Non-Linear Mixed-Effects Models with Stochastic Differential Equations - Implementation of an Estimation Algorithm

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Objectives

The Use of stochastic differential equations (SDEs) rather than ordinary differential equations (ODEs) could potentially strengthen some parts of PK/PD modelling by 1) producing better parameter estimates, 2) as a diagnostic tool, 3) to pinpoint model deficiencies , 4) by incorporating true variations in the parameters, etc (see e.g. [1]). These models offer a general intra-individual error structure where the residuals are decomposed into dynamical noise from the SDEs and uncorrelated measurement noise. The focus of the present study [2] is on two fundamental issues concerning the implementation of SDEs in non-linear mixed effects models. The first is how the likelihood function of non-linear mixed-effects models with SDEs can be approximated to facilitate estimation in these models. The second focus concerns identifiability: Can the inter-individual variability, the measurement- and the dynamical noise be separated?

Methods

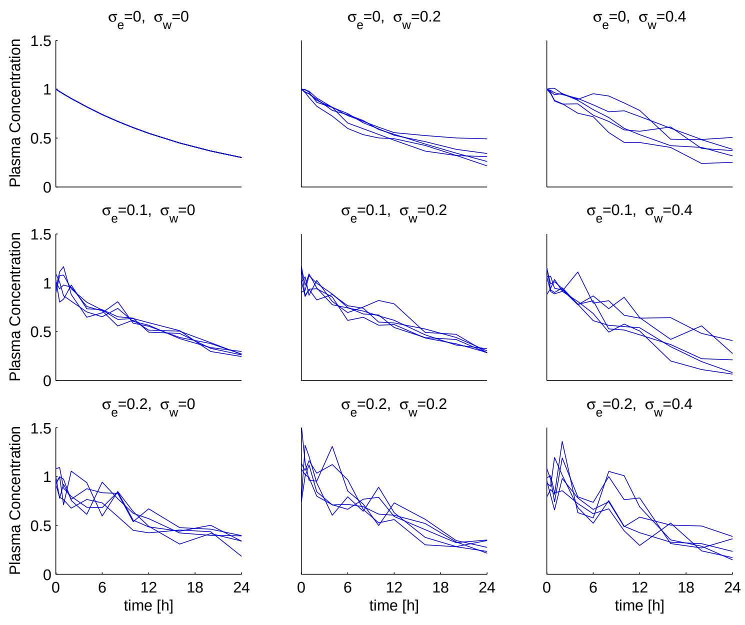
By the introduction of SDEs, the intra-individual residuals will not be uncorrelated, so the likelihood function must be based on the prediction densities conditioned on previous measurements $p(y_j|y_1 \ldots y_{j-1})$. The complete likelihood function was approximated by combining the First Order Conditional Estimation (FOCE) method used in non-linear mixed-effects models, with the Extended Kalman Filter (EKF) [3] used to approximate the conditional densities.

This approximation was implemented in MATLAB for a non-linear mixed-effects model with SDEs corresponding to a one-compartment model:

$$dA = -\frac{CL}{V} A dt + \sigma_W dW$$

The dynamical model was implemented along with proportional measurement error and proportional inter-individual variability on the volume of distribution and clearance.

Figure 1. Simulating Intra-Individual Noise



Simulated individual plasma concentration profiles for various levels and types of measurement noise (σ_e) and dynamical noise (σ_W). Simulations are made with no inter-individual variation, using V = 10 and CL = 0.5.

Conclusions

A novel approximation of the likelihood function was discussed for non-linear mixed-effects models based on SDEs. It was confirmed that inter-individual variability, measurement- and dynamical noise can be separated, such that these models can be treated meaningfully.

[1] N. R. Kristensen. Using Stochastic Differential Equations for PK/PD Model Development. *In Preparation*.

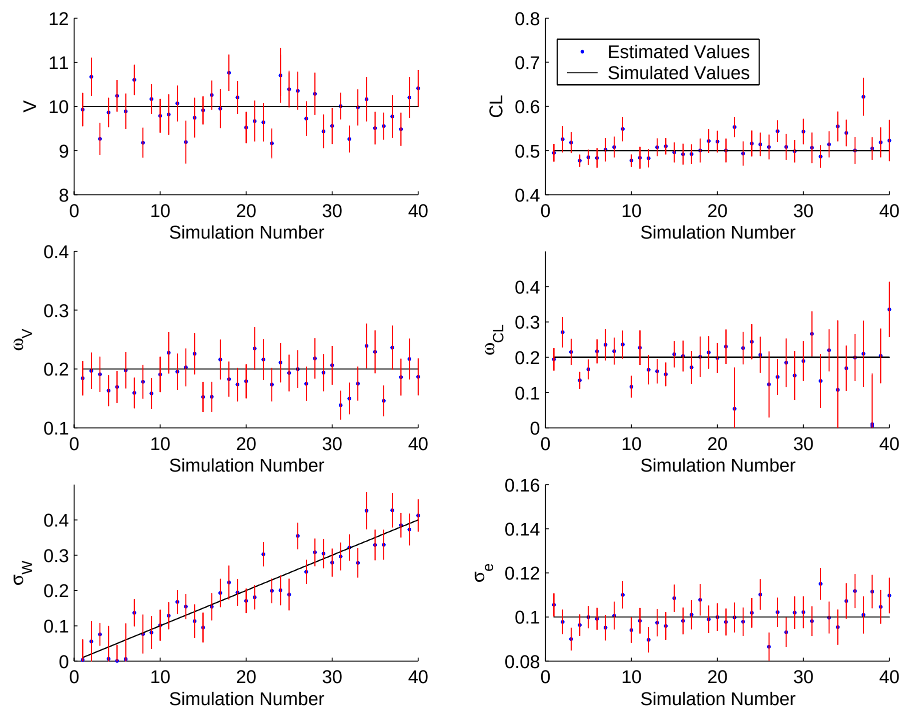
[2] R. Overgaard, et al. Non-Linear Mixed-Effects Models with Stochastic Differential Equations – Implementation of an Estimation Algorithm. Submitted to Journal of Pharmacokinetics and Pharmacodynamics 2004.

[3] A.H Jazwinski. Stochastic Processes and Filtering Theory. Academic Press, New York (1970).

Results

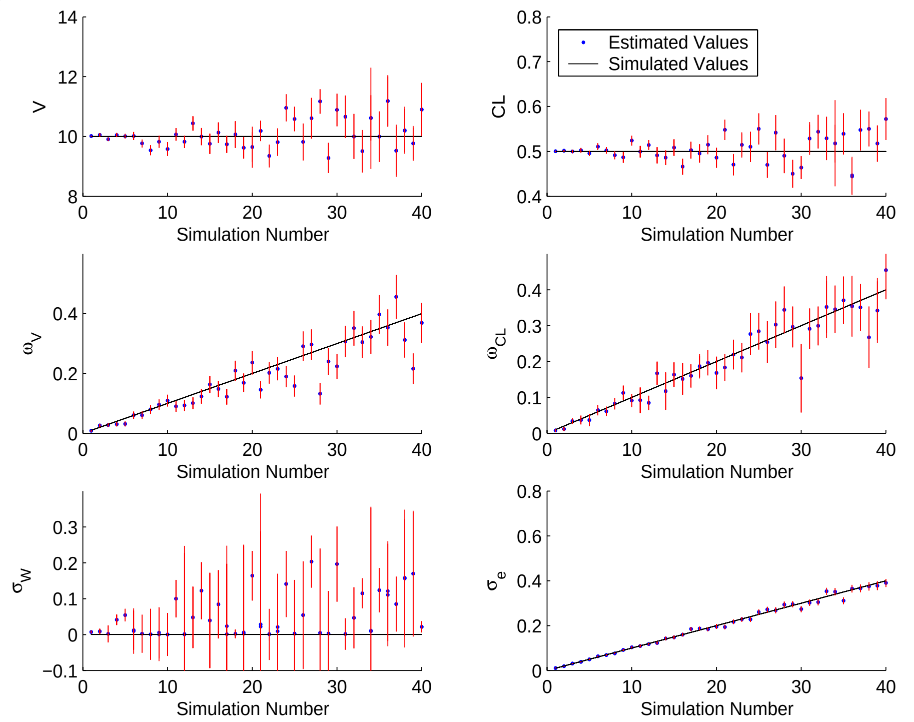
Several simulations and successive estimations with this model have been used to test the estimates produced by the proposed approximation of the likelihood function.

Figure 2. Separating Dynamical Noise (σ_W)



Simulations of 40 different studies of 25 individuals each sampled 12 times demonstrate that higher levels of dynamical noise in the simulations does not produce neither additional measurement noise nor inter-individual variability in the estimates, illustrating that dynamical noise is in fact satisfactorily separable from the remaining noise parameters.

Figure 3. Type I Errors of σ_W



Simulations of 40 different studies of 25 individuals each sampled 12 times demonstrate that the relationship between bias in the dynamical noise and the level of the remaining noise parameters is small. The largest estimate of dynamical noise was around 0.2, which is a modest level of noise compared to the corresponding measurement noise.

Table 1. Sparse Sampling Results

Parameter	Simulated	Mean Estimate	SD of Estimates
Volume [L]	10	10.01	0.212
Clearance [L/h]	0.5	0.508	0.015
ω_V	0.2	0.195	0.016
ω_{CL}	0.2	0.195	0.035
σ_W	0.2	0.198	0.037
σ_e	0.1	0.102	0.010

Statistics based on 50 simulations and successive estimation of studies with 100 individuals each sampled 3 times.