Mixed-Effects Modeling Using Stochastic Differential Equations – Application to Pharmacokinetic Modeling

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Background and motivation

Nonlinear mixed-effects modeling is a popular tool for studying variability within and between individuals of a population. We have extended the ordinary differential equation setting commonly used in nonlinear mixed-effects models to include stochastic differential equations. The new approach is used to account for model misspecification and uncertainty in the underlying dynamics. The framework is applied to a pharmacokinetic model of nicotinic acid.

The stochastic mixed-effects framework

The state-space model for a single individual is described by a system of stochastic differential equations depending on some input u_i and individual parameters ϕ_i

$$dx_i = f(x_i, u_i, \phi_i)dt + \sigma dW, \quad x_i(0) = x_0(\phi_i)$$

together with a measurement equation

$$y_{ij} = h(x_i, u_i, \phi_i) + e_{ij} \quad e_{ij} \sim N(0, S)$$

where index i and j denote individuals and observations, respectively. In a mixed-effects model the individual parameters are assumed to be described by the functional relationship

$$\phi_i = g(\theta, Z_i, \eta_i)$$

$$\eta_i \sim N(0, \Omega)$$

θ- fixed effects

Z_i- covariates

η_i- random effects

Using the stochastic mixed-effects model approach, we are able to explain three sources of variation: measurement error, model uncertainty and population variability.

Parameter estimation

Parameters are estimated by maximizing the population likelihood function. It is approximated using the so called first order conditional estimation method (FOCE). The expression for the approximate population likelihood (APL) is given by

$$APL(\theta) = \sum_{i=1}^{N} l_i(\eta_i^*) - \frac{1}{2}\log\left|\frac{-\Delta l_i(\eta_i^*)}{2\pi}\right|,$$

where the Hessian matrix is approximated using first-order terms only

$$\Delta l_i \approx -\sum_{j=1}^{n_i} \frac{\partial \varepsilon}{\partial \eta}^T R_{ij}^{-1} \frac{\partial \varepsilon}{\partial \eta} - \Omega^{-1}.$$

The individual likelihood is given by

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

To evaluate the APL, we first need to determine the residual vector and output covariance matrix at all measurements points for each individual. The Extended Kalman Filter (EKF) is a suitable choice to process the data [1], which is applicable also to nonlinear models. Gradients are computed using sensitivity equations.

Stochastic NiAc disposition in obese Zucker rats

We have applied the stochastic mixed-effects framework to model the pharmacokinetics (PK) of nicotinic acid in obese rats. The stochastic PK model is an extension of a previously published deterministic model [2].

We model the pharmacokinetics by a one-compartment model with constant synthesis and nonlinear elimination of nicotinic acid. We are interested in identifying the 7 parameters V_c, $Synt$, V_m, K_m, s, ω_{Vm} and σ. We assume $V_{mi} \sim LN(V_m, \omega_{Vm}^2)$.

$$V_c\, dc_i = \left(u + Synt - \frac{V_{mi}c_i}{K_m + c_i}\right)dt + \sigma c_i\, dW$$

$$y_{ik} = c(t_{ik}) + \epsilon_{ik}$$

$$\epsilon_{ik} \sim N(0, c(t_{ik}) * s)$$

V_c – Compartment volume
$Synt$ – Synthesis rate
V_m – Maximal rate
K_m – MM-constant
σ – System noise factor
s – Measurement var.

Parameter estimates (RSE %)

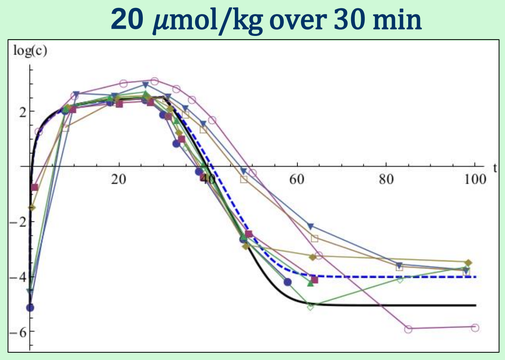
V_c – 0.32 (5.5)
$Synt$ – 0.0018 (24.3)
V_m – 1.35 (16.7)
K_m – 13.6 (21.5)
s – 0.058 (23.5)
σ – 0.033 (15.7)
ω_{Vm} – 0.13 (27.0)

Highlights

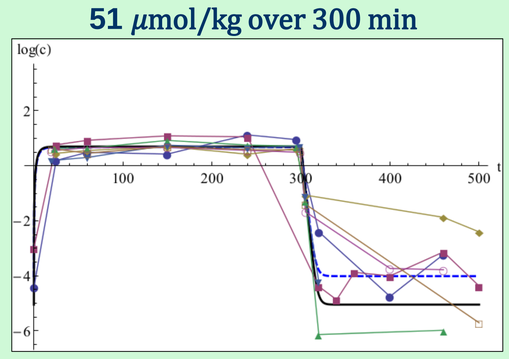
- Combination of SDEs and mixed-effects models
- The framework allows for three source of variation in data
- Highly efficient gradient calculation using sensitivities
- Improved individual model fits for the NiAc data

Fitted population model

20 μmol/kg over 30 min

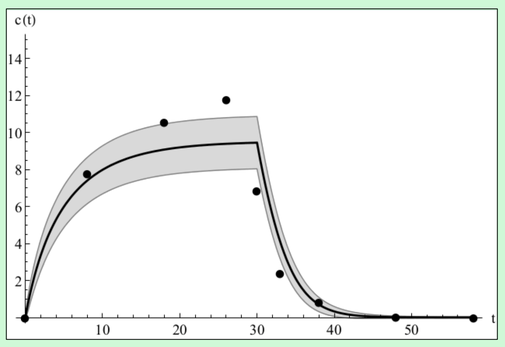


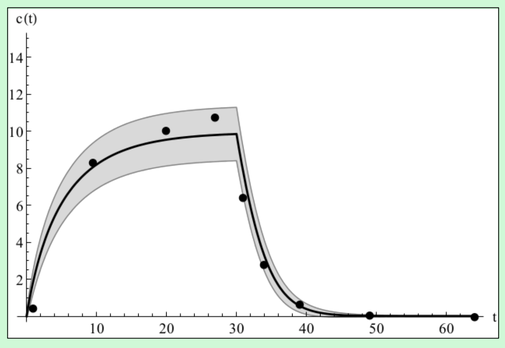
51 μmol/kg over 300 min



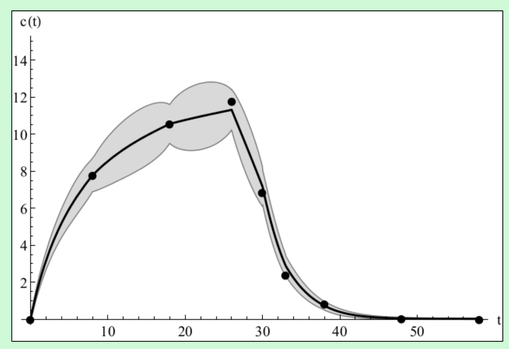
Fitted individual models

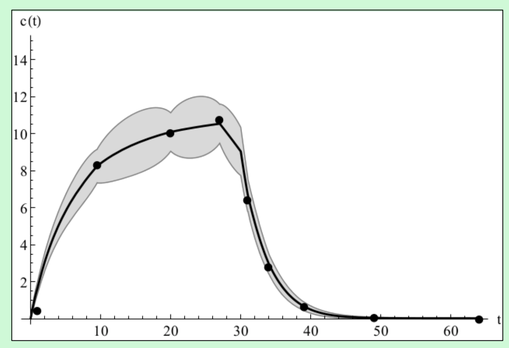
ODEs





SDEs





Acknowledgements

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References

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