UNIVERSIDADE ESTADUAL DE CAMPINAS
UNICAMP

IMECC 50 ANOS

33rd New England Statistics Symposium (NESS)

Flexible longitudinal linear mixed models for multiple censored responses data

Larissa Avila Matos

Co-Authors: Victor H. Lachos, Luis M. Castro and Ming-Hui Chen

May 10, 2019

Contents

Summary

Motivation

- Mixed-effects models are commonly used to fit longitudinal or repeated measures data.
- In longitudinal studies, it is common to observe more than one series of responses repeatedly measured in each subject across time. This type of data is called multivariate longitudinal data and is analyzed (in general) using the multivariate linear mixed effect (MLME) model proposed by Shah et al.
- Studies of HIV viral dynamics, often considered to be a key issue in AIDS research, consider repeated/longitudinal measures over a period of treatment routinely analyzed using MLME to assess rates of changes in HIV-1 RNA level or viral load.
- The number of RNA copies (viral load) in blood plasma and its evolutionary trajecto-ries play a prominent role in the diagnosis of HIV-1 disease progression after an ARV treatment regimen.
- However, depending on the diagnostic assays used, measurements of viral loads may be subject to upper or lower detection limits, values above or below these limits are not quantified.

Motivating dataset : AIDS clinical trials

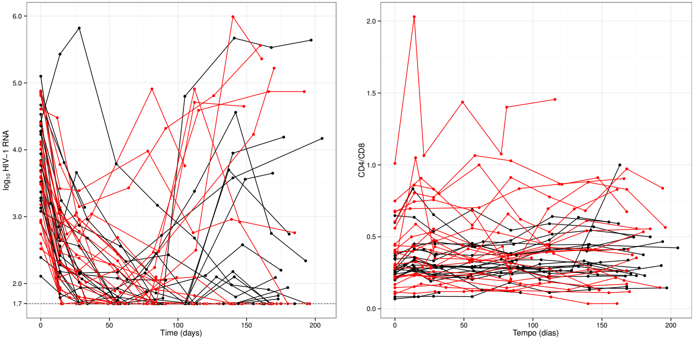
- **A5055 study**

  → 44 infected patients with the human immunodeficiency virus type 1 (HIV-1);

  → These patients were treated with one of two potent ARV therapies;

  → 2 response variables: the viral load ($\log_{10}$(RNA)) and the CD4/CD8, where CD4 and CD8 two immunologic markers frequently used to monitor disease progression in AIDS studies ;

  → 33.5% (106 out of 316) of measurements lies below the limits of assay quantification (left-censored).



→ Black lines indicate patients under treatment 1 and red lines indicate patients under treatment 2

Recent Works

Longitudinal Models

Censored longitudinal models with normal distribution

- Samson *et al.* (2006) [*Computational Statistical & Data Analysis*]
- Vaida *et al.* (2007) [*Computational Statistical & Data Analysis*]
- Vaida & Liu (2009) [*Journal of Computational and Graphical Statistics*]
- Matos *et al.* (2013a) [*Computational Statistical & Data Analysis*]

Censored longitudinal models with heavy-tailed distribution

- Lachos *et al.* (2011) [*Biometrics*]
- **Garay et al. (2014)** [*Statistical Methods in Medical Research*]
- **Matos et al. (2013b)** [*Statistica Sinica*]
- **Wang et al. (2015)** [*Statistical Methods in Medical Research*]

Proposta

- **Goal:** model variables with multiple censored responses using distributions with heavy tails.
- **Classical solution:** In the frequentist context, the main hypothesis assumed is that the random terms follows a multivariate normal or Student-t distribution; and the EM algorithm is used to estimate the parameters.
- **Problem:** Some data sets are not compatible with the assumption of normality, either by the heavy tail or by the presence of atypical values. And depending on the distribution chosen for the random terms the EM algorithm can not be implemented.
- **Proposal:** Use more flexible distributions for random terms. In this case, we will work with the so-called Scale mixture of normal distributions (SMN) and for the estimation procedure we will adopt the SAEM algorithm.

Summary

Scale mixture of normal distributions (SMN)

Andrews & Mallows (1974); Lange & Sinsheimer (1993)

Stochastic representation

$$\mathbf{y} = \boldsymbol{\mu} + \kappa(\mathrm{U})^{1/2}\mathbf{Z}, \quad (1)$$

- $\mu \in \mathbb{R}$ is a location vector;
- $Z \sim N(0, \boldsymbol{\Sigma})$;
- U is a positive random variable with cumulative distribution function (cdf) $\mathrm{H}(u|\boldsymbol{\nu})$ and probability density function (pdf) $h(u|\boldsymbol{\nu})$;
- $\boldsymbol{\nu}$ is a scalar or parameter vector indexing the distribution of U;
- $\kappa(\mathrm{U})$ is the weight function;
- $Z \perp \mathrm{U}$;
- Notation: $\mathbf{y} \sim \mathrm{SMN}_p(\boldsymbol{\mu}, \boldsymbol{\Sigma}; \mathrm{H})$.

Scale mixture of normal distributions (SMN)

- Conditional distribution:

$$\begin{aligned} \mathbf{y}|\mathrm{U}=u &\sim N(\boldsymbol{\mu},\kappa(u)\boldsymbol{\Sigma}), \\ \mathrm{U}=u &\sim h(u|\boldsymbol{\nu}). \end{aligned} \tag{2}$$

- The pdf of **y** is given by:

$$f(\mathbf{y}) = \int_0^\infty \phi_p(\mathbf{y};\boldsymbol{\mu},\kappa(u)\boldsymbol{\Sigma})d\mathrm{H}(u|\boldsymbol{\nu}). \tag{3}$$

Scale mixture of normal distributions (SMN)

Special cases: $\mathbf{y} \in \mathbb{R}^p$

- **The multivariate normal distribution**
  - $P(U = 1) = 1$;
  - Distribution function: $\mathrm{N}(\mathbf{y}|\boldsymbol{\mu}, \boldsymbol{\Sigma}) = \phi_p(\mathbf{y}; \boldsymbol{\mu}, \boldsymbol{\Sigma})$.

- **The multivariate Student?s-t distribution**
  - $\mathrm{U} = Gama(\nu/2, \nu/2)$;
  - $\kappa(u) = 1/u$;
  - Distribution function:

$$\mathrm{T}(\mathbf{y}|\boldsymbol{\mu}, \boldsymbol{\Sigma}, \nu) = \frac{\Gamma(\frac{p+\nu}{2})}{\Gamma(\frac{\nu}{2})\pi^{p/2}} \nu^{-p/2} |\boldsymbol{\Sigma}|^{-1/2} \left(1 + \frac{d}{\nu}\right)^{-(p+\nu)/2},$$

where $d = (\mathbf{y} - \boldsymbol{\mu})^\top \boldsymbol{\Sigma}^{-1} (\mathbf{y} - \boldsymbol{\mu})$.

- **The multivariate slash distribution**

  - $\mathrm{U} = Beta(\nu, 1)$;
  - $\kappa(u) = 1/u$;
  - Distribution function:

$$\mathrm{SL}(\mathbf{y}|\boldsymbol{\mu}, \boldsymbol{\Sigma}, \nu) = \nu \int_0^1 u^{\nu-1} \phi_p(\mathbf{y}; \boldsymbol{\mu}, u^{-1}\boldsymbol{\Sigma}) du, \quad u \in (0, 1), \quad \nu > 0.$$

- **The multivariate contaminated normal distribution**

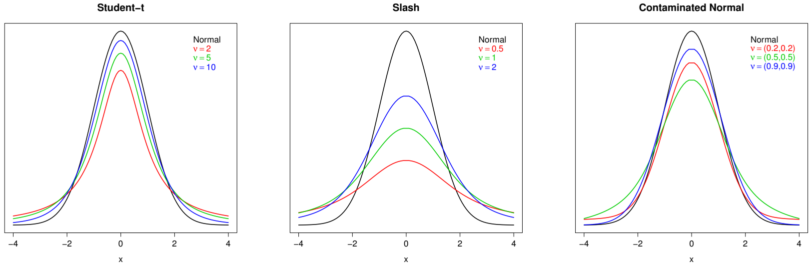
  - U is a discrete random variable taking one of two states and with probability function given by $h(u|\boldsymbol{\nu}) = \nu \mathbb{I}_{\{\gamma\}}(u) + (1-\nu)\mathbb{I}_{\{1\}}(u)$ and $\boldsymbol{\nu} = (\nu, \gamma)$;
  - $\kappa(u) = 1/u$;
  - Distribution function:

$$\mathrm{CN}(\mathbf{y}|\boldsymbol{\mu}, \boldsymbol{\Sigma}, \boldsymbol{\nu}) = \nu \phi_p(\mathbf{y}; \boldsymbol{\mu}, \gamma^{-1}\boldsymbol{\Sigma}) + (1-\nu)\phi_p(\mathbf{y}; \boldsymbol{\mu}, \boldsymbol{\Sigma}).$$

  The parameter ν can be interpreted as the proportion of outliers while γ may be interpreted as a scale factor.

Scale mixture of normal distributions (SMN)

- The univariate case:



SAEM Algorithm

EM Algorithm - Dempster *et al.* (1977)

Let $\boldsymbol{\theta}$ be the parameter vector and $\boldsymbol{y}_c = (\mathbf{y}^\top, \boldsymbol{q}^\top)$ be the vector of complete data, i.e., the observed data $\mathbf{y}^\top$ and the missing/censored data (or the latent variables, depending on the situation) $\boldsymbol{q}^\top$. The EM algorithm consists basically of two steps: the expectation (E-step) and the maximization (M-step).

- **E-Step:** Calculate the conditional expectation

$$Q(\boldsymbol{\theta} \mid \widehat{\boldsymbol{\theta}}^{(k)}) = E\left[\ell_c(\boldsymbol{\theta} \mid \mathbf{y}_c) \mid \mathbf{y}, \widehat{\boldsymbol{\theta}}^{(k)}\right],$$

  where $\widehat{\boldsymbol{\theta}}^{(k)}$ is the estimate of $\boldsymbol{\theta}$ at the k-th iteration.

- **M-Step:** Update $\boldsymbol{\theta}^{(k)}$ according to

$$\widehat{\boldsymbol{\theta}}^{(k+1)} = \underset{\theta}{\text{argmax}} Q(\boldsymbol{\theta} \mid \widehat{\boldsymbol{\theta}}^{(k)}).$$

SAEM Algorithm

MCEM Algorithm - Wei & Tanner (1990)

- **E-Step: MC:**

  1. **Simulation-step:** Draw $\mathbf{q}^{(k,l)}$ $(l = 1, \ldots, m)$ from the conditional distribution $f(\mathbf{q}|\mathbf{y}, \widehat{\boldsymbol{\theta}}^{(k-1)})$;
  2. **Approximation-step:** Using $\mathbf{q}^{(k,l)}$ $(l = 1, \ldots, m)$, calculate the conditional expectation $Q(\boldsymbol{\theta} \mid \widehat{\boldsymbol{\theta}}^{(k)})$ through the approximation,

$$Q(\boldsymbol{\theta}|\widehat{\boldsymbol{\theta}}^{(k)}) = \frac{1}{m}\sum_{l=1}^{m} \ell_c(\boldsymbol{\theta}|\mathbf{q}^{(k,l)}, \mathbf{y}).$$

- **M-Step:** Update $\boldsymbol{\theta}^{(k)}$ according to

$$\widehat{\boldsymbol{\theta}}^{(k+1)} = \underset{\theta}{\operatorname{argmax}} Q(\boldsymbol{\theta}|\widehat{\boldsymbol{\theta}}^{(k)}).$$

SAEM Algorithm

SAEM Algorithm - Delyon *et al.* (1999)

- **E-Step:**

  1. **Simulation-step:** Draw $\mathbf{q}^{(k,l)}$ $(l = 1, \ldots, m)$ from the conditional distribution $f(\mathbf{q}|\mathbf{y}, \widehat{\boldsymbol{\theta}}^{(k-1)})$;
  2. **Stochastic-approximation-step:** Update $Q(\boldsymbol{\theta}|\widehat{\boldsymbol{\theta}}^{(k)})$ according to

  $$Q(\boldsymbol{\theta}|\widehat{\boldsymbol{\theta}}^{(k)}) = Q(\boldsymbol{\theta}|\widehat{\boldsymbol{\theta}}^{(k-1)}) + \delta_k \left[\frac{1}{m} \sum_{l=1}^{m} \ell_c(\boldsymbol{\theta}|\mathbf{q}^{(k,l)}, \mathbf{y}) - Q(\boldsymbol{\theta}|\widehat{\boldsymbol{\theta}}^{(k-1)}) \right],$$

  where $\ell_c(\boldsymbol{\theta} \mid \mathbf{y}_c) = \sum_{i=1}^{n} \ell_i(\boldsymbol{\theta} \mid \mathbf{y}_c)$ is the complete log-likelihood function and δ_k is a smoothness parameter, *i.e.*, a decreasing sequence of positive numbers such that $\sum_{k=1}^{\infty} \delta_k = \infty$ and $\sum_{k=1}^{\infty} \delta_k^2 < \infty$.

- **M-Step:** Update $\boldsymbol{\theta}^{(k)}$ according to

$$\widehat{\boldsymbol{\theta}}^{(k+1)} = \underset{\theta}{\operatorname{argmax}} Q(\boldsymbol{\theta}|\widehat{\boldsymbol{\theta}}^{(k)}).$$

SAEM Algorithm

SAEM Algorithm - Delyon *et al.* (1999)

- As proposed by Galarza *et al.* (2015), we will consider the following smoothing parameter

$$\delta_k = \begin{cases} 1, & \text{if} \quad 1 \leq k \leq cW; \\ \frac{1}{k - cW}, & \text{if} \quad cW + 1 \leq k \leq W, \end{cases} \qquad (4)$$

  where,

  - W is the maximum number of iterations; and
  - c is a cut point $(0 \leq c \leq 1)$ which determines the percentage of the initial iterations.

  - Other proposals for the smoothing parameter δ_k can be found in Kuhn & Lavielle (2005), Jank (2006), among others.

SMN-CR model

Correlation structures - Muñoz *et al.* (1992)

Damped exponential correlation (DEC):

$$\mathrm{E}_i = \mathrm{E}_i(\boldsymbol{\phi}, \mathbf{t}_i) = \left[\phi_1^{|t_{ij}-t_{ik}|^{\phi_2}}\right], \ i = 1, \ldots, n, \ \ j, k = 1, \ldots, n_i, \qquad (5)$$

- ϕ_1: describes the autocorrelation between observations separated by the absolute length of two time points;
- ϕ_2: permits acceleration of the exponential decay of the autocorrelation function, defining a continuous-time autoregressive model.

For the DEC structure, we have that:

(a) if $\phi_2 = 0$, then E_i generates the compound symmetry correlation structure;

(b) when $0 < \phi_2 < 1$, then E_i presents a decay rate between the compound symmetry structure and the first-order AR (AR (1)) model;

(c) if $\phi_2 = 1$, then E_i generates an AR(1) structure;

(d) when $\phi_2 > 1$, E_i presents a decay rate faster than the AR(1) structure; and

(e) if $\phi_2 \to \infty$, then E_i represents the first-order moving average model, MA(1).

Summary

The SMN multivariate linear mixed model for censored responses

Let $\mathbf{Y}_i = [\mathbf{y}_{i1} : \ldots : \mathbf{y}_{ir}]$, then

$$\mathbf{y}_i = \mathbf{X}_i\boldsymbol{\beta} + \mathbf{Z}_i\mathbf{b}_i + \boldsymbol{\epsilon}_i, \quad i = 1, \ldots, n; \tag{6}$$

with:

- $\mathbf{y}_i = \text{vec}(\mathbf{Y}_i) = (\mathbf{y}_{i1}^\top, \ldots, \mathbf{y}_{ir}^\top)^\top$, where $\mathbf{y}_{ij} = (y_{ij1}, \ldots, y_{ijn_i})^\top$ is an $n_i \times 1$ vector of the jth outcome For the ith subject;
- $\mathbf{X}_i = \text{Bdiag}\{\mathbf{X}_{i1}, \ldots, \mathbf{X}_{ir}\}$, where $\mathbf{X}_{ij}$ is an $n_i \times p_j$ design matrix for fixed effects corresponding to the jth outcome of the ith subject;
- $\mathbf{Z}_i = \text{Bdiag}\{\mathbf{Z}_{i1}, \ldots, \mathbf{Z}_{ir}\}$, where $\mathbf{Z}_{ij}$ is an $n_i \times q_j$ design matrix for random effects corresponding to the jth outcome of the ith subject, generally a subset of $\mathbf{X}_{ij}$;
- $\boldsymbol{\beta} = (\boldsymbol{\beta}_1^\top, \ldots, \boldsymbol{\beta}_r^\top)^\top$ is the $p \times 1$ vector of fixed effects associated with the design matrix $\mathbf{X}_i$, $p = \sum_{j=1}^r p_j$;
- $\mathbf{b}_i = (\mathbf{b}_{i1}^\top, \ldots, \mathbf{b}_{ir}^\top)^\top$ is the $q \times 1$ vector of random effects associated with the design matrix $\mathbf{Z}_i$, $q = \sum_{j=1}^r q_j$;
- $\boldsymbol{\epsilon}_i = \text{vec}(\mathrm{E}_i) = (\boldsymbol{\epsilon}_{i1}^\top, \ldots, \boldsymbol{\epsilon}_{ir}^\top)^\top$ is the $s_i \times 1$ vector of random errors ($s_i = n_i \times r$), where $\mathrm{E}_i = [\boldsymbol{\epsilon}_{i1} : \ldots : \boldsymbol{\epsilon}_{ir}]$ and $\boldsymbol{\epsilon}_{ij}$ corresponds to the error for the jth outcome of the ith subject.

Modelo linear multivariado mistos censurado

- Instead of the usual assumption of normality for the errors and random effects, we replace the multivariate normal distribution with the multivariate SMN distribution. Therefore, the model can be expressed as

$$\begin{aligned}\mathbf{y}_i \mid \mathbf{b}_i &\overset{\text{ind.}}{\sim} \mathrm{SMN}_{s_i}(\mathbf{X}_i\boldsymbol{\beta} + \mathbf{Z}_i\mathbf{b}_i, \mathbf{R}_i; \mathrm{H}_1),\\ \mathbf{b}_i &\overset{\text{ind.}}{\sim} \mathrm{SMN}_q(\mathbf{0}, \mathbf{D}; \mathrm{H}_2), \quad i = 1, \ldots, n. \end{aligned} \tag{7}$$

- Using the stochastic representation (1), the hierarchical representation (four stages) of the model defined in (6) is given by

$$\begin{aligned}\mathbf{y}_i \mid \mathbf{b}_i, \kappa_i &\overset{\text{ind.}}{\sim} \mathrm{N}_{s_i}(\mathbf{X}_i\boldsymbol{\beta} + \mathbf{Z}_i\mathbf{b}_i, \kappa_i^{-1}\mathbf{R}_i),\\ \mathbf{b}_i \mid \tau_i &\overset{\text{ind.}}{\sim} \mathrm{N}_q(\mathbf{0}, \tau_i^{-1}\mathbf{D}),\\ \kappa_i &\overset{\text{ind.}}{\sim} \mathrm{H}_1(\nu),\\ \tau_i &\overset{\text{ind.}}{\sim} \mathrm{H}_2(\eta); \end{aligned} \tag{8}$$

where $\mathbf{R}_i = \boldsymbol{\Sigma} \otimes \boldsymbol{\Omega}_i$.

The SMN-MLMEC model

Censored Response

Recall that we are interested in the case where left-censored observations can occur. That is, the observed data for the i-th subject is represented by $(\mathbf{V}_i, \mathbf{C}_i)$, where

- $\mathbf{V}_i$ is the vector of uncensored observation or limit of quantification; and
- $\mathbf{C}_i$ is the vector of censoring indicator whose value equals one if censored observation and zero if uncensored observation,

such that, considering the left censored case, we have that

$$\begin{aligned} y_{ijk} &\leq V_{ijk} \quad \text{se} \quad C_{ijk} = 1, \\ y_{ijk} &= V_{ijk} \quad \text{se} \quad C_{ijk} = 0, \end{aligned}$$

with $i = 1, \ldots, n$, $j = 1, \ldots, n_i$ and $k = 1, \ldots, r$; where $\mathbf{V}_i = [V_{i1} : \ldots : V_{ir}]$ is an $n_i \times r$ matrix and $\mathbf{C}_i = [C_{i1} : \ldots : C_{ir}]$ is an $n_i \times r$matrix.

- For ease of presentation, we assume that the data are left-censored. The extensions to arbitrary censoring are immediate.

The SMN-MLMEC model

- The estimation procedure of the proposed model is derived through the the complete data log-likelihoodfunction, given by:

$$
\begin{aligned}
\ell_c(\boldsymbol{\theta}|\mathbf{y}_c) &= \sum_{i=1}^{n}[\log f(\mathbf{y}_i|\mathbf{b}_i,\kappa_i) + \log f(\mathbf{b}_i|\tau_i) + \log h_1(\kappa_i|\nu) + \log h_2(\tau_i|\eta)] \\
&= -\frac{1}{2}\sum_{i=1}^{n}\log|\mathbf{R}_i| - \frac{1}{2}\sum_{i=1}^{n}\kappa_i(\mathbf{y}_i - \mathbf{X}_i\boldsymbol{\beta} - \mathbf{Z}_i\mathbf{b}_i)^\top\mathbf{R}_i^{-1}(\mathbf{y}_i - \mathbf{X}_i\boldsymbol{\beta} - \mathbf{Z}_i\mathbf{b}_i) \\
&- \frac{1}{2}\sum_{i=1}^{n}\log|\mathbf{D}| - \frac{1}{2}\sum_{i=1}^{n}\tau_i\mathbf{b}_i^\top\mathbf{D}^{-1}\mathbf{b}_i + \sum_{i=1}^{n}\log h_1(\kappa_i|\nu) + \sum_{i=1}^{n}\log h_2(\tau_i|\eta) + K,
\end{aligned}
$$

where K is a constant that does not depend on the parameter vector $\boldsymbol{\theta} = (\boldsymbol{\beta}, \boldsymbol{\sigma}, \boldsymbol{\alpha}, \boldsymbol{\phi}, \nu, \eta)$, and $\mathbf{y}_c = (\mathbf{V}^\top, \mathbf{C}^\top, \mathbf{y}^\top, \boldsymbol{b}^\top, \boldsymbol{\kappa}^\top, \boldsymbol{\tau}^\top)^\top$ (augmenting data).

The SMN-MLMEC model

Maximum likelihood estimation - SAEM

- Q-function: For the i-th subject,

$$
\begin{aligned}
Q_i\left(\boldsymbol{\theta}|\widehat{\boldsymbol{\theta}}^{(k)}\right) &= \widehat{\ell h_{1i}}^{(k)} + \widehat{\ell h_{2i}}^{(k)} - \frac{1}{2}\log|\widehat{\mathbf{D}}^{(k)}| - \frac{1}{2}\mathrm{tr}\left(\widehat{\tau \mathbf{b}_i^2}^{(k)}\widehat{\mathbf{D}}_i^{-1(k)}\right) - \frac{1}{2}\sum_{i=1}^{n}\log|\widehat{\mathbf{R}}_i^{(k)}| \\
&- \frac{1}{2}\left[\mathrm{tr}\left(\widehat{\kappa \mathbf{y}_i^2}^{(k)}\widehat{\mathbf{R}}_i^{-1(k)}\right) - 2\widehat{\boldsymbol{\beta}}^{(k)\top}\mathbf{X}_i^\top\widehat{\mathbf{R}}_i^{-1(k)}\widehat{\kappa \mathbf{y}_i}^{(k)} + 2\widehat{\boldsymbol{\beta}}^{(k)\top}\mathbf{X}_i^\top\widehat{\mathbf{R}}_i^{-1(k)}\mathbf{Z}_i\widehat{\kappa \mathbf{b}_i}^{(k)}\right. \\
&- \left. 2\mathrm{tr}\left(\mathbf{Z}_i^\top\widehat{\mathbf{R}}_i^{-1(k)}\widehat{\kappa \mathbf{y}\mathbf{b}_i}^{(k)}\right) + \mathrm{tr}\left(\mathbf{Z}_i^\top\widehat{\mathbf{R}}_i^{-1(k)}\mathbf{Z}_i\widehat{\kappa \mathbf{b}_i^2}^{(k)}\right) + \widehat{\kappa}_i^{(k)}\widehat{\boldsymbol{\beta}}^{(k)\top}\mathbf{X}_i^\top\widehat{\mathbf{R}}_i^{-1(k)}\mathbf{X}_i\widehat{\boldsymbol{\beta}}^{(k)}\right],
\end{aligned}
$$

with

$$
\begin{aligned}
&\widehat{\ell h_{1i}}^{(k)} = E\left[\log h_1(\kappa_i|\nu)|\mathbf{V}_i,\mathbf{C}_i,\widehat{\boldsymbol{\theta}}^{(k)}\right], \quad \widehat{\ell h_{2i}}^{(k)} = E\left[\log h_2(\tau_i|\eta)|\mathbf{V}_i,\mathbf{C}_i,\widehat{\boldsymbol{\theta}}^{(k)}\right], \\
&\widehat{\kappa \mathbf{y}_i^2}^{(k)} = E\left[\kappa_i\mathbf{y}_i\mathbf{y}_i^\top|\mathbf{V}_i,\mathbf{C}_i,\widehat{\boldsymbol{\theta}}^{(k)}\right], \quad \widehat{\kappa \mathbf{y}_i}^{(k)} = E\left[\kappa_i\mathbf{y}_i|\mathbf{V}_i,\mathbf{C}_i,\widehat{\boldsymbol{\theta}}^{(k)}\right], \\
&\widehat{\kappa \mathbf{b}_i^2}^{(k)} = E\left[\kappa_i\mathbf{b}_i\mathbf{b}_i^\top|\mathbf{V}_i,\mathbf{C}_i,\widehat{\boldsymbol{\theta}}^{(k)}\right], \quad \widehat{\kappa \mathbf{b}_i}^{(k)} = E\left[\kappa_i\mathbf{b}_i|\mathbf{V}_i,\mathbf{C}_i,\widehat{\boldsymbol{\theta}}^{(k)}\right], \\
&\widehat{\tau \mathbf{b}_i^2}^{(k)} = E\left[\tau_i\mathbf{b}_i\mathbf{b}_i^\top|\mathbf{V}_i,\mathbf{C}_i,\widehat{\boldsymbol{\theta}}^{(k)}\right], \quad \widehat{\kappa \mathbf{y}\mathbf{b}_i}^{(k)} = E\left[\kappa_i\mathbf{y}_i\mathbf{b}_i^\top|\mathbf{V}_i,\mathbf{C}_i,\widehat{\boldsymbol{\theta}}^{(k)}\right], \\
&\widehat{\kappa}_i^{(k)} = E\left[\kappa_i|\mathbf{V}_i,\mathbf{C}_i,\widehat{\boldsymbol{\theta}}^{(k)}\right].
\end{aligned}
$$

The SMN-MLMEC model

SAEM - E-step

- **Simulation-step:** Gibbs Sampler

Passo 1. Sample $\mathbf{y}_i^c$ from $f(\mathbf{y}_i^c|\mathbf{V}_i^c, \mathbf{y}_i^o, \mathbf{b}_i^{(k,l-1)}, \kappa_i^{(k,l-1)}, \tau_i^{(k,l-1)}, \widehat{\boldsymbol{\theta}}^{(k)})$, where

$$\mathbf{y}_i^c|\mathbf{V}_i^c, \mathbf{y}_i^o, \mathbf{b}_i, \kappa_i, \tau_i, \boldsymbol{\theta} \sim \mathrm{TN}_{s_i^c}(\boldsymbol{\mu}_i, \kappa_i^{-1}\mathbf{S}_i; \mathbb{A}_i),$$

with $\mathbb{A}_i = \{\mathbf{y}_i^c = (y_{i1}^c, \ldots, y_{is_i^c}^c)^\top | y_{i1}^c \leq V_{i1}^c, \ldots, y_{is_i^c}^c \leq V_{is_i^c}^c\}$,

$$\begin{aligned} \boldsymbol{\mu}_i &= (\mathbf{X}_i^c\boldsymbol{\beta} + \mathbf{Z}_i^c\mathbf{b}_i) + \mathbf{R}_i^{co}(\mathbf{R}_i^{oo})^{-1}(\mathbf{y}_i^o - \mathbf{X}_i^o\boldsymbol{\beta} - \mathbf{Z}_i^o\mathbf{b}_i) \quad \text{and} \\ \mathbf{S}_i &= \mathbf{R}_i^{cc} - \mathbf{R}_i^{co}(\mathbf{R}_i^{oo})^{-1}\mathbf{R}_i^{oc}. \end{aligned}$$

Then, $\mathbf{y}_i^{(k,l)} = (y_{i1}, \ldots, y_{is_i^o}, y_{is_i^o+1}^{c(k,l)}, \ldots, y_{is_i}^{c(k,l)})$ is a sample generated for the s_i^o observed values (uncensored cases) and the censored cases.

Passo 2. Sample $\mathbf{b}_i^{(k,l)}$ from $f(\mathbf{b}_i|\mathbf{y}_i^{(k,l)}, \kappa_i^{(k,l-1)}, \tau_i^{(k,l-1)}, \widehat{\boldsymbol{\theta}}^{(k)})$, where

$$\mathbf{b}_i|\mathbf{y}_i, \kappa_i, \tau_i \sim \mathrm{N}_q(\boldsymbol{\Psi}_i\mathbf{Z}_i^\top\mathbf{R}_i^{-1}\kappa_i(\mathbf{y}_i - \mathbf{X}_i\boldsymbol{\beta}), \boldsymbol{\Psi}_i),$$

with $\boldsymbol{\Psi} = (\kappa_i\mathbf{Z}_i^\top\mathbf{R}_i^{-1}\mathbf{Z}_i + \tau_i\mathbf{D}^{-1})^{-1}$ (Arellano-Valle *et al.*, 2005, Lemma 2).

The SMN-MLMEC model

SAEM - E-step

Passo 3. Sample $\kappa_i^{(k,l)}$ from $f(\kappa_i|\mathbf{y}_i^{(k,l)}, \mathbf{b}_i^{(k,l)}, \tau_i^{(k,l-1)}, \widehat{\boldsymbol{\theta}}^{(k)})$.

Passo 4. Sample $\tau_i^{(k,l)}$ from $f(\tau_i|\mathbf{y}_i^{(k,l)}, \mathbf{b}_i^{(k,l)}, \kappa_i^{(k,l)}, \widehat{\boldsymbol{\theta}}^{(k)})$.

Observação: Note that, since $\mathbf{y}_i \mid \mathbf{b}_i$ is independent of τ_i; $\mathbf{b}_i$ is independent of κ_i; and κ_i and τ_i are mutually independent, we have

$$f(\kappa_i|\mathbf{y}_i, \mathbf{b}_i, \tau_i) \propto f(\mathbf{y}_i|\mathbf{b}_i, \kappa_i) f(\kappa_i)$$

and

$$f(\tau_i|\mathbf{y}_i, \mathbf{b}_i, \kappa_i) \propto f(\mathbf{b}_i|\tau_i) f(\tau_i).$$

The SMN-MLMEC model

SAEM - E-step

Distribution of ϵ_i	Distribution of κ_i	Distribution of $\kappa_i \mid \mathbf{y}_i, \mathbf{b}_i, \tau_i$
$\mathrm{T}_{si}(\mathbf{0}, \mathbf{R}_i, \nu)$	$\text{Gamma}(\nu/2, \nu/2)$	$\text{Gamma}\left((\nu + s_i)/2, (D^2_{e_i} + \nu)/2\right)$
$\mathrm{SL}_{si}(\mathbf{0}, \mathbf{R}_i, \nu)$	$\text{Beta}(\nu, 1)$	$\text{TGamma}\left(\nu + s_i/2, D^2_{e_i}/2, 1\right)$
$\mathrm{CN}_{si}(\mathbf{0}, \mathbf{R}_i, \nu_1, \nu_2)$	$\nu_1 \mathbb{I}_{\{\nu_2\}}(\kappa_i) + (1 - \nu_1)\mathbb{I}_{\{1\}}(\kappa_i)$	$P(\kappa_i = \nu_2) = 1 - P(\kappa_i = 1) = p_1/p_1 + p_2$ $p_1 = \nu_1 \nu_2^{s_i/2} exp\{-\frac{1}{2} D^2_{e_i} \nu_2\}$ $p_2 = (1 - \nu_1) exp\{-\frac{1}{2} D^2_{e_i}\}$

$D^2_{e_i} = (\mathbf{y}_i - \mathbf{X}_i\boldsymbol{\beta} - \mathbf{Z}_i\mathbf{b}_i)^\top \mathbf{R}_i^{-1}(\mathbf{y}_i - \mathbf{X}_i\boldsymbol{\beta} - \mathbf{Z}_i\mathbf{b}_i)$

Distribution of $\mathbf{b}_i$	Distribution of τ_i	Distribution of $\tau_i \mid \mathbf{y}_i, \mathbf{b}_i, \kappa_i$
$\mathrm{T}_q(\mathbf{0}, \mathbf{D}, \eta)$	$\text{Gamma}(\eta/2, \eta/2)$	$\text{Gamma}\left((\eta + q)/2, (D^2_{\mathbf{b}_i} + \eta)/2\right)$
$\mathrm{SL}_q(\mathbf{0}, \mathbf{D}, \eta)$	$\text{Beta}(\eta, 1)$	$\text{TGamma}\left(\eta + q/2, D^2_{\mathbf{b}_i}/2, 1\right)$
$\mathrm{CN}_q(\mathbf{0}, \mathbf{D}, \eta_1, \eta_2)$	$\eta_1 \mathbb{I}_{\{\eta_2\}}(\tau_i) + (1 - \eta_1)\mathbb{I}_{\{1\}}(\tau_i)$	$P(\tau_i = \eta_2) = 1 - P(\tau_i = 1) = q_1/q_1 + q_2$ $q_1 = \eta_1 \eta_2^{q/2} exp\{-\frac{1}{2} D^2_{\mathbf{b}_i} \eta_2\}$ $q_2 = (1 - \eta_1) exp\{-\frac{1}{2} D^2_{\mathbf{b}_i}\}$

$D^2_{\mathbf{b}_i} = \mathbf{b}_i^\top \mathbf{D}^{-1} \mathbf{b}_i$

The SMN-MLMEC model

SAEM - E-step

- **Stochastic-approximation-step:** $(\mathbf{y}_i^{(k,l)}, \mathbf{b}_i^{(k,l)}, \kappa_i^{(k,l)}, \tau_i^{(k,l)})$, $l = 1, \ldots, m$:

$$
\begin{aligned}
\widehat{\kappa\mathbf{y}_i^2}^{(k)} &= \widehat{\kappa\mathbf{y}_i^2}^{(k-1)} + \delta_k \left(\frac{1}{m} \sum_{l=1}^{m} \kappa_i^{(k,l)} \mathbf{y}_i^{(k,l)} \mathbf{y}_i^{(k,l)\top} - \widehat{\kappa\mathbf{y}_i^2}^{(k-1)} \right), \\
\widehat{\kappa\mathbf{y}_i}^{(k)} &= \widehat{\kappa\mathbf{y}_i}^{(k-1)} + \delta_k \left(\frac{1}{m} \sum_{l=1}^{m} \kappa_i^{(k,l)} \mathbf{y}_i^{(k,l)} - \widehat{\kappa\mathbf{y}_i}^{(k-1)} \right), \\
\widehat{\kappa\mathbf{b}_i^2}^{(k)} &= \widehat{\kappa\mathbf{b}_i^2}^{(k-1)} + \delta_k \left(\frac{1}{m} \sum_{l=1}^{m} \kappa_i^{(k,l)} \mathbf{b}_i^{(k,l)} \mathbf{b}_i^{(k,l)\top} - \widehat{\kappa\mathbf{b}_i^2}^{(k-1)} \right), \\
\widehat{\kappa\mathbf{b}_i}^{(k)} &= \widehat{\kappa\mathbf{b}_i}^{(k-1)} + \delta_k \left(\frac{1}{m} \sum_{l=1}^{m} \kappa_i^{(k,l)} \mathbf{b}_i^{(k,l)} - \widehat{\kappa\mathbf{b}_i}^{(k-1)} \right), \\
\widehat{\kappa\mathbf{yb}_i}^{(k)} &= \widehat{\kappa\mathbf{yb}_i}^{(k-1)} + \delta_k \left(\frac{1}{m} \sum_{l=1}^{m} \kappa_i^{(k,l)} \mathbf{y}_i^{(k,l)} \mathbf{b}_i^{(k,l)\top} - \widehat{\kappa\mathbf{yb}_i}^{(k-1)} \right), \\
\widehat{\tau\mathbf{b}_i^2}^{(k)} &= \widehat{\tau\mathbf{b}_i^2}^{(k-1)} + \delta_k \left(\frac{1}{m} \sum_{l=1}^{m} \tau_i^{(k,l)} \mathbf{b}_i^{(k,l)} \mathbf{b}_i^{(k,l)\top} - \widehat{\tau\mathbf{y}_i^2}^{(k-1)} \right), \\
\widehat{\kappa_i}^{(k)} &= \widehat{\kappa_i}^{(k-1)} + \delta_k \left(\frac{1}{m} \sum_{l=1}^{m} \kappa_i^{(k,l)} - \widehat{\kappa_i}^{(k-1)} \right), \\
\widehat{\ell h_{1i}}^{(k)} &= \widehat{\ell h_{1i}}^{(k-1)} + \delta_k \left(\frac{1}{m} \sum_{l=1}^{m} \log h_1(\kappa_i^{(k,l)} | \widehat{\nu}^{(k-1)}) - \widehat{\ell h_{1i}}^{(k-1)} \right), \\
\widehat{\ell h_{2i}}^{(k)} &= \widehat{\ell h_{2i}}^{(k-1)} + \delta_k \left(\frac{1}{m} \sum_{l=1}^{m} \log h_2(\tau_i^{(k,l)} | \widehat{\eta}^{(k-1)}) - \widehat{\ell h_{2i}}^{(k-1)} \right).
\end{aligned}
$$

The SMN-MLMEC model

SAEM - CM-step

Update $\widehat{\boldsymbol{\theta}}^{(k)}$ by the maximization of $Q(\boldsymbol{\theta}|\widehat{\boldsymbol{\theta}}^{(k)})$, which leads to the following expressions:

$$\widehat{\boldsymbol{\beta}}^{(k+1)} = \left(\sum_{i=1}^{n} \widehat{\kappa_i}^{(k)} \mathbf{X}_i^\top \widehat{\mathbf{R}}_i^{-1(k)} \mathbf{X}_i\right)^{-1} \sum_{i=1}^{n} \mathbf{X}_i^\top \widehat{\mathbf{R}}_i^{-1(k)} \left(\widehat{\kappa \mathbf{y}_i}^{(k)} - Z_i \widehat{\kappa \mathbf{b}_i}^{(k)}\right),$$

$$\widehat{\sigma^2_{jl}}^{(k+1)} = \begin{cases} \left(\sum_{i=1}^n n_i\right)^{-1} \sum_{i=1}^n \mathrm{tr}\left(\widehat{\boldsymbol{\Omega}}_i^{-1(k)} \widehat{\kappa \boldsymbol{\epsilon}}_{ijl}^{(k)}\right) & \text{for } j = l, \\ \left(2\sum_{i=1}^n n_i\right)^{-1} \sum_{i=1}^n \mathrm{tr}\left[\widehat{\boldsymbol{\Omega}}_i^{-1(k)} \left(\widehat{\kappa \boldsymbol{\epsilon}}_{ijl}^{(k)} + \widehat{\kappa \boldsymbol{\epsilon}}_{ilj}^{(k)}\right)\right] & \text{for } j \neq l, \end{cases}$$

$$\widehat{\boldsymbol{\phi}}^{(k+1)} = \underset{\boldsymbol{\phi} \in (0,1) \times \mathbb{R}^+}{\mathrm{argmax}} \left\{ -\frac{r}{2} \sum_{i=1}^{n} \log |\boldsymbol{\Omega}_i(\boldsymbol{\phi}, \mathbf{t}_i)| - \frac{1}{2} \sum_{i=1}^{n} \mathrm{tr}\left[\left(\widehat{\boldsymbol{\Sigma}}^{(k)} \otimes \boldsymbol{\Omega}_i(\boldsymbol{\phi}, \mathbf{t}_i)\right)^{-1} \widehat{\kappa \mathrm{E}_i}\right] \right\},$$

$$\widehat{\mathbf{D}}^{(k+1)} = \frac{1}{n} \sum_{i=1}^{n} \widehat{\tau \mathbf{b}_i^2}^{(k)},$$

$$\widehat{\nu}^{(k+1)} = \underset{\nu}{\mathrm{argmax}} \sum_{i=1}^{n} \widehat{\ell h_{1i}}^{(k)}(\nu),$$

$$\widehat{\eta}^{(k+1)} = \underset{\eta}{\mathrm{argmax}} \sum_{i=1}^{n} \widehat{\ell h_{2i}}^{(k)}(\eta).$$

The likelihood function for the observed data can be computed as

$$L_o(\boldsymbol{\theta}; \mathbf{y}^{obs}) = \prod_{i=1}^{n} \int \left[\int_0^{\infty} f(\mathbf{y}_i | \mathbf{b}_i, \kappa_i; \boldsymbol{\theta}) h_1(\kappa_i) d\kappa_i \right] f(\mathbf{b}_i | \boldsymbol{\theta}) d\mathbf{b}_i.$$

Partitioning $\mathbf{y}_i$, we obtain

$$\begin{aligned} L_o(\boldsymbol{\theta}; \mathbf{y}^{obs}) &= \prod_{i=1}^{n} \int \left[\int_0^{\infty} \phi_{s_i^o}(\mathbf{y}_i^o; \mathbf{X}_i^c \boldsymbol{\beta} - \mathbf{Z}_i^c \mathbf{b}_i, \kappa_i^{-1} \mathbf{R}_i^{oo}) \Phi_{s_i^c}(\mathbf{V}_i^c; \boldsymbol{\mu}_i, \kappa_i^{-1} \mathbf{S}_i) h_1(\kappa_i) d\kappa_i \right] \\ &\times \quad f(\mathbf{b}_i | \boldsymbol{\theta}) d\mathbf{b}_i = \prod_{i=1}^{n} \int g(\mathbf{y}_i | \mathbf{b}_i, \kappa_i; \boldsymbol{\theta}) f(\mathbf{b}_i | \boldsymbol{\theta}) d\mathbf{b}_i \qquad (9) \end{aligned}$$

where

$g(\mathbf{y}_i | \mathbf{b}_i, \kappa_i; \boldsymbol{\theta}) = \int_0^{\infty} \phi_{s_i^o}(\mathbf{y}_i^o; \mathbf{X}_i^c \boldsymbol{\beta} - \mathbf{Z}_i^c \mathbf{b}_i, \kappa_i^{-1} \mathbf{R}_i^{oo}) \Phi_{s_i^c}(\mathbf{V}_i^c; \boldsymbol{\mu}_i, \kappa_i^{-1} \mathbf{S}_i) h_1(\kappa_i | \nu) d\kappa_i.$

The SMN-MLMEC model

Likelihood estimation

The integral involved in (9) can be computed using an importance sampling strategy for any continuous distribution. In fact, we have

$$L_o(\boldsymbol{\theta}; \mathbf{y}^{obs}) = \prod_{i=1}^{n} \int g(\mathbf{y}_i|\mathbf{b}_i, \kappa_i; \boldsymbol{\theta}) \frac{f(\mathbf{b}_i|\boldsymbol{\theta})}{f^{\star}(\mathbf{b}_i|\boldsymbol{\theta})} d\mathbf{b}_i,$$

where $f^{\star}$ is the importance distribution. Consequently, $L_o(\boldsymbol{\theta}; \mathbf{y}_i^{obs})$ is estimated through the following approximation:

$$L_o(\boldsymbol{\theta}; \mathbf{y}^{obs}) = \prod_{i=1}^{n} \left[\frac{1}{M} \sum_{m=1}^{M} g(\mathbf{y}_i|\mathbf{b}_{im}, \kappa_i; \boldsymbol{\theta}) \frac{f(\mathbf{b}_{im}|\boldsymbol{\theta})}{f^{\star}(\mathbf{b}_{im}|\boldsymbol{\theta})} \right],$$

with $\mathbf{b}_{i1}, \ldots, \mathbf{b}_{im}$ begin draw from $f^{\star}(\mathbf{b}_i|\boldsymbol{\theta})$.

- **AIC and BIC**

$$\text{AIC} = 2\,m - 2\,\ell_{max} \;\text{ and }\; \text{BIC} = m\,log\,N - 2\,\ell_{max}.$$

- **Decompositions AIC of BIC (Zhang et al., 2014)**

Let $\mathbf{y}^{\star}_{i1} = (\mathbf{y}^{\top}_{i1}, \ldots, \mathbf{y}^{\top}_{ir^{\star}})^{\top}$ and $\mathbf{y}^{\star}_{i2} = (\mathbf{y}^{\top}_{ir^{\star}+1}, \ldots, \mathbf{y}^{\top}_{ir})^{\top}$, where $\mathbf{y}_i = (\mathbf{y}^{\star\top}_{i1}, \mathbf{y}^{\star\top}_{i2})^{\top}$ and $r^{\star} \in \{1, \ldots, r\}$; then, the AIC and BIC have the following decompositions:

$$\text{AIC} = \text{AIC}_{\mathbf{y}^{\star}_1} + \text{AIC}_{\mathbf{y}^{\star}_2|\mathbf{y}^{\star}_1} \;\text{ and }\; \text{BIC} = \text{BIC}_{\mathbf{y}^{\star}_1} + \text{BIC}_{\mathbf{y}^{\star}_2|\mathbf{y}^{\star}_1}.$$

- **Model assessment criteria**

$$\Delta\text{AIC} = \text{AIC}_{\mathbf{y}^{\star}_{2,0}} - \text{AIC}_{\mathbf{y}^{\star}_2|\mathbf{y}^{\star}_1} \;\text{ and }\; \Delta\text{BIC} = \text{BIC}_{\mathbf{y}^{\star}_{2,0}} - \text{BIC}_{\mathbf{y}^{\star}_2|\mathbf{y}^{\star}_1}.$$

The model with a large value of *Delta*AIC or *Delta*BIC fits the data better.

Summary

Analysis of a real data set

A5055 clinical trial

$$
\begin{aligned}
y_{i1k} &= \beta_{10} + \beta_{11} t_{ik} + \beta_{12}\text{treat}_i + \beta_{13} t_{ik}^{0.5} + \beta_{14}\text{treat}_i \times t_{ik} + b_{i10} + b_{i11} t_{ik} + e_{i1k}, \\
y_{i2k} &= \beta_{20} + \beta_{21} t_{ik} + \beta_{22}\text{treat}_i + \beta_{23}\text{treat}_i \times t_{ik} + b_{i20} + b_{i21} t_{ik} + e_{i2k},
\end{aligned}
$$

i=1,. . . ,44,

- y_{i1k} is the $\log_{10}$ (RNA) response for subject i measured at t_k;
- y_{i2k} is the log(CD4/CD8) response for subject i i measured at t_k;
- 316 observations;
- 33% of all viral load measurements are below the detection limit;
- $t_{ik} = \text{day}_{ik}/7$ (week), for $k = 1, \ldots, s_i$, where day=: 0, 7, 14, 28, 56, 84, 112, 140 e 168;
- treat_i is a treatment indicator (= 0 for treatment 1; = 1 pfor treatment 2);
- b_{ij0} and b_{ij1} are the random intercept and random slope, respectively, for y_{ijk}, $j = 1, 2$.

- This data set was previously analyzed by Wang *et al.* (2015).

Analysis of a real data set

A5055 clinical trial

Model comparison criteria for the scale mixtures of normal?multivariate censored linear mixed effect models under the damped exponential correlation (DEC) structure:

	Distribuição ϵ / Distribuição $\mathbf{b}$								
	N/N	SL/N	T/N	N/SL	N/T	SL/SL	SL/T	T/SL	T/T
AIC	789.85	742.18	739.59	791.98	792.29	744.47	744.54	741.85	741.51
BIC	896.62	853.41	850.81	903.20	903.51	860.14	860.21	857.52	857.19

Analysis of a real data set

A5055 clinical trial

Maximum-likelihood estimates with standard errors under the T/N-MLMEC model:

Structure	Parameters	Estimate (SE)	Parameters	Estimate (SE)	Parameters	Estimate (SE)
DEC	β_{10}	3.743 (0.134)	d_{11}	0.1446 (0.0829)	σ_{11}	0.409 (0.076)
	β_{11}	0.130 (0.026)	d_{21}	0.0011 (0.0133)	σ_{21}	-0.039 (0.020)
	β_{12}	-0.005 (0.067)	d_{22}	-0.0884 (0.1182)	σ_{22}	0.050 (0.011)
	β_{13}	-0.957 (0.098)	d_{31}	-0.0011 (0.0033)	ϕ_1	0.704 (0.065)
	β_{14}	-0.007 (0.025)	d_{32}	0.0034 (0.0027)	ϕ_2	0.632 (0.131)
	β_{20}	-1.284 (0.077)	d_{33}	-0.0122 (0.0116)	ν	4.737 (0.003)
	β_{21}	0.005 (0.005)	d_{41}	-0.0004 (0.0004)		
	β_{22}	0.252 (0.084)	d_{42}	0.2727 (0.0861)		
	β_{23}	-0.003 (0.007)	d_{43}	0.0008 (0.0015)		
			d_{44}	0.0001 (0.0001)		
	loglik	-344.79	AIC	739.59	BIC	850.81
UNC	β_{10}	3.718 (0.135)	d_{11}	0.4089 (0.1463)	σ_{11}	0.263 (0.053)
	β_{11}	0.129 (0.026)	d_{21}	-0.0112 (0.0153)	σ_{21}	-0.024 (0.012)
	β_{12}	0.003 (0.091)	d_{22}	-0.0964 (0.1251)	σ_{22}	0.028 (0.005)
	β_{13}	-0.955 (0.075)	d_{31}	0.0002 (0.0030)	ν	4.340 (0.004)
	β_{14}	-0.008 (0.027)	d_{32}	0.0054 (0.0029)		
	β_{20}	-1.278 (0.076)	d_{33}	-0.0132 (0.0116)		
	β_{21}	0.005 (0.004)	d_{41}	-0.0006 (0.0004)		
	β_{22}	0.286 (0.081)	d_{42}	0.2953 (0.0785)		
	β_{23}	-0.006 (0.006)	d_{43}	0.0002 (0.0015)		
			d_{44}	0.0001 (0.0001)		
	loglik	-357.97	AIC	761.94	BIC	864.26

Analysis of a real data set

A5055 clinical trial

Decompositions of AIC and BIC under the best scale mixtures of normal?multivariate censored linear mixed effect model:

AIC	739.59	BIC	850.81
$\text{AIC}_{\mathbf{y}_2^\star \mid \mathbf{y}_1^\star}$	92.65	$\text{BIC}_{\mathbf{y}_2^\star \mid \mathbf{y}_1^\star}$	158.80
$\text{AIC}_{\mathbf{y}_{2,0}^\star}$	125.26	$\text{BIC}_{\mathbf{y}_{2,0}^\star}$	166.58
ΔAIC	32.61	ΔBIC	7.77

Summary

Simulation Studies

- **Simulation I:** This study provides an extensive simulation scheme designed to examine the empirical performance of the parameter estimates under different specifications of the parameters $\boldsymbol{\nu}$ and β. Recall that those parameters are involved in the distribution of the mixture variables, controlling the heavy-tailed behavior of our resulting model, say, the SMN-MLMEC model.
- **Simulation II:** The second simulation scheme focuses on the study of the finite sample properties of the parameter estimates under different censoring proportions. We generate random samples from a SL/SL-MLMEC model, ie, we consider a SMN-MLMEC model where the distribution of the error term and the random effect follows a slash distri- bution. In this scheme, we fit several heavy-tailed SMN-MLMEC models and compare them using the AIC and BIC measures.
- **Simulation III:** Finally,the third simulation scheme studies the effect of the misspecification of thedistribution of the error and random effect terms on the parameter estimates. As in the previous scenario, we draw random samples from an SL/SL-MLMEC model, fitting different heavy-tailed SMN-MLMEC models, including the normal one. We compare these models using the AIC measures and log-likelihood values.

Summary

References I

Andrews, D. F. & Mallows, C. L. (1974). Scale mixtures of normal distributions. *Journal of the Royal Statistical Society. Series B*, pages 99–102.

Arellano-Valle, R. B., Bolfarine, H. & Lachos, V. (2005). Skew-normal linear mixed models. *Journal of Data Science*, **3**, 415–438.

Delyon, B., Lavielle, M. & Moulines, E. (1999). Convergence of a stochastic approximation version of the em algorithm. *Annals of Statistics*, pages 94–128.

Dempster, A., Laird, N. & Rubin, D. (1977). Maximum likelihood from incomplete data via the EM algorithm. *Journal of the Royal Statistical Society, Series B,*, **39**, 1–38.

Garay, A. M., Castro, L. M., Leskow, J. & Lachos, V. H. (2014). Censored linear regression models for irregularly observed longitudinal data using the multivariate-t distribution. *Statistical Methods in Medical Research*, page DOI: 10.1177/0962280214551191.

Jank, W. (2006). Implementing and diagnosing the stochastic approximation EM algorithm. *Journal of Computational and Graphical Statistics*, **15**(4), 803–829.

Kuhn, E. & Lavielle, M. (2005). Maximum likelihood estimation in nonlinear mixed effects models. *Computational Statistics & Data Analysis*, **49**(4), 1020–1038.

Lachos, V. H., Bandyopadhyay, D. & Dey, D. K. (2011). Linear and nonlinear mixed-effects models for censored hiv viral loads using normal/independent distributions. *Biometrics*, **67**, 1594–1604.

Lange, K. L. & Sinsheimer, J. S. (1993). Normal/independent distributions and their applications in robust regression. *Journal of Computational and Graphical Statistics*, **2**, 175–198.

Matos, L., Lachos, V., Balakrishnan, N. & Labra, F. (2013a). Influence diagnostics in linear and nonlinear mixed-effects models with censored data. *Computational Statistical & Data Analysis*, **57**(1), 450–464.

Matos, L., Prates, M., Chen, M.-H. & Lachos, V. (2013b). Likelihood based inference for linear and nonlinear mixed-effects models with censored response using the multivariate-t distribution. *Statistica Sinica*, **23**, 1323–1345.

Muñoz, A., Carey, V., Schouten, J. P., Segal, M. & Rosner, B. (1992). A parametric family of correlation structures for the analysis of longitudinal data. *Biometrics*, **48**, 733–742.

Samson, A., Lavielle, M. & Mentré, F. (2006). Extension of the SAEM algorithm to left-censored data in nonlinear mixed-effects model: application to HIV dynamics model. *Computational Statistics & Data Analysis*, **51**(3), 1562–1574.

References II

Vaida, F. & Liu, L. (2009). Fast implementation for normal mixed effects models with censored response. *Journal of Computational and Graphical Statistics*, **18**(4), 797–817.

Vaida, F., Fitzgerald, A. & DeGruttola, V. (2007). Efficient hybrid EM for linear and nonlinear mixed effects models with censored response. *Computational Statistics & Data Analysis*, **51**(12), 5718–5730.

Wang, W.-L., Lin, T.-I. & Lachos, V. H. (2015). Extending multivariate-t linear mixed models for multiple longitudinal data with censored responses and heavy tails. *Statistical Methods in Medical Research*, page doi: 0962280215620229.

Wei, G. C. & Tanner, M. A. (1990). A Monte Carlo implementation of the EM algorithm and the poor man's data augmentation algorithms. *Journal of the American Statistical Association*, **85**(411), 699–704.

Zhang, D., Chen, M.-H., Ibrahim, J. G., Boye, M. E., Wang, P. & Shen, W. (2014). Assessing model fit in joint models of longitudinal and survival data with applications to cancer clinical trials. *Statistics in Medicine*, **33**(27), 4715–4733.

Acknowledgments