Hierarchical mixture models for longitudinal immunologic data with heterogeneity, non-normality, and missingness

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Introduction

● **Longitudinal data**

  The longitudinal data refers to multi-dimensional data frequently involving measurements over time. Nowadays, with the development of the big data in medical field, the longitudinal data analysis has received a great deal of attention in many studies.

  **Joint modeling analysis**, as the most effective method to analyze longitudinal data, is now an active area of statistics research. However, following issues standout:

  - Response followed heterogeneous characteristics
  - Response contains non-ignorable missingness
  - Model error is skew distributed

● **The majority of literatures for the joint modeling have focused on developing models to capture only specific aspect of the motivating studies:**

  - Assume all subjects come from a homogeneous population
  - Assume the model error is normally distributed
  - Assume all the collected data are “perfectly” measured and without considering the missingness
First, the homogeneous assumption
- Finite mixture models with nonlinear (piecewise) mean functions

The feature of longitudinal data
Introduction

The feature of longitudinal data

- Second, the normally (symmetrically) assumption of model random errors
  - Asymmetric distribution such as skew-t (ST) and skew-normal (SN) distributions should be more appropriate.

- Last, the non-ignorable missing observations in response.
Relatively few studies focus on simultaneous inference for longitudinal data with features of heterogeneity, non-normality and non-ignorable missingness in response.

Motivated by an AIDS study to consider:
- A Finite Mixture of Changepoint (piecewise) Mixed Effects (FMCME) models with skew distributions, which include ST and SN distributions, to simultaneously account for response with skewness, heterogeneity and non-ignorable missingness.

Propose a Bayesian inferential approach:
- To estimate both model parameters and class membership probabilities based on a finite mixture model with piecewise mean functions.
Motivating AIDS Clinical Data Set

- A randomized, open-label clinical study with 96 weeks comparing the treatment of 2 different 4-drug regimens (lamivudine, zidovudine, and indinavir with either efavirenz (arm one) or nelfinavir (arm two) with a standard three-drug regimen of lamivudine, zidovudine, and indinavir (arm three)) for 517 HIV patients.

- **Excluded:** 30, had less than three CD4 measurements.

- **Dropped out:** 107 (22% of 487), may be related to drug-associated toxicities or other problems.

- **Measurement point:** study weeks 0, 4, and 8, and every 8 weeks thereafter.

- **Total missingness:** 898 missing measurements out of 6241 CD4 observations from 487 subjects and the number of measurements for each subject varies from 3 to 14.

- The CD4 cell counts are standardized to obtain stable estimates.
CD4 trajectory profiles can be roughly classified into three classes

- Class 1: CD4 count increase rapidly and followed by a stable constant
- Class 2: CD4 count increase rapidly and then followed by a slow increase
- Class 3: CD4 count increase rapidly but followed by a gradual decrease

The classes 1 and 2 indicate a CD4 recovery and successful treatment without serious clinical problems arisen, while the class 3 implies the CD4 decline which may result in viral load rebound, provides the evidence of treatment failure.
A unified function to describe the CD4 counts changing pattern

\[ y(t) = \beta_0 + \beta_1(t - \tau)_- + \beta_2(t - \tau)_+ \]  \hspace{1cm} (1)

- \( \tau \) denote the time of the changepoint;
- \( x_-\min(x, 0) \) and \( x_-\min(x, 0) \) for variable \( x \);
- \( \beta_1 > 0, \beta_2 = 0 \) presents class 1; \( \beta_1 > 0, \beta_2 > 0 \) presents class 2;
  \( \beta_1 > 0, \beta_2 < 0 \) presents class 3.
Discuss Mixture models

A mixture of hierarchical changepoint models with ST distribution for immunological CD4 response

Assume there are $K$ plausible nonlinear trajectory classes with mean functions $g_k(\cdot)(k = 1, \ldots, K)$, $g_k(\cdot)$ with unknown probability $\pi_k = P(C_i = k)$ which satisfies $\sum_{k=1}^{K} \pi_k = 1$, where $C_i$ is a latent indicator.

Given $C_i = k$, the statistical piecewise trajectory model with $ST$ distribution for individual $i$ can be formulated as

$$(y_i | c_i = k) = g_k(t_i, A_k\beta_i) + e_i, \quad e_i \sim ST_{ni,v}(-J(v)\delta I_{ni}, \sigma^2 I_{ni}, \delta I_{ni}) \quad (2)$$

- $t_i = (t_{i1}, \ldots, t_{in_i})^T$, $\beta_i = (\beta_{1i}, \ldots, \beta_{si})^T$ is a individual parameters for the $i$th individual;
- $J(v) = (v/\pi)^{1/2}\{\Gamma[(v-1)/2]/\Gamma(v/2)\}$, $\Gamma(\cdot)$ is a Gamma function;
- $e_i = (e_{i1}, \ldots, e_{in_i})^T$ follows a multivariate ST distribution with degrees of freedom $v$, unknown variance parameter $\sigma^2$ and skewness parameter $\delta$;
- $A_k(s \times s)(k = 1, \ldots, K)$ is known square indicator matrix: diagonal elements are either 0 or 1 and off-diagonal elements are all 0.
A mixture of hierarchical changepoint model with ST distribution for immunological CD4 response

- Conditionally

\[(y_i | c_i = k) \sim ST_{ni,v}(g_k(t_i, A_k \beta_i) - J(v)\delta I_{ni}, \sigma^2 I_{ni}, \delta I_{ni}) \]  \hspace{1cm} (3)

- Marginally

\[y_i \sim \sum_{k=1}^{K} \pi_k ST_{ni,v}(g_k(t_i, A_k \beta_i) - J(v)\delta I_{ni}, \sigma^2 I_{ni}, \delta I_{ni}) \]  \hspace{1cm} (4)

Model (4) defines a FMCME model. The vector of mixture probabilities \( \pi = (\pi_1, ..., \pi_k)^T \) can be also viewed as the mixture weights of all plausible components within the finite mixture model framework.
Discuss Mixture models

- Three functions of K=3 components in the mixed model

Trajectory pattern(class) 1: \( g_1(t_{ij}, A_1\beta_i) = \beta_0 + \beta_{1i}(t_{ij} - \tau_i) \)

Trajectory pattern(class) 2: \( g_2(t_{ij}, A_2\beta_i) = \beta_0 + \beta_{1i}(t_{ij} - \tau_i) + \beta_{2i}(t_{ij} - \tau_i) \)

Trajectory pattern(class) 3: \( g_3(t_{ij}, A_3\beta_i) = \beta_0 + \beta_{1i}(t_{ij} - \tau_i) - \beta_{2i}(t_{ij} - \tau_i) \)

\[ \beta_{1i} \geq 0, \beta_{2i} \geq 0; b_i = (b_{1i}, b_{2i}, b_{3i}, b_{4i})^T; \]

\[ \beta_i = (\beta_{0i}, \log(\beta_{1i}), \log(\beta_{2i}), \log(\tau_i))^T \] presents individual parameter;

\[ \beta = (\beta_0, \log(\beta_1), \log(\beta_2), \log(\tau_i))^T \] presents population parameter;

- The individual random-effects are assumed to follow a normal distribution

\[ \beta_i = \beta + b_i, \quad b_i \sim N_4(0, \Sigma) \]
Discuss Mixture models

Missing data models

(1) Non-ignorable missing data model

\[ f(r_i | \eta) = \prod_{i=1}^{n} \prod_{i=1}^{n_i} [P(r_{ij} = 1 | \eta)]^{r_{ij}} [1 - P(r_{ij} = 1 | \eta)]^{1-r_{ij}} \]  

\[
\text{logit}[P(r_{ij} = 1 | \eta)] = \eta_0 + \eta_1 y_{ij}, \quad \eta = (\eta_0, \eta_1)^T
\]

Let \( r_i = (r_{i1}, ..., r_{in_i})^T \) be a vector of missing response indicators such that \( r_{ij} = 1 \) if \( y_{ij} \) is missing and 0 otherwise; The missingness of the CD4 response depends on current CD4 value, which may be missing and the missing mechanism is non-ignorable.

(2) Ignorable missing data model

For comparison, we also consider the following ignorable missing model (denote by IM) for CD4 response, with \( y_{id}(d \leq j) \) being the last observed CD4 response for the \( i \) th subject.

\[
\text{logit}[P(r_{0i} = 1 | \eta)] = \eta_0 + \eta_1 y_{id}, \quad d \leq j
\]  

(8)
Parameter estimation of Mixed models

◆ Prior distributions for unknown parameters

Let \( \theta = \{ \beta, \eta, \sigma^2, \Sigma, \nu, \delta \} \) be the collection of unknown parameters in all models except for the mixture weight \( \pi \) in (4). Under the Bayesian framework, we specify weakly informative prior unknown population parameters in these models as follows

\[
\begin{align*}
\beta & \sim N_4(0, 10^2 I_4), \\
\sigma & \sim IG(10^{-2}, 10^{-2}), \\
\Sigma & \sim IW(10^{-2} I_4, 5) \\
\eta & \sim N_2(0, 10^2 I_2), \\
\delta & \sim N(0, 10^2), \\
\nu & \sim Exp(0.1)I(\nu > 2)
\end{align*}
\]

◆ The latent indicating variables \( c_i(i = 1, \cdots, n) \) follow a Categorical distribution (Cat)

\[
c_i \sim Cat((1, 2, 3), (\pi_1, \pi_2, \pi_3))
\]

in which \( \pi = (\pi_1, \pi_2, \pi_3)^T \) follows a Dirichlet distribution (Dir)

\[
\pi \sim Dir(\phi_1, \phi_2, \phi_3)
\]

Hyperparameters \( \phi_1 = \phi_2 = \phi_3 = 1 \) are set to be equal because we initially assume all individuals have equal probabilities of coming from any one of three classes.
Two basic steps of the MCMC scheme for mixture model

1. Sampling class membership indicators $c_i$, conditional on population parameters, $\theta$, and individual random effects, $b_i$

$$P(c_i = k | b_i) = \frac{\pi_k f(y_i | b_i, c_i = k, \theta)}{\sum_{m=1}^{3} \pi_m f(y_i | b_i, c_i = m, \theta)} , \quad (11)$$

Update the probability $\pi$ for next iteration from distribution

$$\left( \pi | \text{num}_1, \text{num}_2, \text{num}_3 \right) \sim \text{Dir}(\phi_1 + \text{num}_1, \phi_2 + \text{num}_2, \phi_3 + \text{num}_3) \quad (12)$$

$$\text{num}_k = \sum_{i=1}^{n} I(c_i = k), (k = 1, 2, 3), \quad I(\bullet) \text{ is an indicator function.}$$

2. Sampling parameters $\theta$ and individual random effects $b_i$, conditional on class membership indicators $C = (c_1, ..., c_n)^T$.

$$y_i | w_i, u_i, b_i, r_i, c_i \sim N_{ni}(g_{ci}(t_i, A_{ci}, \beta_i) + \delta[w_i - J(\mathbf{v})I_{ni}], u_i^{-1}\sigma^2 I_{ni})$$

$$w_i | u_i \sim N_{ni}(0, u_i^{-1}I_{ni}) I(w_i > 0), u_i \sim \Gamma(v/2, v/2), \quad (13)$$

$$b_i \sim N(0, \Sigma), r_{ij} | \eta \sim \text{Bernoulli}(P_{ij})$$
Parameter estimation of Mixed models

Inferential procedure

- Let $f(· | ·)$ denote a conditional density function and $h(·)$ be prior density function.
- After specifying the mixture models for the observed data $D = \{y_{obs,i}, t_i, r_i, (i = 1, ..., n)\}$, the joint posterior density of $\theta$ conditional on $D$ and $c$ can be given by

$$f(\theta|D, c) \propto \left\{ \prod_{i} \int f(y_i|w_i, u_i, b_i, r_i, c_i)f(w_i|u_i, w_i > 0)f(u_i)f(r_i|\eta)f(b_i)dy_{mis,i}db_i \right\} h(\theta)$$

$$= \left\{ \prod_{i} \int f(y_{obs,i}, w_i, u_i, b_i, r_i, c_i)f(w_i|u_i, w_i > 0)f(u_i)f(r_i|\eta)f(b_i)db_i \right\} h(\theta) (13)$$

- The integrals in (13) are of high dimension and do not have a closed form;
- The MCMC procedure can be used to sample population parameters $\theta$, and random effects $b_i$, from conditional posterior distributions, based on (13), using the Gibbs sampler along with the Metropolis-Hastings (M-H) algorithm.
Model implementation and model validation

- Analysis of AIDS data
- Simulation data
Results

Results
Model implementation

Fit the FMCME models with a skew distribution to the data.

Three statistical models with different distribution specifications for model error in the FMCME models (4)–(6) for CD4 response in conjunction with the missing data model (7) are employed to compare the performance of model fitting, and estimate of both model parameters and class membership probabilities at individual and population levels:

- Model ST: A FMCME model with the ST distribution for model error
- Model SN: A FMCME model with the SN distribution for model error
- Model N: A FMCME model with the normal (N) distribution for model error
Analysis of AIDS Clinical Data

- **Model implementation**
  - Applying asymmetric distributions for model error (Models ST and SN) to investigate how asymmetric distributions contribute to modeling results and parameter estimation in comparison with a normal distribution for model error (Model N);
  - Compare the joint modeling approach (JM) with 'naive' method (NM), which ignores missing CD4 response in the mixture models (4), to investigate how the missing data in CD4 contribute to modeling results;
  - Non-ignorable missing data model (7) is replaced by the ignorable missing data model (8) for inference to investigate how non-ignorable and ignorable missing data mechanisms influence modeling results;
  - Sensitivity analysis for various non-ignorable missing data models to check how parameter estimates are sensitive to different missing data mechanisms.

- **The MCMC procedure is implemented using WinBUGS software interacted with a function bugs in the package R2WinBUGS of R.**

- **Convergence of the generated samples is assessed using standard tools such as trace plots and Gelman-Rubin (GR) diagnostics.**
Gelman-Rubin (GR) diagnostics plot based on the FMCME model with an ST distribution (Model ST) for three Markov chains for representative parameters;

The top curve tends to 1, indicating that the algorithm has approached convergence.
## Comparison of modeling results

<table>
<thead>
<tr>
<th>Missing</th>
<th>Method</th>
<th>Model</th>
<th>$\beta_0$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>$\tau$</th>
<th>$\delta$</th>
<th>$\sigma^2$</th>
<th>$v$</th>
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<td>JM</td>
<td>ST</td>
<td>PM</td>
<td>0.135</td>
<td>0.081</td>
<td>0.010</td>
<td>37.07</td>
<td>0.228</td>
<td>0.011</td>
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<td></td>
<td></td>
<td></td>
<td>Lcl</td>
<td>0.011</td>
<td>0.031</td>
<td>0.009</td>
<td>15.31</td>
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<td>0.350</td>
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<td></td>
<td></td>
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<td>SD</td>
<td>0.093</td>
<td>0.059</td>
<td>0.001</td>
<td>22.81</td>
<td>0.009</td>
<td>0.001</td>
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<td>SD</td>
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<td>0.007</td>
<td>19.93</td>
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<td>11.98</td>
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<td>SD</td>
<td>0.078</td>
<td>0.339</td>
<td>0.181</td>
<td>32.26</td>
<td>0.098</td>
<td>0.003</td>
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</table>
Analysis of AIDS Clinical Data

- Comparison of modeling comparison

Goodness of fit: the diagnostic plot of the observed values versus fitted values of standardized CD4 (left panel), and Q–Q plot of different distributions(right panel) based on Model ST.
Analysis of AIDS Clinical Data

- Comparison of modeling comparison

Goodness of fit: the diagnostic plot of the observed values versus fitted values of standardized CD4 (left panel), and Q–Q plot of different distributions (right panel) based on Model SN.
Goodness of fit: the diagnostic plot of the observed values versus fitted values of standardized CD4 (left panel), and Q–Q plot of different distributions (right panel) based on Model N.
### Analysis of AIDS Clinical Data

#### Model Selection Criteria

<table>
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<th>Missing</th>
<th>Method</th>
<th>Model</th>
<th>DIC</th>
<th>EPD</th>
<th>SSR</th>
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<tbody>
<tr>
<td>NIM</td>
<td>JM</td>
<td>ST</td>
<td>3844.6</td>
<td>0.045</td>
<td>139.5</td>
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<td>NIM</td>
<td>JM</td>
<td>SN</td>
<td>3994.1</td>
<td>0.083</td>
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<td>NM</td>
<td>JM</td>
<td>ST</td>
<td>4188.3</td>
<td>0.082</td>
<td>254.9</td>
</tr>
<tr>
<td>IM</td>
<td>JM</td>
<td>ST</td>
<td>4037.5</td>
<td>0.081</td>
<td>250.3</td>
</tr>
</tbody>
</table>

EPD: expected predictive deviance, $E\{\sum_{i,j}(y_{rep,ij} - y_{obs,ij})^2\}$;  
DIC: deviance information criterion; 
SSR: sums of squared residuals.

- Further, the estimates of parameters $\eta$ in non-ignorable missing data model (7) based on Model ST are $\hat{\eta} = (-2.998(0.059), 0.055(0.065))^T$.
- The conducted hypothesis $H_0 : \eta = 0$, $H_1 : \eta \neq 0$; $p=0.008$.  

Sensitivity for missing data models based on Model ST

The sensitivity analysis are conducted based on the mixture model with the ST distribution for CD4 response in conjunction with several alternative missing data models:

- Model I: Model (4) with logit\[P(r_{ij} = 1|\boldsymbol{\eta}) = \eta_0 + \eta_1 y_{ij};\]
- Model II: Model (4) with logit\[P(r_{ij} = 1|\boldsymbol{\eta}) = \eta_0 + \eta_1 r_{i,j-1} + \eta_2 y_{ij};\]
- Model III: Model (4) with logit\[P(r_{ij} = 1|\boldsymbol{\eta}) = \eta_0 + \eta_1 y_{i,j-1} + \eta_2 y_{ij};\]
- Model IV: Model (4) with logit\[P(r_{ij} = 1|\boldsymbol{\eta}) = \eta_0 + \eta_1 y_{ij} + \eta_2 b_{1i} + \eta_3 b_{2i} + \eta_4 b_{3i} + \eta_5 b_{4i};\]
### Comparison of modeling results

<table>
<thead>
<tr>
<th>Model</th>
<th>DIC</th>
<th>EPD</th>
<th>(\hat{\tau}) (SD)</th>
</tr>
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<tbody>
<tr>
<td>Model I</td>
<td>3844.6</td>
<td>0.045</td>
<td>37.07(22.81)</td>
</tr>
<tr>
<td>Model II</td>
<td>3858.2</td>
<td>0.052</td>
<td>37.01(21.91)</td>
</tr>
<tr>
<td>Model III</td>
<td>3873.1</td>
<td>0.050</td>
<td>37.05(22.10)</td>
</tr>
<tr>
<td>Model IV</td>
<td>3902.3</td>
<td>0.057</td>
<td>37.21(22.57)</td>
</tr>
</tbody>
</table>

EPD: expected predictive deviance, calculated as \(E\{\sum_{i,j}(y_{rep,ij} - y_{obs,ij})^2\}\); DIC: deviance information criterion; \(\hat{\tau}\) (SD): estimated posterior mean \(\hat{\tau}\) and associated standard deviation (SD) of population changepoint.
Cluster all individuals’ membership into three trajectory classes based on Model ST can be formulated as below:

\[ p_{ik} = E[I(c_i = k)] = \frac{1}{M} \sum_{m=1}^{M} I(c_i^{(m)} = k) \]

- \( p_{ik} \) denotes the posterior probability of individual \( i \) belong to the \( k \) th (\( k = 1,2,3 \)) class at individual level, ;
- \( c_i^{(m)} \) is class membership of individual \( i \) drawn from the posterior distribution (11) in the \( m \) th MCMC iteration (\( m=1,\ldots,M \)) and \( M \) is a total number of iterations.

- **Analysis results based on model ST**
Barplot displays the probabilities for the selected 20 individuals at individual level (from the 21st to the 40th patient).

- Probability corresponding to individual patient who is classified as either drug resistance or not may help physicians to refine treatment strategy.

- The population proportion of individuals in each class

  $\pi_1(95\%CI), \%=31.13(28.86\sim33.35)$

  $\pi_2(95\%CI), \%=40.58(38.22\sim43.05)$

  $\pi_3(95\%CI), \%=28.29(26.31\sim30.37)$
The three trajectory classes:

1. \( \hat{y}(t) = 0.0135 + 0.081(t - 37.07)_- \)
2. \( \hat{y}(t) = 0.0135 + 0.081(t - 37.07)_- + 0.010(t - 37.07)_+ \)
3. \( \hat{y}(t) = 0.0135 + 0.081(t - 37.07)_- - 0.010(t - 37.07)_+ \)

\( \hat{y}(t) \) is the standardized CD4 scale.

For three trajectory classes indicate that the CD4 count increases rapidly at the beginning of treatment (from entry time to approximate 37 weeks), but after 37 weeks the CD4 count maintains a stable (class 1), has a gradual increase (class 2), and starts to decline.
Simulation study

- Simulation studies to assess the performance of the three models (Models ST, SN, and N) and two methods (JM and NM)

To simulate a heterogeneous population, 10%, 45%, and 45% trajectory mean values of responses, out of 300 individuals, are generated based on the three mean functions (5). In the simulation, the non-ignorable missing data model (7) is adopted and the measurement time points used are similar to those in the CD4 data. The true values of model parameters are similar to those in the data example so that all simulated data make biological sense.

- True values of model parameters:

  \[
  \beta_0 = 0.135, \quad \beta_1 = 0.081, \quad \beta_2 = 0.010, \quad \tau = 37.07
  \]

  \[
  E = \text{diag}(0.61, 4.69, 0.51, 36.21)
  \]

  \[
  \eta_0 = -3.00, \eta_1 = 0.055 \text{ in the non-ignorable missing data model (7) to get an approximately average missing response rate of 20%. We let the first two responses on each individual be always observed, so that each individual has at least two observed responses.} \]
A summary of Monte Carlo (MC) simulation results for MC estimates of fixed-effects $\beta$, skewness $\delta$ as well as bias and mean-square-error (MSE) for Models ST, SN and N based on 200 simulated data sets with $\Gamma(2,1)$ distribution for the model error.

<table>
<thead>
<tr>
<th>Method</th>
<th>Model</th>
<th>$\beta_0$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>$\tau$</th>
<th>$\delta$</th>
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</thead>
<tbody>
<tr>
<td>Ture value</td>
<td>0.135</td>
<td>0.081</td>
<td>0.101</td>
<td>37.07</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>JM</td>
<td>ST</td>
<td>MC mean</td>
<td>0.132</td>
<td>0.078</td>
<td>0.013</td>
<td>39.17</td>
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<tr>
<td></td>
<td></td>
<td>Bias</td>
<td>1.65</td>
<td>-4.37</td>
<td>-19.2</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSE</td>
<td>9.35</td>
<td>7.66</td>
<td>19.8</td>
<td>10.2</td>
</tr>
<tr>
<td>JM</td>
<td>SN</td>
<td>MC mean</td>
<td>0.139</td>
<td>0.071</td>
<td>0.019</td>
<td>42.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bias</td>
<td>1.89</td>
<td>-5.01</td>
<td>-20.2</td>
<td>14.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSE</td>
<td>12.5</td>
<td>7.40</td>
<td>24.5</td>
<td>12.7</td>
</tr>
<tr>
<td>JM</td>
<td>N</td>
<td>MC mean</td>
<td>0.122</td>
<td>0.061</td>
<td>0.023</td>
<td>50.27</td>
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<tr>
<td></td>
<td></td>
<td>Bias</td>
<td>2.78</td>
<td>-9.32</td>
<td>-45.0</td>
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<tr>
<td></td>
<td></td>
<td>MSE</td>
<td>20.5</td>
<td>13.5</td>
<td>42.6</td>
<td>15.7</td>
</tr>
<tr>
<td>NM</td>
<td>ST</td>
<td>MC mean</td>
<td>0.127</td>
<td>0.091</td>
<td>0.020</td>
<td>45.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bias</td>
<td>1.99</td>
<td>-7.04</td>
<td>-21.2</td>
<td>19.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSE</td>
<td>13.1</td>
<td>10.3</td>
<td>34.6</td>
<td>16.7</td>
</tr>
</tbody>
</table>
The developed Bayesian approach to the FMCME models can perfectly provide estimates of both model parameters and class membership probabilities at individual and population levels, allowing accurate inference of parameters while adjusting for heterogeneity, skewness, and missingness in the longitudinal analysis.

The developed FMCME models have generally broader applications whenever the relevant technical specifications are met and longitudinal measurements are assumed to arise from two or more identifiable subclasses within a population.

The proposed modeling approach can be easily implemented using the publicly available WinBUGS and R packages. This makes this approach quite powerful and accessible to practicing statisticians in the fields.
Discussions

Outlooks

◆ The number of components in this analysis is determined empirically based on the viral load trajectory patterns and clinical interpretability, more effectively methods can be considered to identify the heterogeneity and explore the exact components.

◆ The individual-variation of CD4 measurements may indicate different changepoint of all trajectories, as well as the different changing rate of CD4 cell count in different phages.

◆ The missing data models discussed in this research can be extended to incorporate latent class as covariate. The study of such extended missing data models are interesting is a direction for further research.
The end

Thank you for your attention!