Descriptive Discriminant Analysis for Repeated Measures Data

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By

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Abstract

Background: Linear discriminant analysis (DA) encompasses procedures for classifying observations into groups (predictive discriminant analysis, PDA) and describing the relative importance of variables for distinguishing between groups (descriptive discriminant analysis, DDA) in multivariate data. In recent years, there has been increased interest in DA procedures for repeated measures data. PDA procedures that assume parsimonious repeated measures mean and covariance structures have been developed, but corresponding DDA procedures have not been proposed. Most DA procedures for repeated measures data rest on the assumption of multivariate normality, which may not be satisfied in biostatistical applications. For example, health-related quality of life (HRQOL) measures, which are increasingly being used as outcomes in clinical trials and cohort studies, are likely to exhibit skewed or heavy-tailed distributions. As well, measures of relative importance based on discriminant function coefficients (DFCs) for DDA procedures have not been proposed for repeated measures data. **Purpose:** The purpose of this research is to develop repeated measures discriminant analysis (RMDA) procedures based on parsimonious covariance structures, including compound symmetric and first order autoregressive structures, and that are robust (i.e., insensitive) to multivariate non-normal distributions. It also extends these methods to evaluate the relative importance of variables in multivariate repeated measures (i.e., doubly multivariate) data. **Method**: Monte Carlo studies were conducted to investigate the performance of the proposed RMDA procedures under various degrees of group mean separation, repeated measures correlation structures, departure from multivariate normality, and magnitude of covariance mis-specification. Data from the Manitoba Inflammatory Bowel Disease Cohort Study, a prospective longitudinal cohort study about the psychosocial

determinants of health and well-being, are used to illustrate their applications. **Results**: The conventional maximum likelihood (ML) estimates of DFCs for RMDA procedures based on parsimonious covariance structures exhibited substantial bias and error when the covariance structure was mis-specified or when the data followed a multivariate skewed or heavy-tailed distribution. The DFCs of RMDA procedures based on robust estimators obtained from coordinatewise trimmed means and Winsorized variances, were less biased and more efficient when the data followed a multivariate non-normal distribution, but were sensitive to the effects of covariance mis-specification. Measures of relative importance for doubly multivariate data based on linear combinations of the within-variable DFCs resulted in the highest proportion of correctly ranked variables. **Conclusions**: DA procedures based on parsimonious covariance structures and robust estimators will produce unbiased and efficient estimates of variable relative importance of variables in repeated measures data and can be used to test for change in relative importance over time. The choice among these RMDA procedures should be guided by preliminary descriptive assessments of the data.

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Dedication

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Chapter 1. Introduction

Linear discriminant analysis (DA) is a multivariate procedure for predicting group membership (predictive discriminant analysis, PDA) and describing group separation (descriptive discriminant analysis, DDA) in multivariate data for two or more groups of study participants. PDA focuses on the development of efficient classification rules, while DDA identifies the relative importance of variables for discriminating between groups using measures based on discriminant function coefficients (DFCs)[1-2].

In recent years, there has been increased interest in DA procedures for repeated measures data, which arise when measurements are collected at two or more occasions for a single variable (i.e., univariate repeated measures data) or multiple variables (i.e., multivariate repeated measures data or doubly multivariate data). The linear DA procedure has some limitations when applied to repeated measures data; it assumes complete observations, a multivariate normal distribution, and equal numbers of observations for each study participant. DA procedures for repeated measures data have been developed based on growth curve, covariance pattern, and mixed-effects models[5-8], but these procedures are for predicting group membership and not for describing the relative importance of variables for describing group differences (i.e., DDA).

DA procedures for repeated measures data have a number of applications. They have been used to predict pregnancy outcomes (i.e., normal versus abnormal) based on diagnostic test results collected over time[3], and to classify study participants as depressed or not depressed based on depression scale scores collected over time[4].

DDA procedures have also been applied to health-related quality of life (HRQOL) data[9], although not to repeated measures HRQOL data. HRQOL data consist of individuals' ratings on

multiple inter-related dimensions (i.e., domains) that encompass physical, mental, and social health. Longitudinal HRQOL studies examine trajectories of change in health status repeatedly over time and the psychosocial factors associated with change[10-11].

Applying DDA procedures to non-normal data may lead to biased conclusions about the variables that discriminate between groups[1]. PDA procedures have been developed for multivariate non-normal data and are based on multivariate generalization of Box and Cox[12] transformation[13], rank transformation[14], and non-parametric approaches such as kernel density estimation[1]. Robust DDA procedures have not been developed for multivariate repeated measures data. Therefore, the development of DDA procedures that are robust to non-normality in high-dimensional repeated measures data and their application for evaluating variable importance in studies of HRQOL data, which are often characterized by non-normal distributions[15], represents an opportunity for research.

1.1 Purpose and Objectives

The purpose of this research is to develop DDA procedures for the analysis of repeated measures data. The objectives are to develop:

1. DDA procedures based on parsimonious covariance structures for repeated measures data;
2. DDA procedures based on robust estimators for non-normal data;
3. Techniques based on repeated measures DDA procedures for describing the relative importance of variables in multivariate repeated measures data.

1.2 Rationale for Thesis

Health-related quality of life (HRQOL) measures are employed in clinical, observational, comparative effectiveness, and health services research studies as predictors, mediators, moderators or outcome variables to investigate factors affected by, and affecting health. For example, HRQOL data collected at one point in time might be used to predict mortality or morbidity one or five years later. HRQOL measures are also used to investigate the effectiveness of both clinical and population-based interventions, such as new treatments for chronic disease[16-17].

DDA procedures developed in this research will be particularly useful for assessing the relative importance of HRQOL dimensions that discriminate between groups of study participants measured over time. The ability to make statements like "… was the most important HRQoL dimension" or "… had the greatest impact of all the dimensions" can help clinicians to understand the aspects of HRQOL that are amenable to change. This in turn may help to inform treatment decisions. When comparing chronic disease patients to healthy controls, DDA procedures can provide information about the domains on which the disease has the greatest effect, which might be useful in the development of clinical interventions.

In clinical investigations, differences between treatment and control groups are often investigated on multiple correlated outcomes. The familywise Type I error rate (FWR), the probability of erroneously rejecting at least one null hypothesis, may be allocated unequally amongst primary and secondary outcomes[18-19]. The DDA procedures developed in this research could be used to assign weights to the outcomes. They can also be used to detect response shift, which is a change in patients' self-evaluation of their perceptions, feelings, or behaviours over time[20-21]. DDA procedures can be used for variable selection, to develop parsimonious statistical

models.

1.3 Organization of Thesis

This thesis is organized into three sections and is comprised of four manuscripts. Three of the manuscripts are published, and the last is in preparation for peer-review submission. Section I begins with *Manuscript 1*, "*Discriminant analysis for repeated measures data: a review*", which is presented in *Chapter 2*. This manuscript reviews the literature on DA procedures for repeated measures data, including procedures based on covariance structure, mixed-effects, and growth curve models. Their implementation is illustrated using an example dataset. *Chapter 3* is a linking chapter that summarizes the strengths and limitations of existing DA procedures. *Manuscript 2* is presented in *Chapter 4*, "*Discriminant analysis for repeated measures data: effects of mean and covariance misspecification on bias and error in discriminant function coefficients*". The effects of covariance structure misspecification on bias and error in the discriminant function coefficients of repeated measures DA procedures were investigated using Monte Carlo methods.

Section II begins with *Chapter 5*, which examines the strengths and limitations of existing robust DA procedures for multivariate non-normal data. These include trimmed estimators, which have been shown to possess good theoretical properties for non-normal data, are computationally efficient, and are relatively straightforward to implement. The theory underlying trimmed estimators for multivariate data is reviewed and trimming approaches for multivariate and repeated measures data are presented. *Manuscript 3* is presented in *Chapter 6*, "*Robust descriptive discriminant analysis for repeated measures data*". The manuscript

investigates the development of robust DDA procedures based on trimmed means and Winsorized covariances. The effects of population distribution on bias and error in the discriminant function coefficients of DDA procedures based on least squares or maximum likelihood estimators, as well as trimmed estimators, were evaluated using Monte Carlo methods.

Section III focuses on measures of relative importance for variables in multivariate repeated measures data. The section begins with a review of existing measures of relative importance based on DDA models in *Chapter 7*. *Chapter 8* investigates methods based on RMDA procedures for evaluating the relative importance of variables in multivariate repeated measures data. Discriminant function coefficients are used in combination with dimension reduction techniques to evaluate the relative importance of variables in multivariate repeated measures data. Monte Carlo technique was used to evaluate the methods under a variety of data-analytic conditions. Data from the Manitoba Inflammatory Bowel Disease (IBD) cohort study is used to demonstrate the implementation of the procedures.

Chapter 9 summarizes the key findings and research conclusions. Limitations of the research and opportunities for future research are also presented.

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Section I. Repeated Measures Discriminant Analysis

Chapter 2. Discriminant Analysis for Repeated Measures Data: A Review

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This manuscript has been modified to meet the dissertation requirements of the University of Saskatchewan. My contribution to this published manuscript includes the review of the literature, statistical analysis using an example dataset, and preparation of manuscripts for publication.

Abbreviation

AIC = Akaike information criterion

APER = Apparent error rate

AR-1 = First-order autoregressive

CS = Compound Symmetric

DA = Discriminant analysis

DDA = Descriptive discriminant analysis

DRD = Discriminant –regression-discriminant

HAM-D = Hamilton Depression Rating Scale

MANOVA = Multivariate Analysis of Variance

MAR = Missing at Random

MER = Misclassification error rate

PDA = Predictive discriminant analysis

UN = Unstructured

Abstract

Discriminant analysis (DA) encompasses procedures for classifying observations into groups (i.e., predictive discriminative analysis) and describing the relative importance of variables for distinguishing amongst groups (i.e., descriptive discriminative analysis). In recent years, a number of developments have occurred in DA procedures for the analysis of data from repeated measures designs. Specifically, DA procedures have been developed for repeated measures data characterized by missing observations and/or unbalanced measurement occasions, as well as high-dimensional data in which measurements are collected repeatedly on two or more variables. This paper reviews the literature on DA procedures for univariate and multivariate repeated measures data, focusing on covariance pattern and linear mixed-effects models. A numeric example illustrates their implementation using SAS software.

Keywords: repeated measures; longitudinal; multivariate; classification; missing data

2.1 Introduction

Linear discriminant analysis (DA), first introduced by Fisher[1] and discussed in detail by Huberty and Olejnik[2], is a multivariate technique to classify study participants into groups (predictive discriminant analysis; PDA) and describe group differences (descriptive discriminant analysis; DDA). DA is widely used in applied psychological research to develop accurate and efficient classification rules and to assess the relative importance of variables for discriminating between groups.

To illustrate, consider the study of Onur, Alkin, and Tural[3]. The authors investigated clinical measures to distinguish patients with respiratory panic disorder from patients with non-respiratory panic disorder. The authors developed a classification rule in a training dataset, that is, in a sample of patients with panic disorder (N = 124) in which patients with the respiratory subtype (n_1 = 79) could be identified. Data were collected for all patients on eight measures of panic-agoraphobia spectrum symptoms and traits. Using PDA, a classification rule was developed with these eight measures; the rule accurately assigned 86.1% of patients to the correct subtype. DDA results showed that four of the measures were most important for discriminating between patients with and without respiratory panic disorder. The rule developed in the training dataset is used to classify new patients with panic disorder into subtype groups in order to "tailor more specific treatment targets" (p. 485).

DA has been applied to a diverse range of studies within the psychology discipline. For example, in neuropsychology it has been used to distinguish children with autism from healthy controls[4], in educational psychology it has been applied in studies about intellectually gifted students[5], and in clinical psychology it has been applied in addictions research[6]. Sherry[7] discusses some applications in counseling psychology.

DA is usually applied to multivariate problems in which data are collected at a single point in time. Multivariate textbooks that include sections on DA[8-10] as well as DA textbooks[2,11] provide little, if any, discussion about procedures for repeated measures designs, in which study participants provide responses at two or more measurement occasions. Repeated measures designs arise in many disciplines, including social and behavioral science disciplines. A review of DA procedures for repeated measures data is therefore timely given that a number of developments have occurred in procedures for data characterized by missing observations and/or unbalanced measurement occasions and high-dimensional data in which measurements are collected repeatedly on two or more variables.

The purpose of this manuscript is to (a) provide examples of the types of research problems to which repeated measures DA procedures can be applied, (b) describe several repeated measures DA procedures, focusing on those based on covariance pattern and linear mixed-effects regression models, and (c) illustrate the implementation of these procedures.

2.2 Statistical Concepts in Discriminant Analysis

Let $\mathbf{y}_{ij}$ be a $q \times 1$ vector of observed measurements on q variables in a training dataset, in which group membership is known, for the ith study participant ($i = 1, ..., n_j$) in the jth group ($j = 1, 2$). While this manuscript focuses on the analysis of two-group designs, the procedures have been generalized to multi-group problems[1,11]. It is assumed that $\mathbf{y}_{ij} \sim N_q(\boldsymbol{\mu}_j, \boldsymbol{\Sigma}_j)$, where $\boldsymbol{\mu}_j$ and $\boldsymbol{\Sigma}_j$ are the population mean vector and covariance matrix for the jth group and are estimated by $\hat{\boldsymbol{\mu}}_j$ and $\hat{\boldsymbol{\Sigma}}_j$, respectively.

The linear DA classification rule is: Assign the ijth study participant to group 1 if

$$\lambda(\mathbf{y}_{ij}) = \left[\mathbf{y}_{ij} - \frac{1}{2}(\hat{\boldsymbol{\mu}}_1 + \hat{\boldsymbol{\mu}}_2) \right]^{\mathrm{T}} \hat{\mathbf{a}} > \ln(\frac{\hat{\pi}_2}{\hat{\pi}_1}), \quad (1)$$

else assign the study participant to group 2. In equation 1, $^{\mathrm{T}}$ is the transpose operator, $\hat{\mathbf{a}} = \hat{\boldsymbol{\Sigma}}^{-1}(\hat{\boldsymbol{\mu}}_1 - \hat{\boldsymbol{\mu}}_2)$, the estimate of the linear discriminant function, **a**, where

$$\hat{\boldsymbol{\Sigma}} = \frac{(n_1 - 1)\hat{\boldsymbol{\Sigma}}_1 + (n_2 - 1)\hat{\boldsymbol{\Sigma}}_2}{n_1 + n_2 - 2}. \quad (2)$$

The parameters π_1 and π_1 are the *a priori* probabilities that observations belong to populations 1 and 2, respectively and may be estimated by,

$$\hat{\pi}_j = \frac{n_j}{N}, \quad (3)$$

where $N = n_1 + n_2$. Standardized discriminant function coefficients are obtained by multiplying $\hat{\mathbf{a}}$ by a diagonal matrix of variable standard deviations. The relative importance of the variables for discriminating between groups can be assessed by the magnitude of the absolute value of these standardized coefficients, although other measures of relative importance, which are functions of the discriminant function coefficients, have also been proposed[12-13].

The accuracy of the classification rule is described by the misclassification error rate (MER), the probability that an individual is incorrectly allocated to the *j*th population. The MER is estimated by the apparent error rate[8,10],

$$APER = \frac{N - n_{11} - n_{22}}{N}, \quad (4)$$

where n_{11} and n_{22} are the number of study participants correctly assigned to groups 1 and 2, respectively.

The group membership of a new study participant is predicted using the classification rule developed in the training dataset. However, prior to applying this rule to new data, the rule

should be validated in order to assess its generalizability. Internal and external validation techniques are discussed in a number of sources, including Timm[10] and McLachlan[11].

Papers that provide a more detailed introduction to the theory and application of classical linear DA include Huberty[14] and Sherry[7]. A critical evaluation of the differences between DA and logistic regression, another method that is commonly applied to classification problems, is provided by Lei and Koehly[15]. In general, DA is preferred when its underlying derivational assumptions are satisfied because DA will have greater statistical power than logistic regression.

2.3 Examples of Potential Applications of Repeated Measures Discriminant Analysis

Repeated measures DA procedures are applied to data collected on multiple occasions for the same individual; often these data will arise in studies about development, maturation, or aging processes. Below, we discuss a number of examples of the kinds of studies in which repeated measures DA can be used.

Levesque, Ducharme, Zarit, Lachance, and Giroux[16] were interested in classifying husbands, who were care providers for functionally or cognitively impaired wives, into three psychological distress groups based on changes in exposure to stress over time. The variables in the study included objective stressors, such as wives' functional impairment and memory and behavioral problems, as well as subjective stressors such as role overload and relationship deprivation. All variables were collected at two measurement occasions. Measures of change over time, as well as some of the baseline measurements, were used to develop the classification model using conventional linear DA. A total of $N = 205$ study participants provided data at the

baseline measurement occasion. More than one quarter (28.2%) of participants dropped out of the study between the first and second measurement occasions; these individuals were excluded from the analysis.

A second example comes from the study of Rietveld et al.[17]. The researchers were interested in discriminating monozygotic from dizygotic twins using measures of twin similarity and confusion collected at ages six, eight, and 10 years. Self-report data on these measures were obtained from both mothers and fathers. Classical linear DA was used to construct a separate classification rule for each measurement occasion and for each parent, resulting in a total of six rules. The rules were used to describe differences in classification accuracy over time and between parents. Loss to follow up was substantial. While 691 twin pairs were initially recruited into the study, by the third measurement occasion (i.e., age 10), mothers' evaluations were only available for 324 (46.9%) twin pairs and fathers' evaluations were only available for 279 (40.4%) pairs. The classification rules were validated using a leave-one-out internal validation method.

de Coster, Leentjens, Lodder, and Verhey[18] applied classical linear DA to develop a classification rule for first-time stroke patients using data collected on the 17 items of the Hamilton Rating Scale for Depression (HAM-D) at one, three, six, and nine months post stroke. A total of 206 patients were classified as depressed or not depressed; the depression diagnosis was assigned based on the Structured Clinical Interview for the DSM-IV. The measurements collected prior to the diagnosis of depression were used to classify patients into groups using classical linear DA. The following HAM-D items were most important for discriminating between depressed and non-depressed patients: depressed mood, reduced appetite, thoughts of suicide, psychomotor retardation, psychic anxiety, and fatigue. Loss to follow up was small (i.e.,

about 10%).

2.4 Repeated Measures Discriminant Analysis

While the previous section illustrates the kinds of studies in which repeated measures DA procedures can be applied, the authors of these studies used the classical linear DA procedure instead. The application of classical linear DA to repeated measures data has been criticized for a number of reasons[19-20]: (a) observations with missing values are removed from analysis via casewise deletion, (b) covariates are difficult to include, and (c) the classical DA procedure cannot be applied to high dimensional data in which *N* is less than the product of the number of repeated measurements and the number of variables.

Research about repeated measures DA has primarily been undertaken for PDA procedures, rather than DDA procedures. Early research about PDA focused on procedures based on the growth curve model[21-23] as well as a stagewise discriminant, regression, discriminant (DRD) procedure[24]. Under the latter procedure, DA is applied separately to the data from each measurement occasion. The discriminant function coefficients estimated at each measurement occasion are then entered into a linear regression model and DA is applied to the slope and intercept coefficients from this regression model. In terms of DDA procedures, Albert and Kshirsagar[25] developed two procedures for univariate repeated measures data, which are used to evaluate the relative importance of the measurement occasions for discriminating amongst groups. The first procedure is based on repeated measures multivariate analysis of variance (MANOVA) while the second procedure is based on the growth curve model of Pothoff and Roy[26].

To introduce DA procedures for repeated measures data, denote $\mathbf{y}_l$ ($l = 1, \ldots, N$) as the vector of observations for the lth study participant, where the first n_j observation vectors are for participants in group 1 and the remaining observation vectors are for individuals in group 2. In the case of univariate repeated measures data, that is, data that are collected on multiple measurement occasions for a single variable, $\mathbf{y}_l$ has dimension $p_l \times 1$, where p_l is the number of measurement occasions for the lth individual. In multivariate repeated measures data, that is, data that are collected on multiple measurement occasions for two or more variables, $\mathbf{y}_l$ has dimension $qp_l \times 1$, where q is the number of variables. For simplicity, all procedures will be described for the case $p_l = p$.

2.4.1 The Covariance Pattern Model

The covariance pattern model was originally proposed by Jenrich and Schlutcher[27]. For univariate repeated measures data, the model is given by

$$\mathbf{y}_l = \mathbf{X}_l\boldsymbol{\beta} + \boldsymbol{\varepsilon}_l, \tag{5}$$

where $\boldsymbol{\beta}$ is the $k \times 1$ vector of parameters to be estimated, $\mathbf{X}_l$ is the $p \times k$ design matrix that defines groups membership, and $\boldsymbol{\varepsilon}_l \sim N_p(\mathbf{0}, \boldsymbol{\Sigma})$. Group means are computed from estimates of the fixed effects parameters, that is, $\hat{\boldsymbol{\mu}}_l = \mathrm{E}(\mathbf{y}_l) = \mathbf{X}_l\hat{\boldsymbol{\beta}}$. This model assumes $\boldsymbol{\Sigma}$ has a functional form such as compound symmetric (CS) or first-order autoregressive (AR-1). The CS covariance structure assumes equal correlation between pairs of measurement occasions and constant variance across the occasions. The assumption of equi-correlation, regardless of the time lag between measurement occasions, may not be realistic in data collected over time, where the magnitude of correlation often decreases as the time lag between measurement occasions

increases. The AR-1 covariance structure assumes the correlation between pairs of measurement occasions decays over time but the variance remains constant across the occasions [28]. By assuming a functional form for **Σ**, the number of variance and covariance parameters to estimate is reduced, which may result in improved classification accuracy and is advantageous to ensure the data are not overfit when total sample size is small relative to the number of measurement occasions. For example, in a study with $p = 4$ repeated measurements, there are $p(p + 1)/2 = 4(5)/2 = 10$ parameters to estimate when **Σ** is unstructured as compared to two parameters to estimate (one correlation and one variance) when a CS or AR-1 structure is assumed.

Repeated measures DA procedures based on the covariance pattern model can accommodate time-invariant covariates, that is, explanatory variables that do not change across the measurement occasions[28]. The inclusion of covariates in the model may help to improve classification accuracy. As well, it is possible to specify a mean structure for the model, such as assuming that the means remain constant over time [29], which reduces the number of mean parameters to estimate and therefore may further improve classification accuracy.

Repeated measures DA based on the covariance pattern model for univariate repeated measures data is described by Roy and Khattree[29]. Under a CS structure, the authors showed, via statistical proof that the classification rule does not depend on **Σ**. That is, assign the lth subject to group 1 if

$$\lambda(\mathbf{y}_l) = \sum_{k=1}^{p} y_{lk} \geq \left(\frac{\hat{\mu}_1 + \hat{\mu}_2}{2} \right) p, \tag{6}$$

else, allocate to group 2. In equation 6, y_{lk} is the observation for the lth study participant on the kth repeated measurement, $\hat{\mu}_j = p^{-1} \sum_{k=1}^{p} \hat{\mu}_{jk}$ and $\hat{\mu}_{jk}$ is the estimated mean for the jth group on the

*k*th repeated measurement. By comparison, for an AR-1 structure the classification rule depends on the correlation parameter, ρ, as well as the estimated group means.

Repeated measures DA based on the covariance pattern model have also been described for multivariate repeated measures data[30-32]. Briefly, the covariance matrix of the repeated measurements is assumed to have a Kronecker product structure, denoted by the notation $\boldsymbol{\Sigma} = \boldsymbol{\Sigma}_p \otimes \boldsymbol{\Sigma}_q$, where $\boldsymbol{\Sigma}_p$ is the covariance matrix of the repeated measurements and $\boldsymbol{\Sigma}_q$ is the covariance matrix of the variables. A Kronecker product structure assumes that the covariance matrix of the repeated measurements is constant across all variables; adopting this structure results in a substantial reduction in the number of parameters to estimate. For example, with p = 4 and q = 3, there are a total of 4(5)/2 + 3(4)/2 = 16 covariance parameters to estimate under a Kronecker product structure as compared to 12(13)/2 = 78 parameters to estimate when an unstructured covariance is assumed. Roy and Khatree[30] also describe models in which the multivariate mean vector is assumed to have a specific function form (i.e., constant mean) over time, although they do not investigate the effects of classification accuracy when the mean structure is misspecified. Misspecification of the covariance structure in both univariate and multivariate repeated measures analyses may result in increased misclassification rates. The effects of misspecification are considered in a subsequent section of this manuscript. Graphic exploration of the data, likelihood ratio tests, and penalized log-likelihood measures such as the Akaike information criterion (AIC) have been recommended to guide the selection of a well-fitted model with an appropriate covariance structure [28].

2.4.2 The Linear Mixed-Effects Model

For univariate repeated measures data, the linear mixed-effects model is

$$\mathbf{y}_l = \mathbf{X}_l\boldsymbol{\beta} + \mathbf{Z}_l\mathbf{d}_l + \boldsymbol{\varepsilon}_l\,, \tag{7}$$

where $\boldsymbol{\beta}$ is the $k \times 1$ vector of fixed effect parameters, $\mathbf{X}_l$ is the $p \times k$ matrix of corresponding covariates, and $\mathbf{Z}_l$ is the $p \times s$ design matrix associated with the $s \times 1$ vector of subject-specific random effects $\mathbf{d}_l$. The error vector $\boldsymbol{\varepsilon}_l \sim N_p(\mathbf{0}, \mathbf{U}_l)$ and the random effects vector $\mathbf{d}_l \sim N_s(\mathbf{0}, \mathbf{G}_l)$ are assumed to be independent. The subject-specific covariance matrix is defined as

$$\boldsymbol{\Sigma}_l = \mathbf{Z}_l\mathbf{G}_l\mathbf{Z}_l^{\mathrm{T}} + \mathbf{U}_l\,. \tag{8}$$

A repeated measures DA procedure based on the mixed-effects model was first proposed by Choi[33]. Subsequently, Tomasko et al.[20] developed procedures that assume various covariance structures (such as CS and AR-1) for $\mathbf{U}$, the covariance matrix of the residual errors; the application of these procedures was illustrated by Wernecke, Kalb, Schink, and Wegner[34]. The classification rule is: Assign the lth study participant to group 1 if

$$\lambda(\mathbf{y}_l) = \left[\mathbf{y}_l - \frac{1}{2}(\hat{\boldsymbol{\mu}}_{1l} + \hat{\boldsymbol{\mu}}_{2l})\right]^{\mathrm{T}} \hat{\boldsymbol{\Sigma}}_l^{-1}(\hat{\boldsymbol{\mu}}_{1l} - \hat{\boldsymbol{\mu}}_{2l}) > \ln(\frac{\hat{\pi}_2}{\hat{\pi}_1})\,, \tag{9}$$

else, assign the participant to group 2. In equation 9, $\hat{\boldsymbol{\mu}}_{jl}$ is the lth subject-specific mean for the jth group. Maximum likelihood methods are used to estimate $\hat{\boldsymbol{\mu}}_{jl}$ and $\hat{\boldsymbol{\Sigma}}^{-1}$. A strength of DA based on the linear mixed-effects model is that both time-varying and time-invariant covariates can be accommodated in the model; covariate information may help to reduce misclassification error. Moreover, this model can accommodate an unequal number of measurements per individual.

Gupta[35] extended Choi's[33] methodology to develop DA procedures based on the linear

mixed-effects model for multivariate repeated measures data. Roy[19] proposed a classification procedure for incomplete multivariate repeated measures data based on the multivariate linear mixed-effects model that assumes a Kronecker product structure for the covariance matrix of the residual errors. Marshall, De la Cruz-Mesia, Quitanna, and Baron[36] developed classification procedures based on the bivariate non-linear mixed-effects model that assumes a Kronecker product structure for the residual error covariance matrix.

2.4.3 Comparisons Amongst Procedures

Research about the performance of different repeated measures DA procedures has been limited. Roy and Khattree[30-31] used simulation techniques to compare procedures based on different covariance structures for univariate and multivariate repeated measures data. They found that for univariate repeated measures data, the average *APER* for a procedure based on an unstructured covariance was larger than the *APER* for procedures based on CS and AR-1 structures, regardless of the form of the population covariance. However, for multivariate repeated measures data, a misspecified Kronecker product covariance structure resulted in a higher *APER* than a correctly specified Kronecker product covariance structure. One study that investigated DA procedures based on the mixed-effects model[20] found that when sample size was small, procedures that specified a covariance structure for the residual errors generally had lower *APER*s than a procedure that adopted an unstructured covariance. However, for moderate to large sample sizes, the increase in classification accuracy was often negligible. None of the comparative studies that have been conducted to date have investigated the effect of a misspecified mean structure on the *APER*.

The effect of missing data on classification accuracy was studied by Roy[19]. She compared the accuracy of a classification procedure based on the multivariate mixed-effects model to the accuracy of a non-parametric classification procedure that used a multiple imputation method to fill in the missing observations. The assumption underlying both models is that the data are missing at random (MAR)[37]. She found that the *APER* for the mixed-effects procedure was less than the median error rate for the procedure based on the multiple imputation method. Roy suggested that because the multiple imputation method introduces noise into the data, it may not always be the optimal method to use.

2.5 Implementing Repeated Measures Discriminant Analysis

Covariance pattern models and mixed-effects models can be fit to univariate and multivariate repeated measures data using the MIXED procedure in SAS[38]. These models have been described in several sources[39-41]. Covariance pattern models are specified using a REPEATED statement to identify the repeated measurements and define a functional form for the covariance matrix. Mixed-effects models are specified using a RANDOM statement to identify one or more subject-specific effects; a REPEATED statement may also be included to define a functional form for the covariance matrix of the residuals. In multivariate repeated measures data, the MIXED procedure can also be used to specify a Kronecker product structure for the covariance matrix. However, the MIXED statement is limited to specifying $\mathbf{\Sigma}_p$ as unstructured, AR-1, or CS, and $\mathbf{\Sigma}_q$ as unstructured. The parameter estimates and covariances are extracted from the MIXED output using ODS output and the classification rule is defined to calculate the *APER*. This last step can be completed using programming software such as

SAS/IML.

To illustrate, we use a numeric example based on the dataset described by Nunez-Anton and Woodworth[42], which consists of the percent correct scores on a sentence test administered to two groups of study participants wearing different hearing implants[1]. The purpose of the analysis is to develop a classification rule to distinguish between the two type of implants. All study participants were deaf prior to connection of the implants. Data are available for 19 participants in group 1 and 16 participants in group 2, and measurements were obtained at one, nine, 18, and 30 months after connection of the implants. A total of 14 study participants had complete data at all four measurement occasions. The pattern of missing data is intermittent. For this analysis we assume that the data follow a multivariate normal distribution and also that the missing observations are MAR[37].

Table 2-1 provides information about the number of complete observations, means, and standard deviations for each measurement occasions for the two groups. The raw data are provided in Appendix 1, along with the SAS code to define the dataset, *audio*.

Table 2-1. Means and Standard Deviations for Percent Correct Sentence Test Scores in Two Cochlear Implant Groups

	Month 1	**Month 9**	**Month 18**	**Month 30**
	Group 1			
n_1	16	19	14	9
$\hat{\mu}_1$	29.3	39.3	42.9	43.1
SD	18.5	18.2	16.2	16.8
	Group 2			
n_2	15	16	12	9
$\hat{\mu}_2$	41.6	60.6	69.5	77.8
SD	26.4	21.7	22.0	15.9

Note: SD = standard deviation.

First we define the SAS syntax for classical linear DA. This syntax specifies a pooled covariance matrix, assumes a normal distribution of responses, and adopts *a priori* probabilities that are proportional to group sizes.

```
proc discrim data=audio method=normal pool=yes;
  class group;
  priors proportional;
  var month1 month9 month18 month30;
run;
```

Using this code, *APER* = 20.2%. However, this error rate does not take into account the 21 study participants who were excluded from the analysis because of one or more missing observations and therefore could not be classified.

A repeated measures DA procedure based on a mixed-effects model is an appropriate choice for these data given that there are an unequal number of measurements for study participants. A model with an AR-1 covariance structure is implemented using the following SAS syntax.

```
data audio_long1;
  set audio;
  time=1; y=month1; output;
  time=9; y=month9; output;
  time=18; y=month18; output;
  time=30; y=month30; output;
  drop month1 month9 month18 month30;
run;

data audio_long; set audio_long1;
  int=1;
  timeg=time*group;
run;

proc sort data=audio_long;
  by id;
run;

proc mixed data=audio_long method=ml;
  class id group;
  model y=time group time*group/ solution;
  random intercept / subject=id v=1 solution;
  repeated / type=ar(1) subject=id;
```

```
  ods output v=vmat solutionf=parms_mat;
run;
```

The dataset *audio_long1* converts the data into a person-period format and in *audio_long*, we create new variables called timeg (interaction) and int (model intercept). The MIXED syntax specifies the use of maximum likelihood estimation and implements a model containing the fixed effects of time, group, and their interaction. The RANDOM statement specifies a random intercept and requests the estimated covariance matrix for subject 1. The REPEATED statement specifies an AR-1 structure for the residual errors. The ODS statement indicates that $\hat{\boldsymbol{\Sigma}}_1$ will be output to a new dataset named *vmat*, while the fixed-effects parameters are output to the dataset *parms_mat*. Two additional models were fit to these data (syntax not shown), to identify a well-fitting model for these data. One model included a random intercept and random slope, and the second included the quadratic term for time as an additional model covariate. The former did not result in improved model fit, as judged by the AIC, and the latter resulted in problems with estimation of the covariance parameters. Appendix 2 provides example code used to extract the ODS output into SAS/IML to implement the linear classification rule.

Fit statistics and *APERs* are provided in Table 2-2 for three models, to illustrate the effect of modifying the covariance structure on classification accuracy.

Table 2-2: Fit Statistics and Apparent Error Rates (APER) for the Mixed-Effects Model with Three Covariance Structures

Structure of $\hat{\Sigma}_l$	**AIC**	n_{11}	n_{22}	***APER* (%)**
AR-1	877.2	12	12	31.4
CS	886.2	12	13	28.6
UN	876.3	14	16	14.3

Note: AR-1 = first-order autoregressive; CS = compound symmetric; UN = unstructured; AIC = Aikake Information Criterion; n_{11} and n_{22} are the number of study participants correctly classified to groups 1 and 2, respectively; *APER* = apparent error rate.

Overall, the model with an unstructured covariance had the lowest value of the AIC and also resulted in the lowest *APER*. While no guidelines exist about acceptable magnitude of the *APER*, it is possible to test for differences in *APER* values across models[11, 43].

Example syntax is provided in Appendix 2 that could be used to fit both a CS and AR-1 covariance pattern to these data. Given that the covariance pattern model is only applicable to datasets with complete observations, this syntax is provided for illustration purposes.

2.6 Discussion

While research about repeated measures DA spans more than a 30-year period, there have been a number of recent developments in PDA procedures based on covariance pattern and mixed-effects models for univariate and multivariate repeated measures data. These developments provide applied researchers with a number of options to develop accurate and efficient classification rules when data are collected repeatedly on the same subjects. Several of these procedures can be implemented using standard statistical software, although some supplementary programming is required to implement the classification rule.

There are opportunities for further research about repeated measures DA procedures. For example, there has been limited research about procedures for non-normal data and heterogeneous group covariances. While the misclassification error rate of classical linear DA is reasonably robust (i.e., insensitive) to outliers[44], heavy-tailed distributions may result in some loss of classification accuracy and inflate the standard errors of discriminant function coefficients. Non-parametric DA procedures, which do not assume a normal distribution of responses, such as nearest neighbor classification procedures, have been investigated for repeated measures data[45]. PDA procedures based on the multivariate Box and Cox transformation[46] and a rank transformation method[47], which Baron[48] found to perform well for a number of different non-normal distributions, as well as distribution-free methods[49], have not yet been investigated for repeated measures data. Roy and Khattree[29-30] developed PDA procedures for heterogeneous group covariances based on the covariance pattern model while Marshall and Baron[50] proposed PDA procedures based on the mixed-effects model for conditions of covariance heterogeneity, which can be implemented using SAS software. Roy and Khattree[30] showed in a single numeric example that when covariances are heterogeneous, a PDA procedure for unequal group covariances had a lower *APER* than a procedure that assumed homogeneity of group covariances. Additional research is needed to compare the classification accuracy of these procedures across a range of conditions of heterogeneity, particularly when group sizes are unequal, and to develop software to implement these procedures. As well, comparisons with conventional linear DA could also be undertaken.

Non-ignorable missing data, that is, data that are missing not at random (Little & Rubin, 1987) is likely to affect the accuracy of DA classification rules. Pattern mixture and selection models [51-53] have been proposed to adjust for potential bias in mixed-effects models when it

cannot be assumed that the mechanism of missingness is ignorable. Further research could investigate the development of DA procedures based on these models.

Finally, other models could be investigated for repeated measures data. Examples include extensions of the growth curve model[25] to include random effects and machine learning models for high dimensional data[54].

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Appendix 2-1. Example Dataset for Repeated Measures Discriminant Analysis

Id	group	month1	month9	month18	month30
1	1	28	33	47	59
2	1	.	13	21	26
3	1	50	46	.	.
4	1	13	30	42	.
5	1	43	61	67	.
6	1	.	59	57	61
7	1	21	38	.	.
8	1	.	10	20	31
9	1	14	35	37	44
10	1	16	33	45	52
11	1	31	50	43	62
12	1	4	11	14	15
13	1	0	18	35	38
14	1	50	55	59	.
15	1	38	59	61	.
16	1	67	68	.	.
17	1	46	58	52	.
18	1	25	42	.	.
19	1	22	27	.	.
20	2	33	66	.	.

21	2	18	72	89	93
22	2	68	86	87	89
23	2	55	59	.	.
24	2	.	81	83	90
25	2	46	60	63	77
26	2	45	66	89	97
27	2	15	43	58	60
28	2	9	29	43	78
29	2	66	81	83	.
30	2	0	30	40	63
31	2	70	79	.	.
32	2	41	48	70	.
33	2	89	91	97	.
34	2	53	60	.	.
35	2	11	19	32	53

Note: Missing observations are denoted by a period (.).

The SAS code used to define the dataset is:

```
data audio;
input id group month1 month9 month18 month30;
cards;
```

Appendix 2-2. Illustration of SAS syntax to Implement Discriminant Analysis Procedures based on Mixed-Effects and Covariance Structure Models

Mixed-effects model

This SAS/IML syntax reads the SAS datasets from the ODS output (see section 5) for the MIXED procedure and demonstrates the application of the classification rule to the data for the first study participant.

```
proc iml;
 reset noname;
 use audio_long;
 read all var {id int time group timeg y} into tempmat where (y >= 0);
 use parms_mat;
 read all var {'estimate'} into beta;
 beta1a=beta[1:3];
 beta1b=beta[5];
 beta1=beta1a//beta1b;
 use vmat;
 read all var {'index' 'col1' 'col2' 'col3' 'col4'} into vmat;
 ntot=35;
 n1=19;
 n2=16;
 discrim=j(ntot,1,.);
 count=j(ntot,1,.);
```

```
**this portion of the code applies the classification rule to the data for subject id=1**;
 subj=1;
 xmatss1=tempmat[1:4,2:5];
 xmatss2=xmatss1;
 xmatss2[,3]=0;
 ymatss=tempmat[1:4,6];
 vmatss=vmat[1:4,3:6];
 mu1=xmatss1*beta1;
 mu2=xmatss2*beta1;
 discrim[subj]=(ymatss-0.5*(mu1+mu2))`*(inv(vmatss)*(mu1-mu2));
 print 'Discriminant function for subject id=1';
 print discrim[format=6.2];
 if discrim[subj] >=ln(n2/n1) then count[subj]=1;
  else count[subj]=0;
quit;
```

Covariance pattern model

This SAS/IML syntax applies the DA classification rule defined in equation 6, which is based on a CS covariance structure. It also applies a classification rule based on an AR-1 covariance structure. Unlike the previous analyses, neither of these models includes subject-specific effects.

```
**DA BASED ON COVARIANCE PATTERN MODEL WITH CS STRUCTURE**;
```

```
proc iml;
reset noname;
use audio;
read all var {month1 month9 month18 month30} into y;
p=4;
n1=19;
n2=16;
nsum = n1+n2;
dsum = j(nsum,1,.);
do i = 1 to nsum;
  d1 = sum(y[i,]);
  if i = 1 then dsum = d1;
  else dsum = dsum//d1;
end;
y1 = y[1:n1,];
y2 = y[(n1+1):nsum, ];
ybar1 = y1[+,]/n1;
ybar2 = y2[+,]/n2;
ybar = ybar1//ybar2;
yp = j(1,p,1);
mu1 = yp*(ybar1`)/p;
mu2 = yp*(ybar2`)/p;
d = j(nsum,1,.);
```

```
countn = 0;
countn1 = 0;
do t = 1 to nsum;
  if dsum[t] >= (mu1 + mu2)#p/2 then countn = countn + 1;
end;
do t = 1 to n1;
  if dsum[t] >= (mu1 + mu2)#p/2 then countn1 = countn1 + 1;
end;
a = n1 - countn1;
aper = (countn - countn1 + a)*100/nsum;
print 'APER';
print aper[format=6.2];
quit;
```

```
**DA BASED ON COVARIANCE PATTERN MODEL WITH AR-1 STRUCTURE**;
proc mixed data = audio_long method = ml;
class id group;
model y = time group time*group /solution;
repeated / type = ar(1) subject = id;
ods output covparms = cov;
run;

proc iml;
```

```
reset noname;
use audio;
read all var {month1 month9 month18 month30} into z;
use cov;
read all var {'estimate'} into v;
rho = v[1];
n1=19;
n2=16;
nsum =n1+n2;
p = 4;
dtot = j(nsum, 1, .);
dtot2 = j(nsum,1, .);
do i = 1 to nsum;
  dtot[i] = sum(z[i,]);
end;
do k = 1 to nsum;
  dtot2[k] = sum(z[k,2:p-1]);
end;
mdtot = dtot/p;
mdtot2 = dtot2/(p-2);

z1 = z[1:n1, ];
z2 = z[(n1+1):nsum, ];
```

```
zbar1 = z1[+,]/n1;
zbar2 = z2[+,]/n2;
zbar = zbar1//zbar2;
zp = j(1,p,1);
mu1 = zp*(zbar1`)/p;
mu2 = zp*(zbar2`)/p;
/**Allocation Rule****/
zcount = 0;
zcount1=0;
do ir = 1 to nsum;
  if (p*mdtot[ir] - rho*(p-2)*mdtot2[ir])>= (1/2)*(p - rho*(p-2))*(mu1+ mu2) then zcount
= zcount+1;
end;
do ir = 1 to n1;
if (p*mdtot[ir] - rho*(p-2)*mdtot2[ir])>= (1/2)*(p - rho*(p-2))*(mu1+mu2) then zcount1
= zcount1+1;
end;
z1= n1 - zcount1;
aper = (zcount - zcount1+ z1)*100/nsum;
print ’APER';
print aper[format = 6.2];
quit;
```

Chapter 3: Descriptive Discriminant Analysis for Repeated Measures Data

Abbreviations

AR-1 = First-order autoregression

CS = Compound symmetry

DA = Discriminant analysis

DDA = Descriptive discriminant analysis

DFC = Discriminant function coefficient

MANOVA = Multivariate analysis of variance

RMDA = Repeated measures discriminant analysis

RMDDA = Repeated measures descriptive discriminant analysis

3.1 Introduction

The previous chapter reviews various repeated measures discriminant analysis (RMDA) procedures for predicting group membership and describing group separation in univariate and multivariate repeated measures data. This includes discriminant analysis (DA) procedures based on growth curve, mixed-effects, and covariance structure models[1-3]. Although these procedures are based on different underlying assumptions, they result in better classification accuracy than the conventional DA procedure when the underlying model assumptions are satisfied. DA procedures based mixed-effects models are advantageous over the conventional DA procedure in that it can be accommodate both time variant and time invariant covariates and can also be used to predict group memberships when in studies with missing observations. Similarly, DA procedures based on covariance structure models, which assume constant means and parsimonious covariance structures are advantageous when the sample size is small. A summarized description of strengths and limitations of the existing RMDA procedures is provided in Table 3-1. Although these RMDA procedures have been specifically developed for prediction of group membership in repeated measures data, there is less emphasis on the description of group separations (i.e., descriptive discriminant analysis, DDA).

Table 3-1. Repeated Measures Models for Discriminant Analysis

Model	Description	Advantages	Limitations
Covariance Structure Models	1. The proposed DA procedures assume constant repeated measures means and parsimonious covariance structures for univariate and multivariate repeated measures data. 2. Estimation of the DFCs is based on the maximum likelihood estimation method.	1. Can be used in studies with small sample size. 2. Results in better classification accuracy than the conventional DA procedure.	1. Assumes complete data on all measurement occasions 2. Classification accuracy may be reduced due to mis-specification of covariance structure. 3. The assumption of constant means may not be tenable in repeated measures studies with non-constant means.
Mixed-effects models	1. The proposed DA procedure is based means and covariances estimated from a mixed-effects model that assume parsimonious	1. DA procedure can be used when data are missing at random. 2. Can accommodate covariates to improve	1. Can be computationally intensive in multivariate repeated measures data.

	structure for the residual covariance matrix for univariate and multivariate repeated measures data	classification accuracy.	
Growth Curve Models	1. DA procedure based on growth curve model assumes parsimonious growth structure for the group means.	1. Developed for exploratory data analysis in univariate repeated measures data.	1. Require complete data on all variables and for each measurement occasion. 2. May not be appropriate when the sample size is smaller than data dimension

3.2 Descriptive Discriminant Analysis for Repeated Measures Data

In medical and biological studies, one or more outcomes are repeatedly measured at two or measurement occasions on study participants over time. Researchers are sometimes interested in understanding the differences between longitudinal profiles across groups. For example, in longitudinal studies investigating growth or maturation processes in children at fixed time points, clinicians are sometimes interested in identifying how groups of children may be distinguished according to their aspects of growth patterns. Descriptive discriminant analysis[4] is one multivariate technique that can be adopted.

Let $\mathbf{Y}_{ij}$ be the $p \times 1$ random vector of observed measurements for the ith study participant (i = 1, ...,n_j; $N = n_1 + n_2$) in the jth group (j = 1, 2). It is assumed that $\mathbf{Y}_{ij} \sim \mathrm{N}_p(\boldsymbol{\mu}_j, \boldsymbol{\Sigma}_j)$, where $\boldsymbol{\mu}_j$ and $\boldsymbol{\Sigma}_j$ are the population mean vector and covariance for the jth group. DDA can be expressed as a regression model, where discriminant function score l_{ij} is expressed as

$$l_{ij} = c + \hat{\mathbf{a}}\mathbf{y}_{ij} \tag{1}$$

where

$$c = -\frac{1}{2}(\hat{\boldsymbol{\mu}}_1 + \boldsymbol{\mu}_2)^{\mathrm{T}} \hat{\boldsymbol{\Sigma}}^{-1}(\hat{\boldsymbol{\mu}}_1 - \hat{\boldsymbol{\mu}}_2), \tag{2}$$

and $\hat{\mathbf{a}}$ corresponds to the vector of discriminant function coefficients given by

$$\hat{\mathbf{a}} = \hat{\boldsymbol{\Sigma}}^{-1}(\hat{\boldsymbol{\mu}}_1 - \hat{\boldsymbol{\mu}}_2), \tag{3}$$

$$\hat{\boldsymbol{\Sigma}} = \frac{(n_1 - 1)\hat{\boldsymbol{\Sigma}}_1 + (n_2 - 1)\hat{\boldsymbol{\Sigma}}_2}{N - 2}, \tag{4}$$

and

$$\hat{\boldsymbol{\mu}}_j = \frac{\sum_{i=1}^{n_j} \mathbf{y}_{ij}}{n_j}. \tag{5}$$

The discriminant function coefficients (DFCs) can be used to rank order variables according to their ability to discriminate between groups[5-6]. Although the conventional DDA procedure may be used to describe group separation in repeated measures data, it does not take advantage of the special structure the data and may not be appropriate in studies with sample sizes.

Descriptive discriminant analysis procedures for repeated measures data that assume parsimonious means and/or covariance structures are alternative approach to describing group separation in repeated measures data. Earlier references to repeated measures descriptive discriminant analysis (RMDDA) include the two RMDDA procedures developed by Albert and

Kshirsagar[7] to evaluate the relative importance of the measurement occasions for discriminating amongst groups. The first procedure is based on repeated measures multivariate analysis of variance (MANOVA) while the second procedure is based on the growth curve model of Pothoff and Roy[8]. While the former places no restriction on the means and covariance structures, the latter assume parsimonious growth curve structures for the group means and developed goodness of fit tests to determine the appropriate growth curve for the means. However, these two procedures make no assumptions about the covariance structures for the data.

In this chapter and subsequent ones, we investigate the use of DFCs derived from RMDA procedures that assume parsimonious covariance and mean structures for describing group separation in repeated measures data. More specifically, RMDA procedures that assume parsimonious means and/or covariance structures are investigated. This includes RMDA procedures that assume constant means and compound symmetric (CS) or first order autoregressive (AR-1) covariance structures for predicting group memberships in univariate repeated measures data. Also, RMDA procedures that assume structured and unstructured group means and Kronecker product covariance structures have also been developed for multivariate repeated measures data. These procedures are particularly advantageous for describing group separation in high-dimensional longitudinal studies where the sample size is small relative to the dimension of the data.

However, previous research on the DFCs from the conventional DDA procedure for multivariate group designs has shown that DFCs are sensitive to a variety of data characteristics, which may consequently influence the ability to correctly rank order a set of correlated variables. William and Titus[9] used Monte Carlo methods to investigate the influence of several data characteristics on bias and error in the DFCs of the conventional DA procedure. Their study

showed that the bias and error in the estimated DFCs are influenced by the number of outcomes, the magnitude of separation between group means, and the magnitude of correlation among the variables. However, conclusions from this study are limited because the conditions investigated are limited to normally distributed data and for certain selected mean configurations and correlation structures.

For RMDA procedures that assume parsimonious structures on the means and covariances, previous research suggests that the assumption of parsimony improves the accuracy of prediction of group membership[3], a mis-specification of the covariance structure may influence the classification accuracy of the procedures[10]. To investigate the accuracy and precision of DFCs derived from RMDA procedures for describing group separation, we hypothesize that in addition to the influence of a variety of data characteristics, the DFCs of these procedures may be influenced by the assumption of parsimony on the means and covariance structures as well as covariance and mean structure mis-specification.

The next chapter is a manuscript that investigates the effects of the assumptions of parsimony and mis-specification of RM mean and covariance structures on bias and error in the discriminant function coefficients of repeated measures DA procedures based on constant mean structures using Monte Carlo techniques. This manuscript has been accepted for publication in the *Journal of Modern Applied Statistical Methods*

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Chapter 4. Discriminant Analysis for Repeated Measures Data: Effects of Mean and Covariance Mis-specification on Bias and Error in Discriminant Function Coefficients

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A shortened version of this chapter has been accepted for publication in *Journal of Modern Applied Statistical Methods as of May* 2011. This chapter contains additional details in the Appendix. This manuscript has been re-organized in this chapter to meet the dissertation requirements of the University of Saskatchewan. My contribution to this published manuscript includes the review of the literature, statistical analysis using an example dataset, and preparation of the manuscript for publication.

Abbreviations

AR-1 = First-order autoregressive

CS = Compound Symmetric

DA = Discriminant Analysis

DDA = Descriptive discriminant analysis

DFC = Discriminant function coefficients

MER = Misclassification error rate

ML = Maximum likelihood

MSE = Mean square error

PDA = Predictive discriminant analysis

RM = Repeated measurements

STAR = DA based on structured means and covariances with a AR-1 structure

STCS = DA based on structured means and covariances with a CS structure

STUN = DA based on structured means and unstructured covariances

UN = Unstructured

UNUN = DA based on unstructured means and covariances

Abstract

Discriminant analysis (DA) procedures based on parsimonious mean and/or covariance structures have recently been proposed for repeated measures (RM) data. This paper investigates bias and means square error of discriminant function coefficients (DFCs) of these DA procedures when mean and/or covariance structures are correctly specified and misspecified.

Key Words: bias; discriminant function coefficients; mean square error; multivariate; model misspecification

4.1 Introduction

Linear discriminant analysis (DA) is a multivariate procedure, originally proposed by Fisher[1], for predicting group membership (predictive discriminant analysis; PDA) and/or describing group separation (descriptive discriminant analysis; DDA) on multiple variables[2]. The classical linear PDA procedure has also been applied to repeated measures (RM) data[3-4], in which study participants are measured on a single variable at two or more occasions. Classical linear DA will not result in an efficient classification rule in multivariate or RM data when there are a large number of variables or measurement occasions relative to sample size. In recent years, a number of PDA procedures for RM data have been proposed[5-9]. Specifically, Roy and Khattree[6-7] developed DA procedures based on parsimonious mean and covariance structures for both univariate (i.e., measurements on one outcome variable) and multivariate (i.e., measurements on two or more outcome variables) RM data to address the issue of classification efficiency when sample size is small. For univariate RM data, the proposed procedures based on a constant RM mean vector and either a compound symmetric (CS) or first-order autoregressive (AR-1) covariance. While these procedures can result in efficient classification rules in high-dimensional data[8], they can also result in inflated misclassification error rates (MERs) when the mean and/or covariance structure is/are incorrectly specified.

Although these procedures were originally developed for PDA, the discriminant function coefficients (DFCs) that are produced can be used for DDA, that is, to quantify the relative importance of the measurement occasions for discriminating amongst groups[10]. In classical linear DA, it is known that bias and error variation of DFCs is influenced by a variety of characteristics of the data, including degree and pattern of separation between groups (i.e., group mean vectors),

and magnitude of correlation among the outcome variables[11-12]. However, to date, there has been little, if any research, about the effects of mis-specifying the mean and/or covariance structure on DDA procedures for RM data.

The purpose of this study is to investigate the effects of RM mean and/or covariance misspecification on bias and error in DFCs of DDA procedures based on constant mean vectors and/or structured covariance matrices in univariate RM data. The manuscript is organized as follows: First, the investigated DA procedures are described. The results of a Monte Carlo study, which was conducted to investigate the effects of mean and covariance structure mis-specification under a variety of data-analytic conditions, are presented. The manuscript concludes with some considerations about selecting a DDA procedure for RM data.

4.2 Estimation of DFCs in DA Procedures for RM Data

Throughout this manuscript, we focus on the case of $g = 2$ groups, although all procedures can also be generalized to $g > 2$. In general, the number of uncorrelated DFC vectors is equal to $g - 1$.

Let $\mathbf{y}_{ij}$ be the $p \times 1$ random vector of observed measurements for the ith study participant ($i = 1, ..., n_j$; $N = n_1 + n_2$) in the jth group ($j = 1, 2$). It is assumed that $\mathbf{y}_{ij} \sim N_p(\boldsymbol{\mu}_j, \boldsymbol{\Sigma}_j)$, where $\boldsymbol{\mu}_j$ and $\boldsymbol{\Sigma}_j$ are the population mean vector and covariance for the jth group and are estimated by $\hat{\boldsymbol{\mu}}_j$ and $\hat{\boldsymbol{\Sigma}}_j$, respectively. The linear DFC vector is estimated by

$$\hat{\mathbf{a}} = \hat{\boldsymbol{\Sigma}}^{-1}(\hat{\boldsymbol{\mu}}_1 - \hat{\boldsymbol{\mu}}_2). \quad (1)$$

For the conventional linear DA procedure,

$$\hat{\boldsymbol{\Sigma}} = \frac{(n_1 - 1)\hat{\boldsymbol{\Sigma}}_1 + (n_2 - 1)\hat{\boldsymbol{\Sigma}}_2}{N - 2}, \tag{2}$$

and

$$\hat{\boldsymbol{\mu}}_j = \bar{\mathbf{y}}_j, \tag{3}$$

where $\bar{\mathbf{y}}_j = \frac{\sum_{i=1}^{n_j} \mathbf{y}_{ij}}{n_j}$. These quantities are estimated using the least-squares approach.

Roy and Khatree[6] proposed a DA procedure based on constant RM mean vectors and CS covariance structure. With a CS structure, $\boldsymbol{\Sigma}$ has diagonal elements σ^2 and off-diagonal elements $\sigma^2\rho$. For constant RM mean vectors, $\hat{\boldsymbol{\mu}}_j = c_j \mathbf{1}_p$ and the maximum likelihood (ML) estimate of c_j is

$$\hat{c}_j = \frac{\mathbf{1}_p^{\mathrm{T}} \bar{\mathbf{y}}_j}{p}, \tag{4}$$

where $\mathbf{1}_p$ is a $p \times 1$ vector of ones, $^{\mathrm{T}}$ is the transpose operator, and $\bar{\mathbf{y}}_j$ is the sample mean vector for the jth group. The ML estimates of σ^2 and ρ can be obtained by simultaneously solving the following system of equations.

$$-Np(1-\rho)(1+(p-1)\rho)\sigma^2 + (1+(p-1)\rho)(a_1 + a_2) - \rho(b_1 + b_2) = 0, \tag{5}$$

and

$$-N(p-1)p(1+(p-1)\rho)(1-\rho)\rho\sigma^2 - (a_1 + a_2)(1+(p-1)\rho)^2 + (b_1 + b_2)(\rho^2(p-1)+1) = 0, \tag{6}$$

where $a_1 = \mathrm{tr}(\mathbf{W}_1)$, $a_2 = \mathrm{tr}(\mathbf{W}_2)$, $b_1 = \mathrm{tr}(\mathbf{J}\mathbf{W}_1)$, $b_2 = \mathrm{tr}(\mathbf{J}\mathbf{W}_2)$, $\mathbf{J} = \mathbf{1}_p\mathbf{1}_p^{\mathrm{T}}$,

$$\mathbf{W}_j = \sum_{i=1}^{n_j} (\mathbf{y}_{ij} - \bar{\mathbf{y}}_j)(\mathbf{y}_{ij} - \bar{\mathbf{y}}_j)^{\mathrm{T}}, \tag{7}$$

and tr is the trace operator. The DFCs are estimated by substituting the ML estimates of $\boldsymbol{\Sigma}$ and $\boldsymbol{\mu}_j$ in equation 1.

Roy and Khattree[6] proposed a DA procedure based on constant RM mean vectors and AR-1 covariance structure. With an AR-1 structure, Σ has diagonal elements σ^2 and off-diagonal elements $\sigma^2\rho^l$, where l is the number of lags between measurement occasions. Estimates of c_j, σ^2, and ρ are obtained by simultaneously solving

$$(p-2)\rho c_j - pc_j + pm_{j1} - (p-2)\rho m_{j2} = 0, \tag{8}$$

$$\begin{aligned} &Np\sigma^2(1-\rho^2) - (\beta_1\rho^2 - 2\gamma_1\rho + \alpha_1) + n_1c_1(\beta_2\rho^2 - 2\gamma_2\rho + \alpha_2) \\ &+ n_2c_2(\beta_3\rho^2 - 2\gamma_3\rho + \alpha_3) - (n_1c_1^2 + n_2c_2^2)((p-2)\rho^2 - 2(p-1)\rho + p) = 0, \end{aligned} \tag{9}$$

and

$$\begin{aligned} &N(p-1)\sigma^2\rho - N(p-1)\sigma^2\rho^3 - \{\rho(\alpha_1+\beta_1) - \gamma_1\rho^2 - \gamma_1\} \\ &+ n_1c_1\{\rho(\alpha_2+\beta_2) - \gamma_2\rho^2 - \gamma_2\} + n_2c_2\{\rho(\alpha_3+\beta_3) - \gamma_3\rho^2 - \gamma_3\} \\ &- (n_1c_1^2 + n_2c_2^2)\{\rho(2p-2) - (p-1)\rho^2 - (p-1)\} = 0. \end{aligned} \tag{10}$$

The details of these equations are provided in the Appendix. The estimates of the DFCs are obtained by substituting the ML estimates of $\boldsymbol{\Sigma}$ and $\boldsymbol{\mu}_j$ in equation 1.

For DA procedure based on constant RM mean vectors and unstructured covariance, the ML estimate of $\boldsymbol{\mu}_j$ is as shown in equation 3 and $\boldsymbol{\Sigma}$ is estimated as

$$\hat{\boldsymbol{\Sigma}} = \frac{\sum_{j=1}^{2} \mathbf{W}_j}{N}, \tag{11}$$

where $\mathbf{W}_j$ is obtained from equation 7.

4.3 Methodology

The investigated procedures in the Monte Carlo study were: (a) DA procedure based on unstructured mean vectors and unstructured covariances (UN), (b) DA procedure based on constant mean vectors and unstructured covariances (STUN), (c) DA procedure based on constant mean vectors and CS covariances (STCS), and (d) DA based on constant mean vectors and AR-1 covariances (STAR).

The following conditions were manipulated in the study: (a) number of repeated measurements (p), (b) total sample size (N), (c) group sizes, (d) pattern and magnitude of correlation among the repeated measurements, and (e) RM mean vector configuration. The number of groups ($g = 2$) and the population distribution (normal) were fixed.

The number of RMs was set at $p = 3, 5, 7$, and 9. Previous studies have considered values of p ranging from 3 to 10[6,7,11]. Total sample sizes of $N = 60, 90$, and 120 were investigated, giving N/p ranging from 6.6 to 40.0.

Although previous simulation studies about DA procedures for RM data have primarily focused on equal group size conditions[6-7], unequal group sizes have also been investigated for multivariate designs[13-14]. The unequal group sizes selected for this study were $(n_1, n_2) = (24, 36)$ for $N = 60$, (36, 54) for $N = 90$, and (48, 72) for $N = 120$. These were selected based on previous research[13, 15].

The standard errors of DFCs are known to be influenced by the magnitude of correlation amongst the variables[16]. Six population correlation structures were investigated: (a) $\mathbf{Q}_1$: CS structure with parameter $\rho = 0.3$, (b) $\mathbf{Q}_2$: CS structure with $\rho = 0.7$, (c) $\mathbf{Q}_3$: AR-1 structure with $\rho = 0.3$, (d) $\mathbf{Q}_4$: AR-1 structure with $\rho = 0.7$, (e) $\mathbf{Q}_5$: unstructured with average correlation amongst the off-diagonal elements of 0.3, and (e) $\mathbf{Q}_6$: unstructured with average correlation amongst the

off-diagonal elements of 0.7.

Pseudorandom observation vectors $\mathbf{y}_{ij}$ were generated from a multivariate normal distribution with mean $\boldsymbol{\mu}_j$ and correlation matrix $\mathbf{Q}_{mj} = \mathbf{Q}_m$ ($m = 1, \ldots, 6$). A vector of standard normal deviates, $\mathbf{C}_{ij}$, was transformed to a vector of multivariate observations via $\mathbf{y}_{ij} = \boldsymbol{\mu}_j + \mathbf{L}\mathbf{C}_{ij}^{\mathrm{T}}$. Cholesky decomposition was used to obtain $\mathbf{L}$, an upper triangular matrix of dimension p satisfying the equality $\mathbf{L}^{\mathrm{T}}\mathbf{L} = \mathbf{Q}_{mj}$. Then $\mathbf{y}_{ij}$ was multiplied by $\mathbf{V}_j$, a diagonal matrix with elements σ_j to obtain multivariate observations with the desired variances and covariances, such that $\boldsymbol{\Sigma}_j = \mathbf{V}_j\mathbf{Q}_{mj}\mathbf{V}_j^{\mathrm{T}}$. We selected $\sigma_1^2 = \sigma_2^2 = 1$ for all investigated conditions.The RANNOR function in SAS[17] was used to generate the standard normal deviates. A variety of mean vector conditions have been investigated in previous research [6,11]. In this study, three configurations for $\boldsymbol{\mu}_1$ were selected for each value of p (Table 4-1); for all conditions, $\boldsymbol{\mu}_2$ was the null vector. Configuration I had constant means for all RM occasions in both groups. Configuration II had non-constant RM mean with a polynomial pattern for the RM occasions in the first group and constant means in the second group. For Configuration III, a monotonic decreasing linear pattern was specified for the means in the first group and the means in the second group were constant.

Table 4-1. Configurations of $\boldsymbol{\mu}_1$ Investigated in the Simulation Study

P	I	II	III
3	(0.5,0.5,0.5)	(0.5,1,0.5)	(0.5,0.25,0)
5	(0.5,0.5,0.5,0.5,0.5)	(0.5,1,1.5,1,0.5)	(1,0.75,0.5,0.25,0)
7	(0.5,0.5,0.5,0.5,0.5,0.5,0.5)	(0.5,1,1.5,2,1.5,1,0.5)	(1.5,1.25,1,0.75,0.5,0.25,0)
9	(0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5)	(0.5,1,1.5,2,2.5,2,1.5,1,0.5)	(2,1.75,1.5,1.25,1,0.75,0.5,0.25,0)

Note: $\boldsymbol{\mu}_2$ was equal to the null vector for all conditions.

Overall 1493 combinations of simulation conditions were investigated with 5,000 replications

for each combination. The study was conducted using SAS/IML software[17]. Two measures of performance were used to evaluate the DFCs: mean square error (MSE) and norm of the average bias[18]. The former is

$$b = \| \frac{1}{M} \sum_{k=1}^{M} (\hat{\mathbf{a}}_k - \mathbf{a}) \|, \tag{12}$$

and the latter is

$$e = \frac{1}{M} \sum_{k=1}^{M} \| \hat{\mathbf{a}}_k - \mathbf{a} \|^2, \tag{13}$$

where $\mathbf{a}$ is the population vector of DFCs, $\|\mathbf{x}\|$ is the norm of $\mathbf{x}$ and M is the number of replications (i.e., M = 5000). Both measures takes values on the interval [0, ∞) and the smaller the bias or error in the DFCs, the better. To adjust for the confounding effect of degree of separation between the two group means on bias and error, the MSE and bias in the DFCs were standardized using the distance between the two group mean vectors. Therefore,

$$b_{st} = \frac{b}{\| \boldsymbol{\mu}_1 - \boldsymbol{\mu}_2 \|}, \tag{14}$$

and

$$e_{st} = \frac{e}{\| \boldsymbol{\mu}_1 - \boldsymbol{\mu}_2 \|}. \tag{15}$$

4.4 Results

The average standardized MSE and bias values are summarized in Tables 4-2 to 4-5 for the four investigated values of p.

As Table 4-2 reveals for p = 3, when the observations in both groups were sampled from populations with constant mean vectors (i.e., configuration I), MSE was smallest (and similar)

for both the STCS and STAR DA procedures and largest for the UN procedure. When the data were sampled from a population with a non-constant mean configuration (i.e., configurations II or III), MSE and bias were smallest for either the UN or STCS procedure and were substantially largest for the STUN and STAR procedures. For example, under a CS covariance structure and when $\rho = 0.7$ and $p = 3$, the UN and STAR procedures had the smallest and largest average MSE, respectively, when data were sampled from a population with mean configuration II, while the UN and STUN procedures had the smallest and largest MSE respectively, when data were sampled from a population with mean configuration III.

For DA procedures based on constant mean vectors (i.e., STUN, STCS, and STAR), the average MSE decreased as the correlation among the RMs increased when the mean and covariance structure were correctly specified. This finding was observed regardless of the number of RMs. But when either the covariance or mean structure was misspecified, the average MSE increased as the correlation among the repeated measurements increased. For example, when $p = 3$ and under AR-1 population covariance structure, the average MSE for the UN procedure was 0.35 and 0.64 when $\rho = 0.3$ and $\rho = 0.7$, respectively, while the average MSE of the STAR procedure were 0.07 and 0.05 when $\rho = 0.3$ and $\rho = 0.7$, respectively, when data were sampled from a population with constant mean configuration (Table 4-2).

For DA procedures based on structured covariances, the average MSE and bias increased when the covariance structure was misspecified and the mean structures were correctly specified, regardless of the number of RMs. For example, under a AR-1 population covariance structure and when $\rho = 0.3$ and $p = 3$, the average MSE and bias of the STCS procedure were 1.3 and 2.0 times the average MSE of the STAR procedure, respectively, when the data were sampled from a population with mean configuration I. Similarly, the average MSE and bias of DA procedures

based on structured covariances increased under a correctly specified population covariance but a misspecified mean structure. For example, when $p = 3$ and $\rho = 0.3$ under AR-1 population covariance structure, the average MSE and bias of the STAR procedure when the data were sampled from a population with mean configuration II were 6.4 and 7.0 times the average MSE and bias of the STAR procedure under a constant mean configuration, respectively.

For the STUN procedure, the average bias increased when the mean and covariance structures were misspecified, but STCS procedure had the smallest MSE when the data were sampled from a population with a constant mean configuration, regardless of the number of RM. For example, when $p = 7$, under an unstructured population covariance structure and when $\rho = 0.3$ and $p = 7$, the average MSE and bias of the STUN procedure were 0.70 and 2.75 times the average MSE and bias of the STCS procedures, respectively, when the data were sampled from a population with a constant mean configuration (Table 4-4).

Moreover, for each DA procedure, the average MSE and bias due to misspecification of the covariance structure increased as the magnitude of correlation and number of RMs increased. For example, when $p = 5$ and under a CS population covariance structure, the average MSEs of the STAR procedure were 2.6 and 5.5 times the average MSE of the STCS procedure for $\rho = 0.3$ and $\rho = 0.7$, respectively, when data were sampled from a population with a constant mean configuration (Table 3). The corresponding bias values for the STAR procedure were 4.2 and 10.7 times the bias of the STCS procedure when $\rho = 0.3$ and $\rho = 0.7$, respectively. Similarly, when $p = 9$, the average MSEs of the STCS procedure were 8,3 and 11.0 times the average MSE of the STAR procedure for $\rho = 0.3$ and $\rho = 0.7$, respectively, while the corresponding average bias values were 11.0 times the average bias of the STCS procedure when $\rho = 0.3$ and $\rho = 0.7$ (Table 4-5).

Finally, analyses revealed that the average MSE for each of the DA procedures decreased as the sample size increased. For example, the average MSEs of UN procedure were 7.82, 3.77, and 2.50 when N = 60, 90, and 120 respectively. In contrast, the average bias for each DA procedure remained largely unchanged as the sample size increased, regardless of the mean configuration and number of RM. For example, the overall average bias of the STAR procedure were 2.12, 2.10 and 2.10 when N = 60, 90, and 120, respectively.

Table 4-2. Average Standardized MSE and Bias by Covariance Structure, Magnitude of Correlation, and Mean Configuration for $p = 3$

Covariance Structure	ρ	Mean Configuration	MSE				Bias			
			UN	STUN	STCS	STAR	UN	STUN	STCS	STAR
CS	0.3	I	0.34	0.11	**0.07**	0.09	0.08	0.08	**0.07**	0.15
		II	0.31	0.45	0.38	0.52	**0.09**	0..52	0.52	0.61
		III	0.52	0.64	0.61	0.63	**0.13**	0.98	0.98	0.98
	0.7	I	0.65	0.12	**0.05**	0.09	0.06	0.05	**0.05**	0.21
		II	0.65	1.89	1.81	2.38	**0.14**	1.20	1.20	1.38
		III	1.16	3.00	2.95	2.99	**0.25**	2.27	2.27	2.29
AR(1)	0.3	I	0.35	0.14	0.09	**0.07**	0.08	0.08	0.15	**0.08**
		II	0.30	0.56	0.33	0.44	**0.09**	0.59	0.47	0.56
		III	0.48	0.43	0.41	0.41	**0.11**	0.75	0.77	0.75
	0.7	I	0.64	0.13	0.08	**0.05**	0.06	0.06	0.22	**0.06**
		II	0.66	3.29	2.44	3.10	**0.16**	1.61	1.40	1.58
		III	1.01	1.11	1.06	1.06	**0.16**	1.34	1.36	1.34
UN	0.3	I	0.38	**0.13**	0.08	0.16	0.08	**0.08**	0.15	0.27
		II	**0.34**	0.33	0.41	0.53	**0.10**	0.42	0.54	0.60
		III	**0.61**	1.20	1.25	1.31	**0.18**	1.40	1.45	1.47
	0.7	I	0.67	**0.12**	0.05	0.12	0.06	**0.05**	0.08	0.27
		II	**0.66**	1.47	1.52	2.03	**0.13**	1.05	1.10	1.27
		III	**1.29**	4.34	4.41	4.48	**0.32**	2.77	2.81	2.83

Note: See Table 4-1 for a description of the mean configurations; CS = compound symmetric; AR-1 = first-order autoregressive; UN = unstructured; ρ = correlation parameter; UN = unstructured mean and covariance; STUN = structured mean and unstructured covariance; STCS = structured mean and CS covariance; STAR = structured mean and AR-1 covariance. Numbers in bold correspond to bias and error values of DA procedures for which the mean and covariance structures are correctly specified.

Table 4-3. Average Standardized MSE and Bias by Covariance Structure, Magnitude of Correlation and Mean Configuration for $p = 5$

Covariance Structure	ρ	Mean Configuration	MSE				Bias			
			UN	STUN	STCS	STAR	UN	STUN	STCS	STAR
CS	0.3	I	0.56	0.14	**0.05**	0.13	0.06	0.06	**0.05**	0.21
		II	0.53	0.96	0.80	1.09	0.09	0.60	0.60	0.69
		III	0.63	1.21	1.13	1.16	0.12	0.89	0.89	0.91
	0.7	I	1.10	0.16	**0.02**	0.11	0.04	0.04	**0.03**	0.23
		II	1.35	4.40	4.19	5.20	0.18	1.39	1.39	1.54
		III	1.80	6.06	5.95	6.00	0.27	2.08	2.08	2.09
AR(1)	0.3	I	0.56	0.20	0.08	**0.05**	0.09	0.09	0.14	**0.07**
		II	0.46	0.76	0.37	0.48	0.09	0.48	0.38	0.45
		III	0.55	0.57	0.47	0.45	0.10	0.55	0.56	0.55
	0.7	I	1.06	0.21	0.08	**0.04**	0.05	0.05	0.22	**0.04**
		II	0.96	2.42	1.51	2.01	0.11	0.99	0.83	0.95
		III	1.08	0.86	0.76	0.72	0.10	0.72	0.74	0.72
UN	0.3	I	0.66	**0.20**	0.14	0.20	0.08	**0.08**	0.31	0.35
		II	**0.64**	2.26	1.33	1.67	**0.11**	0.96	0.77	0.86
		III	**0.75**	1.61	1.63	1.61	**0.15**	1.03	1.08	1.07
	0.7	I	1.15	**0.17**	0.03	0.10	0.04	**0.03**	0.07	0.22
		II	**1.40**	4.81	4.44	5.35	**0.18**	1.45	1.42	1.56
		III	**2.04**	7.57	7.66	7.76	**0.30**	2.33	2.36	2.37

Note: See Table 4-1 for a description of the mean configurations; CS = compound symmetric; AR-1 = first-order autoregressive; UN = unstructured; ρ = correlation parameter; UN = unstructured mean and covariance; STUN = structured mean and unstructured covariance; STCS = structured mean and CS covariance; STAR = structured mean and AR-1 covariance. Numbers in bold correspond to bias and error values of DA procedures for which the mean and covariance structures are correctly specified

Table 4-4. Average Standardized MSE and Bias by Covariance Structure, Magnitude of Correlation and Mean Configuration for $p = 9$

Covariance Structure	ρ	Mean Configuration	MSE				Bias			
			UN	STUN	STCS	STAR	UN	STUN	STCS	STAR
CS	0.3	I	1.33	0.31	**0.03**	0.25	0.07	0.07	**0.03**	0.33
		II	1.54	2.56	2.04	2.51	0.13	0.66	0.66	0.74
		III	1.64	2.88	2.53	2.59	0.16	0.84	0.84	0.85
	0.7	I	2.18	0.29	**0.01**	0.11	0.03	0.03	**0.02**	0.22
		II	5.14	11.58	10.97	12.40	0.29	1.54	1.54	1.64
		III	6.12	14.07	13.66	13.72	0.37	1.96	1.96	1.96
AR(1)	0.3	I	1.19	0.47	0.07	**0.04**	0.12	0.12	0.13	**0.07**
		II	0.98	1.41	0.51	0.75	0.09	0.41	0.31	0.40
		III	1.40	1.38	0.74	0.78	0.13	0.44	0.44	0.47
	0.7	I	2.17	0.46	0.07	**0.02**	0.07	0.07	0.19	**0.03**
		II	2.05	2.51	0.86	1.22	0.09	0.58	0.43	0.51
		III	2.03	1.27	0.69	0.70	0.10	0.41	0.43	0.41
UN	0.3	I	1.95	**0.47**	0.09	0.33	0.08	**0.07**	0.22	0.41
		II	**4.73**	10.85	12.28	12.84	0.32	1.46	1.63	1.67
		III	**6.85**	35.01	30.47	30.74	0.43	2.40	2.26	2.27
	0.7	I	2.86	**0.37**	0.01	0.12	0.04	**0.03**	0.06	0.23
		II	**8.52**	24.32	23.45	25.40	0.43	2.26	2.25	2.35
		III	**10.07**	32.21	31.44	32.00	0.56	2.98	2.97	2.99

Note: See Table 4-1 for a description of the mean configurations; CS = compound symmetric; AR-1 = first-order autoregressive; UN = unstructured; ρ = correlation parameter; UN = unstructured mean and covariance; STUN = structured mean and unstructured covariance; STCS = structured mean and CS covariance; STAR = structured mean and AR-1 covariance; Numbers in bold correspond to bias and error values of DA procedures for which the mean and covariance structures are correctly specified.

4.5 Conclusions

This manuscript investigated the effects of RM mean and/or covariance structure misspecification on bias and error in DFCs for DA procedures based on parsimonious mean and/or covariance structures. As expected, the bias and error in the DFCs of the investigated procedures increased when the RM mean and/or covariance structures were misspecified. The average bias and error variation due to misspecification of the RM mean structure was greater than the average bias and error variation due to RM covariance structure misspecification for all of the investigated procedures. While DA procedures based on parsimonious RM mean and covariance structures had negligible bias when the mean and covariances are correctly specified, the UN DA procedure had the smallest bias when the data were sampled from a population with non-constant mean configuration.

Based on the study findings, we recommend adopting a DA procedure based on unstructured mean vectors and covariance matrices when the researcher has prior knowledge to suggest that the mean longitudinal profile for each group will change across the repeated measures occasions. If the mean longitudinal profile in each group is not expected to increase or decrease across the measurement occasions, either the STCS or STAR procedure are recommended because they require estimation of a fewer number of parameters, although any of the procedures can be expected to perform well in terms of both bias and error variation.

To reduce the effect of mean and/or covariance structure misspecification on bias and error in the DFCs, preliminary tests of model fit could be undertaken before adopting a DDA procedure for RM data. Graphical exploration of the data, likelihood ratio tests, or penalized log-likelihood measures like the Akaike information criterion have all been proposed to guide the

specification of mean and covariance structures[19].

The limitations of this study should be noted. We focused on normally distributed data. The impact of mean and/or covariance misspecification on bias and error in the DFCs when data are sampled from non-normal distribution has not been investigated. While mild departures from multivariate non-normality are known to have little effect on classification accuracy of conventional DA procedure[20], classification accuracy can be severely affected under large departures[21-22]. Inferences about DFCs of the linear DA procedures may also be affected by the degree of departure from the assumption of multivariate normality[22]. The DA procedures considered in manuscript also focused only on complete data, an assumption which may not be satisfied in RM studies, which are often characterized by missing observations and unbalanced measurements occasions[23]. In the simulation study, the RM variances were assumed to be constant across variables and groups. Linear DA procedures rest on the assumption of covariance homogeneity[2]. Departures from this assumption may result in reduced classification accuracy[24]. DFCs have been shown to be relatively robust to violation of this assumption when the data are normally distributed[25], but it is not known if this robustness will continue to be evident when the covariance and/or mean vector is misspecified.

A number of opportunities for future research exist in the development of DDA procedures for RM data. Although several studies have examined the effects of population distribution on classification accuracy, there is limited investigation of the effects of population distribution and other data characteristics on bias and error in DFCs. Existing studies in this area have only focused on the effects of sample size, number of outcome variables, and mean configuration on bias and variation in DFCs when data were sampled from normally distributed data[12, 26]. This study investigated DA procedures based on constant mean vectors and/or structured covariances.

However, the assumption of a constant repeated measures group mean structure may not be tenable when the interest is in the assessment of the relative importance of measurement occasions that discriminate between groups. DA procedures based on non-constant mean vectors and CS or AR-1 covariance structures can be further investigated. These procedures which assume non-constant mean configurations and parsimonious structures will be useful for assessing the relative importance of information collected at each measurement occasions in univariate repeated measures studies.

In summary, although the adoption of a DA procedure based on a parsimonious mean and/or covariance structure can reduce the number of parameters to estimate, which is beneficial when sample size is small[6], this study shows that bias and error variation in the DFCs can be large, particularly when there is misspecification of the RM mean structure. A researcher's choice of a DA procedure for RM data is dependent, in part, on the trade-off between parsimony in parameter estimation and bias and/or error in the DFCs.

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Appendix I: Maximum Likelihood Estimation for RMDA Procedures

For DDA with constant mean structure, let $\boldsymbol{\Theta}$ be a column vector of model parameters, where the first two elements denote the mean parameters and the last two elements correspond to σ^2 and ρ, respectively. Let $\mathbf{y}_{ij}$ be $1 \times p$ vector of repeated measurements on the ith participant ($i = 1, 2\ldots., n_j$, $j = 1, 2$; $N = n_1 + n_2$) in the jth group, and $\mathbf{Y}_j$ denote the $n_j \times p$ data matrix for the jth group. Then the log of the joint likelihood function L is

$$\log(\boldsymbol{\Theta} \mid y_1, \mathbf{y}_2, ..., \mathbf{y}_N) = -\frac{Np}{2}\log 2\pi - \frac{N}{2}\log|\boldsymbol{\Sigma}| - \frac{1}{2}\mathrm{tr}\{\sum_{j=1}^{2}\sum_{i=1}^{n_j}(\mathbf{y}_{ij} - \boldsymbol{\mu}_j)^{\mathrm{T}}\boldsymbol{\Sigma}^{-1}(\mathbf{y}_{ij} - \boldsymbol{\mu}_j)\}, \qquad \text{(A-1)}$$

where $^{\mathrm{T}}$ is the transpose operator.

Assuming a constant mean structure for the group means,

$$\boldsymbol{\mu}_j = c_j \mathbf{1}_p, \qquad \text{(A-2)}$$

where c_j is the mean for the measurement occasions for the jth group and $\mathbf{1}_p$ is a $p \times 1$ vector of ones). Equation 4 in the text simplifies to

$$\log(\boldsymbol{\Theta} \mid \mathbf{Y}_1, \mathbf{Y}_2) = -\frac{Np}{2}\log 2\pi - \frac{N}{2}\log|\boldsymbol{\Sigma}| - \frac{1}{2}\mathrm{tr}(\boldsymbol{\Sigma}^{-1}\mathbf{W})$$
$$-\frac{1}{2}\mathrm{tr}(\sum_{j=1}^{2} n_j(\bar{\mathbf{y}}_j - c_j\mathbf{1}_p)\boldsymbol{\Sigma}^{-1}(\bar{\mathbf{y}}_j - c_j\mathbf{1}_p)), \qquad \text{(A-3)}$$

where $\mathbf{W} = \mathbf{W}_1 + \mathbf{W}_2$, $\mathbf{W}_j = \sum_{i=1}^{n_j}(\mathbf{y}_{ij} - \bar{\mathbf{y}}_j)(\mathbf{y}_{ij} - \bar{\mathbf{y}}_j)^{\mathrm{T}}$, and tr is the trace operator. Equating the first order derivatives of equation A-3 to zero, the ML estimate of the mean values for the jth group, c_j is as given in equation 4.

Assuming a CS covariance structure for $\boldsymbol{\Sigma}_j$,

$$\boldsymbol{\Sigma} = \sigma^2[(1-\rho)\mathbf{I}_p + \rho\mathbf{1}_p\mathbf{1}_p^{\mathrm{T}}], \qquad \text{(A-4)}$$

where ρ is the magnitude of correlation among the repeated measurements, σ^2 is repeated measures variance assumed to be constant across measurement occasions, and $\mathbf{I}_p$ is the $p \times p$ identity matrix. Then,

$$|\mathbf{\Sigma}| = \sigma^{2p}[1+(p-1)\rho](1-\rho)^{p-1}, \tag{A-5}$$

and

$$\mathbf{\Sigma}^{-1} = \frac{1}{\sigma^2(1-\rho)}[\mathbf{I}_p - \frac{\rho}{1+(p-1)\rho}\mathbf{1}_p\mathbf{1}_p^{\mathrm{T}}], \tag{A-6}$$

where $\mathbf{\Sigma}$ is positive definite, and $\left(\frac{-1}{p-1}\right) < \rho < 1$. Substituting the values of $|\mathbf{\Sigma}|$ and $\mathbf{\Sigma}^{-1}$ in equations A-4 and A-5 into the log of the likelihood function (equation A-2) gives

$$-\frac{Np}{2}\log 2\pi - \frac{N}{2}\log\sigma^2 + \frac{N}{2}\log(1+(p-1)\rho) + \frac{N(p-1)}{2}\log(1-\rho)$$
$$-\frac{1}{2\sigma^2(1-\rho)}tr(\mathbf{W}) - \frac{\rho}{1+(p-1)\rho}\mathrm{tr}(\mathbf{JW}), \tag{A-7}$$

where $\mathbf{W}$ is as defined in equation 7, and $\mathbf{J}$ is a $p \times p$ matrix of ones. The first order derivatives of the log-likelihood function with respect to σ^2 and ρ are as given in equations 5 and 6 The maximum likelihood (ML) estimates of σ^2 and ρ are obtained by setting f_1 and f_2 to zero and solving the equations. The ML estimates of the DFCs for this DDA procedure are obtained by substituting the ML estimates of c_j , σ^2 , and ρ into equation 1.

DDA based on Constant Means and AR-1 Covariance Structure

Assuming a first-order autoregressive structure for $\mathbf{\Sigma}$,

$$|\mathbf{\Sigma}| = \sigma^{2p}(1-\rho^2)^{p-1}, \tag{A-8}$$

$$\mathbf{\Sigma}^{-1} = \frac{\mathbf{\Sigma_0}}{\sigma^2(1-\rho^2)^{p-1}}, \tag{A-9}$$

where

$$\mathbf{\Sigma_0} = \begin{bmatrix} 1 & -\rho & 0 & .... & 0 & 0 \\ -\rho & 1+\rho^2 & -\rho & 0 & .... & 0 \\ 0 & -\rho & 1+\rho^2 & -\rho & .... & 0 \\ ... & ... & ... & ... & .... & .... \\ 0 & 0 & .... & 0 & 1+\rho^2 & -\rho \\ 0 & 0 & .... & 0 & -\rho & 1 \end{bmatrix} . \tag{A-10}$$

The first order derivatives of the log of the joint likelihood function of equation A-2 is given in equation 8. Here,

$$m_{j1} = \frac{\mathbf{1}_p^{\mathrm{T}}\bar{\mathbf{y}}_j}{p}, \tag{A-11}$$

$$m_{j2} = \frac{\mathbf{1}_p^{\mathrm{T}}\bar{\mathbf{y}}_j - \bar{\mathbf{y}}_{j1} - \bar{\mathbf{y}}_{jp}}{(p-2)}, \tag{A-12}$$

and $\bar{\mathbf{y}}_{j1}$ and $\bar{\mathbf{y}}_{jp}$, are respectively, the first and *p*th elements of the vector $\bar{\mathbf{y}}_j$

Substituting the values of $|\mathbf{\Sigma}|$ and $\mathbf{\Sigma}^{-1}$ from equations A-8 and A-9 into the log-likelihood function (equation A-2) gives

$$= -\frac{Np}{2}\log 2\pi - \frac{Np}{2}\log\sigma^2 - \frac{N(p-1)}{2}\log(1-\rho^2) - \frac{1}{2}\mathrm{tr}\left(\frac{\mathbf{\Sigma}_0}{\sigma^2(1-\rho^2)}\mathbf{W}^*\right), \tag{A-13}$$

where

$$\mathbf{W}^{*} = \mathbf{W}_0 - n_1 c_1 \mathbf{W}_5 - n_2 c_2 \mathbf{W}_6 + (n_1 c_1^2 + n_2 c_2^2)\mathbf{J}, \tag{A-14}$$

$$\mathbf{W}_3 = \bar{\mathbf{y}}_1 \bar{\mathbf{y}}_1^{\mathrm{T}}, \tag{A-15}$$

$$\mathbf{W}_4 = \bar{\mathbf{y}}_2 \bar{\mathbf{y}}_{2_1}^{\mathrm{T}}, \tag{A-16}$$

$$\mathbf{W}_5 = (\mathbf{1}_p \bar{\mathbf{y}}_1^{\mathrm{T}} + \bar{\mathbf{y}}_1 \mathbf{1}_{\mathrm{p}}^{\mathrm{T}}), \quad , \tag{A-17}$$

$$\mathbf{W}_6 = (\mathbf{1}_p \bar{\mathbf{y}}_2^{\mathrm{T}} + \bar{\mathbf{y}}_2 \mathbf{1}_{\mathrm{p}}^{\mathrm{T}}), \tag{A-18}$$

and $\mathbf{W}_0 = \sum_{t=1}^{4} \mathbf{W}_t$.

The first-order derivatives of equation A-10 with respect to ρ and σ^2 are given in equation 8 and 9, Where

$$\beta_1 = tr(\mathbf{W}_0) - \mathbf{W}_{0,11} - \mathbf{W}_{0,pp}, \tag{A-19}$$

$$\beta_2 = \alpha_1 - \mathbf{W}_{5,11} - \mathbf{W}_{5,pp}, \tag{A-20}$$

$$\beta_3 = \alpha_3 - \mathbf{W}_{6,11} - \mathbf{W}_{6,pp}, \tag{A-21}$$

$$\alpha_1 = tr(\mathbf{W}_0 + \mathbf{W}_1 + \mathbf{W}_2 + \mathbf{W}_3 + \mathbf{W}_4), \tag{A-22}$$

$$\alpha_2 = \mathrm{tr}(\mathbf{W}_5), \tag{A-23}$$

and

$$\alpha_3 = \mathrm{tr}(\mathbf{W}_6). \tag{A-24}$$

Also,

$$\gamma_1 = \sum_{k=2}^{p} \mathbf{W}_{0k-1,k} , \tag{A-25}$$

$$\gamma_2 = \sum_{k=2}^{p} \mathbf{W}_{5k-1,k} , \tag{A-26}$$

and

$$\gamma_3 = \sum_{k=2}^{p} \mathbf{W}_{6k-1,k}, \tag{A-27}$$

where $\mathbf{W}_{uk\text{-}1,k}$ is the (k-1,k)th element of $\mathbf{W}_u$ (u = 0 ,…, 6) and k = 1 ,…, p. The ML estimates of c_1, c_2, σ^2 and ρ are obtained by solving the systems of equations 8, 9, and 10 simultaneously. The ML estimates of the vector of DFCs for this DDA procedure is obtained by substituting the ML estimates of c_1, c_2, σ^2, and ρ into equation 1.

Section II: Robust Discriminant Analysis for Non-Normal Data

Chapter 5. Discriminant Analysis for Non-normal Data

Abbreviations

CT = Coordinatewise trimming

DA = Discriminant analysis

DDA = Descriptive discriminant analysis

DFC = Discriminant function coefficient

HRQOL = Health-related quality of life

MCD = Minimum covariance determinant

MER = Misclassification error rates

MCD = Minimum covariance determinant

ML = Maximum likelihood

MVE = Minimum volume ellipsoid

PDA = Predictive discriminant analysis

RMDA = Repeated measures discriminant analysis

TL = Trimmed likelihood

5.1 Introduction

The previous section examines discriminant analysis (DA) procedures that assume parsimonious covariance and mean structures for normally distributed repeated measures data[1-3]. However, these DA procedures rest on the assumptions of multivariate normality and covariance homogeneity, which may not be satisfied in practice. Normality of the outcome variables may not be a tenable assumption in clinical investigations. For example, patient-reported outcomes such as health-related quality of life measures frequently exhibit heavy-tails and skewed distributions[4]. Also, treatment groups may exhibit greater variability than control groups[5-6].

The linear DA procedure will sometimes result in smaller misclassification error rates (MERs) for predictive discriminant analysis (PDA) in multivariate non-normal than normal data[7-9]. It may also frequently produce incorrect variable rankings for descriptive discriminant analysis (DDA) when the data are non-normal[10]. Although several DA procedures that are insensitive (i.e., robust) to departures from multivariate normality assumptions in multivariate group designs, there are limited investigations about robust DDA procedures for rank ordering variables in non-normal data. Also, robust repeated measures discriminant analysis (RMDA) procedures for describing group separations in non-normal repeated measures data have not been developed.

This chapter reviews the literature on robust DA procedures for multivariate data and repeated measures data.

5.2 Robust Discriminant Analysis for Multivariate Group Designs

DA classification procedures that are robust to departures from multivariate normal distributions

have been developed for predicting group memberships in multivariate group designs. These include (a) DA procedures based on rank transformation of the data, and (b) DA procedures based on robust estimators of means and covariances. The former includes procedures based on rank transformation of the data[11], rank cut-offs[12], and non-linear transformation of the data[13]. While these procedures have been shown to improve classification accuracy[5], DA based on transformation of the non-normal data may not be appropriate when there are between-group interactions because the ranks are not a linear function of the original scores[14-15].

DA procedures based on robust estimators of means and covariance matrices have been proposed for predicting group memberships in non-normal data. The robustness of an estimator is typically quantified via the breakdown point, the minimum proportion of outliers in the data that can inflate the estimators arbitrarily far from their true values. The breakdown point for least squares estimators is zero[16]. Among the robust estimators of means and covariance is the class of M-estimators of mean and covariance which was first proposed by Huber[17]. In M-estimators, a weighted function of the Mahalanobis distances (M-distances) of the observations is applied to the data such that observations with large M- distances are given reduced weights while observations with smaller M-distances are given larger weights. DA procedures based on M-estimators of mean and covariances have been shown to improve classification accuracy than the conventional DA based on least squares estimators when data are non-normal[18]. Campbell[19-20] also proposed robust DA coefficients based on M-estimators applied to canonical scores of the data. However, DA procedures based on M-estimators have low breakdown points as the data dimension increases[21].

DA procedures have also been developed based on robust estimators with high breakdown points for classification in non-normal multivariate data. This includes S-estimators[22-23],

minimum covariance determinant (MCD) estimators, and minimum volume ellipsoid (MVE) estimators[24]. In MCD and MVE estimators, the means and covariance estimates are obtained from a subset of the data with the smallest covariance determinant or volume ellipsoid. Robust DA procedures based on MCD or MVE estimators are obtained by replacing the conventional least squares estimates with the MCD or MVE estimates of the mean and covariances, respectively. However, these procedures may be computationally intensive for high-dimensional multivariate data and may not result in improved classification accuracy when there are no outliers in the data[22].

DA procedures have been developed based on trimmed estimators, for which means and covariance estimates are computed based on a subset of the original data obtained by removing a predetermined proportion of the observations from each tail of the distribution of the original data. The trimming approach, which was first developed for testing differences between group means when data are non-normal and group covariances are homogeneous, are intuitively appealing estimators because of their computational simplicity and good theoretical properties[25]. Ahmed and Lachenbruch[26] proposed robust DA procedures based on applying DA to a subset of the original data obtained by removing observations with extreme Mahalanobis scores. This includes a DA procedure based on the iterative trimming suggestion of Gnanadesikan and Kettenring[27] in which 5% or 10% of the observations with the largest Mahalanobis distances are trimmed, and the classification rule is developed based on the mean and covariance estimates of the remaining observations. Another approach uses a classification rule developed from a subset of the original data obtained by trimming the discriminant scores of the observations. These robust DA procedures showed better classification accuracy than the classical DA based on least squares estimators in non-normal data. However, Campbell[19] notes that the former and latter DA

procedures may not achieve the optimal classification accuracy in non-normal data because the Mahalalnobis scores of the observations is influenced by the outliers.

5.2 Trimmed Estimation in Multivariate and Repeated Measures Data

Tukey & McLaughlin[28] first proposed trimmed estimators based on the Student *t* test for testing differences between population means. Let $Y_{(1)} \leq Y_{(2)} \leq \ldots. \leq Y_{(n)}$ denote the order statistics for a random sample of size *n* drawn from a population with a continuous symmetric distribution function $F((\frac{Y-\mu}{\sigma}))$ and unknown mean μ and standard deviation σ. Define $g_j = [\delta n]$, where δ represents the proportion of the observations to be trimmed, or censored, from each tail of the distribution and $[x]$ is the integer less than or equal to *x*. Then the δ-trimmed mean is

$$\overline{Y}_t = \frac{\sum_{i=g+1}^{n-g} Y_i}{n-2g}. \qquad (1)$$

This trimmed mean has been shown to asymptotically follow a normal distribution by the following theorem.

Theorem: Univariate Trimming

For a continuous symmetric population with distribution function *F*, let ς_δ denote the δ quantile, i.e., $F(\varsigma_\delta) = \delta$. As $n \rightarrow \infty$,

$$\sqrt{n}(\overline{Y}_t - \mu) \rightarrow \mathrm{N}(0, \sigma^2(\delta)), \qquad (2)$$

where $\sigma^2(\delta) = (1-2\delta)^{-2}\left[\int_{\varsigma_\delta}^{\varsigma_{1-\delta}} t^2 dF(t) + 2\delta\varsigma_\delta^2\right]$.

Tukey & Mclaughlin[26] were the first to Studentize trimmed means. They proposed the trimmed *t* statistic

$$\tilde{t} = \frac{Y_t - \mu}{\sqrt{s_w^2/(h(h-1)}}, \quad (3)$$

where s_w^2 is the Winsorized sums of squared deviations, and $h = n - 2g$ is the effective number of observations.

Other variants of this test statistic have been developed including Yuen's *t*-statistic[29-30]. Wilcox[31] proposed the Winsorized variance as a consistent estimator of the variance of the trimmed data instead of the trimmed variance data when testing for differences between population means for non-normal data. He showed that test procedures based on trimmed means and Winsorized variances are more robust to the effects of variance heterogeneity and non-normality than test procedures based on least squares estimators.

Several trimmed estimators of means and covariances have been developed for non-normal multivariate data. We review a number of trimming approaches that has not previously been used to develop robust DA procedures.

Srivasta and Mudholkar[32] proposed an extension of univariate trimming to multivariate data. This approach is based on coordinate trimming of the multivariate data to develop robust estimators of means and covariance matrices.

Let $\mathbf{Y}_i = (Y_{i1}, Y_{i2,}\ldots, Y_{ip})^T$ ($i = 1, \ldots, n$) denote an independent and identically distributed random vector from a population with $\boldsymbol{\mu} = (\mu_1 \ldots \mu_p)^T$ and $\boldsymbol{\Sigma}$, where ^{T} is the transpose operator. Let $F(Y_1\ Y_{2,}\ldots, Y_p)$ define the joint distribution function, $F_{lk}(Y_l, Y_k)$ denote the bivariate distribution function for Y_l, and Y_k, and $F_k(y_k)$ ($l, k = 1, 2,\ldots., p$) denote the marginal distribution function for the kth variable. The parameters $\boldsymbol{\mu}$ and $\boldsymbol{\Sigma}$ are estimated by $\hat{\boldsymbol{\mu}} = (\bar{Y}_1\ \bar{Y}_2\ \ldots\ \bar{Y}_p)^T$ and $\hat{\boldsymbol{\Sigma}}$, respectively. Let $Y_{(1)k} \le Y_{(2)k} \le \ldots. \le Y_{(n)k}$ denote the order statistic of the sample for the kth variable.

The trimmed mean $\hat{\boldsymbol{\mu}}_t = (\bar{Y}_{1t}\, \bar{Y}_{2t}, \ldots, \bar{Y}_{pt})^T$ where

$$\bar{Y}_{kt} = \frac{1}{n-2g}\sum_{i=g+1}^{n-g} Y_{(i)k} \tag{4}$$

is the trimmed mean for the kth outcome variable, and $g = [\delta n]$, where δ represents the proportion of the observations to be trimmed, or censored, from each tail of the distribution and $[x]$ is the integer less than or equal to x. The trimmed mean has been shown to asymptotically follow a multivariate normal distribution by the following theorem.

Theorem: Multivariate Coordinate Trimming[32,33]

Asymptotically, as $n \to \infty$,

$$\sqrt{n}(\hat{\boldsymbol{\mu}}_t - \boldsymbol{\mu}) \to N_p(\mathbf{0}, \boldsymbol{\Sigma}_{(w)}). \tag{5}$$

The Winsorized covariance has been shown as a consistent estimator of $\boldsymbol{\Sigma}_{(w)}$. The estimated Winsorized covariance is

$$\mathbf{S}_w = (s_m), \tag{6}$$

where

$$s_m = \frac{\sum_{i=1}^{n_j}(z_{im} - \bar{z}_m)(z_{il} - \bar{z}_l)}{n-1}, \tag{7}$$

is the variance for the mth and lth outcome, and

$$\bar{y}_{wm} = \frac{1}{n}\sum_{i=1}^{n} z_{im}, \tag{8}$$

is the group winsorized mean for the mth outcome, where

$$z_{im} = y_{(g+1)m} \quad \text{if } y_{im} \le y_{(g+1)m}$$

$$= y_{im} \quad \text{if } y_{(g+1)m} < y_{im} < y_{(n-g)m}$$

$$= y_{(n-g)m} \quad \text{if } y_{im} \geq y_{(n-g)m}, \text{ for } i = 1, \ldots, n. \square \tag{9}$$

Robust estimators based on coordinatewise trimming (CT) of the data have been adopted in previous studies for multivariate and repeated measures procedures. For example, Srivastava and Mudholkar[32] developed a robust Hottelling T^2-statistic based on 15% coordinate-wise trimming of the non-normal multivariate data. Keselman et al.[34] proposed robust non-pooled Welch-type and Huynh Improved General Approximation test statistics based on CT of the data for testing main and interaction effects in repeated measures designs when data are non-normal.

Trimmed likelihood (TL) estimation is another approach that has been proposed for obtaining robust estimates of means and covariances for likelihood-based models [35-36] but has not been used to develop robust DA procedures for non-normal repeated measures data. Under this approach, robust estimates of the mean and covariance are obtained by trimming the likelihood function rather than directly trimming the data. The trimmed likelihood is expressed as

$$TL(\boldsymbol{\mu}, \boldsymbol{\Sigma}) = \prod_{i=1}^{n-g} f(\mathbf{y}_{(1)}, \ldots, \mathbf{y}_{(n-g)} \mid \boldsymbol{\mu}, \boldsymbol{\Sigma}). \tag{10}$$

The robust estimates of the mean and covariance are obtained by maximizing the trimmed likelihood function. Because the likelihood is scalar-valued, this trimming approach can be done on univariate as well as multivariate data. However, in elliptical distributions, the maximum trimmed likelihood approach is equivalent to trimming the Mahalanobis distance as suggested by Ahmed and Lachenrbuch[27], which may not be efficient due to the distortion of the sample mean and covariance matrices.

Another general class of trimmed estimators for likelihood-based models adopts two-stage

trimming, in which initial robust estimation (e.g., trimming, MCD or MVE) are used to select a sub-sample of the data prior on which likelihood-based inferences are made. Previous work in this area includes the two-stage robust estimator of Broffit, Clarke, and Lachenbruch[37] in which a proportion of observations with the largest Mahalanobis distance are trimmed prior to maximization of the likelihood function. Cuesta-Albertos, Matran, and Mayo-Iscar[38] also suggested an iterative two-stage method in which the robust estimation is used to obtain a suitably trimmed dataset on which ML estimation is conducted. This approach has been shown to result in high-breakdown estimators of means and covariances when data are non-normal, however, its extension to discriminant analysis have not been investigated.

5.3 Discussion

This chapter reviews existing robust DA procedures that have been developed for non-normal data. This includes DA procedures based on rank transformation of the non-normal data and other computer-intensive empirical methods for developing robust estimators. More specifically, trimmed estimation methods for multivariate group designs and repeated measures data, which are computationally efficient with good asymptotic properties, are reviewed. This chapter reviews a number of other trimmed estimation approaches that has not been previously investigated for developing robust DA procedures. While all these approaches have been shown to be robust to non-normality, the choice among these robust estimation approaches remains unclear as there are no previous investigations comparing these estimation methods. While CT estimation method is not as computationally intensive as other robust methods, it is less sensitive to outlying observations because observations considered to be an outlier based on one variable but not an outlier on the other variables are not necessarily removed from the data.

For RMDA procedures that are developed for repeated measures data, there are no previous investigations of robust RMDA procedures for non-normal repeated measures data. Although the existing robust DA procedures for multivariate group designs can be extended to repeated measures data, they do not take advantage of the special structure in the data and may be not be useful for describing group separation in high dimensional non-normal data. While previous research has shown that the bias and error in the DFCs of the conventional DA procedures have been, there is limited investigation of the effects of non-normality on the bias and error in discriminant function coefficients (DFCs) of the conventional DA and RMDA procedures that assume parsimonious covariance structures. These procedures are useful for evaluating the relative importance of variables in longitudinal studies such as health-related quality of life (HRQOL) studies that are often characterized by non-normal distributions.

The RMDA procedures that assume constant means have been described in the previous chapters. These procedures have been shown to improve the accuracy of the classification rule for repeated measures data and advantageous when the sample size is small relative to the number of repeated measures data. However, the assumption of constant repeated measures mean may not be tenable in longitudinal studies that investigate longitudinal changes on one or more variables over time. For example, in longitudinal studies of growth or maturation processes in groups of children or adolescents, the assumption of constant group means may not be tenable when the interest is in describing the differences in the longitudinal profiles of groups[39-40]. In the next chapter, we propose new RMDA procedures that assume unstructured group means and parsimonious covariance structures. Also robust RMDA procedures that assume parsimonious means and/or covariance structures are developed for describing group separation in non-normal repeated measures data.

Despite the benefits of adopting DA procedures based on robust estimators, one limitation of robust estimators is increased bias in the parameter estimates as the breakdown point increases[41]. Our goal in developing robust RMDA procedures is to derive robust DFCs with smaller bias and errors that can be used to describe group separation in non-normal repeated measures data. In the next chapter, we investigate the influence of population distribution on bias and error of DFCs of the robust RMDA procedures under a variety of data analytic conditions in repeated measures data.

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Chapter 6. Robust Descriptive Discriminant Analysis for Repeated Measures Data

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The manuscript presented in this chapter has been accepted for publication in *Computational Statistics and Data Analysis*. It has been re-organized in this chapter to meet the dissertation requirements of the University of Saskatchewan. The candidate's contributions include the development of new robust descriptive discriminant analysis procedures, design and implementation of Monte Carlo study, statistical analysis of the example dataset, and preparation of the published manuscript

Abbreviations

AR-1 = First-order autogressive structure

CS = Compound symmetric structure

CT = Coordinatewise trimming

DA = Discriminant analysis

DDA = Descriptive discriminant analysis

DFC = Discriminant function coefficients

HT-I = Non-normal distribution with moderately heavy tails

HT-II = Non-normal distribution with extremely heavy tails

MCD = Minimum covariance determinant

MER = Misclassification error rates

ML = Maximum likelihood

MVE = Minimum volume ellipsoid

PDA = Predictive discriminant analysis

RMDA = Repeated measures discriminant analysis

RMSE = Root mean square error

SK-I = Non-normal distribution with moderate skewness

SK-II = Non-normal distribution with extreme skeweness

STAR = DA based on structured means and covariances with a AR-1 structure

STCS = DA based on structured means and covariances with a CS structure

UN = Unstructured

UNUN = DA based on unstructured means and covariances

UNCS = DA based on unstructured means and covariances with a CS structure

UNAR = DA based on unstructured means and covariances with a AR-1 structure

Abstract

Discriminant analysis (DA) procedures based on parsimonious mean and/or covariance structures have recently been proposed for repeated measures data. However, these procedures rest on the assumption of a multivariate normal distribution. This study examines repeated measures DA (RMDA) procedures based on maximum likelihood (ML) and coordinatewise trimming (CT) estimation methods and investigates bias and root mean square error (RMSE) in discriminant function coefficients (DFCs) using Monte Carlo techniques. Study parameters include population distribution, covariance structure, sample size, mean configuration, and number of repeated measurements. The results show that for ML estimation, bias in DFC estimates was usually largest when then data were normally distributed, but there was no consistent trend in RMSE. For non-normal distributions, the average bias of CT estimates for procedures that assume unstructured group means and structured covariances was at least 40% smaller than the values for corresponding procedures based on ML estimators. The average RMSE for the former procedures was at least 10% smaller than the average RMSE for the latter procedures, but only when the data were sampled from extremely skewed or heavy-tailed distributions. This finding was observed even when the covariance and mean structures of the RMDA procedure were mis-specified. The proposed robust procedures can be used to identify measurement occasions that make the largest contribution to group separation when the data are sampled from multivariate skewed or heavy-tailed distributions.

Key Words: bias; covariance structure; discriminant function coefficients; repeated measurements; root mean square error

6.1. Introduction

Linear discriminant analysis (DA)[1] is a multivariate procedure for predicting group membership (predictive discriminant analysis; PDA) and/or describing group separation (descriptive discriminant analysis; DDA) on a set of correlated variables. The former focuses on the accuracy of classification while the latter uses discriminant function coefficients (DFCs) to rank order variables according to their contributions to group separation[2]. The linear DA procedure makes no assumptions about the structures of the means or covariances of the variables other than the assumption of homoscedasticity (i.e., equality) of group covariances. Recently, several repeated measures DA (RMDA) procedures based on parsimonious mean and covariance structures, including constant means and compound symmetric (CS) or first-order autoregressive (AR-1) covariances, have been developed for PDA[3-6]. These procedures are efficient when sample size is small relative to the number of repeated measurements, although mis-specification of the mean or covariance structure may influence bias and accuracy.

Previous research has shown that while the linear DA procedure will sometimes result in smaller misclassification error rates (MERs) for PDA in multivariate non-normal than normal data[7-9], it will also frequently produce incorrect variable ranks for DDA when the data are non-normal[10] . Thus, departures from the assumption of multivariate normality may have serious consequences for researchers who adopt the linear DA procedure. However, the effects of non-normality on the performance of RMDA procedures based on parsimonious mean and covariance structures have received little, if any, attention.

Several linear DA procedures that are robust (i.e., insensitive) to departures from the assumption of multivariate normality have been proposed[11-12] by replacing the conventional least-squares estimators of means and covariances with robust estimators, including M-

estimators[13], S-estimators[14,15] , minimum covariance determinant (MCD) estimators[16-17], minimum volume ellipsoid (MVE) estimators[17, 18], and estimators based on the trimmed Mahalanobis distance (M-distance)[19,20];. Some of these estimators have shown poor performance for PDA. Specifically, M-estimators may result in high MERs in high-dimensional data[21]. Moreover, estimators based on trimmed M-distances may be sensitive to multivariate outliers[13]

One approach that has not previously been used to develop robust DA procedures is to adopt estimators based on coordinatewise trimming (CT). In univariate data, trimmed means possess good theoretical properties for heavy-tailed and skewed distributions, are computationally efficient, and straightforward to implement[22]. To implement CT, the coordinates of the multivariate data are independently trimmed by removing a pre-determined proportion of the observations from each tail of the distribution. Trimmed means and Winsorized covariances are then computed from the CT data; the latter are the theoretically correct estimators of variance corresponding to the trimmed mean. Robust estimators based on CT have been adopted in previous studies about multivariate and repeated measures procedures[23-25].

RMDA procedures have a number of applications for describing group differences or predicting group membership. de Coster, Leentjens, Lodder, and Verhey[26] used DA to develop a classification rule for stroke patients. Self-reported depression scores at one, three, six, and nine months post stroke were used to discriminate between patients with and without a clinical diagnosis of depression. RMDA procedures can also be used to identify the ages at which there are significant differences between the growth curves of male and female adolescents[27-28].

In this study, we investigate robust RMDA procedures based on parsimonious means and/or covariances in which the conventional maximum likelihood (ML) estimates of the means and covariances are replaced by ML estimates of means and covariance parameters based on CT. The

effects of population shape and other data characteristics on bias and error in DFCs are investigated using Monte Carlo techniques.

6.2. DFC Estimation for RMDA Procedures

This section focuses on the two-group problem, although all of the procedures can be generalized to multi-group designs. Let $\mathbf{y}_{ij}$ be the $p \times 1$ vector of observed measurements for the ith study participant (i = 1, ..., n_j) in the jth group (j = 1, 2). Initially we assume that $\mathbf{y}_{ij} \sim N_p(\boldsymbol{\mu}_j, \boldsymbol{\Sigma}_j)$, where $\boldsymbol{\mu}_j$ and $\boldsymbol{\Sigma}_j$ are the population mean and covariance for the jth group and are estimated by $\hat{\boldsymbol{\mu}}_j$ and $\hat{\boldsymbol{\Sigma}}_j$, respectively. For the linear DA procedure, the DFC vector is estimated by

$$\hat{\mathbf{a}} = \hat{\boldsymbol{\Sigma}}^{-1}(\hat{\boldsymbol{\mu}}_1 - \hat{\boldsymbol{\mu}}_2), \tag{1}$$

where

$$\hat{\boldsymbol{\Sigma}} = \frac{(n_1 - 1)\hat{\boldsymbol{\Sigma}}_1 + (n_2 - 1)\hat{\boldsymbol{\Sigma}}_2}{n_1 + n_2 - 2}. \tag{2}$$

The number of uncorrelated discriminant functions that separates g groups is equal to $g - 1$. For the linear DA procedure, least-squares and ML estimators of the means and covariances are equivalent (McLachlan, 1992).

RMDA procedures based on constant mean vectors and compound symmetric (CS) or first-order autoregressive (AR-1) covariances for multivariate normal data have been described previously[4, 29], but are included here for completeness. For the CS structure, $\boldsymbol{\Sigma}$ has diagonal elements of σ^2 and off-diagonal elements of $\sigma^2\rho$, where ρ is the correlation parameter. For the AR-1 structure, the covariance elements are equal to $\sigma^2\rho^{|k-l|}$ for the kth and lth measurement occasions (k, l = 1 ,…, p). The DFCs for each procedure are obtained by substituting ML estimates of $\boldsymbol{\Sigma}$, $\boldsymbol{\mu}_1$, and $\boldsymbol{\mu}_2$ into equation 1. However, the assumption of constant $\boldsymbol{\mu}_1$ and $\boldsymbol{\mu}_2$ may not be tenable for repeated measures data and therefore procedures for unstructured means are

developed next.

For a RMDA procedure that assumes a CS structure for $\mathbf{\Sigma}$ and unstructured means, let $\mathbf{\Theta}$ be a column vector of model parameters where the first $2p$ elements denote the mean parameters and the last two elements correspond to σ^2 and $\sigma^2\rho$, respectively. Let $\mathbf{Y}_j$ denote the $n_j \times p$ data matrix for the jth group and $n = n_1 + n_2$. Then the joint log-likelihood function is

$$\log l(\mathbf{\Theta} \mid \mathbf{Y}_1, \mathbf{Y}_2) = -\frac{np}{2}\log 2\pi - \frac{n}{2}\log|\mathbf{\Sigma}| - \frac{1}{2}\mathrm{tr}\{\sum_{j=1}^{2}\sum_{i=1}^{n_j}(\mathbf{y}_{ij} - \mathbf{\mu}_j)^{\mathrm{T}}\mathbf{\Sigma}^{-1}(\mathbf{y}_{ij} - \mathbf{\mu}_j)\}, \quad (3)$$

where $^{\mathrm{T}}$ is the transpose operator. The ML estimate of $\mathbf{\mu}_j$ is $\hat{\mathbf{\mu}}_j$ and the estimates of ρ and σ^2 are obtained by solving

$$-np(1-\rho)(1+(p-1)\rho)\sigma^2 + (1+(p-1)\rho)(a_8 + a_9) - \rho(b_8 + b_9) = 0, \quad (4)$$

and

$$\begin{aligned} &-n(p-1)p(1+(p-1)\rho)(1-\rho)\rho\sigma^2 - (a_8 + a_9)(1+(p-1)\rho)^2 \\ &+ (b_8 + b_9)(\rho^2(p-1)+1) = 0, \end{aligned} \quad (5)$$

where $a_8 = \mathrm{tr}(\mathbf{W}_1)$, $a_9 = \mathrm{tr}(\mathbf{W}_2)$, $b_8 = \mathrm{tr}(\mathbf{J}\mathbf{W}_1)$, $b_9 = \mathrm{tr}(\mathbf{J}\mathbf{W}_2)$, $\mathbf{W}_j = \sum_{i=1}^{n_j}(\mathbf{y}_{ij} - \bar{\mathbf{y}}_j)^{\mathrm{T}}(\mathbf{y}_{ij} - \bar{\mathbf{y}}_j)$,

and

$$\bar{\mathbf{y}}_j = \frac{\sum_{i=1}^{n_j}\mathbf{y}_{ij}}{n_j}, \quad (6)$$

$\mathbf{J} = \mathbf{1}_p\mathbf{1}_p^{\mathrm{T}}$, and $\mathbf{1}_p$ is a $p \times 1$vector of ones. The DFCs are estimated by substituting the ML estimates of ρ, σ^2, and $\mathbf{\mu}_j$ into equation 1. The Appendix provides further details.

For a RMDA procedure with an AR-1 structure for $\mathbf{\Sigma}$ and unstructured mean vectors, the ML estimate of $\mathbf{\mu}_j$ is defined previously and the estimates of ρ and σ^2 are obtained by solving

$$-np\sigma^2(1-\rho^2) + \beta\rho^2 - 2\rho\gamma + \alpha = 0, \quad (7)$$

and

$$n(p-1)\sigma^2\rho^3 - \gamma\rho^2 - n(p-1)\sigma^2 - (\alpha+\beta)\rho - \gamma = 0, \quad (8)$$

where $\text{tr}(\mathbf{\Sigma}_0\mathbf{W}) = \rho\beta_1 - 2\rho\gamma + \alpha$, $\beta = \text{tr}(\mathbf{W}) - \mathbf{W}_{11} - \mathbf{W}_{pp}$, $\gamma = \sum_{\substack{1\le l<p,\\ m=l+1}} \mathbf{W}_{lm}$, $\alpha = tr(\mathbf{W})$,

$\mathbf{W} = \mathbf{W}_1 + \mathbf{W}_2$, and $\mathbf{W}_{ij}$ is the (i, j)th element of **W.** The DFC estimates are obtained by substituting the ML estimates of $\mathbf{\Sigma}$ (based on ρ and σ^2), $\boldsymbol{\mu}_1$, and $\boldsymbol{\mu}_2$ into equation 1. The Appendix provides further details.

6. 3. CT Estimation of DFCs

For CT of repeated measurements, let $y_{(1)jm} \le y_{(2)jm} \le .... \le y_{(n_j)jm}$ denote the order statistics for the jth group and the mth ($m = 1, \ldots, p$) occasion. Define $g_j = [\delta n_j]$, where δ represents the proportion of the observations to be trimmed, or censored, from each tail of the distribution and $[x]$ is the integer less than or equal to x. When symmetric trimming is adopted, so that the same number of observations are removed from each tail of the distribution, the effective sample size for the jth group is $f_j = n_j - 2g_j$. The trimmed mean for the jth group on the mth occasion is

$$\bar{y}_{tjm} = \frac{1}{f_j}\sum_{i=g_j+1}^{n_j-g_j} y_{(i)jm}\,. \quad (8)$$

Define z_{ijm} as

$$z_{ijm} = y_{(g_j+1)jm} \quad \text{if } y_{ijm} \le y_{(g_j+1)jm}$$

$$= y_{ijm} \quad \text{if } y_{(g_j+1)jm} < y_{ijm} < y_{(n_j-g_j)jm}$$

$$= y_{(n_j-g_j)jm} \quad \text{if } y_{ijm} \ge y_{(n_j-g_j)jm}\,.$$

Then

$$\bar{z}_{wjm} = \frac{1}{n_j}\sum_{i=1}^{n_j} z_{ijm}, \tag{9}$$

is the *j*th Winsorized mean for the *m*th occasion. The Winsorized sum of squared deviations for the *m*th and *l*th occasions in the *j*th group is

$$ss_{wjml} = \sum_{i=1}^{n_j}(z_{ijm} - \bar{z}_{wjm})(z_{ijl} - \bar{z}_{wjl}), \tag{10}$$

and $\mathbf{S}_{\underline{wj}} = (ss_{wjml})$ is the Winsorized sums of squares and cross product matrix. The pooled Winsorized covariance is

$$\mathbf{\Sigma}_w = \frac{\mathbf{S}_{w1} + \mathbf{S}_{w2}}{f_1 + f_2 - 2}. \tag{11}$$

For the linear DA procedure, CT is used to define a subsample of observations; trimmed means and Winsorized covariances are computed as described. Robust estimates of the DFCs of procedures that assume unstructured or structured means and structured covariances are derived by maximizing the likelihood of the CT data. More specifically, CT is used to define a subsample of observations for which means and covariances are estimated by solving the systems of equations defined previously. Given that CT estimators are derived by trimming each coordinate[22, 30 - 31], they share similar robustness properties to univariate trimmed estimators.

6.4. Simulation Study

A Monte Carlo study was conducted to examine bias and error in DFCs for the following procedures: (a) conventional DA procedure that assumes unstructured means and covariances (UNUN), (b) RMDA procedure that assumes unstructured means and CS covariances (UNCS), (c) RMDA procedure that assumes unstructured means and AR-1 covariances (UNAR), (d)

RMDA procedure that assumes structured (i.e., constant) means and CS covariances (STCS), and (e) RMDA procedure that assumes structured means and AR-1 covariances (STAR). The DFCs of each procedure were estimated using ML methods applied to the original and CT data.

The following conditions were investigated: (a) number of repeated measurements (p), (b) total sample size (n), (c) group sizes, (d) pattern and magnitude of correlation among the repeated measurements, (e) mean configuration, and (f) population distribution. All procedures were investigated for two independent groups.

The number of repeated measurements was set at p = 3, 5, and 7. Previous studies about RMDA procedures have considered p ranging from 3 to 10[4]. Total sample sizes of n = 60, 100, and 140 were investigated. Although previous simulation studies for RMDA procedures have primarily focused on equal group sizes[4-5], unequal group sizes have also been shown to affect the MER of DA procedures[8, 14], and may therefore influence bias and RMSE of DFCs. For n = 60, the group sizes were (n_1, n_2) = (30, 30), (24, 36), and (15, 45). For n = 100, they were (n_1, n_2) = (50, 50), (40, 60), and (25, 75). For n = 140, the group sizes were (n_1, n_2) = (70, 70), (56, 84) and (35, 105). These group sizes, which represents small to large degrees of group size imbalance, were chosen based on previous research[8,15, 29, 32] (Baron, 1991; Sajobi et al., in press; Van Aelst & Willems, 2010). For the unequal group size cases, the coefficient of group size variation ranged from 0.2 to 0.5[33] (Lix & Fouladi, 2007).

Error in DFCs is known to be influenced by both the magnitude and pattern of correlation amongst the observations[34] (Thomas & Zumbo, 1996). Therefore, six correlation structures were investigated: (a) $\mathbf{Q}_1$: CS with ρ = 0.3 (b) $\mathbf{Q}_2$: CS with ρ = 0.6, (c) $\mathbf{Q}_3$: AR-1 with ρ = 0.3, (d) $\mathbf{Q}_4$: AR-1 with ρ = 0.6, (e) $\mathbf{Q}_5$: UN with average ρ = 0.6, and (f) $\mathbf{Q}_6$: UN with average ρ = 0.6.

The data were generated from multivariate normal and non-normal distributions. For the

former, the marginal skewness and kurtosis values are $\gamma_1 = 0$ and $\gamma_2 = 0$, respectively. Pseudorandom observation vectors $\mathbf{y}_{ij}$ were generated from a multivariate distribution with mean $\boldsymbol{\mu}_j$ and correlation matrix $\mathbf{Q}_{sj} = \mathbf{Q}_s$ ($s = 1, \ldots, 6$). A $p \times 1$ vector of standard normal deviates, $\mathbf{C}_{ij}$, was transformed to a vector of multivariate observations via $\mathbf{y}_{ij} = \boldsymbol{\mu}_j + \mathbf{L}\mathbf{C}_{ij}$. The Cholesky decomposition was used to obtain $\mathbf{L}$, an upper triangular matrix of dimension p satisfying the equality $\mathbf{L}^{\mathrm{T}}\mathbf{L} = \mathbf{Q}_{sj}$. Then $\mathbf{y}_{ij}$ was multiplied by $\mathbf{V}_j$, a diagonal matrix with elements σ_j, to obtain multivariate observations with the desired variances and covariances such that $\boldsymbol{\Sigma}_j = \mathbf{V}_j\mathbf{Q}_{sj}\mathbf{V}_j^{\mathrm{T}}$. For all the investigated conditions, $\boldsymbol{\Sigma}_1 = \boldsymbol{\Sigma}_2$.

When the assumption of multivariate normality was violated, we considered conditions in which the data from the two groups were sampled from the same distribution as well as conditions in which the data for the two groups were sampled from different distributions. For the former, we considered two skewed distributions with $\gamma_1 = 1.8$ and $\gamma_2 = 5.9$ (SK-I) and $\gamma_1 = 13.2$ and $\gamma_2 = 42892.9$ (SK-II), respectively. Two heavy-tailed distributions were investigated, with $\gamma_1 = 0$ and $\gamma_2 = 33$ (HT-I) for the first while the second was similar to a heavy-tailed Cauchy distribution for which γ_1 and γ_2 are undefined (HT-II). For the latter, we investigated the case in which observations in group 1 were sampled from a HT-II distribution while the observations in group 2 were sampled from a SK-II distribution and denoted this condition by HT-II/SK-II. These non-normal distributions represent moderate and extreme departures from multivariate normality and have been investigated in previous studies employing trimmed estimators[35, 36] (Berkovits, Hancock, & Nevitt, 2000; Keselman et al., 2007). Field and Genton[37] describe a family of multivariate non-normal distributions obtained by modifying the quantiles. The variables g and h, which control the magnitude of γ_1 and γ_2, are used to transform a standard normal variate, C, as follows:

$$y_{ijm} = \frac{\exp(gC_{ijm})}{g} \exp \frac{h}{2} C_{ijm}^2 \ . \tag{12}$$

When $g = 0$, this equation reduces to

$$y_{ijm} = \exp(\frac{h}{2} C_{ijm}^2) C_{ijm} \ . \tag{13}$$

The g and h parameters provide a convenient approach to generate data from multivariate distributions. When $g = h = 0$, the distribution is multivariate normal. The parameter h determines the heaviness of the tails of a distribution while the parameter g controls the magnitude of skewness.

Three configurations for $\boldsymbol{\mu}_1$ were selected based on previous research (Table 1) and $\boldsymbol{\mu}_2 = 0.5\mathbf{1}_p$ for all conditions[4, 38]. Configuration I had constant means across the repeated measurements in both groups. Configuration II had non-constant means in a quadratic pattern for the first group. For configuration III, a monotonic decreasing linear pattern was specified for $\boldsymbol{\mu}_1$. These configurations represent the types of structures common in repeated measures studies[39].

Table 6-1. Configurations of $\boldsymbol{\mu}_1$ for the Monte Carlo Study

Configuration	$p = 3$	$p = 5$	$p = 7$
I	(1, 1, 1)	(1, 1, 1, 1, 1)	(1, 1, 1, 1, 1, 1, 1)
II	(1, 1.5, 1)	(1, 1.5, 2, 1.5, 1)	(1, 1.5, 2, 2.5, 2, 1.5, 1)
III	(1, 0.75, 0.5)	(1.5, 1.25, 1, 0.75, 0.5)	(2, 1.75, 1.5, 1.25, 1, 0.75, 0.5)

Note: $\boldsymbol{\mu}_2 = 0.5\mathbf{1}_p$ for all conditions.

For the robust procedures, a 20% symmetric trimming rule was adopted as recommended by Wilcox[22]. All combinations of conditions were investigated for each procedure and each method of estimation, resulting in a total of 3 x 3 x 3 x 6 x 3 x 6= 2916 combinations. There were 10,000

replications for each combination.

The Monte Carlo study was conducted using SAS/IML version 9.2[40]. The RANNOR function was used to generate the standard normal deviates.

Two quantitative measures to evaluate bias and error in DFCs are the norm of the average bias and root mean square error (RMSE)[15]. Let $\hat{\mathbf{a}}_k$ be the estimated vector of DFCs for the kth simulation run ($k = 1, \ldots, M$), and $\mathbf{a}$, the vector of population DFCs obtained from the population covariances and group means. Bias is defined as

$$b = \| \frac{1}{M} \sum_{k=1}^{M} (\hat{\mathbf{a}}_k - \mathbf{a}) \|, \tag{14}$$

and RMSE is defined as

$$e = \sqrt{\frac{1}{M} \sum_{k=1}^{M} \| \hat{\mathbf{a}}_k - \mathbf{a} \|^2}, \tag{15}$$

where $\|\boldsymbol{x}\|$ is the norm of vector $\boldsymbol{x}$. Both measures take values on the interval $[0, \infty)$ and smaller values are better. Absolute values of average bias and RMSE are reported, along with relative bias and RMSE for CT estimation.

6.5. Results

Tables 2 and 3 contain the results for average bias and RMSE, respectively, for the DFCs when the data were sampled from multivariate normal and non-normal distributions for each of the six correlation structures. When conventional ML estimators were adopted, the average bias values for procedures that assume unstructured group means (i.e., UNUN, UNCS, and UNAR) were smallest when the data were normal but largest when they were non-normal. In contrast, the average bias values for procedures that assume constant group means (i.e., STCS and STAR) were smallest for the HT-I distribution and largest for the HT-II/SK-II distribution. The average

bias values for the investigated procedures based on ML estimators were sometimes influenced by the correlation structure. For the UNUN procedure, average bias values were similar across the six correlation structures. For all the procedures based on ML estimators, the average bias was smallest for a CS or AR-1 correlation structure and largest for a UN structure (i.e, $\mathbf{Q}_5$ or $\mathbf{Q}_6$).

When CT estimation was adopted, average bias values for the UNUN, UNCS, and UNAR procedures were smallest for the SK-I distribution and largest for the HT-II/SK-II condition. In contrast, the average bias values for the STCS and STAR procedures were smallest when the data were sampled from the SK-II distribution and largest for the normal distribution. For the UNUN, UNCS and UNAR procedures, average bias was smallest for either a CS (i.e., $\mathbf{Q}_1$ and $\mathbf{Q}_2$) or AR-1 (i.e., $\mathbf{Q}_3$ and $\mathbf{Q}_4$) structure. For the STCS and STAR procedures, bias was smallest for the $\mathbf{Q}_2$ and $\mathbf{Q}_3$ structures but largest for the $\mathbf{Q}_5$ and $\mathbf{Q}_6$ structures, regardless of the population distribution.

When the data were sampled from multivariate non-normal distributions, average bias values were generally lower for robust than ML estimators. However, this depended on the procedure and the correlation structure. For example, for the SK-I distribution with $\mathbf{Q}_6$, average bias for the UNCS procedure based on ML and CT estimators were 0.45 and 0.32, respectively, whereas the average bias values for the STCS procedure were 1.29 and 1.41, respectively. The average bias values for UNUN, UNCS, and UNAR procedure based on CT estimators exhibited smaller variability (i.e., standard deviation) than the corresponding ML estimates, although this again depends on the covariance structure and population distribution. In contrast, the average bias values for the STCS and STAR procedures based on ML estimators had larger standard deviation values than those of the corresponding procedures based on ML estimators when data were normal but not under non-normal distributions.

Table 6-2. Mean(SD) Bias of Discriminant Function Coefficients by Population Distribution and Correlation Structure

Distribution	Correlation Structure	ML Estimation					CT Estimation				
		UNUN	UNCS	UNAR	STCS	STAR	UNUN	UNCS	UNAR	STCS	STAR
Normal	$\mathbf{Q}_1$	0.05(0.05)	0.06(0.05)	0.28(0.16)	0.75(0.33)	0.78(0.33)	0.13(0.07)	0.11(0.05)	0.32(0.14)	0.89(0.30)	0.90(0.29)
	$\mathbf{Q}_2$	0.04(0.04)	0.04(0.05)	0.05(0.05)	0.34(0.25)	0.33(0.25)	0.18(0.06)	0.15(0.05)	0.15(0.05)	0.46(0.20)	0.43(0.20)
	$\mathbf{Q}_3$	0.05(0.05)	0.16(0.06)	0.06(0.05)	0.51(0.21)	0.51(0.23)	0.13(0.05)	0.22(0.08)	0.11(0.05)	0.66(0.18)	0.64(0.19)
	$\mathbf{Q}_4$	0.06(0.06)	0.35(0.14)	0.08(0.06)	0.87(0.29)	0.86(0.43)	0.11(0.05)	0.40(0.19)	0.09(0.04)	1.00(0.26)	0.98(0.38)
	$\mathbf{Q}_5$	0.06(0.05)	0.54(0.34)	0.67(0.42)	1.04(0.55)	1.06(0.53)	0.14(0.06)	0.51(0.32)	0.68(0.40)	1.15(0.52)	1.16(0.50)
	$\mathbf{Q}_6$	0.07(0.05)	0.32(0.13)	0.70(0.43)	1.39(0.67)	1.54(0.67)	0.18(0.12)	0.31(0.14)	0.69(0.38)	1.51(0.63)	1.65(0.63)
SK-I	$\mathbf{Q}_1$	0.19(0.06)	0.22(0.06)	0.34(0.16)	0.64(0.38)	0.68(0.36)	0.08(0.04)	0.07(0.05)	0.28(0.16)	0.80(0.32)	0.83(0.31)
	$\mathbf{Q}_2$	0.19(0.06)	0.22(0.05)	0.23(0.05)	0.38(0.18)	0.38(0.18)	0.10(0.05)	0.08(0.04)	0.07(0.04)	0.40(0.22)	0.38(0.22)
	$\mathbf{Q}_3$	0.18(0.06)	0.23(0.06)	0.21(0.06)	0.43(0.22)	0.41(0.28)	0.07(0.04)	0.17(0.07)	0.06(0.04)	0.58(0.19)	0.57(0.21)
	$\mathbf{Q}_4$	0.21(0.07)	0.37(0.08)	0.24(0.06)	0.77(0.30)	0.74(0.47)	0.08(0.04)	0.35(0.15)	0.07(0.06)	0.90(0.28)	0.89(0.41)
	$\mathbf{Q}_5$	0.23(0.06)	0.62(0.33)	0.71(0.42)	0.97(0.56)	1.00(0.54)	0.13(0.08)	0.52(0.34)	0.66(0.42)	1.08(0.54)	1.10(0.52)
	$\mathbf{Q}_6$	0.26(0.08)	0.45(0.18)	0.77(0.47)	1.29(0.72)	1.44(0.71)	0.11(0.05)	0.32(0.14)	0.70(0.43)	1.41(0.66)	1.56(0.67)
SK-II	$\mathbf{Q}_1$	0.65(0.11)	0.72(0.12)	0.74(0.14)	0.74(0.21)	0.76(0.21)	0.34(0.06)	0.36(0.08)	0.45(0.14)	0.58(0.39)	0.66(0.36)
	$\mathbf{Q}_2$	0.72(0.06)	0.81(0.04)	0.81(0.04)	0.78(0.04)	0.78(0.04)	0.23(0.09)	0.28(0.09)	0.28(0.09)	0.39(0.17)	0.40(0.17)
	$\mathbf{Q}_3$	0.63(0.08)	0.69(0.06)	0.70(0.06)	0.66(0.10)	0.67(0.09)	0.30(0.07)	0.34(0.08)	0.34(0.08)	0.42(0.21)	0.43(0.25)
	$\mathbf{Q}_4$	0.68(0.13)	0.73(0.13)	0.74(0.13)	0.78(0.21)	0.80(0.24)	0.37(0.10)	0.46(0.07)	0.43(0.09)	0.71(0.30)	0.69(0.45)
	$\mathbf{Q}_5$	0.84(0.21)	1.02(0.34)	1.03(0.37)	1.05(0.42)	1.06(0.42)	0.51(0.19)	0.72(0.34)	0.78(0.41)	0.95(0.54)	0.98(0.52)
	$\mathbf{Q}_6$	0.95(0.37)	1.09(0.46)	1.18(0.54)	1.26(0.65)	1.30(0.65)	0.66(0.24)	0.72(0.32)	0.92(0.51)	1.21(0.76)	1.34(0.74)
HT-I	$\mathbf{Q}_1$	0.33(0.07)	0.36(0.07)	0.43(0.16)	0.58(0.39)	0.64(0.37)	0.10(0.06)	0.10(0.08)	0.28(0.17)	0.73(0.34)	0.77(0.33)
	$\mathbf{Q}_2$	0.34(0.06)	0.38(0.06)	0.38(0.06)	0.45(0.13)	0.46(0.13)	0.06(0.05)	0.06(0.06)	0.06(0.06)	0.35(0.24)	0.34(0.24)
	$\mathbf{Q}_3$	0.31(0.07)	0.34(0.07)	0.34(0.06)	0.42(0.20)	0.43(0.23)	0.07(0.05)	0.17(0.06)	0.09(0.07)	0.51(0.20)	0.51(0.24)

	$\mathbf{Q}_4$	0.35(0.08)	0.43(0.06)	0.37(0.08)	0.72(0.31)	0.68(0.48)	0.14(0.06)	0.35(0.11)	0.16(0.07)	0.83(0.29)	0.82(0.44)
	$\mathbf{Q}_5$	0.41(0.09)	0.72(0.33)	0.78(0.41)	0.95(0.54)	0.97(0.53)	0.20(0.12)	0.56(0.34)	0.67(0.43)	1.03(0.55)	1.05(0.52)
	$\mathbf{Q}_6$	0.46(0.15)	0.60(0.24)	0.86(0.49)	1.22(0.76)	1.37(0.73)	0.24(0.07)	0.39(0.18)	0.74(0.47)	1.35(0.69)	1.49(0.69)
HT-II	$\mathbf{Q}_1$	0.45(0.09)	0.51(0.09)	0.55(0.15)	0.62(0.32)	0.65(0.32)	0.19(0.07)	0.20(008)	0.33(0.16)	0.66(0.37)	0.71(0.36)
	$\mathbf{Q}_2$	0.48(0.06)	0.55(0.05)	0.55(0.05)	0.56(0.05)	0.57(0.09)	0.09(0.08)	0.13(0.08)	0.13(0.08)	0.34(0.23)	0.35(0.22)
	$\mathbf{Q}_3$	0.43(0.08)	0.48(0.08)	0.49(0.07)	0.49(0.15)	0.50(0.16)	0.15(0.07)	0.22(0.07)	0.19(0.08)	0.45(0.22)	0.45(0.27)
	$\mathbf{Q}_4$	0.47(0.10)	0.55(0.09)	0.53(0.10)	0.71(0.29)	0.72(0.38)	0.23(0.07)	0.38(0.08)	0.27(0.08)	0.77(0.31)	0.74(0.48)
	$\mathbf{Q}_5$	0.57(0.13)	0.85(0.35)	0.89(0.41)	0.98(0.52)	1.00(0.51)	0.32(0.16)	0.63(0.36)	0.72(0.46)	0.99(0.58)	1.03(0.55)
	$\mathbf{Q}_6$	0.64(0.23)	0.80(0.33)	0.98(0.51)	1.20(0.75)	1.31(0.72)	0.41(0.12)	0.51(0.23)	0.80(0.49)	1.28(0.73)	1.42(0.71)
HT-II/SK-II	$\mathbf{Q}_1$	0.65(0.10)	0.72(0.08)	0.75(0.09)	0.84(0.16)	0.85(0.15)	0.33(0.10)	0.31(0.07)	0.41(0.13)	0.61(0.39)	0.68(0.37)
	$\mathbf{Q}_2$	0.75(0.13)	0.84(0.09)	0.84(0.09)	0.83(0.12)	0.83(0.12)	0.17(0.08)	0.20(0.08)	0.20(0.07)	0.36(0.20)	0.37(0.19)
	$\mathbf{Q}_3$	0.66(0.12)	0.72(0.10)	0.73(0.10)	0.75(0.15)	0.76(0.13)	0.24(0.05)	0.24(0.06)	0.26(0.06)	0.43(0.22)	0.42(0.28)
	$\mathbf{Q}_4$	0.65(0.11)	0.71(0.10)	0.71(0.09)	0.88(0.16)	0.90(0.17)	0.41(0.14)	0.45(0.10)	0.37(0.08)	0.73(0.31)	0.69(0.48)
	$\mathbf{Q}_5$	0.82(0.13)	1.01(0.29)	1.03(0.32)	1.12(0.38)	1.13(0.37)	0.54(0.26)	0.68(0.36)	0.75(0.43)	0.96(0.55)	0.99(0.53)
	$\mathbf{Q}_6$	0.86(0.22)	1.00(0.34)	1.11(0.47)	1.33(0.57)	1.35(0.58)	0.74(0.07)	0.70(0.17)	0.90(0.45)	1.24(0.75)	1.38(0.73)

Note: Normal distribution has skewness (γ_1) = 0 and kurtosis (γ_2) = 0; SK-I has γ_1 = 1.8 and γ_2 = 5.9; SK-II has γ_1 = 13.2 and γ_2 = 42892.9; HT-I has γ_1 = 0 and γ_2 = 33; HT-II has $\gamma_1 = \infty$ and $\gamma_2 = \infty$. $\mathbf{Q}_1$ = CS with ρ = 0.3; $\mathbf{Q}_2$ = CS with ρ = 0.6; $\mathbf{Q}_3$ = AR-1 with ρ = 0.3; $\mathbf{Q}_4$ = AR-1 with ρ = 0.6; $\mathbf{Q}_5$ = UN with average ρ = 0.3; $\mathbf{Q}_6$ = UN with average ρ = 0.6. ρ = correlation parameter. UNUN = UN group means and UN covariances; UNCS = UN group means and CS covariances; UNAR = UN group means and AR-1 covariances; STCS = Structured group mean vectors and CS-covariance structure; STAR = Structured group mean vectors and AR-1 covariance. AR-1 = First-order autoregressive; CS = compound symmetric; UN = unstructured; SD = Standard deviation

Table 6-3. Average (SD) RMSE of Discriminant Function Coefficients by Population Distribution and Correlation Structure

Distribution	Correlation Structure	ML Estimation					CT Estimation				
		UNUN	UNCS	UNAR	STCS	STAR	UNUN	UNCS	UNAR	STCS	STAR
Normal	$\mathbf{Q}_1$	0.55(0.17)	0.47(0.17)	0.55(0.12)	0.77(0.34)	0.80(0.33)	0.69(0.18)	0.57(0.18)	0.64(0.12)	0.91(0.31)	0.92(0.30)
	$\mathbf{Q}_2$	0.42(0.l2)	0.34(0.13)	0.33(0.13)	0.36(0.25)	0.36(0.25)	0.55(0.12)	0.44(0.12)	0.44(0.13)	0.48(0.22)	0.45(0.21)
	$\mathbf{Q}_3$	0.52(0.14)	0.44(0.13)	0.43(0.15)	0.53(0.23)	0.53(0.25)	0.65(0.15)	0.55(0.13)	0.53(0.16)	0.68(0.20)	0.66(0.21)
	$\mathbf{Q}_4$	0.78(0.24)	0.65(0.16)	0.67(0.23)	0.89(0.29)	0.88(0.43)	0.93(0.26)	0.78(0.17)	0.78(0.25)	1.03(0.27)	1.01(0.39)
	$\mathbf{Q}_5$	0.59(0.20)	0.76(0.27)	0.83(0.35)	1.05(0.55)	1.08(0.53)	0.72(0.21)	0.81(0.23)	0.89(0.32)	1.17(0.52)	1.18(0.50)
	$\mathbf{Q}_6$	0.83(0.35)	0.79(0.28)	1.12(0.31)	1.41(0.67)	1.56(0.66)	1.02(0.37)	0.89(0.32)	1.20(0.30)	1.54(0.62)	1.68(0.62)
SK-I	$\mathbf{Q}_1$	0.58(0.15)	0.50(0.15)	0.57(0.12)	0.67(0.36)	0.72(0.35)	0.68(0.18)	0.56(0.19)	0.63(0.13)	0.84(0.32)	0.86(0.32)
	$\mathbf{Q}_2$	0.46(0.11)	0.39(0.12)	0.39(0.13)	0.40(0.19)	0.40(0.19)	0.54(0.13)	0.41(0.14)	0.41(0.14)	0.42(0.24)	0.41(0.24)
	$\mathbf{Q}_3$	0.55(0.13)	0.45(0.14)	0.47(0.14)	0.46(0.24)	0.46(0.27)	0.64(0.15)	0.52(0.14)	0.52(0.17)	0.61(0.22)	0.60(0.23)
	$\mathbf{Q}_4$	0.78(0.21)	0.63(0.15)	0.68(0.20)	0.80(0.30)	0.79(0.44)	0.91(0.25)	0.73(0.17)	0.77(0.24)	0.94(0.28)	0.93(0.41)
	$\mathbf{Q}_5$	0.63(0.17)	0.80(0.28)	0.86(0.36)	0.99(0.55)	1.02(0.53)	0.71(0.22)	0.81(0.25)	0.88(0.33)	1.11(0.53)	1.12(0.51)
	$\mathbf{Q}_6$	0.86(0.27)	0.83(0.21)	1.15(0.32)	1.33(0.69)	1.47(0.69)	0.97(0.34)	0.87(0.29)	1.19(0.30)	1.46(0.64)	1.60(0.65)
SK-II	$\mathbf{Q}_1$	0.76(0.09)	0.78(0.10)	0.79(0.13)	0.78(0.20)	0.79(0.20)	0.68(0.14)	0.62(0.15)	0.69(0.12)	0.68(0.32)	0.73(0.32)
	$\mathbf{Q}_2$	0.79(0.06)	0.84(0.04)	0.85(0.04)	0.80(0.05)	0.80(0.05)	0.53(0.13)	0.47(0.15)	0.47(0.15)	0.43(0.19)	0.43(0.19)
	$\mathbf{Q}_3$	0.73(0.08)	0.74(0.07)	0.75(0.07)	0.69(0.10)	0.70(0.10)	0.65(0.13)	0.56(0.14)	0.59(0.15)	0.48(0.22)	0.50(0.24)
	$\mathbf{Q}_4$	0.86(0.10)	0.80(0.12)	0.83(0.11)	0.82(0.20)	0.83(0.23)	0.83(0.15)	0.71(0.14)	0.78(0.14)	0.78(0.27)	0.79(0.37)
	$\mathbf{Q}_5$	0.95(0.19)	1.06(0.33)	1.07(0.35)	1.08(0.41)	1.09(0.41)	0.80(0.19)	0.90(0.28)	0.95(0.34)	1.00(0.51)	1.03(0.50)
	$\mathbf{Q}_6$	1.14(0.28)	1.19(0.40)	1.28(0.48)	1.30(0.62)	1.34(0.62)	1.03(0.13)	1.01(0.17)	1.23(0.35)	1.30(0.68)	1.41(0.67)
HT-I	$\mathbf{Q}_1$	0.61(0.13)	0.56(0.12)	0.61(0.12)	0.64(0.35)	0.68(0.35)	0.65(0.18)	0.56(0.19)	0.63(0.13)	0.78(0.33)	0.81(0.33)

	$\mathbf{Q}_2$	0.52(0.10)	0.49(0.11)	0.49(0.11)	0.47(0.15)	0.48(0.15)	0.51(0.13)	0.40(0.15)	0.40(0.15)	0.39(0.25)	0.38(0.25)
	$\mathbf{Q}_3$	0.58(0.12)	0.50(0.13)	0.53(0.13)	0.45(0.22)	0.47(0.24)	0.62(0.15)	0.51(0.15)	0.52(0.17)	0.55(0.23)	0.55(0.25)
	$\mathbf{Q}_4$	0.79(0.17)	0.65(0.13)	0.71(0.16)	0.76(0.30)	0.76(0.42)	0.87(0.23)	0.71(0.17)	0.76(0.22)	0.88(0.29)	0.88(0.41)
	$\mathbf{Q}_5$	0.69(0.14)	0.86(0.28)	0.90(0.36)	0.98(0.53)	1.00(0.52)	0.70(0.21)	0.83(0.26)	0.89(0.33)	1.06(0.54)	1.08(0.52)
	$\mathbf{Q}_6$	0.90(0.18)	0.91(0.16)	1.18(0.34)	1.29(0.70)	1.42(0.69)	0.94(0.30)	0.88(0.25)	1.20(0.31)	1.40(0.66)	1.54(0.66)
HT-II	$\mathbf{Q}_1$	0.68(0.10)	0.65(0.10)	0.68(0.12)	0.67(0.30)	0.71(0.29)	0.67(0.17)	0.58(0.18)	0.65(0.13)	0.72(0.34)	0.77(0.34)
	$\mathbf{Q}_2$	0.63(0.09)	0.63(0.09)	0.64(0.09)	0.59(0.11)	0.60(0.11)	0.52(0.14)	0.42(0.16)	0.42(0.16)	0.39(0.24)	0.39(0.23)
	$\mathbf{Q}_3$	0.65(0.10)	0.59(0.11)	0.62(0.11)	0.53(0.17)	0.55(0.18)	0.64(0.15)	0.52(0.16)	0.54(0.17)	0.51(0.24)	0.51(0.26)
	$\mathbf{Q}_4$	0.84(0.12)	0.71(0.12)	0.76(0.11)	0.77(0.27)	0.78(0.35)	0.87(0.20)	0.70(0.16)	0.77(0.20)	0.83(0.30)	0.83(0.42)
	$\mathbf{Q}_5$	0.80(0.13)	0.95(0.31)	0.98(0.38)	1.02(0.50)	1.04(0.49)	0.75(0.21)	0.87(0.27)	0.92(0.35)	1.04(0.56)	1.07(0.53)
	$\mathbf{Q}_6$	1.01(0.13)	1.02(0.20)	1.22(0.38)	1.27(0.68)	1.37(0.67)	0.97(0.22)	0.92(0.20)	1.21(0.33)	1.35(0.68)	1.48(0.67)
HT-II/SK-II	$\mathbf{Q}_1$	0.81(0.10)	0.81(0.09)	0.84(0.09)	0.92(0.15)	0.93(0.14)	0.65(0.14)	0.54(0.14)	0.62(0.10)	0.66(0.35)	0.71(0.34)
	$\mathbf{Q}_2$	0.87(0.13)	0.90(0.11)	0.90(0.11)	0.88(0.14)	0.88(0.13)	0.48(0.10)	0.35(0.10)	0.35(0.10)	0.38(0.19)	0.38(0.19)
	$\mathbf{Q}_3$	0.83(0.11)	0.80(0.11)	0.82(0.11)	0.82(0.16)	0.83(0.15)	0.59(0.10)	0.45(0.11)	0.48(0.11)	0.45(0.22)	0.46(0.26)
	$\mathbf{Q}_4$	0.91(0.10)	0.81(0.12)	0.86(0.09)	0.96(0.15)	0.98(0.15)	0.82(0.17)	0.66(0.14)	0.71(0.14)	0.77(0.29)	0.77(0.41)
	$\mathbf{Q}_5$	0.97(0.13)	1.08(0.27)	1.10(0.29)	1.19(0.35)	1.19(0.35)	0.79(0.26)	0.84(0.31)	0.89(0.37)	0.98(0.54)	1.01(0.52)
	$\mathbf{Q}_6$	1.10(0.12)	1.14(0.26)	1.27(0.37)	1.40(0.53)	1.42(0.53)	1.02(0.13)	0.92(0.11)	1.17(0.31)	1.30(0.70)	1.43(0.69)

Note: Normal distribution has skewness (γ_1) = 0 and kurtosis (γ_2) = 0; SK-I has γ_1 = 1.8 and γ_2 = 5.9; SK-II has γ_1 = 13.2 and γ_2 = 42892.9; HT-I has γ_1 = 0 and γ_2 = 33; HT-II has $\gamma_1 = \infty$ and $\gamma_2 = \infty$. $\mathbf{Q}_1$ = CS with ρ = 0.3; $\mathbf{Q}_2$ = CS with ρ = 0.6; $\mathbf{Q}_3$ = AR-1 with ρ = 0.3; $\mathbf{Q}_4$ = AR-1 with ρ = 0.6; $\mathbf{Q}_5$ = UN with average ρ = 0.3; $\mathbf{Q}_6$ = UN with average ρ = 0.6. ρ = correlation parameter. UNUN = UN group means and UN covariances; UNCS = UN group means and CS covariances; UNAR = UN group means and AR-1 covariances; STCS = Structured group mean vectors and CS-covariance structure; STAR = Structured group mean vectors and AR-1 covariance. AR-1 = First-order autoregressive; CS = compound symmetric; UN = unstructured; SD = Standard deviation

Table 6-4. Mean (SD) Bias of Discriminant Function Coefficients by Population Distribution and Mean Configuration

Distribution	Mean Configuration	ML Estimation					CT Estimation				
		UNUN	UNCS	UNAR	STCS	STAR	UNUN	UNCS	UNAR	STCS	STAR
Normal	I	0.08(0.04)	0.19(0.14)	0.19(0.15)	0.34(0.20)	0.33(0.23)	0.08(0.05)	0.19(0.13)	0.22(0.17)	0.52(0.19)	0.51(0.21)
	II	0.02(0.02)	0.21(0.24)	0.27(0.36)	0.93(0.45)	1.05(0.54)	0.19(0.05)	0.31(0.20)	0.35(0.30)	1.04(0.45)	1.14(0.54)
	III	0.07(0.07)	0.33(0.29)	0.46(0.49)	1.18(0.51)	1.15(0.53)	0.16(0.08)	0.35(0.28)	0.45(0.45)	1.27(0.51)	1.23(0.52)
SK-I	I	0.21(0.03)	0.30(0.11)	0.27(0.11)	0.25(0.15)	0.24(0.19)	0.09(0.07)	0.18(0.15)	0.18(0.16)	0.41(0.18)	0.39(0.20)
	II	0.17(0.04)	0.31(0.22)	0.38(0.33)	0.87(0.44)	0.99(0.51)	0.09(0.04)	0.24(0.22)	0.29(0.35)	0.97(0.45)	1.08(0.53)
	III	0.25(0.09)	0.44(0.28)	0.60(0.46)	1.11(0.51)	1.10(0.53)	0.10(0.05)	0.33(0.29)	0.45(0.49)	1.21(0.51)	1.18(0.52)
SK-II	I	0.61(0.09)	0.67(0.11)	0.66(0.12)	0.57(0.13)	0.58(0.12)	0.37(0.11)	0.41(0.11)	0.38(0.10)	0.22(0.13)	0.23(0.15)
	II	0.74(0.18)	0.85(0.24)	0.88(0.27)	0.94(0.33)	0.98(0.35)	0.39(0.19)	0.44(0.26)	0.50(0.34)	0.83(0.43)	0.96(0.47)
	III	0.89(0.26)	1.01(0.35)	1.06(0.40)	1.13(0.44)	1.13(0.44)	0.45(0.26)	0.60(0.34)	0.72(0.47)	1.08(0.50)	1.07(0.51)
HT-I	I	0.33(0.04)	0.40(0.09)	0.36(0.09)	0.24(0.13)	0.24(0.16)	0.15(0.10)	0.22(0.14)	0.20(0.15)	0.32(0.18)	0.31(0.20)
	II	0.33(0.08)	0.44(0.21)	0.50(0.30)	0.84(0.42)	0.96(0.48)	0.11(0.07)	0.23(0.24)	0.30(0.36)	0.92(0.44)	1.04(0.52)
	III	0.44(0.13)	0.58(0.28)	0.72(0.44)	1.08(0.50)	1.08(0.51)	0.15(0.11)	0.36(0.30)	0.50(0.49)	1.16(0.51)	1.14(0.52)
HT-II	I	0.44(0.05)	0.51(0.09)	0.48(0.09)	0.33(0.13)	0.34(0.13)	0.24(0.12)	0.29(0.13)	0.26(0.13)	0.24(0.16)	0.23(0.19)
	II	0.48(0.11)	0.60(0.22)	0.65(0.29)	0.86(0.39)	0.95(0.43)	0.20(0.13)	0.30(0.25)	0.36(0.36)	0.88(0.44)	1.00(0.51)
	III	0.61(0.18)	0.76(0.32)	0.87(0.42)	1.09(0.49)	1.09(0.50)	0.25(0.18)	0.45(0.32)	0.59(0.49)	1.13(0.51)	1.11(0.53)
HT-II/SK-II	I	0.73(0.10)	0.75(0.12)	0.74(0.12)	0.74(0.09)	0.74(0.09)	0.42(0.24)	0.39(0.17)	0.32(0.13)	0.21(0.14)	0.20(0.17)
	II	0.66(0.14)	0.80(0.21)	0.82(0.24)	0.94(0.33)	0.97(0.35)	0.44(0.24)	0.42(0.28)	0.49(0.35)	0.85(0.43)	0.97(0.49)
	III	0.80(0.20)	0.95(0.30)	1.02(0.36)	1.20(0.42)	1.20(0.42)	0.35(0.21)	0.49(0.32)	0.63(0.47)	1.10(0.51)	1.09(0.52)

Note: Normal distribution has skewness (γ_1) = 0 and kurtosis (γ_2) = 0; SK-I has γ_1 = 1.8 and γ_2 = 5.9; SK-II has γ_1 = 13.2 and γ_2 = 42892.9; HT-I has γ_1 = 0

and $\gamma_2 = 33$; HT-II has $\gamma_1 = \infty$ and $\gamma_2 = \infty$. See Table 1 for a description of mean configurations. UNUN = UN group means and UN covariances; UNCS = UN group means and CS covariances; UNAR = UN group means and AR-1 covariances; STCS = Structured group mean vectors and CS-covariance structure; STAR = Structured group mean vectors and AR-1 covariance. AR-1 = First-order autoregressive; CS = compound symmetric; UN = unstructured; SD = Standard deviation

Table 6-5. Mean (SD) RMSE of Discriminant Function Coefficients by Population Distribution and Mean Configuration

Distribution	Mean Configuration	ML Estimation					CT Estimation				
		UNUN	UNCS	UNAR	STCS	STAR	UNUN	UNCS	UNAR	STCS	STAR
Normal	I	0.79(0.32)	0.70(0.27)	0.69(0.28)	0.36(0.20)	0.36(0.22)	0.95(0.35)	0.82(0.29)	0.82(0.30)	0.54(0.19)	0.53(0.21)
	II	0.47(0.14)	0.42(0.20)	0.50(0.29)	0.93(0.45)	1.06(0.54)	0.61(0.16)	0.51(0.17)	0.58(0.26)	1.04(0.45)	1.14(0.54)
	III	0.58(0.17)	0.59(0.24)	0.77(0.41)	1.21(0.51)	1.19(0.53)	0.73(0.18)	0.69(0.21)	0.84(0.38)	1.32(0.50)	1.28(0.53)
SK-I	I	0.79(0.27)	0.70(0.22)	0.69(0.23)	0.30(0.15)	0.29(0.18)	0.93(0.32)	0.80(0.27)	0.79(0.28)	0.45(0.18)	0.43(0.21)
	II	0.51(0.14)	0.46(0.20)	0.55(0.30)	0.87(0.44)	0.99(0.51)	0.59(0.16)	0.48(0.18)	0.56(0.28)	0.97(0.44)	1.09(0.53)
	III	0.63(0.16)	0.64(0.26)	0.82(0.42)	1.15(0.51)	1.14(0.53)	0.70(0.17)	0.67(0.23)	0.85(0.40)	1.26(0.51)	1.24(0.53)
SK-II	I	0.78(0.07)	0.75(0.08)	0.75(0.08)	0.62(0.11)	0.62(0.11)	0.84(0.19)	0.76(0.14)	0.75(0.16)	0.35(0.14)	0.35(0.15)
	II	0.85(0.19)	0.89(0.24)	0.92(0.27)	0.95(0.33)	0.99(0.34)	0.67(0.20)	0.59(0.24)	0.67(0.32)	0.85(0.42)	0.97(0.47)
	III	0.99(0.26)	1.06(0.35)	1.11(0.39)	1.16(0.43)	1.16(0.44)	0.76(0.22)	0.79(0.32)	0.94(0.42)	1.14(0.50)	1.13(0.51)
HT-I	I	0.78(0.21)	0.71(0.16)	0.70(0.18)	0.32(0.12)	0.32(0.15)	0.89(0.29)	0.78(0.24)	0.77(0.26)	0.38(0.18)	0.37(0.20)
	II	0.57(0.13)	0.55(0.21)	0.62(0.29)	0.85(0.42)	0.97(0.48)	0.57(0.16)	0.48(0.20)	0.57(0.30)	0.93(0.44)	1.05(0.52)
	III	0.70(0.16)	0.73(0.28)	0.89(0.41)	1.13(0.50)	1.12(0.51)	0.68(0.17)	0.68(0.25)	0.86(0.41)	1.22(0.51)	1.20(0.52)
HT-II	I	0.79(0.16)	0.73(0.10)	0.72(0.11)	0.42(0.10)	0.43(0.11)	0.88(0.26)	0.77(0.21)	0.76(0.23)	0.34(0.17)	0.34(0.19)
	II	0.68(0.15)	0.68(0.22)	0.74(0.28)	0.87(0.39)	0.96(0.43)	0.61(0.18)	0.51(0.22)	0.60(0.32)	0.89(0.44)	1.01(0.50)
	III	0.82(0.18)	0.87(0.21)	0.99(0.41)	1.14(0.49)	1.13(0.49)	0.72(0.18)	0.72(0.28)	0.89(0.42)	1.20(0.51)	1.18(0.52)
HT-II/SK-II	I	0.96(0.08)	0.88(0.08)	0.89(0.07)	0.84(0.08)	0.84(0.08)	0.81(0.27)	0.67(0.22)	0.65(0.22)	0.29(0.15)	0.29(0.17)
	II	0.84(0.15)	0.87(0.21)	0.90(0.24)	0.99(0.33)	1.02(0.34)	0.71(0.23)	0.56(0.26)	0.64(0.34)	0.86(0.43)	0.98(0.49)
	III	0.94(0.18)	1.01(0.29)	1.10(0.35)	1.26(0.41)	1.25(0.41)	0.65(0.17)	0.65(0.29)	0.82(0.43)	1.12(0.51)	1.11(0.52)

Note: Normal distribution has skewness (γ_1) = 0 and kurtosis (γ_2) = 0; SK-I has γ_1 = 1.8 and γ_2 = 5.9; SK-II has γ_1 = 13.2 and γ_2 = 42892.9; HT-I has γ_1 = 0

and $\gamma_2 = 33$; HT-II has $\gamma_1 = \infty$ and $\gamma_2 = \infty$. See Table 1 for a description of mean configurations. UNUN = UN group means and UN covariances; UNCS = UN group means and CS covariances; UNAR = UN group means and AR-1 covariances; STCS = Structured group mean vectors and CS-covariance structure; STAR = Structured group mean vectors and AR-1 covariance. AR-1 = First-order autoregressive; CS = compound symmetric; UN = unstructured; SD = Standard deviation

For RMSE, the bias values were consistently lowest for the UNUN, UNCS, and UNAR procedures when ML estimators were adopted, but tended to be smaller for the normal distribution than for non-normal distributions (Table 3). For the STCS and STAR procedures, values were lower for non-normal than normal distributions. A comparison of procedures based on ML and CT estimation revealed that when the data were normally distributed, the latter procedures resulted in slightly higher average RMSE values than the former. RMSE was generally lower for CT estimation than for ML estimation when the data were non-normal, but again this depended on the procedure, the degree of departure from multivariate normality, and the correlation structure.

Average bias and RMSE for each of the mean configurations and population distributions are reported in Tables 4 and 5, respectively. For UNCS and UNAR procedures, the average bias values (Table 4) were usually smaller for Configuration I, which had a constant mean pattern, than for Configurations II and III, which had non-constant mean patterns, regardless of the method of estimation and population distribution. For the STCS and STAR procedures, the differences amongst the mean configurations were usually much larger. For example, the average bias values for the STCS and STAR procedures under Configuration II were about 1.5 times the values under Configuration I, when the data were sampled from the HT-II/SK-II distribution.

For CT estimation, average bias values for UNUN, UNCS, and UNAR procedures were smaller than the values for the corresponding procedures based on ML estimators when the data were sampled from non-normal distributions. For example, for Configuration III, the average values for the UNAR procedure based on CT and ML estimators were 1.02 and 0.63, respectively, for the SK-II/HT-II condition. For STCS and STAR procedures, the average bias values were smaller for CT estimation than for ML estimation, but this again depended on the

mean configuration and the population distribution.

Moreover, the average RMSE values for STAR and STAR procedures (Table 5) were smallest under Configuration I and largest under Configuration II or III, regardless of the population distribution and estimation method. However, the average RMSE when the mean structure was mis-specified increased for non-normal distributions. For example, the average RMSE of the STCS procedure based on ML estimation for Configuration II was 2.6, 2.9, and 1.5 times greater than the average RMSE of the STCS procedure for Configuration I when data are sampled from normal, SK-I, and SK-II distributions, respectively.

The average RMSE for the corresponding robust procedures were smaller than the corresponding procedure based on ML estimators when the data were sampled from SK-II or HT-II distributions but not the SK-I or HT-I distributions.

For robust UNUN, UNCS, and UNAR procedures, average RMSE values were smallest for Configuration II and largest for Configuration I, regardless of the distribution. For Configurations II and III, the average RMSE values for these procedures were smaller than the corresponding procedures based on ML estimators when the data were sampled from a non-normal distribution, except the SK-I distribution. Overall, the average RMSE values for procedures based on CT estimators exhibited more variability than procedures based on ML estimators.

Figure 1 provides average relative bias and RMSE for the procedures based on CT estimation for non-normal distributions for different numbers of repeated measurements. While the average relative bias for all the robust procedures increased with p, the average relative RMSE values for these procedures remained largely unchanged for both skewed and heavy-tailed distributions. But the average relative bias and RMSE for all the procedures increased as p

increased for the HT-II/SK-II distribution. Finally, the relative average bias and RMSE for robust procedures that assume unstructured group means (i.e., UNUN, UNCS, and UNAR) decreased as *n* increased when the data were sampled from non-normal distributions (Figure 2). However, the change in average relative bias and RMSE for the robust procedures that assume constant group means (i.e., STCS and STAR) was negligible as *n* increased.

Figure 6-1. Relative Average Bias and RMSE of Robust RMDA Procedures for Non-Normal Population Distributions and Number of Repeated Measurements

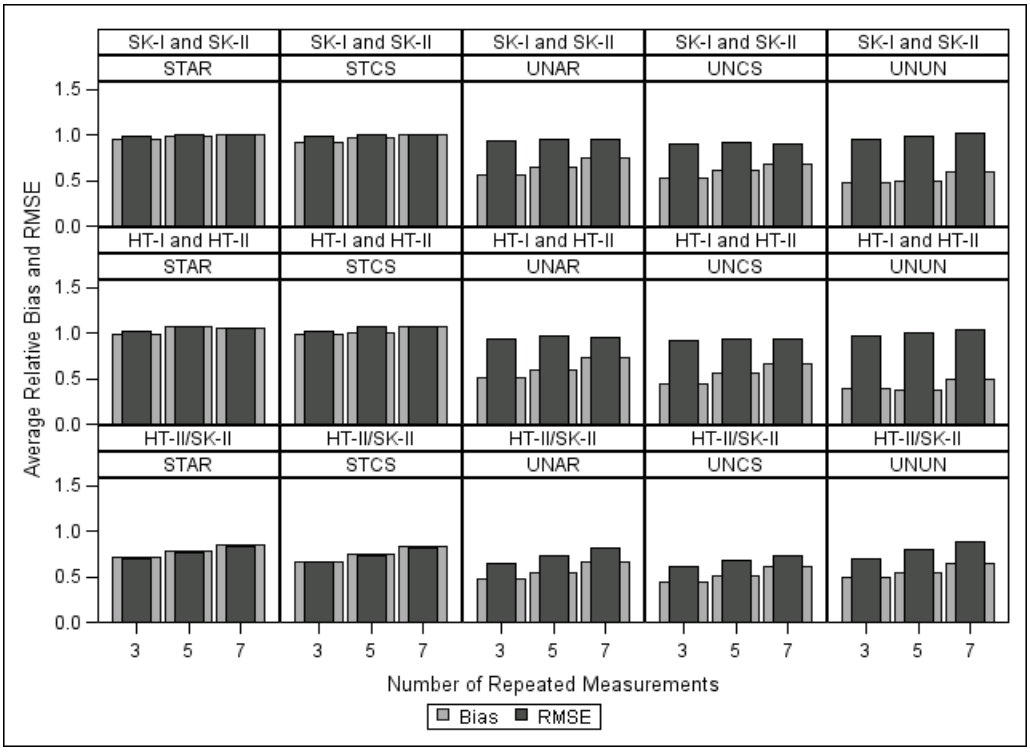
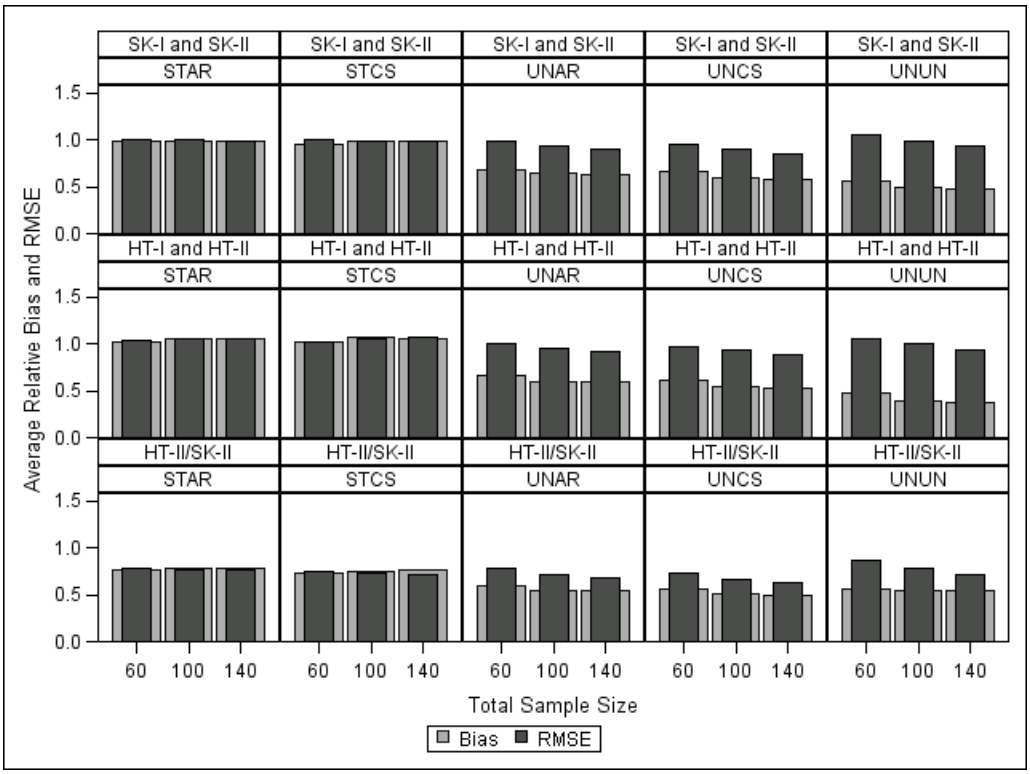


Figure 6-2. Relative Average Bias and RMSE of Robust RMDA Procedures for Non-Normal Population Distributions and Total Sample Size



6.6 Numeric Example

Data to illustrate the procedures are from the Manitoba Inflammatory Bowel Disease (IBD) Cohort Study, a prospective longitudinal study, initiated in 2002, of patients recently diagnosed with Crohn's disease or ulcerative colitis[41-42]. Data were collected at six-month intervals using self-report instruments. Study participants were assigned to active ($n_1 = 265$) and inactive ($n_2 = 116$) disease groups based on self-reported IBD symptoms at study entry. Differences between active and inactive groups of participants on scores for a disease-specific measure of quality of life, the IBD questionnaire (IBDQ), were investigated for the first two years of the study (i.e., first five measurement occasions). The primary research question is whether active and inactive disease groups differ in their longitudinal profiles of quality of life.

The group means and descriptive measures of skewness and kurtosis for a modified set of IBDQ data are reported in Table 6. A mean imputation method was adopted to ensure complete data at all occasions[43]. Marginal measures of skewness and kurtosis suggest a moderate departure from the assumption of a normal distribution in the active disease group when compared with the inactive group (Table 6). A linearly increasing trend was observed (i.e., poorer quality of life) for the active disease group, while a constant trend was observed for the inactive group. We use the pooled covariance to estimate the DFCs (equation 2)

$$\hat{\boldsymbol{\Sigma}} = \begin{bmatrix} 663.23 & 384.72 & 350.76 & 297.14 & 309.32 \\ & 699.44 & 487.39 & 398.63 & 353.05 \\ & & 795.76 & 455.31 & 379.60 \\ & & & 677.50 & 441.17 \\ & & & & 690.39 \end{bmatrix}.$$

The ML and robust estimates of the DFCs for each RMDA procedure are reported in Table 7. These were implemented using a SAS program written by the authors[40]; the program is provided in Appendix II. There are substantial differences in the estimated DFCs for the

procedures and for ML and robust estimation methods, leading to different conclusions about the rank order of the repeated measurements for group discrimination. For the UNCS and UNAR procedures, the CT estimates were larger than those of the UNCS procedure based on ML estimators for all measurement occasions, except Month 18. For the UNUN procedure, the CT estimates were larger than the ML estimates for Months 0, 18, and 24. In contrast, the CT estimates for the STCS and STAR procedures were larger than the corresponding ML estimates for the first three occasions.

Table 6-6. Descriptive Statistics for the Inflammatory Bowel Disease Questionnaire by Disease Activity Group

Occasion (Month)	**Active Disease Group**			**Inactive Disease Group**		
	Mean (SD)	γ_1	γ_2	**Mean (SD)**	γ_1	γ_2
0	158.37(27.94)	1.52	3.28	185.59(23.40)	0.97	2.28
6	165.53(28.53)	1.31	2.52	186.13(22.19)	0.34	-1.76
12	166.26(31.83)	-1.73	4.40	188.27(18.76)	-0.76	0.25
18	169.53(28.75)	-0.98	1.06	188.60(19.82)	-0.81	0.77
24	171.88(27.77)	-1.98	5.70	188.09(23.25)	-0.67	0.19

SD = Standard deviation; γ_1 = skewness; γ_2 = kurtosis

Table 6-7. Discriminant Function Coefficients for Discriminant Analysis Procedures Applied to the Inflammatory Bowel Disease Questionnaire Data

Occasion (Month)	**UNUN**	**UNCS**	**UNAR**	**STCS**	**STAR**
ML Estimation					
0	-0.43	-0.22	-0.09	0.21	0.19
6	-0.29	-0.13	-0.17	0.15	0.07
12	0.30	0.69	1.00	0.59	0.30
18	0.43	0.56	0.28	0.54	0.28
24	0.10	0.43	0.32	0.55	0.53
CT Estimation					
0	-0.69	-0.30	-0.13	0.29	0.28
6	0.10	-0.19	-0.23	0.21	0.11
12	0.24	0.74	1.06	0.63	0.33
18	0.56	0.46	0.20	0.47	0.25
24	0.19	0.45	0.38	0.51	0.49

UNUN = UN group means and UN covariances; UNCS = UN group means and CS covariances; UNAR = UN group means and AR-1 covariances; STCS = Structured group means and CS-covariance; STAR = Structured group means and AR-1 covariance. AR-1 = First-order autoregressive; CS = compound symmetric; UN = unstructured

6.7 Discussion and Conclusions

In this study, we investigated RMDA procedures based on structured and unstructured means and covariances with ML estimation and robust RMDA procedures based on CT and illustrated their implementation using a numeric example. As expected, bias and error in the DFCs of the investigated procedures were influenced by the shape of the population distribution, but the effect of non-normality was associated with the population correlation structure and mean configuration. Mis-specification of the mean and/or covariance structure resulted in increased

average bias and RMSE, but the effect was smaller when the data were multivariate non-normal than when they were multivariate normal. Among all the investigated procedures, DA procedures that assume unstructured group means and parsimonious covariance structures (i.e., UNCS and UNAR) were less sensitive to mis-specification of the mean structure while the UNUN procedure was least sensitive to mis-specification of the covariance structure regardless of the population distribution.

As expected, RMDA procedures based on CT estimators were less sensitive to distribution shape when compared to procedures based on ML estimation when the data were sampled from non-normal distributions. More specifically, the DFCs of the UNCS and UNAR procedures based on CT estimators were less biased and had less error than DFCs of other RMDA procedures for extreme departures from a multivariate normal distribution. However, the DFCs of these procedures may not always be more efficient than other procedures for moderate departures from a multivariate normal distribution.

Based on the findings of this study, we recommend adopting a RMDA procedure based on unstructured group means (i.e., UNUN, UNCS or UNAR) when the data are normally distributed and their corresponding robust alternatives when there are indications of strong departure from the multivariate normality assumption. However, the RMDA procedures based on CT estimators may not be efficient in non-normal distributions when the group mean or covariance structure is mis-specified. Therefore, we recommend that the choice among these RMDA procedures based on unstructured group means should be guided by other data characteristics such as structure and magnitude of correlations among the repeated measurements. A preliminary descriptive analysis of the data could be undertaken to guide a researcher's choice among these procedures. Also, tests of model fit such as likelihood ratio tests, or penalized log-likelihood measures like the

Akaike information criterion might be used to guide the specification of mean and covariance structures[39].

One criticism of CT estimators is that they rely on asymptotic normality of the trimmed data[25] and may be less efficient when the sample size is small and when data are normally distributed[22]. But as shown in the Monte Carlo study, the robust RMDA procedures that assume no parsimony on the group means showed negligible differences in bias and RMSE for the conventional and robust estimators under small sample size conditions and when the data were normally distributed. Hence, they may be adopted by applied researchers when there are slight departures from the assumption of multivariate normality.

This study has some limitations. The simulation study focused on conditions in which group covariances were equal; this may not be a reasonable assumption in all data-analytic problems. In addition, complete data were generated for all measurement occasions.

A number of opportunities exist in the development of robust RMDA procedures. While this study showed that procedures based on trimmed estimators control bias and error under departures from the multivariate normality assumption, further investigation about the effects of population distribution on the ability of these procedures to correctly rank order repeated measurements with respect to their relative contributions to group separation are needed[44]. Further research is needed to ascertain if reduction in bias and/or error in the DFCs of robust DA procedures can lead to more accurate rank ordering of the repeated measurements under strong departures from multivariate normality and other data-analytic conditions.

While RMDA procedures based on CT estimation controlled the bias in the DFCs when the data were non-normal for correctly specified covariance and mean structures, the RMSE was only controlled under the most extreme departures from non-normality. Therefore, while the

robust RMDA procedures investigated in this study show promise, further research is warranted to investigate other approaches such as trimmed estimation methods based on robust Mahalanobis distances[45] and trimmed likelihood estimation methods[46-47].

In conclusion, robust RMDA procedures are recommended for describing group separation in non-normal repeated measures data. The assumption of parsimonious covariance structures in these procedures are advantageous when sample size is small relative to the number of measurement occasions. The procedures can be applied in growth, developmental, or maturation studies to quantify the relative contribution of the repeated measurements to group discrimination under substantial departures from a multivariate normal distribution.

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Appendix I: Maximum Likelihood Estimation for Parameters of RMDA Procedures that assume Unstructured Means and Parsimonious Covariances

RMDA Procedure with Unstructured Means and CS Covariances (UNCS)

Assuming a CS structure for $\mathbf{\Sigma}$,

$$\mathbf{\Sigma} = \sigma^2[(1-\rho)\mathbf{I}_p + \rho\mathbf{1}_p\mathbf{1}_p^{\mathrm{T}}], \tag{A-1}$$

$$|\mathbf{\Sigma}| = \sigma^{2p}[1+(p-1)\rho](1-\rho)^{p-1}, \tag{A-2}$$

and

$$\mathbf{\Sigma}^{-1} = \frac{1}{\sigma^2(1-\rho)}[\mathbf{I}_p - \frac{\rho}{1+(p-1)\rho}\mathbf{1}_p\mathbf{1}_p^{\mathrm{T}}], \tag{A-3}$$

where $\mathbf{I}_p$ is the $p\times p$ identity matrix, $\mathbf{1}_p$ is a $p\times 1$ vector of ones, $\mathbf{\Sigma}$ is positive definite, and $\left(\frac{-1}{p-1}\right) < \rho < 1$. Then the log of the likelihood function in equation 3 (section 6.2) is

$$\log l = -\frac{np}{2}\log 2\pi - \frac{n}{2}\log|\mathbf{\Sigma}| - \frac{1}{2}\mathrm{tr}(\mathbf{\Sigma}^{-1}\mathbf{W}) - \frac{1}{2}\{\sum_{j=1}^{2} n_j(\mathbf{y}_j - \boldsymbol{\mu}_j)^{\mathrm{T}}\mathbf{\Sigma}^{-1}(\mathbf{y}_j - \boldsymbol{\mu}_j)\}, \tag{A-4}$$

where $\mathbf{W}_j = \sum_{i=1}^{n_j}(\mathbf{y}_{ij} - \bar{\mathbf{y}}_j)^{\mathrm{T}}(\mathbf{y}_{ij} - \bar{\mathbf{y}}_j)$, and $\mathbf{W} = \mathbf{W}_1 + \mathbf{W}_2$. To estimate ρ and σ^2, equation A-4 becomes

$$\log l = -\frac{np}{2}\log 2\pi - \frac{np}{2}\log(\sigma^2) - \frac{n}{2}\log[1+(p-1)\rho] - \frac{n(p-1)\log(1-\rho)}{2} - \frac{a_8+a_9}{2\sigma^2(1-\rho)} + \frac{\rho(b_8+b_9)}{2\sigma^2(1-\rho)[1+(p-1)\rho]}, \tag{A-5}$$

where $a_8 = \mathrm{tr}(\mathbf{W}_1)$, $a_9 = \mathrm{tr}(\mathbf{W}_2)$, $b_8 = \mathrm{tr}(\mathbf{J}\mathbf{W}_1)$, $b_9 = \mathrm{tr}(\mathbf{J}\mathbf{W}_2)$, and $\mathbf{J} = \mathbf{1}_p\mathbf{1}_p^{\mathrm{T}}$.

The first order derivatives of equation A-5 with respect to σ^2 and ρ yield to the expressions in equations 4 and 5 in section 6.2, respectively.

RMDA Procedure with Unstructured Means and AR-1 Covariances (UNAR)

For a AR-1 structured $\boldsymbol{\Sigma}$,

$$|\boldsymbol{\Sigma}| = \sigma^{2p}(1-\rho^2)^{p-1}, \tag{A-6}$$

and

$$\boldsymbol{\Sigma}^{-1} = \frac{\boldsymbol{\Sigma}_0}{\sigma^2(1-\rho^2)^{p-1}}, \tag{A-7}$$

where

$$\boldsymbol{\Sigma}_0 = \begin{bmatrix} 1 & -\rho & 0 & \ldots & \ldots & 0 \\ -\rho & 1+\rho^2 & -\rho & 0 & & 0 \\ 0 & -\rho & 1+\rho^2 & -\rho & .... & 0 \\ . & \ldots & .... & .... & \ldots & . \\ 0 & \ldots & \ldots & \ldots & 1+\rho^2 & -\rho \\ 0 & \ldots & .... & \ldots & -\rho & 1 \end{bmatrix}.$$

The joint log-likelihood function in equation 3 (see section 6.2) can be expressed as

$$\log l = -\frac{np}{2}\log 2\pi - \frac{np}{2}\log\sigma^2 - \frac{n(p-1)}{2}\log(1-\rho^2) - \frac{\mathrm{tr}(\boldsymbol{\Sigma}_0\mathbf{W})}{2\sigma^2(1-\rho^2)}, \tag{A-8}$$

where $\mathrm{tr}(\boldsymbol{\Sigma}_0\mathbf{W}) = \rho\beta_1 - 2\rho\gamma + \alpha$, $\beta = \mathrm{tr}(\mathbf{W}) - \mathbf{W}_{11} - \mathbf{W}_{pp}$, $\gamma = \sum_{\substack{1\le l<p,\\ m=l+1}} \mathbf{W}_{lm}$, $\alpha = tr(\mathbf{W})$,

$\mathbf{W} = \mathbf{W}_1 + \mathbf{W}_2$, and $\mathbf{W}_{ij}$ is the (i, j)th element of $\mathbf{W}$. Equation A-8 simplifies to

$$\log l = -\frac{np}{2}\log 2\pi - \frac{np}{2}\log\sigma^2 - \frac{n(p-1)}{2}\log(1-\rho^2) - \frac{\beta\rho^2 - 2\rho\gamma + \alpha}{2\sigma^2(1-\rho^2)}. \tag{A-9}$$

The first order derivatives of equation A-9 with respect to σ^2 and ρ yields the expressions in equations 7 and 8 (section 6.2), respectively.

Appendix II: Supplementary Documentation

Description

This supplementary documentation contains SAS programming syntax (SAS Institute Inc., 2008) to illustrate the implementation of repeated measures discriminant analysis procedures in non-normal repeated measures data.

The documentation begins with syntax to read data from a .txt or .dat file into a file named 'rsdata' and a temporary SAS dataset called rmdaappendix. If the data are not in a .txt or .dat file, then the syntax at the beginning of the program will change. Consult your SAS user's manual or contact the authors if you require assistance to prepare your dataset for use.

The documentation illustrates the syntax for data that contain six repeated measurements on a HRQOL outcome. The data for the six repeated measurements are name y1, y2, y3, y4, y5,and y6. The data also contain the numeric variable grp, which is used to discriminate between the two study groups. The grp variable takes on values of 0 and 1. In this example, there are 45 observations (i.e., individuals) in group 1 and 25 observations in group 2. The group sizes must be specified in the SAS program.

The components of the program that require user input are highlighted in boldface font.

The program will generate an error if there are missing data for any of the variables in the dataset.

Reference

SAS Institute Inc. (2008). *SAS/IML user's guide, version 9.2.* Cary, NC: SAS Institute Inc.

SAS Syntax

```
**read in the data**;
filename rmdata 'Note to users: the dataset path and filename is inserted between the single quotation marks';
data rmdappendix;
  infile rmdata;
  input  grp y1 y2 y3 y4 y5 y6;
  run;
**Use the IML procedure to read the dataset and its specifications**;
proc iml;
use rmdappendix;
read all var {y1 y2 y3 y4 y5 y6} into Y;
read all var {grp} into X;
x = design(x);
dv = ncol(y);
grpsz1 = 45; grpsz2 = 25;
ng = 2;
per = 0.2;
nj = {45 25};
ntot = 70;
bhat = inv(x`*x)*x`*y;
bhatw = bhat;
ss1 = J(dv,dv,0); ss2 = j(dv,dv,0);
```

```
ss1=((y#x[,1]-x[,1]*bhatw[1,])`*(y#x[,1]-x[,1]*bhatw[1,]));
ss2=((y#x[,2]-x[,2]*bhatw[2,])`*(y#x[,2]-x[,2]*bhatw[2,]));
sig = (ss1 +ss2)/(ntot-2);

/*************************************************************************
Module name: Trmn
Module Outputs:
bhat:  Output matrix of least squares or trimmed means for each variable.
bhatw: Output matrix of group least squares or winsorized means for each variable
ytw:   Output matrix of least squares of winsorized observations
*************************************************************************/
start trmn(trim, y, x, nj, bhat, bhatw, ytw, df) global(per,dv,ng);
ntot = sum(nj);
if trim=0 then do;
  bhat=inv(x`*x)*x`*y;
  bhatw=bhat;
  ytw = y;
  df=nj-1;
end;
if trim =1 then do;
  bhat=J(ng,dv,0);
  bhatw=bhat;
  ytw = J(ntot,dv,0);
  df=J(1,ng,0);
  f=1;
```

```
m=0;
do j=1 to ng;
  samp=nj[j];
  l=m+samp;
  g=int(per#samp);
  df[j]=samp-2#g-1;
 do  k = 1 to ncol(y);
    temp = y[f:l, k];
    nv = temp;
    temp[rank(nv),] = nv;
    trimy = temp[g+1: samp-g,];
    trimmn = sum(trimy)/(df[j]+1);
    bhat[j,k] = trimmn;
          mint = min(trimy);
          maxt = max(trimy);
    do p=1 to nrow(nv);
       if nv[p]<=mint then nv[p] = mint;
       if nv[p]>=maxt then nv[p] = maxt;
    end;
    ytw[f:l,k]=nv;
    bhatw[j,k]=sum(nv)/samp;
   end;
   m = l;
```

```
    f=f+nj[j];
  end;
end;
finish;
/*************************************************************************
Module Name:   class_unstrmeanmod
Module Output: Output vector of discriminant function coefficients based on UNUN procedure
*************************************************************************/
start  class_unstrmeanmod (y, x,bhat, bhatw,grpsz1,grpsz2,dv,dcoef1);
one = j(dv,1, 1);
n = nrow(y);
ybard=bhat[1,]-bhat[2,];
ss1=((y#x[,1]-x[,1]*bhatw[1,])`*(y#x[,1]-x[,1]*bhatw[1,]));
ss2=((y#x[,2]-x[,2]*bhatw[2,])`*(y#x[,2]-x[,2]*bhatw[2,]));
sig = (ss1 +ss2)/(n-2);
dcoef1= inv(sig)*(ybard)`;
finish class_unstrmeanmod;
/*************************************************************************
Module Name:   ddacs_mod
Module Output: Output vector of discriminant function coefficients based on UNCS Procedure
*************************************************************************/
start ddacs_mod(y,x,bhat, bhatw, grpsz1, grpsz2, dv,dcoef2);
n = nrow(y);
```

```
b3 = J(dv,1,0);

ybar = y[+,]/n;

gp1 = y[1:grpsz1, ];

gp2 = y[grpsz1+1:n,];

jn = J(dv,dv,1);

ybard=bhat[1,]-bhat[2,];

w1=((y#x[,1]-x[,1]*bhatw[1,])`*(y#x[,1]-x[,1]*bhatw[1,]));

w2=((y#x[,2]-x[,2]*bhatw[2,])`*(y#x[,2]-x[,2]*bhatw[2,]));

a8 = trace(w1); a9 = trace(w2); b8 = trace(jn*w1); b9 = trace(jn*w2);

/**** Estimating an initial estimate of rho****/

ybarn = repeat(ybar,n,1);

gp = y - ybarn;

gpass = gp[##,];

sq_gp = repeat(sqrt(gpass),n,1);

gpa = gp/sq_gp;

S = t(gpa)*(gpa);

rho1 = (s[+,+] - trace(s))/(dv*(dv-1));

sige = 0; iter = 0; converge = 0.0000001;

/***Evaluating the functions***/

do until(maxab< converge);

sig = ((1 + (dv-1)*rho1)*(a8+a9) - rho1*(b8+b9))/ (n*dv*(1-rho1)*(1 + (dv-1)*rho1));

absig = abs(sige - sig);

sige = sig;
```

```
/***Derivatives Function***/

k0 = n*(dv-1)*dv*sig;

pp = -((dv-2)*k0 - ((a8+a9)*(dv-1)**2) + (b8+b9)*(dv-1))/((dv-1)*k0);

qq =-(k0 - 2*(a8+a9)*(dv-1))/((dv-1)*k0);

rr        = -(b8 + b9 - a8 - a9)/((dv-1)*k0);

aa = (1/3)*(3*qq-pp**2);

bb = (1/27)*(2*pp**3 - 9*pp*qq + 27*rr);

d = (bb**2)/4 + (aa**3)/27;

if d < 0 then s1 = 0;

else s1 = d**0.5;

s2 = (-bb/2 + s1)**(1/3);

ar = -bb/2 - s1;

if ar < 0 then do;

ar1 = -ar;

ar2 = ar1**(1/3);

s3 = -ar2;

end;

else do;

s3 = ar**(1/3);

end;

rho2 = s2 + s3 - pp/3;

iter = iter +1;

abr1 = abs(rho1 - rho2);
```

```
rho1 = rho2;
maxab = max(absig//abr1);
end;
sigm = (sig)*(( (1-rho2)*i(dv) + rho2*jn));
dcoef2 = inv(sigm)*(ybard)`;
finish ddacs_mod;
/*************************************************************************
Module Name:    ddar
Module Output: Output vector of discriminant function coefficients based on UNAR
*************************************************************************/
start ddar (y, x, bhat, bhatw,grpsz1, grpsz2, dv,dcoef3);
n = nrow(y);
ybar = y[+,]/n;
gp1 = y[1:grpsz1, ];
gp2 = y[grpsz1+1:n,];
gpbar1 = gp1[+,]/grpsz1;
gpbar2 = gp2[+,]/grpsz2;
ybard=bhat[1,]-bhat[2,];
w1=((y#x[,1]-x[,1]*bhatw[1,])`*(y#x[,1]-x[,1]*bhatw[1,]));
w2=((y#x[,2]-x[,2]*bhatw[2,])`*(y#x[,2]-x[,2]*bhatw[2,]));
w0 = w1 + w2;
a1 = trace(w0);
beta1 = trace(w0) - w0[1,1] - w0[dv,dv];
gama1 = 0;
```

```
do i = 1 to dv-1;
gama1 = gama1 + w0[i,i+1];
end;
/**** Estimating an initial estimate of rho****/
ybarn = repeat(ybar,n,1);
gp = y - ybarn;
gpass = gp[##,];
sq_gp = repeat(sqrt(gpass),n,1);
gpa = gp/sq_gp;
S = t(gpa)*(gpa);
rho1 = (s[+,+] - trace(s))/(dv*(dv-1));
sige = 0; iter = 0; converge = 0.0000001;
do until (maxab< converge);
sig = (beta1*rho1**2  - (2*gama1*rho1) + a1)/(n*dv*(1-rho1**2));
sige = sig;
absig = abs(sige - sig);
pp = -(gama1) /(n*(dv-1)*sig);
qq =-(n*(dv-1)*sig - (a1+beta1))/(n*(dv-1)*sig);
rr  = -(gama1)/(n*(dv-1)*sig);
aa = (1/3)*(3*qq-pp**2);
bb = (1/27)*(2*pp**3 - 9*pp*qq + 27*rr);
d = (bb**2)/4 + (aa**3)/27;
if d < 0 then s1 = 0;
```

```
else s1 = d**0.5;
s2 = (-bb/2 + s1)**(1/3);
ar = -bb/2 - s1;
if ar < 0 then do;
ar1 = -ar;
ar2 = ar1**(1/3);
s3 = -ar2;
end;
else do;
s3 = ar**(1/3);
end;
rho2 = s2 + s3 - pp/3;
iter = iter +1;
abr1 = abs(rho1 - rho2);
rho1 = rho2;
maxab = max(absig//abr1);
end;
v = J(dv,dv,0);
do i = 1 to dv;
do j = 1 to dv;
v[i,j] = sig*rho2**(abs(i-j));
end; end;
dcoef3 = inv(v)*(ybard)`;
```

```
finish ddar;
/*************************************************************************
Module Name: royddacs_mod
Module Output: Output vector of discriminant function coefficients based on STCS Procedure
*************************************************************************/
start royddacs_mod(y,x, bhat, bhatw, grpsz1, grpsz2, dv,dcoef4);
n = nrow(y);
one = j(dv, 1, 1);
b3 = J(dv,1,0);
ybar = y[+,]/n;
gp1 = y[1:grpsz1, ];
gp2 = y[grpsz1+1:n,];
gpbar1 = gp1[+,]/grpsz1;
gpbar2 = gp2[+,]/grpsz2;
mu1 = bhat[1,]*one/dv;
mu2 = bhat[2,]*one/dv;
mn1 =  mu1* one;
mn2 = mu2 * one;
w1 = J(dv,dv,0);
w2 = J(dv,dv,0);
jn = J(dv,dv,1);
ybard=bhat[1,]-bhat[2,];
w1=((y#x[,1]-x[,1]*bhatw[1,])`*(y#x[,1]-x[,1]*bhatw[1,]));
```

```
w2=((y#x[,2]-x[,2]*bhatw[2,])`*(y#x[,2]-x[,2]*bhatw[2,]));

a8 = trace(w1); a9 = trace(w2); b8 = trace(jn*w1); b9 = trace(jn*w2);

/**** Estimating an initial estimate of rho****/

ybarn = repeat(ybar,n,1);

gp = y - ybarn;

gpass = gp[##,];

sq_gp = repeat(sqrt(gpass),n,1);

gpa = gp/sq_gp;

s = t(gpa)*(gpa);

rho1 = (s[+,+] - trace(s))/(dv*(dv-1));

sige = 0; iter = 0; converge = 0.0000001;

/***Evaluating the functions***/

do until(maxab< converge);

sig = ((1 + (dv-1)*rho1)*(a8+a9) - rho1*(b8+b9))/ (n*dv*(1-rho1)*(1 + (dv-1)*rho1));

absig = abs(sige - sig);

sige = sig;

/***Derivatives Function***/

k0 = n*(dv-1)*dv*sig;

pp = -((dv-2)*k0 - ((a8+a9)*(dv-1)**2) + (b8+b9)*(dv-1))/((dv-1)*k0);

qq =-(k0 - 2*(a8+a9)*(dv-1))/((dv-1)*k0);

rr        = -(b8 + b9 - a8 - a9)/((dv-1)*k0);

aa = (1/3)*(3*qq-pp**2);

bb = (1/27)*(2*pp**3 - 9*pp*qq + 27*rr);
```

```
d = (bb**2)/4 + (aa**3)/27;
if d < 0 then s1 = 0;
else s1 = d**0.5;
s2 = (-bb/2 + s1)**(1/3);
ar = -bb/2 - s1;
if ar < 0 then do;
ar1 = -ar;
ar2 = ar1**(1/3);
s3 = -ar2;
end;
else do;
s3 = ar**(1/3);
end;
rho2 = s2 + s3 - pp/3;
iter = iter +1;
abr1 = abs(rho1 - rho2);
rho1 = rho2;
maxab = max(absig//abr1);
end;
sigm = (sig)*(( (1-rho2)*i(dv) + rho2*jn));
dcoef4 = inv(sigm)*(mn1 - mn2);
finish royddacs_mod;
```

```
/*************************************************************************
Module Name: royddar_mod
Module Output: Output vector of discriminant function coefficients based on STAR Procedure
*************************************************************************/
start royddar (y,x, bhat, bhatw, grpsz1, grpsz2, dv,dcoef5);
one = J(dv, 1, 1);
n = nrow(y);
ybar = y[+,]/n;
gp1 = y[1:grpsz1, ];
gp2 = y[grpsz1+1:n,];
gpbar1 = gp1[+,]/grpsz1;
gpbar2 = gp2[+,]/grpsz2;
mu1 = bhat[1,]*one/dv;
mu2 = bhat[2,]*one/dv;
mn1 =  mu1* one;
mn2 = mu2 * one;
ybard=bhat[1,]-bhat[2,];
w1=((y#x[,1]-x[,1]*bhatw[1,])`*(y#x[,1]-x[,1]*bhatw[1,]));
w2=((y#x[,2]-x[,2]*bhatw[2,])`*(y#x[,2]-x[,2]*bhatw[2,]));
w3 = bhatw[1,]`*bhatw[1,];
w4 = bhatw[2,]`*bhatw[2,];
w5 = one*bhatw[1,] + bhatw[1,]`*one`;
w6 = one*bhatw[2,] + bhatw[2,]`*one`;
```

```
w0 = w1 + w2+ grpsz1*w3 + grpsz2*w4;

a1 = trace(w0);

a2 = trace(w5);

a3 = trace(w6);

beta1 = trace(w0) - w0[1,1] - w0[dv,dv];

beta2 = trace(w5) - w5[1,1] - w5[dv,dv];

beta3 = trace(w6) - w6[1,1] - w6[dv,dv];

gama1 = 0;

gama2 = 0;

gama3 = 0;

do i = 1 to dv-1;

gama1 = gama1 + w0[i,i+1];

gama2 = gama2 + w5[i, i+1];

gama3 = gama3  + w6[i, i+1];

end;

cc = grpsz1*(mu1**2) + grpsz2*(mu2**2);

/**** Estimating an initial estimate of rho****/

ybarn = repeat(ybar,n,1);

gp = y - ybarn;

gpass = gp[##,];

sq_gp = repeat(sqrt(gpass),n,1);

gpa = gp/sq_gp;

s = t(gpa)*(gpa);
```

```
rho1 = (s[+,+] - trace(s))/(dv*(dv-1));
sige = 0; iter = 0; converge = 0.0000001;
do until (maxab< converge);
sig = ((beta1 - grpsz1*mu1*beta2 - grpsz2*mu2*beta3 + cc*(dv - 2))*(rho1**2) -  2*(gama1 -
grpsz1*mu1*gama2 - grpsz2*mu2*gama3 + cc*(dv-1))*(rho1) +
(a1 - grpsz1*mu1*a2 - grpsz2*mu2*a3 + cc*dv))/(n*dv*(1-rho1**2));
sige = sig;
absig = abs(sige - sig);
pp = -(gama1-grpsz1*mu1*gama2 - grpsz2*mu2*gama3 + cc*(dv-1)) /(n*(dv-1)*sig);
qq =-(n*(dv-1)*sig - (a1+beta1) + grpsz1*mu1*(a2+ beta2) + grpsz2*mu2*(a3 + beta3) -
cc*(2*dv-2))/(n*(dv-1)*sig);
rr  = -(gama1- grpsz1*mu1*gama2 - grpsz2*mu2*gama3 + cc*(dv-1) )/(n*(dv-1)*sig);
aa = (1/3)*(3*qq-pp**2);
bb = (1/27)*(2*pp**3 - 9*pp*qq + 27*rr);
d = (bb**2)/4 + (aa**3)/27;
if d < 0 then s1 = 0;
else s1 = d**0.5;
s2 = (-bb/2 + s1)**(1/3);
ar = -bb/2 - s1;
if ar < 0 then do;
ar1 = -ar;
ar2 = ar1**(1/3);
s3 = -ar2;
```

```
end;
else do;
s3 = ar**(1/3);
end;
rho2 = s2 + s3 - pp/3;
iter = iter +1;
abr1 = abs(rho1 - rho2);
rho1 = rho2;
maxab = max(absig//abr1);
end;
v = J(dv,dv,0);
do i = 1 to dv;
do j = 1 to dv;
v[i,j] = sig*rho2**(abs(i-j));
end; end;
dcoef5 = inv(v)*(mn1 - mn2);
finish royddar;
****Compute Discriminant Function Coefficients based on ML Estimation;
trim = 0;
cal trmn(trim, y, x, nj, bhat, bhatw, ytw, df);
call class_unstrmeanmod (y, x,bhat, bhatw,grpsz1,grpsz2,dv,dcoef1);
call ddacs_mod(y,x,bhat, bhatw, grpsz1, grpsz2, dv,dcoef2);
call ddar (y,x, bhat, bhatw, grpsz1, grpsz2,dv,dcoef3);
```

```
call royddacs_mod(y, x, bhat, bhatw, grpsz1, grpsz2,dv, dcoef4);
call royddar (y,x, bhat, bhatw, grpsz1, grpsz2,dv,dcoef5);
****Compute Discriminant Function Coefficients based on CT Estimation;
trim = 1;
call trmn(trim, y, x, nj, bhat, bhatw, ytw, df);
call class_unstrmeanmod (ytw, x,bhat, bhatw,grpsz1,grpsz2,dv,tdcoef1);
call ddacs_mod(ytw,x,bhat, bhatw, grpsz1, grpsz2, dv,tdcoef3);
call ddar (ytw,x, bhat, bhatw, grpsz1, grpsz2,dv,tdcoef3);
call royddacs_mod(ytw, x, bhat, bhatw, grpsz1, grpsz2,dv, tdcoef4);
call royddar (ytw,x, bhat, bhatw, grpsz1, grpsz2,dv,tdcoef5);
Print 'Vector of DFCs for UNUN Procedure based on ML Estimators;' dcoef1[format =8.2];
Print 'Vector of DFCs for UNUN Procedure based on CT Estimators;' tdcoef1[format =8.2];
Print 'Vector of DFCs for UNCS Procedure based on ML Estimators;' dcoef2[format =8.2];
Print 'Vector of DFCs for UNCS Procedure based on CT Estimators;' tdcoef2[format =8.2];
Print 'Vector of DFCs for UNAR Procedure based on ML Estimators;' dcoef3[format =8.2];
Print 'Vector of DFCs for UNAR Procedure based on CT Estimators;' tdcoef3[format =8.2];
Print 'Vector of DFCs for STCS Procedure based on ML Estimators;' dcoef4[format =8.2];
Print 'Vector of DFCs for STCS Procedure based on CT Estimators;' tdcoef4[format =8.2];
Print 'Vector of DFCs for STAR Procedure based on ML Estimators;' dcoef5[format =8.2];
Print 'Vector of DFCs for STAR Procedure based on CT Estimators;' tdcoef5[format =8.2];
quit;
```

Section III. Variable Importance Measures for Multivariate Repeated Measures Data

Chapter 7. Variable Importance Measures

Abbreviations

DA = Discriminant analysis

DDA = Descriptive discriminant analysis

DFC = Discriminant function coefficient

DRC = Discriminant ratio coefficient

FTR = *F*-to-remove statistic

HRQOL = Health-related quality of life

MANOVA = Multivariate analysis of variance

RMDA = Repeated measures discriminant analysis

SDFC = Standardized discriminant function coefficient

SC = Structure coefficient

TDRC = Total discriminant ratio coefficient

7.1 Introduction

In clinical investigations involving the comparison of two groups (i.e., treatment and control), data are often collected on a battery of outcomes. It is often desirable to test for differences between groups and to identify the variables that predict differences between groups. Global tests of group differences can be obtained using multivariate procedures, such as multivariate analysis of variance (MANOVA)[1-2]. Following a significant overall test of differences between groups, researchers may be interested in identifying the domains that discriminate between groups. The conventional approach is to conduct multiple tests of significance for evaluating group differences on the outcomes using an appropriate multiple testing procedure to control the overall probability of type I error[3-4]. The variables that are statistically significant are considered to be the most important variables that discriminate between groups.

Relative importance analysis is another approach for identifying the most important variables that discriminate between groups. The concept of variable importance, which has been historically subject to diverse interpretations in the statistics literature and in many disciplines[5-7], was first developed within the regression model framework for quantifying the relative importance of explanatory variables in predicting an outcome. In recent years, the concept of variable importance has been extended to describe the relative importance of outcome variables in multivariate group designs using descriptive discriminant analysis (DDA) models.

In DDA, one or more linear combinations of the variables that maximize group separation are identified and the discriminant function coefficients (DFCs) from DDA are used to rank the variables according to their contribution to group separation[8]. Several measures of relative importance based on DFCs have been proposed including standardized discriminant function

coefficients (SDFCs)[9-10], structure coefficients (SCs), discriminant ratio coefficients (DRCs)[11], total discriminant ratio coefficients (TDRCs)[12], and *F*-to-remove (FTR) statistics[9,13]. Relative importance measures can be used to rank order outcome variables based on their ability to discriminate between groups. These measures are now being adopted for identifying variables that discriminate between groups in several disciplines[14,15]. They are also useful for testing hypothesis about differences in the DFCs and/or ranks of variables[16].

In this chapter, measures of relative importance derived from the DFCs of DDA are described. A number of issues that arise in the assessment of relative importance of variables are also discussed.

7.2 Description of Measures of Relative Importance for Multivariate Group Designs

In two-group multivariate designs, Huberty and Wisenbaker[9] defined variable importance as the relative contribution of a variable to group discrimination. More specifically, they defined the relative importance of a variable as (a) its contribution to a latent variable, (b) its contribution to a linear discriminant function, and (c) its contribution to a grouping variable effect. These measures, which are functions of the DFCs, are used to rank the variables based on their contribution to group separation.

Let $\mathbf{y}_{ij}$ be the $p \times 1$ vector of observed measurements for the ith study participant (i = 1,..., n_j) in the jth group (j = 1, 2, $N = n_1 + n_2$). Assume that $\mathbf{y}_{ij} \sim N_p(\boldsymbol{\mu}_j, \boldsymbol{\Sigma}_j)$, where $\boldsymbol{\mu}_j$ and $\boldsymbol{\Sigma}_j$ are the population mean and covariance for the jth group and are estimated by $\hat{\boldsymbol{\mu}}_j$ and $\hat{\boldsymbol{\Sigma}}_j$, respectively. For the linear discriminant analysis (DA) procedure, the DFC vector is estimated by

$$\hat{\mathbf{a}} = \hat{\boldsymbol{\Sigma}}^{-1}(\hat{\boldsymbol{\mu}}_1 - \hat{\boldsymbol{\mu}}_2), \tag{1}$$

where

$$\hat{\boldsymbol{\Sigma}} = \frac{(n_1 - 1)\hat{\boldsymbol{\Sigma}}_1 + (n_2 - 1)\hat{\boldsymbol{\Sigma}}_2}{n_1 + n_2 - 2}. \tag{2}$$

The number of uncorrelated discriminant functions that separates g groups is equal to $g - 1$.

The SDFC is one commonly adopted measure of relative importance. It is a unitless measure that range from -1 to 1. The SDFC quantifies the relative importance of a variable by taking into account the presence of other variables in the study. While there have been arguments in favour of using SDFCs to measure relative importance[17,18], they are known to be sensitive to correlation among the variables[18].

The SDFC for the *k*th variable is,

$$a_k^* = a_k s_k, \tag{3}$$

where a_k and s_k are the DFC and standard deviation on the *k*th variable, respectively. SDFCs can be positive or negative, and the absolute magnitude determines relative importance.

The SC is the correlation between a DFC and the individual variable. SCs are particularly useful for assessing variable importance because they provide direct information about the relationship between a discriminant function and an outcome variable. However, Rencher and Scott[19] have argued against using SCs because they do not take into account the presence of other variables.

DRC[9,10] measures the relative importance of a variable as a proportion of the group differences explained by this variable. The DRC is given by

$$q_k = a_k^* f_k, \tag{4}$$

where a_k^* and f_k are the SDFC and SC for the *k*th variable, respectively. DRC values typical range

between 0 and 1, although negative values indicate potential collinearity among the variables or the presence of suppressor variables. Suppression occurs when a variable makes little or no direct contribution to group separation on its own but contributes to group separation indirectly through another variable.

Thomas and Zumbo[13] proposed the TDRC to measure relative importance. The TDRC for the *k*th variable is

$$t_k = \frac{|a_k|\mathbf{S}_{\mathrm{T}kk}}{\sqrt{(\mathbf{a}\mathbf{S}_{\mathrm{T}}\mathbf{a})}}, \tag{5}$$

where $\mathbf{S}_{\mathrm{T}kk}$ is the (k,k)th element of $\mathbf{S}_{\mathrm{T}}$, $\mathbf{S}_{\mathrm{T}} = \mathbf{T}/(N-1)$, $\mathbf{T} = \mathbf{H} + \mathbf{E}$,

$$\mathbf{E} = \sum_{j=1}^{2}\sum_{i=1}^{n_j}(\mathbf{y}_{ij} - \bar{\mathbf{y}}_j)(\mathbf{y}_{ij} - \bar{\mathbf{y}}_j)^{\mathrm{T}}, \tag{6}$$

is the error sum of squares and cross product matrix,

$$\mathbf{H} = \sum_{j=1}^{2} n_j(\mathbf{y}_j - \bar{\mathbf{y}})(\mathbf{y}_j - \bar{\mathbf{y}})^{\mathrm{T}}, \tag{7}$$

is the hypothesis sum of squares and cross product matrix, and $^{\mathrm{T}}$ is the transpose operator. TDRCs can take values within the interval $[0, \infty)$, with a larger value indicating greater relative importance.

The FTR[9,13] for the *k*th variable is

$$F_{(k)} = \frac{k_2(a_k / s_{(kk)})^2}{(\bar{z}_1 - \bar{z}_2) + k_3 - (a_k / s_{(kk)})^2}, \tag{8}$$

where $k_2 = (N - 2 - p)$, $k_3 = N^2 / n_1 n_2$, a_k is the DFC for the *k*th variable, $\bar{z}_1$ and $\bar{z}_2$ are the group means for the discriminant function score corresponding to **a**, and $s_{(kk)}$ is the positive square root

Table 7-1. Measures of Relative Importance for Multivariate Group Designs

Measure	Description	Advantages	Limitations
SDFC	1. A product of the estimated DFC and the standard deviation on each variable. 2. Ranks variables based on the absolute values of the SDFC	1. It is a unitless measure 2. Evaluates importance while accounting for the presence of other study variables 3. Available in existing software	1. It is sensitive to correlation among the variables 2. May not be appropriate when there are suppressor variables in the study
SC	1. A measure of correlation between each variable and the discriminant function score. 2. SC values range between 0 and 1.	1. Evaluates the importance of a variable as its contribution to the discriminant function. 2. Available in existing software	1. A univariate measure of correlation that does not account for the presence of other study variables
DRC	1. A product of the SDFC and the structure coefficient. It quantifies the relative importance of a variable as the proportion of the group differences explained by	1. It satisfies all axioms about variable importance. 2. Recommended as the most reliable measure of relative importance. 3. Robust to several data	1. It is sensitive to correlation among the variables. 2. Not to easy to compute in existing software

	the variable. 2. DRC values range between 0 and 1.	characteristics	
TDRC	1. A variant of the SDFC that uses the total error sum of squares and cross product matrix to standardize the DFCs. 2. TDRC takes values in the interval [0, ∞).	1. TDRC has been recommended as a measure for identifying suppressor variables when used in conjunction with the DRC.	1. It is sensitive to the magnitude of correlation among the variables.
FTR statistic	1. A variant of the step-wise multivariate analysis of variance (MANOVA) measure. 2. The FTR statistic takes values in the interval [0, ∞)	1. The FTR statistic quantifies the importance of a variable as its contribution to a grouping effect. 2. Evaluates the unique contribution of a variable to a grouping effect	1. The FTR statistic does not account for the presence of other study variables.

of the *k*th diagonal element of the inverse of **E**, which is defined in equation 6. The FTR can take values within the interval [0, ∞), with a larger value indicating greater relative importance.

The strengths and limitations of these measures of relative importance are summarized in

Table 7-1.

7.3 Statistical Inference about Variable Importance

While measures of relative importance can be used in exploratory analyses to identify the most important variables, there are limited investigations about whether the size of the DFC for a variable is large enough to suggest that the variable is important. The conventional rule of thumb is one approach often used by applied researchers to evaluate if the magnitude of the relative importance measure is large enough to determine if a variable is important. This includes setting cut off points, to determine what size is important[20,21]. For example, variables with DRC values above 1/2*p* can be considered important while variables with negative DRC values are suggested to be suppressor variables with no direct contribution to group separation. However, given that sample estimates of DFCs of variable rankings ignore the sample error in that data, such rules of thumb are sensitive to sample size and the number of variables in the study.

Assessing statistical significance of a variable's DFC provides an alternative approach for evaluating the size of a variable's DFC in relation to variable importance. A number of parametric and non-parametric tests of significance of DFCs have been described in the literature..

Statistical significance based on the theoretical distribution of the DFCs is another valid approach proposed for testing if a variable's rank is significantly different from zero. Parametric tests based on asymptotic theory have been developed to test for statistical significance of DFCs[16, 22]. For example, Rao[16] proposed an *F*-test to evaluate statistical significance of a variable's contribution to group separation. This test is given as

$$F_k^* = \frac{(n-p)(D^2 - D_{(-k)}^2)}{k_3(n-p) + D_{(k)}^2} \sim F(1, n-p), \tag{9}$$

where $D^2 = (\bar{\mathbf{y}}_1 - \bar{\mathbf{y}}_2)^{\mathrm{T}} \mathbf{S}^{-1} (\bar{\mathbf{y}}_1 - \bar{\mathbf{y}}_2)$, and $D_{(k)}^2$ is the value of D^2 when the *k*th variable is omitted from the analysis. For this test, the null hypothesis is that the DFC for the *k*th variable is equal to zero (i.e., H_0: $a_k = 0$; H_1: $a_k \neq 0$). A statistically significant a_k suggests that the *k*th variable's contribution to group separation is statistically significant.

More recently, Bodnar and Okhirin[23] derived a more general statistic for testing statistical significance of a variable's DFCs or testing differences between the DFCs of two variables. Define *T* as

$$T = \sqrt{n-p+1} \frac{\mathbf{L}\hat{\mathbf{a}}}{\sqrt{\mathbf{L}^{\mathrm{T}} \hat{\mathbf{\Sigma}}^{-1} \mathbf{L}} \sqrt{1 + (\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)^{\mathrm{T}} \hat{\mathbf{R}}_L (\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)}} \sim t_{n-p+1}, \tag{10}$$

where $\hat{\mathbf{R}} = \hat{\mathbf{\Sigma}}^{-1} - \hat{\mathbf{\Sigma}}^{-1} \mathbf{L}^{\mathrm{T}} \mathbf{L} \hat{\mathbf{\Sigma}}^{-1} / \mathbf{L}^{T} \hat{\mathbf{\Sigma}}^{-1} \mathbf{L}$, and $\mathbf{L}$ is a contrast vector corresponding to the variable DFCs being tested. Similarly, these parametric tests can be used to derive confidence intervals for the DFC for each variable. However, these parametric tests are sensitive to departures from the underlying assumptions of DDA and may not perform well when the sample size is small.

Re-sampling based statistical methods[10, 24] that repeatedly sample from the original data, are alternative methods for testing hypothesis about statistical significance of DFCs or for testing differences between the ranks of two variables. Dalgleish[24] tested for statistical significance of structure coefficients by constructing approximate confidence intervals using a Jacknife technique and concluded that bootstrap confidence intervals provide a more reliable way to evaluate statistical significance of a variable's importance. For the FTR statistic, Huberty and Wisenbaker[10] proposed two statistical tests based on bootstrap methods for testing if a variable is statistically important and whether two variables are statistically equal in importance. Given that

resampling-based methods do not assume a parametric distribution, they are particularly useful for assessing statistical significance of a variable's importance when the data distribution is not known. This methodology has been used with other variable importance measures (such as relative weights and Pratt's index) in the regression literature for testing hypotheses and constructing confidence intervals[25, 26].

7.4 Discussion

While previous research has shown that there is a lack of agreement about the "best" measure of relative importance, these measures may not always result in consistent rankings of a set of variables[27-28]. Dissimilarities in rankings may arise, in part, because of data characteristics and deviations from the assumptions of multivariate normality and homogeneity (i.e., equality) of group covariance matrices. When the assumptions of the DDA model are satisfied, these measures result in correct rank ordering of the variables because DDA has greater statistical power to discriminate between groups. However, under assumption violations, these measures may result in incorrect rank ordering of the variables[19].

Moreover, data characteristics such as collinearity and suppression effects can also influence the consistency of variable rankings for these measures. For example, when the DRC is used to rank order the variables according to their contribution to group separation, an exclusion of variables with large negative DRC values (due to suppression or collinearity) from the analysis has been recommended[12]. In contrast, other variable importance measures, which are not sensitive to suppression effect, may rank this variable as important. Hence, DRCs may result in a different rank ordering of the variables than other measures of relative importance when suppressor variables are excluded from the analysis.

Although variable importance measures have been developed mainly for descriptive

purposes, they are also useful for inferential analyses. For example,tests of the significance of sample variable ranks may be conducted in order to generalize conclusions about variable importance to the population. Hypotheses about whether there is a statistically significant change in a variable importance over two measurement occasions may also be tested using measures of relative importance. However, although a number of approaches for evaluating statistical significance of variable importance ranking have been described in section 7.3, the statistical power and Type I error rates of these tests have not been investigated. Moreover, the measures of relative importance described here have only been applied to rank order a set of correlated variables in multivariate data collected at a single time point. There is limited investigation about their application in evaluating the relative importance of variables in multivariate repeated measures data. Such data often arise in longitudinal studies in which multiple outcomes are measured at two or more measurement occasions. In these studies, researchers seek to understand the most important HRQOL dimensions on which the differences between groups are maximized. Measures of relative importance have potential applications in identifying the most importance variables on which group

The measures of importance described in this chapter assume complete data on all variables, with casewise deletion of study participants with incomplete data. However, casewise deletion can result in biased estimates of relative importance when the mechanism of missingness is not random[29]. While an imputation method[29] could be adopted when there are missing values, the statistical theory underlying DA procedures based on imputation methods are yet to be developed.

There are additional considerations when conducting a relative importance analysis. The conclusion that one variable is more important than another can only be applied to the set of

variables under investigation. Hence, changing the variable set included in the analysis may result in different conclusions about relative importance. As well, relative importance may be associated with covariates such as age and sex. Stratified analyses might be conducted to assess the influence of covariates on the results. Alternatively, covariates can be incorporated into the mean of the DA model by conditioning on the covariates and by adopting a multivariate analysis of covariance model[30].

Relative importance measures have a number of potential uses in exploratory and inferential research. In exploratory research, they can be used to identify a small set of domains on which to focus in future studies. The measures could be used to assign weights to the domains when using a multiple testing procedure to control the overall probability of a Type I error; procedures in which the weights are assigned *a priori* have been shown to result in substantially improved power to detect group differences on the most important variables[31-32].

More recently, DA procedures that assume parsimonious means and covariance structures have been developed for predicting group memberships in repeated measures data[33-35]. Although these procedures are advantageous for classification in studies with small sample size, there are limited investigations of their application for describing the relative importance of variables/measurement occasions in repeated measures data. Given that the DFCs of DDA procedures can be used to quantify the relative importance of variable in multivariate group designs, DFCs from the repeated measures discriminant analysis (RMDA) procedures can also be used to describe the relative contribution of variables and measurement occasions in multivariate repeated measures data. Measures of relative importance based on these RMDA procedures could be useful in longitudinal health-related quality of life (HRQOL) studies in which researchers seek to understand the most important HRQOL domains on which the

differences between groups are maximized[36]. The next chapter proposes new methods for evaluating the relative importance of variables in multivariate repeated measures data with a numeric example from a longitudinal HRQOL study.

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Chapter 8. Evaluation of Variable Importance in Multivariate Repeated Measures Data

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Abbreviations

AR-1 = First-order autoregressive structure

CS = Compound symmetric structure

DDA = Descriptive discriminant analysis

DFC = Discriminant function coefficient

HRQOL = Health-related quality of life

IBDQ = Inflammatory Bowel Disease Questionnaire

ML = Maximum likelihood

RMDA = Repeated measures discriminant analysis

SDFC = Standardized discriminant function coefficient

UN = Unstructured

UNAR = DA based on unstructured means and covariances with a AR-1 structure

UNCS = DA based on unstructured means and covariances with a CS structure

UNUN = DA based on unstructured means and covariances

Abstract

Repeated measures discriminant analysis (RMDA) procedures that assume parsimonious covariance structures have been recently developed for predicting group membership in multivariate repeated measures data, in which two or more outcome variables are repeatedly measured at more than two measurement occasions. However, there is less emphasis on the use of the discriminant function coefficients of these procedures for evaluating the relative importance of variables in multivariate repeated measures data. This study compares standardized discriminant function coefficients (SDFCs) of two RMDA procedures based on their ability to correctly rank order variables according to their ability to discriminate between groups. These include the stagewise RMDA procedure and an RMDA procedure that assume Kronecker product covariance structures. Monte Carlo techniques were used to evaluate the SDFCs of these procedures for different conditions of number of variables, total sample size, mean configuration, and correlation structure. Percentages of any-variable and average per-variable correct rankings were evaluated. Overall, SDFC based on the average of with-variable DFCs for RMDA procedure that assume Kronecker product covariance structure resulted in the highest percentages of correct rankings and largest concordance values. Moreover, the SDFCs for these RMDA procedures are sensitive to the magnitude of separation between group means, and the magnitude of variable correlation. Variable importance measures are an important tool identifying the most importance outcome that discriminate between groups in multivariate repeated measures data.

Key words: relative importance; multivariate repeated measures data; discriminant analysis; Kronecker product; covariance structure

8.1 Introduction

Multivariate repeated measures data in which $q \geq 2$ outcome variables are measured at $p \geq 2$ measurement occasions are common in medical and social science research studies that compares groups of individuals for efficacy of treatment or interventions. For example, a recent review of research studies on psychotherapy for the treatment of youth mental health disorders suggests that this literature abounds with studies in which participants exposed to child-, parent-, family-, or teacher-focused interventions were compared with participants randomized to a placebo condition, standard case management protocol, or alternate treatment, on multiple measures of patient symptoms, behaviours, level of functioning, and psychosocial responses[1]. Longitudinal health-related quality of life data are another example of multivariate repeated measures data. They consist of individuals' ratings on multiple inter-related domains, such as mental health, physical function, and social function, which are collected at multiple occasions following disease diagnosis or treatment[2-3].

There are several reasons why a researcher might test for group differences on multiple outcome variables that are measured on multiple occasions. Researchers may be interested modeling the joint evolution of outcome variables or in understanding how that evolution differs for different groups of study participants. In clinical trials, for example, differences between treatment and control groups or severely ill versus less severely ill patients may be examined. There may be limited research knowledge about which outcome(s) will be the responsive to treatment.

While multivariate data are usually characterized by between variable correlations, multivariate repeated measures data contain two sources of correlation: (a) within-variable correlation, which arises because the repeated measurements for each outcome variable are

correlated and (b) between-variable correlation, which arises because the responses on the outcome variables at each measurement occasion are correlated. Statistical procedures that accounts for both correlation sources include procedures for testing omnibus hypotheses of no group differences[4-6] such as repeated measures analysis of variance (RMANOVA) and analysis of covariance (ANCOVA). Post-hoc multiple testing procedures[7] have also been proposed for identifying the outcomes on which group differences exist in multivariate repeated measures studies. Moreover, classification models, such as repeated measures discriminant analysis (RMDA) procedures that assume structured covariances, have been proposed for predicting disease status in multivariate repeated measures data[8-11]. One model is based on a stage-wise discriminant analysis procedure, in which within-variable growth trends are summarized using regression functions (Stage 1) and a DA classification rule is developed based on the subject–specific predicted scores from the regression functions (Stage 2). More recently, RMDA models that assume parsimonious means and/or covariances have been developed for discrimination in multivariate repeated measures data[12-13]. These procedures, which assume Kronecker product structure, are particularly advantageous when the sample size is small relative to data dimension. However, these procedures have focused on prediction and not description of group separation.

Variable importance analysis based on discriminant function coefficients provides an alternative approach for identifying the most important outcomes that are responsive to treatment in multivariate repeated measures data. These measures have been developed to rank a set of variables according to their ability to discriminate between groups in multivariate data[14-15], but there have been few studies in which these methods have been extended to multivariate repeated measures data. Methods that have been proposed to evaluate the variable importance in multivariate repeated measures studies include assigning ranks to a set of variables using

discriminant function coefficients (DFCs) from descriptive discriminant analysis (DDA) to the baseline data[16-17], or ranking variables based on measures of relative importance derived from applying DDA to subject-specific longitudinal change scores[18-19]. These methods do not account for within-variable and between-variable correlation and may be inefficient when the sample size is small relative to the number of variables.

Given this background, the purpose of this study is to develop variable importance measures based on the DFCs of RMDA procedures that assume Kronecker product covariance structures for evaluating variable importance in multivariate repeated measures data. Their performance under a variety of data analytic conditions is examined using Monte Carlo techniques and data from the longitudinal cohort study are used to demonstrate their implementation.

8.2 Methods

Let $\mathbf{y}_{ij}$ be the $pq \times 1$ vector of observed measurements corresponding to p repeated measurements on each of the q outcome variables for the ith study participant in the jth group ($i = 1, ..., n_j$; $j = 1, 2$; $n = n_1 + n_2$).The vectors are structured such that the repeated measurements are nested within each variable. Assume that $\mathbf{y}_{ij} \sim N_{pq}(\boldsymbol{\mu}_j, \boldsymbol{\Omega}_j)$, where $\boldsymbol{\mu}_j$ and $\boldsymbol{\Omega}_j = \boldsymbol{\Omega}$ are the population mean and covariance for the jth group and are estimated by $\hat{\boldsymbol{\mu}}_j$ and $\hat{\boldsymbol{\Omega}}$, respectively. Here, we describe three methods for evaluating the relative importance of variables in multivariate repeated measures data.

Method 1 is a stagewise procedure, in which DFCs are estimated separately for each outcome variable using RMDA procedure and then used to estimate subject-specific discriminant function score for each variable (stage 1). Standardized discriminant function coefficients

(SDFC), which are estimated from the discriminant function score data, are then used to rank order the variables (stage 2). Possible choices for RMDA procedures for estimating DFCs for each outcome variable include RMDA procedures such as the RMDA based on unstructured means and compound symmetric covariance (UNCS) and RMDA based on unstructured means and first order autoregressive (AR-1) covariances (UNAR), which have been previously proposed by Sajobi et al [20].

Let $\boldsymbol{\mu}_{jk}$ and $\boldsymbol{\Omega}_{kk}$ denote $p\times1$ vector of repeated measures means and $p\times p$ covariance matrix, respectively, for the kth (k = 1,2, ...q) variable in the jth group. Here, $\boldsymbol{\Omega}_{kk}$ corresponds to the kth matrix on the diagonal of $\boldsymbol{\Omega}$. Define $\mathbf{w} = (\mathbf{w}_k)$ as a $p\times q$ matrix of DFCs such that

$$\mathbf{w}_k = \boldsymbol{\Omega}_{kk}^{-1}(\boldsymbol{\mu}_{1k} - \boldsymbol{\mu}_{2k}), \tag{1}$$

where $\mathbf{w}_k$, the kth column of $\mathbf{w}$, is a $p\times1$ vector of DFCs for the kth outcome variable. The ML estimates of $\boldsymbol{\mu}_{jk}$ and $\boldsymbol{\Omega}_{kk}$ will depend on the choice of RMDA procedure adopted. The discriminant function score for the ith individual on the kth variable in the jth group as

$$\mathrm{z}^{*}_{ijk} = \mathbf{w}_k^{\mathrm{T}}\mathbf{y}_{ijk}, \tag{2}$$

where $\mathbf{z}^{*}_{j} = (z^{*}_{ijk})$ is the $n_j \times q$ matrix of discriminant function scores for the jth group, and $\mathbf{z}^{*}_{j} \sim \mathrm{N}_q(\mathbf{m}_j, \boldsymbol{\Lambda})$. Define $\mathbf{w}^{*}$ as

$$\mathbf{w}^{*} = \boldsymbol{\Lambda}^{-1}(\mathbf{m}_1 - \mathbf{m}_2). \tag{3}$$

where $\mathbf{m}_j$ and $\boldsymbol{\Lambda}$ are estimated by

$$\hat{\mathbf{m}}_j = \frac{\sum_{i=1}^{n_j}\mathbf{z}^{*}_{ij}}{n_j}, \tag{4}$$

and

$$\hat{\mathbf{\Lambda}} = \frac{\sum_{j=1}^{2}\sum_{i=1}^{n_j}(\mathbf{y}_{ij}^{*} - \hat{\mathbf{m}}_j)(\mathbf{y}_{ij}^{*} - \hat{\mathbf{m}}_j)^{\mathrm{T}}}{n-1}, \tag{5}$$

respectively.

Standardized DFCs (SDFCs) based on $\mathbf{w}^{*}$ are used to rank the variables based on their contribution to group separation. The SDFC for the *k*th variable is

$$s_k^{*} = w_k^{*}\sqrt{\hat{\mathbf{\Lambda}}_{kk}}, \tag{6}$$

where w_k^{*} is the *k*th (*k* = 1 , 2,…, *q*) element of $\hat{\mathbf{w}}^{*}$, and $\hat{\mathbf{\Lambda}}_{kk}$ is the *k*th element on the diagonal of $\hat{\mathbf{\Lambda}}$.

Methods 2 and 3 are the SDFCs based on linear combinations of within-variable DFCs of a RMDA procedure that adopts unstructured means and Kronecker product covariance structure. The choice of this procedure is consistent with conclusions from previous research that RMDA procedures that assume no parsimony on the mean structures results in DFCs with less bias and error (see Chapter 6).

For a Kronecker product covariance, $\mathbf{\Omega} = \mathbf{\Sigma} \otimes \mathbf{V}$, where $\mathbf{\Sigma}$ and $\mathbf{V}$ are *q*×*q* positive definite variance-covariance matrix for the outcome variables and *p*×*p* positive definite correlation matrix among the repeated measurements, respectively, and $\otimes$ is the Kronecker product operator. SDFCs for Methods 2 and 3 are developed from RMDA procedure whose Kronecker product covariance is characterized by unstructured $\mathbf{\Sigma}$ and unstructured $\mathbf{V}$. For this RMDA procedure, the vector of DFCs is given by

$$\mathbf{a} = (\mathbf{\Sigma} \otimes \mathbf{V})^{-1}(\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)^{\mathrm{T}}. \tag{7}$$

Let $\mathbf{C}^{\mathrm{T}}$ be a *q*×1 transformation that summarizes the within-variable DFCs into a single score for each variable and observation. The vector of linearly transformed DFCs is given as

$$\mathbf{a}^{*} = \mathbf{M}\mathbf{a} = (\mathbf{I}_q \otimes \mathbf{C}^{\mathrm{T}})\mathbf{a} \tag{8}$$

$$= (\mathbf{I}_q \otimes \mathbf{C}^{\mathrm{T}})(\boldsymbol{\Sigma}^{-1} \otimes \mathbf{V}^{-1})(\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)^{\mathrm{T}}. \tag{9}$$

This simplifies to

$$\mathbf{a}^{*} = \alpha(\boldsymbol{\Sigma}^{-1} \otimes \mathbf{C}^{\mathrm{T}})(\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)^{\mathrm{T}}, \tag{10}$$

where α is a constant that is dependent on the choice of $\mathbf{C}$, $\mathbf{M} = (\mathbf{I}_q \otimes \mathbf{C}^{\mathrm{T}})$, and $\mathbf{I}_q$ is a $q \times q$ identity matrix. Estimates of $\boldsymbol{\Sigma}$, ρ, $\boldsymbol{\mu}_1$, and $\boldsymbol{\mu}_2$ are obtained via the maximum likelihood (ML) estimation method as described in the Appendix. The vector of SDFCs is given by $\mathbf{d} = (d_k)$, where

$$d_k = a_k^{*}\sqrt{\boldsymbol{\Omega}_{kk}^{*}}, \tag{11}$$

d_k is the kth element of $\mathbf{d}$, a_k^{*} is the kth ($k = 1, 2, \ldots, q$) element of $\hat{\mathbf{a}}^{*}$, and $\hat{\boldsymbol{\Omega}}_{kk}^{*}$ is the kth diagonal element of $\boldsymbol{\Omega}^{*} = (\mathbf{I}_q \otimes \mathbf{C}^{\mathrm{T}})\boldsymbol{\Omega}(\mathbf{I}_q \otimes \mathbf{C})$. The outcome variables are ranked based on the magnitude of the transformed SDFC, with a value of one representing the variable with the largest absolute value.

For Method 2, $\mathbf{C} = \frac{\mathbf{1}_p}{p}$, which corresponds to the average of all repeated measurements on each variable. In contrast, $\mathbf{C}$ is a $p \times 1$ vector such that the first and last elements are 1 and -1, respectively, and the remaining entries of $\mathbf{C}$ are zero.

In the following theorem, we show that the rank ordering of variables based on Methods 2 and 3 are equivalent to the ranking ordering of variables based on the SDFCs derived from applying DDA to a linear transformation of the $\mathbf{y}_{ij}$.

Theorem

Assume that $\mathbf{y}_{ij} \sim \mathrm{N}_{pq}(\boldsymbol{\mu}_j, \boldsymbol{\Omega})$, where $\boldsymbol{\Omega} = \boldsymbol{\Sigma} \otimes \mathbf{V}$, $\boldsymbol{\Sigma}$ is the unstructured between variable variance-covariance matrix, $\mathbf{V}$ is the $p \times p$ positive definite CS correlation structure among the repeated measurements. Define $\mathbf{y}_{ij}^*$ as $\mathbf{y}_{ij}^* = \mathbf{M}\mathbf{y}_{ij}$ where $\mathbf{y}_{ij}^* \sim \mathrm{N}_q(\mathbf{M}\boldsymbol{\mu}_j, \mathbf{M}(\Sigma \otimes \mathbf{V})\mathbf{M}^{\mathrm{T}})$ is a $q \times 1$ vector of transformed measurements obtained by based on the transformed within-variable repeated measurements, and $\mathbf{M} = (\mathbf{I}_q \otimes \mathbf{C}^{\mathrm{T}})$. Then,

$$\mathbf{M}\mathbf{a} \propto \mathbf{a}^*, \tag{12}$$

and

$$r(\mathbf{M}\mathbf{a}) = r(\mathbf{a}^*), \tag{13}$$

where $\mathbf{a}$ is the vector of DFCs obtained by applying DDA to the original data, $\mathbf{a}^*$ is the vector of DFCs obtained from applying DDA to the transformed data, and r is a step function that ranks the elements of a vector according to the magnitude of the elements.

Proof

The vector of DFCs, **a,** can be expressed as

$$\mathbf{a} = (\boldsymbol{\Sigma} \otimes \mathbf{V})^{-1}(\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)^{\mathrm{T}}. \tag{14}$$

This simplifies to the expression in equation 10. For the transformed data, the left hand side of the equality in equation 12 can be expressed as

$$\mathbf{a}^* = (\mathbf{M}(\boldsymbol{\Sigma} \otimes \mathbf{V})\mathbf{M}^{\mathrm{T}})^{-1}\mathbf{M}(\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2). \tag{15}$$

This simplifies to

$$\mathbf{a}^* = \frac{(\boldsymbol{\Sigma}^{-1} \otimes \mathbf{C}_p)(\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)}{\beta}, \tag{16}$$

where $\beta = \mathbf{C}\mathbf{V}\mathbf{C}^{\mathrm{T}}$. Hence,

$$r(\mathbf{Ma}) = r(\mathbf{a}^*), \tag{17}$$

and the theorem is proved.

8.3 Simulation Study

Monte Carlo techniques were used to evaluate the performance of our proposed methods for evaluating variable importance in multivariate repeated measures data. The following methods were investigated: (a) SDFCs based on a sequential procedure (Method 1) which uses a DA procedure based on unstructured means and covariances (UNUN) to evaluate DFCs in the first step, (b) SDFCs based on a sequential procedure (Method 1) which uses a DA procedure based on unstructured means and CS covariances (UNCS) to evaluate DFCs in the first step, (c) SDFCs based on a sequential RMDA procedure (Method 1) in which a DA procedure based on unstructured means and first order autoregressive covariances (UNAR) is used to evaluate the DFCs in the first step, (d) SDFCs derived from average within-variable DFCs of a RMDA procedure based on a Kronecker product covariance structure (Method 2), (e) SDFCs derived from the difference between the first and last within-variable DFCs of a RMDA procedure based on a Kronecker product covariance structure (Method 3).

The number of outcome variables was set at q = 5 and 7, while the number of repeated measurements was held constant at p = 3. Previous studies about RMDA procedures have considered q ranging from 3 to 10[20,21]. Total sample sizes of n = 50, 100, and 240 were investigated, which gives n/pq values ranging from 2.4 to 16. Based on previous simulations studies[21, 22], both equal and unequal sample size conditions were investigated. For n = 50, the group sizes were (n_1, n_2) = (30, 30), (n_1, n_2) = (20, 30), and (n_1, n_2) = (30, 20). For n = 100, they

were (n_1, n_2) = (50, 50), (n_1, n_2) = (40, 60), and (n_1, n_2) = (60, 40). For n = 240, they were (n_1, n_2) = (120, 120), (n_1, n_2) = (96, 144), and (n_1, n_2) = (144, 96).

The mean structure and magnitude of separation between group means have also been shown to influence the estimation of DFCs and rank ordering of the variables[14,15]. In this study, the mean vectors had the configuration $\boldsymbol{\mu}_j = \boldsymbol{\mu}_{jp} \otimes \boldsymbol{\mu}_{jq}$, where $\boldsymbol{\mu}_{jp}$ is the p×1 mean vector for the measurement occasions and $\boldsymbol{\mu}_{jq}$ is the q×1 mean vector for the outcome variables for the jth group. Table 8-1 describes the three configurations for $\boldsymbol{\mu}_{1q}$ and $\boldsymbol{\mu}_{1p}$ that were investigated and their corresponding magnitude of group differences (i.e., Mahalanobis distance, $D^2 = (\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)^{\mathrm{T}} \boldsymbol{\Omega}^{-1} (\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)$). For configuration I, a monotonic decreasing linear pattern was specified for $\boldsymbol{\mu}_{1q}$, while while a constant trend was assumed for $\boldsymbol{\mu}_{1p}$. For Configuration II, non-constant means in a quadratic pattern was specified for $\boldsymbol{\mu}_{1q}$, while a constant trend was assumed for $\boldsymbol{\mu}_{1p}$. For Configuration III, a polynomial trend was specified for $\boldsymbol{\mu}_{1q}$, while a decreasing linear trend was specified for $\boldsymbol{\mu}_{1p}$. In all cases, $\boldsymbol{\mu}_{2p}$ and $\boldsymbol{\mu}_{2q}$ were vectors of zeros. These configurations represent the types of structures common in repeated measures studies[23].

Data were generated from a multivariate normal distribution with mean $\boldsymbol{\mu}_j$ and covariance matrix $\boldsymbol{\Omega}$, which has Kronecker product structure of the form $\mathbf{L}\boldsymbol{\rho}\mathbf{L}^{\mathrm{T}}$, where $\mathbf{L}$ is a diagonal matrix with $\boldsymbol{\sigma} = \boldsymbol{\sigma}_p \otimes \boldsymbol{\sigma}_q$ on the diagonal, $\boldsymbol{\sigma}_p$ is the vector of standard deviations for the repeated measurements, and $\boldsymbol{\sigma}_q$ is the vector of standard deviations for the outcome variables. As well, a Kronecker product correlation structure was assumed for $\boldsymbol{\rho}$ such that $\boldsymbol{\rho} = \boldsymbol{\rho}_p \otimes \boldsymbol{\rho}_q$, where $\boldsymbol{\rho}_p$ is a CS correlation matrix for the measurement occasions and $\boldsymbol{\rho}_q$ is an unstructured correlation matrix for the outcome variables, respectively. Three values were considered for $\boldsymbol{\rho}_p$: (a) $\boldsymbol{\rho}_p = (\rho_p) = 0.1$, (b) $\boldsymbol{\rho}_p = (\rho_p) = 0.4$, and (c) $\boldsymbol{\rho}_p = (\rho_p) = 0.7$. For the correlation among the outcome variables, two population matrices were considered: (a) unstructured with average correlation among the off-

diagonal elements of 0.4 ($\mathbf{Q}_{q1}$) and (b) unstructured with average correlation among the off-diagonal elements of 0.7 ($\mathbf{Q}_{q2}$). For all investigated conditions, $\sigma_1^2 = \sigma_2^2 = \mathbf{1}_{pq}$, and $\mathbf{\Omega}_1 = \mathbf{\Omega}_2$.

All combinations of conditions were investigated for each method, resulting in a total of 324 combinations. There were 5000 replications for each combination. The simulation study was conducted using SAS/IML version 9.2[24].

For every set of conditions, the variables were ranked based on the magnitude of the SDFCs with a value of one representing the variable with the largest absolute value. Ties in ranks were resolved by assigning mid-ranks[15, 25]. The population ranks were obtained by rank ordering the population DFCs, which were calculated from the population means and covariance matrices. The proportion of correctly ranked variables was estimated for each method by comparing the sample ranks for the variables with the population ranks and computing the any-variable and per-variable correct ranking percentages[26]. The former is the average percentage of simulations in which the sample ranks were the same as the corresponding population ranks for any variable, while the latter is the percent of simulations in which any variable was correctly ranked and is averaged across all variables.

Table 8-1. Configurations of $\boldsymbol{\mu}_{1p}$ and $\boldsymbol{\mu}_{1q}$ for the Monte Carlo Study

Configuration	$\boldsymbol{\mu}_{1p}$	$\boldsymbol{\mu}_{1q}$			
	$p=3$	$q = 5$	D^2	$q = 7$	D^2
I	(1, 1, 1.5)	(2.5, 2, 1.5, 1 0.5)	58.44	(3.5,3, 2.5,2,1.5,1,0.5)	148.75
II	(1, 1, 1)	(0.5, 1, 1.5, 1, 0.5)	14.25	(0.5,1,1.5,2,1.5,1,0.5)	33
III	(1, 0.7, 0.5)	(1.5,0.5,1 1.5, 0.5)	10.88	(1.5,1,0.5,1,1.5,1,0.5)	12.5

Note: $\boldsymbol{\mu}_{2q}$ and $\boldsymbol{\mu}_{2p}$ are both null vectors for all conditions.

8.4 Results

Tables 8-2 and 8-3 describe the average any-variable and average per-variable correct ranking percentages for the three methods. Overall, Method 2, in which the SDFCs are based on the average within-variable DFCs of a RMDA procedure that assumes a Kronecker product covariance structure, achieved the highest proportion of correctly-ranked variables, while Method 3, in which the SDFC vector is estimated from the within-variable difference scores, achieved the smallest proportion of correctly ranked variables. For each method, the proportion of correctly ranked variables were largest when $q = 5$ and smallest when $q = 7$, regardless of the mean configuration and total sample size.

The performance of these methods was influenced by the type of mean configuration for the data. The average any-variable correct ranking percentage for Method 1 was largest when the data for group 1 were sampled from a population with mean configuration I and smallest when the data for group 1 were sampled from a population with mean configuration III, when $q = 5$. However, when $q = 7$, the average any-variable correct ranking percentages were largest when the data were drawn from a population with mean configuration I and smallest when drawn from a population with mean configuration II. There were negligible differences in the average any-variable and per-variable correct ranking percentages when UNUN, UNCS, and UNAR procedures were adopted to estimate the DFCs, regardless of the population mean configuration.

For Method 2, the average any-variable correct ranking percentage values were largest under configuration I and smallest under mean configuration III, although the difference between the correct ranking percentage values for this method when the data were sampled from mean configuration I and II were negligible, for $q = 5$. For method 3, the average correct ranking percentage values were largest when the data were sampled from a population with mean

configuration I but smallest when sampled from a population with mean configuration II.

Similar trends were observed for average per-variable correct ranking results. However, for Methods 1 and 3, the difference between the average per-variable correct ranking percentages under mean configuration II and III were negligible when $q = 7$ (Table 8-2).

The average any-variable and per-variable correct ranking percentages for these methods by mean configuration and variable correlations are described in Table 8-3. For method 1, the average any-variable correct ranking percentages under $\mathbf{Q}_{q1}$ were higher than the value under $\mathbf{Q}_{q2}$ when the data were sampled from a population with mean configuration I or III. However, for Configuration II, the changes in any-variable correct ranking percentage were substantially higher under $\mathbf{Q}_{q2}$ than under $\mathbf{Q}_{q1}$. For Method 2, the average any-variable correct ranking percentage was slightly higher under $\mathbf{Q}_{q2}$ than under $\mathbf{Q}_{q1}$ when the data were sampled from a population with mean configuration I. For other mean configurations, the average any-variable correct ranking percentage values for Method 2 decreased as the magnitude of variable correlation decreased. For Method 3, there was also a slight increase in average any-variable correct ranking percentage under $\mathbf{Q}_{q2}$ than under $\mathbf{Q}_{q1}$. But for other mean configurations, the change in percentage values under $\mathbf{Q}_{q1}$ and $\mathbf{Q}_{q2}$ were negligible.

In terms of the per-variable correct ranking percentages, the percentages for Method 2 and Method 3 were largest under $\mathbf{Q}_{q1}$ but smallest under $\mathbf{Q}_{q2}$, regardless of the mean configuration. For example, the average any-variable correct ranking percentage for Method 2 under $\mathbf{Q}_{q1}$ was about 5% higher than the value under $\mathbf{Q}_{q2}$ when the data were sampled from a population with mean configuration For Method 1, the average per-variable correct ranking percentage values were largest under $\mathbf{Q}_{q1}$ but smallest under $\mathbf{Q}_{q2}$, only when the data were sampled from a population with mean configuration I or III. When the data were sampled from a

population with mean configuration II, the average correct ranking percentage values for Method 1 was about 2.5% smaller under $\mathbf{Q}_{q1}$ than the corresponding values for $\mathbf{Q}_{q2}$.

Finally, the average any-variable and per-variable correct ranking rates for each of the methods decrease as the sample size increased. While, there were no substantial changes in the any-variable correct ranking percentage values of Method 1 and Method 3 as n increased, the change in percentage values for Method 2 was about 10%. For each method, the change in the per-variable correct ranking percentage values as n increased was not more than 2%.

Table 8-1. Average Any-Variable and Average Per-Variable Correct Ranking Percentages for Standardized Discriminant Function Coefficients by Number of Outcomes (q) and Variable Mean Configuration

q	Mean Configuration	Method 1			Method 2	Method 3
		UNUN	UNCS	UNAR		
Any-Variable Correct Ranking (%)						
5	I	80.80	80.54	80.45	96.75	84.03
	II	56.27	56.14	55.86	76.23	14.18
	III	22.09	22.07	22.13	37.49	20.97
7	I	74.35	74.03	74.00	98.15	81.03
	II	41.06	40.87	40.62	98.57	17.46
	III	50.41	50.26	50.44	53.4	46.66
	Average	**53.96**	**53.79**	**53.72**	**75.79**	**43.80**
Per-Variable Correct Ranking (%)						
5	I	28.03	27.87	27.76	43.11	29.83
	II	11.25	11.23	11.17	15.25	2.84
	III	4.42	4.41	4.43	7.50	4.19
7	I	18.23	18.08	17.98	22.89	20.56
	II	5.87	5.84	5.80	14.01	2.49
	III	7.20	7.18	7.21	7.62	6.67
	Average	**12.46**	**12.39**	**12.35**	**18.27**	**11.02**

Table 8-3. Average Any-Variable and Per-Variable Correct Ranking Percentages for Standardized Discriminant Function Coefficients by Variable Mean Configuration and Covariance Structure

Mean Configuration	Variable Correlation	Method 1			Method 2	Method 3
		UNUN	UNCS	UNAR		
Any-Variable Correct Ranking (%)						
I	$\mathbf{Q}_{q1}$	81.50	81.43	81.46	96.39	80.90
	$\mathbf{Q}_{q2}$	72.70	72.13	71.97	98.79	84.75
II	$\mathbf{Q}_{q1}$	43.71	43.65	43.19	94.94	19.13
	$\mathbf{Q}_{q2}$	55.49	55.44	55.20	77.08	11.77
II	$\mathbf{Q}_{q1}$	37.04	37.00	37.17	51.16	33.95
	$\mathbf{Q}_{q2}$	35.47	35.33	35.41	39.66	33.68
Per-Variable Correct Ranking (%)						
I	$\mathbf{Q}_{q1}$	24.93	24.85	24.79	35.67	26.70
	$\mathbf{Q}_{q2}$	21.13	20.88	20.72	30.22	23.57
II	$\mathbf{Q}_{q1}$	7.65	7.60	7.54	16.20	3.31
	$\mathbf{Q}_{q2}$	10.00	10.00	9.97	12.99	1.94
II	$\mathbf{Q}_{q1}$	5.93	5.93	5.96	8.73	5.47
	$\mathbf{Q}_{q2}$	5.69	5.66	5.67	6.39	5.39

Note: See Table 8-1 for a description of repeated measures and variable mean configurations. UNUN = RMDA based on unstructured means and covariances; UNCS = RMDA based on unstructured means and CS covariances;UNAR = RMDA based on unstructured means and AR(1) covariances; $\mathbf{Q}_{p1}$ = UN with average $\boldsymbol{\rho}_q = 0.3$; $\mathbf{Q}_2$ = UN with average $\boldsymbol{\rho}_q = 0.6$. $\boldsymbol{\rho}_q$ = correlation among the outcomes

8.5 Numeric Example

Data to illustrate the implementation of these methods for evaluating relative importance of variables in multivariate repeated measures data were from the Manitoba Inflammatory Bowel Disease (IBD) Cohort Study, which was introduced in Chapter 6. This is a prospective longitudinal study, initiated in 2002, of patients who were recently diagnosed with Crohn's disease or ulcerative colitis. Data were collected at six-month intervals using self-report instruments. Study participants were assigned to active ($n_1 = 265$) and inactive ($n_2 = 116$) disease groups based on self-reported IBD symptoms at study entry. Health-related quality of life (HRQOL) data is collected in the Cohort Study using disease-specific and generic HRQOL instruments, including the Inflammatory Bowel Disease Questionnaire (IBDQ)[27]. The IBDQ is a disease-specific instrument that has 32 items grouped into four domains: bowel symptoms (10 items), systemic symptoms (five items), emotional factors (12 items), and social factors (five items). Each item is scored on a 7-point Likert scale, ranging from 1 (worst of health) to 7 (best of health). The average score on each domain ranges from 1 to 7, with higher scores indicating better HRQOL. More details about this study and the self-report instruments have been described elsewhere[28-29].

Data on disease activity were missing for 2% of the participants. Participants with at least one missing HRQOL domain score constituted 23% and 16% of the total sample at months 0 and 24, respectively. To reduce the number of missing observations, a mean imputation method[30] was adopted.

Differences between active and inactive groups of participants on scores for the four IBDQ domains were investigated for the first two years of the study (i.e., first five measurement occasions). The primary research question is to identify which domains are the most important

that explain differences between the longitudinal profiles of quality of life for active and inactive groups. The methods described in this research were used to identify the most important IBDQ domains. These methods were implemented using a SAS program written by the authors[24]; the program is provided in Appendix II.

Table 8-4. Descriptive Statistics for IBDQ Domain Scores

IBDQ Domains	Month 0	Month 6	Month 12	Month 18	Month 24
Active Disease (n_1 = 265)					
Bowel Symptom	4.92(1.03)	5.15(1.01)	5.20(1.07)	5.27(1.01)	5.34(1.01)
Emotional Health	4.92(1.01)	5.16(1.00)	5.16(1.08)	5.26(0.97)	5.36(0.97)
Systemic Symptoms	4.07(1.19)	4.34(1.20)	4.34(1.26)	4.49(1.22)	4.49(1.26)
Social Function	5.63(1.30)	5.97(1.10)	5.87(1.31)	6.10(1.10)	6.09(1.12)
Inactive Disease (n_2 = 116)					
Bowel Symptom	6.00(0.78)	5.92 (0.85)	5.94(0.77)	5.99(0.73)	5.95(0.83)
Emotional Health	5.80(0.90)	5.76 (0.83)	5.85(0.71)	5.80(0.73)	5.85(0.79)
Systemic Symptoms	5.10(1.06)	5.09(1.03)	5.12(0.97)	5.24(1.00)	5.13(1.08)
Social Function	6.63(0.63)	6. 60(0.49)	6.67(0.46)	6.71(0.51)	6.59(0.74)

Note: Reported values are means (SD); IBDQ = Inflammatory Bowel Disease Questionnaire

The IBDQ domains scores were summarized using means and standard deviations at each measurement occasion (Table 8-4). While the domains in active disease groups exhibited an increasing trend over time, there were no significant changes in the mean scores for the domains over time in the inactive disease group. Statistical tests of significance of difference between IBDQ domain scores for both active and inactive disease groups suggests the group mean scores are significantly different on each of the IBDQ domains at study baseline.

The SDFCs and the corresponding ranks for each method are described in Table 8-5. Method 1 identified the IBDQ emotional health domain and bowel symptoms as the first and

second most important domains, respectively. Method 2 identified the IBDQ bowel symptoms and social functioning domains as the first and second most important outcome variables for discriminating between groups. Method 3 identified the IBDQ bowel symptom and systemic symptoms domains as the first and second most important domains that discriminate between groups.

Table 8-5. Standardized Discriminant Function Coefficients and Relative Importance Ranks of IBDQ Domains

IBDQ Domains	Method 1 UNUN		Method 1 UNCS		Method 1 UNAR		Method 2		Method 3	
	a*	*r*	a*	*r*	a*	r	a*	*r*	a*	*r*
Bowel Symptoms	0.07	2	0.09	2	0.05	3	0.15	1	0.22	1
Emotional Health	-0.09	1	-0.11	1	-0.07	1	0.05	4	0.06	4
Systemic Symptoms	-0.01	4	-0.01	4	0.06	2	0.09	3	0.21	2
Social Functioning	0.07	3	0.07	3	-0.01	4	0.14	2	0.11	3

IBDQ = Inflammatory Bowel Disease Questionnaire; a* = standardized discriminant function coefficient; *r* = relative importance rank; UNUN = DA based on unstructured covariances; UNCS = RMDA based on covariances with a CS structure; UNAR = RMDA based on covariances with a AR-1 structure.

8.6 Discussion

This study proposes new methods for evaluating the relative importance of variables in multivariate repeated measures data. These methods are based on the DFCs derived from stage-wise RMDA and RMDA procedures in combination with dimension reduction techniques. These procedures for evaluating the relative importance of variables are advantageous when the sample size is small relative to the data dimension. Their performance under a variety of data-analytic conditions was investigated using Monte Carlo techniques and a numeric example was used to illustrate their application.

Our study results suggests the performance of these methods in correctly rank ordering a set of variables in multivariate repeated measures design is influenced by the magnitude of separation between groups, the magnitude of covariance among the variables, and the size of the outcome variable set. While these procedures differ in their sensitivity to data characteristics, Method 2, which is based on the SDFCs derived from the average of the within-variable DFCs of a RMDA procedure that assumes unstructured means and Kronecker product covariances, maintained the highest any-variable and per-variable correct ranking percentages in almost all the investigated conditions. While Method 1 was less sensitive to the mean configuration and correlations among the variables, methods based on the RMDA procedures that assume a Kronecker product covariance structure (i.e., Methods 2 and 3) were more sensitive to the configuration of the group means and the magnitude of correlation among the variables. The percentage of correctly ranked variables for each method decreased as the number of outcome variables increased.

Moreover, conclusions from the numeric example suggest that bowel symptoms and emotional health domains are the most important domains that discriminate between active and

inactive groups. These findings about the importance of these two IBDQ domains are consistent with findings from previous studies about the importance of these domains in predicting longitudinal change in the quality of life of active and inactive disease groups in the IBD population.

Based on the findings of this study, we recommend that Method 2 be adopted for evaluating the relative variable importance in multivariate repeated measures data because it achieved the highest correct ranking rates among the methods investigated. However, previous research has shown that RMDA procedures may be sensitive to mis-specification of the covariance structure[20,12], which may in turn influence the rank ordering of variables. We therefore, recommend that a preliminary evaluation of mean and covariance structure fit such as log-likelihood ratio test (LRT) be conducted prior to choosing a method. For example, the LRT developed by Roy and Khattree may be used for testing whether a Kronecker product structure is a good fit for the data[12,31].

The limitations of these methods for evaluating relative variable importance in multivariate repeated measures data should be noted. Although previous research notes that dimension reduction techniques are relatively straightforward to implement, they may result in loss of information about within-variable temporal trends[32], which may influence the conclusions about the rank ordering of variables based on the DFCs of RMDA procedures. The simulation study focused on conditions in which group covariances were equal; this may not be a reasonable assumption in all data-analytic problems. In addition, complete data were generated for all measurement occasions. In this study, the SDFC, which is most commonly adopted measure of relative importance estimated from the DDA model[15], was used to rank order the variables according to their contribution to group separation. Other measures of relative importance such

as the *F*-to-remove statistic and discriminant ratio coefficients[14,25], which could also be used to evaluate importance of variables, they were not investigated in this study.

While multivariate repeated measures data are often characterized by observations with missing data, the methods described in this study assume complete data on all participants and at each measurement occasion with casewise deletion of observations due to missing data. However, casewise deletion can result in biased estimates of relative importance when the mechanism of missingness is not random[30]. This is evident in the numeric example where about 24% of the observations have missing values. Although mean imputation method was used to adjust for missing observations, there are no optimal methods to control bias in the DFC estimates. Also, multiple imputation[30, 33] might be used instead of mean imputation because the former results in more efficient estimates of the variability than the latter. However, implementing multiple imputation method for the procedures described in this study may be computationally intensive. Therefore, the choice between these imputation methods may be influenced by considerations about the trade-offs between computational burden and accuracy of parameter estimates.

In summary, this study investigates new methods to evaluate the relative importance of variables in multivariate repeated measures data. These methods are based on DFCs from RMDA procedures that assume parsimonious covariance structures. Measures of relative importance have a number of potential uses for researchers who are interested in studying the longitudinal change on multiple outcomes. They can be used to identify the set of outcomes that are most responsive to treatment interventions in longitudinal studies.

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Appendix I: Estimation of Transformed Discriminant Function Coefficients of Variable Importance Measures for Multivariate Repeated Measures Discriminant Analysis Procedures

Let $\mathbf{y}_{ij}$ be the *pq*-variate normally distributed multivariate repeated measures data corresponding to *p* repeated measurements on each of the *q* variables in the jth group ($i = 1, ..., n_j$; $j = 1, 2$; $n = n_1 + n_2$). Assume that $\mathbf{y}_{ij} \sim N_{pq}(\boldsymbol{\mu}_j, \boldsymbol{\Omega})$, where $\boldsymbol{\Omega} = \boldsymbol{\Sigma} \otimes \mathbf{V}$, $\boldsymbol{\Sigma}$ is the unstructured between variable variance-covariance matrix, $\mathbf{V}$ is the $p \times p$ positive definite compound symmetric structure among the repeated measurements. The log of the likelihood function $l = L(\boldsymbol{\mu}_{j1}, \boldsymbol{\mu}_{j2}, \boldsymbol{\Omega} | \mathbf{y}_{1j, \ldots}, \mathbf{y}_{nj}; n = n_1 + n_2)$ is

$$\log l = \frac{-np}{2}\log 2\pi - \frac{n}{2}\log|\boldsymbol{\Sigma}\otimes\mathbf{V}| - \frac{1}{2}\mathrm{tr}((\boldsymbol{\Sigma}\otimes\mathbf{V})^{-1}\sum_{j=1}^{2}(\mathbf{y}_{ij}-\boldsymbol{\mu}_j)(\mathbf{y}_{ij}-\boldsymbol{\mu}_j) \quad \text{(A-1)}$$

$$\log l = \frac{-np}{2}\log 2\pi - \frac{n}{2}\log|\boldsymbol{\Sigma}\otimes\mathbf{V}| - \frac{1}{2}\mathrm{tr}((\boldsymbol{\Sigma}\otimes\mathbf{V})^{-1}\sum_{j=1}^{2}\mathbf{W}_j + n_j(\bar{\mathbf{y}}_j-\boldsymbol{\mu}_j)(\bar{\mathbf{y}}_j-\boldsymbol{\mu}_j), \quad \text{(A-2)}$$

$$\log l = \frac{-np}{2}\log 2\pi - \frac{n}{2}\log|\boldsymbol{\Sigma}\otimes\mathbf{V}| - \frac{1}{2}\mathrm{tr}((\boldsymbol{\Sigma}^{-1}\otimes\mathbf{V}^{-1})\sum_{j=1}^{2}\mathbf{W}_j + n_j(\bar{\mathbf{y}}_j-\boldsymbol{\mu}_j)(\bar{\mathbf{y}}_j-\boldsymbol{\mu}_j) \quad \text{(A-3)}$$

where $\mathbf{W}_j = \sum_{i=1}^{n_j}(\mathbf{y}_{ij}-\bar{\mathbf{y}}_j)^{\mathrm{T}}(\mathbf{y}_{ij}-\bar{\mathbf{y}}_j)$.

The ML estimate of $\boldsymbol{\mu}_j$ is obtained by equating the first-order derivatives of equation A-3 to zero. To obtain the ML estimates of ρ, and $\boldsymbol{\Sigma}$, A-3 simplifies to

$$\log l = -\frac{npq}{2}\log 2\pi - \frac{np}{2}\log|\boldsymbol{\Sigma}| - \frac{nq}{2}\log|\mathbf{V}| - \frac{1}{2}tr(\boldsymbol{\Sigma}^{-1}\otimes\mathbf{V}^{-1})\mathbf{W}, \quad \text{(A-4)}$$

For a compound symmetric correlation matrix, $\mathbf{V}$,

$$\mathbf{V} = \sigma^2[(1-\rho)\mathbf{I}_p + \rho\mathbf{1}_p\mathbf{1}_p^{\mathrm{T}}], \quad \text{(A-5)}$$

$$|\mathbf{V}| = \sigma^{2p}[1+(p-1)\rho](1-\rho)^{p-1}, \quad \text{(A-6)}$$

and

$$\mathbf{V}^{-1} = \frac{1}{\sigma^2(1-\rho)}[\mathbf{I}_p - \frac{\rho}{1+(p-1)\rho}\mathbf{1}_p\mathbf{1}_p^{\mathrm{T}}], \tag{A-7}$$

where where ρ is the common correlation for the repeated measurements, σ^2 is repeated measures variance assumed to be constant across measurement occasions, $\mathbf{I}_p$ is the $p\times p$ identity matrix, $\mathbf{1}_p$ is a $p\times 1$ vector of ones, $\mathbf{V}$ is positive definite, and $\left(\frac{-1}{p-1}\right) < \rho < 1$. Substituting the values of $|\mathbf{V}|$ and $\mathbf{V}^{-1}$ in equations A-6 and A-7 into the log of the likelihood function (equation A-4) gives

$$\log l = -\frac{npq}{2}\log 2\pi - \frac{n(p-1)q}{2}\log(1-\rho) - \frac{nq}{2}\log\{1+(p-1)\rho\} - \frac{np}{2}\log|\mathbf{\Sigma}| - \frac{k_1}{2(1-\rho)} + \frac{\rho k_2}{2(1-\rho)\{1+(p-1)\rho\}}, \tag{A-8}$$

where $k_1 = \mathrm{tr}(\mathbf{I}_p \otimes \mathbf{\Sigma}^{-1})\mathbf{W}$, $k_2 = \mathrm{tr}(\mathbf{J}_p \otimes \mathbf{\Sigma}^{-1})\mathbf{W}$, $\mathbf{W} = \mathbf{W}_1 + \mathbf{W}_2$, and $\mathbf{J} = \mathbf{1}_p\mathbf{1}_p^{\mathrm{T}}$.

The first order derivative of equation A-8 with respect to ρ and $\mathbf{\Sigma}$ yields

$$(p-1)k_0\rho^3 - \{k_0 - (p-1)k_0 + (p-1)k_1 - (p-1)k_2\}\rho^2 + \{2(p-1)k_1 - k_0\}\rho - (k_1 - k_2), \tag{A-9}$$

and

$$\mathbf{\Sigma} - \frac{1}{np}\sum_{j=1}^{2}\sum_{i=1}^{n_j}\sum_{l=1}^{p}\sum_{m=1}^{p}\upsilon_j^{lm}(\mathbf{y}_{ijm} - \bar{\mathbf{y}}_{jm})(\mathbf{y}_{ijm} - \bar{\mathbf{y}}_{jm})^{\mathrm{T}}, \tag{A-10}$$

where $k_0 = nq(p-1)p$, $k_1 = \mathrm{tr}(\mathbf{I}_p \otimes \mathbf{\Sigma}^{-1})\mathbf{W}$, $k_2 = \mathrm{tr}(\mathbf{J}_p \otimes \mathbf{\Sigma}^{-1})\mathbf{W}$, $\mathbf{W} = \mathbf{W}_1 + \mathbf{W}_2$, $\mathbf{J} = \mathbf{1}_p\mathbf{1}_p^{\mathrm{T}}$, $\mathbf{I}_p$ is a $p\times p$ identity matrix, $\mathbf{1}_p$ is a $p\times 1$ vector of ones, and υ^{lm} is the (l,m)th element of $\mathbf{V}$. The ML estimates of ρ and $\mathbf{\Sigma}$ are obtained by equating A-9 and A-10 to zero and solving the systems of equations simultaneously.

For Method 2, $\mathbf{C} = \frac{\mathbf{1}_p}{p}$. Then the transformed DFC vector is

$$\mathbf{a}^* = (\mathbf{I}_q \otimes \mathbf{C}^{\mathrm{T}})(\boldsymbol{\Sigma}^{-1} \otimes \mathbf{V}^{-1})(\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)^{\mathrm{T}}, \tag{A-11}$$

$$\mathbf{a}^* = (\boldsymbol{\Sigma}^{-1} \otimes \mathbf{C}^{\mathrm{T}}\mathbf{V}^{-1})(\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)^{\mathrm{T}}. \tag{A-12}$$

This simplifies to

$$\mathbf{a}^* = \frac{(\boldsymbol{\Sigma}^{-1} \otimes \mathbf{C}^{\mathrm{T}})(\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)^{\mathrm{T}}}{\alpha}, \tag{A-13}$$

where

$$\alpha = \frac{1}{1 + (p-1)\rho_p}. \tag{A-14}$$

For Method 3, **C** is a $p \times 1$ vector such that the first and *p*th elements are 1 and -1, respectively, while the remaining elements are zero. Then

$$\mathbf{a}^* = \frac{(\boldsymbol{\Sigma}^{-1} \otimes \mathbf{C}^{\mathrm{T}})(\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)^{\mathrm{T}}}{\alpha}, \tag{A-15}$$

where

$$\alpha = \frac{1}{1 - \rho}. \tag{A-16}$$

Appendix II: Supplementary SAS Program Documentation

Description

This supplementary documentation contains SAS programming syntax (SAS Institute Inc., 2008) to illustrate the implementation of methods for evaluating variable importance in multivariate repeated measures data.

The documentation begins with syntax to read data from a .txt or .dat file into a file named ‘mrdata’ and a temporary SAS dataset called ‘mrmappendix’. If the data are not in a .txt or .dat file, then the syntax at the beginning of the program will change. Consult your SAS user’s manual or contact the authors if you require assistance to prepare your dataset for use.

This documentation demonstrates the SAS syntax for multivariate repeated measures data that contains three outcome variables that were measured at 3 measurement occasions. The data for first variable for the three measurement occasions are named y11, y12, and y13, respectively. The data for the second outcome variable for the three measurement occasions are named y21, y22, and y23, respectively. The data for the third outcome variable are named y31, y32, and y33, respectively. The data also contain the numeric variable grp, which is used to discriminate between the two study groups. The grp variable takes on values of 0 and 1. In this example, there are 54 observations (i.e., individuals) in group 1 and 76 observations in group 2. The group sizes must be specified in the SAS program.

The components of the program that require user input are highlighted in boldface font. The program will generate an error if there are missing data for any of the variables in the dataset.

Reference

SAS Institute Inc. (2008). *SAS/IML user's guide, version 9.2.* Cary, NC: SAS Institute Inc.

```
**Read in the data**;
filename mrmdata 'Note to users: the dataset path and filename is inserted between the single
quotation marks';
data mrmappendix;
  infile mrmdata;
  input  grp y11 y12 y13 y21 y22 y23 y31 y32 y33;
  run;
**Use the IML procedure to read the dataset and its specifications**;
proc iml;
use mrmappendix;
read all var { y11 y12 y13 y21 y22 y23 y31 y32 y33} into y;
read all var {grp} into x;
knum = 3;  lnum = 3;
dv = knum#lnum;
grpsz1 = 54; grpsz2 = 76;
c1 = {1 1 1}/3;
c2 = {1 0 -1}/3;
/*****************************************************************
Module Name: stagewiseda
Module Output:
sdfc: Standardized discrimiant function coefficients based on UNUN Procedure
rsdfc1: Variable Ranking based on sdfc1
*****************************************************************/
start  stagewise_unun(y,knum,lnum, grpsz1,grpsz2,dv,dcoef1, ddcoef1,sdfc1, rsdfc1);
```

```
one = j(dv,1, 1);  n = nrow(y);
dfs = J(n, knum,0);  adc = J(1,knum,0);
dcoef1 = J(lnum, knum, 0);  dcoef = J(lnum, knum, 0);
gp1 = y[1: grpsz1, ]; gp2 = y[(grpsz1+1):n, ];
ybar1 = gp1[+,]/grpsz1;  ybar2 = gp2[+,]/grpsz2;
ss1 = J(dv,dv,0); ss2 = J(dv,dv,0);
do i = 1 to grpsz1;
ss1 = ss1+ (gp1[i,]- ybar1)`*(gp1[i,]- ybar1);
end;
do i = 1 to grpsz2;
ss2 =  ss2+ (gp2[i,]- ybar2)`*(gp2[i,]- ybar2);
end;
sig = (ss1 +ss2)/(n-1);
/***Estimate DFCs for data on each variable (Stage 1)*****/
do m = 1 to knum;
dcoef1[,m] = inv(sig[(((m-1)*lnum)+1): (m*lnum), (((m-1)*lnum)+1): (m*lnum)])*(
(ybar1[,(((m-1)*lnum)+1): m*lnum]) - (ybar2[,(((m-1)*lnum)+1): m*lnum]))`;
adc[,m]= sqrt((dcoef1[,m])`*(sig[(((m-1)*lnum)+1): (m*lnum), (((m-1)*lnum)+1):
(m*lnum)])*dcoef1[,m]);
dcoef[,m]=(dcoef1[,m])/adc[,m];
dfs[,m] = y[,(((m-1)*lnum)+1):(m*lnum)]*dcoef[,m];
end;
/**Compute Discriminant function Scores for each variable based on DFCs in Stage 1****/
```

```
dfs1 = dfs[1:grpsz1,];  dfs2 = dfs[(grpsz1 + 1): n, ];

dfbar1 = dfs1[+,]/grpsz1;    dfbar2 = dfs2[+,]/grpsz2;

/***Estimate DFCs based on the discriminant function scores (Stage 2) *****/

dss1 = J(knum,knum,0); dss2 = j(knum,knum, 0);

do i = 1 to knum;

dss1 = dss1+ (dfs1[i,]- dfbar1)`*(dfs1[i,]- dfbar1);

dss2 =  dss2+ (dfs2[i,]- dfbar2)`*(dfs2[i,]- dfbar2);

end;

dsig = (dss1 +dss2)/(n-2);

ddcoef1 = inv(dsig)*(dfbar1 - dfbar2)`;

dadc =(ddcoef1`*(dsig)*ddcoef1);

sddcoef1 = ddcoef1/dadc;

****Compute SDFCs and Variable Ranks***;

sdfc1 = J(knum,1,0);

do k = 1 to knum;

sdfc1[k] = sddcoef1[k]*sqrt(dsig[k,k]);

end;

rsdfc1 = knum-ranktie(abs(sdfc1))+1;

finish stagewise_unun;

/*************************************************************************
```

Module Name: stagewise_uncs

Module Output:

sdfc2: Standardized discrimiant function coefficients based on UNCS Procedure

```
rsdfc2: Variable Ranking based on sdfc2
**************************************************************************/
start stagewise_uncs(y,knum, lnum,grpsz1, grpsz2, dv, ddcoef2, sdfc2, rsdfc2);
n = nrow(y);
dcoef2 = J(lnum, knum, 0);    dcoef22 = J(lnum, knum, 0);
dcoef = J(lnum, knum, 0);  dfs = J(n,knum,0);  adc2 = J(1,knum,0);
ybard = J(1,dv,0); msigm = J(dv,dv,0);  ybar = y[+,]/n;
gp1 = y[1: grpsz1, ]; gp2 = y[(grpsz1+1):n, ];
ybar1 = gp1[+,]/grpsz1;    ybar2 = gp2[+,]/grpsz2;
ss1 = J(dv,dv,0);  ss2 = J(dv,dv,0);
do i = 1 to grpsz1;
ss1 = ss1+ (gp1[i,]- ybar1)`*(gp1[i,]- ybar1);
end;
/****Estimate the ML Estimates of CS covariance parameters for Repeated Measurements on
Each Variable***/
do i = 1 to grpsz2;
ss2 =  ss2+ (gp2[i,]- ybar2)`*(gp2[i,]- ybar2);
end;
sig1 = ss1/(grpsz1-1); sig2 = ss2/(grpsz2-1);
w = (ss1 +ss2)/(n-1);
jn = J(lnum,lnum,1);
a8 = J(1,knum, 0);  a9 = J(1,knum, 0);  b8 = J(1,knum, 0);  b9 = J(1,knum, 0);
k0 = J(1,knum,0); pp = J(1,knum,0);  qq = J(1,knum,0);  rr = J(1,knum,0);  aa = J(1,knum,0); bb
```

```
= J(1,knum,0);
d = J(1,knum,0);  s1 = J(1,knum,0);  s2 = J(1,knum,0); s3= J(1,knum,0); ar = J(1,knum,0); ar1 =
J(1,knum,0);  ar2= J(1,knum,0);
mrho1= J(1,knum,0);  mrho2 = J(1,knum,0);  abr1= J(1,knum,0);
msig = J(1,knum,0);    msige = J(1,knum,0); au = J(1,knum,0);
do m = 1 to knum;
ym = y[, (((m-1)*lnum)+1): m*lnum];
ybard[,(((m-1)*lnum)+1): m*lnum]  = (ybar1[,(((m-1)*lnum)+1): m*lnum]) - (ybar2[,(((m-
1)*lnum)+1): m*lnum]);
mybar = ybar[, (((m-1)*lnum)+1): m*lnum];
w1 =  sig1[(((m-1)*lnum)+1): (m*lnum), (((m-1)*lnum)+1): (m*lnum)];
w2 = sig2[(((m-1)*lnum)+1): (m*lnum), (((m-1)*lnum)+1): (m*lnum)];
a8[,m] = trace(w1); a9[,m] = trace(w2); b8[,m] = trace(jn*w1); b9[,m] = trace(jn*w2);
mybarn = repeat(mybar,n,1);
mgp = ym - mybarn;
mgpass = mgp[##,];
msq_gp = repeat(sqrt(mgpass),n,1);
mgpa = mgp/msq_gp;
S = t(mgpa)*(mgpa);
mrho1[,m] = (s[+,+] - trace(s))/(lnum*(lnum-1));
do until(maxab< converge);
 iter = 0; converge = 0.00001;
msig[,m] = ((1 + (lnum-1)*mrho1[,m])*(a8[,m]+a9[,m]) - mrho1[,m]*(b8[,m]+b9[,m]))/
```

```
(n*lnum*(1-mrho1[,m])*(1 + (lnum-1)*mrho1[,m]));

absig = abs(msige[,m] - msig[,m]);

msige[,m] = msig[,m];

k0[,m] = n*(lnum-1)*lnum*msig[,m];

pp[,m] = -((lnum-2)*k0[,m] - ((a8[,m]+a9[,m])*(lnum-1)**2) + (b8[,m]+b9[,m])*(lnum-

1))/((lnum-1)*k0[,m]);

qq[,m] =-(k0[,m] - 2*(a8[,m]+a9[,m])*(lnum-1))/((lnum-1)*k0[,m]);

rr[,m]   = -(b8[,m]+b9[,m] - a8[,m] - a9[,m])/((lnum-1)*k0[,m]);

aa[,m] = (1/3)*(3*qq[,m]-pp[,m]**2);

bb[,m] = (1/27)*(2*pp[,m]**3 - 9*pp[,m]*qq[,m] + 27*rr[,m]);

d[,m] = (bb[,m]**2)/4 + (aa[,m]**3)/27;

if d[,m] < 0 then s1[,m] = 0;

else s1[,m] = d[,m]**0.5;

au[,m] =  -bb[,m]/2 + s1[,m];

if au[,m] < 0 then s2[,m] =0;

else s2[,m] = (au[,m])**(1/3);

ar[,m] = -bb[,m]/2 - s1[,m];

if ar[,m] < 0 then do;

ar1[,m] = -ar[,m];

ar2[,m] = ar1[,m]**(1/3);

s3[,m] = -ar2[,m];

end;

else do;
```

```
s3[,m] = ar[,m]**(1/3);
end;
mrho2[,m] = s2[,m] + s3[,m] - pp[,m]/3;
iter = iter +1;
abr1[,m] = abs(mrho1[,m] - mrho2[,m]);
mrho1[,m] = mrho2[,m];
maxab = max(absig//abr1[,m]);
end;
msigm[(((m-1)*lnum)+1): (m*lnum), (((m-1)*lnum)+1): (m*lnum)] = (msig[,m])*( (1-
mrho2[,m])*i(lnum) + mrho2[,m]*jn);
end;
***Compute the DFCs and Discriminant Function Scores for Each Variable (Stage 1);
do m = 1 to knum;
dcoef2[,m]  = inv(msigm[(((m-1)*lnum)+1): (m*lnum), (((m-1)*lnum)+1):
(m*lnum)])*(ybard[,(((m-1)*lnum)+1): m*lnum])`;
adc2[,m]= sqrt((dcoef2[,m])`*(msigm[(((m-1)*lnum)+1): (m*lnum), (((m-1)*lnum)+1):
(m*lnum)])*dcoef2[,m]);
dcoef22[,m]=(dcoef2[,m])/adc2[,m];
dfs[,m] = y[,(((m-1)*lnum)+1):(m*lnum)]*dcoef2[,m];
end;
dfs1 = dfs[1:grpsz1,];
dfs2 = dfs[(grpsz1 + 1): n, ];
dfbar1 = dfs1[+,]/grpsz1;
```

```
dfbar2 = dfs2[+,]/grpsz2;
/***Estimate DFCs based on the discriminant function scores (Stage 2)*/
dss1 = J(knum,knum,0); dss2 = j(knum,knum, 0);
do i = 1 to knum;
dss1 = dss1+ (dfs1[i,]- dfbar1)`*(dfs1[i,]- dfbar1);
dss2 =  dss2+ (dfs2[i,]- dfbar2)`*(dfs2[i,]- dfbar2);
end;
dsig = (dss1 +dss2)/(n-1);
ddcoef2 = inv(dsig)*(dfbar1 - dfbar2)`;
dadcd = (ddcoef2`*(dsig)*ddcoef2);
ddcoef2_t = ddcoef2/dadcd;
****Compute SDFCs and Variable Ranks***;
sdfc2 = J(knum,1,0);
do k = 1 to knum;
sdfc2[k] = ddcoef2_t[k]*sqrt(dsig[k,k]);
end;
rsdfc2 = knum-ranktie(abs(sdfc2))+1;
finish stagewise_uncs;
/*************************************************************************
Module Name: stagewise_unar
Module Output:
sdfc3: Standardized discrimiant function coefficients based on UNAR Procedure
rsdfc3: Variable Ranking based on sdfc3
```

```
**************************************************************************/
start stagewise_unar(y,knum, lnum,grpsz1, grpsz2, dv,ddcoef3, sdfc3, rsdfc3);
n = nrow(y); dcoef3 = J(lnum, knum, 0);
dcoef33 = J(lnum, knum, 0);  dfs = J(n,knum,0);
adc3 = J(1,knum,0); ybard = J(1,dv,0); msigm = J(dv,dv,0); ybar = y[+,]/n;
gp1 = y[1: grpsz1, ]; gp2 = y[(grpsz1+1):n, ];
ybar1 = gp1[+,]/grpsz1; ybar2 = gp2[+,]/grpsz2;
ss1 = J(dv,dv,0); ss2 = J(dv,dv,0);
/****Estimate the ML Estimates of CS covariance parameters for Repeated Measurements on
Each Variable***/
do i = 1 to grpsz1;
ss1 = ss1+ (gp1[i,]- ybar1)`*(gp1[i,]- ybar1);
end;
do i = 1 to grpsz2;
ss2 =  ss2+ (gp2[i,]- ybar2)`*(gp2[i,]- ybar2);
end;
sig1 = ss1/(grpsz1-1); sig2 = ss2/(grpsz2-1);
ws = (ss1 + ss2);
gama1 = J(1, knum, 0); jn = J(lnum,lnum,1);
beta1 = J(1, knum, 0);   a1 = J(1,knum, 0);    a9 = J(1,knum, 0);
b8 = J(1,knum, 0);  b9 = J(1,knum, 0);
k0 = J(1,knum,0); pp = J(1,knum,0);  qq = J(1,knum,0);  rr = J(1,knum,0);  aa = J(1,knum,0); bb
= J(1,knum,0);
```

```
d = J(1,knum,0);  s1 = J(1,knum,0);  s2 = J(1,knum,0); s3= J(1,knum,0); ar = J(1,knum,0); ar1 =
J(1,knum,0);  ar2= J(1,knum,0);
mrho1= J(1,knum,0);  mrho2 = J(1,knum,0);  abr1= J(1,knum,0);
msig = J(1,knum,0);    msige = J(1,knum,0); au = J(1,knum,0);
do m = 1 to knum;
ym = y[, (((m-1)*lnum)+1): m*lnum];
ybard[,(((m-1)*lnum)+1): m*lnum]  = (ybar1[,(((m-1)*lnum)+1): m*lnum]) - (ybar2[,(((m-
1)*lnum)+1): m*lnum]);
mybar = ybar[, (((m-1)*lnum)+1): m*lnum];
w = ws[((m-1)*lnum+1) : m*lnum,  ((m-1)*lnum+1) : m*lnum];
a1[,m] = trace(w);
beta1[,m] = trace(w) - w[1,1] - w[lnum,lnum];
do i = 1 to lnum-1;
gama1[,m] = gama1[,m] + w[i,i+1];
end;
mybarn = repeat(mybar,n,1);
mgp = ym - mybarn;
mgpass = mgp[##,];
msq_gp = repeat(sqrt(mgpass),n,1);
mgpa = mgp/msq_gp;
s = t(mgpa)*(mgpa);
mrho1[,m] = (s[+,+] - trace(s))/(lnum*(lnum-1));
do until (maxab< converge);
```

```
iter = 0; converge = 0.000001;
msig[,m] = (beta1[,m]*mrho1[,m]**2  - (2*gama1[,m]*mrho1[,m]) + a1[,m])/(n*lnum*(1-
mrho1[,m]**2));
msige[,m] = msig[,m];
absig = abs(msige[,m] - msig[,m]);
pp[,m] = -(gama1[,m]) /(n*(lnum-1)*msig[,m]);
qq[,m] =-(n*(lnum-1)*msig[,m] - (a1[,m]+beta1[,m]))/(n*(lnum-1)*msig[,m]);
rr[,m]  = -(gama1[,m])/(n*(lnum-1)*msig[,m]);
aa[,m] = (1/3)*(3*qq[,m]-pp[,m]**2);
bb[,m] = (1/27)*(2*pp[,m]**3 - 9*pp[,m]*qq[,m] + 27*rr[,m]);
d[,m] = (bb[,m]**2)/4 + (aa[,m]**3)/27;
if d[,m] < 0 then s1[,m] = 0;
else s1[,m] = d[,m]**0.5;
au[,m] =  -bb[,m]/2 + s1[,m];
if au[,m] < 0 then s2[,m] =0;
else s2[,m] = (au[,m])**(1/3);
ar[,m] = -bb[,m]/2 - s1[,m];
if ar[,m] < 0 then do;
ar1[,m] = -ar[,m];
ar2[,m] = ar1[,m]**(1/3);
s3[,m] = -ar2[,m];
end;
else do;
```

```
s3[,m] = ar[,m]**(1/3);
end;
mrho2[,m] = s2[,m] + s3[,m] - pp[,m]/3;
iter = iter +1;
abr1[,m] = abs(mrho1[,m] - mrho2[,m]);
mrho1[,m] = mrho2[,m];
maxab = max(absig//abr1[,m]);
end;
v = J(lnum, lnum, 0);
do i = 1 to lnum;
do j = 1 to lnum;
v[I,J] =  msig[,m]*mrho2[,m]**(abs(i-j));
end;end;
msigm[(((m-1)*lnum)+1): (m*lnum), (((m-1)*lnum)+1): (m*lnum)] =  v;
end;
***Compute the DFCs and Discriminant Function Scores for Each Variable (Stage 1);
do m = 1 to knum;
dcoef3[,m]  = inv(msigm[(((m-1)*lnum)+1): (m*lnum), (((m-1)*lnum)+1):
(m*lnum)])*(ybard[,(((m-1)*lnum)+1): m*lnum])`;
adc3[,m]= sqrt((dcoef3[,m])`*(msigm[(((m-1)*lnum)+1): (m*lnum), (((m-1)*lnum)+1):
(m*lnum)])*dcoef3[,m]);
dcoef33[,m]=(dcoef3[,m])/adc3[,m];
dfs[,m] = y[,(((m-1)*lnum)+1):(m*lnum)]*dcoef3[,m];
```

```
end;
dfs1 = dfs[1:grpsz1,];  dfs2 = dfs[(grpsz1 + 1): n, ];
dfbar1 = dfs1[+,]/grpsz1;  dfbar2 = dfs2[+,]/grpsz2;
/**Compute Discriminant function Scores for each variable based on DFCs in Stage 1*/
dss1 = J(knum,knum,0);  dss2 = j(knum,knum, 0);
do i = 1 to knum;
dss1 = dss1+ (dfs1[i,]- dfbar1)`*(dfs1[i,]- dfbar1);
dss2 =  dss2+ (dfs2[i,]- dfbar2)`*(dfs2[i,]- dfbar2);
end;
dsig = (dss1 +dss2)/(n-1);
ddcoef3 = inv(dsig)*(dfbar1 - dfbar2)`;
dadcd3 = (ddcoef3`*(dsig)*ddcoef3);
ddcoef3 = ddcoef3/dadcd3;
****Compute SDFCs and Variable Ranks***;
sdfc3 = J(knum,1,0);
do k = 1 to knum;
sdfc3[k] = ddcoef3[k]*sqrt(dsig[k,k]);
end;
rsdfc3 = knum-ranktie(abs(sdfc3))+1;
finish stagewise_unar;

/*************************************************************************
Module Name: mrmda
```

Module Output:

sdfc4: Standardized discrimiant function coefficients for Method 2

rsdfc4: Variable Ranking based on sdfc4

sdfc5: Standardized discrimiant function coefficients for Method 3

rsdfc5: Variable Ranking based on sdfc4

**********/

```
start mrmda (y, knum, lnum, grpsz1, grpsz2, dv, c1, c2, tdcoef, sdfc4, sdfc5,rsdfc4, rsdfc5);
n = nrow(y);
mdcoef = J(dv, 1, 0);
one = J(lnum,1,1);
ybar = y[+,]/n;
gp1 = y[1: grpsz1, ]; gp2 = y[(grpsz1+1):n, ];
ybar1 = gp1[+,]/grpsz1;
ybar2 = gp2[+,]/grpsz2;
w = J(dv,dv,0);
/***ML Estimation of Kronecker product covariance parameters (i.e, V and Sigma)*/
do i = 1 to n;
w = w + (y[i,]- ybar)`*(y[i,]- ybar);
end;
mya = J(n,dv,0);
do i =1 to n;
mya[i,] = y[i,] - ybar;
end;
```

```
yass=mya[##, ];
sq_assm= repeat(sqrt(yass),n,1);
yan=mya/sq_assm;
v0=t(yan)*yan;
vi = J(knum, knum, 0);
do k = 1 to lnum;
vi = vi + v0[((k-1)*knum+1): k*knum, ((k-1)*knum+1): k*knum];
end;
vi=vi/knum;
rest= (vi[+,+]-trace(vi))/(lnum*(lnum-1));
ve=(1-rest) *I(lnum) + rest#(one*t(one));
 jj = I(lnum); v = J(lnum,lnum,0);
tau = I(lnum) @ I(knum);
/* Calculating the mle's mlv and mlsig of V and Sigma.*/
mlsige=j(knum,knum,0); iter=0; converge = 0.001;
do until (maxab<converge);
ive=inv(ve);
 do l = 1 to lnum;
 do m = 1 to lnum;
 v[l,m] = t(jj[,l])*ive*jj[,m];
 end;end;
sigma_e=j(knum,knum,0);
subba = J(n,dv, 0);
```

```
subb = J(n, dv, 0);
do i = 1 to n;
subba[i, ]= y[i,] - ybar;
end;
do k = 1 to lnum;
subb[,((k-1)*knum)+1 : k*knum] = t(tau[((k-1)*knum)+1 : k*knum, ]* t(subba));
end;
do l = 1 to lnum;
do m = 1 to lnum;
sigma_e = sigma_e + v[l, m]*(t(subb[,((m-1)*knum)+1 : m*knum])* subb[, ((l-1)*knum)+1 :
l*knum]);
end; end;
mlsig=sigma_e/(n*lnum);
absig=abs(trace(mlsige-mlsig));
mlsige=mlsig;
imlsig=inv(mlsig);
k3=trace((I(lnum)@imlsig)*w);
k4=trace(((one*t(one))@imlsig)*w);
s=lnum-1; ko=n*knum*s*lnum;
pp=(ko-s*ko+(k3*s**2)-s*k4)/(s*ko); qq=(2*s*k3-ko)/(s*ko); rr=(k3-k4)/(s*ko);
aa=(1/3)*(3*qq-pp**2); bb=(1/27)*(2*pp**3 -9*pp*qq + 27*rr);
discrim=(abs(bb)**2)/4+(abs(aa)**3)/27;
if discrim > 0 then do;
```

```
s1 = (discrim)**0.5;
end;
else do;
s1 =0;
end;
sn = -bb/2+ s1;
if sn > 0 then do;
s2=(sn)**(1/3);
end;
else do;
s2 = (abs(sn))**(1/3);
end;
ar=-(bb/2)- s1;
if ar <0 then
do;
ar1=-ar; ar2=ar1**(1/3); s3=-ar2;
end;
else
do;
s3=ar**(1/3);
end;
ro2=abs(s2+s3-(pp/3));
mlv=(1-ro2)*I(lnum)+ro2*one*t(one);
```

```
ve=mlv;
iter=iter+1;
abr1=abs(rest-ro2);
rest=ro2;
maxab=max(absig//abr1);
end;
omega = mlsig @ ve;
****Compute overall DFCs and its linear transformation based on c1 and c2**;
mdcoef = inv(omega) *(ybar1 - ybar2)`;
madc = sqrt(abs(mdcoef`*omega*mdcoef));
mdcoef = mdcoef/madc;
m1 = i(knum)@c1;
m2 = i(knum)@c2;

tdcoef1 = m1*mdcoef;
tdcoef2 = m2*mdcoef;
tomega1 = m1*omega*m1`;
tomega2 = m2*omega*m2`;
****Compute transformed SDFCs and Variable Rankings***;
sdfc4 = J(knum,1,0);
do k = 1 to knum;
sdfc4[k] = tdcoef1[k]*sqrt(abs(tomega1[k,k]));
end;
```

```
rsdfc4 = knum-ranktie(abs(sdfc4))+1;
sdfc5 = J(knum,1,0);
do k = 1 to knum;
sdfc5[k] = tdcoef2[k]*sqrt((tomega2[k,k]));
end;
rsdfc5 = knum-ranktie(abs(sdfc5))+1;
finish mrmda;
call stagewise_unun(y,knum,lnum, grpsz1,grpsz2,DV,dcoef1,ddcoef1, sdfc1, rsdfc1);
call stagewise_uncs(y,knum, lnum,grpsz1, grpsz2, dv, ddcoef2, sdfc2,rsdfc2);
call stagewise_unar(y,knum, lnum,grpsz1, grpsz2, dv, ddcoef3, sdfc3, rsdfc3);
call mrmda (y, knum, lnum, grpsz1, grpsz2, dv, c1, c2, tdcoef, sdfc4, sdfc5,rsdfc4, rsdfc5);
Print 'Vector of SDFC for stagewise RMDA-UNUN procedure (Method 1) ;' sdfc1[format =8.2];
Print 'Vector of Variable Rank DFCs for SDFCs based on Stagewise RMDA(Method 1) ;'
rsdfc1[format =8.2];
Print 'Vector of SDFCs for stagewise RMDA procedure based on UNCS procedure(Method 1) ;'
sdfc2[format =8.2];
Print 'Vector of Variable Rank DFCs for SDFCs derived from Stagewise RMDA-UNCS
procedure(Method 1)  ;' rsdfc2[format =8.2];
Print 'Vector of SDFCs for stagewise RMDA-UNAR procedure(Method 1);' sdfc3[format =8.2];
Print 'Vector of Variable Rank DFCs based on SDFCs of Stagewise RMDA-UNAR
procedure(Method 1);' rsdfc3[format =8.2];
Print 'Vector of SDFCs for transformed SDFCs of RMDA procedure that assume Kronecker
product covariance (Method 2);' sdfc4[format =8.2];
```

```
Print 'Vector of Variable Ranks for transformed SDFCs of RMDA procedure that assume
Kronecker product covariance (Method 2);' rsdfc4[format =8.2];
Print 'Vector of SDFCs for transformed SDFCs of RMDA procedure that assume Kronecker
product covariance (Method 3);' sdfc5[format =8.2];
Print 'Vector of Variable Ranks for transformed SDFCs of RMDA procedure that assume
Kronecker product covariance (Method 3);' rsdfc5[format =8.2];
quit;
```

Chapter 9. Discussion and Conclusions

Abbreviations

CT = Coordinatewise trimming

DA = Discriminant analysis

DDA = Descriptive discriminant analysis

DFC = Discriminant function coefficient

HRQOL = Health-related quality of life

IBD = Inflammatory bowel disease

IBDQ = Inflammatory Bowel Disease Questionnaire

LR = Logistic regression

MAR = Missing at random

MNAR = Missing not at random

ML = Maximum likelihood

MSE = Mean square error

RMDA = Repeated measures discriminant analysis

RMSE = Root mean square error

SDFC = Standardized discriminant function coefficient

9.1 Summary

The objectives of this research were to develop descriptive discriminant analysis (DDA) procedures based on parsimonious covariance structures that are also insensitive to non-normality in repeated measures data and to develop techniques based on repeated measures DDA procedures for evaluating the relative importance of variables that discriminate between groups in multivariate repeated measures data.

Repeated measures discriminant analysis (RMDA) procedures that assume parsimonious covariance structures (and possibly even parsimonious mean structures) have been developed based on growth curve, mixed-effects, and covariance structure models[1] for classifying observations in univariate and multivariate repeated measures data. As Huberty and Wisenbaker[2] note, discriminant analysis (DA) procedures can also be used to identify the relative importance of variables for discriminating between groups. There has been little, if any research on the topic of DDA for repeated measures data.

This dissertation begins by investigating RMDA procedures based on covariance structure models for describing group separation in univariate repeated measures data. The bias and error in the discriminant function coefficients (DFCs) of RMDA procedures that assume parsimonious covariance structures were investigated under a variety of data-analytic conditions using Monte Carlo methods. Bias in the DFCs was influenced by mis-specification of the covariance structure of the data. The magnitude of bias due to mis-specification was largest under normally distributed data, but it was attenuated for multivariate non-normal data. As expected, mean square error (MSE) was smallest for all procedures when the covariance was correctly specified and largest when it was mis-specified. The effect of mis-specification on the errors of the DFCs was attenuated when the data were multivariate non-normal. Parsimony of the

covariance structure resulted in smaller error but larger bias in the DFCs estimates. The DFCs of the linear DA procedure that assumes unstructured covariances was less biased but also less efficient.

Robust RMDA procedures that are insensitive to departures from the assumption of multivariate normality were developed for describing group separation in non-normal data. These robust RMDA procedures were developed based on coordinatewise trimming (CT) of the repeated measures data and applying maximum likelihood (ML) estimators to the trimmed data. The CT approach was adopted because of its computational simplicity and good theoretical properties that have been demonstrated in previous research for multivariate data. The DFCs of these procedures were less biased than the DFCs of the RMDA procedures based on ML estimators for untrimmed data. The impact of mis-specification of the covariance structure on bias in the DFCs of robust RMDA procedures was smaller than for RMDA procedures based on ML estimators when the data were sampled from non-normal distributions.

The root mean square error (RMSE) of the estimated DFCs was influenced by the population distribution, covariance structure, and mean structure. The DFCs of robust RMDA procedures that did not place any restrictions on the group means were more efficient (i.e., smaller RMSE) than the DFCs of the corresponding procedures based on ML estimators when the population covariance structure was mis-specified. Error in the DFCs increased as the magnitude of the correlation among the repeated measurements.

New measures of relative importance based on DFCs from RMDA procedures were developed for identifying the variables that discriminate between groups in multivariate repeated measures data. These new measures are the standardized discriminant function coefficients (SDFCs) based on a stage-wise RMDA procedure and linear transformations of the DFCs of a

multivariate RMDA procedure that assumes a Kronecker product covariance covariance structure. Statistical derivations about the equivalence of variable ranks for based on SDFCs obtained from linear transformation of the DFCs of the RMDA procedures and variable ranks based on SDFCs obtained from linear transformations of the variables were provided. A comparison of these methods using Monte Carlo techniques suggests that SDFCs based on the average of within-variable DFCs of a RMDA procedure with a Kronecker product covariance structure resulted in the highest proportion of correctly ranked variables among the investigated procedures. However, the proportion of correctly ranked variables was sensitive to data-analytic characteristics, including the magnitude of separation between the group means, the structure and magnitude of correlation among the outcomes, and the number of study variables. This finding was also demonstrated in the numeric example, where there were disimilarities in the rank order of inflammatory bowel disease (IBDQ) domains from different relative importance measures.

9.2 Discussion

Mis-specification of the covariance structure for DA procedures results in reduced classification accuracy[3-4]. The current research has shown that covariance mis-specification can also result in increased bias and error in the DFCs of RMDA procedures. While conventional RMDA procedures are sensitive to departures from a multivariate normal distribution, the proposed robust RMDA procedures resulted in reduced bias and error in non-normal distributions. The DFCs of RMDA procedures based on coordinatewise trimming (CT) of the non-normal data were less biased and more efficient than those of RMDA procedures based on ML estimators under strong departures from multivariate normal distribution. For moderately skewed and or heavy-tailed distribution, the DFCs of the former procedures were similar to those of the latter procedures. However, it is important to note that there were no disadvantages

associated with using robust RMDA procedures when the data were normally distributed. These findings are consistent with previous research showing that trimmed means and Winsorized estimators perform equally well under normally distributed data and small sample sizes[5]. Thus, robust RMDA procedures should be routinely used because they can offer distinct advantages when the data demonstrate significant departures from multivariate normality.

Our findings about bias and error in the DFCs of RMDA procedures that assume parsimonious covariance structures are consistent with previous research findings[6-7]. Adopting a DA procedure based on a simplified covariance structure will substantially reduce the number of parameters to estimate, but bias in the parameter estimates can sometimes be large and will increase as the degree of deviance between the model and the data increases. A researcher's choice of a DA procedure for repeated measures data is dependent, in part, on the trade-off between parsimony and bias and/or error in the DFCs when describing differences between groups.

Data characteristics such as the magnitude of separation between group means and magnitude and pattern of correlation among the variables influenced the proposed methods for evaluating variable importance in multivariate repeated measures data. These results corroborate previous findings about the sensitivity of measures of relative importance to a variety of data analytic conditions[8-9]. However, a mis-specification of the within-variable correlation structure did not have a large influence on the ability of the proposed methods to correctly rank order the variables according to their contributions to group separation in multivariate repeated measures data. This might be attributed to the fact that the proposed methods adopt dimension reduction techniques to summarize within-variable measurements on each variable. Previous research has shown that while dimension reduction techniques are straightforward to implement, they may

result in some loss of information about the temporal trends in the data[10].

Data from the Manitoba Inflammatory Bowel Disease (IBD) Cohort Study[11] were used to illustrate the application of robust RMDA procedures for describing group separation (Chapter 6). It was also used to illustrate the application of methods for evaluating the relative importance of variables in multivariate repeated measures data (Chapter 8). The choice of this dataset for the numeric examples was motivated by its characteristics, namely (a) moderate to strong correlations among the domains, (b) high-dimensional data for multiple domains and measurement occasions, and (c) moderate to extreme departures from multivariate normality assumptions. Through the numeric examples, software to implement the procedures was presented. This detailed information on the application of the proposed procedures can benefit applied statisticians as well as clinicians who will implement the proposed methods in their own research. Our analysis suggests that the IBD Questionnaire (IBDQ) bowel symptoms and emotional health domains were the most important domains that discriminated between active and inactive disease groups within the first two years of the study. These findings are consistent with previous research based on data collected at study baseline[12].

9.3 Research Strengths and Limitations

This research has a number of strengths. The robust RMDA procedures developed in this study are based on CT of the repeated measures data, which is straightforward to implement. This estimation method, which replaces the conventional mean and covariance with trimmed means and Winsorized covariances, possesses good theoretical properties in both skewed and heavy-tailed distributions[13]. Another advantage of this robust estimation approach is that observations considered to be “outliers” with respect to some coordinates are not completely eliminated from the sample, which preserves information on the non-outlying coordinates[15].

To evaluate the relative importance of variables in multivariate repeated measures data, DFCs from the RMDA procedures were used in combination with dimension reduction techniques to rank variables according to their contribution to group separation. These proposed methods for evaluating relative importance of variables in multivariate repeated measures data are intuitively appealing, easy to implement, and are advantageous when the sample size is small relative to the data dimension[10]. In addition, the methods described in this study were also found to be less sensitive to mis-specification of the covariance structure for multivariate repeated measures data.

However, the limitations of this research should be noted. An assumption that underlies the methods investigated in this research is homogeneity of group covariances. This assumption may not always be satisfied in clinical studies in which there is more variability in the treatment group than the control group[16]. Previous research has shown that the conventional DA procedure based on least squares estimators is less sensitive to heterogeneity of group covariances when the data are normally distributed and more sensitive to heterogeneity in non-normal distributions[17]. Quadractic DA procedures that allow for heterogeneity in group covariances have been developed for repeated measures data, but their emphasis is on prediction and not description. The impact of group covariance heterogeneity on the ranking accuracy of the investigated procedures is not known for multivariate non-normal data.

The investigated RMDA procedures assume complete data on all observations and across repeated measurements, with casewise deletion of observations occurring when there is missing data. However, casewise deletion may result in biased estimates of DFCs when the mechanism of missingness is not random[18] and loss of statistical power due to smaller sample size.

The DFCs of RMDA procedures can be used to evaluate the importance of

variables/measurement occasions in discriminating between groups. However, sample statistics cannot be generalized to the population. Inferential methods for DFCs and the corresponding ranks have been proposed and could also be applied to repeated measures data. For example, Huberty and Wisenbaker[2] adopted bootstrap methods to test whether DFCs are significantly different from zero. A recent paper on statistical inference for relative importance measures was proposed by our research group, but was beyond the scope of this dissertation[19].

The conclusion that one variable is more important than another variable can only be applied to the set of variables under investigation. Therefore, changing the mix of variables included in a study could change a researcher's conclusions about variable importance[2]. Finally, variable selection techniques were not applied to the data prior to conducting DDA[20-21]. It is assumed that the set of variables are determined a *priori* and selected based on theoretical considerations. This is a reasonable approach in the analysis of multi-dimensional HRQOL data, where researchers are unlikely to have a plan to exclude some domains from the analysis.

9.4 Future Research

This research study have focused on the development of repeated measures DDA procedures and their application in evaluating variable importance in multivariate repeated measures data. Topics for future investigations in this topic area are numerous. These include the development of robust RMDA procedures for evaluating variable importance in multivariate repeated measures data characterized by non-normal distributions, non-ignorable missing data, and/or measurement error. As well, statistical inference about variable importance measures also represents an area for further exploration.

While robust RMDA procedures have been developed based on the CT estimation method for repeated measures data, further research could investigate high breakdown robust

estimators for describing group separation in multivariate repeated measures data, including minimum covariance determinant estimators and trimmed likelihood estimation methods[22-23], which have been proposed for developing robust maximum likelihood estimators of means and covariances. Unlike the CT estimation which independently trims the data on each measurement occasion separately, these highbreakdwon estimators are advantageous because they account for both within-variable and between-variable correlations among the variable in developing robust estimators of means and covariances[24, 25].

An assumption underlying the methods in the dissertation is that the outcome variables are measured without error. However, this assumption may not be tenable in longitudinal health-related quality of life (HRQOL) studies where proxy measurements may be obtained for study participants who are unable to self-report their quality of life. Previous research has shown that the presence of measurement error in variables may influence the classification accuracy of the DA classification rule and result in incorrect rank ordering of the variables that discriminate between groups[26]. One method to address measurement error in discriminant analysis models is the moment reconstruction method, a form of regression calibration for logistic regression[27]. However, there is limited investigation about methods for correcting measurement error in continuous variables when adopting RMDA procedures.

The methods used to evaluate the relative importance of variables in multivariate repeated measures data rests on the assumption of multivariate normality. The sensitivity of these procedures to multivariate non-normal repeated measures data has not been investigated. Although robust RMDA procedures based on CT have been proposed in this study, the extension of these procedures to multivariate repeated measures data has not been investigated. Such procedures are particularly relevant for evaluating variable importance in non-normal

multivariate repeated measures data. Further research will investigate whether the CT approach is unbiased and efficient when each repeated measurement on each variable is trimmed separately and then a linear combination of the observations is created. The application of this robust procedure for evaluating the relative importance of variables in multivariate non-normal repeated measures data will also be investigated.

In two-group repeated measures studies there is only one statistically significant discriminant function. However, for multi-group designs, more than one statistically significant discriminant function may exist; consequently the assessment of variable importance may not be straightforward. Huberty and Wisenbaker[2] proposed using a weighted linear combination of the DFCs on each variable to evaluate variable importance in multi-group designs. Further research is needed to develop this approach for constructing relative importance measures in multi-group repeated measures data.

The RMDA procedures developed in this study do not accommodate missing observations. Previous research has investigated RMDA procedures based on multiple imputation methods and mixed-effects models when the data are characterized by missing observations[20]. The RMDA procedure based on the mixed-effects model, which classifies observations into groups based on their subject-specific means and covariances[28-30], have been shown to result in better classification accuracy than the conventional DA procedure based on multiply imputed data, when the missing data are assumed to be missing at random (MAR). RMDA procedures based on mixed-effects models can also accommodate unbalanced repeated measures data and MAR observations. However, there no current research on RMDA procedures that can accommodate missing not at random (MNAR) pattern of missingness (i.e., non-ignorable missing data) in multivariate repeated measures data. While pattern-mixture[31] and

selection[32] models approaches have been proposed to address non-ignorable missing data in multivariate repeated measures data, RMDA procedures based on these statistical techniques have not been developed.

Inferential techniques for DFCs were not investigated in this study. Tests of statistical significance for DFCs include parametric tests based on asymptotic *F*- or *t*-distributions[33-34]. Resampling-based methods have also been developed. Moreover, statistical inference about a variable's importance or changes in the importance of a variable over time has received little attention in the literature. Future research could investigate inferential methods of variable importance in both univariate and multivariate repeated measures data.

9.5 Conclusions and Recommendations

This study investigated RMDA procedures based on parsimonious covariance structures that are insensitive to non-normal repeated measures data and investigated their potential use for evaluating the relative importance of variables in multivariate repeated measures data. Although robust DA procedures have been proposed for classifying observations into groups when data are non-normal[35-36], this is the first study to develop robust RMDA procedures that assume parsimonious covariance structures for non-normal repeated measures data. The DFC estimates of RMDA procedures proposed in this study were found to be influenced by a number of data characteristics including population distribution, the magnitude of separation between group means, mean configuration, number of outcome variables, and the magnitude of correlation among the repeated measurements/variables. Similarly, the proposed methods for evaluating variable importance in multivariate repeated measures data were also influenced by these characteristics.

Choosing a procedure for discriminant analysis of repeated measures data should be

guided by careful consideration of: (a) study design features such as total sample size and number of variables/repeated measurements, (b) distributional shape, and (c) data characteristics such as correlation structure, mean structure, and correlations.

The relationship between the sample size and number of variables and/or repeated measurements will determine whether a discriminant analysis procedure with a simplified covariance structure should be selected. While it is possible to conduct statistical tests of departures from the assumptions of normality[37-38], these tests are sensitive to sample size[38]. Instead, descriptive measures of skewness and kurtosis should be used to select a procedure. Preliminary assessment of the mean and covariance structures of the data can be conducted. While graphical exploratory analysis may be used to identify the mean structure, statistical tests of model fit such as likelihood ratio tests, or penalized log-likelihood measures like the Akaike information criterion[40] may be adopted to guide the specification of both the mean and covariance structures.

For applied researchers, descriptive discriminant analysis methods can be used instead of multiple tests of significance to identify the measurement occasions/variable on which group differences might exist. Software and documentation to support its use by applied researchers is provided to facilitate uptake of these methods.

In summary, this study developed DDA procedures with parsimonious covariance structures and based on robust estimators for describing group separation in repeated measures data. Methods for evaluating the relative importance of variables that discriminate between groups in multivariate repeated measures data were also developed. This study contributes to the statistical literature on methods for analyzing high-dimensional multivariate repeated measures data. The proposed procedures have a number of uses for researchers who conduct longitudinal

studies about HRQOL; they can be used to assign weights to the domains when using a multiple testing procedure to control the overall probability of a Type I error in multivariate repeated measures data. Also, they can be used to identify the domains that are most responsive to change over time, in order to develop additional questions about these domains in future studies.

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