Evaluation of the Fisher information matrix in nonlinear mixed effect models without linearization

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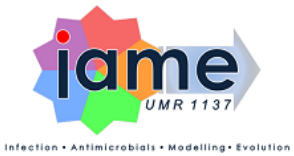

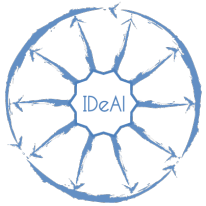

Outline

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Longitudinal data

- Longitudinal or repeated measurements
- Several observations per patient across time
- Within and between subject variability

$\Rightarrow$ Non Linear Mixed Effect Models

- Estimation of parameters of the model: by Maximum Likelihood
  $\Rightarrow$ No analytical form of the likelihood
  $\Rightarrow$ Specific software available

Design

- How to design these studies ?
  - Number of subjects
  - Number of points per subject
- Objective: predict the precision in estimation

  $\Rightarrow$ Relative Standard Error (RSE)

FIM in NLMEM

Instead of performing clinical trial simulations
$\Rightarrow$ Evaluation of the Fisher Information Matrix (FIM)

- Inverse FIM = lower bound of the variance-covariance matrix of any unbiased parameters estimator (Cramer-Rao inequality)
- FIM $\Rightarrow$ Evaluate and optimize designs
- In NLMEM: no analytical form
- $\Rightarrow$ First-order (FO) linearization
  Performs very well, but cannot applied to:
  - Complex nonlinear models
  - Discrete data

Mentré et al. Biometrika 84, 429–442 (1997).

Outline

Nonlinear mixed effect models

For continuous data:

$$y_i = f(g(\mu, b_i), \xi_i) + \varepsilon_i$$

For discrete data:

$$p(y_i, \psi | b_i) = \prod_{j=1}^{n_i} h(y_{ij}, g(\mu, b_i), \xi_i)$$

with

- $y_i = (y_{i1}, \ldots, y_{in_i})^T$ response for individual i $(i = 1, \ldots, N)$
- f, h structural model
- ξ_i elementary design for subject i
- g individual parameters vector, function of μ and b_i
- μ vector of fixed effects
- b_i vector of random effects for individual i, $b_i \sim \mathcal{N}(0, \Omega)$
- ε_i vector of residual errors, $\varepsilon_i \sim \mathcal{N}(0, \Sigma)$ and Σ diagonal matrix
- ψ vector of all parameters, $\psi = (\mu, \Omega, \Sigma)$

Fisher Information Matrix (FIM)

Population FIM:

$$M(\psi, \Xi) = \sum_{i=1}^{N} M(\psi, \xi_i)$$

with Ξ population design ($\Xi = (\xi_1, \ldots, \xi_N)^{\mathsf{T}}$)

Individual FIM:

$$M(\psi, \xi) = E\left(\frac{\partial \log(L(y,\psi))}{\partial \psi} \frac{\partial \log(L(y,\psi))}{\partial \psi}^T\right)$$

with the likelihood:

$$L(y, \psi) = \int_b p(y|b, \psi) p(b) db$$

where $p(y|b, \psi)$: conditional density of y given the random effects b

$p(b)$: density of b

Proposed approach

$$M(\psi,\xi) = E\left(\frac{\partial \log(L(y,\psi))}{\partial \psi}\frac{\partial \log(L(y,\psi))}{\partial \psi}^T\right)$$

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$$= \int_y \underbrace{\left(\frac{\partial \log(L(y,\psi))}{\partial\psi}\frac{\partial \log(L(y,\psi))}{\partial\psi}^T\right)}_{A_y} \cdot L(y,\psi)dy$$

Monte Carlo - MC

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Monte Carlo - MC

After calculation... $A_y \iff$

$$\int_{b_1} \frac{\partial(\log(p(y|b_1,\psi)p(b_1)))}{\partial\psi_k}\frac{p(y|b_1,\psi)p(b_1)}{\int p(y|b,\psi)p(b)db}db_1 . \int_{b_2} \frac{\partial(\log(p(y|b_2,\psi)p(b_2)))}{\partial\psi_l}\frac{p(y|b_2,\psi)p(b_2)}{\int p(y|b,\psi)p(b)db}db_2$$

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Markov Chains Monte Carlo - MCMC

MC-MCMC algorithm for FIM evaluation

$$\int_y \int_{b_1} \frac{\partial(\log(p(y|b_1,\psi)p(b_1)))}{\partial\psi_k} \underbrace{\frac{p(y|b_1,\psi)p(b_1)}{\int p(y|b,\psi)p(b)db}}_{\text{conditional density of } b \text{ given } y} db_1 . \int_{b_2} \frac{\partial(\log(p(y|b_2,\psi)p(b_2)))}{\partial\psi_l} \underbrace{\frac{p(y|b_2,\psi)p(b_2)}{\int p(y|b,\psi)p(b)db}}_{\text{conditional density of } b \text{ given } y} db_2 . \underbrace{L(y,\psi)}_{\text{marginal density of } y} dy$$

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(I) Draw an R-sample of y from its marginal distribution.

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(III) Using MCMC, draw two series of M-samples of b from its conditional density given y.

MC-MCMC algorithm for FIM evaluation

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(V) Using MC, estimate $\int_y$ by the mean according to y of the product of the previous partial derivatives.

Partial derivatives of the conditional log-likelihood

$$\frac{\partial \left(\log(p(y|b,\psi)p(b))\right)}{\partial \psi_k}$$

- By hand. For continuous data:

$$\frac{\partial \left(\log(p(y|b,\psi)p(b))\right)}{\partial \psi_k} = -\frac{1}{2}\left[Tr\left(V_b^{-1}\frac{\partial V_b}{\partial \psi_k}\right) - 2(y-E_b)^T V_b^{-1}\frac{\partial E_b}{\partial \psi_k} - (y-E_b)^T V_b^{-1}\frac{\partial V_b}{\partial \psi_k}V_b^{-1}(y-E_b) + Tr\left(\Omega^{-1}\frac{\partial \Omega}{\partial \psi_k}\right) - b^T\Omega^{-1}\frac{\partial \Omega}{\partial \psi_k}\Omega^{-1}b\right]$$

with $E_b = f(g(\mu, b), \xi)$ and $V_b = \Sigma$

- Numerically **for all types of distributions**

STAN* for MCMC

STAN

- Markov Chain Monte Carlo (MCMC) sampler (as JAGS, BUGS, ...)
  - To sample in posterior distributions
  - Based on constructing a Markov chain that has the desired distribution as its stationary distribution
- STAN uses Hamiltonian Monte Carlo (HMC)
  - non-random walk Monte Carlo method vs. Metropolis-Hastings, Gibbs sampling, ...
  - More complex but more efficient, faster convergence
    $\Rightarrow$ Able to overcome some issues inherent in Gibbs sampling
- STAN calculates the gradient of the log probability function (necessary for HMC)

* Stan Development Team. Gelman, Carpenter, ... Columbia University
2014. Stan: A C++ Library for Probability and Sampling, Version 2.5.0. http://mc-stan.org

Outline

FIM evaluation

We compared 3 approaches:

- Linearization (FO) using PFIM 4.0
- AGQ-based approach (AGQ) implemented in R
- MCMC-based approach (MCMC) implemented in R (using rstan)

with clinical trial simulations (CTS):

- Simulate 1000 datasets Y with $\Psi = \Psi_T$ using R
- For each Y: estimate $\hat{\Psi}$ using Monolix 4.3

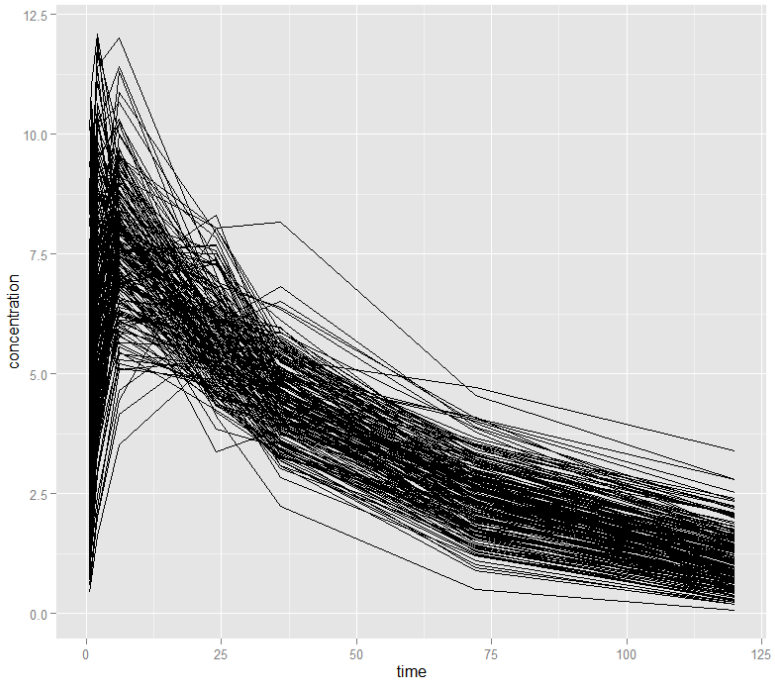
in terms of

- RSE / RRMSE: $RRMSE = \sqrt{\frac{1}{1000}\sum(\hat{\Psi} - \Psi_T)^2}\,/\Psi_T$
- Calculation time

Example 1: PK Warfarin

PKW: One compartment model with first order absorption and elimination:

$$f(\phi = (k_a, V, CL), t) = \frac{70}{V} \frac{k_a}{k_a - \frac{CL}{V}} \left(e^{-\frac{CL}{V} t} - e^{-k_a t} \right)$$



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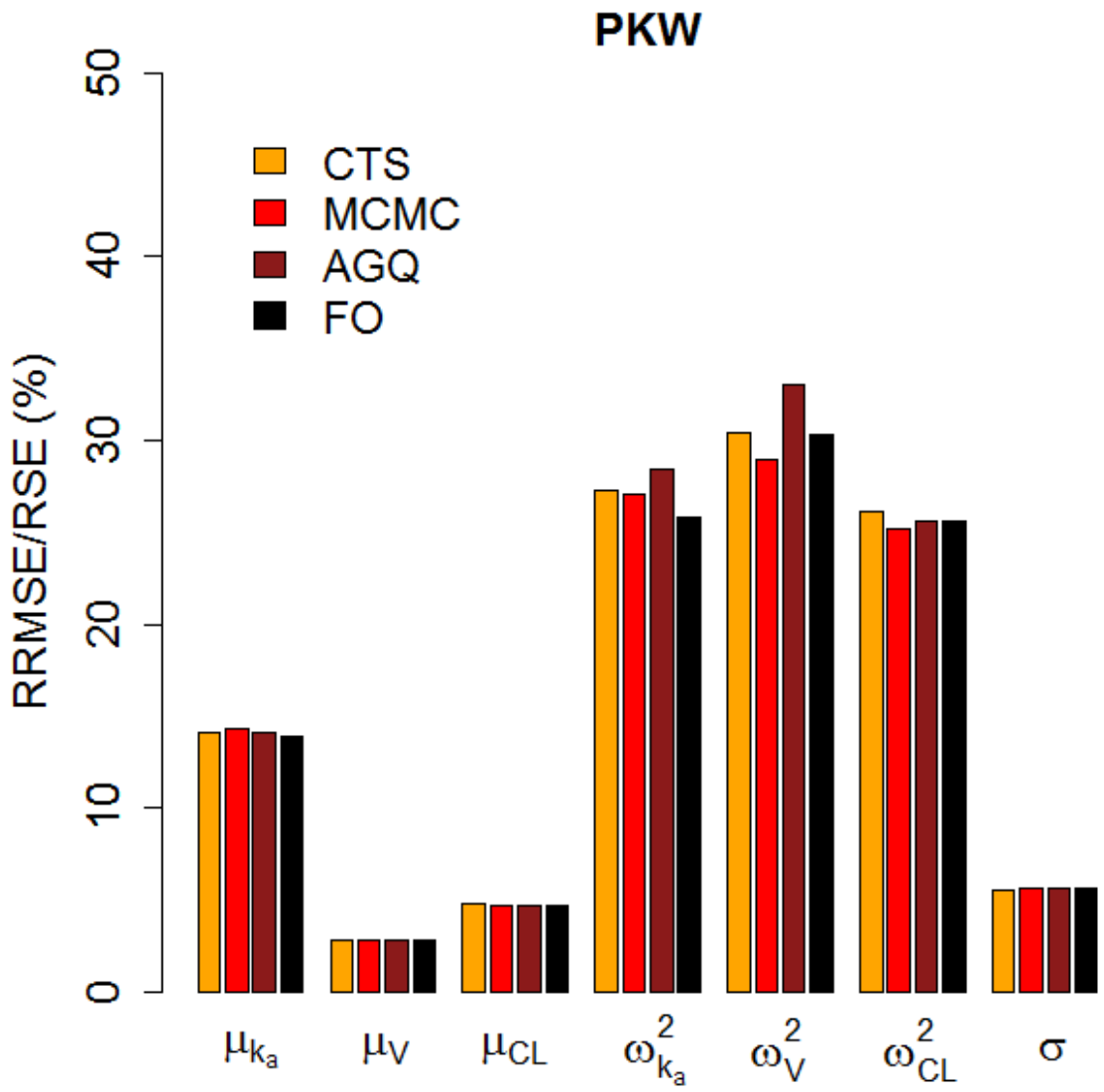
- Fixed effects: $(\mu_{k_a}, \mu_V, \mu_{CL}) = (1.00, 8.00, 0.15)$
- Exponential random effects with variances: $(\omega^2_{k_a}, \omega^2_V, \omega^2_{CL}) = (0.60, 0.02, 0.07)$
- Proportional residual error: $\sigma_{\text{slope}} = 0.1$
- 8 times: $t = \xi = (0.5, 1, 2, 6, 24, 36, 72, 120)$
- $N = 32$ patients

Nyberg et al. Br J Clin Pharmacol 79, 6–17 (2015).

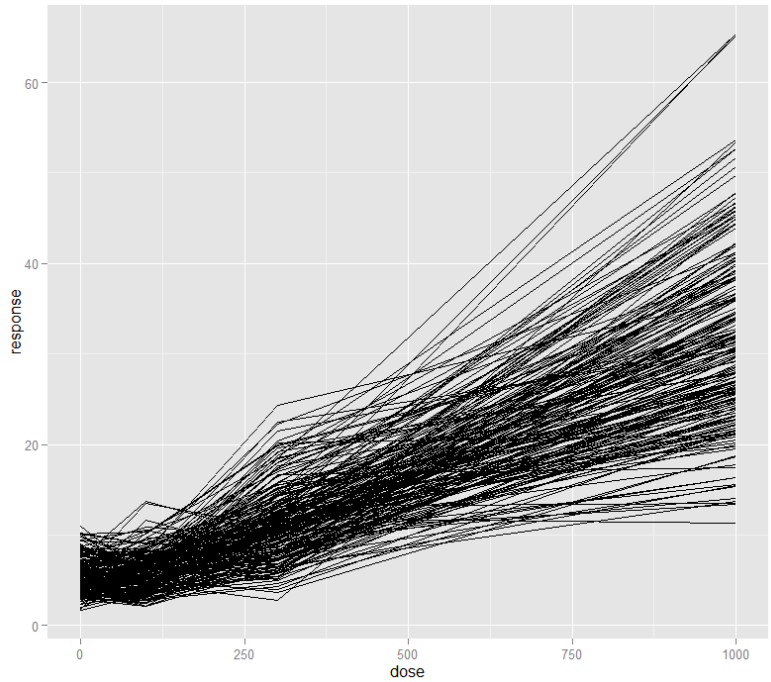
Example 1 - RSE/RRMSE



Example 2: Sigmoïd E_{max} model

SC1: Sigmoïd E_{max} model:

$$f(\phi = (E_0, E_{max}, ED_{50}, \gamma), d) = E_0 + \frac{E_{max} d^{\gamma}}{ED_{50}^{\gamma} + d^{\gamma}}$$



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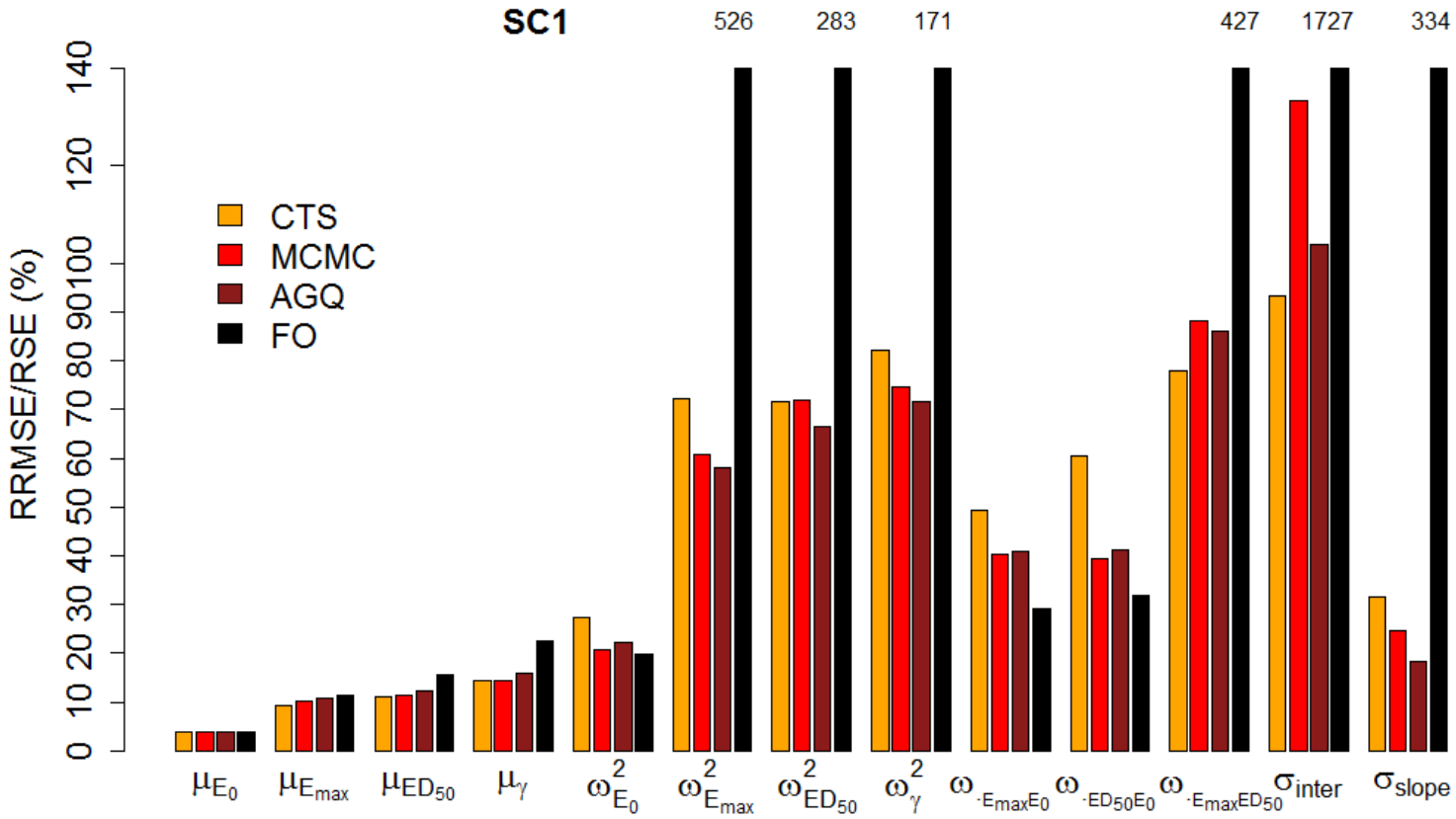
$$f(\phi = (E_{max}, ED_{50}), d) = E_0 + \frac{E_{max} d^\gamma}{ED_{50}^\gamma + d^\gamma}$$

- Fixed effects: $(\mu_{E_0}, \mu_{E_{max}}, \mu_{ED_{50}}, \mu_\gamma) = (5, 30, 500, 3)$
- Exponential random effects with variance-covariance:

$$\Omega = \begin{pmatrix} 0.09 & 0.06 & 0.06 & 0 \\ 0.06 & 0.09 & 0.06 & 0 \\ 0.06 & 0.06 & 0.09 & 0 \\ 0 & 0 & 0 & 0.09 \end{pmatrix}$$

- Combined residual error: $(\sigma_{\text{inter}}, \sigma_{\text{slope}}) = (0.2, 0.2)$
- 4 doses: $d = (0, 100, 300, 1000)$
- $N = 100$ patients

Example 2 - RSE/RRMSE

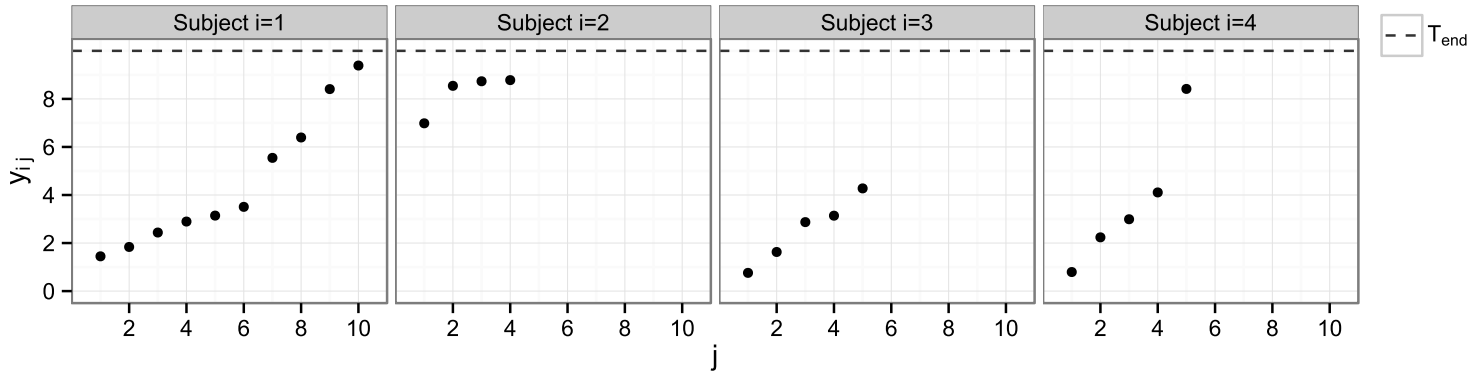


Example 3: Repeated time-to-event

RRTE: Exponential distribution for repeated time-to-event with constant hazard:

$$P(y|b) = \lambda_1 \exp(-\lambda_1 t)$$

- Fixed effects: $\mu_1 = 1.0$
- Exponential random effects: $\lambda_1 = \mu_1 \exp(b)$ with variances: $\omega_1^2 = 0.1$
- Censoring time: 10
- $N = 50$ patients



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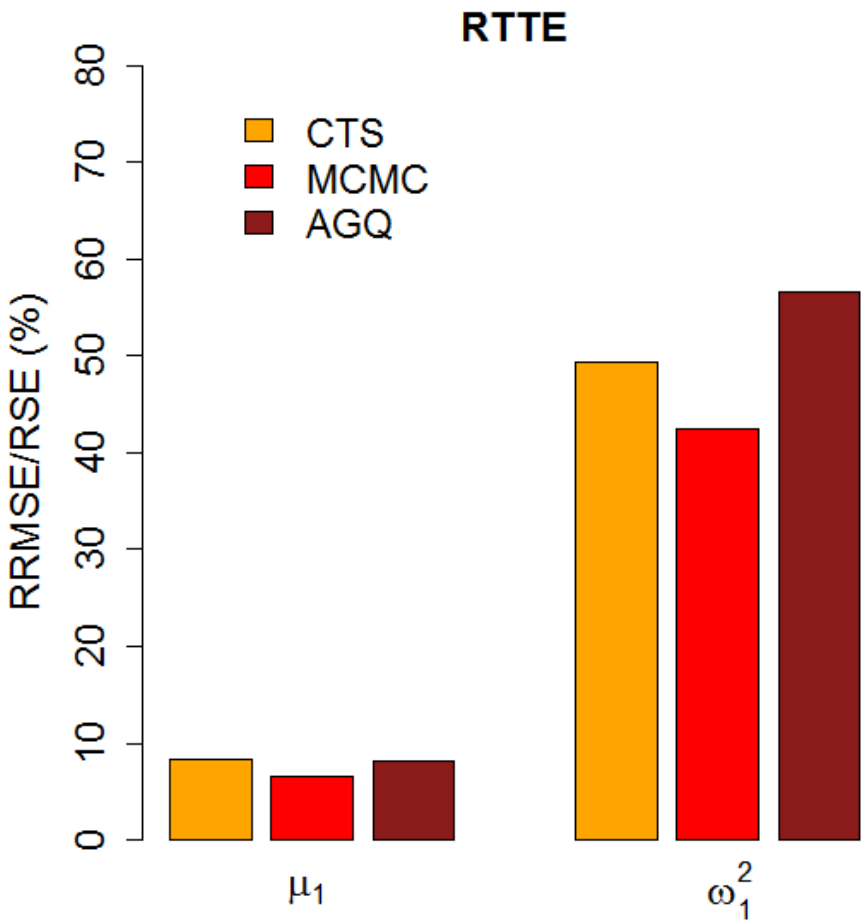
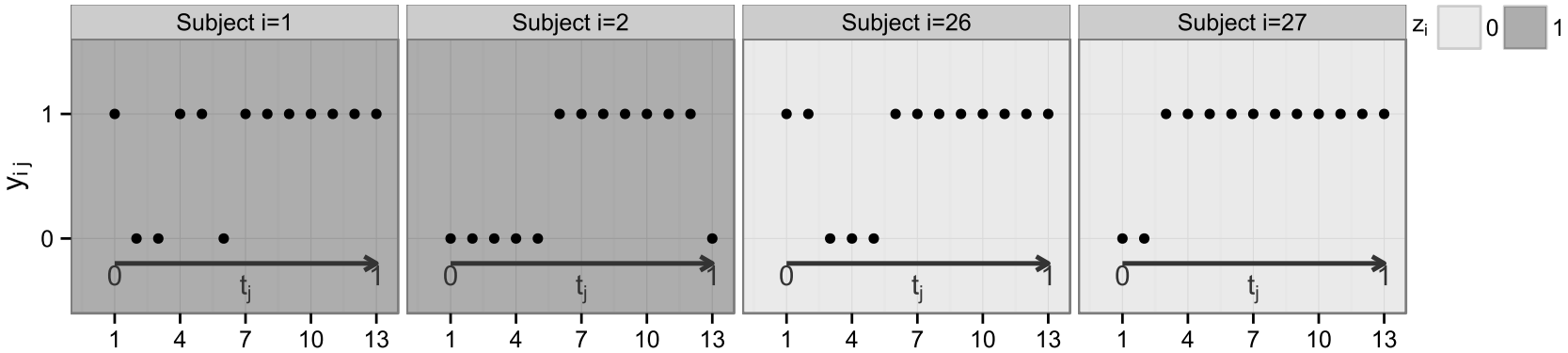


Example 4: Longitudinal binary

LLB: Probability of response at time t:

$$P(y = 1|b) = \frac{\exp(\beta_1 + \beta_2(1 - \mu_3\delta)t)}{1 + \exp(\beta_1 + \beta_2(1 - \mu_3\delta)t)}$$

- Fixed effects: $(\mu_1, \mu_2, \mu_3) = (-1.0, 4.0, 0.4)$
- Additive random effects with variances: $(\omega_1^2, \omega_2^2) = (0.5, 4.0)$
- 2 groups: $\delta = 0$ and $\delta = 1$
- 13 time points equally spaced between 0 and 1 time units for each patient
- $N = 25$ patients per group



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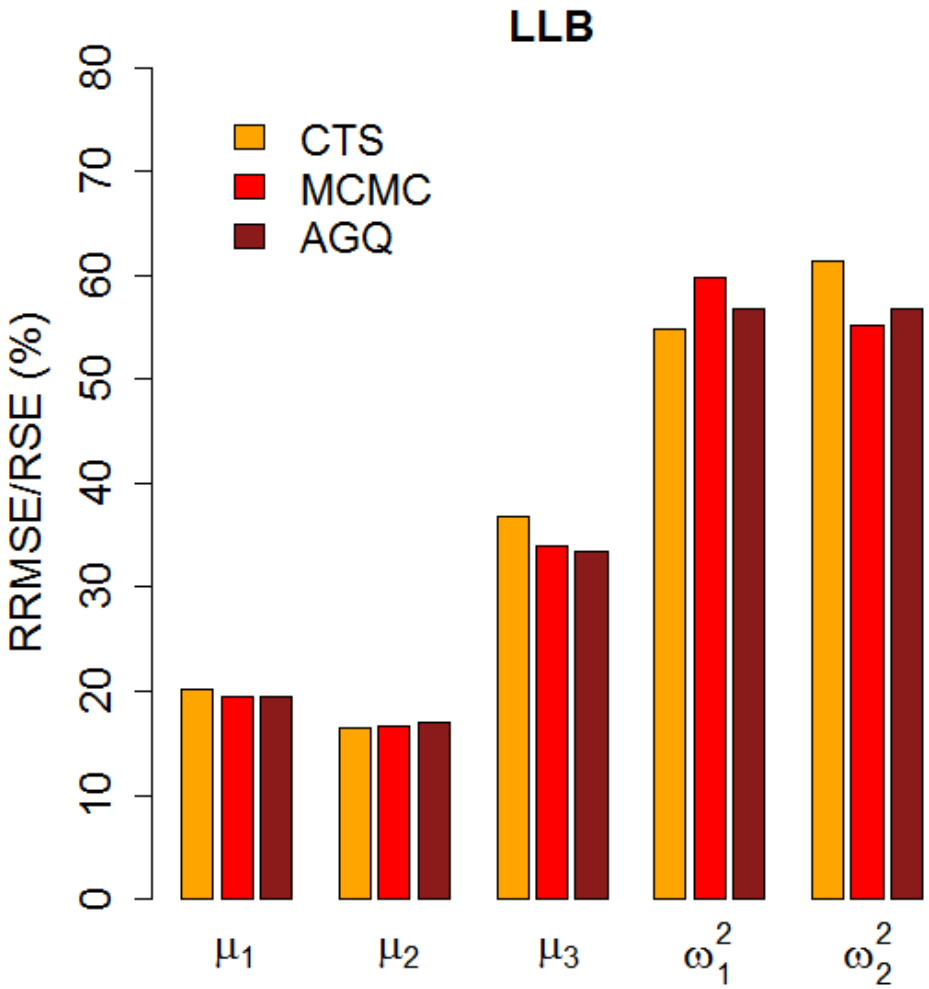
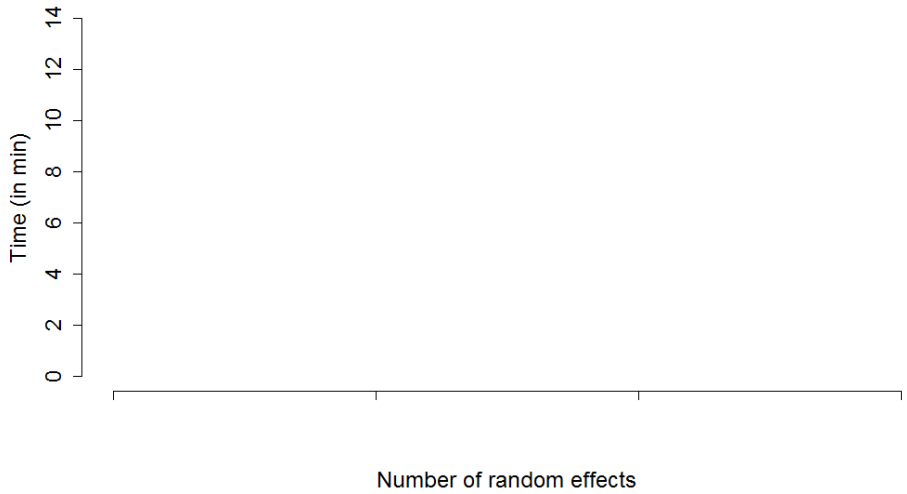


Comparison: calculation time

		PKW	SC1	RTTE	LLB
	CTS	>5h	>5h	>5h	>5h
Time:	MCMC	≈ 6min	≈ 8min	≈ 2min	≈ 4min
	AGQ	≈ 2min	≈ 13min	≈ 10s	≈ 2min
	FO	<5s	<5s	-	-



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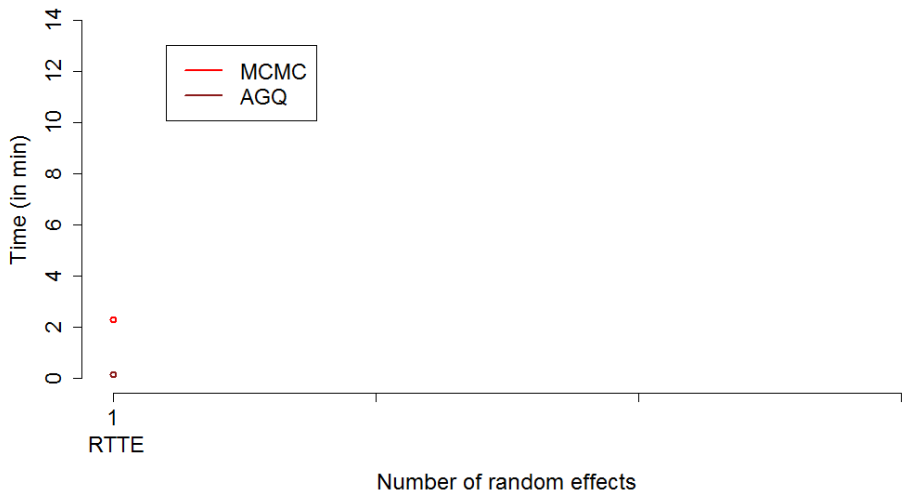

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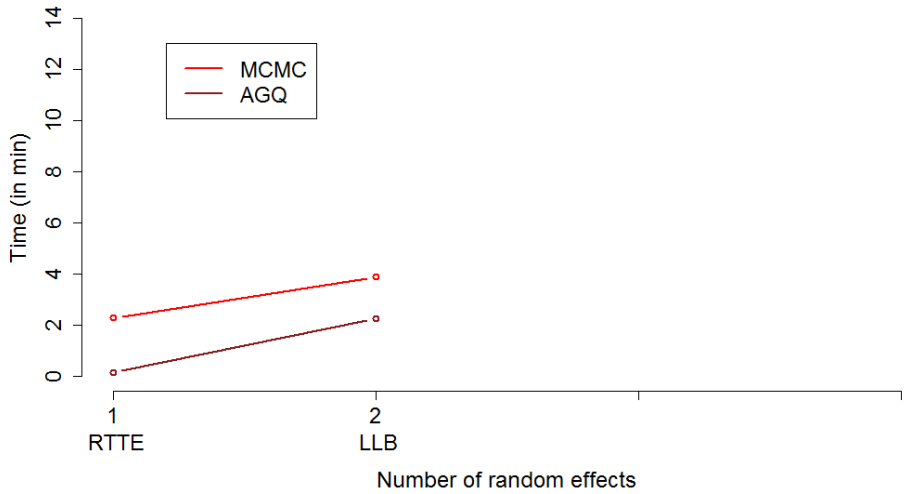

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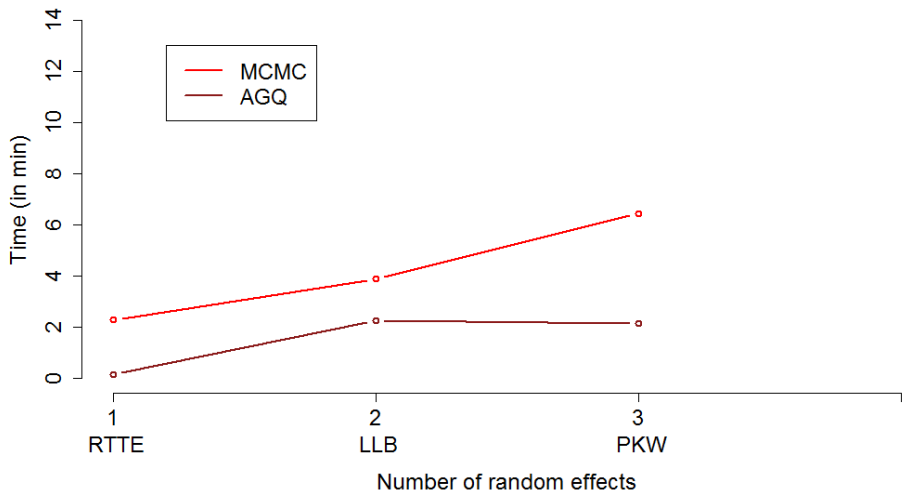

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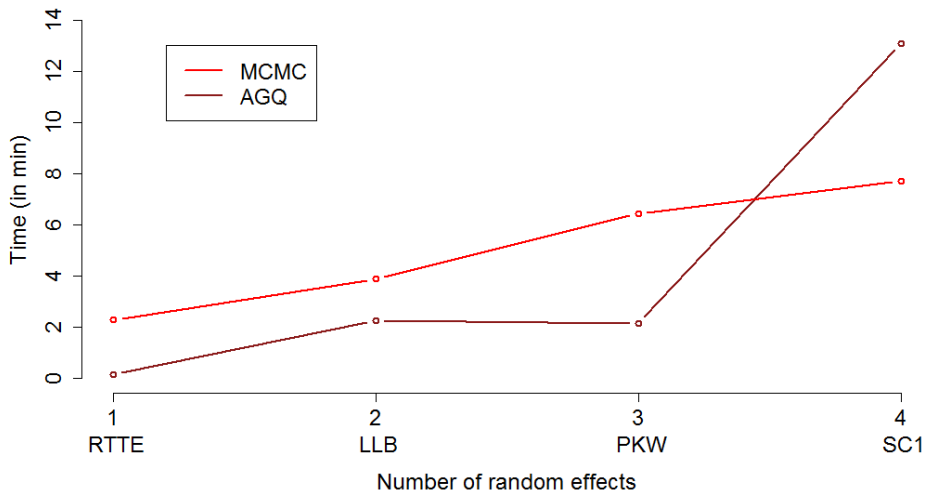

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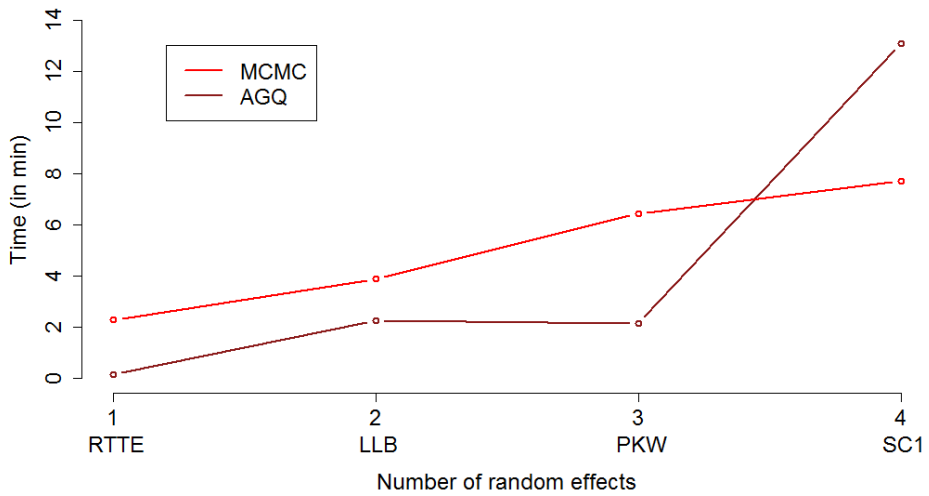

- AGQ: time increases exponentially with the number of random parameters
- MCMC: time increases linearly

Outline

Conclusion

- Need of new methods for FIM evaluation
- Developed a MC-MCMC-based method for evaluating FIM
- Advantages:
  - Adapted for discrete and continuous models
  - No model linearization
  - Very high agreement with clinical trial results
- Drawbacks:
  - Much slower than FO approximation
- Perspectives:
  - Publish R package *MIXFIM* on CRAN (*rstan* 07/2015)
    - Show convergence, stochastic error
    - Investigate design optimization
  - Use model averaging to account for model uncertainty

Thank you for your attention!

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