Sensitivity Equations Provide More Robust Gradients and Faster Computation of the FOCE Approximation to the Population Likelihood

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Background

The first order conditional estimation (FOCE) method [1] is still one of the parameter estimation workhorses for nonlinear mixed effects (NLME) modeling used in population pharmacokinetics and pharmacodynamics [2]. We propose a novel implementation of the FOCE and FOCEI methods where instead of obtaining the gradients needed for the two levels of quasi-Newton optimizations from the standard finite difference approximation, gradients are computed using so called sensitivity equations [3].

The Approximate Population Likelihood

The state-space model for a single individual is described by a system of ordinary differential equations and a corresponding set of measurement equations

$$\frac{d\mathrm{x}_i(t)}{dt} = \mathrm{f}(\mathrm{x}_i(t), t, \mathrm{Z}_i(t), \boldsymbol{\theta}, \boldsymbol{\eta}_i)$$
$$\mathrm{x}_i(t_0) = \mathrm{x}_{0i}(\mathrm{Z}_i(t_0), \boldsymbol{\theta}, \boldsymbol{\eta}_i)$$

$$\mathrm{y}_{ij} = \mathrm{h}(\mathrm{x}_{ij}, t_{j_i}, \mathrm{Z}_i(t_{j_i}), \boldsymbol{\theta}, \boldsymbol{\eta}_i) + \mathrm{e}_{ij}$$
$$\mathrm{e}_{ij} \in N(\mathbf{0}, \mathrm{R}_{ij}(\mathrm{x}_{ij}, t_{j_i}, \mathrm{Z}_i(t_{j_i}), \boldsymbol{\theta}, \boldsymbol{\eta}_i))$$
$$\hat{\mathrm{y}}_{ij} = \mathrm{E}[\mathrm{y}_{ij}]$$

where indices i and j denote individuals and observations, respectively. Furthermore, $\boldsymbol{\theta}$ are fixed effects parameters, $\mathbf{Z}_i(t_{j_i})$ are covariates, $\boldsymbol{\eta}_i \sim N(0, \boldsymbol{\Omega})$ are random effect parameters, and $\mathbf{R}_{ij}$ are measurement error covariance matrices.

Given a set of experimental observations, $\mathbf{d}_{ij}$, for the individuals $i = 1, \dots, N$ at the time points t_{j_i}, where $j_i = 1, \dots n_i$, we define the residuals $\epsilon_{ij} = \mathrm{d}_{ij} - \hat{\mathrm{y}}_{ij}$

The approximate log-likelihood function is obtained using the Laplacian approximation, which involves a second order Taylor expansion wrt $\boldsymbol{\eta}_i$ of l_i around points $\boldsymbol{\eta}_i^*$ that maximize the individual l_i.

$$\log L(\boldsymbol{\theta}) \approx \log L_F(\boldsymbol{\theta}) = \sum_{i=1}^{N} \left(l_i(\boldsymbol{\eta}_i^*) - \frac{1}{2} \log\det\left[\frac{-\mathbf{H}_i(\boldsymbol{\eta}_i^*)}{2\pi}\right] \right)$$

where

$$l_i = -\frac{1}{2}\sum_{j=1}^{n_i}\left(\boldsymbol{\epsilon}_{ij}^T \mathbf{R}_{ij}^{-1}\boldsymbol{\epsilon}_{ij} + \log\det(2\pi\mathbf{R}_{ij})\right) - \frac{1}{2}\boldsymbol{\eta}_i^T\boldsymbol{\Omega}^{-1}\boldsymbol{\eta}_i - \frac{1}{2}\log\det(2\pi\boldsymbol{\Omega})$$

The Inner Optimization Problem

The inner optimization problem consists of finding the $\boldsymbol{\eta}_i$ that maximize the individual l_i (for a given $\boldsymbol{\theta}$). Gradient based optimization methods need accurate gradients. The k^{th} component of the gradient of the log-likelihood wrt $\boldsymbol{\eta}_i$

$$\frac{dl_i}{d\eta_{ik}} = -\frac{1}{2}\sum_{j=1}^{n_i}\left(2\boldsymbol{\epsilon}_{ij}^T\mathbf{R}_{ij}^{-1}\frac{d\boldsymbol{\epsilon}_{ij}}{d\eta_{ik}} - \boldsymbol{\epsilon}_{ij}^T\mathbf{R}_{ij}^{-1}\frac{d\mathbf{R}_{ij}}{d\eta_{ik}}\mathbf{R}_{ij}^{-1}\boldsymbol{\epsilon}_{ij} + \mathrm{tr}\left[\mathbf{R}_{\mathrm{ij}}^{-1}\frac{d\mathbf{R}_{ij}}{d\eta_{ik}}\right]\right) - \boldsymbol{\eta}_i^T\boldsymbol{\Omega}^{-1}\frac{d\boldsymbol{\eta}_i}{d\eta_{ik}}$$

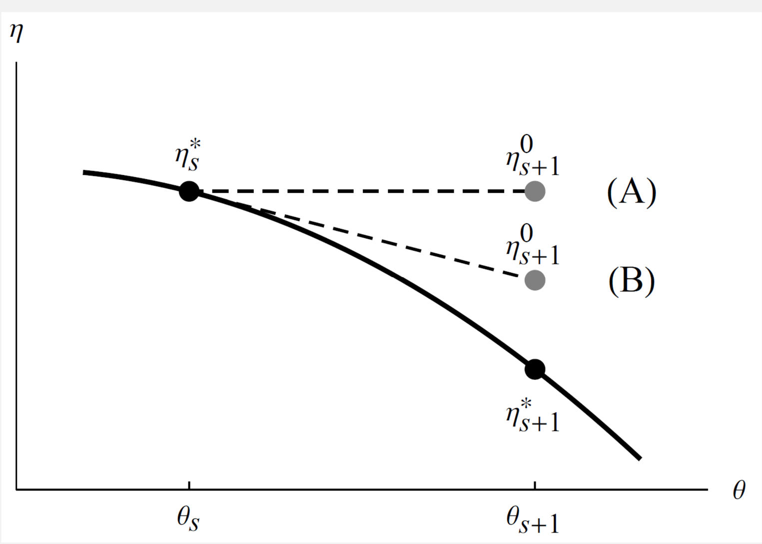
where

$$\frac{d\boldsymbol{\epsilon}_{ij}}{d\eta_{ik}} = \frac{d(\mathbf{d}_{ij} - \hat{\mathbf{y}}_{ij})}{d\eta_{ik}} = -\left(\frac{\partial\mathbf{h}}{\partial\eta_{ik}} + \frac{\partial\mathbf{h}}{\partial\mathbf{x}_{ij}}\frac{d\mathbf{x}_{ij}}{d\eta_{ik}}\right) \quad \text{and} \quad \frac{d\mathbf{R}_{ij}}{d\eta_{ik}} = \frac{\partial\mathbf{R}_{ij}}{\partial\eta_{ik}} + \frac{\partial\mathbf{R}_{ij}}{\partial\mathbf{x}_{ij}}\frac{d\mathbf{x}_{ij}}{d\eta_{ik}}$$

The *sensitivity* differential equations wrt η_{ik}

$$\frac{d}{dt}\left(\frac{d\mathbf{x}_i}{d\eta_{ik}}\right) = \frac{\partial\mathbf{f}}{\partial\eta_{ik}} + \frac{\partial\mathbf{f}}{\partial\mathbf{x}_i}\left(\frac{d\mathbf{x}_i}{d\eta_{ik}}\right) \qquad \left(\frac{d\mathbf{x}_i}{d\eta_{ik}}\right)(t_0) = \frac{\partial\mathbf{x}_{0i}}{\partial\eta_{ik}}$$

Starting Values for Random Parameters



Using that $\boldsymbol{\eta}_i^* = \boldsymbol{\eta}_i^*(\boldsymbol{\theta})$ is a function of $\boldsymbol{\theta}$ and that we have $\frac{d\boldsymbol{\eta}_i^*}{d\boldsymbol{\theta}}$ give improved starting values of the inner optimization problem

$$\eta_{s+1}^0 = \eta_s^* + \frac{d\eta_s^*}{d\theta}(\theta_{s+1} - \theta_s)$$

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The Outer Optimization Problem

The outer optimization problem consists of finding the $\boldsymbol{\theta}$ that maximizes the log-likelihood. The m^{th} component of the gradient of the log-likelihood wrt $\boldsymbol{\theta}$

$$\frac{d\log L_F}{d\theta_m} = \sum_{i=1}^{N}\left(\frac{dl_i(\boldsymbol{\eta}_i^*)}{d\theta_m} - \frac{1}{2}\mathrm{tr}\left[\mathbf{H}_i^{-1}(\boldsymbol{\eta}_i^*)\frac{d\mathbf{H}_i(\boldsymbol{\eta}_i^*)}{d\theta_m}\right]\right)$$

where the total derivatives of l_i and $\mathbf{H}_i$ wrt $\boldsymbol{\theta}$ can be expressed in terms of solutions to sensitivity differential equations, e.g.,

$$\frac{dl_i(\boldsymbol{\eta}_i^*)}{d\theta_m} = \left.\frac{dl_i(\boldsymbol{\eta}_i)}{d\theta_m}\right|_{\boldsymbol{\eta}_i=\boldsymbol{\eta}_i^*(\boldsymbol{\theta})} = \left[-\frac{1}{2}\sum_{j=1}^{n_i}\left(2\boldsymbol{\epsilon}_{ij}^T\mathbf{R}_{ij}^{-1}\frac{d\boldsymbol{\epsilon}_{ij}}{d\theta_m} - \boldsymbol{\epsilon}_{ij}^T\mathbf{R}_{ij}^{-1}\frac{d\mathbf{R}_{ij}}{d\theta_m}\mathbf{R}_{ij}^{-1}\boldsymbol{\epsilon}_{ij} + \mathrm{tr}\left[\mathbf{R}_{\mathrm{ij}}^{-1}\frac{d\mathbf{R}_{ij}}{d\theta_m}\right]\right) + \frac{1}{2}\boldsymbol{\eta}_i\boldsymbol{\Omega}^{-1}\frac{d\boldsymbol{\Omega}}{d\theta_m}\boldsymbol{\Omega}^{-1}\boldsymbol{\eta}_i - \frac{1}{2}\mathrm{tr}\left[\boldsymbol{\Omega}^{-1}\frac{d\boldsymbol{\Omega}}{d\theta_m}\right]\right]_{\boldsymbol{\eta}_i=\boldsymbol{\eta}_i^*(\boldsymbol{\theta})}$$

$$\frac{d\boldsymbol{\epsilon}_{ij}^*}{d\theta_m} = \left.\frac{d\boldsymbol{\epsilon}_{ij}}{d\theta_m}\right|_{\boldsymbol{\eta}_i=\boldsymbol{\eta}_i^*(\boldsymbol{\theta})} + \left.\frac{d\boldsymbol{\epsilon}_{ij}}{d\boldsymbol{\eta}_i}\right|_{\boldsymbol{\eta}_i=\boldsymbol{\eta}_i^*(\boldsymbol{\theta})}\frac{d\boldsymbol{\eta}_i^*}{d\theta_m} \quad \text{where} \quad \frac{d\boldsymbol{\epsilon}_{ij}}{d\theta_m} = \frac{d(\mathbf{d}_{ij} - \hat{\mathbf{y}}_{ij})}{d\theta_m} = -\left(\frac{\partial\mathbf{h}}{\partial\theta_m} + \frac{\partial\mathbf{h}}{\partial\mathbf{x}_{ij}}\frac{d\mathbf{x}_{ij}}{d\theta_m}\right)$$

The sensitivity differential equations wrt θ_m

$$\frac{d}{dt}\left(\frac{d\mathbf{x}_i}{d\theta_m}\right) = \frac{\partial\mathbf{f}}{\partial\theta_m} + \frac{\partial\mathbf{f}}{\partial\mathbf{x}_i}\left(\frac{d\mathbf{x}_i}{d\theta_m}\right) \qquad \left(\frac{d\mathbf{x}_i}{d\theta_m}\right)(t_0) = \frac{\partial\mathbf{x}_{0i}}{\partial\theta_m}$$

How to find $\frac{d\boldsymbol{\eta}_i^*}{d\boldsymbol{\theta}}$?

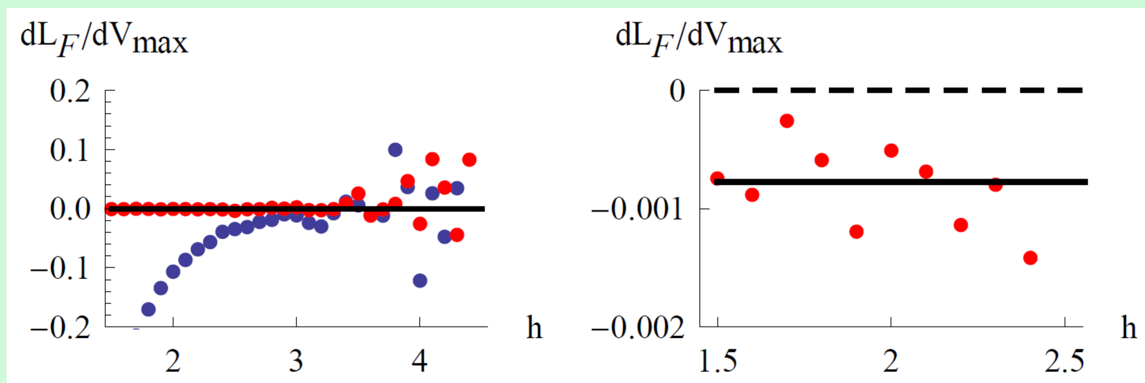
$$\left.\frac{dl_i}{d\boldsymbol{\eta}_i}\right|_* = 0\ \forall\theta \Rightarrow \frac{d}{d\boldsymbol{\theta}}\left(\left.\frac{dl_i}{d\boldsymbol{\eta}_i}\right|_*\right) = 0 \Rightarrow \left.\frac{d^2l_i}{d\boldsymbol{\eta}_i d\boldsymbol{\theta}}\right|_* + \left.\frac{d^2l_i}{d\boldsymbol{\eta}_i^2}\right|_*\frac{d\boldsymbol{\eta}_i^*}{d\boldsymbol{\theta}} = 0 \Rightarrow \frac{d\boldsymbol{\eta}_i^*}{d\boldsymbol{\theta}} = -\left(\left.\frac{d^2l_i}{d\boldsymbol{\eta}_i^2}\right|_*\right)^{-1}\left.\frac{d^2l_i}{d\boldsymbol{\eta}_i d\boldsymbol{\theta}}\right|_*$$

* indicates the substitution $\boldsymbol{\eta}_i = \boldsymbol{\eta}_i^*(\boldsymbol{\theta})$

Second order sensitivities are also required: $\frac{d^2\boldsymbol{x}_i}{d\eta_{ik}d\theta_m}$ and $\frac{d^2\boldsymbol{x}_i}{d\eta_{ik}d\eta_{il}}$.

Precision, Accuracy, and Performance

Two different levels of magnification of an element of the log-likelihood gradient as a function of the finite difference step, h.



Forward diff (blue)

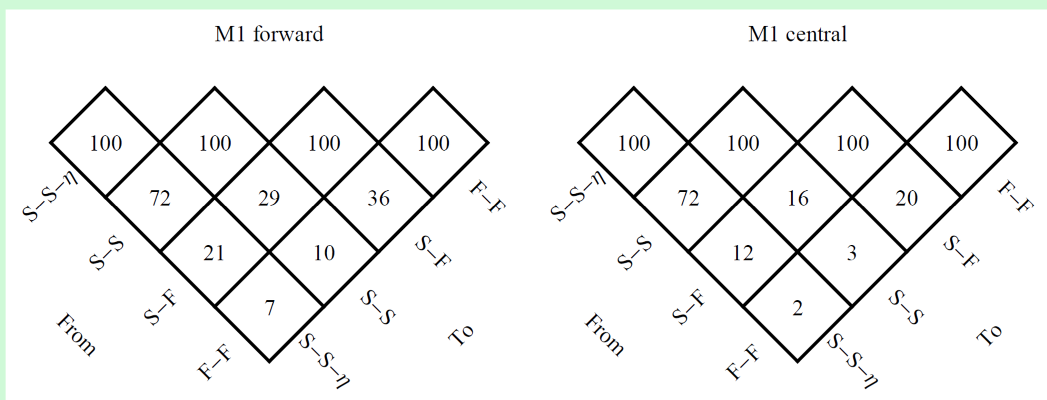
$$\frac{\log L_F(\theta_m(1+10^{-h})) - \log L_F(\theta_m)}{\theta_m 10^{-h}}$$

Central diff (red)

$$\frac{\log L_F(\theta_m(1+10^{-h})) - \log L_F(\theta_m(1-10^{-h}))}{2\theta_m 10^{-h}}$$

Sensitivity based (solid black line)

Benchmarking – relative estimation times



Model M1: 2-compartment, nonlinear elimination

S-F- η: **S**ensitivities (inner), **F**inite differences (outer), improved $\boldsymbol{\eta}$ starting values

Example: F-F (central diff) to S-S-η gives 50-fold decreased computational time

Highlights

- Robust computation of gradients
- Methodology applies to both individual and population log-likelihoods
- Improves computational speed compared to finite differences

References

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