Bayesian analysis for heavy-tailed nonlinear mixed effects models

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May 2013

Bayes 2013, Rotterdam

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- Introduction
- Motivating example
- Nonlinear mixed effects models
- Heavy-tailed nonlinear mixed effects models
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Introduction

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- Random effects and errors are usually assumed to be independent and normally distributed.
- We assume that the random effects and errors jointly follow heavy tailed distributions for the random effects and errors.
- This assumption may produce more robust estimates against outlying or influential observations (see, for instance, Meza et al., 2011 and Russo et al., 2009).

Motivating example: Theophylline concentration

Kinetics of anti-asthmatic agent theophylline (Pinheiro & Bates 2000)

- Y: Theophylline Concentration (mg / L) (response variable)
- T: Time (h) (covariate)
- D: Applied dose (mg / kg)

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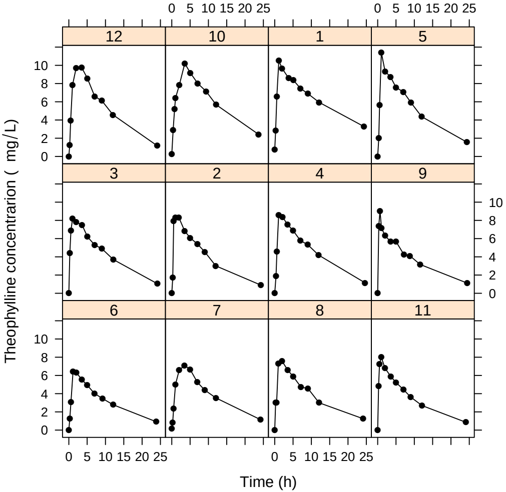
$$\mathrm{E}(Y) = D \exp(lK_e + lK_a - lC_l) \frac{[\exp(-e^{lK_e} T) - \exp(-e^{lK_a} T)]}{e^{lK_a} - e^{lK_e}}$$

- lK_a: logarithm of the absorption rate,
- lK_e: logarithm of the elimination rate
- lC_l: the logarithm of clearance.

Motivating example: Theophylline concentration

In an experiment, serum concentration (in mg/L) of theophylline was measured in eleven times (in h) after the administration of D dose (in mg/kg) in each of twelve patients.

Motivating example: Theophylline data



Theophylline concentration versus time

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where

- $\phi_{1i} = lK_e + b_{1i}$
- $\phi_{2i} = lK_a + b_{2i}$
- $\phi_{3i} = lC_l + b_{3i}$
- lK_e, lK_a and lC_l are fixed effects
- b_{1i}, b_{2i} and b_{3i} are random effects
- ϵ_{ij} are random errors.

Nonlinear model with random effects

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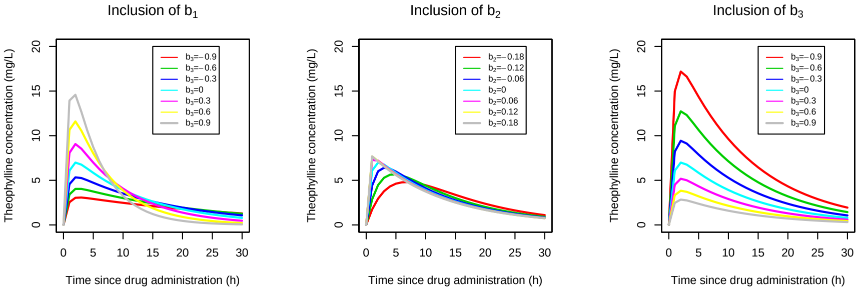
Here we assume the random effects and errors to jointly follow a multivariate scale mixture of normal distributions.

Interpretation of random effects in the nonlinear model



Interpretation of random effects in the nonlinear model

Nonlinear mixed-effects models

Suppose that $\mathbf{y} = (\mathbf{y}_1^\top, \ldots, \mathbf{y}_n^\top)^\top$ is a vector of observed continuous multivariate responses with $\mathbf{y}_i$ a $(n_i \times 1)$ vector containing the observations for the experimental unit i, $i = 1, \ldots, n$, such that

$$\begin{aligned} \mathbf{y}_i &= \mathbf{g}(\phi_i, \mathbf{X}_i) + \boldsymbol{\epsilon}_i, \;\; i = 1, \ldots, n, \\ \phi_i &= \boldsymbol{\beta} + \mathbf{b}_i, \end{aligned} \tag{1}$$

with

- $\mathbf{X}_i = (\mathbf{X}_{i1}, \ldots, \mathbf{X}_{in_i})^\top$ a matrix of explanatory variables for the i-th unit,
- $\mathbf{b}_i$ is a $(q \times 1)$ vector of random effects,
- $\boldsymbol{\epsilon}_i$ is an $(n_i \times 1)$ vector of random errors values for $i = 1, \ldots, n$,
- $\boldsymbol{\beta}$ is a $(p \times 1)$ location vector.

Heavy-tailed nonlinear mixed-effects models

Let a $m-$dimensional random vector $\mathbf{W}$ follows a scale mixture of normal distribution (SMN) in its stochastic form, that is

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

where

- $\boldsymbol{\mu}$ is the location vector,
- 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 vector parameter indexing the distribution of U,
- $\kappa(U)$ is the weight function,
- $\mathbf{Z} \sim N(\mathbf{0}, \boldsymbol{\Sigma})$
- $\mathbf{Z}$ and U independent.

Heavy-tailed nonlinear mixed-effects models

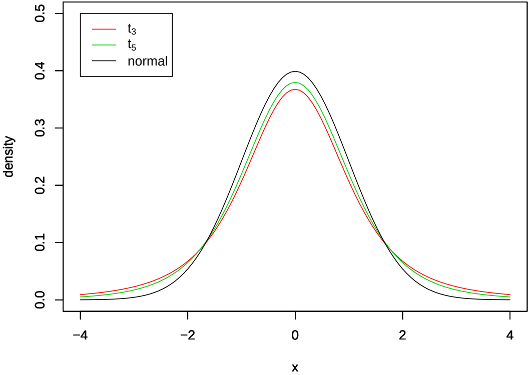
Characterization of some SMN distributions.

Distribution	$\kappa(u)$	U
$\text{MN}_m(\boldsymbol{\mu}, \boldsymbol{\Sigma})$	1	$U = 1$
$\text{MSt}_m(\boldsymbol{\mu}, \boldsymbol{\Sigma}, \nu)$	$\frac{1}{u}$	$U \overset{\text{ind.}}{\sim} \text{Gamma}\left(\frac{\nu}{2}, \frac{\nu}{2}\right)$, $u > 0, \nu > 0$
$\text{MSI}_m(\boldsymbol{\mu}, \boldsymbol{\Sigma}, \nu)$	$\frac{1}{u}$	$U \sim Beta(\nu, 1)$, $0 < u < 1, \nu > 0$
$\text{MCN}_m(\boldsymbol{\mu}, \boldsymbol{\Sigma}, \nu, \gamma)$	$\frac{1}{u}$	$h(u, \boldsymbol{\nu}) = \nu \mathbb{I}_{(u=\gamma)} + (1-\nu)\mathbb{I}_{(u=1)}$, $u = \gamma, 1; 0 \leq \nu \leq 1,\ 0 \leq \gamma \leq 1$,

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

Heavy-tailed nonlinear mixed-effects models

Scale mixture of normal distributions include symmetrical distributions with heavier tailed than the Gaussian distributions, including the normal itself.



Normal and Student-t distributions

Heavy-tailed nonlinear mixed-effects models

In the nonlinear model

$$\mathbf{y}_i = \mathbf{g}(\phi_i, \mathbf{X}_i) + \epsilon_i, \ i = 1, \ldots, n,$$
$$\phi_i = \boldsymbol{\beta} + \mathbf{b}_i,$$

we assume that

$$\begin{pmatrix} \epsilon_i \\ \mathbf{b}_i \end{pmatrix} \overset{ind.}{\sim} \mathrm{SMN}_{n_i+q}\left(\begin{pmatrix} \mathbf{0} \\ \mathbf{0} \end{pmatrix}, \begin{pmatrix} \boldsymbol{\Sigma}_i & \mathbf{0} \\ \mathbf{0} & \mathbf{D} \end{pmatrix}; \mathrm{H} \right), \quad (2)$$

where $\mathbf{D}$ and $\boldsymbol{\Sigma}_i$ are positive-definite dispersion matrices. For simplicity, we assume that $\mathbf{D} = \mathrm{diag}(\boldsymbol{\tau})$ and $\boldsymbol{\Sigma}_i = \sigma^2 \mathbf{I}_{n_i}$ for $i = 1, \ldots, n$ and $\sigma > 0$ a scalar.

Application

In the nonlinear model for the theophylline data:

$\boldsymbol{\theta} = (\boldsymbol{\beta}, \sigma^2, \boldsymbol{\tau})^\top = (lKe, lKa, lCl, \sigma^2, \tau_1, \tau_2, \tau_3)^\top$

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Prior distributions:

- $\boldsymbol{\beta}_i \sim N(0, v)$,
- $\tau_i \sim \text{Gamma}(a_i, b_i)$,
- $\sigma^2 \sim \text{Gamma}(c, d)$.

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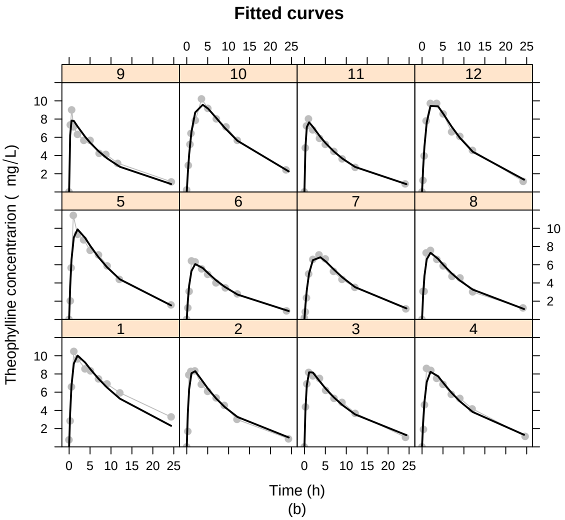
The Monte Carlo estimates using OpenBUGS were obtained generating chains of size 30000 spaced by 50 (burn-in of 5000). The posterior means and the corresponding standard deviations of the posterior distributions are presented in the following slides.

Results: Theophylline data

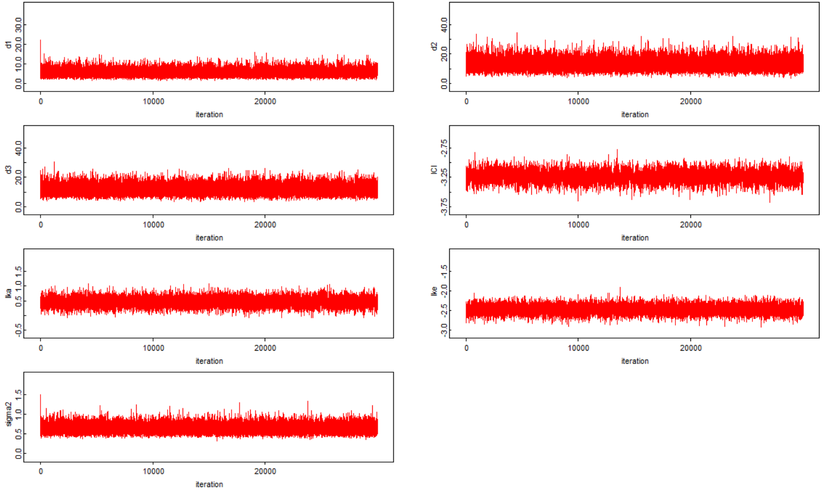
	Normal		Student-t_4		Slash$_4$	
	mean	(sd)	mean	(sd)	mean	(sd)
lK_e	-2.465	(0.102)	-2.452	(0.099)	-2.450	(0.099)
lK_a	0.462	(0.142)	0.460	(0.146)	0.459	(0.147)
lC_l	-3.232	(0.095)	-3.221	(0.097)	-3.220	(0.094)
$(\sigma^2)^{-1}$	0.636	(0.104)	0.552	(0.145)	0.123	(0.035)
$(\tau_1)^{-1}$	5.580	(1.691)	5.053	(1.492)	5.052	(1.505)
$(\tau_2)^{-1}$	13.060	(3.458)	13.150	(3.451)	13.210	(3.451)
$(\tau_3)^{-1}$	11.830	(3.087)	11.740	(3.082)	11.760	(3.085)
DIC	323.5		303.6		298.3	

Results: Theophylline data



Fitted curves for theophylline problem under **Slash**$_4$ model.

Convergence



Convergence of chains in **Slash**$_4$ case

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- For nonlinear mixed effects models, convergence may be difficult to reach depending on the initial values.

Discussion and remarks

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- Considering a stochastic formulation in a bayesian approach, we propose the use of heavy-tailed distributions in a bayesian context to provide alternatives to the gaussian model.
- Easy implementation in Bayesian approach.

Discussion and remarks

- Nonlinear mixed effects models plays an important role in nonlinear problems with correlated data.
- Considering a stochastic formulation in a bayesian approach, we propose the use of heavy-tailed distributions in a bayesian context to provide alternatives to the gaussian model.
- Easy implementation in Bayesian approach.
- Estimation of individual profiles.

Work in progress

- Model diagnostics
- Robustness assessment
- Other nonlinear data sets.

References

- Meza, C., Osorio, F. and De la Cruz, R. (2012) Estimation in nonlinear mixed-effects models using heavy-tailed distributions. Statistics and Computing 22, 121-139.
- Pinheiro, J. C. and Bates, D. M. (2000) Mixed-Effects Models in S and S-Plus, Springer, New York.
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Thank you!