Exact Gradients Improve Parameter Estimation in Nonlinear Mixed Effects Models with Stochastic Dynamics

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Background

Nonlinear mixed effects (NLME) models based on stochastic differential equations (SDEs) have evolved into a promising approach for analysis of PKPD data [1-3]. We present an exact-gradient version of the first order conditional estimation (FOCE) method for SDE-NLME models, and show that it enables faster estimation and better gradient precision/accuracy compared to finite difference (FD) gradients. This method is an extension of our previous work on regular NLME models [4].

The SDE-NLME framework

The SDE-NLME model

The hierarchical dynamic model is described by a system of SDEs

$$d\boldsymbol{x}_i = \boldsymbol{f}(\boldsymbol{x}_i, \boldsymbol{u}_i, t, \boldsymbol{\theta}, \boldsymbol{\eta}_i)dt + \mathbf{G}(\boldsymbol{x}_i, \boldsymbol{u}_i, t, \boldsymbol{\theta}, \boldsymbol{\eta}_i)d\boldsymbol{w}_i \qquad \boldsymbol{\eta}_i \sim N(\mathbf{0}, \boldsymbol{\Omega})$$

$$\boldsymbol{x}_i(t_0) = \boldsymbol{x}_0(\boldsymbol{\theta}, \boldsymbol{\eta}_i) \qquad d\boldsymbol{w}_i \sim N(\mathbf{0}, dt\,\mathbf{I})$$

together with an observation equation

$$\boldsymbol{y}_{ij} = \boldsymbol{h}(\boldsymbol{x}_{ij}, \boldsymbol{u}_i, t_{ij}, \boldsymbol{\theta}, \boldsymbol{\eta}_i) + \boldsymbol{e}_{ij} \qquad \boldsymbol{e}_{ij} \sim N(\mathbf{0}, \boldsymbol{\Sigma})$$

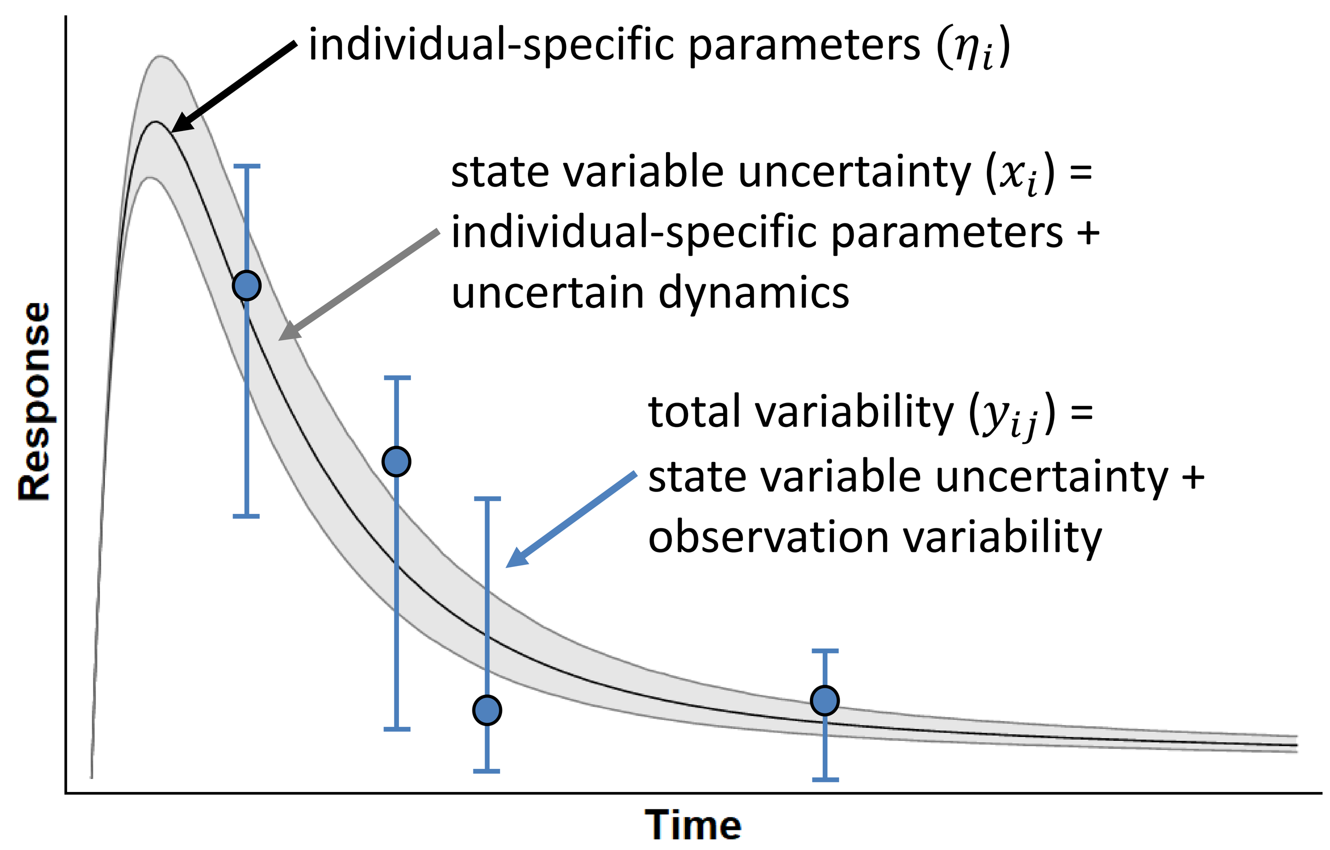
Parameter estimation combines three methods

- Likelihood approximation: FOCE method
- State variable estimation: Extended Kalman Filter (EKF)
- Optimization of the likelihood: nested optimization (inner and outer level) using an exact gradient approach

The exact gradient approach

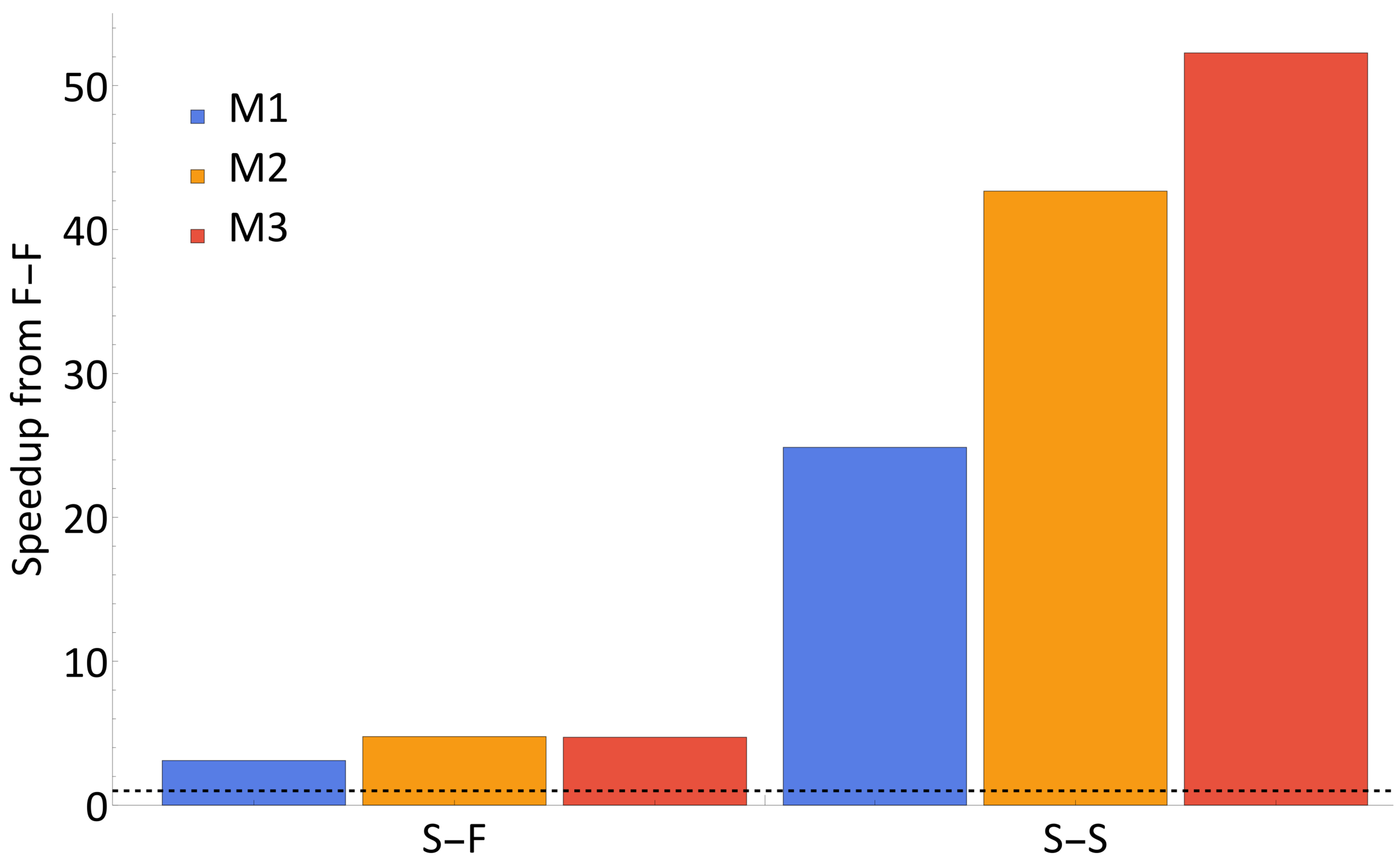
- Symbolic differentiation of the likelihood w.r.t. model parameters
- Requires forward sensitivity equations for the model and the EKF
- Benchmarked using three common PKPD models: two-compartment PK with first order absorption (M1), M1 combined with direct response (M2), and M1 combined with turnover response (M3)

Three sources of variability

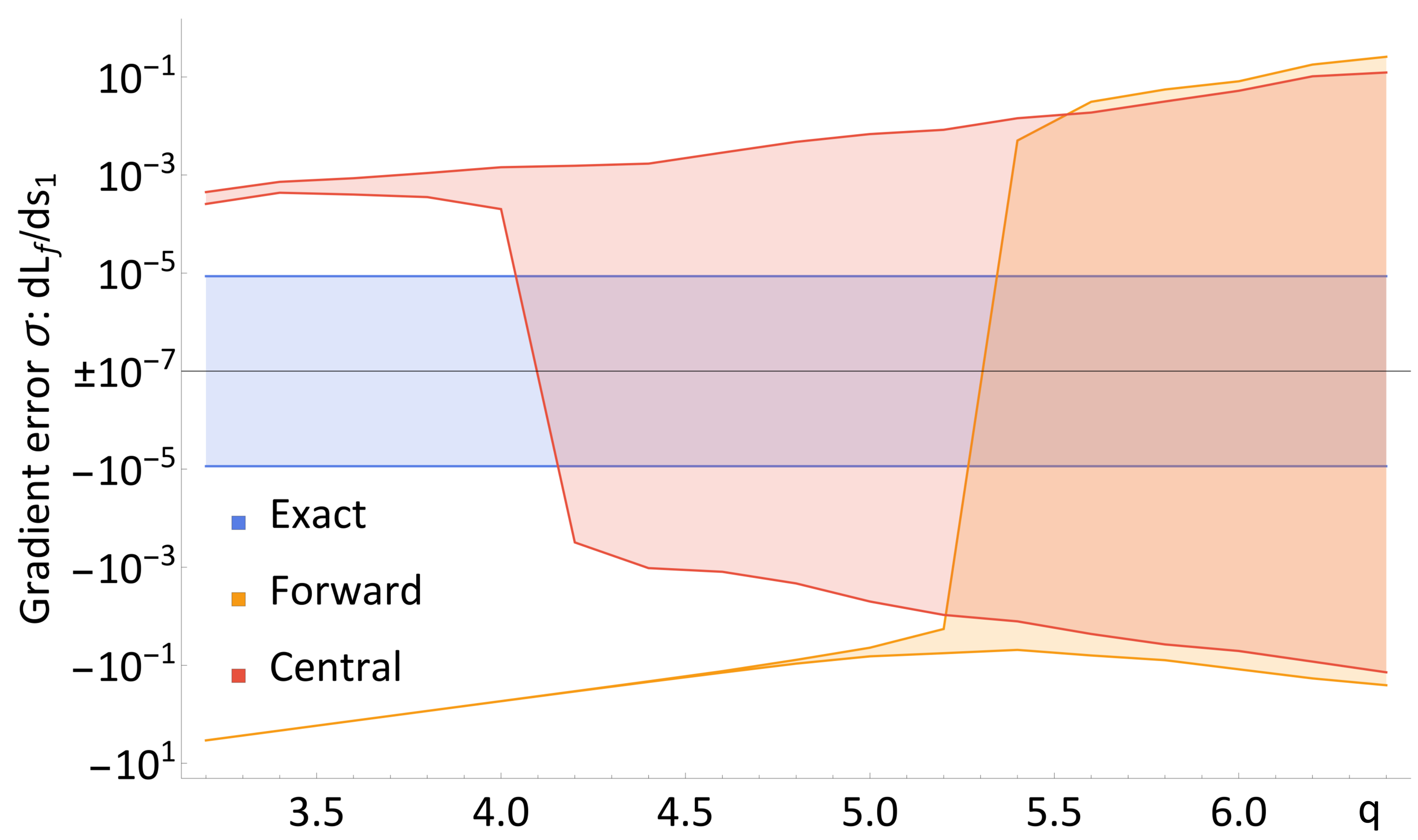


- SDEs are used to model uncertainty in the dynamics of the underlying biological process
- SDE-NLME models account for three sources of variability in PKPD data: observation errors, between subject variability, and state variable uncertainty

Exact gradients improve speed, accuracy, and precision



Relative speed-up for exact gradients compared to using central FDs (dashed line) for three benchmark PKPD models (M1-M3). S-F shows the speed-up using exact gradients in the inner problem only. S-S shows the speed-up using exact gradients in both inner and outer problems.



Monte Carlo sample distributions of numerical errors in the gradient computation using exact gradients (blue), forward FDs (yellow), and central FDs (red), for different step-sizes 10^{-q}. For large step sizes (small q), FDs are biased but precise. Accuracy of FDs increase when step sizes decrease (large q), but FDs simultaneously suffers from a loss of precision compared to exact gradients.

Summary and conclusions

- A method for computing the exact gradients of the FOCE likelihood approximation for SDE-NLME models has been developed and implemented in Mathematica (Wolfram Research)
- The method has been benchmarked using three standard PKPD models of different complexity
- Relative run-times improved up to 50-fold when FDs were replaced by exact gradients
- Exact gradients are unbiased and precise, compared to FD gradients

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