THE UNIVERSITY OF TEXAS AT SAN ANTONIO, COLLEGE OF BUSINESS

Working Paper SERIES

February 17, 2008

Wp# 0037MSS-253-2008

Testing of a Structured Covariance Matrix for Three-level Repeated Measures Data

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Abstract

This paper considers the problem of estimating, and testing for, a Kronecker product covariance structure of three-level (multiple time points (p), multiple sites (u), and multiple response variables (q)) multivariate data. Testing of such covariance structures is potentially important when not enough samples are available to estimate the unstructured variance-covariance matrix. This hypothesis testing procedure not only can test the hypothesis on three-level multivariate data, but also can test the hypotheses on two-level multivariate data as special cases. We provide the maximum likelihood estimates of the unknown population parameters. The test is implemented with a real data set.

AMS 2000 subject classification: Primary 62H15; Secondary 62H12.

Key words: Kronecker product covariance structure, maximum likelihood estimates, equicorrelated partitioned matrix, three-level multivariate data.

JEL Code: C30

1 Introduction

In this article we develop a likelihood ratio test for a Kronecker product covariance structure for three-level multivariate data, where more than one response variable is measured on each experimental unit on more than one site at several time points (spatial). It is very common in clinical trial study to collect measurements on more than one response variable at different body positions (sites) repeatedly over time.

Consider an example of clinical trial study of a clinical evaluation for a bone densitometry study where bone mineral density (BMD) were obtained from each patient on each femoral (right and left femoral, $u = 2$). Two BMD measurements ($q = 2$) were taken, one in the femoral neck and the other one in the trochanter region. These four measurements were observed over a period of two years ($p = 2$). Consider another example, also from a clinical trial study, where researchers measure levels of fat byproducts at different parts of the body repeatedly over time. These kinds of data we name as three-level multivariate data or triply multivariate data. Different time points as well as different sites may have different measurement variations for the variables, and we must take these variations into account while analyzing these kinds of data. Several authors (Boik, 1991; Chaganty and Naik, 2002; Galecki, 1994; Naik and Rao, 2001; Roy and Khattree, 2003, 2005 a,b; Roy, 2006 a, b; Shults and Morrow, 2002) have observed many advantages of using Kronecker product structure or separable covariance structure over the usual unstructured variance-covariance matrix for analyzing doubly multivariate data. Shults, Whitt and Kumanyika (2004) and Roy and Leiva (2006) used Kronecker product structure while analyzing triply multivariate data or three-level multivariate data. Shults et al. (2004) used Kronecker product structure in the framework of generalized estimating equations, while Roy and Leiva (2006) used the Kronecker product structure in developing classification rules for three-level multivariate data. The main advantage of using Kronecker product structured variance-covariance matrix over the unstructured one is that the number of unknown parameters declines substantially; thus helps us in analyzing data in a small sample set-up in expensive clinical trials such as alzheimer disease, parkinson decease and AIDS. However, one needs to be very careful with the assumption of Kronecker product structured variance-covariance matrix, especially for three-level multivariate data, as incorrect assumption may result in invalid conclusion. Thus, testing of the validity of the Kronecker product structure is crucial before using it for any statistical analysis.

This article deals with the hypothesis testing of a Kronecker product structured variance-covariance matrix for three-level multivariate data. Hypotheses testing problems on doubly multivariate data using Kronecker product structure have recently been studied by many authors (Lu and Zimmerman, 2005; Roy and Khattree, 2003, 2005 b, c; Roy, 2006 c). Regrettably, none of them gave a solution for hypothesis testing problem on three-level or three-factor multivariate data. Very recently Roy and Leiva (2007) have studied the hypotheses testing problems on Kronecker product covariance structures for triply multivariate data by assuming an autoregressive of order one $\big(\text{AR}(1)\big)$ as well as a compound symmetry (CS) correlation structure on repeated measurements over time. However, pattern on the repeated measurements sometimes may not be of direct interest, or the covariance matrix does not follow one of these standard structures. In this case one needs to work with the unstructured variance-covariance matrix on repeated measurements over time instead of a restricted AR(1) or CS structure. By unstructured variance-covariance matrix we mean the mean vectors and the variances and covariances are arbitrary, in contrast to the structured one. Lu and Zimmerman (2005) recommended an extension of the separability of two-factor case $\mathbf{\Sigma}_1 \otimes \mathbf{\Sigma}_2$ to three-factor case as $\mathbf{\Sigma}_1 \otimes \mathbf{\Sigma}_2 \otimes \mathbf{\Sigma}_3$, where $\mathbf{\Sigma}_i,\ i = 1, 2, 3$ are three unstructured variance-covariance (positive definite) matrices for three levels. In this paper we alternatively propose a covariance structure $\mathbf{\Omega}$ (defined in (1.1)) for three-factor or three-level multivariate data, which is also an extension of $\mathbf{\Sigma}_1 \otimes \mathbf{\Sigma}_2$, and at the same time more parsimonious than that of the extension suggested by Lu and Zimmerman for $u > q$. Furthermore, our new covariance structure $\mathbf{\Omega}$ not only is an extension of Lu and Zimmerman (2005) and Roy and Khattree's (2003) separable covariance structures, where both the components of the Kronecker product have unstructured variance-covariance matrix, but also is an extension of Roy and Khattree's (2005 c) separable covariance structure where one of its components has a CS structure (explained in Section 3). Thus, our new covariance structure can be perceived as a more general extension to three-level multivariate data. We will discuss later in this section some of the interesting interpretations of this new covariance structure $\mathbf{\Omega}$. In this paper we propose a likelihood ratio test for testing this new covariance structure where repeated measurements over time has unstructured covariance matrix by using an "equicorrelated (partitioned) matrix" (Leiva, 2007) on the measurement vector over sites. This parsimonious covariance sytucture is very relevant in the context of many statistical analyses, especially in discriminant analysis, when not enough samples are available to estimate the unstructured variance-covariance matrix.

Let $\boldsymbol{y}_{r,ts}$ be a q-variate vector of measurements on the r^{th} individual at the s^{th} site (location) and at the t^{th} time point; $r = 1, \ldots, n$, $s = 1, \ldots, u$, $t = 1, \ldots, p$. Let $\boldsymbol{y}_{r,t}$ be the uq-variate vector of all measurements corresponding to the r^{th} individual at the t^{th} time point, that is, for each r, and t, $\boldsymbol{y}_{r,t}$ is obtained by stacking all q responses of the r^{th} individual at the t^{th} time point at the first site (location), then stacking all its q responses at the second site and so on. Let $\boldsymbol{y}_r = (\boldsymbol{y}'_{r,1}, \boldsymbol{y}'_{r,2}, \ldots, \boldsymbol{y}'_{r,p})'$ be the puq-variate vector of all measurements corresponding to the r^{th} individual. Finally, let $\boldsymbol{Y} = [\boldsymbol{y}_1, \boldsymbol{y}_2, \ldots, \boldsymbol{y}_n]$ be random samples of size n from population $N_{puq}(\boldsymbol{\mu}, \mathbf{\Omega})$, where $\boldsymbol{\mu} \in \mathbb{R}^{puq}$ and $\mathbf{\Omega}$ is assumed to be a $puq \times puq-$dimensional positive definite matrix. Thus, the number of unknown parameters to be estimated is $puq(puq + 1)/2$; which can increase very rapidly with the increase of the dimension of any of the factors. So, researchers typically rely on structured covariance matrix which depends on a smaller set of unknown parameters. The problem, though, is knowing what the structure is. A form of covariance structure $\mathbf{\Omega}$ suitable for three-level multivariate data can be assumed as

$$\underset{puq\times puq}{\mathbf{\Omega}} = \underset{p\times p}{\boldsymbol{V}} \otimes \underset{uq\times uq}{\mathbf{\Gamma}}, \tag{1.1}$$

where $\boldsymbol{V}$ is an unstructured variance covariance matrix, and $\mathbf{\Gamma}$ is an equicorrelated (partitioned) variance covariance matrix of the form

$$\mathbf{\Gamma} = \mathbf{I}_u \otimes (\mathbf{\Sigma}_0 - \mathbf{\Sigma}_1) + \mathbf{J}_u \otimes \mathbf{\Sigma}_1, \tag{1.2}$$

where $\mathbf{I}_u$ is the $u \times u$ identity matrix, $\mathbf{1}_u$ is the $u \times 1$ vector containing all elements as unity, $\mathbf{J}_u = \mathbf{1}_u \mathbf{1}_u'$ and $\otimes$ represents the Kronecker product. $\mathbf{\Sigma}_0$ is a positive definite symmetric unstructured $q \times q$ matrix, and $\mathbf{\Sigma}_1$ is a symmetric $q \times q$ matrix. The matrix $\mathbf{\Gamma}$ is called equicorrelated partitioned matrix with equicorrelation matrices $\mathbf{\Sigma}_0$ and $\mathbf{\Sigma}_1$. The $q \times q$ block diagonals $\mathbf{\Sigma}_0$ represents the variance-covariance matrix of the q response variables at any given site and at any given time point, whereas the $q \times q$ block off diagonals $\mathbf{\Sigma}_1$ represents the covariance matrix of the q response variables between any two site pairs and at any given time point. We assume $\mathbf{\Sigma}_0$ is constant for all sites and time points. Also, $\mathbf{\Sigma}_1$ is the same for all site pairs and for all time points. The $p \times p$ matrix $\boldsymbol{V}$ is the variance-covariance matrix of the repeated measurements over time on a given response variable and at any given site, and is assumed to be same for all response variables and for all sites. We assume $\boldsymbol{V}$ as positive definite and symmetric.

Now, what are the merits of this new covariance structure (1.1) over the unstructured variance-covariance matrix? First of all, if the number of subjects n is not greater than the number of repeated measurements puq, the estimate of the variance-covariance matrix $\mathbf{\Omega}$ becomes a singular one. If the number of subjects $n \geq puq$, but relatively small, the estimate of $\mathbf{\Omega}$ becomes unstable. Moreover, if the dimension of $\mathbf{\Omega}$ is large, the estimation becomes computationally demanding. To avoid all these problems, one may model $\mathbf{\Omega}$ as (1.1). This matrix has only $\frac{p(p+1)}{2} + q(q+1) - 1$ unknown parameters, which is much less than $\frac{puq(puq+1)}{2}$. The apparent advantage of this model (1.1) is that the number of parameters to be estimated is greatly reduced, and thus the statistical analysis can be accomplished in a small sample set-up. Furthermore, if the covariance structure (1.1) is the correct one and the unstructured covariance matrix is used, the estimates will be most awful.

The number of unknown parameters in model (1.1) is $\frac{p(p+1)}{2} + q(q+1) - 1$, whereas the number of unknown parameters under three-factor separability is $\frac{p(p+1)}{2} + \frac{q(q+1)}{2} + \frac{u(u+1)}{2} - 2$. Thus, if u is greater than q, the model (1.1) is more parsimonious than the three-factor separability model, the extension suggested by Lu and Zimmerman (2005). Therefore, the model (1.1) not only is a more general extension to three-level multivariate data, but also is more parsimonious if u is greater than q.

2 Matrix Results

It is known form Lemma 4.3 of Ritter and Gallegos (2002), and Leiva (2007) that a $uq \times uq$ matrix of the form

$$\mathbf{\Gamma} = \mathbf{I}_u \otimes (\mathbf{\Sigma}_0 - \mathbf{\Sigma}_1) + \mathbf{J}_u \otimes \mathbf{\Sigma}_1,$$

is non singular, if both $\mathbf{\Sigma}_0 - \mathbf{\Sigma}_1$ and $\mathbf{\Sigma}_0 + (u-1)\mathbf{\Sigma}_1$ are non singular matrices. Then the inverse of $\mathbf{\Gamma}$ is given by

$$\mathbf{\Gamma}^{-1} = \mathbf{I}_u \otimes (\mathbf{\Sigma}_0 - \mathbf{\Sigma}_1)^{-1} + \mathbf{J}_u \otimes \frac{1}{u}\left[(\mathbf{\Sigma}_0 + (u-1)\mathbf{\Sigma}_1)^{-1} - (\mathbf{\Sigma}_0 - \mathbf{\Sigma}_1)^{-1}\right].$$

That is, $\mathbf{\Gamma}^{-1}$ also has the form

$$\mathbf{\Gamma}^{-1} = \mathbf{I}_u \otimes \boldsymbol{H} + \mathbf{J}_u \otimes \boldsymbol{K}, \tag{2.3}$$

where

$$\boldsymbol{H} = (\mathbf{\Sigma}_0 - \mathbf{\Sigma}_1)^{-1},$$

and

$$\boldsymbol{K} = \frac{1}{u}\left[(\mathbf{\Sigma}_0 + (u-1)\mathbf{\Sigma}_1)^{-1} - (\mathbf{\Sigma}_0 - \mathbf{\Sigma}_1)^{-1}\right].$$

This result generalizes the one given by Bartlett (1951) for the case $q = 1$. The determinant of $\mathbf{\Gamma}$ is given by

$$|\mathbf{\Gamma}| = |\mathbf{\Sigma}_0 - \mathbf{\Sigma}_1|^{u-1} |\mathbf{\Sigma}_0 + (u-1)\mathbf{\Sigma}_1|. \tag{2.4}$$

3 The Hypothesis and the likelihood ratio test

We consider the likelihood ratio test for the following general hypothesis testing (a) for three-level multivariate data, where $\mathbf{\Gamma}$ is an $uq \times uq$ equicorrelated (partitioned) variance-covariance matrix as defined in (1.2). We assume that $n > puq$.

$$(a) \qquad H_1 : \mathbf{\Omega} = \boldsymbol{V} \otimes \mathbf{\Gamma},\ \boldsymbol{V} \text{ unstructured} \quad \text{vs.} \quad K_1 : \mathbf{\Omega} \text{ unstructured}.$$

In particular, when $q = 1$, the data reduces to doubly multivariate data and the hypothesis (a) reduces to

$$(b) \qquad H_2 : \mathbf{\Omega} = \boldsymbol{V} \otimes \mathbf{\Delta},\ \boldsymbol{V} \text{ unstructured} \quad \text{vs.} \quad K_2 : \mathbf{\Omega} \text{ unstructured},$$

where $\boldsymbol{\Delta}$ is a $u \times u$ CS variance-covariance matrix. This hypothesis tests the separability of the variance-covariance matrix of doubly multivariate data with structured correlation (CS) in one multivariate level. Thus, the data corresponding to any given time point are equicorrelated across sites, i.e., spatially equicorrelated. This kind of situation may occur when repeated measurements are made at different parts of the body. For example the measurements in both the eyes, or the measurements in both the kidneys, or the measurements of fat byproducts at different parts of the body. This hypothesis is discussed in detail in Roy and Khattree (2005 c).
Likewise, when $u = 1$, the data reduces to doubly multivariate data too and the hypothesis (a) reduces to

$$(c) \qquad H_3 : \boldsymbol{\Omega} = \boldsymbol{V} \otimes \boldsymbol{\Sigma}_0,\ \boldsymbol{V} \text{ unstructured} \quad \text{vs.} \quad K_3 : \boldsymbol{\Omega} \text{ unstructured},$$

where $\boldsymbol{\Sigma}_0$ is a $q \times q$ positive definite unstructured variance-covariance matrix as defined earlier. This hypothesis (c) tests the separability of the variance covariance matrix of doubly multivariate data with unstructured variance-covariance matrices in both the multivariate levels. This hypothesis is discussed by Roy and Khattree in 2003, and by Lu and Zimmerman in detail in 2005. Thus, we see that the model (1.1) is a natural extension to three-level multivariate data from two-level multivariate data. In this article we discuss the general hypothesis (a) which is implemented with a real data set.

We obtain a likelihood based test procedure for testing the Kronecker product covariance structure as defined in (1.1) over the unstructured variance covariance matrix $\boldsymbol{\Omega}$. The likelihood ratio $\Lambda = \frac{\max_{H_1} L}{\max_{K_1} L}$, or a function of it, is used as the test statistic to test the null hypothesis H_1. It is well known that for large sample size and under normality assumption, $-2\ln\Lambda$ is approximately distributed as χ^2_ν under H_1. The degrees of freedom ν is equal to the number of parameters estimated under K_1 minus the number estimated under H_1.

Let a random sample of size n, $\boldsymbol{Y} = [\boldsymbol{y}_1, \boldsymbol{y}_2, \ldots, \boldsymbol{y}_n]$ be drawn from $N_{puq}(\boldsymbol{\mu}, \boldsymbol{\Omega})$. The log likelihood function $\ln L(\boldsymbol{\mu}, \boldsymbol{V}, \boldsymbol{\Gamma}; \boldsymbol{Y})$ under H_1 is given by

$$\begin{aligned} \ln L(\boldsymbol{\mu}, \boldsymbol{V}, \boldsymbol{\Gamma}; \boldsymbol{Y}) \;=\; & -\frac{npuq}{2}\ln(2\pi) - \frac{n}{2}\ln|\boldsymbol{V}\otimes\boldsymbol{\Gamma}| - \frac{1}{2}\mathrm{tr}\,(\boldsymbol{V}\otimes\boldsymbol{\Gamma})^{-1}\boldsymbol{S} \\ & -\frac{n}{2}\mathrm{tr}\,(\boldsymbol{V}\otimes\boldsymbol{\Gamma})^{-1}(\overline{\boldsymbol{y}}-\boldsymbol{\mu})(\overline{\boldsymbol{y}}-\boldsymbol{\mu})', \end{aligned}$$

where

$$\boldsymbol{S} = \sum_{r=1}^{n}(\boldsymbol{y}_r - \overline{\boldsymbol{y}})(\boldsymbol{y}_r - \overline{\boldsymbol{y}})', \tag{3.5}$$

and $\overline{\boldsymbol{y}} = \frac{1}{n}\sum_{i=1}^{n}\boldsymbol{y}_i$. For arbitrary values of $\boldsymbol{V}$ and $\boldsymbol{\Gamma}$, the maximum of $\ln L(\boldsymbol{\mu}, \boldsymbol{V}, \boldsymbol{\Gamma}; \boldsymbol{Y})$

is attained when $\boldsymbol{\mu} = \overline{\boldsymbol{y}}$. Therefore, the MLE of $\boldsymbol{\mu}$ is

$$\widehat{\boldsymbol{\mu}} = \overline{\boldsymbol{y}}. \tag{3.6}$$

Consequently, by replacing $\boldsymbol{\mu}$ by $\widehat{\boldsymbol{\mu}}$ the log likelihood function reduces to

$$\ln L(\widehat{\boldsymbol{\mu}}, \boldsymbol{V}, \boldsymbol{\Gamma}; \boldsymbol{Y}) = -\frac{npuq}{2}\ln(2\pi) - \frac{n}{2}\ln\left(|\boldsymbol{V}|^{uq}\,|\boldsymbol{\Gamma}|^{p}\right) - \frac{1}{2}\mathrm{tr}\left(\boldsymbol{V}^{-1}\otimes\boldsymbol{\Gamma}^{-1}\right)\boldsymbol{S}. \tag{3.7}$$

Using (2.3) and (2.4) an alternative expression for $\ln L$ is given by

$$\begin{aligned}\ln L(\widehat{\boldsymbol{\mu}}, \boldsymbol{V}, \boldsymbol{\Gamma}; \boldsymbol{Y}) \;=\; & -\frac{npuq}{2}\ln(2\pi) - \frac{nuq}{2}\ln|\boldsymbol{V}| - \frac{np\,(u-1)}{2}\ln|\boldsymbol{\Sigma}_0 - \boldsymbol{\Sigma}_1| \\ & -\frac{np}{2}\ln|\boldsymbol{\Sigma}_0 + (u-1)\,\boldsymbol{\Sigma}_1| \\ & -\frac{1}{2}\sum_{r=1}^{n}\sum_{m=1}^{p}\sum_{l=1}^{p}\sum_{s=1}^{u} v^{lm}\left(\boldsymbol{y}_{r,ls} - \overline{\boldsymbol{y}}_{ls}\right)'\boldsymbol{H}\left(\boldsymbol{y}_{r,ms} - \overline{\boldsymbol{y}}_{ms}\right) \\ & -\frac{1}{2}\sum_{r=1}^{n}\sum_{m=1}^{p}\sum_{l=1}^{p}\sum_{s=1}^{u}\sum_{s^*=1}^{u} v^{lm}\left(\boldsymbol{y}_{r,ls} - \overline{\boldsymbol{y}}_{ls}\right)'\boldsymbol{K}\left(\boldsymbol{y}_{r,ms^*} - \overline{\boldsymbol{y}}_{ls^*}\right),\end{aligned}$$

where v^{lm} represents the $(l, m)^{\text{th}}$ element of $\boldsymbol{V}^{-1}$. This can also be written as

$$\begin{aligned}\ln L \;=\; & -\frac{npuq}{2}\ln(2\pi) - \frac{nuq}{2}\ln|\boldsymbol{V}| - \frac{np\,(u-1)}{2}\ln\left|\boldsymbol{H}^{-1}\right| - \frac{np}{2}\ln\left|\boldsymbol{M}^{-1}\right| \\ & -\frac{1}{2}\mathrm{tr}\boldsymbol{H}\boldsymbol{B}_1 - \frac{1}{2}\mathrm{tr}\boldsymbol{K}\boldsymbol{B}_2,\end{aligned} \tag{3.8}$$

where

$$\begin{aligned}\boldsymbol{H}^{-1} &= \boldsymbol{\Sigma}_0 - \boldsymbol{\Sigma}_1, \\ \boldsymbol{M}^{-1} &= \boldsymbol{\Sigma}_0 + (u-1)\,\boldsymbol{\Sigma}_1, \\ \boldsymbol{B}_1 &= \sum_{r=1}^{n}\sum_{m=1}^{p}\sum_{l=1}^{p}\sum_{s=1}^{u} v^{lm}\left(\boldsymbol{y}_{r,ls} - \overline{\boldsymbol{y}}_{ls}\right)\left(\boldsymbol{y}_{r,ms} - \overline{\boldsymbol{y}}_{ms}\right)', \\ \text{and } \boldsymbol{B}_2 &= \sum_{r=1}^{n}\sum_{m=1}^{p}\sum_{l=1}^{p}\sum_{s=1}^{u}\sum_{s^*=1}^{u} v^{lm}\left(\boldsymbol{y}_{r,ls} - \overline{\boldsymbol{y}}_{ls}\right)\left(\boldsymbol{y}_{r,ms^*} - \overline{\boldsymbol{y}}_{ms^*}\right)'.\end{aligned}$$

Using (3.8) we get

$$\begin{aligned}\ln L \;=\; & -\frac{npuq}{2}\ln(2\pi) - \frac{nuq}{2}\ln|\boldsymbol{V}| - \frac{np\,(u-1)}{2}\ln\left|\boldsymbol{H}^{-1}\right| - \frac{np}{2}\ln\left|\boldsymbol{M}^{-1}\right| \\ & -\frac{1}{2}\mathrm{tr}\boldsymbol{H}\left(\boldsymbol{B}_1 - \frac{1}{u}\boldsymbol{B}_2\right) - \frac{1}{2}\mathrm{tr}\boldsymbol{M}\frac{1}{u}\boldsymbol{B}_2.\end{aligned}$$

Differentiating the above equation with respect to $\boldsymbol{H}^{-1}$ and $\boldsymbol{M}^{-1}$ separately, and then equating them to zero we get

$$\widehat{\boldsymbol{H}^{-1}} = \frac{1}{np\,(u-1)}\left(\boldsymbol{B}_1 - \frac{1}{u}\boldsymbol{B}_2\right),$$

and

$$\widehat{\boldsymbol{M}^{-1}} = \frac{1}{npu}\boldsymbol{B}_2.$$

Therefore

$$\widehat{\boldsymbol{H}} = (\widehat{\boldsymbol{H}^{-1}})^{-1}, \tag{3.9}$$

and

$$\widehat{\boldsymbol{K}} = \frac{1}{u}\left(\widehat{\boldsymbol{M}} - \widehat{\boldsymbol{H}}\right). \tag{3.10}$$

After some simplifications for each $\boldsymbol{V}$ we get

$$\widehat{\boldsymbol{\Sigma}}_0 = \frac{1}{npu}\boldsymbol{B}_1, \tag{3.11}$$

and

$$\widehat{\boldsymbol{\Sigma}}_1 = \frac{1}{npu\,(u-1)}\left(\boldsymbol{B}_2 - \boldsymbol{B}_1\right). \tag{3.12}$$

From (3.7) we get

$$\ln L(\widehat{\boldsymbol{\mu}}, \boldsymbol{V}, \boldsymbol{\Gamma}; \boldsymbol{Y}) = -\frac{npuq}{2}\ln(2\pi) - \frac{nuq}{2}\ln(|\boldsymbol{V}|) - \frac{np}{2}\ln(|\boldsymbol{\Gamma}|) - \frac{1}{2}\mathrm{tr}\left(\boldsymbol{V}^{-1}\otimes\boldsymbol{\Gamma}^{-1}\right)\boldsymbol{S}.$$

Substituting the value of $\boldsymbol{\Gamma}^{-1}$ from (2.3) we get

$$\begin{aligned}\ln L(\widehat{\boldsymbol{\mu}}, \boldsymbol{V}, \boldsymbol{\Gamma}; \boldsymbol{Y}) = &-\frac{npuq}{2}\ln(2\pi) - \frac{nuq}{2}\ln(|\boldsymbol{V}| - \frac{np}{2}\ln(|\boldsymbol{\Gamma}|)\\ &-\frac{1}{2}\mathrm{tr}\left(\boldsymbol{V}^{-1}\otimes\mathbf{I}_u\otimes\boldsymbol{H}\right)\boldsymbol{S} - \frac{1}{2}\mathrm{tr}\left(\boldsymbol{V}^{-1}\otimes\mathbf{J}_u\otimes\boldsymbol{K}\right)\boldsymbol{S}.\end{aligned}$$

After some simplifications we get

$$\ln L(\widehat{\boldsymbol{\mu}}, \boldsymbol{V}, \boldsymbol{\Gamma}; \boldsymbol{Y}) = -\frac{npuq}{2}\ln(2\pi) + \frac{nuq}{2}\ln\left|\boldsymbol{V^{-1}}\right| - \frac{np}{2}\ln(|\boldsymbol{\Gamma}|) - \frac{1}{2}\mathrm{tr}\left(\boldsymbol{V}^{-1}(\boldsymbol{A}+\boldsymbol{B})\right),$$

where the $(l,m)^{\text{th}}$ element of the matrix $\boldsymbol{A}$ is given by

$$a_{lm} = \sum_{r=1}^{n}\sum_{s=1}^{u}(\boldsymbol{y}_{r,ls} - \overline{\boldsymbol{y}}_{ls})'\boldsymbol{H}(\boldsymbol{y}_{r,ms} - \overline{\boldsymbol{y}}_{ms}), \quad \text{for} \quad l,m = 1,\ldots,p,$$

and the $(l,m)^{\text{th}}$ element of the matrix $\boldsymbol{B}$ is given by

$$b_{lm} = \sum_{r=1}^{n}\sum_{s=1}^{u}\sum_{s^\star=1}^{u}(\boldsymbol{y}_{r,ls} - \overline{\boldsymbol{y}}_{ls})'\boldsymbol{K}(\boldsymbol{y}_{r,ms^\star} - \overline{\boldsymbol{y}}_{ms^\star}), \quad \text{for} \quad l,m = 1,\ldots,p.$$

Differentiating the above log likelihood function with respect to $\boldsymbol{V}^{-1}$ and equating it to zero we get

$$\widehat{\boldsymbol{V}} = \frac{1}{nuq}\left(\boldsymbol{A}+\boldsymbol{B}\right). \tag{3.13}$$

Note that $\widehat{\boldsymbol{V}}$ depends on $\boldsymbol{\Gamma}$ through $\boldsymbol{H}$ and $\boldsymbol{K}$, and that the maximum value of $\ln L(\widehat{\boldsymbol{\mu}}, \widehat{\boldsymbol{V}}, \boldsymbol{\Gamma}; \boldsymbol{Y})$ also depends on $\boldsymbol{\Gamma}$. The maximum likelihood estimates $\widehat{\boldsymbol{\Sigma}}_0$, $\widehat{\boldsymbol{\Sigma}}_1$ and $\widehat{\boldsymbol{V}}$ are obtained by simultaneously and iteratively solving (3.11), (3.12) and (3.13). The computations can be carried out by the algorithm presented below. The MLE of $\boldsymbol{\Gamma}$ is obtained as

$$\widehat{\boldsymbol{\Gamma}} = \mathbf{I}_u \otimes \left(\widehat{\boldsymbol{\Sigma}}_0 - \widehat{\boldsymbol{\Sigma}}_1\right) + \mathbf{J}_u \otimes \widehat{\boldsymbol{\Sigma}}_1. \tag{3.14}$$

Therefore, the maximum of log likelihood function under H_1 is given by

$$\max_{H_1} L(\boldsymbol{\mu}, \boldsymbol{V}, \boldsymbol{\Gamma}; \boldsymbol{Y}) = (2\pi)^{-\frac{npuq}{2}} |\widehat{\boldsymbol{V}}|^{-\frac{uqn}{2}} |\widehat{\boldsymbol{\Gamma}}|^{-\frac{pn}{2}} e^{-\frac{1}{2}\mathrm{tr}(\widehat{\boldsymbol{V}} \otimes \widehat{\boldsymbol{\Gamma}})^{-1}\boldsymbol{S}}.$$

The maximum of log likelihood function under K_1 is straight forward and is given by

$$\max_{K_1} L(\boldsymbol{\mu}, \boldsymbol{\Omega}; \boldsymbol{Y}) = (2\pi)^{-\frac{npuq}{2}} |\boldsymbol{S}|^{-\frac{n}{2}} n^{\frac{npuq}{2}} e^{-\frac{npuq}{2}},$$

where $\boldsymbol{S}$ has been defined before in (3.5). Therefore, the likelihood ratio is given by

$$\Lambda = \frac{\max_{H_1} L}{\max_{K_1} L} = \frac{|\widehat{\boldsymbol{V}}|^{-\frac{uqn}{2}} |\widehat{\boldsymbol{\Gamma}}|^{-\frac{pn}{2}} e^{-\frac{1}{2}\mathrm{tr}(\widehat{\boldsymbol{V}} \otimes \widehat{\boldsymbol{\Gamma}})^{-1}\boldsymbol{S}}}{|\boldsymbol{S}|^{-\frac{n}{2}} n^{\frac{npuq}{2}} e^{-\frac{npuq}{2}}}.$$

The associated degrees of freedom ν for the null distribution of $-2\ln\Lambda$ is given by,

$$\nu = \frac{puq(puq+1)}{2} - \frac{p(p+1)}{2} - q(q+1) + 1.$$

This is because, without loss of generality $\boldsymbol{V} \otimes \boldsymbol{\Gamma}$ can be constraint to $v_{11} = 1$, where v_{11} is the first diagonal element of $\boldsymbol{V}$.

4 An example

In this section we demonstrate the proposed hypothesis testing (a) procedure with a real data set. The data is given by Fernando Saraví, MD, PhD, at the Nuclear Medicine School, Mendoza, Argentina. Twelve patients ($n = 12$) were chosen for a bone densitometry study. Bone mineral density (BMD) were obtained by a technique known as dual X-ray absorptiometry (DXA) using a GE Lunar Prodigy machine. The measurements were obtained from the hip region. In each femoral (right and left femoral, $u = 2$) two BMD measurements ($q = 2$) were taken, one at the femoral neck and the other one at the trochanter region. These four measurements were observed over a period of two years ($p = 2$). We find that the covariance structure of the two measurements at femoral neck and trochanter region at two sites over the period of two years is $\boldsymbol{V} \otimes \boldsymbol{\Gamma}$ with $p-$value $= 0.1352$. The test statistic value $-2\ln\Lambda$ is 36.2954 with 28 degrees of freedom. The maximum likelihood estimate of $\boldsymbol{V}$ is

$$\widehat{\boldsymbol{V}} = \begin{bmatrix} 1 & 0.9196 \\ 0.9196 & 1.0755 \end{bmatrix}.$$

We see that the variance of the BMD measurements both at the femoral neck and the trochanter region at the 2^{nd} year is slightly higher than the variance at the 1^{st} year, and this is true for both the sites. The maximum likelihood estimate of $\boldsymbol{\Gamma}$ is

$$\widehat{\boldsymbol{\Gamma}} = \begin{bmatrix} 0.0057 & 0.0045 & 0.0029 & 0.0036 \\ 0.0045 & 0.0072 & 0.0036 & 0.0060 \\ 0.0029 & 0.0036 & 0.0057 & 0.0045 \\ 0.0036 & 0.0060 & 0.0045 & 0.0072 \end{bmatrix}.$$

This shows that the variance of the BMD measurements at the trochanter region is slightly higher than the variance of the same at the femoral neck. Also, the covariance of the BMD measurements in each femoral at the trochanter region is higher than the covariance of the same in each femoral at the femoral neck.

5 Concluding Remarks

In this article, we study the hypothesis testing of a Kronecker product structured covariance matrix for three-level multivariate data. This covariance structure is very important for statistical analysis, in particular for high dimensional data, where computation of the unstructured variance covariance matrix is practically impossible. The proposed methodology can readily be generalized to more than three levels.

Acknowledgement

The first author thanks the College of Business at the University of Texas at San Antonio for the summer research grant.

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