathbf{\Sigma}_{t \times t} = \sigma_s^2\mathbf{J}_t + \sigma_e^2\mathbf{I}_t$. This means that all variances of each repeated measurement are equal and all covariances (off-diagonal elements) among the two different repeated measurements are equal. Unfortunately, in some repeated measurement designs, the covariance between two levels of the repeated measurements will not conform to the sphericity requirement. McCall and Appelbaum (1973: 401) illustrated an example in the area of developmental or learning psychology showing that adjacent measurement occasions are more highly correlated than non-adjacent measurement occasions, with the correlation between these measurements decreasing the farther apart the measurements are in the series.

Boik (1981: 241) showed that the Type I error rates of the mixed model test of the within-subject effect and the interaction effect are greatly inflated when $\mathbf{\Sigma}_{t\times t}$ does not satisfy the sphericity condition, so the test for the Univariate Mixed Model should be avoided.

To correct for the non-sphericity problem, Greenhouse and Geisser (1959: 99) and Huynh and Feldt (1976: 71) proposed adjusted-df Univariate tests which are robust alternatives to the conventional F test. Both works gave an approximate-df procedure by reducing the numerator and denominator degrees of freedom of the mixed model F test of the within-subject effect and the interaction effect.

Whether the sphericity condition is met or not, one can use the Multivariate Linear Model to analyze univariate repeated measurement designs. This is because this analysis does not require the sphericity assumption but instead requires the homogeneity of the covariance matrices at all levels of the group factor as well as normality and independence of observations across subjects (Sahinler and Gorgulu, 2006: 453). However, if $\mathbf{\Sigma}_{t\times t}$ is found to satisfy the sphericity assumption, univariate mixed model exact F tests are more powerful than multivariate tests of the group × time, group and time factors. The Univariate Mixed Model Exact F Test of mean group differences is more powerful than the multivariate test of mean vector differences since the F Test is one contrast of all possible contrasts for the Multivariate test. The Univariate Exact F Test of the time factor is more powerful than the more restrictive multivariate test and the Univariate Mixed Model F Test of the interaction factor is more powerful than the multivariate test of parallelism since the Univariate F Test has more degrees of freedom of error, $uv_e = (t-1)(n-g)$, where v_e is the degrees of freedom for the corresponding multivariate test (Timm, 2002: 285).

1.2.2 Multivariate Repeated Measurement Design

When p response variables are repeated measurements at t occasions on each subject in g groups, this design is called the *Multivariate Repeated Measurement Design*. From the data layout in Table 1.1, each scalar response y_{ijk} is replaced by

$\mathbf{y}_{ijk} = (y_{ijk}^{(1)}, y_{ijk}^{(2)}, \ldots, y_{ijk}^{(p)})'$, a $p \times 1$ vector of the i^{th} subject in the j^{th} group at k^{th} time, for $i = 1, 2, \ldots, n_j$, $\sum_{j=1}^{g} n_j = n$, $j = 1, 2, \ldots, g$, $k = 1, 2, \ldots, t$. Analysis of such data is further complicated by the existence of correlation both among the measurements taken at different points in time and among the dependent variables. Similar to the Univariate Repeated Measurement Design, there are two different models for analyzing repeated measurements of multivariate outcomes, DMM and MMM. An introduction of these models is briefly reviewed in the following section and the details of these analyses are given in Chapter 2.

1.2.2.1 Doubly Multivariate Linear Model Analysis

Let $\mathbf{Y}_{ij} = (\mathbf{y}_{ij1}, \mathbf{y}_{ij2}, \ldots, \mathbf{y}_{ijt})'$ be a $t \times p$ matrix and let $\mathbf{y}_{ij} = \text{vec}(\mathbf{Y}_{ij})$ denote a $pt \times 1$ response vector formed by stacking columns of $\mathbf{Y}_{ij}$. Taking $\mathbf{y}_{ij}'$ in each row, $\mathbf{Y}_{n \times pt} = (\mathbf{y}_{11}, \mathbf{y}_{21}, \ldots, \mathbf{y}_{n_1 1}, \mathbf{y}_{12}, \mathbf{y}_{22}, \ldots, \mathbf{y}_{n_2 2}, \ldots, \mathbf{y}_{1g}, \mathbf{y}_{2g}, \ldots, \mathbf{y}_{n_g g})'$ is obtained. The matrix form of DMM is

$$\mathbf{Y}_{n \times pt} = \mathbf{X}_{n \times g} \mathbf{B}_{g \times pt} + \mathbf{U}_{n \times pt}, \tag{1.25}$$

where $\mathbf{Y}$ is an $n \times pt$ response matrix, $\mathbf{X}$ is an $n \times g$ between subject design matrix having $rank(\mathbf{X}) = g$, $\mathbf{B}$ is a $g \times pt$ unknown parameter matrix and $\mathbf{U}$ is an $n \times pt$ random error matrix.

Each row vector of $\mathbf{U}$, denoted by $\boldsymbol{u}_{ij}'$, is assumed to be identically independently multivariate normally distributed with a zero mean vector and a $pt \times pt$ covariance matrix $\boldsymbol{\Sigma}_{pt \times pt}$, denoted as $\mathbf{u}_{ij} \sim N_{pt}(\mathbf{0}, \boldsymbol{\Sigma}_{pt \times pt})$, where $\boldsymbol{\Sigma}_{pt \times pt}$ is positive definite. Subsequently, $\mathbf{u} = vec(\mathbf{U})$ is an $npt \times 1$ vector assumed to be distributed as

$$\mathbf{u} = vec(\mathbf{U}) \sim N_{npt}(\mathbf{0}, \boldsymbol{\Sigma}_{pt \times pt} \otimes \mathbf{I}_n), \tag{1.26}$$

where $\otimes$ denotes the Kronecker product operator between matrices ($\mathbf{A} \otimes \mathbf{B} = [a_{ij}\mathbf{B}]$).

According to DMM in (1.25) and under the normality assumption (1.26), we obtain

$$\boldsymbol{y}_{npt \times 1} = vec(\mathbf{Y}_{n \times pt}) \sim N_{npt}\left((\mathbf{I}_{pt} \otimes \mathbf{X}) vec(\mathbf{B}_{g \times pt}), \boldsymbol{\Sigma}_{pt \times pt} \otimes \mathbf{I}_n\right). \tag{1.27}$$

The maximum likelihood estimators of $\mathbf{B}_{g \times pt}$ and $\boldsymbol{\Sigma}_{pt \times pt}$ respectively are

$$\hat{\mathbf{B}}_{g\times pt} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y},$$

$$\hat{\mathbf{\Sigma}}_{pt\times pt} = \frac{(\mathbf{Y}_{n\times pt} - \mathbf{X}\hat{\mathbf{B}}_{g\times pt})'(\mathbf{Y}_{n\times pt} - \mathbf{X}\hat{\mathbf{B}}_{g\times pt})}{n-g}.$$

To test the time effect, group effect and interaction group × time effect, multivariate general linear hypotheses are formulated in the form

$$H_0 : \mathbf{CB}_{g\times pt}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{\Gamma}_{0(v_h\times pu)} \text{ or } H_0 : \mathbf{\Gamma}_{v_h\times pu} = \mathbf{\Gamma}_{0(v_h\times pu)}, \qquad (1.28)$$

where $\mathbf{C}$ is a $v_h \times g$ matrix having $rank(\mathbf{C}) = v_h \leq g$ and $\mathbf{A}$ is a $t\times u$ matrix having $rank(\mathbf{A}) = u \leq t$. The rows of $\mathbf{C}$ consist of the coefficients of v_h estimable between group functions. The columns of $\mathbf{A}$ consist of the coefficients of u linear functions (e.g. contrasts) of t time periods. Without loss of generality, the matrix $\mathbf{A}$ is assumed to satisfy $\mathbf{A}'\mathbf{A} = \mathbf{I}_u$.

To obtain the DMM analysis, t time periods in model (1.25) are first reduced to u linear functions of the time periods by multiplying the post matrix $\mathbf{I}_p \otimes \mathbf{A}$ to obtain a reduced model

$$\mathbf{Y}_{n\times pt}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{XB}_{g\times pt}(\mathbf{I}_p \otimes \mathbf{A}) + \mathbf{U}(\mathbf{I}_p \otimes \mathbf{A}).$$

Under assumption (1.28), we obtain

$$vec\left(\mathbf{Y}_{n\times pt}(\mathbf{I}_p \otimes \mathbf{A})\right) \sim N_{npu}\left((\mathbf{I}_{pu} \otimes \mathbf{X})vec(\mathbf{B}_{g\times pt}(\mathbf{I}_p \otimes \mathbf{A})), \mathbf{\Phi} \otimes \mathbf{I}_n\right),$$

where

$$\mathbf{\Phi} = (\mathbf{I}_p \otimes \mathbf{A})'\mathbf{\Sigma}_{pt\times pt}(\mathbf{I}_p \otimes \mathbf{A}).$$

When $v_e = n - g > pu$, Wilks' Lambda (or likelihood ratio statistic) to test $H : \mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{\Gamma}_0$ is given by

$$\Lambda = \frac{\left|\mathbf{S}_{e(pu\times pu)}\right|}{\left|\mathbf{S}_{e(pu\times pu)} + \mathbf{S}_{h(pu\times pu)}\right|},$$

where $\mathbf{S}_{e(pu\times pu)}$ and $\mathbf{S}_{h(pu\times pu)}$ are the $pu \times pu$ sum of squares and cross product (SSCP) matrices corresponding respectively to the error and hypothesis defined by

$$\mathbf{S}_{e(pu\times pu)} = (\mathbf{I}_p \otimes \mathbf{A})'\mathbf{Y}'_{n\times pt}[\mathbf{I}_n - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}']\mathbf{Y}_{n\times pt}(\mathbf{I}_p \otimes \mathbf{A}),$$

$$\mathbf{S}_{h(pu\times pu)} = (\mathbf{C}\hat{\mathbf{B}}_{g\times pt}(\mathbf{I}_p \otimes \mathbf{A}) - \mathbf{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\mathbf{B}}_{g\times pt}(\mathbf{I}_p \otimes \mathbf{A}) - \mathbf{\Gamma}_0).$$

The null hypothesis $H:\mathbf{CB}_{g\times pt}(\mathbf{I}_p\otimes\mathbf{A})=\mathbf{\Gamma}_0$ is rejected if $\Lambda<U^{\alpha}(pu,v_h,v_e)$, where $U^{\alpha}(pu,v_h,v_e)$ are upper $(1-\alpha)100\%$ critical values of Wilks' Lambda statistic with parameters pu, where $u=rank(\mathbf{A})$, $v_h=rank(\mathbf{C})$ and $v_e=n-g$. The table of $U^{\alpha}(pu,v_h,v_e)$ at $\alpha=.05$ is provided in Rencher (2002: 566-573).

1.2.2.2 Multivariate Mixed Model Analysis

According to the Univariate Mixed Model (1.16), the p-variate mixed model of a $p\times 1$ vector $\boldsymbol{y}_{ijk}$ on the i^{th} subject in the j^{th} group at the k^{th} time, $i=1,\ldots,n_j$, $j=1,\ldots,g$, $n_1+n_2+\cdots+n_g=n$ and $k=1,\ldots,t$ can be analyzed by MMM defined as

$$\mathbf{y}_{ijk}=\boldsymbol{\mu}+\boldsymbol{\alpha}_j+\boldsymbol{\beta}_k+(\boldsymbol{\alpha\beta})_{jk}+\mathbf{s}_{(j)i}+\mathbf{e}_{ijk}, \tag{1.29}$$

where $\mathbf{y}_{ijk}$ is a $p\times 1$ response vector on i^{th} subject in j^{th} group at k^{th} time,

$\boldsymbol{\mu}$ is a $p\times 1$ overall mean vector,

$\boldsymbol{\alpha}_j$ is a $p\times 1$ vector of fixed effects for j^{th} group,

$\boldsymbol{\beta}_k$ is a $p\times 1$ vector of fixed effects for k^{th} time,

$(\boldsymbol{\alpha\beta})_{jk}$ is a $p\times 1$ vector of interaction effects between j^{th} group and k^{th} time,

$\mathbf{s}_{(j)i}$ is a $p\times 1$ vector of random deviation of i^{th} subject within j^{th} group, and

$\mathbf{e}_{ijk}$ is a $p\times 1$ random error on the i^{th} subject in the j^{th} group at the k^{th} time.

The model (1.29) can be written in the form of a mean model defined by

$$\mathbf{y}_{ijk}=\boldsymbol{\mu}_{jk}+\mathbf{s}_{(j)i}+\mathbf{e}_{ijk}, \tag{1.30}$$

where $\boldsymbol{\mu}_{jk}=\boldsymbol{\mu}+\boldsymbol{\alpha}_j+\boldsymbol{\beta}_k+(\boldsymbol{\alpha\beta})_{jk}$ is a $p\times 1$ mean vector of the j^{th} group at the k^{th} occasion and $\mathbf{u}_{ijk}=\mathbf{s}_{(j)i}+\mathbf{e}_{ijk}$ is a $p\times 1$ random vector. Assume that $\mathbf{s}_{(j)i}$ and $\mathbf{e}_{ijk}$ are respectively normally distributed as

$$\mathbf{s}_{(j)i}\sim N_p(\mathbf{0},\mathbf{\Sigma}_s), \tag{1.31}$$

$$\mathbf{e}_{ijk}\sim N_p(\mathbf{0},\mathbf{\Sigma}_e), \tag{1.32}$$

where $\mathbf{\Sigma}_s$ is a $p\times p$ covariance matrix and $\mathbf{\Sigma}_e$ is a $p\times p$ covariance matrix.

Let $\mathbf{Y}^*_{ij}=(\mathbf{y}_{ij1},\mathbf{y}_{ij2},\ldots,\mathbf{y}_{ijt})'$ and $\mathbf{E}^*_{ij}=(\mathbf{e}_{ij1},\mathbf{e}_{ij2},\ldots,\mathbf{e}_{ijt})'$ be $t\times p$ matrices of responses and errors respectively for each subject and $\boldsymbol{\mu}^*_j=(\boldsymbol{\mu}_{j1},\boldsymbol{\mu}_{j2},\ldots,\boldsymbol{\mu}_{jt})'$ be a

$t \times p$ matrix of parameters for each group, then the MMM for the i^{th} subject in the j^{th} group can be written as

$$\mathbf{Y}_{ij}^{*} = \boldsymbol{\mu}_{j} + \mathbf{1}_{t}\mathbf{s}'_{(j)i} + \mathbf{E}_{ij}^{*}, \tag{1.33}$$

or equivalently

$$\mathbf{Y}_{ij}^{*} = \boldsymbol{\mu}_{j} + \mathbf{U}_{ij}^{*}, \tag{1.34}$$

where $\mathbf{U}_{ij}^{*} = \mathbf{1}_{t}\mathbf{s}'_{(j)i} + \mathbf{E}_{ij}^{*}$.

By using the $vec(.)$ operator to stack the columns, and letting $\mathbf{u}_{ij}^{*} = vec((\mathbf{U}_{ij}^{*})')$ be $pt \times 1$ vectors, we obtain

$$\operatorname{cov}(\mathbf{u}_{ij}^{*}) = \boldsymbol{\Sigma}_{ij}^{*} = (\mathbf{1}_{t}\mathbf{1}'_{t} \otimes \boldsymbol{\Sigma}_{s}) + (\mathbf{I}_{t} \otimes \boldsymbol{\Sigma}_{e}). \tag{1.35}$$

This $pt \times pt$ covariance matrix $\boldsymbol{\Sigma}_{ij}^{*}$ for each subject has a compound symmetrical structure. It is clear that homegeneity of covariances is satisfied, i.e. $\boldsymbol{\Sigma}_{ij}^{*} = \boldsymbol{\Sigma}_{pt\times pt}^{*}$ for all $i = 1,\ldots,n_{j}$, $j = 1,\ldots,g$, which is a requirement for Scheffé's MMM. Assume that

$$\mathbf{u}_{ij}^{*} \sim N_{pt}(\mathbf{0}, \boldsymbol{\Sigma}^{*}), \tag{1.36}$$

then, according to Scheffé's MMM (1.34) and under the normality assumption (1.36),

$$\boldsymbol{y}_{ij}^{*} = vec(\mathbf{Y}_{ij}^{*}) \sim N_{pt}(vec(\boldsymbol{\mu}_{j}^{*}), \boldsymbol{\Sigma}^{*}). \tag{1.37}$$

By taking each $t \times p$ matrix $\mathbf{Y}_{ij}^{*}$ in each column, where the columns of $\mathbf{Y}_{ij}^{*}$ are t times and the rows are p response variables, and similarly taking each $\mathbf{U}_{ij}^{*}$ in each column, the response matrix $\mathbf{Y}_{nt\times p}^{*}$, error matrix $\mathbf{U}_{nt\times p}^{*}$ and $\mathbf{B}_{gt\times p}^{*}$ are obtained. Subsequently, MMM is defined by

$$\mathbf{Y}_{nt\times p}^{*} = (\mathbf{X}_{n\times g} \otimes \mathbf{I}_{t})\mathbf{B}_{gt\times p}^{*} + \mathbf{U}_{nt\times p}^{*}, \tag{1.38}$$

where $\mathbf{Y}^{*}$ is an $nt \times p$ response matrix for n subjects, $\mathbf{X}$ is an $n\times g$ between subject design matrix of $rank(\mathbf{X}) = g$, $\mathbf{B}^{*}$ is a $gt \times p$ unknown parameter matrix of fixed effects and $\mathbf{U}^{*}$ is an $nt \times p$ random error matrix. The layouts of these matrices are shown in Chapter 2. Assume that

$$vec((\mathbf{U}_{nt\times p}^{*})') \sim N_{npt}(\mathbf{0}_{npt\times 1}, \mathbf{I}_{n} \otimes \boldsymbol{\Sigma}_{pt\times pt}^{*}), \tag{1.39}$$

which has a block diagonal structure of covariance matrix and $\mathbf{\Sigma}^*_{pt\times pt}$ has a compound symmetrical structure as defined in (1.35).

The reduced model to analyze contrast among the t times is obtained by multiplying the model by the post matrix $\mathbf{M}^* = \mathbf{I}_n \otimes \mathbf{A}'_{u\times t}$, i.e.

$$(\mathbf{I}_n \otimes \mathbf{A}'_{u\times t})\mathbf{Y}^*_{nt\times p} = (\mathbf{I}_n \otimes \mathbf{A}'_{u\times t})(\mathbf{X}_{n\times g} \otimes \mathbf{I}_t)\mathbf{B}^*_{gt\times p} + (\mathbf{I}_n \otimes \mathbf{A}'_{u\times t})\mathbf{U}^*_{nt\times p}$$
$$= (\mathbf{X}_{n\times g} \otimes \mathbf{A}'_{u\times t})\mathbf{B}^*_{gt\times p} + (\mathbf{I}_n \otimes \mathbf{A}'_{u\times t})\mathbf{U}^*_{nt\times p}. \tag{1.40}$$

The MLE of $\mathbf{B}^*_{gt\times p}$ from the reduced model (1.40) is $\mathbf{B}^*_{gt\times p} = [(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}' \otimes \mathbf{I}_t]\mathbf{Y}'^*_{nt\times p}$.

The MMM (1.38) is related to the DMM (1.25) and to show this relationship, the response matrix $\mathbf{Y}_{n\times pt}$ from (1.25) is rearranged by ordering the elements in each column according to time and within each time according to the dependent variables, leading to a rearranged DMM represented as

$$\tilde{\mathbf{Y}}_{n\times pt} = \tilde{\mathbf{X}}_{n\times g}\tilde{\mathbf{B}}_{g\times pt} + \tilde{\mathbf{U}}_{n\times pt}. \tag{1.41}$$

Under the multivariate normality assumption,

$$vec(\tilde{\mathbf{U}}'_{n\times pt}) \sim N_{npt}(\mathbf{0}_{npt\times 1}, \mathbf{I}_n \otimes \tilde{\mathbf{\Sigma}}_{pt\times pt}), \tag{1.42}$$

where the covariance matrix $\tilde{\mathbf{\Sigma}}_{pt\times pt}$ is a $pt\times pt$ covariance matrix which is the rearrangement of the covariance matrix $\mathbf{\Sigma}_{pt\times pt}$ by reordering within each column according to time and within time according to the response variables.

Note that $vec((\tilde{\mathbf{Y}}_{n\times pt})') = vec((\mathbf{Y}^*_{nt\times p})')$, $vec((\tilde{\mathbf{B}}_{n\times pt})') = vec((\mathbf{B}^*_{nt\times p})')$, and $vec((\tilde{\mathbf{U}}_{n\times pt})') = vec((\mathbf{U}^*_{nt\times p})')$. The covariance matrix $\mathbf{\Sigma}^*_{pt\times pt}$ from (1.35) is a special structure of $\tilde{\mathbf{\Sigma}}_{pt\times pt}$ in (1.42).

A reduced model of the rearranged DMM (1.41) is defined by multiplying the post matrix $\mathbf{A}_{t\times u} \otimes \mathbf{I}_p$ as

$$\tilde{\mathbf{Y}}_{n\times pt}(\mathbf{A}_{t\times u} \otimes \mathbf{I}_p) = \tilde{\mathbf{X}}_{n\times g}\tilde{\mathbf{B}}_{g\times pt}(\mathbf{A}_{t\times u} \otimes \mathbf{I}_p) + \tilde{\mathbf{U}}_{n\times pt}(\mathbf{A}_{t\times u} \otimes \mathbf{I}_p),$$
$$\tilde{\mathbf{Y}}_M = \tilde{\mathbf{X}}_{n\times g}\tilde{\mathbf{B}}_M + \tilde{\mathbf{U}}_M, \tag{1.43}$$

where $\tilde{\mathbf{Y}}_M = \tilde{\mathbf{Y}}_{n\times pt}(\mathbf{A}_{t\times u} \otimes \mathbf{I}_p)$, $\tilde{\mathbf{B}}_M = \tilde{\mathbf{B}}_{g\times pt}(\mathbf{A}_{t\times u} \otimes \mathbf{I}_p)$ and $\tilde{\mathbf{U}}_M = \tilde{\mathbf{U}}_{n\times pt}(\mathbf{A}_{t\times u} \otimes \mathbf{I}_p)$, under the normality assumption (1.42). Subsequently,

$$vec(\tilde{\mathbf{U}}'_M) \sim N_{npu}(\mathbf{0}, \mathbf{I}_n \otimes \tilde{\mathbf{\Phi}}_{pu\times pu}),$$

where $\tilde{\mathbf{\Phi}}$ is a $pu \times pu$ covariance matrix, defined as

$$\tilde{\mathbf{\Phi}} = (\mathbf{A}' \otimes \mathbf{I}_p)\tilde{\mathbf{\Sigma}}_{pt\times pt}(\mathbf{A} \otimes \mathbf{I}_p). \tag{1.44}$$

If $\tilde{\mathbf{\Sigma}}_{pt\times pt} = \mathbf{\Sigma}^*_{pt\times pt} = (\mathbf{1}_t\mathbf{1}'_t \otimes \mathbf{\Sigma}_s) + (\mathbf{I}_t \otimes \mathbf{\Sigma}_e)$, the covariance matrix $\tilde{\mathbf{\Phi}}$ satisfies multivariate sphericity such that

$$\tilde{\mathbf{\Phi}} = \mathbf{I}_u \otimes \mathbf{\Sigma}_e. \tag{1.45}$$

Given the multivariate sphericity condition (1.45) and the reduced MMM (1.40), the Multivariate General Linear Hypothesis for testing for the effect of the time and group factors and the interaction effect between the group and time factors is

$$H:(\mathbf{C}\otimes\mathbf{A}')\mathbf{B}^*_{gt\times p} = \mathbf{\Gamma}^*_{0(uv_h\times p)} \quad \text{or} \quad H:\mathbf{\Gamma}^* = \mathbf{\Gamma}^*_{0(uv_h\times p)}, \tag{1.46}$$

where $\mathbf{C}$ is a $v_h \times g$ between group contrast matrix having $rank(\mathbf{C}) = v_h \le g$ and $\mathbf{A}$ is a $t \times u$ within subject contrast matrix such that $\mathbf{A}'\mathbf{A} = \mathbf{I}_u$ and $rank(\mathbf{A}) = u \le t$. Hypothesis (1.46) is identical to (1.28) in DMM analysis.

When $uv_e = u(n-g) > p$, the classical Wilks' Lambda statistic for testing $H:(\mathbf{C}\otimes\mathbf{A}')\mathbf{B}^*_{gt\times p} = \mathbf{\Gamma}^*_{0(uv_h\times p)}$ using the reduced MMM (1.40) under the multivariate sphericity condition (1.45) is given by

$$\Lambda = \frac{\left|\mathbf{S}^*_{e(p\times p)}\right|}{\left|\mathbf{S}^*_{e(p\times p)} + \mathbf{S}^*_{h(p\times p)}\right|} = \left|\mathbf{I}_p + \mathbf{S}^*_{h(p\times p)}\mathbf{S}^{*-1}_{e(p\times p)}\right|^{-1},$$

where $\mathbf{S}^*_{e(p\times p)}$ and $\mathbf{S}^*_{h(p\times p)}$ are the $p \times p$ sum of squares and cross product (SSCP) matrices corresponding to error and the hypothesis respectively defined by

$$\mathbf{S}^*_{e(p\times p)} = (\mathbf{Y}^*_{nt\times p})'[(\mathbf{I}_n - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}) \otimes \mathbf{A}\mathbf{A}']\mathbf{Y}^*_{nt\times p},$$

$$\mathbf{S}^*_{h(p\times p)} = (\mathbf{Y}^*_{nt\times p})'\left\{\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}' \otimes \mathbf{A}\mathbf{A}'\right\}\mathbf{Y}^*_{nt\times p}.$$

The hypothesis $H:(\mathbf{C}\otimes\mathbf{A}')\mathbf{B}^*_{gt\times p} = \mathbf{\Gamma}^*_{0(uv_h\times p)}$ is rejected if $\Lambda < U^\alpha(p, uv_h, uv_e)$ where $U^\alpha(p, uv_h, uv_e)$ are the upper $(1-\alpha)100\%$ critical values of Wilks' Lambda statistic with parameters, p , $u = rank(\mathbf{A})$, $v_h = rank(\mathbf{C})$ and $v_e = n - g$. The values table of $U^{\alpha}(p, uv_h, uv_e)$ at $\alpha = .05$ is provided by Rencher (2002: 566-573).

The DMM and MMM analyses require the multivariate normality assumption, homogeneity of the group covariance matrices and independence of the selected subjects. In addition, MMM analysis requires the multivariate sphericity condition where the covariance matrix of the orthogonalized contrasts must be proportional to an identity matrix for each dependent variable as defined in (1.45). If the data do not satisfy the multivariate sphericity condition, then DMM is commonly adopted in practice (Naik and Rao, 2001: 91-94; Timm, 2002: 400-404) .

1.3 Problems of High Dimensional Data

DMM analysis of multivariate repeated measurements is based on classical multivariate tests which are a function of $\mathbf{S}_h\mathbf{S}_e^{-1}$, where $\mathbf{S}_e$ and $\mathbf{S}_h$ are the $pu \times pu$ SSCP matrices corresponding respectively to error and the hypothesis. The MANOVA of DMM requires an assumption that the degrees of freedom of the SSCP error matrix $\mathbf{S}_e$ is larger than the *pu*-dimensional of $\mathbf{S}_e$, i.e. $v_e = n - g > pu$. For MMM analysis, classical multivariate tests are a function of $\mathbf{S}_h^*(\mathbf{S}_e^*)^{-1}$, where $\mathbf{S}_e^*$ and $\mathbf{S}_h^*$ are the $p \times p$ SSCP matrices. Similar to DMM, the MANOVA of MMM requires that the degrees of freedom of the error SSCP matrix $\mathbf{S}_e^*$ is larger than the dimension of $\mathbf{S}_e^*$, i.e. $uv_e = u(n-g) > p$.

In an example a study involving high dimensional data, deoxyribonucleic acid (DNA) microarray time course experiments, gene expression is available on thousands of genes of an individual which can be measured several times but there are only a few individuals in the dataset. These experiments are of a high dimensional multivariate repeated measurements design where the number of response variables (or *p* genes) is much larger than the sample size (or individuals) *n*. In the analysis of these high dimensional data, the classical multivariate tests of the DMM and MMM analyses are not suitable because the data fail the requirement that the degrees of freedom of the SSCP matrix due to error are larger than its dimension. Therefore, the development of test statistics of DMM and MMM applicable to the High Dimensional Multivariate Repeated Measurements Design are of interest.

1.4 Objectives of the Study

This dissertation focuses on the analysis of the High Dimensional Multivariate Repeated Measurements Design. The objective of this study is to propose tests for analyzing multivariate repeated measurements data in a high dimension framework. The proposed tests are modifications of MANOVA using two models: DMM and Scheffé's MMM under a high dimension framework, where $p \to \infty$, $n \to \infty$ and the dimension of the SSCP matrix due to error is larger than its degrees of freedom, such that $pu > v_e$ in the DMM analysis and $p > uv_e$ in the MMM analysis.

The approximate or asymptotic distributions of the proposed tests under the null and non-null hypotheses are derived and used to compare the performances of the proposed tests.

1.5 Scope of the Study

The scope of this study is as follows**:**

1. A multivariate repeated measurements design has p response variables observed on n subjects in g groups over t times when $p \to \infty$, $n \to \infty$, and t is fixed.

2. An analysis of the Multivariate Repeated Measurements Design is considered under the assumptions of normality, independent subjects and homogeneity of variances among the groups.

3. A set of multivariate repeated measurement data is complete and within-subjects balanced. This means that there is no missing data and repeated measurements on each subject are equal.

4. Multivariate tests for the Multivariate Linear Hypothesis are considered in two models: DMM with an unstructured covariance matrix and Scheffé's MMM with a compound symmetry covariance matrix structure that satisfies the multivariate sphericity condition.

In this dissertation, the multivariate tests for analyzing multivariate repeated measurements designs in a high dimensional framework are worked on. A literature review concerning DMM and MMM analyses and some high dimensional MANOVA tests is given in Chapter 2. The proposed tests of DMM and MMM analyses and their null and non-null distributions are derived in Chapter 3. The approximate or asymptotic distributions of the test statistics are derived and power comparisons of the test statistics are evaluated using a simulation study provided in Chapter 4 and an application of the analysis of the High Dimensional Multivariate Repeated Measurement Design is given in Chapter 5. A summary and conclusions of this dissertation's work is discussed in Chapter 6.

CHAPTER 2

LITERATURE REVIEW

2.1 The Doubly Multivariate Linear Model (DMM)

In a univariate repeated measurements design having t time periods, each subject gives a t-repeated response. As described in section 1.2.1.2, the $t \times 1$ response vector $\mathbf{y}_{ij} = (y_{ij1}, y_{ij2}, \dots, y_{ijt})'$ for each i^{th} subject in the j^{th} group can be analyzed according to the Multivariate Linear Model $\mathbf{y}_{ij} = \boldsymbol{\mu} + \boldsymbol{\alpha}_j + \boldsymbol{\varepsilon}_{ij}$ or $\mathbf{y}_{ij} = \boldsymbol{\mu}_j + \boldsymbol{\varepsilon}_{ij}$, where $\boldsymbol{\alpha}_j$ is a vector of the main effect corresponding to t repeated measures for the treatment or group factor, $\boldsymbol{\varepsilon}_{ij}$ is an error vector for each subject and $\boldsymbol{\mu}_j = \boldsymbol{\mu} + \boldsymbol{\alpha}_j$. This model seems to only include a treatment factor but it can be used in a profile analysis to obtain tests on the time and interaction factors.

When p response variables are observed on n subjects at each t occasion, each subject gives a pt-dimensional response. The multivariate linear model analysis of univariate repeated measurements designs of the t-dimensional response vector $\mathbf{y}_{ij}$ is extended to the DMM of a $t \times p$ response matrix $\mathbf{Y}_{ij}$, for each i^{th} subject in the j^{th} group. Note that if the number of variables $p = 1$, this is a multivariate linear model of the repeated measurements of one response over t occasions, as described in section 1.2.1.2.

Let $\mathbf{y}_{ijk}$ be a $p \times 1$ vector of p-variate responses on the i^{th} subject in the j^{th} group at the k^{th} occasion, for $i = 1, \dots, n_j$, $j = 1, \dots, g$, $n_1 + n_2 + \dots + n_g = n$ and $k = 1, \dots, t$, and let $\mathbf{Y}_{ij} = (\mathbf{y}_{ij1}, \mathbf{y}_{ij2}, \dots, \mathbf{y}_{ijt})'$ be $t \times p$ response matrices on the i^{th} subject in the j^{th} group, then the data layout of a multivariate repeated measurements design are as shown in Table 2.1.

Table 2.1 The Data Layout of a Multivariate Repeated Measurements Design

Treatment Group (j)	Subject (i)	Response Matrix $\mathbf{Y}'_{ij}$		Condition (Time) 1	2	$\cdots$	t
1	1	$\mathbf{Y}'_{11}$	=	$(\mathbf{y}_{111}$	$\mathbf{y}_{112}$	$\cdots$	$\mathbf{y}_{11t})$
	2	$\mathbf{Y}'_{21}$	=	$(\mathbf{y}_{211}$	$\mathbf{y}_{212}$	$\cdots$	$\mathbf{y}_{21t})$
	$\vdots$	$\vdots$		$\vdots$	$\vdots$		$\vdots$
	n_1	$\mathbf{Y}'_{n_1 1}$	=	$(\mathbf{y}_{n_1 11}$	$\mathbf{y}_{n_1 12}$	$\cdots$	$\mathbf{y}_{n_1 1t})$
2	1	$\mathbf{Y}'_{12}$	=	$(\mathbf{y}_{121}$	$\mathbf{y}_{122}$	$\cdots$	$\mathbf{y}_{12t})$
	2	$\mathbf{Y}'_{22}$	=	$(\mathbf{y}_{221}$	$\mathbf{y}_{222}$	$\cdots$	$\mathbf{y}_{22t})$
	$\vdots$	$\vdots$		$\vdots$	$\vdots$		$\vdots$
	n_2	$\mathbf{Y}'_{n_2 2}$	=	$(\mathbf{y}_{n_2 21}$	$\mathbf{y}_{n_2 22}$	$\cdots$	$\mathbf{y}_{n_2 2t})$
$\vdots$	$\vdots$	$\vdots$		$\vdots$	$\vdots$		$\vdots$
g	1	$\mathbf{Y}'_{1g}$	=	$(\mathbf{y}_{1g1}$	$\mathbf{y}_{1g2}$	$\cdots$	$\mathbf{y}_{1gt})$
	2	$\mathbf{Y}'_{2g}$	=	$(\mathbf{y}_{2g1}$	$\mathbf{y}_{2g2}$	$\cdots$	$\mathbf{y}_{2gt})$
	$\vdots$	$\vdots$		$\vdots$	$\vdots$		$\vdots$
	n_g	$\mathbf{Y}'_{n_g g}$	=	$(\mathbf{y}_{n_g g1}$	$\mathbf{y}_{n_g g2}$	$\cdots$	$\mathbf{y}_{n_g gt})$

According to the response data, let $\boldsymbol{\mu}_{jk}$ be a $p \times 1$ population mean vector for the j^{th} group at the k^{th} occasion, for $j = 1,\ldots,g$, $k = 1,\ldots,t$, and let $\boldsymbol{\mu}_j = (\boldsymbol{\mu}_{j1}, \boldsymbol{\mu}_{j2}, \ldots, \boldsymbol{\mu}_{jt})'$ be the $t \times p$ population mean matrices for the j^{th} group, then the matrix of population means $\boldsymbol{\mu}_j$ are as shown in Table 2.2.

Table 2.2 Population Mean Matrices

Treatment Group (j)	Cell Mean Matrix		Condition (Time) 1	2	$\cdots$	t
1	$\boldsymbol{\mu}'_1$	=	$(\boldsymbol{\mu}_{11}$	$\boldsymbol{\mu}_{12}$	$\cdots$	$\boldsymbol{\mu}_{1t})$
2	$\boldsymbol{\mu}'_2$	=	$(\boldsymbol{\mu}_{21}$	$\boldsymbol{\mu}_{22}$	$\cdots$	$\boldsymbol{\mu}_{2t})$
$\vdots$	$\vdots$		$\vdots$	$\vdots$		$\vdots$
g	$\boldsymbol{\mu}'_g$	=	$(\boldsymbol{\mu}_{g1}$	$\boldsymbol{\mu}_{g2}$	$\cdots$	$\boldsymbol{\mu}_{gt})$

The data setup shown in Table 2.1 is identical to the data of a one-way multivariate repeated measurements design. The Multivariate Linear Model of the $t \times p$ response matrix $\mathbf{Y}_{ij}$ is identical to a one-way MANOVA and can be written as

$$\mathbf{Y}_{ij} = \boldsymbol{\mu}_j + \mathbf{U}_{ij}, \qquad \text{for } i = 1,\ldots,n_j,\ j = 1,\ldots,g, \quad (2.1)$$

where $\boldsymbol{\mu}_j$ is a $t \times p$ cell mean matrix for the j^{th} group and $\mathbf{U}_{ij}$ is a $t \times p$ error matrix for the i^{th} subject in the j^{th} group. The $t \times p$ matrices of $\mathbf{Y}_{ij}$, $\boldsymbol{\mu}_j$ and $\mathbf{U}_{ij}$ are respectively defined by

$$\mathbf{Y}_{ij} = \begin{bmatrix} y_{ij1}^{(1)} & y_{ij1}^{(2)} & \cdots & y_{ij1}^{(p)} \\ y_{ij2}^{(1)} & y_{ij2}^{(2)} & \cdots & y_{ij2}^{(p)} \\ \vdots & \vdots & & \vdots \\ y_{ijt}^{(1)} & y_{ijt}^{(2)} & \cdots & y_{ijt}^{(p)} \end{bmatrix},$$

$$\boldsymbol{\mu}_j = \begin{bmatrix} \mu_{j1}^{(1)} & \mu_{j1}^{(2)} & \cdots & \mu_{j1}^{(p)} \\ \mu_{j2}^{(1)} & \mu_{j2}^{(2)} & \cdots & \mu_{j2}^{(p)} \\ \vdots & \vdots & & \vdots \\ \mu_{jt}^{(1)} & \mu_{jt}^{(2)} & \cdots & \mu_{jt}^{(p)} \end{bmatrix},$$

and

$$\mathbf{U}_{ij} = \begin{bmatrix} u_{ij1}^{(1)} & u_{ij1}^{(2)} & \cdots & u_{ij1}^{(p)} \\ u_{ij2}^{(1)} & u_{ij2}^{(2)} & \cdots & u_{ij2}^{(p)} \\ \vdots & \vdots & & \vdots \\ u_{ijt}^{(1)} & u_{ijt}^{(2)} & \cdots & u_{ijt}^{(p)} \end{bmatrix}.$$

2.1.1 The Matrix Form of the Doubly Multivariate Linear Model

Let $\mathbf{y}_{ij} = \text{vec}(\mathbf{Y}_{ij})$ denote the $pt \times 1$ random response vector formed by stacking the columns of $t \times p$ response matrices $\mathbf{Y}_{ij}$, for $i = 1,\ldots,n_j$, $j = 1,\ldots,g$, such that

$$\mathbf{y}_{ij} = vec(\mathbf{Y}_{ij}) = vec\begin{bmatrix} y_{ij1}^{(1)} & y_{ij1}^{(2)} & \cdots & y_{ij1}^{(p)} \\ y_{ij2}^{(1)} & y_{ij2}^{(2)} & \cdots & y_{ij2}^{(p)} \\ \vdots & \vdots & & \vdots \\ y_{ijt}^{(1)} & y_{ijt}^{(2)} & \cdots & y_{ijt}^{(p)} \end{bmatrix}$$

$$= \left(y_{ij1}^{(1)}, y_{ij2}^{(1)}, \ldots y_{ijt}^{(1)}, \quad y_{ij1}^{(2)}, y_{ij2}^{(2)}, \ldots y_{ijt}^{(2)}, \quad \ldots, \quad y_{ij1}^{(p)}, y_{ij2}^{(p)}, \ldots y_{ijt}^{(p)} \right)'.$$

By taking each $\mathbf{y}'_{ij}$ in each row, an $n \times pt$ response matrix for n subjects is obtained, i.e. $\mathbf{Y} = (\mathbf{y}_{11}, \mathbf{y}_{21}, \ldots, \mathbf{y}_{n_1 1}, \mathbf{y}_{12}, \mathbf{y}_{22}, \ldots, \mathbf{y}_{n_2 2}, \ldots, \mathbf{y}_{1g}, \mathbf{y}_{2g}, \ldots, \mathbf{y}_{n_g g})'$, giving the DMM as

$$\mathbf{Y}_{n \times pt} = \mathbf{X}_{n \times g} \mathbf{B}_{g \times pt} + \mathbf{U}_{n \times pt}, \tag{2.2}$$

where $\mathbf{Y}$ is an $n \times pt$ response matrix for n subjects, $\mathbf{X}$ is an $n \times g$ between subject design matrix of $rank(\mathbf{X}) = g$, $\mathbf{B}$ is a $g \times pt$ unknown parameter matrix of fixed effects and $\mathbf{U}$ is an $n \times pt$ random error matrix. The layouts of these matrices are as follows:

$$\mathbf{Y}_{n \times pt} = \left[\begin{array}{c} \mathbf{y}'_{11} \\ \mathbf{y}'_{21} \\ \vdots \\ \mathbf{y}'_{n_1 1} \\ \hline \mathbf{y}'_{12} \\ \mathbf{y}'_{22} \\ \vdots \\ \mathbf{y}'_{n_2 2} \\ \hline \vdots \\ \hline \mathbf{y}'_{1g} \\ \mathbf{y}'_{2g} \\ \vdots \\ \mathbf{y}'_{n_g g} \end{array}\right] = \left[\begin{array}{ccc|ccc|c|ccc} y^{(1)}_{111} & \cdots & y^{(1)}_{11t} & y^{(2)}_{111} & \cdots & y^{(2)}_{11t} & \cdots & y^{(p)}_{111} & \cdots & y^{(p)}_{11t} \\ y^{(1)}_{211} & \cdots & y^{(1)}_{21t} & y^{(2)}_{211} & \cdots & y^{(2)}_{21t} & \cdots & y^{(p)}_{211} & \cdots & y^{(p)}_{21t} \\ \vdots & & \vdots & \vdots & & \vdots & & \vdots & & \vdots \\ y^{(1)}_{n_1 11} & \cdots & y^{(1)}_{n_1 1t} & y^{(2)}_{n_1 11} & \cdots & y^{(2)}_{n_1 1t} & \cdots & y^{(p)}_{n_1 11} & \cdots & y^{(p)}_{n_1 1t} \\ \hline y^{(1)}_{121} & \cdots & y^{(1)}_{12t} & y^{(2)}_{121} & \cdots & y^{(2)}_{12t} & \cdots & y^{(p)}_{121} & \cdots & y^{(p)}_{12t} \\ y^{(1)}_{221} & \cdots & y^{(1)}_{22t} & y^{(2)}_{221} & \cdots & y^{(2)}_{22t} & \cdots & y^{(p)}_{221} & \cdots & y^{(p)}_{22t} \\ \vdots & & \vdots & \vdots & & \vdots & & \vdots & & \vdots \\ y^{(1)}_{n_2 21} & \cdots & y^{(1)}_{n_2 2t} & y^{(2)}_{n_2 21} & \cdots & y^{(2)}_{n_2 2t} & \cdots & y^{(p)}_{n_2 21} & \cdots & y^{(p)}_{n_2 2t} \\ \hline \vdots & & \vdots & \vdots & & \vdots & & \vdots & & \vdots \\ \hline y^{(1)}_{1g1} & \cdots & y^{(1)}_{1gt} & y^{(2)}_{1g1} & \cdots & y^{(2)}_{1gt} & \cdots & y^{(p)}_{1g1} & \cdots & y^{(p)}_{1gt} \\ y^{(1)}_{2g1} & \cdots & y^{(1)}_{2gt} & y^{(2)}_{2g1} & \cdots & y^{(2)}_{2gt} & \cdots & y^{(p)}_{2g1} & \cdots & y^{(p)}_{2gt} \\ \vdots & & \vdots & \vdots & & \vdots & & \vdots & & \vdots \\ y^{(1)}_{n_g g1} & \cdots & y^{(1)}_{n_g gt} & y^{(2)}_{n_g g1} & \cdots & y^{(2)}_{n_g gt} & \cdots & y^{(p)}_{n_g g1} & \cdots & y^{(p)}_{n_g gt} \end{array}\right],$$

$$\mathbf{X}_{n \times g} = \begin{bmatrix} \mathbf{1}_{n_1} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \mathbf{1}_{n_2} & \cdots & \mathbf{0} \\ \vdots & \vdots & \ddots & \vdots \\ \mathbf{0} & \mathbf{0} & \cdots & \mathbf{1}_{n_g} \end{bmatrix},$$

$$\mathbf{B}_{g \times pt} = \begin{bmatrix} \boldsymbol{\beta}'_1 \\ \boldsymbol{\beta}'_2 \\ \vdots \\ \boldsymbol{\beta}'_g \end{bmatrix} = \left[\begin{array}{ccc|ccc|c|ccc} \mu^{(1)}_{11} & \cdots & \mu^{(1)}_{1t} & \mu^{(2)}_{11} & \cdots & \mu^{(2)}_{1t} & \cdots & \mu^{(p)}_{11} & \cdots & \mu^{(p)}_{1t} \\ \mu^{(1)}_{21} & \cdots & \mu^{(1)}_{2t} & \mu^{(2)}_{21} & \cdots & \mu^{(2)}_{2t} & \cdots & \mu^{(p)}_{21} & \cdots & \mu^{(p)}_{2t} \\ \vdots & & \vdots & \vdots & & \vdots & & \vdots & & \vdots \\ \mu^{(1)}_{g1} & \cdots & \mu^{(1)}_{gt} & \mu^{(2)}_{g1} & \cdots & \mu^{(2)}_{gt} & \cdots & \mu^{(p)}_{g1} & \cdots & \mu^{(p)}_{gt} \end{array}\right],$$

where $\boldsymbol{\beta}_j = vec(\boldsymbol{\mu}_j)$ denotes the $pt \times 1$ unknown parameter vector formed by stacking the columns of $t \times p$ parameter matrix $\boldsymbol{\mu}_j$, and similarly,

$$
\mathbf{U}_{n\times pt} = \left[\begin{array}{c} \mathbf{u}'_{11} \\ \mathbf{u}'_{21} \\ \vdots \\ \mathbf{u}'_{n_1 1} \\ \hline \mathbf{u}'_{12} \\ \mathbf{u}'_{22} \\ \vdots \\ \mathbf{u}'_{n_2 2} \\ \hline \vdots \\ \hline \mathbf{u}'_{1g} \\ \mathbf{u}'_{2g} \\ \vdots \\ \mathbf{u}'_{n_g g} \end{array}\right] = \left[\begin{array}{ccc|ccc|c|ccc}
u_{111}^{(1)} & \cdots & u_{11t}^{(1)} & u_{111}^{(2)} & \cdots & u_{11t}^{(2)} & \cdots & u_{111}^{(p)} & \cdots & u_{11t}^{(p)} \\
u_{211}^{(1)} & \cdots & u_{21t}^{(1)} & u_{211}^{(2)} & \cdots & u_{21t}^{(2)} & \cdots & u_{211}^{(p)} & \cdots & u_{21t}^{(p)} \\
\vdots & & \vdots & \vdots & & \vdots & & \vdots & & \vdots \\
u_{n_1 11}^{(1)} & \cdots & u_{n_1 1t}^{(1)} & u_{n_1 11}^{(2)} & \cdots & u_{n_1 1t}^{(2)} & \cdots & u_{n_1 11}^{(p)} & \cdots & u_{n_1 1t}^{(p)} \\ \hline
u_{121}^{(1)} & \cdots & u_{12t}^{(1)} & u_{121}^{(2)} & \cdots & u_{12t}^{(2)} & & u_{121}^{(p)} & \cdots & u_{12t}^{(p)} \\
u_{221}^{(1)} & \cdots & u_{22t}^{(1)} & u_{221}^{(2)} & \cdots & u_{22t}^{(2)} & & u_{221}^{(p)} & \cdots & u_{22t}^{(p)} \\
\vdots & & \vdots & \vdots & & \vdots & & \vdots & & \vdots \\
u_{n_2 21}^{(1)} & \cdots & u_{n_2 2t}^{(1)} & u_{n_2 21}^{(2)} & \cdots & u_{n_2 2t}^{(2)} & & u_{n_2 21}^{(p)} & \cdots & u_{n_2 2t}^{(p)} \\ \hline
\vdots & & \vdots & \vdots & & \vdots & & \vdots & & \vdots \\ \hline
u_{1g1}^{(1)} & \cdots & u_{1gt}^{(1)} & u_{1g1}^{(2)} & \cdots & u_{1gt}^{(2)} & & u_{1g1}^{(p)} & \cdots & u_{1gt}^{(g)} \\
u_{2g1}^{(1)} & \cdots & u_{2gt}^{(1)} & u_{2g1}^{(2)} & \cdots & u_{2gt}^{(2)} & & u_{2g1}^{(p)} & \cdots & u_{2gt}^{(p)} \\
\vdots & & \vdots & \vdots & & \vdots & & \vdots & & \vdots \\
u_{n_g g1}^{(1)} & \cdots & u_{n_g gt}^{(1)} & u_{n_g g1}^{(2)} & \cdots & u_{n_g gt}^{(2)} & & u_{n_g g1}^{(p)} & \cdots & u_{n_g gt}^{(p)}
\end{array}\right].
$$

Each row of the vectors of $\mathbf{U}$, denoted by $\mathbf{u}'_{ij}$, is assumed to be identically independently multivariate normally distributed with a $pt \times 1$ zero mean vector and a $pt \times pt$ covariance matrix $\boldsymbol{\Sigma}$,

$$
\mathbf{u}_{ij} \sim N_{pt}(\mathbf{0}_{pt\times 1}, \boldsymbol{\Sigma}_{pt\times pt}), \tag{2.3}
$$

where $\boldsymbol{\Sigma}$ is a $pt \times pt$ positive definite matrix defined as

$$
\boldsymbol{\Sigma} = \left[\begin{array}{cccc|cccc|c|cccc}
\sigma_1^{(1)}\sigma_1^{(1)} & \sigma_1^{(1)}\sigma_2^{(1)} & \cdots & \sigma_1^{(1)}\sigma_t^{(1)} & \sigma_1^{(1)}\sigma_1^{(2)} & \sigma_1^{(1)}\sigma_2^{(2)} & \cdots & \sigma_1^{(1)}\sigma_t^{(2)} & \cdots & \sigma_1^{(1)}\sigma_1^{(p)} & \sigma_1^{(1)}\sigma_2^{(p)} & \cdots & \sigma_1^{(1)}\sigma_t^{(p)} \\
\sigma_2^{(1)}\sigma_1^{(1)} & \sigma_2^{(1)}\sigma_2^{(1)} & \cdots & \sigma_2^{(1)}\sigma_t^{(1)} & \sigma_2^{(1)}\sigma_1^{(2)} & \sigma_2^{(1)}\sigma_2^{(2)} & \cdots & \sigma_2^{(1)}\sigma_t^{(2)} & \cdots & \sigma_2^{(1)}\sigma_1^{(p)} & \sigma_2^{(1)}\sigma_2^{(p)} & \cdots & \sigma_2^{(1)}\sigma_t^{(p)} \\
\vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots & & \vdots & \vdots & \ddots & \\
\sigma_t^{(1)}\sigma_1^{(1)} & \sigma_t^{(1)}\sigma_2^{(1)} & \cdots & \sigma_t^{(1)}\sigma_t^{(1)} & \sigma_t^{(1)}\sigma_1^{(2)} & \sigma_t^{(1)}\sigma_2^{(2)} & \cdots & \sigma_t^{(1)}\sigma_t^{(2)} & \cdots & \sigma_t^{(1)}\sigma_1^{(p)} & \sigma_t^{(1)}\sigma_2^{(p)} & \cdots & \sigma_t^{(1)}\sigma_t^{(p)} \\ \hline
\sigma_1^{(2)}\sigma_1^{(1)} & \sigma_1^{(2)}\sigma_2^{(1)} & \cdots & \sigma_1^{(2)}\sigma_t^{(1)} & \sigma_1^{(2)}\sigma_1^{(2)} & \sigma_1^{(2)}\sigma_2^{(2)} & \cdots & \sigma_1^{(2)}\sigma_t^{(2)} & \cdots & \sigma_1^{(2)}\sigma_1^{(p)} & \sigma_1^{(2)}\sigma_2^{(p)} & \cdots & \sigma_1^{(2)}\sigma_2^{(p)} \\
\sigma_2^{(2)}\sigma_1^{(1)} & \sigma_2^{(2)}\sigma_2^{(1)} & \cdots & \sigma_2^{(2)}\sigma_t^{(1)} & \sigma_2^{(2)}\sigma_1^{(2)} & \sigma_2^{(2)}\sigma_2^{(2)} & \cdots & \sigma_2^{(2)}\sigma_t^{(2)} & \cdots & \sigma_2^{(2)}\sigma_1^{(p)} & \sigma_2^{(2)}\sigma_2^{(p)} & \cdots & \sigma_2^{(2)}\sigma_t^{(p)} \\
\vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots & & \vdots & \vdots & \ddots & \vdots \\
\sigma_t^{(2)}\sigma_1^{(1)} & \sigma_t^{(2)}\sigma_2^{(1)} & \cdots & \sigma_t^{(2)}\sigma_t^{(1)} & \sigma_t^{(2)}\sigma_1^{(2)} & \sigma_t^{(2)}\sigma_2^{(2)} & \cdots & \sigma_t^{(2)}\sigma_t^{(2)} & \cdots & \sigma_t^{(2)}\sigma_1^{(p)} & \sigma_t^{(2)}\sigma_2^{(p)} & \cdots & \sigma_t^{(2)}\sigma_t^{(p)} \\ \hline
\vdots & \vdots & & \vdots & \vdots & \vdots & & \vdots & \ddots & \vdots & \vdots & & \vdots \\ \hline
\sigma_1^{(p)}\sigma_1^{(1)} & \sigma_1^{(p)}\sigma_2^{(1)} & \cdots & \sigma_1^{(p)}\sigma_t^{(1)} & \sigma_1^{(p)}\sigma_1^{(2)} & \sigma_1^{(p)}\sigma_2^{(2)} & \cdots & \sigma_1^{(p)}\sigma_t^{(2)} & \cdots & \sigma_1^{(p)}\sigma_1^{(p)} & \sigma_1^{(p)}\sigma_2^{(p)} & \cdots & \sigma_1^{(p)}\sigma_t^{(p)} \\
\sigma_2^{(p)}\sigma_1^{(1)} & \sigma_2^{(p)}\sigma_2^{(1)} & \cdots & \sigma_2^{(p)}\sigma_t^{(1)} & \sigma_2^{(p)}\sigma_1^{(2)} & \sigma_2^{(p)}\sigma_2^{(2)} & \cdots & \sigma_2^{(p)}\sigma_t^{(2)} & \cdots & \sigma_2^{(p)}\sigma_1^{(p)} & \sigma_2^{(p)}\sigma_2^{(p)} & \cdots & \sigma_2^{(p)}\sigma_t^{(p)} \\
\vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots & & \vdots & \vdots & \ddots & \vdots \\
\sigma_t^{(p)}\sigma_1^{(1)} & \sigma_t^{(p)}\sigma_2^{(1)} & \cdots & \sigma_t^{(p)}\sigma_t^{(1)} & \sigma_t^{(p)}\sigma_1^{(2)} & \sigma_t^{(p)}\sigma_2^{(2)} & \cdots & \sigma_t^{(p)}\sigma_t^{(2)} & \cdots & \sigma_t^{(p)}\sigma_1^{(p)} & \sigma_t^{(p)}\sigma_2^{(p)} & \cdots & \sigma_t^{(p)}\sigma_t^{(p)}
\end{array}\right].
$$

Note that the covariance matrix $\boldsymbol{\Sigma}_{pt\times pt}$ can be partitioned into sub-matrices $\boldsymbol{\Sigma}_{ll'}$, such that

$$\mathbf{\Sigma}_{pt\times pt}=\begin{bmatrix}\mathbf{\Sigma}_{11} & \mathbf{\Sigma}_{12} & \cdots & \mathbf{\Sigma}_{1p}\\ \mathbf{\Sigma}_{21} & \mathbf{\Sigma}_{22} & \cdots & \mathbf{\Sigma}_{2p}\\ \vdots & \vdots & \ddots & \vdots\\ \mathbf{\Sigma}_{p1} & \mathbf{\Sigma}_{p2} & \cdots & \mathbf{\Sigma}_{pp}\end{bmatrix},$$

where $\mathbf{\Sigma}_{ll'}=\left[\sigma_k^{(l)}\sigma_{k'}^{(l')}\right]$ is a $t\times t$ covariance matrix of t repeated measurements between the l^{th} and l'^{th} response variables, where $l=1,2,\ldots,p$ and $l'=1,2,\ldots,p$.

By taking the standard $vec(\cdot)$ operator that stacks the columns of a matrix $\mathbf{U}$, the $npt\times 1$ error vector $\mathbf{u}=vec(\mathbf{U})$ is obtained,

$$\mathbf{u}_{npt\times 1}=vec(\mathbf{U})\sim N_{npt}(\mathbf{0}_{npt\times 1},\mathbf{\Sigma}_{pt\times pt}\otimes\mathbf{I}_n). \tag{2.4}$$

According to the DMM in (2.2) and under the normality assumption (2.3), each row of the response matrix $\mathbf{Y}$ independently distributes as multivariate normal,

$$\mathbf{y}_{ij}\sim N_{pt}((\mathbf{I}_{pt}\otimes x_{ij})\boldsymbol{\beta}_j,\mathbf{\Sigma}_{pt\times pt}),$$

leading to

$$\mathbf{y}_{npt\times 1}=vec(\mathbf{Y}_{n\times pt})\sim N_{npt}\left((\mathbf{I}_{pt}\otimes\mathbf{X})vec(\mathbf{B}),\mathbf{\Sigma}_{pt\times pt}\otimes\mathbf{I}_n\right). \tag{2.5}$$

2.1.2 Estimation Theory

Recall the DMM $\mathbf{Y}_{n\times pt}=\mathbf{X}_{n\times g}\mathbf{B}_{g\times pt}+\mathbf{U}_{n\times pt}$ (2.2), by taking the $vec(\cdot)$ operator on both sides, we obtain

$$\begin{aligned}vec(\mathbf{Y}_{n\times pt})&=vec(\mathbf{X}_{n\times g}\mathbf{B}_{g\times pt}+\mathbf{U}_{n\times pt})\\ &=vec(\mathbf{XB})+vec(\mathbf{U})\\ &=(\mathbf{I}_{pt}\otimes\mathbf{X})vec(\mathbf{B})+vec(\mathbf{U}).\end{aligned} \tag{2.6}$$

Let $\mathbf{y}_{npt\times 1}=vec(\mathbf{Y}_{n\times pt})$, $\boldsymbol{\beta}_{gpt\times 1}=vec(\mathbf{B}_{g\times pt})$, $\mathbf{u}_{npt\times 1}=vec(\mathbf{U}_{n\times pt})$ and $\mathbf{D}_{npt\times gpt}=\mathbf{I}_{pt}\otimes\mathbf{X}_{n\times g}$, then model (2.6) can be written as

$$\mathbf{y}_{npt\times 1}=\mathbf{D}_{npt\times gpt}\boldsymbol{\beta}_{gpt\times 1}+\mathbf{u}_{npt\times 1}, \tag{2.7}$$

which is a general linear model with an unknown $\mathbf{\Sigma}_{pt\times pt}$.

Assume that $\mathbf{u}_{npt\times 1}=vec(\mathbf{U})\sim N_{n,pt}(\mathbf{0}_{npt\times 1},\mathbf{\Sigma}_{pt\times pt}\otimes\mathbf{I}_n)$, then

$$\mathbf{y}_{npt\times 1}=vec(\mathbf{Y}_{n\times pt})\sim N_{npt}\left((\mathbf{I}_{pt}\otimes\mathbf{X})vec(\mathbf{B}),\mathbf{\Sigma}_{pt\times pt}\otimes\mathbf{I}_n\right), \tag{2.8}$$

or equivalently,

$$\mathbf{y}_{npt\times 1} \sim N_{npt}\left(\mathbf{D}_{npt\times gpt}\boldsymbol{\beta}_{gpt\times 1}, \boldsymbol{\Omega}_{npt\times npt}\right), \tag{2.9}$$

where $\boldsymbol{\Omega} = \boldsymbol{\Sigma}_{pt\times pt} \otimes \mathbf{I}_n$.

To estimate $\mathbf{B}_{g\times pt}$ or $\boldsymbol{\beta}_{gpt\times 1} = vec(\mathbf{B}_{g\times pt})$, the generalized least square theorem as below.

Theorem 2.1 Let $\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$, $E(\mathbf{y}) = \mathbf{X}\boldsymbol{\beta}$, $\text{cov}(\mathbf{y}) = \sigma^2\mathbf{V}$, where $\mathbf{X}$ is a full rank matrix and $\mathbf{V}$ is a known positive definite matrix, then the BLUE of $\boldsymbol{\beta}$ is

$$\hat{\boldsymbol{\beta}} = (\mathbf{X}'\mathbf{V}^{-1}\mathbf{X}')^{-1}\mathbf{X}'\mathbf{V}^{-1}\mathbf{y} \quad \text{and} \quad \text{cov}(\hat{\boldsymbol{\beta}}) = (\mathbf{X}'\mathbf{V}^{-1}\mathbf{X}')^{-1}.$$

Proof. See Rencher (2000: 149).

Theorem 2.2 For the Doubly Multivariate Linear Model, $\mathbf{Y}_{n\times pt} = \mathbf{X}_{n\times g}\mathbf{B}_{g\times pt} + \mathbf{U}_{n\times pt}$, where $\mathbf{X}_{n\times g}$ is a matrix of $rank(\mathbf{X}) = g$, let $\mathbf{y}_{npt\times 1} = vec(\mathbf{Y}_{n\times pt})$, $\mathbf{D}_{npt\times gpt} = \mathbf{I}_{pt} \otimes \mathbf{X}_{n\times g}$, $\boldsymbol{\beta}_{gpt\times 1} = vec(\mathbf{B}_{g\times pt})$, then $E(\mathbf{y}) = \mathbf{D}\boldsymbol{\beta}$ and $\text{cov}(\mathbf{y}) = \boldsymbol{\Omega} = \boldsymbol{\Sigma}_{pt\times pt} \otimes \mathbf{I}_n$, where $\boldsymbol{\Sigma}_{pt\times pt}$ is an unknown positive definite covariance matrix.

(i) The BLUE of $\mathbf{B}$ is

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

(ii) The covariance of $\hat{\boldsymbol{\beta}} = vec(\hat{\mathbf{B}})$ is

$$\text{cov}(\hat{\boldsymbol{\beta}}) = \boldsymbol{\Sigma} \otimes (\mathbf{X}'\mathbf{X})^{-1}$$

(iii) The unbiased estimator of $tr(\boldsymbol{\Sigma})$ is

$$tr(\hat{\boldsymbol{\Sigma}}) = \frac{1}{n-g}tr[(\mathbf{Y}-\mathbf{XB})'(\mathbf{Y}-\mathbf{XB})]$$

Proof. Since the DMM $\mathbf{Y}_{n\times pt} = \mathbf{X}_{n\times g}\mathbf{B}_{g\times pt} + \mathbf{U}_{n\times pt}$ can be expressed as the general linear model (2.7), then $\mathbf{y}_{npt\times 1} = \mathbf{D}_{npt\times gpt}\boldsymbol{\beta}_{gpt\times 1} + \mathbf{u}_{npt\times 1}$, where $\mathbf{y}_{npt\times 1} = vec(\mathbf{Y}_{n\times pt})$, $\mathbf{D}_{npt\times gpt} = \mathbf{I}_{pt} \otimes \mathbf{X}_{n\times g}$, $\boldsymbol{\beta}_{gpt\times 1} = vec(\mathbf{B}_{g\times pt})$ and $\mathbf{u}_{npt\times 1} = vec(\mathbf{U}_{n\times pt})$. From model (2.7), $E(\mathbf{y}) = \mathbf{D}\boldsymbol{\beta}$ and $\text{cov}(\mathbf{y}) = \boldsymbol{\Omega} = \boldsymbol{\Sigma}_{pt\times pt} \otimes \mathbf{I}_n$, as described in (2.9).

(i) First consider that the BLUE of $\boldsymbol{\beta}_{gpt\times 1} = vec(\mathbf{B}_{g\times pt})$ if $\boldsymbol{\Omega} = \boldsymbol{\Sigma}_{pt\times pt} \otimes \mathbf{I}_n$ is known. By applying theorem 2.1 with a known $\boldsymbol{\Omega}$, the BLUE of $\boldsymbol{\beta}$ is

$$\hat{\boldsymbol{\beta}} = (\mathbf{D}'\boldsymbol{\Omega}^{-1}\mathbf{D})^{-1}\mathbf{D}'\boldsymbol{\Omega}^{-1}\mathbf{y}. \tag{2.10}$$

By substituting $\mathbf{D} = \mathbf{I}_{pt} \otimes \mathbf{X}_{n\times g}$ in (2.10), we obtain

$$\begin{aligned}
\hat{\boldsymbol{\beta}} = vec(\hat{\mathbf{B}}) &= (\mathbf{D}'\boldsymbol{\Omega}^{-1}\mathbf{D})^{-1}\mathbf{D}'\boldsymbol{\Omega}^{-1}\mathbf{y} \\
&= \left[(\mathbf{I}_{pt} \otimes \mathbf{X})'(\boldsymbol{\Sigma} \otimes \mathbf{I}_n)^{-1}(\mathbf{I}_{pt} \otimes \mathbf{X})\right]^{-1}(\mathbf{I}_{pt} \otimes \mathbf{X})'(\boldsymbol{\Sigma} \otimes \mathbf{I}_n)^{-1}\mathbf{y} \\
&= \left[(\mathbf{I}_{pt} \otimes \mathbf{X}')(\boldsymbol{\Sigma}^{-1} \otimes \mathbf{I}_n)(\mathbf{I}_{pt} \otimes \mathbf{X})\right]^{-1}(\mathbf{I}_{pt} \otimes \mathbf{X}')(\boldsymbol{\Sigma}^{-1} \otimes \mathbf{I}_n)\mathbf{y} \\
&= \left[(\mathbf{I}_{pt} \otimes \mathbf{X}')(\boldsymbol{\Sigma}^{-1} \otimes \mathbf{X})\right]^{-1}(\boldsymbol{\Sigma}^{-1} \otimes \mathbf{X}')\mathbf{y} \\
&= \left[(\boldsymbol{\Sigma}^{-1} \otimes \mathbf{X}'\mathbf{X})\right]^{-1}(\boldsymbol{\Sigma}^{-1} \otimes \mathbf{X}')\mathbf{y} \\
&= \left(\boldsymbol{\Sigma} \otimes (\mathbf{X}'\mathbf{X})^{-1}\right)\left(\boldsymbol{\Sigma}^{-1} \otimes \mathbf{X}'\right)\mathbf{y} \\
&= (\boldsymbol{\Sigma}\boldsymbol{\Sigma}^{-1} \otimes (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}')\mathbf{y} \\
&= (\mathbf{I}_{pt} \otimes (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}')\mathbf{y} \\
&= (\mathbf{I}_{pt} \otimes (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}')vec(\mathbf{Y}) \\
&= vec\left[(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}\right].
\end{aligned}$$

Hence, the BLUE of $\mathbf{B}$ is $\hat{\mathbf{B}} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}$.

When $\boldsymbol{\Omega}$ is unknown, (2.9) can be used because the estimator of $\boldsymbol{\beta}$ does not depend on $\boldsymbol{\Sigma}$, and so $\boldsymbol{\Sigma}$ drops out in the derivation of $\hat{\boldsymbol{\beta}}$.

(ii) From Theorem 2.1, the covariance matrix of $\hat{\boldsymbol{\beta}}$ is obtained as

$$\begin{aligned}
\operatorname{cov}(\hat{\boldsymbol{\beta}}) &= (\mathbf{D}'\boldsymbol{\Omega}^{-1}\mathbf{D})^{-1} \\
&= \left[(\mathbf{I}_{pt} \otimes \mathbf{X})'(\boldsymbol{\Sigma} \otimes \mathbf{I}_n)^{-1}(\mathbf{I}_{pt} \otimes \mathbf{X})\right]^{-1} \\
&= \left[(\mathbf{I}_{pt} \otimes \mathbf{X}')(\boldsymbol{\Sigma}^{-1} \otimes \mathbf{X})\right]^{-1} \\
&= \left[(\boldsymbol{\Sigma}^{-1} \otimes \mathbf{X}'\mathbf{X})\right]^{-1} \\
&= \boldsymbol{\Sigma} \otimes (\mathbf{X}'\mathbf{X})^{-1}.
\end{aligned}$$

(iii) Using the General Linear Model $\mathbf{y}_{npt\times 1} = \mathbf{D}_{npt\times gpt}\boldsymbol{\beta}_{gpt\times 1} + \mathbf{u}_{npt\times 1}$, where $E(\mathbf{y}) = \mathbf{D}\boldsymbol{\beta}$ and $\mathrm{cov}(\mathbf{y}) = \boldsymbol{\Omega} = \boldsymbol{\Sigma}_{pt\times pt} \otimes \mathbf{I}_n$, the quadratic form is firstly considered,

$$(\mathbf{y}-\mathbf{D}\hat{\boldsymbol{\beta}})'(\mathbf{y}-\mathbf{D}\hat{\boldsymbol{\beta}})$$

$$= [\mathbf{y}-(\mathbf{I}_{pt}\otimes\mathbf{X})(\mathbf{I}_{pt}\otimes(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{y})]'[\mathbf{y}-(\mathbf{I}_{pt}\otimes\mathbf{X})(\mathbf{I}_{pt}\otimes(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{y})]$$

$$= [\mathbf{y}-(\mathbf{I}_{pt}\otimes\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{y})]'[\mathbf{y}-(\mathbf{I}_{pt}\otimes\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{y})]$$

$$= \mathbf{y}'[\mathbf{I}_{npt}-(\mathbf{I}_{pt}\otimes\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}')]'[\mathbf{I}_{npt}-(\mathbf{I}_{pt}\otimes\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}')]\mathbf{y}$$

$$= \mathbf{y}'[\mathbf{I}_{npt}-(\mathbf{I}_{pt}\otimes\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}')]\mathbf{y}\,.$$

Using the expectation of the quadratic form (Rencher, 2000: 95), then

$$E[(\mathbf{y}-\mathbf{D}\hat{\boldsymbol{\beta}})'(\mathbf{y}-\mathbf{D}\hat{\boldsymbol{\beta}})] = tr\left[(\mathbf{I}_{npt}-(\mathbf{I}_{pt}\otimes\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'))(\boldsymbol{\Sigma}\otimes\mathbf{I}_n)\right]$$
$$+(\mathbf{I}_{pt}\otimes\mathbf{X})\boldsymbol{\beta})'[\mathbf{I}_{npt}-(\mathbf{I}_{pt}\otimes\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}')](\mathbf{I}_{pt}\otimes\mathbf{X})\boldsymbol{\beta}\,.$$

Since,

$$tr\left[(\mathbf{I}_{npt}-(\mathbf{I}_{pt}\otimes\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'))(\boldsymbol{\Sigma}\otimes\mathbf{I}_n)\right] = tr(\boldsymbol{\Sigma}_{pt}\otimes\mathbf{I}_n) - tr(\boldsymbol{\Sigma}_{pt}\otimes\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}')$$
$$= tr(\boldsymbol{\Sigma}_{pt})tr(\mathbf{I}_n) - tr(\boldsymbol{\Sigma}_{pt})tr(\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}')$$
$$= tr(\boldsymbol{\Sigma}_{pt})(n) - tr(\boldsymbol{\Sigma}_{pt})(g)$$
$$= (n-g)tr(\boldsymbol{\Sigma}_{pt})\,,$$

and $(\mathbf{I}_{pt}\otimes\mathbf{X})\boldsymbol{\beta})'[\mathbf{I}_{npt}-(\mathbf{I}_{pt}\otimes\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}')](\mathbf{I}_{pt}\otimes\mathbf{X})\boldsymbol{\beta}$

$$= (\mathbf{I}_{pt}\otimes\mathbf{X})\boldsymbol{\beta})'(\mathbf{I}_{pt}\otimes\mathbf{X})\boldsymbol{\beta}) - (\mathbf{I}_{pt}\otimes\mathbf{X})\boldsymbol{\beta})'(\mathbf{I}_{pt}\otimes\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}')(\mathbf{I}_{pt}\otimes\mathbf{X})\boldsymbol{\beta}$$
$$= \boldsymbol{\beta}'(\mathbf{I}_{pt}\otimes\mathbf{X}'\mathbf{X})\boldsymbol{\beta} - \boldsymbol{\beta}'(\mathbf{I}_{pt}\otimes\mathbf{X}'\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{X})\boldsymbol{\beta}$$
$$= \boldsymbol{\beta}'(\mathbf{I}_{pt}\otimes\mathbf{X}'\mathbf{X})\boldsymbol{\beta} - \boldsymbol{\beta}'(\mathbf{I}_{pt}\otimes\mathbf{X}'\mathbf{X})\boldsymbol{\beta}$$
$$= 0\,,$$

we obtain

$$\frac{1}{n-g}E[(\mathbf{y}-\mathbf{D}\hat{\boldsymbol{\beta}})'(\mathbf{y}-\mathbf{D}\hat{\boldsymbol{\beta}})] = \frac{1}{n-g}(n-g)tr(\boldsymbol{\Sigma}) = tr(\boldsymbol{\Sigma})\,.$$

Thus $(\mathbf{y}-\mathbf{D}\hat{\boldsymbol{\beta}})'(\mathbf{y}-\mathbf{D}\hat{\boldsymbol{\beta}})$ is an unbiased estimator of $tr(\boldsymbol{\Sigma})$.

Next, using the identity that $vec(\mathbf{ABC}) = (\mathbf{C}' \otimes \mathbf{A})vec(\mathbf{B})$, therefore

$$\begin{aligned}(\mathbf{y} - \mathbf{D}\boldsymbol{\beta}) &= vec(\mathbf{Y}) - (\mathbf{I}_{pt} \otimes \mathbf{X}_{n\times g})vec(\mathbf{B}) \\ &= vec(\mathbf{Y}) - vec(\mathbf{XB}) \\ &= vec(\mathbf{Y} - \mathbf{XB}),\end{aligned}$$

and subsequently

$$\begin{aligned}(\mathbf{y} - \mathbf{D}\boldsymbol{\beta})'(\mathbf{y} - \mathbf{D}\boldsymbol{\beta}) &= [vec(\mathbf{Y} - \mathbf{XB})]'[vec(\mathbf{Y} - \mathbf{XB})] \\ &= tr[(\mathbf{Y} - \mathbf{XB})'(\mathbf{Y} - \mathbf{XB})].\end{aligned}$$

Note that $tr(\mathbf{A}'\mathbf{B}) = \left[vec(\mathbf{A})\right]'\left[vec(\mathbf{B})\right]$.

Thus $tr(\hat{\boldsymbol{\Sigma}}) = \dfrac{1}{n-g} tr[(\mathbf{Y} - \mathbf{XB})'(\mathbf{Y} - \mathbf{XB})]$ is an unbiased estimator of $tr(\boldsymbol{\Sigma})$. □

Note that, using Theorem 2.2 and under the normality assumption,

$$\hat{\boldsymbol{\beta}} \sim N_{gpt}\left(vec(\mathbf{B}), \boldsymbol{\Sigma} \otimes (\mathbf{X}'\mathbf{X})^{-1}\right). \tag{2.11}$$

Theorem 2.3 For the DMM $\mathbf{Y}_{n\times pt} = \mathbf{X}_{n\times g}\mathbf{B}_{g\times pt} + \mathbf{U}_{n\times pt}$, where $\mathbf{X}$ is of full rank g and under the normality assumption (2.4), where $\boldsymbol{\Sigma}$ is a $pt \times pt$ unknown nonsingular covariance matrix, the maximum likelihood estimators (MLE) of $\mathbf{B}$ and $\boldsymbol{\Sigma}$ are

$$\hat{\mathbf{B}} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}, \tag{2.12}$$

$$\hat{\boldsymbol{\Sigma}} = \frac{(\mathbf{Y} - \mathbf{X}\hat{\mathbf{B}})'(\mathbf{Y} - \mathbf{X}\hat{\mathbf{B}})}{n}. \tag{2.13}$$

Proof. Using the general linear model (2.7) and the normality assumption (2.9) such that

$$\mathbf{y}_{npt\times 1} = \mathbf{D}_{npt\times gpt}\boldsymbol{\beta}_{gpt\times 1} + \mathbf{u}_{npt\times 1},$$

assume that

$$\mathbf{y} \sim N_{npt}\left(\mathbf{D}\boldsymbol{\beta}, \boldsymbol{\Omega}\right),$$

where $\mathbf{y} = vec(\mathbf{Y})$, $\boldsymbol{\beta} = vec(\mathbf{B})$, $\mathbf{u} = vec(\mathbf{U})$, $\mathbf{D} = \mathbf{I}_{pt} \otimes \mathbf{X}_{n\times g}$ and $\boldsymbol{\Omega} = \boldsymbol{\Sigma} \otimes \mathbf{I}_n$, then the density of $\mathbf{y} = vec(\mathbf{Y})$ is

$$(2\pi)^{-npt/2}\left|\boldsymbol{\Omega}\right|^{-1/2}\exp\left[-\frac{1}{2}(\mathbf{y} - \mathbf{D}\boldsymbol{\beta})'\boldsymbol{\Omega}^{-1}(\mathbf{y} - \mathbf{D}\boldsymbol{\beta})\right]. \tag{2.14}$$

While (2.13) may be used to find the maximum likelihood estimators of $\boldsymbol{\beta}$ and $\boldsymbol{\Omega}$, and hence $\boldsymbol{\Sigma}$, it is convenient to use a matrix normal distribution for the response matrix $\mathbf{Y}_{n\times pt}$. By using a simplification of (2.13), first observe that

$$\left|\boldsymbol{\Omega}\right|^{-1/2} = \left|\boldsymbol{\Sigma}\otimes\mathbf{I}_n\right|^{-1/2} = \left|\boldsymbol{\Sigma}\right|^{-n/2}\left|\mathbf{I}_n\right|^{-pt/2} = \left|\boldsymbol{\Sigma}\right|^{-n/2} \tag{2.15}$$

(using the identity that $\left|\mathbf{A}_m\otimes\mathbf{B}_n\right| = \left|\mathbf{A}\right|^n\left|\mathbf{B}\right|^m$).

Since $(\mathbf{y}-\mathbf{D}\boldsymbol{\beta}) = vec(\mathbf{Y}-\mathbf{XB})$, the component of (2.13) can be written in the form

$$\begin{aligned}(\mathbf{y}-\mathbf{D}\boldsymbol{\beta})'\boldsymbol{\Omega}^{-1}(\mathbf{y}-\mathbf{D}\boldsymbol{\beta}) &= [vec(\mathbf{Y}-\mathbf{XB})]'(\boldsymbol{\Sigma}\otimes\mathbf{I}_n)^{-1}[vec(\mathbf{Y}-\mathbf{XB})]\\ &= [vec(\mathbf{Y}-\mathbf{XB})]'[vec(\mathbf{Y}-\mathbf{XB})]\boldsymbol{\Sigma}^{-1}\\ &= tr[(\mathbf{Y}-\mathbf{XB})'(\mathbf{Y}-\mathbf{XB})\boldsymbol{\Sigma}^{-1}]\\ &= tr[\boldsymbol{\Sigma}^{-1}(\mathbf{Y}-\mathbf{XB})'(\mathbf{Y}-\mathbf{XB})]\ .\end{aligned} \tag{2.16}$$

By substituting (2.15) and (2.16) into (2.14), the matrix form of the multivariate normal distribution for $\mathbf{Y}_{n\times pt}$ is

$$L(\mathbf{Y}) = (2\pi)^{-npt/2}\left|\boldsymbol{\Sigma}\right|^{-n/2} etr\left[-\frac{1}{2}\boldsymbol{\Sigma}^{-1}(\mathbf{Y}-\mathbf{XB})'(\mathbf{Y}-\mathbf{XB})\right], \tag{2.17}$$

then

$$\ln L(\mathbf{Y}) = -npt\ln 2\pi + \frac{n}{2}\ln\left|\boldsymbol{\Sigma}^{-1}\right| + tr\left[-\frac{1}{2}\boldsymbol{\Sigma}^{-1}(\mathbf{Y}-\mathbf{XB})'(\mathbf{Y}-\mathbf{XB})\right].$$

By differentiating $\ln L(\mathbf{Y})$ with respect to $\mathbf{B}$, we obtain

$$\begin{aligned}\frac{\partial}{\partial\mathbf{B}}\ln L(\mathbf{Y}) &= \frac{\partial}{\partial\mathbf{B}}tr\left[-\frac{1}{2}\boldsymbol{\Sigma}^{-1}(\mathbf{Y}-\mathbf{XB})'(\mathbf{Y}-\mathbf{XB})\right]\\ &= \frac{\partial}{\partial\mathbf{B}}tr\left[-\frac{1}{2}\boldsymbol{\Sigma}^{-1}(\mathbf{Y}'\mathbf{Y}-\mathbf{B}'\mathbf{X}'\mathbf{Y}-\mathbf{Y}'\mathbf{XB}+2\mathbf{B}'\mathbf{X}'\mathbf{XB})\right]\\ &= -\frac{1}{2}\boldsymbol{\Sigma}^{-1}(-2\mathbf{X}'\mathbf{Y}+2\mathbf{X}'\mathbf{XB})\\ &= \mathbf{0}_{pt\times pt}\end{aligned}$$

(note that $\frac{\partial}{\partial\mathbf{X}}tr(\mathbf{AX}) = \frac{\partial}{\partial\mathbf{X}}tr(\mathbf{AX})' = \mathbf{A}'$, and $\frac{\partial}{\partial\mathbf{X}}tr(\mathbf{A}'\mathbf{X}'\mathbf{XA}) = 2\mathbf{X}'\mathbf{XA}$).

Subsequently, the first normal equation is obtained;

$$\mathbf{\Sigma}^{-1}(\mathbf{X}'\mathbf{Y}+\mathbf{X}'\mathbf{X}\mathbf{B})=0$$

$$\mathbf{X}'\mathbf{X}\mathbf{B}=\mathbf{X}'\mathbf{Y}$$

$$\hat{\mathbf{B}}=(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}.$$

Since $\mathbf{\Sigma}$ and $\mathbf{\Sigma}^{-1}$ have a one-to-one correspondence, i.e. each covariance matrix $\mathbf{\Sigma}$ can be matched to each of its inverse matrices, maximization with respect to $\mathbf{\Sigma}^{-1}$ is the same as maximization with respect to $\mathbf{\Sigma}$. It is also more convenient to take the derivative of $\ln L(\mathbf{Y})$ with respect to $\mathbf{\Sigma}^{-1}$.

It can be shown that (Muller and Stewart, 2006: 251), if $\mathbf{A}$ is symmetric and nonsingular, then

$$\frac{\partial}{\partial \mathbf{A}}\ln\left|\mathbf{A}\right|=2\mathbf{A}^{-1}-diag(\mathbf{A}^{-1}),$$

and if $\mathbf{X}$ is symmetric and $\mathbf{A}$ is fixed, then

$$\frac{\partial}{\partial \mathbf{X}}\mathbf{A}'\mathbf{X}\mathbf{A}=2\mathbf{A}'\mathbf{A}-diag(\mathbf{A}'\mathbf{A}).$$

The differentiation of $\ln L(\mathbf{Y})$ with respect to $\mathbf{\Sigma}^{-1}$ can be expressed as

$$\frac{\partial}{\partial \mathbf{\Sigma}^{-1}}\ln L(\mathbf{Y})=\frac{\partial}{\partial \mathbf{\Sigma}^{-1}}\left[\frac{n}{2}\ln\left|\mathbf{\Sigma}^{-1}\right|\right]-\frac{1}{2}tr\left[\frac{\partial}{\partial \mathbf{\Sigma}^{-1}}\mathbf{\Sigma}^{-1}(\mathbf{Y}-\mathbf{X}\mathbf{B})'(\mathbf{Y}-\mathbf{X}\mathbf{B})\right]$$

$$=\frac{n}{2}\left[2\mathbf{\Sigma}-diag(\mathbf{\Sigma})\right]-\frac{1}{2}tr\left\{2(\mathbf{Y}-\mathbf{X}\mathbf{B})'(\mathbf{Y}-\mathbf{X}\mathbf{B})-diag\left[(\mathbf{Y}-\mathbf{X}\mathbf{B})'(\mathbf{Y}-\mathbf{X}\mathbf{B})\right]\right\}$$

$$=\frac{n}{2}\left[2\mathbf{\Sigma}-diag(\mathbf{\Sigma})\right]-\frac{1}{2}\left\{2(\mathbf{Y}-\mathbf{X}\mathbf{B})'(\mathbf{Y}-\mathbf{X}\mathbf{B})-diag\left[(\mathbf{Y}-\mathbf{X}\mathbf{B})'(\mathbf{Y}-\mathbf{X}\mathbf{B})\right]\right\}$$

$$=\mathbf{0}_{pt\times pt}.$$

After this, the second normal equation is obtained;

$$\frac{n}{2}\left[2\mathbf{\Sigma}-diag(\mathbf{\Sigma})\right]=\frac{1}{2}\left\{2(\mathbf{Y}-\mathbf{X}\mathbf{B})'(\mathbf{Y}-\mathbf{X}\mathbf{B})-diag\left[(\mathbf{Y}-\mathbf{X}\mathbf{B})'(\mathbf{Y}-\mathbf{X}\mathbf{B})\right]\right\}$$

$$2\mathbf{\Sigma}-diag(\mathbf{\Sigma})=2\left[\frac{(\mathbf{Y}-\mathbf{X}\mathbf{B})'(\mathbf{Y}-\mathbf{X}\mathbf{B})}{n}\right]-diag\left[\frac{(\mathbf{Y}-\mathbf{X}\mathbf{B})'(\mathbf{Y}-\mathbf{X}\mathbf{B})}{n}\right].$$

Hence,

$$\hat{\mathbf{\Sigma}}=\frac{(\mathbf{Y}-\mathbf{X}\mathbf{B})'(\mathbf{Y}-\mathbf{X}\mathbf{B})}{n}.\qquad\square$$

2.1.3 The Multivariate General Linear Hypothesis

For the analysis of the Multivariate Repeated Measurements Design using DMM, the three multivariate hypotheses of interest are:

H_{01} : The p-variate profiles for the g groups are parallel

H_{02} : There are no p-variate differences among the g groups

H_{03} : There are no p-variate differences among the t times

To test these three hypotheses of group differences (the effect of the group factor), time differences (the effect of the time factor) and parallelism of the profiles (the effect of interaction between the group and time factors) of p-variate responses, the multivariate general linear hypothesis can be formulated in the form

$$H : \mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{\Gamma}_0, \tag{2.18}$$

where $\mathbf{C}$ is a $v_h \times g$ between group contrast matrix having $rank(\mathbf{C}) = v_h \le g$ and $\mathbf{A}$ is a $t \times u$ within subject contrast matrix having $rank(\mathbf{A}) = u \le t$. Without loss of generality, it may be assumed that $\mathbf{A}'\mathbf{A} = \mathbf{I}_u$.

The $\mathbf{C}$ matrix defines contrasts between groups or levels of predictors by computing linear combinations of coefficients of predictor variables, such as the mean. The $\mathbf{C}$ matrix implicitly computes and explicitly allows the testing of linear combinations of the columns of $\mathbf{X}$, the predictor variables.

The $\mathbf{A}$ matrix defines contrasts within levels of the response variables (times) by computing linear combinations of coefficients of response variables, again such as the mean. The $\mathbf{A}$ matrix implicitly computes and explicitly allows testing linear combinations of the columns of $\mathbf{Y}$, the response variable in the model $\mathbf{Y} = \mathbf{XB} + \mathbf{U}$.

To test H_{01}, the parallelism or interaction factor between group and time, the hypothesis is stated as

$$H_{01} : \left[\begin{array}{c:c:c} \mu_{11}^{(1)} - \mu_{12}^{(1)} & \cdots & \mu_{11}^{(p)} - \mu_{12}^{(p)} \\ \mu_{12}^{(1)} - \mu_{13}^{(1)} & \cdots & \mu_{12}^{(p)} - \mu_{13}^{(p)} \\ \vdots & \cdots & \vdots \\ \mu_{1(t-1)}^{(1)} - \mu_{1t}^{(1)} & \cdots & \mu_{1(t-1)}^{(p)} - \mu_{1t}^{(p)} \end{array}\right] = \cdots = \left[\begin{array}{c:c:c} \mu_{g1}^{(1)} - \mu_{g2}^{(1)} & \cdots & \mu_{g1}^{(p)} - \mu_{g2}^{(p)} \\ \mu_{g2}^{(1)} - \mu_{g3}^{(1)} & \cdots & \mu_{g2}^{(p)} - \mu_{g3}^{(p)} \\ \vdots & \cdots & \vdots \\ \mu_{g(t-1)}^{(1)} - \mu_{gt}^{(1)} & \cdots & \mu_{g(t-1)}^{(p)} - \mu_{gt}^{(p)} \end{array}\right].$$

Equivalently, by representing H_{01} in terms of the elements of $\mathbf{B}$ as $H_{01} : \mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{\Gamma}_0$, the matrices $\mathbf{C}$, $\mathbf{A}$ and $\mathbf{\Gamma}_0$ are taken in the form

$$\mathbf{C}_{(g-1)\times g} = \left[\begin{array}{cccc:c} 1 & 0 & \dots & 0 & -1 \\ 0 & 1 & \dots & 0 & -1 \\ \vdots & \vdots & \ddots & \vdots & -1 \\ 0 & 0 & \dots & 1 & -1 \end{array}\right],\ \mathbf{A}_{t\times(t-1)} = \begin{bmatrix} 1 & 0 & \dots & 0 \\ -1 & 1 & \dots & 0 \\ 0 & -1 & \dots & 0 \\ \vdots & \vdots & \ddots & 0 \\ 0 & 0 & \dots & 1 \\ 0 & 0 & \dots & -1 \end{bmatrix} \text{ and } \boldsymbol{\Gamma}_0 = \mathbf{0}_{(g-1)\times p(t-1)}.$$

Subsequently,

$$H_{01} : \left[\boldsymbol{\Gamma}_1 \mid \boldsymbol{\Gamma}_2 \mid \dots \mid \boldsymbol{\Gamma}_p\right] = \mathbf{0}_{(g-1)\times p(t-1)},$$

where $\boldsymbol{\Gamma}_l$ is a $(g-1)\times(t-1)$ sub-matrix of $\boldsymbol{\Gamma} = \mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A})$ for each l^{th} variable, for $l = 1, 2, \dots, p$, such that

$$\boldsymbol{\Gamma}_l = \begin{bmatrix} (\mu_{11}^{(l)} - \mu_{12}^{(l)}) - (\mu_{g1}^{(1)} - \mu_{g2}^{(1)}) & (\mu_{12}^{(l)} - \mu_{13}^{(l)}) - (\mu_{g2}^{(l)} - \mu_{g3}^{(l)}) & \dots & (\mu_{1(t-1)}^{(l)} - \mu_{1t}^{(l)}) - (\mu_{g(t-1)}^{(l)} - \mu_{gt}^{(l)}) \\ (\mu_{21}^{(l)} - \mu_{22}^{(l)}) - (\mu_{g1}^{(l)} - \mu_{g2}^{(1)}) & (\mu_{22}^{(l)} - \mu_{23}^{(l)}) - (\mu_{g2}^{(l)} - \mu_{g3}^{(l)}) & \dots & (\mu_{2(t-1)}^{(l)} - \mu_{2t}^{(l)}) - (\mu_{g(t-1)}^{(l)} - \mu_{gt}^{(l)}) \\ \vdots & \vdots & \dots & \vdots \\ (\mu_{(g-1)1}^{(l)} - \mu_{(g-1)2}^{(l)}) - (\mu_{g1}^{(l)} - \mu_{g2}^{(l)}) & (\mu_{(g-1)2}^{(l)} - \mu_{(g-1)3}^{(l)}) - (\mu_{g2}^{(l)} - \mu_{g3}^{(l)}) & \dots & (\mu_{(g-1)(t-1)}^{(l)} - \mu_{(g-1)t}^{(l)}) - (\mu_{g(t-1)}^{(l)} - \mu_{gt}^{(l)}) \end{bmatrix}.$$

To test H_{02}, the differences in group mean vectors, the hypothesis is stated as

$$H_{02} : \begin{bmatrix} \mu_{11}^{(1)} & \mu_{11}^{(2)} & \dots & \mu_{11}^{(p)} \\ \mu_{12}^{(1)} & \mu_{12}^{(2)} & \dots & \mu_{12}^{(p)} \\ \vdots & \vdots & \dots & \vdots \\ \mu_{1t}^{(1)} & \mu_{1t}^{(2)} & \dots & \mu_{1t}^{(p)} \end{bmatrix} = \begin{bmatrix} \mu_{21}^{(1)} & \mu_{21}^{(2)} & \dots & \mu_{21}^{(p)} \\ \mu_{22}^{(1)} & \mu_{22}^{(2)} & \dots & \mu_{22}^{(p)} \\ \vdots & \vdots & \dots & \vdots \\ \mu_{2t}^{(1)} & \mu_{2t}^{(2)} & \dots & \mu_{2t}^{(p)} \end{bmatrix} = \dots = \begin{bmatrix} \mu_{g1}^{(1)} & \mu_{g1}^{(2)} & \dots & \mu_{g1}^{(p)} \\ \mu_{g2}^{(1)} & \mu_{g2}^{(2)} & \dots & \mu_{g2}^{(p)} \\ \vdots & \vdots & \dots & \vdots \\ \mu_{gt}^{(1)} & \mu_{gt}^{(2)} & \dots & \mu_{gt}^{(p)} \end{bmatrix}.$$

Equivalently, by representing it as $H_{02} : \mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A}) = \boldsymbol{\Gamma}_0$, the matrices $\mathbf{C}$, $\mathbf{A}$ and $\boldsymbol{\Gamma}_0$ are

$$\mathbf{C}_{(g-1)\times g} = \left[\begin{array}{cccc:c} 1 & 0 & \dots & 0 & -1 \\ 0 & 1 & \dots & 0 & -1 \\ \vdots & \vdots & \ddots & \vdots & -1 \\ 0 & 0 & \dots & 1 & -1 \end{array}\right],\ \mathbf{A} = \mathbf{I}_t \text{ and } \boldsymbol{\Gamma}_0 = \mathbf{0}_{(g-1)\times pt}, \text{ leading to}$$

$$H_{02} : \left[\begin{array}{ccc:c:ccc} \mu_{11}^{(1)} - \mu_{g1}^{(1)} & \dots & \mu_{1t}^{(1)} - \mu_{gt}^{(1)} & \dots & \mu_{11}^{(p)} - \mu_{g1}^{(p)} & \dots & \mu_{1t}^{(p)} - \mu_{gt}^{(p)} \\ \mu_{21}^{(1)} - \mu_{g1}^{(1)} & \dots & \mu_{2t}^{(1)} - \mu_{gt}^{(1)} & \dots & \mu_{21}^{(p)} - \mu_{g1}^{(p)} & \dots & \mu_{2t}^{(p)} - \mu_{gt}^{(p)} \\ \vdots & \dots & \vdots & \dots & \vdots & \dots & \vdots \\ \mu_{(g-1)1}^{(l)} - \mu_{g1}^{(1)} & \dots & \mu_{(g-1)t}^{(1)} - \mu_{gt}^{(1)} & \dots & \mu_{(g-1)1}^{(p)} - \mu_{g1}^{(p)} & \dots & \mu_{(g-1)t}^{(p)} - \mu_{gt}^{(p)} \end{array}\right] = \mathbf{0}_{(g-1)\times p}.$$

To test H_{03}, the differences in time, the hypothesis is stated as

$$H_{03}:\begin{bmatrix} \mu_{11}^{(1)} & \mu_{11}^{(2)} & \cdots & \mu_{11}^{(p)} \\ \mu_{21}^{(1)} & \mu_{21}^{(2)} & \cdots & \mu_{21}^{(p)} \\ \vdots & \vdots & \cdots & \vdots \\ \mu_{g1}^{(1)} & \mu_{g1}^{(2)} & \cdots & \mu_{g1}^{(p)} \end{bmatrix} = \begin{bmatrix} \mu_{12}^{(1)} & \mu_{12}^{(2)} & \cdots & \mu_{12}^{(p)} \\ \mu_{22}^{(1)} & \mu_{22}^{(2)} & \cdots & \mu_{22}^{(p)} \\ \vdots & \vdots & \cdots & \vdots \\ \mu_{g2}^{(1)} & \mu_{g2}^{(2)} & \cdots & \mu_{g2}^{(p)} \end{bmatrix} = \cdots = \begin{bmatrix} \mu_{1t}^{(1)} & \mu_{1t}^{(2)} & \cdots & \mu_{1t}^{(p)} \\ \mu_{2t}^{(1)} & \mu_{2t}^{(2)} & \cdots & \mu_{2t}^{(p)} \\ \vdots & \vdots & \cdots & \vdots \\ \mu_{gt}^{(1)} & \mu_{gt}^{(2)} & \cdots & \mu_{gt}^{(p)} \end{bmatrix}.$$

Equivalently, by representing it as $H_{03}:\mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{\Gamma}_0$, the matrices $\mathbf{C}$, $\mathbf{A}$ and $\mathbf{\Gamma}_0$ are

$$\mathbf{C} = \mathbf{I}_g,\ \mathbf{A}_{t\times(t-1)} = \begin{bmatrix} 1 & 0 & \cdots & 0 \\ 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \cdots & \vdots \\ 0 & 0 & \cdots & 1 \\ \hline -1 & -1 & \cdots & -1 \end{bmatrix} = \begin{bmatrix} \mathbf{I}_{(t-1)} \\ \hline -\mathbf{1}'_{1\times(t-1)} \end{bmatrix},\ \text{and}\ \mathbf{\Gamma}_0 = \mathbf{0}_{g\times p(t-1)},$$

then

$$H_{03}:\left[\begin{array}{ccc|c|ccc} \mu_{11}^{(1)}-\mu_{1t}^{(1)} & \cdots & \mu_{1(t-1)}^{(1)}-\mu_{1t}^{(1)} & \cdots & \mu_{11}^{(p)}-\mu_{1t}^{(p)} & \cdots & \mu_{1(t-1)}^{(p)}-\mu_{1t}^{(p)} \\ \mu_{21}^{(1)}-\mu_{2t}^{(1)} & \cdots & \mu_{1(t-1)}^{(1)}-\mu_{1t}^{(1)} & \cdots & \mu_{21}^{(p)}-\mu_{2t}^{(p)} & \cdots & \mu_{2(t-1)}^{(p)}-\mu_{2t}^{(p)} \\ \vdots & \cdots & \vdots & \cdots & \vdots & \cdots & \vdots \\ \mu_{g1}^{(1)}-\mu_{gt}^{(1)} & \cdots & \mu_{1(t-1)}^{(1)}-\mu_{1t}^{(1)} & \cdots & \mu_{g1}^{(p)}-\mu_{gt}^{(p)} & \cdots & \mu_{g(t-1)}^{(p)}-\mu_{gt}^{(p)} \end{array}\right] = \mathbf{0}_{g\times p(t-1)}.$$

Alternatively, by selecting the with-subject contrast matrix $\mathbf{A}$ such that $\mathbf{A}'\mathbf{A} = \mathbf{I}_u$, the three hypotheses are stated as follows.

To test the group × time interaction effect, the matrices $\mathbf{C}$, $\mathbf{\Gamma}_0$ and $\mathbf{A}$ are taken in the form

$$\mathbf{C}_{(g-1)\times g} = \left[\begin{array}{cccc|c} 1 & 0 & \cdots & 0 & -1 \\ 0 & 1 & \cdots & 0 & -1 \\ \vdots & \vdots & \ddots & \vdots & -1 \\ 0 & 0 & \cdots & 1 & -1 \end{array}\right],\ \mathbf{\Gamma}_0 = \mathbf{0}_{(g-1)\times p(t-1)}\ \text{and}$$

the orthogonal matrices $\mathbf{A}_{t\times(t-1)}$, for t = 2, 3 and 4, are respectively

$$\mathbf{A}_{2\times1} = \begin{bmatrix} 1/\sqrt{2} \\ -1/\sqrt{2} \end{bmatrix},\ \mathbf{A}_{3\times2} = \begin{bmatrix} 1/\sqrt{2} & -1/\sqrt{6} \\ 0 & 2/\sqrt{6} \\ -1/\sqrt{2} & -1/\sqrt{6} \end{bmatrix},\ \mathbf{A}_{4\times3} = \begin{bmatrix} 1/\sqrt{2} & -1/\sqrt{6} & -1/\sqrt{12} \\ 0 & 2/\sqrt{6} & -1/\sqrt{12} \\ -1/\sqrt{2} & -1/\sqrt{6} & -1/\sqrt{12} \\ 0 & 0 & 3/\sqrt{12} \end{bmatrix}.$$

For example, if $t=3$, the following hypothesis is obtained;

$$H_{01}:\left[\boldsymbol{\Gamma}^{(1)} \;\vdots\; \boldsymbol{\Gamma}^{(2)} \;\vdots\; \ldots \;\vdots\; \boldsymbol{\Gamma}^{(p)}\right]=\mathbf{0}_{(g-1)\times 2p},$$

where $\boldsymbol{\Gamma}_l$ is a $(g-1)\times 2$ sub-matrix of $\boldsymbol{\Gamma}=\mathbf{CB}(\mathbf{I}_p\otimes\mathbf{A})$ for each l^{th} variable such that

$$\boldsymbol{\Gamma}_l=\begin{bmatrix} \dfrac{(\mu_{11}^{(l)}-\mu_{13}^{(l)})-(\mu_{g1}^{(l)}-\mu_{g3}^{(l)})}{\sqrt{2}} & \dfrac{(-\mu_{11}^{(l)}+2\mu_{12}^{(l)}-\mu_{13}^{(l)})-(-\mu_{g1}^{(l)}+2\mu_{g2}^{(l)}-\mu_{g3}^{(l)})}{\sqrt{6}} \\ \dfrac{(\mu_{21}^{(l)}-\mu_{23}^{(l)})-(\mu_{g1}^{(l)}-\mu_{g3}^{(l)})}{\sqrt{2}} & \dfrac{(-\mu_{21}^{(l)}+2\mu_{22}^{(l)}-\mu_{23}^{(l)})-(-\mu_{g1}^{(l)}+2\mu_{g2}^{(l)}-\mu_{g3}^{(l)})}{\sqrt{6}} \\ \vdots & \vdots \\ \dfrac{(\mu_{(g-1)1}^{(l)}-\mu_{g3}^{(l)})-(\mu_{(g-1)1}^{(l)}-\mu_{g3}^{(l)})}{\sqrt{2}} & \dfrac{(-\mu_{(g-1)1}^{(l)}+2\mu_{(g-1)2}^{(l)}-\mu_{(g-1)3}^{(l)})-(-\mu_{g1}^{(l)}+2\mu_{g2}^{(l)}-\mu_{g3}^{(l)})}{\sqrt{6}} \end{bmatrix},$$

for $l=1,2,\ldots,p$.

To test the H_{02}, differences in the group means (averaged over time), the matrices $\mathbf{C}$, $\mathbf{A}$ and $\boldsymbol{\Gamma}_0$ are given by

$$\mathbf{C}_{(g-1)\times g}=\left[\begin{array}{cccc|c} 1 & 0 & \ldots & 0 & -1 \\ 0 & 1 & \ldots & 0 & -1 \\ \vdots & \vdots & \ddots & \vdots & -1 \\ 0 & 0 & \ldots & 1 & -1 \end{array}\right],\ \mathbf{A}_{t\times 1}=\begin{bmatrix} 1/\sqrt{t} \\ 1/\sqrt{t} \\ \vdots \\ 1/\sqrt{t} \end{bmatrix} \text{ and } \boldsymbol{\Gamma}_0=\mathbf{0}_{(g-1)\times p}.$$

Using the matrices $\mathbf{C}$, $\mathbf{A}$ and $\boldsymbol{\Gamma}_0$, it is possible to obtain the hypothesis

$$H_{02}:\begin{bmatrix} \dfrac{\sum_{k=1}^{t}\mu_{1k}^{(1)}}{\sqrt{t}}-\dfrac{\sum_{k=1}^{t}\mu_{gk}^{(1)}}{\sqrt{t}} & \dfrac{\sum_{k=1}^{t}\mu_{1k}^{(2)}}{\sqrt{t}}-\dfrac{\sum_{k=1}^{t}\mu_{gk}^{(2)}}{\sqrt{t}} & \ldots & \dfrac{\sum_{k=1}^{t}\mu_{1k}^{(p)}}{\sqrt{t}}-\dfrac{\sum_{k=1}^{t}\mu_{gk}^{(p)}}{\sqrt{t}} \\ \dfrac{\sum_{k=1}^{t}\mu_{2k}^{(1)}}{\sqrt{t}}-\dfrac{\sum_{k=1}^{t}\mu_{gk}^{(1)}}{\sqrt{t}} & \dfrac{\sum_{k=1}^{t}\mu_{2k}^{(2)}}{\sqrt{t}}-\dfrac{\sum_{k=1}^{t}\mu_{gk}^{(2)}}{\sqrt{t}} & \ldots & \dfrac{\sum_{k=1}^{t}\mu_{2k}^{(p)}}{\sqrt{t}}-\dfrac{\sum_{k=1}^{t}\mu_{gk}^{(p)}}{\sqrt{t}} \\ \vdots & \vdots & \ldots & \vdots \\ \dfrac{\sum_{k=1}^{t}\mu_{(g-1)k}^{(1)}}{\sqrt{t}}-\dfrac{\sum_{k=1}^{t}\mu_{gk}^{(1)}}{\sqrt{t}} & \dfrac{\sum_{k=1}^{t}\mu_{(g-1)k}^{(2)}}{\sqrt{t}}-\dfrac{\sum_{k=1}^{t}\mu_{gk}^{(2)}}{\sqrt{t}} & \ldots & \dfrac{\sum_{k=1}^{t}\mu_{(g-1)k}^{(p)}}{\sqrt{t}}-\dfrac{\sum_{k=1}^{t}\mu_{gk}^{(p)}}{\sqrt{t}} \end{bmatrix}=\mathbf{0}_{(g-1)\times p}.$$

To test H_{03}, differences in the time means (averaged over group) , the matrices $\mathbf{C}$ and $\mathbf{\Gamma}_0$ are taken as

$$\mathbf{C} = \begin{bmatrix} \frac{1}{g} & \frac{1}{g} & \dots & \frac{1}{g} \end{bmatrix} \text{ for equal number of subjects in each group,}$$

$$\mathbf{C} = \begin{bmatrix} \frac{n_1}{n} & \frac{n_2}{n} & \dots & \frac{n_g}{n} \end{bmatrix} \text{ for unequal number of subjects in each group,}$$

$\mathbf{\Gamma}_0 = [0]_{1\times p(t-1)}$ and the orthogonal matrices $\mathbf{A}_{t\times(t-1)}$, for t = 2, 3 and 4, are respectively

$$\mathbf{A}_{2\times1} = \begin{bmatrix} 1/\sqrt{2} \\ -1/\sqrt{2} \end{bmatrix},\ \mathbf{A}_{3\times2} = \begin{bmatrix} 1/\sqrt{2} & -1/\sqrt{6} \\ 0 & 2/\sqrt{6} \\ -1/\sqrt{2} & -1/\sqrt{6} \end{bmatrix},\ \mathbf{A}_{4\times3} = \begin{bmatrix} 1/\sqrt{2} & -1/\sqrt{6} & -1/\sqrt{12} \\ 0 & 2/\sqrt{6} & -1/\sqrt{12} \\ -1/\sqrt{2} & -1/\sqrt{6} & -1/\sqrt{12} \\ 0 & 0 & 3/\sqrt{12} \end{bmatrix}.$$

For example, if $t = 3$, the following hypothesis is obtained;

$$H_{03} : \left[\mathbf{\Gamma}^{(1)} \mid \mathbf{\Gamma}^{(2)} \mid \dots \mid \mathbf{\Gamma}^{(p)}\right] = \mathbf{0}_{(g-1)\times 2p},$$

where $\mathbf{\Gamma}_l$ is a 1×2 sub-matrix of $\mathbf{\Gamma} = \mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A})$ for each l^{th} variable, $l = 1,2,\dots,p$.

If the number of subjects in each group are equal, then

$$\underset{(1\times2)}{\mathbf{\Gamma}_l} = \begin{bmatrix} \dfrac{\sum_{j=1}^{g}(\mu_{j1}^{(l)} - \mu_{j3}^{(l)})}{g\sqrt{2}} & \dfrac{\sum_{j=1}^{g}(-\mu_{j1}^{(l)} + 2\mu_{12}^{(l)} - \mu_{j3}^{(l)})}{g\sqrt{6}} \end{bmatrix}.$$

If there are an unequal number of subjects in each group, then

$$\underset{(1\times2)}{\mathbf{\Gamma}_l} = \begin{bmatrix} \dfrac{\sum_{j=1}^{g} n_j(\mu_{j1}^{(l)} - \mu_{j3}^{(l)})}{n\sqrt{2}} & \dfrac{\sum_{j=1}^{g} n_j(-\mu_{j1}^{(l)} + 2\mu_{12}^{(l)} - \mu_{j3}^{(l)})}{n\sqrt{6}} \end{bmatrix}.$$

2.1.4 Classical Test Statistics

To analyze contrasts among the t time periods of p-variate responses, $pt \times pu$, the post matrix $\mathbf{M} = \mathbf{I}_p \otimes \mathbf{A}$, $rank(\mathbf{M}) = pu \le pt$, is multiplied into DMM (2.2) to obtain a reduced model

$$\mathbf{Y}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{XB}(\mathbf{I}_p \otimes \mathbf{A}) + \mathbf{U}(\mathbf{I}_p \otimes \mathbf{A}),$$
$$\mathbf{YM} = \mathbf{XBM} + \mathbf{UM},$$
$$\mathbf{Y}_M = \mathbf{XB}_M + \mathbf{U}_M, \tag{2.19}$$

where $\mathbf{Y}_M = \mathbf{Y}(\mathbf{I}_p \otimes \mathbf{A})$, $\mathbf{B}_M = \mathbf{B}(\mathbf{I}_p \otimes \mathbf{A})$ and $\mathbf{U}_M = \mathbf{U}(\mathbf{I}_p \otimes \mathbf{A})$.

Using the $vec(.)$ operator into model (2.19), we obtain

$$\begin{aligned} vec(\mathbf{Y}_M) &= vec(\mathbf{XB}_M) + vec(\mathbf{U}_M) \\ &= (\mathbf{I}_{pu} \otimes \mathbf{X}')vec(\mathbf{B}_M) + vec(\mathbf{U}_M). \end{aligned} \tag{2.20}$$

Let $\mathbf{y}_M = vec(\mathbf{Y}_M)$, $\boldsymbol{\beta}_M = vec(\mathbf{B}_M)$, $\mathbf{u}_M = vec(\mathbf{U}_M)$ and $\mathbf{X}_M = \mathbf{I}_{pu} \otimes \mathbf{X}_{n\times g}$, then model (2.20) can be written as

$$\underset{(npu\times 1)}{\mathbf{y}_M} = \underset{(npu\times gpu)}{\mathbf{X}_M}\ \underset{(gpu\times 1)}{\boldsymbol{\beta}_M} + \underset{(npu\times 1)}{\mathbf{u}_M}. \tag{2.21}$$

Recall assumption (2.5) that $\mathbf{y} = vec(\mathbf{Y}) \sim N_{npt}\left((\mathbf{I}_{pt} \otimes \mathbf{X})vec(\mathbf{B}), \boldsymbol{\Sigma}_{pt\times pt} \otimes \mathbf{I}_n\right)$, then from model (2.20), we obtain

$$\mathbf{y}_M = vec(\mathbf{Y}_M) \sim N_{npu}\left((\mathbf{I}_{pu} \otimes \mathbf{X})vec(\mathbf{B}_M), \boldsymbol{\Phi}_{pu\times pu} \otimes \mathbf{I}_n\right), \tag{2.22}$$

where
$$\boldsymbol{\Phi}_{pu\times pu} = (\mathbf{I}_p \otimes \mathbf{A})'\boldsymbol{\Sigma}_{pt\times pt}(\mathbf{I}_p \otimes \mathbf{A}). \tag{2.23}$$

Using the notation of model (2.21), we obtain

$$\mathbf{y}_M \sim N_{npu}\left(\mathbf{X}_M\boldsymbol{\beta}_M, \boldsymbol{\Phi} \otimes \mathbf{I}_n\right). \tag{2.24}$$

Thus the reduced model (2.21) of $\mathbf{y}_M$ is a generalized linear model with covariance matrix $\boldsymbol{\Phi} \otimes \mathbf{I}_n$.

To test multivariate linear hypothesis (2.18), let $\boldsymbol{\Gamma} = \mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{CB}_M$ be a $v_h \times pu$ matrix of parameters. According to Theorem 2.2 and reduced model (2.19), the BLUE of $\boldsymbol{\Gamma}$ is

$$\hat{\boldsymbol{\Gamma}} = \mathbf{C}\hat{\mathbf{B}}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{C}\hat{\mathbf{B}}\mathbf{M} = \mathbf{C}\hat{\mathbf{B}}_M, \tag{2.25}$$

where $\hat{\mathbf{B}} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}$.

The estimator $\hat{\boldsymbol{\Gamma}}$ is also the MLE or minimum variance unbiased estimator of $\boldsymbol{\Gamma}$ and does not depend on $\boldsymbol{\Sigma}$, i.e. the MLE is invariant to the assumed structure of $\boldsymbol{\Sigma}$ (Kim and Timm, 2007: 225).

From the multivariate normality assumption of primary estimator $\hat{\boldsymbol{\beta}}$ defined in (2.11), $\hat{\boldsymbol{\beta}} \sim N_{gpt}\left(vec(\mathbf{B}), \boldsymbol{\Sigma} \otimes (\mathbf{X}'\mathbf{X})^{-1}\right)$, the estimator $\hat{\boldsymbol{\beta}}_M$ of reduce model (2.21) and $\hat{\boldsymbol{\gamma}} = vec(\hat{\boldsymbol{\Gamma}})$ are assumed distributed as

$$\hat{\boldsymbol{\beta}}_M = vec(\hat{\mathbf{B}}_M) \sim N_{gpt}\left(vec(\mathbf{B}_M), \mathbf{M}'\boldsymbol{\Sigma}\mathbf{M} \otimes (\mathbf{X}'\mathbf{X})^{-1}\right), \tag{2.26}$$

$$\hat{\boldsymbol{\gamma}} = vec(\hat{\boldsymbol{\Gamma}}) = vec(\mathbf{C}\hat{\mathbf{B}}_M) \sim N_{v_h pu}\left(vec(\mathbf{C}\mathbf{B}_M), \boldsymbol{\Phi} \otimes \mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}'\right). \tag{2.27}$$

Note that the distribution of $\hat{\boldsymbol{\Gamma}}$ depends on $\boldsymbol{\Sigma}$ so that inferences about $\boldsymbol{\Gamma}$ depend on the structure of $\boldsymbol{\Sigma}$.

Using the estimator $\hat{\boldsymbol{\Gamma}}$ of $\boldsymbol{\Gamma}$, a well known multivariate test statistic, Wilks' Lambda Criterion, is derived to test the Multivariate General Linear Hypothesis (2.18) given in Theorem 2.4.

Theorem 2.4. To test the Multivariate Linear Hypothesis $H: \mathbf{C}\mathbf{B}_M = \boldsymbol{\Gamma}_0$, where $\mathbf{C}$ is a $v_h \times g$ between group contrast matrix of $rank(\mathbf{C}) = v_h \le g$, $\mathbf{A}$ is a $t \times u$ within subject contrast matrix of $rank(\mathbf{A}) = u \le t$, $\mathbf{A}'\mathbf{A} = \mathbf{I}_u$ and $\mathbf{B}_M = \mathbf{B}(\mathbf{I}_p \otimes \mathbf{A})$, consider the reduced DMM in (2.19), $\mathbf{Y}_M = \mathbf{X}\mathbf{B}_M + \mathbf{U}_M$, where $\mathbf{X}$ is a design matrix of full rank g, $\mathbf{Y}_M = \mathbf{Y}(\mathbf{I}_p \otimes \mathbf{A})$, $\mathbf{U}_M = \mathbf{U}(\mathbf{I}_p \otimes \mathbf{A})$ and assume that $\mathbf{y}_M = vec(\mathbf{Y}_M)$ $\sim N_{npu}((\mathbf{I}_{pu} \otimes \mathbf{X})vec(\mathbf{B}_M), \boldsymbol{\Phi} \otimes \mathbf{I}_n)$, where $\boldsymbol{\Phi} = (\mathbf{I}_p \otimes \mathbf{A})'\boldsymbol{\Sigma}(\mathbf{I}_p \otimes \mathbf{A})$ is a $pu \times pu$ unknown nonsingular covariance matrix. When $v_e = n - g > pu$, Wilks' Lambda test is given by

$$\Lambda = \frac{|\mathbf{S}_e|}{|\mathbf{S}_e + \mathbf{S}_h|} = \left|\mathbf{I}_{pu} + \mathbf{S}_h\mathbf{S}_e^{-1}\right|^{-1}, \tag{2.28}$$

where $\mathbf{S}_e$ and $\mathbf{S}_h$ are the $pu \times pu$ sum of squares and product (SSCP) matrices corresponding to error and the hypothesis defined by

$$\mathbf{S}_e = (\mathbf{I}_p \otimes \mathbf{A})'\mathbf{Y}'[\mathbf{I}_n - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}']\mathbf{Y}(\mathbf{I}_p \otimes \mathbf{A}) \tag{2.29}$$

$$\mathbf{S}_h = (\mathbf{C}\hat{\mathbf{B}}(\mathbf{I}_p \otimes \mathbf{A}) - \boldsymbol{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\mathbf{B}}(\mathbf{I}_p \otimes \mathbf{A}) - \boldsymbol{\Gamma}_0). \tag{2.30}$$

The null hypothesis $H: \mathbf{C}\mathbf{B}_M = \boldsymbol{\Gamma}_0$ is rejected if $\Lambda < c$.

Proof. First, the unrestricted and restricted maximum likelihood estimators of $\mathbf{B}_M = \mathbf{B}(\mathbf{I}_p \otimes \mathbf{A})$ and $\mathbf{\Phi}$, which are the functions of primary parameters $\mathbf{B}$ and $\mathbf{\Sigma}$, are derived.

By applying Theorem 2.3 to reduced model (2.19) and under the multivariate normality assumption (2.22), the unrestricted MLEs of $\mathbf{B}_M$ and $\mathbf{\Phi}$ are

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

$$\hat{\mathbf{\Sigma}}_M = \frac{(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M)'(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M)}{n} \quad .$$

The restricted MLEs of $\mathbf{B}_M$ and $\mathbf{\Phi}$ under the restriction that $\mathbf{C}\mathbf{B}_M = \mathbf{\Gamma}_0$ are (Kim and Timm, 2007: 148)

$$\hat{\mathbf{B}}_{M(\omega)} = \hat{\mathbf{B}}_M - (\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0),$$

$$= \hat{\mathbf{B}}_M - \mathbf{W},$$

where $\mathbf{W} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0)$, and

$$\hat{\mathbf{\Sigma}}_{M(\omega)} = \frac{(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_{M(\omega)})'(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_{M(\omega)})}{n}.$$

Next, the likelihood ratio test for $H: \mathbf{C}\mathbf{B}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{\Gamma}_0$ is derived as

$$\Lambda = \frac{\max\limits_{\omega} L(\mathbf{Y}_M)}{\max L(\mathbf{Y}_M)}$$

$$= \frac{(2\pi)^{-npu/2}\left|\hat{\mathbf{\Phi}}_\omega\right|^{-\frac{n}{2}} \exp\left[tr\left(-\frac{1}{2}\hat{\mathbf{\Phi}}_\omega^{-1}(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_{M(\omega)})'(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_{M(\omega)})\right)\right]}{(2\pi)^{-npu/2}\left|\hat{\mathbf{\Phi}}\right|^{-\frac{n}{2}} \exp\left[tr\left(-\frac{1}{2}\hat{\mathbf{\Phi}}^{-1}(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M)'(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M)\right)\right]}$$

$$= \frac{\left|\hat{\mathbf{\Phi}}_\omega\right|^{-\frac{n}{2}} \exp\left[tr\left(-\frac{n}{2}\right)\right]}{\left|\hat{\mathbf{\Phi}}\right|^{-\frac{n}{2}} \exp\left[tr\left(-\frac{n}{2}\right)\right]}$$

$$= \left|\frac{\mathbf{\Phi}}{\mathbf{\Phi}_\omega}\right|^{\frac{n}{2}}.$$

Thus,

$$\Lambda^{2/n} = \left|\frac{\hat{\mathbf{\Phi}}}{\hat{\mathbf{\Phi}}_{\omega}}\right| = \left|\frac{(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M)'(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M)}{(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_{M(\omega)})'(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_{M(\omega)})}\right|, \tag{2.31}$$

i.e. the null hypothesis $H: \mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{\Gamma}_0$ is rejected if $\Lambda^{2/n} < c_0$ or $\Lambda < c_1$, where $c_1 = (c_0)^{n/2}$.

Denote the numerator term of the determinant in (2.31) by $\mathbf{S}_e$, then

$$\begin{aligned}
\mathbf{S}_e &= (\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M)'(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M) \\
&= \mathbf{M}'\mathbf{Y}'(\mathbf{I} - \mathbf{X}\hat{\mathbf{B}})'(\mathbf{I} - \mathbf{X}\hat{\mathbf{B}})\mathbf{Y}\mathbf{M} \\
&= (\mathbf{I}_p \otimes \mathbf{A})'\mathbf{Y}'[\mathbf{I}_n - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}']\mathbf{Y}(\mathbf{I}_p \otimes \mathbf{A}).
\end{aligned} \tag{2.32}$$

Express the denominator term of determinant in (2.31) as

$$\begin{aligned}
(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_{M(\omega)})'(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_{M(\omega)}) &= [(\mathbf{Y}_M - \mathbf{X}(\hat{\mathbf{B}}_M - \mathbf{W})]'[(\mathbf{Y}_M - \mathbf{X}(\hat{\mathbf{B}}_M - \mathbf{W})] \\
&= [(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M) - \mathbf{XW}]'[(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M) - \mathbf{XW}] \\
&= (\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M)'(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M) - (\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M)'(\mathbf{XW}) \\
&\quad - (\mathbf{XW})'(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M) + (\mathbf{XW})'(\mathbf{XW}).
\end{aligned} \tag{2.33}$$

Consider the second term of (2.33);

$$\begin{aligned}
(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M)'(\mathbf{XW}) &= (\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M)'\left\{\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0)\right\} \\
&= (\mathbf{Y}_M'\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1} - \hat{\mathbf{B}}_M'\mathbf{X}'\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1})\left\{\mathbf{C}'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0)\right\} \\
&= (\hat{\mathbf{B}}_M' - \hat{\mathbf{B}}_M')\left\{\mathbf{C}'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0)\right\} \\
&= \mathbf{0}_{pu \times pu}.
\end{aligned}$$

Consider the third term of (2.33);

$$\begin{aligned}
(\mathbf{XW})'(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M) &= \left\{\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0)\right\}'(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M) \\
&= \left\{(\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\right\}(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M) \\
&= \left\{(\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}\mathbf{C}\right\}[\hat{\mathbf{B}}_M - \hat{\mathbf{B}}_M] \\
&= \mathbf{0}_{pu \times pu}.
\end{aligned}$$

Consider the fourth term of (2.33);

$$(\mathbf{XW})'(\mathbf{XW}) = \mathbf{W}'\mathbf{X}'\mathbf{XW}$$

$$= \left\{(\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\right\}(\mathbf{X}'\mathbf{X})$$

$$\times\left\{(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0)\right\}$$

$$= (\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}'][\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}$$

$$\times(\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0)$$

$$= (\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0).$$

Therefore, (2.32) becomes

$$(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M)'(\mathbf{XW}) = (\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M)'(\mathbf{Y}_M - \mathbf{X}\hat{\mathbf{B}}_M)$$

$$+(\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0)$$

$$= \mathbf{S}_e + \mathbf{S}_h,$$

where

$$\mathbf{S}_h = (\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\mathbf{B}}_M - \mathbf{\Gamma}_0)$$

$$= (\hat{\mathbf{\Gamma}} - \mathbf{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\hat{\mathbf{\Gamma}} - \mathbf{\Gamma}_0). \tag{2.34}$$

Substitute $\mathbf{S}_e$ and $\mathbf{S}_h$, defined by (2.32) and (2.34) respectively, into (2.31), Wilks' Lambda (likelihood ratio statistic), to test $H:\mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{\Gamma}_0$ when $v_e > pu$ is given by

$$\Lambda = \frac{|\mathbf{S}_e|}{|\mathbf{S}_e + \mathbf{S}_h|}$$

$$= \frac{|\mathbf{S}_e\mathbf{S}_e^{-1}|}{|\mathbf{S}_e\mathbf{S}_e^{-1} + \mathbf{S}_h\mathbf{S}_e^{-1}|}$$

$$= \frac{|\mathbf{I}_{pu}|}{|\mathbf{I}_{pu} + \mathbf{S}_h\mathbf{S}_e^{-1}|}$$

$$= |\mathbf{I}_{pu} + \mathbf{S}_h\mathbf{S}_e^{-1}|^{-1}. \tag{2.35}$$

Next it will be shown that the likelihood ratio statistic (2.35) is a function of the eigenvalues of $\mathbf{S}_h\mathbf{S}_e^{-1}$.

Let $\mathbf{K}$ be a $pu \times pu$ orthogonal matrix whose columns are the eigenvectors corresponding to eigenvalues $d_1,\ldots,d_s$ of $\mathbf{S}_h\mathbf{S}_e^{-1}$, $\mathbf{KK}'=\mathbf{I}_{pu}$. Subsequently, $\mathbf{K}(\mathbf{S}_h\mathbf{S}_e^{-1})\mathbf{K}'=\mathbf{D}$, where $\mathbf{D}=diag(d_1,\ldots,d_s)$ and $s=rank(\mathbf{S}_h\mathbf{S}_e^{-1})=\min(v_h, pu)$. Thus

$$\begin{aligned}\Lambda &= \left|\mathbf{I}_{pu}+\mathbf{S}_h\mathbf{S}_e^{-1}\right|^{-1}\\ &= \left|\mathbf{KI}_{pu}\mathbf{K}'+\mathbf{KS}_h\mathbf{S}_e^{-1}\mathbf{K}'\right|^{-1}\\ &= \left|\mathbf{I}_{pu}+\mathbf{D}\right|^{-1}\\ &= \prod_{i=1}^{s}(1+d_i)^{-1}\,. \qquad \square\end{aligned}$$

Under the multivariate normality assumption and $v_e > pu$, the matrices $\mathbf{S}_e$ and $\mathbf{S}_h$ have independent Wishart distributions (Boik, 1988: 472) defined by

$$\mathbf{S}_e \sim W_{pu}(\mathbf{\Phi}, v_e)\,, \tag{2.36}$$

$$\mathbf{S}_h \sim W_{pu}(\mathbf{\Phi}, v_h, \mathbf{\Phi}^{-1}\mathbf{\Delta})\,, \tag{2.37}$$

where $v_e = n - rank(\mathbf{X}) = n - g$, $v_h = rank(\mathbf{C})$ and the noncentrality matrix is

$$\mathbf{\Delta} = (\mathbf{\Gamma}-\mathbf{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{\Gamma}-\mathbf{\Gamma}_0)\,. \tag{2.38}$$

In order to find the *p*-value corresponding to the likelihood ratio statistic (Wilks' Lambda), the transformed F value of Rao's F approximation is calculated as below (Boik, 1988: 472):

$$F_\Lambda = (\Lambda^{-c}-1)(\frac{v_1}{v_2}) \sim F_{v_1,v_2}\,, \tag{2.39}$$

where

$$c=\left(\frac{(pu)^2+v_h^2-5}{(v_h pu)^2-4}\right)^{1/2},\ v_1 = v_h pu \ \text{ and } \ v_2 = g^{-1}[v_e - \tfrac{1}{2}(pu - v_h + 1)] - \tfrac{1}{2}(v_h pu - 2)\,.$$

2.2 The Multivariate Mixed Model (MMM)

2.2.1 Scheffé's Mixed Model Specification

From the layout of the Multivariate Repeated Measurements Design in Table 2.1, one can analyze these data by using the MMM which is an extension of Scheffé's Univariate Mixed Model. First, the p-variate Scheffé Mixed Model of the $p \times 1$ vector $\mathbf{y}_{ijk}$ on the i^{th} subject in the j^{th} group at the k^{th} time, where $i = 1, \ldots, n_j$, $j = 1, \ldots, g$, $n_1 + n_2 + \cdots + n_g = n$ and $k = 1, \ldots, t$ is defined. The mixed-effect model for multivariate repeated measurements is

$$\mathbf{y}_{ijk} = \boldsymbol{\mu} + \boldsymbol{\alpha}_j + \boldsymbol{\beta}_k + (\boldsymbol{\alpha\beta})_{jk} + \mathbf{s}_{(j)i} + \mathbf{e}_{ijk}, \tag{2.40}$$

where

$\mathbf{y}_{ijk}$ is a $p \times 1$ response vector on i^{th} subject in j^{th} group at k^{th} occasion,

$\boldsymbol{\mu}$ is a $p \times 1$ overall mean vector,

$\boldsymbol{\alpha}_j$ is a $p \times 1$ vector of fixed effects for group j,

$\boldsymbol{\beta}_k$ is a $p \times 1$ vector of fixed effects for time k,

$(\boldsymbol{\alpha\beta})_{jk}$ is a $p \times 1$ vector of interaction effects between group j and time k,

$\mathbf{s}_{(j)i}$ is a $p \times 1$ vector of random deviation of subject i within group j, and

$\mathbf{e}_{ijk}$ is a $p \times 1$ random error on the i^{th} subject in the j^{th} group at the k^{th} occasion.

The model (2.40) can be written in the form of a mean model defined by

$$\mathbf{y}_{ijk} = \boldsymbol{\mu}_{jk} + \mathbf{s}_{(j)i} + \mathbf{e}_{ijk}, \tag{2.41}$$

where $\boldsymbol{\mu}_{jk} = \boldsymbol{\mu} + \boldsymbol{\alpha}_j + \boldsymbol{\beta}_k + (\boldsymbol{\alpha\beta})_{jk}$ is a $p \times 1$ mean vector of the j^{th} group at the k^{th} occasion and $\mathbf{u}_{ijk} = \mathbf{s}_{(j)i} + \mathbf{e}_{ijk}$ is a $p \times 1$ random vector. Assume that $\mathbf{s}_{(j)i}$ and $\mathbf{e}_{ijk}$ are normally distributed as

$$\mathbf{s}_{(j)i} \sim N_p(\mathbf{0}, \boldsymbol{\Sigma}_s) \tag{2.42}$$

and

$$\mathbf{e}_{ijk} \sim N_p(\mathbf{0}, \boldsymbol{\Sigma}_e), \tag{2.43}$$

where $\boldsymbol{\Sigma}_s$ and $\boldsymbol{\Sigma}_e$ are the $p \times p$ covariance matrices of $\mathbf{s}_{(j)i}$ and $\mathbf{e}_{ijk}$, respectively.

Let $\mathbf{Y}_{ij}^* = (\mathbf{y}_{ij1}, \mathbf{y}_{ij2}, \ldots, \mathbf{y}_{iji})'$ and $\mathbf{E}_{ij}^* = (\mathbf{e}_{ij1}, \mathbf{e}_{ij2}, \ldots, \mathbf{e}_{ijt})'$ be the $t \times p$ matrices of responses and errors for each subject and $\boldsymbol{\mu}_j^* = (\boldsymbol{\mu}_{j1}, \boldsymbol{\mu}_{j2}, \ldots, \boldsymbol{\mu}_{jt})'$ be a $t \times p$ matrix of parameters for each group, then the MMM for the i^{th} subject in the j^{th} group can be written as

$$\mathbf{Y}_{ij}^* = \boldsymbol{\mu}_j + \mathbf{1}_t \mathbf{s}'_{(j)i} + \mathbf{E}_{ij}^*, \tag{2.44}$$

or equivalently

$$\mathbf{Y}_{ij}^* = \boldsymbol{\mu}_j + \mathbf{U}_{ij}^*, \tag{2.45}$$

where $\mathbf{U}_{ij}^* = \mathbf{1}_t \mathbf{s}'_{(j)i} + \mathbf{E}_{ij}^*$. The matrices $\mathbf{Y}_{ij}^*$, $\boldsymbol{\mu}_j^*$ and $\mathbf{U}_{ij}^*$ are respectively defined by

$$\mathbf{Y}_{ij}^* = \begin{bmatrix} y_{ij1}^{(1)} & y_{ij1}^{(2)} & \cdots & y_{ij1}^{(p)} \\ y_{ij2}^{(1)} & y_{ij2}^{(2)} & \cdots & y_{ij2}^{(p)} \\ \vdots & \vdots & \ddots & \vdots \\ y_{ijt}^{(1)} & y_{ijt}^{(2)} & \cdots & y_{ijt}^{(p)} \end{bmatrix},$$

$$\boldsymbol{\mu}_j^* = \begin{bmatrix} \mu_{j1}^{(1)} & \mu_{j1}^{(2)} & \cdots & \mu_{j1}^{(p)} \\ \mu_{j2}^{(1)} & \mu_{j2}^{(2)} & \cdots & \mu_{j2}^{(p)} \\ \vdots & \vdots & \ddots & \vdots \\ \mu_{jt}^{(1)} & \mu_{jt}^{(2)} & \cdots & \mu_{jt}^{(p)} \end{bmatrix}, \text{ and}$$

$$\mathbf{U}_{ij}^* = \begin{bmatrix} u_{ij1}^{(1)} & u_{ij1}^{(2)} & \cdots & u_{ij1}^{(p)} \\ u_{ij2}^{(1)} & u_{ij2}^{(2)} & \cdots & u_{ij2}^{(p)} \\ \vdots & \vdots & \ddots & \vdots \\ u_{ijt}^{(1)} & u_{ijt}^{(2)} & \cdots & u_{ijt}^{(p)} \end{bmatrix}$$

$$= \begin{bmatrix} s_{ij}^{(1)} & s_{ij}^{(2)} & \cdots & s_{ij}^{(p)} \\ s_{ij}^{(1)} & s_{ij}^{(2)} & \cdots & s_{ij}^{(p)} \\ \vdots & \vdots & \ddots & \vdots \\ s_{ij}^{(1)} & s_{ij}^{(2)} & \cdots & s_{ij}^{(p)} \end{bmatrix} + \begin{bmatrix} e_{ij1}^{(1)} & e_{ij1}^{(2)} & \cdots & e_{ij1}^{(p)} \\ e_{ij2}^{(1)} & e_{ij2}^{(2)} & \cdots & e_{ij2}^{(p)} \\ \vdots & \vdots & \ddots & \vdots \\ e_{ijt}^{(1)} & e_{ijt}^{(2)} & \cdots & e_{ijt}^{(p)} \end{bmatrix}.$$

Using the $vec(.)$ operator to stack the columns, let $\mathbf{u}_{ij}^* = vec((\mathbf{U}_{ij}^*)')$ be $pt \times 1$ vectors, $\mathbf{u}_{ij}^* = (u_{ij1}^{(1)}, u_{ij1}^{(2)}, \ldots, u_{ij1}^{(p)}, u_{ij2}^{(1)}, u_{ij2}^{(2)}, \ldots, u_{ij2}^{(p)}, \ldots, u_{ijt}^{(1)}, u_{ijt}^{(2)}, \ldots, u_{ijt}^{(p)})'$. This leads to

$$\begin{aligned} \mathbf{u}_{ij}^* = vec((\mathbf{U}_{ij}^*)') &= vec(\mathbf{s}_{(j)i} \mathbf{1}'_t) + vec((\mathbf{E}_{ij}^*)') \\ &= (\mathbf{1}_t \otimes \mathbf{I}_p) vec(\mathbf{s}_{(j)i}) + vec((\mathbf{E}_{ij}^*)') \\ &= (\mathbf{1}_t \otimes \mathbf{I}_p) \mathbf{s}_{(j)i} + vec((\mathbf{E}_{ij}^*)'), \end{aligned}$$

then

$$\begin{aligned}
\boldsymbol{\Sigma}_{ij}^{*} &= \operatorname{cov}(\mathbf{u}_{ij}^{*}) = \operatorname{cov}\left((\mathbf{1}_t \otimes \mathbf{I}_p)\mathbf{s}_{(j)i} + vec((\mathbf{E}_{ij}^{*})')\right) \\
&= (\mathbf{1}_t \otimes \mathbf{I}_p) \operatorname{cov}(\mathbf{s}_{(j)i})(\mathbf{1}_t \otimes \mathbf{I}_p)' + \operatorname{cov}\left(vec((\mathbf{E}_{ij}^{*})')\right) \\
&= (\mathbf{1}_t \otimes \mathbf{I}_p)\boldsymbol{\Sigma}_s(\mathbf{1}_t \otimes \mathbf{I}_p)' + \left(\mathbf{I}_t \otimes \boldsymbol{\Sigma}_e\right) \\
&= (\mathbf{1}_t\mathbf{1}_t' \otimes \boldsymbol{\Sigma}_s) + \left(\mathbf{I}_t \otimes \boldsymbol{\Sigma}_e\right) \qquad (2.46) \\
&= \begin{bmatrix} \boldsymbol{\Sigma}_s + \boldsymbol{\Sigma}_e & \boldsymbol{\Sigma}_s & \cdots & \boldsymbol{\Sigma}_s \\ \boldsymbol{\Sigma}_s & \boldsymbol{\Sigma}_s + \boldsymbol{\Sigma}_e & \cdots & \boldsymbol{\Sigma}_s \\ \vdots & \vdots & \ddots & \vdots \\ \boldsymbol{\Sigma}_s & \boldsymbol{\Sigma}_s & \cdots & \boldsymbol{\Sigma}_s + \boldsymbol{\Sigma}_e \end{bmatrix}.
\end{aligned}$$

The covariance matrix $\boldsymbol{\Sigma}_{ij}^{*}$ has a compound symmetry structure and it is clear that the homegeneity of covariance matrices is satisfied, i.e. $\boldsymbol{\Sigma}_{ij}^{*} = \boldsymbol{\Sigma}^{*}$ for all $i = 1,\ldots,n_j$, $j = 1,\ldots,g$, which is a requirement for Scheffe's MMM model. Under normality assumptions (2.42) and (2.43),

$$\mathbf{u}_{ij}^{*} \sim N_{pt}(\mathbf{0}_{pt\times 1}, \boldsymbol{\Sigma}_{pt\times pt}^{*}) . \qquad (2.47)$$

According to Scheffe's MMM model (3.6) and under normality assumption (2.47),

$$\boldsymbol{y}_{ij}^{*} = vec(\mathbf{Y}_{ij}^{*}) \sim N_{pt}(vec(\boldsymbol{\mu}_{j}^{*}), \boldsymbol{\Sigma}_{pt\times pt}^{*}) . \qquad (2.48)$$

Taking each $t \times p$ matrix $\mathbf{Y}_{ij}^{*}$ in each column, where the columns of $\mathbf{Y}_{ij}^{*}$ are t occasions and the rows are p response variables, and similarly taking each $\mathbf{U}_{ij}^{*}$ in each column, the response matrix $\mathbf{Y}_{nt\times p}^{*}$ and error matrix $\mathbf{U}_{nt\times p}^{*}$ are obtained and represented as

$$\mathbf{Y}^*_{nt\times p} = \begin{bmatrix} \mathbf{Y}^*_{11} \\ \mathbf{Y}^*_{21} \\ \vdots \\ \mathbf{Y}^*_{n_1 1} \\ \hline \mathbf{Y}^*_{12} \\ \mathbf{Y}^*_{22} \\ \vdots \\ \mathbf{Y}^*_{n_2 2} \\ \hline \vdots \\ \hline \mathbf{Y}^*_{1g} \\ \mathbf{Y}^*_{2g} \\ \vdots \\ \mathbf{Y}^*_{n_g g} \end{bmatrix} \quad \text{and} \quad \mathbf{U}^*_{nt\times p} = \begin{bmatrix} \mathbf{U}^*_{11} \\ \mathbf{U}^*_{21} \\ \vdots \\ \mathbf{U}^*_{n_1 1} \\ \hline \mathbf{U}^*_{12} \\ \mathbf{U}^*_{22} \\ \vdots \\ \mathbf{U}^*_{n_2 2} \\ \hline \vdots \\ \hline \mathbf{U}^*_{1g} \\ \mathbf{U}^*_{2g} \\ \vdots \\ \mathbf{U}^*_{n_g g} \end{bmatrix}. \tag{2.49}$$

In a similar manner, by taking each $\boldsymbol{\mu}^*_{ij}$ in each column, an unknown parameter matrix is obtained;

$$\mathbf{B}^*_{gt\times p} = \begin{bmatrix} \boldsymbol{\mu}^*_1 \\ \boldsymbol{\mu}^*_2 \\ \vdots \\ \boldsymbol{\mu}^*_g \end{bmatrix}. \tag{2.50}$$

Using the form of matrices $\mathbf{Y}^*_{nt\times p}$, $\mathbf{U}^*_{nt\times p}$, and $\mathbf{B}^*_{gt\times p}$, MMM is defined as

$$\mathbf{Y}^*_{nt\times p} = (\mathbf{X}_{n\times g} \otimes \mathbf{I}_t)\mathbf{B}^*_{gt\times p} + \mathbf{U}^*_{nt\times p}, \tag{2.51}$$

where $\mathbf{Y}^*$ is an $nt\times p$ response matrix for n subjects, $\mathbf{X}$ is an $n\times g$ between subject design matrix of $rank(\mathbf{X}) = g$, $\mathbf{B}^*$ is a $gt\times p$ unknown parameter matrix of fixed effects and $\mathbf{U}^*$ is an $nt\times p$ random error matrix. The layouts of these matrices are as follows:

$$
\mathbf{Y}^{*}_{nt\times p}=\left[\begin{array}{cccc}
y_{111}^{(1)} & y_{111}^{(2)} & \cdots & y_{111}^{(p)} \\
y_{112}^{(1)} & y_{112}^{(2)} & \cdots & y_{112}^{(p)} \\
\vdots & \vdots & & \vdots \\
y_{11t}^{(1)} & y_{11t}^{(2)} & \cdots & y_{11t}^{(p)} \\
\hdashline
\vdots & \vdots & \vdots & \vdots \\
\hdashline
y_{n_1 11}^{(1)} & y_{n_1 11}^{(2)} & \cdots & y_{n_1 11}^{(p)} \\
y_{n_1 12}^{(1)} & y_{n_1 12}^{(2)} & \cdots & y_{n_1 12}^{(p)} \\
\vdots & \vdots & & \vdots \\
y_{n_1 1t}^{(1)} & y_{n_1 1t}^{(2)} & \cdots & y_{n_1 1t}^{(p)} \\
\hdashline
\vdots & \vdots & & \vdots \\
\hdashline
y_{1g1}^{(1)} & y_{1g1}^{(2)} & \cdots & y_{1g1}^{(p)} \\
y_{1g2}^{(1)} & y_{1g2}^{(2)} & \cdots & y_{1g2}^{(p)} \\
\vdots & \vdots & & \vdots \\
y_{1gt}^{(1)} & y_{1gt}^{(2)} & \cdots & y_{1gt}^{(p)} \\
\hdashline
\vdots & \vdots & & \vdots \\
\hdashline
y_{n_g g1}^{(1)} & y_{n_g g1}^{(2)} & \cdots & y_{n_g g1}^{(p)} \\
y_{n_g g2}^{(1)} & y_{n_g g2}^{(2)} & \cdots & y_{n_g g2}^{(p)} \\
\vdots & \vdots & & \vdots \\
y_{n_g gt}^{(1)} & y_{n_g gt}^{(2)} & \cdots & y_{n_g gt}^{(p)}
\end{array}\right], \qquad
\mathbf{U}^{*}_{nt\times p}=\left[\begin{array}{cccc}
u_{111}^{(1)} & u_{111}^{(2)} & \cdots & u_{111}^{(p)} \\
u_{112}^{(1)} & u_{112}^{(2)} & \cdots & u_{112}^{(p)} \\
\vdots & \vdots & & \vdots \\
u_{11t}^{(1)} & u_{11t}^{(2)} & \cdots & u_{11t}^{(p)} \\
\hdashline
\vdots & \vdots & \vdots & \vdots \\
\hdashline
u_{n_1 11}^{(1)} & u_{n_1 11}^{(2)} & \cdots & u_{n_1 11}^{(p)} \\
u_{n_1 12}^{(1)} & u_{n_1 12}^{(2)} & \cdots & u_{n_1 12}^{(p)} \\
\vdots & \vdots & & \vdots \\
u_{n_1 1t}^{(1)} & u_{n_1 1t}^{(2)} & \cdots & u_{n_1 1t}^{(p)} \\
\hdashline
\vdots & \vdots & & \vdots \\
\hdashline
u_{1g1}^{(1)} & u_{1g1}^{(2)} & \cdots & u_{1g1}^{(p)} \\
u_{1g2}^{(1)} & u_{1g2}^{(2)} & \cdots & u_{1g2}^{(p)} \\
\vdots & \vdots & & \vdots \\
u_{1gt}^{(1)} & u_{1gt}^{(2)} & \cdots & u_{1gt}^{(p)} \\
\hdashline
\vdots & \vdots & & \vdots \\
\hdashline
u_{n_g g1}^{(1)} & u_{n_g g1}^{(2)} & \cdots & u_{n_g g1}^{(p)} \\
u_{n_g g2}^{(1)} & u_{n_g g2}^{(2)} & \cdots & u_{n_g g2}^{(p)} \\
\vdots & \vdots & & \vdots \\
u_{n_g gt}^{(1)} & u_{n_g gt}^{(2)} & \cdots & u_{n_g gt}^{(p)}
\end{array}\right],
$$

$$
\mathbf{B}^{*}_{gt\times p}=\left[\begin{array}{cccc}
\mu_{11}^{(1)} & \mu_{11}^{(2)} & \cdots & \mu_{11}^{(p)} \\
\mu_{12}^{(1)} & \mu_{12}^{(2)} & \cdots & \mu_{12}^{(p)} \\
\vdots & \vdots & \ddots & \vdots \\
\mu_{1t}^{(1)} & \mu_{1t}^{(2)} & \cdots & \mu_{1t}^{(p)} \\
\hdashline
\mu_{21}^{(1)} & \mu_{11}^{(2)} & \cdots & \mu_{11}^{(p)} \\
\mu_{22}^{(1)} & \mu_{22}^{(2)} & \cdots & \mu_{22}^{(p)} \\
\vdots & \vdots & \ddots & \vdots \\
\mu_{2t}^{(1)} & \mu_{2t}^{(2)} & \cdots & \mu_{2t}^{(p)} \\
\hdashline
\vdots & \vdots & & \vdots \\
\hdashline
\mu_{g1}^{(1)} & \mu_{g1}^{(2)} & \cdots & \mu_{g1}^{(p)} \\
\mu_{g2}^{(1)} & \mu_{g2}^{(2)} & \cdots & \mu_{g2}^{(p)} \\
\vdots & \vdots & \ddots & \vdots \\
\mu_{gt}^{(1)} & \mu_{gt}^{(2)} & \cdots & \mu_{gt}^{(p)}
\end{array}\right], \qquad
\mathbf{X}_{n\times g}=\begin{bmatrix}
\mathbf{1}_{n_1} & \mathbf{0} & \cdots & \mathbf{0} \\
\mathbf{0} & \mathbf{1}_{n_2} & \cdots & \mathbf{0} \\
\vdots & \vdots & \ddots & \vdots \\
\mathbf{0} & \mathbf{0} & \cdots & \mathbf{1}_{n_g}
\end{bmatrix}.
$$

According to normality assumption (3.8), for each subject, $\mathbf{u}_{ij}^* = vec(\mathbf{U}_{ij}^*)$ $\sim N_{pt}(\mathbf{0}, \mathbf{\Sigma}^*)$, the distribution of an $npt \times 1$ random error vector $vec(\mathbf{U}^{*\prime})$ $= [(\mathbf{u}_{11}^*)', (\mathbf{u}_{21}^*)', \ldots, (\mathbf{u}_{n_1 1}^*)', (\mathbf{u}_{12}^*)', (\mathbf{u}_{22}^*), \ldots, (\mathbf{u}_{n_2 2}^*)', \ldots, (\mathbf{u}_{1g}^*)', (\mathbf{u}_{2g}^*)', \ldots (\mathbf{u}_{n_g g}^*)]'$ is obtained as

$$vec(\mathbf{U}^{*\prime}) \sim N_{npt}(\mathbf{0}_{npt\times 1}, \mathbf{I}_n \otimes \mathbf{\Sigma}^*), \tag{2.52}$$

which has a covariance matrix with a block diagonal structure and $\mathbf{\Sigma}_{pt\times pt}^*$ has a compound symmetry structure as defined in (2.46).

2.2.2 Parameter Estimation

To find the estimator of $\mathbf{B}_{gt\times p}^*$ from MMM in (2.51), Theorem 2.3 is applied. By Theorem 2.3, from the DMM $\mathbf{Y}_{n\times pt} = \mathbf{X}_{n\times g}\mathbf{B}_{g\times pt} + \mathbf{U}_{n\times pt}$, the MLE of $\mathbf{B}_{g\times pt}$ is $\hat{\mathbf{B}} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}^*$. By substituting $\mathbf{X}_{n\times g}$ by $\mathbf{X}_{n\times g} \otimes \mathbf{I}_t$, the MLE of $\mathbf{B}^*$ is obtained as

$$\begin{aligned}
\hat{\mathbf{B}}^* &= [(\mathbf{X}\otimes\mathbf{I}_t)'(\mathbf{X}\otimes\mathbf{I}_t)]^{-1}(\mathbf{X}\otimes\mathbf{I}_t)'\mathbf{Y}^* \\
&= (\mathbf{X}'\mathbf{X}\otimes\mathbf{I}_t)^{-1}(\mathbf{X}\otimes\mathbf{I}_t)'\mathbf{Y}^* \\
&= [(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\otimes\mathbf{I}_t]\mathbf{Y}^* \ .
\end{aligned} \tag{2.53}$$

The estimator of $\mathbf{\Sigma}^*$ from the MMM in (2.51) is also obtained by applying Theorem 2.3. By substituting $\mathbf{Y}_{n\times pt}$, $\mathbf{X}_{n\times g}$ and $\hat{\mathbf{B}}_{g\times pt}$ in (2.13) by $\mathbf{Y}_{nt\times p}^*$, $\mathbf{X}_{n\times g}\otimes\mathbf{I}_t$ and $\hat{\mathbf{B}}_{gt\times p}^*$, respectively, the MLE of $\mathbf{\Sigma}_{pt\times pt}^*$ is obtained as

$$\hat{\mathbf{\Sigma}}^* = \frac{(\mathbf{Y}^*-(\mathbf{X}\otimes\mathbf{I}_t)\hat{\mathbf{B}}^*)'(\mathbf{Y}^*-(\mathbf{X}\otimes\mathbf{I}_t)\hat{\mathbf{B}}^*)}{n}.$$

Consider $\mathbf{Y}^* - (\mathbf{X}_{n\times g}\otimes\mathbf{I}_t)\hat{\mathbf{B}}^*$,

$$\begin{aligned}
\mathbf{Y}^* - (\mathbf{X}\otimes\mathbf{I}_t)\hat{\mathbf{B}}^* &= \mathbf{Y}^* - (\mathbf{X}\otimes\mathbf{I}_t)[(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\otimes\mathbf{I}_t]\mathbf{Y}^* \\
&= \mathbf{Y}^* - (\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\otimes\mathbf{I}_t)\mathbf{Y}^* \\
&= [\mathbf{I}_{nt} - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\otimes\mathbf{I}_t]\mathbf{Y}^*,
\end{aligned}$$

then

$$\hat{\boldsymbol{\Sigma}}^* = \frac{\mathbf{Y}^{*\prime}[\mathbf{I}_{nt} - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}' \otimes \mathbf{I}_t]'[\mathbf{I}_{nt} - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}' \otimes \mathbf{I}_t]\mathbf{Y}^*}{n}$$

$$= \frac{\mathbf{Y}^{*\prime}[\mathbf{I}_{nt} - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}' \otimes \mathbf{I}_t]\mathbf{Y}^*}{n} .$$

2.2.3 The Multivariate General Linear Hypothesis

The Multivariate General Linear Hypothesis for testing the effect of the time and group factors, and the interaction effect between the group and time factors, is

$$H : (\mathbf{C} \otimes \mathbf{A}')\mathbf{B}^* = \boldsymbol{\Gamma}_{\mathbf{0}}^* \quad \text{or} \quad H : \boldsymbol{\Gamma}^*_{uv_h \times p} = \boldsymbol{\Gamma}^*_0 , \tag{2.54}$$

where $\mathbf{C}$ is a $v_h \times g$ between group contrast matrix having $rank(\mathbf{C}) = v_h \le g$ and $\mathbf{A}$ is a $t \times u$ within subject contrast matrix having $rank(\mathbf{A}) = u \le t$, where $\mathbf{A}$ is assumed to be an orthogonal matrix satisfying $\mathbf{A}'\mathbf{A} = \mathbf{I}_u$.

To test the group × time interaction effect, the matrices $\mathbf{C}$, $\mathbf{A}$ and $\boldsymbol{\Gamma}_0$ are taken in the form

$$\mathbf{C}_{(g-1)\times g} = \left[\begin{array}{cccc:c} 1 & 0 & \dots & 0 & -1 \\ 0 & 1 & \dots & 0 & -1 \\ \vdots & \vdots & \ddots & \vdots & -1 \\ 0 & 0 & \dots & 1 & -1 \end{array}\right], \quad \boldsymbol{\Gamma}_0 = \mathbf{0}_{(g-1)(t-1)\times p} ,$$

and the orthogonal matrices of $\mathbf{A}_{t\times(t-1)}$ for $t =$ 2, 3 and 4 are respectively

$$\mathbf{A}_{2\times1} = \begin{bmatrix} 1/\sqrt{2} \\ -1/\sqrt{2} \end{bmatrix}, \quad \mathbf{A}_{3\times2} = \begin{bmatrix} 1/\sqrt{2} & -1/\sqrt{6} \\ 0 & 2/\sqrt{6} \\ -1/\sqrt{2} & -1/\sqrt{6} \end{bmatrix}, \quad \mathbf{A}_{4\times3} = \begin{bmatrix} 1/\sqrt{2} & -1/\sqrt{6} & -1/\sqrt{12} \\ 0 & 2/\sqrt{6} & -1/\sqrt{12} \\ -1/\sqrt{2} & -1/\sqrt{6} & -1/\sqrt{12} \\ 0 & 0 & 3/\sqrt{12} \end{bmatrix}.$$

For example, where $t =$ 3, the following hypothesis is obtained;

$$H_{01}: \begin{bmatrix} \frac{(\mu_{11}^{(1)}-\mu_{13}^{(1)})-(\mu_{g1}^{(1)}-\mu_{g3}^{(1)})}{\sqrt{2}} & \cdots & \frac{(\mu_{11}^{(p)}-\mu_{13}^{(p)})-(\mu_{g1}^{(p)}-\mu_{g3}^{(p)})}{\sqrt{2}} \\ \frac{(-\mu_{11}^{(1)}+\mu_{12}^{(1)}-\mu_{13}^{(1)})-(-\mu_{g1}^{(1)}+\mu_{g2}^{(1)}-\mu_{g3}^{(1)})}{\sqrt{6}} & \cdots & \frac{(-\mu_{11}^{(p)}+\mu_{12}^{(p)}-\mu_{13}^{(p)})-(-\mu_{g1}^{(p)}+\mu_{g2}^{(p)}-\mu_{g3}^{(p)})}{\sqrt{6}} \\ \frac{(\mu_{21}^{(1)}-\mu_{23}^{(1)})-(\mu_{g1}^{(1)}-\mu_{g3}^{(1)})}{\sqrt{2}} & \cdots & \frac{(\mu_{21}^{(p)}-\mu_{23}^{(p)})-(\mu_{g1}^{(p)}-\mu_{g3}^{(p)})}{\sqrt{2}} \\ \frac{(-\mu_{21}^{(1)}+\mu_{22}^{(1)}-\mu_{23}^{(1)})-(-\mu_{g1}^{(1)}+\mu_{g2}^{(1)}-\mu_{g3}^{(1)})}{\sqrt{6}} & \cdots & \frac{(-\mu_{21}^{(p)}+\mu_{22}^{(p)}-\mu_{23}^{(p)})-(-\mu_{g1}^{(p)}+\mu_{g2}^{(p)}-\mu_{g3}^{(p)})}{\sqrt{6}} \\ \vdots & \cdots & \vdots \\ \frac{(\mu_{(g-1)1}^{(1)}-\mu_{g3}^{(1)})-(\mu_{(g-1)1}^{(1)}-\mu_{g3}^{(1)})}{\sqrt{2}} & \cdots & \frac{(\mu_{(g-1)1}^{(p)}-\mu_{(g-1)3}^{(p)})-(\mu_{g1}^{(p)}-\mu_{g3}^{(p)})}{\sqrt{2}} \\ \frac{(-\mu_{(g-1)1}^{(1)}+\mu_{(g-1)2}^{(1)}-\mu_{(g-1)3}^{(1)})-(-\mu_{g1}^{(1)}+\mu_{g2}^{(1)}-\mu_{g3}^{(1)})}{\sqrt{6}} & \cdots & \frac{(-\mu_{(g-1)1}^{(p)}+\mu_{(g-1)2}^{(p)}-\mu_{(g-1)3}^{(p)})-(-\mu_{g1}^{(p)}+\mu_{g2}^{(p)}-\mu_{g3}^{(p)})}{\sqrt{6}} \end{bmatrix}$$

$$= \mathbf{0}_{(g-1)(t-1)\times p}.$$

To test the group effect averaged over time, the matrices $\mathbf{C}$, $\mathbf{A}$ and $\mathbf{\Gamma}_0$ for $H_{02}:(\mathbf{C}\otimes\mathbf{A}')\mathbf{B}^* = \mathbf{\Gamma}_{\mathbf{0}}^*$ are given by

$$\mathbf{C}_{(g-1)\times g} = \left[\begin{array}{cccc|c} 1 & 0 & \dots & 0 & -1 \\ 0 & 1 & \dots & 0 & -1 \\ \vdots & \vdots & \dots & \vdots & -1 \\ 0 & 0 & \dots & 1 & -1 \end{array}\right], \quad \mathbf{A}_{t\times 1} = \begin{bmatrix} 1/\sqrt{t} \\ 1/\sqrt{t} \\ \vdots \\ 1/\sqrt{t} \end{bmatrix} \quad \text{and} \quad \mathbf{\Gamma}_0 = \mathbf{0}_{(g-1)\times p}.$$

Using matrices $\mathbf{C}$, $\mathbf{A}$ and $\mathbf{\Gamma}_0$, the following hypothesis is obtained;

$$H_{02}: \begin{bmatrix} \frac{\sum_{k=1}^{t}\mu_{1k}^{(1)}}{\sqrt{t}} - \frac{\sum_{k=1}^{t}\mu_{gk}^{(1)}}{\sqrt{t}} & \frac{\sum_{k=1}^{t}\mu_{1k}^{(2)}}{\sqrt{t}} - \frac{\sum_{k=1}^{t}\mu_{gk}^{(2)}}{\sqrt{t}} & \cdots & \frac{\sum_{k=1}^{t}\mu_{1k}^{(p)}}{\sqrt{t}} - \frac{\sum_{k=1}^{t}\mu_{gk}^{(p)}}{\sqrt{t}} \\ \frac{\sum_{k=1}^{t}\mu_{2k}^{(1)}}{\sqrt{t}} - \frac{\sum_{k=1}^{t}\mu_{gk}^{(1)}}{\sqrt{t}} & \frac{\sum_{k=1}^{t}\mu_{2k}^{(2)}}{\sqrt{t}} - \frac{\sum_{k=1}^{t}\mu_{gk}^{(2)}}{\sqrt{t}} & \cdots & \frac{\sum_{k=1}^{t}\mu_{2k}^{(p)}}{\sqrt{t}} - \frac{\sum_{k=1}^{t}\mu_{gk}^{(p)}}{\sqrt{t}} \\ \vdots & \vdots & \cdots & \vdots \\ \frac{\sum_{k=1}^{t}\mu_{(g-1)k}^{(1)}}{\sqrt{t}} - \frac{\sum_{k=1}^{t}\mu_{gk}^{(1)}}{\sqrt{t}} & \frac{\sum_{k=1}^{t}\mu_{(g-1)k}^{(2)}}{\sqrt{t}} - \frac{\sum_{k=1}^{t}\mu_{gk}^{(2)}}{\sqrt{t}} & \cdots & \frac{\sum_{k=1}^{t}\mu_{(g-1)k}^{(p)}}{\sqrt{t}} - \frac{\sum_{k=1}^{t}\mu_{gk}^{(p)}}{\sqrt{t}} \end{bmatrix} = \mathbf{0}_{(g-1)\times p}$$

To test H_{03}, the differences in time average over group, the matrices $\mathbf{C}$, $\mathbf{A}$ and $\mathbf{\Gamma}_0$ for $H_{03}:(\mathbf{C}\otimes\mathbf{A}')\mathbf{B}^* = \mathbf{\Gamma}_{\mathbf{0}}^*$ are

$\mathbf{C} = \begin{bmatrix} \frac{1}{g} & \frac{1}{g} & \dots & \frac{1}{g} \end{bmatrix}$ for an equal number of subjects in each group, and

$\mathbf{C} = \begin{bmatrix} \frac{n_1}{n} & \frac{n_2}{n} & \cdots & \frac{n_g}{n} \end{bmatrix}$ for an unequal number of subjects in each group,

$\mathbf{\Gamma}_0 = \mathbf{0}_{1\times p(t-1)}$, and the orthogonal matrices of $\mathbf{A}_{t\times(t-1)}$ for $t = 2$, 3 and 4 are respectively

$$\mathbf{A}_{2\times1} = \begin{bmatrix} 1/\sqrt{2} \\ -1/\sqrt{2} \end{bmatrix},\ \mathbf{A}_{3\times2} = \begin{bmatrix} 1/\sqrt{2} & -1/\sqrt{6} \\ 0 & 2/\sqrt{6} \\ -1/\sqrt{2} & -1/\sqrt{6} \end{bmatrix},\ \mathbf{A}_{4\times3} = \begin{bmatrix} 1/\sqrt{2} & -1/\sqrt{6} & -1/\sqrt{12} \\ 0 & 2/\sqrt{6} & -1/\sqrt{12} \\ -1/\sqrt{2} & -1/\sqrt{6} & -1/\sqrt{12} \\ 0 & 0 & 3/\sqrt{12} \end{bmatrix}.$$

For example, if $t = 3$ and the number of subjects in each group are equal, the following hypothesis is obtained;

$$H_{03}: \begin{bmatrix} \dfrac{\sum_{j=1}^{g}(\mu_{j1}^{(1)} - \mu_{j3}^{(1)})}{g\sqrt{2}} & \dfrac{\sum_{j=1}^{g}(\mu_{j1}^{(2)} - \mu_{j3}^{(2)})}{g\sqrt{2}} & \cdots & \dfrac{\sum_{j=1}^{g}(\mu_{j1}^{(p)} - \mu_{j3}^{(p)})}{g\sqrt{2}} \\ \dfrac{\sum_{j=1}^{g}(\mu_{j1}^{(1)} + 2\mu_{j2}^{(1)} - \mu_{j3}^{(1)})}{g\sqrt{6}} & \dfrac{\sum_{j=1}^{g}(\mu_{j1}^{(2)} + 2\mu_{j2}^{(2)} - \mu_{j3}^{(2)})}{g\sqrt{6}} & \cdots & \dfrac{\sum_{j=1}^{g}(\mu_{j1}^{(p)} + 2\mu_{j2}^{(p)} - \mu_{j3}^{(p)})}{g\sqrt{6}} \end{bmatrix}$$

$$= \mathbf{0}_{(t-1)\times p}.$$

If there are an unequal number of subjects in each group, the hypothesis H_{03} is

$$H_{03}: \begin{bmatrix} \dfrac{\sum_{j=1}^{g}n_j(\mu_{j1}^{(1)} - \mu_{j3}^{(1)})}{n\sqrt{2}} & \dfrac{\sum_{j=1}^{g}n_j(\mu_{j1}^{(2)} - \mu_{j3}^{(2)})}{n\sqrt{2}} & \cdots & \dfrac{\sum_{j=1}^{g}n_j(\mu_{j1}^{(p)} - \mu_{j3}^{(p)})}{n\sqrt{2}} \\ \dfrac{\sum_{j=1}^{g}n_j(\mu_{j1}^{(1)} + 2\mu_{j2}^{(1)} - \mu_{j3}^{(1)})}{n\sqrt{6}} & \dfrac{\sum_{j=1}^{g}n_j(\mu_{j1}^{(2)} + 2\mu_{j2}^{(2)} - \mu_{j3}^{(2)})}{n\sqrt{6}} & \cdots & \dfrac{\sum_{j=1}^{g}n_j(\mu_{j1}^{(p)} + 2\mu_{j2}^{(p)} - \mu_{j3}^{(p)})}{n\sqrt{6}} \end{bmatrix}$$

$$= \mathbf{0}_{(t-1)\times p}.$$

2.2.4 The Multivariate Sphericity Condition

The MMM defined in (2.51) is related to the DMM defined in (2.2). In order to show this relationship, the response matrix $\mathbf{Y}_{n\times pt}$ of DMM in (2.2) is rearranged by ordering the elements in each column according to time and within each time according to the dependent variables, to obtain a rearranged response matrix $\tilde{\mathbf{Y}}_{n\times pt}$ as

$$
\tilde{\mathbf{Y}}_{n\times pt}=\left[\begin{array}{ccc|ccc|c|ccc}
y_{111}^{(1)} & \cdots & y_{111}^{(p)} & y_{112}^{(1)} & \cdots & y_{112}^{(p)} & \cdots & y_{11t}^{(1)} & \cdots & y_{11t}^{(p)} \\
y_{211}^{(1)} & \cdots & y_{211}^{(p)} & y_{212}^{(1)} & \cdots & y_{212}^{(p)} & \cdots & y_{21t}^{(1)} & \cdots & y_{21t}^{(p)} \\
\vdots & & \vdots & \vdots & & \vdots & & \vdots & & \vdots \\
y_{n_1 11}^{(1)} & \cdots & y_{n_1 11}^{(p)} & y_{n_1 12}^{(1)} & \cdots & y_{n_1 12}^{(p)} & \cdots & y_{n_1 1t}^{(1)} & \cdots & y_{n_1 1t}^{(p)} \\
\hline
y_{121}^{(1)} & \cdots & y_{121}^{(p)} & y_{122}^{(1)} & \cdots & y_{122}^{(p)} & \cdots & y_{12t}^{(1)} & \cdots & y_{12t}^{(p)} \\
y_{221}^{(1)} & \cdots & y_{221}^{(p)} & y_{222}^{(1)} & \cdots & y_{222}^{(p)} & \cdots & y_{22t}^{(1)} & \cdots & y_{22t}^{(p)} \\
\vdots & & \vdots & \vdots & & \vdots & & \vdots & & \vdots \\
y_{n_2 21}^{(1)} & \cdots & y_{n_2 21}^{(p)} & y_{n_2 22}^{(1)} & \cdots & y_{n_2 22}^{(p)} & \cdots & y_{n_2 2t}^{(1)} & \cdots & y_{n_2 2t}^{(p)} \\
\hline
\vdots & & \vdots & \vdots & & \vdots & & \vdots & & \vdots \\
\hline
y_{1g1}^{(1)} & \cdots & y_{1g1}^{(p)} & y_{1g2}^{(1)} & \cdots & y_{1g2}^{(p)} & \cdots & y_{1gt}^{(1)} & \cdots & y_{1gt}^{(p)} \\
y_{2g1}^{(1)} & \cdots & y_{2g1}^{(p)} & y_{2g2}^{(1)} & \cdots & y_{2g2}^{(p)} & \cdots & y_{2gt}^{(1)} & \cdots & y_{2gt}^{(p)} \\
\vdots & & \vdots & \vdots & & \vdots & & \vdots & & \vdots \\
y_{n_g g1}^{(1)} & \cdots & y_{n_g g1}^{(p)} & y_{n_g g2}^{(1)} & \cdots & y_{n_g g2}^{(p)} & \cdots & y_{n_g gt}^{(1)} & \cdots & y_{n_g gt}^{(p)}
\end{array}\right].
$$

Corresponding to the rearranged response matrix, $\tilde{\mathbf{Y}}_{n\times pt}$, the columns of matrix $\mathbf{U}_{n\times pt}$ and $\mathbf{B}_{g\times pt}$ are rearranged in the same manner, denoted by $\tilde{\mathbf{U}}_{n\times pt}$ and $\tilde{\mathbf{B}}_{g\times pt}$ respectively,

$$
\tilde{\mathbf{B}}_{g\times pt}=\left[\begin{array}{ccc|ccc|c|ccc}
\mu_{11}^{(1)} & \cdots & \mu_{11}^{(p)} & \mu_{12}^{(1)} & \cdots & \mu_{12}^{(p)} & \cdots & \mu_{1t}^{(1)} & \cdots & \mu_{1t}^{(p)} \\
\mu_{21}^{(1)} & \cdots & \mu_{2t}^{(p)} & \mu_{22}^{(1)} & \cdots & \mu_{22}^{(p)} & \cdots & \mu_{2t}^{(1)} & \cdots & \mu_{2t}^{(p)} \\
\vdots & \ddots & \vdots & \vdots & \ddots & \vdots & & \vdots & \ddots & \vdots \\
\mu_{g1}^{(1)} & \cdots & \mu_{g1}^{(p)} & \mu_{g2}^{(1)} & \cdots & \mu_{g2}^{(p)} & \cdots & \mu_{gt}^{(1)} & \cdots & \mu_{gt}^{(p)}
\end{array}\right].
$$

Thus the rearranged DMM is obtained and represented as

$$\tilde{\mathbf{Y}}_{n\times pt}=\tilde{\mathbf{X}}_{n\times g}\tilde{\mathbf{B}}_{g\times pt}+\tilde{\mathbf{U}}_{n\times pt}. \tag{2.55}$$

Under the normality assumption,

$$vec(\tilde{\mathbf{U}}')\sim N_{npt}(\mathbf{0}_{npt\times 1},\mathbf{I}_n\otimes\tilde{\mathbf{\Sigma}}_{pt\times pt}), \tag{2.56}$$

where $\tilde{\mathbf{\Sigma}}$ is a rearranged $pt\times pt$ covariance matrix $\mathbf{\Sigma}_{pt\times pt}$ obtained by ordering within each column according to time and within time according to the response variables, i.e.

$$\tilde{\mathbf{\Sigma}} = \begin{bmatrix} \tilde{\mathbf{\Sigma}}_{11} & \tilde{\mathbf{\Sigma}}_{12} & \cdots & \tilde{\mathbf{\Sigma}}_{1t} \\ \tilde{\mathbf{\Sigma}}_{21} & \tilde{\mathbf{\Sigma}}_{22} & \cdots & \tilde{\mathbf{\Sigma}}_{2t} \\ \vdots & \vdots & \ddots & \vdots \\ \tilde{\mathbf{\Sigma}}_{t1} & \tilde{\mathbf{\Sigma}}_{t2} & \cdots & \tilde{\mathbf{\Sigma}}_{tt} \end{bmatrix}, \tag{2.57}$$

where $\tilde{\mathbf{\Sigma}}_{kk'}$ is a $p \times p$ sub-covariance matrix of p variables at the k^{th} and $k'^{\text{ th}}$ measurement (or time) , for $k = 1, 2 \ldots, t$ and $k' = 1, 2 \ldots, t$, defined by

$$\tilde{\mathbf{\Sigma}}_{kk'} = \begin{bmatrix} \sigma_k^{(1)}\sigma_{k'}^{(1)} & \sigma_k^{(1)}\sigma_{k'}^{(2)} & \cdots & \sigma_k^{(1)}\sigma_{k'}^{(p)} \\ \sigma_k^{(2)}\sigma_{k'}^{(1)} & \sigma_k^{(2)}\sigma_{k'}^{(2)} & \cdots & \sigma_k^{(2)}\sigma_{k'}^{(p)} \\ \vdots & \vdots & \ddots & \vdots \\ \sigma_k^{(p)}\sigma_{k'}^{(1)} & \sigma_k^{(p)}\sigma_{k'}^{(2)} & \cdots & \sigma_k^{(p)}\sigma_{k'}^{(p)} \end{bmatrix}.$$

Note that $vec(\tilde{\mathbf{Y}}'_{n\times pt}) = vec(\mathbf{Y}'^{*}_{nt\times p})$, $vec(\tilde{\mathbf{B}}'_{g\times pt}) = vec(\mathbf{B}'^{*}_{gt\times p})$ and $vec(\tilde{\mathbf{U}}'_{n\times pt})$ $= vec(\mathbf{U}'^{*}_{nt\times p})$. Subsequently, the normality assumption (2.52) of $vec(\mathbf{U}'^{*}_{nt\times p})$ is equivalent to the normality assumption (2.56) of $vec(\tilde{\mathbf{U}}'_{n\times pt})$, where $vec(\mathbf{U}'^{*}_{nt\times p})$ has the compound symmetry covariance matrix in (2.46) which is a special structure of $\tilde{\mathbf{\Sigma}}_{pt\times pt}$ in (2.57).

The reduced model of the rearranged DMM (2.55) is defined by multiplying the post matrix $\mathbf{A}_{t\times u} \otimes \mathbf{I}_p$ as

$$\tilde{\mathbf{Y}}_{n\times pt}(\mathbf{A}_{t\times u} \otimes \mathbf{I}_p) = \tilde{\mathbf{X}}_{n\times g}\tilde{\mathbf{B}}_{g\times pt}(\mathbf{A}_{t\times u} \otimes \mathbf{I}_p) + \tilde{\mathbf{U}}_{n\times pt}(\mathbf{A}_{t\times u} \otimes \mathbf{I}_p),$$

$$\tilde{\mathbf{Y}}_M = \tilde{\mathbf{X}}_{n\times g}\tilde{\mathbf{B}}_M + \tilde{\mathbf{U}}_M, \tag{2.58}$$

where $\tilde{\mathbf{Y}}_M = \tilde{\mathbf{Y}}_{n\times pt}(\mathbf{A}_{t\times u} \otimes \mathbf{I}_p), \tilde{\mathbf{B}}_M = \tilde{\mathbf{B}}_{g\times pt}(\mathbf{A}_{t\times u} \otimes \mathbf{I}_p)$ and $\tilde{\mathbf{U}}_M = \tilde{\mathbf{U}}_{n\times pt}(\mathbf{A}_{t\times u} \otimes \mathbf{I}_p)$.

Using the vec(.) operator into (2.58), the $n \times pu$ vector of $vec(\tilde{\mathbf{U}}'_M)$ $= vec[(\tilde{\mathbf{U}}_{n\times pt}(\mathbf{A}_{t\times u} \otimes \mathbf{I}_p))'] = (\mathbf{A}_{t\times u} \otimes \mathbf{I}_p)vec(\tilde{\mathbf{U}}'_{n\times pt})$ is obtained. Under the normality assumption that $vec(\tilde{\mathbf{U}}'_{n\times pt}) \sim N_{npt}(\mathbf{0}_{npt\times 1}, \mathbf{I}_n \otimes \tilde{\mathbf{\Sigma}}_{pt\times pt})$, then

$$vec(\tilde{\mathbf{U}}'_M) \sim N_{npt}(\mathbf{0}_{npt\times 1}, \mathbf{I}_n \otimes \tilde{\mathbf{\Phi}}_{pu\times pu}),$$

where $\tilde{\mathbf{\Phi}}$ is a $pu \times pu$ covariance matrix defined as

$$\tilde{\mathbf{\Phi}}_{pu\times pu} = (\mathbf{A}' \otimes \mathbf{I}_p)\tilde{\mathbf{\Sigma}}_{pt\times pt}(\mathbf{A} \otimes \mathbf{I}_p). \tag{2.59}$$

Since the within-subject contrast matrix $\mathbf{A}_{t\times u}$ is orthogonal, then $\mathbf{A}'\mathbf{A} = \mathbf{I}_u$ and $\mathbf{A}'\mathbf{1}_t = \mathbf{0}$, and the covariance matrix $\mathbf{\Sigma}^*_{pt\times pt}$, which is a special compound symmetry structure of $\tilde{\mathbf{\Sigma}}_{pt\times pt}$. The reduced covariance matrix $\tilde{\mathbf{\Phi}}_{pu\times pu}$ (2.59) can be formed as

$$
\begin{aligned}
\tilde{\mathbf{\Phi}} = \mathbf{\Phi}^* &= (\mathbf{A}'\otimes\mathbf{I}_p)\mathbf{\Sigma}^*(\mathbf{A}\otimes\mathbf{I}_p) \\
&= (\mathbf{A}'\otimes\mathbf{I}_p)\left[(\mathbf{1}_t\mathbf{1}_t'\otimes\mathbf{\Sigma}_s)+(\mathbf{I}_t\otimes\mathbf{\Sigma}_e)\right](\mathbf{A}\otimes\mathbf{I}_p) \\
&= (\mathbf{A}'\otimes\mathbf{I}_p)(\mathbf{1}_t\mathbf{1}_t'\otimes\mathbf{\Sigma}_s)(\mathbf{A}\otimes\mathbf{I}_p)+(\mathbf{A}'\otimes\mathbf{I}_p)(\mathbf{I}_t\otimes\mathbf{\Sigma}_e)(\mathbf{A}\otimes\mathbf{I}_p) \\
&= (\mathbf{A}'\mathbf{1}_t\mathbf{1}_t'\mathbf{A}\otimes\mathbf{\Sigma}_s)+(\mathbf{A}'\mathbf{A}\otimes\mathbf{\Sigma}_e) \\
&= \mathbf{I}_u\otimes\mathbf{\Sigma}_e\,. \qquad (2.60)
\end{aligned}
$$

The covariance matrix $\tilde{\mathbf{\Phi}}_{pu\times pu}$ in (2.60) satisfies the multivariate sphericity condition which is a necessary and sufficient condition for the SSCP matrices of $\mathbf{S}_e^*$ and $\mathbf{S}_h^*$ to be distributed according to the Wishart distribution (Boik 1988: 475).

2.2.5 The Classic Test Statistic

To obtain the test statistic of (2.54), the MMM defined in (2.51) is reduced by multiplying the model by the post matrix $\mathbf{M}^* = \mathbf{I}_n\otimes\mathbf{A}'_{u\times t}$, i.e.

$$
\begin{aligned}
(\mathbf{I}_n\otimes\mathbf{A}'_{u\times t})\mathbf{Y}^*_{nt\times p} &= (\mathbf{I}_n\otimes\mathbf{A}'_{u\times t})(\mathbf{X}_{n\times g}\otimes\mathbf{I}_t)\mathbf{B}^*_{gt\times p}+(\mathbf{I}_n\otimes\mathbf{A}'_{u\times t})\mathbf{U}^*_{nt\times p} \\
&= (\mathbf{X}_{n\times g}\otimes\mathbf{A}'_{u\times t})\mathbf{B}^*_{gt\times p}+(\mathbf{I}_n\otimes\mathbf{A}'_{u\times t})\mathbf{U}^*_{nt\times p}\,. \qquad (2.61)
\end{aligned}
$$

From the reduced MMM in (2.61), it can be seen that the design matrix, which has the form $\mathbf{X}_{n\times g}\otimes\mathbf{A}'_{u\times t}$, is separable, and that the hypothesis test matrix is also separable in that it takes the required form $\mathbf{C}\otimes\mathbf{A}'$ using the standard multivariate linear models and the univariate mixed model. Establishing an expression for the SSCP matrix due to error, say $\mathbf{S}_e^*$, is only complicated by the fact that the design matrix involves a Kronecker product. To find $\mathbf{S}_e^*$, recall that in the DMM

$$
\mathbf{S}_e = \mathbf{Y}'_{n\times pt}[\mathbf{I}_n - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}']\mathbf{Y}_{n\times pt}\,, \qquad (2.62)
$$

and then by substituting $\mathbf{Y}_{n\times pt}$ and $\mathbf{X}_{n\times g}$ in (2.62) by $(\mathbf{I}_n \otimes \mathbf{A}'_{u\times t})\mathbf{Y}^*_{nt\times p}$ and $\mathbf{X}_{n\times g} \otimes \mathbf{A}'_{u\times t}$ from the reduced MMM (2.61) , we obtain

$$
\begin{aligned}
\mathbf{S}_e^* &= \mathbf{Y}^{*\prime}(\mathbf{I}_n \otimes \mathbf{A})\{\mathbf{I}_{nu} - (\mathbf{X}\otimes\mathbf{A}')[(\mathbf{X}\otimes\mathbf{A}')'(\mathbf{X}\otimes\mathbf{A}')]^{-1}(\mathbf{X}\otimes\mathbf{A}')'\}(\mathbf{I}_n \otimes \mathbf{A}')\mathbf{Y}^* \\
&= \mathbf{Y}^{*\prime}(\mathbf{I}_n \otimes \mathbf{A})\{\mathbf{I}_{nu} - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}' \otimes \mathbf{A}'(\mathbf{A}\mathbf{A}')^{-1}\mathbf{A}\}(\mathbf{I}_n \otimes \mathbf{A}')\mathbf{Y}^* \\
&= \mathbf{Y}^{*\prime}(\mathbf{I}_n \otimes \mathbf{A}\mathbf{A}')\mathbf{Y}^* - \mathbf{Y}^{*\prime}(\mathbf{I}_n \otimes \mathbf{A})[\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}' \otimes \mathbf{A}'(\mathbf{A}\mathbf{A}')^{-1}\mathbf{A}](\mathbf{I}_n \otimes \mathbf{A}')\mathbf{Y}^* \\
&= \mathbf{Y}^{*\prime}(\mathbf{I}_n \otimes \mathbf{A}\mathbf{A}')\mathbf{Y}^* - \mathbf{Y}^{*\prime}[\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}' \otimes \mathbf{A}\mathbf{A}'(\mathbf{A}\mathbf{A}')^{-1}\mathbf{A}\mathbf{A}']\mathbf{Y}^* \\
&= \mathbf{Y}^{*\prime}(\mathbf{I}_n \otimes \mathbf{A}\mathbf{A}')\mathbf{Y}^* - \mathbf{Y}^{*\prime}[\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}' \otimes \mathbf{A}\mathbf{A}']\mathbf{Y}^* \\
&= \mathbf{Y}^{*\prime}[(\mathbf{I}_n - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}) \otimes \mathbf{A}\mathbf{A}']\mathbf{Y}^* . \qquad (2.63)
\end{aligned}
$$

Let $\hat{\mathbf{\Gamma}}^*_{uv_h\times p} = (\mathbf{C}\otimes\mathbf{A}')\hat{\mathbf{B}}^*_{gt\times p}$, where $\hat{\mathbf{B}}^*$ is defined by (2.53), then the SSCP matrix due to the hypothesis becomes

$$
\mathbf{S}_h^* = \left(\hat{\mathbf{\Gamma}}^* - \mathbf{\Gamma}_0^*\right)\left[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}'\right]^{-1}\left(\hat{\mathbf{\Gamma}}^* - \mathbf{\Gamma}_0^*\right)'. \qquad (2.64)
$$

However, because one usually tests $H_0 : (\mathbf{C}\otimes\mathbf{A}')\mathbf{B}^* = \mathbf{0}$, $\mathbf{S}_h^*$ from (2.64), this reduces to

$$
\begin{aligned}
\mathbf{S}_h^* &= \hat{\mathbf{B}}^{*\prime}(\mathbf{C}'\otimes\mathbf{A})[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\otimes\mathbf{A}')\hat{\mathbf{B}}^* \\
&= \mathbf{Y}^{*\prime}((\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\otimes\mathbf{I}_t)'(\mathbf{C}'\otimes\mathbf{A})[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\otimes\mathbf{A}')((\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\otimes\mathbf{I}_t)\mathbf{Y}^* \\
&= \mathbf{Y}^{*\prime}(\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}'\otimes\mathbf{A})[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\otimes\mathbf{A}')\mathbf{Y}^* \\
&= \mathbf{Y}^{*\prime}\left\{\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\otimes\mathbf{A}\mathbf{A}'\right\}\mathbf{Y}^* . \qquad (2.65)
\end{aligned}
$$

Since the MMM is related to the rearranged DMM, it is possible to rewrite $\mathbf{S}_e^*$ and $\mathbf{S}_h^*$, as defined in (2.64) and (2.65) respectively, by using $\mathbf{S}_e$ and $\mathbf{S}_h$ in (2.29) and (2.30) from the DMM analysis. Boik (1991: 1238) gave the forms of $\mathbf{S}_e^*$ and $\mathbf{S}_h^*$ in the MMM analysis based on Thompson's (1973: 545) Generalized Trace Operator of $\mathbf{S}_e$ and $\mathbf{S}_h$ in the DMM. Let $\mathbf{D}$ be a $pu\times pu$ matrix and let $\mathbf{D}_{ll'}$ be the $u\times u$ sub-matrix of the l^{th} and l'^{th} response variables, $l, l' = 1, 2, \ldots, p$. Subsequently, the

Generalized Trace Operator of $\mathbf{D}$, denoted by $T_p(\mathbf{D})$, is a $p \times p$ matrix represented as

$$T_p(\mathbf{D}) = \left[tr(\mathbf{D}_{ll'})\right]_{p \times p}.$$

From the DMM, partitioning the $pu \times pu$ sum of squares and cross product matrices $\mathbf{S}_e$ and $\mathbf{S}_h$ in (2.29) and (2.30), and also partitioning the $pu \times pu$ covariance matrix $\mathbf{\Phi}$ in (2.23) and the noncentrality matrix $\mathbf{\Delta}$ in (2.38) into $u \times u$ submatrices, i.e. $\mathbf{S}_e = \left[(\mathbf{S}_e)_{ll'}\right]$, $\mathbf{S}_h = \left[(\mathbf{S}_h)_{ll'}\right]$, $\mathbf{\Phi} = \left[\mathbf{\Phi}_{ll'}\right]$ and $\mathbf{\Delta} = \left[\mathbf{\Delta}_{ll'}\right]$, for $l, l' = 1, 2, \ldots, p$, we obtain

$$\mathbf{S}_e^* = T_p(\mathbf{S}_e), \tag{2.66}$$

$$\mathbf{S}_h^* = T_p(\mathbf{S}_h), \tag{2.67}$$

$$\mathbf{\Phi}^* = T_p(\mathbf{\Phi}), \tag{2.68}$$

$$\text{and} \quad \mathbf{\Delta}^* = T_p(\mathbf{\Delta}). \tag{2.69}$$

If the multivariate sphericity condition (2.60) is satisfied, the error and hypothesis SSCP matrices $\mathbf{S}_e^*$ (2.66) and $\mathbf{S}_h^*$ (2.67) are independently distributed as

$$\mathbf{S}_e^* \sim W_p\left(u^{-1}\mathbf{\Phi}^*, uv_e\right), \tag{2.70}$$

$$\text{and } \mathbf{S}_h^* \sim W_p\left(u^{-1}\mathbf{\Phi}^*, uv_h, (u\mathbf{\Phi}^*)^{-1}\mathbf{\Delta}^*\right). \tag{2.71}$$

Therefore, when $uv_e > p$, the classical likelihood ratio statistic, or Wilks' Lambda, for testing $H: (\mathbf{C} \otimes \mathbf{A}')\mathbf{B}^* = \mathbf{\Gamma}_\mathbf{0}^*$ is given by

$$\Lambda = \frac{\left|\mathbf{S}_e^*\right|}{\left|\mathbf{S}_e^* + \mathbf{S}_h^*\right|} = \left|\mathbf{I}_{pu} + \mathbf{S}_h^*\mathbf{S}_e^{*-1}\right|^{-1} = \prod_{i=1}^{s^*}(1 + d_i^*)^{-1}, \tag{2.72}$$

where $d_1^*, \ldots, d_s^*$ are eigenvalues of $\mathbf{S}_h^*\mathbf{S}_e^{*-1}$, $s^* = \min(uv_e, uv_h)$.

In the same way as with the DMM test, Wilks' Lambda criterion of the MMM test can be transformed to the F value of Rao's F approximation such that

$$F_{\Lambda^*} = ((\Lambda^*)^{-c} - 1)(\frac{v_1}{v_2}) \sim F_{v_1, v_2}, \tag{2.73}$$

where

$$c = \left\{ \frac{p^2 + (uv_h)^2 - 5}{(puv_h)^2 - 4} \right\}^{1/2},$$

$$v_1 = puv_h,$$

and
$$v_2 = g^{-1}[uv_e - \tfrac{1}{2}(p - uv_h + 1)] - \tfrac{1}{2}(puv_h - 2).$$

When multivariate sphericity is not satisfied, the MMM is not valid but the DMM can be used. However, one does not want to assume a general structure. Boik (1991: 1239), Galecki (1994: 3108-3112) and Naik and Rao (2001: 95-100) proposed an alternative structure of the covariance matrix that is the Kronecker product structure $\mathbf{\Sigma}_{t\times t} \otimes \mathbf{\Sigma}_{p\times p}$, where $\mathbf{\Sigma}_{t\times t}$ is a covariance of repeated measurements and $\mathbf{\Sigma}_{p\times p}$ is a covariance of dependent response variables. Boik (1991: 1239) gave an ε-adjustment MMM test to correct the degrees of freedom of the Wishart distribution for tests of the time and interaction effects. He showed that the adjusted df MMM test is more powerful than the DMM test when the sample size is very small. However, if the sample size is large, the DMM test is preferred.

Vallejo, Fidalgo, and Fernández (1981 quoted in Vallejo, Fidalgo, and Fernández, 2001: 2) studied the performance of an unadjusted MMM test, the ε_1-adjusted MMM test based on the generalization of Greenhouse and Geisser's (1959: 101) test proposed by López and Ato (1994: 457), the ε- adjusted MMM test developed by Boik (1991: 1239) and a DMM test. They found that when multivariate sphericity is not satisfied, the unadjusted MMM test was liberal, Greenhouse-Geisser's ε_1-adjusted test was conservative, and Boik's ε-adjusted test was robust if and only if the covariance matrix has the Kronecker product structure $\mathbf{\Sigma}_{t\times t} \otimes \mathbf{\Sigma}_{p\times p}$. As the degree of the Kronecker product structure $(\mathbf{\Sigma}_{t\times t} \otimes \mathbf{\Sigma}_{p\times p})$ decreased, Boik's test became conservative. On the other hand, the DMM test maintained Type I error rates at the nominal alpha level across the values of ε and showed a significant increase in power over the other evaluated tests. Boik (1991: 1250) reported similar results in that the ε-adjusted MMM test is most accurate when the covariance matrix has the Kronecker product structure and is more efficient than the DMM test when the sample size is very small. If the sample size is reasonably large, there is no advantage in using adjusted MMM tests.

2.3 Tests of High Dimensional MANOVA

Some authors' works have shown that dealing with high dimensional datasets with fewer observations than dimensions is frequently encountered. Srivastava (2007: 55) has developed a multivariate theory for analyzing multivariate data sets that have fewer observations than dimensions. He considered the problems of testing the hypothesis concerning the mean vector in one sample, the equality of two sample mean vectors in the two-sample case, as well as MANOVA issues.

Fujikoshi, Himmeno and Wakaki (2004: 21) derived an asymptotic expansion of the Dempster test when both n and p are large, and $p/n \to \gamma \in (0,\infty)$. They found that Dempster's test performs better than three classical test statistics when the variation of the eigenvalues of the covariance matrix is small. Srivastava and Fujikoshi (2006: 1929) proposed a high-dimensional test in the MANOVA model with fewer observations than dimensions. They proposed two test statistics adapted from Dempster's and the likelihood ratio tests using the Moore-Penrose inverse matrix of the sum of squares and products due to error (or 'within' matrix). The asymptotic distributions of their statistics under the null hypothesis as well as under the alternatives were given under certain mild conditions. A power comparison among their statistics was made and the results show that the adapted version of the likelihood ratio test appears to perform better for large p and small n. Scott (2007: 1827) proposed a number of high-dimensional tests for testing the equality of the mean vectors in a one-way multivariate analysis of variance.

However, there have only been a few recent attempts on the issue of high dimensionality for repeated measure data. Bathke (2002: 120) proved that the classical ANOVA F-test is still asymptotically normal when the number of levels of a factor converges to infinity but the number of replications is finite, assuming independent observations. He proved asymptotic normality without relying on the normality assumption for the model. Bathke and Harrar (2008: 590-598) derived asymptotic distributions of different multivariate tests for a factorial structure when the number of treatments tends to infinity while the number of replications is relatively small. Their test statistics are nonparametric and do not require any special structure of the covariance matrix.

Ahmad, Werner and Bruner (2008: 417-421) derived one sample statistic for the analysis of a repeated measurements design when the dimension of repeated measurements, denoted by d, is large compared with the sample size n, i.e. $d > n$. They gave a modified version of an ANOVA-type statistic based on Box's approximation (Box, 1954, quoted in Ahmad et al. 2008: 417). Ahmad (2008:11-58) worked on his doctoral dissertation to develop one and two sample test statistics for the analysis of repeated measurements designs when the dimensions $d > n$.

A summary of high-dimensional tests in MANOVA as described above are reviewed as follows:

Let $\mathbf{Y}$ be an $n \times p$ observation matrix which is obtained by independently observing a p dimensional variate $\boldsymbol{y} = (y_1, \ldots, y_p)'$ for n objects. A multivariate linear model for $\mathbf{Y}_{n\times p}$ is expressed as

$$\mathbf{Y}_{n\times p} = \mathbf{X}_{n\times q}\mathbf{B}_{q\times p} + \mathbf{E}_{n\times p},$$

where $\mathbf{X}$ is a known $n\times q$ design matrix of $rank(\mathbf{X}) = q$, $\mathbf{B}$ is a $q\times p$ unknown parameter matrix and $\mathbf{E}$ is an $n\times p$ error matrix. It is assumed that the row vectors of $\mathbf{E}$ are i.i.d. as multivariate normal distributions with a zero mean vector and a $p\times p$ unknown nonsingular covariance matrix $\mathbf{\Sigma}_{p\times p}$, denoted by $\boldsymbol{e}_i \sim N_p(\mathbf{0}_{p\times 1}, \mathbf{\Sigma}_{p\times p})$. The maximum likelihood estimators of $\mathbf{B}_{q\times p}$ and $\mathbf{\Sigma}_{p\times p}$ are

$$\hat{\mathbf{B}}_{g\times p} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}_{n\times p},$$

$$\begin{aligned}\hat{\mathbf{\Sigma}}_{p\times p} &= \frac{(\mathbf{Y}_{n\times p} - \mathbf{X}\hat{\mathbf{B}}_{q\times p})'(\mathbf{Y}_{n\times p} - \mathbf{X}\hat{\mathbf{B}}_{q\times p})}{n} \\ &= \frac{\mathbf{Y}'_{n\times p}[\mathbf{I}_n - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}']\mathbf{Y}_{n\times p}}{n}.\end{aligned}$$

For testing the linear hypothesis

$$H_0 : \mathbf{CB}_{q\times p} = \mathbf{0} \text{ versus } H_A : \mathbf{CB}_{q\times p} \neq \mathbf{0}, \tag{2.72}$$

where $\mathbf{C}$ is a $k\times q$ matrix of $rank(\mathbf{C}) = k \le g$, let $\mathbf{S}_{e(p\times p)}$ and $\mathbf{S}_{h(p\times p)}$ be the $p\times p$ matrices of the sums of squares and products due to error and the hypothesis defined by

$$\mathbf{S}_{e(p\times p)} = \mathbf{Y}'_{n\times p}[\mathbf{I}_n - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}']\mathbf{Y}_{n\times p},$$

$$\mathbf{S}_{h(p\times p)} = (\mathbf{C}\hat{\mathbf{B}}_{g\times p})'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}\mathbf{C}\hat{\mathbf{B}}_{g\times p} \ .$$

Under the assumption of normality, $\mathbf{S}_{e(p\times p)}$ and $\mathbf{S}_{h(p\times p)}$ are independently distributed as a central Wishart distribution $W_p(\mathbf{\Sigma}_{p\times p}, m)$, where $m = n-k$, and a noncentral Wishart distribution $W_p(\mathbf{\Sigma}_{p\times p}, k, \mathbf{DD}')$, where $\mathbf{D}$ is a $p\times k$ matrix such that

$$\mathbf{DD}' = (\mathbf{CB})'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}\mathbf{CB}.$$

Under the assumptions that $m = n-k \geq p$ and $\mathbf{\Sigma}$ is nonsingular, the following four well known classical statistics have been used:

(1) Wilks' Lambda Criterion

$$\Lambda = \frac{\left|\mathbf{S}_{e(p\times p)}\right|}{\left|\mathbf{S}_{h(p\times p)} + \mathbf{S}_{e(p\times p)}\right|} = \sum_{i=1}^{s} \frac{l_i}{1+l_i}$$

(2) The Lawley – Hotelling Trace Criterion

$$T_0^2 = tr(\mathbf{S}_{h(p\times p)}\mathbf{S}_{e(p\times p)}^{-1}) = \sum_{i=1}^{s} l_i$$

(3) The Bartlett-Nanda-Pillai Trace Criterion

$$V = tr[\mathbf{S}_{h(p\times p)}(\mathbf{S}_{e(p\times p)} + \mathbf{S}_{h(p\times p)})^{-1}] = \sum_{i=1}^{s} \frac{l_i}{1+l_i}$$

(4) The Roy Maximum Root Criterion

$$\theta = l_1/(1+l_1)$$

where $s = \min(p,q)$ and $l_1 > \ldots > l_s > 0$ are non-zero eigenvalues of $\mathbf{S}_{h(p\times p)}\mathbf{S}_{e(p\times p)}^{-1}$.

When $m = n-k < p$, $\mathbf{S}_{e(p\times p)}$ becomes singular of rank $m < p$, it will be impossible to use these classical statistics. For such cases, some tests which can be used for testing the hypothesis when $m < p$ are reviewed.

2.3.1 Dempster's Test

Dempster (1958: 998, 1960: 42-44) first proposed a non-exact test for one and two high dimensional samples cases. For testing (2.72), Srivastava and Fujikoshi (2006: 1929) gave a generalization of Dempster's test.

First, they defined $a_i = tr(\mathbf{\Sigma}^i_{p\times p})/p$, for $i = 1,\ldots,4$ and $b = a_1^2/a_2$, and assumed that $0 < \lim_{p\to\infty} a_i = a_{i0} < \infty$, for $i = 1,\ldots,4$. It has been shown in Srivastava (2005: 252) that the consistent estimators of a_1, a_2 and b as $n \to \infty$ and $p \to \infty$ are

$$\hat{a}_1 = tr(\mathbf{S}_{e(p\times p)})/mp\,,$$

$$\hat{a}_2 = \frac{1}{(m-1)(m+2)p}\left[tr(\mathbf{S}^2_{e(p\times p)}) - \frac{1}{m}(tr(\mathbf{S}_{e(p\times p)}))^2\right],$$

$$\hat{b} = \hat{a}_1^2/\hat{a}_2\,.$$

The generalization of Dempster's test proposed by Srivastava and Fujikoshi (2006: 1929) is defined by

$$T_D = \frac{m\ tr(\mathbf{S}_{h(p\times p)})}{k\ tr(\mathbf{S}_{e(p\times p)})}.$$

The exact distribution of T_D even under the hypothesis is difficult to obtain. An approximate distribution of T_D under the hypothesis is

$$T_D \sim F_{[k\hat{d}],[m\hat{d}]}\,,$$

where $F_{a,b}$ denotes the F-distribution with a and b degrees of freedom, and $\lfloor x \rfloor$ denotes the largest integer $\le x$. Srivastava (2007: 67) proposed estimating d using $\hat{d} = p\hat{b}$.

Fujikoshi et al. (2004: 20) studied the asymptotic distribution of the Dempster's test under a high dimension framework:

(A1) With k fixed, $n \to \infty$, $p \to \infty$, $\dfrac{p}{n} \to \gamma \in (0,\infty)$.

(A2) Assume that, for the null case,

$$a_i = \frac{tr(\mathbf{\Sigma}^i_{p\times p})}{p} = O(1)\ ,\ i = 1,2\,.$$

(A3) For the non-null case, assume that

$$a_i = \frac{tr(\mathbf{\Sigma}^i_{p\times p}\mathbf{\Xi})}{p} = O(1) \quad i = 1,2\,,$$

where $\mathbf{\Xi} = \mathbf{\Sigma}^{-1/2}_{p\times p}(\mathbf{CB}_{q\times p})'(\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}')(\mathbf{CB}_{q\times p})\mathbf{\Sigma}^{-1/2}_{p\times p}$.

Under the null hypothesis, $\mathbf{S}_{e(p\times p)}$ and $\mathbf{S}_{h(p\times p)}$ are independently distributed as central Wishart distributions, $W_p(\mathbf{\Sigma}_{p\times p}, m)$ and $W_p(\mathbf{\Sigma}_{p\times p}, k)$, respectively.

Let

$$\tilde{T}_D = \sqrt{p}\left\{m\frac{tr(\mathbf{S}_{h(p\times p)})}{tr(\mathbf{S}_{e(p\times p)})} - k\right\}$$

$$= \sqrt{p}\left\{m\frac{tr(\mathbf{S}_{h(p\times p)})}{mp\hat{a}_1} - k\right\} = \frac{tr(\mathbf{S}_{h(p\times p)})}{\sqrt{p}\hat{a}_1} - v_h\sqrt{p}\,. \tag{2.73}$$

Let U and V be defined by

$$U = \frac{tr(\mathbf{S}_{h(p\times p)}) - ktr(\mathbf{\Sigma}_{p\times p})}{\sqrt{2ktr(\mathbf{\Sigma}^2_{p\times p})}}, \quad V = \frac{tr(\mathbf{S}_{e(p\times p)}) - mtr(\mathbf{\Sigma}_{p\times p})}{\sqrt{2mtr(\mathbf{\Sigma}^2_{p\times p})}},$$

then, when considering the characteristic functions of U and V, it can be seen that U and V are asymptotically distributed as a normal distribution $N(0,1)$. Using (2.73), $\tilde{T}_D$ can be expanded as (Fujikoshi et al. 2004: 21-24)

$$\tilde{T}_D = \sqrt{p}\left\{\frac{U\sqrt{2mpk}\sqrt{tr(\mathbf{\Sigma}^2_{p\times p})/p} + pk\sqrt{m}tr(\mathbf{\Sigma}_{p\times p})/p}{V\sqrt{2p}\sqrt{(tr(\mathbf{\Sigma}_{p\times p}))^2/p} + p\sqrt{m}tr(\mathbf{\Sigma}_{p\times p})/p} - k\right\}$$

$$= \frac{\sqrt{2ktr(\mathbf{\Sigma}^2_{p\times p})/p}}{tr(\mathbf{\Sigma}_{p\times p})/p}U + o(1).$$

Therefore, under assumptions (A1) and (A2), it holds that

$$\frac{\tilde{T}_D}{\sigma_D} \xrightarrow{d} N(0,1),$$

where $\xrightarrow{d}$ denotes convergences in distribution, and

$$\sigma_D = \frac{\sqrt{2ktr(\mathbf{\Sigma}^2_{p\times p})/p}}{tr(\mathbf{\Sigma}_{p\times p})/p}.$$

Since $\mathbf{\Sigma}_{p\times p}$ is usually unknown, it is necessary to use the consistent estimator of σ_D, which is given by

$$\hat{\sigma}_D = \frac{\sqrt{2k\left\{tr(\mathbf{S}^2_{e(p\times p)})/m^2 - (tr(\mathbf{S}_{e(p\times p)}))^2/m^3\right\}/p}}{tr(\mathbf{S}_{e(p\times p)})/mp}.$$

2.3.2 Bai and Saranadasa's Test

Bai and Saranadasa (1996: 318-320) proposed a test for the two-sample high dimensional problem. Srivastava and Fujikoshi (2006: 1930) gave a generalization of Bai and Saranadasa's test for the MANOVA problem with fewer observations than dimensions.

In the same way as for the generalization of Dempster's test, $a_i = tr(\mathbf{\Sigma}^i_{p\times p})/p$, for $i = 1,\ldots,4$, and $b = (a_1^2/a_2)$ are defined, and it is assumed that

$$0 < \lim_{p\to\infty} a_i = a_{i0} < \infty,\ i = 1,\ldots,4,\ \text{and} \tag{2.83}$$

$$0 < \lim_{p\to\infty} \frac{tr(\mathbf{\Sigma}^i_{p\times p}\mathbf{\Xi})}{p} < \infty, i = 1,2, \tag{2.84}$$

where $\mathbf{\Xi} = \mathbf{\Sigma}^{-1/2}_{p\times p}\mathbf{DD}'\mathbf{\Sigma}^{-1/2}_{p\times p}$.

The consistent estimators of a_1, a_2 and b as $n\to\infty$ and $p\to\infty$ are defined by (2.79), (2.80) and (2.81).

The generalization of Bai and Saranadasa's test proposed by Srivastava and Fujikoshi (2006: 1930) is defined by

$$\begin{aligned}
T_{BS} &= \left[\frac{p\hat{b}}{2k(1+n^{-1}k)}\right]^{\frac{1}{2}}\left[\frac{tr(\mathbf{S}_{h(p\times p)}) - pk\hat{a}_1}{p\hat{a}_1}\right] \\
&= \left[\frac{p}{2k\hat{a}_2(1+n^{-1}k)}\right]^{\frac{1}{2}}\left[p^{-1}tr(\mathbf{S}_{h(p\times p)}) - k\hat{a}_1\right] \\
&= \left[2k\hat{a}_2(1+v_e^{-1}v_h)\right]^{\frac{1}{2}}\left[\frac{tr(\mathbf{S}_{h(p\times p)})}{\sqrt{p}} - \frac{k}{\sqrt{m}}\frac{tr(\mathbf{S}_{e(p\times p)})}{\sqrt{mp}}\right].
\end{aligned}$$

Under the normality assumption (2.74), if (Srivastava and Fujikoshi, 2006: 1933)

$$\frac{\max_{1\le i\le p}\lambda_i/\sqrt{p}}{\sqrt{a_2}} \to 0 \ \text{as}\ p\to\infty,$$

then the asymptotic distribution of T_{BS} under the null hypothesis (2.75) is a standard normal distribution given by

$$\lim_{n\to\infty}\lim_{p\to\infty}\left[P_0(T_{BS} < z) - \mathbb{N}(z)\right] = 0,$$

where P_0 denotes that the probability is being calculated under the hypothesis and $\mathbb{N}(z)$ is a cumulative standard normal distribution at z.

The asymptotic distribution of T_{BS} under the non-null hypothesis is standard normal given by

$$\lim_{n\to\infty}\lim_{p\to\infty}\left[P_1(T_{BS} > z)\right] = \lim_{n\to\infty}\lim_{p\to\infty}\mathbb{N}\left[-\frac{\sigma_1}{\sigma_1^*}z + \frac{tr(\mathbf{\Sigma}_{p\times p}\mathbf{\Xi})}{\sigma_1^*\sqrt{p}}\right],$$

where P_1 denotes that the probability is being calculated under the local alternative hypothesis, and $\sigma_1^2 = 2ka_2(1+n^{-1}k)$ and $\sigma_1^{*2} = \sigma_1^2 + 4tr(\mathbf{\Sigma}_{p\times p}^2\mathbf{\Xi})/p$.

2.3.3 An Adapted Version of Wilks' Lambda, Lawley-Hotelling's and the Bartlett-Nanda-Pillai Tests

Srivastava and Fujikoshi (2006: 1930) proposed test statistics for testing (2.72) when $m = n-k < p$. These statistics are adapted versions of Wilks' Lambda Criterion, Lawley-Hotelling's Criterion and the Bartlett-Nanda-Pillai Criterion by using the Moore-Penrose inverse of $\mathbf{S}_e$, say $\mathbf{S}_e^+$. The Moore-Penrose inverse of $a\times b$ matrix $\mathbf{A}$ is denoted by $\mathbf{A}^+$ which satisfies the four conditions: (i) $\mathbf{AA}^+\mathbf{A} = \mathbf{A}$, (ii) $\mathbf{A}^+\mathbf{AA}^+ = \mathbf{A}^+$, (iii) $(\mathbf{AA}^+)' = \mathbf{AA}^+$ and (iv) $(\mathbf{A}^+\mathbf{A})' = \mathbf{A}^+\mathbf{A}$. The Moore-Penrose inverse is unique and is equal to the inverse of the nonsingular $a\times a$ square matrix **A**.

In the same way as with Dempster's test, define $a_i = tr(\mathbf{\Sigma}_{p\times p}^i)/p$, $i = 1,\ldots,4$ and $b = a_1^2/a_2$ and assume that $0 < \lim_{p\to\infty} a_i = a_{i0} < \infty$, $i = 1,\ldots,4$. The consistent estimators of a_1, a_2 and b as $n\to\infty$ and $p\to\infty$ are

$$\hat{a}_1 = tr(\mathbf{S}_{e(p\times p)})/mp,$$

$$\hat{a}_2 = \frac{1}{(m-1)(m+2)p}\left[tr(\mathbf{S}_{e(p\times p)}^2) - \frac{1}{m}(tr(\mathbf{S}_{e(p\times p)}))^2\right],$$

$$\hat{b} = \hat{a}_1^2/\hat{a}_2.$$

The adapted versions of Wilks' Lambda, Lawley-Hotelling's and Bartlett-Nanda-Pillai Criterions, as proposed by Srivastava and Fujikoshi (2006 : 1930), are

$$T_W = -p\hat{b}\log\left|\mathbf{I}_p + \mathbf{S}_{h(p\times p)}\mathbf{S}^{+}_{e(p\times p)}\right|,$$

$$= -p\hat{b}\log\prod_{i=1}^{s}(1+c_i)^{-1},$$

$$T_{LH} = -p\hat{b}\sum_{i=1}^{s}c_i,$$

$$T_{BNP} = -p\hat{b}\sum_{i=1}^{s}\frac{c_i}{1+c_i},$$

where c_i are the non-zero eigenvalues of $\mathbf{S}_{h(p\times p)}\mathbf{S}^{+}_{e(p\times p)}$ and $s = \min(p,k)$.

Srivastava and Fujikoshi (2006: 1931-1932) showed that, as $p \to \infty$, the tests T_W, T_{LH} and T_{BNP} are asymptotically equivalent when they only consider the null and non-null distributions of T_W. Under the null hypothesis, it can be shown that (Srivastava and Fujikoshi, 2006: 1934)

$$\lim_{n\to\infty}\lim_{p\to\infty}\left[P_0\left(\frac{T_1^* - mk}{\sqrt{2mk}} < z\right) - \mathbb{N}(z)\right] = 0,$$

and, under the local alternative hypothesis (Srivastava and Fujikoshi, 2006: 1938),

$$\lim_{n\to\infty}\lim_{p\to\infty}\left[P_1\left(\frac{T_1^* - mk}{\sqrt{2mk}} > z\right)\right] = \mathbb{N}\left(-z + \frac{mtr(\mathbf{\Sigma}_{p\times p}\mathbf{\Xi})}{pa_2\sqrt{2mk}}\right).$$

CHAPTER 3

TESTS FOR HIGH DIMENSIONAL MULTIVARIATE REPEATED MEASUREMENTS DESIGN

3.1 High Dimensional DMM Tests

As described in section 2.1, the DMM is

$$\mathbf{Y}_{n\times pt} = \mathbf{X}_{n\times g}\mathbf{B}_{g\times pt} + \mathbf{U}_{n\times pt}, \tag{3.1}$$

where $\mathbf{Y}$ is an $n\times pt$ response matrix for n subjects, $\mathbf{X}$ is an $n\times g$ between subject design matrix of $rank(\mathbf{X}) = g$, $\mathbf{B}$ is a $g\times pt$ unknown parameter matrix of fixed effects and $\mathbf{U}$ is an $n\times pt$ random error matrix. It is assumed that the $npt\times 1$ error vector $\mathbf{u} = vec(\mathbf{U})$ is distributed as

$$\mathbf{u}_{npt\times 1} = vec(\mathbf{U}_{n\times pt}) \sim N_{npt}(\mathbf{0}_{npt\times 1}, \mathbf{\Sigma}_{pt\times pt} \otimes \mathbf{I}_n), \tag{3.2}$$

where $\mathbf{\Sigma}$ is a $pt\times pt$ unknown positive definite covariance matrix.

From Theorem 2.2 and (2.12), the BLUE or MLE of $\mathbf{B}$ is given by

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

and, from (2.13), the MLE of $\mathbf{\Sigma}$ is

$$\hat{\mathbf{\Sigma}} = \frac{(\mathbf{Y}-\mathbf{XB})'(\mathbf{Y}-\mathbf{XB})}{n-g}.$$

The Multivariate General Linear Hypothesis of interest can be put into the form

$$H: \mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{\Gamma}_0, \tag{3.3}$$

where $\mathbf{C}$ is a $v_h \times g$ between group contrast matrix having $rank(\mathbf{C}) = v_h \le g$ and $\mathbf{A}$ is a $t\times u$ within-subject contrast matrix of $rank(\mathbf{A}) = u \le t$. Without loss of generality, it can be assumed that $\mathbf{A}'\mathbf{A} = \mathbf{I}_u$.

For testing the contrasts among the t time periods of p-variate responses in (3.3), the post $\mathbf{M} = \mathbf{I}_p \otimes \mathbf{A}$ is multiplied into the DMM (3.1) to obtain

$$\mathbf{Y}_M = \mathbf{X}\mathbf{B}_M + \mathbf{U}_M, \tag{3.4}$$

where $\mathbf{Y}_M = \mathbf{Y}(\mathbf{I}_p \otimes \mathbf{A})$, $\mathbf{B}_M = \mathbf{B}(\mathbf{I}_p \otimes \mathbf{A})$ and $\mathbf{U}_M = \mathbf{U}(\mathbf{I}_p \otimes \mathbf{A})$.

By assuming the multivariate normality assumption (3.2) and the reduced DMM (3.4),

$$vec(\mathbf{Y}_M) \sim N_{npu}\left((\mathbf{I}_{pu} \otimes \mathbf{X})vec(\mathbf{B}_M), \mathbf{\Phi}_{pu\times pu} \otimes \mathbf{I}_n\right), \tag{3.5}$$

where

$$\mathbf{\Phi}_{pu\times pu} = (\mathbf{I}_p \otimes \mathbf{A})'\mathbf{\Sigma}_{pt\times pt}(\mathbf{I}_p \otimes \mathbf{A}). \tag{3.6}$$

Under the assumptions in (3.4) and (3.5), the test statistic for testing (3.3) is obtained by performing a multivariate linear model analysis on the pu-dimensional model in (3.4).

As shown in Theorem 2.4, from the reduced DMM (3.4), the $pu \times pu$ sum of squares and product (SSCP) matrices corresponding to error and the hypothesis, $\mathbf{S}_e$ and $\mathbf{S}_h$, are defined by

$$\mathbf{S}_e = \mathbf{Y}'_M[\mathbf{I}_n - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}']\mathbf{Y}_M \tag{3.7}$$

and
$$\mathbf{S}_h = (\mathbf{C}\hat{\mathbf{B}}_M)'\left[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}'\right]^{-1}(\mathbf{C}\hat{\mathbf{B}}_M). \tag{3.8}$$

Assuming (3.5) is correct, the matrices $\mathbf{S}_e$ and $\mathbf{S}_h$ are independently distributed as central and non-central Wishart distributions, as defined by (Boik, 1988: 472),

$$\mathbf{S}_e \sim W_{pu}(\mathbf{\Phi}, v_e) \tag{3.9}$$

and
$$\mathbf{S}_h \sim W_{pu}(\mathbf{\Phi}, v_h, \mathbf{\Phi}^{-1}\mathbf{\Delta}), \tag{3.10}$$

where $v_e = n - rank(\mathbf{X}) = n - g$, $v_h = rank(\mathbf{C})$ and the noncentrality matrix is

$$\mathbf{\Delta} = (\mathbf{\Gamma} - \mathbf{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{\Gamma} - \mathbf{\Gamma}_0). \tag{3.11}$$

If the degrees of freedom of the error SSCP matrix $\mathbf{S}_e$ is fewer than its dimensions, $v_e < pu$, then the error SSCP matrix $\mathbf{S}_e$ has $rank(\mathbf{S}_e) = v_e < pu$, and so $\mathbf{S}_e$ is singular (Muller and Stewart, 2006: 194). Thus, in this particular high dimensional situation, the classical Wilks' Lambda statistic (2.28) given in Theorem 2.4 does not exist.

To obtain a test statistic for high dimensional data in the DMM, Dempster's test and Bai and Saranadasa's test, as proposed by Srivastava (2006: 1929-1930), can be applied to DMM analysis when $v_e < pu$ by defining

$$a_i = \frac{tr(\mathbf{\Phi}^i)}{pu} \quad , \qquad \text{for } \ i = 1, \ldots, 4\,, \tag{3.12}$$

and

$$b = \frac{a_1^2}{a_2}. \tag{3.13}$$

It is assumed that:

(1) $p \to \infty$, $n \to \infty$, t is fixed and $v_e < pu$ (3.14)

(2) $\lim\limits_{p\to\infty} a_i = a_{i0}$, for $i = 1, \ldots, 4$, and $0 < a_{i0} < \infty$ (3.15)

(3) For the local alternative hypothesis,

$$0 < \lim_{p\to\infty} \frac{tr(\mathbf{\Phi}^i \mathbf{\Xi})}{pu} < \infty \ , \quad \text{for } i = 1, \ldots, 4\,, \tag{3.16}$$

where $\mathbf{\Xi} = \mathbf{\Phi}^{-1/2} \mathbf{\Delta} \mathbf{\Phi}^{-1/2}$ and $\mathbf{\Delta} = (\mathbf{\Gamma} - \mathbf{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{\Gamma} - \mathbf{\Gamma}_0)$

Lemma 3.1 Under assumptions (3.5) and (3.13), as $n \to \infty$, consistent estimators of a_1 and a_2 are respectively given by

$$\hat{a}_1 = \frac{tr(\mathbf{S}_e)}{v_e pu} \tag{3.17}$$

and

$$\hat{a}_2 = \frac{1}{(v_e - 1)(v_e + 2)pu}\left[tr(\mathbf{S}_e^2) - \frac{1}{v_e}(tr(\mathbf{S}_e))^2 \right]. \tag{3.18}$$

Proof. See Appendix A.

Corollary 3.1 The consistent estimators of b are

$$\hat{b} = \frac{\hat{a}_1^2}{\hat{a}_2}, \tag{3.19}$$

where $\hat{a}_1$ and $\hat{a}_2$ are given by (3.17) and (3.18), respectively.

3.1.1 Generalization of Dempster's Test

Dempster (1958: 998, 1960: 42-44) first proposed a non-exact test for the difference between two population mean vectors in two high dimensional sample cases. Srivastava and Fujikoshi (2006: 1929) gave a generalization of Dempster's test for high dimensional MANOVA which is adapted in this dissertation for testing the Multivariate General Linear Hypothesis (3.3), $H:\mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{\Gamma}_0$, in DMM analysis as follows:

$$T_1 = \frac{v_e \; tr(\mathbf{S}_h)}{v_h \; tr(\mathbf{S}_e)} \; . \tag{3.20}$$

Lemma 3.2 The proposed test T_1 is invariant under the group of orthogonal linear transformations $\mathbf{Y}_M \to c\mathbf{Y}_M\mathbf{\Upsilon}$, where c is a nonzero constant and $\mathbf{\Upsilon} \in \mathbf{O}_{pu}$, $\mathbf{O}_{pu}$ is a group of $pu \times pu$ orthogonal matrices such that $\mathbf{\Upsilon\Upsilon}' = \mathbf{I}_{pu}$.

Proof. From the reduced DMM (3.4), let $\mathbf{\Upsilon}$ be a $pu \times pu$ orthogonal matrix such that $\mathbf{\Upsilon\Upsilon}' = \mathbf{I}_{pu}$, then the orthogonal linear transformation of the reduced DMM yields

$$\mathbf{Y}_M\mathbf{\Upsilon} = \mathbf{XB}_M\mathbf{\Upsilon} + \mathbf{U}_M\mathbf{\Upsilon} \tag{3.21}$$

and, under the multivariate normality assumption (3.5),

$$vec(\mathbf{Y}_M\mathbf{\Upsilon}) \sim N_{npu}\left((\mathbf{I}_{pu} \otimes \mathbf{X})vec(\mathbf{B}_M\mathbf{\Upsilon}), \mathbf{\Phi}_\Upsilon \otimes \mathbf{I}_n\right),$$

where $\mathbf{\Phi}_\Upsilon = \mathbf{\Upsilon}'\mathbf{\Phi\Upsilon}$. Using the orthogonal linear transformed model defined in (3.21), the error SSCP and hypothesis matrices, $\mathbf{S}_e$ (3.7) and $\mathbf{S}_h$ (3.8), are transformed as

$$\mathbf{\Upsilon}'\mathbf{S}_e\mathbf{\Upsilon} = (\mathbf{Y}_M\mathbf{\Upsilon})'[\mathbf{I}_n - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'](\mathbf{Y}_M\mathbf{\Upsilon}) \tag{3.22}$$

and $$\mathbf{\Upsilon}'\mathbf{S}_h\mathbf{\Upsilon} = (\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}_M\mathbf{\Upsilon})'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}_M\mathbf{\Upsilon}) . \tag{3.23}$$

Therefore, the proposed test T_1 in (3.20) becomes

$$T_1 = \frac{v_e \; tr(\mathbf{\Upsilon}'\mathbf{S}_h\mathbf{\Upsilon})}{v_h \; tr(\mathbf{\Upsilon}'\mathbf{S}_e\mathbf{\Upsilon})} = \frac{v_e \; tr(\mathbf{S}_h\mathbf{\Upsilon\Upsilon}')}{v_h \; tr(\mathbf{S}_e\mathbf{\Upsilon\Upsilon}')} = \frac{v_e \; tr(\mathbf{S}_h)}{v_h \; tr(\mathbf{S}_e)} .$$

Thus the proposed test T_1 is invariant under the orthogonal linear transformation of $\mathbf{Y}_M$. □

Taking spectral decomposition, which is a particular case of orthogonal linear transformation, let $\boldsymbol{\Upsilon}$ be a $pu \times pu$ orthogonal eigenvector matrix corresponding to eigenvalues $\lambda_1, \ldots, \lambda_{pu}$ of $\boldsymbol{\Phi}$. From the Orthogonal Linear Transformation Model (3.21) and under the multivariate normality assumption (3.5),

$$vec(\mathbf{Y}_M \boldsymbol{\Upsilon}) \sim N_{npu}\left((\mathbf{I}_{pu} \otimes \mathbf{X})vec(\mathbf{B}_M \boldsymbol{\Upsilon}), \boldsymbol{\Phi}_{\Upsilon} \otimes \mathbf{I}_n\right),$$

where $\boldsymbol{\Phi}_{\Upsilon} = \boldsymbol{\Upsilon}' \boldsymbol{\Phi} \boldsymbol{\Upsilon} = diag(\lambda_1, \ldots, \lambda_{pu})$.

By applying Lemma 3.2, the proposed test T_1 is invariant under this orthogonal linear transformation. Thus, without loss of generality, it may assumed that the covariance matrix in (3.6) is a diagonal matrix

$$\boldsymbol{\Phi}_{pu \times pu} = \boldsymbol{\Phi}_{\Upsilon} = diag(\lambda_1, \ldots, \lambda_{pu}), \tag{3.24}$$

where $\lambda_1 > \lambda_2 \ldots > \lambda_{pu}$ are eigenvalues of $\boldsymbol{\Phi}$.

Next, an approximate distribution of T_1 under the null hypothesis is derived by assuming that the covariance matrix is diagonal, as defined in (3.24). The result is given in Theorem 3.1.

Theorem 3.1. Under the null hypothesis (3.3) and assumption (3.15),

$$P_0\left(T_1 < f\right) \doteq F(f, \lfloor v_h d \rfloor, \lfloor v_e d \rfloor),$$

where P_0 denotes that the probability is being calculated under the null hypothesis and $F(f, v_1, v_2)$ denotes the cumulative F distribution at f with v_1 and v_2 degrees of freedom, $\lfloor x \rfloor$ denotes the largest integer $\leq x$, and d is defined by

$$d = \frac{(tr(\boldsymbol{\Phi}_{\Upsilon}))^2}{tr(\boldsymbol{\Phi}_{\Upsilon}^2)} = \frac{pua_1^2}{a_2} = pub.$$

Since d is the function of unknown parameter $\boldsymbol{\Phi}_{\Upsilon}$, it can be estimated by

$$\hat{d} = \frac{pu\hat{a}_1^2}{\hat{a}_2} = pu\hat{b}.$$

Proof. Under the null hypothesis, $\mathbf{S}_e$ and $\mathbf{S}_h$ are independently distributed as central Wishart distributions, $W_{pu}(\boldsymbol{\Phi}, v_e)$ and $W_{pu}(\boldsymbol{\Phi}, v_h)$, respectively (Boik, 1988: 472).

Glueck and Muller (1988: 2139) reported that the trace of a central Wishart matrix is equal to a weighted sum of central chi-squared random variables. Thus traces of $\mathbf{S}_e$ and $\mathbf{S}_h$ can be written in the form

$$tr(\mathbf{S}_e) = \sum_{k=1}^{pu} \lambda_k u_{1k} \tag{3.25}$$

and

$$tr(\mathbf{S}_h) = \sum_{k=1}^{pu} \lambda_k u_{2k} \ , \tag{3.26}$$

where u_{1k} and u_{2k} are independently distributed as chi-squared random variables with v_e and v_h degrees of freedom, respectively.

Muller and Barton (1989: 554) explained that the distribution of the weighted sum (finite positive weights) of a set of independent central chi-squared random variables may be approximated by a single scaled central chi-squared distribution, denoted by $w\chi_r^2$. The approximation always produces at least the first correct moment and special cases are sufficient to at least insure the correct first and second moments. To choose an approximating central chi-squared distribution, one must solve for degrees of freedom and a positive weight, say r and w, to define the approximate distribution by equating moments to those of the approximated random variable.

From (3.25) and (3.26), the first and second moments of $tr(\mathbf{S}_e)$ and $tr(\mathbf{S}_h)$ are

$$E\left[tr(\mathbf{S}_e)\right] = v_e \sum_{k=1}^{pu} \lambda_k \ , \quad \mathrm{var}\left[tr(\mathbf{S}_e)\right] = 2v_e \sum_{k=1}^{pu} \lambda_k^2 \tag{3.27}$$

and

$$E\left[tr(\mathbf{S}_h)\right] = v_h \sum_{k=1}^{pu} \lambda_k \ , \quad \mathrm{var}\left[tr(\mathbf{S}_h)\right] = 2v_h \sum_{k=1}^{pu} \lambda_k^2 \ . \tag{3.28}$$

To find the approximate central chi-squared distributions of $tr(\mathbf{S}_e)$ and $tr(\mathbf{S}_h)$, denoted by $tr(\mathbf{S}_e) \sim w_e \chi_{r_e}^2$ and $tr(\mathbf{S}_h) \sim w_h \chi_{r_h}^2$, respectively, the degrees of freedom r_e and positive weight w_e can be solved by equating the moments defined in (3.27) and the moment of the approximate central chi-squared distribution of $tr(\mathbf{S}_e)$ and, similarly, the degrees of freedom r_h and positive weight w_h can be solved by equating moments defined in (3.28) and the moment of the approximate central chi-squared distribution of $tr(\mathbf{S}_h)$. Since $\mathbf{S}_e$ and $\mathbf{S}_h$ are independent, $tr(\mathbf{S}_e)$ and $tr(\mathbf{S}_h)$

are also independent, and the first and second moments of the approximate central chi-squared distribution of $tr(\mathbf{S}_e)$ and $tr(\mathbf{S}_h)$ are

$$E\left[tr(\mathbf{S}_e)\right] = w_e r_e, \quad \text{var}\left[tr(\mathbf{S}_e)\right] = 2w_e^2 r_e \tag{3.29}$$

and
$$E\left[tr(\mathbf{S}_h)\right] = w_h r_h, \quad \text{var}\left[tr(\mathbf{S}_h)\right] = 2w_h^2 r_h . \tag{3.30}$$

By equating the first and second moments of $tr(\mathbf{S}_e)$ from (3.27) and (3.29), the following two equations are obtained to solve for w_e and r_e:

$$w_e r_e = v_e \sum_{k=1}^{pu} \lambda_k \tag{3.31}$$

and
$$2(w_e)^2 r_e = 2v_e \sum_{k=1}^{pu} \lambda_k^2 . \tag{3.32}$$

When dividing equation (3.32) by (3.31), the solution for w_e is

$$w_e = \frac{\sum_{k=1}^{pu} \lambda_k^2}{\sum_{k=1}^{pu} \lambda_k} = \frac{a_2}{a_1},$$

and, when substituting the solution for w_e in (3.31), the solution for r_e is

$$r_e = v_e \frac{\left(\sum_{k=1}^{pu} \lambda_k\right)^2}{\sum_{k=1}^{pu} \lambda_k^2} = v_e pu \frac{a_1^2}{a_2} = v_e pub .$$

Similarly, by equating the first and second moments of $tr(\mathbf{S}_h)$ from (3.28) and (3.30), the following two equations are obtained to solve for w_h and r_h:

$$w_h r_h = v_h \sum_{k=1}^{pu} \lambda_k \tag{3.33}$$

and
$$2(w_h)^2 r_h = 2v_h \sum_{k=1}^{pu} \lambda_k^2 . \tag{3.34}$$

When solving (3.33) and (3.34) in the same manner, it can be seen that

$$w_h = \frac{\sum_{k=1}^{pu} \lambda_k^2}{\sum_{k=1}^{pu} \lambda_k} = \frac{a_2}{a_1}$$

and $$r_h = v_h \frac{\left(\sum_{k=1}^{pu} \lambda_k\right)^2}{\sum_{k=1}^{pu} \lambda_k^2} = v_h pu \frac{a_1^2}{a_2} = v_h pub .$$

To simplify the notation of the degrees of freedom of r_e and r_h, the notation d, where $d = pub$, can be used and then r_e and r_h can be written as $r_e = v_e d$ and $r_h = v_h d$. Under the null hypothesis, the distribution of T_1 is approximated by

$$\begin{aligned} P(T_1 < f) &= P(\frac{tr(\mathbf{S}_h)/v_h}{tr(\mathbf{S}_e)/v_e} < f) \\ &\doteq P(\frac{w_h \chi^2_{v_h d}/v_h}{w_e \chi^2_{v_e d}/v_e} < f) \\ &\doteq P(\frac{\chi^2_{v_h d}/v_h}{\chi^2_{v_e d}/v_e} < f) \qquad (\because\ w_h = w_e) \\ &\doteq P(F_{v_h d, v_e d} < f) . \end{aligned}$$

Since d consists of an unknown parameter b, then by using Lemma 3.1, d is estimated by $\hat{d} = pu\hat{b}$. □

By applying Theorem 3.1, the null hypothesis (3.3), $H: \mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{\Gamma}_0$, is rejected at significance level α if $T_1 > f_{\alpha, \lfloor v_h \hat{d} \rfloor, \lfloor v_e \hat{d} \rfloor}$, where f_{α, v_1, v_2} is the upper $(1-\alpha)100$ critical value of the F random variable with v_1 and v_2 degrees of freedom, $v_h = rank(\mathbf{C})$, $v_e = n - g$, $\hat{d} = pu\hat{b}$ and $\hat{b}$ is given in Corollary 3.1.

Next, the approximate non-null distribution of T_1 is derived to find the power of the test. The approximate non-null distribution of T_1 is given in Theorem 3.2.

Theorem 3.2 Under the local alternative hypothesis and assumption (3.16) **,**

$$P_1\left(T_1 < f\right) \doteq F\left(f, \lfloor r_h \rfloor, \lfloor r_e \rfloor, \delta\right),$$

where w_h, w_e , r_h , r_e and δ are respectively defined by

$$w_h = \frac{v_h tr(\mathbf{\Phi}_\Upsilon^2) + 2tr(\mathbf{\Phi}_\Upsilon^2 \mathbf{\Xi})}{v_h tr(\mathbf{\Phi}_\Upsilon) + 2tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi})} , \quad w_e = \frac{tr(\mathbf{\Phi}_\Upsilon^2)}{tr(\mathbf{\Phi}_\Upsilon)} ,$$

$$r_h = \frac{v_h tr(\mathbf{\Phi}_\Upsilon)}{w_h} \quad , \quad r_e = \frac{v_e[tr(\mathbf{\Phi}_\Upsilon)]^2}{tr(\mathbf{\Phi}_\Upsilon^2)} \quad \text{and} \quad \delta = \frac{tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi})}{w_h} \ .$$

Note that P_1 denotes that the probability is being calculated under the local alternative hypothesis and $F(f, v_1, v_2, \delta)$ denotes the cumulative probability of a non-central F distribution at f with v_1 and v_2 degrees of freedom and a non-centrality parameter δ, and $\lfloor x \rfloor$ denotes the largest integer $\le x$.

Proof. Under the local alternative hypothesis, $\mathbf{S}_e$ and $\mathbf{S}_h$ are independently distributed as central and non-central Wishart distributions, $W_{pu}(\mathbf{\Phi}, v_e)$ and $W_{pu}(\mathbf{\Phi}, v_h, \mathbf{\Phi}^{-1}\mathbf{\Delta})$, respectively (Boik, 1988: 472), then the traces of $\mathbf{S}_e$ and $\mathbf{S}_h$ can be written in the form (Glueck and Muller, 1988: 2139)

$$tr(\mathbf{S}_e) = \sum_{k=1}^{pu} \lambda_k u_{1k} \tag{3.35}$$

and

$$tr(\mathbf{S}_h) = \sum_{k=1}^{pu} \lambda_k u_{2k} \ , \tag{3.36}$$

where u_{1k} is a central chi-squared random variable with v_e degrees of freedom and u_{2k} is a non-central chi-squared random variable with v_h degrees of freedom and non-centrality parameter δ_k, which are diagonal elements of $\mathbf{\Phi}^{-1}\mathbf{\Delta}$. The first two moments of $tr(\mathbf{S}_e)$ and $tr(\mathbf{S}_h)$ from (3.17) and (3.18) are

$$E\left[tr(\mathbf{S}_e)\right] = v_e \sum_{k=1}^{pu} \lambda_k \ , \quad \mathrm{var}\left[tr(\mathbf{S}_e)\right] = 2v_e \sum_{k=1}^{pu} \lambda_k^2 \tag{3.37}$$

and

$$E\left[tr(\mathbf{S}_h)\right] = \sum_{k=1}^{pu} \lambda_k (v_h + \delta_k) \ , \quad \mathrm{var}\left[tr(\mathbf{S}_h)\right] = \sum_{k=1}^{pu} \lambda_k^2 (2v_h + 4\delta_k) \ . \tag{3.38}$$

To find the approximate central and noncentral chi-squared distribution of $tr(\mathbf{S}_e)$ and $tr(\mathbf{S}_h)$, denoted by $tr(\mathbf{S}_e) \sim w_e \chi^2_{r_e}$ and $tr(\mathbf{S}_h) \sim w_h \chi^2_{r_h, \delta}$, the degrees of freedom r_e and positive weight w_e can be solved by equating moments defined in (3.37) and the moment of the approximate central chi-squared distribution of $tr(\mathbf{S}_e)$. The degrees of freedom r_h, positive weight w_h and noncentrality parameter δ can be solved by equating moments defined in (3.38) and the moment of the approximate noncentral chi-squared distribution of $tr(\mathbf{S}_h)$ (Muller and Barton, 1989: 554). Since $\mathbf{S}_e$ and $\mathbf{S}_h$ are independent, $tr(\mathbf{S}_e)$ and $tr(\mathbf{S}_h)$ are also independent and the first and second moments of the approximate central chi-squared distribution of $tr(\mathbf{S}_e)$ and $tr(\mathbf{S}_h)$ are

$$E\left[tr(\mathbf{S}_e)\right] = w_e r_e, \quad \mathrm{var}\left[tr(\mathbf{S}_e)\right] = 2w_e^2 r_e, \tag{3.39}$$

$$E\left[tr(\mathbf{S}_h)\right] = w_h(r_h + \delta), \quad \mathrm{var}\left[tr(\mathbf{S}_h)\right] = w_h^2(2r_h + 4\delta). \tag{3.40}$$

By equating the first and second moments of $tr(\mathbf{S}_e)$ from (3.37) and (3.39) so as to solve w_e and r_e, it is found that their solutions are

$$w_e = \frac{\sum_{k=1}^{pu} \lambda_k^2}{\sum_{k=1}^{pu} \lambda_k} = \frac{a_2}{a_1}$$

and
$$r_e = v_e \frac{\left(\sum_{k=1}^{pu} \lambda_k\right)^2}{\sum_{k=1}^{pu} \lambda_k^2} = v_e pu \frac{a_1^2}{a_2} = v_e pub.$$

To find w_h , r_h and δ, the first and second moments of $tr(\mathbf{S}_h)$ from (3.38) and (3.40) are equaled , and the two equations are obtained as

$$w_h(r_h + \delta) = v_h \sum_{k=1}^{pu} \lambda_k + \sum_{k=1}^{pu} \lambda_k \delta_k \tag{3.41}$$

and
$$w_h{}^2(2r_h + 4\delta) = 2v_h \sum_{k=1}^{pu} \lambda_k^2 + 4v_h \sum_{k=1}^{pu} \lambda_k \delta_k . \tag{3.42}$$

Using the notation S_1 and S_2 for the two terms on the right hand side of (3.41) and S_3 and S_4 for the two terms on the right hand side of (3.42), equations (3.41) and (3.42) become

$$w_h(r_h + \delta) = S_1 + S_2 \tag{3.43}$$

and
$$w_h{}^2(2r_h + 4\delta) = 2S_3 + 4S_4, \tag{3.44}$$

where $S_1 = v_h \sum_{k=1}^{pu} \lambda_k$, $S_2 = \sum_{k=1}^{pu} \lambda_k \delta_k$, $S_3 = v_h \sum_{k=1}^{pu} \lambda_k^2$ and $S_4 = \sum_{k=1}^{pu} \lambda_k^2 \delta_k$.

To find w_h, equation (3.44) is divided by (3.43), leading to

$$w_h = \frac{S_3 + 2S_4}{S_1 + 2S_2} = \frac{v_h \sum_{k=1}^{pu} \lambda_k^2 + 2\sum_{k=1}^{pu} \lambda_k^2 \delta_k}{v_h \sum_{k=1}^{pu} \lambda_k + 2\sum_{k=1}^{pu} \lambda_k \delta_k} = \frac{v_h pua_2 + 2tr(\mathbf{\Phi}_\Upsilon^2 \mathbf{\Xi}))}{v_h pua_1 + 2tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi})},$$

$$r_h = \frac{S_1}{w_h} = \frac{v_h \sum_{k=1}^{pu} \lambda_k}{w_h} = \frac{v_h tr(\mathbf{\Phi}_\Upsilon)}{w_h}$$

and
$$\delta = \frac{S_2}{w_h} = \frac{\sum_{k=1}^{pu} \lambda_k \delta_k}{w_h} = \frac{tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi})}{w_h}.$$

Therefore, under the local alternative hypothesis, the non-null distribution of T_1 is approximated by

$$P(T_1 < f) = P\left\{ \frac{tr(\mathbf{S}_h)/v_h}{tr(\mathbf{S}_e)/v_e} < f \right\}$$

$$\doteq P\left\{ \frac{w_h \chi^2_{r_h,\delta}/v_h}{w_e \chi^2_{r_e}/v_e} < f \right\}$$

$$\doteq P\left\{ \frac{\chi^2_{r_h,\delta}/r_h}{\chi^2_{r_e}/r_e} < \frac{w_e}{w_h} \cdot \frac{v_h r_e}{v_e r_h} f \right\},$$

since
$$\frac{w_e}{w_h} \cdot \frac{v_h r_e}{v_e r_h} = \frac{a_2}{a_1 w_h} \cdot \frac{v_h \left(v_e pu \frac{a_1^2}{a_2} \right)}{v_e \left(\frac{v_h pua_1}{w_h} \right)} = 1,$$

$$\doteq F\left(f, \lfloor r_h \rfloor, \lfloor r_e \rfloor, \delta\right). \qquad \square$$

3.1.2 Generalization of Bai and Saranadasa's Test

Bai and Saranadasa (1996: 318-320) proposed test statistics for testing the difference between two population mean vectors of the two-sample high dimensional problem. Srivastava and Fujikoshi (2006: 1930) gave a generalization of Bai and Saranadasa's test for MANOVA problems with fewer observations than dimensions.

Accordingly, an adaption of the generalization of Bai and Saranadasa's test for testing hypothesis (3.3) provided in this dissertation is given by

$$T_2 = \left\{ 2v_h a_2 \left(1 + \frac{v_h}{v_e} \right) \right\}^{-1/2} \frac{1}{\sqrt{pu}} \left[tr(\mathbf{S}_h) - \frac{v_h}{v_e} tr(\mathbf{S}_e) \right]. \tag{3.45}$$

Next, the asymptotic distribution of T_2 is derived under the null hypothesis given in Theroem 3.3. The following Lemma 3.2 is an asymptotic standard normal distribution theory for a large p which is given for use in the proof of Theorem 3.3.

Lemma 3.3 If $z_1, z_2, \ldots$ are independent identically distributed random variables, each with mean 0 and variance 1, and if c_k, $i = 1, 2, \ldots, p$, for $p = 1, 2, \ldots,$ is a fixed array of constants with

$$\sum_{i=1}^{p} c_k^2 = 1, \quad \text{for } p = 1, 2, \ldots,$$

then, if

$$\max_{1 \le k \le p} |c_k| \to 0 \quad \text{as} \quad p \to \infty,$$

$$\lim_{p \to \infty} P(\sum_{k=1}^{p} c_k z_k < z) = \mathbb{N}(z).$$

Proof. Refer to Gnedenko and Kolmogorov (1954: 103).

Theorem 3.3 Under the null hypothesis (3.3) and assumption (3.15)

$$\lim_{n \to \infty} \lim_{p \to \infty} P_0(T_2 < z) = \mathbb{N}(z),$$

where P_0 denotes the probability of being calculated under the local null hypothesis and $\mathbb{N}(z)$ denotes the cumulative standard normal distribution.

Proof. Under the null hypothesis, $\mathbf{S}_e$ and $\mathbf{S}_h$ are independently distributed as central Wishart distributions, $W_{pu}(\mathbf{\Phi}, v_e)$ and $W_{pu}(\mathbf{\Phi}, v_h)$, respectively. Subsequently, $tr(\mathbf{S}_e)$ and $tr(\mathbf{S}_h)$ equal a weighted sum of central chi-squared random variables (Glueck and Muller, 1988: 2139) defined by

$$tr(\mathbf{S}_e) = \sum_{k=1}^{pu} \lambda_k u_{1k}$$

and
$$tr(\mathbf{S}_h) = \sum_{k=1}^{pu} \lambda_k u_{2k} ,$$

where u_{1k} and u_{2k} are independently distributed as chi-square random variables with v_e and v_h degrees of freedom, denoted by $u_{1k} \sim \chi^2_{v_e}$ and $u_{2k} \sim \chi^2_{v_h}$.

From (3.45), let

$$\begin{aligned} T_0 &= \frac{1}{\sqrt{pu}}\left[tr(\mathbf{S}_h) - \frac{v_h}{v_e} tr(\mathbf{S}_e) \right] \\ &= \frac{1}{\sqrt{pu}}\left[\sum_{k=1}^{pu} \lambda_k u_{2k} - \frac{v_h}{v_e} \sum_{k=1}^{pu} \lambda_k u_{1k} \right] \\ &= \frac{1}{\sqrt{pu}}\left[\sum_{k=1}^{pu} \lambda_k (u_{2k} - \frac{v_h}{v_e} u_{1k}) \right]. \end{aligned}$$

Since the expectation and variance of $u_{2k} - \frac{v_h}{v_e} u_{1k}$ are

$$E\left(u_{2k} - \frac{v_h}{v_e} u_{1k} \right) = E(u_{2k}) - \frac{v_h}{v_e} E(u_{1k}) = v_h - \frac{v_h}{v_e} \cdot v_e = 0 \tag{3.46}$$

and
$$\begin{aligned} \operatorname{var}\left(u_{2k} - \frac{v_h}{v_e} u_{1k} \right) &= \operatorname{var}(u_{2k}) + \left(\frac{v_h}{v_e} \right)^2 \operatorname{var}(u_{1k}) \\ &= 2v_h + \left(\frac{v_h}{v_e} \right)^2 2v_e = 2v_h + \frac{2v_h^2}{v_e} . \end{aligned} \tag{3.47}$$

Subsequently, we obtain

$$E(T_0) = \frac{1}{\sqrt{pu}} \sum_{k=1}^{pu} \lambda_k E(u_{2k} - \frac{v_h}{v_e} u_{1k}) = 0$$

and
$$\begin{aligned} \operatorname{var}(T_0) &= \frac{1}{pu} \sum_{k=1}^{pu} \lambda_k^2 \operatorname{var}\left(u_{2k} - \frac{v_h}{v_e} u_{1k} \right) \\ &= \frac{1}{pu} \sum_{k=1}^{pu} \lambda_k^2 \left(2v_h + \frac{2v_h^2}{v_e} \right) \\ &= a_2 \left(2v_h + \frac{2v_h^2}{v_e} \right) \end{aligned}$$

$$= 2v_h a_2\left(1+\frac{v_h}{v_e}\right) = \sigma_0^2 < \infty .$$

Writing the test statistic T_2 defined by (3.45) in terms of T_0 gives

$$T_2 = \left\{2v_h a_2\left(1+\frac{v_h}{v_e}\right)\right\}^{-1/2} \frac{1}{\sqrt{pu}}\left[tr(\mathbf{S}_h) - \frac{v_h}{v_e} tr(\mathbf{S}_e)\right]$$

$$= \left\{2v_h a_2\left(1+\frac{v_h}{v_e}\right)\right\}^{-1/2} T_0 . \tag{3.48}$$

Using the expectation and variance of T_0, the expectation and variance of T_2 are obtained in (3.48) as follows:

$$E(T_2) = 0 ,$$

and

$$\operatorname{var}(T_2) = \left\{2v_h a_2\left(1+\frac{v_h}{v_e}\right)\right\}^{-1} \operatorname{var}(T_0)$$

$$= \left\{2v_h a_2\left(1+\frac{v_h}{v_e}\right)\right\}^{-1} 2v_h a_2\left(1+\frac{v_h}{v_e}\right) = 1 .$$

Correspondingly from Lemma 3.3, it is deemed that T_2 from (3.48) can be written as $T_2 = \sum_{k=1}^{pu} c_k z_k$, where

$$c_k = \frac{1}{\sqrt{pua_2}}\lambda_k \quad \text{and} \quad z_k = \left\{2v_h\left(1+\frac{v_h}{v_e}\right)\right\}^{-1/2}\left(u_{2k} - \frac{v_h}{v_e}u_{1k}\right) .$$

Subsequently ,

$$\sum_{k=1}^{pu} c_k^2 = \frac{1}{a_2}\cdot\frac{1}{pu}\sum_{k=1}^{pu}\lambda_k^2 = \frac{a_2}{a_2} = 1 ,$$

and, from (3.26) and (3.27),

$$E(z_k) = 0 \quad \text{and} \quad \operatorname{var}(z_k) = 1 .$$

Therefore, if

$$\max_{1\le k\le p}\left|c_k\right| = \max_{1\le k\le p}\frac{1}{\sqrt{pua_2}}\lambda_k \to 0 , \qquad \text{as } p\to\infty , \tag{3.49}$$

T_2 is asymptotically standard normally distributed as $p\to\infty$.

From assumption (3.15), a_2 is assumed to be constant as $p \to \infty$, so c_k converges in probability to a constant, and it is additionally assumed that $\lambda_k = O(p^m)$, for $0 \le m < \frac{1}{2}$, to satisfy condition (3.49). Hence, from Slutsky's Theorem and Lemma 3.2,

$$\lim_{n\to\infty}\lim_{p\to\infty} P_0(T_2 < z) = \mathbb{N}(z).$$

This completes the proof. □

By Theorem 3.3, the null hypothesis (3.3), $H : \mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{\Gamma}_0$, is rejected at significance level α if $T_2 > z_\alpha$, where z_α denotes the upper $(1-\alpha)$ 100%.

Next, the asymptotic non-null distribution of T_2 is derived so as to find the power of the test. Recall that under the local alternative hypothesis, $\mathbf{S}_e$ and $\mathbf{S}_h$ are independently distributed and are, respectively,

$$\mathbf{S}_e \sim W_{pu}(\mathbf{\Phi}, v_e)$$

and $$\mathbf{S}_h \sim W_{pu}(\mathbf{\Phi}, v_h, \mathbf{\Phi}^{-1}\mathbf{\Delta}),$$

with a non-centrality matrix

$$\mathbf{\Delta} = (\mathbf{\Gamma} - \mathbf{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{\Gamma} - \mathbf{\Gamma}_0).$$

Subsequently, we obtain

$$tr(\mathbf{S}_e) = \sum_{k=1}^{pu} \lambda_k u_{1k}$$

and $$tr(\mathbf{S}_h) = \sum_{k=1}^{pu} \lambda_k u_{2k},$$

where u_{1k} are central chi-squared random variables with v_e degrees of freedom and u_{2k} are non-central chi-squared random variables with v_h degrees of freedom and non-centrality parameter δ_k, which is comprised of diagonal elements of $\mathbf{\Phi}^{-1}\mathbf{\Delta}$.

Define

$$u_1 = \frac{1}{\sqrt{pu}}[tr(\mathbf{S}_h) - v_h tr(\mathbf{\Phi}_\Upsilon) - tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi})]$$

and $$u_2 = \frac{1}{\sqrt{v_e pu}}[tr(\mathbf{S}_e) - v_e tr(\mathbf{\Phi}_\Upsilon)].$$

The following Lemma 3.4 gives the asymptotic distributions of u_1 and u_2 (Srivastrava, 2006: 1935).

Lemma 3.4 As $p \to \infty$ and, under assumptions (3.5) and (3.6),

$$u_1 \xrightarrow{d} N\left\{0, 2v_h a_2 + 4tr(\mathbf{\Phi}_\Upsilon^2 \mathbf{\Xi}) / pu\right\}$$

and $$u_2 \xrightarrow{d} N(0, 2a_2),$$

where $\xrightarrow{d}$ denotes 'converges in distribution'.

Proof. The characteristic function of u_1 is given by

$$\begin{aligned}
\Psi_{u_1}(t) &= E(\exp(itu_1)) \\
&= E\left\{\exp\left(\frac{it}{\sqrt{pu}} tr(\mathbf{S}_h)\right)\right\} \times E\left\{\exp\left(-\frac{it}{\sqrt{pu}}[v_h tr(\mathbf{\Phi}_\Upsilon) + tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi})]\right)\right\} \\
&= \left| I_{pu} - \frac{2it}{\sqrt{pu}} \mathbf{\Phi}_\Upsilon \right|^{-\frac{1}{2}v_h} \exp\left(-\frac{it}{\sqrt{pu}} tr\left[\mathbf{\Phi}_\Upsilon \left(I_{pu} - \frac{2it}{\sqrt{pu}} \mathbf{\Phi}_\Upsilon\right)^{-1} \mathbf{\Xi}\right]\right) \\
&\quad \times \exp\left(-\frac{it}{\sqrt{pu}}[v_h tr(\mathbf{\Phi}_\Upsilon) + tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi})]\right).
\end{aligned}$$

Now, by expanding,

$$\begin{aligned}
\log\left| I_{pu} - \frac{2it}{\sqrt{pu}} \mathbf{\Phi}_\Upsilon \right|^{-\frac{1}{2}v_h} &= -\frac{1}{2} v_h \log\left| I_{pu} - \frac{2it}{\sqrt{pu}} \mathbf{\Phi}_\Upsilon \right| \\
&= \frac{1}{2} v_h \left[\frac{2it}{\sqrt{pu}} tr(\mathbf{\Phi}_\Upsilon) + \left(\frac{2it}{\sqrt{pu}}\right)^2 tr(\mathbf{\Phi}_\Upsilon^2)\right] + o(1) \\
&= \frac{it}{\sqrt{pu}} v_h tr(\mathbf{\Phi}_\Upsilon) + \left(\frac{it}{\sqrt{pu}}\right)^2 2v_h tr(\mathbf{\Phi}_\Upsilon^2) + o(1),
\end{aligned}$$

and $\frac{it}{\sqrt{pu}} tr\left[\mathbf{\Phi}_\Upsilon \left(I_{pu} - \frac{2it}{\sqrt{pu}} \mathbf{\Phi}_\Upsilon\right)^{-1} \mathbf{\Xi}\right]$

$$= \frac{it}{\sqrt{pu}} tr\left[\mathbf{\Phi}_{\Upsilon} \left(I_{pu} + \frac{2it}{\sqrt{pu}} \mathbf{\Phi}_{\Upsilon} + \left(\frac{2it}{\sqrt{pu}} \right)^{2} \mathbf{\Phi}_{\Upsilon}^{2} \right) \mathbf{\Xi} + o(1) \right]$$

$$= \frac{it}{\sqrt{pu}} tr\left[\mathbf{\Phi}_{\Upsilon}\mathbf{\Xi} + \frac{2it}{\sqrt{pu}} \mathbf{\Phi}_{\Upsilon}^{2}\mathbf{\Xi} + \left(\frac{2it}{\sqrt{pu}} \right)^{2} \mathbf{\Phi}_{\Upsilon}^{3}\mathbf{\Xi} + o(1) \right]$$

$$= \frac{it}{\sqrt{pu}} tr(\mathbf{\Phi}_{\Upsilon}\mathbf{\Xi}) + \left(\frac{2it}{\sqrt{pu}} \right)^{2} tr(\mathbf{\Phi}_{\Upsilon}^{2}\mathbf{\Xi}) + o(1) .$$

Hence,

$$\log E(\exp(itu_1)) = \log \left| I_{pu} - \frac{2it}{\sqrt{pu}} \mathbf{\Phi}_{\Upsilon} \right|^{-\frac{1}{2}v_h} - \frac{it}{\sqrt{pu}} tr\left[\mathbf{\Phi}_{\Upsilon} \left(I_{pu} - \frac{2it}{\sqrt{pu}} \mathbf{\Phi}_{\Upsilon} \right)^{-1} \mathbf{\Xi} \right]$$

$$- \frac{it}{\sqrt{pu}} [v_h tr(\mathbf{\Phi}_{\Upsilon}) + tr(\mathbf{\Phi}_{\Upsilon}\mathbf{\Xi})]$$

$$= \frac{it}{\sqrt{pu}} v_h tr(\mathbf{\Phi}_{\Upsilon}) + \left(\frac{it}{\sqrt{pu}} \right)^{2} 2v_h tr(\mathbf{\Phi}_{\Upsilon}^{2}) + \frac{it}{\sqrt{pu}} tr(\mathbf{\Phi}_{\Upsilon}\mathbf{\Xi})$$

$$+ \left(\frac{2it}{\sqrt{pu}} \right)^{2} tr(\mathbf{\Phi}_{\Upsilon}^{2}\mathbf{\Xi}) - \frac{it}{\sqrt{pu}} [v_h tr(\mathbf{\Phi}_{\Upsilon}) + tr(\mathbf{\Phi}_{\Upsilon}\mathbf{\Xi})] + o(1)$$

$$= (it)^2 \frac{2v_h tr(\mathbf{\Phi}_{\Upsilon}^{2})}{pu} + (it)^2 \frac{4tr(\mathbf{\Phi}_{\Upsilon}^{2}\mathbf{\Xi})}{pu} + o(1) .$$

Therefore,

$$\Psi_{u_1}(t) = E(\exp(itu_1))$$

$$= \exp\left((it)^2 \frac{2v_h tr(\mathbf{\Phi}_{\Upsilon}^{2})}{pu} + (it)^2 \frac{4tr(\mathbf{\Phi}_{\Upsilon}^{2}\mathbf{\Xi})}{pu} + o(1) \right)$$

$$= \exp\left\{ \frac{1}{2} \left((it)^2 \frac{2v_h tr(\mathbf{\Phi}_{\Upsilon}^{2})}{pu} + (it)^2 \frac{4tr(\mathbf{\Phi}_{\Upsilon}^{2}\mathbf{\Xi})}{pu} \right) \right\}$$

$$\times \exp\left\{ \frac{1}{2} \left((it)^2 \frac{2v_h tr(\mathbf{\Phi}_{\Upsilon}^{2})}{pu} + (it)^2 \frac{4tr(\mathbf{\Phi}_{\Upsilon}^{2}\mathbf{\Xi})}{pu} \right) \right\}$$

$$= \exp\left(\frac{1}{2} (it)^2 \left\{ \frac{2v_h tr(\mathbf{\Phi}_{\Upsilon}^{2})}{pu} + \frac{4tr(\mathbf{\Phi}_{\Upsilon}^{2}\mathbf{\Xi})}{pu} \right\} \right) \times (1 + o(1)) .$$

As $p \to \infty$, this function is in the form of a characteristic function of a normal distribution with mean parameter $\frac{2v_h tr(\mathbf{\Phi}_\Upsilon^2)}{pu} = 2v_h a_2$ and covariance parameter $\frac{4tr(\mathbf{\Phi}_\Upsilon^2 \mathbf{\Xi})}{pu}$. Thus, as $p \to \infty$,

$$u_1 \sim N\left(0, 2v_h a_2 + \frac{4tr(\mathbf{\Phi}_\Upsilon^2 \mathbf{\Xi})}{pu}\right).$$

The characteristic function of u_2 is given by

$$\begin{aligned}
\Psi_{u_2}(t) &= E[\exp(itu_2)] \\
&= E\left\{\exp\left(\frac{it}{\sqrt{v_e pu}} tr(\mathbf{S}_e)\right)\right\} \times E\left\{\exp\left(-\frac{it}{\sqrt{v_e pu}} v_e tr(\mathbf{\Phi}_\Upsilon)\right)\right\} \\
&= \left| I_{pu} - \frac{2it}{\sqrt{v_e pu}} \mathbf{\Phi}_\Upsilon \right|^{-\frac{1}{2}v_e} \exp\left(-\frac{it}{\sqrt{v_e pu}} v_e tr(\mathbf{\Phi}_\Upsilon)\right).
\end{aligned}$$

As before, we have

$$\begin{aligned}
\log\left| I_{pu} - \frac{2it}{\sqrt{v_e pu}} \mathbf{\Phi}_\Upsilon \right|^{-\frac{1}{2}v_e} &= -\frac{1}{2} v_e \log\left| I_{pu} - \frac{2it}{\sqrt{v_e pu}} \mathbf{\Phi}_\Upsilon \right| \\
&= \frac{1}{2} v_e \left[\frac{2it}{\sqrt{v_e pu}} tr(\mathbf{\Phi}_\Upsilon) + \left(\frac{2it}{\sqrt{v_e pu}}\right)^2 tr(\mathbf{\Phi}_\Upsilon^2)\right] + o(1) \\
&= itv_e \frac{tr(\mathbf{\Phi}_\Upsilon)}{\sqrt{v_e pu}} + (it)^2 \frac{2tr(\mathbf{\Phi}_\Upsilon^2)}{pu} + o(1).
\end{aligned}$$

Hence,

$$\begin{aligned}
\log E[\exp(itu_2)] &= \left| I_{pu} - \frac{2it}{\sqrt{v_e pu}} \mathbf{\Phi}_\Upsilon \right|^{-\frac{1}{2}v_e} - \frac{it}{\sqrt{v_e pu}} v_e tr(\mathbf{\Phi}_\Upsilon) \\
&= \frac{it}{\sqrt{v_e pu}} v_e tr(\mathbf{\Phi}_\Upsilon) + (it)^2 \frac{2tr(\mathbf{\Phi}_\Upsilon^2)}{pu} - \frac{it}{\sqrt{v_e pu}} v_e tr(\mathbf{\Phi}_\Upsilon) + o(1) \\
&= (it)^2 \frac{2tr(\mathbf{\Phi}_\Upsilon^2)}{pu} + o(1).
\end{aligned}$$

Therefore, we obtain

$$\Psi_{u_2}(t) = E[\exp(itu_2)]$$

$$= \exp\left((it)^2 \frac{2tr(\mathbf{\Phi}_\Upsilon^2)}{pu} + o(1) \right)$$

$$= \exp\left(\frac{1}{2}(it)^2 \frac{2tr(\mathbf{\Phi}_\Upsilon^2)}{pu} \right) \times \exp\left(\frac{1}{2}(it)^2 \frac{2tr(\mathbf{\Phi}_\Upsilon^2)}{pu} \right) \times o(1)$$

$$= \exp\left(\frac{1}{2}(it)^2 \frac{2tr(\mathbf{\Phi}_\Upsilon^2)}{pu} \right) \times (1 + o(1)).$$

As $p \to \infty$, this characteristic function is in the form of a characteristic function of a normal distribution with a zero mean parameter and covariance $\frac{2tr(\mathbf{\Phi}_\Upsilon^2)}{pu} = 2a_2$. Thus, as $p \to \infty$,

$$u_2 \sim N\left(0, 2a_2\right).$$

□

Theorem 3.4 Under the local alternative hypothesis and assumption (3.16),

$$\lim_{p\to\infty} P_1(T_2 > z) = \lim_{p\to\infty} \mathbb{N}\left(-\frac{\sigma_0}{\sigma_2} z_\alpha + \frac{tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi})}{\sigma_2 \sqrt{pu}} \right),$$

where P_1 denotes the probability as being calculated under the local alternative hypothesis and $\mathbb{N}(z)$ denotes the cumulative standard normal distribution.

Proof. Consider

$$u_1 - \frac{v_h}{\sqrt{v_e}} u_2 = \frac{1}{\sqrt{pu}} [tr(\mathbf{S}_h) - v_h tr(\mathbf{\Phi}_\Upsilon) - tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi})] - \frac{v_h}{\sqrt{v_e}} \frac{1}{\sqrt{v_e pu}} [tr(\mathbf{S}_e) - v_e tr(\mathbf{\Phi}_\Upsilon)]$$

$$= \frac{1}{\sqrt{pu}} \left\{ tr(\mathbf{S}_h) - v_h tr(\mathbf{\Phi}_\Upsilon) - tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi}) - \frac{v_h}{v_e} [tr(\mathbf{S}_e) - v_e tr(\mathbf{\Phi}_\Upsilon)] \right\}$$

$$= \frac{1}{\sqrt{pu}} \left\{ tr(\mathbf{S}_h) - tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi}) - \frac{v_h}{v_e} tr(\mathbf{S}_e) \right\}$$

$$= \sigma_0 T_2 - \frac{tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi})}{\sqrt{pu}}.$$

Note that u_1 and u_2 are independently distributed. From Lemma 3.4,

$$E\left(u_1 - \frac{v_h}{\sqrt{v_e}}u_2\right) = E(u_1) - \frac{v_h}{\sqrt{v_e}}E(u_2) = 0,$$

$$\begin{aligned}\operatorname{var}\left(u_1 - \frac{v_h}{\sqrt{v_e}}u_2\right) &= \operatorname{var}(u_1) + \frac{v_h^2}{v_e}\operatorname{var}(u_2)\\ &= 2v_h a_2 + \frac{4tr(\mathbf{\Phi}_\Upsilon^2\mathbf{\Xi})}{pu} + \frac{v_h^2}{v_e}2a_2\\ &= 2v_h a_2(1+\frac{v_h}{v_e}) + \frac{4tr(\mathbf{\Phi}_\Upsilon^2\mathbf{\Xi})}{pu}.\end{aligned}$$

Thus, by Lemma 3.4, as $p \to \infty$,

$$u_1 - \frac{v_h}{\sqrt{v_e}}u_2 \xrightarrow{d} N\left\{0,\ 2v_h a_2(1+\frac{v_h}{v_e}) + \frac{4tr(\mathbf{\Phi}_\Upsilon^2\mathbf{\Xi})}{pu}\right\}.$$

Let

$$\begin{aligned}\sigma_2^2 &= 2v_h a_2(1+\frac{v_h}{v_e}) + \frac{4tr(\mathbf{\Phi}_\Upsilon^2\mathbf{\Xi})}{pu},\\ &= \sigma_0^2 + \frac{4tr(\mathbf{\Phi}_\Upsilon^2\mathbf{\Xi})}{pu}.\end{aligned}$$

Hence, as $p \to \infty$,

$$\frac{1}{\sigma_2}\left(u_1 - \frac{v_h}{\sqrt{v_e}}u_2\right) = \frac{1}{\sigma_2}\left(\sigma_0 T_2 - \frac{tr(\mathbf{\Phi}_\Upsilon\mathbf{\Xi})}{\sqrt{pu}}\right) \xrightarrow{d} N(0,1).$$

Thus,

$$\begin{aligned}P_1(T_2 > z_\alpha) &= P_1\left(\sigma_0 T_2 > \sigma_0 z_\alpha\right)\\ &= P_1\left(\sigma_0 T_2 - \frac{tr(\mathbf{\Phi}_\Upsilon\mathbf{\Xi})}{\sqrt{pu}} > \sigma_0 z_\alpha - \frac{tr(\mathbf{\Phi}_\Upsilon\mathbf{\Xi})}{\sqrt{pu}}\right)\\ &= P_1\left\{\frac{1}{\sigma_2}\left(\sigma_0 T_2 - \frac{tr(\mathbf{\Phi}_\Upsilon\mathbf{\Xi})}{\sqrt{pu}}\right) > \frac{1}{\sigma_2}\left(\sigma_0 z_\alpha - \frac{tr(\mathbf{\Phi}_\Upsilon\mathbf{\Xi})}{\sqrt{pu}}\right)\right\}\\ &= P_1\left\{Z > \frac{\sigma_0}{\sigma_2}z_\alpha - \frac{tr(\mathbf{\Phi}_\Upsilon\mathbf{\Xi})}{\sqrt{pu}}\right\},\end{aligned}$$

$$\lim_{p\to\infty} P_1(T_2 > z_\alpha) = \lim_{p\to\infty} P_1\left\{ Z > \frac{\sigma_0}{\sigma_2} z_\alpha - \frac{tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi})}{\sqrt{pu}} \right\}$$

$$= \lim_{p\to\infty} \left\{ 1 - \mathbb{N}\left(\frac{\sigma_0}{\sigma_2} z_\alpha - \frac{tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi})}{\sigma_2\sqrt{pu}} \right) \right\}$$

$$= \lim_{p\to\infty} \mathbb{N}\left[-\left(\frac{\sigma_0}{\sigma_2} z_\alpha - \frac{tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi})}{\sigma_2\sqrt{pu}} \right) \right]$$

$$= \lim_{p\to\infty} \mathbb{N}\left(-\frac{\sigma_0}{\sigma_2} z_\alpha + \frac{tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi})}{\sigma_2\sqrt{pu}} \right). \qquad \square$$

3.2 High Dimensional MMM Tests

As described in Section 2.2, MMM is defined by

$$\mathbf{Y}^*_{nt\times p} = (\mathbf{X}_{n\times g} \otimes \mathbf{I}_t)\mathbf{B}^*_{gt\times p} + \mathbf{U}^*_{nt\times p}, \tag{3.50}$$

where $\mathbf{Y}^*$ is an $nt \times p$ response matrix for n subjects, $\mathbf{X}$ is an $n \times g$ between subject design matrix of $rank(\mathbf{X}) = g$, $\mathbf{B}^*$ is a $gt \times p$ unknown parameter matrix of fixed effects and $\mathbf{U}^*$ is an $nt \times p$ random error matrix. Assume that

$$vec(\mathbf{U}^{*\prime}) \sim N_{npt}(\mathbf{0}_{npt\times 1}, \mathbf{I}_n \otimes \mathbf{\Sigma}^*_{pt\times pt}), \tag{3.51}$$

whose covariance matrix has a block diagonal structure and $\mathbf{\Sigma}^*$ has compound symmetry structures defined as

$$\mathbf{\Sigma}^* = (\mathbf{1}_t\mathbf{1}_t' \otimes \mathbf{\Sigma}_s) + (\mathbf{I}_t \otimes \mathbf{\Sigma}_e). \tag{3.52}$$

The MLE of $\mathbf{B}^*$ and $\mathbf{\Sigma}^*$ are

$$\hat{\mathbf{B}}^* = [(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}' \otimes \mathbf{I}_t]\mathbf{Y}^* \tag{3.53}$$

and

$$\mathbf{\Sigma}^* = \frac{\mathbf{Y}^{*\prime}[\mathbf{I}_{nt} - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}' \otimes \mathbf{I}_t]\mathbf{Y}^*}{n}. \tag{3.54}$$

The general multivariate linear hypothesis for testing the effects of the time and group factors, and the interaction effect between the group and time factors, is

$$H: (\mathbf{C} \otimes \mathbf{A}')\mathbf{B}^* = \mathbf{\Gamma}^*_{\mathbf{0}} \quad \text{or} \quad H: \mathbf{\Gamma}^*_{v_h u\times p} = \mathbf{\Gamma}^*_0, \tag{3.55}$$

where $\mathbf{C}$ is a $v_h \times g$ between group contrast matrix having $rank(\mathbf{C}) = v_h \le g$ and $\mathbf{A}$ is a $t \times u$ within subject contrast matrix such that $\mathbf{A}'\mathbf{A} = \mathbf{I}_u$ and $rank(\mathbf{A}) = u \le t$.
To obtain the test statistic of (3.55), the MMM defined in (3.50) is reduced to

$$(\mathbf{I}_n \otimes \mathbf{A}'_{u\times t})\mathbf{Y}^*_{nt\times p} == (\mathbf{X}_{n\times g} \otimes \mathbf{A}'_{u\times t})\mathbf{B}^*_{gt\times p} + (\mathbf{I}_n \otimes \mathbf{A}'_{u\times t})\mathbf{U}^*_{nt\times p} \quad . \tag{3.56}$$

It is assumed that the multivariate sphericity condition (2.61) holds, i.e.

$$\mathbf{\Phi}^* = (\mathbf{A}' \otimes \mathbf{I}_p)\mathbf{\Sigma}^*(\mathbf{A} \otimes \mathbf{I}_p) = \mathbf{I}_u \otimes \mathbf{\Sigma}_e \,. \tag{3.57}$$

The $pu \times pu$ error and hypothesis SSCP matrices corresponding to error and hypothesis, $\mathbf{S}^*_e$ and $\mathbf{S}^*_h$ are defined by

$$\mathbf{S}^*_e = \mathbf{Y}^{*\prime}[(\mathbf{I}_n - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}) \otimes \mathbf{A}\mathbf{A}']\mathbf{Y}^* \tag{3.58}$$

and $$\mathbf{S}^*_h = \mathbf{Y}^{*\prime}\left\{\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}' \otimes \mathbf{A}\mathbf{A}'\right\}\mathbf{Y}^* . \tag{3.59}$$

Alternatively, using Thompson's (1973: 545) Generalized Trace Operator, we obtain (Boik, 1991: 1238)

$$\mathbf{S}^*_e = T_p(\mathbf{S}_e),\ \mathbf{S}^*_h = T_p(\mathbf{S}_h),\ \mathbf{\Phi}^* = T_p(\mathbf{\Phi}) \text{ and } \mathbf{\Delta}^* = T_p(\mathbf{\Delta}), \tag{3.60}$$

where $T_p(\mathbf{D}) = \left[tr(\mathbf{D}_{ll'})\right]_{p\times p}$; $\mathbf{D}_{ll'}$ is a $u \times u$ submatrix of the l^{th} and l'^{th} response variables, for $l, l' = 1, 2, \ldots, p$. $\mathbf{S}_e$, $\mathbf{S}_h$, $\mathbf{\Phi}$ and $\mathbf{\Delta}$ are defined by (3.7), (3.8), (3.67) and (3.11) respectively in the DMM analysis.

Under assumption (3.51) and if multivariate sphericity (3.57) is satisfied, the matrices $\mathbf{S}^*_e$ and $\mathbf{S}^*_h$ are independently distributed as central and non-central Wishart distributions as defined by (Boik, 1998: 474-475);

$$\mathbf{S}^*_e \sim W_p\left(u^{-1}\mathbf{\Phi}^*, uv_e\right) \tag{3.61}$$

and $$\mathbf{S}^*_h \sim W_p\left(u^{-1}\mathbf{\Phi}^*, uv_h, (u\mathbf{\Phi}^*)^{-1}\mathbf{\Delta}^*\right), \tag{3.62}$$

where $v_e = n - rank(\mathbf{X}) = n - g$, $v_h = rank(\mathbf{C})$, $u = rank(\mathbf{A})$ and the noncentrality matrix is $\mathbf{\Delta}^* = T_p(\mathbf{\Delta})$, where $\mathbf{\Delta} = (\mathbf{\Gamma} - \mathbf{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{\Gamma} - \mathbf{\Gamma}_0)$ is as in (3.11).

For the high dimensional problem of MMM, if $uv_e < p$, the error SSCP matrix $\mathbf{S}^*_e$ is singular with $rank(\mathbf{S}^*_e) = uv_e < p$. Thus a classic multivariate test, such as

Wilks' Lambda criterion defined in (2.72), is not available for high dimensional MMM analysis.

In the same manner as in high dimensional DMM, this dissertation proposes modifications of Dempster's and Bai and Saranadasa's tests to analyze the MMM when $v_e u < p$.

Define

$$a_i^* = \frac{tr((\mathbf{\Phi}^*)^i)}{p} \quad , \qquad \text{for } i = 1,\dots,4, \tag{3.63}$$

and

$$b^* = \frac{(a_1^*)^2}{a_2^*}. \tag{3.64}$$

For MMM analysis, it is assumed that:

(1) $p \to \infty$, $n \to \infty$, t is fixed and $v_e u < p$ (3.65)

(2) $\lim\limits_{p\to\infty} a_i^* = a_{i0}^*$, for $i = 1,\dots,4$, and $0 < a_{i0}^* < \infty$ (3.66)

(3) For the local alternative hypothesis,

$$0 < \lim_{p\to\infty} \frac{tr\left((\mathbf{\Phi}^*)^i \mathbf{\Xi}^*)\right)}{p} < \infty \quad , \text{for } i = 1,\dots,4, \tag{3.67}$$

where $\mathbf{\Xi}^* = (\mathbf{\Phi}^*)^{-1/2} \mathbf{\Delta}^* (\mathbf{\Phi}^*)^{-1/2}$ and $\mathbf{\Delta}^*$ is as defined in (3.60)

Lemma 3.5 Under assumptions (3.51) and (3.66), and as $n \to \infty$, the consistent estimators of a_1 and a_2 are respectively given by

$$\hat{a}_1^* = \frac{tr(\mathbf{S}_e^*)}{uv_e p}, \tag{3.68}$$

$$\hat{a}_2^* = \frac{1}{(uv_e - 1)(uv_e + 2)p}\left[tr\left((\mathbf{S}_e^*)^2\right) - \frac{1}{uv_e}\left(tr(\mathbf{S}_e^*)\right)^2\right]. \tag{3.69}$$

Proof. This is similar to the proof of Lemma 3.2 given in Appendix A by substituting $\mathbf{S}_e^*$ instead of $\mathbf{S}_e$, p instead of pu, and uv_e instead of v_e.

Corollary 3.2 The consistent estimator of b^* is given by

$$\hat{b}^* = \frac{(\hat{a}_1^*)^2}{\hat{a}_2^*}, \tag{3.70}$$

where $\hat{a}_1^*$ and $\hat{a}_2^*$ are given by (3.68) and (3.69), respectively.

3.2.1 Generalization of Dempster's Test

Correspondingly, the generalization of Dempster's test in DMM analysis as defined by (3.20), the generalization of Dempster's test in MMM analysis, denoted by T_1^*, for testing hypothesis (3.55) is

$$T_1^* = \frac{uv_e \; tr(\mathbf{S}_h^*)}{uv_h \; tr(\mathbf{S}_e^*)}. \tag{3.71}$$

The approximate distribution of T_1^* under the null hypothesis is derived and given in Theorem 3.5.

Theorem 3.5. Under the null hypothesis (3.55) and assumption (3.51) and (3.66), if multivariate sphericity (3.57) is satisfied,

$$P_0(T_1^* < f) \doteq F(f, \lfloor uv_h d^* \rfloor, \lfloor uv_e d^* \rfloor),$$

where P_0 denotes that the probability is being calculated under the null hypothesis and $F(f, v_1, v_2)$ denotes the cumulative F distribution at f with v_1 and v_2 degrees of freedom, and $\lfloor x \rfloor$ denotes the largest integer $\leq x$. d^* is defined by

$$d^* = \frac{[tr(\mathbf{\Phi}_\Upsilon^*)]^2}{tr((\mathbf{\Phi}_\Upsilon^*)^2)} = \frac{p(a_1^*)^2}{a_2^*} = pb^*.$$

Since d^* is the function of unknown parameter $\mathbf{\Phi}_\Upsilon^*$, d^* can be estimated by

$$\hat{d}^* = \frac{p(\hat{a}_1^*)^2}{\hat{a}_2^*} = p\hat{b}^* \; .$$

Proof. Under the null hypothesis and if multivariate sphericity (3.57) is satisfied, $\mathbf{S}_e^*$ and $\mathbf{S}_h^*$ are independently distributed as central Wishart distributions, $W_p(\mathbf{\Phi}_\Upsilon^*, uv_e)$

and $W_p(\mathbf{\Phi}^*_\Upsilon, uv_h)$, respectively (Boik, 1988: 474-475). Subsequently, traces of $\mathbf{S}^*_e$ and $\mathbf{S}^*_h$ can be written in the form (Glueck and Muller, 1988: 2139)

$$tr(\mathbf{S}^*_e) = \sum_{k=1}^{p} \lambda^*_k u^*_{1k} \tag{3.72}$$

and

$$tr(\mathbf{S}^*_h) = \sum_{k=1}^{p} \lambda^*_k u^*_{2k} , \tag{3.73}$$

where u^*_{1k} and u^*_{2k} are independently distributed as chi-squared random variables with uv_e and uv_h degrees of freedom, respectively.

$tr(\mathbf{S}^*_e)$ and $tr(\mathbf{S}^*_h)$ are the finite positive weighted sums of a set of independent central chi-squared random variables which can be approximated by a single scaled central chi-squared distribution (Muller and Barton, 1989: 554). To define the approximate distribution, the first and second moments of (3.72) and (3.73) are equated to those of the approximated single scaled central chi-squared distribution. The first and second moments $tr(\mathbf{S}^*_e)$ and $tr(\mathbf{S}^*_h)$, defined by (3.72) and (3.73), are

$$E\left[tr(\mathbf{S}^*_e)\right] = uv_e \sum_{k=1}^{p} \lambda^*_k , \quad \mathrm{var}\left[tr(\mathbf{S}^*_e)\right] = 2uv_e \sum_{k=1}^{p} (\lambda^*_k)^2 \tag{3.74}$$

and

$$E\left[tr(\mathbf{S}^*_h)\right] = uv_h \sum_{k=1}^{p} \lambda^*_k , \quad \mathrm{var}\left[tr(\mathbf{S}^*_h)\right] = 2uv_h \sum_{k=1}^{p} (\lambda^*_k)^2 . \tag{3.75}$$

Defining the approximate central chi-squared distributions of $tr(\mathbf{S}^*_e)$ and $tr(\mathbf{S}^*_h)$ as $tr(\mathbf{S}^*_e) \sim w^*_e \chi^2_{r^*_e}$ and $tr(\mathbf{S}^*_h) \sim w^*_h \chi^2_{r^*_h}$, the degrees of freedom r^*_e and positive weight w^*_e can be solved by equating the moments defined in (3.74) and the moment of the approximate $w\chi^2_{r^*_e}$ distribution. Similarly, the degrees of freedom r^*_h and positive weight w^*_h can be solved by equating the moments defined in (3.75) and the moments of the approximate $w^*_h \chi^2_{r^*_h}$ distribution of $tr(\mathbf{S}_h)$. The first and second moments of the approximate central chi-squared distributions of $tr(\mathbf{S}^*_e)$ and $tr(\mathbf{S}^*_h)$ are

$$E\left[tr(\mathbf{S}^*_e)\right] = w^* r^*_e , \quad \mathrm{var}\left[tr(\mathbf{S}^*_e)\right] = 2(w^*)^2 r^*_e \tag{3.76}$$

and $$E\left[tr(\mathbf{S}_h^*)\right] = w^* r_h^*,\ \mathrm{var}\left[tr(\mathbf{S}_h^*)\right] = 2(w^*)^2 r_h^*. \tag{3.77}$$

Equating the first and second moments of $tr(\mathbf{S}_e^*)$ from (3.74) and (3.76) and the first and second of $tr(\mathbf{S}_h^*)$ from (3.75) and (3.77), the two following equations are obtained to solve for w^*, r_e^* and r_h^* as follows:

$$w_e^* r_e^* = uv_e \sum_{k=1}^{p} \lambda_k^* \quad \text{and} \quad 2(w_e^*)^2 r_e^* = 2uv_e \sum_{k=1}^{p} (\lambda_k^*)^2,$$

$$w_h^* r_h^* = uv_h \sum_{k=1}^{p} \lambda_k^* \quad \text{and} \quad 2(w_h^*)^2 r_h^* = 2uv_h \sum_{k=1}^{p} (\lambda_k^*)^2.$$

The solutions of the above four equations are

$$w_e^* = w_h^* = \frac{\sum_{k=1}^{p} (\lambda_k^*)^2}{\sum_{k=1}^{p} \lambda_k^*} = \frac{a_2^*}{a_1^*},$$

$$r_e^* = uv_e \frac{\left(\sum_{k=1}^{p} \lambda_k^*\right)^2}{\sum_{k=1}^{p} (\lambda_k^*)^2} = uv_e p \frac{(a_1^*)^2}{a_2^*} = uv_e pb^*$$

and $$r_h^* = uv_h \frac{\left(\sum_{k=1}^{p} \lambda_k^*\right)^2}{\sum_{k=1}^{p} (\lambda_k^*)^2} = uv_h p \frac{(a_1^*)^2}{a_1^*} = uv_h pb^*.$$

Using notation d, where $d = pb^*$, to simplify the notation of the degrees of freedom, $r_e^* = uv_e d^*$ and $r_h^* = uv_h d^*$, then, under the null hypothesis, the distribution of T_1^* is approximated by

$$\begin{aligned}
P(T_1^* < f) &= P\left(\frac{tr(\mathbf{S}_e^*)/uv_h}{tr(\mathbf{S}_h^*)/uv_e} < f\right) \\
&\doteq P\left(\frac{w_h^* \chi^2_{uv_h d^*}/uv_h}{w_e^* \chi^2_{uv_e d^*}/uv_e} < f\right) \\
&\doteq P\left(\frac{\chi^2_{uv_h d^*}/uv_h d^*}{\chi^2_{uv_e d^*}/uv_e d^*} < f\right) \\
&\doteq P(F_{uv_h d^*, uv_e d^*} < f).
\end{aligned}$$

Since d^* consists of an unknown parameter b^*, by Corollary 3.2, d^* is estimated by $\hat{d}^* = p\hat{b}^*$.

By Theorem 3.5, the null hypothesis (3.55), $H:(\mathbf{C}\otimes\mathbf{A}')\mathbf{B}^*=\mathbf{\Gamma}_{\mathbf{0}}^*$, is rejected at significance level α if $T_1^*>F(1-\alpha,\lfloor uv_h d^*\rfloor,\lfloor uv_e d^*\rfloor)$, where $v_h=rank(\mathbf{C})$, $v_e=n-g$, $\hat{d}^*=pu\hat{b}^*$ and $\hat{b}^*$ is defined by Corollary 3.2.

Next, the approximate non-null distribution of T_1^* is derived so as to find the power of the test. The approximate non-null distribution of T_1 is given in Theorem 3.6.

Theorem 3.6 Under the local alternative hypothesis and assumptions (3.51), (3.66) and (3.67), if multivariate sphericity (3.57) is satisfied, then

$$P_1\left(T_1^*<f\right)\doteq F\left(f,\lfloor r_h^*\rfloor,\lfloor r_h^*\rfloor,\delta^*\right),$$

where w_h^*, w_e^*, r_h^*, r_e^* and δ^* are respectively defined by

$$w_h^*=\frac{uv_h tr((\mathbf{\Phi}_\Upsilon^*)^2)+2tr((\mathbf{\Phi}_\Upsilon^*)\mathbf{\Xi}^*))}{uv_h tr(\mathbf{\Phi}_\Upsilon^*)+2tr(\mathbf{\Phi}_\Upsilon^*\mathbf{\Xi}^*)}\ ,\quad w_e^*=\frac{tr((\mathbf{\Phi}_\Upsilon^*)^2)}{tr(\mathbf{\Phi}_\Upsilon^*)},$$

$$r_h^*=\frac{uv_h tr(\mathbf{\Phi}_\Upsilon^*)}{w_h^*}\ ,\quad r_e^*=\frac{uv_e^*(tr(\mathbf{\Phi}_\Upsilon^*))^2}{tr((\mathbf{\Phi}_\Upsilon^*)^2)}\ \text{and}\ \delta^*=\frac{tr((\mathbf{\Phi}_\Upsilon^*)\mathbf{\Xi}^*)}{w^* tr(\mathbf{\Phi}_\Upsilon^*)}\ .$$

Note that P_1 denotes that the probability is being calculated under the local alternative hypothesis and $F\,(f,v_1,v_2,\delta)$ denotes the cumulative non-central F distribution with v_1 and v_2 degrees of freedom and non-centrality parameter δ, and $[x]$ denotes the largest integer $\leq x$.

Proof. Under the local alternative hypothesis, if multivariate sphericity (3.57) is satisfied, $\mathbf{S}_e^*$ and $\mathbf{S}_h^*$ are independently distributed as central and non-central Wishart distributions, $W_p(\mathbf{\Phi}^*,uv_e)$ and $W_p\left(\mathbf{\Phi}^*,uv_h,\mathbf{\Phi}^{*-1}\mathbf{\Delta}^*\right)$, respectively. Subsequently, traces of $\mathbf{S}_e^*$ and $\mathbf{S}_h^*$ can be written in the form

$$tr(\mathbf{S}_e^*)=\sum_{k=1}^{p}\lambda_k^* u_{1k}^* \tag{3.78}$$

and

$$tr(\mathbf{S}_h^*)=\sum_{k=1}^{p}\lambda_k^* u_{2k}^*\ , \tag{3.79}$$

where u_{1k}^* are central chi-squared random variables with uv_e degrees of freedom and u_{2k}^* are non-central chi-squared random variables with uv_h degrees of freedom and non-centrality parameter δ_k^*, which is comprised of diagonal elements of $(\mathbf{\Phi}_\Upsilon^*)^{-1}\mathbf{\Delta}^*$. To approximate the distributions of $tr(\mathbf{S}_e^*)$ and $tr(\mathbf{S}_h^*)$, their first and second moments are derived as

$$E\left[tr(\mathbf{S}_e^*)\right] = uv_e\sum_{k=1}^{p}\lambda_k^*, \quad \text{var}\left[tr(\mathbf{S}_e^*)\right] = 2uv_e\sum_{k=1}^{p}(\lambda_k^*)^2 \tag{3.80}$$

and
$$E\left[tr(\mathbf{S}_h^*)\right] = \sum_{k=1}^{p}\lambda_k^*(uv_h + \delta_k^*), \quad \text{var}\left[tr(\mathbf{S}_h^*)\right] = \sum_{k=1}^{p}(\lambda_k^*)^2(2uv_h + 4\delta_k^*). \tag{3.81}$$

To find the approximate central and noncentral chi-squared distributions of $tr(\mathbf{S}_e^*)$ and $tr(\mathbf{S}_h^*)$, denoted by $tr(\mathbf{S}_e^*) \sim w_e^*\chi_{r_e^*}^2$ and $tr(\mathbf{S}_h^*) \sim w_h^*\chi_{r_h^*,\delta^*}^2$, the first and second moments of $tr(\mathbf{S}_e^*)$ and $tr(\mathbf{S}_h^*)$ of the approximated chi-squared distributions are defined by

$$E\left[tr(\mathbf{S}_e^*)\right] = w_e^*r_e^*, \quad \text{var}\left[tr(\mathbf{S}_e^*)\right] = 2(w_e^*)^2 r_e^* \tag{3.82}$$

and
$$E\left[tr(\mathbf{S}_h^*)\right] = w^*(r_h^* + \delta^*), \quad \text{var}\left[tr(\mathbf{S}_h^*)\right] = (w^*)^2(2r_h^* + 4\delta^*). \tag{3.83}$$

By equating the first and second moments of $tr(\mathbf{S}_e^*)$ from (3.80) and (3.82) and solving for w_e^* and r_e^*, the solutions are

$$w_e^* = \frac{\sum_{k=1}^{p}(\lambda_k^*)^2}{\sum_{k=1}^{p}\lambda_k^*}$$

and
$$r_e^* = \frac{\left(\sum_{k=1}^{p}\lambda_k^*\right)^2}{\sum_{k=1}^{p}(\lambda_k^*)^2} = \frac{uv_e(tr(\mathbf{\Phi}_\Upsilon^*))^2}{tr((\mathbf{\Phi}_\Upsilon^*))^2}.$$

By equating the first and second moments of $tr(\mathbf{S}_h^*)$ from (3.81) and (3.83), we obtain

$$w^*(r_h^* + \delta^*) = uv_h\sum_{k=1}^{p}\lambda_k^* + \sum_{k=1}^{p}\lambda_k^*\delta_k^* \tag{3.84}$$

and
$$(w^*)^2(2r_h^* + 4\delta^*) = 2uv_h\sum_{k=1}^{p}(\lambda_k^*)^2 + 4\sum_{k=1}^{pu}(\lambda_k^*)^2\delta_k^* . \tag{3.85}$$

Using the notations S_1 and S_2 for the two terms on the right hand side of (3.84) and S_3 and S_4 for the two terms on right hand side of (3.85) to solve for w_h^*, r_h^* and δ^*, the solutions are

$$w_h^* = \frac{S_3^* + 2S_4^*}{S_1^* + 2S_2^*} = \frac{uv_h \sum_{k=1}^{p} (\lambda_k^*)^2 + 2\sum_{k=1}^{p} (\lambda_k^*)^2 \delta_k^*}{uv_h \sum_{k=1}^{p} \lambda_k^* + 2\sum_{k=1}^{p} \lambda_k^* \delta_k^*} = \frac{uv_h p a_2^* + 2tr((\mathbf{\Phi}_\Upsilon^*)^2 \mathbf{\Xi}^*))}{uv_h p a_1^* + 2tr(\mathbf{\Phi}_\Upsilon^* \mathbf{\Xi}^*)} \ ,$$

$$r_h^* = \frac{S_1^*}{w_h^*} = \frac{uv_h \sum_{k=1}^{p} \lambda_k^*}{w_h^*} = \frac{uv_h tr(\mathbf{\Phi}_\Upsilon^*)}{w_h^*},$$

and
$$\delta^* = \frac{S_2^*}{w_h^*} = \frac{\sum_{k=1}^{p} \lambda_k^* \delta_k^*}{w_h^*} = \frac{tr(\mathbf{\Phi}_\Upsilon^* \mathbf{\Xi})}{w_h^*}.$$

Therefore, under the local alternative hypothesis, the non-null distribution of T_1^* is approximated by

$$\begin{aligned}
P(T_1^* < f) &= P\left\{ \frac{tr(\mathbf{S}_h^*)/uv_h}{tr(\mathbf{S}_e^*)/uv_e} < f \right\} \\
&\doteq P\left\{ \frac{w_h^* \chi^2_{r_h^*,\delta^*}/uv_h}{w_e^* \chi^2_{r_e^*}/uv_e} < f \right\} \\
&\doteq P\left\{ \frac{\chi^2_{r_h^*,\delta^*}/r_h^*}{\chi^2_{r_e^*}/r_e^*} < \frac{w_e^*}{w_h^*} \cdot \frac{uv_h r_e^*}{uv_e r_h^*} f \right\} \\
&\doteq F\left(f, \lfloor r_h^* \rfloor, \lfloor r_e^* \rfloor, \delta^*\right).
\end{aligned}$$

□

3.2.2 Generalization of Bai and Saranadasa's Test

Similarly to Section 2.1.2, the generalization of Bai and Saranadasa's test is adapted for testing hypothesis (3.55) in MMM analysis. The test statistic is given by

$$T_2^* = \left\{ 2uv_h a_2^* \left(1 + \frac{v_h}{v_e}\right) \right\}^{-1/2} \frac{1}{\sqrt{p}} \left[tr(\mathbf{S}_h^*) - \frac{v_h}{v_e} tr(\mathbf{S}_e^*) \right]. \tag{3.86}$$

Next, the asymptotic distribution of T_2^* is derived under the null hypothesis given in Theorem 3.7.

Theorem 3.7 Under the null hypothesis (3.55) and assumptions (3.51) and (3.66), if multivariate sphericity (3.57) is satisfied, then

$$\lim_{n\to\infty}\lim_{p\to\infty} P_0(T_2^* < z) = \mathbb{N}(z),$$

where P_0 denotes that the probability is being calculated under the local null hypothesis and $\mathbb{N}(z)$ denotes the cumulative standard normal distribution.

Proof. Under the null hypothesis, if multivariate sphericity (3.57) is satisfied, then

$$\mathbf{S}_e^* \sim W_p(\mathbf{\Phi}^*, uv_e) \text{ and } \mathbf{S}_h^* \sim W_p(\mathbf{\Phi}^*, uv_h),$$

$$\text{and} \quad tr(\mathbf{S}_e^*) = \sum_{k=1}^{p} \lambda_k^* u_{1k}^* \quad \text{and} \quad tr(\mathbf{S}_h^*) = \sum_{k=1}^{p} \lambda_k^* u_{2k}^*,$$

where $u_{1k}^* \sim \chi^2_{v_e^*}$ and $u_{2k}^* \sim \chi^2_{v_h^*}$.

Let

$$T_0^* = \frac{1}{\sqrt{p}}\left[tr(\mathbf{S}_h^*) - \frac{v_h}{v_e} tr(\mathbf{S}_e^*) \right]$$

$$= \frac{1}{\sqrt{p}}\left[\sum_{k=1}^{p} \lambda_k^* (u_{2k}^* - \frac{v_h}{v_e} u_{1k}^*) \right]. \tag{3.87}$$

Consider that

$$E\left(u_{2k}^* - \frac{v_h}{v_e} u_{1k}^* \right) = 0, \tag{3.88}$$

and

$$\text{var}\left(u_{2k}^* - \frac{v_h}{v_e} u_{1k}^* \right) = 2uv_h + \frac{2uv_h^2}{v_e}. \tag{3.89}$$

Therefore,

$$E(T_0) = 0$$

$$\text{and} \qquad \text{var}(T_0^*) = \frac{1}{p}\sum_{k=1}^{p} (\lambda_k^*)^2 \left(2uv_h + \frac{2uv_h^2}{v_e} \right)$$

$$= a_2^*\left(2uv_h + \frac{2uv_h^2}{v_e}\right)$$

$$= 2uv_h a_2^*\left(1+\frac{v_h}{v_e}\right) = (\sigma_0^*)^2 < \infty . \tag{3.90}$$

From (3.86) and (3.87), T_2^* can be written in the form of T_0^* as

$$T_2^* = \left\{2uv_h a_2^*\left(1+\frac{v_h}{v_e}\right)\right\}^{-1/2} \frac{1}{\sqrt{p}}\left[tr(\mathbf{S}_h^*) - \frac{v_h}{v_e} tr(\mathbf{S}_e^*)\right]$$

$$= \left\{2uv_h a_2^*\left(1+\frac{v_h}{v_e}\right)\right\}^{-1/2} T_0^* , \tag{3.91}$$

and the expectation and variance of T_2^* are

$$E(T_2^*) = 0 \quad \text{and} \quad \mathrm{var}(T_2^*) = 1 .$$

Correspondingly from Lemma 3.3, it is possible that T_2^* from (3.91) can be written as $T_2^* = \sum_{k=1}^{p} c_k^* z_k^*$, where

$$c_k^* = \frac{1}{\sqrt{pa_2^*}}\lambda_k^* \qquad \text{and} \qquad z_k^* = \left\{2uv_h\left(1+\frac{v_h}{v_e}\right)\right\}^{-1/2}\left(u_{2k}^* - \frac{v_h}{v_e}u_{1k}^*\right),$$

after which we get

$$\sum_{k=1}^{p}(c_k^*)^2 = \frac{1}{a_2^*}\cdot\frac{1}{p}\sum_{k=1}^{p}(\lambda_k^*)^2 = \frac{a_2^*}{a_2^*} = 1$$

and, from (3.88) and (3.89), we obtain

$$E(z_k^*) = 0 \quad \text{and} \quad \mathrm{var}(z_k^*) = 1 .$$

Therefore, if

$$\max_{1\le k\le p}\left|c_k^*\right| = \max_{1\le k\le p}\frac{1}{\sqrt{pa_2^*}}\lambda_k^* \to 0 \qquad \text{as } p\to\infty , \tag{3.92}$$

T_2^* is asymptotically standard normally distributed as $p\to\infty$.

From assumption (3.66), a_2^* is assumed to be constant as $p\to\infty$, c_k^* converges in probability to a constant, and it is additionally assumed that $\lambda_k^* = O(p^m)$, for $0 \le m < \frac{1}{2}$, satisfies condition (3.92). Hence, from Slutsky's Theorem and Lemma 3.3,

$$\lim_{n\to\infty}\lim_{p\to\infty} P(T_2^* < z) = \mathbb{N}(z) . \qquad \square$$

By applying Theorem 3.7, the null hypothesis (3.55), $H:(\mathbf{C}\otimes\mathbf{A}')\mathbf{B}^* = \mathbf{\Gamma}_\mathbf{0}^*$, is rejected at significance level α if $T_2^* > z_\alpha$, where z_α denotes the upper $(1-\alpha)$ 100%. To derive the asymptotic distribution of T_2^* under the local alternative hypothesis, u_1^* and u_2^* are defined as shown below and the asymptotic distribution of u_1^* and u_2^* are stated in Lemma 3.6.

Let

$$u_1^* = \frac{1}{\sqrt{p}}[tr(\mathbf{S}_h^*) - uv_h tr(\mathbf{\Phi}_\Upsilon^*) - tr(\mathbf{\Phi}_\Upsilon^*\mathbf{\Xi}^*)]$$

and
$$u_2^* = \frac{1}{\sqrt{uv_e p}}[tr(\mathbf{S}_e^*) - uv_e tr(\mathbf{\Phi}_\Upsilon^*)] .$$

Lemma 3.6 As $p\to\infty$ and under assumptions (3.51), (3.66) and (3.67),

$$u_1^* \xrightarrow{d} N\left\{0, 2uv_h a_2^* + 4tr((\mathbf{\Phi}_\Upsilon^*)^2\mathbf{\Xi}^*)/p\right\}$$

and
$$u_2^* \xrightarrow{d} N(0, 2a_2^*) ,$$

where $\xrightarrow{d}$ denotes 'converges in distribution' .

Proof. The characteristic function of u_1^* is given by

$$\begin{aligned}
\Psi_{u_1}(t) &= E[\exp(itu_1^*)] \\
&= E\left(\exp(\frac{it}{\sqrt{p}}tr(\mathbf{S}_h^*))\right) \times E\left(\exp(-\frac{it}{\sqrt{p}}[uv_h tr(\mathbf{\Phi}_\Upsilon^*) + tr(\mathbf{\Phi}_\Upsilon^*\mathbf{\Xi}^*)]\right) \\
&= \left| I_{pu} - \frac{2it}{\sqrt{p}}\mathbf{\Phi}_\Upsilon^* \right|^{-\frac{1}{2}uv_h} \exp\left\{ -\frac{it}{\sqrt{p}} tr\left(\mathbf{\Phi}_\Upsilon^* \left(I_p - \frac{2it}{\sqrt{p}}\mathbf{\Phi}_\Upsilon^* \right)^{-1} \mathbf{\Xi}^* \right) \right\} \\
&\quad \times \exp\left\{ -\frac{it}{\sqrt{p}}[uv_h tr(\mathbf{\Phi}_\Upsilon^*) + tr(\mathbf{\Phi}_\Upsilon^*\mathbf{\Xi}^*)] \right\} .
\end{aligned}$$

Now, by expansion,

$$\log\left|I_p - \frac{2it}{\sqrt{p}}\mathbf{\Phi}_\Upsilon^*\right|^{-\frac{1}{2}uv_h} = -\frac{1}{2}uv_h \log\left|I_p - \frac{2it}{\sqrt{p}}\mathbf{\Phi}_\Upsilon^*\right|$$

$$= \frac{1}{2}uv_h\left[\frac{2it}{\sqrt{p}}tr(\mathbf{\Phi}_\Upsilon^*) + \left(\frac{2it}{\sqrt{p}}\right)^2 tr((\mathbf{\Phi}_\Upsilon^*)^2)\right] + o(1)$$

$$= \frac{it}{\sqrt{p}}uv_h tr(\mathbf{\Phi}_\Upsilon^*) + \left(\frac{it}{\sqrt{p}}\right)^2 2uv_h tr((\mathbf{\Phi}_\Upsilon^*))^2 + o(1),$$

and $-\frac{it}{\sqrt{p}}tr\left(\mathbf{\Phi}_\Upsilon^*\left(I_p - \frac{2it}{\sqrt{p}}\mathbf{\Phi}_\Upsilon^*\right)^{-1}\mathbf{\Xi}^*\right)$

$$= \frac{it}{\sqrt{p}}tr\left[\mathbf{\Phi}_\Upsilon^*\left(I_p + \frac{2it}{\sqrt{p}}\mathbf{\Phi}_\Upsilon^* + \left(\frac{2it}{\sqrt{p}}\right)^{\mathbf{2}}(\mathbf{\Phi}_\Upsilon^*)^2\right)\mathbf{\Xi}^* + o(1)\right]$$

$$= \frac{it}{\sqrt{p}}tr\left[\mathbf{\Phi}_\Upsilon^*\mathbf{\Xi}^* + \frac{2it}{\sqrt{p}}(\mathbf{\Phi}_\Upsilon^*)^2\mathbf{\Xi}^* + \left(\frac{2it}{\sqrt{p}}\right)^{\mathbf{2}}(\mathbf{\Phi}_\Upsilon^*)^3\mathbf{\Xi}^* + o(1)\right]$$

$$= \frac{it}{\sqrt{p}}tr(\mathbf{\Phi}_\Upsilon^*\mathbf{\Xi}^*) + \left(\frac{2it}{\sqrt{p}}\right)^{\mathbf{2}} tr(\mathbf{\Phi}_\Upsilon^*)^2\mathbf{\Xi}^*) + o(1).$$

Hence,

$$\log E(e^{itu_1^*}) = \log\left|I_p - \frac{2it}{\sqrt{p}}\mathbf{\Phi}_\Upsilon^*\right|^{-\frac{1}{2}uv_h} - \frac{it}{\sqrt{p}}tr\left[\mathbf{\Phi}_\Upsilon^*\left(I_p - \frac{2it}{\sqrt{p}}\mathbf{\Phi}_\Upsilon^*\right)^{-1}\mathbf{\Xi}^*\right]$$

$$-\frac{it}{\sqrt{p}}[uv_h tr(\mathbf{\Phi}_\Upsilon^*) + tr(\mathbf{\Phi}_\Upsilon^*\mathbf{\Xi})]$$

$$= \frac{it}{\sqrt{p}}uv_h tr(\mathbf{\Phi}_\Upsilon^*) + \left(\frac{it}{\sqrt{p}}\right)^2 2uv_h tr((\mathbf{\Phi}_\Upsilon^*)^2) + \frac{it}{\sqrt{p}}tr(\mathbf{\Phi}_\Upsilon^*\mathbf{\Xi}^*)$$

$$+\left(\frac{2it}{\sqrt{p}}\right)^{\mathbf{2}} tr((\mathbf{\Phi}_\Upsilon^*)^2\mathbf{\Xi}^*) - \frac{it}{\sqrt{p}}[uv_h tr(\mathbf{\Phi}_\Upsilon^*) + tr(\mathbf{\Phi}_\Upsilon^*\mathbf{\Xi}^*)] + o(1)$$

$$= (it)^2\frac{2uv_h tr((\mathbf{\Phi}_\Upsilon^*)^2)}{p} + (it)^{\mathbf{2}}\frac{4tr((\mathbf{\Phi}_\Upsilon^*)^2\mathbf{\Xi}^*)}{p} + o(1).$$

Therefore,

$$\Psi_{u_1}(t) = E(\exp(itu_1^*))$$

$$= \exp\left\{(it)^2 \frac{2uv_h tr((\mathbf{\Phi}_\Upsilon^*)^2)}{p} + (it)^2 \frac{4tr((\mathbf{\Phi}_\Upsilon^*)^2 \mathbf{\Xi}^*)}{p} + o(1)\right\}$$

$$= \exp\left\{\frac{1}{2}\left((it)^2 \frac{2uv_h tr((\mathbf{\Phi}_\Upsilon^*)^2)}{p} + (it)^2 \frac{4tr((\mathbf{\Phi}_\Upsilon^*)^2 \mathbf{\Xi}^*)}{p}\right)\right\}$$

$$\times \exp\left\{\frac{1}{2}\left((it)^2 \frac{2uv_h tr((\mathbf{\Phi}_\Upsilon^*)^2)}{p} + (it)^2 \frac{4tr((\mathbf{\Phi}_\Upsilon^*)^2 \mathbf{\Xi}^*)}{p}\right)\right\} \times o(1)$$

$$= \exp\left\{\frac{1}{2}(it)^2\left(\frac{2uv_h tr((\mathbf{\Phi}_\Upsilon^*)^2)}{p} + \frac{4tr((\mathbf{\Phi}_\Upsilon^*)^2 \mathbf{\Xi}^*)}{p}\right)\right\} \times (1 + o(1)) .$$

As $p \to \infty$, this function is in the form of a characteristic function of a normal distribution with mean parameter $\frac{2uv_h tr((\mathbf{\Phi}_\Upsilon^*))^2}{p}$ and covariance parameter $\frac{4tr((\mathbf{\Phi}_\Upsilon^*)\mathbf{\Xi}^*)}{p}$. Thus, as $p \to \infty$,

$$u_1^* \sim N\left(\frac{2uv_h tr((\mathbf{\Phi}_\Upsilon^*))^2}{p}, \frac{4tr((\mathbf{\Phi}_\Upsilon^*)\mathbf{\Xi}^*)}{p}\right).$$

The characteristic function of u_2^* is given by

$$\Psi_{u_2^*}(t) = E(\exp(itu_2^*))$$

$$= E\left\{\exp\left(\frac{it}{\sqrt{uv_e p}} tr(\mathbf{S}_e^*)\right)\right\} \times E\left\{\exp\left(-\frac{it}{\sqrt{uv_e p}} uv_e tr(\mathbf{\Phi}_\Upsilon^*)\right)\right\}$$

$$= \left|I_p - \frac{2it}{\sqrt{uv_e p}} \mathbf{\Phi}_\Upsilon^*\right|^{-\frac{1}{2}v_e} \exp\left(-\frac{it}{\sqrt{uv_e p}} uv_e tr(\mathbf{\Phi}_\Upsilon^*)\right).$$

As before, we have

$$\log\left|I_p-\frac{2it}{\sqrt{uv_e p}}\mathbf{\Phi}_\Upsilon^*\right|^{-\frac{1}{2}uv_e} = -\frac{1}{2}uv_e\log\left|I_p-\frac{2it}{\sqrt{uv_e p}}\mathbf{\Phi}_\Upsilon^*\right|$$

$$=\frac{1}{2}uv_e\left[\frac{2it}{\sqrt{uv_e p}}tr(\mathbf{\Phi}_\Upsilon^*)+\left(\frac{2it}{\sqrt{uv_e p}}\right)^2 tr((\mathbf{\Phi}_\Upsilon^*))^2\right]+o(1)$$

$$=ituv_e\frac{tr(\mathbf{\Phi}_\Upsilon^*)}{\sqrt{uv_e p}}+(it)^2\frac{2tr((\mathbf{\Phi}_\Upsilon^*))^2}{p}+o(1).$$

Hence,

$$\log E(\exp(itu_2^*))=\left|I_p-\frac{2it}{\sqrt{uv_e p}}\mathbf{\Phi}_\Upsilon^*\right|^{-\frac{1}{2}v_e}-\frac{it}{\sqrt{uv_e p}}uv_e tr(\mathbf{\Phi}_\Upsilon^*)$$

$$=ituv_e\frac{tr(\mathbf{\Phi}_\Upsilon^*)}{\sqrt{uv_e p}}+(it)^2\frac{2tr((\mathbf{\Phi}_\Upsilon^*))^2}{p}-\frac{it}{\sqrt{uv_e p}}uv_e tr(\mathbf{\Phi}_\Upsilon^*)+o(1)$$

$$=(it)^2\frac{2tr((\mathbf{\Phi}_\Upsilon^*)^2)}{p}+o(1).$$

Therefore, we have

$$\Psi_{u_2^*}(t)=E(\exp(itu_2^*))$$

$$=\exp\left((it)^2\frac{2tr((\mathbf{\Phi}_\Upsilon^*)^2)}{p}+o(1)\right)$$

$$=\exp\left(\frac{1}{2}(it)^2\frac{2tr((\mathbf{\Phi}_\Upsilon^*)^2)}{p}\right)\times\exp\left(\frac{1}{2}(it)^2\frac{2tr((\mathbf{\Phi}_\Upsilon^*)^2)}{p}\right)\times o(1)$$

$$=\exp\left(\frac{1}{2}(it)^2\frac{2tr((\mathbf{\Phi}_\Upsilon^*)^2)}{p}\right)\times(1+o(1)) \; .$$

As $p\to\infty$, the characteristic function of u_2^* is the same as the characteristic function of a normal distribution with a zero mean parameter and covariance $\frac{2tr((\mathbf{\Phi}_\Upsilon^*)^2)}{p}=2a_2^*$. Thus, as $p\to\infty$,

$$u_2^*\sim N\left(0,2a_2^*\right).$$ □

Theorem 3.8 Under the local alternative hypothesis and assumptions (3.51) and (3.67), if multivariate sphericity (3.57) is satisfied, then

$$\lim_{p\to\infty} P_1(T_2^* > z) = \lim_{p\to\infty} \mathbb{N}\left(-\frac{\sigma_0}{\sigma_2} z_\alpha + \frac{tr(\mathbf{\Phi}_\Upsilon^* \mathbf{\Xi}^*)}{\sigma_2 \sqrt{p}}\right).$$

Proof. Consider

$$u_1^* - \frac{uv_h}{\sqrt{uv_e}} u_2^* = \frac{1}{\sqrt{p}}\left\{tr(\mathbf{S}_h^*) - uv_h tr(\mathbf{\Phi}_\Upsilon^*) - tr(\mathbf{\Phi}_\Upsilon^*\mathbf{\Xi}^*)] - \frac{uv_h}{uv_e}[tr(\mathbf{S}_e^*) - uv_e tr(\mathbf{\Phi}_\Upsilon^*)]\right\}$$

$$= \frac{1}{\sqrt{p}}\left\{tr(\mathbf{S}_h^*) - tr(\mathbf{\Phi}_\Upsilon^*\mathbf{\Xi}^*) - \frac{v_h}{v_e} tr(\mathbf{S}_e^*)\right\}$$

$$= \sigma_0^* T_2^* - \frac{tr(\mathbf{\Phi}_\Upsilon^*\mathbf{\Xi}^*)}{\sqrt{p}},$$

where T_2^* and σ_0^* are defined as in (3.91) and (3.87), respectively.

Note that u_1^* and u_2^* are independently distributed and, from Lemma 3.5, we obtain

$$E\left(u_1^* - \frac{v_h}{\sqrt{v_e}} u_2^*\right) = 0$$

and

$$\operatorname{var}\left(u_1^* - \frac{v_h}{\sqrt{v_e}} u_2^*\right) = 2uv_h a_2^* + \frac{4tr((\mathbf{\Phi}_\Upsilon^*)^2\mathbf{\Xi}^*)}{p} + \frac{v_h^2}{v_e} 2a_2^*$$

$$= 2uv_h a_2^*(1 + \frac{v_h}{v_e}) + \frac{4tr((\mathbf{\Phi}_\Upsilon^*)^2\mathbf{\Xi}^*)}{p}$$

$$= (\sigma_0^*)^2 + \frac{4tr((\mathbf{\Phi}_\Upsilon^*)^2\mathbf{\Xi}^*)}{p}$$

$$= (\sigma_2^*)^2 < \infty .$$

Thus, from Lemma 3.6, as $p \to \infty$,

$$u_1^* - \frac{v_h}{\sqrt{v_e}} u_2^* \xrightarrow{d} N\left\{0,\ 2uv_h a_2^*(1 + \frac{v_h}{v_e}) + \frac{4tr((\mathbf{\Phi}_\Upsilon^*)^2\mathbf{\Xi}^*)}{p}\right\}.$$

Hence, as $p \to \infty$,

$$\frac{1}{\sigma_2^*}\left(u_1^* - \frac{v_h}{\sqrt{v_e}}u_2^*\right) = \frac{1}{\sigma_2^*}\left(\sigma_0^* T_2^* - \frac{tr(\mathbf{\Phi}_\Upsilon^* \mathbf{\Xi}^*)}{\sqrt{p}}\right) \xrightarrow{d} N(0,1).$$

Thus,

$$P_1(T_2^* > z_\alpha) = P_1\left(\sigma_0^* T_2^* > \sigma_0^* z_\alpha\right)$$

$$= P_1\left(\sigma_0^* T_2^* - \frac{tr(\mathbf{\Phi}_\Upsilon^* \mathbf{\Xi}^*)}{\sqrt{p}} > \sigma_0^* z_\alpha - \frac{tr(\mathbf{\Phi}_\Upsilon^* \mathbf{\Xi}^*)}{\sqrt{p}}\right)$$

$$= P_1\left\{\frac{1}{\sigma_2^*}\left(\sigma_0^* T_2^* - \frac{tr(\mathbf{\Phi}_\Upsilon^* \mathbf{\Xi}^*)}{\sqrt{p}}\right) > \frac{1}{\sigma_2^*}\left(\sigma_0^* z_\alpha - \frac{tr(\mathbf{\Phi}_\Upsilon^* \mathbf{\Xi}^*)}{\sqrt{p}}\right)\right\}$$

$$= P_1\left\{Z > \frac{\sigma_0^*}{\sigma_2^*} z_\alpha - \frac{tr(\mathbf{\Phi}_\Upsilon^* \mathbf{\Xi}^*)}{\sigma_2^* \sqrt{p}}\right\} ,$$

and
$$\lim_{p\to\infty} P_1(T_2^* > z_\alpha) = \lim_{p\to\infty} P_1\left\{Z > \frac{\sigma_0^*}{\sigma_2^*} z_\alpha - \frac{tr(\mathbf{\Phi}_\Upsilon^* \mathbf{\Xi}^*)}{\sigma_2^* \sqrt{p}}\right\}$$

$$= \lim_{p\to\infty}\left\{1 - \mathbb{N}\left(\frac{\sigma_0^*}{\sigma_2^*} z_\alpha - \frac{tr(\mathbf{\Phi}_\Upsilon^* \mathbf{\Xi}^*)}{\sigma_2^* \sqrt{p}}\right)\right\}$$

$$= \lim_{p\to\infty} \mathbb{N}\left[-\left(\frac{\sigma_0^*}{\sigma_2^*} z_\alpha - \frac{tr(\mathbf{\Phi}_\Upsilon^* \mathbf{\Xi}^*)}{\sigma_2^* \sqrt{p}}\right)\right]$$

$$= \lim_{p\to\infty} \mathbb{N}\left(-\frac{\sigma_0^*}{\sigma_2^*} z_\alpha + \frac{tr(\mathbf{\Phi}_\Upsilon^* \mathbf{\Xi}^*)}{\sigma_2^* \sqrt{p}}\right). \qquad \square$$

CHAPTER 4

SIMULATION STUDY

4.1 Simulation Design

In this chapter, the performance of the proposed tests, T_1 and T_2 for the high dimensional DMM and T_1^* and T_2^* for the high dimensional MMM, are evaluated using simulation studies. Both under the null and local alternate hypotheses and using the upper 5% limit, the powers of the test statistics are evaluated using a Monte Carlo simulation and are calculated based on 5,000 iterations.

4.1.1 Multivariate Repeated Measurements Design

Multivariate repeated measurements were simulated using three groups (g = 3) and repeated three times ($t = 3$). The number of observations were set for four cases as 15, 30, 60 and 90 ($n = 15, 30, 60, 90$). There were two cases of an equal number of subjects in each group, $n = 15$ ($n_1 = n_2 = n_3 = 5$) and $n = 60$ ($n_1 = n_2 = n_3 = 20$), and two cases of an unequal number of subjects in each group, $n = 30$ ($n_1 = 8$, $n_2 = 10$, $n_3 = 12$) and $n = 90$ ($n_1 = 25$, $n_2 = 30$, $n_3 = 35$).

The dimensions of the response variables were chosen for each case of observations. For $n = 15$, the dimensions were set at 30, 45, 60 and 75, for $n = 30$, the dimensions were set at 60, 90, 120 and 150, for $n = 60$, the dimensions were set at 120, 180, 240 and 300 and, for $n = 90$, the dimensions were set at 180, 270, 360 and 450.

Using the DMM $\mathbf{Y}_{n\times pt} = \mathbf{X}_{n\times g}\mathbf{B}_{g\times pt} + \mathbf{U}_{n\times pt}$, an $n \times pt$ error matrix $\mathbf{U}$ was firstly generated for each group by using a multivariate normal distribution with a zero mean matrix and a positive definited covariance matrix $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{\Sigma}$.

The simulation was studied in two cases of $\mathbf{\Sigma}$: $\mathbf{\Sigma}=\mathbf{I}_{pt}$ and $\mathbf{\Sigma}=1.5\mathbf{I}_{pt}+0.5\mathbf{J}_{pt}$. After this, the $n\times pt$ response matrix $\mathbf{Y}$ was constructed using the DMM $\mathbf{Y}_{n\times pt}=\mathbf{X}_{n\times g}\mathbf{B}_{g\times pt}+\mathbf{U}_{n\times pt}$, where $\mathbf{X}$ is a $n\times g$ constant design matrix and $\mathbf{B}$ is a $g\times pt$ parameter matrix. The design matrix $\mathbf{X}$ and parameter matrix $\mathbf{B}$ are defined by

$$\mathbf{X}_{n\times 3}=\begin{bmatrix}\mathbf{1}_{n_1} & \mathbf{0} & \mathbf{0}\\ \mathbf{0} & \mathbf{1}_{n_2} & \mathbf{0}\\ \mathbf{0} & \mathbf{0} & \mathbf{1}_{n_3}\end{bmatrix}, \text{ where } \mathbf{1}_m \text{ is an } m\times 1 \text{ vector of ones, and} \tag{4.1}$$

$$\mathbf{B}_{3\times 3p}=\left[\begin{array}{ccc|ccc|c|ccc}\mu_{11}^{(1)} & \mu_{12}^{(1)} & \mu_{13}^{(1)} & \mu_{11}^{(2)} & \mu_{21}^{(2)} & \mu_{13}^{(2)} & \cdots & \mu_{11}^{(p)} & \mu_{12}^{(p)} & \mu_{13}^{(p)}\\ \mu_{21}^{(1)} & \mu_{22}^{(1)} & \mu_{23}^{(1)} & \mu_{21}^{(2)} & \mu_{22}^{(2)} & \mu_{23}^{(2)} & \cdots & \mu_{21}^{(p)} & \mu_{22}^{(p)} & \mu_{23}^{(p)}\\ \mu_{31}^{(1)} & \mu_{32}^{(1)} & \mu_{33}^{(1)} & \mu_{31}^{(2)} & \mu_{32}^{(2)} & \mu_{33}^{(2)} & & \mu_{31}^{(p)} & \mu_{32}^{(p)} & \mu_{33}^{(p)}\end{array}\right]. \tag{4.2}$$

For testing the null hypothesis (2.18), $H:\mathbf{CB}(\mathbf{I}_p\otimes\mathbf{A})=\mathbf{\Gamma}_0$, the parameter matrix $\mathbf{B}$ (4.2) was set so that $\mathbf{B}=\mathbf{B_0}$ and for testing the local alternative hypothesis, $\mathbf{B}=\mathbf{B}_1$, as follows:

$$\mathbf{B}_0=\left[\mu^{(1)}\mathbf{J}_{3\times 3}\quad \mu^{(2)}\mathbf{J}_{3\times 3}\quad \cdots\quad \mu^{(p)}\mathbf{J}_{3\times 3}\right]_{3\times 3p}$$

$$=\left[\begin{array}{ccc|ccc|c|ccc}\mu^{(1)} & \mu^{(1)} & \mu^{(1)} & \mu^{(2)} & \mu^{(2)} & \mu^{(2)} & \cdots & \mu^{(p)} & \mu^{(p)} & \mu^{(p)}\\ \mu^{(1)} & \mu^{(1)} & \mu^{(1)} & \mu^{(2)} & \mu^{(2)} & \mu^{(2)} & \cdots & \mu^{(p)} & \mu^{(p)} & \mu^{(p)}\\ \mu^{(1)} & \mu^{(1)} & \mu^{(1)} & \mu^{(2)} & \mu^{(2)} & \mu^{(2)} & \cdots & \mu^{(p)} & \mu^{(p)} & \mu^{(p)}\end{array}\right] \tag{4.3}$$

where $\mu^{(l)}\sim U(5,6)$, for $l=1,2,\ldots,p$.

$$\mathbf{B}_1=\mathbf{B}_0+\delta\left[\mathbf{D}_{3\times 3}\quad \mathbf{D}_{3\times 3}\quad \cdots\quad \mathbf{D}_{3\times 3}\right], \tag{4.4}$$

where

$$\mathbf{D}_{3\times 3}=\begin{bmatrix}1 & 0.5 & 0.25\\ 0.5 & 0.25 & 0\\ 0 & 0 & 0\end{bmatrix} \text{ and } \delta=0.1,0.2,0.3,0.4,0.5,$$

$$=\left[\begin{array}{ccc|c|ccc}\mu^{(1)}+\delta & \mu^{(1)}+0.5\delta & \mu^{(1)}+0.25\delta & \cdots & \mu^{(p)}+\delta & \mu^{(p)}+0.5\delta & \mu^{(p)}+0.25\delta\\ \mu^{(1)}+0.5\delta & \mu^{(1)}+0.25\delta & \mu^{(1)} & \cdots & \mu^{(p)}+0.5\delta & \mu^{(p)}+0.25\delta & \mu^{(p)}\\ \mu^{(1)} & \mu^{(1)} & \mu^{(1)} & \cdots & \mu^{(p)} & \mu^{(p)} & \mu^{(p)}\end{array}\right].$$

4.1.2 Between- and Within-Subjects Contrast Matrices

To test the Multivariate General Linear Hypothesis (2.18), $H:\mathbf{CB}_0(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{\Gamma}_0$, the $v_h \times g$ between-subjects contrast matrix $\mathbf{C}$ of $rank(\mathbf{C}) = v_h \le g$ and the $t \times u$ within-subjects contrast matrix $\mathbf{A}$ of $rank(\mathbf{A}) = u \le t$ were set for testing the group × time interaction effect , and the group and time effects, as follows:

$$\mathbf{C}_{2\times 3} = \begin{bmatrix} 1 & 0 & -1 \\ 0 & 1 & -1 \end{bmatrix} \text{ and } \mathbf{A}_{3\times 3} = \begin{bmatrix} 1/\sqrt{2} & -1/\sqrt{6} \\ 0 & 2/\sqrt{6} \\ -1/\sqrt{2} & -1/\sqrt{6} \end{bmatrix} \text{ for the group} \times \text{time effect} \quad (4.5)$$

$$\mathbf{C}_{2\times 3} = \begin{bmatrix} 1 & 0 & -1 \\ 0 & 1 & -1 \end{bmatrix} \text{ and } \mathbf{A}_{3\times 1} = \begin{bmatrix} 1/\sqrt{3} \\ 1/\sqrt{3} \\ 1/\sqrt{3} \end{bmatrix} \text{ for the group effect} \quad (4.6)$$

$$\mathbf{C}_{1\times 3} = \begin{bmatrix} 1 & 1 & 1 \end{bmatrix} \text{ and } \mathbf{A}_{3\times 3} = \begin{bmatrix} 1/\sqrt{2} & -1/\sqrt{6} \\ 0 & 2/\sqrt{6} \\ -1/\sqrt{2} & -1/\sqrt{6} \end{bmatrix} \text{ for the time effect} \quad (4.7)$$

From the contrast matrices $\mathbf{C}$ and $\mathbf{A}$ as defined above, the mean matrix $\mathbf{B} = \mathbf{B}_0$, defined in (4.3), was used to test the null hypothesis $H:\mathbf{CB}_0(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{0}$ as follows:

For testing the group ×time effect, the null hypothesis is

$$H_{01}: \left[\mathbf{\Gamma}^{(1)} \mid \mathbf{\Gamma}^{(2)} \mid \ldots \mid \mathbf{\Gamma}^{(p)}\right] = \mathbf{0}_{2\times 2p}, \quad (4.8)$$

where

$$\mathbf{\Gamma}^{(l)} = \begin{bmatrix} \dfrac{(\mu_{11}^{(l)} - \mu_{13}^{(l)}) - (\mu_{31}^{(l)} - \mu_{33}^{(l)})}{\sqrt{2}} & \dfrac{(-\mu_{11}^{(l)} + 2\mu_{12}^{(l)} - \mu_{13}^{(l)}) - (-\mu_{31}^{(l)} + 2\mu_{32}^{(l)} - \mu_{33}^{(l)})}{\sqrt{6}} \\ \dfrac{(\mu_{21}^{(l)} - \mu_{23}^{(l)}) - (\mu_{31}^{(l)} - \mu_{33}^{(l)})}{\sqrt{2}} & \dfrac{(-\mu_{21}^{(l)} + 2\mu_{22}^{(l)} - \mu_{23}^{(l)}) - (-\mu_{31}^{(l)} + 2\mu_{32}^{(l)} - \mu_{33}^{(l)})}{\sqrt{6}} \end{bmatrix}$$

for $l = 1, 2, \ldots, p$.

For testing the group effect, the null hypothesis is

$$H_{02}:\begin{bmatrix} \dfrac{\sum_{k=1}^{3}\mu_{1k}^{(1)}}{\sqrt{3}}-\dfrac{\sum_{k=1}^{3}\mu_{3k}^{(1)}}{\sqrt{3}} & \dfrac{\sum_{k=1}^{3}\mu_{1k}^{(2)}}{\sqrt{3}}-\dfrac{\sum_{k=1}^{3}\mu_{3k}^{(2)}}{\sqrt{3}} & \cdots & \dfrac{\sum_{k=1}^{3}\mu_{1k}^{(p)}}{\sqrt{3}}-\dfrac{\sum_{k=1}^{3}\mu_{3k}^{(p)}}{\sqrt{3}} \\ \dfrac{\sum_{k=1}^{3}\mu_{2k}^{(1)}}{\sqrt{3}}-\dfrac{\sum_{k=1}^{3}\mu_{3k}^{(1)}}{\sqrt{3}} & \dfrac{\sum_{k=1}^{3}\mu_{2k}^{(2)}}{\sqrt{3}}-\dfrac{\sum_{k=1}^{3}\mu_{3k}^{(2)}}{\sqrt{3}} & \cdots & \dfrac{\sum_{k=1}^{3}\mu_{2k}^{(p)}}{\sqrt{3}}-\dfrac{\sum_{k=1}^{3}\mu_{3k}^{(p)}}{\sqrt{3}} \end{bmatrix}$$

$$= \mathbf{0}_{2\times p}. \tag{4.9}$$

For testing the time effect, the null hypothesis is

$$H_{03}:\left[\boldsymbol{\Gamma}^{(1)} \;\vdots\; \boldsymbol{\Gamma}^{(2)} \;\vdots\; \ldots \;\vdots\; \boldsymbol{\Gamma}^{(p)}\right] = \mathbf{0}_{1\times 2p}, \tag{4.10}$$

where $\boldsymbol{\Gamma}_l$ is a 1×2 sub-matrix of $\boldsymbol{\Gamma} = \mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A})$ for each l^{th} variable such that

$$\underset{(1\times 2)}{\boldsymbol{\Gamma}_l} = \begin{bmatrix} \dfrac{\sum_{j=1}^{g}(\mu_{j1}^{(l)}-\mu_{j3}^{(l)})}{\sqrt{2}} & \dfrac{\sum_{j=1}^{g}(-\mu_{j1}^{(l)}+2\mu_{12}^{(l)}-\mu_{j3}^{(l)})}{\sqrt{6}} \end{bmatrix}, \text{ for } l=1,2,\ldots,p.$$

To test the local alternative hypothesis, the mean matrix $\mathbf{B}=\mathbf{B}_1$, defined in (4.4), was used for testing $H:\mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A}) = \boldsymbol{\Gamma}_0$ for the group × time interaction effect , and the group and time effects, as follows:

For testing the group ×time effect, the local alternative hypothesis is

$$H_{a1}:\left[\boldsymbol{\Gamma}^{(1)} \;\vdots\; \boldsymbol{\Gamma}^{(2)} \;\vdots\; \ldots \;\vdots\; \boldsymbol{\Gamma}^{(p)}\right]$$

$$= \left[\begin{array}{cc|cc|c|cc} \dfrac{0.75\delta}{\sqrt{2}} & 0 & \dfrac{0.75\delta}{\sqrt{2}} & 0 & \cdots & \dfrac{0.75\delta}{\sqrt{2}} & 0 \\ \dfrac{0.5\delta}{\sqrt{2}} & \dfrac{0.25\delta}{\sqrt{2}} & \dfrac{0.5\delta}{\sqrt{2}} & \dfrac{0.25\delta}{\sqrt{2}} & \cdots & \dfrac{0.5\delta}{\sqrt{2}} & \dfrac{0.25\delta}{\sqrt{2}} \end{array}\right]_{2\times 2p}, \tag{4.11}$$

where

$$\boldsymbol{\Gamma}^{(l)} = \begin{bmatrix} \dfrac{(\mu_{11}^{(l)}-\mu_{13}^{(l)})-(\mu_{31}^{(l)}-\mu_{33}^{(l)})}{\sqrt{2}} & \dfrac{(-\mu_{11}^{(l)}+2\mu_{12}^{(l)}-\mu_{13}^{(l)})-(-\mu_{31}^{(l)}+2\mu_{32}^{(l)}-\mu_{33}^{(l)})}{\sqrt{6}} \\ \dfrac{(\mu_{21}^{(l)}-\mu_{23}^{(l)})-(\mu_{31}^{(l)}-\mu_{33}^{(l)})}{\sqrt{2}} & \dfrac{(-\mu_{21}^{(l)}+2\mu_{22}^{(l)}-\mu_{23}^{(l)})-(-\mu_{31}^{(l)}+2\mu_{32}^{(l)}-\mu_{33}^{(l)})}{\sqrt{6}} \end{bmatrix}$$

for $l=1,2,\ldots,p$.

For testing the group effect , the local alternative hypothesis is

$$H_{a2}:\begin{bmatrix} \frac{1}{\sqrt{3}}\left(\sum_{k=1}^{3}\mu_{1k}^{(1)}-\sum_{k=1}^{3}\mu_{3k}^{(1)}\right) & \frac{1}{\sqrt{3}}\left(\sum_{k=1}^{3}\mu_{1k}^{(2)}-\sum_{k=1}^{3}\mu_{3k}^{(2)}\right) & \cdots & \frac{1}{\sqrt{3}}\left(\sum_{k=1}^{3}\mu_{1k}^{(p)}-\sum_{k=1}^{3}\mu_{3k}^{(p)}\right) \\ \frac{1}{\sqrt{3}}\left(\sum_{k=1}^{3}\mu_{2k}^{(1)}-\sum_{k=1}^{3}\mu_{3k}^{(1)}\right) & \frac{1}{\sqrt{3}}\left(\sum_{k=1}^{3}\mu_{2k}^{(2)}-\sum_{k=1}^{3}\mu_{3k}^{(2)}\right) & \cdots & \frac{1}{\sqrt{3}}\left(\sum_{k=1}^{3}\mu_{2k}^{(p)}-\sum_{k=1}^{3}\mu_{3k}^{(p)}\right) \end{bmatrix}$$

$$=\begin{bmatrix} \frac{1.5\delta}{\sqrt{3}} & \frac{1.5\delta}{\sqrt{3}} & \cdots & \frac{1.5\delta}{\sqrt{3}} \\ \frac{0.5\delta}{\sqrt{3}} & \frac{0.5\delta}{\sqrt{3}} & \cdots & \frac{0.5\delta}{\sqrt{3}} \end{bmatrix}_{2\times p}. \tag{4.12}$$

For testing the time effect, the local alternative hypothesis is

$$H_{a3}:\left[\mathbf{\Gamma}^{(1)} \mid \mathbf{\Gamma}^{(2)} \mid \ldots \mid \mathbf{\Gamma}^{(p)}\right]$$

$$=\left[\frac{1.5\delta}{\sqrt{2}} \quad \frac{0.5\delta}{\sqrt{6}} \;\middle|\; \frac{1.5\delta}{\sqrt{2}} \quad \frac{0.5\delta}{\sqrt{6}} \;\middle|\; \cdots \;\middle|\; \frac{1.5\delta}{\sqrt{2}} \quad \frac{0.5\delta}{\sqrt{6}}\right]_{1\times 2p}, \tag{4.13}$$

where $\mathbf{\Gamma}_l$ is a 1×2 sub-matrix of $\mathbf{\Gamma}=\mathbf{CB}(\mathbf{I}_p\otimes\mathbf{A})$ for each l^{th} variable such that

$$\underset{(1\times 2)}{\mathbf{\Gamma}_l}=\left[\frac{1}{\sqrt{2}}\sum_{j=1}^{g}(\mu_{j1}^{(l)}-\mu_{j3}^{(l)}) \quad \frac{1}{\sqrt{6}}\sum_{j=1}^{g}(-\mu_{j1}^{(l)}+2\mu_{12}^{(l)}-\mu_{j3}^{(l)})\right],\ \text{for } l=1,2,\ldots,p.$$

4.1.3 Computation of the Test Statistics

To test the Multivariate General Linear Hypothesis (2.18), the four proposed test statistics, T_1 (3.20) and T_2 (3.45) in DMM analysis, and T_1^* (3.71) and T_2^* (3.86) in MMM analysis, were computed from the generated response matrix described in section (4.1.1). The hypothesis (2.18) is rejected at significance level α if

$$T_1=\frac{v_e\ tr(\mathbf{S}_h)}{v_h\ tr(\mathbf{S}_e)}>F(f_{1-\alpha},\lfloor v_h\hat{d}\rfloor,\lfloor v_e\hat{d}\rfloor), \tag{4.14}$$

$$T_2=\left\{2v_h\hat{a}_2\left(1+\frac{v_h}{v_e}\right)\right\}^{-1/2}\frac{1}{\sqrt{pu}}\left[tr(\mathbf{S}_h)-\frac{v_h}{v_e}tr(\mathbf{S}_e)\right]>z_{1-\alpha}, \tag{4.15}$$

$$T_1^*=\frac{uv_e\ tr(\mathbf{S}_h^*)}{uv_h\ tr(\mathbf{S}_e^*)}>F(f_{1-\alpha},\lfloor uv_h d^*\rfloor,\lfloor uv_e d^*\rfloor), \tag{4.16}$$

and $$T_2^*=\left\{2uv_h\hat{a}_2^*\left(1+\frac{v_h}{v_e}\right)\right\}^{-1/2}\frac{1}{\sqrt{p}}\left[tr(\mathbf{S}_h^*)-\frac{v_h}{v_e}tr(\mathbf{S}_e^*)\right]>z_{1-\alpha}, \tag{4.17}$$

where $v_e = n - g$, $v_h = rank(\mathbf{C})$. The $pu \times pu$ error and hypothesis SSCP matrices, $\mathbf{S}_e$ and $\mathbf{S}_h$ in the DMM analysis, are computed by

$$\mathbf{S}_e = (\mathbf{I}_p \otimes \mathbf{A})'\mathbf{Y}'[\mathbf{I}_n - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}']\mathbf{Y}(\mathbf{I}_p \otimes \mathbf{A})$$

and $$\mathbf{S}_h = (\mathbf{C}\hat{\mathbf{B}}(\mathbf{I}_p \otimes \mathbf{A}))'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}\mathbf{C}\hat{\mathbf{B}}(\mathbf{I}_p \otimes \mathbf{A}),$$

where $\hat{\mathbf{B}} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}$, and similarly, the $p \times p$ error and hypothesis SSCP matrices, $\mathbf{S}_e^*$ and $\mathbf{S}_h^*$, are obtained using Thompson's Generalized Trace Operator of $\mathbf{S}_e$ and $\mathbf{S}_h$ such that

$$\mathbf{S}_e^* = T_p(\mathbf{S}_e) = \begin{bmatrix} tr(\mathbf{S}_e^{(11)}) & tr(\mathbf{S}_e^{(12)}) & \cdots & tr(\mathbf{S}_e^{(1p)}) \\ tr(\mathbf{S}_e^{(21)}) & tr(\mathbf{S}_e^{(22)}) & \cdots & tr(\mathbf{S}_e^{(2p)}) \\ \vdots & \vdots & \ddots & \vdots \\ tr(\mathbf{S}_e^{(p1)}) & tr(\mathbf{S}_e^{(p2)}) & \cdots & tr(\mathbf{S}_e^{(pp)}) \end{bmatrix}$$

$$= \begin{bmatrix} \sum_{k=1}^{u} s_{e_{kk}}^{(11)} & \sum_{k=1}^{u} s_{e_{kk}}^{(12)} & \cdots & \sum_{k=1}^{u} s_{e_{kk}}^{(1p)} \\ \sum_{k=1}^{u} s_{e_{kk}}^{(21)} & \sum_{k=1}^{u} s_{e_{kk}}^{(22)} & \cdots & \sum_{k=1}^{u} s_{e_{kk}}^{(2p)} \\ \vdots & \vdots & \ddots & \vdots \\ \sum_{k=1}^{u} s_{e_{kk}}^{(p1)} & \sum_{k=1}^{u} s_{e_{kk}}^{(p2)} & \cdots & \sum_{k=1}^{u} s_{e_{kk}}^{(pp)} \end{bmatrix}, \tag{4.18}$$

$$\mathbf{S}_h^* = T_p(\mathbf{S}_h) = \begin{bmatrix} tr(\mathbf{S}_h^{(11)}) & tr(\mathbf{S}_h^{(12)}) & \cdots & tr(\mathbf{S}_h^{(1p)}) \\ tr(\mathbf{S}_h^{(21)}) & tr(\mathbf{S}_h^{(22)}) & \cdots & tr(\mathbf{S}_h^{(2p)}) \\ \vdots & \vdots & \ddots & \vdots \\ tr(\mathbf{S}_h^{(p1)}) & tr(\mathbf{S}_h^{(p2)}) & \cdots & tr(\mathbf{S}_h^{(pp)}) \end{bmatrix},$$

$$= \begin{bmatrix} \sum_{k=1}^{u} s_{h_{kk}}^{(11)} & \sum_{k=1}^{u} s_{h_{kk}}^{(12)} & \cdots & \sum_{k=1}^{u} s_{h_{kk}}^{(1p)} \\ \sum_{k=1}^{u} s_{h_{kk}}^{(21)} & \sum_{k=1}^{u} s_{h_{kk}}^{(22)} & \cdots & \sum_{k=1}^{u} s_{h_{kk}}^{(2p)} \\ \vdots & \vdots & \ddots & \vdots \\ \sum_{k=1}^{u} s_{h_{kk}}^{(p1)} & \sum_{k=1}^{u} s_{h_{kk}}^{(p2)} & \cdots & \sum_{k=1}^{u} s_{h_{kk}}^{(pp)} \end{bmatrix} \tag{4.19}$$

where $\mathbf{S}_e^{(ll')}$ and $\mathbf{S}_h^{(ll')}$ are the $u \times u$ sub-matrices of $\mathbf{S}_e$ and $\mathbf{S}_h$ of the l^{th} and $l'^{\text{ th}}$ response variables, for $l = 1, 2, \ldots, p$ and $l' = 1, 2, \ldots, p$, such that

$$\mathbf{S}_e^{(ll')} = \begin{bmatrix} s_{e11}^{(ll')} & s_{e12}^{(ll')} & \cdots & s_{e1u}^{(ll')} \\ s_{e21}^{(ll')} & s_{e22}^{(ll')} & \cdots & s_{e2u}^{(ll')} \\ \vdots & \vdots & \ddots & \vdots \\ s_{eu1}^{(ll')} & s_{eu2}^{(ll')} & \cdots & s_{euu}^{(ll')} \end{bmatrix} \quad \text{and} \quad \mathbf{S}_h^{(ll')} = \begin{bmatrix} s_{h11}^{(ll')} & s_{h12}^{(ll')} & \cdots & s_{h1u}^{(ll')} \\ s_{h21}^{(ll')} & s_{h22}^{(ll')} & \cdots & s_{h2u}^{(ll')} \\ \vdots & \vdots & \ddots & \vdots \\ s_{hu1}^{(ll')} & s_{hu2}^{(ll')} & \cdots & s_{huu}^{(ll')} \end{bmatrix}.$$

The matrices $\mathbf{C}$ and $\mathbf{A}$ taken in the form of (4.5), (4.6), and (4.7) were used to compute $\mathbf{S}_e$ and $\mathbf{S}_h$ for testing the group × time interaction effect , and the group time effects. The degrees of freedom (df) of $\mathbf{S}_e$ and $\mathbf{S}_h$ are $v_e = n - g$ and $v_h = rank(\mathbf{C})$ and the degrees of freedom (*df*) of $\mathbf{S}_e^*$ and $\mathbf{S}_h^*$are uv_e and uv_h.

Note that, in the DMM, $tr(\mathbf{S}_e) = \sum_{l=1}^{p}\sum_{k=1}^{u} s_{e_{kk}}^{(ll)}$, $tr(\mathbf{S}_e^2) = \sum_{l=1}^{p}\sum_{k=1}^{u} (s_{e_{kk}}^{(ll)})^2$, $tr(\mathbf{S}_h) = \sum_{l=1}^{p}\sum_{k=1}^{u} s_{h_{kk}}^{(ll)}$ and $tr(\mathbf{S}_h^2) = \sum_{l=1}^{p}\sum_{k=1}^{u} (s_{h_{kk}}^{(ll)})^2$. In the MMM, it was shown that $tr(\mathbf{S}_e^*) = \sum_{l=1}^{p}\sum_{k=1}^{u} s_{e_{kk}}^{(ll)}$, $tr((\mathbf{S}_e^*)^2) = \sum_{l=1}^{p}\left(\sum_{k=1}^{u} s_{e_{kk}}^{(ll)}\right)^2$, $tr(\mathbf{S}_h^*) = \sum_{l=1}^{p}\sum_{k=1}^{u} s_{h_{kk}}^{(ll)}$ and $tr((\mathbf{S}_h^*)^2) = \sum_{l=1}^{p}\left(\sum_{k=1}^{u} s_{h_{kk}}^{(ll)}\right)^2$.

Thus, we obtain

$$tr(\mathbf{S}_e) = tr(\mathbf{S}_e^*) \text{ and } tr(\mathbf{S}_h) = tr(\mathbf{S}_h^*), \tag{4.20}$$

$$tr(\mathbf{S}_e^2) \le tr((\mathbf{S}_e^*)^2) \text{ and } tr(\mathbf{S}_h^2) \le tr((\mathbf{S}_h^*)^2). \tag{4.21}$$

The consistent estimators $\hat{a}_1$ and $\hat{a}_2$ defined in Lemma 3.1 and $\hat{a}_1^*$ and $\hat{a}_2^*$ in Lemma 3.5 were used to analyze the DMM and MMM tests:

$$\hat{a}_1 = \frac{tr(\mathbf{S}_e)}{v_e p u},$$

$$\hat{a}_2 = \frac{1}{(v_e - 1)(v_e + 2) p u}\left[tr(\mathbf{S}_e^2) - \frac{1}{v_e}(tr(\mathbf{S}_e))^2 \right],$$

$$\hat{a}_1^* = \frac{tr(\mathbf{S}_e^*)}{u v_e p}$$

and $$\hat{a}_2^* = \frac{1}{(uv_e - 1)(uv_e + 2) p}\left[tr\left((\mathbf{S}_e^*)^2\right) - \frac{1}{uv_e}\left(tr(\mathbf{S}_e^*)\right)^2 \right].$$

$\hat{a}_2$ and $\hat{a}_2^*$ were used to compute the test statistics T_2 and T_2^*. $\hat{a}_1$, $\hat{a}_2$, $\hat{a}_1^*$ and $\hat{a}_2^*$ were used to compute the degrees of freedom of the approximate F distributions of T_1 and T_2 in the forms $\hat{d} = \frac{pu\hat{a}_1^2}{\hat{a}_2}$ and $\hat{d}^* = \frac{p(\hat{a}_1^*)^2}{\hat{a}_2^*}$. Note that, from (4.20) and (4.21), $\hat{a}_1 = \hat{a}_1^*$ but $\hat{a}_2 \neq \hat{a}_2^*$.

To test the interaction or time effects, the dimensions of the SSCP matrices $\mathbf{S}_e$ and $\mathbf{S}_h$ are $pu \times pu$ and the dimensions of the SSCP matrices $\mathbf{S}_e^*$ and $\mathbf{S}_h^*$ are $p \times p$. When comparing the test statistics T_1 with T_1^* (3.45) and T_2 with T_2^*, it was found that $T_1 = T_1^*$ and $T_2 = T_2^*$ since $\hat{a}_2 \neq \hat{a}_2^*$.

To test the group effect, $rank(\mathbf{A}) = u = 1$ and $\mathbf{S}_e$ and $\mathbf{S}_h$ are $p \times p$ SSCP matrices which are the same as $\mathbf{S}_e^*$ and $\mathbf{S}_h^*$. From (4.21), $tr(\mathbf{S}_e^2) = tr((\mathbf{S}_e^*)^2)$ and $tr(\mathbf{S}_h^2) = tr((\mathbf{S}_h^*)^2)$, then $\hat{a}_1 = \hat{a}_1^*$ and $\hat{a}_2 = \hat{a}_2^*$. Therefore $T_1 = T_1^*$ and $T_2 = T_2^*$, this implies that the results of the DMM test are the same as for the MMM test.

4.1.4 Attained Significance Levels

To compare the four test statistics, T_1 (4.8) and T_2 (4.9) for DMM and T_1^* (4.10) and T_2^* (4.11) for MMM, it was necessary to define the attained significance levels. Let $f_{1-\alpha,v_1,v_2}$ and $f_{1-\alpha,v_1^*,v_2^*}$ be $100(1-\alpha)\%$ quantiles of the approximated null distribution of the test statistics T_1 and T_1^*, where $v_1 = \lfloor v_h\hat{d} \rfloor$, $v_2 = \lfloor v_e\hat{d} \rfloor$, $v_1^* = \lfloor uv_h\hat{d}^* \rfloor$ and $v_2^* = \lfloor uv_e\hat{d}^* \rfloor$. Let $z_{1-\alpha}$ be the $100(1-\alpha)\%$ quantile of the asymptotic null distribution of the test statistics T_2 and T_2^*. With $m = 5{,}000$ replications of the data set simulated under the null hypothesis at nominal significance level $\alpha = .05$, the attained significance levels of T_1, T_2, T_1^* and T_2^* were computed as

$$\hat{\alpha}_1 = \frac{(\#\text{ of } T_1 > f_{0.95,v_1,v_2})}{m}, \qquad \hat{\alpha}_1^* = \frac{(\#\text{ of } T_1^* > f_{0.95,v_1^*,v_1^*})}{m} \tag{4.22}$$

$$\hat{\alpha}_2 = \frac{(\#\text{ of } T_2 > z_{0.95})}{m} \quad \text{and} \quad \hat{\alpha}_2^* = \frac{(\#\text{ of } T_2^* > z_{0.95})}{m}. \tag{4.23}$$

4.1.5 Empirical Power of Tests

To compute the empirical power of the tests, critical points $f_{1-\alpha,v_1,v_2}$ and $f_{1-\alpha,v_1^*,v_2^*}$ for T_1 and T_1^* respectively and critical point $z_{1-\alpha}$ for T_2 and T_2^* were used at significance level $\alpha = .05$. With $m = 5{,}000$ replications of the data set simulated under the local alternative hypothesis with given choice of $\mathbf{CBM} \neq \mathbf{0}$, the empirical powers of the tests, using T_1, T_2, T_1^* and T_2^* respectively, are

$$\hat{\beta}_1 = \frac{(\#\text{ of } T_1 > f_{.95,v_1,v_2})}{m}, \quad \hat{\beta}_1^* = \frac{(\#\text{ of } T_1^* > f_{0.95,v_1^*,v_1^*})}{m}, \tag{4.24}$$

$$\hat{\beta}_2 = \frac{(\#\text{ of } T_2 > Z_{0.95})}{m} \text{ and } \hat{\beta}_2^* = \frac{(\#\text{ of } T_2^* > Z_{0.95})}{m}. \tag{4.25}$$

4.2 Attained Significance Levels

The simulation results of the attained significance levels of T_1, T_2, T_1^* and T_2^*, respectively denoted by $\hat{\alpha}_1$, $\hat{\alpha}_2$, $\hat{\alpha}_1^*$ and $\hat{\alpha}_2^*$ in (4.18) and (4.19), for testing the interaction effect, and the group and time effects, were calculated in each case of the number of variables (p) and number of subjects (n). The dimension (dim) of the error SSCP matrix $\mathbf{S}_e$, degrees of freedom (df) of $\mathbf{S}_e$ and the ratio of dimension and degrees of freedom $\mathbf{S}_e$, $r = \dim/df$, were computed in each case of p and n to indicate the high dimensional framework such that $\dim > df$ or $r > 1$.

4.2.1 Case $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$

The simulation results of the attained significance levels of the four proposed tests, T_1 and T_2 from the high dimensional DMM analysis and T_1^* and T_2^* from the high dimensional MMM analysis, to test the interaction effect, and the group and time effects, are respectively shown in Tables 4.1 to 4.3.

The results in Table 4.1 can be summarized in that the attained significance levels of the T_1 and T_1^* tests of interaction effect range from 0.0468 to 0.0572 and 0.0480 to 0.0564, respectively, which are reasonably close to the nominal level

$\alpha = .05$ for all cases of n and p. The attained significance levels of the T_2 and T_2^* tests of the interaction effect respectively range from 0.0522 to 0.0652 and 0.0516 to 0.0650, close to the nominal 0.05 level, when $n = 60$ and $n = 90$. Unfortunately, when n is small, the attained significance levels of the T_2 and T_2^* tests range from 0.0598 to 0.0762 and 0.0596 to 0.0742 which, in some cases, is not close to the nominal .05 level, especially when $n = 15$.

Figure 4.1 shows that the attained significance levels of the T_1 and T_1^* tests from the DMM and MMM analyses seem to behave in a similar manner and close to the nominal .05 level for all cases of n and p. The attained significance levels of the T_2 and T_2^* tests also have similar results but they are larger than those of the T_1 and T_1^* tests for all cases of n and p. When n increases, the gap between the graphs of the two types of tests decreases and the attained significance levels of the T_2 and T_2^* tests are close to those of the T_1 and T_1^* tests when n is large.

For testing the group effect, the test results for DMM and MMM were the same. Table 4.2 shows that the attained significance levels of the $T_1 (= T_1^*)$ test range from 0.0442 to 0.0544, close to the nominal .05 level, for all cases of n and p. The attained significance levels of the $T_2 (= T_2^*)$ test range from 0.0496 to 0.0598 which are close to the nominal .05 level when n = 60 to 90, but they range from 0.0598 to 0.0806 when n = 10 to 30 which, in some cases, is not close to the nominal 0.05 level, especially when n = 15.

Figure 4.2 shows that the attained significance levels of the $T_1 (= T_1^*)$ tests from the DMM and MMM analyses are close to the .05 level for all cases of n and p. The attained significance levels of the $T_2 (= T_2^*)$ tests are larger than those of the T_1 $(= T_1^*)$ tests for all cases of n and p. When n increases, the gap between the graphs of the two types of tests decreases and the attained significance levels of the $T_2 (= T_2^*)$ tests are close to those of the T_1 and T_1^* tests when n is large.

Table 4.1 The Attained Significance Levels of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Null Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$

		DMM					MMM				
p	n	dim ($2p$)	df (v_e)	r	Attained Significance Level		dim (p)	df ($2v_e$)	r	Attained Significance Level	
					$\hat{\alpha}_1$	$\hat{\alpha}_2$				$\hat{\alpha}_1^*$	$\hat{\alpha}_2^*$
30	15	60	12	5.00	0.0524	0.0756	30	24	1.25	0.0512	0.0724
45	15	90	12	7.50	0.0500	0.0744	40	24	1.88	0.0492	0.0688
60	15	120	12	10.00	0.0558	0.0762	60	24	2.50	0.0532	0.0742
75	15	150	12	12.50	0.0498	0.0720	70	24	3.13	0.0518	0.0708
60	30	120	27	4.44	0.0512	0.0658	60	54	1.11	0.0524	0.0644
90	30	180	27	6.67	0.0510	0.0614	90	54	1.67	0.0486	0.0606
120	30	240	27	8.89	0.0502	0.0620	120	54	2.22	0.0506	0.0604
150	30	300	27	11.11	0.0508	0.0598	150	54	2.78	0.0488	0.0596
120	60	240	57	4.21	0.0572	0.0652	120	114	1.05	0.0564	0.0650
180	60	360	57	6.32	0.0522	0.0584	180	114	1.58	0.0526	0.0596
240	60	480	57	8.42	0.0510	0.0550	240	114	2.11	0.0510	0.0556
300	60	600	57	10.53	0.0498	0.0570	300	114	2.63	0.0496	0.0572
180	90	360	87	4.14	0.0522	0.0566	180	174	2.30	0.0520	0.0562
270	90	540	87	6.21	0.0500	0.0548	270	174	2.35	0.0504	0.0550
360	90	720	87	8.28	0.0492	0.0538	360	174	2.36	0.0492	0.0532
450	90	900	87	10.34	0.0468	0.0522	450	174	2.36	0.0480	0.0516

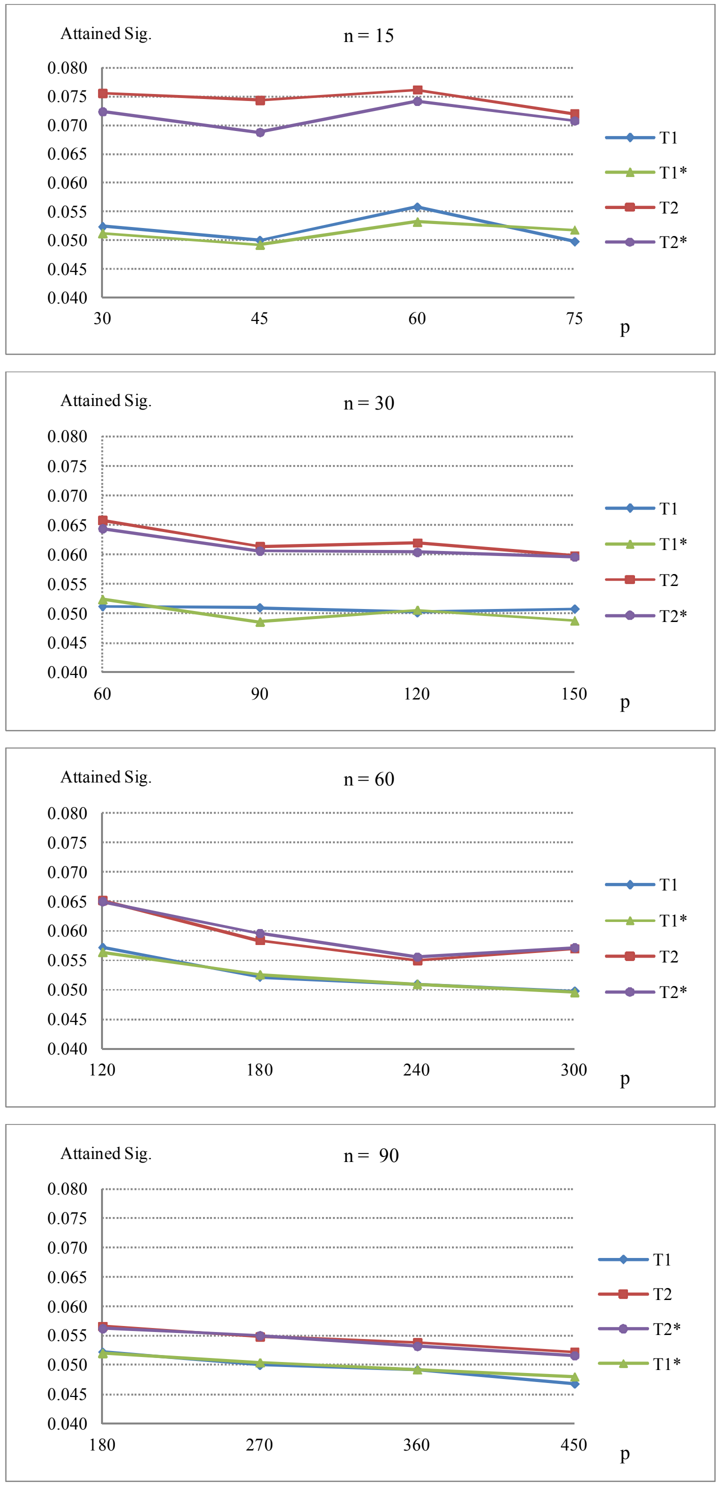


Figure 4.1 The Attained Significance Levels of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Null Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$

Table 4.2 The Attained Significance Levels of the T_1, T_2, T_1^* and T_2^* Tests of the Group Effect under the Null Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$

p	n	DMM*				
		dim (p)	df (v_e)	r	Attained Significance Level	
					$\hat{\alpha}_1 = \hat{\alpha}_1^*$	$\hat{\alpha}_2 = \hat{\alpha}_2^*$
30	15	30	12	2.50	0.0544	0.0806
45	15	45	12	3.75	0.0502	0.0764
60	15	60	12	5.00	0.0528	0.0740
75	15	75	12	6.25	0.0482	0.0726
60	30	60	27	2.22	0.0496	0.0644
90	30	90	27	3.33	0.0498	0.0632
120	30	120	27	4.44	0.0470	0.0606
150	30	150	27	5.56	0.0480	0.0598
120	60	120	57	2.11	0.0500	0.0568
180	60	180	57	3.16	0.0484	0.0548
240	60	240	57	4.21	0.0456	0.0522
360	60	360	57	6.32	0.0536	0.0598
180	90	180	87	2.07	0.0468	0.0522
270	90	270	87	3.10	0.0454	0.0512
360	90	360	87	4.14	0.0442	0.0496
450	90	450	87	5.17	0.0520	0.0562

Note: * The results of the T_1^* and T_2^* tests from MMM are the same as those of the T_1 and T_2 tests from DMM, as described in Section 4.1.3

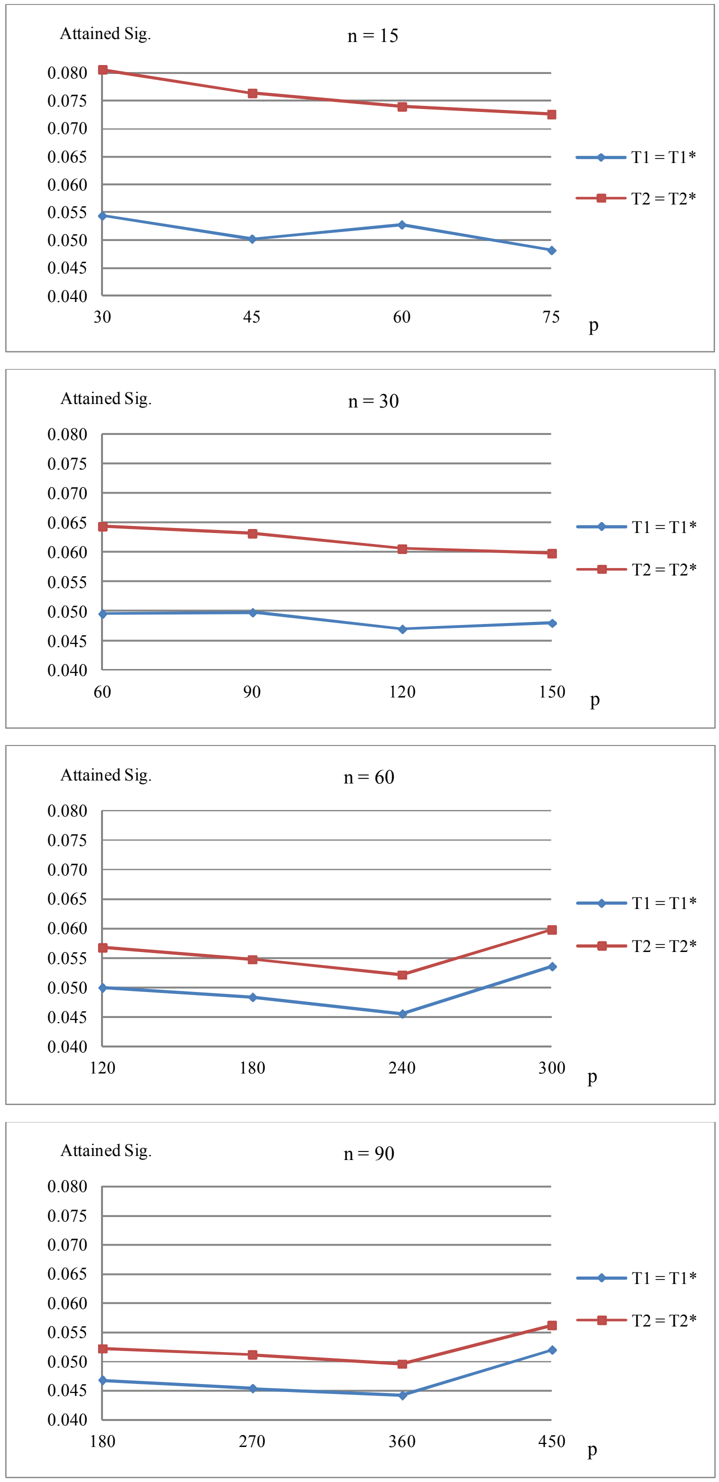


Figure 4.2 The Attained Significance Levels of the T_1, T_2, T_1^* and T_2^* Tests of the Group Effect under the Null Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$

Table 4.3 can be summarized as the attained significance levels of the T_1 and T_1^* tests of the time effect respectively range from 0.0444 to 0.0568 and 0.0436 to 0.0560, which are reasonably close to the nominal .05 level, for all cases of n and p. The attained significance levels of the T_2 and T_2^* tests of the time effect range from 0.0510 to 0.0604 and 0.0516 to 0.0600, respectively, close to the nominal 0.05 level, when $n = 60$ and $n = 90$. Unfortunately, when n is small, the attained significance levels of the T_2 and T_2^* tests range from 0.0564 to 0.0780 and 0.0562 to 0.0762 which, in some cases, are not close to the nominal .05 level, especially when $n = 15$.

The plots of the attained significance levels of the four tests for the time effect in Figure 4.3 show that the two lines of attained significance levels of the T_1 and T_1^* tests are similar and close to the nominal .05 level for all cases of n and p. The two lines of attained significance levels of the T_2 and T_2^* tests are also similar but those of T_2 and T_2^* are larger than those of the T_1 and T_1^* tests for all cases of n and p. When n increases, the gap between the graphs of the two types of tests decreases and the attained significance levels of the T_2 and T_2^* tests are close to those of the T_1 and T_1^* tests when n is large.

Table 4.3 The Attained Significance Levels of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Null Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$

p	n	DMM dim $(2p)$	DMM df (v_e)	DMM r	DMM Attained Significance Level $\hat{\alpha}_1$	DMM Attained Significance Level $\hat{\alpha}_2$	MMM dim (p)	MMM df $(2v_e)$	MMM r	MMM Attained Significance Level $\hat{\alpha}_1^*$	MMM Attained Significance Level $\hat{\alpha}_2^*$
30	15	60	12	5.00	0.0568	0.0780	30	24	1.25	0.0560	0.0762
45	15	90	12	7.50	0.0520	0.0694	45	24	1.88	0.0522	0.0686
60	15	120	12	10.00	0.0566	0.0762	60	24	2.50	0.0556	0.0734
75	15	150	12	12.50	0.0496	0.0630	75	24	3.13	0.0476	0.0614
60	30	120	27	4.44	0.0444	0.0564	60	54	1.11	0.0436	0.0562
90	30	180	27	6.67	0.0486	0.0588	90	54	1.67	0.0480	0.0582
120	30	240	27	8.89	0.0520	0.0622	120	54	2.22	0.0520	0.0624
150	30	300	27	11.11	0.0516	0.0584	150	54	2.78	0.0518	0.0592
120	60	240	57	4.21	0.0464	0.0542	120	114	1.05	0.0458	0.0542
180	60	360	57	6.32	0.0482	0.0538	180	114	1.58	0.0482	0.0538
240	60	480	57	8.42	0.0518	0.0574	240	114	2.11	0.0508	0.0576
300	60	600	57	10.53	0.0540	0.0604	300	114	2.63	0.0540	0.0600
180	90	360	87	4.14	0.0500	0.0546	180	174	1.03	0.0506	0.0550
270	90	540	87	6.21	0.0496	0.0522	270	174	1.55	0.0486	0.0524
360	90	720	87	8.28	0.0514	0.0550	360	174	2.07	0.0516	0.0554
450	90	900	87	10.34	0.0468	0.0510	450	174	2.59	0.0466	0.0516

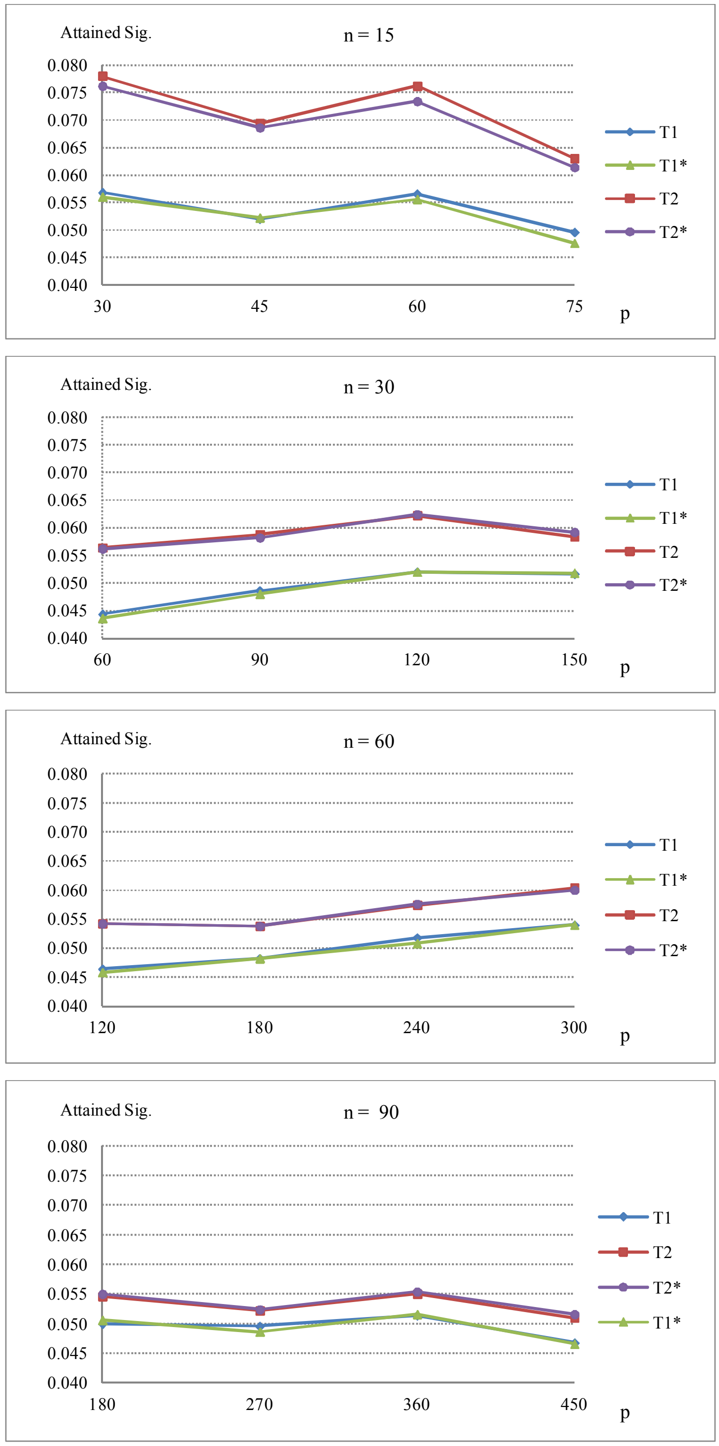


Figure 4.3 The Attained Significance Levels of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Null Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$

4.2.2 Case $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$

The simulation results of the attained significance levels of T_1 and T_2 for the DMM analysis, and T_1^* and T_2^* for the MMM analysis, for testing the interaction effect, and the group and time effects, when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ are shown in Tables 4.4 to 4.6.

The results in Table 4.4 can be summarized as the attained significance levels of the T_1 and T_1^* tests of the interaction effect range from 0.0444 to 0.0574 and 0.0416 to 0.0556, respectively, which are reasonably close to the nominal .05 level, for all cases of n and p. The attained significance levels of the T_2 and T_2^* tests of the interaction effect respectively range from 0.0528 to 0.0624 and 0.0524 to 0.0610, close to the nominal 0.05 level, when n = 60 to n = 90. However, when n = 15 to n = 30, the attained significance levels of the T_2 and T_2^* tests range from 0.0572 to 0.818 and 0.0576 to 0.0772 which, in some cases, are not close to the nominal 0.05 level.

Figure 4.4 shows that the two plots of the attained significance levels of the T_1 and T_1^* tests from the DMM and MMM analyses are similar and close to the nominal .05 level for all cases of n and p. The two plots of the attained significance levels of the T_2 and T_2^* tests are similar but larger than those of the T_1 and T_1^* tests for all cases of n and p. When n increases, the gap between the graphs of two types of tests decreases and the attained significance levels of the T_2 and T_2^* tests are close to those of the T_1 and T_1^* tests when n is large.

Table 4.4 The Attained Significance Levels of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Null Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$

p	n	DMM dim $(2p)$	DMM df (v_e)	DMM r	DMM Attained Significance Level $\hat{\alpha}_1$	DMM Attained Significance Level $\hat{\alpha}_2$	MMM dim (p)	MMM df $(2v_e)$	MMM r	MMM Attained Significance Level $\hat{\alpha}_1^*$	MMM Attained Significance Level $\hat{\alpha}_2^*$
30	15	60	12	5.00	0.0444	0.0652	30	24	1.25	0.0416	0.0630
45	15	90	12	7.50	0.0538	0.0778	45	24	1.88	0.0518	0.0754
60	15	120	12	10.00	0.0500	0.0716	60	24	2.50	0.0498	0.0692
75	15	150	12	12.50	0.0574	0.0818	75	24	3.13	0.0556	0.0772
60	30	120	27	4.44	0.0512	0.0622	60	54	1.11	0.0514	0.0630
90	30	180	27	6.67	0.0494	0.0628	90	54	1.67	0.0492	0.0616
120	30	240	27	8.89	0.0528	0.0644	120	54	2.22	0.0532	0.0648
150	30	300	27	11.11	0.0476	0.0572	150	54	2.78	0.0476	0.0576
120	60	240	57	4.21	0.0488	0.0562	120	114	1.05	0.0480	0.0564
180	60	360	57	6.32	0.0490	0.0542	180	114	1.58	0.0484	0.0542
240	60	480	57	8.42	0.0556	0.0624	240	114	2.11	0.0552	0.0610
300	60	600	57	10.53	0.0510	0.0562	300	114	2.63	0.0518	0.0552
180	90	360	87	4.14	0.0470	0.0528	180	174	1.03	0.0464	0.0528
270	90	540	87	6.21	0.0510	0.0582	270	174	1.55	0.0520	0.0578
360	90	720	87	8.28	0.0494	0.0532	360	174	2.07	0.0492	0.0524
450	90	900	87	10.34	0.0516	0.0556	450	174	2.59	0.0522	0.0550

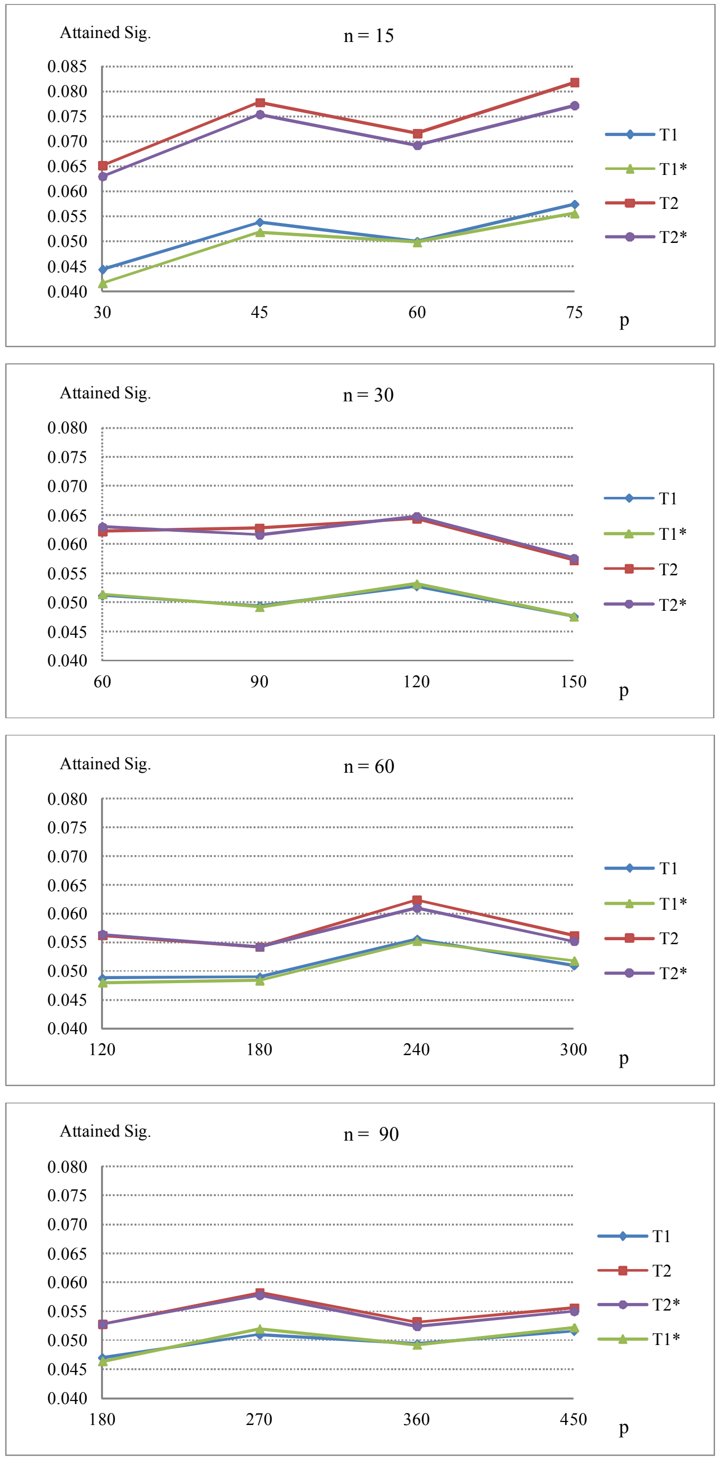


Figure 4.4 The Attained Significance Levels of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Null Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$

For testing the group effect, the performance of the tests for DMM and MMM are the same. Table 4.5 shows that the attained significance levels of the T_1 $(=T_1^*)$ test range from 0.0466 to 0.0544, reasonably close to the nominal 0.05 level, for all cases of n and p. The attained significance levels of the T_2 $(=T_2^*)$ test range from 0.0530 to 0.0610, reasonably close to the nominal 0.05 level, when n = 60 and 90, but the range broadened to 0.0590 to 0.0820 when n = 15 and 30, which is outside the nominal .05 level.

Figure 4.5 shows that the attained significance levels of the $T_1(=T_1^*)$ tests from the DMM and MMM analyses are close to the .05 level for all cases of n and p . The attained significance levels of $T_2(=T_2^*)$ are larger than those of the $T_1(=T_1^*)$ tests for all cases of n and p. When n increases, the gap between the graphs of the two types of tests decreases and the attained significance levels of the $T_2(=T_2^*)$ tests are close to those of the T_1 and T_1^* tests when n is large.

The results in Table 4.6 can be summarized as the attained significance levels of the T_1 and T_1^* tests of the time effect respectively range from 0.0458 to 0.0548 and 0.0452 to 0.0546, which are reasonably close to the nominal .05 level, for all cases of n and p. The attained significance levels of the T_2 and T_2^* tests of the time effect range from 0.0498 to 0.0594 and 0.0498 to 0.592, respectively, close to the nominal .05 level, when n = 60 and n = 90. Nevertheless, when n is small, the attained significance levels of the T_2 and T_2^* tests range from 0.0556 to 0.0704 and 0.0552 to 0.0698, respectively, which, in some cases, are not close to the nominal 0.05 level.

Figure 4.6 shows the plots of the attained significance levels of the four tests for the time effect. The two plots of the attained significance levels of the T_1 and T_1^* tests are similar and close to the 0.05 level for all cases of n and p. The two plots of attained significance levels of the T_2 and T_2^* tests are also similar but the attained significance levels of T_2 and T_2^* are larger than those of the T_1 and T_1^* tests for all cases of n and p. When n increases, the gap between the graphs of the two types of tests decreases and the attained significance levels of the T_2 and T_2^* tests are close to those of the T_1 and T_1^* tests when *n* is large.

Table 4.5 The Attained Significance Levels of the T_1, T_2, T_1^* and T_2^* Tests of the Group Effect under the Null Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$

p	n	DMM*				
		dim (p)	df (v_e)	r	$\hat{\alpha}_1 = \hat{\alpha}_1^*$	$\hat{\alpha}_2 = \hat{\alpha}_2^*$
30	15	30	12	2.50	0.0530	0.0820
45	15	45	12	3.75	0.0486	0.0748
60	15	60	12	5.00	0.0508	0.0724
75	15	75	12	6.25	0.0506	0.0724
60	30	60	27	2.22	0.0514	0.0644
90	30	90	27	3.33	0.0496	0.0640
120	30	120	27	4.44	0.0544	0.0644
150	30	150	27	5.56	0.0486	0.0590
120	60	120	57	2.11	0.0520	0.0610
180	60	180	57	3.16	0.0488	0.0566
240	60	240	57	4.21	0.0494	0.0582
360	60	360	57	6.32	0.0500	0.0566
180	90	180	87	2.07	0.0516	0.058
270	90	270	87	3.10	0.0466	0.0542
360	90	360	87	4.14	0.0516	0.0572
450	90	450	87	5.17	0.0502	0.0530

Note: * The results of the T_1^* and T_2^* tests from MMM are the same as those of the T_1 and T_2 tests from DMM, as described in Section 4.1.3

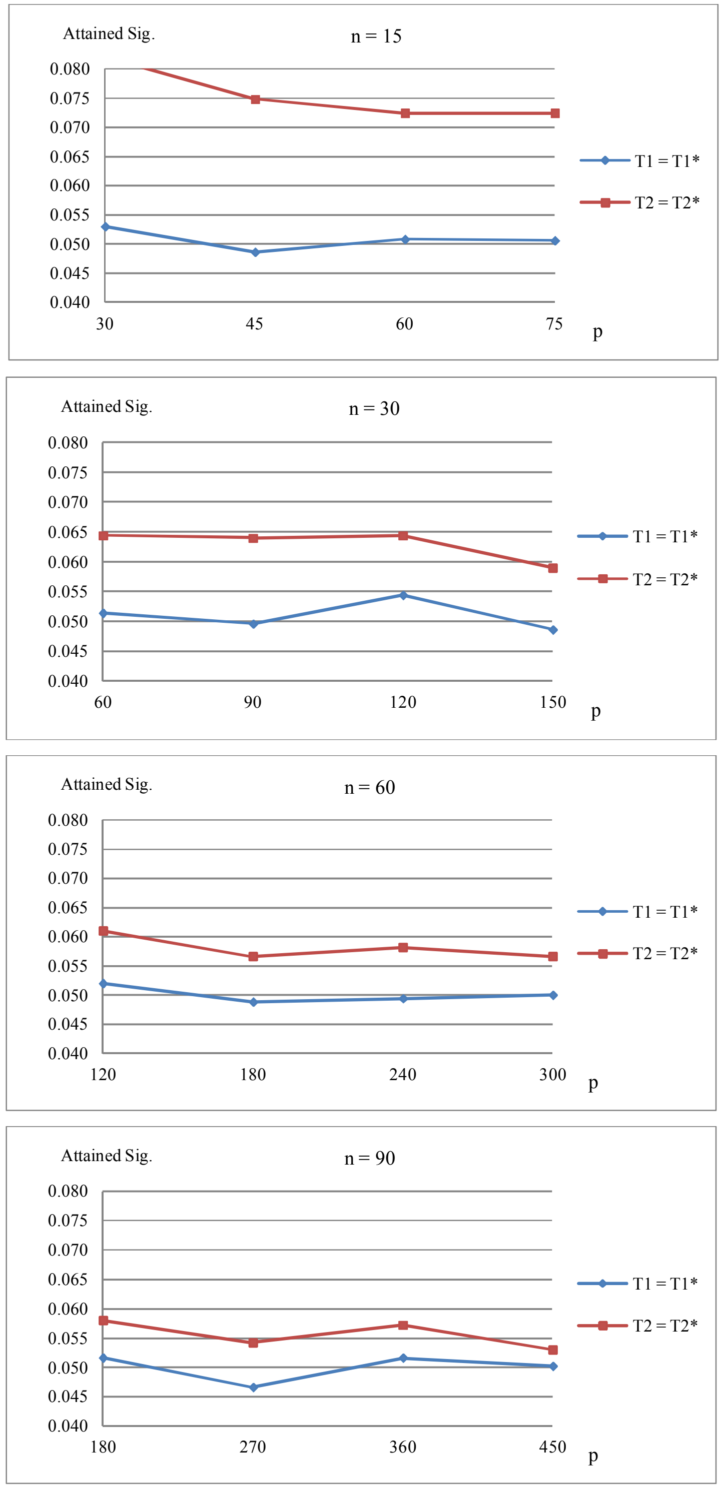


Figure 4.5 The Attained Significance Levels of the T_1, T_2, T_1^* and T_2^* Tests of the Group Effect under the Null Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$

The results in Table 4.6 can be summarized as the attained significance levels of the T_1 and T_1^* tests of the time effect respectively range from 0.0458 to 0.0548 and 0.0452 to 0.0546, which are reasonably close to the nominal .05 level for all cases of n and p. The attained significance levels of the T_2 and T_2^* tests of the time effect range from 0.0498 to 0.0594 and 0.0498 to 0.592, respectively, again close to the nominal .05 level, when n = 60 and n = 90. Nevertheless, when n is small, the attained significance levels of the T_2 and T_2^* tests range from 0.0556 to 0.0704 and 0.0552 to 0.0698 which, in some cases, are not close to the nominal 0.05 level.

Figure 4.6 shows the plots of the attained significance levels of the four tests for the time effect. The two plots of the attained significance levels of the T_1 and T_1^* tests are similar and close to the 0.05 level for all cases of n and p. The two plots of the attained significance levels of the T_2 and T_2^* tests are also similar but larger than those of the T_1 and T_1^* tests for all cases of n and p. When n increases, the gap between the graphs of the two types of tests decreases and the attained significance levels of the T_2 and T_2^* tests are close to those of the T_1 and T_1^* tests when n is large.

Table 4.6 The Attained Significance Levels of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Null Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$

		DMM					MMM				
p	n	dim $(2p)$	df (v_e)	r	Attained Significance Level		dim (p)	df $(2v_e)$	r	Attained Significance Level	
					$\hat{\alpha}_1$	$\hat{\alpha}_2$				$\hat{\alpha}_1^*$	$\hat{\alpha}_2^*$
30	15	60	12	5.00	0.0492	0.0668	30	24	1.25	0.0492	0.0658
45	15	90	12	7.50	0.0520	0.0704	45	24	1.88	0.0516	0.0698
60	15	120	12	10.00	0.0500	0.0654	60	24	2.50	0.0500	0.0646
75	15	150	12	12.50	0.0512	0.0672	75	24	3.13	0.0514	0.0672
60	30	120	27	4.44	0.0458	0.0556	60	54	1.11	0.0452	0.0552
90	30	180	27	6.67	0.0538	0.0646	90	54	1.67	0.0546	0.0636
120	30	240	27	8.89	0.0548	0.0612	120	54	2.22	0.0542	0.0612
150	30	300	27	11.11	0.0490	0.0566	150	54	2.78	0.0492	0.0558
120	60	240	57	4.21	0.0510	0.0592	120	114	1.05	0.0514	0.0588
180	60	360	57	6.32	0.0520	0.0562	180	114	1.58	0.0514	0.0564
240	60	480	57	8.42	0.0534	0.0582	240	114	2.11	0.0522	0.0590
300	60	600	57	10.53	0.0476	0.0544	300	114	2.63	0.0470	0.0538
180	90	360	87	4.14	0.0544	0.0594	180	174	1.03	0.0540	0.0592
270	90	540	87	6.21	0.0494	0.0526	270	174	1.55	0.0492	0.0528
360	90	720	87	8.28	0.0492	0.0534	360	174	2.07	0.0492	0.0528
450	90	900	87	10.34	0.0460	0.0498	450	174	2.59	0.0456	0.0498

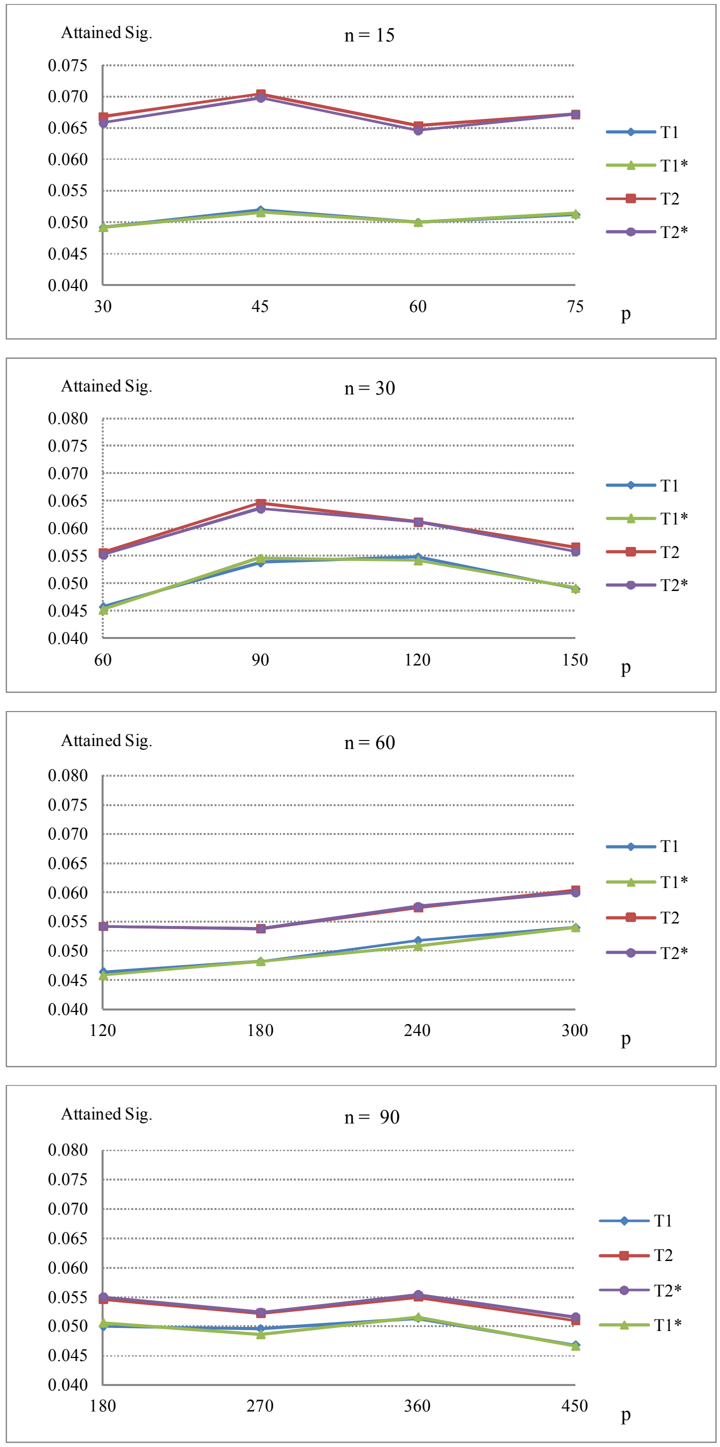


Figure 4.6 The Attained Significance Levels of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Null Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$

4.3 The Empirical Powers of the Test Statistics

The simulation results of the empirical powers of the T_1, T_2, T_1^* and T_2^* tests, repectively denoted by $\hat{\beta}_1$, $\hat{\beta}_2$, $\hat{\beta}_1^*$ and $\hat{\beta}_2^*$ in (4.20) and (4.21), for testing the interaction effect, and the group and time effects, were calculated for each case of *p* and *n*.

4.3.1 Case $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$

4.3.1.1 The Interaction Effect

The empirical powers of the interaction effect tests under the local alternative hypothesis (4.11) when $n = 15$, 30, 60, 90 and $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ are shown in Tables 4.7 to 4.10, respectively.

The results in Tables 4.7 to 4.10 can be summarized as follows. In each table, which shows the results of the empirical powers of the interaction effect tests for each case of *n*, the empirical powers of the T_1, T_2, T_1^* and T_2^* tests increase as *p* increases. For both the DMM and MMM analyses, the empirical powers of the T_2 tests are higher than the empirical powers of the T_1 test and likewise for the T_2^* test when compared to the T_1^* test. Additionally, the empirical powers of the tests from the DMM and MMM are similar but those of the T_1 and T_2 tests from DMM are slightly higher than those of the T_1^* and T_2^* tests from MMM.

From Figures 4.7 to 4.10, each figure gives two plots of the empirical powers between the T_1 and T_2 tests and between the T_1^* and T_2^* tests for each case of *n*, and both plots from the DMM and MMM analyses in each figure are similar. From the DMM analysis, the empirical powers of the T_1 and T_2 tests vary directly in relation to the values of the constant δ given in the local alternative hypothesis, and increase when *p* increases for all cases of *n*. The empirical powers of T_2 are higher than T_1 for all cases of δ and *p*. From the MMM analysis, the variations of the empirical powers of T_1^* and T_2^* tests are the same as those of DMM. When comparing the four cases of n, the plots show that the empirical powers of the T_1, T_2, T_1^* and T_2^* tests increase when n increases.

Table 4.7 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 15$

DMM												
p	dim (pu)	df (v_e)	$\hat{\beta}_1$ $\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\hat{\beta}_2$ $\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
30	60	12	0.0448	0.0526	0.0648	0.0902	0.1278	0.0756	0.0642	0.0744	0.0952	0.1266
45	90	12	0.0566	0.0664	0.0858	0.1188	0.1654	0.0744	0.0802	0.0936	0.1156	0.1540
60	120	12	0.0534	0.0644	0.0870	0.1262	0.1934	0.0762	0.0754	0.0880	0.1186	0.1706
75	150	12	0.0626	0.0766	0.1056	0.1556	0.2312	0.0720	0.0858	0.1032	0.1362	0.1926
MMM												
p	dim (p)	df (uv_e)	$\hat{\beta}_1^*$ $\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\hat{\beta}_2^*$ $\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
30	30	24	0.0434	0.0514	0.0628	0.0856	0.1246	0.0638	0.0716	0.0924	0.1256	0.1752
45	45	24	0.0542	0.0644	0.0830	0.1142	0.1632	0.0774	0.0890	0.1114	0.1542	0.2168
60	60	24	0.0498	0.0608	0.0834	0.1250	0.1986	0.0726	0.0868	0.1158	0.1710	0.2408
75	75	24	0.0594	0.0738	0.1028	0.1522	0.2288	0.0826	0.1014	0.1356	0.1920	0.2830

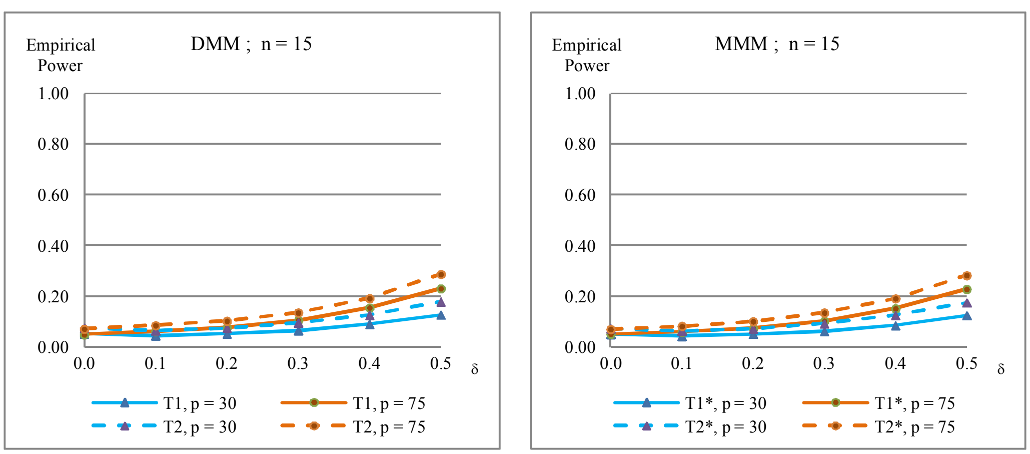


Figure 4.7 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 15$

Table 4.8 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 30$

DMM												
p	dim (pu)	df (v_e)	$\hat{\beta}_1$					$\hat{\beta}_2$				
			$\delta=0.1$	$\delta=0.2$	$\delta=0.3$	$\delta=0.4$	$\delta=0.5$	$\delta=0.1$	$\delta=0.2$	$\delta=0.3$	$\delta=0.4$	$\delta=0.5$
60	120	27	0.0572	0.0856	0.1496	0.2616	0.4452	0.0696	0.1030	0.1722	0.2964	0.4894
90	180	27	0.0618	0.0958	0.1800	0.3490	0.5966	0.0762	0.1128	0.2090	0.3844	0.6362
120	240	27	0.0652	0.1120	0.2140	0.4218	0.7000	0.0780	0.1326	0.2382	0.4602	0.7358
150	300	27	0.0582	0.1068	0.2316	0.4710	0.7870	0.0682	0.1272	0.2620	0.5080	0.8088
MMM												
p	dim (p)	df (uv_e)	$\hat{\beta}_1^*$					$\hat{\beta}_2^*$				
			$\delta=0.1$	$\delta=0.2$	$\delta=0.3$	$\delta=0.4$	$\delta=0.5$	$\delta=0.1$	$\delta=0.2$	$\delta=0.3$	$\delta=0.4$	$\delta=0.5$
60	60	54	0.0434	0.0514	0.0628	0.0856	0.1246	0.0638	0.0716	0.0924	0.1256	0.1752
90	90	54	0.0542	0.0644	0.0830	0.1142	0.1632	0.0774	0.0890	0.1114	0.1542	0.2168
120	120	54	0.0498	0.0608	0.0834	0.1250	0.1986	0.0726	0.0868	0.1158	0.1710	0.2408
150	150	54	0.0594	0.0738	0.1028	0.1522	0.2288	0.0826	0.1014	0.1356	0.1920	0.2830

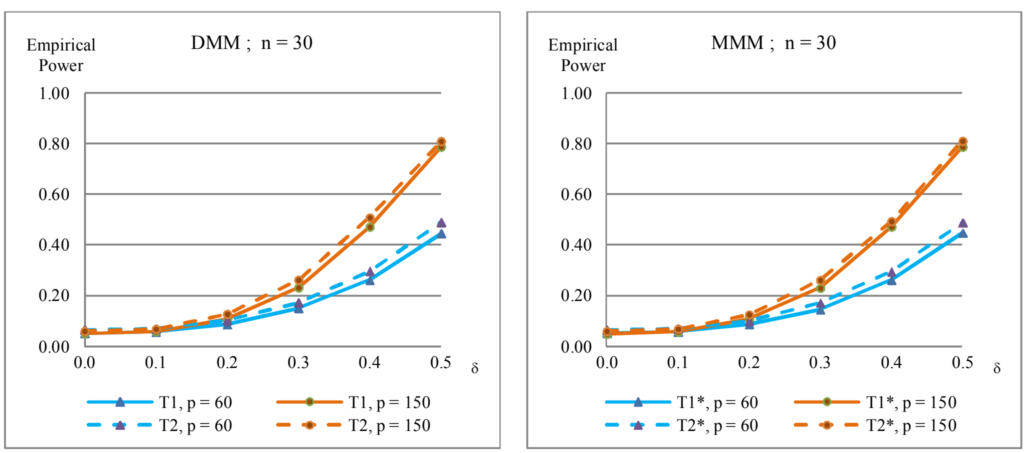


Figure 4.8 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 30$

Table 4.9 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 60$

			DMM									
p	dim (pu)	df (v_e)	$\hat{\beta}_1$					$\hat{\beta}_2$				
			$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
120	240	57	0.0760	0.1884	0.5108	0.8758	0.9936	0.0830	0.2044	0.5332	0.8888	0.9936
180	360	57	0.0800	0.2376	0.6362	0.9638	0.9998	0.0890	0.2566	0.6572	0.9617	0.9998
240	480	57	0.0948	0.2988	0.7582	0.9912	1.0000	0.1016	0.3184	0.7726	0.9926	1.0000
300	600	57	0.0914	0.3202	0.8218	0.9966	1.0000	0.0994	0.3412	0.8344	0.9972	1.0000

			MMM									
p	dim (p)	df (uv_e)	$\hat{\beta}_1^*$					$\hat{\beta}_2^*$				
			$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
120	120	114	0.0752	0.1878	0.5092	0.8758	0.9936	0.0838	0.2040	0.5342	0.8882	0.9946
180	180	114	0.0794	0.2390	0.6356	0.9646	0.9998	0.0878	0.2578	0.6560	0.9682	0.9998
240	240	114	0.0938	0.2980	0.7554	0.9914	1.0000	0.1018	0.3182	0.7742	0.9926	1.0000
300	300	114	0.0908	0.3204	0.8224	0.9968	1.0000	0.0996	0.3410	0.8340	0.9972	1.0000

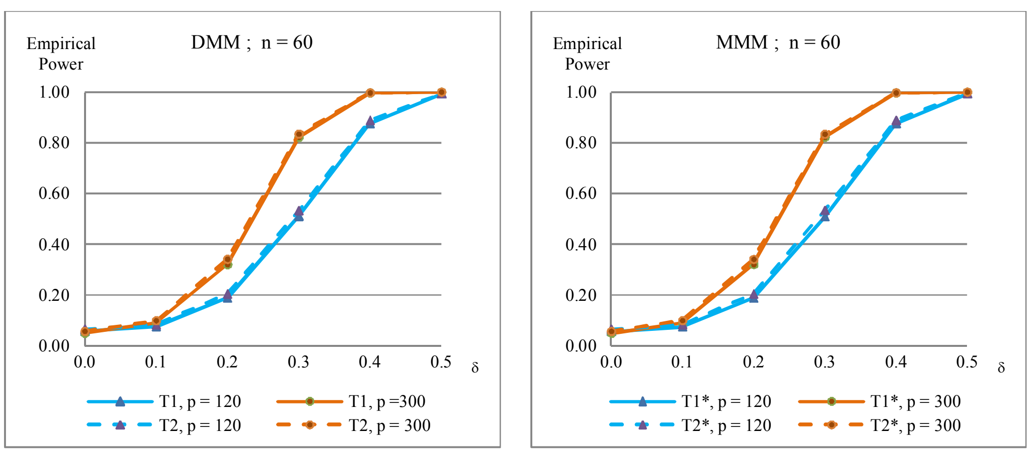


Figure 4.9 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 60$

Table 4.10 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 90$

			DMM									
p	dim (pu)	df (v_e)	$\hat{\beta}_1$					$\hat{\beta}_2$				
			δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5	δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5
180	360	87	0.1006	0.3930	0.9016	0.9996	1.0000	0.1074	0.4104	0.9082	0.9996	1.0000
270	540	87	0.1146	0.5004	0.9732	1.0000	1.0000	0.1232	0.5168	0.9744	1.0000	1.0000
360	720	87	0.1296	0.6068	0.9912	1.0000	1.0000	0.1380	0.6204	0.9916	1.0000	1.0000
450	900	87	0.1368	0.6900	0.9981	1.0000	1.0000	0.1448	0.7034	0.9977	1.0000	1.0000
			MMM									
p	dim (p)	df (uv_e)	$\hat{\beta}_1^*$					$\hat{\beta}_2^*$				
			δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5	δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5
180	180	174	0.0752	0.1878	0.5092	0.8758	0.9936	0.0838	0.2040	0.5342	0.8882	0.9946
270	270	174	0.0794	0.2390	0.6356	0.9646	0.9998	0.0878	0.2578	0.6560	0.9682	0.9998
360	360	174	0.0938	0.2980	0.7554	0.9914	1.0000	0.1018	0.3182	0.7742	0.9926	1.0000
450	450	174	0.0908	0.3204	0.8224	0.9968	1.0000	0.0996	0.3410	0.8340	0.9972	1.0000

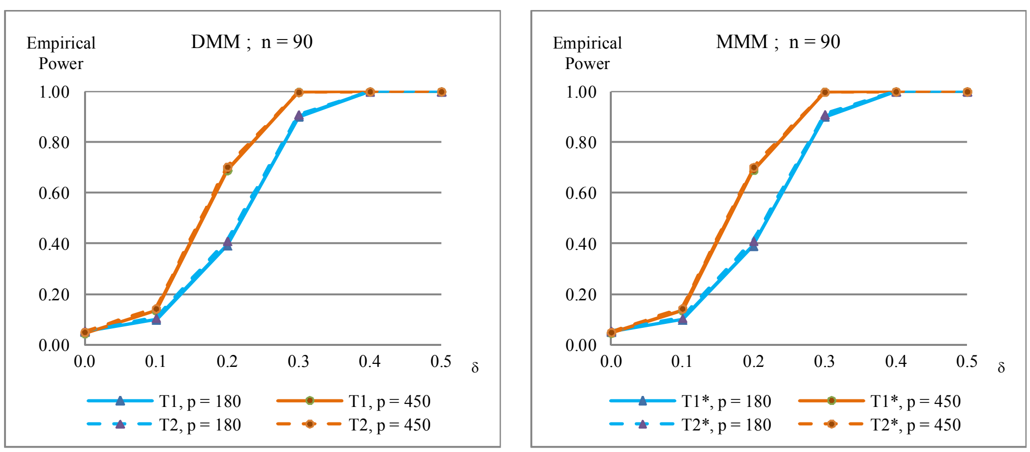


Figure 4.10 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 90$

4.3.1.2 The Group Effect

The empirical powers of the group effect tests under the local alternative hypothesis (4.12) when $n = 15$, 30, 60, 90 and $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ are respectively shown in Tables 4.11 to 4.14.

The results in Tables 4.11 to 4.14 can be summarized as follows. In each table, which shows the results of the empirical powers of the group effect tests for $n = 15$, 30, 60, 90, respectively, the test statistics from MMM are the same as those from DMM, as described in Section 4.1.3, so tables only show the results of the empirical powers of the T_1 and T_2 tests from DMM. They show that the empirical powers of the T_1 and T_2 tests increase as p increases and that the empirical powers of the T_2 test are higher than those of the T_1 test. As previously mentioned, these results are the same as for the MMM analysis.

From Figures 4.11 to 4.14, each of these figures gives the plot of the empirical powers of the T_1 and T_2 tests of the group effect from the DMM for $n = 15, 30, 60, 90$, respectively. The plots in each of the four figures are similar and can be described as follows. From the DMM (or MMM) analysis, the empirical powers of T_1 (or T_1^*) and T_2 (or T_2^*) tests are directly related to the values of constant δ given in the local alternative hypothesis $\mathbf{\Gamma}_1$, and increase when p increases for all cases of n. The empirical powers of the T_2 test are higher than those of the T_1 test for all cases of δ and p. When comparing the four cases of n, the plots show that the empirical powers of the T_1 and T_2 tests increase when n increases.

Table 4.11 The Empirical Powers of the T_1 and T_2 Tests of the Group Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 15$

			DMM*									
p	dim (p)	df (v_e)	$\hat{\beta}_1$					$\hat{\beta}_2$				
			$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
30	30	12	0.0448	0.0526	0.0648	0.0902	0.1278	0.0756	0.0642	0.0744	0.0952	0.1266
45	45	12	0.0566	0.0664	0.0858	0.1188	0.1654	0.0744	0.0802	0.0936	0.1156	0.1540
60	60	12	0.0534	0.0644	0.0870	0.1262	0.1934	0.0762	0.0754	0.0880	0.1186	0.1706
75	75	12	0.0626	0.0766	0.1056	0.1556	0.2312	0.0720	0.0858	0.1032	0.1362	0.1926

Note: * The results of the T_1^* and T_2^* tests from MMM are the same as those of the T_1 and T_2 tests from DMM, as described in Section 4.1.3

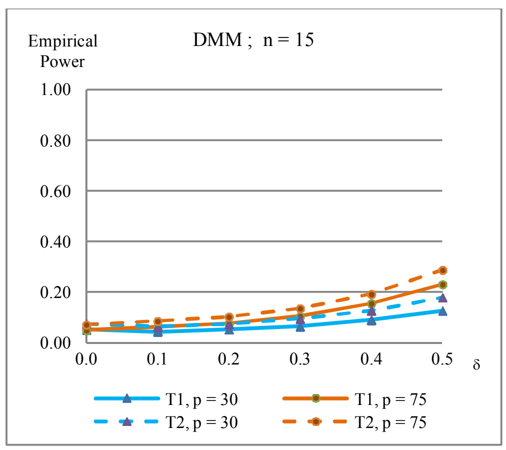


Figure 4.11 The Empirical Powers of the T_1 and T_2 Tests of the Group Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 15$

Table 4.12 The Empirical Powers of the T_1 and T_2 Tests of the Group Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 30$

			DMM*									
			$\hat{\beta}_1$					$\hat{\beta}_2$				
p	dim (p)	df (v_e)	δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5	δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5
60	120	27	0.0668	0.1436	0.3222	0.6314	0.8900	0.0876	0.1722	0.3706	0.6760	0.9106
90	180	27	0.0720	0.1712	0.4170	0.7720	0.9692	0.0892	0.1994	0.4602	0.8050	0.9754
120	240	27	0.0770	0.1916	0.4866	0.8560	0.9908	0.0928	0.2194	0.5298	0.8806	0.9930
150	300	27	0.0760	0.2153	0.5698	0.9218	0.9979	0.0912	0.2315	0.6096	0.9348	0.9971

Note: * The results of the T_1^* and T_2^* tests from MMM are the same as those of the T_1 and T_2 tests from DMM, as described in Section 4.1.3

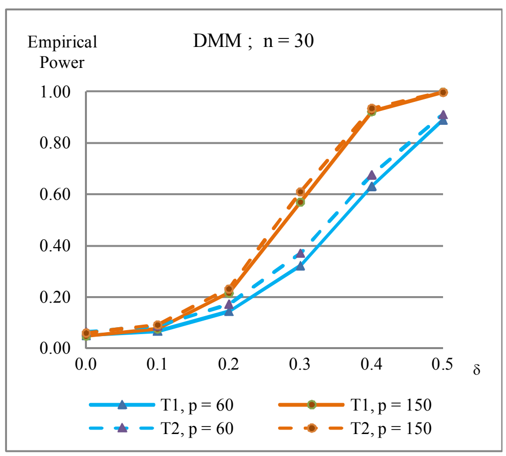


Figure 4.12 The Empirical Powers of the T_1 and T_2 Tests for the Group Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 30$

Table 4.13 The Empirical Powers of the T_1 and T_2 Tests of the Group Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 60$

			DMM*									
p	dim (p)	df (v_e)	$\hat{\beta}_1$					$\hat{\beta}_2$				
			$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
120	120	57	0.1134	0.4546	0.9344	0.9998	1.0000	0.1258	0.4826	0.9458	0.9998	1.0000
180	180	57	0.1296	0.5994	0.9856	1.0000	1.0000	0.1480	0.6206	0.9882	1.0000	1.0000
240	240	57	0.1330	0.6914	0.9978	1.0000	1.0000	0.1484	0.7146	0.9978	1.0000	1.0000
300	300	57	0.1614	0.7752	0.9994	1.0000	1.0000	0.1830	0.7896	0.9998	1.0000	1.0000

Note: * The results of the T_1^* and T_2^* tests from MMM are the same as those of the T_1 and T_2 tests from DMM, as described in Section 4.1.3

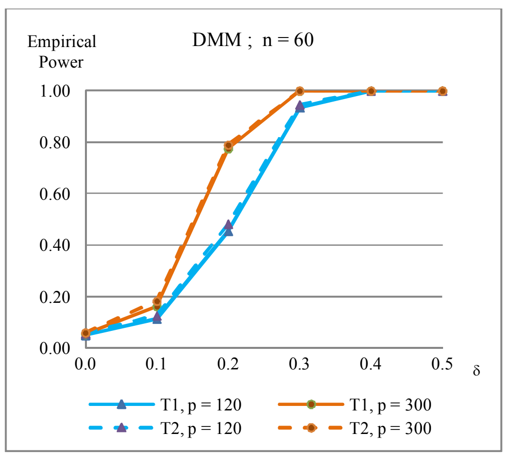


Figure 4.13 The Empirical Powers of the T_1 and T_2 Tests of the Group Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 60$

Table 4.14 The Empirical Powers of the T_1 and T_2 Tests of the Group Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 90$

			DMM*									
p	dim (p)	df (v_e)	$\hat{\beta}_1$					$\hat{\beta}_2$				
			δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5	δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5
180	180	87	0.1806	0.8540	1.0000	1.0000	1.0000	0.1966	0.8666	1.0000	1.0000	1.0000
270	270	87	0.2218	0.9476	1.0000	1.0000	1.0000	0.2388	0.9540	1.0000	1.0000	1.0000
360	360	87	0.2750	0.9832	1.0000	1.0000	1.0000	0.2868	0.9844	1.0000	1.0000	1.0000
450	450	87	0.3066	0.9942	1.0000	1.0000	1.0000	0.3224	0.9946	1.0000	1.0000	1.0000

Note: * The results of the T_1^* and T_2^* tests from MMM are the same as those of the T_1 and T_2 tests from DMM, as described in Section 4.1.3

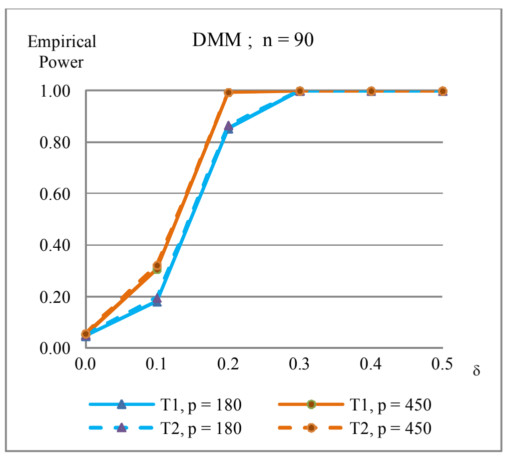


Figure 4.14 The Empirical Powers of the T_1 and T_2 Tests of the Group Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 90$

4.3.1.3 The Time Effect

The empirical powers of the time effect tests under the local alternative hypothesis (4.13) when $n = 15$, 30, 60, 90 and $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ are respectively shown in Tables 4.15 to 4.18.

The results in Tables 4.15 to 4.18 can be summarized as follows. In each table, which shows the results of the empirical powers of the time effect tests for $n = 15$, 30, 60, 90, respectively, the empirical powers of the T_1, T_2, T_1^* and T_2^* tests increase as p increases. For both the DMM and MMM analyses, the empirical powers of the T_2 tests are higher than those of the T_1 test, and those of the T_2^* test are higher than those of the T_1^* the test. Additionally, the empirical powers of the tests from DMM and MMM are similar, but those of the T_1 and T_2 tests from DMM are slightly higher than those of the T_1^* and T_2^* tests for MMM.

From Figures 4.15 to 4.18, each of these figures gives plots of the empirical powers of the T_1 and T_2 tests of the interaction effect from DMM and the empirical powers of the T_1^* and T_2^* tests from MMM, for $n = 15$, 30, 60, 90. Both plots from the DMM and MMM analyses in each of the four figures are similar and can be described as follows. From the DMM analysis, the empirical powers of the T_1 and T_2 tests vary directly with δ, the constants given in the local alternative hypothesis $\mathbf{\Gamma}_1$, and increase when p increases for all cases of n. The empirical powers of T_2 are higher than T_1 for all cases of δ and p. From the MMM analysis, the variations of the empirical powers of the T_1^* and T_2^* tests are the same as for DMM. When comparing the four cases of n, the plots show that the empirical powers of T_1, T_2, T_1^* and T_2^* increase when n increases.

Table 4.15 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 15$

			DMM									
p	dim (pu)	df (v_e)	$\hat{\beta}_1$					$\hat{\beta}_2$				
			$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
30	60	12	0.0550	0.0750	0.1150	0.1890	0.3090	0.0752	0.0974	0.1460	0.2338	0.3660
45	90	12	0.0594	0.0806	0.1310	0.2402	0.4084	0.0768	0.1042	0.1646	0.2856	0.4616
60	120	12	0.0606	0.0876	0.1562	0.2866	0.4922	0.0748	0.1134	0.1876	0.3318	0.5456
75	150	12	0.0592	0.0882	0.1756	0.3304	0.5588	0.0738	0.1132	0.2082	0.3740	0.6050
			MMM									
p	dim (p)	df (uv_e)	$\hat{\beta}_1^*$					$\hat{\beta}_2^*$				
			$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
30	30	24	0.0530	0.0750	0.1152	0.1856	0.3058	0.0742	0.0950	0.1438	0.2314	0.3638
45	45	24	0.0594	0.0792	0.1316	0.2362	0.4028	0.0746	0.1016	0.1650	0.2874	0.4618
60	60	24	0.0582	0.0872	0.1542	0.2854	0.4940	0.0760	0.1110	0.1892	0.3290	0.5466
75	75	24	0.0576	0.0854	0.1692	0.3298	0.5568	0.0724	0.1108	0.2068	0.3712	0.6030

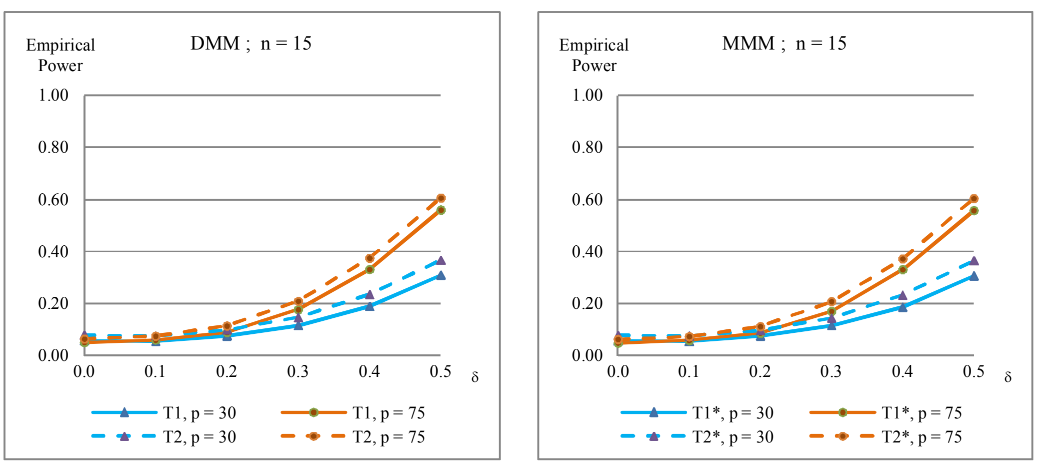


Figure 4.15 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 15$

Table 4.16 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 30$

			DMM									
p	dim (pu)	df (v_e)	$\hat{\beta}_1$					$\hat{\beta}_2$				
			δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5	δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5
60	120	27	0.0642	0.1372	0.3398	0.6572	0.9068	0.0768	0.1612	0.3728	0.6894	0.9234
90	180	27	0.0742	0.1704	0.4220	0.7842	0.9738	0.0850	0.1964	0.4544	0.8040	0.9782
120	240	27	0.0786	0.1890	0.5066	0.8726	0.9920	0.0882	0.2092	0.5392	0.8880	0.9932
150	300	27	0.0754	0.2290	0.5944	0.9292	0.9992	0.0876	0.2470	0.6186	0.9378	0.9994
			MMM									
p	dim (p)	df (uv_e)	$\hat{\beta}_1^*$					$\hat{\beta}_2^*$				
			δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5	δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5
60	60	54	0.0632	0.1366	0.3390	0.6572	0.9060	0.0764	0.1580	0.3748	0.6874	0.9232
90	90	54	0.0742	0.1684	0.4216	0.7850	0.9750	0.0844	0.1944	0.4528	0.8060	0.9786
120	120	54	0.0786	0.1916	0.5086	0.8728	0.9926	0.0880	0.2098	0.5396	0.8892	0.9934
150	150	54	0.0742	0.2274	0.5936	0.9292	0.9994	0.0872	0.2474	0.6182	0.9384	0.9994

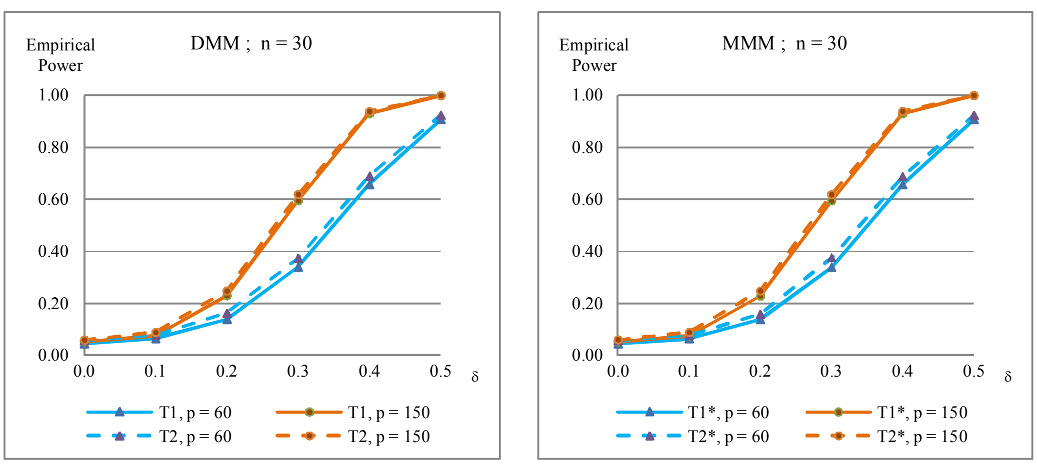


Table 4.16 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 30$

Table 4.17 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 60$

DMM												
p	dim (pu)	df (v_e)	$\hat{\beta}_1$					$\hat{\beta}_2$				
			$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
120	240	27	0.1128	0.4650	0.9364	0.9998	1.0000	0.1220	0.4870	0.9440	0.9998	1.0000
180	360	27	0.1314	0.5938	0.9860	1.0000	1.0000	0.1424	0.6142	0.9876	1.0000	1.0000
240	480	27	0.1360	0.7012	0.9978	1.0000	1.0000	0.1452	0.7166	0.9984	1.0000	1.0000
300	600	27	0.1584	0.7818	0.9996	1.0000	1.0000	0.1676	0.7968	0.9996	1.0000	1.0000
MMM												
p	dim (p)	df (uv_e)	$\hat{\beta}_1^*$					$\hat{\beta}_2^*$				
			$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
120	120	54	0.1118	0.4662	0.9368	0.9998	1.0000	0.1218	0.4878	0.9448	0.9998	1.0000
180	180	54	0.1314	0.5942	0.9864	1.0000	1.0000	0.1432	0.6134	0.9872	1.0000	1.0000
240	240	54	0.1358	0.7012	0.9982	1.0000	1.0000	0.1476	0.7170	0.9982	1.0000	1.0000
300	300	54	0.1574	0.7820	0.9996	1.0000	1.0000	0.1674	0.7960	0.9996	1.0000	1.0000

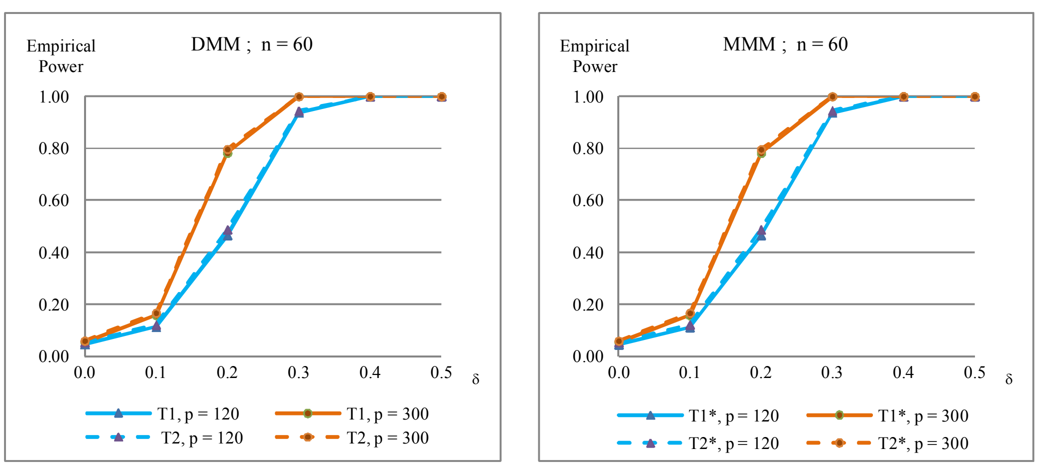
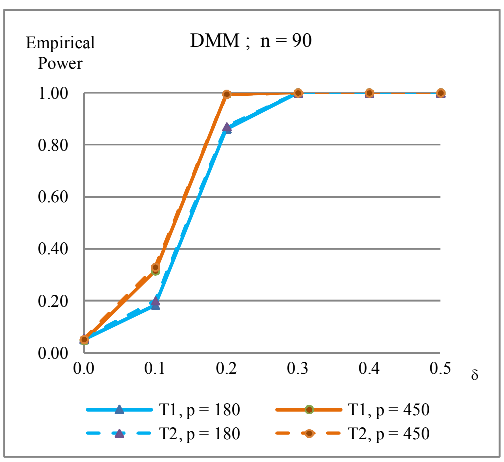


Figure 4.17 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 60$

Table 4.18 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 90$

			DMM									
p	dim (pu)	df (v_e)	$\hat{\beta}_1$					$\hat{\beta}_2$				
			δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5	δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5
180	360	27	0.1842	0.8612	1.0000	1.0000	1.0000	0.2004	0.8698	1.0000	1.0000	1.0000
270	540	27	0.2242	0.9542	1.0000	1.0000	1.0000	0.2362	0.9582	1.0000	1.0000	1.0000
360	720	27	0.2690	0.9826	1.0000	1.0000	1.0000	0.2832	0.9836	1.0000	1.0000	1.0000
450	900	27	0.3146	0.9942	1.0000	1.0000	1.0000	0.3292	0.9950	1.0000	1.0000	1.0000
			MMM									
p	dim (p)	df (uv_e)	$\hat{\beta}_1^*$					$\hat{\beta}_2^*$				
			δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5	δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5
180	180	54	0.1842	0.8604	1.0000	1.0000	1.0000	0.1996	0.8692	1.0000	1.0000	1.0000
270	270	54	0.2250	0.9542	1.0000	1.0000	1.0000	0.2376	0.9578	1.0000	1.0000	1.0000
360	360	54	0.2684	0.9837	1.0000	1.0000	1.0000	0.2840	0.9823	1.0000	1.0000	1.0000
450	450	54	0.3138	0.9942	1.0000	1.0000	1.0000	0.3292	0.9952	1.0000	1.0000	1.0000



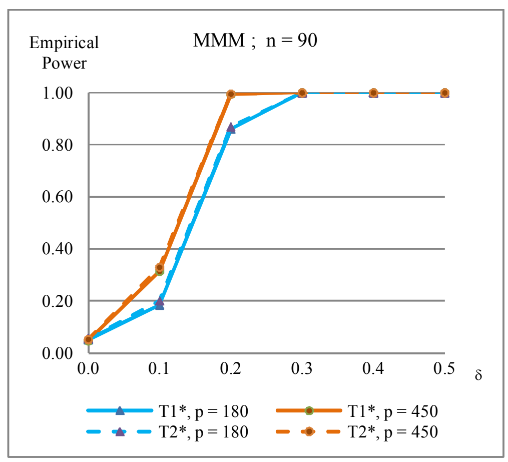


Figure 4.18 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2 = \mathbf{\Sigma}_3 = \mathbf{I}_{pt}$ and $n = 90$

4.3.2 Case $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$

4.3.2.1 The Interaction Effect

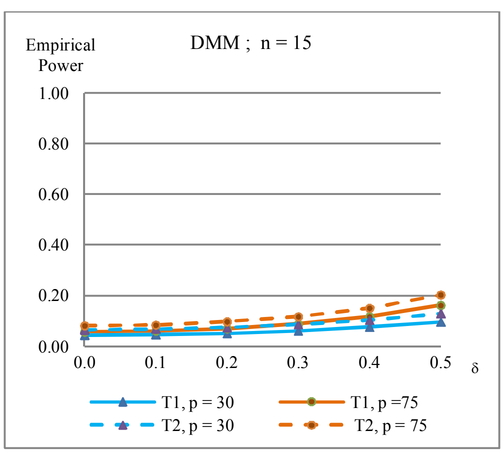
The empirical powers of the interaction effect tests under the local alternative hypothesis (4.11) when $n = 15$, 30, 60, 90, and $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$, are respectively shown in Tables 4.19 to 4.22.

The results in Tables 4.19 to 4.22 can be summarized as follows. In each table showing the results of the empirical powers of the interaction effect tests in each case of $n = 15$, 30, 60, 90, respectively, the empirical powers of the T_1, T_2, T_1^* and T_2^* tests increase as *p* increases. For both the DMM and MMM analyses, the empirical powers of the T_2 test are higher than those of the T_1 test, and those of the T_2^* test are higher than those of the T_1^* test. Additionally, the empirical powers of the tests from DMM and MMM are similar but those of the T_1 and T_2 tests from DMM are slightly higher than the T_1^* and T_2^* tests for MMM.

From Figures 4.19 to 4.22, each of these figures gives one plot of the empirical powers of the T_1 and T_2 tests for the interaction effect from DMM and the other plot of the empirical powers for the T_1^* and T_2^* tests from MMM, for $n = 15$, 30, 60, 90. Both plots from the DMM and MMM analyses in each of the four figures are similar and can be described as follows. From the DMM analysis, the empirical powers of the T_1 and T_2 tests vary directly with δ, the constants given in local alternative hypothesis $\mathbf{\Gamma}_1$, and increase when *p* increases for all cases of *n*. The empirical powers of T_2 are higher than T_1 for all cases of δ and *p*. From the MMM analysis, the variations of empirical powers of the T_1^* and T_2^* tests are the same as for DMM. When comparing the four cases of *n*, the plots show that the empirical powers of T_1, T_2, T_1^* and T_2^* increase when *n* increases.

Table 4.19 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 15$

DMM													
p	dim (pu)	df (v_e)	$\hat{\beta}_1$ $\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\hat{\beta}_2$ $\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
30	60	12	0.0454	0.0514	0.0606	0.0760	0.0956	0.0684	0.0744	0.0862	0.1032	0.1288
45	90	12	0.0570	0.0636	0.0746	0.0950	0.1250	0.0830	0.0902	0.1048	0.1282	0.1614
60	120	12	0.0530	0.0596	0.0750	0.0968	0.1338	0.0762	0.0870	0.1026	0.1294	0.1766
75	150	12	0.0612	0.0702	0.0878	0.1170	0.1622	0.0846	0.0980	0.1176	0.1512	0.2036
MMM												
p	dim (p)	df (uv_e)	$\hat{\beta}_1^*$ $\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\hat{\beta}_2^*$ $\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
30	30	24	0.0428	0.0490	0.0576	0.0706	0.0912	0.0660	0.0712	0.0830	0.1008	0.1276
45	45	24	0.0560	0.0622	0.0730	0.0900	0.1190	0.0790	0.0862	0.1014	0.1240	0.1592
60	60	24	0.0508	0.0554	0.0710	0.0940	0.1324	0.0722	0.0826	0.0996	0.1298	0.1748
75	75	24	0.0592	0.0680	0.0878	0.1134	0.1584	0.0804	0.0940	0.1154	0.1490	0.2038



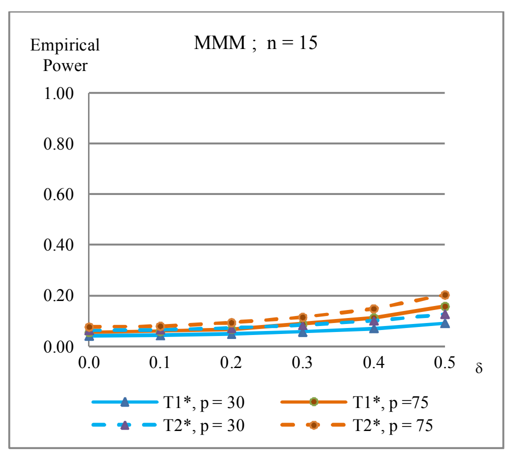


Figure 4.19 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 15$

Table 4.20 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 30$

			DMM									
	dim	df	$\hat{\beta}_1$					$\hat{\beta}_2$				
p	(pu)	(v_e)	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
60	120	27	0.0562	0.0714	0.1064	0.1722	0.2702	0.0684	0.0880	0.1264	0.1986	0.3042
90	180	27	0.0552	0.0826	0.1288	0.2124	0.3680	0.0724	0.0992	0.1482	0.2426	0.4046
120	240	27	0.0612	0.0856	0.1456	0.2586	0.4464	0.0740	0.1026	0.1670	0.2918	0.4810
150	300	27	0.0554	0.0822	0.1520	0.2842	0.4988	0.0660	0.0974	0.1734	0.3156	0.5348

			MMM									
	dim	df	$\hat{\beta}_1^*$					$\hat{\beta}_2^*$				
p	(p)	(uv_e)	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
60	60	54	0.0574	0.0734	0.1054	0.1706	0.2680	0.0678	0.0878	0.1274	0.1970	0.3028
90	90	54	0.0570	0.0810	0.1258	0.2118	0.3664	0.0714	0.0982	0.1472	0.2438	0.4080
120	120	54	0.0618	0.0886	0.1448	0.2588	0.4456	0.0742	0.1024	0.1658	0.2898	0.4814
150	150	54	0.0552	0.0810	0.1513	0.2852	0.5026	0.0658	0.0956	0.1583	0.3150	0.5356

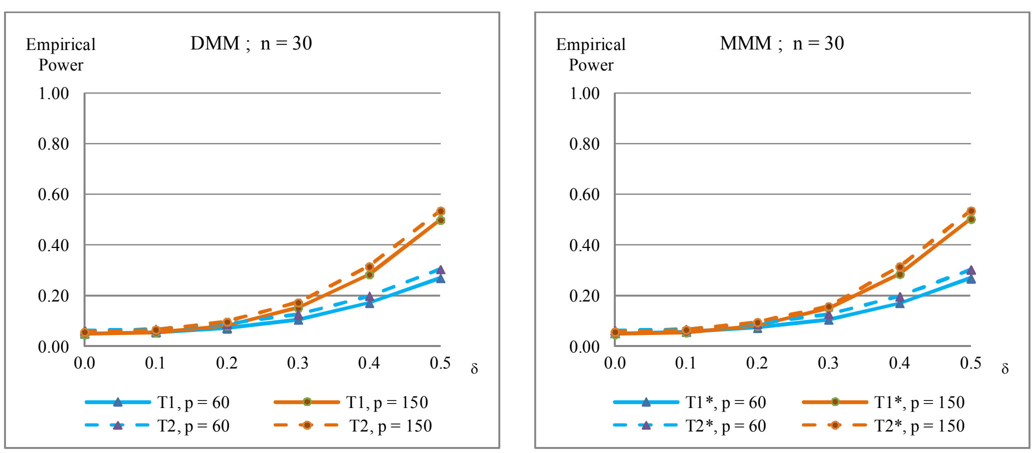


Figure 4.20 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 30$

Table 4.21 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 60$

			DMM									
p	dim (pu)	df (v_e)	$\hat{\beta}_1$					$\hat{\beta}_2$				
			$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
120	240	27	0.0656	0.1244	0.3058	0.6198	0.8960	0.0738	0.1378	0.3268	0.6420	0.9082
180	360	27	0.0672	0.1556	0.3994	0.7620	0.9704	0.0738	0.1658	0.4206	0.7792	0.9736
240	480	27	0.0778	0.1900	0.4962	0.8644	0.9936	0.0862	0.2054	0.5132	0.8756	0.9152
300	600	27	0.0768	0.2004	0.5360	0.9154	0.9978	0.0840	0.2152	0.5554	0.9258	0.9982
			MMM									
p	dim (p)	df (uv_e)	$\hat{\beta}_1^*$					$\hat{\beta}_2^*$				
			$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
120	120	54	0.0654	0.1232	0.3034	0.6190	0.8962	0.0736	0.1364	0.3246	0.6404	0.9062
180	180	54	0.0660	0.1550	0.3992	0.7610	0.9702	0.0740	0.1660	0.4206	0.7804	0.9738
240	240	54	0.0782	0.1900	0.4952	0.8658	0.9938	0.0860	0.2050	0.5140	0.8758	0.9948
300	300	54	0.0776	0.2152	0.5340	0.9160	0.9982	0.0840	0.2168	0.5550	0.9232	0.9978

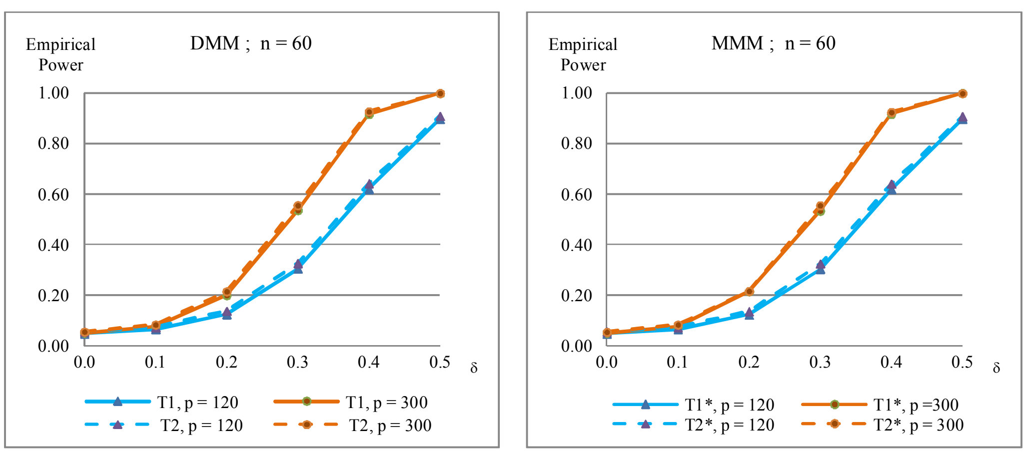
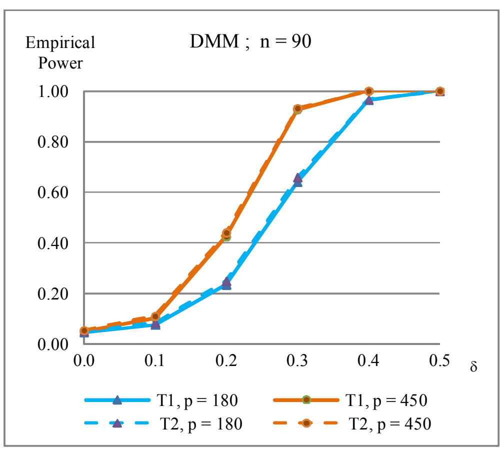


Figure 4.21 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 60$

Table 4.22 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 90$

			DMM									
p	dim (pu)	df (v_e)	$\hat{\beta}_1$					$\hat{\beta}_2$				
			$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
180	360	27	0.0770	0.2354	0.6416	0.9638	0.9996	0.0850	0.2500	0.6594	0.9674	0.9996
270	540	27	0.0918	0.2966	0.7768	0.9940	1.0000	0.0996	0.3138	0.7896	0.9942	1.0000
360	720	27	0.0962	0.3600	0.8774	0.9996	1.0000	0.1032	0.3748	0.8854	0.9998	1.0000
450	900	27	0.1042	0.4252	0.9266	1.0000	1.0000	0.1114	0.4410	0.9318	1.0000	1.0000
			MMM									
p	dim (p)	df (uv_e)	$\hat{\beta}_1^*$					$\hat{\beta}_2^*$				
			$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
180	180	54	0.0780	0.2364	0.6426	0.9640	0.9996	0.0856	0.2496	0.6578	0.9670	0.9998
270	270	54	0.0912	0.2970	0.7766	0.9940	1.0000	0.0988	0.3128	0.7894	0.9944	1.0000
360	360	54	0.0968	0.3612	0.8770	0.9996	1.0000	0.1034	0.3764	0.8856	0.9998	1.0000
450	450	54	0.1042	0.4252	0.9268	1.0000	1.0000	0.1112	0.4396	0.9324	1.0000	1.0000



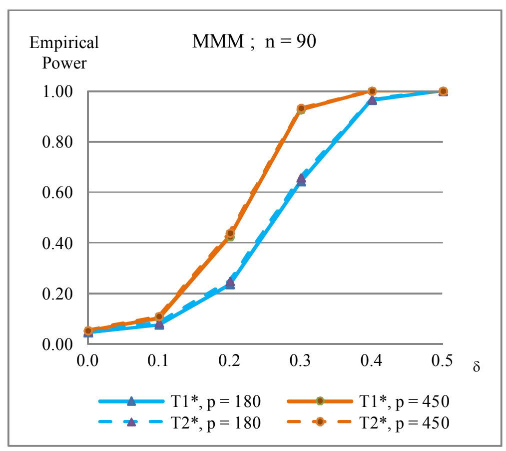


Figure 4.22 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Interaction Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 90$

4.3.2.2 The Group effect

The empirical powers of the group effect tests under the local alternative hypothesis (4.12) when $n = 15$, 30, 60, 90, and $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$, are respectively shown in Tables 4.23 to 4.26.

The results in Tables 4.23 to 4.26 can be summarized as follows. In each table, the results of the empirical powers of the group effect tests in each case of $n = 15$, 30, 60, 90, respectively, the same pattern of results was obtained as in Section 4.3.1.2. The DMM and MMM test statistics are the same as shown in Section 4.1.3, so only the results of the empirical powers of the T_1 and T_2 tests from the DMM analysis are discussed here. The results show that the empirical powers of the T_1 and T_2 tests increase as p increases. The empirical powers of the T_2 test are higher than those of the T_1 test. These results are the same as in the MMM analysis.

From Figures 4.23 to 4.26, each of them shows a plot of the empirical powers of the T_1 and T_2 tests of the group effect from the DMM for each case of $n = 15, 30, 60, 90$, respectively. The plots in each of the four figures are similar and can be described as follows. From the DMM (or MMM) analysis, the empirical powers of the T_1 (or T_1^*) and T_2 (or T_2^*) tests vary directly with the δ constants given in the local alternative hypothesis $\mathbf{\Gamma}_1$, and increase when p increases for all cases of n. The empirical powers of the T_2 test are higher than those of the T_1 test for all cases of δ and p. When comparing the four cases of n, the plots show that the empirical powers of the T_1 and T_2 tests increase when n increases.

Table 4.23 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Group Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 15$

			DMM*									
p	dim (p)	*df* (v_e)	$\hat{\beta}_1$					$\hat{\beta}_2$				
			$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
30	30	12	0.0562	0.0632	0.0714	0.0862	0.1086	0.0862	0.0944	0.1076	0.1278	0.1570
45	45	12	0.0514	0.0584	0.0722	0.0932	0.1286	0.0772	0.0884	0.1074	0.1374	0.1726
60	60	12	0.0516	0.0594	0.0730	0.0964	0.1404	0.0762	0.0868	0.1052	0.1386	0.1910
75	75	12	0.0534	0.0620	0.0808	0.1134	0.1576	0.0756	0.0916	0.1136	0.1510	0.2062

Note: * The results of the T_1^* and T_2^* tests from MMM are the same as those of the T_1 and T_2 tests from DMM, as described in Section 4.1.3

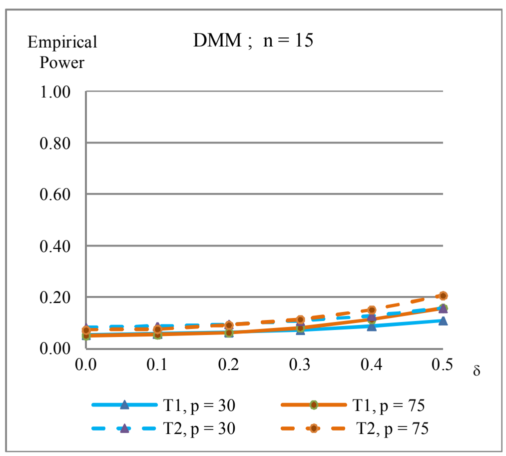


Figure 4.23 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Group Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 15$

Table 4.24 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Group Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 30$

			DMM*									
			$\hat{\beta}_1$					$\hat{\beta}_2$				
p	dim (p)	df (v_e)	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
60	60	27	0.0568	0.0756	0.1134	0.1810	0.2924	0.0708	0.0936	0.1378	0.2156	0.3360
90	90	27	0.0574	0.0772	0.1302	0.2272	0.3796	0.0682	0.0972	0.1568	0.2640	0.4258
120	120	27	0.0622	0.0864	0.1454	0.2540	0.4448	0.0718	0.1068	0.1712	0.2908	0.4884
150	150	27	0.0578	0.0876	0.1558	0.2956	0.5196	0.0702	0.1058	0.1798	0.3310	0.5592

Note: * The results of the T_1^* and T_2^* tests from MMM are the same as those of the T_1 and T_2 tests from DMM, as described in Section 4.1.3

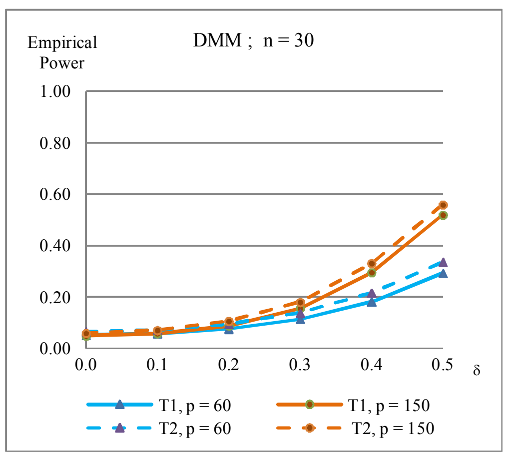


Figure 4.24 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Group Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 30$

Table 4.25 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Group Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 60$

			DMM*									
p	dim (p)	df (v_e)	$\hat{\beta}_1$ $\delta=0.1$	$\hat{\beta}_1$ $\delta=0.2$	$\hat{\beta}_1$ $\delta=0.3$	$\hat{\beta}_1$ $\delta=0.4$	$\hat{\beta}_1$ $\delta=0.5$	$\hat{\beta}_2$ $\delta=0.1$	$\hat{\beta}_2$ $\delta=0.2$	$\hat{\beta}_2$ $\delta=0.3$	$\hat{\beta}_2$ $\delta=0.4$	$\hat{\beta}_2$ $\delta=0.5$
120	120	57	0.0684	0.1384	0.3156	0.6280	0.9004	0.0800	0.1528	0.3404	0.6554	0.9116
180	180	57	0.0722	0.1688	0.4172	0.7786	0.9738	0.0824	0.1846	0.4416	0.7970	0.9770
240	240	57	0.0686	0.1802	0.4952	0.8740	0.9952	0.0770	0.1948	0.5178	0.8870	0.9948
300	300	57	0.0772	0.2172	0.5846	0.9326	0.9990	0.0862	0.2372	0.6058	0.9384	0.9992

Note: * The results of the T_1^* and T_2^* tests from MMM are the same as those of the T_1 and T_2 tests from DMM, as described in Section 4.1.3

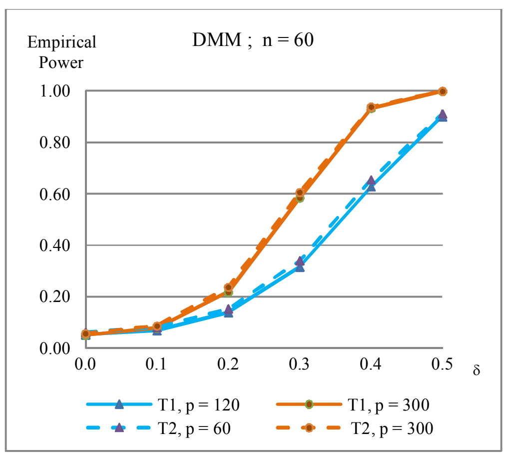


Figure 4.25 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Group Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 60$

Table 4.26 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Group Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 90$

			DMM*									
p	dim	df	$\hat{\beta}_1$					$\hat{\beta}_2$				
	(p)	(v_e)	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
180	180	87	0.0816	0.2500	0.6702	0.9644	0.9998	0.0898	0.2678	0.6902	0.9694	1.0000
270	270	87	0.0856	0.3208	0.8116	0.9952	1.0000	0.0934	0.3412	0.8212	0.9958	1.0000
360	360	87	0.0990	0.3856	0.8928	0.9994	1.0000	0.1090	0.4010	0.9006	0.9994	1.0000
450	450	87	0.1016	0.4386	0.9472	1.0000	1.0000	0.1098	0.4580	0.9508	1.0000	1.0000

Note: * The results of the T_1^* and T_2^* tests from MMM are the same as those of the T_1 and T_2 tests from DMM, as described in Section 4.1.3

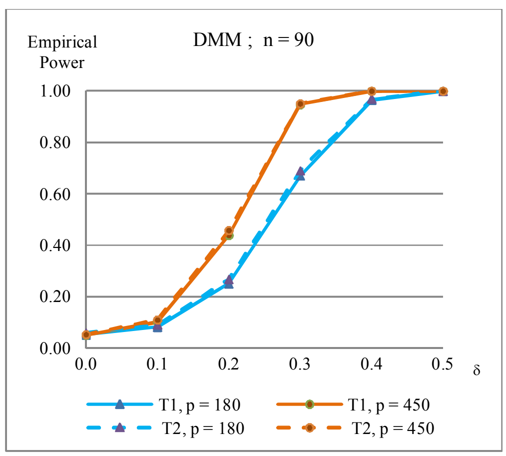


Figure 4.26 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Group Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 90$

4.3.2.3 The Time Effect

The empirical powers of the time effect tests under the local alternative hypothesis (4.13) when $n = 15$, 30, 60, 90, and $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$, are respectively shown in Tables 4.27 to 4.30.

The results in Tables 4.27 to 4.30 can be summarized as follows. In each table showing the results of the empirical powers of the time effect tests in each case of $n = 15$, 30, 60, 90, respectively, the empirical powers of the T_1, T_2, T_1^* and T_2^* tests increase as p increases. For both the DMM and MMM analyses, the empirical powers of the T_2 test are higher than those of the T_1 test, and those of the T_2^* test are higher than those of the T_1^* test. Additionally, the empirical powers of the tests from DMM and MMM are similar but those of the T_1 and T_2 tests for DMM are slightly higher than the T_1^* and T_2^* tests for MMM.

From Figures 4.27 to 4.30, each of them gives one plot of the empirical powers of the T_1 and T_2 tests of the time effect from DMM and the other plot of the empirical powers for the T_1^* and T_2^* tests from MMM, for $n = 15$, 30, 60, 90, respectively. Both plots from the DMM and MMM analyses in each of the four figures are similar and can be described as follows. From the DMM analysis, the empirical powers of the T_1 and T_2 tests vary directly with δ, the constants given in local alternative hypothesis $\mathbf{\Gamma}_1$, and increase when p increases for all cases of n. The empirical powers of T_2 are higher than those of T_1 for all cases of δ and p. From the MMM analysis, the variations of the empirical powers of the T_1^* and T_2^* tests are the same as for DMM. When comparing the four cases of n, the plots show that the empirical powers of T_1, T_2, T_1^* and T_2^* increase when n increases.

Table 4.27 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 15$

DMM													
p	dim	df	$\hat{\beta}_1$					$\hat{\beta}_2$					
	(pu)	(v_e)	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
30	60	12	0.0526	0.0658	0.0892	0.1292	0.1982	0.0706	0.0866	0.1164	0.1640	0.2426
45	90	12	0.0568	0.0712	0.0990	0.1540	0.2506	0.0736	0.0914	0.1260	0.1916	0.2954
60	120	12	0.0572	0.0772	0.1130	0.1814	0.2994	0.0734	0.0952	0.1406	0.2198	0.3464
75	150	12	0.0570	0.0774	0.1196	0.2070	0.3470	0.0704	0.0976	0.1496	0.2406	0.3906
MMM													
p	dim	df	$\hat{\beta}_1^*$					$\hat{\beta}_2^*$					
	(p)	(uv_e)	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
30	30	24	0.0512	0.0624	0.0888	0.1298	0.1940	0.0706	0.0848	0.1156	0.1616	0.2388
45	45	24	0.0556	0.0710	0.1000	0.1548	0.2472	0.0726	0.0900	0.1266	0.1900	0.2954
60	60	24	0.0564	0.0748	0.1118	0.1816	0.2994	0.0726	0.0940	0.1398	0.2174	0.3470
75	75	24	0.0562	0.0738	0.1160	0.2044	0.3446	0.0696	0.0940	0.1472	0.2276	0.3916

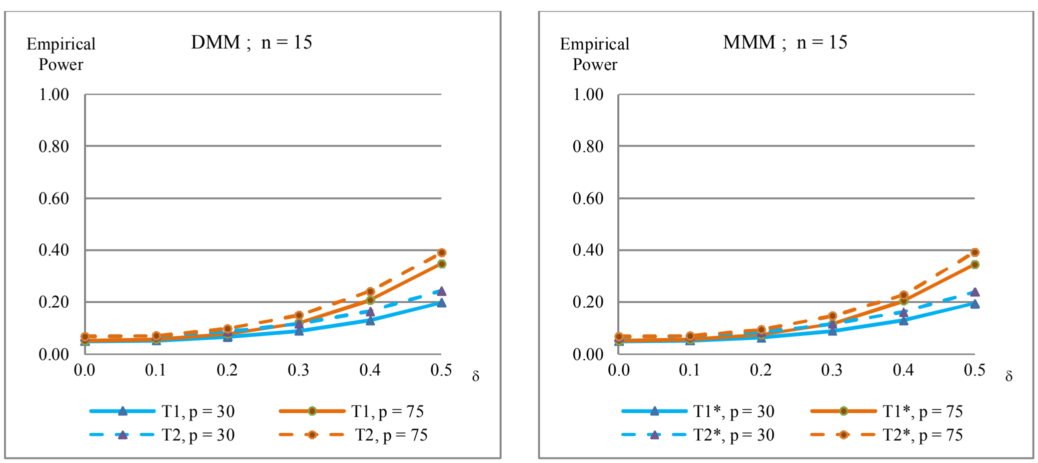


Figure 4.27 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 15$

Table 4.28 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 30$

			DMM									
p	dim (pu)	df (v_e)	$\hat{\beta}_1$					$\hat{\beta}_2$				
			δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5	δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5
60	120	27	0.0566	0.1012	0.2068	0.4132	0.6830	0.0718	0.1178	0.2356	0.4454	0.7144
90	180	27	0.0676	0.1154	0.2620	0.5178	0.8134	0.0764	0.1312	0.2900	0.5472	0.8334
120	240	27	0.0710	0.1304	0.3122	0.6166	0.8950	0.0786	0.1478	0.3368	0.6450	0.9064
150	300	27	0.0660	0.1466	0.3652	0.7054	0.9468	0.0748	0.1638	0.3916	0.7282	0.9522

			MMM									
p	dim (p)	df (uv_e)	$\hat{\beta}_1^*$					$\hat{\beta}_2^*$				
			δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5	δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5
60	60	54	0.0570	0.1012	0.2044	0.4124	0.6814	0.0704	0.1184	0.2346	0.4444	0.7136
90	90	54	0.0662	0.1156	0.2597	0.5194	0.8148	0.0754	0.1312	0.2850	0.5446	0.8342
120	120	54	0.0694	0.1290	0.3080	0.6148	0.8944	0.0780	0.1468	0.3376	0.6474	0.9062
150	150	54	0.0650	0.1454	0.3650	0.7048	0.9464	0.0732	0.1638	0.3930	0.7266	0.9518

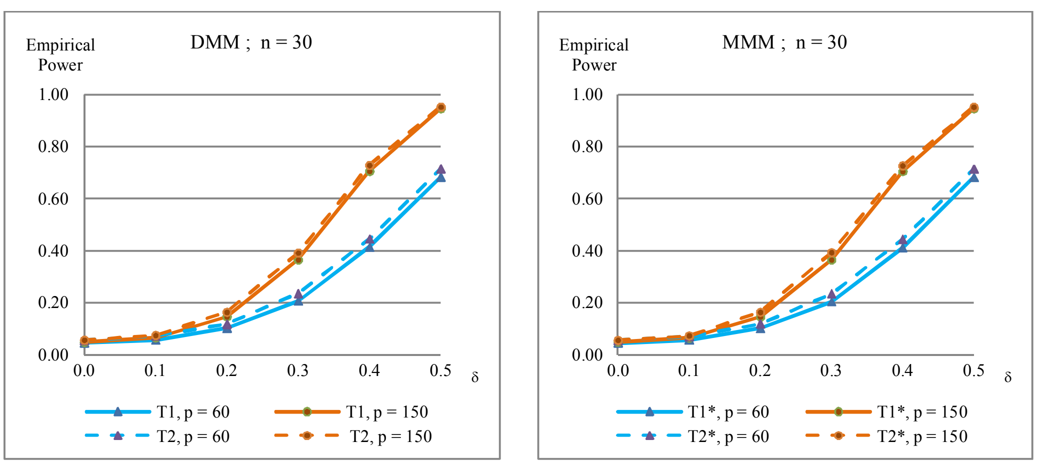


Figure 4.28 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 30$

Table 4.29 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 60$

DMM												
p	dim (pu)	df (v_e)	$\hat{\beta}_1$					$\hat{\beta}_2$				
			$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
120	240	27	0.0876	0.2824	0.7148	0.9776	1.0000	0.0976	0.3030	0.7332	0.9820	1.0000
180	360	27	0.0982	0.3698	0.8570	0.9976	1.0000	0.1098	0.3882	0.8686	0.9978	1.0000
240	480	27	0.1006	0.4360	0.9328	0.9998	1.0000	0.1084	0.4582	0.9374	0.9998	1.0000
300	600	27	0.1090	0.5062	0.9704	1.0000	1.0000	0.1174	0.5256	0.9730	1.0000	1.0000
MMM												
p	dim (p)	df (uv_e)	$\hat{\beta}_1^*$					$\hat{\beta}_2^*$				
			$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$	$\delta = 0.1$	$\delta = 0.2$	$\delta = 0.3$	$\delta = 0.4$	$\delta = 0.5$
120	120	54	0.0868	0.2804	0.7152	0.9782	1.0000	0.0974	0.3020	0.7328	0.9810	1.0000
180	180	54	0.0992	0.3702	0.8574	0.9974	1.0000	0.1094	0.3880	0.8686	0.9980	1.0000
240	240	54	0.1000	0.4358	0.9328	0.9998	1.0000	0.1088	0.4572	0.9382	0.9998	1.0000
300	300	54	0.1092	0.5064	0.9708	1.0000	1.0000	0.1176	0.5252	0.9730	1.0000	1.0000

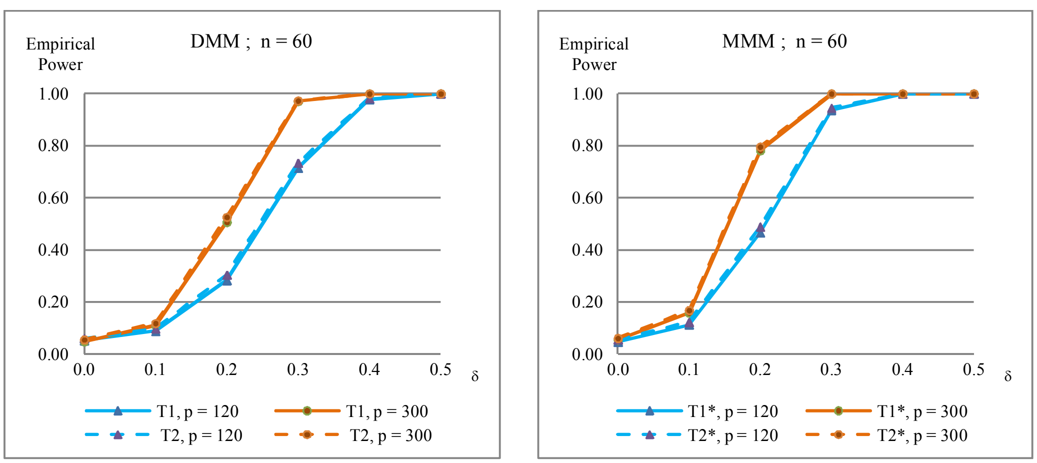
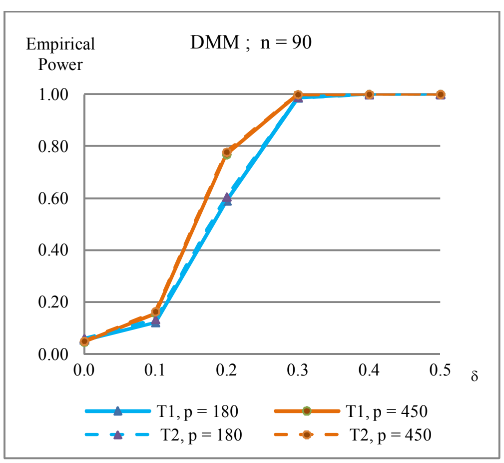


Figure 4.29 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 60$

Table 4.30 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 90$

			DMM									
p	dim (pu)	df (v_e)	$\hat{\beta}_1$					$\hat{\beta}_2$				
			δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5	δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5
180	360	27	0.1216	0.5888	0.9864	1.0000	1.0000	0.1334	0.6048	0.9880	1.0000	1.0000
270	540	27	0.1170	0.5858	0.9888	1.0000	1.0000	0.1262	0.6012	0.9896	1.0000	1.0000
360	720	27	0.1404	0.6918	0.9972	1.0000	1.0000	0.1494	0.7056	0.9976	1.0000	1.0000
450	900	27	0.1558	0.7684	0.9994	1.0000	1.0000	0.1636	0.7778	0.9994	1.0000	1.0000
			MMM									
p	dim (p)	df (uv_e)	$\hat{\beta}_1^*$					$\hat{\beta}_2^*$				
			δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5	δ = 0.1	δ = 0.2	δ = 0.3	δ = 0.4	δ = 0.5
180	180	54	0.1214	0.5876	0.9864	1.0000	1.0000	0.1314	0.6052	0.9880	1.0000	1.0000
270	270	54	0.1160	0.5858	0.9890	1.0000	1.0000	0.1254	0.6024	0.9894	1.0000	1.0000
360	360	54	0.1408	0.6910	0.9972	1.0000	1.0000	0.1490	0.7054	0.9976	1.0000	1.0000
450	450	54	0.1552	0.7668	0.9994	1.0000	1.0000	0.1648	0.7764	0.9994	1.0000	1.0000



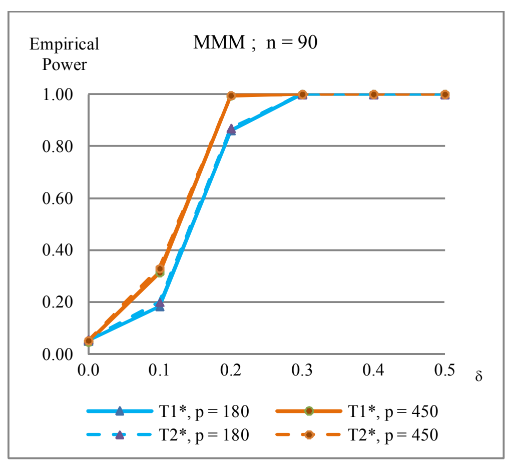


Figure 4.30 The Empirical Powers of the T_1, T_2, T_1^* and T_2^* Tests of the Time Effect under the Local Alternative Hypothesis when $\mathbf{\Sigma} = 1.5\mathbf{I}_{pt} + 0.5\mathbf{J}_{pt}$ and $n = 90$

CHAPTER 5

APPLICATION TO MICROARRAY TIME COURSE EXPERIMENTS

5.1 Microarray Time Course Experiments

Microarray time course experiments typically involve gene expression measurements for thousands of genes over relatively few time points under one or more biological conditions. The time points at which samples are taken are usually determined by the investigator's judgment concerning the biological events of interest and are frequently irregularly spaced for periodic time course experiments. Microarray time course studies usefully provide the ability to monitor the temporal behavior of a biological process of interest through the measurement of expression levels of thousands of genes simultaneously (Tai and Speed, 2005: 1).

5.1.1 Experiment Design

Time course experiments can be classified based on different criteria: the number of time points, the number of biological conditions and the independence between time points. First, the number of time points can be 3-6 for short time courses and more than 6 for long ones. From the second criteria, time course data can be divided into single or multiple series data depending on whether one experimental group or more are evaluated. Finally, time course experiments can be classified into longitudinal and cross-sectional data. In longitudinal time courses, individuals are sampled at different time points whereas in cross-sectional experiments samples at different times are from different and independent individuals (Roldán, 2009: 8).

There are three major types of biological question in the study of microarray time course experiments. One type of experiment aims at understanding the gene-expression basis of physiological phenomena or the developmental process which are related to long, longitudinal and single time course data. Another type of experiment tries to determine the gene expression response to treatments and frequently uses short and multiple time series. Finally, time course experiments are also designed to study gene regulatory networks or interaction between genes which associate with a single series of time course data (Roldán, 2009: 9).

5.1.2 Gene expression microarray data

The gene expression microarray is the one technique for measuring gene expression. Microarrays quantify gene expression by measuring the hybridization of DNA immobilized on a small glass matrix to mRNA representation from the sample under study. This microarray technology can measure the expression of all of the genes of an organism. There are two main microarray transcriptomic techniques, cDNA arrays and oligonucleotide arrays, which can be used in combination with one or two dye labeling strategies. Traditionally, cDNA arrays are coupled to two color arrays whereas the use of oligonucleotide arrays of either one or two colors were commercially imposed in the last few years. The most popular oligonucleotide chip is commercialized by the Affymetrix company, with trademark name GeneChip, which uses probe sets along with one color technology (Roldán, 2009: 5).

The gene expression information obtained from a microarray is organized into a data matrix where the rows represent the genes and the columns the different situations or arrays. This data matrix is called a gene expression profile at the different expression values that one gene has for different conditions, treatments or tissues (row of the data matrix). Before applying data analysis to find responses to the biological questions of interest, data pre-processing steps, which are usually logarithm transformations, the treatment of missing values and outliers, replicate handling and normalization, are required to prepare the gene expression microarray data for posterior statistical analysis (Roldán, 2009: 16).

5.1.3 Statistical Analysis of Microarray Time Course Data

5.1.3.1 Identifying Differentially Expressed Genes

One of the main goals in microarray studies is to identify genes with different expression under the experimental condition of the study or, in other words, to analyze if the different experimental conditions have an influence on gene expression. This main purpose usually involves hypothesis testing methods, which implies as many statistical tests as variables and the appearance of a multiple testing scenario that demands adjustment of the single test *p*-values. To identify a differentially expressed gene for a single gene, classical statistical univariate methods, such as the student t-test, the ANOVA-F test or mixed models, have been applied. In recent genetic research, detecting sets of genes which are significant with respect to treatment is the point of focus and many researchers have proposed newly developed multivariate methods to analyze microarray time course experiments, such as the multivariate two-sample test (Chen and Qin, 2010:5), MANOVA (Tsai and Chen, 2009:1), robustified MANOVA (Xu and Cui, 2008: 2) or the unified mixed effect model (Wang, Chen and Wolfinger, 2009: 1).

5.1.3.2 Multiple Testing Correction

Performing more than one statistical inference procedure on the same data set is called multiple inference or multiple testing. In microarray experiments, several thousand genes or gene sets are simultaneously measured across different conditions. When detecting differentially expressed genes or gene sets across those conditions, each gene or gene set is considered independently from one another. Incidences of false positives are genes that are found to be statistically different between conditions but are not in reality. A false positive is proportional to the number of tests performed and the critical significance level (p-value cutoff) (Agilent Technologies, 2005: 2).

Consider the problem of testing m null hypotheses simultaneously, of which m_0 are true and R is the number of hypotheses rejected. Table 5.1 defines some of the random variables related to the m hypothesis tests. The specific m hypotheses are assumed to be known in advance. R is an observable random variable and U, V, S and T are unobservable random variables. If each individual null hypothesis is tested separately at level α, then $R = R(\alpha)$ is increasing in α.

Table 5.1 Number of Errors committed when testing m Null Hypotheses

	Declared Non Significant	Declared Significant	Total
True Null Hypothesis	U	V	m_0
Untrue Null Hypothesis	T	S	$m - m_0$
	m-R	R	m

The family-wise type I error rate (FWER) is the probability of making one or more false discoveries, or type I errors, among the hypotheses when performing multiple testing. In other words, the procedure will almost definitely wrongly conclude that there is at least a difference in one test. From Table 5.1, FWER = $P(V \geq 1) = 1 - (1 - \alpha)^m$. In spite of selecting a very low significance level, FWER increases considerably. For instance, in an experiment with 1,000 genes or gene sets and two conditions, there are 1,000 statistical tests; taking α = 0.05, the FWER = 1.000.

Multiple testing correction is a procedure to adjust p-values derived from multiple statistical tests to correct for the occurrence of false positives. A simple procedure is the Bonferroni correction that consists of choosing a global significance level and working for each comparison at the FWER/q level. The Bonferroni corrected p-value is the $q \cdot$p-value and the null hypothesis is rejected when it is less than the global significance at level α. Unfortunately, this correction is very strong for gene expression analysis due to the large number of comparisons needed. The required significance level for each contrast will be so small that almost no statistically significant gene would be found in the results, yielding many false negatives (Roldán, 2009: 33). For instance, if testing 1,000 genes or gene sets with a control family-wise error rate at most 0.05, the highest accepted individual p-value is 0.00005, making the correction very stringent. Another procedure to control the FWER is the Holm-Bonferroni step-down correction, which is less stringent than the Bonferroni correction. However, the control of the FWER is conservative.

An alternative to controlling false positives, called false discovery rate (FDR), was introduced by Benjamini and Hochberg (1995: 290). The FDR of a group of tests is the expected value of the ratio of falsely rejected hypotheses to all rejected hypotheses, i.e. the expected value of V/R in Table 5.1. If the null hypotheses are true, the FDR is equivalent to the FWER, therefore control of the FDR implies control of the FWER in a weak sense. When $m_0 < m$, the FDR is smaller than or equal to the FWER. If a procedure controls the FDR only, it can be less stringent and a gain in power may be expected (Benjamini and Hochberg, 1995: 291).

Benjamini and Hochberg's false discovery rate procedure firstly orders the p-values associated with the employed statistics for m null hypotheses $p_{(1)}, p_{(2)}, \ldots, p_{(m)}$ and, secondarily, the largest p-value remains as is after which the second largest p-value is multiplied by the total number of genes or gene sets in the gene list divided by its rank. The corrected p-value is the $m/(m-1)\cdot$p-value and, if less than 0.05, is significant. After this, the third p-value is multiplied as was the second one, the corrected p-value is the $m/(m-2)\cdot$p-value which, if less than 0.05, is significant, and so on.

5.2 Analysis of the Clinical Study of the Burn Injury Time Course Experiment

A large-scale clinical study of burn patients was analyzed to characterize the gene expression impact of demographic factors important to patients' outcome after injury. This clinical study by the National Institute of General Medical Sciences in the US, called the Inflammation and Host Response to Injury (Burns) program, includes gene expression data of blood samples from pediatric and adult patients measured at different times after severe burn injury and from healthy controls. The data set was analyzed by Zhou et al. (2010a: 1) using a time course ANOVA (TANOVA) methodology on the effect of age on a patient's genomic response to burn injury. This statistical analysis is a univariate test detecting differentially expressed genes (DEG) at each gene level. Since each gene does not function individually in isolation and tends to work with other genes to achieve certain biological tasks, the multivariate approach is used to identify sets of burn injury patients' expressed genes which are significant with respect to the age factor.

To test whether different expressed gene sets in the burn injury data are significant with respect to the interaction, age and time effects, the proposed tests in this dissertation for the high dimensional DMM and MMM were applied. The burn injury time course data was retrieved from the Gene Expression Omnibus GEO) database, www.ncbi.nlm.nih.gov/geo (accession no. GSE19743).

5.2.1 Clinical Study Information

5.2.1.1 Patients

Zhou et al. (2010b: 1) gave details of the patients' enrollment in the burn injury microarray time course experiment:

One hundred and eighty six burn patients with burns over 20% of the total body surface area (TBSA) and 101 healthy controls were enrolled in a prospective longitudinal study. Patients were enrolled by the participating burn centers: Loyola University, Massachusetts General Hospital, Parkland Memorial Hospital, Shriners Hospital for Children–Galveston, University of Texas Medical Branch and the University of Washington. Criteria for enrollment included hospital admission within 96 hours of injury with a burn size >20% of TBSA requiring surgical treatment. The study was reviewed and approved by the Institutional Review Board at each clinical site; genomic analyses were performed at the University of Florida–Gainesville, and permission for these studies was also obtained from their Institutional Review Board. Prior to study, each patient, parent, or child's legal guardian signed a written informed consent form. Blood was drawn within 10 days of burning and then at subsequent times throughout the first 3 years following injury. Non-burned volunteers, or patients more than three years post burn, were enrolled as control patients. Control samples were obtained at a single time point from volunteers or from individuals undergoing elective operative interventions. Demographics and clinical data were recorded in the trial database.

5.2.1.2 Sample Collection and Microarray Processing

Zhou et al. (2010b: 1) gave details of sample collection and microarray processing of burn injury microarray time course experiment:

Blood was drawn within 10 days of burning (early stage) and again 11–49 days post burn (middle stage). Non-burned volunteers, or patients more than three years post burn, were enrolled as controls. Control samples were obtained at a single time point from volunteers or from individuals undergoing elective operative interventions. Peripheral blood was collected and lysis buffer (bicarbonate-buffered ammonium chloride solution, 0.826% NH_4Cl, 0.1% $KHCO_3$, 0.0037% Na_4EDTA in H_2O) was added at a ratio of 20:1 (lysis buffer:blood). Samples were then incubated at room temperature until erythrocyte lysis was complete (5–7 min). Leukocytes were recovered by centrifugation (400 g, 48 C) and washed once in ice-cold phosphate buffered saline. Leukocyte pellets were then resuspended in 8 ml buffer RLT (Qiagen) and the samples sheared 10 times with an 18-gauge needle attached to a 10-ml syringe. Samples were then immediately frozen and kept at –80ºC until RNA extraction was required. Total cellular RNA was isolated from the leukocyte pellets using a commercial kit (RNeasy, Qiagen). Purity was confirmed by spectrophotometry (A260⁄A280 ratio) and capillary electrophoresis (Agilent 2100 Bioanalyser, Agilent Inc). cRNA synthesis was performed using 4-mg total cellular RNA, hybridized onto Hu133 plus 2.0 oligonucleotide arrays (Affymetrix), and processed according to the protocol outlined by Affymetrix, with a few modifications.

A total of 54,675 probe sets on the Hu133 plus 2.0 arrays were analyzed. Normalization of signal intensity was performed using dChip (Li and Wong, 2001:31) and the expression level was modeled using the perfect-match-only option.

5.2.2 Gene Set Mapping

Gene sets are technically defined in the Gene Ontology (GO) system that provides the structured and controlled vocabularies producing names of gene sets (also called GO terms). There are three groups of Gene Ontology of interest: Biological Processes (BP), Cellular Components (CC) and Molecular Functions (MF). There are 29,230 genes functionally defined based on the biological process of GO and are mapped to unique GO terms in the BP categories. There are 1108 GO terms in the BP parent-categories, 247 in the CC parent-categories and 471 in MF parent-categories. Within three parent-categories, there are 191 gene sets in BP, 40 gene sets in CC and 146 gene sets in MF containing only single genes and the largest gene set contains 3049 genes in BP, 7729 genes in CC and 4440 genes in MF.

From a high dimensional framework perspective, the number of genes must be larger than the sample size. Analysis of the burn injury time course data is focused on the size of the GO categories: 70 to 2000 genes. In order to reduce the redundancy in GO, all child-categories, if the corresponding parent-category was within the size limitation, were removed. If the parent-category exceeded the size limitation, the child-categories were considered for the mapping of the GO categories. After the mapping process, the gene expression levels were left with 70 gene sets in BP, 76 gene sets in CC and 64 gene sets in MF for analysis.

5.2.3 Testing of the Interaction, Age and Time Effects in Burn Injuries for each Gene Set

As described in Section 5.2.2, the gene expression levels of blood samples from the 26 pediatric and 31 adult patients were repeatedly measured at two time points after severe burn injury: the early stage (0-10 days) and the middle stage (11-49 days). For each patient, the gene expression levels were mapped into 70 gene sets in the BP category, 76 gene sets in the CC category and 64 gene sets in the MF category. The total gene sets in the three categories was 210. In each gene set, the number of genes (p), which ranged from 70 to 2000, was larger than the number of patients (or subjects, n = 57).

Each set of gene expressions from the burn injury time course experiment is of the high dimensional multivariate repeated measurement design, i.e. p gene expressions in each gene set are repeatedly measured in blood sampled from each patient in two age groups ($g=2$) at two time periods ($t=2$). The numbers of subjects in each age group are unequal: $n_1 = 26$ and $n_2 = 31$.

Let $\mathbf{Y}_{i1} = (\boldsymbol{y}_{i11}, \boldsymbol{y}_{i12})'$ be a $t \times p$ matrix of gene expression levels measured on the i^{th} pediatric patient, for $i = 1,\ldots,n_1$ and $\mathbf{Y}_{i2} = (\boldsymbol{y}_{i21}, \boldsymbol{y}_{i22})'$ be a $t \times p$ matrix of gene expression levels measured on the i^{th} adult patient, for $i = 1,\ldots,n_2$. The layout of data is shown in Table 5.2.

Since there are two time-point measurements, the within-subject contrast matrix A is of $rank(\mathbf{A}) = 1$. Therefore, the proposed tests of DMM and MMM analyses are the same, i.e. $T_1 = T_1^*$ and $T_2 = T_2^*$. To analyze the burn injury time course data, only the two proposed tests in DMM analysis, T_1 and T_2, were applied to detect the different expression levels of the gene sets affected by the age, time and interaction factors for each of the 210 gene sets in the three categories.

Table 5.2 Burn Injury Time Course Data

Treatment Group (j)	Subject (i)	Response Matrix $\mathbf{Y}'_{ij}$		Condition (Time) 1	2
1	1	$\mathbf{Y}'_{11}$	=	$(\boldsymbol{y}_{111}$	$\boldsymbol{y}_{112})$
	2	$\mathbf{Y}'_{21}$	=	$(\boldsymbol{y}_{211}$	$\boldsymbol{y}_{212})$
	$\vdots$	$\vdots$		$\vdots$	$\vdots$
	n_1 (=26)	$\mathbf{Y}'_{n_1 1}$	=	$(\boldsymbol{y}_{n_1 11}$	$\boldsymbol{y}_{n_1 12}$
2	1	$\boldsymbol{Y}'_{12}$	=	$(\boldsymbol{y}_{121}$	$\boldsymbol{y}_{122})$
	2	$\mathbf{Y}'_{22}$	=	$(\boldsymbol{y}_{221}$	$\boldsymbol{y}_{222})$
	$\vdots$	$\vdots$		$\vdots$	$\vdots$
	n_2 (=31)	$\mathbf{Y}'_{n_2 2}$	=	$(\boldsymbol{y}_{n_1 21}$	$\boldsymbol{y}_{n_2 22})$

The DMM in (2.2) for the $n \times pt$ matrix of gene expression levels, denoted by $\mathbf{Y}$, for each gene set consisting of p genes is

$$\mathbf{Y} = \mathbf{XB} + \mathbf{U}. \tag{5.1}$$

The layouts of the $\mathbf{Y}$, $\mathbf{X}$ and $\mathbf{B}$ matrices of each gene set are as follows:

$$\mathbf{Y}_{(n \times 2p)} = \begin{bmatrix} \boldsymbol{y}'_{11} \\ \boldsymbol{y}'_{21} \\ \vdots \\ \boldsymbol{y}'_{n_1 1} \\ \hline \boldsymbol{y}'_{12} \\ \boldsymbol{y}'_{22} \\ \vdots \\ \boldsymbol{y}'_{n_2 2} \end{bmatrix} = \left[\begin{array}{cc:cc:c:cc} y_{111}^{(1)} & y_{112}^{(1)} & y_{111}^{(2)} & y_{112}^{(2)} & \cdots & y_{111}^{(p)} & y_{112}^{(p)} \\ y_{211}^{(1)} & y_{212}^{(1)} & y_{211}^{(2)} & y_{212}^{(2)} & \cdots & y_{211}^{(p)} & y_{212}^{(p)} \\ \vdots & \vdots & \vdots & \vdots & & \vdots & \vdots \\ y_{n_1 11}^{(1)} & y_{n_1 12}^{(1)} & y_{n_1 11}^{(2)} & y_{n_1 12}^{(2)} & \cdots & y_{n_1 11}^{(p)} & y_{n_1 12}^{(p)} \\ \hdashline y_{121}^{(1)} & y_{122}^{(1)} & y_{121}^{(2)} & y_{122}^{(2)} & \cdots & y_{121}^{(p)} & y_{122}^{(p)} \\ y_{221}^{(1)} & y_{222}^{(1)} & y_{221}^{(2)} & y_{222}^{(2)} & \cdots & y_{221}^{(p)} & y_{222}^{(p)} \\ \vdots & \vdots & \vdots & \vdots & & \vdots & \vdots \\ y_{n_2 21}^{(1)} & y_{n_2 22}^{(1)} & y_{n_2 21}^{(2)} & y_{n_2 22}^{(2)} & \cdots & y_{n_2 21}^{(p)} & y_{n_2 22}^{(p)} \end{array} \right],$$

$$\mathbf{X}_{n\times 2} = \begin{bmatrix} \mathbf{1}_{n_1} & \mathbf{0} \\ \mathbf{0} & \mathbf{1}_{n_2} \end{bmatrix},$$

$$\mathbf{B}_{(2\times 2p)} = \begin{bmatrix} \boldsymbol{\mu}_1' \\ \boldsymbol{\mu}_2' \end{bmatrix} = \left[\begin{array}{cc|cc|c|cc} \mu_{11}^{(1)} & \mu_{12}^{(1)} & \mu_{11}^{(2)} & \mu_{12}^{(2)} & & \mu_{11}^{(p)} & \mu_{12}^{(p)} \\ \mu_{21}^{(1)} & \mu_{22}^{(1)} & \mu_{21}^{(2)} & \mu_{22}^{(2)} & & \mu_{21}^{(1)} & \mu_{22}^{(1)} \end{array}\right].$$

Three null hypotheses for testing the interaction, age and time effects are as follows:

H_{01} : the p average gene expressions of each gene set in each GO category are parallel

H_{02} : the p average gene expressions of each gene set in each GO category are not differentially expressed among the age groups

H_{03} : the p average gene expressions of each gene set in each GO category are not differentially expressed over time

The Multivariate General Linear Hypothesis for testing the age × time interaction, age and time effects for each gene set is

$$H : \mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{0}, \tag{5.2}$$

and the contrast matrices $\mathbf{C}$ and $\mathbf{A}$, satisfying $\mathbf{A}'\mathbf{A} = 1$, are defined as

$$\mathbf{C} = \begin{bmatrix} 1 & -1 \end{bmatrix},\ \mathbf{A} = \begin{bmatrix} 1/\sqrt{2} \\ -1/\sqrt{2} \end{bmatrix},\quad \text{for the } H_{01}\text{, age} \times \text{time effect test},$$

$$\mathbf{C} = \begin{bmatrix} 1 & -1 \end{bmatrix},\ \mathbf{A} = \begin{bmatrix} 1/\sqrt{2} \\ 1/\sqrt{2} \end{bmatrix},\quad \text{for the } H_{02}\text{, age effect test, and}$$

$$\mathbf{C} = \begin{bmatrix} \frac{n_1}{n} & \frac{n_2}{n} \end{bmatrix} = \begin{bmatrix} \frac{26}{57} & \frac{31}{57} \end{bmatrix},\ \mathbf{A} = \begin{bmatrix} 1/\sqrt{2} \\ -1/\sqrt{2} \end{bmatrix},\quad \text{for the } H_{03}\text{, time effect test.}$$

Therefore, the multivariate hypotheses (5.2) for H_{01}, H_{02}, H_{03} are stated as

$$H_{01} : \begin{bmatrix} \frac{(\mu_{11}^{(1)} - \mu_{12}^{(1)}) - (\mu_{21}^{(1)} - \mu_{22}^{(1)})}{\sqrt{2}} & \cdots & \frac{(\mu_{11}^{(p)} - \mu_{12}^{(p)}) - (\mu_{21}^{(p)} - \mu_{22}^{(p)})}{\sqrt{2}} \end{bmatrix} = \mathbf{0}_{1\times p},$$

$$H_{02} : \begin{bmatrix} \frac{\sum_{k=1}^{2} \mu_{1k}^{(1)} - \sum_{k=1}^{2} \mu_{2k}^{(1)}}{\sqrt{2}} & \frac{\sum_{k=1}^{2} \mu_{1k}^{(2)} - \sum_{k=1}^{2} \mu_{2k}^{(2)}}{\sqrt{2}} & \cdots & \frac{\sum_{k=1}^{2} \mu_{1k}^{(p)} - \sum_{k=1}^{2} \mu_{2k}^{(p)}}{\sqrt{2}} \end{bmatrix} = \mathbf{0}_{1\times p},$$

$$H_{03}:\left[\begin{array}{cccc}\dfrac{\sum_{j=1}^{g}(\mu_{j1}^{(1)}-\mu_{j2}^{(1)})}{\sqrt{2}} & \dfrac{\sum_{j=1}^{g}(\mu_{j1}^{(2)}-\mu_{j2}^{(2)})}{\sqrt{2}} & \cdots & \dfrac{\sum_{j=1}^{g}(\mu_{j1}^{(2)}-\mu_{j2}^{(2)})}{\sqrt{2}}\end{array}\right]=\mathbf{0}_{1\times p}.$$

The $p\times p$ SSCP matrices due to error and the hypothesis, $\mathbf{S}_e$ and $\mathbf{S}_h$, for each gene set, are calculated by

$$\mathbf{S}_e=(\mathbf{I}_p\otimes\mathbf{A})'\mathbf{Y}'[\mathbf{I}_n-\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}']\mathbf{Y}(\mathbf{I}_p\otimes\mathbf{A}) \tag{5.3}$$

and
$$\mathbf{S}_h=(\mathbf{C}\hat{\mathbf{B}}(\mathbf{I}_p\otimes\mathbf{A}))'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}\mathbf{C}\hat{\mathbf{B}}(\mathbf{I}_p\otimes\mathbf{A}), \tag{5.4}$$

where $\hat{\mathbf{B}}=(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}$. Using the $\mathbf{S}_h$ and $\mathbf{S}_e$ matrices, the proposed tests T_1 and T_2 for testing hypothesis (5.2) are calculated as

$$T_1=\frac{v_e\ tr(\mathbf{S}_h)}{v_h\ tr(\mathbf{S}_e)} \tag{5.5}$$

and
$$T_2=\left\{2v_h\hat{a}_2\left(1+\frac{v_h}{v_e}\right)\right\}^{-1/2}\frac{1}{\sqrt{p}}\left[tr(\mathbf{S}_h)-\frac{v_h}{v_e}tr(\mathbf{S}_e)\right], \tag{5.6}$$

where $v_e=n-g=55$, $v_h=1$ and

$$\hat{a}_1=\frac{tr(\mathbf{S}_e)}{v_e p}, \tag{5.7}$$

$$\hat{a}_2=\frac{1}{(v_e-1)(v_e+2)p}\left[tr(\mathbf{S}_e^2)-\frac{1}{v_e}(tr(\mathbf{S}_e))^2\right], \tag{5.8}$$

$$\hat{b}=\frac{\hat{a}_2}{(\hat{a}_1)^2}. \tag{5.9}$$

At the 5% significance level, the unadjusted p-values of the proposed test T_1 are calculated using the upper cumulative F distribution with $\lfloor v_h\hat{d}\rfloor$ and $\lfloor v_e\hat{d}\rfloor$ degrees of freedom, $1-F(T_1,\lfloor v_h\hat{d}\rfloor,\lfloor v_e\hat{d}\rfloor)$, where $\hat{d}=p\hat{a}_1^2/\hat{a}_2$, and those of the proposed test T_2 are calculated by $1-\mathbb{N}(T_2)$, where $\mathbb{N}(z)$ is a cumulative standard normal distribution. The adjusted p-values for multiple testing corrections are derived from 70 statistical tests in the BP category, 76 statistical tests in the CC category and 64 statistical tests in the MF category to control FDR at the 5% level. If the FDR adjusted p-value of each gene set is less than 0.05, the null hypothesis (5.2) is rejected.

5.2.4 Numerical Example of analysis of each gene set

Each gene set in the three GO categories was analyzed by DMM analysis. To give an example of the data analysis, the first set of genes in the BP category, defined in GO terms as GO:0000079 (*regulation of cyclin-dependent protein kinase activity*), were selected. The data of this example are 71 gene expression levels of blood samples from the 26 pediatric and 31 adult patients at two time points after severe burn injury.

The three null hypotheses of testing the interaction, age and time effects are as follows:

H_{01}: 71 average gene expression profiles of the *regulation of cyclin-dependent protein kinase activity* gene set in the BP category are parallel.

H_{02}: 71 average gene expressions of the *regulation of cyclin-dependent protein kinase activity* gene set in the BP category are not differentially expressed between age groups.

H_{03}: 71 average gene expressions of the *regulation of cyclin-dependent protein kinase activity* gene set in the BP category are not differentially expressed over time.

For each test for effect, the 71×71 SSCP matrices due to error and the hypothesis, $\mathbf{S}_e$ and $\mathbf{S}_h$, of this gene set were calculated by (5.3) and (5.4) and the traces of these matrices obtained. The consistent estimators, $\hat{a}_1$, $\hat{a}_2$ and $\hat{b}$, are respectively calculated by (5.7), (5.8) and (5.9). The proposed tests, T_1 and T_2, and the p-values of the tests were calculated in the testing of the interaction, age and time effect matrices defined in (5.5) and (5.6).

To test H_{01} (the age × time effect), $tr(\mathbf{S}_e) =$ 64,157,238, $tr(\mathbf{S}_h) =$ 297,221.27, $\hat{a}_1 =$ 16,429.5103, $\hat{a}_2 =$ 6,809,442,590 and $\hat{b} =$ 0.03964 were calculated, followed by

$$T_1 = \frac{v_e \; tr(\mathbf{S}_h)}{v_h \; tr(\mathbf{S}_e)}$$

$$= \frac{(55)(297{,}221.27)}{(1)(64{,}157{,}238)} = 0.25,$$

$$T_2 = \left\{ 2v_h \hat{a}_2 \left(1 + \frac{v_h}{v_e} \right) \right\}^{-1/2} \frac{1}{\sqrt{p}} \left[tr(\mathbf{S}_h) - \frac{v_h}{v_e} tr(\mathbf{S}_e) \right],$$

$$= \left\{ 2(1)(6{,}809{,}442{,}590) \left(1 + \frac{1}{55} \right) \right\}^{-1/2} \frac{1}{\sqrt{71}} \left[(297{,}221.27) - \frac{1}{55}(64{,}157{,}238) \right]$$

$$= \frac{1}{117{,}745.59} \frac{-869{,}273.97}{8.426} = -0.876 .$$

The p-value of T_1 is $1 - F(T_1, \lfloor v_h \hat{d} \rfloor, \lfloor v_e \hat{d} \rfloor)$, where $\hat{d} = p\hat{b} = (71)(0.039640)$ $= 2.814$. The degrees of freedom are $v_h \hat{d} = 2.814$ and $v_e \hat{d} = (55)(2.814) = 154.77$, and then $P(T_1 > 0.25) = 1 - F(0.25, 8, 154) = 0.8458 > 0.05$. Therefore, the null hypothesis H_{01} is not rejected.

The p-value of T_2 is $P(T_2 > -0.876) = 1 - \mathbb{N}(-0.876) = 0.8095 > 0.05$, so the null hypothesis H_{01} is not rejected.

To test H_{02} (the age effect), $tr(\mathbf{S}_e) = 127{,}792{,}271$, $tr(\mathbf{S}_h) = 2{,}172{,}514.2$, $\hat{a}_1 =$ 32,725.294, $\hat{a}_2 =$ 26,770,108,472 and $\hat{b} =$ 0.040005 were calculated, followed by

$$T_1 = \frac{v_e \; tr(\mathbf{S}_h)}{v_h \; tr(\mathbf{S}_e)}$$

$$= \frac{(55)(2{,}172{,}514.2)}{(1)(127{,}792{,}271)} = 0.935,$$

$$T_2 = \left\{ 2v_h \hat{a}_2 \left(1 + \frac{v_h}{v_e} \right) \right\}^{-1/2} \frac{1}{\sqrt{p}} \left[tr(\mathbf{S}_h) - \frac{v_h}{v_e} tr(\mathbf{S}_e) \right],$$

$$= \left\{ 2(1)(26{,}770{,}108{,}472) \left(1 + \frac{1}{55} \right) \right\}^{-1/2} \frac{1}{\sqrt{71}} \left[(2{,}172{,}514.2) - \frac{1}{55}(127{,}792{,}271) \right]$$

$$= \frac{1}{233{,}460.79} \frac{-150{,}981.64}{8.426} = -0.076 .$$

The p-value of T_1 is $1-F(T_1,\lfloor v_h\hat{d}\rfloor,\lfloor v_e\hat{d}\rfloor)$, where $\hat{d}=p\hat{b}=(71)(0.040005)$ $=2.840$. The degrees of freedom are $v_h\hat{d}=2.840$ and $v_e\hat{d}=(55)(2.840)=156.2$, and then $P(T_1>0.94)=1-F(0.94,2,156)=0.4214>0.05$. Therefore, the null hypothesis H_{02} is not rejected.

The p-value of T_2 is $P(T_2>-0.076)=1-\mathbb{N}(-0.076)=0.5306>0.05$, so the null hypothesis H_{02} is not rejected.

To test H_{03} (the time effect), $tr(\mathbf{S}_e)=$ 64,157,238, $tr(\mathbf{S}_h)=$ 376,028.56, $\hat{a}_1=16{,}429.5103$, $\hat{a}_2=$ 6,809,442,590 and $\hat{b}=$ 0.03964 were calculated, followed by

$$T_1=\frac{v_e\ tr(\mathbf{S}_h)}{v_h\ tr(\mathbf{S}_e)}$$

$$=\frac{(55)(376{,}028.56)}{(1)(64{,}157{,}238)}=0.32,$$

$$T_2=\left\{2v_h\hat{a}_2\left(1+\frac{v_h}{v_e}\right)\right\}^{-1/2}\frac{1}{\sqrt{p}}\left[tr(\mathbf{S}_h)-\frac{v_h}{v_e}tr(\mathbf{S}_e)\right]$$

$$=\left\{2(1)(6{,}809{,}442{,}590)\left(1+\frac{1}{55}\right)\right\}^{-1/2}\frac{1}{\sqrt{71}}\left[(376{,}028.56)-\frac{1}{55}(64{,}157{,}238)\right]$$

$$=\frac{1}{117{,}745.59}\frac{-790{,}466.676}{8.426}=-0.80.$$

The p-value of T_1 is $1-F(T_1,\lfloor v_h\hat{d}\rfloor,\lfloor v_e\hat{d}\rfloor)$, where $\hat{d}=p\hat{b}=(71)(0.039640)$ $=2.814$. The degrees of freedom are $v_h\hat{d}=2.814$ and $v_e\hat{d}=(55)(2.814)=154.77$, and then $P(T_1>0.32)=1-F(0.32,8,154)=0.7965>0.05$. Therefore, the null hypothesis H_{03} is not rejected.

The p-value of T_2 is $P(T_2>-0.80)=1-\mathbb{N}(-0.80)=0.7872>0.05$, so the null hypothesis H_{03} is not rejected.

From the results of the three hypotheses tests on one gene set, 71 average gene expression profiles of the *regulation of cyclin-dependent protein kinase activity* gene set in the BP category are parallel and are not differentially expressed between age groups or over time.

The other gene sets were analogously analyzed using the DMM analysis. The results of the DMM analyses for each of the 70 gene sets in the BP category, 76 gene sets in the CC category and 64 gene sets in the MF category are shown in the next section. The adjusted p-values for multiple testing corrections were derived to control FDR at 5% level.

5.3 The Results of the Multiple Tests in the Analysis of Burn Injury Data

5.3.1 Significant Differential Gene Expressions in the BP Categories

The results of testing the age × time, age and time effects for each of the 70 gene sets in the BP category are shown in Tables 5.3 - 5.5. From both of the T_1 and T_2 tests, it was found that there were 10 gene sets in the BP group that were significantly differentially expressed over the age × time effect, 49 gene sets differentially expressed by the age group and 54 gene sets differentially expressed over time.

The gene sets in the BP category which were significantly differentially expressed over the age × time interaction are classified as follows: regulation (including *regulation of cell growth*), transcription (including *transcription--regulation of transcription, DNA-dependent*), metabolic processes (including *lipid metabolic process*, *metabolic process*, *ATP biosynthetic process*) and transport (including *transport*, *transport--transport*, *negative regulation of transcription from RNA polymerase II promoter*, *intracellular protein transport*, *transport--ion transport*)**.**

The gene sets in the BP category which were significantly differentially expressed by the age effect are classified as follows: transport (including *transport--transport*, *transport—ion transport*, *transport--intracellular protein transport*), metabolic and cellular processes (including *cell adhesion, angiogenesis, carbohydrate metabolic process*, *metabolic process*), transcription (including *negative regulation of transcription from RNA polymerase II promoter*, *regulation of transcription*, *transcription*, *DNA-dependent*) and genetic information (including *protein folding*, *mRNA processing*).

The gene sets in the BP category which were significantly differentially expressed over time are classified as follows: transduction (including *transduction*, *small GTPase mediated signal transduction*), metabolic process (including *lipid metabolic process*, *metabolic process*), transport (including *intracellular protein transport, transport-- transport*, *transport--ion transport*), transcription (including *transcription--regulation of transcription, DNA-dependent*), cell proliferation and genetic information (including *multicellular organismal development*, *cell cycle*, *nuclear mRNA splicing*, *via spliceosome*), and stress response (including *immune response*, *chemotaxis*).

Table 5.3 Significant Differential Gene Expression in the BP Category over the Age × Time Effect Test in Burn Injury Patients

BP Category	Description	Size (p)	Age × Time Effect					
			T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0000079	regulation of cyclin-dependent protein kinase activity	71	0.25	0.8458	0.9109	-0.88	0.8095	0.8586
GO:0000082	G1/S transition of mitotic cell cycle	101	0.18	0.8502	0.8883	-0.85	0.8012	0.8628
GO:0000122	negative regulation of transcription from RNA polymerase II promoter	463	1.91*	0.0002	0.0012	4.48*	3.80E-06	2.95E-05
GO:0000165	MAPKKK cascade	93	1.79	0.1122	0.2619	1.26	0.1039	0.2424
GO:0000187	activation of MAPK activity	100	1.37	0.2547	0.4245	0.29	0.3852	0.5737
GO:0000226	microtubule cytoskeleton organization	75	0.46	0.8481	0.8995	-0.96	0.8302	0.8674
GO:0000398	nuclear mRNA splicing, via spliceosome	289	1.20	0.2723	0.4236	0.51	0.3034	0.4827
GO:0001501	skeletal system development	275	1.67	0.1397	0.2963	1.07	0.1432	0.3038
GO:0001503	ossification	98	0.11	0.8009	0.8899	-0.70	0.7588	0.8431
GO:0001525	angiogenesis	211	1.37	0.1351	0.2956	1.11	0.1325	0.2898
GO:0001558	regulation of cell growth	231	16.59*	5.23E-12	1.83E-10	21.97*	2.67E-107	1.87E-105
GO:0001666	response to hypoxia	142	0.41	0.6158	0.7184	-0.52	0.6977	0.8140
GO:0001701	in utero embryonic development	110	1.43	0.1779	0.3366	0.87	0.1916	0.3626
GO:0005975	carbohydrate metabolic process	423	0.74	0.8800	0.9059	-1.13	0.8712	0.8968
GO:0006091	generation of precursor metabolites and energy	82	0.92	0.4876	0.6321	-0.14	0.5563	0.7347
GO:0006139	nucleobase-containing compound metabolic process	128	0.84	0.5265	0.6465	-0.25	0.6000	0.7499
GO:0006260	DNA replication	212	1.18	0.3053	0.4547	0.17	0.4323	0.6304
GO:0006281	DNA repair	228	2.06	0.0740	0.2466	1.62	0.0522	0.1739
GO:0006333	chromatin assembly or disassembly	85	0.60	0.5569	0.6721	-0.40	0.6572	0.7932
GO:0006334	nucleosome assembly	135	0.90	0.5255	0.6568	-0.21	0.5846	0.7578
GO:0006350 // GO:0006355	transcription // regulation of transcription, DNA-dependent // regulation of transcription, DNA-dependent	1183	5.08*	7.47E-16	5.23E-14	14.87*	2.61E-50	9.14E-49
GO:0006350 // GO:0006355 // GO:0006355	transcription // regulation of transcription, DNA-dependent //	416	1.75	0.0441	0.1716	1.94	0.0263	0.1024
GO:0006350 // GO:0006355 // GO:0006357	transcription // regulation of transcription, DNA-dependent // regulation of transcription from RNA polymerase II promoter	208	1.85	0.0288	0.1439	2.22	0.0131	0.0573
GO:0006350 // GO:0006355 // GO:0006366	transcription // regulation of transcription, DNA-dependent // transcription from RNA polymerase II promoter	163	2.02*	7.12E-07	1.25E-05	6.15*	3.81E-10	5.33E-09
GO:0006350 // GO:0006355 // GO:0007275	transcription // regulation of transcription, DNA-dependent // multicellular organismal development	158	2.63	0.0100	0.0635	3.11*	0.0009	0.0060
GO:0006350 // GO:0006355 // GO:0016578	transcription // regulation of transcription, DNA-dependent // chromatin modification	77	2.02	0.0295	0.1379	2.26	0.0120	0.0558
GO:0006350 // GO:0006355 // GO:0045449	transcription // regulation of transcription, DNA-dependent //	90	1.77	0.0705	0.2466	1.63	0.0517	0.1808

Table 5.3 (Continued)

BP Category	Description	Size (p)	Age × Time Effect T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0006355	regulation of transcription, DNA-dependent	309	1.28	0.1681	0.3361	0.95	0.1720	0.3541
GO:0006364	rRNA processing	156	0.73	0.4688	0.6192	-0.25	0.6001	0.7370
GO:0006396	RNA processing	125	1.79	0.1619	0.3333	0.87	0.1913	0.3720
GO:0006397	mRNA processing	232	1.16	0.2976	0.4528	0.44	0.3301	0.5135
GO:0006412	translation	616	0.71	0.5961	0.7073	-0.42	0.6639	0.7877
GO:0006457	protein folding	277	1.25	0.2582	0.4203	0.54	0.2943	0.4905
GO:0006461	protein complex assembly	138	0.52	0.6932	0.7955	-0.62	0.7333	0.8280
GO:0006464	protein modification process	365	2.31	0.0978	0.2632	1.37	0.0857	0.2306
GO:0006468	protein phosphorylation	945	1.77	0.0137	0.0800	2.59	0.0048	0.0279
GO:0006470	protein dephosphorylation	218	0.79	0.7125	0.8044	-0.62	0.7330	0.8411
GO:0006486	protein glycosylation	93	0.32	0.8057	0.8812	-0.81	0.7923	0.8666
GO:0006508	proteolysis	748	1.56	0.0970	0.2828	1.37	0.0850	0.2379
GO:0006511	ubiquitin-dependent protein catabolic process	750	1.13	0.3343	0.4875	0.30	0.3835	0.5835
GO:0006629	lipid metabolic process	428	1.80	NaN	NaN	NaN	NaN	NaN
GO:0006694	steroid biosynthetic process	72	1.97	0.0211	0.1137	2.44*	0.0074	0.0397
GO:0006754	ATP biosynthetic process	127	2.79*	0.0001	0.0009	5.28*	6.36E-08	7.42E-07
GO:0006810	transport	244	1.86	0.0036	0.0252	3.26*	0.0006	0.0039
GO:0006810 // GO:0006810	transport // transport	314	1.76*	0.0000	0.0001	5.21*	9.65E-08	9.65E-07
GO:0006810 // GO:0006811	transport // ion transport	696	1.53	0.0000	0.0002	4.71*	1.26E-06	1.10E-05
GO:0006810 // GO:0006886	transport // intracellular protein transport	213	1.04	0.4019	0.5742	0.16	0.4346	0.6208
GO:0006810 // GO:0015031	transport // protein transport	259	1.25	0.2102	0.3679	0.76	0.2239	0.4019
GO:0006886	intracellular protein transport	73	5.77*	4.29E-06	6.01E-05	8.57*	5.35E-18	1.25E-16
GO:0006897	endocytosis	130	1.63	0.0983	0.2548	1.37	0.0858	0.2224
GO:0006915	apoptosis	353	1.30	0.1773	0.3448	0.90	0.1843	0.3685
GO:0006928	apoptosis	133	0.89	0.4409	0.6052	-0.13	0.5520	0.7576
GO:0006935	chemotaxis	93	1.75	0.1312	0.2962	1.12	0.1320	0.2981
GO:0006950	response to stress	81	2.18	0.0789	0.2403	1.58	0.0574	0.1828
GO:0006952	defense response	120	1.84	0.1023	0.2470	1.34	0.0900	0.2251
GO:0006954	inflammatory response	89	0.87	0.5237	0.6665	-0.23	0.5917	0.7531
GO:0006955	immune response	430	1.20	0.2347	0.4006	0.67	0.2512	0.4289
GO:0007010	cytoskeleton organization	102	2.04	0.0439	0.1808	2.01	0.0223	0.0920
GO:0007018	microtubule-based movement	89	2.57	0.0347	0.1519	2.28	0.0112	0.0558
GO:0007049	cell cycle	340	1.23	0.2628	0.4181	0.53	0.2966	0.4828
GO:0007155	cell adhesion	735	1.24	0.1009	0.2523	1.31	0.0945	0.2282
GO:0007165	signal transduction	1305	2.60*	NaN	NaN	NaN	NaN	NaN
GO:0007186	G-protein coupled receptor protein signaling pathway	77	0.87	0.4392	0.6149	-0.14	0.5562	0.7487
GO:0007242	intracellular signaling cascade	129	1.90	0.0636	0.2344	1.72	0.0427	0.1572
GO:0007264	small GTPase mediated signal transduction	149	0.98	0.4683	0.6304	-0.05	0.5195	0.7273
GO:0007275	multicellular organismal development	389	1.23	0.2052	0.3780	0.79	0.2161	0.3980
GO:0007601	visual perception	77	1.78	0.0784	0.2495	1.55	0.0604	0.1838
GO:0008152	metabolic process	457	2.99*	2.08E-07	4.84E-06	7.50*	3.31E-14	5.79E-13
GO:0032313	regulation of Rab GTPase activity	84	1.39	0.2081	0.3736	0.72	0.2355	0.4121
GO:0055114	oxidation-reduction process	120	1.75	0.0973	0.2726	1.38	0.0837	0.2442

*significant at the FDR 0.05 level

Table 5.4 Significant Differential Gene Expression in the BP Category by the Age Effect Test in Burn Injury Patients

BP Category	Description	Size (p)	Age Effect					
			T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0000079	regulation of cyclin-dependent protein kinase activity	71	0.94	0.4214	0.4469	-0.08	0.5306	0.5543
GO:0000082	G1/S transition of mitotic cell cycle	101	2.76*	0.0444	0.0597	2.13*	0.0167	0.0238
GO:0000122	negative regulation of transcription from RNA polymerase II promoter	463	4.02*	2.19E-18	2.55E-17	14.64*	7.79E-49	6.82E-48
GO:0000165	MAPKKK cascade	93	1.97	0.0836	0.1009	1.52	0.0647	0.0781
GO:0000187	activation of MAPK activity	100	3.11	0.0697	0.0903	1.71	0.0433	0.0561
GO:0000226	microtubule cytoskeleton organization	75	1.95	0.0631	0.0834	1.73	0.0415	0.0548
GO:0000398	nuclear mRNA splicing, via spliceosome	289	4.24*	3.47E-08	1.35E-07	9.22*	1.54E-20	5.98E-20
GO:0001501	skeletal system development	275	2.18	0.0411	0.0587	2.08	0.0187	0.0256
GO:0001503	ossification	98	2.21	0.1350	0.1575	0.97	0.1669	0.1947
GO:0001525	angiogenesis	211	11.66*	1.34E-30	2.35E-29	31.42*	6.21E-217	2.17E-215
GO:0001558	regulation of cell growth	231	0.97	0.4309	0.4502	-0.05	0.5194	0.5509
GO:0001666	response to hypoxia	142	4.97*	0.0135	0.0210	3.56*	0.0002	0.0003
GO:0001701	in utero embryonic development	110	6.23*	3.18E-07	1.06E-06	9.98*	9.18E-24	4.02E-23
GO:0005975	carbohydrate metabolic process	423	5.76*	4.14E-29	5.79E-28	22.02*	9.59E-108	1.34E-106
GO:0006091	generation of precursor metabolites and energy	82	5.59*	0.0002	0.0004	6.66*	1.33E-11	3.32E-11
GO:0006139	nucleobase-containing compound metabolic process	128	2.26	0.0412	0.0577	2.10*	0.0179	0.0251
GO:0006260	DNA replication	212	2.59	0.0704	0.0896	1.70	0.0446	0.0567
GO:0006281	DNA repair	228	2.59*	0.0293	0.0437	2.41*	0.0080	0.0119
GO:0006333	chromatin assembly or disassembly	85	5.28*	0.0044	0.0074	4.53*	2.98E-06	5.34E-06
GO:0006334	nucleosome assembly	135	1.79	0.0428	0.0588	1.97*	0.0247	0.0332
GO:0006350// GO:0006355	transcription // regulation of transcription, DNA-dependent // regulation of transcription, DNA-dependent	1183	2.19*	0.0003	0.0007	4.41*	5.25E-06	9.18E-06
GO:0006350// GO:0006355// GO:0006355	transcription // regulation of transcription, DNA-dependent //	416	2.87*	0.0003	0.0006	4.93*	4.16E-07	8.32E-07
GO:0006350// GO:0006355// GO:0006357	transcription // regulation of transcription, DNA-dependent // regulation of transcription from RNA polymerase II promoter	208	3.06*	0.0002	0.0004	5.27*	6.96E-08	1.43E-07
GO:0006350// GO:0006355// GO:0006366	transcription // regulation of transcription, DNA-dependent // transcription from RNA polymerase II promoter	163	3.26*	4.45E-17	3.89E-16	12.88*	2.75E-38	2.14E-37
GO:0006350// GO:0006355// GO:0007275	transcription // regulation of transcription, DNA-dependent // multicellular organismal development	158	3.32*	0.0002	0.0004	5.41*	3.23E-08	7.07E-08
GO:0006350// GO:0006355// GO:0016578	transcription // regulation of transcription, DNA-dependent // chromatin modification	77	3.90*	3.16E-08	1.30E-07	8.93*	2.19E-19	8.06E-19
GO:0006350// GO:0006355// GO:0045449	transcription // regulation of transcription, DNA-dependent //	90	1.51	0.1242	0.1474	1.18	0.1192	0.1414

Table 5.4 (Continued)

BP Category	Description	Size (p)	Age Effect T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0006355	regulation of transcription, DNA-dependent	309	3.80*	7.62E-14	5.76E-13	12.15*	2.82E-34	1.75E-33
GO:0006364	rRNA processing	156	7.06*	0.0010	0.0017	6.22	2.48E-10	5.63E-10
GO:0006396	RNA processing	125	1.19*	0.3163	0.3309	0.23*	0.4090	0.4278
GO:0006397	mRNA processing	232	4.91*	1.32E-11	8.17E-11	12.19*	1.78E-34	1.21E-33
GO:0006412	translation	616	2.85*	0.0077	0.0119	3.34*	0.0004	0.0006
GO:0006457	protein folding	277	9.17*	4.40E-12	2.99E-11	16.51*	1.51E-61	1.71E-60
GO:0006461	protein complex assembly	138	3.91*	0.0052	0.0082	3.96*	3.69E-05	5.83E-05
GO:0006464	protein modification process	365	10.87*	1.58E-05	3.99E-05	10.54*	2.83E-26	1.48E-25
GO:0006468	protein phosphorylation	945	3.31*	3.68E-11	1.93E-10	10.11*	2.56E-24	1.16E-23
GO:0006470	protein dephosphorylation	218	3.37*	6.10E-07	1.89E-06	7.52*	2.67E-14	7.89E-14
GO:0006486	protein glycosylation	93	4.08*	0.0017	0.0029	4.71*	1.25E-06	2.30E-06
GO:0006508	proteolysis	748	3.96*	7.75E-08	2.77E-07	8.71*	1.52E-18	5.15E-18
GO:0006511	ubiquitin-dependent protein catabolic process	750	2.51*	0.0004	0.0007	4.60*	2.16E-06	3.86E-06
GO:0006629	lipid metabolic process	428	3.75	NaN	NaN	NaN	NaN	NaN
GO:0006694	steroid biosynthetic process	72	4.19*	1.95E-07	6.63E-07	8.60*	3.93E-18	1.22E-17
GO:0006754	ATP biosynthetic process	127	3.10*	2.31E-06	6.82E-06	6.86*	3.53E-12	9.24E-12
GO:0006810	transport	244	3.38*	1.47E-08	6.23E-08	8.64*	2.76E-18	8.95E-18
GO:0006810// GO:0006810	transport // transport	314	4.28*	8.10E-94	2.75E-92	35.76*	1.99E-280	1.35E-278
GO:0006810// GO:0006811	transport // ion transport	696	2.87*	2.86E-98	1.94E-96	31.02*	1.41E-211	3.20E-210
GO:0006810// GO:0006886	transport // intracellular protein transport	213	3.87*	1.36E-11	7.69E-11	11.02*	1.46E-28	8.29E-28
GO:0006810// GO:0015031	transport // protein transport	259	4.04*	3.13E-09	1.42E-08	9.75*	9.29E-23	3.71E-22
GO:0006886	intracellular protein transport	73	3.08*	0.0021	0.0034	4.15*	1.64E-05	2.66E-05
GO:0006897	endocytosis	130	4.08*	3.93E-06	1.07E-05	7.46*	4.47E-14	1.27E-13
GO:0006915	apoptosis	353	2.45*	0.0006	0.0011	4.36*	6.45E-06	1.07E-05
GO:0006928	apoptosis	133	2.39	0.0706	0.0858	1.69	0.0458	0.0556
GO:0006935	chemotaxis	93	1.54	0.1811	0.1986	0.82	0.2048	0.2246
GO:0006950	response to stress	81	1.62	0.1672	0.1864	0.89	0.1871	0.2086
GO:0006952	defense response	120	5.41*	0.0001	0.0003	6.70*	1.06E-11	2.67E-11
GO:0006954	inflammatory response	89	1.42	0.2247	0.2388	0.61	0.2696	0.2864
GO:0006955	immune response	430	3.27	3.39E-06	9.60E-06	6.87*	3.14E-12	8.53E-12
GO:0007010	cytoskeleton organization	102	3.49	0.0007	0.0012	4.90*	4.77E-07	9.02E-07
GO:0007018	microtubule-based movement	89	2.11	0.0770	0.0919	1.59	0.0555	0.0662
GO:0007049	cell cycle	340	3.45*	1.18E-05	3.10E-05	6.57*	2.47E-11	5.79E-11
GO:0007155	cell adhesion	735	5.50*	5.61E-47	1.27E-45	27.86*	4.35E-171	7.39E-170
GO:0007165	signal transduction	1305	3.38	NaN	NaN	NaN	NaN	NaN
GO:0007186	G-protein coupled receptor protein signaling pathway	77	0.62	0.5962	0.5962	-0.45	0.6742	0.6742
GO:0007242	intracellular signaling cascade	129	1.33	0.2134	0.2304	0.72	0.2360	0.2547
GO:0007264	small GTPase mediated signal transduction	149	3.14*	0.0001	0.0003	5.40*	3.29E-08	6.78E-08
GO:0007275	multicellular organismal development	389	3.68*	1.16E-10	5.65E-10	10.26*	5.23E-25	2.54E-24
GO:0007601	visual perception	77	3.93*	0.0002	0.0004	5.78*	3.69E-09	8.09E-09
GO:0008152	metabolic process	457	4.73*	3.18E-17	3.09E-16	15.11*	6.89E-52	6.70E-51
GO:0032313	regulation of Rab GTPase activity	84	2.59*	0.0165	0.0244	2.79*	0.0026	0.0039
GO:0055114	oxidation-reduction process	120	2.10*	0.0344	0.0488	2.18*	0.0145	0.0205

*significant at the FDR 0.05 level

Table 5.5 Significant Differential Gene Expression in the BP Category over the Time Effect Test in Burn Injury Patients

BP Category	Description	Size (p)	Time Effect					
			T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0000079	regulation of cyclin-dependent protein kinase activity	71	0.33	0.7965	0.8199	-0.80	0.7872	0.8103
GO:0000082	G1/S transition of mitotic cell cycle	101	7.52*	0.0005	0.0009	6.84*	3.89E-12	8.78E-12
GO:0000122	negative regulation of transcription from RNA polymerase II promoter	463	2.77*	6.40E-11	2.64E-10	9.52*	8.77E-22	2.46E-21
GO:0000165	MAPKKK cascade	93	0.47	0.7799	0.8149	-0.79	0.7859	0.8211
GO:0000187	activation of MAPK activity	100	2.71	0.0748	0.0988	1.63	0.0515	0.0680
GO:0000226	microtubule cytoskeleton organization	75	2.02	0.0761	0.0986	1.59	0.0563	0.0729
GO:0000398	nuclear mRNA splicing, via spliceosome	289	6.38*	4.76E-12	2.08E-11	14.01*	6.65E-45	2.74E-44
GO:0001501	skeletal system development	275	3.04*	0.0080	0.0116	3.43*	0.0003	0.0005
GO:0001503	ossification	98	2.15	0.1367	0.1679	0.95	0.1717	0.2073
GO:0001525	angiogenesis	211	2.03	0.0037	0.0057	3.38*	0.0004	0.0005
GO:0001558	regulation of cell growth	231	10.36*	2.15E-09	7.17E-09	16.48*	2.54E-61	1.27E-60
GO:0001666	response to hypoxia	142	0.70	0.4607	0.4886	-0.25	0.5984	0.6347
GO:0001701	in utero embryonic development	110	1.24	0.1839	0.2182	0.84	0.1997	0.2369
GO:0005975	carbohydrate metabolic process	423	2.99*	1.00E-09	3.69E-09	9.05*	6.97E-20	1.88E-19
GO:0006091	generation of precursor metabolites and energy	82	1.48*	0.1569	0.1894	0.97	0.1650	0.2026
GO:0006139	nucleobase-containing compound metabolic process	128	0.96	0.4064	0.4377	0.04	0.4845	0.5383
GO:0006260	DNA replication	212	1.18	0.3550	0.3945	0.02	0.4923	0.5385
GO:0006281	DNA repair	228	3.16*	0.0044	0.0066	3.94*	4.04E-05	6.42E-05
GO:0006333	chromatin assembly or disassembly	85	1.08	0.3755	0.4107	-0.01	0.5024	0.5411
GO:0006334	nucleosome assembly	135	4.23*	3.87E-05	8.47E-05	6.62*	1.79E-11	3.92E-11
GO:0006350 // GO:0006355	transcription // regulation of transcription, DNA-dependent // regulation of transcription, DNA-dependent	1183	7.27*	2.24E-28	2.24E-27	25.02*	1.96E-138	1.96E-137
GO:0006350 // GO:0006355 // GO:0006355	transcription // regulation of transcription, DNA-dependent //	416	2.54*	0.0004	0.0008	4.73*	1.12E-06	2.06E-06
GO:0006350 // GO:0006355 // GO:0006357	transcription // regulation of transcription, DNA-dependent // regulation of transcription from RNA polymerase II promoter	208	5.27*	2.38E-09	7.58E-09	10.92*	4.85E-28	1.62E-27
GO:0006350 // GO:0006355 // GO:0006366	transcription // regulation of transcription, DNA-dependent // transcription from RNA polymerase II promoter	163	3.58*	3.92E-21	3.05E-20	14.90*	1.54E-50	7.20E-50
GO:0006350 // GO:0006355 // GO:0007275	transcription // regulation of transcription, DNA-dependent // multicellular organismal development	158	5.07*	6.49E-06	1.57E-05	8.04*	4.43E-16	1.07E-15
GO:0006350 // GO:0006355 // GO:0016578	transcription // regulation of transcription, DNA-dependent // chromatin modification	77	4.62*	5.36E-07	1.50E-06	8.91*	2.58E-19	6.70E-19
GO:0006350 // GO:0006355 // GO:0045449	transcription // regulation of transcription, DNA-dependent //	90	8.96*	1.53E-13	7.66E-13	18.05*	4.20E-73	2.26E-72

Table 5.5 (Continued)

BP Category	Description	Size (p)	Time Effect					
			T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0006355	regulation of transcription, DNA-dependent	309	3.69*	2.73E-09	8.30E-09	9.60*	3.84E-22	1.12E-21
GO:0006364	rRNA processing	156	1.63	0.2151	0.2510	0.53	0.2985	0.3483
GO:0006396	RNA processing	125	12.01*	2.23E-06	5.79E-06	12.37*	1.84E-35	6.79E-35
GO:0006397	mRNA processing	232	2.60*	0.0002	0.0004	5.00*	2.89E-07	5.47E-07
GO:0006412	translation	616	2.58*	0.0328	0.0442	2.34*	0.0097	0.0134
GO:0006457	protein folding	277	2.61*	0.0044	0.0066	3.58*	0.0002	0.0003
GO:0006461	protein complex assembly	138	1.97	0.0944	0.1180	1.41	0.0789	0.0986
GO:0006464	protein modification process	365	4.53*	0.0133	0.0190	3.41*	0.0003	0.0005
GO:0006468	protein phosphorylation	945	2.54*	2.20E-05	5.14E-05	5.78*	3.64E-09	7.50E-09
GO:0006470	protein dephosphorylation	218	2.33*	0.0012	0.0021	4.01*	3.04E-05	5.07E-05
GO:0006486	protein glycosylation	93	7.78*	0.0001	0.0002	8.00*	6.39E-16	1.49E-15
GO:0006508	proteolysis	748	2.42*	0.0027	0.0043	3.75*	0.0001	0.0001
GO:0006511	ubiquitin-dependent protein catabolic process	750	1.98	0.0265	0.0364	2.33*	0.0098	0.0132
GO:0006629	lipid metabolic process	428	3.79*					
GO:0006694	steroid biosynthetic process	72	2.81*	0.0003	0.0005	5.08*	1.89E-07	3.68E-07
GO:0006754	ATP biosynthetic process	127	2.90*	2.26E-05	5.11E-05	6.03*	8.06E-10	1.71E-09
GO:0006810	transport	244	9.09*	1.67E-35	2.34E-34	29.98*	8.34E-198	1.95E-196
GO:0006810 // GO:0006810	transport // transport	314	4.32*	7.40E-43	2.59E-41	24.42*	5.56E-132	4.86E-131
GO:0006810 // GO:0006811	transport // ion transport	696	3.22*	1.06E-40	2.48E-39	20.99*	3.96E-98	3.08E-97
GO:0006810 // GO:0006886	transport // intracellular protein transport	213	1.98*	0.0009	0.0015	3.96*	3.70E-05	6.02E-05
GO:0006810 // GO:0015031	transport // protein transport	259	2.51*	0.0004	0.0008	4.54*	2.79E-06	5.00E-06
GO:0006886	intracellular protein transport	73	14.19*	3.38E-17	2.15E-16	26.46*	1.32E-154	1.54E-153
GO:0006897	endocytosis	130	4.73*	1.03E-06	2.78E-06	8.64*	2.79E-18	6.96E-18
GO:0006915	apoptosis	353	16.82	1.95E-46	1.37E-44	46.87*	0.00E+00	0.00E+00
GO:0006928	apoptosis	133	1.15	0.3073	0.3469	0.24	0.4045	0.4567
GO:0006935	chemotaxis	93	19.26*	4.46E-15	2.40E-14	27.21*	2.18E-163	3.06E-162
GO:0006950	response to stress	81	2.01	0.0814	0.1036	1.55	0.0608	0.0773
GO:0006952	defense response	120	3.69*	0.0034	0.0054	4.10*	2.06E-05	3.51E-05
GO:0006954	inflammatory response	89	7.25*	4.12E-08	1.20E-07	11.78*	2.34E-32	8.18E-32
GO:0006955	immune response	430	9.64*	1.10E-31	1.29E-30	29.15*	4.05E-187	7.09E-186
GO:0007010	cytoskeleton organization	102	8.04*	1.03E-09	3.60E-09	13.59*	2.33E-42	9.06E-42
GO:0007018	microtubule-based movement	89	8.07*	3.17E-06	7.91E-06	9.93*	1.56E-23	4.76E-23
GO:0007049	cell cycle	340	8.78*	3.48E-15	2.03E-14	19.00*	8.53E-81	5.43E-80
GO:0007155	cell adhesion	735	2.90*	3.66E-13	1.71E-12	10.71*	4.79E-27	1.52E-26
GO:0007165	signal transduction	1305	4.04*					
GO:0007186	G-protein coupled receptor protein signaling pathway	77	1.45	0.2326	0.2669	0.51	0.3064	0.3516
GO:0007242	intracellular signaling cascade	129	7.68*	4.80E-10	1.87E-09	14.12*	1.41E-45	6.17E-45
GO:0007264	small GTPase mediated signal transduction	149	18.15*	1.53E-36	2.69E-35	43.37*	0.00E+00	0.00E+00
GO:0007275	multicellular organismal development	389	6.30*	6.16E-20	4.31E-19	18.79*	4.69E-79	2.74E-78
GO:0007601	visual perception	77	3.66*	0.0003	0.0005	5.49*	1.98E-08	3.95E-08
GO:0008152	metabolic process	457	5.90*	1.45E-23	1.27E-22	20.69*	2.35E-95	1.64E-94
GO:0032313	regulation of Rab GTPase activity	84	2.14	0.0253	0.0354	2.44*	0.0073	0.0102
GO:0055114	oxidation-reduction process	120	3.13*	0.0024	0.0040	4.16*	1.58E-05	2.77E-05

*significant at the FDR 0.05 level

5.3.2 Significant Differential Gene Expressions in the CC Category

Tables 5.6 - 5.8 show the results of testing of the interaction, age and time effects for each of the gene sets in the CC category. The two proposed tests gave the number of gene sets in the CC category which were significantly differentially expressed over the age × time, age and time factors as 23, 55 and 69, respectively.

The gene sets in the CC category which were significant differentially expressed over age × time are classified as follows: membrane (including *membrane—integral to membrane*, *plasma membrane—integral to plasma*, *Golgi membrane*, *plasma membrane—membrane*), intracellular (including *intracellular—cytosol*, *endoplasmic reticulum*, *lysosome*, *cytoplasm—membrane*, *microtubule*, *nucleus*, *intermediate filament*, *cytoplasm—cytosol*, *nucleus—nucleus—transcription factor complex*, *nucleus—cytoplasm*, *cytoplasm—endosome*, *cytoplasm—cytosleleton*, *chromatin*, *intracellular—nucleus*, *proteasome complex*, *nucleus—transcription factor complex*) and cell fraction (including *membrane fraction*, *soluble fraction*).

The gene sets in the CC category which were significantly differentially expressed by age group are classified as follows: membrane (including *plasma membrane—membrane*, *integral to plasma membrane*, *Golgi membrane*), intracellular (including *cytoplasm—cytoplasm*, *cytoplasm—cytosol*, *intracellular—nucleus*, *mitochondrion*, *cytoplasm—cytoskeleton*, *cytoplasm—plasma membrane*, *nucleus—nucleus—nucleus*, *nucleosome*, *endoplasmic reticulum*, *nucleus—transcription factor complex*, *mitochodrion—mitochodrion*, *nucleus—cytoplasm*) and extracellular (including *extracellular—region-non-traceable author statement*, *extracellular—proteinaceous extracellular matrix*, *extracellular—plasma membrane*).

The gene sets in CC category which were significantly differentially expressed over time are classified as follows: membrane (including *membrane*, *plasma membrane—integral to plasma membrane*, *plasma membrane—plasma membrane*), intracellular (including *nucleus—nucleus—nucleolus*, *nucleus—nucleolus*, *nucleus—transcription factor complex*, *nucleus—spliceosome*, *nucleus*, *nucleus—nucleus pore*, *endosome, nucleus—nucleus—nucleoplasm*, *peroxisome*, *Golgi apparatus*, *nucleus—cytoplasm*, *cytoplasm—cytoplasm*, *mitochondrion—mitochondrion*, *chromosome,* *centromeric region*) and cell fraction (including *soluble fraction*, *membrane fraction*).

Table 5.6 Significant Differential Gene Expressions in the CC Category over Age × Time Effect Test in Burn Injury Patients

CC Category	Description	Size (p)	Age × Time Effect					
			T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0000119	mediator complex	75	0.67	0.5630	0.6209	-0.39	0.6511	0.7182
GO:0000139	Golgi membrane	739	1.97*	0.0071	0.0294	3.01*	0.0013	0.0055
GO:0000151	ubiquitin ligase complex	136	0.46	0.8312	0.8540	-0.91	0.8185	0.8296
GO:0000502	proteasome complex	76	3.55	0.0188	0.0565	2.96*	0.0015	0.0057
GO:0000775	chromosome, centromeric region	91	1.49	0.0893	0.1915	1.43	0.0771	0.1651
GO:0000785	chromatin	143	2.75*	0.0143	0.0466	2.93*	0.0017	0.0060
GO:0000786	nucleosome	130	1.22	0.2808	0.4129	0.46	0.3217	0.4731
GO:0001726	ruffle	124	0.05	0.8591	0.8707	-0.72	0.7634	0.7952
GO:0005576	extracellular region	659	0.95	0.4907	0.5662	-0.11	0.5444	0.6379
GO:0005576// GO:0005576	extracellular region//non-traceable author statement	684	1.03	0.4157	0.5111	0.14	0.4458	0.5765
GO:0005576// GO:0005578	extracellular region//proteinaceous extracellular matrix	489	1.19	0.2659	0.4155	0.55	0.2929	0.4673
GO:0005576// GO:0005615	extracellular region//extracellular space	495	1.05	0.3827	0.4865	0.07	0.4702	0.5782
GO:0005576// GO:0005624	extracellular region//membrane fraction	90	0.58	0.5627	0.6299	-0.42	0.6617	0.7192
GO:0005576// GO:0005737	extracellular region//cytoplasm	138	1.21	0.3037	0.4218	0.23	0.4096	0.5390
GO:0005576// GO:0005886	extracellular region// plasma membrane	227	0.85	0.6108	0.6639	-0.39	0.6503	0.7280
GO:0005576// GO:0016020	extracellular region//membrane	74	0.35	0.7113	0.7514	-0.65	0.7431	0.7850
GO:0005615	extracellular space	162	0.96	0.4551	0.5417	-0.07	0.5274	0.6279
GO:0005622	intracellular	636	2.44	0.0221	0.0637	2.56	0.0052	0.0150
GO:0005622// GO:0005622	Intracellular//intracellular	78	0.72	0.6354	0.6808	-0.48	0.6858	0.7348
GO:0005622// GO:0005624	Intracellular//membrane fraction	79	1.15	NaN	NaN	NaN	NaN	NaN
GO:0005622// GO:0005634	Intracellular//nucleus	1095	2.02	0.0175	0.0547	2.57*	0.0052	0.0155
GO:0005622// GO:0005634// GO:0005634	Intracellular//nucleus//nucleus	715	1.01	0.4377	0.5295	0.03	0.4880	0.5903
GO:0005622// GO:0005634// GO:0005737	Intracellular//nucleus//cytoplasm	209	1.63	0.1544	0.2968	0.97	0.1655	0.3182
GO:0005622// GO:0005737	Intracellular//cytoplasm	516	1.40	0.2215	0.3955	0.64	0.2602	0.4539
GO:0005622// GO:0005739	Intracellular//mitochondrion	108	0.82	0.4614	0.5407	-0.20	0.5773	0.6661
GO:0005622// GO:0005829	Intracellular//cytosol	131	1.82*	2.95E-64	2.21E-62	20.89*	3.51E-97	1.32E-95

Table 5.6 (Continued)

CC Category	Description	Size (p)	Age × Time Effect T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0005622// GO:0005886	Intracellular//plasma membrane	88	0.53	0.8622	0.8622	-1.02	0.8455	0.8455
GO:0005624	membrane fraction	764	1.87*	1.03E-10	1.29E-09	7.91*	1.25E-15	1.17E-14
GO:0005625	soluble fraction	224	1.56	0.0270	0.0723	2.16*	0.0153	0.0397
GO:0005634	nucleus	1782	1.81*	4.99E-08	4.68E-07	6.54*	3.16E-11	2.63E-10
GO:0005634// GO:0005634	nucleus//nucleus	636	1.75*	0.0071	0.0281	2.89*	0.0019	0.0065
GO:0005634// GO:0005634// GO:0005634	nucleus//nucleus//nucleus	489	1.04	0.4126	0.5157	0.13	0.4500	0.5721
GO:0005634// GO:0005634// GO:0005654	nucleus//nucleus//nucleoplasm	210	1.25	0.2489	0.4148	0.59	0.2779	0.4632
GO:0005634// GO:0005634// GO:0005667	nucleus//nucleus//transcription factor complex	81	4.56*	0.0001	0.0007	6.40*	8.00E-11	6.00E-10
GO:0005634// GO:0005634// GO:0005681	nucleus//nucleus//spliceosome	107	1.94	0.0606	0.1420	1.76	0.0389	0.0913
GO:0005634// GO:0005634// GO:0005730	nucleus//nucleus//nucleolus	180	1.53	0.1016	0.2117	1.34	0.0908	0.1892
GO:0005634// GO:0005634// GO:0005737	nucleus//nucleus//cytoplasm	627	1.26	0.2048	0.3746	0.78	0.2175	0.4079
GO:0005634// GO:0005643	nucleus//nuclear pore	103	1.18	0.3165	0.4239	0.32	0.3762	0.5225
GO:0005634// GO:0005654	nucleus//nucleoplasm	271	1.24	0.2663	0.4076	0.52	0.3032	0.4738
GO:0005634// GO:0005667	nucleus//transcription factor complex	98	2.29	0.0351	0.0908	2.21*	0.0134	0.0358
GO:0005634// GO:0005681	nucleus//spliceosome	140	1.63	0.1053	0.2135	1.31	0.0946	0.1918
GO:0005634// GO:0005730	nucleus//nucleolus	344	1.74	0.0807	0.1833	1.53	0.0636	0.1445
GO:0005634// GO:0005737	nucleus//cytoplasm	1625	1.66*	0.0001	0.0008	4.31*	0.0000	4.02E-05
GO:0005737	cytoplasm	1090	1.23	0.2516	0.4015	0.59	0.2786	0.4543
GO:0005737// GO:0005737	cytoplasm//cytoplasm	702	1.67*	0.0054	0.0240	2.97*	0.0015	0.0059
GO:0005737// GO:0005739	cytoplasm//mitochondrion	249	3.69*	0.0002	0.0012	5.55*	1.41E-08	8.79E-08
GO:0005737// GO:0005768	cytoplasm//endosome	84	3.95*	0.0002	0.0009	5.83*	2.79E-09	1.90E-08
GO:0005737// GO:0005783	cytoplasm//endoplasmic reticulum	94	0.54	0.7720	0.8042	-0.78	0.7814	0.8028
GO:0005737// GO:0005794	cytoplasm//Golgi apparatus	108	1.21	0.2909	0.4195	0.42	0.3363	0.4850
GO:0005737// GO:0005829	cytoplasm//cytosol	234	2.32*	0.0001	0.0005	5.12*	1.53E-07	8.80E-07
GO:0005737// GO:0005856	cytoplasm//cytoskeleton	488	1.62*	0.0123	0.0419	2.58*	0.0049	0.0154

Table 5.6 (Continued)

CC Category	Description	Size (p)	Age × Time Effect T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0005737// GO:0005886	cytoplasm//plasma membrane	340	1.75	0.0426	0.1066	1.96	0.0250	0.0626
GO:0005737// GO:0016020	cytoplasm//membrane	150	7.47*	1.17E-11	1.75E-10	14.71*	2.89E-49	3.61E-48
GO:0005739	mitochondrion	208	2.63*	0.0003	0.0014	4.80*	8.13E-07	4.36E-06
GO:0005739	mitochondrion	208	2.63*	0.0003	0.0014	4.80*	8.13E-07	4.36E-06
GO:0005739// GO:0005739	mitochondrion//mitochondrion	338	1.23	0.2278	0.3884	0.69	0.2458	0.4390
GO:0005739// GO:0005741	mitochondrion//mitochondrial outer membrane	73	1.18	0.3131	0.4269	0.34	0.3663	0.5183
GO:0005739// GO:0005743	mitochondrion//mitochondrial inner membrane	279	1.21	0.2774	0.4161	0.48	0.3140	0.4709
GO:0005739// GO:0005759	mitochondrion//mitochondrial matrix	77	0.74	0.5241	0.5955	-0.31	0.6217	0.7065
GO:0005764	lysosome	192	13.35*	3.13E-12	5.87E-11	19.93*	1.09E-88	2.04E-87
GO:0005768	endosome	109	3.21*	0.0106	0.0399	3.27*	0.0005	0.0024
GO:0005777	peroxisome	82	2.45	0.0243	0.0675	2.50*	0.0062	0.0171
GO:0005783	endoplasmic reticulum	904	8.23*	1.81E-19	4.53E-18	20.73*	8.72E-96	2.18E-94
GO:0005794	Golgi apparatus	273	1.26	0.2910	0.4118	0.31	0.3781	0.5155
GO:0005813	centrosome	97	1.10	0.3354	0.4337	0.10	0.4595	0.5744
GO:0005829	cytosol	297	1.88	0.0847	0.1869	1.50	0.0668	0.1474
GO:0005856	cytoskeleton	85	1.49	0.2276	0.3970	0.51	0.3060	0.4683
GO:0005874	microtubule	108	21.29*	3.24E-08	3.47E-07	19.59*	1.02E-85	1.53E-84
GO:0005882	intermediate filament	111	5.99*	1.68E-07	1.40E-06	10.07*	3.89E-24	4.17E-23
GO:0005886// GO:0005886	plasma membrane//plasma membrane	330	1.50	0.1415	0.2793	1.07	0.1421	0.2804
GO:0005886// GO:0005887	plasma membrane//integral to plasma	492	1.71*	0.0008	0.0037	3.75*	0.0001	0.0004
GO:0005886// GO:0016020	plasma membrane//membrane	965	1.56*	0.0109	0.0389	2.61*	0.0046	0.0149
GO:0005887	integral to plasma membrane	409	1.20	0.2506	0.4086	0.61	0.2722	0.4640
GO:0008076	voltage-gated potassium channel complex	98	1.53	0.1896	0.3556	0.77	0.2196	0.4017
GO:0016020	membrane	121	2.20	0.0598	0.1447	1.81*	0.0352	0.0852
GO:0016020// GO:0016021	membrane//integral to membrane	2239	5.75*	2.11E-35	7.92E-34	24.45*	2.63E-132	1.97E-130
GO:0016020// GO:0016021// GO:0016021	membrane//integral to membrane// integral to membrane	204	1.17	0.3216	0.4232	0.31	0.3796	0.5084

*significant at the FDR 0.05 level

Table 5.7 Significant Differential Gene Expressions in the CC Category by Age Effect Test in Burn Injury Patients

CC Category	Description	Size (p)	Age Effect					
			T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0000119	mediator complex	75	3.48*	0.0371	0.0497	2.39*	0.0085	0.0114
GO:0000139	Golgi membrane	739	2.94*	5.25E-07	1.77E-06	7.18*	3.56E-13	9.71E-13
GO:0000151	ubiquitin ligase complex	136	1.97	0.0581	0.0750	1.80*	0.0361	0.0466
GO:0000502	proteasome complex	76	0.74	0.4675	0.4675	-0.24	0.5962	0.5962
GO:0000775	chromosome, centromeric region	91	1.44	0.0629	0.0797	1.65	0.0499	0.0633
GO:0000785	chromatin	143	3.88*	0.0001	0.0003	5.85*	2.51E-09	5.40E-09
GO:0000786	nucleosome	130	5.85*	2.24E-08	9.34E-08	10.71*	4.37E-27	2.39E-26
GO:0001726	ruffle	124	1.08	0.3188	0.3328	0.06	0.4760	0.4898
GO:0005576	extracellular region	659	3.18*	3.66E-05	0.0001	5.96*	1.29E-09	2.86E-09
GO:0005576//GO:0005576	extracellular region//non-traceable author statement	684	5.20*	6.12E-62	1.45E-60	31.40*	1.08E-216	7.68E-215
GO:0005576//GO:0005578	extracellular region//proteinaceous extracellular matrix	489	5.43*	5.20E-17	4.11E-16	15.93*	2.11E-57	2.50E-56
GO:0005576//GO:0005615	extracellular region//extracellular space	495	2.02	0.0756	0.0941	1.60	0.0545	0.0679
GO:0005576//GO:0005624	extracellular region//membrane fraction	90	5.05*	0.0102	0.0144	3.82*	0.0001	0.0001
GO:0005576//GO:0005737	extracellular region//cytoplasm	138	4.01*	0.0041	0.0067	4.16*	1.61E-05	2.73E-05
GO:0005576//GO:0005886	extracellular region// plasma membrane	227	4.65*	3.65E-10	1.99E-09	10.99*	2.17E-28	1.28E-27
GO:0005576//GO:0016020	extracellular region//membrane	74	1.98	0.1180	0.1374	1.20	0.1154	0.1343
GO:0005615	extracellular space	162	4.49*	0.0002	0.0004	6.03*	8.35E-10	1.91E-09
GO:0005622	intracellular	636	5.71*	3.30E-06	9.03E-06	8.64*	2.75E-18	9.78E-18
GO:0005622//GO:0005622	Intracellular//intracellular	78	3.57*	0.0025	0.0043	4.28*	9.39E-06	1.71E-05
GO:0005622//GO:0005624	Intracellular//membrane fraction	79	4.51*	0.0021	0.0039	4.74*	1.05E-06	2.01E-06
GO:0005622//GO:0005634	Intracellular//nucleus	1095	6.56*	2.57E-18	2.61E-17	18.07*	2.89E-73	4.11E-72
GO:0005622//GO:0005634//GO:0005634	Intracellular//nucleus//nucleus	715	4.93*	4.46E-11	2.64E-10	11.87*	8.02E-33	5.69E-32
GO:0005622//GO:0005634//GO:0005737	Intracellular//nucleus//cytoplasm	209	6.53*	1.15E-06	3.72E-06	9.63*	2.91E-22	1.22E-21
GO:0005622//GO:0005737	Intracellular//cytoplasm	516	3.77*	1.28E-05	3.14E-05	6.78*	6.18E-12	1.62E-11
GO:0005622//GO:0005739	Intracellular//mitochondrion	108	0.97	0.4018	0.4075	-0.03	0.5124	0.5197
GO:0005622//GO:0005829	Intracellular//cytosol	131	2.37*	0.0241	0.0328	2.49*	0.0065	0.0088
GO:0005622//GO:0005886	Intracellular//plasma membrane	88	5.15*	0.0002	0.0004	6.37*	9.73E-11	2.38E-10
GO:0005624	membrane fraction	764	3.23	NaN	NaN	NaN	NaN	NaN
GO:0005625	soluble fraction	224	3.23*	4.59E-22	6.52E-21	14.80*	7.37E-50	6.54E-49

Table 5.7 (Continued)

CC Category	Description	Size (p)	Age Effect T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0005634	nucleus	1782	3.28	NaN	NaN	NaN	NaN	NaN
GO:0005634// GO:0005634	nucleus//nucleus	636	4.50*	8.85E-49	1.57E-47	26.03*	1.14E-149	2.02E-148
GO:0005634// GO:0005634// GO:0005634	nucleus//nucleus//nucleus	489	2.87*	2.75E-09	1.39E-08	8.53*	7.29E-18	2.46E-17
GO:0005634// GO:0005634// GO:0005654	nucleus//nucleus//nucleoplasm	210	2.00*	0.0044	0.0071	3.24*	0.0006	0.0009
GO:0005634// GO:0005634// GO:0005667	nucleus//nucleus//transcription factor complex	81	2.58*	0.0089	0.0129	3.15*	0.0008	0.0012
GO:0005634// GO:0005634// GO:0005681	nucleus//nucleus//spliceosome	107	3.96*	2.63E-06	7.48E-06	7.51*	3.00E-14	8.53E-14
GO:0005634// GO:0005634// GO:0005730	nucleus//nucleus//nucleolus	180	1.40	0.1132	0.1362	1.25	0.1059	0.1274
GO:0005634// GO:0005634// GO:0005737	nucleus//nucleus//cytoplasm	627	2.75*	1.75E-06	5.19E-06	6.64*	1.62E-11	4.10E-11
GO:0005634// GO:0005643	nucleus//nuclear pore	103	1.78	8.33E-02	0.1020	1.50	0.0662	0.0810
GO:0005634// GO:0005654	nucleus//nucleoplasm	271	2.44*	0.0059	0.0091	3.32*	0.0005	0.0007
GO:0005634// GO:0005667	nucleus//transcription factor complex	98	7.44*	4.40E-08	1.64E-07	11.64*	1.30E-31	8.41E-31
GO:0005634// GO:0005681	nucleus//spliceosome	140	4.35*	1.43E-06	4.41E-06	8.03*	4.69E-16	1.51E-15
GO:0005634// GO:0005730	nucleus//nucleolus	344	3.46*	8.65E-05	0.0002	5.81*	3.14E-09	6.56E-09
GO:0005634// GO:0005737	nucleus//cytoplasm	1625	3.28	NaN	NaN	NaN	NaN	NaN
GO:0005737	cytoplasm	1090	2.40*	3.44E-06	9.06E-06	6.10*	5.31E-10	1.26E-09
GO:0005737// GO:0005737	cytoplasm//cytoplasm	702	4.65*	7.87E-67	2.79E-65	31.10*	1.03E-212	3.67E-211
GO:0005737// GO:0005739	cytoplasm//mitochondrion	249	2.35*	0.0064	0.0096	3.23*	0.0006	0.0009
GO:0005737// GO:0005768	cytoplasm//endosome	84	3.33*	0.0003	0.0005	5.26*	7.40E-08	1.46E-07
GO:0005737// GO:0005783	cytoplasm//endoplasmic reticulum	94	1.50	0.1744	0.1935	0.88	0.1904	0.2112
GO:0005737// GO:0005794	cytoplasm//Golgi apparatus	108	2.45*	0.0067	0.0100	3.25*	0.0006	0.0009
GO:0005737// GO:0005829	cytoplasm//cytosol	234	3.03*	8.38E-19	9.92E-18	13.20*	4.20E-40	3.31E-39
GO:0005737// GO:0005856	cytoplasm//cytoskeleton	488	2.46*	1.40E-14	9.91E-14	10.53*	3.17E-26	1.61E-25
GO:0005737// GO:0005886	cytoplasm//plasma membrane	340	4.31*	7.56E-09	3.35E-08	9.75*	8.98E-23	3.98E-22
GO:0005737// GO:0016020	cytoplasm//membrane	150	1.51	0.0498	0.0655	1.80*	0.0357	0.0470

Table 5.7 (Continued)

CC Category	Description	Size (p)	Age Effect T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0005739	mitochondrion	208	4.71*	8.04E-18	7.14E-17	15.38*	1.19E-53	1.21E-52
GO:0005739// GO:0005739	mitochondrion//mitochondrion	338	3.20*	1.99E-07	7.07E-07	7.71*	6.24E-15	1.93E-14
GO:0005739// GO:0005741	mitochondrion//mitochondrial outer membrane	73	3.27*	0.0022	0.0039	4.21*	1.29E-05	2.29E-05
GO:0005739// GO:0005743	mitochondrion//mitochondrial inner membrane	279	4.21*	3.74E-08	1.47E-07	9.17*	2.46E-20	9.69E-20
GO:0005739// GO:0005759	mitochondrion//mitochondrial matrix	77	1.98	0.1167	0.1381	1.21	0.1133	0.1340
GO:0005764	lysosome	192	5.10*	1.27E-05	0.0000	7.67*	8.85E-15	2.62E-14
GO:0005768	endosome	109	3.45*	0.0018	0.0034	4.39*	5.60E-06	1.05E-05
GO:0005777	peroxisome	82	3.10	0.0033	0.0055	3.92*	4.48E-05	0.0001
GO:0005783	endoplasmic reticulum	904	3.37*	6.76E-09	3.20E-08	8.85*	4.50E-19	1.68E-18
GO:0005794	Golgi apparatus	273	1.59	0.1843	0.2013	0.78	0.2164	0.2363
GO:0005813	centrosome	97	1.46	0.2340	0.2517	0.49	0.3135	0.3372
GO:0005829	cytosol	297	2.40*	0.0236	0.0328	2.51*	0.0061	0.0084
GO:0005856	cytoskeleton	85	1.35	0.2639	0.2797	0.37	0.3562	0.3774
GO:0005874	microtubule	108	2.00	0.1445	0.1655	0.95	0.1715	0.1933
GO:0005882	intermediate filament	111	2.40*	0.0050	0.0079	3.38*	0.0004	0.0006
GO:0005886	plasma membrane	330	2.74*	0.0014	0.0027	4.16*	1.61E-05	2.79E-05
GO:0005886// GO:0005886	plasma membrane//plasma membrane	492	2.95	NaN	NaN	NaN	NaN	NaN
GO:0005886// GO:0005887	plasma membrane//integral to plasma	965	2.58*	6.05E-84	4.30E-82	27.44*	4.40E-166	1.04E-164
GO:0005886// GO:0016020	plasma membrane//membrane	409	2.99*	9.78E-13	6.31E-12	10.50*	4.26E-26	2.02E-25
GO:0005887	integral to plasma membrane	98	1.63	0.1515	0.1707	0.99	0.1606	0.1839
GO:0008076	voltage-gated potassium channel complex	121	4.17*	0.0005	0.0010	5.42*	2.93E-08	5.94E-08
GO:0016020	membrane	2239	3.11	NaN	NaN	NaN	NaN	NaN
GO:0016020// GO:0016021	membrane//integral to membrane	204	1.13	0.3366	0.3464	0.29	0.3874	0.4045
GO:0016020// GO:0016021// GO:0016021	membrane//integral to membrane// integral to membrane	75	3.48*	0.0371	0.0497	2.39*	0.0085	0.0114

*significant at the FDR 0.05 level

Table 5.8 Significant Differential Gene Expressions in the CC Category over Time Effect Test in Burn Injury Patients

CC Category	Description	Size (p)	Time Effect					
			T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0000119	mediator complex	75	8.17*	0.0001	0.0001	8.46*	1.39E-17	3.15E-17
GO:0000139	Golgi membrane	739	2.70*	0.0001	0.0001	5.30*	5.92E-08	9.25E-08
GO:0000151	ubiquitin ligase complex	136	2.03	0.0638	0.0714	1.74*	0.0412	0.0461
GO:0000502	proteasome complex	76	3.85*	0.0131	0.0175	3.32*	0.0005	0.0006
GO:0000775	chromosome, centromeric region	91	5.06*	1.30E-10	4.89E-10	11.69*	7.00E-32	2.10E-31
GO:0000785	chromatin	143	2.15	0.0502	0.0588	1.94*	0.0265	0.0310
GO:0000786	nucleosome	130	1.40	0.1819	0.1921	0.86	0.1955	0.2066
GO:0001726	ruffle	124	0.27	0.6400	0.6486	-0.55	0.7092	0.7188
GO:0005576	extracellular region	659	2.46*	0.0045	0.0063	3.46*	0.0003	0.0004
GO:0005576// GO:0005576	extracellular region//non-traceable author statement	684	3.17*	2.30E-09	7.20E-09	8.92*	2.23E-19	5.23E-19
GO:0005576// GO:0005578	extracellular region//proteinaceous extracellular matrix	489	3.77*	7.00E-07	1.42E-06	7.82*	2.57E-15	4.82E-15
GO:0005576// GO:0005615	extracellular region//extracellular space	495	1.25	0.2880	0.3000	0.37	0.3574	0.3723
GO:0005576// GO:0005624	extracellular region//membrane fraction	90	4.34*	0.0149	0.0193	3.33*	0.0004	0.0006
GO:0005576// GO:0005737	extracellular region//cytoplasm	138	6.89*	0.0008	0.0013	6.28*	1.64E-10	2.73E-10
GO:0005576// GO:0005886	extracellular region// plasma membrane	227	2.48*	0.0021	0.0030	3.85*	0.0001	0.0001
GO:0005576// GO:0016020	extracellular region//membrane	74	3.76*	0.0254	0.0312	2.77*	0.0028	0.0036
GO:0005615	extracellular space	162	2.45*	0.0216	0.0270	2.58*	0.0050	0.0061
GO:0005622	intracellular	636	3.54*	0.0016	0.0023	4.51*	3.25E-06	4.87E-06
GO:0005622// GO:0005622	Intracellular//intracellular	78	6.96*	5.26E-07	1.13E-06	10.26*	5.54E-25	1.54E-24
GO:0005622// GO:0005624	Intracellular//membrane fraction	1095	2.25*	0.0071	0.0098	3.14*	0.0008	0.0011
GO:0005622// GO:0005634	Intracellular//nucleus	715	2.68*	0.0010	0.0016	4.27*	9.69E-06	1.43E-05
GO:0005622// GO:0005634// GO:0005634	Intracellular//nucleus//nucleus	209	2.20	0.0570	0.0647	1.85*	0.0324	0.0374
GO:0005622// GO:0005634// GO:0005737	Intracellular//nucleus//cytoplasm	516	2.47*	0.0308	0.0373	2.35*	0.0094	0.0114
GO:0005622// GO:0005737	Intracellular//cytoplasm	108	0.68	0.5326	0.5472	-0.34	0.6349	0.6523
GO:0005622// GO:0005739	Intracellular//mitochondrion	131	0.94	0.9499	0.9499	-1.62	0.9474	0.9474
GO:0005622// GO:0005829	Intracellular//cytosol	88	5.29*	3.78E-07	8.34E-07	9.23*	1.33E-20	3.21E-20
GO:0005622// GO:0005886	Intracellular//plasma membrane	764	3.20*	1.17E-38	1.75E-37	19.96*	6.00E-89	4.09E-88
GO:0005624	membrane fraction	224	3.97*	3.63E-12	1.70E-11	11.47*	9.83E-31	2.83E-30
GO:0005625	soluble fraction	1782	4.74*	2.18E-62	1.63E-60	30.29*	8.98E-202	1.68E-200

Table 5.8 (Continued)

CC Category	Description	Size (p)	Time Effect T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0005634	nucleus	636	5.04*	1.60E-17	1.34E-16	15.69*	9.06E-56	5.23E-55
GO:0005634// GO:0005634	nucleus//nucleus	489	3.55*	5.18E-08	1.30E-07	8.45*	1.47E-17	3.23E-17
GO:0005634// GO:0005634// GO:0005634	nucleus//nucleus//nucleus	210	4.93*	1.18E-07	2.76E-07	9.38*	3.19E-21	8.26E-21
GO:0005634// GO:0005634// GO:0005654	nucleus//nucleus//nucleoplasm	81	12.53*	1.06E-13	6.10E-13	20.68*	2.73E-95	2.05E-94
GO:0005634// GO:0005634// GO:0005667	nucleus//nucleus//transcription factor complex	107	5.07*	1.36E-05	2.43E-05	7.62*	1.29E-14	2.36E-14
GO:0005634// GO:0005634// GO:0005681	nucleus//nucleus//spliceosome	180	4.72*	8.55E-08	2.07E-07	9.33*	5.29E-21	1.32E-20
GO:0005634// GO:0005634// GO:0005730	nucleus//nucleus//nucleolus	627	16.07*	3.31E-46	1.24E-44	45.98*	0.00E+00	0.00E+00
GO:0005634// GO:0005634// GO:0005737	nucleus//nucleus//cytoplasm	103	8.67*	3.03E-09	8.74E-09	13.62*	1.61E-42	6.35E-42
GO:0005634// GO:0005643	nucleus//nuclear pore	271	10.82*	2.36E-16	1.77E-15	21.37*	1.41E-101	1.18E-100
GO:0005634// GO:0005654	nucleus//nucleoplasm	98	7.98*	4.42E-08	1.14E-07	12.01*	1.54E-33	5.24E-33
GO:0005634// GO:0005667	nucleus//transcription factor complex	140	22.71*	3.49E-32	4.37E-31	45.47*	0.00E+00	0.00E+00
GO:0005634// GO:0005681	nucleus//spliceosome	344	12.64*	1.11E-17	1.04E-16	24.10*	1.37E-128	1.28E-127
GO:0005634// GO:0005730	nucleus//nucleolus	1625	4.73*	3.85E-41	7.23E-40	24.32*	5.50E-131	5.89E-130
GO:0005634// GO:0005737	nucleus//cytoplasm	1090	6.49*	3.67E-12	1.62E-11	14.16*	7.74E-46	3.41E-45
GO:0005737	cytoplasm	702	2.78*	1.98E-08	5.51E-08	7.93*	1.11E-15	2.14E-15
GO:0005737// GO:0005737	cytoplasm//cytoplasm	249	8.26*	3.86E-11	1.61E-10	14.97*	5.71E-51	2.86E-50
GO:0005737// GO:0005739	cytoplasm//mitochondrion	84	8.13*	3.41E-10	1.22E-09	14.06*	3.16E-45	1.32E-44
GO:0005737// GO:0005768	cytoplasm//endosome	94	4.16*	0.0005	0.0008	5.37*	3.83E-08	6.11E-08
GO:0005737// GO:0005783	cytoplasm//endoplasmic reticulum	108	1.89	0.0539	0.0622	1.84*	0.0331	0.0376
GO:0005737// GO:0005794	cytoplasm//Golgi apparatus	234	3.14*	2.33E-08	6.24E-08	8.27*	6.97E-17	1.45E-16
GO:0005737// GO:0005829	cytoplasm//cytosol	488	2.66*	5.99E-07	1.25E-06	6.87*	3.32E-12	5.65E-12
GO:0005737// GO:0005856	cytoplasm//cytoskeleton	340	5.51*	5.09E-10	1.66E-09	11.70*	6.11E-32	1.91E-31
GO:0005737// GO:0005886	cytoplasm//plasma membrane	150	6.15*	2.72E-09	8.15E-09	11.71*	5.36E-32	1.75E-31
GO:0005737// GO:0016020	cytoplasm//membrane	208	3.44*	2.20E-06	4.13E-06	7.16*	4.02E-13	7.02E-13

Table 5.8 (Continued)

CC Category	Description	Size (p)	Time Effect T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0005739	mitochondrion	338	3.71*	2.66E-07	6.05E-07	8.09*	2.91E-16	5.75E-16
GO:0005739// GO:0005739	mitochondrion//mitochondrion	73	8.95*	5.07E-11	2.00E-10	15.44*	4.55E-54	2.44E-53
GO:0005739// GO:0005741	mitochondrion//mitochondrial outer membrane	279	6.38*	5.04E-10	1.72E-09	12.48*	4.67E-36	1.67E-35
GO:0005739// GO:0005743	mitochondrion//mitochondrial inner membrane	77	2.07	0.1100	0.1179	1.26	0.1035	0.1109
GO:0005739// GO:0005759	mitochondrion//mitochondrial matrix	192	7.36*	9.17E-07	1.76E-06	10.26*	5.55E-25	1.49E-24
GO:0005764	lysosome	109	3.05*	0.0142	0.0187	3.03*	0.0012	0.0016
GO:0005768	endosome	82	15.13*	2.13E-15	1.33E-14	24.33*	4.43E-131	5.54E-130
GO:0005777	peroxisome	904	6.16*	1.24E-13	6.65E-13	14.82*	5.76E-50	2.70E-49
GO:0005783	endoplasmic reticulum	273	2.73	0.0459	0.0546	2.10*	0.0180	0.0214
GO:0005794	Golgi apparatus	97	35.62*	1.33E-12	6.67E-12	34.22*	6.26E-257	1.56E-255
GO:0005813	centrosome	297	2.58*	0.0191	0.0243	2.70*	0.0035	0.0044
GO:0005829	cytosol	85	2.39	0.0927	0.1008	1.42	0.0777	0.0845
GO:0005856	cytoskeleton	108	9.43*	0.0002	0.0004	8.14*	2.06E-16	4.17E-16
GO:0005874	microtubule	111	5.13*	2.83E-06	5.18E-06	8.32*	4.24E-17	9.08E-17
GO:0005882	intermediate filament	330	2.40*	0.0105	0.0144	2.99*	0.0014	0.0018
GO:0005886	plasma membrane	492	3.40*	2.61E-16	1.78E-15	12.77*	1.24E-37	4.66E-37
GO:0005886// GO:0005886	plasma membrane//plasma membrane	965	5.18*	3.60E-25	3.85E-24	19.43*	2.32E-84	1.45E-83
GO:0005886// GO:0005887	plasma membrane//integral to plasma	409	3.42*	8.72E-07	1.72E-06	7.45*	4.52E-14	8.07E-14
GO:0005886// GO:0016020	plasma membrane//membrane	98	4.24*	0.0018	0.0027	4.73*	1.13E-06	1.73E-06
GO:0005887	integral to plasma membrane	121	1.96	0.0907	0.1001	1.45	0.0740	0.0816
GO:0008076	voltage-gated potassium channel complex	2239	6.41*	2.90E-41	7.24E-40	27.84*	6.58E-171	9.88E-170
GO:0016020	membrane	204	3.91*	0.0004	0.0007	5.38*	3.69E-08	6.01E-08
GO:0016020// GO:0016021	membrane//integral to membrane	75	8.17*	0.0001	0.0001	8.46*	1.39E-17	3.15E-17
GO:0016020// GO:0016021// GO:0016021	membrane//integral to membrane// integral to membrane	739	2.70*	0.0001	0.0001	5.30*	5.92E-08	9.25E-08

*significant at the FDR 0.05 level

5.3.3 Significant Differential Gene Expressions in the MF Category

The results of testing the interaction, age and time effects for each of the gene sets in the MF category are shown in Tables 5.9 to 5.11. From both the T_1 and T_2 tests, the results show that there were 21 gene sets in the MF group significantly differentially expressed by the age × time factor, 52 gene sets differentially expressed by the age factor and 56 gene sets differentially expressed by the time factor.

The gene sets in the MF category which were significantly differentially expressed over age × time effect are in the following classifications: binding (including *binding, iron ion binding*, *protein binding*, *receptor binding*, *RNA binding*, *DNA binding— protein binding*, *DNA binding— zinc ion binding, chromatin binding*, *antigen binding*), transcription regulator activity (including *transcription corepressor factor activity*, *transcription coactivator factor activity*, *transcription factor activity*), catalytic activity (including *catalytic activity*, *guanyl-nucleotide exchange factor activity*, *ubiquitin-protein ligase activity, hormone activity*, *signal transducer activity*, *peptidase activity*, *transferase activity*) and structural molecular activity (including *structural constituent of ribosome*).

The MF gene sets which were significantly differentially expressed by the age effect are in the following classifications: binding (including *nucleotide binding—magnesium ion binding*, *DNA binding—zinc ion binding*, *nucleotide binding—aminoacy1-tRNA ligase activity*, *DNA binding—DNA binding*, *iron ion binding*, *chromatin binding*, *magnesium ion binding, binding*, *zinc ion binding*, *protein binding*), catalytic activity (including *catalytic activity*, *methyltransferase activity*, *ion channel activity*, *monooxygenase activity*, *cytokine activity*), structural molecular activity (including, *structural constituent of ribosome*, *extracellular matrix structural constituent*), transcription regulator activity (including *transcription coactivator activity*, *transcription factor activity*, *transcription corepressor activity*), and translation regulator activity (including *translation initiation factor activity*).

The MF gene sets which were significantly differentially expressed over the time factor are in the following classifications: binding (including *nucleotide binding—magnesium ion binding*, *iron ion binding*, *protein binding—zinc iron ion binding*, *antigen binding,* *chromatin binding*, *DNA binding—zinc iron ion binding*), catalytic activity (including *aminopeptiase activity*, *receptor activity*, *catalytic activity*, *phosphoprotein phosphatase activity*, *GTPase activator activity*, *metalloendopeptidase activity*, *hydrolase activity*, *cytokine activity*, *ion channel activity*, *methyltrasferase activity*), structural molecular activity (including *structural constituent of ribosome*, *guanyl-nucleotide exchange factor activity*, *structural molecular activity*, *extracellular matrix structural constituent*) and transcription and translation regulator activity (including *transcription factor activity*, *translation initiation factor activity*).

Table 5.9 Significant Differential Gene Expressions in the MF Category over Age × Time Effect in Burn Injury Patients

MF Category	Description	Size (p)	Age × Time Effect					
			T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0000166// GO:0000287	nucleotide binding//magnesium ion binding	563	1.96	0.0300	0.0787	2.23*	0.0128	0.0336
GO:0000166// GO:0003676	nucleotide binding//nucleic acid binding	975	0.75	0.6741	0.6962	-0.55	0.7083	0.7437
GO:0000166// GO:0003677	nucleotide binding//DNA binding	136	0.75	0.4599	0.5268	-0.23	0.5918	0.6779
GO:0000166// GO:0003774	nucleotide binding//motor activity	219	0.38	0.6642	0.6974	-0.58	0.7207	0.7443
GO:0000166// GO:0003824	nucleotide binding//catalytic activity	151	0.51	0.7501	0.7501	-0.73	0.7670	0.7670
GO:0000166// GO:0003924	nucleotide binding//GTPase activity	344	1.43	0.1863	0.3172	0.83	0.2039	0.3381
GO:0000166// GO:0004672	nucleotide binding//protein kinase activity	777	1.10	0.3546	0.4468	0.26	0.3964	0.4995
GO:0000166// GO:0004812	nucleotide binding//aminoacyl-tRNA ligase activity	81	0.58	0.5637	0.6122	-0.42	0.6618	0.7189
GO:0000166// GO:0005515	nucleotide binding//protein binding	205	1.39	0.2543	0.3641	0.37	0.3563	0.4581
GO:0000166// GO:0005524	nucleotide binding//ATP binding	158	0.70	0.5086	0.5722	-0.31	0.6212	0.6989
GO:0000166// GO:0005525	nucleotide binding//GTP binding	137	1.08	0.3637	0.4492	0.26	0.3989	0.4928
GO:0000287	magnesium ion binding	457	1.30	0.2582	0.3615	0.51	0.3059	0.4282
GO:0003676	magnesium ion binding	72	0.76	0.7476	0.7596	-0.71	0.7615	0.7738
GO:0003676// GO:0003677	magnesium ion binding//DNA binding	1383	1.70	0.0732	0.1707	1.59	0.0557	0.1300
GO:0003676// GO:0003723	magnesium ion binding//RNA binding	122	0.95	0.4346	0.5167	-0.07	0.5293	0.6176
GO:0003676// GO:0005515	magnesium ion binding//protein binding	120	1.84	0.1511	0.2800	0.94	0.1730	0.3114
GO:0003676// GO:0008270	magnesium ion binding//zinc ion binding	142	1.39	0.2418	0.3543	0.52	0.3019	0.4322
GO:0003677	DNA binding	232	1.51	0.1890	0.3133	0.78	0.2164	0.3496
GO:0003677// GO:0000037	DNA binding//	1027	1.29	0.1900	0.3069	0.84	0.2004	0.3413
GO:0003677// GO:0003677	DNA binding// DNA binding	682	1.22	0.2866	0.3842	0.43	0.3332	0.4466
GO:0003677// GO:0003682	DNA binding//chromatin binding	90	0.97	NaN	NaN	NaN	NaN	NaN
GO:0003677// GO:0005515	DNA binding//protein binding	206	1.68*	0.0027	0.0108	3.26*	0.0006	0.0019
GO:0003677// GO:0008270	DNA binding//zinc ion binding	164	1.90*	0.0014	0.0058	3.68*	0.0001	0.0005
GO:0003682	chromatin binding	88	1.83*	0.0139	0.0399	2.61*	0.0046	0.0137

Table 5.9 (Continued)

MF Category	Description	Size (p)	Age × Time Effect T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0003700	transcription factor activity	221	2.54*	1.03E-05	0.0001	5.89*	1.95E-09	1.75E-08
GO:0003713	transcription coactivator activity	110	2.62*	0.0031	0.0116	3.72*	0.0001	0.0005
GO:0003714	transcription corepressor activity	78	3.72*	5.80E-06	0.0001	7.04*	9.50E-13	1.20E-11
GO:0003723	RNA binding	564	1.67*	0.0052	0.0171	2.99*	0.0014	0.0046
GO:0003735	structural constituent of ribosome	188	1.79*	0.0077	0.0242	2.88*	0.0020	0.0062
GO:0003743	translation initiation factor activity	75	1.22	0.2672	0.3659	0.53	0.2997	0.4391
GO:0003755	peptidyl-prolyl cis-trans isomerase activity	89	1.05	0.3900	0.4725	0.08	0.4690	0.5682
GO:0003779	actin binding	684	1.20	0.1599	0.2879	0.99	0.1608	0.2979
GO:0003823	antigen binding	114	1.85	0.0354	0.0892	2.10*	0.0179	0.0451
GO:0003824	catalytic activity	1355	1.69*	0.0009	0.0045	3.68*	0.0001	0.0005
GO:0004177	aminopeptidase activity	76	1.44	0.2269	0.3404	0.59	0.2792	0.4188
GO:0004197	cysteine-type endopeptidase activity	126	0.63	0.6136	0.6553	-0.47	0.6821	0.7284
GO:0004221	ubiquitin thiolesterase activity	121	1.84	0.0879	0.1787	1.47	0.0712	0.1446
GO:0004222	metalloendopeptidase activity	191	2.08	0.0497	0.1205	1.93	0.0268	0.0650
GO:0004497	monooxygenase activity	159	1.78	0.1332	0.2543	1.10	0.1362	0.2599
GO:0004721	phosphoprotein phosphatase activity	229	1.35	0.2006	0.3159	0.78	0.2188	0.3446
GO:0004842	ubiquitin-protein ligase activity	271	2.52*	0.0011	0.0048	4.16*	1.56E-05	0.0001
GO:0004866	endopeptidase inhibitor activity	151	1.24	0.2888	0.3714	0.39	0.3472	0.4557
GO:0004871	signal transducer activity	997	2.56*	2.70E-13	8.50E-12	10.13*	2.12E-24	3.33E-23
GO:0004872	receptor activity	1359	1.16	0.2873	0.3771	0.48	0.3161	0.4329
GO:0005085	guanyl-nucleotide exchange factor activity	271	3.46*	0.0002	0.0016	5.40*	3.35E-08	2.64E-07
GO:0005096	GTPase activator activity	327	1.33	0.1783	0.3121	0.89	0.1867	0.3267
GO:0005102	receptor binding	244	2.18*	0.0001	0.0006	4.99*	3.04E-07	1.74E-06
GO:0005125	cytokine activity	201	1.87	0.0246	0.0675	2.32*	0.0102	0.0279
GO:0005179	hormone activity	82	3.72*	0.0005	0.0024	5.22*	8.89E-08	6.22E-07
GO:0005198	structural molecule activity	339	1.41	0.1022	0.2012	1.32	0.0931	0.1833
GO:0005201	extracellular matrix structural constituent	90	1.69	0.0811	0.1762	1.52	0.0647	0.1455
GO:0005215	transporter activity	526	2.14*	0.0004	0.0023	4.31*	8.31E-06	4.36E-05
GO:0005216	ion channel activity	396	1.22	0.2258	0.3469	0.70	0.2420	0.3718
GO:0005488	binding	923	9.58*	1.08E-34	6.79E-33	30.58*	1.28E-205	8.07E-204
GO:0005506	iron ion binding	150	12.73*	3.92E-08	6.18E-07	15.01*	3.01E-51	9.47E-50
GO:0005509	calcium ion binding//protein binding	603	3.28*	0.0004	0.0023	5.08*	1.93E-07	1.21E-06
GO:0005515	protein binding	1845	3.13*	3.33E-13	7.00E-12	10.92*	4.68E-28	9.83E-27
GO:0005515// GO:0005515	protein binding//protein binding	865	1.40*	0.0129	0.0388	2.45*	0.0071	0.0205
GO:0005515// GO:0008270	protein binding//zinc ion binding	467	1.45	0.0777	0.1749	1.51	0.0652	0.1416
GO:0008168	methyltransferase activity	110	0.63	0.5299	0.5856	-0.36	0.6411	0.7086
GO:0008233	peptidase activity	76	2.66*	0.0046	0.0163	3.54*	0.0002	0.0007
GO:0008270	zinc ion binding	374	1.66	0.0851	0.1788	1.48	0.0698	0.1465
GO:0016740	transferase activity	86	4.26*	0.0001	0.0008	6.22*	2.55E-10	2.67E-09
GO:0016787	hydrolase activity	129	0.99	0.4362	0.5089	-0.01	0.5057	0.6011

*significant at the FDR 0.05 level

Table 5.10 Significant Differential Gene Expression in the MF Category by Age Effect Test in Burn Injury Patients

MF Category	Description	Size (p)	Age Effect					
			T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0000166// GO:0000287	nucleotide binding//magnesium ion binding	563	2.68*	0.0012	0.0023	4.19*	1.39E-05	2.38E-05
GO:0000166// GO:0003676	nucleotide binding//nucleic acid binding	975	2.78*	0.0008	0.0016	4.43*	4.69E-06	8.27E-06
GO:0000166// GO:0003677	nucleotide binding//DNA binding	136	0.62	0.5167	0.5254	-0.35	0.6366	0.6474
GO:0000166// GO:0003774	nucleotide binding//motor activity	219	3.85*	0.0260	0.0306	2.76*	0.0029	0.0034
GO:0000166// GO:0003824	nucleotide binding//catalytic activity	151	3.66*	0.0033	0.0046	4.14*	1.72E-05	2.87E-05
GO:0000166// GO:0003924	nucleotide binding//GTPase activity	344	2.81*	0.0022	0.0035	3.98*	3.50E-05	0.0001
GO:0000166// GO:0004672	nucleotide binding//protein kinase activity	777	4.45*	3.40E-23	4.08E-22	17.39*	4.55E-68	5.46E-67
GO:0000166// GO:0004812	nucleotide binding//aminoacyl-tRNA ligase activity	81	3.11*	0.0421	0.0486	2.22*	0.0132	0.0152
GO:0000166// GO:0005515	nucleotide binding//protein binding	205	1.31	0.2744	0.2888	0.35	0.3633	0.3824
GO:0000166// GO:0005524	nucleotide binding//ATP binding	158	2.59	0.0768	0.0838	1.61	0.0535	0.0583
GO:0000166// GO:0005525	nucleotide binding//GTP binding	137	1.79*	0.0066	0.0086	2.95*	0.0016	0.0019
GO:0000287	magnesium ion binding	457	4.10*	2.14E-05	0.0001	6.80*	5.25E-12	1.43E-11
GO:0003676	magnesium ion binding	72	5.65*	0.0015	0.0026	5.39*	3.44E-08	7.64E-08
GO:0003676// GO:0003677	magnesium ion binding//DNA binding	1383	8.34*	4.05E-16	1.87E-15	18.74*	1.19E-78	1.78E-77
GO:0003676// GO:0003723	magnesium ion binding//RNA binding	122	1.99	0.0959	0.1027	1.40*	0.0809	0.0867
GO:0003676// GO:0005515	magnesium ion binding//protein binding	120	2.51	0.0503	0.0569	1.99*	0.0233	0.0264
GO:0003676// GO:0008270	magnesium ion binding//zinc ion binding	142	2.05	0.0719	0.0799	1.64	0.0500	0.0555
GO:0003677	DNA binding	232	5.31*	5.87E-06	1.60E-05	8.13*	2.07E-16	5.91E-16
GO:0003677// GO:0000037	DNA binding//	1027	5.36*	1.41E-19	1.21E-18	17.16*	2.84E-66	2.84E-65
GO:0003677// GO:0003677	DNA binding// DNA binding	682	2.35*	0.0018	0.0030	3.84*	0.0001	0.0001
GO:0003677// GO:0003682	DNA binding//chromatin binding	90	5.50*	0.0029	0.0043	4.89*	5.04E-07	1.04E-06
GO:0003677// GO:0005515	DNA binding//protein binding	206	4.08*	5.03E-75	3.02E-73	31.23*	2.17E-214	1.30E-212
GO:0003677// GO:0008270	DNA binding//zinc ion binding	164	2.68*	3.39E-17	1.85E-16	11.97*	2.68E-33	1.24E-32
GO:0003682	chromatin binding	88	3.51*	2.80E-10	1.05E-09	9.85*	3.54E-23	1.25E-22
GO:0003700	transcription factor activity	221	4.83*	1.06E-46	2.12E-45	26.23*	5.55E-152	1.67E-150
GO:0003713	transcription coactivator activity	110	3.27*	1.34E-05	3.49E-05	6.39*	8.07E-11	1.94E-10
GO:0003714	transcription corepressor activity	78	1.96	0.0050	0.0068	3.17*	0.0008	0.0010
GO:0003723	RNA binding	564	3.34*	1.86E-61	5.59E-60	25.90*	3.03E-148	6.07E-147

Table 5.10 (Continued)

MF Category	Description	Size (p)	Age Effect T_1	raw p-value	fdr p-value	T_2	raw p-value	fdr p-value
GO:0003735	structural constituent of ribosome	188	3.75*	1.48E-19	1.11E-18	14.73*	2.19E-49	1.64E-48
GO:0003743	translation initiation factor activity	75	2.25*	0.0023	0.0036	3.67*	0.0001	0.0002
GO:0003755	peptidyl-prolyl cis-trans isomerase activity	89	3.12*	0.0031	0.0044	3.95*	3.84E-05	0.0001
GO:0003779	actin binding	684	3.75	NaN	NaN	NaN	NaN	NaN
GO:0003823	antigen binding	114	3.10*	2.85E-06	8.56E-06	6.79*	5.58E-12	1.46E-11
GO:0003824	catalytic activity	1355	3.03	NaN	NaN	NaN	NaN	NaN
GO:0004177	aminopeptidase activity	76	3.67*	0.0087	0.0109	3.55*	0.0002	0.0003
GO:0004197	cysteine-type endopeptidase activity	126	3.07*	0.0098	0.0120	3.28*	0.0005	0.0007
GO:0004221	ubiquitin thiolesterase activity	121	3.32*	0.0080	0.0102	3.49*	0.0002	0.0003
GO:0004222	metalloendopeptidase activity	191	6.70*	0.0000	1.43E-05	9.06*	6.60E-20	2.20E-19
GO:0004497	monooxygenase activity	159	3.82*	0.0013	0.0023	4.75*	1.01E-06	1.95E-06
GO:0004721	phosphoprotein phosphatase activity	229	3.00*	3.63E-05	0.0001	5.83*	2.81E-09	6.50E-09
GO:0004842	ubiquitin-protein ligase activity	271	4.50*	2.02E-11	8.06E-11	11.64*	1.37E-31	5.85E-31
GO:0004866	endopeptidase inhibitor activity	151	3.51*	0.0010	0.0020	4.70*	1.28E-06	2.32E-06
GO:0004871	signal transducer activity	997	3.16	NaN	NaN	NaN	NaN	NaN
GO:0004872	receptor activity	1359	2.82*	2.55E-15	1.09E-14	11.42*	1.59E-30	6.34E-30
GO:0005085	guanyl-nucleotide exchange factor activity	271	2.94*	0.0003	0.0007	4.95*	3.66E-07	7.85E-07
GO:0005096	GTPase activator activity	327	2.53*	0.0002	0.0005	4.83*	6.91E-07	1.38E-06
GO:0005102	receptor binding	244	2.97*	2.44E-30	3.66E-29	17.02*	2.91E-65	2.50E-64
GO:0005125	cytokine activity	201	2.10*	0.0014	0.0025	3.79*	0.0001	0.0001
GO:0005179	hormone activity	82	2.54*	0.0118	0.0142	2.98*	0.0015	0.0018
GO:0005198	structural molecule activity	339	3.91*	2.67E-16	1.33E-15	13.51*	6.90E-42	3.76E-41
GO:0005201	extracellular matrix structural constituent	90	2.40*	0.0029	0.0044	3.64*	0.0001	0.0002
GO:0005215	transporter activity	526	3.02*	1.21E-18	7.28E-18	13.12*	1.33E-39	6.66E-39
GO:0005216	ion channel activity	396	3.53*	2.89E-10	1.02E-09	9.86*	3.11E-23	1.17E-22
GO:0005488	binding	923	3.21*	7.64E-19	5.09E-18	13.53*	5.39E-42	3.23E-41
GO:0005506	iron ion binding	150	3.55*	0.0052	0.0069	3.84*	0.0001	0.0001
GO:0005509	calcium ion binding//protein binding	603	4.32*	8.41E-07	2.66E-06	8.20*	1.21E-16	3.64E-16
GO:0005515	protein binding	1845	2.66	NaN	NaN	NaN	NaN	NaN
GO:0005515// GO:0005515	protein binding//protein binding	865	2.97	NaN	NaN	NaN	NaN	NaN
GO:0005515// GO:0008270	protein binding//zinc ion binding	467	3.38*	9.62E-21	9.62E-20	14.58*	1.89E-48	1.26E-47
GO:0008168	methyltransferase activity	110	1.11	0.3406	0.3523	0.12	0.4519	0.4674
GO:0008233	peptidase activity	76	4.35*	6.72E-07	2.24E-06	8.31*	4.78E-17	1.51E-16
GO:0008270	zinc ion binding	374	2.69*	0.0004	0.0008	4.71*	1.24E-06	2.33E-06
GO:0016740	transferase activity	86	2.60*	0.0021	0.0035	3.89*	4.97E-05	0.0001
GO:0016787	hydrolase activity	129	3.73*	2.27E-05	0.0001	6.53*	3.34E-11	8.35E-11

*significant at the FDR 0.05 level

Table 5.11 Significant Differential Gene Expression in the MF Category over Time Effect Test in Burn Injury Patients

MF Category	Description	Size (p)	Time Effect T_1	raw p-alue	fdr p-value	T_2	raw p-alue	fdr p-value
GO:0000166// GO:0000287	nucleotide binding//magnesium ion binding	563	3.27*	0.0002	0.0004	5.27*	6.88E-08	1.17E-07
GO:0000166// GO:0003676	nucleotide binding//nucleic acid binding	975	2.26*	0.0150	0.0190	2.74*	3.11E-03	0.0038
GO:0000166// GO:0003677	nucleotide binding//DNA binding	136	4.59*	0.0155	0.0191	3.36*	3.89E-04	0.0005
GO:0000166// GO:0003774	nucleotide binding//motor activity	219	0.56	0.5552	0.5552	-0.41	6.60E-01	0.6601
GO:0000166// GO:0003824	nucleotide binding//catalytic activity	151	3.22*	0.0103	0.0132	3.29*	4.92E-04	0.0006
GO:0000166// GO:0003924	nucleotide binding//GTPase activity	344	1.70	0.0996	0.1100	1.36	8.69E-02	0.0960
GO:0000166// GO:0004672	nucleotide binding//protein kinase activity	777	3.41*	1.33E-05	2.89E-05	6.50*	3.91E-11	7.47E-11
GO:0000166// GO:0004812	nucleotide binding//aminoacyl-tRNA ligase activity	81	4.94*	0.0082	0.0112	3.96*	3.69E-05	0.0001
GO:0000166// GO:0005515	nucleotide binding//protein binding	205	1.69	0.1918	0.2048	0.66	2.56E-01	0.2730
GO:0000166// GO:0005524	nucleotide binding//ATP binding	158	0.71	0.5046	0.5212	-0.30	6.18E-01	0.6281
GO:0000166// GO:0005525	nucleotide binding//GTP binding	137	3.17*	1.78E-06	4.01E-06	7.01*	1.23E-12	2.59E-12
GO:0000287	magnesium ion binding	457	4.55*	0.0002	0.0004	6.05*	7.30E-10	1.28E-09
GO:0003676	magnesium ion binding	72	0.93	0.5454	0.5542	-0.22	5.87E-01	0.6060
GO:0003676// GO:0003677	magnesium ion binding//DNA binding	1383	2.38*	0.0079	0.0110	3.14*	8.46E-04	0.0011
GO:0003676// GO:0003723	magnesium ion binding//RNA binding	122	5.74*	0.0003	0.0005	6.46*	5.33E-11	9.88E-11
GO:0003676// GO:0005515	magnesium ion binding//protein binding	120	1.29	0.2812	0.2952	0.32	3.74E-01	0.3927
GO:0003676// GO:0008270	magnesium ion binding//zinc ion binding	142	1.64	0.1714	0.1862	0.85*	1.97E-01	0.2140
GO:0003677	DNA binding	232	2.77*	0.0205	0.0243	2.71*	3.41E-03	0.0041
GO:0003677// GO:0000037	DNA binding//	1027	2.47*	0.0009	0.0014	4.22*	1.21E-05	1.90E-05
GO:0003677// GO:0003677	DNA binding// DNA binding	682	2.01	0.0444	0.0500	1.99*	2.32E-02	0.0260
GO:0003677// GO:0003682	DNA binding//chromatin binding	90	2.88	NaN	NaN	NaN	NaN	NaN
GO:0003677// GO:0005515	DNA binding//protein binding	206	2.84*	7.64E-10	2.67E-09	8.81*	6.44E-19	1.76E-18
GO:0003677// GO:0008270	DNA binding//zinc ion binding	164	4.03*	1.23E-13	7.04E-13	12.34*	2.71E-35	1.00E-34
GO:0003682	chromatin binding	88	4.94*	5.75E-12	3.02E-11	12.45*	6.91E-36	2.72E-35
GO:0003700	transcription factor activity	221	3.52*	6.15E-10	2.28E-09	9.65*	2.50E-22	8.29E-22
GO:0003713	transcription coactivator activity	110	2.73*	0.0021	0.0031	3.98*	3.51E-05	0.0001
GO:0003714	transcription corepressor activity	78	4.23*	4.43E-07	1.16E-06	8.36*	3.15E-17	7.94E-17
GO:0003723	RNA binding	564	6.97*	7.23E-36	2.28E-34	26.84*	5.16E-159	1.08E-157

Table 5.11 (Continued)

MF Category	Description	Size (p)	Time Effect T_1	raw p-alue	fdr p-value	T_2	raw p-alue	fdr p-value
GO:0003735	structural constituent of ribosome	188	4.66*	5.85E-14	4.10E-13	13.30*	1.09E-40	4.90E-40
GO:0003743	translation initiation factor activity	75	3.01*	0.0004	0.0007	4.88*	5.32E-07	8.82E-07
GO:0003755	peptidyl-prolyl cis-trans isomerase activity	89	3.05*	0.0098	0.0132	3.27*	5.45E-04	0.0007
GO:0003779	actin binding	684	4.03*	2.97E-19	2.34E-18	15.04*	2.01E-51	1.27E-50
GO:0003823	antigen binding	114	12.28*	1.98E-23	2.08E-22	27.84*	6.94E-171	2.19E-169
GO:0003824	catalytic activity	1355	8.94*	1.06E-68	6.65E-67	42.39*	0.00E+00	0.00E+00
GO:0004177	aminopeptidase activity	76	3.55*	0.0099	0.0130	3.42*	3.11E-04	0.0004
GO:0004197	cysteine-type endopeptidase activity	126	10.80*	4.32E-07	1.18E-06	12.63*	6.98E-37	2.93E-36
GO:0004221	ubiquitin thiolesterase activity	121	9.79*	2.64E-10	1.11E-09	15.44*	4.51E-54	3.15E-53
GO:0004222	metalloendopeptidase activity	191	4.79*	0.0001	0.0001	6.75*	7.52E-12	1.53E-11
GO:0004497	monooxygenase activity	159	16.34*	8.72E-12	4.23E-11	21.56*	2.27E-103	2.87E-102
GO:0004721	phosphoprotein phosphatase activity	229	2.81*	0.0019	0.0029	4.06*	2.43E-05	3.74E-05
GO:0004842	ubiquitin-protein ligase activity	271	2.65*	0.0006	0.0009	4.52*	3.12E-06	5.04E-06
GO:0004866	endopeptidase inhibitor activity	151	5.52*	3.27E-05	6.44E-05	7.48*	3.76E-14	8.45E-14
GO:0004871	signal transducer activity	997	3.92*	4.82E-30	1.01E-28	18.97*	1.41E-80	1.27E-79
GO:0004872	receptor activity	1359	5.96*	6.31E-14	3.98E-13	14.78*	1.05E-49	5.99E-49
GO:0005085	guanyl-nucleotide exchange factor activity	271	7.37*	8.06E-11	3.63E-10	13.96*	1.30E-44	6.29E-44
GO:0005096	GTPase activator activity	327	3.77*	1.51E-06	3.65E-06	7.56*	2.02E-14	4.72E-14
GO:0005102	receptor binding	244	3.05*	3.26E-09	1.03E-08	8.70*	1.69E-18	4.44E-18
GO:0005125	cytokine activity	201	1.87*	0.0243	0.0284	2.33*	9.96E-03	0.0114
GO:0005179	hormone activity	82	7.18*	1.67E-08	4.77E-08	11.84*	1.17E-32	4.09E-32
GO:0005198	structural molecule activity	339	3.33*	4.45E-07	1.12E-06	7.59*	1.61E-14	3.91E-14
GO:0005201	extracellular matrix structural constituent	90	2.58*	0.0051	0.0073	3.45*	2.77E-04	0.0004
GO:0005215	transporter activity	526	3.40*	3.12E-09	1.04E-08	9.09*	5.04E-20	1.44E-19
GO:0005216	ion channel activity	396	3.22*	1.69E-06	3.94E-06	7.07*	7.98E-13	1.73E-12
GO:0005488	binding	923	7.28*	1.02E-24	1.28E-23	22.38*	2.84E-111	4.47E-110
GO:0005506	iron ion binding	150	8.12*	2.00E-05	4.19E-05	9.11*	4.17E-20	1.25E-19
GO:0005509	calcium ion binding//protein binding	603	4.01*	2.42E-05	4.91E-05	6.69*	1.09E-11	2.14E-11
GO:0005515	protein binding	1845	5.07*	2.72E-29	4.28E-28	20.89*	3.24E-97	3.40E-96
GO:0005515// GO:0005515	protein binding//protein binding	865	3.61*	3.37E-23	3.04E-22	15.93*	2.11E-57	1.66E-56
GO:0005515// GO:0008270	protein binding//zinc ion binding	467	3.71*	8.48E-09	2.55E-08	9.14*	3.24E-20	1.02E-19
GO:0008168	methyltransferase activity	110	3.88*	0.0248	0.0284	2.81*	2.48E-03	0.0031
GO:0008233	peptidase activity	76	2.88*	0.0023	0.0034	3.99*	3.32E-05	4.98E-05
GO:0008270	zinc ion binding	374	2.18*	0.0171	0.0207	2.63*	4.23E-03	0.0049
GO:0016740	transferase activity	86	8.55*	3.36E-10	1.32E-09	14.40*	2.51E-47	1.32E-46
GO:0016787	hydrolase activity	129	4.37*	0.0001	0.0002	6.24*	2.16E-10	3.89E-10

*significant at the FDR 0.05 level

5.4 Discussion of the Analysis of Burn Injury Data

As described in Sections 5.2 and 5.3, the proposed high dimensional DMM analysis was applied to a large-scale clinical study of burn patients' data. This clinical study by the Inflammation and Host Response to Injury program included gene expression data of blood samples from pediatric and adult patients measured at different times after severe burn injury and from healthy controls. This burn injury data was firstly analyzed by Zhou et al. (2010a: 1) using a factorial analysis of time course microarrays. They were interested in genes that exhibited a dynamic response to burn injury (i.e. show different dynamic patterns in burn patients over time when compared to normal controls) and in how the response may depend on the additional factor of age. In this case, they used a factorial design with two binary factors (burn status and age group) and longitudinal time-course measurements, and developed a method to simultaneously handle the time course and factorial structure in the microarray data.

In this researcher's method**,** multivariate repeated measurement analysis of time course microarrays were used to only analyze the burn patients group. Of interest were groups of genes that are differentially expressed by the age × time, age and time factors. A split-plot design was used where the burn injury patients were randomly nested within the age group (whole plot) factor which is crossed with the time (split-plot) factor. The genes were mapped in sets of GO terms in three categories, BP, CC and MF, and each gene set was analyzed by using high dimensional DMM and MMM analyses.

The results of the high dimensional DMM analysis and factorial analysis of time of burn injury data can be summarized in the following sections.

5.4.1 High Dimensional DMM Analysis

The gene expression levels of blood samples from 26 pediatric and 31 adult burn injury patients were repeatedly measured at two time points after severe burn injury: the early stage (0-10 days) and the middle stage (11-49 days). There were 29,230 genes functionally defined based on the biological process of GO and were mapped to unique GO terms in BP, CC and MF categories. The analysis of burn injury time course data was focused on the sizes of the GO categories, 70 to 2000 genes. After the mapping processes, the gene expression levels were left with 70 gene sets in the BP category, 76 gene sets in CC and 64 gene sets in MF for analysis.

To test whether differentially expressed gene sets in burn injury data are significant with respect to the age × time, age and time effects, high dimensional DMM and MMM analyses were applied for each gene set. Since there were two time-point measurements, the DMM and MMM analyses are the same. The adjusted p-values for multiple testing corrections were derived to control FDR at the 5% level.

5.4.1.1 The Age × Time Effect on Burn Injury Patients

The results of testing the age×time effect for each of the 70, 76 and 64 gene sets in the BP, CC and MF categories showed that there were 10, 23 and 21 gene sets significantly differentially expressed over the age×time effect in the three categories, respectively.

The 4 of 10 GO gene sets in the BP category which were most significantly differentially expressed over the age × time interaction effect are: *regulation of cell growth* (231 genes, p value of T_1: 1.83E-10, p value of T_2 : 1.87E-105), *transcription* (1,183 genes, p value of T_1: 5.23E-14, p value of T_2 : 2.61E-50), *metabolic process* (457 genes, p value of T_1: 4.48E-06 , p value of T_2 : 5.79E-13) and *intercellular protein transport* (73 genes, p value of T_1: 6.01E-05, p value of T_2 : 1.25E-16).

In the CC category, the 4 of 23 gene sets which were most significantly differentially expressed over age × time are: *intracellular-cytosol* (131 genes, p value of T_1: 2.21E-62, p value of T_2 : 1.32E-95), *membrane fraction* (764 genes, p value of T_1: 1.29E-09, p value of T_2 : 1.17E-14), *cytoplasm-membrane* (150 genes, p value of T_1: 1.75E-10, p value of T_2 : 3.61E-48) and *nucleus* (1,782 genes, p value of T_1: 4.68E-07, p value of T_2 : 2.63E-10).

The 4 of 21 gene sets in the MF category which were most significantly differentially expressed over the age × time effect are: *binding* (923 genes, p value of T_1: 6.79E-33, p value of T_2 : 8.07E-204), *protein binding* (1,845 genes, p value of T_1: 7.00E-12, p value of T_2 : 9.83E-27), *signal transducer activity*

(997 genes, p value of T_1: 8.50E-12, p value of T_2: 3.33E-23) and *transcription corepressor activity* (78 genes, p value of T_1: 0.0001, p value of T_2: 1.20E-11).

5.4.1.2 The Age Effect on Burn Injury Patients

There were 49 of 70 gene sets from BP, 55 of 76 gene sets from CC and 52 of 64 gene sets from MF which showed significant differential expression over the age factor.

The 4 of 49 GO gene sets in the BP category which were significantly differentially expressed between age groups are: *transport- transport* (314 genes, p value of T_1: 2.75E-92, p value of T_2: 1.35E-278), *transport-ion transport* (696 genes, p value of T_1: 1.94E-96, p value of T_2: 3.20E-210), *angiogenesis* (211 genes, p value of T_1: 2.35E-29, p value of T_2: 2.17E-215) and *carbohydrate metabolic process* (423 genes, p value of T_1: 5.79E-28, p value of T_2: 1.34E-106).

The 4 of 55 GO gene sets in the CC category which were significantly differentially expressed between age groups are: *extracellular region--non-traceable author statement* (684 genes, p value of T_1: 1.45E-60, p value of T_2: 7.68E-215), *cytoplasm—cytoplasm* (702 genes, p value of T_1: 2.79E-65, p value of T_2: 1.03E-212), *nucleus—nucleus* (636 genes, p value of T_1: 1.57E-47, p value of T_2: 2.02E-148) and *plasma membrane—integral to plasma* (965 genes, p value of T_1: 4.30E-82, p value of T_2: 1.04E-164).

The 4 of 52 GO gene sets in the MF category which were significantly differentially expressed between age groups are: *DNA binding—protein binding* (206 genes, p value of T_1: 3.02E-73, p value of T_2: 1.30E-212), *transcription factor activity* (221 genes, p value of T_1: 2.12E-45, p value of T_2: 1.67E-150), *RNA binding* (564 genes, p value of T_1: 5.59E-60, p value of T_2: 6.07E-147) and *nucleotide binding—protein kinase activity* (777 genes, p value of T_1: 4.08E-22, p value of T_2: 5.46E-67).

5.4.1.3 The Time Effect on Burn Injury Patients

For each of the 70, 76 and 64 gene sets in the BP, CC and MF categories, there were 54, 69 and 56 gene sets significantly differentially expressed over the time effect in the three categories, respectively.

The 4 of 54 GO gene sets in the BP category that were mostly significant differentially expressed over time are: *transport* (244 genes, p value of T_1: 2.34E-34, p value of T_2 : 1.95E-196), *immune response* (430 genes, p value of T_1: ,1.29E-30, p value of T_2 : 7.09E-186), *chemotaxis* (93 genes, p value of T_1: 2.40E-14, p value of T_2 : 3.06E-162) and *intracellular protein transport* (73 genes, p value of T_1 : 2.15E-16, p value of T_2 : 1.54E-153).

Within the CC categories, the 4 of 69 gene sets significantly differentially expressed over time are: *soluble fraction* (1782 genes, p value of T_1: 1.63E-60, p value of T_2 : 1.68E-200), *voltage-gate potassium channel complex* (2239 genes, p value of T_1: 7.24E-40, p value of T_2 : 9.88E-170), *nucleus-nucleolus* (1625 genes, p value of T_1: 7.23E-40, p value of T_2 : 5.89E-130) and *nucleus—transcription factor* (1782 genes, p value of T_1: 7.23E-40, p value of T_2 : 5.89E-130).

There were 4 of 56 MF gene sets significantly differentially expressed over time: *RNA binding* (564 genes, p value of T_1: 2.28E-34, p value of T_2 : 1.08E-157), *binding* (923 genes, p value of T_1: 1.28E-23, p value of T_2: 4.47E-110), *catalytic activity* (1,355 genes, p value of T_1: 6.65E-67, p value of T_2 : 0), and *antigen activity* (114 genes, p value of T_1: 2.08E-22, p value of T_2 : 1.27E-50).

5.4.2 Factorial Time Course Microarray Analysis

The method of Zhou et al. (2010a: 1) draws on the idea from the classical statistical method of ANOVA to analyze factor effects on gene expression. The ANOVA structure was used to model the dependency of gene expression on the experimental factors by conducting a series of statistical tests on the factor effects for each gene. The best ANOVA structure was selected to model the gene expression pattern and classify the genes into five mutually exclusive groups (C1-C5). C1 is a group of genes that have different expression patterns in the interactive effect of the two (burn and age) factors, while C2 is a group of genes that have differential expression patterns in both the age and burn factors, but the two effects are independent. The C3 and C4 groups are two group of genes that have differential expression patterns in the main effect of one factor, the age or burn factor, respectively. C5 is a group of remaining genes that either have constant expression patterns or are not affected by any factor. In this way, Zhou et al. (2010a: 2) proposed the time course ANOVA (TANOVA) method to characterize the gene expression impact of the age factor to patients' outcomes after injury. The analysis identified many genes responsive to burn injury, including those with responses that are age-specific.

The data set included burn and control groups and two age groups: 26 children and 31 adults. For each patient, two time-point measurements were considered in the analysis, the early stage and the middle stage, post burn. Since there is a single array for each control subject, the array was duplicated to obtain pseudo time-course data. To achieve a better balance on the confounding factors between the two age groups, Zhou et al. (2010a: 4) sampled two datasets by randomly deleting one adult with inhalation injury and four adult patients without inhalation injury. The resulting datasets both had 26 adult patients balanced with the pediatric group. TANOVA was then applied to each of the two data sets to classify the probe sets into five groups (C1-C5). The classification was done by a stepwise significance test. The threshold of each test was chosen to control a false discovery rate (FDR) < 0.01. The common probe sets in each group shared by both datasets were analyzed.

Their analysis was done on the 8,639 probe sets with a coefficient of variation > 0.06 and median expression across arrays > 7 (log2 scale). The number of shared probe sets in C1, C2, C3 and C4 were 866, 642, 5807 and 73, respectively. Genes in C1 and C2 showed significant age effect after burn injury, while C3 was affected only by burn and C4 only by age. Thus the vast majority of probe sets (C1+C2+C3 = 7,315) were perturbed by burn injury, and 21% of these ((C1+C2)/(C1+C2+C3) = 1,508/7,315) revealed differences between adults and children.

In the C1 group, there were 866 probe sets showing significant age-dependent changes over time course after burn injury. Hypermetabolism and inflammation are two hallmarks of the body's response to burn injury. Their analysis revealed that significantly enriched pathways in the interaction effect include: glycosphingolipid biosynthesis-globoseries (5 genes, p value: 8.19E-5), primary immunodeficiency (10 genes, p value: 0.001), keratin sulfate biosynthesis (5 genes, p value: 0.007), ubiquinone biosynthesis (8 genes, p value: 0.01), death receptor signaling (7 genes, p value: 0.01) and mitochondrial dysfunction (12 genes, p value: 0.01). These specific metabolic and inflammatory genes and pathways are differentially perturbed in the two age groups and are potential contributors to the pathophysiological differences in pediatric and adult patients.

Genes in C2 are influenced by both age and burn, but the two factor effects are independent. In C2 group, 642 probe sets were significantly differentially expressed between the two age groups. Significantly enriched pathways in the age effect include: notch signaling (4 genes, p value: 0.002), mitochondrial dysfunction (11 genes, p value: 0.004) aminophosphonate metabolism (4 genes, p value: 0.005), clathrin-mediate endocytosis signaling (11 genes, p value: 0.005), virus entry via endocytic pathways (9 genes, p value: 0.005) and ubiquinone biosynthesis (7 genes, p value: 0.006).

C3 genes are burn responsive without age group differences. As expected, significant pathways in C3 are involved in the cellular immune response and metabolic processes, such as glutamate metabolism (14 genes, p value: 0), T helper cell differentiation (14 genes, p value: 0), fatty acid biosynthesis (5 genes, p value: 0), nucleotide sugars metabolism (6 genes, p value: 0), role of pattern recognition receptors in recognition of bacteria and viruses (34 genes, p value: 0.005), CD28 signaling in T helper cells (49 genes, p value: 0.006) and calcium-induced T lymphocyte apoptosis (29 genes, p value: 0.007). Finally, C4 genes are related only to age and not burn injury. It includes genes (RHOB, PPP1CA, and MA2K7) involved in the production of nitric oxide and reactive oxygen species in macrophages which are related to the aging process.

CHAPTER 6

SUMMARY AND CONCLUSIONS

6.1 Summary and Conclusions

A multivariate repeated measurements design is a design where p response variables are observed repeatedly over t times on each subject in g groups. There are two different approaches for analyzing multivariate repeated measures, the Doubly Multivariate Model (DMM) and the Multivariate Mixed Model (MMM). These analyses are based on the classical multivariate test which requires an assumption that sample size is larger than the dimension of the response variables. The data in DMM analysis consists of pt response variables on each of n subject and requires that $n > pt$, whereas MMM consists of p response variables on each of nt subject and requires that $nt > p$. In DNA microarray time course experiments, gene expression is available on thousands of genes of an individual and is measured several times, but there are only a few individuals in the data set. These experiments require high dimensional multivariate repeated measurements designs where the dimension of the response variables is larger than sample size. Therefore the classical multivariate tests of both cases are not valid to analyze these high dimensional data.

In this study, the multivariate tests for analyzing multivariate repeated measurement designs in a high dimensional framework are modified, the approximate or asymptotic distributions of the test statistics are derived and a power comparison of the test statistics is considered. The modified statistics for the DMM and MMM analyses are derived in Chapters 2 and 3, respectively, and the proposed tests in both cases were evaluated using a simulation study given in Chapter 4. The proposed tests were also applied to analyze the microarray time course experiment detailed in Chapter 5.

6.1.1 The Proposed Tests and their Distributions

6.1.1.1 Doubly Multivariate Model Analysis

DMM is defined by $\mathbf{Y} = \mathbf{XB} + \mathbf{U}$, where $\mathbf{Y}$ is an $n \times pt$ response matrix for n subjects, $\mathbf{X}$ is an $n \times g$ between subject design matrix of $rank(\mathbf{X}) = g$, $\mathbf{B}$ is a $g \times pt$ unknown parameter matrix of fixed effects and $\mathbf{U}$ is an $n \times pt$ random error matrix in which each row vector is assumed to be i.i.d. as multivariate normal, i.e. $\boldsymbol{u}_{npt\times 1} = vec(\mathbf{U}) \sim N_{npt}(\mathbf{0}_{npt\times 1}, \mathbf{\Sigma} \otimes \mathbf{I}_n)$.

The Multivariate General Linear Hypothesis for testing the effect of the time and group factors, and the interaction effect between the group and time factors, is $H : \mathbf{CB}(\mathbf{I}_p \otimes \mathbf{A}) = \mathbf{\Gamma}_0$, where $\mathbf{C}$ is a $v_h \times g$ between group contrast matrix having $rank(\mathbf{C}) = v_h \le g$, $\mathbf{A}$ is a $t \times u$ within subject contrast matrix having $rank(\mathbf{A}) = u \le t$, and $\mathbf{A}'\mathbf{A} = \mathbf{I}_u$.

Defining $a_i = tr(\mathbf{\Phi}^j)/pu$, for $i = 1,\ldots,4$, $b = a_1^2/a_2$, and without loss of generality, the $pu \times pu$ covariance matrix of error matrix $\mathbf{U}$ is assumed to be a diagonal matrix, $\mathbf{\Phi} = \mathbf{\Phi}_\Upsilon = diag(\lambda_1,\ldots,\lambda_{pu})$. Under the following assumptions:

(1) $p \to \infty$, $n \to \infty$, t is fixed and $n < pt$,

(2) $\lim_{p\to\infty} a_i = a_{i0}$, for $i = 1,\ldots,4$ and $0 < a_{i0} < \infty$,

(3) For the local alternative hypothesis,

$$0 < \lim_{p\to\infty} \frac{tr(\mathbf{\Phi}^j \mathbf{\Xi})}{pu} < \infty, \quad \text{for } i = 1,\ldots,4,$$

where $a_i = \dfrac{tr(\mathbf{\Phi}^j)}{pu}$, $\mathbf{\Xi} = \mathbf{\Phi}^{-1/2}\mathbf{\Delta}\mathbf{\Phi}^{-1/2}$ and $\mathbf{\Delta} = (\mathbf{\Gamma} - \mathbf{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{\Gamma} - \mathbf{\Gamma}_0)$, the consistent estimators of a_1, a_2 and b are respectively given by Lemma 3.1 as

$$\hat{a}_1 = \frac{tr(\mathbf{S}_e)}{v_e pu},$$

$$\hat{a}_2 = \frac{1}{(v_e - 1)(v_e + 2)p}\left[tr(\mathbf{S}_e^2) - \frac{1}{v_e}(tr(\mathbf{S}_e))^2 \right]$$

and $$\hat{b} = \frac{\hat{a}_1^2}{\hat{a}_2},$$

where $\mathbf{S}_e$ is the $pu \times pu$ SSCP matrix corresponding to error

$$\mathbf{S}_e = (\mathbf{I}_p \otimes \mathbf{A})'\mathbf{Y}'[\mathbf{I}_n - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}']\mathbf{Y}(\mathbf{I}_p \otimes \mathbf{A}), \tag{6.1}$$

and the $pu \times pu$ SSCP matrix due to the hypothesis is defined as

$$\mathbf{S}_h = (\mathbf{C}\hat{\mathbf{B}}(\mathbf{I}_p \otimes \mathbf{A}) - \mathbf{\Gamma}_0)'[\mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}']^{-1}(\mathbf{C}\hat{\mathbf{B}}(\mathbf{I}_p \otimes \mathbf{A}) - \mathbf{\Gamma}_0). \tag{6.2}$$

The adaptations of generalized versions of Dempster's test and Bai and Saranadasa's test (Srivastava and Fujikoshi , 2006 :) for testing multivariate linear hypotheses in DMM, proposed as T_1 and T_2, respectively, are

$$T_1 = \frac{v_e \; tr(\mathbf{S}_h)}{v_h \; tr(\mathbf{S}_e)}$$

and $$T_2 = \left\{2v_h\hat{a}_2\left(1+\frac{v_h}{v_e}\right)\right\}^{-1/2}\frac{1}{\sqrt{pu}}\left[tr(\mathbf{S}_h) - \frac{v_h}{v_e}tr(\mathbf{S}_e)\right].$$

From Theorems 3.1 and 3.2, the approximate null and non-null distributions of proposed test T_1, respectively, are

$$T_1 \mathrel{\dot{\sim}} F(f, \lfloor v_h d \rfloor, \lfloor v_e d \rfloor)$$

and $$T_1 \sim F\left(f, \lfloor r_h \rfloor, \lfloor r_e \rfloor, \delta\right),$$

where $F(f, v_1, v_2)$ denotes the cumulative F distribution at f with v_1 and v_2 degrees of freedom, and $\lfloor x \rfloor$ denotes the largest integer $\leq x$. d, w_h, w_e, r_h, r_e and δ are respectively defined by

$$d = \frac{[tr(\mathbf{\Phi}_\Upsilon)]^2}{tr(\mathbf{\Phi}_\Upsilon^2)} = \frac{pua_1^2}{a_2} = pub,$$

$$w_h = \frac{v_h tr(\mathbf{\Phi}_\Upsilon^2) + 2tr(\mathbf{\Phi}_\Upsilon^2\mathbf{\Xi})}{v_h tr(\mathbf{\Phi}_\Upsilon) + 2tr(\mathbf{\Phi}_\Upsilon\mathbf{\Xi})}, \quad w_e = \frac{tr(\mathbf{\Phi}_\Upsilon^2)}{tr(\mathbf{\Phi}_\Upsilon)},$$

$$r_h = \frac{v_h tr(\mathbf{\Phi}_\Upsilon)}{w_h}, \quad r_e = \frac{v_e[tr(\mathbf{\Phi}_\Upsilon)]^2}{tr(\mathbf{\Phi}_\Upsilon^2)}, \text{ and}$$

$$\delta = \frac{tr(\mathbf{\Phi}_\Upsilon\mathbf{\Xi})}{w_h}.$$

As $n \to \infty$ and $p \to \infty$, the asymptotic null distribution and non-null distribution of proposed test T_1 are respectively given in Theorems 3.3 and 3.4 as

$$\lim_{p\to\infty} P(T_2 > z) = \lim_{p\to\infty} \mathbb{N}(z)$$

and
$$\lim_{p\to\infty} P(T_2 > z) = \lim_{p\to\infty} \mathbb{N}\left(-\frac{\sigma_0}{\sigma_2} z_\alpha + \frac{tr(\mathbf{\Phi}_\Upsilon \mathbf{\Xi})}{\sigma_2 \sqrt{pu}} \right).$$

6.1.1.2 Multivariate Mixed Model Analysis

MMM is defined by $\mathbf{Y}^* = (\mathbf{X} \otimes \mathbf{I}_t)\mathbf{B}^* + \mathbf{U}^*$, where $\mathbf{Y}^*$ is an $nt \times p$ response matrix for n subjects, $\mathbf{X}$ is an $n \times g$ between subject design matrix of $rank(\mathbf{X}) = g$, $\mathbf{B}^*$ is a $gt \times p$ unknown parameter matrix of fixed effects and $\mathbf{U}^*$ is an $nt \times p$ random error matrix assumed to be multivariate normally distributed. $vec(\mathbf{U}^{*\prime}) \sim N_{npt}(\mathbf{0}_{npt\times 1}, \mathbf{I}_n \otimes \mathbf{\Sigma}^*)$, where $\mathbf{\Sigma}^*$ has compound symmetry structures.

As described in Chapter 3, MMM is related to a rearranged DMM, so $\mathbf{S}_e^*$ and $\mathbf{S}_h^*$ can be written using $\mathbf{S}_e$ and $\mathbf{S}_h$ in (6.1) and (6.2), respectively. Boik (1991: 1238) gave the forms of $\mathbf{S}_e^*$ and $\mathbf{S}_h^*$ for the MMM analysis based on Thompson's generalized trace operator of $\mathbf{S}_e$ and $\mathbf{S}_h$. Let $\mathbf{D}$ be a $pu \times pu$ matrix and let $\mathbf{D}_{ij}$ be the ij^{th} $u \times u$ submatrix, where $i, j = 1, 2, \ldots, p$, then the generalized trace operator of $\mathbf{D}$, denoted by $T_p(\mathbf{D})$, is a $p \times p$ matrix written as

$$T_p(\mathbf{D}) = \left[tr(\mathbf{D}_{ij}) \right]_{p\times p}.$$

By partitioning the $pu \times pu$ sum of squares and cross product matrices $\mathbf{S}_e$ and $\mathbf{S}_h$ from (6.1) and (6.2), $pu \times pu$ covariance matrix $\mathbf{\Phi}$ and non-centrality matrix $\mathbf{\Delta}$ respectively, into $u \times u$ submatrices, i.e. $\mathbf{S}_e = \left[\mathbf{S}_{eij} \right], \mathbf{S}_h = \left[\mathbf{S}_{hij} \right]$, $\mathbf{\Phi} = \left[\mathbf{\Phi}_{ij} \right]$ and $\mathbf{\Delta} = \left[\mathbf{\Delta}_{ij} \right]$, for $i, j = 1, 2, \ldots, p$, we define

$$\mathbf{S}_e^* = T_p(\mathbf{S}_e),$$

$$\mathbf{S}_h^* = T_p(\mathbf{S}_h),$$

$$\mathbf{\Phi}^* = T_p(\mathbf{\Phi})$$

and $$\mathbf{\Delta}^* = T_p(\mathbf{\Delta}) .$$

The necessary and sufficient condition for $\mathbf{S}_e^*$ and $\mathbf{S}_h^*$ to be distributed accordingly as a Wishart distribution (Boik, 1988: 475) is that covariance matrix $\mathbf{\Phi}^*$ satisfies the condition of multivariate sphericity,

$$\mathbf{\Phi}^* = \mathbf{I}_u \otimes \mathbf{\Psi} , \tag{3.31}$$

where $\mathbf{\Phi}^* = (\mathbf{A}' \otimes \mathbf{I}_p)\mathbf{\Sigma}^*(\mathbf{A} \otimes \mathbf{I}_p)$ and $\mathbf{\Psi}$ is a $p \times p$ positive definite matrix of covariance among p-variate responses.

Defining $a_i^* = tr((\mathbf{\Phi}^*)^j)/p$, for $i = 1,\ldots,4$, and $b^* = (a_1^*)^2/a_2^*$, without loss of generality, the $pu \times pu$ covariance matrix of error matrix $\mathbf{U}^*$ is assumed to be a diagonal matrix, $\mathbf{\Phi}^* = \frac{1}{u} T_p(\mathbf{\Phi})$.

Under the following assumptions

(1) $p \to \infty$, $n \to \infty$, t is fixed and $nt < p$,

(2) $\lim\limits_{p\to\infty} a_i^* = a_{i0}^*$, for $i = 1,\ldots,4$ and $0 < a_{i0}^* < \infty$, and

(3) For the local alternative hypothesis,

$$0 < \lim_{p\to\infty} \frac{tr\left((\mathbf{\Phi}^*)^j \mathbf{\Xi}^*)\right)}{p} < \infty, \text{ for } \quad i = 1,\ldots,4 ,$$

where $\mathbf{\Xi}^* = (\mathbf{\Phi}^*)^{-1/2}\mathbf{\Delta}^*(\mathbf{\Phi}^*)^{-1/2}$, the consistent estimators of a_1, a_2 and b are respectively given by Lemma 3.5 as

$$\hat{a}_1^* = \frac{tr(\mathbf{S}_e^*)}{uv_e p},$$

$$\hat{a}_2^* = \frac{1}{(uv_e - 1)(uv_e + 2)p}\left[tr\left((\mathbf{S}_e^*)^2\right) - \frac{1}{uv_e}\left(tr(\mathbf{S}_e^*)\right)^2 \right]$$

and $$\hat{b}^* = \frac{(\hat{a}_1^*)^2}{\hat{a}_2^*} .$$

The generalized Dempster's test and Bai and Saranadasa's test for testing multivariate linear hypothesis are again adapted for the MMM analysis and proposed as T_1^* and T_2^*, respectively:

$$T_1^* = \frac{uv_e \; tr(\mathbf{S}_h^*)}{uv_h \; tr(\mathbf{S}_e^*)}$$

and $$T_2^* = \left\{ 2uv_h a_2^* \left(1 + \frac{v_h}{v_e} \right) \right\}^{-1/2} \frac{1}{\sqrt{p}} \left[tr(\mathbf{S}_h^*) - \frac{v_h}{v_e} tr(\mathbf{S}_e^*) \right].$$

From Theorems 3.5 and 3.6, the approximate null distribution of proposed test T_1^* is $T_1^* \dot{\sim} F(f, \lfloor uv_h d^* \rfloor, \lfloor uv_e d^* \rfloor)$ and under the local alternative hypothesis, $T_1^* \dot{\sim} F\left(f, \lfloor r_h^* \rfloor], \lfloor r_h^* \rfloor, \delta^* \right)$. d, w_h^*, w_e^*, r_h^*, r_e^* and δ^* are respectively defined by

$$\hat{d}^* = \frac{p(\hat{a}_1^*)^2}{\hat{a}_2^*} = p\hat{b}^*,$$

$$w_h^* = \frac{uv_h tr((\mathbf{\Phi}_\Upsilon^*)^2) + 2tr((\mathbf{\Phi}_\Upsilon^*)\mathbf{\Xi}^*))}{uv_h tr(\mathbf{\Phi}_\Upsilon^*) + 2tr(\mathbf{\Phi}_\Upsilon^* \mathbf{\Xi}^*)}, \quad w_e^* = \frac{tr((\mathbf{\Phi}_\Upsilon^*)^2)}{tr(\mathbf{\Phi}_\Upsilon^*)},$$

$$r_h^* = \frac{uv_h tr(\mathbf{\Phi}_\Upsilon^*)}{w_h^*}, \quad r_e^* = \frac{uv_e^*(tr(\mathbf{\Phi}_\Upsilon^*))^2}{tr((\mathbf{\Phi}_\Upsilon^*)^2)}, \text{ and}$$

$$\delta^* = \frac{tr((\mathbf{\Phi}_\Upsilon^*)\mathbf{\Xi}^*)}{w^* tr(\mathbf{\Phi}_\Upsilon^*)}.$$

As $n \to \infty$ and $p \to \infty$, the asymptotic null distribution and non-null distribution of proposed test T_2^* are respectively given in Theorems 3.7 and 3.8 as

$$\lim_{n\to\infty} \lim_{p\to\infty} P(T_2^* < z) = \mathbb{N}(z)$$

and $$\lim_{p\to\infty} P(T_2^* > z) = \lim_{p\to\infty} \mathbb{N}\left(-\frac{\sigma_0}{\sigma_2} z_\alpha + \frac{tr(\mathbf{\Phi}_\Upsilon^* \mathbf{\Xi}^*)}{\sigma_2 \sqrt{p}} \right).$$

6.1.2 Simulation Study Results

A simulation study was carried out to evaluate the performance of the proposed tests in the DMM and MMM analyses. The attained significance levels of T_1, T_2, T_1^* and T_2^* are computed as

$$\hat{\alpha}_1 = \frac{(\#\text{ of } T_1 > f_{0.95,v_1,v_2})}{m}, \quad \hat{\alpha}_1^* = \frac{(\#\text{ of } T_1^* > f_{0.95,v_1^*,v_1^*})}{m}$$

$$\hat{\alpha}_2 = \frac{(\#\text{ of } T_2 > Z_{0.95})}{m} \quad \text{and} \quad \hat{\alpha}_2^* = \frac{(\#\text{ of } T_2^* > Z_{0.95})}{m}.$$

Under the local alternative hypothesis, the empirical powers of T_1, T_2, T_1^* and T_2^*, respectively, are

$$\hat{\beta}_1 = \frac{(\#\text{ of } T_1 > f_{0.95,v_1,v_2})}{m}, \quad \hat{\beta}_1^* = \frac{(\#\text{ of } T_1^* > f_{0.95,v_1^*,v_1^*})}{m},$$

$$\hat{\beta}_2 = \frac{(\#\text{ of } T_2 > Z_{0.95})}{m} \quad \text{and} \quad \hat{\beta}_2^* = \frac{(\#\text{ of } T_2^* > Z_{0.95})}{m}.$$

The attained significance levels of the T_1 and T_1^* tests on the interaction, group and time effects in the DMM and MMM analyses seemed to behave similarly and were close to the nominal 0.05 level for all cases of n and p. The attained significance levels of the T_2 and T_2^* tests also behaved similarly but were larger than those of the T_1 and T_1^* tests for all cases of n and p. When n increases, the gap between the graphs of the two types of test decreases and the attained significance levels of the T_2 and T_2^* tests are close to those of the T_1 and T_1^* tests when n is large.

The results of the empirical powers of the interaction, group and time effects tests on each case of $n = 15$, 30, 60, 90 show that the empirical powers of the T_1, T_2, T_1^* and T_2^* tests increase as p increases. In both of the DMM and MMM analyses, the empirical powers of the T_2 tests are higher than those of the T_1 test and those of the T_2^* test are higher than those of the T_1^* test. Additionally, the empirical powers of the tests in the DMM and MMM analyses are similar but those of the T_1 and T_2 tests in the DMM analysis are slightly higher than those of the T_1^* and T_2^* tests in the MMM analysis.

6.1.3 Application of the Proposed Tests

The proposed tests of the analysis of high dimensional multivariate repeated measurements were applied to the analysis of data from the burn injury microarray time course study. In this study, the gene expression levels of blood samples from 26 pediatric and 31 adult patients were repeatedly measured at two time points after severe burn injury, the early stage (0-10 days) and the middle stage (11-49 days). For each patient, gene expression levels were mapped into 70 gene sets in the biological process (BP) category, 76 gene sets in the cellular component (CC) category and 64 gene sets in the molecular function (MF) category, in which each gene set ranged from 70 to 2000 genes. The DMM analysis was applied in testing the age, time and the interaction effects on each gene set in all three categories.

It was found that there were 10 gene sets in the BP groups significantly differentially expressed over age×time, 49 gene sets differentially expressed between the age groups and 54 gene sets differentially expressed over time. In the CC category, the gene sets significantly differentially expressed over the age × time, age and time factors were 23, 55 and 69 gene sets, respectively. Finally, there were 21 gene sets in the MF groups significantly differentially expressed over the age × time factor, 52 gene sets differentially expressed between the age groups and 56 gene sets differentially expressed over time.

6.2 Discussion

The proposed tests adapted from generalizations of Dempster's test and Bai and Saranadasa's test can be used to analyze high dimensional multivariate repeated measurement designs when the dimension is larger than the observation. These two types of proposed test are based on multivariate analysis of variance in DMM and MMM which both require the normality assumption and homogeneity of covariance matrices among groups. The performances of the proposed tests in the DMM analysis are similar to and slightly higher than those in MMM. Therefore the proposed tests in the DMM analysis could be commonly adopted in practice for high dimensional cases because they do not require the assumption of covariance structure, whereas MMM requires the multivariate sphericity condition. The performances of the proposed tests adapted from generalizations of Dempster's test and Bai and Saranadasa's test are similar but the adaption of a generalized Bai and Saranadasa's test performs well when the sample size is large whereas the generalized Dempster's test performs well for all cases of sample size. Therefore, when sample size is small, the adapted generalization of Dempster's test is available to use in the analysis of high dimensional multivariate repeated measurements.

6.3 Recommendations for Further Research

The problem in the analysis of a high dimensional multivariate test is that the sample covariance matrix is singular and not invertible. To solve this problem, one of the alternative methods is to develop a well-conditioned estimator of the high dimensional covariance matrix that can be used as an estimator for classical test statistics. Another choice is to adapt multivariate tests to use the generalized inverse of sample covariance. A proposed alternative approach is to use a non-parametric test statistic to deal with high dimensional multivariate repeated measurements data.

In this work, the proposed tests were derived under the assumptions of normality and homogeneity of covariance matrices which were not satisfied in some experiments. An extension of the present work could be to develop test statistics for the analysis of high dimensional multivariate repeated measurements under a non-normality assumption and heterogeneity of covariance matrices.

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APPENDIX

Appendix A

Proof of Lemma 3.1

To prove Lemma 3.1, the following Lemmas A.1, A.2 and A.3 are given.

Lemma A.1 Let w be a chi-squared random variable with n degrees of freedom, then

$$E(w^r) = n(n+2)\cdots(n+2r-2), \quad \text{for } r = 1,2,\dots,$$

$$\text{var}(w) = 2n, \qquad \text{var}(w^2) = 8n(n+2)(n+3),$$

$$E(w-n)^3 = 8n, \qquad E(w-n)^4 = 12n(n+4),$$

$$E\left[w^2 - n(n+2)\right]^4 = 3n(n+2)\left[272n^4 + O(n^3)\right].$$

Next, expressions for $tr(\mathbf{S}_e)$, $tr(\mathbf{S}_e^2)$ and $\left(tr(\mathbf{S}_e)\right)^2$ in terms of chi-squared random variables are obtained.

Let $pu \times pu$, $\mathbf{S}_e \sim W_{pu}(\boldsymbol{\Phi}, v_e)$, where $v_e = n - g$, then there exists a $v_e \times pu$ random matrix $\mathbf{Y}_A$ such that $\mathbf{S}_e = \mathbf{Y}_A'\mathbf{Y}_A$, $vec(\mathbf{Y}_A) \sim N_{v_e pu}(\mathbf{0}, \boldsymbol{\Phi} \otimes \mathbf{I}_{v_e})$ (Srivastava and Khatri, 1979: 77). Let $\mathbf{Y}_A = (\boldsymbol{y}_1, \boldsymbol{y}_2, \dots, \boldsymbol{y}_{v_e})'$, then $\boldsymbol{y}_i$ are i.i.d. $N_{pu}(\mathbf{0}, \boldsymbol{\Phi})$.

Let $\boldsymbol{\Upsilon}$ be a $pu \times pu$ orthogonal matrix such that $\boldsymbol{\Upsilon}'\boldsymbol{\Phi}\boldsymbol{\Upsilon} = \boldsymbol{\Phi}_\Upsilon$, where $\boldsymbol{\Phi}_\Upsilon = diag(\lambda_1, \lambda_2, \dots, \lambda_{pu})$ and λ_i are eigenvalues of $\boldsymbol{\Phi}_\Upsilon$. Let $\mathbf{Z} = (z_1, z_2, \dots, z_{v_e})'$, where z_i are i.i.d. $N_{pu}(\mathbf{0}, \mathbf{I}_{pu})$, then

$$\mathbf{Y}_A = \mathbf{Z}\boldsymbol{\Phi}^{1/2} \sim N_{pu}(\mathbf{0}, \boldsymbol{\Phi}), \quad \text{where } \boldsymbol{\Phi} = \boldsymbol{\Phi}^{1/2}\boldsymbol{\Phi}^{1/2}.$$

Therefore,

$$\begin{aligned} tr(\mathbf{S}_e) &= tr(\mathbf{Y}_A'\mathbf{Y}_A) = tr(\mathbf{Y}_A\mathbf{Y}_A') \\ &= tr\left[(\mathbf{Z}\boldsymbol{\Phi}^{1/2})(\mathbf{Z}\boldsymbol{\Phi}^{1/2})'\right] \\ &= tr(\mathbf{Z}\boldsymbol{\Phi}\mathbf{Z}') \end{aligned}$$

$$= tr\left[\mathbf{Z}(\Upsilon\Upsilon')\mathbf{\Phi}(\Upsilon\Upsilon')\mathbf{Z}'\right]$$

$$= tr\left[\mathbf{W}\mathbf{\Phi}_{\Upsilon}\mathbf{W}'\right]$$

$$= \sum_{i=1}^{pu} \lambda_i \boldsymbol{w}_i' \boldsymbol{w}_i \ ,$$

where

$$\mathbf{Z}\Upsilon = \begin{bmatrix} z_1' \\ z_2' \\ \vdots \\ z_{v_e}' \end{bmatrix} (\gamma_1, \gamma_2, \ldots, \gamma_{pu}) \ = \begin{bmatrix} z_1'\gamma_1 & z_1'\gamma_2 & z_1'\gamma_{pu} \\ z_2'\gamma_1 & z_2'\gamma_2 & z_2'\gamma_{pu} \\ \vdots & \vdots & \vdots \\ z_{v_e}'\gamma_1 & z_{v_e}'\gamma_2 & z_{v_e}'\gamma_{pu} \end{bmatrix}$$

$$= (\boldsymbol{w}_1, \boldsymbol{w}_2, \ldots, \boldsymbol{w}_{pu}) = \mathbf{W} \, .$$

Each column of matrix Υ, γ_i is an eigenvector corresponding to eigenvalue λ_i and $\mathbf{W} = (\boldsymbol{w}_1, \boldsymbol{w}_2, \ldots, \boldsymbol{w}_{pu})$ whose $v_e \times 1$ column vectors $\boldsymbol{w}_i$ are i.i.d. $N_{v_e}(\mathbf{0}, \mathbf{I}_{v_e})$. Thus, let $v_{ii} = \boldsymbol{w}_i' \boldsymbol{w}_i$ (a scalar), $\boldsymbol{v}_{ii}$ are i.i.d. chi-squared random variables with v_e degrees of freedom, i.e. $v_{ii} \sim \chi^2_{v_e}$.

Note that

$$\mathbf{W}\mathbf{\Phi}_{\Upsilon}\mathbf{W}' = (\boldsymbol{w}_1, \boldsymbol{w}_2, \ldots, \boldsymbol{w}_{pu}) \begin{bmatrix} \lambda_1 & 0 & \cdots & 0 \\ 0 & \lambda_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \lambda_{pu} \end{bmatrix} \begin{bmatrix} \boldsymbol{w}_1' \\ \boldsymbol{w}_2' \\ \vdots \\ \boldsymbol{w}_{pu}' \end{bmatrix}$$

$$= (\boldsymbol{w}_1\lambda_1, \boldsymbol{w}_2\lambda_2, \ldots, \boldsymbol{w}_{pu}\lambda_{pu}) \begin{bmatrix} \boldsymbol{w}_1' \\ \boldsymbol{w}_2' \\ \vdots \\ \boldsymbol{w}_{pu}' \end{bmatrix}$$

$$= \sum_{i=1}^{pu} \lambda_i \boldsymbol{w}_i \boldsymbol{w}_i', \text{ where } \boldsymbol{w}_i \boldsymbol{w}_i' \text{ is a } v_e \times v_e \text{ matrix,}$$

$$
= \begin{bmatrix} \sum_{i=1}^{pu} \lambda_i w_{1i}^2 & \sum_{i=1}^{pu} \lambda_i w_{1i} w_{2i} & \cdots & \sum_{i=1}^{pu} \lambda_i w_{1i} w_{v_e i} \\ \sum_{i=1}^{pu} \lambda_i w_{2i} w_{1i} & \sum_{i=1}^{pu} \lambda_i w_{2i}^2 & \cdots & \sum_{i=1}^{pu} \lambda_i w_{2i} w_{v_e i} \\ \vdots & \vdots & \ddots & \vdots \\ \sum_{i=1}^{pu} \lambda_i w_{v_e i} w_{1i} & \sum_{i=1}^{pu} \lambda_i w_{v_e i} w_{2i} & \cdots & \sum_{i=1}^{pu} \lambda_i w_{v_e i}^2 \end{bmatrix}.
$$

Subsequently,

$$
\begin{aligned}
tr(\mathbf{W\Phi}_{\Upsilon}\mathbf{W}') &= \sum_{i=1}^{pu} \lambda_i w_{1i}^2 + \sum_{i=1}^{pu} \lambda_i w_{2i}^2 + \ldots + \sum_{i=1}^{pu} \lambda_i w_{v_e i}^2 \\
&= \sum_{j=1}^{v_e} \sum_{i=1}^{pu} \lambda_i w_{ji}^2 \\
&= \sum_{i=1}^{pu} \lambda_i \sum_{j=1}^{v_e} w_{ji}^2 \\
&= \sum_{i=1}^{pu} \lambda_i \boldsymbol{w}_i' \boldsymbol{w}_i \ .
\end{aligned}
$$

Hence, we can express

$$
tr(\mathbf{S}_e) = \sum_{i=1}^{pu} \lambda_i \boldsymbol{w}_i' \boldsymbol{w}_i = \sum_{i=1}^{pu} \lambda_i v_{ii} \,, \tag{a.1}
$$

$$
\left[tr(\mathbf{S}_e) \right]^2 = \left(\sum_{i=1}^{pu} \lambda_i v_{ii} \right)^2 = \sum_{i=1}^{pu} \lambda_i^2 v_{ii}^2 + 2 \sum_{i<j}^{pu} \lambda_i \lambda_j v_{ii} v_{jj} \,, \tag{a.2}
$$

$$
\begin{aligned}
tr(\mathbf{S}_e^2) &= tr\left[(\mathbf{W\Phi}_{\Upsilon}\mathbf{W}')(\mathbf{W\Phi}_{\Upsilon}\mathbf{W}') \right] \\
&= tr\left[\left(\sum_{i=1}^{pu} \lambda_i \boldsymbol{w}_i \boldsymbol{w}_i' \right) \left(\sum_{i=1}^{pu} \lambda_i \boldsymbol{w}_i \boldsymbol{w}_i' \right) \right] \\
&= tr\left[\sum_{i=1}^{pu} \lambda_i^2 \boldsymbol{w}_i \boldsymbol{w}_i' \boldsymbol{w}_i \boldsymbol{w}_i' + 2 \sum_{i<j}^{pu} \lambda_i \lambda_j \boldsymbol{w}_i \boldsymbol{w}_i' \boldsymbol{w}_j \boldsymbol{w}_j' \right] \\
&= \sum_{i=1}^{pu} \lambda_i^2 \left(\boldsymbol{w}_i' \boldsymbol{w}_i \right) tr(\boldsymbol{w}_i \boldsymbol{w}_i') + 2 \sum_{i<j}^{pu} \lambda_i \lambda_j (\boldsymbol{w}_i' \boldsymbol{w}_j) tr(\boldsymbol{w}_i \boldsymbol{w}_i') \qquad (\because \boldsymbol{w}_i' \boldsymbol{w}_j \text{ is scalar}) \\
&= \sum_{i=1}^{pu} \lambda_i^2 \left(\boldsymbol{w}_i' \boldsymbol{w}_i \right) tr(\boldsymbol{w}_i' \boldsymbol{w}_i) + 2 \sum_{i<j}^{pu} \lambda_i \lambda_j (\boldsymbol{w}_i' \boldsymbol{w}_j) tr(\boldsymbol{w}_i' \boldsymbol{w}_i)
\end{aligned}
$$

$$= \sum_{i=1}^{pu} \lambda_i^2 \left(\boldsymbol{w}_i'\boldsymbol{w}_i\right)^2 + 2\sum_{i<j}^{pu} \lambda_i\lambda_j (\boldsymbol{w}_i'\boldsymbol{w}_j)^2$$

$$= \sum_{i=1}^{pu} \lambda_i^2 v_{ii}^2 + 2\sum_{i<j}^{pu} \lambda_i\lambda_j v_{ij}^2 ,$$

where $\boldsymbol{v}_{ii} = \boldsymbol{w}_i'\boldsymbol{w}_i$ and $v_{ij} = \boldsymbol{w}_i'\boldsymbol{w}_j$, $i \neq j$.

Let $\dfrac{1}{(v_e-1)(v_e+2)} = k$, and then, from (3.15) of Lemma 3.1,

$$\hat{a}_2 = \frac{k}{pu}\left[tr(\mathbf{S}_e^2) - \frac{1}{v_e}(tr(\mathbf{S}_e))^2 \right]$$

$$= \frac{k}{pu}\left[\sum_{i=1}^{pu} \lambda_i^2 v_{ii}^2 + 2\sum_{i<j}^{pu} \lambda_i\lambda_j v_{ij}^2 - \frac{1}{v_e}\left(\sum_{i=1}^{pu} \lambda_i^2 v_{ii}^2 + 2\sum_{i<j}^{pu} \lambda_i\lambda_j v_{ii}v_{jj} \right)\right]$$

$$= \frac{k}{pu}\left[\frac{v_e-1}{v_e}\sum_{i=1}^{pu} \lambda_i^2 v_{ii}^2 + 2\sum_{i<j}^{pu} \lambda_i\lambda_j (v_{ij}^2 - \frac{1}{v_e}v_{ii}v_{jj}) \right]$$

$$= k\left[\frac{v_e-1}{v_e pu}\sum_{i=1}^{pu} \lambda_i^2 v_{ii}^2 + \frac{2}{pu}\sum_{i<j}^{pu} \lambda_i\lambda_j s_{ij} \right]$$

$$= k\left(f_1 + f_2\right), \tag{a.3}$$

where $$s_{ij} = v_{ij}^2 - \frac{1}{v_e}v_{ii}v_{jj} = \left(\boldsymbol{w}_i'\boldsymbol{w}_j\right)^2 - \frac{1}{v_e}(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_j'\boldsymbol{w}_j) . \tag{a.4}$$

Lemma A.2 For s_{ij} defined in (a.4), we have

$$E(s_{ij}) = 0, \quad E(s_{ij}s_{ik}) = 0 \quad \text{for all } i, j, k,$$

$$\text{var}(s_{ij}) = 2(v_e+2)(v_e-1) .$$

Proof. Since $\boldsymbol{w}_i$ are i.i.d. $N_{v_e}(\mathbf{0},\mathbf{I}_{v_e})$, then $\boldsymbol{w}_i'\boldsymbol{w}_i = \sum_{k=1}^{v_e} w_{ik}^2 \sim \chi_{v_e}^2$ and

$$\text{var}(\boldsymbol{w}_i\boldsymbol{w}_i') = E(\boldsymbol{w}_i\boldsymbol{w}_i') = \mathbf{I}_{v_e} ,\; E(\boldsymbol{w}_i'\boldsymbol{w}_i) = v_e .$$

(i) $$E(s_{ij}) = E\left[(\boldsymbol{w}_i'\boldsymbol{w}_j)^2 - \frac{1}{v_e}(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_j'\boldsymbol{w}_j) \right]$$

$$= E\left(\boldsymbol{w}_i'\boldsymbol{w}_j\boldsymbol{w}_j'\boldsymbol{w}_i\right) - \frac{1}{v_e}E\left[(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_j'\boldsymbol{w}_j)\right]$$

$$= E\left(\boldsymbol{w}_i'\boldsymbol{w}_i\right) - \frac{1}{v_e} E\left[(\boldsymbol{w}_i'\boldsymbol{w}_i)\right] E\left[(\boldsymbol{w}_j'\boldsymbol{w}_j)\right]$$

$$= v_e - \frac{1}{v_e}(v_e \cdot v_e)$$

$$= 0 .$$

Note that, since $(\boldsymbol{w}_i'\boldsymbol{w}_j)^2$ is a scalar, then

$$E(\boldsymbol{w}_i'\boldsymbol{w}_j)^2 = E\left(tr(\boldsymbol{w}_i'\boldsymbol{w}_j\boldsymbol{w}_i'\boldsymbol{w}_j)\right) = E\left(tr(\boldsymbol{w}_i'\boldsymbol{w}_j\boldsymbol{w}_j'\boldsymbol{w}_i)\right) = E\left(tr(\boldsymbol{w}_i'\boldsymbol{w}_j)(\boldsymbol{w}_j\boldsymbol{w}_j')\right)$$

$$= tr\left(E(\boldsymbol{w}_i'\boldsymbol{w}_i)E(\boldsymbol{w}_j\boldsymbol{w}_j')\right)) = tr\left(E(\boldsymbol{w}_i'\boldsymbol{w}_i)\mathbf{I}_{v_e}\right)$$

$$= E\left(tr(\boldsymbol{w}_i'\boldsymbol{w}_i)\right) = E(\boldsymbol{w}_i'\boldsymbol{w}_i) .$$

(ii) $$E(s_{ij}s_{ik}) = E\left(\left(\boldsymbol{w}_i'\boldsymbol{w}_j\right)^2 - \frac{1}{v_e}(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_j'\boldsymbol{w}_j)\right)\left(\left(\boldsymbol{w}_i'\boldsymbol{w}_k\right)^2 - \frac{1}{v_e}(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_k'\boldsymbol{w}_k)\right)$$

$$= E[(\boldsymbol{w}_i'\boldsymbol{w}_j)^2(\boldsymbol{w}_i'\boldsymbol{w}_k)^2 - \frac{1}{v_e}(\boldsymbol{w}_i'\boldsymbol{w}_j)^2(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_k'\boldsymbol{w}_k)$$

$$-\frac{1}{v_e}(\boldsymbol{w}_i'\boldsymbol{w}_k)^2(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_j'\boldsymbol{w}_j) + \frac{1}{v_e^2}(\boldsymbol{w}_i'\boldsymbol{w}_i)^2(\boldsymbol{w}_j'\boldsymbol{w}_j)(\boldsymbol{w}_k'\boldsymbol{w}_k)] .$$

Since we can find that

$$E[(\boldsymbol{w}_i'\boldsymbol{w}_j)^2(\boldsymbol{w}_i'\boldsymbol{w}_k)^2] = E[(\boldsymbol{w}_i'\boldsymbol{w}_j\boldsymbol{w}_j'\boldsymbol{w}_i)(\boldsymbol{w}_i'\boldsymbol{w}_k\boldsymbol{w}_k'\boldsymbol{w}_i)]$$

$$= E[\{\boldsymbol{w}_i'(\boldsymbol{w}_j\boldsymbol{w}_j')\boldsymbol{w}_i\}\{\boldsymbol{w}_i'(\boldsymbol{w}_k\boldsymbol{w}_k')\boldsymbol{w}_i\}]$$

$$= E[(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_i'\boldsymbol{w}_i)]$$

$$= \mathrm{var}(\boldsymbol{w}_i'\boldsymbol{w}_i) + E[(\boldsymbol{w}_i'\boldsymbol{w}_i)]^2$$

$$= 2v_e + v_e^2 ,$$

$$E[(\boldsymbol{w}_i'\boldsymbol{w}_j)^2(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_k'\boldsymbol{w}_k)] = E[(\boldsymbol{w}_i'\boldsymbol{w}_j\boldsymbol{w}_j'\boldsymbol{w}_i)(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_k'\boldsymbol{w}_k)]$$

$$= E[(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_k'\boldsymbol{w}_k)]$$

$$= E[(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_i'\boldsymbol{w}_i)]E[(\boldsymbol{w}_k'\boldsymbol{w}_k)]$$

$$= v_e(v_e + 2)(v_e)$$

$$= v_e^2(v_e + 2) ,$$

$$
\begin{aligned}
E[(\boldsymbol{w}_i'\boldsymbol{w}_k)^2(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_j'\boldsymbol{w}_j)] &= E[(\boldsymbol{w}_i'\boldsymbol{w}_k\boldsymbol{w}_k'\boldsymbol{w}_i)(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_j'\boldsymbol{w}_j)] \\
&= E[(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_j'\boldsymbol{w}_j)] \\
&= E[(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_i'\boldsymbol{w}_i)]\cdot E[(\boldsymbol{w}_j'\boldsymbol{w}_j)] \\
&= v_e(v_e+2)\cdot v_e \\
&= v_e^2(v_e+2),
\end{aligned}
$$

$$
\begin{aligned}
E[(\boldsymbol{w}_i'\boldsymbol{w}_i)^2(\boldsymbol{w}_j'\boldsymbol{w}_j)(\boldsymbol{w}_k'\boldsymbol{w}_k)] &= E[(\boldsymbol{w}_i'\boldsymbol{w}_i)^2]\cdot E[(\boldsymbol{w}_j'\boldsymbol{w}_j)]\cdot E[(\boldsymbol{w}_k'\boldsymbol{w}_k)] \\
&= v_e(v_e+2)\cdot v_e\cdot v_e \\
&= v_e^3(v_e+2).
\end{aligned}
$$

Hence

$$
\begin{aligned}
E(s_{ij}s_{ik}) &= v_e(v_e+2) - \left(\frac{1}{v_e}v_e^2(v_e+2)\right) - \left(\frac{1}{v_e}v_e^2(v_e+2)\right) + \left(\frac{1}{v_e^2}v_e^3(v_e+2)\right) \\
&= 2v_e(v_e+2) - 2v_e(v_e+2) \quad = 0.
\end{aligned}
$$

(iii) $\operatorname{var}(s_{ij}) = E(s_{ij}^2) - \left[E(s_{ij})\right]^2 = E(s_{ij}^2)$, from (i) $E(s_{ij}) = 0$

To calculate $E(s_{ij}^2)$, note that

$$
\begin{aligned}
s_{ij}^2 &= \left(v_{ij}^2 - \frac{1}{v_e}v_{ii}v_{jj}\right)\left(v_{ij}^2 - \frac{1}{v_e}v_{ii}v_{jj}\right) \\
&= v_{ij}^4 - \frac{2}{v_e}v_{ij}^2v_{ii}v_{jj} + \frac{1}{v_e^2}v_{ii}^2v_{jj}^2,
\end{aligned}
$$

so we must find $E(v_{ij}^4)$, $E(v_{ij}^2v_{ii}v_{jj})$ and $E(v_{ii}^2v_{jj}^2)$.

$$
\begin{aligned}
E(v_{ij}^4) &= E[(\boldsymbol{w}_i'\boldsymbol{w}_j\boldsymbol{w}_j'\boldsymbol{w}_i)^2] \\
&= E[(\boldsymbol{w}_i'\boldsymbol{A}_j\boldsymbol{w}_j)^2],
\end{aligned}
$$

where $\boldsymbol{A}_j = \boldsymbol{w}_j\boldsymbol{w}_j'$.

Let G be an orthogonal matrix such that $\mathbf{G}\mathbf{A}_j\mathbf{G}' = diag(\boldsymbol{w}_j'\boldsymbol{w}_j, 0, \ldots, 0)$, then since for a given $\mathbf{A}_j$, $\boldsymbol{h}_i = \mathbf{G}\boldsymbol{w}_i \sim N_{v_e}(\mathbf{0}, \mathbf{I}_{v_e})$, it follows that $\boldsymbol{h}_i$ is independently distributed of $\mathbf{A}_j$ and $h_{ik} \sim N(0,1)$, $h_{ik}^2 \sim \chi_{(1)}^2$. Subsequently,

$$
\begin{aligned}
E(v_{ij}^4) &= E[(\boldsymbol{w}_i'\mathbf{G}'(\mathbf{G}\boldsymbol{A}_j\mathbf{G}')\mathbf{G}\boldsymbol{w}_i)^2] \\
&= E[(\boldsymbol{h}_i' diag(\boldsymbol{w}_j'\boldsymbol{w}_j, 0, \ldots, 0)\boldsymbol{h}_i)^2] \\
&= E[(h_{i1}^2 \boldsymbol{w}_j'\boldsymbol{w}_j)^2] \\
&= E(h_{i1}^2)^2 E(\boldsymbol{w}_j'\boldsymbol{w}_j)^2 = 3v_e(v_e+2) .
\end{aligned}
$$

Similarly,

$$
\begin{aligned}
E(v_{ij}^2 v_{ii} v_{jj}) &= E[(\boldsymbol{w}_i'\boldsymbol{w}_j\boldsymbol{w}_j'\boldsymbol{w}_j)(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_j'\boldsymbol{w}_j)] \\
&= E[(\boldsymbol{w}_i'\boldsymbol{A}_j\boldsymbol{w}_j)(\boldsymbol{w}_i'\boldsymbol{w}_i)(\boldsymbol{w}_j{}'\boldsymbol{w}_j)], \quad \text{where } \boldsymbol{A}_j = \boldsymbol{w}_j\boldsymbol{w}_j' \\
&= E[(h_{i1}^2 \boldsymbol{w}_j{}'\boldsymbol{w}_j)(\boldsymbol{w}_i'\boldsymbol{G}'\boldsymbol{G}\boldsymbol{w}_i)(\boldsymbol{w}_j{}'\boldsymbol{w}_j)] \\
&= E[(h_{i1}^2)(\boldsymbol{h}_i'\boldsymbol{h}_i)(\boldsymbol{w}_j{}'\boldsymbol{w}_j)^2] \\
&= E[(h_{i1}^2)(\sum_{k=1}^{v_e} h_{ik})(\boldsymbol{w}_j{}'\boldsymbol{w}_j)^2] \\
&= E[(h_{i1}^2 \sum_{k=1}^{v_e} h_{ik}^2)] \cdot E[(\boldsymbol{w}_j{}'\boldsymbol{w}_j)^2] \\
&= E[(h_{i1}^2)(\sum_{k=1}^{v_e} h_{ik}^2)] \cdot E[(\boldsymbol{w}_j{}'\boldsymbol{w}_j)^2] \\
&= E[(h_{i1}^2)^2 + \sum_{k=2}^{v_e} h_{i1}^2 h_{ik}^2)] \cdot E[(\boldsymbol{w}_j{}'\boldsymbol{w}_j)^2] \\
&= [(1)(3) + (v_e - 1)] \cdot v_e(v_e+2) \\
&= v_e(v_e+2)^2 .
\end{aligned}
$$

Finally,

$$
\begin{aligned}
E(v_{ii}^2 v_{jj}^2) &= E(v_{ii}^2)E(v_{jj}^2) \\
&= \left[v_e(v_e+2)\right]^2 .
\end{aligned}
$$

Thus $$\operatorname{var}(s_{ij}) = E(s_{ij}^2) = E\left[v_{ij}^4 - \frac{2}{v_e} v_{ij}^2 v_{ii} v_{jj} + \frac{1}{v_e^2} v_{ii}^2 v_{jj}^2\right]$$

$$= 3v_e(v_e+2) - \frac{2}{v_e} v_e(v_e+2)^2 + \frac{1}{v_e^2}\left[v_e(v_e+2)\right]^2$$

$$= 3v_e(v_e+2) - 2(v_e+2)^2 + (v_e+2)^2$$

$$= 3v_e(v_e+2) - (v_e+2)^2$$

$$= (v_e+2)[3v_e - v_e - 2]$$

$$= 2(v_e+2)(v_e-1)\,. \qquad \square$$

Lemma A.3 Let v_{ii} be i.i.d. as $\chi^2_{v_e}$,

$$f_1 = \frac{v_e - 1}{v_e pu} \sum_{i=1}^{pu} \lambda_i^2 v_{ii}^2 \quad \text{and} \quad f_2 = \frac{2}{pu} \sum_{i<j}^{pu} \lambda_i \lambda_j s_{ij}\,,$$

then

(i) $\operatorname{cov}(f_1, f_2) = 0$,

(ii) $\operatorname{var}(f_1) = \left[\frac{8(v_e+2)(v_e+3)(v_e-1)^2}{v_e^2 pu}\right] a_4$,

(iii) $\operatorname{var}(f_2) = \left[\frac{8(v_e+2)(v_e-1)}{(pu)^2}\right]\left(\sum_{i<j}^{pu} \lambda_i^2 \lambda_j^2\right)$

$$= 4(v_e+2)(v_e-1)\left(a_2^2 - \frac{a_4}{pu}\right) \simeq 4v_e^2\left(a_2^2 - \frac{a_4}{pu}\right).$$

Proof. From Lemma A.2, $E(f_2) = \frac{2}{pu} \sum_{i<j}^{pu} \lambda_i \lambda_j E(s_{ij}) = 0$, then

(i) $\operatorname{cov}(f_1, f_2) = E(f_1 f_2) - E(f_1)E(f_2)$

$$= E(f_1 f_2)$$

$$= \frac{v_e - 1}{v_e pu} \cdot \frac{2}{pu} E\left[\left(\sum_{i=1}^{pu} \lambda_i^2 v_{ii}^2\right)\left(\sum_{i<j}^{pu} \lambda_i \lambda_j s_{ij}\right)\right], \qquad \text{(a.5)}$$

where

$$E\left[\left(\sum_{i=1}^{pu}\lambda_i^2 v_{ii}^2\right)\left(\sum_{i<j}^{pu}\lambda_i\lambda_j s_{ij}\right)\right]=\lambda_1^2 E\left[v_{11}^2\left(\sum_{i<j}^{pu}\lambda_i\lambda_j s_{ij}\right)\right]+\lambda_2^2 E\left[v_{22}^2\left(\sum_{i<j}^{pu}\lambda_i\lambda_j s_{ij}\right)\right]$$

$$+\cdots+\lambda_2^2 E\left[v_{(pu)(pu)}^2\left(\sum_{i<j}^{pu}\lambda_i\lambda_j s_{ij}\right)\right]. \qquad \text{(a.6)}$$

Now let us consider $E(v_{ii}^2 s_{jk})$, when $j \neq k$.

If $i = j \neq k$,

$$\begin{aligned}
E(v_{ii}^2 s_{ik}) &= E\left[v_{ii}^2\left(v_{ik}^2-\frac{1}{v_e}v_{ii}v_{kk}\right)\right]\\
&= E\left[v_{ii}^2 v_{ik}^2-\frac{1}{v_e}v_{ii}^3 v_{kk}\right]\\
&= E\left[(\boldsymbol{w}_i'\boldsymbol{w}_i)^2(\boldsymbol{w}_i'\boldsymbol{w}_k\boldsymbol{w}_k'\boldsymbol{w}_i)-\frac{1}{v_e}(\boldsymbol{w}_i'\boldsymbol{w}_i)^3(\boldsymbol{w}_k'\boldsymbol{w}_k)\right]\\
&= E(\boldsymbol{w}_i'\boldsymbol{w}_i)^2 E(\boldsymbol{w}_i'\boldsymbol{w}_k\boldsymbol{w}_k'\boldsymbol{w}_i)-\frac{1}{v_e}E(\boldsymbol{w}_i'\boldsymbol{w}_i)^3 E(\boldsymbol{w}_k'\boldsymbol{w}_k)\\
&= E(\boldsymbol{w}_i'\boldsymbol{w}_i)^2 E(\boldsymbol{w}_i'\boldsymbol{w}_i)-\frac{1}{v_e}E(\boldsymbol{w}_i'\boldsymbol{w}_i)^3(v_e)\\
&= E(\boldsymbol{w}_i'\boldsymbol{w}_i)^3-E(\boldsymbol{w}_i'\boldsymbol{w}_i)^3=0.
\end{aligned}$$

If $i \neq j \neq k$,

$$\begin{aligned}
E(v_{ii}^2 s_{jk}) &= E\left[v_{ii}^2\left(v_{jk}^2-\frac{1}{v_e}v_{jj}v_{kk}\right)\right]\\
&= E\left[v_{ii}^2 v_{jk}^2-\frac{1}{v_e}v_{ii}^2 v_{jj}v_{kk}\right]\\
&= E\left[(\boldsymbol{w}_i'\boldsymbol{w}_i)^2(\boldsymbol{w}_j'\boldsymbol{w}_k\boldsymbol{w}_k'\boldsymbol{w}_j)-\frac{1}{v_e}(\boldsymbol{w}_j'\boldsymbol{w}_j)^3(\boldsymbol{w}_k'\boldsymbol{w}_k)\right]\\
&= E(\boldsymbol{w}_i'\boldsymbol{w}_i)^2 E(\boldsymbol{w}_j'\boldsymbol{w}_k\boldsymbol{w}_k'\boldsymbol{w}_j)-\frac{1}{v_e}E(\boldsymbol{w}_i'\boldsymbol{w}_i)^2 E(\boldsymbol{w}_j'\boldsymbol{w}_j)E(\boldsymbol{w}_k'\boldsymbol{w}_k)\\
&= E(\boldsymbol{w}_i'\boldsymbol{w}_i)^2 E(\boldsymbol{w}_j'\boldsymbol{w}_j)-\frac{1}{v_e}E(\boldsymbol{w}_i'\boldsymbol{w}_i)^2 E(\boldsymbol{w}_j'\boldsymbol{w}_j)v_e\\
&= E(\boldsymbol{w}_i'\boldsymbol{w}_i)^2 E(\boldsymbol{w}_j'\boldsymbol{w}_j)-E(\boldsymbol{w}_i'\boldsymbol{w}_i)^2 E(\boldsymbol{w}_j'\boldsymbol{w}_j)=0.
\end{aligned}$$

If $i = k \neq j$, $E(v_{ii}^2 s_{ji}) = E\left[v_{ii}^2 \left(v_{ji}^2 - \frac{1}{v_e} v_{jj} v_{ii} \right) \right]$

$$= E\left[v_{ii}^2 v_{ji}^2 - \frac{1}{v_e} v_{ii}^3 v_{jj} \right]$$

$$= E\left[(\boldsymbol{w}_i'\boldsymbol{w}_i)^2 (\boldsymbol{w}_i'\boldsymbol{w}_j \boldsymbol{w}_j'\boldsymbol{w}_i) - \frac{1}{v_e} (\boldsymbol{w}_i'\boldsymbol{w}_i)^3 (\boldsymbol{w}_j'\boldsymbol{w}_j) \right]$$

$$= E(\boldsymbol{w}_i'\boldsymbol{w}_i)^2 E(\boldsymbol{w}_i'\boldsymbol{w}_j \boldsymbol{w}_j'\boldsymbol{w}_i) - \frac{1}{v_e} E(\boldsymbol{w}_i'\boldsymbol{w}_i)^2 E(\boldsymbol{w}_j'\boldsymbol{w}_j) E(\boldsymbol{w}_k'\boldsymbol{w}_k)$$

$$= E(\boldsymbol{w}_i'\boldsymbol{w}_i)^2 E(\boldsymbol{w}_i'\boldsymbol{w}_i) - \frac{1}{v_e} E(\boldsymbol{w}_i'\boldsymbol{w}_i)^3 E(\boldsymbol{w}_j'\boldsymbol{w}_j)$$

$$= E(\boldsymbol{w}_i'\boldsymbol{w}_i)^3 - E(\boldsymbol{w}_i'\boldsymbol{w}_i)^3 = 0.$$

Hence, from (a.6) and (a.7), we obtain

$$E\left[\left(\sum_{i=1}^{pu} \lambda_i^2 v_{ii}^2 \right) \left(\sum_{i<j}^{pu} \lambda_i \lambda_j s_{ij} \right) \right] = 0 \text{, which leads to } \operatorname{cov}(f_1, f_2) = 0 .$$

(ii) $\operatorname{var}(f_1) = \left(\frac{v_e - 1}{v_e pu} \right)^2 \operatorname{var}\left(\sum_{i=1}^{pu} \lambda_i^2 v_{ii}^2 \right)$

$$= \frac{(v_e - 1)^2}{v_e^2 (pu)^2} \left(\sum_{i=1}^{pu} \lambda_i^4 \operatorname{var}(v_{ii}^2) + \sum_{i<j}^{pu} \lambda_i^2 \lambda_2^2 \operatorname{cov}(v_{ii}^2 v_{jj}^2) \right).$$

By Lemma A.1,

$$= \frac{(v_e - 1)^2}{v_e^2 (pu)^2} \left(8 v_e (v_e + 2)(v_e + 3) \sum_{i=1}^{pu} \lambda_i^4 \right)$$

$$= \frac{8(v_e + 2)(v_e + 3)(v_e - 1)^2}{v_e^2 pu} \left(\frac{tr(\boldsymbol{\Phi}_\Upsilon^4)}{pu} \right)$$

$$= \left(\frac{8(v_e + 2)(v_e + 3)(v_e - 1)^2}{v_e^2 pu} \right) a_4 .$$

(iii) $$\operatorname{var}(f_2) = \left(\frac{2}{pu}\right)^2 \operatorname{var}\left(\sum_{i<j}^{pu} \lambda_i \lambda_j s_{ij}\right)$$

$$= \frac{4}{(pu)^2} \operatorname{var}\left(\sum_{i<j}^{pu} \lambda_i \lambda_j s_{ij}\right)$$

$$= \frac{4}{(pu)^2} \sum_{i<j}^{pu} \lambda_i^2 \lambda_j^2 \operatorname{var}(s_{ij}).$$

By Lemma A.2 , $\operatorname{var}(s_{ij}) = 2(v_e+2)(v_e-1)$), then

$$\operatorname{var}(f_2) = \frac{4}{(pu)^2}\left(2(v_e+2)(v_e-1)\sum_{i<j}^{pu} \lambda_i^2 \lambda_j^2\right)$$

$$= \frac{8(v_e+2)(v_e-1)}{(pu)^2}\left(\sum_{i<j}^{pu} \lambda_i^2 \lambda_j^2\right),$$

($\because \left(\sum_{i=1}^{pu} \lambda_i^2\right)^2 = \sum_{i=1}^{pu} \lambda_i^4 + 2\sum_{i<j}^{pu} \lambda_i^2 \lambda_j^2$)

$$= 8(v_e+2)(v_e-1)\cdot \frac{\frac{1}{2}\left[(\sum_{i=1}^{pu} \lambda_i^2)^2 - \sum_{i=1}^{pu} \lambda_i^4 \right]}{(pu)^2}$$

$$= 4(v_e+2)(v_e-1)\cdot \left(\frac{(\sum_{i=1}^{pu} \lambda_i^2)^2}{(pu)^2} - \frac{\sum_{i=1}^{pu} \lambda_i^4}{(pu)^2} \right)$$

$$= 4(v_e+2)(v_e-1)\cdot \left\{ \left(\frac{tr(\mathbf{\Phi}_{\Upsilon}^2)}{pu}\right)^2 - \frac{tr(\mathbf{\Phi}_{\Upsilon}^4)}{(pu)^2} \right\}$$

$$= 4(v_e+2)(v_e-1)\left(a_2^2 - \frac{a_4}{pu}\right) \simeq 4v_e^2\left(a_2^2 - \frac{a_4}{pu}\right).$$ □

Now the proof for Lemma 2.1 will be given using the fact that any estimator is consistent if it is unbiased and its variance goes to zero as $n \to \infty$ (Lehmann and Casella, 1988 :) (theorem 1.8.2).

(1) To show that $\hat{a}_1$ is a consistent estimator of a_1.

From equation (a.1),

$$E(\hat{a}_1) = \frac{1}{v_e pu} E\left[tr(\mathbf{S}_e)\right]$$

$$= \frac{1}{v_e pu} E\left[\sum_{i=1}^{pu} \lambda_i v_{ii}\right] = \frac{1}{v_e pu} \sum_{i=1}^{pu} \lambda_i E(v_{ii})$$

$$= \frac{1}{v_e pu} \sum_{i=1}^{pu} \lambda_i v_e = \frac{1}{pu} \sum_{i=1}^{pu} \lambda_i$$

$$= \frac{tr(\mathbf{\Phi}_\Upsilon)}{pu} = a_1 \quad .$$

Hence , $\hat{a}_1$ is an unbiased estimator of a_1.

$$\operatorname{var}(\hat{a}_1) = \operatorname{var}\left[\frac{1}{v_e pu} tr(\mathbf{S}_e)\right]$$

$$= \frac{1}{(v_e pu)^2} \operatorname{var}\left[\sum_{i=1}^{pu} \lambda_i v_{ii}\right] = \frac{1}{(v_e pu)^2} \sum_{i=1}^{pu} \lambda_i^2 \operatorname{var}(v_{ii})$$

$$= \frac{1}{(v_e pu)^2} 2 v_e \sum_{i=1}^{pu} \lambda_i^2$$

$$= \frac{2}{v_e pu} \cdot \frac{tr(\mathbf{\Phi}_\Upsilon^2)}{pu} = \frac{2}{v_e pu} a_2 ,$$

then we obtain

$$\lim_{n,p\to\infty} \operatorname{var}(\hat{a}_1) = \lim_{n,p\to\infty} \frac{2}{v_e pu} a_2 = 0 .$$

(2) To show that $\hat{a}_2$ is a consistent estimator of a_2.

Let $\dfrac{1}{(v_e - 1)(v_e + 2)} = k$ and $\hat{a}_2 = \dfrac{k}{pu}\left[tr(\mathbf{S}_e^2) - \dfrac{1}{v_e}(tr(\mathbf{S}_e))^2\right]$, then from (a.3),

$$E(\hat{a}_2)=\frac{k}{pu}E\left[tr(\mathbf{S}_e^2)-\frac{1}{v_e}(tr(\mathbf{S}_e))^2\right]$$

$$=k\left\{\frac{v_e-1}{v_e pu}E\left[\sum_{i=1}^{pu}\lambda_i^2 v_{ii}^2\right]+\frac{2}{pu}E\left[\sum_{i<j}^{pu}\lambda_i\lambda_j s_{ij}\right]\right\}$$

$$=k\left\{\frac{v_e-1}{v_e pu}\sum_{i=1}^{pu}\lambda_i^2 E(v_{ii}^2)+\frac{2}{pu}\sum_{i<j}^{pu}\lambda_i\lambda_j E(s_{ij})\right\}$$

$$=k\left\{\frac{v_e-1}{v_e pu}v_e(v_e+2)\sum_{i=1}^{pu}\lambda_i^2+\frac{2}{pu}\sum_{i<j}^{pu}\lambda_i\lambda_j(0)\right\}$$

$$=k\left\{\frac{(v_e-1)(v_e+2)}{pu}tr(\mathbf{\Phi}_\Upsilon^2)\right\}$$

$$=\frac{1}{(v_e-1)(v_e+2)}\cdot\frac{(v_e-1)(v_e+2)}{pu}tr(\mathbf{\Phi}_\Upsilon^2)$$

$$=\frac{tr(\mathbf{\Phi}_\Upsilon^2)}{pu}=a_2\,.$$

Hence, $\hat{a}_2$ is an unbiased estimator of a_2. Next, the variance of $\hat{a}_2$ is found using Lemma A.3.

$$\mathrm{var}(\hat{a}_2)=k^2\ \mathrm{var}\left\{\frac{v_e-1}{v_e pu}\sum_{i=1}^{pu}\lambda_i^2 v_{ii}^2+\frac{2}{pu}\sum_{i<j}^{pu}\lambda_i\lambda_j s_{ij}\right\}$$

$$=k^2\ \mathrm{var}\left\{f_1+f_2\right\}$$

$$=k^2\left[\mathrm{var}(f)+\mathrm{var}(f_2)+\mathrm{cov}(f_1+f_2)\right]$$

$$=k^2\left\{\left[\frac{8(v_e+2)(v_e+3)(v_e-1)^2}{v_e^2 pu}\right]a_4+4(v_e+2)(v_e-1)\left(a_2^2-\frac{a_4}{pu}\right)\right\}$$

$$=k^2\left\{4(v_e+2)(v_e-1)a_2^2+\left(\frac{8(v_e+2)(v_e+3)(v_e-1)^2-4v_e^2(v_e+2)(v_e-1)}{v_e^2 pu}\right)a_4\right\}$$

$$=k^2\left\{4(v_e+2)(v_e-1)a_2^2+\left(\frac{4(v_e+2)(v_e-1)}{v_e^2 pu}\right)\left(2(v_e+3)(v_e-1)-v_e^2\right)a_4\right\}$$

$$=k^2\left\{4(v_e+2)(v_e-1)a_2^2-\left(\frac{4(v_e+2)(v_e-1)\left(v_e^2+4v_e-3\right)}{v_e^2 pu}\right)a_4\right\}$$

$$= \frac{1}{(v_e-1)^2(v_e+2)^2}\left\{4(v_e+2)(v_e-1)a_2^2 + \left(\frac{4(v_e+2)(v_e-1)\left(v_e^2+4v_e-3\right)}{v_e^2 pu}\right)a_4\right\}$$

$$= \frac{4}{(v_e-1)(v_e+2)}\left[a_2^2 - \frac{\left(v_e^2+4v_e-3\right)}{v_e^2 pu}a_4\right].$$

Subsequently, under assumption (3.15) in Chapter 2, we obtain

$$\lim_{n,p\to\infty}\operatorname{var}(\hat{a}_2) = \lim_{n,p\to\infty}\left[\frac{4}{(v_e-1)(v_e+2)}\right]a_2^2 + \lim_{n,p\to\infty}\left[\frac{4\left(v_e^2+4v_e-3\right)}{(v_e+2)(v_e-1)v_e^2 pu}\right]a_4$$

$$= 0. \qquad \square$$

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