Bayesian Inference on Joint Mixture Models for Survival-Longitudinal Data with Multiple Features

Yangxin Huang

Department of Epidemiology and Biostatistics, COPH, USF, Tampa, FL

yhuang@health.usf.edu

January 20, 2017

Outline

- **Introduction: Problems and Objectives**
- **Motivating Data Set**
- **Joint Mixture Models for HIV Dynamics**
- **Simultaneous Bayesian Inference Approach**
- **Analysis of AIDS Clinical Data**
  - **Model implementation**
  - **Results of data analysis**
- **Summary**

Introduction

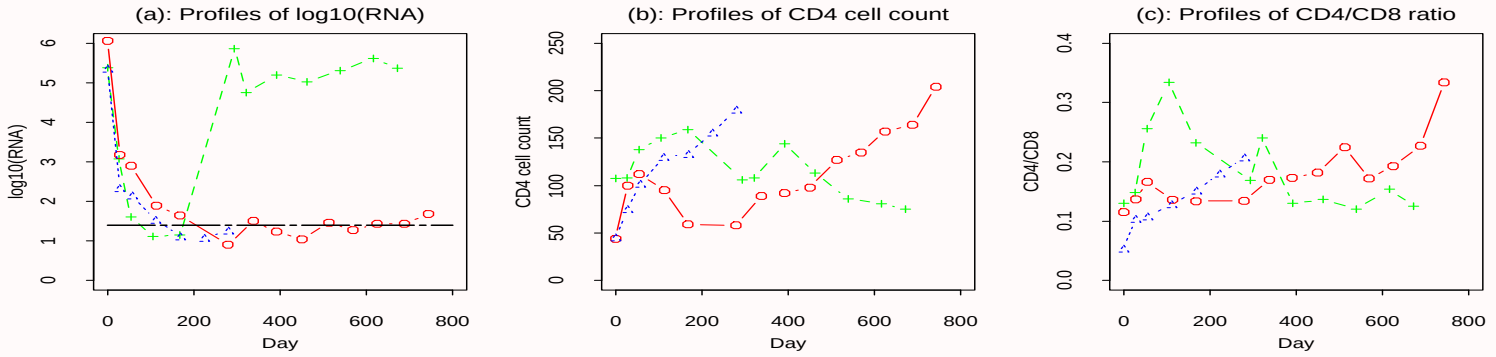
- **Joint modeling analysis of event times and longitudinal measures is an active area of statistics research. However, following issues standout**
  - **Response followed heterogeneous characteristics**
  - **Response suffered from left-censoring due to a limit of detection**
  - **Covariate measured with substantial error**
  - **Shortages of confidence in specifying distribution for a time-to-event**
- **The majority of literature for the joint modeling has focused on developing models to capture only specific aspects of the motivating studies:**
  - **mixture response**
  - **censored response**
  - **covariate measurement error**
  - **longitudinal-survival (or event time) data**

Introduction (*cont.*)

- **No studies have done on simultaneous inference for longitudinal data with features of heterogeneity and left-censoring due to LOD in response and measurement error in covariate as well as event time data incorporated**
- **Propose a Bayesian approach-based mixture of joint models**
- **In particular, motivated by an AIDS study to consider**
  - **a mixture of NLME models for viral load response in connection with a Tobit model to tailor observations below LOD**
  - **a nonparametric mixed-effects model for CD4 covariate process to modulate accuracy from measurement error**
  - **an accelerated failure time (AFT) model with unspecified distribution for time to decline of CD4/CD8**
  - **a mixture of joint models linked through shared random-effects**

Motivating AIDS Clinical Data Set

- **A randomized, open-label study with 96 weeks comparing 2 different 4-drug regimens for 517 subjects**
- **HIV-1 RNA (viral load), CD4 and CD8 data: measured at weeks 0, 4, 8, 16, and every 8 weeks**
- **Baseline and demographic data**
- **34% of viral load observations were measured below the LOD**



Motivating AIDS Clinical Data Set (*cont.*)

- **Viral load trajectory profiles can be roughly classified into three classes (Left panel of Figure in last slide)**
  - **Class 1: patient's viral loads decrease rapidly and constantly in a short-term period (dotted-blue line) due to the fact that some patients withdrew too early to be clustered into either class 2 (without viral load rebound) or class 3 (with viral load rebound)**
  - **Class 2: patient's viral loads decrease at the beginning and then stay stable at a low level (solid-red line)**
  - **Class 3: patient's viral loads decrease at the beginning, but they experience viral load increase, which results in viral load rebound eventually (dashed-green line)**
- **The classes 1 and 2 indicate a confirmed virologic response, while the class 3 implies a virologic failure**

Mixture of Joint Models

- **Discuss mixture of NLME joint models: three processes**
- **Covariate process–measurement error model**

$$z_{ij} = w(t_{ij}) + h_i(t_{ij}) + \epsilon_{ij} \ (\equiv z^*_{ij} + \epsilon_{ij}), \ \boldsymbol{\epsilon}_i \overset{\text{iid}}{\sim} N_{n_i}(\mathbf{0}, \sigma_1^2 \boldsymbol{I}_{n_i}), \quad (1)$$

  - **Nonparametric mixed-effects model**
  - $z^*_{ij} = w(t_{ij}) + h_i(t_{ij})$ **are the true (but unobservable) covariate values at time** t_{ij}
  - **Fixed smooth function** $w(t)$ **represents population average, while the random smooth function** $h_i(t)$ **is introduced to incorporate the large inter-individual variation**
  - $\boldsymbol{\epsilon}_i = (\epsilon_{i1}, \ldots, \epsilon_{in_i})^T$ **follows a multivariate normal distribution**

Mixture of Joint Models (*cont.*)

- **Regression spline used to approximate $w(t)$ and $h_i(t)$ by a linear combination of basis functions $\boldsymbol{\Psi}_p(t) = \{\psi_0(t), \psi_1(t), ..., \psi_{p-1}(t)\}^T$ and $\boldsymbol{\Phi}_q(t) = \{\phi_0(t), \phi_1(t), ..., \phi_{q-1}(t)\}^T$**

$$\begin{aligned} w(t) \approx w_p(t) &= \textstyle\sum_{l=0}^{p-1} \alpha_l \psi_l(t) = \boldsymbol{\Psi}_p(t)^T \boldsymbol{\alpha}, \\ h_i(t) \approx h_{iq}(t) &= \textstyle\sum_{l=0}^{q-1} a_{il} \phi_l(t) = \boldsymbol{\Phi}_q(t)^T \boldsymbol{a}_i, \end{aligned} \tag{2}$$

  - $\boldsymbol{\alpha} = (\alpha_0, \ldots, \alpha_{p-1})^T$ **is a** $p \times 1$ **vector of fixed-effects**
  - $\boldsymbol{a}_i = (a_{i0}, \ldots, a_{i,q-1})^T$ $(q \leq p)$ **is a** $q \times 1$ **vector of random-effects**
  - $\boldsymbol{a}_i \overset{\text{iid}}{\sim} N_q(\mathbf{0}, \boldsymbol{\Sigma}_a)$

- **Approximated LME model**

$$z_{ij} \approx \boldsymbol{\Psi}_p(t_{ij})^T \boldsymbol{\alpha} + \boldsymbol{\Phi}_q(t_{ij})^T \boldsymbol{a}_i + \epsilon_{ij} \approx z^*_{ij} + \epsilon_{ij}, \quad \boldsymbol{\epsilon}_i \overset{\text{iid}}{\sim} N_{n_i}(\mathbf{0}, \sigma_1^2 \boldsymbol{I}_{n_i}), \tag{3}$$

Mixture of Joint Models (*cont.*)

- **Response process–Mixture of NLME Tobit models**

$$
\begin{aligned}
&(\boldsymbol{y}_i|c_i = k) = \boldsymbol{g}_k(\boldsymbol{t}_i, \boldsymbol{A}_k\boldsymbol{\beta}_{ij}) + \boldsymbol{e}_i, \;\; \boldsymbol{e}_i \overset{\text{iid}}{\sim} N_{n_i}(\boldsymbol{0}, \sigma_2^2\boldsymbol{I}_{n_i}), \\
&\boldsymbol{\beta}_{ij} = \boldsymbol{Z}_{ij}\boldsymbol{\beta} + \boldsymbol{X}\boldsymbol{b}_i, \;\; \boldsymbol{b}_i \overset{\text{iid}}{\sim} N_s(\boldsymbol{0}, \boldsymbol{\Sigma_b}),
\end{aligned}
\tag{4}
$$

  - K **plausible nonlinear trajectory classes with mean functions** $g_k(\cdot)$ **(**$k = 1, ..., K$**)**
  - $g_k(\cdot)$ **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**
  - $\boldsymbol{t}_i = (t_{i1}, \ldots, t_{in_i})^T$**,** $\boldsymbol{\beta}_{ij} = (\beta_{1ij}, \ldots, \beta_{sij})^T$**,** $\boldsymbol{\beta} = (\beta_1, ..., \beta_r)^T$
  - $\boldsymbol{Z}_{ij}$ $(s \times r)$ **is a design matrix**
  - $\boldsymbol{X}$ $(s \times m)$ **is random-effects related indicator matrix**
  - $\boldsymbol{A}_k$ **is known** $s \times s$ **square-matrix indicator where diagonal elements are either** 0 **or** 1 **and off-diagonal elements are all** 0**.**
  - $\boldsymbol{A}_k$ **is introduced because the mean functions of** y_{ij}**, specified by the nonlinear functions** $g_k(\cdot)$**, may only involve different subsets of** $\boldsymbol{\beta}_{ij}$**.**

Mixture of Joint Models (*cont.*)

- **Model (4) can be specified conditionally and marginally**

$$(\boldsymbol{y}_i|c_i = k) \sim N_{n_i}(\boldsymbol{g}_k(\boldsymbol{t}_i, \boldsymbol{A}_k\boldsymbol{\beta}_{ij}), \sigma_2^2\boldsymbol{I}_{n_i}), \tag{5}$$

$$\boldsymbol{y}_i \sim \sum_{k=1}^{K} \pi_k N_{n_i}(\boldsymbol{g}_k(\boldsymbol{t}_i, \boldsymbol{A}_k\boldsymbol{\beta}_{ij}), \sigma_2^2\boldsymbol{I}_{n_i}). \tag{6}$$

- **In order to introduce Tobit model to deal with observations below LOD, denote the observed value y_{ij} by (q_{ij}, d_{ij}), where d_{ij} is the censoring indicator and q_{ij} is the latent response variable.**
- **y_{ij} is observed if $d_{ij} = 0$ and y_{ij} is left-censoring if $d_{ij} = 1$; that is, $y_{ij} = q_{ij}$ if $d_{ij} = 0$, and $y_{ij} \leq \rho$ (a known constant LOD) if $d_{ij} = 1$.**
- **Equation (6) along with the Tobit formulation forms the finite mixture of NLME Tobit models**

Mixture of Joint Models (*cont.*)

- **For the viral load responses with 3 classes, we have the mean functions of $K = 3$ components in the mixture model**
  1. **One-compartment model with a constant decay rate for class 1**

$$g_1(t_{ij}, \boldsymbol{A}_1\boldsymbol{\beta}_{ij}) = \log_{10}(e^{p_{1i} - \lambda_{1i} t_{ij}}), \tag{7}$$

  2. **Two-compartment model with constant decay rates for class 2**

$$g_2(t_{ij}, \boldsymbol{A}_2\boldsymbol{\beta}_{ij}) = \log_{10}(e^{p_{1i} - \lambda_{1i} t_{ij}} + e^{p_{2i} - \lambda_{2i} t_{ij}}), \tag{8}$$

  3. **Two-compartment model with constant and time-varying decay rates for class 3**

$$g_3(t_{ij}, \boldsymbol{A}_3\boldsymbol{\beta}_{ij}) = \log_{10}(e^{p_{1i} - \lambda_{1i} t_{ij}} + e^{p_{2i} - \lambda_{2ij} t_{ij}}). \tag{9}$$

$$\beta_{1i} = p_{1i} = \beta_1 + b_{i1},\ \beta_{2i} = \lambda_{1i} = \beta_2 + \beta_3 z_{i0} + b_{i2},\ \beta_{3i} = p_{2i} = \beta_4 + b_{i3},$$
$$\beta_{4i} = \lambda_{2i} = \beta_5 + b_{i4},\ \beta_{5ij} = \lambda_{2ij} = \beta_5 + \beta_6 z^*_{ij} + b_{i4},$$
$$\boldsymbol{\beta}_{ij} = (\beta_{1i}, \beta_{2i}, \beta_{3i}, \beta_{4i}, \beta_{5ij})^T,\ \boldsymbol{\beta} = (\beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6)^T, \boldsymbol{b}_i = (b_{i1}, \ldots, b_{i4})^T,$$
$$\boldsymbol{A}_1 = \mathbf{diag}(1, 1, 0, 0, 0), \boldsymbol{A}_2 = \mathbf{diag}(1, 1, 1, 1, 0), \boldsymbol{A}_3 = \mathbf{diag}(1, 1, 1, 0, 1)$$

Mixture of Joint Models (*cont.*)

$$\boldsymbol{Z}_{ij} = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & z_{i0} & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 & z_{ij}^* \end{pmatrix} \text{ and } \boldsymbol{X} = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 \end{pmatrix}, \qquad (10)$$

- z_{i0} **and** z_{ij}^* **are baseline CD4 and true value of CD4 at time** t_{ij}
- **Decay rate of the second compartment in (9),** β_{5ij}**, is time-varying due to** z_{ij}^***, but other parameters in** $\boldsymbol{\beta}_{ij}$ **are time independent**
- $g_1(\cdot)$ **only involves parameters** β_{1i} **and** β_{2i}**, and** $g_2(\cdot)$ **and** $g_3(\cdot)$ **share the same parameters** β_{1i}**,** β_{2i}**, and** β_{3i} **but have different second-phase decay rate,** β_{4i} **and** β_{5ij}**, respectively**
- $\boldsymbol{A}_1$**,** $\boldsymbol{A}_2$**, and** $\boldsymbol{A}_3$**, determine which elements of** $\boldsymbol{\beta}_{ij}$ **are involved and set other unrelated parameters to be 0 in the mean functions,** $g_k(\cdot)$

Mixture of Joint Models (*cont.*)

- **Survival process– Accelerated failure time (AFT) models with an unspecified distribution**

$$\begin{aligned} \ln(\Im_i) &= \boldsymbol{\gamma}^T \boldsymbol{\tau}_i + \varepsilon_i, \;\; \varepsilon_i \sim G(\cdot), \\ G(\cdot) &\sim DP(\eta G_0),\; G_0 \sim N(\zeta_0, \sigma_0^2),\; \eta \sim \Gamma(\eta_{10}, \eta_{20}). \end{aligned} \tag{11}$$

  - $\boldsymbol{\tau}_i = (1, a_{i0}, a_{i1}, a_{i2}, b_{i2}, b_{i4})^T$ **with unknown coefficients** $\boldsymbol{\gamma} = (\gamma_0, \gamma_1, \ldots, \gamma_5)^T$
  - ε_i **follows an unspecified distribution** $G(\cdot)$ **that is the DP prior**
  - **Parameter** G_0 **is the prior mean of** $G(\cdot)$ **and represents a guess; the other parameter of the DP prior,** η**, reflects the degree of closeness of** $G(\cdot)$ **to the prior mean** G_0**.**
  - **Large values of** η **make** $G(\cdot)$ **very close to** G_0**, while small values of** η **allow** $G(\cdot)$ **to deviate from** G_0
  - **To implement the DP prior** $DP(\eta G_0)$ **, a popular way for specifying the DP prior is the stick-breaking prior representation**

Simultaneous Bayesian Inference

- **Under the umbrella of a mixture of joint models, MCMC procedure consists of the following two iterative steps**

  1. **Sampling class membership indicator c_i, conditional on $\boldsymbol{\theta} = \{\boldsymbol{\alpha}, \boldsymbol{\beta}, \boldsymbol{\gamma}, \sigma_1^2, \sigma_2^2, \boldsymbol{\Sigma}_a, \boldsymbol{\Sigma}_b\}$, $\boldsymbol{a}_i$ and $\boldsymbol{b}_i$**

$$P(c_i = k|\boldsymbol{a}_i, \boldsymbol{b}_i, \boldsymbol{\theta}, \boldsymbol{y}_i) = \frac{\pi_k f(\boldsymbol{y}_i|\boldsymbol{a}_i, \boldsymbol{b}_i, c_i=k, \boldsymbol{\theta})}{\sum_{m=1}^{3} \pi_m f(\boldsymbol{y}_i|\boldsymbol{a}_i, \boldsymbol{b}_i, c_i=m, \boldsymbol{\theta})}, \tag{12}$$

  2. **Sampling parameters $\boldsymbol{\theta}$, and $\boldsymbol{a}_i$ and $\boldsymbol{b}_i$, conditional on class membership indicator c_i**

$$\begin{aligned} &\boldsymbol{z}_i|\boldsymbol{a}_i \sim N_{n_i}(\boldsymbol{z}_i^*, \sigma_1^2 \boldsymbol{I}_{n_i}),\ \boldsymbol{a}_i \sim N_3(\boldsymbol{0}, \boldsymbol{\Sigma}_a), \\ &\boldsymbol{y}_i|\boldsymbol{a}_i, \boldsymbol{b}_i, c_i \sim N_{n_i}(\boldsymbol{g}_{c_i}(\boldsymbol{t}_i, \boldsymbol{A}_{c_i}\boldsymbol{\beta}_i), \sigma_2^2 \boldsymbol{I}_{n_i}),\ \boldsymbol{b}_i \sim N_4(\boldsymbol{0}, \boldsymbol{\Sigma_b}), \\ &\Im_i|\boldsymbol{\tau}_i \sim G\left(\ln(t_i) - \boldsymbol{\gamma}^T \boldsymbol{\tau}_i\right), \end{aligned} \tag{13}$$

Simultaneous Bayesian Inference (*cont.*)

- **Prior distributions for unknown parameters**

$$\boldsymbol{\alpha} \sim N_3(\boldsymbol{\tau}_1, \boldsymbol{\Lambda}_1),\ \boldsymbol{\beta} \sim N_6(\boldsymbol{\tau}_2, \boldsymbol{\Lambda}_2),\ \boldsymbol{\gamma} \sim N_6(\boldsymbol{\tau}_3, \boldsymbol{\Lambda}_3),$$
$$\sigma_1^2 \sim IG(\omega_1, \omega_2),\ \sigma_2^2 \sim IG(\omega_3, \omega_4),\ \boldsymbol{\Sigma}_a \sim IW(\boldsymbol{\Omega}_1, \nu_1),\ \boldsymbol{\Sigma}_b \sim IW(\boldsymbol{\Omega}_2, \nu_2), \tag{14}$$

- **Latent indicating variables c_i $(i = 1, ..., n)$ follow a Categorical distribution(Cat)**

$$c_i \overset{iid}{\sim} Cat((1, 2, 3), (\pi_1, \pi_2, \pi_3)), \tag{15}$$

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

$$\boldsymbol{\pi} \sim Dir(\phi_1, \phi_2, \phi_3). \tag{16}$$

Simultaneous Bayesian Inference (*cont.*)

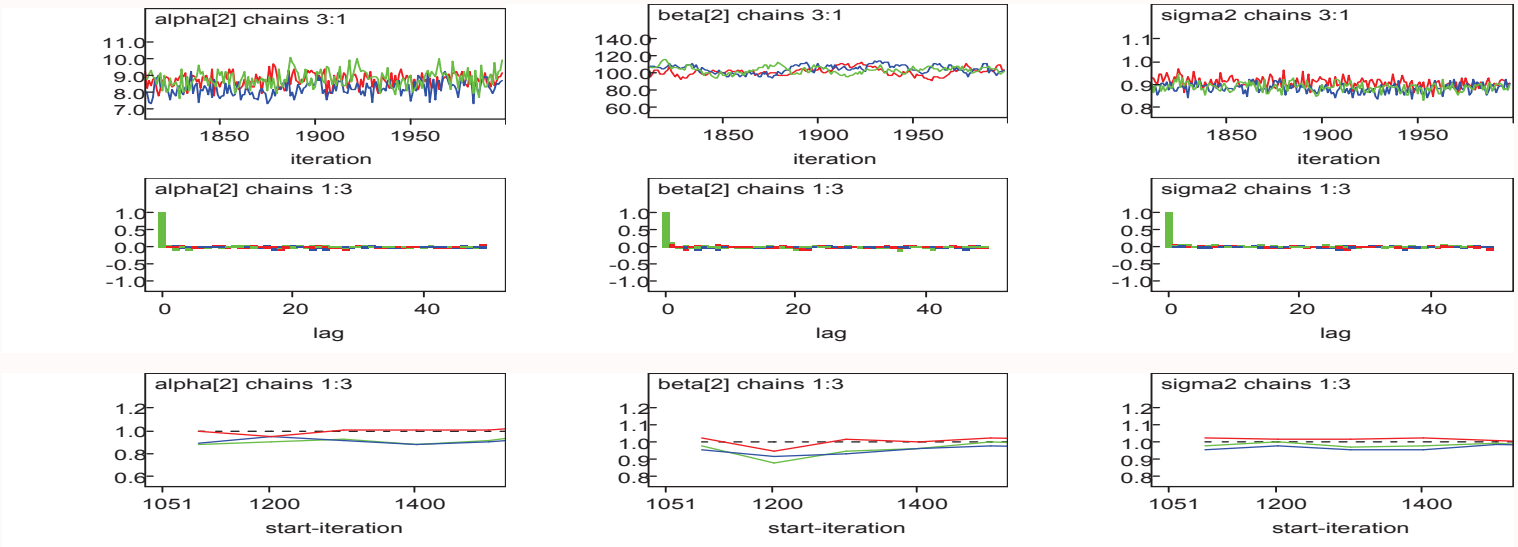
- **Let $f(\cdot|\cdot)$, $F(\cdot|\cdot)$ and $h(\cdot)$ denote a probability density function (pdf), cumulative density function (cdf) and prior density function.**
- **With the specification of the Tobit model, a detectable measurement y_{ij} contributes $f(y_{ij}|\boldsymbol{b}_i, \boldsymbol{a}_i, c_i)$, whereas a non-detectable measurement contributes $F(\rho|\boldsymbol{b}_i, \boldsymbol{a}_i, c_i) \equiv P(y_{ij} < \rho|\boldsymbol{b}_i, \boldsymbol{a}_i, c_i)$ in the likelihood.**
- **After specifying the models for the observed data $\Re$ and prior $h(\boldsymbol{\theta})$, the joint posterior density of $\boldsymbol{\theta}$ based on the observed data $\Re$ and classification indicator $\boldsymbol{c}$**

$$f(\boldsymbol{\theta}|\Re, \boldsymbol{c}) \propto \{\prod_{i=1}^{n} \int\int L_{\boldsymbol{y}_i} f(\boldsymbol{z}_i|\boldsymbol{a}_i) F^*(u_i, v_i|\boldsymbol{\tau}_i) f(\boldsymbol{a}_i) f(\boldsymbol{b}_i) d\boldsymbol{a}_i d\boldsymbol{b}_i\} h(\boldsymbol{\theta}), \tag{17}$$

  - $F^*(u_i, v_i|\boldsymbol{\tau}_i) = G\left(\ln(v_i) - \boldsymbol{\gamma}^T \boldsymbol{\tau}_i\right) - G\left(\ln(u_i) - \boldsymbol{\gamma}^T \boldsymbol{\tau}_i\right)$
  - $L_{\boldsymbol{y}_i} = \prod_{j=1}^{n_i} f(y_{ij}|\boldsymbol{b}_i, \boldsymbol{a}_i, c_i)^{1-d_{ij}} F(\rho|\boldsymbol{b}_i, \boldsymbol{a}_i, c_i)^{d_{ij}}$

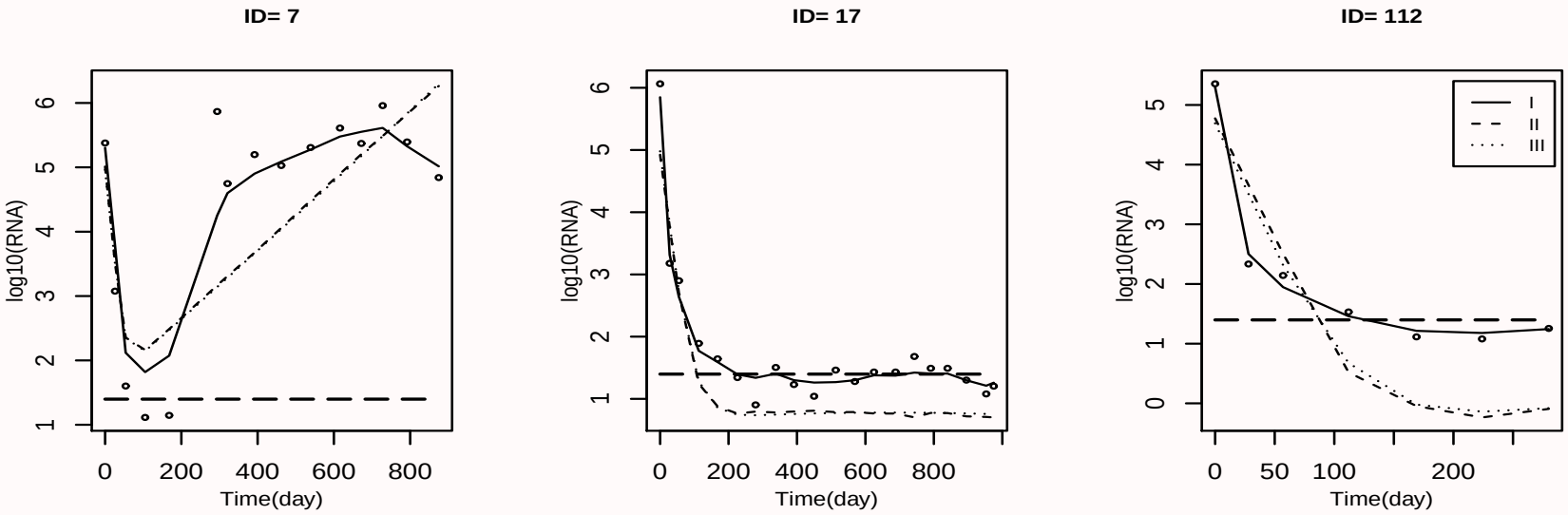
Analysis of AIDS Clinical Data

- **Model implementation**
  - **Compare the joint modeling (JM) approach (Model I) with 'naive" method (NM) (Model II), which ignores measurement error in CD4 covariate**
  - **Investigate a commonly used NLME joint model (Model III, ignoring data feature of heterogeneous population) where the mean function is specified by (9) to compare the proposed mixture of NLME joint model (Model I).**
- **To carry out the Bayesian inference, we took weakly-informative prior distributions for the parameters**
- **The MCMC sampler was implemented using WinBUGS software interacted with R**
- **Convergence of the generated samples was assessed using standard tools such as trace plots and Gelman-Rubin (GR) diagnostics**



- **Trace plots (top panel) that the lines of three different chains mix or cross in trace, implying that convergence is ensured**
- **Autocorrelation plots (middle panel) that autocorrelations are very low with a lag being 50, implying that convergence is obtained**
- **Gelman-Rubin (GR) diagnostics (bottom panel) where the three curves are given: the top curve (red) tends to 1, indicating that the algorithm has approached convergence**

Analysis of AIDS Clinical Data (*cont.*)



- **The estimated individual trajectories for Model I fit the originally observed values above LOD more closely than those for Models II and III which are comparable**
- **The predicted values where the viral load observations are below LOD appear quite different between Model I and Models II and III**

Analysis of AIDS Clinical Data (*cont.*)

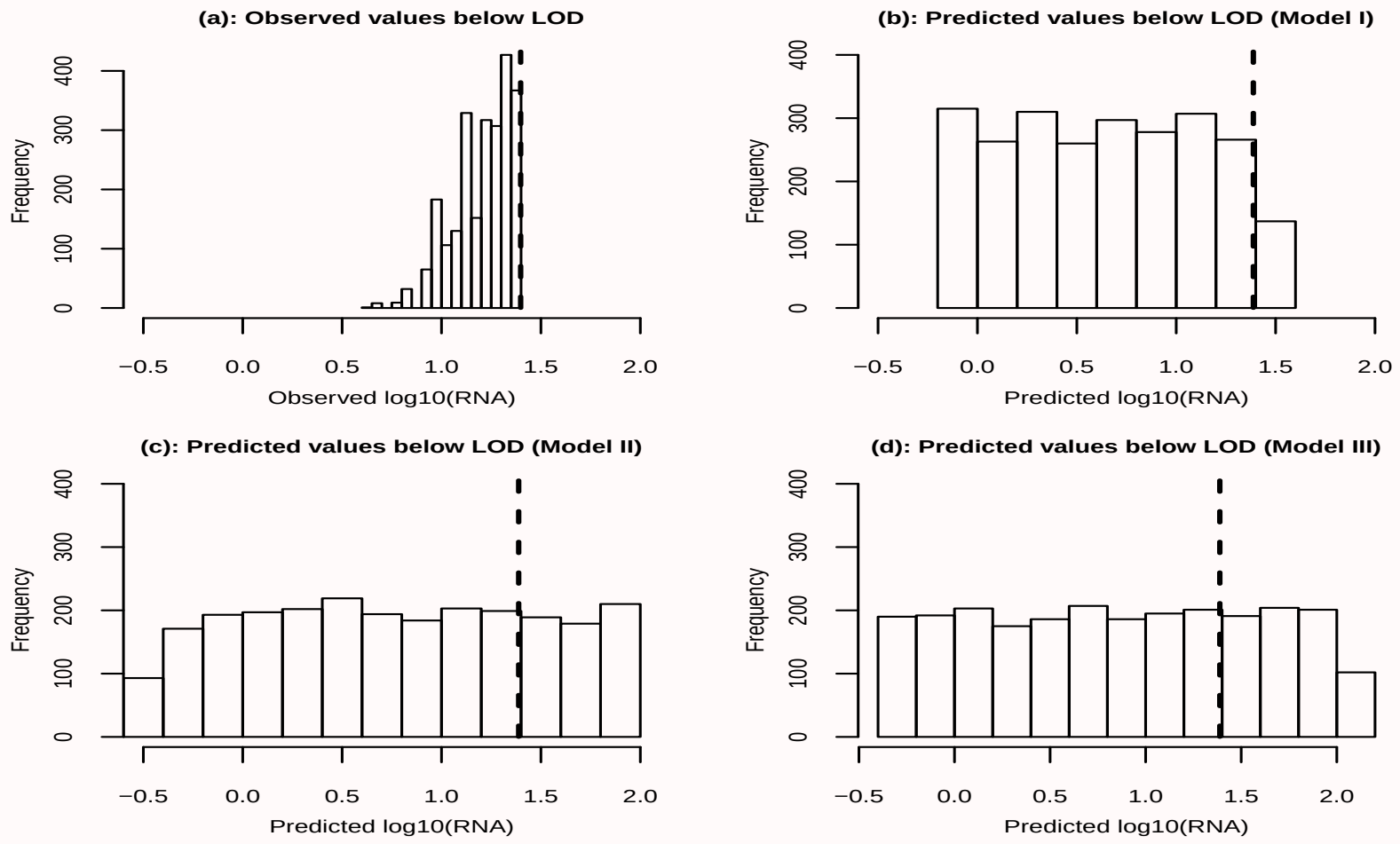
- **In the mixture of NLME response model**
  - **β_5 and β_6, which are parameters related to second-phase viral decay rate, are significantly different from zero for the three Models**
  - **For the estimate of the coefficient of CD4 covariate β_6, although its estimate based on Model I (0.098) is much smaller than the counterpart based on Models II and III (0.245 and 0.157), its estimate is always significantly positive**
  - **This means that CD4 has a significantly positive effect on the second-phase viral decay rate, suggesting that CD4 covariate may be an important predictor of the second-phase viral decay rate**
  - **The estimate of β_3, the coefficient of baseline CD4 count, is significantly positive, indicating that the baseline CD4 has positive effect on the first-phase viral decay rate.**

Analysis of AIDS Clinical Data (*cont.*)

- **In the CD4 covariate model**
  - **α_2 is significantly different from zero with a positive value, suggesting that there is a positive linear relation between CD4 cell count and measurement time**
  - **This result may be explained by the fact that CD4 cell count may increase during treatment, and in turn, indicates an overall improvement of AIDS progression**
- **In the AFT model**
  - **The estimates of parameters do not directly show that the time to CD4/CD8 decrease is highly associated with either the two viral decay rates or the CD4 changes over time, which is different from what was anticipated.**
  - **This finding is consistent with that reported in the literature**

Analysis of AIDS Clinical Data (*cont.*)

- **In comparison JM (Model I) with NM (Model II)**
  - **Estimates of (β_5, β_6), which depend on whether or not to ignore potential CD4 measurement error, that the differences between the NM estimates and JM estimates indicate that CD4 measurement error can not be ignored in the analysis.**
- **In comparison Model I with Model III**
  - **The important differences were found in the estimates of parameters (β_5, β_6), which are associated with the second-phase viral decay rate**
  - **One advantage of Model I over Model III is its flexibility to provide not only estimates of all model parameters, but also evaluate class membership probabilities at both population and individual levels, which is helpful for clinicians to develop individualized treatment**



Histograms of inaccurate raw data (a) below LOD (dash line), and predicted values of viral load below LOD based on Models I (b), II (c) and III (d)

Analysis of AIDS Clinical Data (*cont.*)

- **Treat inaccurate observed viral loads below LOD as missing values and predict them using the mixture of joint models in connection with the Tobit model**
  - **Most observed values are piled up at the range (0.6, 1.4) in the upper-left histogram (Fig. (a))**
  - **For Models I, II and III the predicted values of the unobserved viral load below LOD are spread out**
  - **Models II and III produce the predicted values exceeded the LOD much more than Model I does**
- **When we compare the three models in terms of their distributions in predicting viral loads below LOD**
  - **Model I gives more plausible values ranged within (-0.2, 1.5) than Models II and III do, implying that Model I is the better model**
  - **This finding is also confirmed by the results from DIC**
  - **It is important to consider heterogeneous, LOD and/or covariate measurement error data features**

Analysis of AIDS Clinical Data (*cont.*)

- **One of the primary objectives is to cluster all individuals' membership into 3 classes based on viral load trajectories. At population level,**
  - **The estimates of population proportion and associated 95% CI of (π_1, π_2, π_3) for three classes are 5.29% (3.15%, 7.47%), 57.13% (54.34%, 59.79%) and 37.58% (34.83%, 40.43%), respectively**
  - **A confirmed shorter-term (class 1) and longer-term (class 2) virologic responses were observed in a total of 62.42% of the patients in classes 1 and 2**

Analysis of AIDS Clinical Data (*cont.*)

- **At individual level, barplot below displays the probabilities for the selected 20 individuals**

- **Probability corresponding to individual patient who is classified as either viral load rebound or not may help physicians to refine treatment strategy. For example,**
  - **patient 12 belongs to class 1 because the viral load decreases constantly in a early short-term period with probability 81.5%;**
  - **viral load of patient 17 decreases and then maintain stable, so this patient belongs to class 2 with probability 91.1%;**
  - **patient 7 is in class 3 (indicating viral load rebound) with probability 83.7%.**

Summary

- Constructed a mixture of joint model formulated by the longitudinal (response and covariate) models and time-to-event model linked through shared random-effects
- Developed a Bayesian joint modeling approach-based mixture of joint models that may be preferred over the 'naive' method
- Applied the methodology to AIDS clinical trial study and obtained some important findings

Summary (*cont.*)

- One advantage of mixture joint modeling approach-based models is its flexibility to study simultaneous impact of various data characteristics (heterogeneity, nonlinearity, missingness due to LOD and measurement errors)
- Another advantage of our mixture joint modeling approach is to provide not only all model parameter estimates, but also model-based probabilistic clustering to obtain class membership probabilities at both population and individual levels
- This research is motivated by AIDS clinical study, but the basic concepts of developed modeling method have generally broader applications whenever relevant technical specifications are met.

Summary (*cont.*)

- The mixture components, $g_k(\cdot)$ may have the same family of densities but differ only in specific values of parameters such as in their means, or have completely different functional forms with parameters of different dimensions and meanings across the sub-models, which is the case adopted in this study.
- The number of components in this analysis was determined empirically based on the viral load trajectory patterns and clinical interpretability
- The mixture of joint models can be extended to assume model errors with skew distributions such as skew-normal and skew-t if data exhibit non-normality which is a direction for further research

THE END

Questions and comments?

Thank you for your attention!