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## 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

$$\frac{dx_i}{dt} = f(x_i, u_i, t, \phi_i), \quad x_i(t_0) = x_0(\phi_i)$$

together with an observation model

$$y_{ij} = h(x_{ij}, u_i, t_{ij}, \phi_i) + e_{ij}, \quad e_{ij} \sim N(0, \Sigma)$$

The individual parameters  $\phi_i$  are linked to population parameters by a functional relationship  $\phi_i = g(\theta_{pop}, \eta_i)$  with the random effects  $\eta_i \sim N(0, \Omega)$ .

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

## Parameter estimation

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

Since the random effects  $\eta_i$  are unobserved, the joint probability distribution is marginalized over the unobserved quantities to obtain the likelihood function.

$$L(\theta) = \prod_{i=1}^N \int p(y_i | \eta_i) p(\eta_i) d\eta_i := \prod_{i=1}^N \int \exp(l_i) d\eta_i$$

Due to the normality assumptions in the model we have

$$l_i = -\frac{1}{2} \sum_{j=1}^{n_i} (\epsilon_{ij}^T \Sigma_{ij}^{-1} \epsilon_{ij} + \log \det(2\pi \Sigma_{ij})) - \frac{1}{2} \eta_i^T \Omega^{-1} \eta_i - \frac{1}{2} \log \det(2\pi \Omega)$$

with residual  $\epsilon_{ij} = d_{ij} - h(x_{ij}, u_i, t_{ij}, \phi_i)$ .

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

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

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

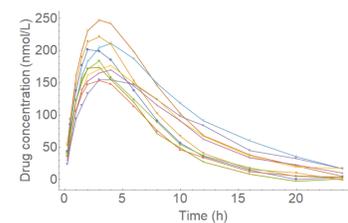
The Hessian  $\Delta l_i$  can further be simplified to give the so called first order conditional estimation (FOCE) approximation.

## 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  $L(\theta)$  and  $\eta_i^*$ .
- 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 == c1 Exp[eta2]
};
obsModel = {c1[t]};
model = {{dynamicModel, obsModel}};
```

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

```
NLMEModelFit[dataset, model,
  {{kA, 1}, {V1, 10}, {c1, 10}}, {eta1, eta2},
  {phi1, phi2, phi3}]
```

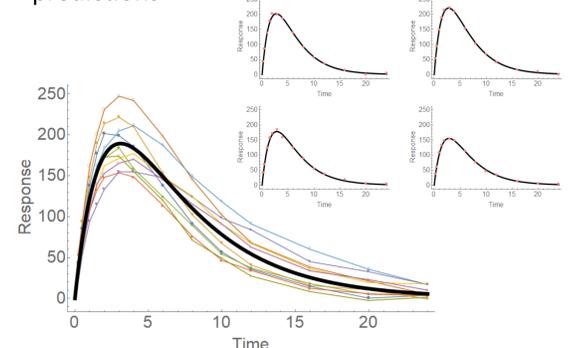
Several options are available:

```
NLMEModelFit[dataset, model,
  {{kA, 1}, {V1, 10}, {c1, 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.

Parameter	Estimate	Standard error	RSE [%]
kA	0.499	0.00912	1.83
V1	29.	1.78	6.13
c1	5.59	0.4	7.15

The model object can be used for easy plotting of predictions



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## References

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