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RESEARCH CENTRE FOR INDUSTRIAL MATHEMATICS

Parameter Estimation for Nonlinear Mixed Effects Models Implemented in Mathematica

Jacob Leander[1,2,3], Joachim Almquist[1,3], Helga Kristín Ólafsdóttir[2], Anna Johnning[1,2], and Mats Jirstrand[1]

[1]Fraunhofer-Chalmers Centre, Gothenburg, Sweden, [2]Department of Mathematical Sciences, Chalmers University of Technology and University of Gothenburg, Gothenburg, Sweden, [3]Quantitative Clinical Pharmacology, Early Clinical Development, IMED Biotech Unit, AstraZeneca, Gothenburg, Sweden

Summary and conclusions

- A Mathematica package for parameter estimation in nonlinear mixed effects models has been implemented and demonstrated.
- The package enables easy-to-use NLME modeling, is free, and can be further demonstrated upon request.

Background

In many applications within biology and medicine, measurements are gathered from several entities in the same experiment. This could for example be patients exposed to a treatment or cells measured after stimuli.

To characterize the variability in response between entities, the nonlinear mixed effects (NLME) model is a suitable statistical model. An NLME model enables quantification of both within- and between subject variability.

The parameter estimation in NLME models is not straightforward, due to the intractable expression of the likelihood function.

In this work we present a Mathematica package for parameter estimation in NLME models where the longitudinal model is defined by differential equations. The parameter estimation problem is solved by the first-order conditional estimation (FOCE) method with exact gradients. The package is demonstrated using data from a simulated drug concentration model.

Statistical model

The dynamical model for an individual is defined by a system of ODEs

$$\frac{d\boldsymbol{x}_i}{dt} = \boldsymbol{f}(\boldsymbol{x}_i, \boldsymbol{u}_i, t, \boldsymbol{\phi}_i), \qquad \boldsymbol{x}_i(t_0) = \boldsymbol{x}_0(\boldsymbol{\phi}_i)$$

together with an observation model

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

The individual parameters $\boldsymbol{\phi}_i$ are linked to population parameters by a functional relationship $\boldsymbol{\phi}_i = g(\boldsymbol{\theta}_{\boldsymbol{pop}}, \boldsymbol{\eta}_i)$ with the random effects $\boldsymbol{\eta}_i \sim N(\boldsymbol{0}, \boldsymbol{\Omega})$.

Extension to a longitudinal model described by stochastic differential equations (SDEs) is also supported.

Parameter estimation

The aim is to estimate the model parameters $\boldsymbol{\theta} = \{\boldsymbol{\theta}_{\boldsymbol{pop}}, \boldsymbol{\Omega}, \boldsymbol{\Sigma}\}$ from a set of observations $\boldsymbol{d}_{ij}, i = 1, \dots, N, j = 1, \dots, n_i$.

Since the random effects $\boldsymbol{\eta}_i$ are unobserved, the joint probability distribution is marginalized over the unobserved quantities to obtain the likelihood function.

$$L(\boldsymbol{\theta}) = \prod_{i=1}^{N} \int p(\boldsymbol{y}_i|\boldsymbol{\eta}_i) p(\boldsymbol{\eta}_i) d\boldsymbol{\eta}_i \coloneqq \prod_{i=1}^{N} \int \exp(l_i) d\boldsymbol{\eta}_i$$

Due to the normality assumptions in the model we have

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

with residual $\boldsymbol{\varepsilon}_{ij} = \boldsymbol{d}_{ij} - \boldsymbol{h}\left(\boldsymbol{x}_{ij}, \boldsymbol{u}_i, t_{ij}, \boldsymbol{\phi}_i\right)$.

Since the integral over $\exp(l_i)$ is problematic, the integral is approximated using a second order Taylor expansion of l_i, which yields the objective function

$$L(\boldsymbol{\theta}) \approx \prod_{i=1}^{N} \left(\exp\left(l_i(\boldsymbol{\eta}_i^*)\right) \det\left[\frac{-\Delta l_i(\boldsymbol{\eta}_i^*)}{2\pi}\right]^{-\frac{1}{2}} \right)$$

where the point $\boldsymbol{\eta}_i^* = \boldsymbol{\eta}_i^*(\boldsymbol{\theta})$ is the value maximizing l_i (for a fixed $\boldsymbol{\theta}$). This leads to a nested optimization problem which is computationally demanding.

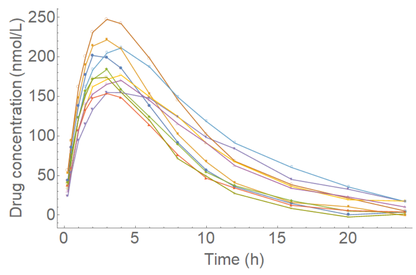
The Hessian Δl_i can further be simplified to give the so called first order conditional estimation (FOCE) approximation.

Exact gradients

- A quasi-Newton method with a finite difference approximation of the gradient has traditionally been used to compute the maximum likelihood estimate.
- In this work, we use sensitivity equations to compute exact gradients for the optimization of $L(\boldsymbol{\theta})$ and $\boldsymbol{\eta}_i^*$.
- The ODE system is differentiated with respect to the model parameters to obtain the sensitivity equations [1,2].
- Exact gradients enable faster and more robust optimization compared to finite differences, and have been implemented in the NLME software NONMEM 7.4 [3].
- The package has previously been used in several applications, see [4,5,6].

Modeling workflow

The measurements are collected as a list of time-value pairs with easy-to-use plotting tools available.



The NLME model is defined by an ODE system and an observation model.

```
dynamicModel = {
   a0'[t] == -phi1 a0[t],
   a0[0] == Dose,
   a1[0] == 0,
   a1'[t] == phi1 a0[t] - phi3 c1[t],
   c1[t] == a1[t] / phi2,
   phi1 == kA ,
   phi2 == V1 Exp[eta1],
   phi3 == cl Exp[eta2]
  };
obsModel = {c1[t]};
model = {{dynamicModel, obsModel}};
```

The estimation requires dataset, model and initial guesses for the population parameters:

```
NLMEDynamicalModelFit[dataset, model,
 {{kA, 1}, {V1, 10}, {cl, 10}}, {eta1, eta2},
 {phi1, phi2, phi3}]
```

Several options are available:

```
NLMEDynamicalModelFit[dataset, model,
 {{kA, 1}, {V1, 10}, {cl, 10}}, {eta1, eta2},
 {phi1, phi2, phi3},
 Sigma → {"Proportional"}, Omega → "Full",
 Parallel → True]
```

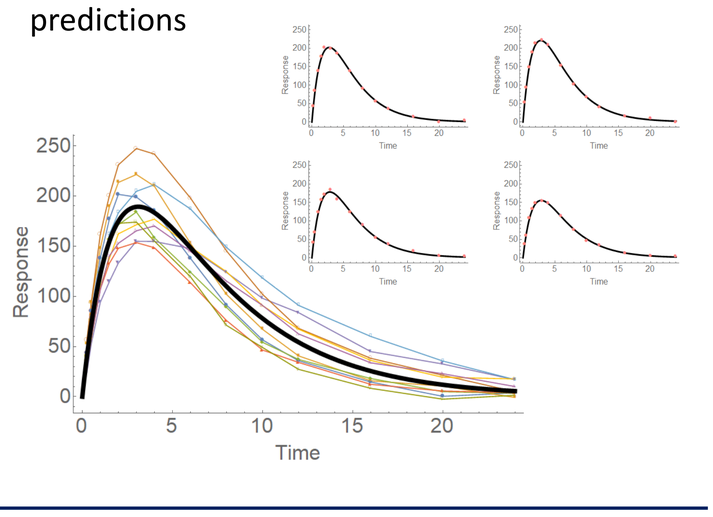
The optimization returns an object which contains the estimated model, including parameter estimates and optimization history.

State variables: 1
Observables: 1
Covariates: 1
Population parameters: 3
Random effects parameters: 2
Covariance matrix form: Diagonal
Individuals: 10
Observations: 140
Ω: $\begin{pmatrix} 0.035852 & 0 \\ 0 & 0.0508928 \end{pmatrix}$
Σ–parameters: {3.20677}

Table:

Parameter	Estimate	Standard error	RSE [%]
kA	0.499	0.00912	1.83
V1	29.	1.78	6.13
cl	5.59	0.4	7.15

The model object can be used for easy plotting of predictions



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