Using Stochastic Differential Equations for PK/PD Model Development

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Outline

- Brief introduction to SDE models
- Quantifying model uncertainty with SDEs
- Tracking time-variations via SDE models
- Iterative model building with SDEs
- Example: Absorption kinetics

Brief introduction to SDE models

- Stochastic state space model:

$$dA = g(A, d, \theta)dt + \sigma_\omega(\theta)d\omega_t$$

$$y_k = f(A, \theta) + e_k \quad , \quad e_k \in N(0, \sigma_e(\theta))$$

A – state variables.

y – output variables.

g – drift term.

d – input variables.

θ – parameters.

σ_ω – diffusion term.

$\{\omega_t\}$ – Wiener process.

$$\Delta\omega_j = \omega_{j+1} - \omega_j \in N(0, (t_{j+1} - t_j)I)$$

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Quantifying model uncertainty with SDEs

- Stochastic state space model:

$$d\mathbf{A} = \mathbf{g}(\mathbf{A}, \mathbf{d}, \boldsymbol{\theta})dt + \boldsymbol{\sigma}_{\boldsymbol{\omega}}(\boldsymbol{\theta})d\boldsymbol{\omega}_t$$

$$\mathbf{y}_k = \mathbf{f}(\mathbf{A}, \boldsymbol{\theta}) + \mathbf{e}_k \quad , \quad \mathbf{e}_k \in N(\mathbf{0}, \boldsymbol{\sigma}_{\mathbf{e}}(\boldsymbol{\theta}))$$

  - By including the diffusion term, reasonable parameter estimates can be obtained despite structural misspecifications in the drift term.
  - Uncertainty due to structural misspecifications can be quantified by means of estimates of the parameters of the diffusion term.

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Quantifying model uncertainty with SDEs

- The parameters of a stochastic state space model can be estimated with a maximum likelihood (ML) approach based on the extended Kalman filter (EKF).

- A software tool (CTSM) is available from http://www.imm.dtu.dk/ctsm.

Tracking time-variations via SDE models

- Stochastic state space model:

$$d\mathbf{A} = \mathbf{g}(\mathbf{A}, \mathbf{d}, \boldsymbol{\theta})dt + \boldsymbol{\sigma}_{\boldsymbol{\omega}}(\boldsymbol{\theta})d\boldsymbol{\omega}_t$$

$$\mathbf{y}_k = \mathbf{f}(\mathbf{A}, \boldsymbol{\theta}) + \mathbf{e}_k \quad , \quad \mathbf{e}_k \in N(\mathbf{0}, \boldsymbol{\sigma}_{\mathbf{e}}(\boldsymbol{\theta}))$$

- Types of state estimates (available in CTSM):
  - Simulated: $\hat{\mathbf{A}}_{k|0}$ - Pure simulation (conventional).
  - Predicted: $\hat{\mathbf{A}}_{k|k-1}$ - EKF with measurement update.
  - Filtered: $\hat{\mathbf{A}}_{k|k}$ - EKF with measurement update.
  - Smoothed: $\hat{\mathbf{A}}_{k|N}$ - Smoothing based on EKF.
- Confidence intervals provided automatically.

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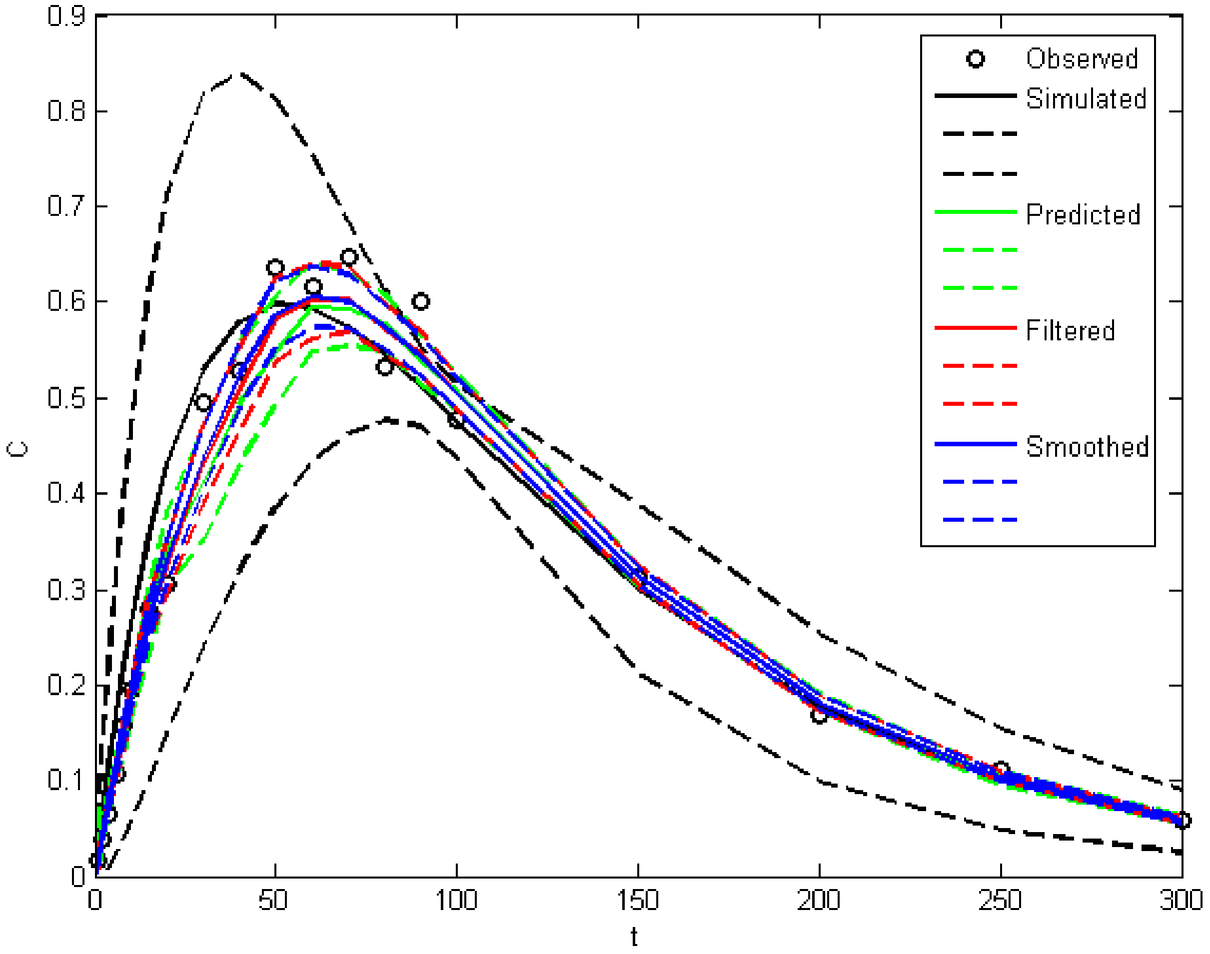
Tracking time-variations via SDE models



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Tracking time-variations via SDE models

- Time-variations in parameters or unknown inputs can be tracked by including these as additional state variables in the model:

$$d\mathbf{A} = \mathbf{g}(\mathbf{A}, \mathbf{d}, \boldsymbol{\theta}, \varphi)dt + \boldsymbol{\sigma}_{\boldsymbol{\omega}}(\boldsymbol{\theta})d\boldsymbol{\omega}_t$$

$$d\varphi = \sigma_\varphi d\omega_t^\varphi$$

$$\mathbf{y}_k = \mathbf{f}(\mathbf{A}, \boldsymbol{\theta}) + \mathbf{e}_k \quad , \quad \mathbf{e}_k \in N(\mathbf{0}, \boldsymbol{\sigma}_{\mathbf{e}}(\boldsymbol{\theta}))$$

  - Resulting model – random walk:

$$\varphi_{k+1} = \varphi_k + \sigma_\varphi \Delta\omega_k^\varphi \quad , \quad \Delta\omega_k^\varphi \in N(0, t_{k+1} - t_k)$$

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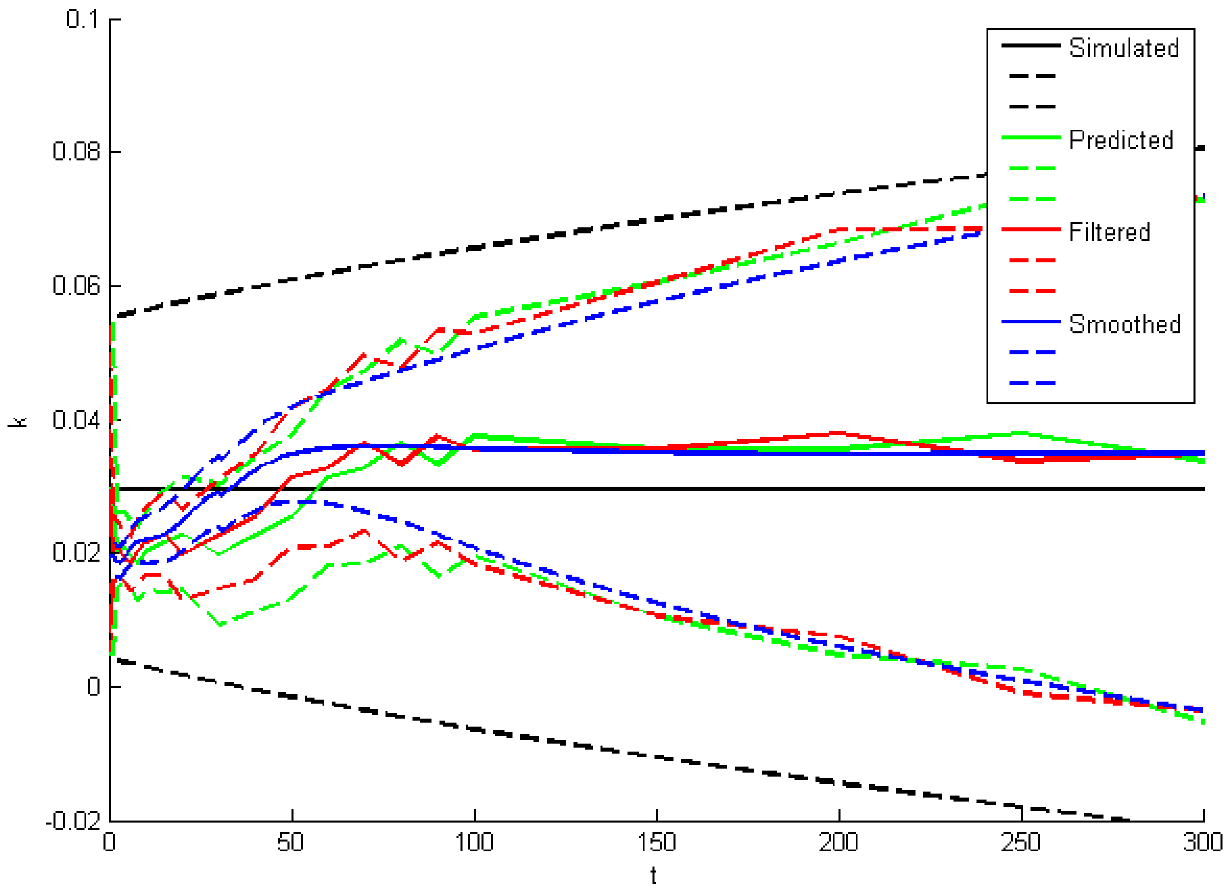
Tracking time-variations via SDE models



Iterative model building with SDEs

- The advantages of using SDE models can be used to formulate a systematic procedure for iterative development of ODE models:
  - Estimates of the parameters of the diffusion term can be used to quantify uncertainty due to model structure misspecifications to detect model errors.
  - Tracking of time-variations in key parameters can be used to determine how to correct the errors.

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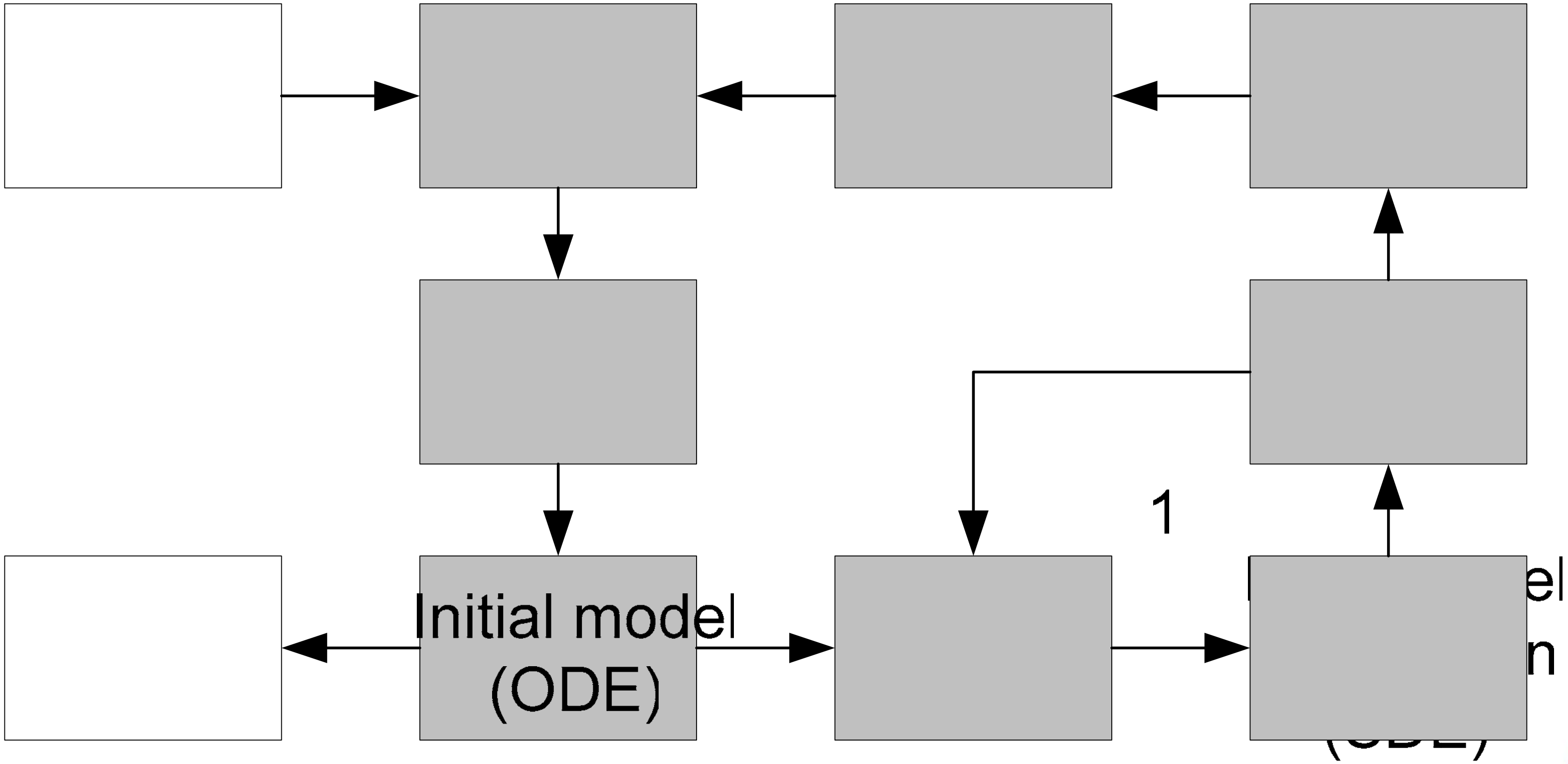
Iterative model building with SDEs



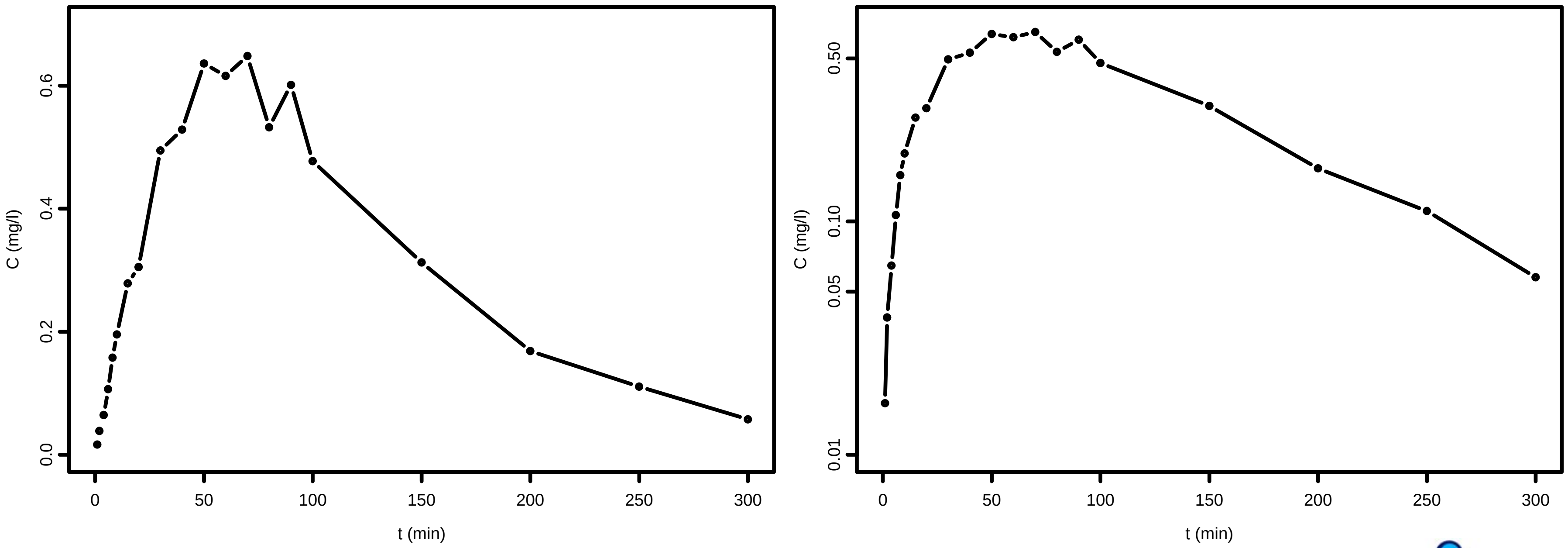
Example: Absorption kinetics

- Problem: To determine absorption kinetics for a drug using a single oral dose.
- Data (simulated*): 20 blood samples from a single individual taken over 5 hours.
- Assumptions:
  - One-compartment model of disposition sufficient.
  - Absorption kinetics unknown - to be determined.

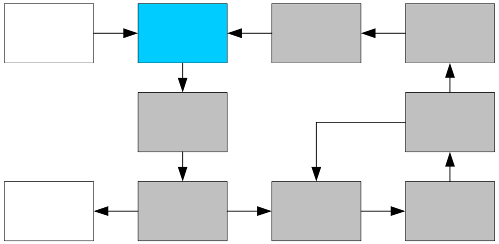
*: Simulation model: One-compartment model with nonlinear absorption (Michaelis-Menten) and first-order elimination.

Example: Absorption kinetics

- Data:



Step 1:



- Formulate an initial ODE model and translate it into an SDE model (the basic model).

$$\frac{dA}{dt} = -k_A A \qquad\qquad dA = -k_A A dt + \sigma_1 d\omega_t^1$$

$$\frac{dC}{dt} = \frac{k_A A}{V} - \frac{CL}{V} C \quad \Rightarrow \quad dC = \left(\frac{k_A A}{V} - \frac{CL}{V} C \right) dt - \frac{\sigma_1}{V} d\omega_t^1 + \sigma_2 d\omega_t^2$$

$$y_k = C(1 + e_k) \;,\; e_k \in N(0, \sigma_e)$$

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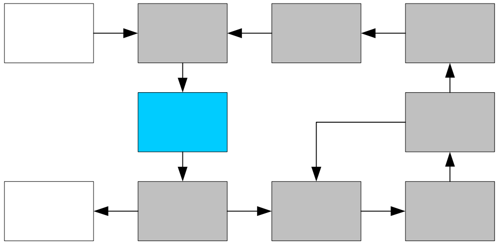


Step 2:

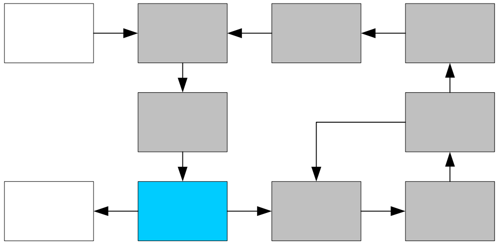
- Estimate the parameters of the basic SDE model from the available data.

$$dA = -k_A A dt + \sigma_1 d\omega_t^1$$

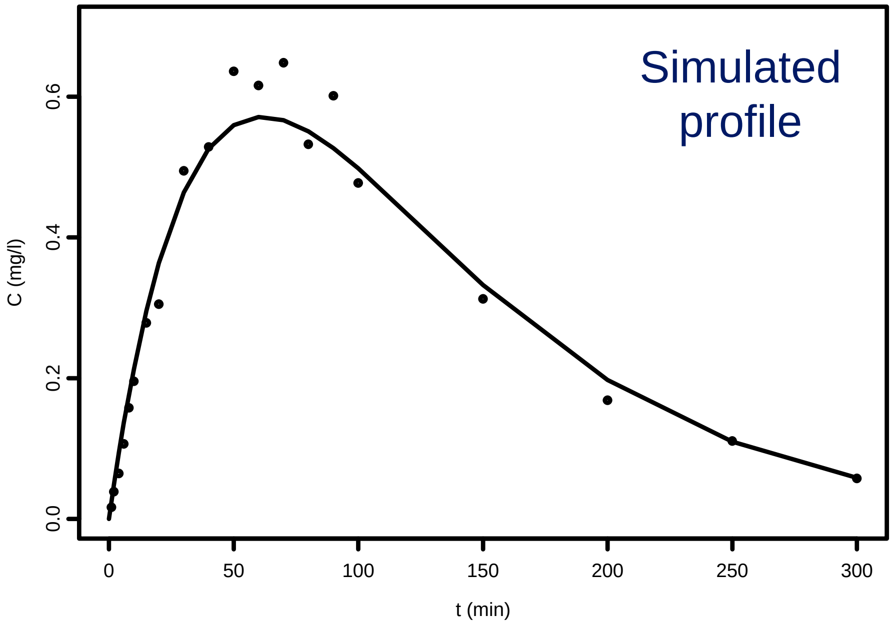
$$dC = \left(\frac{k_A A}{V} - \frac{CL}{V} C \right) dt - \frac{\sigma_1}{V} d\omega_t^1 + \sigma_2 d\omega_t^2$$

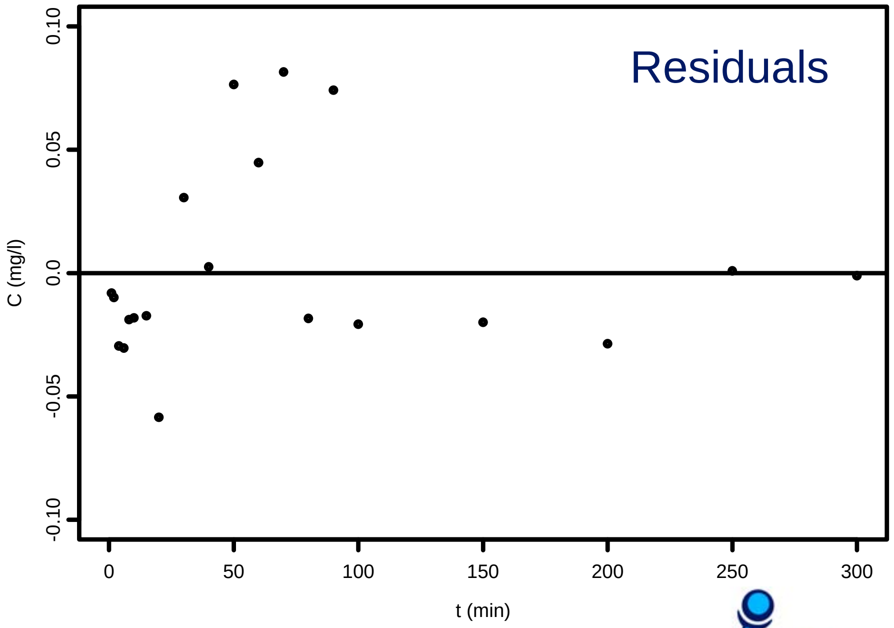
Parameter	k_A	CL	V	σ_1	σ_2	σ_e
Estimate	1.62E-2	5.21E-2	3.22E+0	1.89E-2	1.11E-7	5.74E-3
p-value	0.0007	0.0000	0.0008	0.0283	0.9990	0.0786

Step 3:



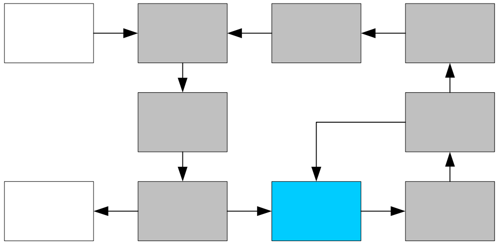
- Evaluate the quality of the basic SDE model using residual analysis and statistical tests.





$-\ln(L(\theta)) = -14.80$

Step 4:



- Formulate an extended model, where a possibly time-varying parameter is included as an additional state variable (random walk).

$$dA = -k_A A dt + \sigma_1 d\omega_t^1$$

$$dC = \left(\frac{k_A A}{V} - \frac{CL}{V} C \right) dt - \frac{\sigma_1}{V} d\omega_t^1 + \sigma_2 d\omega_t^2$$

$$dk_A = \sigma_3 d\omega_t^3$$

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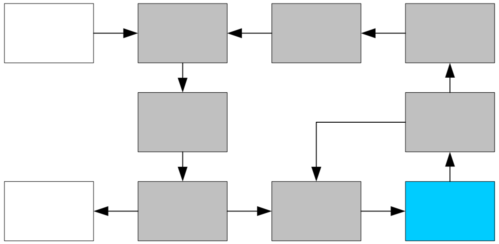
Step 5:



- Estimate the parameters of the extended model from the available data.

$$dA = -k_A A dt + \sigma_1 d\omega_t^1$$

$$dC = \left(\frac{k_A A}{V} - \frac{CL}{V} C \right) dt - \frac{\sigma_1}{V} d\omega_t^1 + \sigma_2 d\omega_t^2$$

$$dk_A = \sigma_3 d\omega_t^3$$

Parameter	$k_{A,0}$	CL	V	σ_1	σ_2	σ_3	σ_e
Estimate	1.71E-2	5.22E-2	4.64E+0	3.0E-20	3.39E-9	1.63E-3	5.16E-3
p-value	0.0000	0.0000	0.0000	1.0000	0.9998	0.0322	0.0111

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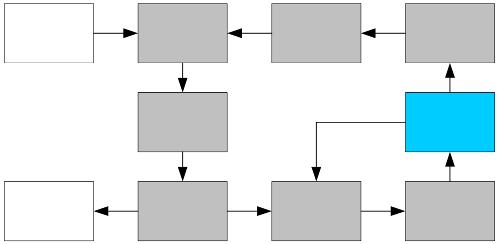
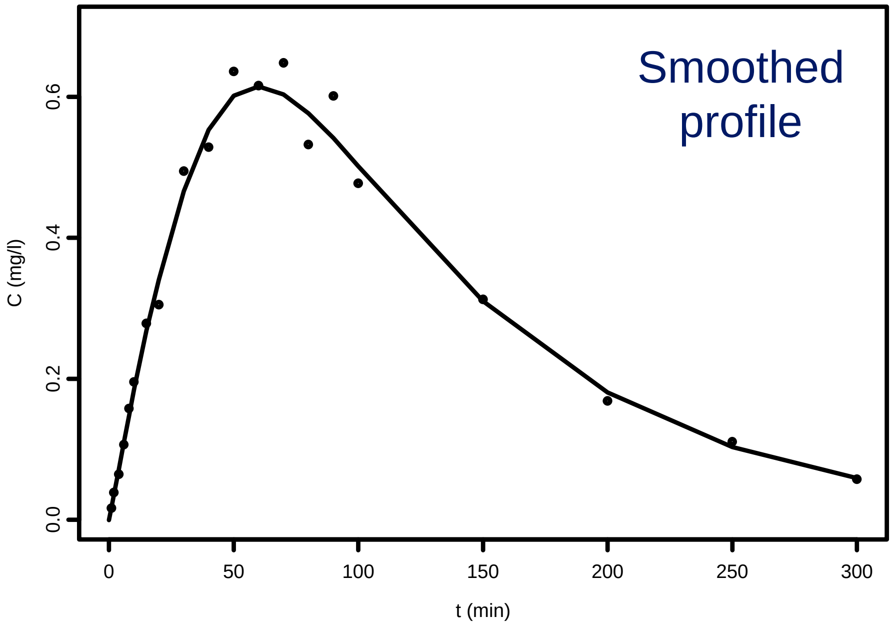
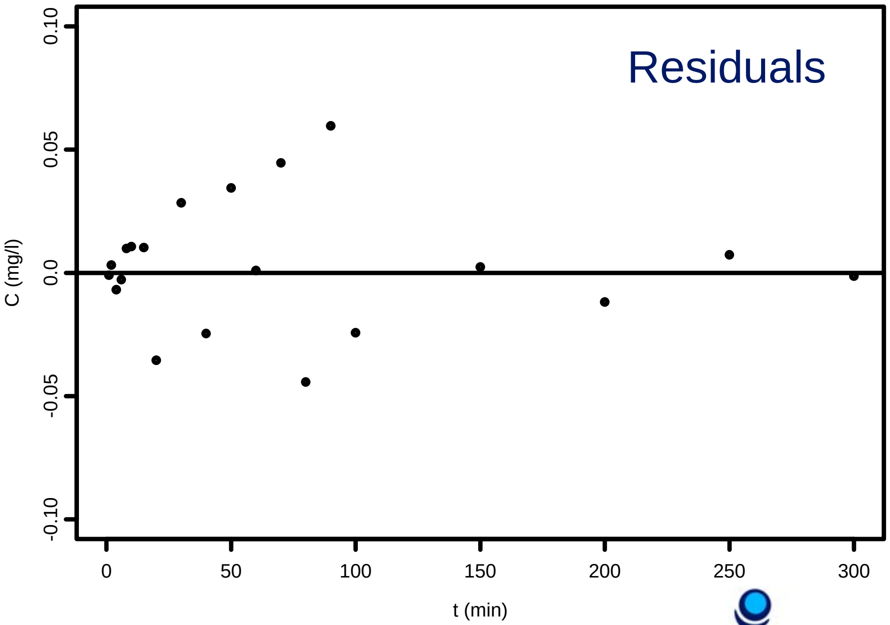
Step 6:



- Determine whether or not the selected parameter is in fact time-varying.





$-\ln(L(\theta)) = -19.21 \quad (\Delta(-\ln(L(\theta)) = -4.41)$

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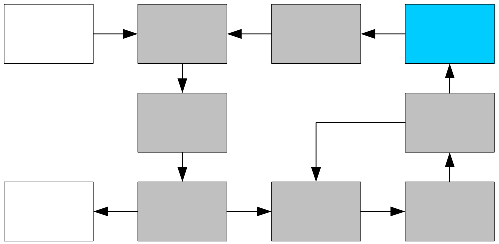
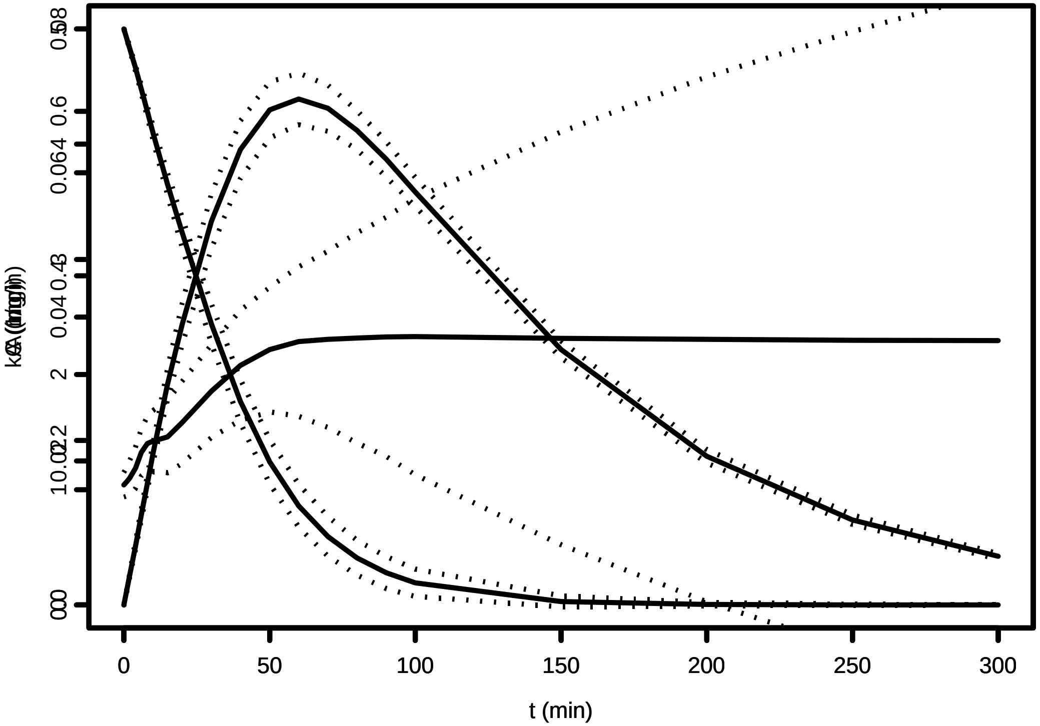
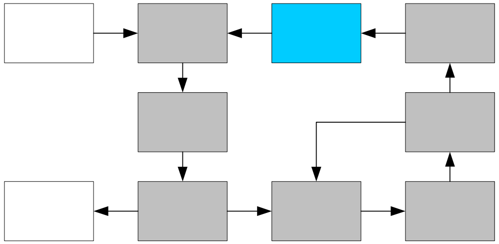
Step 7:



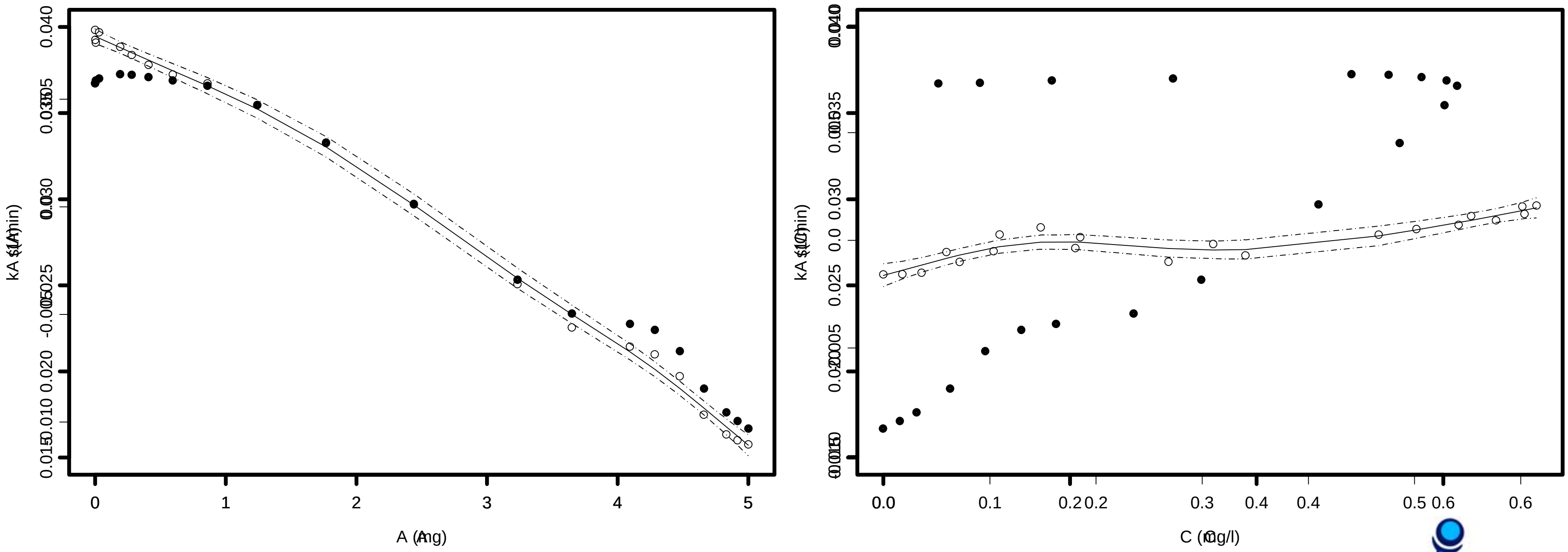
- Determine the nature of the variations in the time-varying parameter.



Step 8:

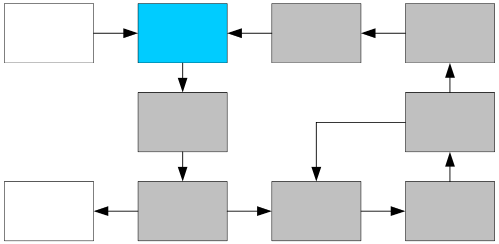


- Analyze the variations in the time-varying parameter to improve the model.



Simple additive model fitted with S-plus function gam.

Step 1 (repeated):



- Re-formulate the basic SDE model.

$$dA = -k_A A\,dt + \sigma_1 d\omega_t^1$$

$$dC = \left(\frac{k_A A}{V} - \frac{CL}{V} C\right) dt - \frac{\sigma_1}{V} d\omega_t^1 + \sigma_2 d\omega_t^2$$

$$\Downarrow$$

$$dA = -\frac{V_{max} A}{K_m + A} dt + \sigma_1 d\omega_t^1$$

$$dC = \left(\frac{V_{max} A}{(K_m + A)V} - \frac{CL}{V} C\right) dt - \frac{\sigma_1}{V} d\omega_t^1 + \sigma_2 d\omega_t^2$$

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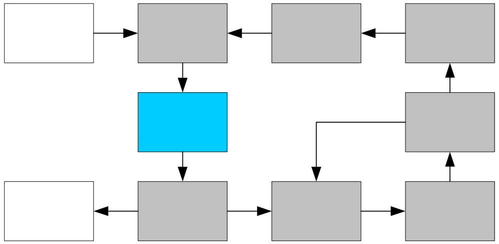
Step 2 (repeated):



- Estimate the parameters of the new SDE model from the available data.

$$dA = -\frac{V_{max}A}{K_m + A}dt + \sigma_1 d\omega_t^1$$

$$dC = \left(\frac{V_{max}A}{(K_m + A)V} - \frac{CL}{V}C\right)dt - \frac{\sigma_1}{V}d\omega_t^1 + \sigma_2 d\omega_t^2$$

Parameter	V_{max}	K_m	CL	V	σ_1	σ_2	σ_e
Estimate	1.15E-1	9.89E-1	5.22E-2	4.99E+0	4.22E-3	1.28E-8	5.37E-3
p-value	0.0000	0.0000	0.0000	0.0000	0.4971	0.9956	0.0024

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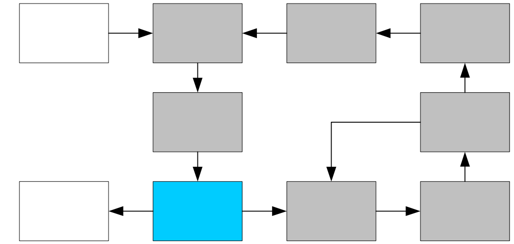
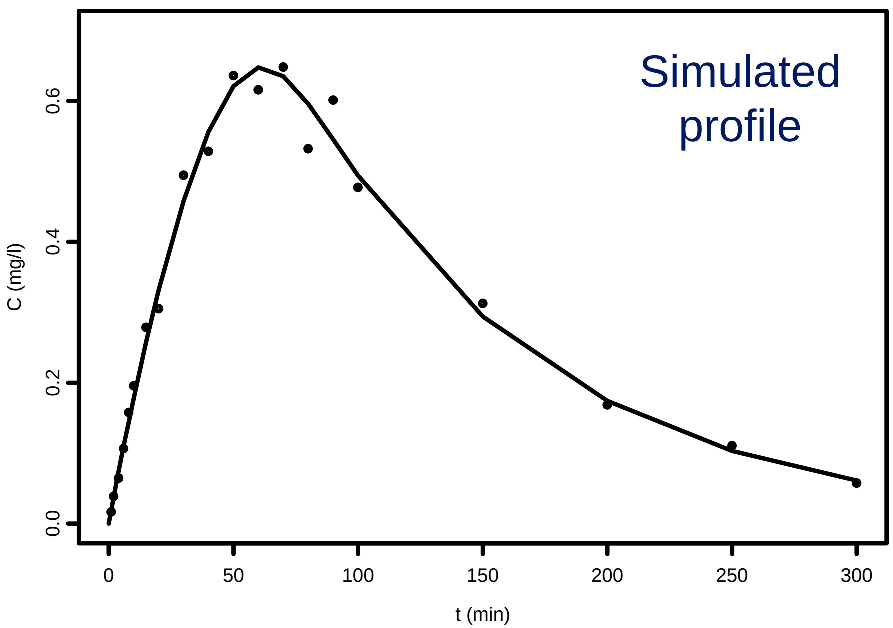
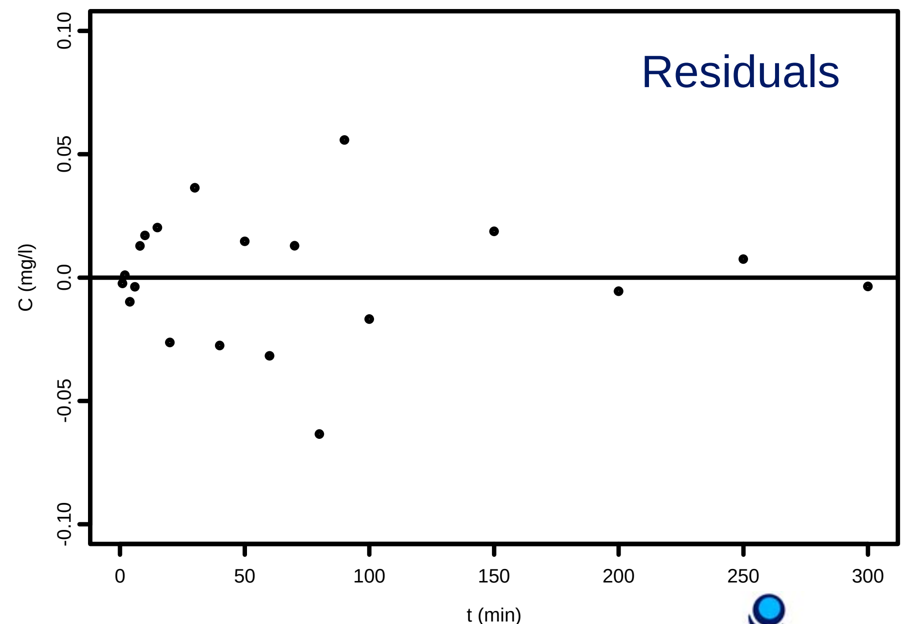


Step 3 (repeated):

- Evaluate the quality of the new SDE model using residual analysis and statistical tests.





$-\ln(L(\theta)) = -23.27 \quad (\Delta(-\ln(L(\theta))) = -4.06)$

Conclusions

- Iterative model building with SDEs can be used for PK/PD model development:
  - Allows systematic quantification of model uncertainty to detect model errors.
  - Facilitates tracking of time-variations in key parameters to correct the errors.
  - Nonparametric modelling can be applied to determine functional relationships.

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The future

- Iterative population model building with SDEs in a nonlinear mixed-effects setting.
    - Parameter estimation and state prediction and filtering possible in NONMEM VI.
    - Smoothing and population-based methodologies for inference-making yet unresolved.