Evaluation of the expected Fisher information matrix without linearization, in nonlinear mixed effect models for discrete and continuous outcomes

Marie-Karolee Riviere, Sebastian Ueckert and France Mentre
INSERM, IAME, UMR 1137, F-75018 Paris, France
Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France

Introduction
Nonlinear mixed effect models (NLMEs) are widely used for the analysis of longitudinal data. Longitudinal data include continuous measures but also discrete measures such as binary, ordinal or count data. To evaluate and compare NLME designs, the Fisher information matrix (FIM) can be used as its inverse is the lower bound of the variance covariance matrix of any unbiased parameter estimator according to the Cramer-Rao inequality. However, in NLMEs, the Fisher information matrix has no analytical form and its calculation, which require multiple integrations, can be challenging. Therefore, an expression based on first-order linearization (FO) around the expectation of the random effects was proposed by Mentre et al. In recent years, estimation algorithms for NLMEs have transitioned from linearization-based approaches towards more exact higher-order methods. Optimal design, on the other hand, has mainly relied on FO to calculate the expected FIM. Although very efficient in general, FO precludes the application of optimal design with complex non-linear models and in studies with discrete endpoints. The objective of this work was to apply integration algorithms, which have proven to be efficient for estimation, to evaluate the asymptotically exact FIM in NLME for both discrete and continuous outcomes.

Methods
Nonlinear mixed effect models

- For continuous data: \( y_i = f(y_i, \mu, \psi_i) + \varepsilon_i \)
- For discrete data: \( P(y_i|\psi_i) = \prod_{j=1}^{n_i} f(y_{ij}, \mu, \psi_i) \)

\( f \)  a structural model
\( \varepsilon_i \)  vector of random effects for individual \( i \)
\( \psi_i \)  random effect parameter vector
\( \mu \)  vector of fixed effects

Markov Chains Monte Carlo - MCMC

- Partial derivatives calculation:
  - Monte Carlo - MC
  - Markov Chain Monte Carlo - MCMC

Fisher Information Matrix

\( M(\psi, \zeta) = \mathbb{E} \left[ \frac{\partial^2 \log L(\psi, \zeta)}{\partial \psi \partial \zeta} \right] \)

Adaptive Gaussian Quadrature - AGQ

\( M(\psi, \zeta) = \int \frac{\partial^2 \log L(\psi, \zeta)}{\partial \psi \partial \zeta} \, L(\psi, \zeta) \, dy \)

Simulation and Results

We compared 3 approaches to evaluate the FIM: MCMC-based approach, AGQ-based approach and Linearization (FO), with clinical trial simulations (CTS). We used several criteria: the RSE / RMSE, and the normalized determinant of the FIM / normalized determinant of the inverse of the observed variance-covariance matrix, and also investigated computation time. We used two continuous examples: a pharmacokinetic Warfarin model (PKW), and an Emam dose-response model (SCI), as well as two discrete examples: a logistic model for longitudinal binary outcome (LLB), and an exponential model with constant hazard for repeated time-to-event (RTTE).

PKW: One compartment model with first order absorption and elimination

\( f(x, \mu, \psi) = \frac{1}{\alpha + \beta x} \left( e^{-\alpha t} - e^{-\beta x t} \right) \)

- Fixed effects: \( \mu \) (0.0, 0.0, 0.15)
- Proportional residual error: 0.25
- \( N = 32 \) patients

LLB: Probability of “no-response” at time \( t \) for group \( \delta \):

\( P(y = 1|t) = \exp(\delta) \exp(-\mu \exp(\delta) t) \)

- Fixed effects: \( \mu \) (1.0, 0.4, 0.4)

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

\( f(t) = \lambda e^{-\lambda t} \)

- Fixed effects: \( \lambda \) (0.1)
- \( N = 50 \) patients

SCI: Signal \( E_{max} \) model

\( f(x) = \frac{E_{max} \cdot D_{max}}{D_{max} + x} \)

- Fixed effects: \( \mu \) (1.5, 0.5, 0.5)
- Proportional residual error: 0.25
- \( N = 100 \) patients

Results:
Both AGQ and MCMC-based approaches showed good performance on scenarios for continuous outcomes with RSE close to the RMSEs obtained by simulations. In general, RSE predicted by linearization gave close results for rich designs, but showed larger deviations for sparse designs and very non-linear models. On the contrary to FO, AGQ and MCMC can be applied to discrete data and showed good performance. Computation of the FIM in AGQ took only seconds for models with few random effects, but time computation increases exponentially with the number of random effects and models with more than 4 random effects became infeasible. The MCMC approach on the other hand was slower than AGQ for simple models, but can be applied to complex ones with similar time calculation.

Conclusion

Two complementary methods for calculating the exact FIM were proposed and evaluated. Both approaches showed similar performance in terms of RSE for model with continuous and discrete data. AGQ is a fast algorithm that can be used for simple models. MCMC suited even for large complex models where FO fails to correctly evaluate the FIM. We developed two R packages that will be soon available.

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