Pharmacokinetics and stochastic differential equations: model and methodology.

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Background and Objectives

A recent evolution of the traditional PK models based on ordinary differential equations (ODEs) consists in adding a system noise to the ODEs to account for more intra-individual variability (see [1], [2], [3]). However, the frequently proposed linear SDE system turns out to be irrelevant.

The objectives of this contribution are :

- to present new SDE models that would best reflect the PK reality,
- to develop some specific maximum estimation procedure for the population parameters in these new models.

Structural Model

Example : Bolus model

1 - ODE model

The time evolution of the quantity of drug (Q) in the central compartment is described by an ordinary differential equation :

$$(1) \qquad dQ(t) = -k\ Q(t)\ dt$$

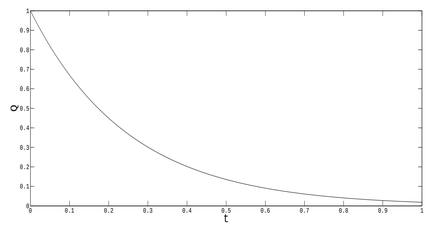


FIGURE : Kinetics simulated according to equation (1) ($k = 4$).

2 - SDE model

A system noise is added to (1) to account for more intra-individual variability(see [1], [2], [3]):

$$(2) \quad dQ(t) = -\ k\ Q(t)\ dt\ +\ \sigma\ dW(t)$$

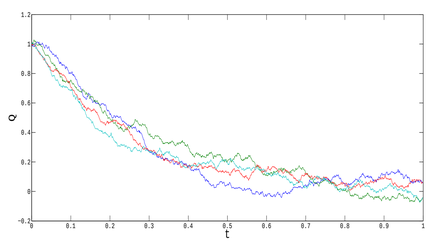


FIGURE : Kinetics simulated according to equation (2) ($k^* = 4, \sigma = 2$).

The kinetics simulated with the linear SDE model are irrelevant:

- provide an overly erratic description of the evolution of the drug concentrations within the compartments of the human body
- do not comply with some constraints on the biological dynamics (sign, monotony)

3 - SDE model (2)

Assuming that the diffusion process randomly perturbs the transfer rate constants of the system is more realistic :

$$(3) \quad dk(t) = (k^* - k(t))dt + \sigma dW(t)$$

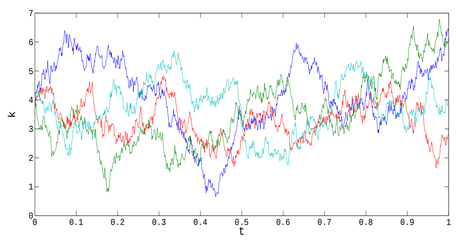


FIGURE : Simulated kinetics of k ($k^* = 4, \sigma = 4$).

The time evolution of Q is then given by

$$(4) \qquad dQ(t) = -k(t)Q(t)dt$$

$Q(t)$ has an explicit expression :

$$Q(t) = Q(0)e^{-\int_0^t k(s)ds}$$

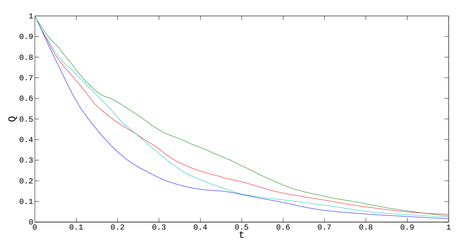


FIGURE : Simulated kinetics of Q ($k^* = 4, \sigma = 4$).

Integrating process k allows a more accurate representation of the biological system : the simulated kinetics are smoother.

4 - New parametrisation of SDE model (2)

Let's introduce the following new process z. Model (3), (4) is equivalent to :

$$(5) \qquad \begin{aligned} dk(t) &= (k^* - k(t))\ dt + \sigma\ dW(t) \\ dz(t) &= k^*\ dt + \sigma\ dW(t) \\ \log Q(t) &= k(t) - z(t) \end{aligned}$$

This new parametrisation allows to come down to a linear Gaussian system, in which the Kalman filter applies.

Statistical Model

Intra-individual model

$$\begin{aligned} dk_i(t) &= (k_i^* - k_i(t))dt + \sigma_i dW_i(t) \\ dQ_i(t) &= -k_i(t)Q_i(t)dt \end{aligned}$$

Observations $$y_{ij} = \log\left(\frac{Q_i(t_{ij})}{V_i}\right) + \gamma_i \epsilon_{ij}$$

Population appraoch : we assume some inter-individual variability on parameters k^*, V, γ, σ:

$$1 \leq i \leq n\ ;\ \psi_i = (k_i^*, V_i, \gamma_i, \sigma_i)$$

$$\psi_i = h(\phi_i)\ ;\ \phi_i \sim \mathcal{N}(\phi_{\text{pop}}, \Omega)$$

Methodology

The SAEM algorithm is used for estimating the population parameters. This requires to compute $p(\mathrm{y}_i|\psi_i)$. By using system (5), it is possible to implement the Kalman filter for computing the conditional likelihoods $p(\mathrm{y}_i|\psi_i)$ and for estimating $k_i(t)$.

Simulation Study

1 - Design for the simulations

- $n = 50$ subjects
- 10 measurments per subject
- 1 dose at $t = 0$
- inter-individual variability on parameters k^* and V : $\psi_i = (k_i^*, V_i)$

$$\log \psi_i \sim \mathcal{N}(\phi_{\text{pop}}, \Omega)$$

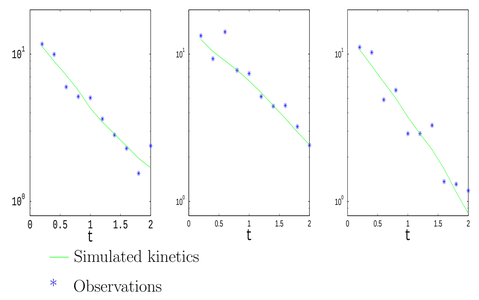


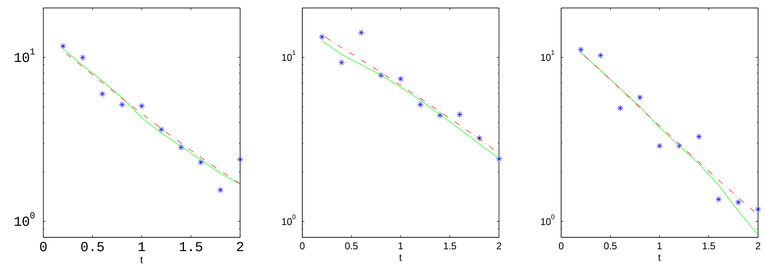
FIGURE : Some simulated kinetics (semi-log scale).

2 - Results

Estimation of the population parameters

Parameter	True value	Estimated value	s.e.	r.s.e. (%)
k^*	1	1.060	0.040	4
V	0.5	0.494	0.014	3
σ	0.5	0.444	0.084	19
γ	0.2	0.204	0.008	4
$\omega^2_{k^*}$	0.1	0.128	0.043	34
ω^2_V	0.1	0.104	0.033	33

Estimation of the individual kinetics (Kalman smoother)



Conclusion

- We have proposed a new category of mixed-effects models based on SDEs for PK modeling and our maximum likelihood estimation procedure shows quite good practical properties.
- We aim to extend in a next future the present approach to more complex compartment models.
- Defining the transfer rate constants as stochastic processes often leads to highly non linear models, in which the present estimation methodology based on the Kalman filter cannot be used. A SAEM based method using the extended Kalman filter or a particle filter should rather be considered.

[1] S. Mortensen, S. Klim, B. Dammann, N. Kristensen, H. Madsen, R. Overgaard "A Matlab framework for estimation of NLME models using stochastic differential equations", Journal of Pharmacokinetics and Pharmacodynamics vol:34, pages: 623-642, 2007.

[2] R. Overgaard, E. Jonsson, C. Tornoe, H. Madsen, "Non-Linear Mixed Effects Models with Stochastic Differential Equations. Implementation of an Estimation Algorithm", PAGE 2004.

[3] Donnet S, Samson A, Parametric inference for mixed models defined by stochastic differential equations, ESAIM P&S, 12:196-218, 2008.

[4] Delattre M, Del Moral P, Lavielle M "The SAEM algorithm in MONOLIX for Non-Linear Mixed Effects Models with Stochastic Differential equations", PAGE 2010.