jmcm: An R Package for Joint Mean-Covariance Modelling of Longitudinal Data

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Abstract

Longitudinal studies commonly arise in various fields such as psychology, social science, economics and medical research, etc. It is of great importance to understand the dynamics in the mean function, covariance and/or correlation matrices of repeated measurements. However, high-dimensionality (HD) and positive-definiteness (PD) constraints are two major stumbling blocks in modelling of covariance and correlation matrices. It is evident that Cholesky-type decomposition based methods are effective in dealing with HD and PD problems, but those methods were not implemented in statistical software yet, causing a difficulty for practitioners to use. In this paper, we first introduce recently developed Cholesky decomposition based methods for joint modelling of mean and covariance structures, namely modified Cholesky decomposition (MCD), alternative Cholesky decomposition (ACD) and hyperspherical parameterization of Cholesky factor (HPC). We then introduce our newly developed R package **jmcm** which is currently able to handle longitudinal data that follows a Gaussian distribution using the MCD, ACD and HPC methods. Demonstration is provided by running the package **jmcm** and comparison of those methods is made through analysing two real data sets.

Keywords: Cholesky decomposition, covariance matrix estimator, longitudinal data, joint mean-covariance models.

1. Introduction

A longitudinal study usually involves repeated observations of the same variables over a long period of time and is often used in psychology, sociology and medical research. The covariance matrix plays a prominent role in analysing data from longitudinal studies since the components of collected measurements within the same subject are not independent. A good covariance modelling approach improves statistical inference of the mean of interest and the covariance structure itself may be of scientific interest in some circumstances (Diggle and Verbyla 1998).

However, modelling of covariance structure is challenging because the estimated covariance matrices in general should be positive definite and there are many parameters in covariance matrices. To overcome these two obstacles, Pourahmadi (1999) advocated a data-driven joint mean-covariance modelling method based on a modified Cholesky decomposition (MCD) of the marginal within-subject covariance matrix. The decomposition leads to a reparameterization where entries can be interpreted in terms of innovation variances and autoregressive coefficients. See Pan and Mackenzie (2003) for a related discussion. Another Cholesky-type

decomposition (ACD) proposed by Chen and Dunson (2003) can be understood as modelling certain innovation variances and moving average parameters, and the method is compared with MCD in details by Pourahmadi (2007). These two Cholesky-type approaches demonstrate parsimonious and effective strategies, but their corresponding variance functions cannot be directly interpreted as those of the repeated observations. Therefore additional efforts are needed for interpreting the variance and covariance functions. More recently, Zhang, Leng, and Tang (2015) considered a regression approach based on the standard Cholesky decomposition of the correlation matrix and the hyperspherical parameterization (HPC) of its Cholesky factor, of which parameters are directly interpretable with respect to variance and correlation. A brief review of these approaches is presented in the following sections. Note this paper is not an exhaustive survey, and many other covariance structure modelling methods are also commonly used in the literature, see Fan, Liao, and Liu (2016) for a more general overview on the estimation of large covariance and precision matrices.

Software for analysis of longitudinal data by some conventional approaches has been implemented in R (R Core Team 2015) environment for many years. For instance, several packages provide functions for determining maximum likelihood estimates of the parameters in linear mixed-effect model (LMM) that incorporates both fixed effects and random effects in the linear predictor, such as the `lme` function in package **nlme** (Pinheiro, Bates, DebRoy, Sarkar, and R Core Team 2015) and the `lmer` function in package **lme4** (Bates, Mächler, Bolker, and Walker 2015). Similar commercial statistical programs are also available for LMM such as `PROC MIXED` in SAS (SAS Institute Inc. 2013), `MIXED` in SPSS (SPSS Inc. 2015) and `fitlme` in MATLAB (The MathWorks Inc. 2015). The method of generalized estimating equation (GEE) (Liang and Zeger 1986) is widely used as it focuses on models for the mean of the correlated observations without fully specifying the joint distribution of the responses. Several implementations of GEE are available through package **gee** (Carey, Lumley, and Ripley 2015) and **geepack** (Halekoh, Højsgaard, and Yan 2006). Gaussian copula model provides a flexible general framework for marginal regression analysis of continuous, discrete and categorical responses, and is available through package **gcmr** (Masarotto, Varin *et al.* 2012). However all of these procedures are based on specific model assumptions like existence of an expectation or homogeneous variances and are not intuitive for a joint mean-covariance modelling framework. In this paper we focus on the joint mean-covariance modelling for both balanced and unbalanced longitudinal data, and we present a user friendly R package **jmcm** (freely available from CRAN at `http://CRAN.R-project.org/package=jmcm`) that can be used to handle such joint models. For efficiency, the core part of package **jmcm** is implemented in compiled C++ code using **Rcpp** (Eddelbuettel and François 2011; Eddelbuettel 2013) and **RcppArmadillo** (Eddelbuettel and Sanderson 2014) for numerical linear algebra. All the implemented R functions are well documented with some examples. The main objective of this paper is to introduce the joint mean-covariance modelling approaches in package **jmcm** to a wide audiences of statisticians and practitioners who need to analyze longitudinal data.

The rest of the paper is organized as follows. In Section 2 we present the joint mean-covariance modelling methods, and discuss different choices for modelling strategies of covariance structure mentioned above. Furthermore, we consider the maximum likelihood estimations for each type of the models, with particular emphasize on numerical optimization techniques. Section 3 provides detailed implementation of the methods introduced in Section 2 using the package **jmcm** and gives a brief illustration of the computational tools and Section 4 concludes the paper with further discussions.

2. Joint mean-covariance modelling framework

2.1. Joint mean-covariance models

Denote longitudinal measurements by $y_i = (y_{i1}, y_{i2}, \cdots, y_{im_i})^\top$ $(i = 1, 2, \cdots, n)$ that are collected from n subjects and measured at times points $t_i = (t_{i1}, t_{i2}, \cdots, t_{im_i})^\top$. Here we assume the number of measurements m_i and time t_i are subject specific, so that unbalanced longitudinal data sets with observations taken at irregular time points can be modelled.

The basic linear model used in joint mean-covariance modelling frame work of longitudinal data analysis can be described by the distribution of a vector-valued random response variable y_i, which is assumed to be multivariate normal,

$$y_i \sim N_{m_i}(\mu_i, \Sigma_i)$$

where $\mu_i = (\mu_{i1}, \mu_{i2}, \cdots, \mu_{im_i})^\top$ is an $m_i \times 1$ vector and Σ_i is an $m_i \times m_i$ within-subject covariance matrix. The mean μ_i of y_i is usually modelled by a linear regression,

$$\mu_i = X_i\beta \tag{1}$$

where X_i denotes an $m_i \times (p+1)$ model matrix with an intercept on the first column followed by covariates of the ith subject, β is a $(p+1) \times 1$ regression coefficient vector. The subject-specific within-subject covariance matrix, Σ_i, may be modelled similarly based on different decomposition approaches, and will be discussed in detail in the following sections.

Estimates of the joint mean-covariance model parameters θ, including $\theta_1 = \beta$ in the mean model and other unspecified parameters θ_2 in the covariance matrices, can be obtained by Maximum Likelihood (ML estimation). In particular, a maximum likelihood estimator (MLE) of the unknown parameter vector is defined as any solution $\hat{\theta}_n$ of:

$$\hat{\theta}_n = arg \min_{\theta \in \Theta} \{-2l(\theta)\} \tag{2}$$

where

$$-2l(\theta) = \sum_{i=1}^{n} \log|\Sigma_i| + \sum_{i=1}^{n} (y_i - \mu_i(\theta_1))^\top \Sigma_i^{-1}(\theta_2)(y_i - \mu_i(\theta_1)) \tag{3}$$

is the minus twice of the log-likelihood function without the constant term. Note that it is the form of the log-likelihood function that is implemented by default in the package, though value of the full log-likelihood including the constant term can be easily obtained by setting a specific option before the model fitting. After obtaining the score functions $U(\theta) = (U(\theta_1)^\top, U(\theta_2)^\top)^\top$ based on $f(\theta) = -2l(\theta)$ by direct calculations, we then estimate θ via the iterative quasi-Newton method (BFGS) that solves the score equations. More specifically, we apply the following quasi-Newton algorithm.

1. Select an initial value $\theta^{(0)} = ((\theta_1^{(0)})^\top, (\theta_2^{(0)})^\top)^\top$. Set the superscript $k = 0$ for iteration number. A convenient initial value for $\theta_1^{(0)} = \beta^{(0)}$ is its ordinary least-squares estimates, $\beta^{(0)} = (\sum_{i=1}^{n} X_i^\top X_i)^{-1}(\sum_{i=1}^{n} X_i^\top y_i)$ while the initial value for θ_2^0 is set to form a diagonal covariance matrix, and will be discussed in details respectively with the choice of covariance structure models later.

2. Initialize score function $U^0 = U(\theta^0)$ and the inverse Hessian H^0 as identity matrix.

3. Update search direction (Newton step) and compute step size $\tilde{\lambda}$ by performing an approximate line minimization

$$p^{(k)} = -H^{(k)}U^{(k)}, \quad \tilde{\lambda} = arg \min_{0<\tilde{\lambda}\leq 1} f(\theta^{(k)} + \tilde{\lambda}p^{(k)}). \tag{4}$$

4. Update θ as

$$\theta^{(k+1)} = \theta^{(k)} + \tilde{\lambda}p^{(k)} \tag{5}$$

and then the new gradient

$$U^{(k+1)} = U(\theta^{(k+1)}). \tag{6}$$

5. Compute the difference $\theta^{(k+1)} - \theta^{(k)}$ and $U^{(k+1)} - U^{(k)}$ and update the inverse Hessian with the BFGS updating formula

$$\begin{aligned} H_{i+1} =& H_i + \frac{(\theta^{(k+1)} - \theta^{(k)})(\theta^{(k+1)} - \theta^{(k)})^\top}{(\theta^{(k+1)} - \theta^{(k)})^\top (U^{(k+1)} - U^{(k)})} \\ & - \frac{[H^{(k)}(U^{(k+1)} - U^{(k)})][H^{(k)}(U^{(k+1)} - U^{(k)})]^\top}{(U^{(k+1)} - U^{(k)})^\top H^{(k)}(U^{(k+1)} - U^{(k)})} \\ & + (U^{(k+1)} - U^{(k)})^\top H^{(k)}(U^{(k+1)} - U^{(k)})uu^\top \end{aligned} \tag{7}$$

where u is defined as the following vector

$$u \equiv \frac{(\theta^{(k+1)} - \theta^{(k)})}{(\theta^{(k+1)} - \theta^{(k)})^\top (U^{(k+1)} - U^{(k)})} - \frac{H^{(k)}(U^{(k+1)} - U^{(k)})}{(U^{(k+1)} - U^{(k)})^\top H^{(k)}(U^{(k+1)} - U^{(k)})}. \tag{8}$$

6. Set $k = k + 1$ and repeat steps 3 to 5 until a pre-specified criterion is met.

See Press, Teukolsky, Vetterling, and Flannery (2007) for a more detailed discussion of BFGS optimization algorithm with line-search and its implementations. Note that currently only BFGS algorithm is implemented in the package since it proves to be one of the best quasi-Newton methods for solving smooth unconstrained optimization problem and works very well in our problem. Other quasi-Newton algorithms will also be implemented as alternatives in the future. In practice, we find the estimates of parameters θ of the joint mean-covariance model can be further improved by solving the parameters one by one with other parameters fixed in the optimization, and will be discussed in more detail in the following sections.

2.2. Modified Cholesky decomposition (MCD)

The two major obstacles in modelling covariance matrices are high-dimensionality (HD) and positive-definiteness (PD). The HD problem usually alleviated from regressions analysis with a large number of covariates and the PD problem can be removed by infusing regression-based ideas into Cholesky decomposition (Pourahmadi 2013). The standard Cholesky decomposition of an $m_i \times m_i$ positive definite covariance matrix is of the following form

$$\Sigma_i = C_i C_i^\top \tag{9}$$

where $C_i = (c_{ijk})$ is a lower triangular matrix with positive diagonal elements and its entries are difficult to interpret (Pinheiro and Bates 1996). We will find that the task of statistical interpretation can be much easier by reducing C_i to unit lower triangular matrices by post- and pre-multiply the inverse of $D_i = diag(c_{i11}, c_{i22}, \cdots, c_{im_im_i})$.

Defining modified Cholesky decomposition (MCD)

The first case, post-multiplying C_i by the inverse of D_i, leads to the modified Cholesky decomposition (MCD) and keeps D_i inside (Zhang and Leng 2012),

$$\Sigma_i = (C_i D_i^{-1})(D_i D_i)(D_i^{-1} C_i^\top) = L_i D_i^2 L_i^\top \tag{10}$$

or in another more commonly used form (Pourahmadi 1999),

$$T_i \Sigma_i T_i^\top = D_i^2 \tag{11}$$

where $T_i = L_i^{-1}$ and $L_i = C_i D_i^{-1}$ can be considered as a standardised version of C_i, dividing each column by its corresponding diagonal entry (Maadooliat, Pourahmadi, and Huang 2013).

The below-diagonal entries of T_i are the negatives of the so-called generalized autoregressive parameters (GARPs), ϕ_{ijk}, in

$$y_{ij} = \mu_{ij} + \sum_{k=1}^{j-1} \phi_{ijk}(y_{ik} - \mu_{ik}) + \epsilon_{ij} \tag{12}$$

the AR model for the actual measurements on subject i. The diagonal entries of D_i^2 are the innovation variance $\sigma_{ij}^2 = Var(\epsilon_{ij})$, see Pourahmadi (1999) for the details. It is helpful to invert Equation 12 by using $y_{i1} = \epsilon_{i1}$ and repeating substitution for y_{it} in terms of ϵ_{it} to obtain

$$y_{ij} - \mu_{ij} = \epsilon_{ij} + \sum_{k=1}^{j-1} \tilde{\phi}_{ijk} \epsilon_{ik} \quad (j = 2, \cdots, m_i) \tag{13}$$

where the matrix form reveals $L_i = (\tilde{\phi}_{ijk})$ so that its entries on the jth row can be interpreted as regression parameters when y_{ij} is regressed on the present and past innovations $\epsilon_{ij}, \epsilon_{i(j-1)}, \cdots, \epsilon_{i1}$. Then we can prove

$$\mathsf{COV}(y_{is}, y_{it}) = \sum_{k=1}^{\min(s,t)} \tilde{\phi}_{isk} \tilde{\phi}_{itk} \sigma_{ik}^2 \tag{14}$$

by setting $\tilde{\phi}_{ijj} = 1$ and $\tilde{\phi}_{ijk} = 0$ for $j < k$ and $1 \le s, t \le m_i$. Thus, the correlation coefficient between y_{is} and y_{it} depends on both the $\tilde{\phi}_{ijk}$'s and the σ_{ij}^2's.

Maximum likelihood estimation of MCD

Using the idea of linear models and employing covariates as in Pan and Mackenzie (2003), the unconstrained parameters $\zeta_{ij} \equiv \log \sigma_{ij}^2$ and ϕ_{ijk} are modelled as

$$\zeta_{ij} = z_{ij}^\top \lambda, \quad \phi_{ijk} = w_{ijk}^\top \gamma \tag{15}$$

where z_{ij} and w_{ijk} are $(d+1)\times 1$ and $(q+1)\times 1$ vectors of covariates, $\lambda = (\lambda_0, \lambda_1, \cdots, \lambda_d)^\top$ and $\gamma = (\gamma_0, \gamma_1, \cdots, \gamma_q)^\top$ are unknown parameters for the innovation variances and autoregressive coefficients, respectively.

Under model in (15), the minus twice log-likelihood function, except for a constant, is given by

$$-2l = \sum_{i=1}^{n} \log |T_i^{-1} D_i^2 T_i^{-\top}| + \sum_{i=1}^{n} r_i^\top T_i^\top D_i^{-2} T_i r_i \tag{16}$$

where $r_{ij} = y_{ij} - x_{ij}^\top \beta$ is the jth element of $r_i = y_i - X_i\beta$, the vector of residuals for ith subject.

The maximum likelihood estimating equations for β, λ and γ become

$$\begin{cases} U_1(\beta) = \sum_{i=1}^{n} X_i^\top \Sigma_i^{-1}(y_i - X_i\beta) \\ U_2(\lambda) = \frac{1}{2}\sum_{i=1}^{n} Z_i^\top (D_i^{-2} e_i - 1_{m_i}) \\ U_3(\gamma) = \sum_{i=1}^{n} G_i^\top D_i^{-2}(r_i - G_i\gamma) \end{cases} \tag{17}$$

where the matrix G_i, of order $m_i \times (q+1)$, has typical row $g_{ij}^\top = \sum_{k=1}^{j-1} r_{ik} w_{ijk}^\top$. Also, $Z_i = (z_{i1}^\top, z_{i2}^\top, \cdots, z_{im_i}^\top)^\top$, $e_i = (e_{i1}, e_{i2}, \cdots, e_{im_i})^\top$ with $e_{ij} = (r_{ij} - \hat{r}_{ij})^2$ and $\hat{r}_{ij} = \sum_{k=1}^{j-1} \phi_{ijk} r_{ik}$, are the $m_i \times (d+1)$ matrix of covariates and the $m_i \times 1$ vector of squared fitted residuals respectively, and 1_{m_i} is the $m_i \times 1$ vector of 1's.

The initial guess $\beta^{(0)}$ can be set by employing a simple linear regression:

```
R> lm.obj <- lm(Y ~ X - 1)
R> bta0 <- coef(lm.obj)
```

After we exact residuals from the linear model, the starting value $\lambda^{(0)}$ is obtained by fitting its linear regression model in (15) while $\gamma^{(0)}$ is simply assumed to be a vector of 0's so that T_i is constructed as an identity matrix :

```
R> resid(lm.obj) -> res
R> lmd0 <- coef(lm(log(res ^ 2) ~ Z - 1))
R> gma0 <- rep(0, lgma)
```

We then estimate θ by minimizing expression in (16) via the iterative quasi-Newton algorithm, as explained in Section 2.1, after substitution of $U(\theta)$ by $(-2U_1(\beta)^\top, -2U_2(\lambda)^\top, -2U_3(\gamma)^\top)^\top$.

Since the solutions satisfy Equation 17 and the parameters β, λ, γ are asymptotically independent (Ye and Pan 2006), the three parameters can also be sequentially solved one by one with other parameters kept fixed. More specifically, we apply the following algorithm.

1. Initialize the parameters as $\theta^{(0)} = ((\beta^{(0)})^\top, (\lambda^{(0)})^\top, (\gamma^{(0)})^\top)^\top$. Set $k = 0$.

2. Compute Σ_i by using $\lambda^{(k)}$ and $\gamma^{(k)}$. Update β as

$$\beta = (\sum_{i=1}^{n} X_i^\top \Sigma_i^{-1} X_i)^{-1} \sum_{i=1}^{n} X_i^\top \Sigma_i^{-1} y_i.$$

3. Given $\beta = \beta^{(k+1)}$ and $\gamma = \gamma^{(k)}$, update λ via the iterative quasi-Newton algorithm after substitution of $f(\theta) = -2l(\theta)$ by $f(\lambda)$ and $U(\theta)$ by $-2U_2(\lambda)$ since there is no explicit form for the solution of λ.

4. Given $\beta = \beta^{(k+1)}$ and $\lambda = \lambda^{(k+1)}$, update γ as

$$\gamma = (\sum_{i=1}^{n} G_i^\top D_i^{-2} G_i)^{-1} \sum_{i=1}^{n} G_i^\top D_i^{-2} r_i.$$

5. Update search direction as

$$p^{(k)} = \theta^{(k+1)} - \theta^{(k)},$$

Compute step size $\tilde{\lambda}$ by performing an approximate line minimization

$$\tilde{\lambda} = arg \min_{0<\tilde{\lambda}\leq 1} f(\theta^{(k)} + \tilde{\lambda} p^{(k)}).$$

6. Update $\theta^{(k+1)}$ again as

$$\theta^{(k+1)} = \theta^{(k)} + \tilde{\lambda} p^{(k)}.$$

7. Set $k = k + 1$ and repeat steps 2 to 6 until a pre-specified criterion is met.

2.3. Alternative Cholesky decomposition (ACD)

Defining alternative Cholesky decomposition (ACD)

The second case, pre-multiplying C_i by the inverse of D_i, leads to alternative Cholesky decomposition (ACD) (Chen and Dunson 2003) and keeps D_i outside,

$$\Sigma_i = D_i(D_i^{-1}C_i)(C_i^\top D_i^{-1})D_i = D_i\tilde{L}_i\tilde{L}_i^\top D_i$$

where $\tilde{L}_i = D_i^{-1}C_i$ is obtained from a slightly different standardised C_i, dividing each row by its corresponding diagonal entry (Maadooliat *et al.* 2013).

For statistical interpretation of the below-diagonal entries of $\tilde{L}_i$, it is clear that $D_i^{-1}(y_i - \mu_i)$ has $\tilde{L}_i\tilde{L}_i^\top$ as the standard Cholesky decomposition of its covariance matrix and $\epsilon_i = (D_i\tilde{L}_i)^{-1}(y_i - \mu_i)$, its vector of innovations, has $\mathsf{COV}(\epsilon_i) = I_{m_i}$. Thus, with $\tilde{L}_i = (\tilde{\phi}_{ijk})$, $D_i = (\sigma_{ij})$ and from $D_i^{-1}(y_i - \mu_i) = \tilde{L}_i\epsilon_i$ we obtain variable-order, MA representation for the standardized $(y_{ij} - \mu_{ij})/\sigma_{ij}$ as

$$(y_{ij} - \mu_{ij})/\sigma_{ij} = \epsilon_{ij} + \sum_{k=1}^{j-1} \tilde{\phi}_{ijk}\epsilon_{ik} \tag{18}$$

Then we can prove

$$\mathsf{COV}(y_{is}, y_{it}) = \sigma_{is}\sigma_{it} \sum_{k=1}^{\min(s,t)} \tilde{\phi}_{itk}\tilde{\phi}_{isk} \tag{19}$$

for any $1 \leq s, t \leq m_i$, so that the correlation coefficient between y_{is} and y_{it} given by

$$\mathsf{CORR}(y_{is}, y_{it}) = \frac{\sum_{k=1}^{\min(s,t)} \tilde{\phi}_{itk}\tilde{\phi}_{isk}}{\sqrt{(\sum_{k=1}^{s} \tilde{\phi}_{isk}^2 \sum_{k=1}^{t} \tilde{\phi}_{itk}^2)}} \tag{20}$$

is determined solely by $\tilde{\phi}_{ijk}$'s.

Maximum likelihood estimation of ACD

Following the similar approach in Pan and Mackenzie (2003), the log-innovation variance $\zeta_{ij} = \log \sigma_{ij}^2$ and moving average parameters $\tilde{\phi}_{ijk}$ in ACD are modelled as

$$\zeta_{ij} = z_{ij}^\top \lambda, \quad \tilde{\phi}_{ijk} = v_{ijk}^\top \gamma \tag{21}$$

where z_{ij} and v_{ijk} are $(d+1) \times 1$ and $(q+1) \times 1$ vectors of covariates, $\lambda = (\lambda_0, \lambda_1, \cdots, \lambda_d)^\top$ and $\gamma = (\gamma_0, \gamma_1, \cdots, \gamma_q)^\top$ are unknown parameters for the innovation variances and moving average regression coefficients, respectively.

Under model in (21), the minus twice log-likelihood function, except for a constant, is given by

$$-2l = \sum_{i=1}^{n} \log |D_i \tilde{L}_i \tilde{L}_i^\top D_i| + \sum_{i=1}^{n} r_i^\top D_i^{-1} \tilde{L}_i^{-\top} \tilde{L}_i^{-1} D_i^{-1} r_i \tag{22}$$

where $r_{ij} = y_{ij} - x_{ij}^\top \beta$ is the jth element of $r_i = y_i - X_i\beta$, the vector of residuals for ith subject.

The score functions can be obtained and simplified as

$$\begin{cases} U_1(\beta) = \sum_{i=1}^{n} X_i^\top \Sigma_i^{-1}(y_i - X_i\beta) \\ U_2(\lambda) = \frac{1}{2}\sum_{i=1}^{n} Z_i^\top (h_i - 1_{m_i}) \\ U_3(\gamma) = \sum_{i=1}^{n} (\epsilon_i^\top \otimes I_{m_i}) \frac{\partial \tilde{L}_i^\top}{\partial \gamma} \tilde{L}_i^{-\top} \epsilon_i \end{cases} \tag{23}$$

where $Z_i = (z_{i1}^\top, z_{i2}^\top, \cdots, z_{im_i}^\top)^\top$, $h_i = diag(\tilde{L}_i^{-1} D_i^{-1} r_i r_i^\top D_i^{-1})$, $\epsilon_i = (\epsilon_{i1}, \cdots, \epsilon_{im_i})^\top = \tilde{L}_i^{-1} D_i^{-1} r_i$, thus $\epsilon_{i1}, \cdots, \epsilon_{im_i}$ are independent standard normal random variables, and I_{m_i} is an $m_i \times m_i$ identity matrix.

Since covariance structure of MCD and ACD are quite close, the initial guess of parameters $\beta^{(0)}$, $\lambda^{(0)}$ and $\gamma^{(0)}$ in ACD can be obtained using the same approach described in initial parameter setting of MCD:

```
R> lm.obj <- lm(Y ~ X - 1)
R> bta0 <- coef(lm.obj)
```

```
R> resid(lm.obj) -> res
R> lmd0 <- coef(lm(log(res ^ 2) ~ Z - 1))
R> gma0 <- rep(0, lgma)
```

We then estimate θ by minimizing expression in (22) via the iterative quasi-Newton algorithm, as explained in Section 2.1, after substitution of $U(\theta)$ by $(-2U_1(\beta)^\top, -2U_2(\lambda)^\top, -2U_3(\gamma)^\top)^\top$. Since the solutions satisfy Equation 23 and the parameters λ and γ are not asymptotically orthogonal (Maadooliat *et al.* 2013), the three parameters can be split into two groups, $\theta_1 = \beta$ and $\theta_2 = (\lambda^\top, \gamma^\top)^\top$ and can be sequentially solved one by one with other parameter kept fixed. More specifically, we apply the following algorithm.

1. Initialize the parameters as $\theta^{(0)} = ((\theta_1^{(0)})^\top, (\theta_2^{(0)})^\top)^\top = ((\beta^{(0)})^\top, (\lambda^{(0)})^\top, (\gamma^{(0)})^\top)^\top$. Set $k = 0$.

2. Compute Σ_i by using $\lambda^{(k)}$ and $\gamma^{(k)}$. Update $\theta_1 = \beta$ as

$$\beta = (\sum_{i=1}^{n} X_i^\top \Sigma_i^{-1} X_i)^{-1} \sum_{i=1}^{n} X_i^\top \Sigma_i^{-1} y_i.$$

3. Given $\beta = \beta^{(k+1)}$, update θ_2 via the iterative quasi-Newton algorithm after substitution of $f(\theta) = -2l(\theta)$ by $f(\theta_2)$ and $U(\theta)$ by $(-2U_2(\lambda)^\top, -2U_3(\gamma)^\top)^\top$.

4. Update search direction as

$$p^{(k)} = \theta^{(k+1)} - \theta^{(k)},$$

   Compute step size $\tilde{\lambda}$ by performing an approximate line minimization

$$\tilde{\lambda} = arg \min_{0<\tilde{\lambda}\leq 1} f(\theta^{(k)} + \tilde{\lambda} p^{(k)}).$$

5. Update $\theta^{(k+1)}$ again as

$$\theta^{(k+1)} = \theta^{(k)} + \tilde{\lambda} p^{(k)}.$$

6. Set $k = k + 1$ and repeat steps 2 to 5 until a pre-specified criterion is met.

2.4. Hyperspherical parameterization of Cholesky factor (HPC)

Even though modified Cholesky decomposition (MCD) (Pourahmadi 1999) and alternative Cholesky decomposition (ACD) (Chen and Dunson 2003) provide parsimonious unconstrained and statistically interpretable parameterization of a covariance matrix, the innovation variance is not same as the marginal variances of the repeated measurements within the same subject.

Defining hyperspherical parameterization of Cholesky factor(HPC)

It is well known that variance-correlation decomposition has the form below

$$\Sigma_i = H_i R_i H_i \tag{24}$$

where $H_i = diag(\sigma_{i1}, \sigma_{i2}, \cdots, \sigma_{im_i})$ with σ_{ij} being the standard deviation of jth measurement for subject i and $R_i = (\rho_{ijk})_{j,k=1}^{m_i}$ is the correlation matrix of y_i with $\rho_{ijk} = \mathsf{CORR}(y_{ij}, y_{ik})$ being the correlation between the jth and kth observations of the ith subject. By using this decomposition, one can directly model the variances and correlations of observations separately.

Not surprisingly, the development of a regression method to model the correlation structure proves to be difficult. Specifically, a correlation matrix must be positive semidefinite and symmetric with 1's as the main diagonal entries and values between -1 and 1 as the off-diagonal entries. The new challenge is mitigated by employ the standard Cholesky decomposition on correlation matrix R_i,

$$R_i = B_i B_i^\top \tag{25}$$

and parameterize its Cholesky factor B_i via hyperspherical co-ordinates (HPC) (Zhang *et al.* 2015),

$$B_i = \begin{bmatrix} 1 & 0 & 0 & \dots & 0 \\ c_{i21} & s_{i21} & 0 & \dots & 0 \\ c_{i31} & c_{i32}s_{i31} & s_{i32}s_{i31} & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ c_{im_i1} & c_{im_i2}s_{im_i1} & c_{im_i3}s_{im_i2}s_{im_i1} & \dots & \prod_{l=1}^{m_i-1} s_{im_il} \end{bmatrix}$$

where $c_{ijk} = \cos(\theta_{ijk})$ and $s_{ijk} = \sin(\theta_{ijk})$.

Equivalently, the non-zeros entries in the lower triangular matrix $B_i = (b_{ijk})$ are given as $b_{i11} = 1$, $b_{ij1} = c_{ij1} = \cos(\theta_{ij1})$ for $j = 1, 2, \cdots, m_i$ and

$$b_{ijk} = \begin{cases} \cos(\theta_{ijk}) \prod_{l=1}^{k-1} \sin(\theta_{ijl}), & 2 \le k < j \le m_i, \\ \prod_{l=1}^{k-1} \sin(\theta_{ijl}), & k = j, j = 2, \cdots, m_i. \end{cases}$$

where θ_{ijk} are some angles in $[0, \pi)$ (Rapisarda, Brigo, and Mercurio 2007)

Maximum likelihood estimation of HPC

The correlation matrix R_i is guaranteed positive semi-definite since it is constructed by its corresponding standard Cholesky factor B_i and the angle parameters in B_i are unconstrained except that $\theta_{ijk} \in [0, \pi)$. We are free to model the log-variances and angles through regression by using some covariates

$$\log \sigma_{ij}^2 = z_{ij}^\top \lambda, \quad \theta_{ijk} = g_{ijk}^\top \gamma \tag{26}$$

As for the range of θ_{ijk}, our experience from data analysis and simulation study indicates all the estimated θ_{ijk}s fall in the range $[0, \pi)$. Transformation such as the inverse tangent transformation can be applied to ensure that θ_{ijk} definitely falls in $[0, \pi)$, and can be implemented in a future version. Under model in (26), the minus twice log-likelihood function, except for a constant, is given by

$$-2l = \sum_{i=1}^{n} \log |H_i B_i B_i^\top H_i| + \sum_{i=1}^{n} r_i' H_i^{-1} B_i^{-\top} B_i^{-1} H_i^{-1} r_i \tag{27}$$

where $r_{ij} = y_{ij} - x_{ij}^\top \beta$ is the jth element of $r_i = y_i - X_i\beta$, the vector of residuals for ith subject.

The score functions can be obtained and simplified as

$$\begin{cases} U_1(\beta) = \sum_{i=1}^{n} X_i^\top \Sigma_i^{-1}(y_i - X_i\beta) \\ U_2(\lambda) = \frac{1}{2}\sum_{i=1}^{n} Z_i^\top (h_i - 1_{m_i}) \\ U_3(\gamma) = \sum_{i=1}^{n}((\epsilon_i^\top \otimes I_{m_i})\frac{\partial B_i^\top}{\partial \gamma} B_i^{\top -1}\epsilon_i - \sum_{j=1}^{m_i}\frac{\partial \log B_{ijj}}{\partial \gamma}) \end{cases} \tag{28}$$

where $Z_i = (z_{i1}^\top, z_{i2}^\top, \cdots, z_{im_i}^\top)^\top$, $h_i = diag(B_i^{-1}H_i^{-1}r_i r_i^\top H_i^{-1})$, $\epsilon_i = (\epsilon_{i1}, \cdots, \epsilon_{im_i})^\top = B_i^{-1}H_i^{-1}r_i$, thus $\epsilon_{i1}, \cdots, \epsilon_{im_i}$ are independent standard normal random variables, and I_{m_i} is an $m_i \times m_i$ identity matrix.

The initial guess $\beta^{(0)}$ can be set by employing a simple linear regression:

```
R> lm.obj <- lm(Y ~ X - 1)
R> bta0 <- coef(lm.obj)
```

After we exact residuals from the linear model, the starting value $\lambda^{(0)}$ is obtained by fitting its linear regression model in (26) while $\gamma^{(0)}$ is simply assumed to be a vector whose first element is $\frac{1}{2}\pi$ and followed by 0's so that B_i is constructed as an identity matrix :

```
R> resid(lm.obj) -> res
R> lmd0 <- coef(lm(log(res ^ 2) ~ Z - 1))
R> gma0 <- c(pi / 2, rep(0, lgma-1))
```

We then estimate θ by minimizing expression in (27) via the iterative quasi-Newton algorithm, as explained in Section 2.1, after substitution of $U(\theta)$ by $(-2U_1(\beta)^\top, -2U_2(\lambda)^\top, -2U_3(\gamma)^\top)^\top$.

Since the solutions satisfy Equation 28 and the parameters λ and γ are not asymptotically independent (Zhang *et al.* 2015), the three parameters can be split into two groups, $\theta_1 = \beta$ and $\theta_2 = (\lambda^\top, \gamma^\top)^\top$ and can be sequentially solved one by one with other parameters kept fixed. More specifically, we apply the following algorithm.

1. Initialize the parameters as $\theta^{(0)} = ((\theta_1^{(0)})^\top, (\theta_2^{(0)})^\top)^\top = ((\beta^{(0)})^\top, (\lambda^{(0)})^\top, (\gamma^{(0)})^\top)^\top$. Set $k = 0$.

2. Compute Σ_i by using $\lambda^{(k)}$ and $\gamma^{(k)}$. Update $\theta_1 = \beta$ as

$$\beta = (\sum_{i=1}^{n} X_i^\top \Sigma_i^{-1} X_i)^{-1} \sum_{i=1}^{n} X_i^\top \Sigma_i^{-1} y_i.$$

3. Given $\beta = \beta^{(k+1)}$, update θ_2 via the iterative quasi-Newton algorithm after substitution of $f(\theta) = -2l(\theta)$ by $f(\theta_2)$ and $U(\theta)$ by $(-2U_2(\lambda)^\top, -2U_3(\gamma)^\top)^\top$.

4. Update search direction as
$$p^{(k)} = \theta^{(k+1)} - \theta^{(k)},$$
Compute step size $\tilde{\lambda}$ by performing an approximate line minimization
$$\tilde{\lambda} = arg \min_{0<\tilde{\lambda}\leq 1} f(\theta^{(k)} + \tilde{\lambda} p^{(k)}).$$

5. Update $\theta^{(k+1)}$ again as
$$\theta^{(k+1)} = \theta^{(k)} + \tilde{\lambda} p^{(k)}.$$

6. Set $k = k + 1$ and repeat steps 2 to 5 until a pre-specified criterion is met.

2.5. Comparison of MCD, ACD and HPC

For modelling the covariance and correlation structure, the three discussed Cholesky-type decomposition-based approaches have been demonstrated to be effective in the sense that estimated covariance and correlation are guaranteed positive (semi)definite, and number of parameters is largely reduced through regression techniques.

It is clear that MCD and ACD has a more close relationship since they are constructed similarly through standardize the Cholesky factor C_i, and the resulting unconstrained parameters have a nice statistical interpretation in terms of innovation variance, autoregressive and moving average parameters respectively. The main drawbacks of these two approaches are the potential needs for a natural order (e.g., time series), which makes it difficult to find a reasonable statistical interpretation and may result in different estimation of covariance and correlation matrix with each single ordering. A recent application of Cholesky-based approach for estimating covariance matrix of multiple stocks within a portfolio and more detailed discussion of ordering problem can be find in Dellaportas and Pourahmadi (2012), Pedeli, Fokianos, and Pourahmadi (2015). Additional effort and extra care are needed in practice for interpreting their corresponding variance and correlation functions. Moreover, owning to the decomposition, resulting correlation function of MCD depends on both the innovation variance and autoregressive parameters, indicating MCD is not robust against the misspecification of innovation variance when correlation is the main interest (Maadooliat *et al.* 2013). We also need to note that MCD is most computationally efficient among three approaches due to the fact that its Fisher information matrix is block diagonal (Ye and Pan 2006).

The parameterization of HPC is very attractive because the resulting parameters are unconstrained and directly interpretable with respect to the variances and correlations. The angles in the Cholesky factor of correlation matrix have a geometric connection with correlations. However, modelling covariance and correlation using HPC can be computationally expensive since it transforms the problem of estimating Cholesky factor into the one that actually first estimates a matrix consists of angles. See details in Zhang *et al.* (2015).

3. Examples of use

3.1. Analysis of a balanced longitudinal dataset

In this section, we provide our first example that illustrates how to apply joint mean-covariance models in analysing a balanced longitudinal data by using **jmcm**. Kenward (1987) reported an experiment on cattle intestinal paasites controls in which the cattle were assigned randomly to two treatment groups A and B, and their weights were recorded. Thirty animals received treatment A and another thirty received treatment B. The animals were weighted $n = 11$ times over a 133-day period; the first 10 measurements on each animal were made at two-week intervals and the final measurement was made one week later. Since no observation was missing, it is considered to be a balanced longitudinal dataset. The data is loaded simply using the `data()` instruction:

```
R> library("jmcm")
R> data("cattle", package = "jmcm")
R> head(cattle)
```

```
  id day group weight
1  1   0     A    233
2  1  14     A    224
3  1  28     A    245
4  1  42     A    258
5  1  56     A    271
6  1  70     A    287
```

We present in Figure 1 the subject-specific longitudinal profiles of the cattle data using following code:

```
R> library("lattice")
R> xyplot(weight ~ day | group, group = id, data = cattle, xlab = "days",
+    ylab = "weight", col = 1, type = "l")
```

and observes that in both groups the variability of weights seems to increase over time with a severe weight loss on the final measurement in group B.

Following Pourahmadi (1999), Pan and Mackenzie (2003), Pan and MacKenzie (2006), Pan and MacKenzie (2007) and Zhang *et al.* (2015), we re-analysed group A data by using a saturated mean model with the common measurement time rescaled to $t = 1, 2, \cdots, 10, 10.5$. The Bayesian Information Criterion (BIC), which is closely related to Akaike Information Criterion (AIC) and introduces a larger penalty term for the number of parameters in the model than the AIC aiming to solve the problem of over-fitting, is used as the criterion to select the optimum model

$$BIC(p, d, q) = -2\hat{l}_{max}/n + (p + d + q + 3)\log(n)/n \tag{29}$$

where p, d and q are respectively the orders of three polynomials and $\hat{l}_{max}$ is the value of maximum log-likelihood function for the given order. By default, the value of likelihood does not include the constant term as defined in Equation (3) but it can be switched to the full likelihood containing the constant term easily by explicitly specifying `control = jmcmControl(ignore.const.term = F)` in `jmcm` function.

The basic use of `jmcm` is to indicate the model formula, data, choice of poly(p, d, q) and covariance structure model. For example, a joint mean-covariance model based on modified Cholesky decomposition (MCD) are estimated using:

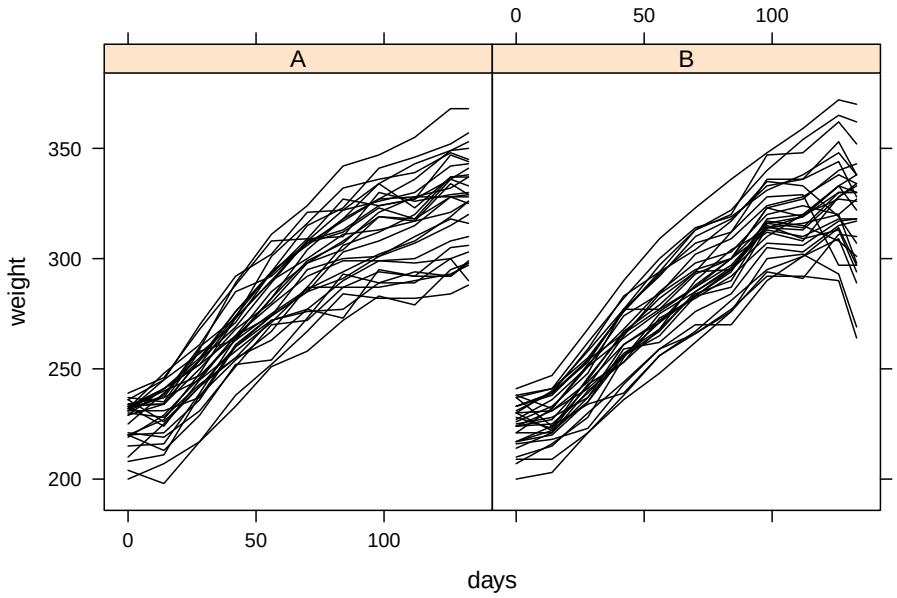

Figure 1: Subject-specific weight against time for group A and B.

```
R> cattleA <- cattle[cattle$group=='A', ]
R> fit1 <- jmcm(weight | id | I(day/14 + 1) ~ 1 | 1, data = cattleA,
+    triple = c(8, 3, 4), cov.method = 'mcd')
R> fit1

Joint mean-covariance model based on MCD ['jmcmMod']
Formula: weight | id | I(day/14 + 1) ~ 1 | 1
Poly: c(8, 3, 4)
Data: cattleA

logLik: -771.0007
BIC: 53.4408

Mean Parameters:
[1]   1.832e+02   1.244e+02  -1.403e+02   7.881e+01  -2.362e+01   4.071e+00
[7]  -4.052e-01   2.162e-02  -4.787e-04
Innovation Variance Parameters:
[1]   5.366409  -0.878890   0.132427  -0.006371
Autoregressive Parameters:
[1]   0.297055   0.619888  -0.396189   0.069150  -0.003696
```

The R package **Formula** of Zeileis and Croissant (2010) is used to extract information from a two-sided linear formula object which is used to describe both longitudinal data and covariates of the model, with the response, subject id and observation time point on the left of a "∼" operator separated by vertical bars ("|") and covariates for the mean model and innovation

variance, also separated by a "|" operator, on the right. Here both covariates for mean model and innovation variance are marked as 1, and only time is used to construct design matrices. Optimal model selection involves identifying the best integer triple poly(p, d, q), specified by option `triple`, representing the degrees of three polynomial functions for the mean structure, log innovation variance and autoregressive coefficients respectively. To make the model fitting comparable with the results reported in the literature, in this paper we focus on the fitting using polynomials in time. The use of other covariates is also possible and will be demonstrated later. By default, the `jmcm` function uses the profile likelihood for having a better estimating result. Alternatively, non-profile method can be applied by specifying `control = jmcmConstrol(profile = F)`. When the estimation for the fitted model is ready, an object of the `S4` class `jmcmMod` is returned from the function and it automatically displays the basic information by calling the generic `print` function. The `getJMCM` function can be used to extract various objects (e.g., estimation of mean vector and covariance matrix) from a fitted joint mean-covariance model. In this example, the global optimum triple poly(8,3,4) reported in Pan and Mackenzie (2003) is modelled, produced a better result with $\hat{l}_{max}$ = -771.0007 and BIC = 53.4408.

Since it is a balanced longitudinal dataset, we produced the sample regressograms and fitted curves for the cattle data using the following function:

```
R> regressogram(fit1, time = 1:11)
```

By examining the log innovation variance versus time in Figure 2, it is clear that curvature pattern is well captured by the fitted polynomial function curve. Figure 2 also indicates a good fit for autoregressive coefficients by examining the autoregressive coefficient versus time lag between measurements and the fitted curve.

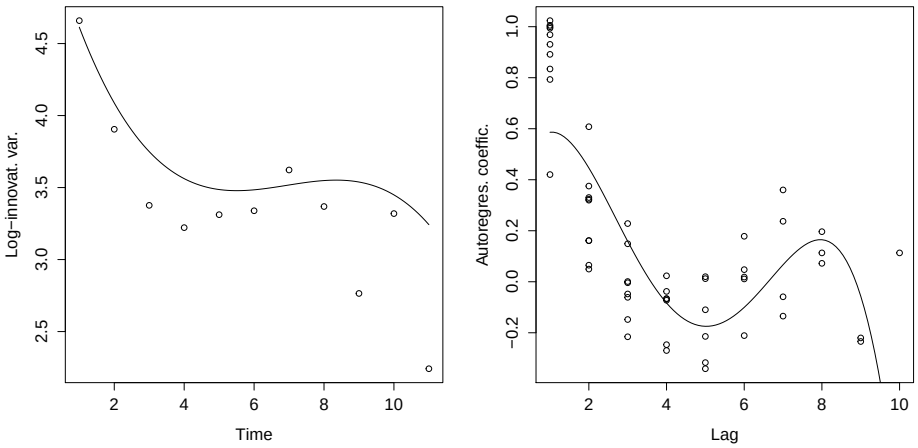

Figure 2: Group A analysis of Kenward's cattle data. Sample regressograms and MCD model fits based on the triple ploy(8, 3, 4) for log innovation variances (left) and autoregressive coefficients (right).

Same triple poly(8,3,4), representing the degrees of three polynomial functions for the mean structure, the log innovation variance and moving average coefficients respectively, is used

in joint mean-covariance model fitting based on ACD for cattle data. The covariance structure option should be specified as `cov.method = 'acd'`. By comparing the maximized log-likelihood and BIC for MCD modelling, we clearly see that ACD method produces a larger likelihood $\hat{l}_{max} = -747.6994$ and a smaller BIC-value 51.8873.

```
R> fit2 <- jmcm(weight | id | I(day/14 + 1) ~ 1 | 1, data = cattleA,
+    triple = c(8, 3, 4), cov.method = 'acd')
R> fit2
```

```
Joint mean-covariance model based on ACD ['jmcmMod']
Formula: weight | id | I(day/14 + 1) ~ 1 | 1
Poly: c(8, 3, 4)
Data: cattleA

logLik: -747.6994
BIC: 51.8873

Mean Parameters:
[1]   1.784e+02   1.360e+02  -1.511e+02   8.400e+01  -2.503e+01   4.299e+00
[7]  -4.267e-01   2.272e-02  -5.020e-04
Innovation Variance Parameters:
[1]   4.959622  -0.625990   0.084538  -0.003963
Moving Average Parameters:
[1]   0.5216849   0.4795778  -0.1049448   0.0105871  -0.0003623
```

Regressograms for ACD can be produced by the same command:

```
R> regressogram(fit2, time = 1:11)
```

By examining the log innovation variance versus time (left) and moving average coefficient versus time lag (right) in Figure 3, similar conclusion can be drawn that the proposed polynomial model fitting well captured trend in sample regressogram.

When the joint mean-covariance model approach based on HPC is applied to the cattle data, the covariance structure option should be specified as `cov.method = 'hpc'`. Same two-sided linear formula object is used to describe both longitudinal data and covariates of the model, but on the right of a "$\sim$" operator, covariates for mean model and variance is specified on the right side of the operator instead of mean model and innovation variance in MCD and ACD. The integer triple poly(p, d, q) is specified by option `triple`, representing the degrees of three polynomial functions for the mean structure, log variance and angles respectively. More specifically, the optimal triple ploy(8, 2, 2) of HPC model fitting reported in Zhang *et al.* (2015) can be reproduced using the following command:

```
R> fit3 <- jmcm(weight | id | I(day/14 + 1) ~ 1 | 1, data = cattleA,
+    triple = c(8, 2, 2), cov.method = 'hpc')
R> fit3
```

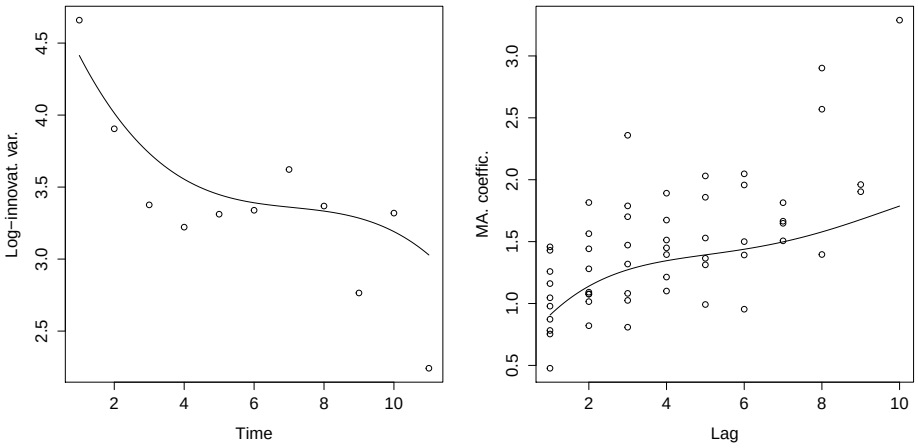

Figure 3: Group A analysis of Kenward's cattle data. Sample regressograms and ACD model fits based on the triple ploy(8, 3, 4) for log innovation variances (left) and moving average coefficients (right).

```
Joint mean-covariance model based on HPC ['jmcmMod']
Formula: weight | id | I(day/14 + 1) ~ 1 | 1
Poly: c(8, 2, 2)
Data: cattleA

logLik: -746.9001
BIC: 51.4939

Mean Parameters:
[1]   1.781e+02   1.373e+02  -1.528e+02   8.500e+01  -2.535e+01   4.359e+00
[7]  -4.330e-01   2.307e-02  -5.101e-04
Variance Parameters:
[1]   4.0263   0.3148  -0.0113
Angle Parameters:
[1]   0.729414   0.092111  -0.004424
```

A slightly better result with $\hat{l}_{max}$ = -746.9001 and BIC = 51.4939 is produced compared to reported $\hat{l}_{max}$ = -755.00 and BIC = 52.03. Similarly, model fitting can be checked by plot the two regressograms using:

```
R> regressogram(fit3, time = 1:11)
```

We need to note that there is no general form for calculating angles. The corresponding angles ϕ_{ijk} of the empirical correlation matrix is calculated iteratively using expression

$$\theta_{ijk} = \arccos(b_{ijk} / \prod_{l=1}^{k-1} \sin(\arccos(\theta_{ijl}))), \quad 1 \leq k < j \leq m_i, \tag{30}$$

where $\prod_1^0$ is taken as 1. By examining the log variance versus time (left) and angle versus time lag (right) in Figure 4, it is clear that curvature patterns on two sample regressograms is well captured by the two fitted model, indicating a good model fitting.

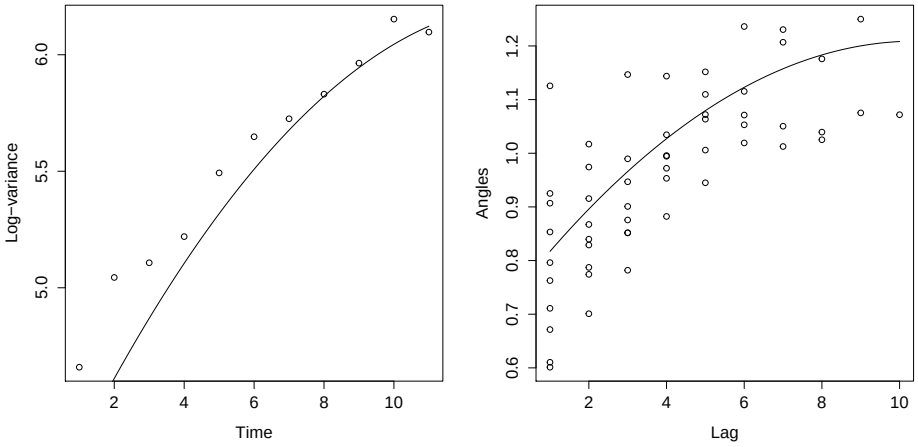

Figure 4: Group A analysis of Kenward's cattle data. Sample regressograms and HPC model fits based on the triple ploy(8, 2, 2) for log variances (left) and angles (right).

The comparisons between MCD, ACD and HPC based joint mean-covariance models on cattle data are made in Table 1 with different choices of triple and execution time (in seconds) are measured for each model fitting. We find that HPC-based model is more desirable in most cases with a larger value in log likelihood and smaller BIC when compared to MCD and ACD based models at the cost of a much longer execution time. From Table 1, we also find that MCD and ACD will produce quite close results in term of value of likelihood and BIC while MCD based model is most time efficient among three approaches. Our tests were conducted under Windows 10 (64-bit version) on ThinkPad T410 equipped with an Intel(R) Core(TM) i5 M 480@2.67GHz with 4.00GB of RAM.

(p,d,q)	No. of	MCD			ACD			HPC		
	parms.	l_{max}	BIC	Time	l_{max}	BIC	Time	l_{max}	BIC	Time
(8,3,4)	18	-771.0007	53.4408	0.53	-747.6994	51.8873	3.54	-745.2783	51.7259	6.61
(8,2,2)	15	-789.6174	54.3418	0.57	-750.8567	51.7577	2.78	-746.9001	51.4939	6.28
(10,10,10)	33	-739.1477	53.0178	4.77	-740.7159	53.1224	88.68	-739.6031	53.0482	128.10
(6,1,1)	11	-823.8421	56.1699	0.47	-763.5859	52.1528	1.33	-759.5982	51.8870	4.09
(3,3,3)	12	-825.3397	56.3831	1.05	-800.8213	54.7486	6.03	-798.1533	54.5707	16.69
(4,4,3)	14	-791.1545	54.3309	0.80	-760.6863	52.2996	3.21	-760.2976	52.2737	10.25
(7,2,2)	14	-791.7968	54.3737	0.47	-755.7579	51.9711	2.14	-751.8171	51.7084	6.17
(8,7,4)	22	-769.5302	53.7962	1.89	-745.1182	52.1688	4.97	-743.1843	52.0398	16.19
(9,1,3)	16	-794.7426	54.7968	0.38	-750.0146	51.8149	2.94	-746.7736	51.5989	9.39
(9,4,3)	19	-783.2143	54.3684	0.61	-746.3733	51.9123	5.41	-744.9879	51.8200	9.98
(9,8,5)	25	-754.3422	53.1238	2.09	-743.2145	52.3820	28.67	-741.6877	52.2802	37.91

Table 1: Kenward's cattle data. Comparison of MCD, ACD and HPC with different triples.

3.2. Analysis of an unbalanced longitudinal dataset

In this section, we apply the proposed joint mean-covariance modelling approach to an unbalanced CD4+ cell dataset analysed by Ye and Pan (2006) and Zhang *et al.* (2015). The dataset comprises a total of 2376 CD4+ cell counts of 369 HIV-infected men covering a period of approximately eight and half year. The number of measurement m_i for each individual varies from 1 to 12 and the times are not equally spaced. The CD4+ cell data are highly unbalanced and included in the package.

```
R> data("aids", package = "jmcm")
R> head(aids)
```

```
       time cd4  age packs drugs sex cesd    id
1 -0.741958 548 6.57     0     0   5    8 10002
2 -0.246407 893 6.57     0     1   5    2 10002
3  0.243669 657 6.57     0     1   5   -1 10002
4 -2.729637 464 6.95     0     1   5    4 10005
5 -2.250513 845 6.95     0     1   5   -4 10005
6 -0.221766 752 6.95     0     1   5   -5 10005
```

We present in Figure 5 the scatter plot of CD4+ cell counts against time, with the first six individuals profiles superimposed:

```
R> library("lattice")
R> xyplot(sqrt(cd4) ~ time, data = aids,
     panel = function(x, y, ...) {
       panel.xyplot(x, y, ...)
       panel.lines(x[aids$id==10002], y[aids$id==10002], col = 2, lwd = 2)
       panel.lines(x[aids$id==10005], y[aids$id==10005], col = 3, lwd = 2)
       panel.lines(x[aids$id==10029], y[aids$id==10029], col = 4, lwd = 2)
       panel.lines(x[aids$id==10039], y[aids$id==10039], col = 5, lwd = 2)
       panel.lines(x[aids$id==10048], y[aids$id==10048], col = 6, lwd = 2)
       panel.lines(x[aids$id==10052], y[aids$id==10052], col = 7, lwd = 2)
     },
     xlab = "Time", ylab = "CD4 cell numbers", col = 1)
```

and observe that the data is highly unbalanced with unclear profile patterns for each individual.

As in Zhang *et al.* (2015), square roots of the CD4 cell counts are used to make the response variable closer to the Normal distribution. The optimal triplet poly(8, 1, 3) of MCD method reported in Zhang *et al.* (2015) is fitted using the following command:

```
R> fit4 <- jmcm(I(sqrt(cd4)) | id | time ~ 1 | 1, data = aids,
+    triple = c(8, 1, 3), cov.method = 'mcd')
R> fit4
```

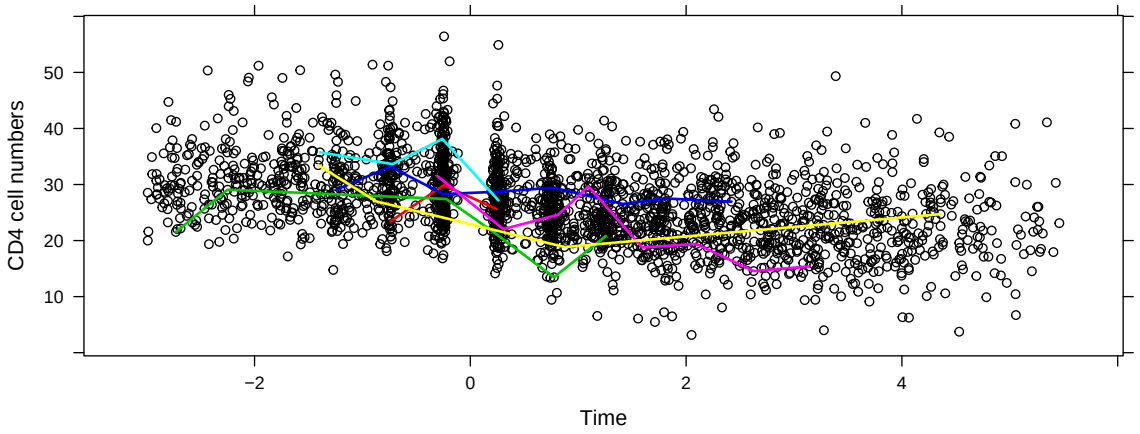

Figure 5: Scatter plot of CD4+ cell counts against time, with the first six individuals profiles superimposed.

```
Joint mean-covariance model based on MCD ['jmcmMod']
Formula: I(sqrt(cd4)) | id | time ~ 1 | 1
Poly: c(8, 1, 3)
Data: aids

logLik: -4979.193
BIC: 27.2278

Mean Parameters:
[1]  29.217447  -4.100596  -1.279396   1.073685   0.195578  -0.166439
[7]  -0.001842   0.009407  -0.001020
Innovation Variance Parameters:
[1]   3.2646  -0.0886
Autoregressive Parameters:
[1]   0.67990  -0.57684   0.17741  -0.01815
```

Here the CD4 data is again re-analysed with MCD based joint mean-covariance model using time as the main covariates and values of $\hat{l}_{max}$ = -4979.193 and smaller BIC = 27.2278 are obtained. Note that `jmcm` function do allow adding other covariates in the mean model and innovation variance model. For instance, the linear formula part of `jmcm` function in this example can be replaced by `I(sqrt(cd4)) | id | time ~ age | age + packs`, which in turn generates the new vectors of covariates for the mean and innovation variance with the following form

$$x_{ij} = (1, t_{ij}, t_{ij}^2, \cdots, t_{ij}^p, age)^\top,$$
$$z_{ij} = (1, t_{ij}, t_{ij}^2, \cdots, t_{ij}^d, age, packs)^\top.$$

The joint mean-covariance model based on ACD and HPC approaches can also be fitted with

other covariate in a similar way, and currently the fitted models can be compared with other model fittings using the value of log likelihood and BIC.

Since CD4+ cell data are unbalanced, sample covariance matrix cannot be obtained and using instruction `regressogram()` with the model fitting result will simply lead to an error message. Instead we produced fitted curves and its 95% confidence interval based on bootstrap using the following function:

```
R> bootcurve(fit4, nboot = 1000)
```

where number of bootstrap replications can be specified by option `nboot` and there are 1000 bootstrap samples in this example. Figure 6 shows the fitted curve of the mean, log innovation variance, autoregressive coefficient and their corresponding 95% confidence intervals. From Figure 6, we also observed the monotone-decreasing relationship of fitted log innovation variance with the time, and a curvature pattern of fitted autoregressive coefficient with the time lag.

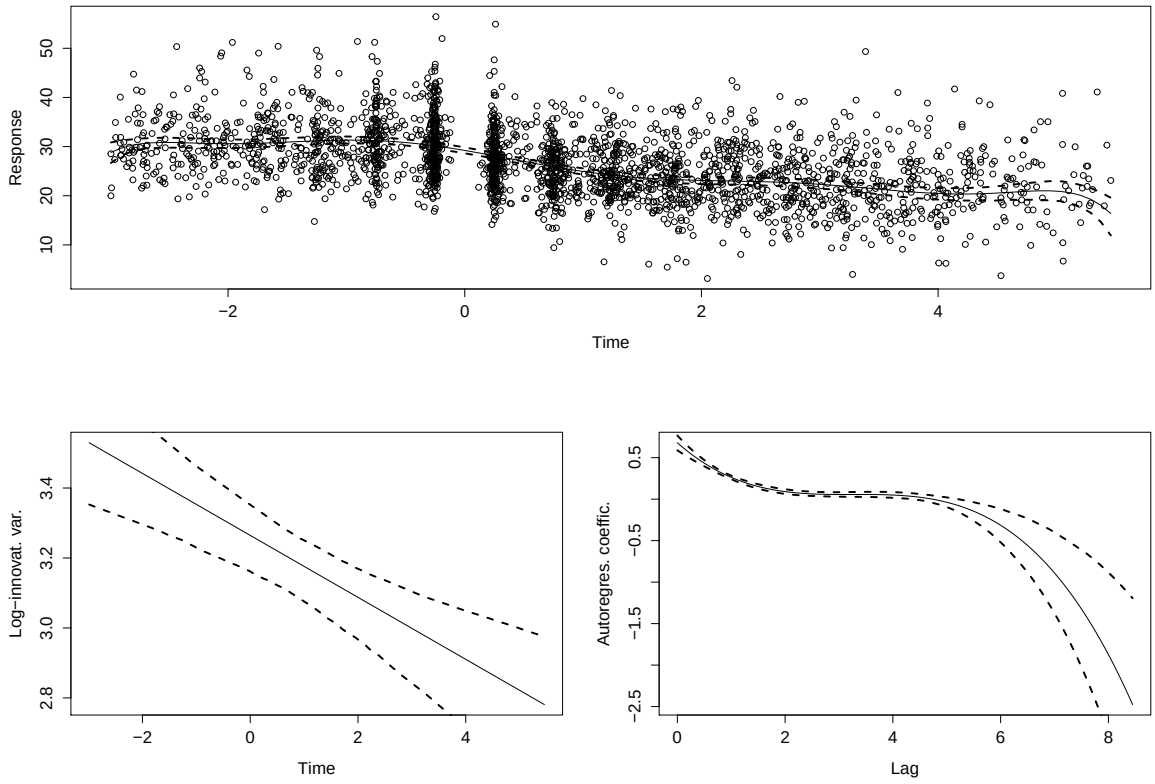

Figure 6: CD4 cell data. MCD model fits based on the triple poly(8,1,3). Fitted curves of the mean against time (top), the log innovation variance against time (left) and the autoregressive coefficient against lag (right): - - - - - -, 95% confidence intervals.

The same triple poly(8,1,3) is used in joint mean-covariance model fitting based on ACD for aids data, and we clearly see that ACD method produces a larger likelihood $\hat{l}_{max}$ = -4927.492 and a smaller BIC-value 26.9476.

```
R> fit5 <- jmcm(I(sqrt(cd4)) | id | time ~ 1 | 1, data = aids,
+    triple = c(8, 1, 3), cov.method = 'acd')
R> fit5

Joint mean-covariance model based on ACD ['jmcmMod']
Formula: I(sqrt(cd4)) | id | time ~ 1 | 1
Poly: c(8, 1, 3)
Data: aids

logLik: -4927.492
BIC: 26.9476

Mean Parameters:
[1]  29.0395978  -4.0577291  -1.0767686   0.9747427   0.1479554  -0.1416514
[7]  -0.0002373   0.0076762  -0.0008416
Innovation Variance Parameters:
[1]   3.2441  -0.1163
Moving Average Parameters:
[1]   0.580633  -0.151159   0.056772  -0.006433
```

Fitted curves for ACD can be produced by the same command:

```
R> bootcurve(fit5, nboot = 1000)
```

From Figure 7, again we observed the monotone-decreasing relationship of fitted log innovation variance with the time, and a curvature pattern of fitted moving average coefficient with the time lag.

When the optimal triplet poly(8, 1, 1) of HPC approach reported in Zhang *et al.* (2015) is fitted, the optimal BIC-value turns out to be 26.7268, and $\hat{l}_{max}$ = -4892.68, producing the best model among the three proposed covariance and correlation structure modelling methods.

```
R> fit6 <- jmcm(I(sqrt(cd4)) | id | time ~ 1 | 1, data = aids,
+    triple = c(8, 1, 1), cov.method = 'hpc')
R> fit6

Joint mean-covariance model based on HPC ['jmcmMod']
Formula: I(sqrt(cd4)) | id | time ~ 1 | 1
Poly: c(8, 1, 1)
Data: aids

logLik: -4892.68
BIC: 26.7268

Mean Parameters:
[1]  29.0352214  -4.1553878  -0.9452119   0.9969254   0.1066325  -0.1394301
[7]   0.0026802   0.0072015  -0.0008294
Variance Parameters:
```

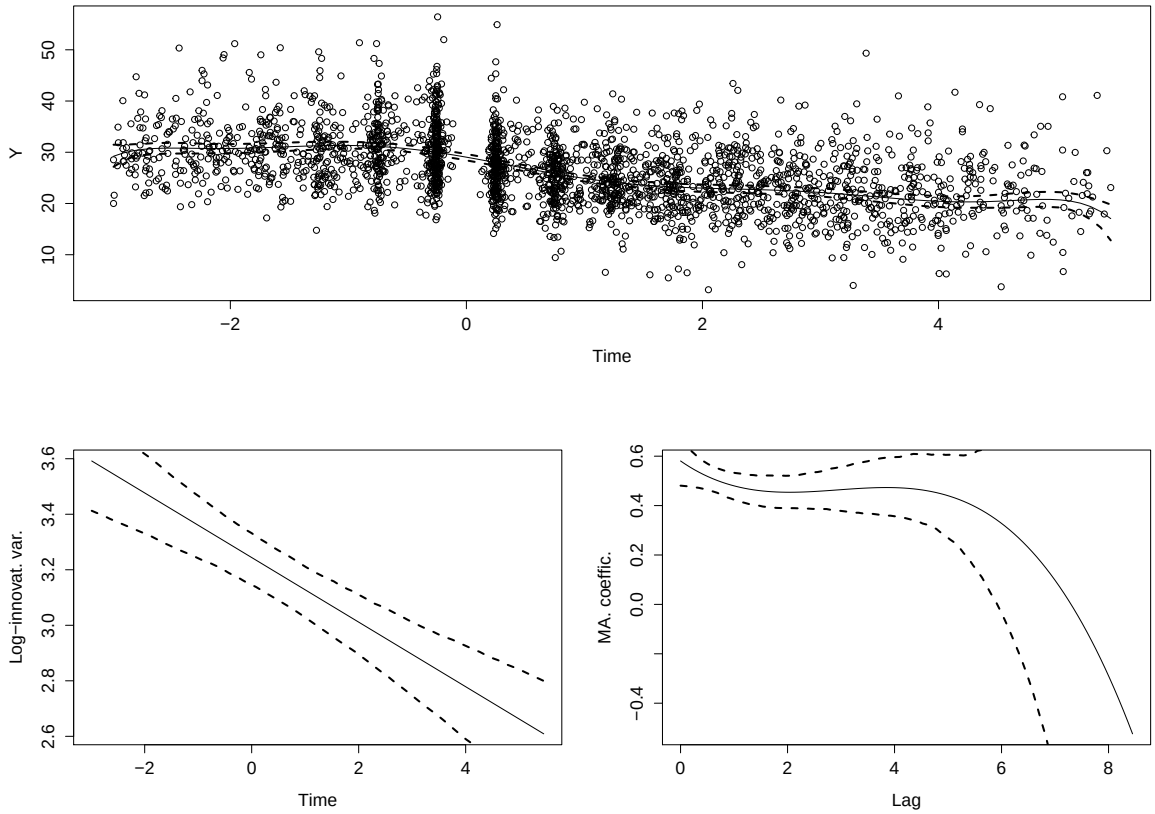

Figure 7: CD4 cell data. ACD model fits based on the triple poly(8,1,3). Fitted curves of the mean against time (top), the log innovation variance against time (left) and the moving average coefficient against lag (right): - - - - - -, 95% confidence intervals.

```
[1]  3.64089  0.03252
Angle Parameters:
[1]  1.06980  0.05357
```

Similarly, model fitting can be checked by plot the fitted curves using

```
R> bootcurve(fit6, nboot = 1000)
```

and from Figure 8, we observe the monotone increasing relationship of fitted log variance with the time, and fitted angles with the time lag.

We also compared the MCD, ACD and HPC based joint mean-covariance models on the CD4+ cell data in Table 2. We find that HPC-based model proves better model fitting in most cases with a larger value in log likelihood and smaller BIC when compared to MCD and ACD based models at the cost of a much longer execution time, ACD based model slightly outperforms compared to MCD, and MCD based model again provides the most time-efficient model fitting.

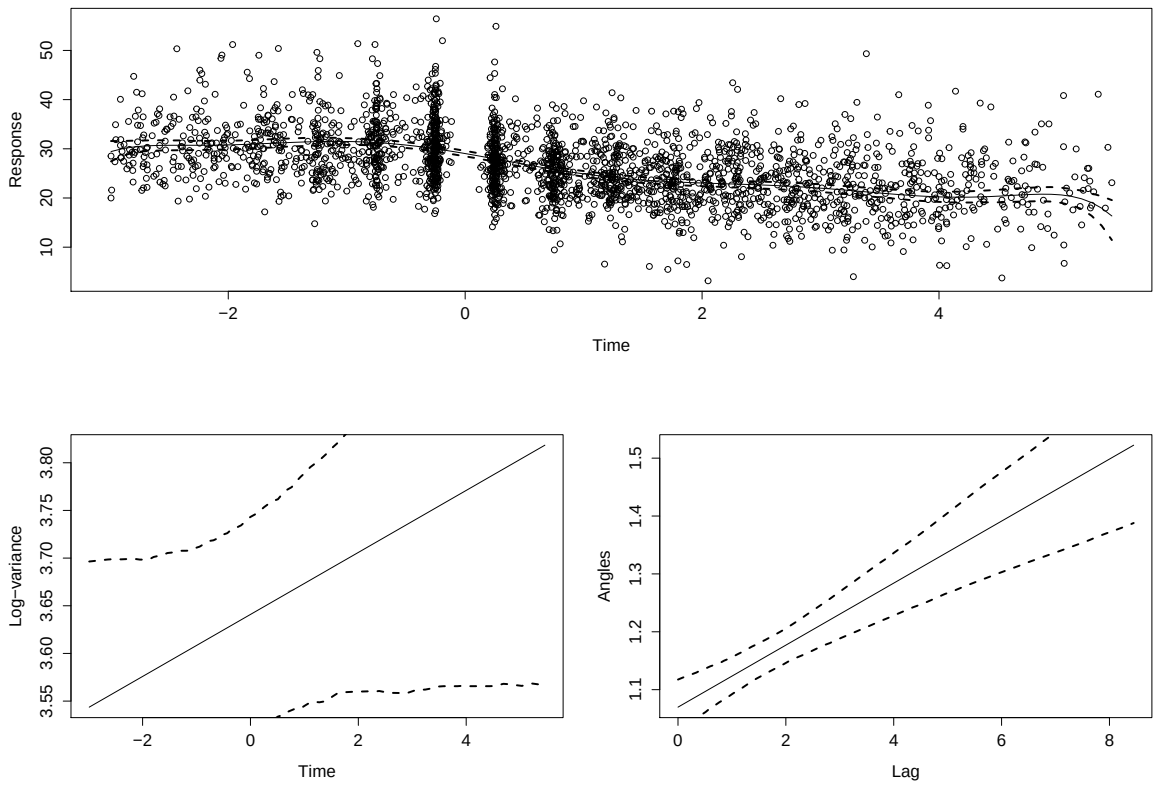

Figure 8: CD4 cell data. HPC model fits based on the triple poly(8,1,1). Fitted curves of the mean against time (top), the log variance against time (left) and the angle against lag (right): - - - - - -, 95% confidence intervals.

4. Conclusion

In this article, we have illustrated the capabilities of package **jmcm** for the joint mean-covariance modelling of both balanced and unbalanced longitudinal data using three popular covariance and correlation structure modelling approaches. In particular, we provide: functions for estimation of MCD, ACD and HPC based joint mean-covariance models, devices for displaying regressograms and fitted model curves. By using these models, the estimated covariance and correlation are guaranteed to be positive (semi)definite and the estimation of high-dimensional covariance and correlation matrix is reduced to solving a series of regression problems. The likelihood-based estimation procedure permits extensions such as regularization-based model selection, so that the package can be compared with other likelihood-based R packages.

However, the package is currently limited to handle longitudinal data with a multivariate Gaussian distribution. It is worthwhile to develop methods further that are robust with non-Normally distributed data by introducing the Cholesky-based covariance structure modelling methods to GEE model and/or Gaussian copula model. We plan to update the package **jmcm** on a regular basis with new statistical procedures available for joint mean-covariance modelling approach.

(p,d,q)	No. of	MCD			ACD			HPC		
	parms.	l_{max}	BIC	Time	l_{max}	BIC	Time	l_{max}	BIC	Time
(8,1,1)	13	-5008.753	27.3560	2.11	-4928.924	26.9233	37.28	-4892.680	26.7268	134.64
(8,1,3)	15	-4979.193	27.2278	2.80	-4927.492	26.9476	39.72	-4890.396	26.7465	112.79
(6,1,1)	11	-5018.470	27.3766	1.88	-4937.227	26.9362	25.06	-4902.175	26.7463	79.32
(3,3,3)	12	-5006.176	27.3260	3.22	-4951.234	27.0282	40.57	-4919.522	26.8563	120.88
(4,4,3)	14	-4995.509	27.3002	3.36	-4934.265	26.9682	56.34	-4902.100	26.7939	177.25
(8,3,3)	17	-4974.683	27.2354	3.31	-4919.700	26.9374	58.68	-4886.337	26.7565	155.85
(8,7,4)	22	-4971.712	27.2994	7.16	-4914.223	26.9878	270.25	-4881.736	26.8117	763.83
(9,1,3)	16	-4974.104	27.2162	3.00	-4918.684	26.9158	63.18	-4881.266	26.7130	120.09
(9,4,3)	19	-4970.209	27.2432	5.06	-4909.363	26.9134	66.25	-4875.877	26.7319	212.51
(9,8,5)	25	-4962.655	27.2983	7.70	-4901.841	26.9687	221.10	-4871.577	26.8047	662.64

Table 2: CD4 cell data. Comparison of MCD, ACD and HPC with different triples.

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