

Population pharmacokinetics and stochastic differential equations: models and methods

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1 Introduction

2 Model

3 Methodology

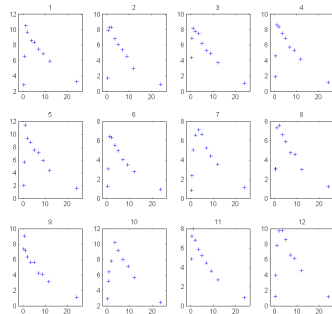
4 Conclusion

Introduction

Pharmacokinetics (PK)

- study of the evolution of a drug in the body
- human body represented as a set of compartments
- transfers between compartments
- statistical models based on ODEs

Example:



Introduction

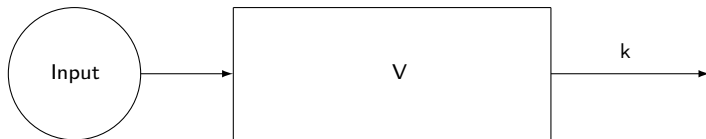
Our objectives:

- to present new SDE (*Stochastic Differential Equations*)-based PK models in a population approach
- to develop some specific estimation procedure for the parameters in these models

Fixed-effects model development

Example: bolus

- Dose administered by rapid injection into a single compartment



Purpose:

- model for $C(t)$ (concentration of drug in the compartment at time t)

Fixed-effects model development: structural model

a) *deterministic model*

- Ordinary differential model

$$dC(t) = -k C(t) dt$$

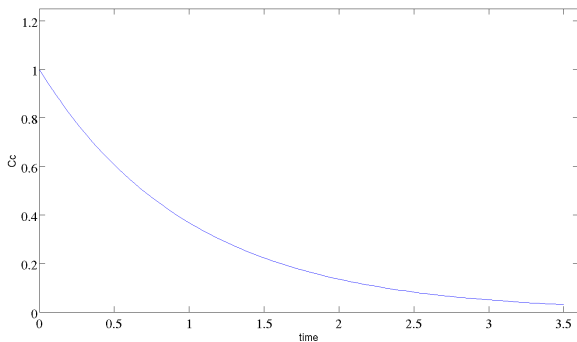


Figure: Evolution of the concentration of a bolus represented by an ODE.

Fixed-effects model development: structural model

b) diffusion model

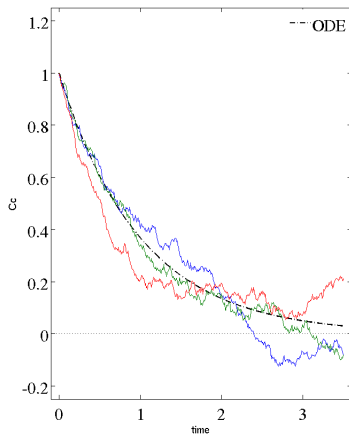
- some perturbation in the evolution of the drug

- diffusion model

$$dC(t) = -k C(t) dt + \gamma(C(t)) dW(t)$$

- Example

$$dC(t) = -k C(t) dt + \gamma C(t) dW(t)$$



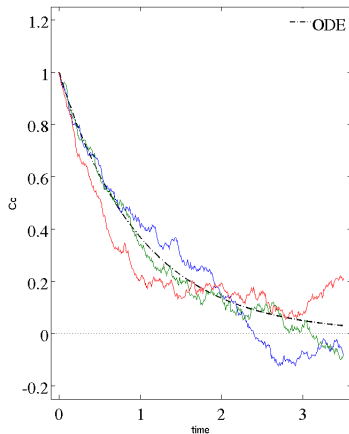
Fixed-effects model development: structural model

b) diffusion model

$$dC(t) = -k C(t) dt + \gamma(C(t)) dW(t)$$

This model is not realistic:

- monotony,
- sign ...



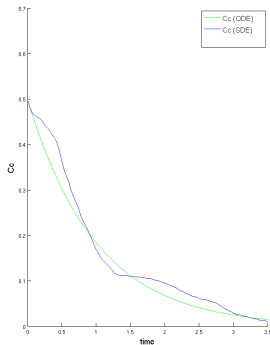
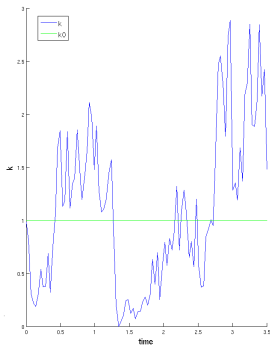
Fixed-effects model development: structural model

b) diffusion model

- More realistic assumption: k is randomly perturbed and driven by a SDE

$$dk(t) = b(k(t)) dt + \gamma(k(t)) dW(t)$$

$$dC(t) = -k(t) C(t) dt$$



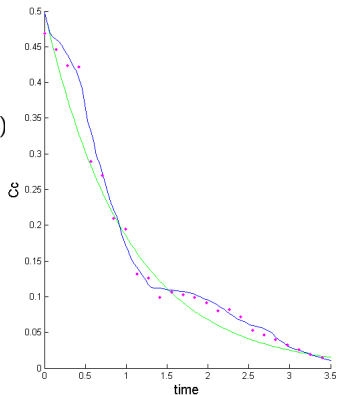
Fixed-effects model development: statistical model

- The kinetics is observed at discrete time points: (y_1, \dots, y_n)

$$dk(t) = b(k(t)) dt + \gamma(k(t)) dW(t)$$

$$dC(t) = -k(t) C(t) dt$$

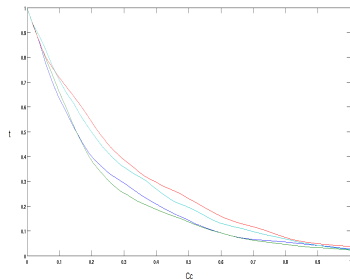
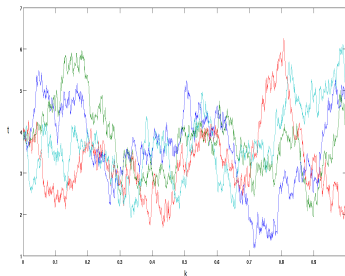
$$y_j = \log C(t_j) + \epsilon_j, \quad \epsilon_j \underset{i.i.d.}{\sim} \mathcal{N}(0, \sigma^2)$$



Mixed-effects model

- N kinetics

$\mathbf{y}_i = (y_{i1}, \dots, y_{i,n_i})$: observations for individual i



- Multiple sources of variability:

- intra-individual variability

- k is a diffusion process
- residual errors

- between-subjects variability

- the parameters of the model are random variables

Mixed-effects bolus model

Mixed diffusion model: example

$$\begin{aligned} dk_i(t) &= \alpha(k_i(t), \phi_i) dt + \gamma(k_i(t), \phi_i) dW_i(t) \\ dC_i(t) &= -k_i(t)C_i(t)dt \\ y_{ij} &= \log(C_i(t_{ij})) + \epsilon_{ij} \end{aligned}$$

$$\begin{aligned} \epsilon_{ij} &\underset{i.i.d.}{\sim} \mathcal{N}(0, \sigma^2(\phi_i)) \\ \phi_i &\underset{i.i.d.}{\sim} \mathcal{N}(\phi_{pop}, \Omega) \end{aligned}$$

$$\begin{aligned} i &= 1, \dots, N, \\ j &= 1, \dots, n_i \end{aligned}$$

General mixed-effects model

Mixed diffusion model: general form

$$\begin{aligned}dX_i(t) &= b(X_i(t), \phi_i) dt + \gamma(X_i(t), \phi_i) dW_i(t), \\y_{ij} &= g(X_i(t_{ij}), \phi_i) + \epsilon_{ij}\end{aligned}$$

$$\begin{aligned}\epsilon_{ij} &\underset{i.i.d.}{\sim} \mathcal{N}(0, \sigma^2(\phi_i)) \\ \phi_i &\underset{i.i.d.}{\sim} \mathcal{N}(\phi_{pop}, \Omega)\end{aligned}$$

The objectives are

- i) to estimate $\theta = (\phi_{pop}, \Omega)$ from the observations $\mathbf{y} = (\mathbf{y}_1, \dots, \mathbf{y}_N)$;
- ii) to estimate the individual parameters ϕ_i , $i = 1, \dots, N$;
- iii) to recover the individual trajectories $X_i(t)$, $i = 1, \dots, N$.

Methodology

- Estimation of θ (MLE)

$$\hat{\theta} = \operatorname{argmax}_{\theta} p(\mathbf{y}; \theta)$$

→ SAEM combined with the extended Kalman filter

- Estimation of ϕ_i (MAP)

$$\hat{\phi}_i = \operatorname{argmax}_{\phi_i} p(\phi_i | \mathbf{y}_i; \hat{\theta})$$

- Estimation of X_i (MAP)

$$\hat{X}(t_{ij}) = \operatorname{argmax}_{X(t_{ij})} p(X(t_{ij}) | \mathbf{y}_i; \hat{\phi}_i)$$

→ Kalman smoother

Likelihood

Mixed diffusion model

$$\begin{aligned}dX_i(t) &= b(X_i(t), \phi_i) dt + \gamma(X_i(t), \phi_i) dW_i(t), \\y_{ij} &= g(X_i(t_{ij}), \phi_i) + \epsilon_{ij}\end{aligned}$$

$$\epsilon_{ij} \underset{i.i.d.}{\sim} \mathcal{N}(0, \sigma^2(\phi_i))$$

$$\phi_i \underset{i.i.d.}{\sim} \mathcal{N}(\phi_{pop}, \Omega)$$

The **likelihood** of the observations has a very complex expression

$$p(Y; \theta) = \prod_{i=1}^N \int p(\mathbf{y}_i, \phi_i; \theta) d\phi_i = \prod_{i=1}^N \int p(\mathbf{y}_i | \phi_i) p(\phi_i; \theta) d\phi_i$$

and

$$p(\mathbf{y}_i | \phi_i) = p(y_{i1} | \phi_i) \prod_{j=1}^{n_i} p(y_{ij} | y_{i,j-1}, \dots, y_{i1}, \phi_i)$$

SAEM algorithm

Iteration k of SAEM algorithm:

- *Simulation of the non observed data*

For $i = 1, \dots, n$, simulate $\phi_i^{(k)}$ under $p(\phi_i | \mathbf{y}_i; \theta_{k-1})$

→ Monte Carlo Markov chains methods

- *Stochastic approximation of the log-likelihood*

$$Q_k(\theta) = Q_{k-1}(\theta) + \gamma_k \left[\sum_{i=1}^n \log p(\mathbf{y}_i, \phi_i^{(k)}; \theta) - Q_{k-1}(\theta) \right]$$

- *Maximization*

$$\theta_k = \operatorname{argmax}_{\theta} Q_k(\theta)$$

SAEM algorithm for mixed effects SDE models

The key of the SAEM algorithm is a quick approximate computation of each individual complete likelihood:

$$\begin{aligned} p(\mathbf{y}_i, \phi_i; \theta) &= p(\mathbf{y}_i | \phi_i; \theta) p(\phi_i; \theta) \\ &= p(\mathbf{y}_i | \phi_i) p(\phi_i; \theta) \end{aligned}$$

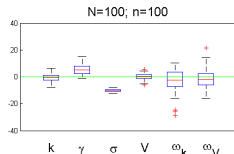
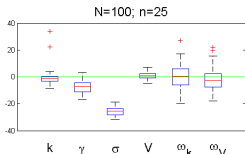
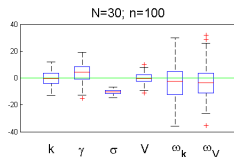
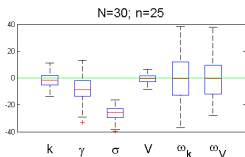
- $p(\phi_i; \theta)$ is explicitly known: $\phi_i \sim \mathcal{N}(\phi_{pop}, \Omega)$
- The **extended Kalman filter** allows to approximate the conditional distribution of the observation $p(\mathbf{y}_i | \phi_i)$ with Gaussian distributions

$$\begin{aligned} dX_i(t) &= b(X_i(t), \phi_i) dt + \gamma(X_i(t), \phi_i) dW_i(t), \\ y_{ij} &= g(X_i(t_{ij}), \phi_i) + \epsilon_{ij} \end{aligned}$$

Simulation study: estimation of the population parameters

$$\begin{aligned}
 dk_i(t) &= (k_i^* - k_i(t)) dt + \gamma \sqrt{k_i(t)} dW_i(t), \\
 dQ_i(t) &= -k_i(t) Q_i(t) dt, \\
 y_{ij} &= \log(Q_i(t)/V_i) + \epsilon_{ij}, \quad \epsilon_{ij} \underset{i.i.d.}{\sim} \mathcal{N}(0, \sigma^2),
 \end{aligned}$$

$$\phi_i = (\log k_i^*, \log V_i) \underset{i.i.d.}{\sim} \mathcal{N}(\phi_{pop}, \Omega), \quad \phi_{pop} = (\log k, \log V).$$



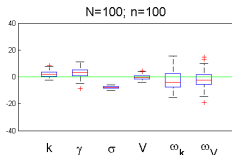
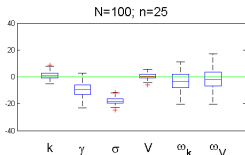
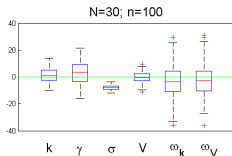
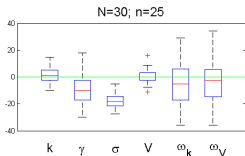
Simulation study: estimation of the population parameters

$$d \log k_i(t) = (\log k_i^* - \log k_i(t)) dt + \gamma dW_i(t),$$

$$dQ_i(t) = -k_i(t) Q_i(t) dt,$$

$$y_{ij} = \log(Q_i(t)/V_i) + \epsilon_{ij}, \quad \epsilon_{ij} \stackrel{i.i.d.}{\sim} \mathcal{N}(0, \sigma^2),$$

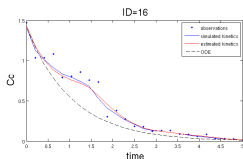
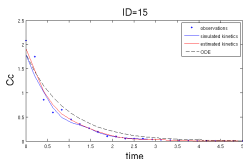
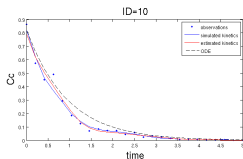
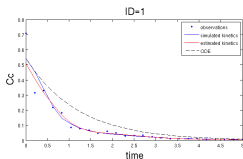
$$\phi_i = (\log k_i^*, \log V_i) \stackrel{i.i.d.}{\sim} \mathcal{N}(\phi_{pop}, \Omega), \quad \phi_{pop} = (\log k, \log V).$$



Simulation study: estimation of the individual trajectories

$$\begin{aligned}
 dk_i(t) &= (k_i^* - k_i(t)) dt + \gamma \sqrt{k_i(t)} dW_i(t), \\
 dQ_i(t) &= -k_i(t) Q_i(t) dt, \\
 y_{ij} &= \log(Q_i(t)/V_i) + \epsilon_{ij}, \quad \epsilon_{ij} \stackrel{i.i.d.}{\sim} \mathcal{N}(0, \sigma^2),
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$$\phi_i = (\log k_i^*, \log V_i) \stackrel{i.i.d.}{\sim} \mathcal{N}(\phi_{pop}, \Omega), \quad \phi_{pop} = (\log k, \log V).$$



Conclusion

- we have proposed a new category of dynamical models for PK application in a population approach;
extension to more general dynamical systems and other application is straightforward
- we have proposed new estimation procedure for these models
 - good practical properties
- Next steps:
 - simulation studies involving more complex models
 - application to real data