# *On the use of stochastic differential mixed effects models for modeling inter occasion variability*

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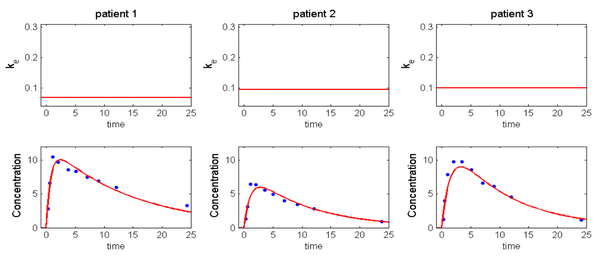
**Objectives:** one objective of WP6.4 of the DDMoRe project is to develop new methods for complex NLMEM. We consider here stochastic differential mixed-effects models used for describing intra-subject variability of certain PK parameters.

## *Models*

**1.** A model without intra subject (or inter occasion) variability assumes that the subject specific parameters do not change over time.

**Example**: PK of theophylline

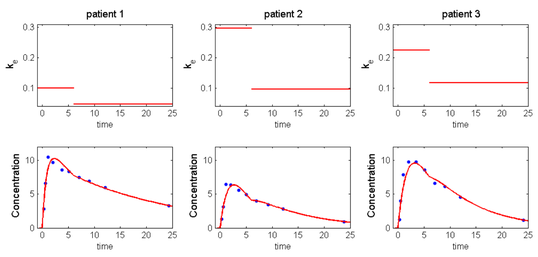
*The PK parameters ($k_a$, V, k) are constant for each patient.*




**2.** A model with intra subject (or inter occasion) variability assumes that the subject specific parameters are piecewise constant.

**Example**: PK of theophylline

*We assume here that the elimination rate constant k can change at t = 6h.*

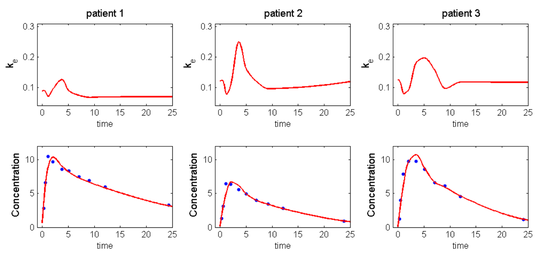



This model is not biologically realistic: the PK parameters are continuous processes.

**3.** A Stochastic Differential Equation (SDE) based model assumes that certain parameters are stochastic processes.

**Example**: PK of theophylline

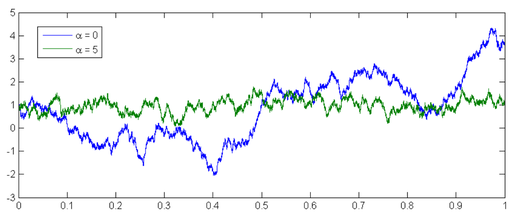
*here, k is a diffusion process*




Here, $l(t) = \log(k)$ is an Ornstein-Uhlenbeck process:

$$\dot{l}(t) = -\alpha(l(t) - l^*) + \gamma\dot{W}(t)$$

- $l^*$ is the mean value of $l = \log(k)$
- $W$ is the standard Wiener process
- $\alpha$ is used to prevent large excursions far from $l^*$




**The complete model**:

$$\begin{aligned}
l_i(t) &= \log\big(k_i(t)\big) \\
\dot{l}_i(t) &= -\alpha(l_i(t) - l_i^*) + \gamma\dot{W}_i(t) \\
\dot{A}_i(t) &= -ka_i\ Ai(t) \\
\dot{C}_i(t) &= (ka_i/V)\ Ai(t) - k_i(t)C_i(t) \\
\log\big(y_{ij}\big) &= \log\big(C_i(t_{ij})\big) + \sigma\xi_{ij} \\
l_i(0) &= l_i^*\ ; A_i(0) = Dose\ ;\ C_i(0) = 0
\end{aligned}$$

In a population context, the parameters of the model $(k_a, V, \alpha, k^*, \gamma)$ are individual parameters and $W$ is a subject specific Wiener process. Then, a methodology is required for estimating

- The populations parameters of the model
- Each individual kinetics $k(t)$ and $C(t)$

## *Methods*

**Mixed effects diffusion model:**

$$\begin{cases} dX_i(t) = b(X_i(t), \phi_i)dt + \gamma(X_i(t), \phi_i)dW_i(t), \\ y_{ij} = g(X_i(t_{ij}), \phi_i) + \xi_{ij} \quad , \quad \xi_{ij}, \underset{i.i.d.}{\sim} \mathcal{N}(0, \sigma^2(\phi_i)), \end{cases}$$

$$\phi_i \sim \pi(\cdot, \theta)$$

We propose:

1) to combine the MCMC-SAEM algorithm with the Extended Kalman Filter for computing the Maximum Likelihood Estimate of $\theta$.

2) to adapt the Extended Kalman Smoother for estimating each individual kinetic.

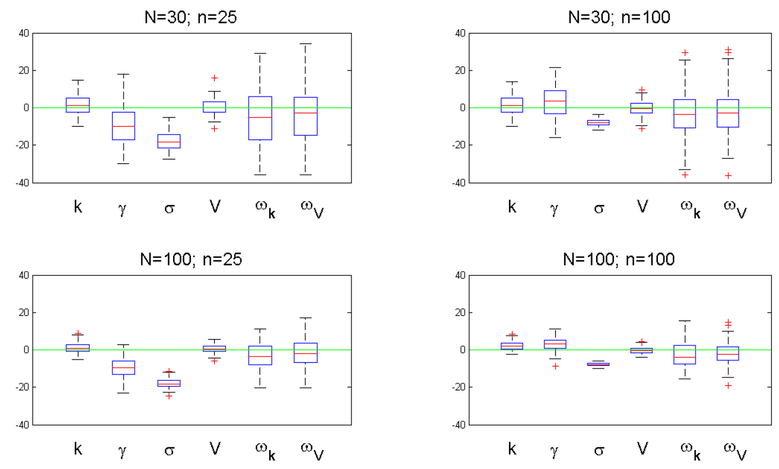
## *Simulation study*

**Bolus with linear elimination:**

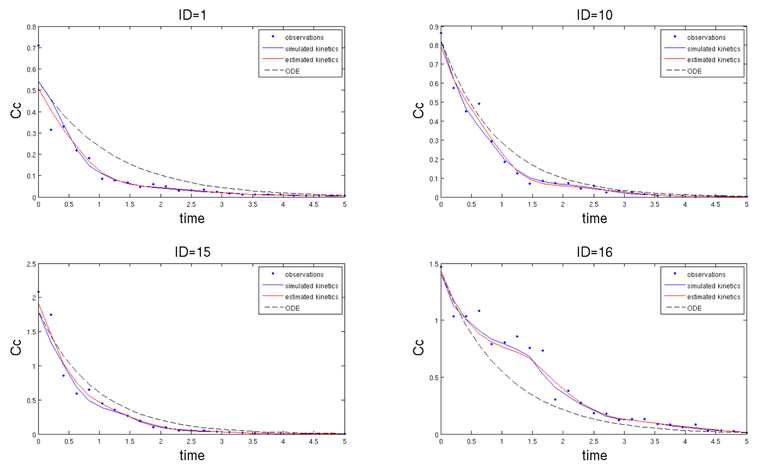
$$\begin{aligned}
l_i(t) &= \log\big(k_i(t)\big) \\
\dot{l}_i(t) &= -\alpha(l_i(t) - l_i^*) + \gamma\dot{W}_i(t) \\
\dot{C}_i(t) &= -k_i(t)C_i(t) \\
\log\big(y_{ij}\big) &= \log\big(C_i(t_{ij})\big) + \sigma\xi_{ij}
\end{aligned}$$

| Parameter | $\theta_0$ |
|---|---|
| $k^*$ | 0.2 |
| $V$ | 0.5 |
| $\gamma$ | 0.3 |
| $\sigma$ | 0.1 |
| $\omega_k$ | 0.3 |
| $\omega_V$ | 0.2 |

($\alpha$ is fixed to 1)




Results of the Monte Carlo simulation study: distribution of the relative estimation errors for different number of subjects *N* and different numbers of observations per subject *n*.




Reconstruction of four individual PK profiles.

**Conclusion:**

Stochastic differential mixed-effects models can satisfactorily model the intra subject variability of PK parameters. The use of the Extended Kalman Filter allowed us to efficiently develop several extensions of methods used for NLMEM.

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