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

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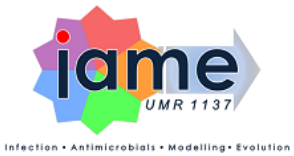

Outline

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Novel approximation for Fisher information matrix (FIM) for non-linear mixed effect models

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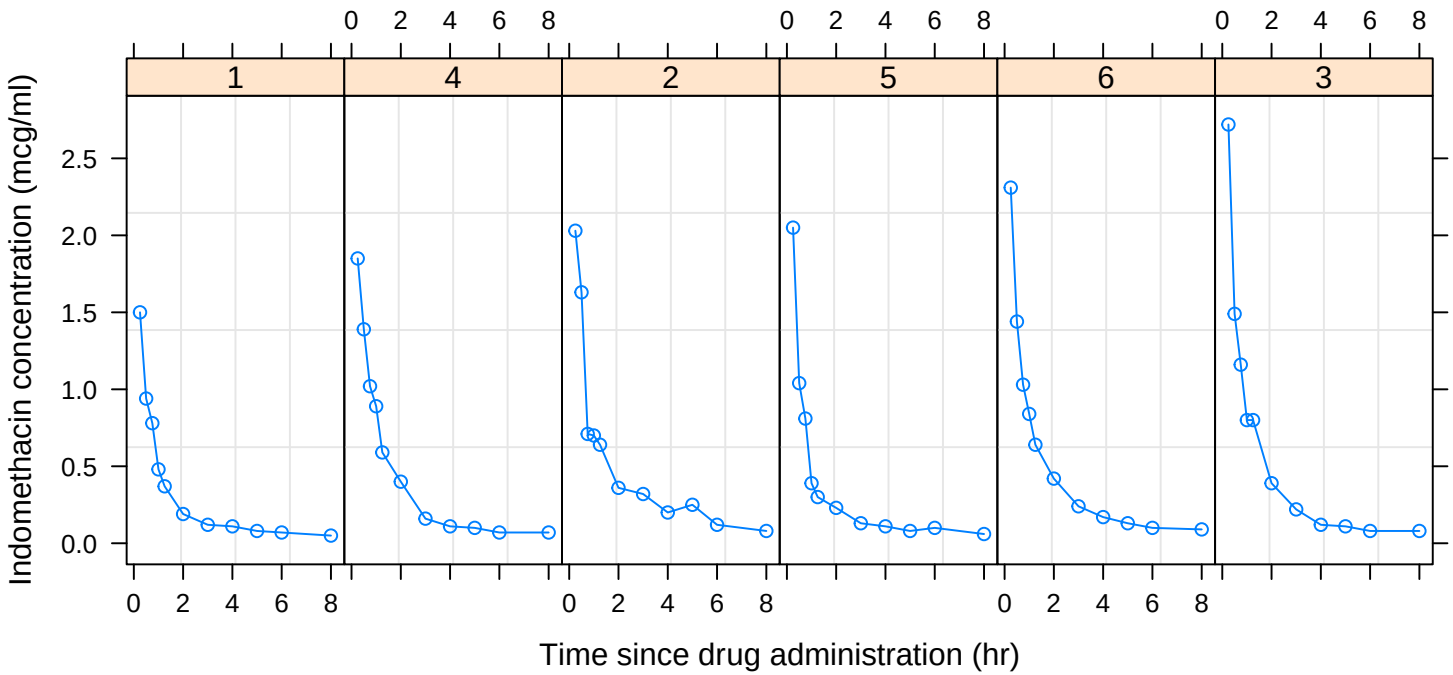
Again? Why?

Pharmacokinetics

. . . characterization of the time course of drug absorption, distribution, metabolism and excretion, and with the relationship of these processes to the intensity and time course of therapeutic and adverse effects of drugs[1]



[1] Wagner 1981

Pharmacokinetics

- Important growth period 1961-1972 (important concepts, journals, . . .)
- Clinical use limited due to need for many measurments per subject
- New approach by Sheiner et al. 1972
  - Pharmacokinetic models (non-linear)
  - Parameters with fixed and random component
  - Many advantages (sparse sampling, individualized dosing, . . .)

Non-linear mixed effect models (NLMEM)

Parameter estimation

- No analytic form for likelihood $\rightarrow$ estimation challenging
- Sheiner et al. 1972 also proposed parameter estimation algorithm – First order (FO) approximation[2]:
  - Model linearized w.r.t. random effect parameters
  - Random effect parameter evaluated at 0
  - Essentially treatment as linear mixed effect model
- Algorithm fast & from 1980 available in software (NONMEM)

[2] MQL approximation in statistics literature

Design

- Design of population pharmacokinetic studies mostly heuristic & rarely took advantage of NLMEM
- Derivation of FIM approximation for NLMEM by Mentré et al. 1997
  - First-order approximation
  - Treatment as linear mixed effect model

Evolution of estimation algorithms

- FO approximation for estimation
  - Biased
  - Asympthotic theory does not apply
  - Problems already for simple models
- NLMEM estimation algorithms:
  - Model linearization around mode (Lindström and Bates 1990)
  - Laplacian approximation (Tierney and Kadane 1986)
  - Importances sampling (Geweke 1989)
  - Gaussian quadrature (Davidian and Gallant 1992)
  - Adaptive gaussian quadrature (Pinheiro and Bates 1995)
  - Stochastic approximation expectation maximization (Kuhn and Lavielle 2004)

Evolution of population FIM approximations

- FO approximation surprisingly accurate for a large class of models[3]
- Population FIM approximations
  - First order conditional approximation (Retout and Mentré 2003)
  - Non-block diagonal FO approximation (Foracchia et al. 2004)
  - First order conditional mode approximation (Nyberg et al. 2012)

FO approximation still most used (PFIM & PopED)

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

Evolution of models

- Advances in estimation methods fostered development of more complex models
  - Complex random effects structures
  - Multiple outcomes
  - Many parameters
  - Discrete outcomes[4]

FO approximation not or less appropriate

[4] Mentré et al. CPT: pharmacomet. syst. pharmacol. 2, e46 (2013)

Objectives

Apply integration algorithms, which have proven to be efficient for estimation, to evaluate the asymptotically exact FIM in NLMEM for both discrete and continuous outcomes

Outline

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Nonlinear mixed effect models

For continuous data:

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

For discrete data:

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

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

Fisher Information Matrix (FIM)

Population FIM:

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

with

ψ vector of all parameters $(\Psi = (\mu, \Omega, \Sigma)^{\mathsf{T}})$

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

$$
\begin{aligned}
M(\psi,\xi) &= E\left(\frac{\partial \log(L(y,\psi))}{\partial\psi}\frac{\partial \log(L(y,\psi))}{\partial\psi}^T\right) \\
&= \int_y \underbrace{\left(\frac{\partial \log(L(y,\psi))}{\partial\psi}\frac{\partial \log(L(y,\psi))}{\partial\psi}^T\right)}_{A_y} \cdot L(y,\psi)dy
\end{aligned}
$$

$$
M(\psi,\xi) = \int_y A_y \quad L(y,\psi)dy \qquad \text{Monte Carlo - MC}
$$

$$
M(\psi,\xi) = \sum_{y_r} A_{y_r}
$$

AGQ MCMC

Outline

Estimation of A_y with AGQ[5]

$$A_y = \frac{\partial \log(L(y,\psi))}{\partial \psi} \frac{\partial \log(L(y,\psi))}{\partial \psi}^T = \frac{\partial L(y,\psi)}{\partial \psi} \frac{\partial L(y,\psi)}{\partial \psi}^T L(y,\Psi))^{-2}$$

with

$$L(y,\psi) = \int_b p(y|b,\psi)p(b)db = \int_\eta p(y|\Omega^{\frac{1}{2}}\eta,\psi)\phi(\eta)\ d\eta \qquad (\eta \stackrel{\text{def}}{=} \Omega^{-\frac{1}{2}} b)$$

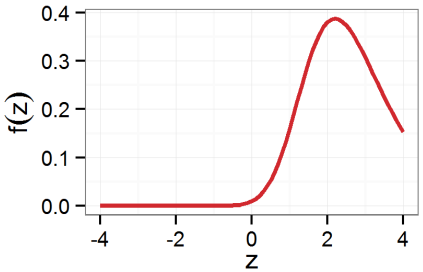
$$\begin{aligned}\frac{\partial L(y,\psi)}{\partial \psi} &= \int_b \frac{\partial (p(y|b,\psi)p(b))}{\partial \psi} db \\ &= \int_\eta \frac{\partial p(y|\Omega^{\frac{1}{2}}\eta,\psi)}{\partial \psi}\phi(\eta)\ d\eta + \\ &\quad \int_\eta -\frac{1}{2}\left[Tr\left(\Omega^{-1}\frac{\partial \Omega}{\partial \psi_k}\right) - \eta^T\Omega^{-\frac{1}{2}}\frac{\partial \Omega}{\partial \psi_k}\Omega^{-\frac{1}{2}}\eta\right] p(y|\Omega^{\frac{1}{2}}\eta,\psi)\phi(\eta)\ d\eta\end{aligned}$$

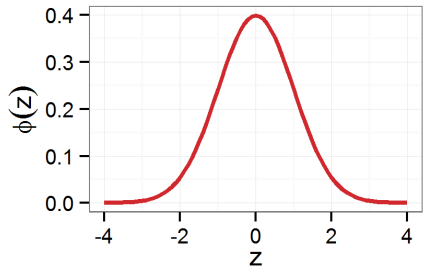
Adaptive Gaussian Quadrature - AGQ

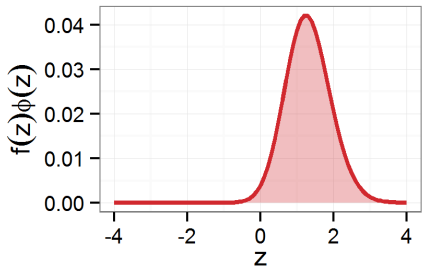
[5] Nguyen & Mentré. Comp. Statistics & Data Analysis 80, 57–69 (2014).

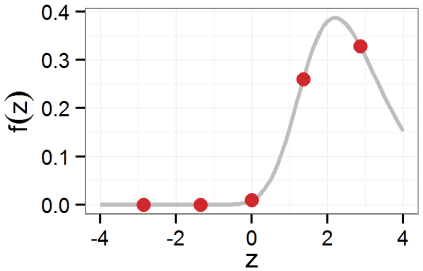
Gaussian Quadrature

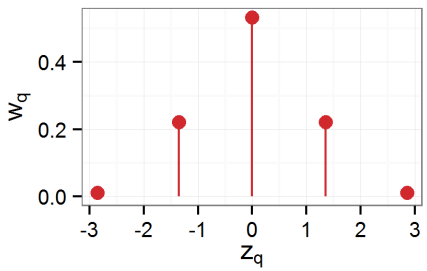
$$\int f(x)\phi(z)dz \approx \sum_{q=1}^{Q} w_q f(z_q)$$

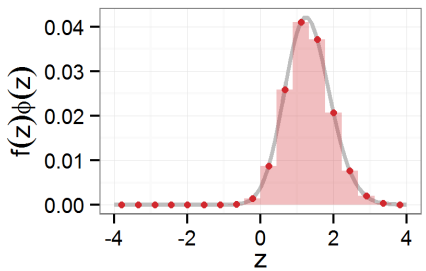








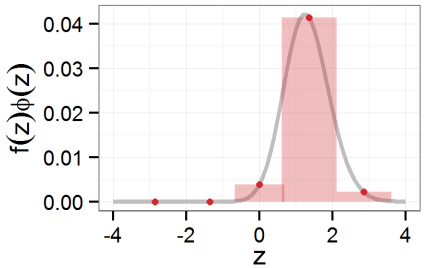




Adaptive Gaussian Quadrature

$$\int f(x)\phi(z)dz \approx \sum_{q=1}^{Q} w_q f(z_q)$$

Center integration grid at mode of $f(x)\phi(z)$



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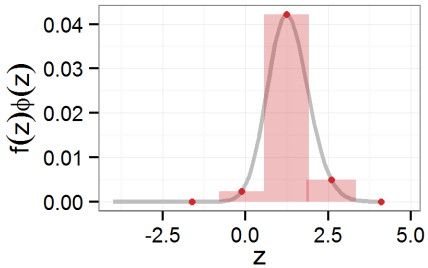
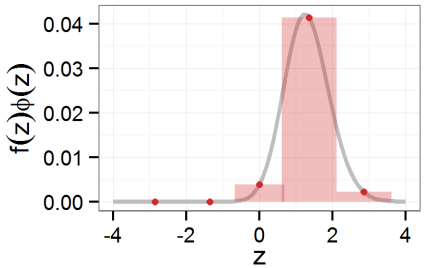


Center integration grid at mode of $f(x)\phi(z)$ & scale by $\frac{\partial^2}{\partial z^2} f(x)\phi(z)$



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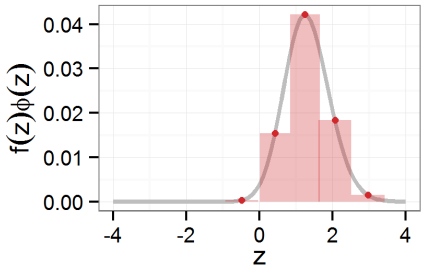

MC-AGQ algorithm for FIM evaluation

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

(II) Determine integration grid

(III) Approximate integrals

MC-AGQ algorithm for FIM evaluation

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

(II) Determine integration grid

- Determine $\hat{\eta} = \arg\max_\eta \log p(y|\Omega^{\frac{1}{2}}\eta, \psi)\phi(\eta)$ through BFGS optimization starting at η.
- Calculate $\frac{\partial^2}{\partial \eta^2} \log p(y|\Omega^{\frac{1}{2}}\eta, \psi)\phi(\eta)|_{\eta=\hat{\eta}}$ through numerical differentiation.
- Calculate quadrature nodes

$$a_{q_1,\ldots,q_d} = \hat{\eta} + \left[-\frac{\partial^2}{\partial \eta^2} \log p(y|\Omega^{\frac{1}{2}}\eta, \psi)\phi(\eta)\Big|_{\eta=\hat{\eta}} \right]^{-\frac{1}{2}} a^*_{q_1,\ldots,q_d}$$

and weights

$$w_{q_1,\ldots,q_d} = \left| \left[-\frac{\partial^2}{\partial \eta^2} \log p(y|\Omega^{\frac{1}{2}}\eta, \psi)\phi(\eta)\Big|_{\eta=\hat{\eta}} \right]^{-\frac{1}{2}} \right| \prod_{k=1}^d w^*_{q_k} \frac{\phi(a_{q_k})}{\phi(a^*_{q_k})}$$

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$\sum_{q_1=1}^{Q} \cdots \sum_{q_d=1}^{Q} w_{q_1,\ldots,q_d} \cdot \tilde{f}(a_{q_1,\ldots,q_d}, \cdot)$

Outline

Reminder

$$
\begin{aligned}
M(\psi,\xi) &= E\left(\frac{\partial \log(L(y,\psi))}{\partial\psi}\frac{\partial \log(L(y,\psi))}{\partial\psi}^T\right) \\
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M(\psi,\xi) = \int_y A_y \quad L(y,\psi)dy \qquad \text{Monte Carlo - MC}
$$

$$
M(\psi,\xi) = \sum_{y_r} A_{y_r}
$$

Estimation of A_y with MCMC

After calculation... A_y in the FIM: $\Longleftrightarrow$

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

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Markov Chains Monte Carlo - MCMC

MC-MCMC algorithm for FIM evaluation

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MC-MCMC algorithm for FIM evaluation

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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

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

(II) For each value of y sampled:

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

  (IV) Estimate $\int_{b_1}$ and $\int_{b_2}$ by the mean of the partial derivatives of the conditional log-likelihood taken in the samples of b drawn in step (III).

MC-MCMC algorithm for FIM evaluation

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

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  (IV) Estimate $\int_{b_1}$ and $\int_{b_2}$ by the mean of the partial derivatives of the conditional log-likelihood taken in the samples of b drawn in step (III).

(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)
  - vs. random walk Monte Carlo methods (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 (using statmod for nodes)
- 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

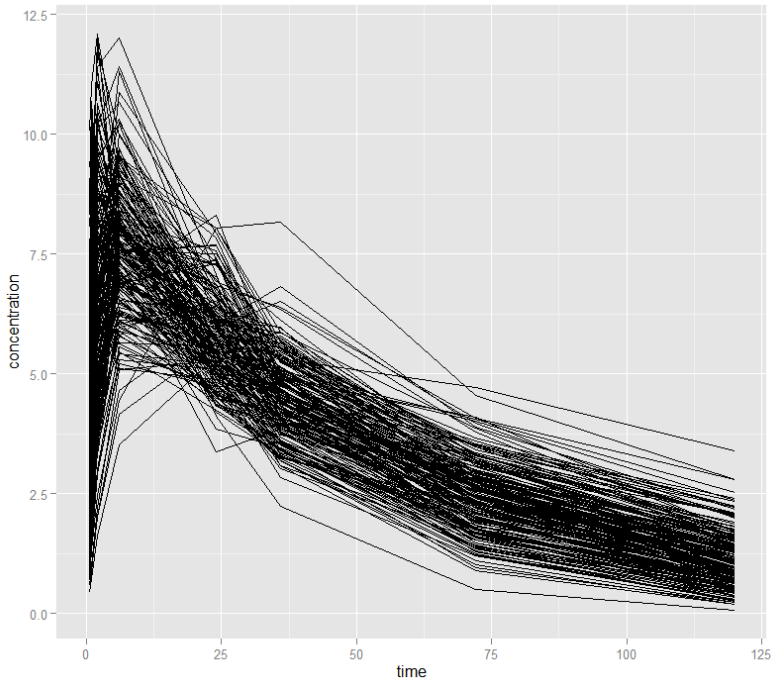
in terms of

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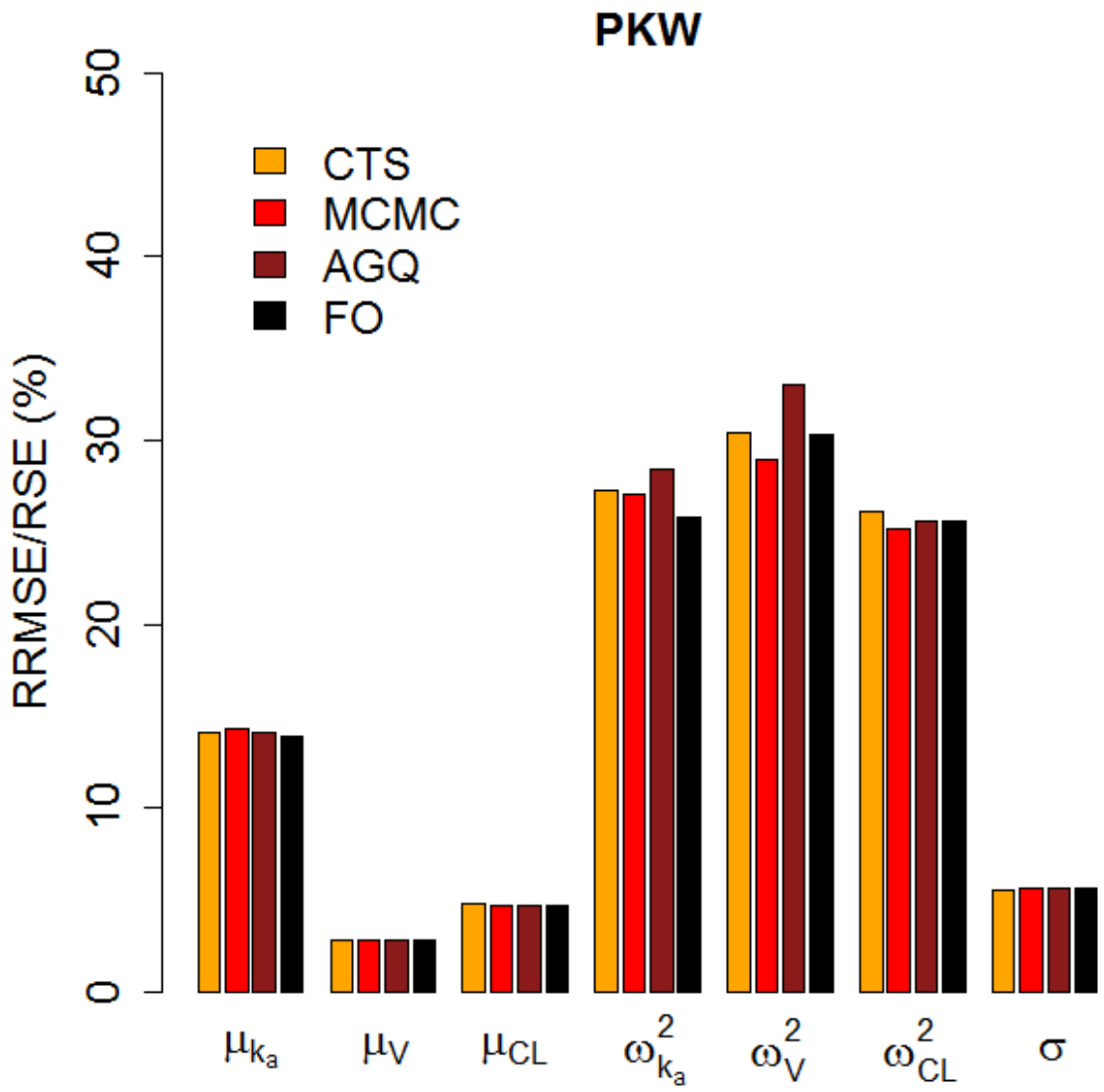
- Fixed effects: $(\mu_{k_a}, \mu_V, \mu_{CL}) = (1.00, 8.00, 0.15)$
- Exponential random effects with variances: $(\omega^2_{k_a}, \omega^2_V, \omega^2_{CL}) = (0.60, 0.02, 0.07)$
- Proportional residual error: $\sigma_{\text{slope}} = 0.1$
- 8 times: $t = (0.5, 1, 2, 6, 24, 36, 72, 120)$
- $N = 32$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

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

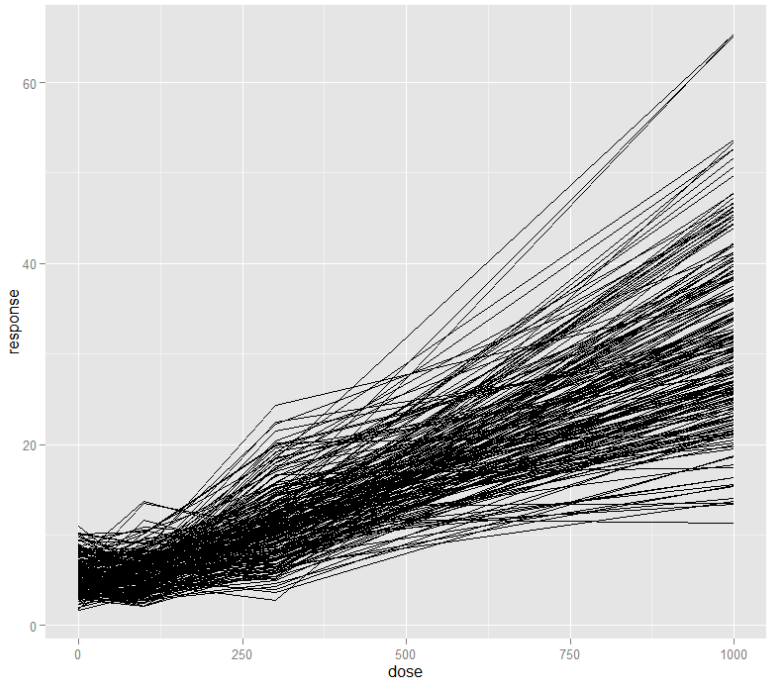
Example 1 - RSE/RRMSE



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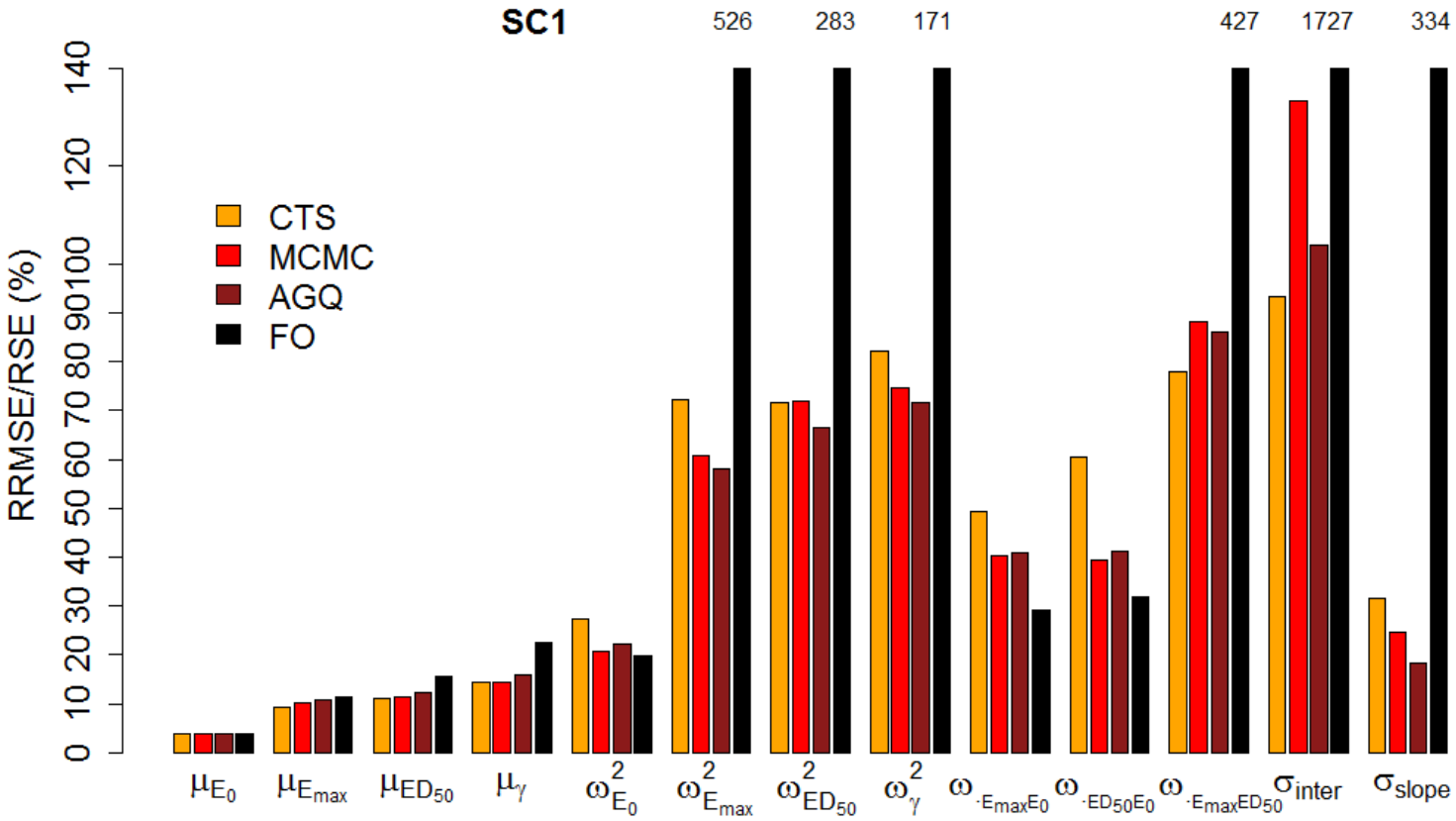
$$f(\phi = (E_0, E_{max}, ED_{50}, \gamma), d) = E_0 + \frac{E_{max} d^\gamma}{ED_{50}^\gamma + d^\gamma}$$

- 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

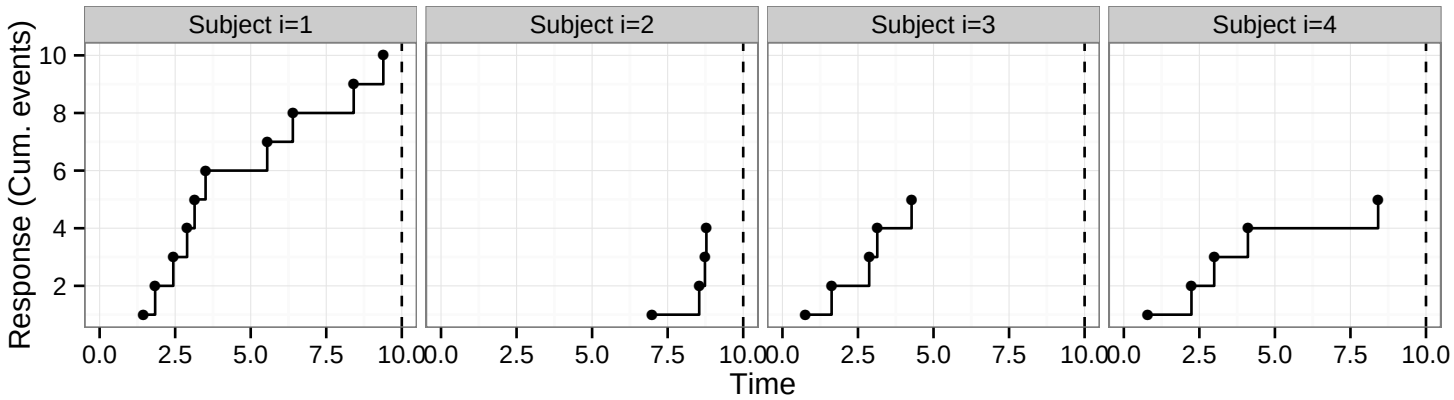


Example 3: Repeated time-to-event

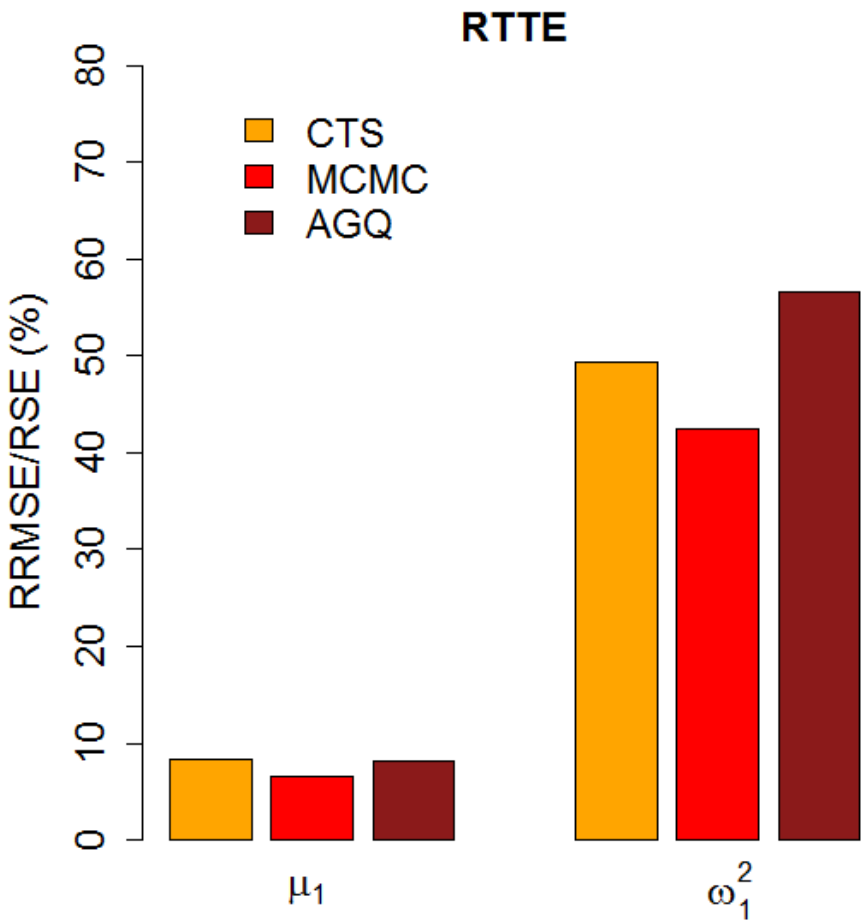
RRTE: Exponential distribution for repeated time-to-event with constant hazard:

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

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



Example 3 - RSE/RRMSE

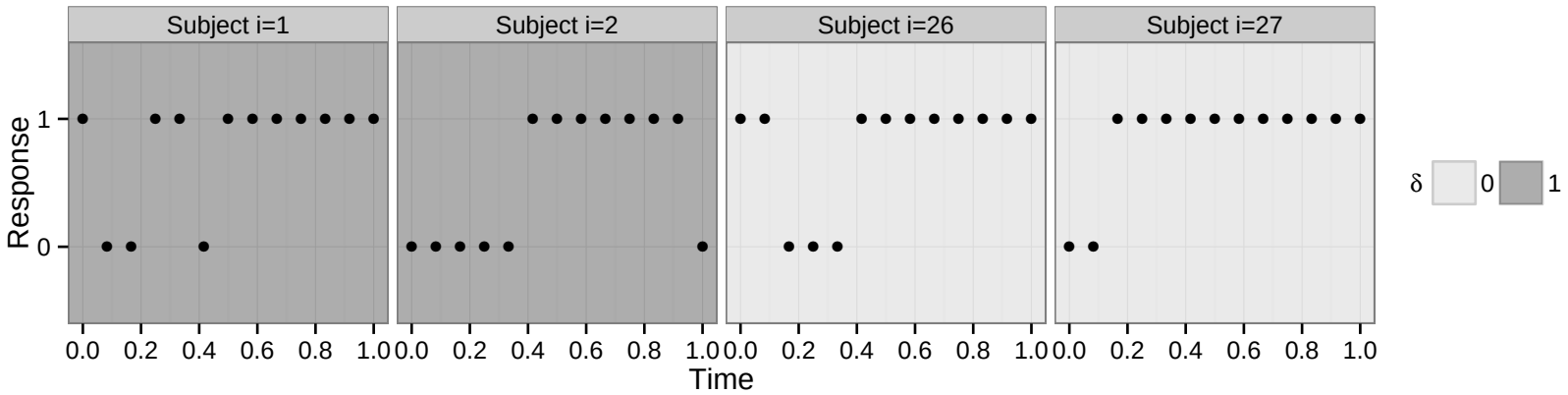


Example 4: Longitudinal binary

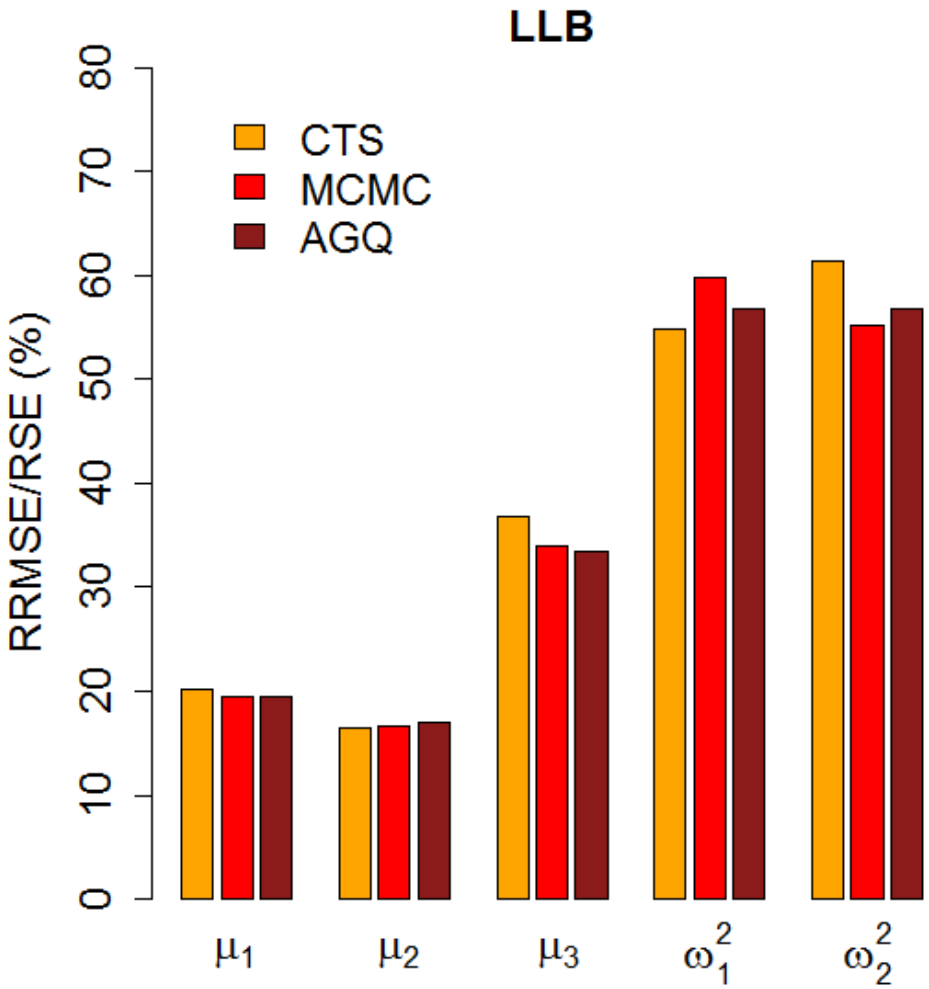
LLB: Probability of response at time t:

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

- 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

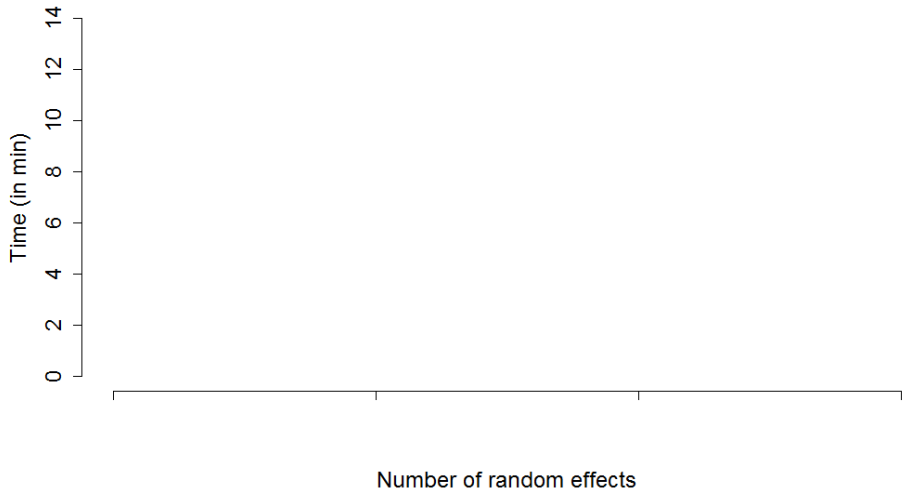


Example 4 - RSE/RRMSE



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	-	-



Comparison: calculation time

		PKW	SC1	RTTE	LLB
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Time:	MCMC	≈ 6min	≈ 8min	≈ 2min	≈ 4min
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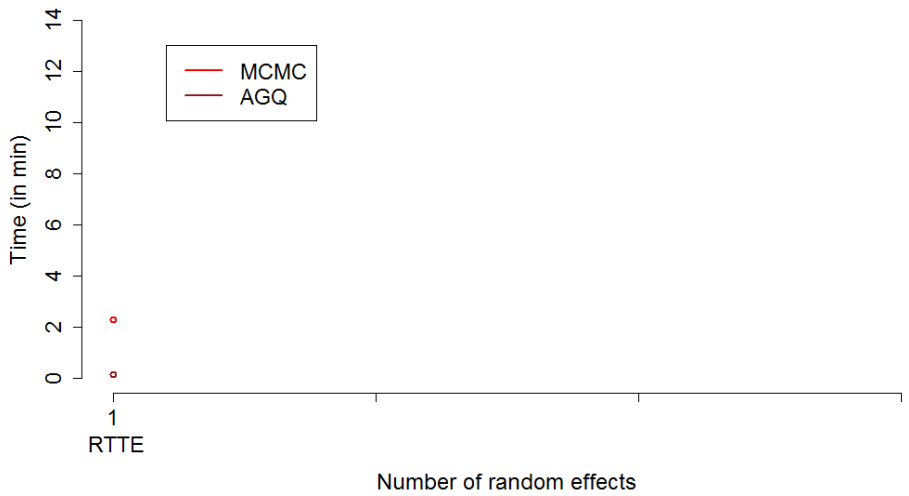

Comparison: calculation time

		PKW	SC1	RTTE	LLB
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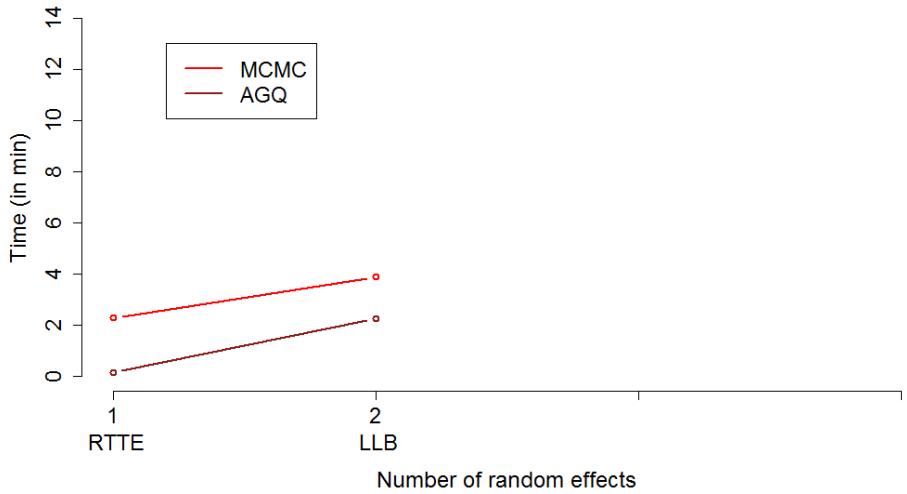

Comparison: calculation time

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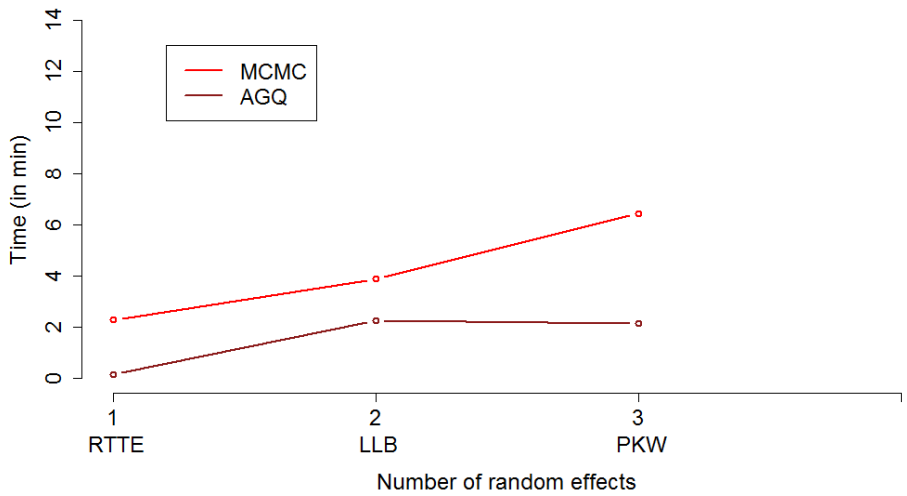

Comparison: calculation time

		PKW	SC1	RTTE	LLB
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	MCMC	≈ 6min	≈ 8min	≈ 2min	≈ 4min
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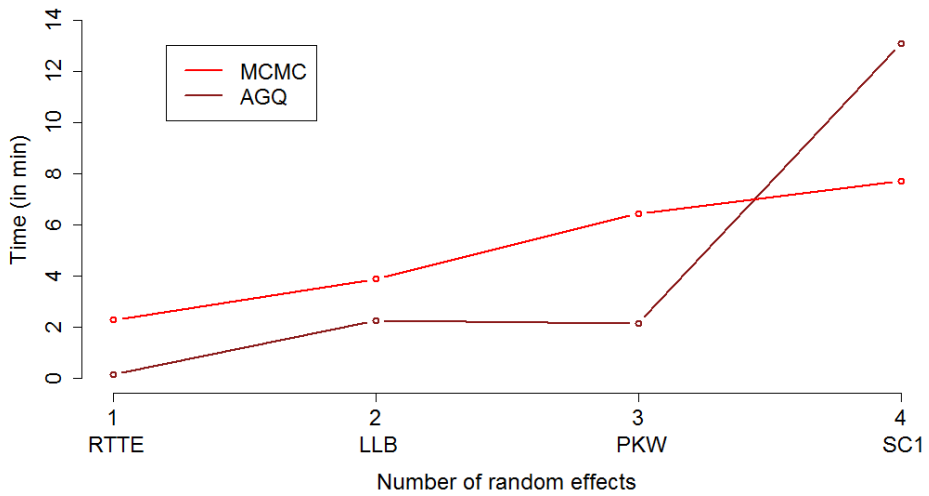

Comparison: calculation time

		PKW	SC1	RTTE	LLB
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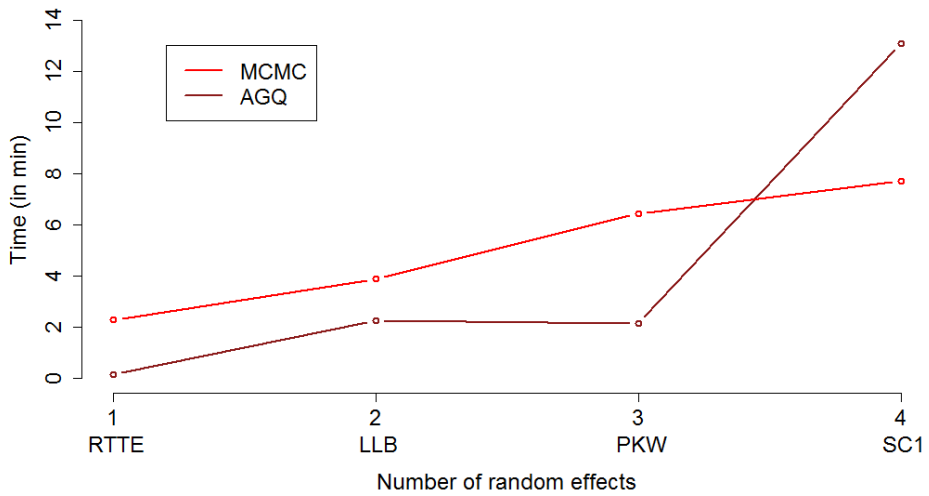

- AGQ: time increases exponentially with the number of random parameters
- MCMC: time increases linearly

Outline

Summary

- Recent NLMEM (multivariate, complex, discrete, ...) require improved method for FIM prediction
- Presented two complementing MC-based methods for calculating FIM
- Advantages:
  - Adapted for discrete and continuous models
  - No model linearization
  - Very high agreement with clinical trial results
- Drawbacks:
  - Much slower than FO approximation
  - Monte-Carlo noise

Perspectives

- Publish R packages on CRAN
- Investigate design optimization:
  - Handling of MC noise (stochastic approximation, simulated annealing, ...)
  - Adaptive approximation (refine approximation during optimization)
- Investigate alternative sampling methods (Latin hypercube sampling, quasi-random sampling, ...)

Thank you for your attention!

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