Population pharmacokinetics and stochastic differential equations: models and methods

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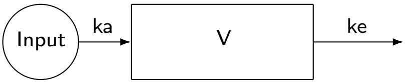
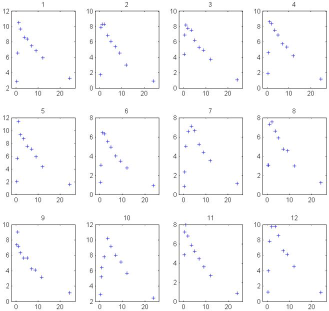
Pharmacokinetics (*PK*)

- 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:



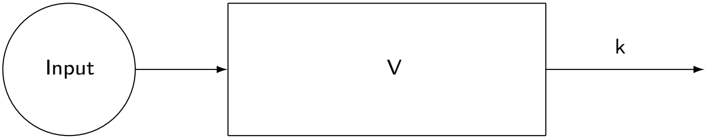


Our objectives:

- 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

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)

a) deterministic model

- dynamical ODE model

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

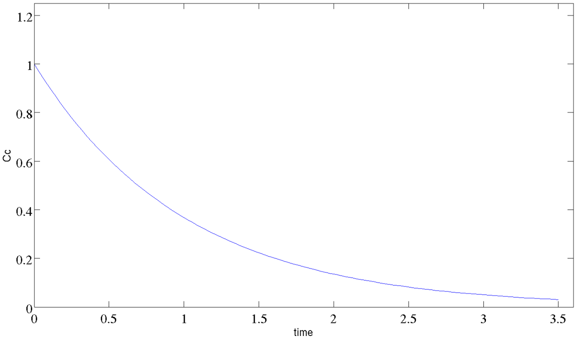


Figure: Evolution of the concentration of a bolus represented by an ODE.

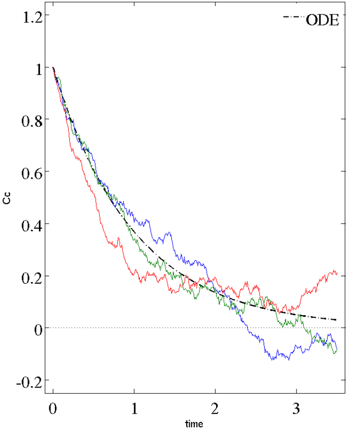
b) diffusion model

- some perturbation in the evolution of the drug
- diffusion model

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

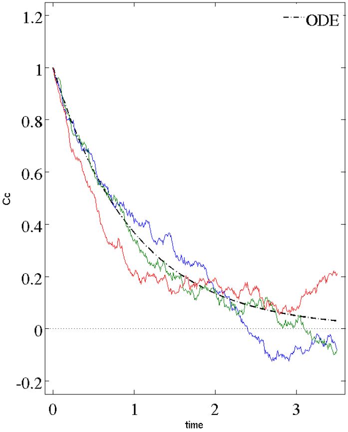
- *Example*

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



b) diffusion model

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



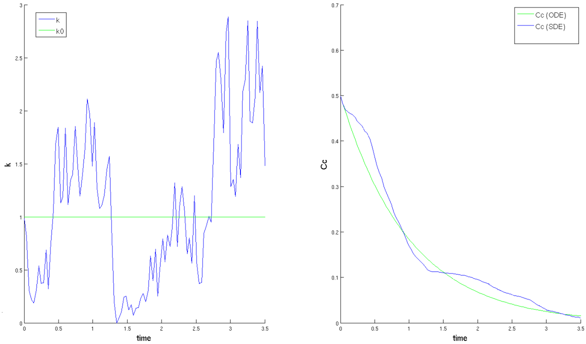
This model is not realistic:

- monotony,
- sign ...

b) diffusion model

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

$$
\begin{aligned}
dk(t) &= b(k(t)) \quad dt \quad + \gamma(k(t))\, dW(t) \\
dC(t) &= -k(t)\, C(t) \quad dt
\end{aligned}
$$

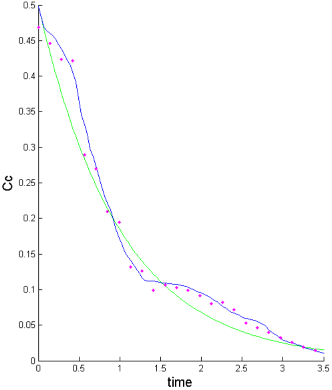


- The kinetics is observed at discrete time points: $(y_1, \ldots, y_n)$

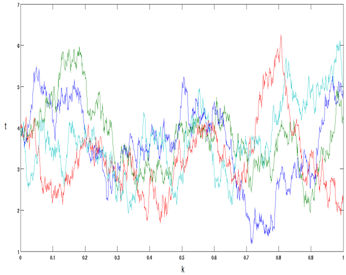
$$dk(t) = b(k(t))\ dt\ +\ \gamma(k(t))\ dW(t)$$

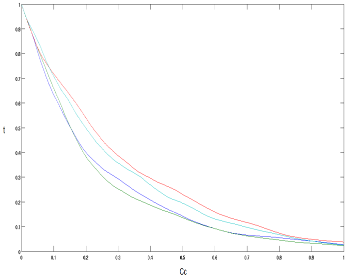
$$dC(t) = -k(t)\ C(t)\ dt$$

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



- N kinetics
  $\mathbf{y}_i = (y_{i1}, \ldots, y_{i,n_i})$: 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 diffusion model: example

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

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

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

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 $\mathbf{y} = (\mathbf{y}_1, \ldots, \mathbf{y}_N)$;

ii) to estimate the individual parameters ϕ_i, $i = 1, \ldots, N$;

iii) to recover the individual trajectories $X_i(t)$, $i = 1, \ldots, N$.

Contribution

- *Estimation of θ (MLE)*

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

$\rightarrow$ *SAEM combined with the extended Kalman filter*

- *Estimation of ϕ_i (MAP)*

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

- *Estimation of X_i (MAP)*

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

$\rightarrow$ *Kalman smoother*

Mixed diffusion model

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

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

The likelihood of the observations has a very complex expression

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

and

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

Iteration k of SAEM algorithm:

- *Simulation of the non observed data*

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

  $\rightarrow$ Monte Carlo Markov chains methods

- *Stochastic approximation of the log-likelihood*

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

- *Maximization*

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

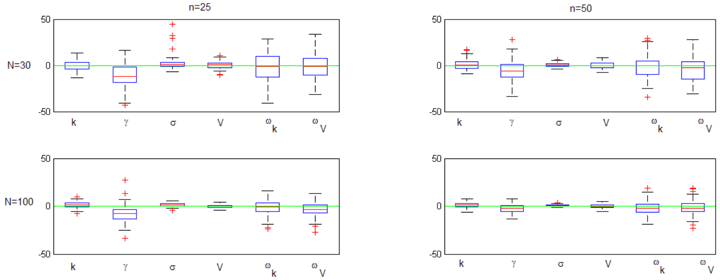
The key of the SAEM algorithm is a quick approximate computation of each individual complete likelihood:

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

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

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

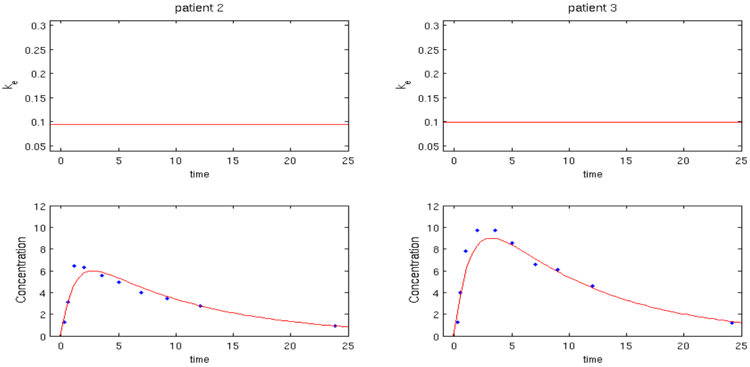
$$d\log k_i(t) = (\log k_i^* - \log k_i(t))\ dt + \gamma\ dW_i(t),$$
$$dQ_i(t) = -k_i(t)\ Q_i(t)\ dt,$$
$$y_{ij} = \log\left(Q_i(t)/V_i\right) + \epsilon_{ij},\ \epsilon_{ij} \underset{i.i.d.}{\sim} \mathcal{N}(0,\sigma^2),$$
$$\phi_i = (\log k_i^*, \log V_i) \underset{i.i.d.}{\sim} \mathcal{N}(\phi_{pop},\Omega),\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



Individual fits for the dynamical ODE model

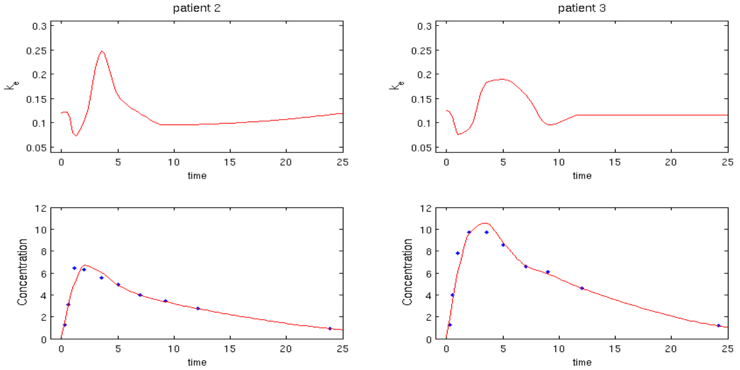
$$dC_i(t) = k_i \frac{D_i}{V_i} e^{-k_i t} - k_{ei} C_i(t) dt$$

$$y_{ij} = C_i(t_{ij}) + \epsilon_{ij} \ , \ \epsilon_{ij} \underset{i.i.d.}{\sim} \mathcal{N}(0, \sigma^2)$$



Individual fit for the diffusion model

$$
\begin{aligned}
dk_{ei}(t) &= -\alpha(k_{ei}(t) - k_{ei0}(t))dt + \gamma\sqrt{k_{ei}(t)}dW_i(t) \\
dC_i(t) &= k_i \frac{D_i}{V_i} e^{-k_i t} - k_{ei} C_i(t)dt \\
y_{ij} &= C_i(t_{ij}) + \epsilon_{ij} \ , \ \epsilon_{ij} \underset{i.i.d.}{\sim} \mathcal{N}(0, \sigma^2)
\end{aligned}
$$



- 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