Modeling & Simulation in Systems Pharmacology

Max von Kleist

DFG Research Center MATHEON
Mathematics for key technologies

April 24, 2014

Organization of this seminar

every thursday 12:00-14:00 (2x45min)

"Topics and schedule"

date	topic		date	topic	
17.04.	~~Overview~~	~~M.v.K.~~	12.06.	proj. feedback	stud. + superv.
24.04.	**Modelling & PK**	M.v.K.	19.06.	proj. feedback	stud. + superv.
08.05.	Parameter Estimation	M.v.K.	**26.06.**	Drug Absorption PBPK	Marco Johanna
15.05.	proj. feedback	stud. + superv.	**03.07.**	Part. coeff. Parameter estimation	Benjamin ?
25.05.	proj. feedback	stud. + superv.	**10.07.**	Dis. Modelling I Dis. Modelling II	? ?
05.06.	proj. feedback	stud. + superv.	**17.07.**	ODE vs. stoch. sim.	Ivo

Project supervision & feedback

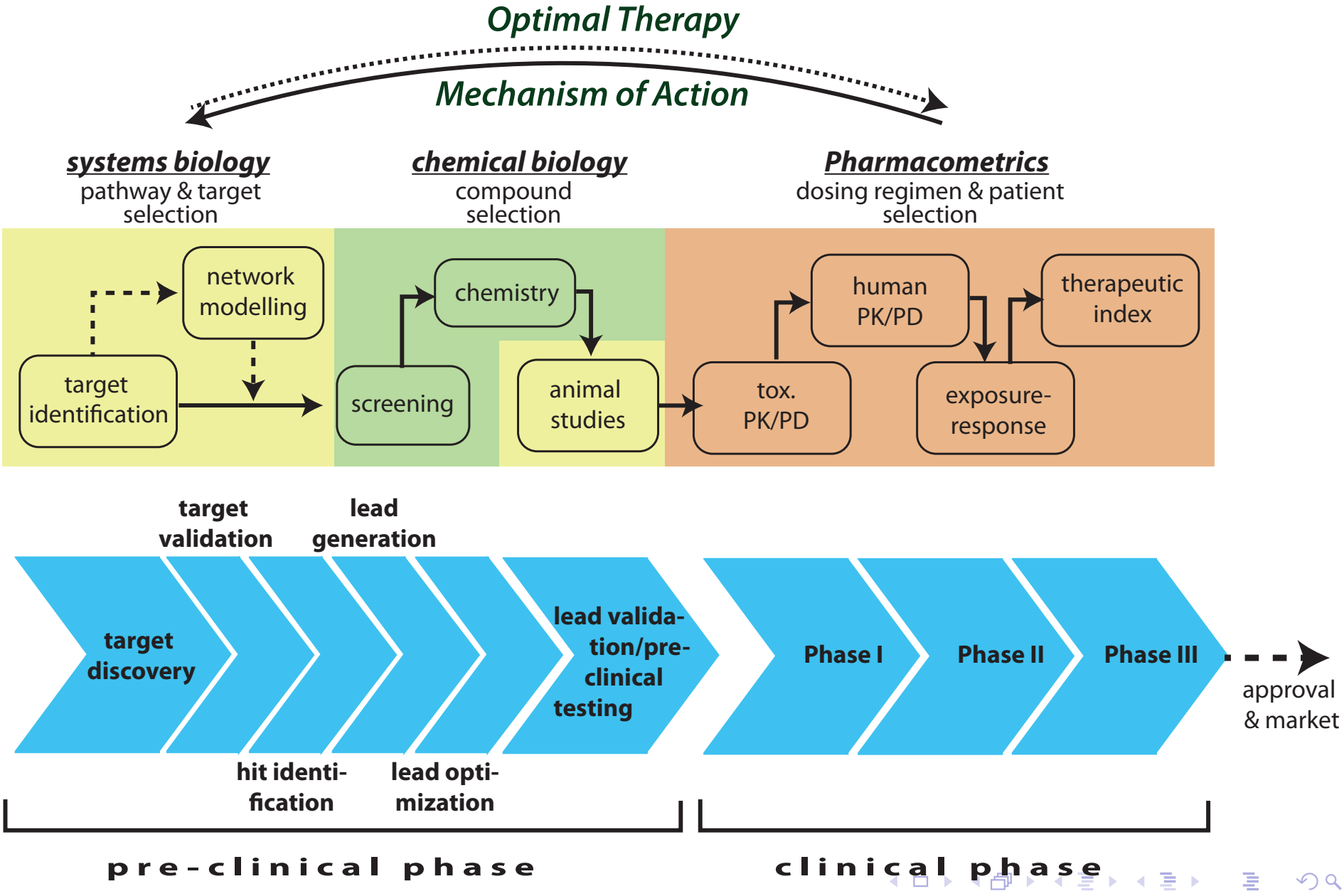
1. **initial meeting:**
   - goal: clarification of the tasks related to the study topic.
   - prepare: read the project portfolio, start the programming tasks, prepare questions
2. **intermediate meeting:**
   - goal: solving particular issues regarding e.g. the programming tasks, obtain feedback & tips, monitor progress
   - prepare: present your achievements up to this time point and discusses ways to present the work
3. **final meeting:**
   - goal: review of the results & presentation and obtain feedback.
   - prepare: presentation of the study topic.
4. **presentation:**
   - goal: present your scientific results in the context of a larger topic. Scientific discussion.

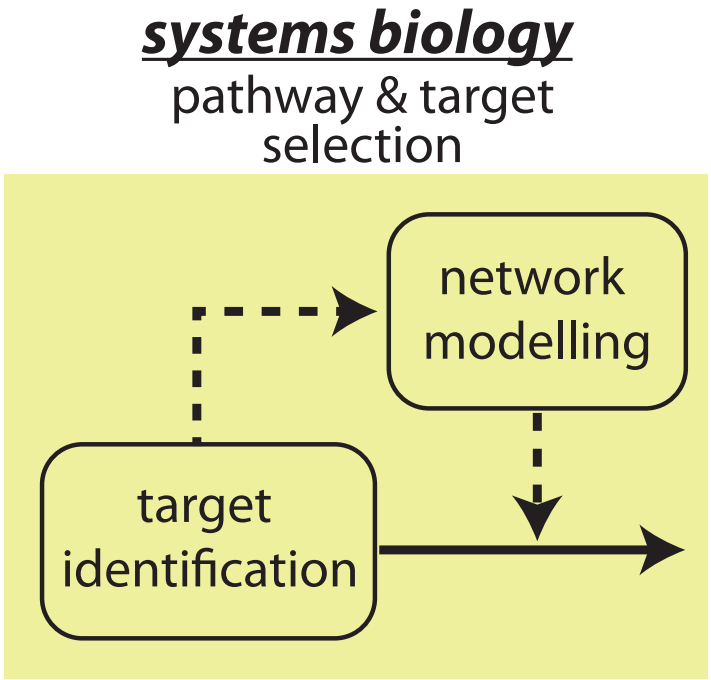
Metting Schedule (preliminary)

topic	1st	2nd	3rd	superv.
Absorption	12.05	28.05	19.06	Sulav M.v.K.
PBPK	12.05	28.05	19.06	M.v.K.
part. coeff.	15.05	05.06	26.06	M.v.K.
param. est.	15.05	05.06	26.06	Kaveh M.v.K.
Dis. Model I	25.05	12.06	03.07	M.v.K.
Dis. Model II	25.05	12.06	03.07	Sulav M.v.K.
ODE vs. stoch sim.	25.05	19.06	10.07	Kaveh M.v.K.

Repetition.

Systems pharm. in drug development



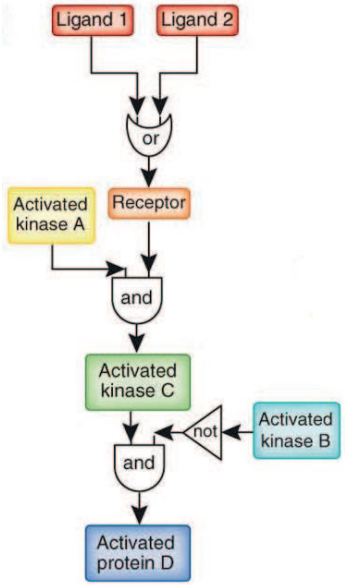

systems biology
pathway & target selection
network modelling
target identification

Modelling Approaches

Protein Interaction Networks

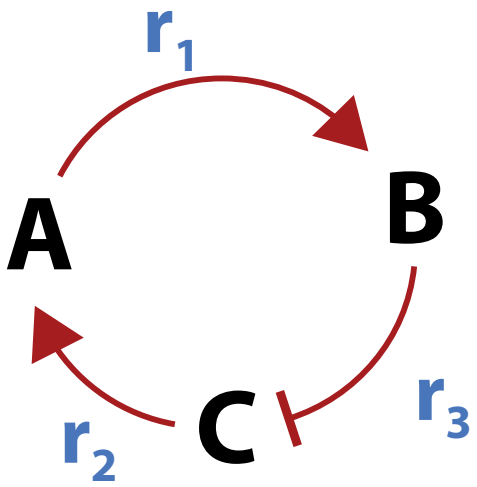
- association/ correlation
- qualitative patterns/trends

Logic models



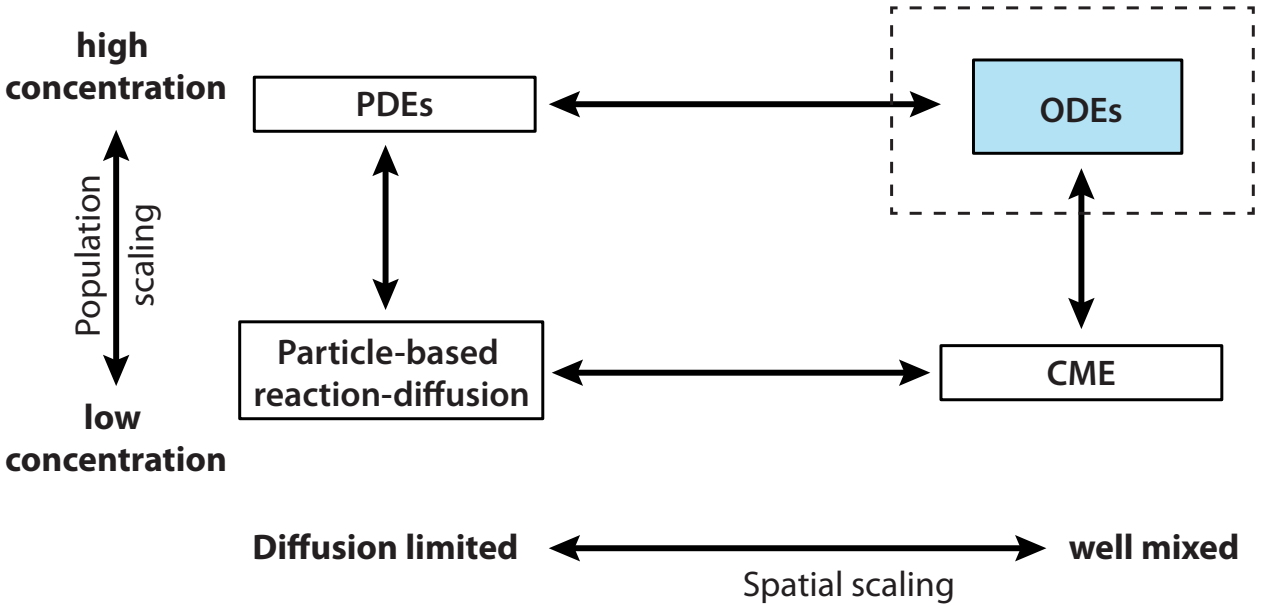
- discrete states ("on/off")
- logic-based functions

Kinetic models

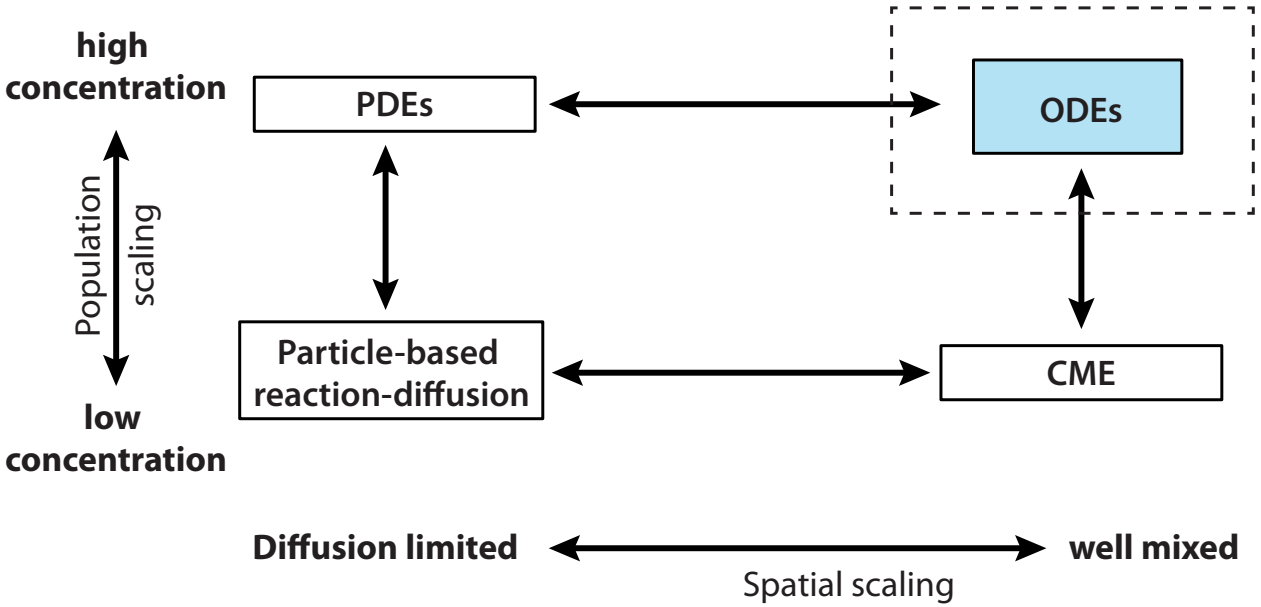


- dynamic range components
- reaction rate laws
- kinetic behavior

Kinetic Modelling Approaches



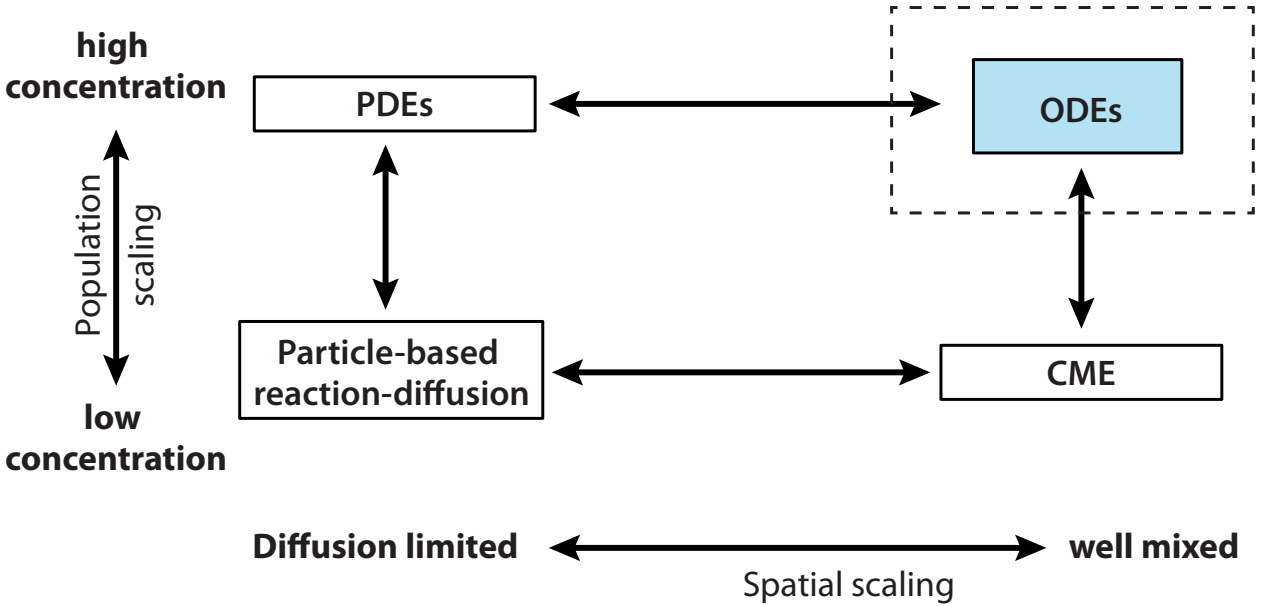
Kinetic Modelling Approaches



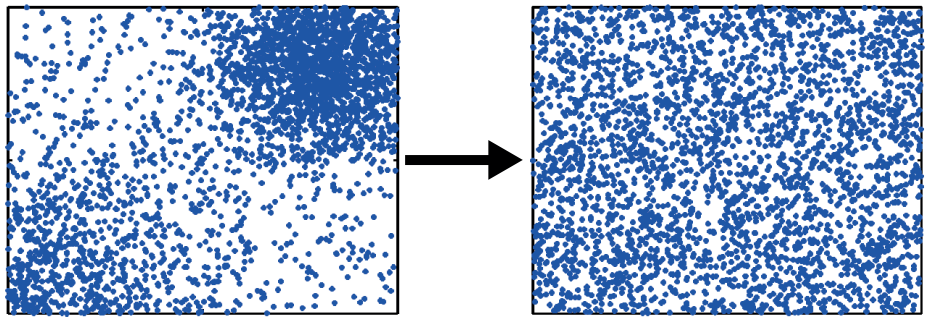
Assumption: All molecules within one reaction compartment (e.g. cytosol, extracell. space, ...) are well-mixed...

- valid for fast diffusing particles (in relation to the timescale of interest).
- timescale of intracellular particle diffusion: $\sim$ sec.

Kinetic Modelling Approaches

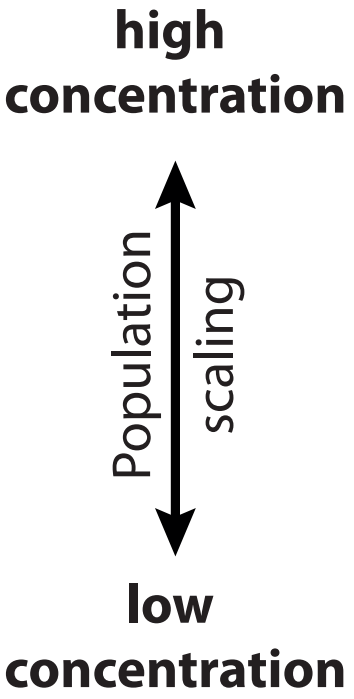


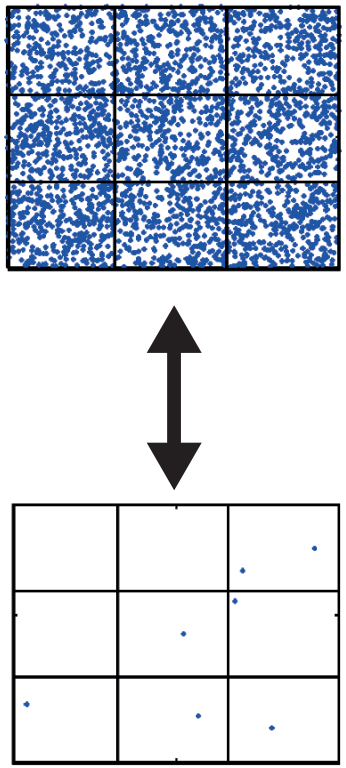
Assumption: All molecules within one reaction compartment (e.g. cytosol, extracell. space, ...) are well-mixed...



Many vs. few particles

Assumption: Many molecules within one reaction compartment, large reaction volume





- many molecules, large reaction volume
- concentrations $x(t) \sim \mathbb{E}(X(t))/\Omega$
- ODE (Chemical Reaction Kinetics)

- few molecules, small reaction volume
- molecular numbers $X(t)$
- CME (Chemical Master Equation)

Modelling Techniques

Model Constituents

- initial conditions
  - x_0 – concentrations at time zero (t_0), e.g. [μmol/L] $\Leftrightarrow$ [μM]
- compartment volumes
  - $V(t)$ – compartment volumes, e.g. [1/L]
  - assume constant volumes $V = V(t) \; \forall \; t$
- reaction rules
  - change vector $s_{\cdot,j}$
  - reaction rates r_j

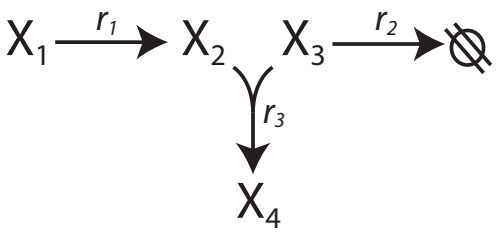
Reaction rules I: Change vector

The single reaction j

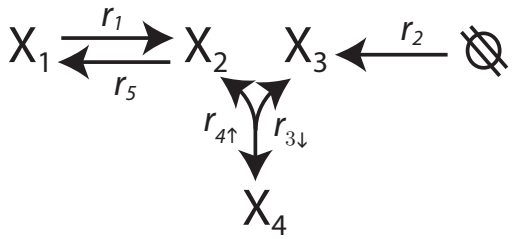
$$\underbrace{\sum_i m_i X_i}_{educts} \xrightarrow{r_j(t)} \underbrace{\sum_i n_i X_i}_{products}$$

has $m_1 \ldots m_q$ *educt* molecules and produces $n_1 \ldots n_q$ *product* molecules of species $1 \ldots q$. Its *stochiometric change vector* is $s_{\cdot,j} = n_{\cdot,j} - m_{\cdot,j}$

Example 1



Example 2



yielding the $\#species \times \#reactions$ *stoichiometric matrix* $S = \{s_{i,j}\}$

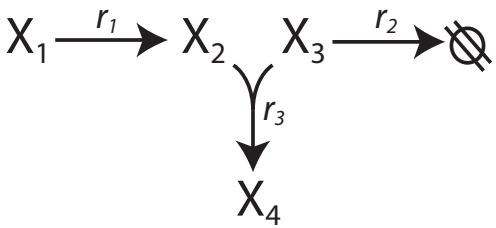
Reaction rules II: Rates

The single reaction j

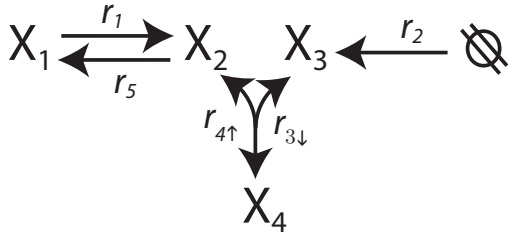
$$\underbrace{\sum_i m_i X_i}_{educts} \xrightarrow{r_j(t,k)} \underbrace{\sum_i n_i X_i}_{products}$$

has reaction rate $r_j(t,k) = k_j \cdot \prod_i X_i^{m_i}(t)$.... (elementary/simple reactions)

Example 1



Example 2



yielding the $\#reactions \times 1$ *reaction rate vector* $R(t,k) = \{r_j(t,k)\}$

Reaction rules III: Rates

- Elementary/simple reactions

order	reaction	rate	unit of k
0^{th}	$\emptyset \xrightarrow{k_\emptyset} \ldots$	$r_0(k) = k_\emptyset$	mole/time
1^{st}	$X_i \xrightarrow{k_1} \ldots$	$r_1(X, k) = k_1 \cdot X_i$	1/time
2^{nd}	$X_i + X_\ell \xrightarrow{k_2} \ldots$	$r_2(X, k) = k_2 \cdot X_i \cdot X_\ell$	1/(time $\cdot$ mole)

Reaction rules III: Rates

- Elementary/simple reactions

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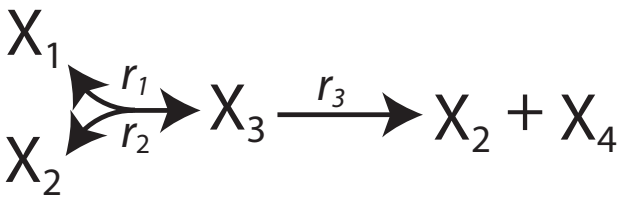
2^{nd}	$X_i + X_\ell \xrightarrow{k_2} \ldots$	$r_2(X,k) = k_2 \cdot X_i \cdot X_\ell$	1/(time · mole)

- Any other reaction functions/propensity functions

$$r_j = f(\mathbf{X}, \mathbf{k}, m, t)$$

$$r_j = \frac{k_{\mathbf{cat}} \cdot (X_2 + X_3)^{m_{2+3}} \cdot X_1^{m_1}(t)}{K_{\mathcal{M}} + X_1^{m_1}(t)}$$



...corresponds to an aggregation/lumping of elementary reactions...

Model Equations (ODEs)

For each species i we have:

$$\frac{\mathrm{d}}{\mathrm{d}t} X_i = \sum_j s_{i,j} \cdot r_j(t, k) \tag{1}$$

which is (matrix multiplication):

$$\frac{\mathrm{d}}{\mathrm{d}t} \mathbf{X} = S \cdot R(t, k) \tag{2}$$

Attention: Units, units, units!

Note I: These describe change in molecule numbers [mol/time] or [molecules/time], not concentrations changes!
If V constant then $\mathbf{x}(t) = \mathbf{X}(t)/V$.

Note II: We have mass conservation $\sum_i X_i(t) \cdot \mathrm{MW}_i = \mathrm{const.}$
(conc. not conserved, nor molecule numbers).

Model Constituents $\Rightarrow$ ODE Model

Setting Up a Model...

Solve...

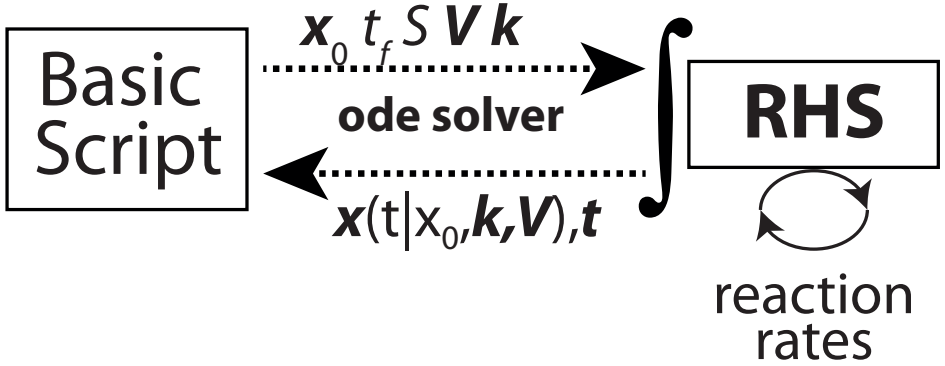
$$\mathbf{V}\frac{\mathrm{d}}{\mathrm{d}t}\mathbf{x} = S \cdot R_V(t,k) \tag{3}$$

with initial conditions $x(t_0) = X(t_0)/V$.

We need:

- Stoichiometric matrix $S = \{s_{i,j}\}$ ... constant
- Volumes **V** ... we assume them to be constant for simplicity
- Initial conditions $\mathbf{x}(t_0)$
- Volume scaled reactions rates $R_V(t) = \{r_{j,V}(t,k)\}$ ... are functions of parameters k and the state vector (which changes in time)

Example: Matlab:Volumes



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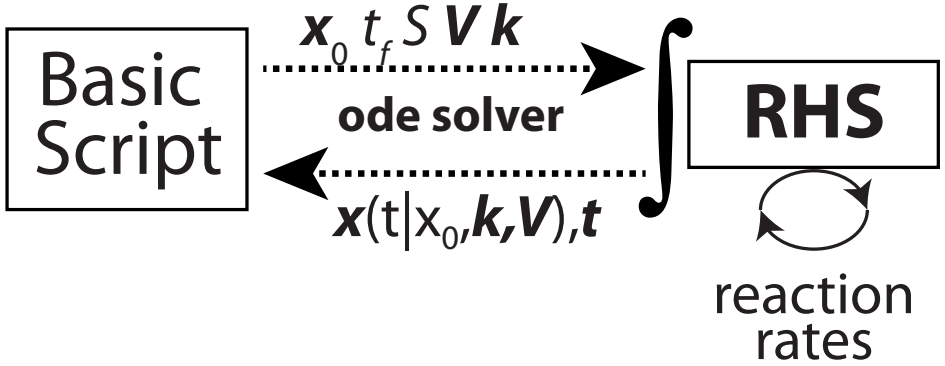
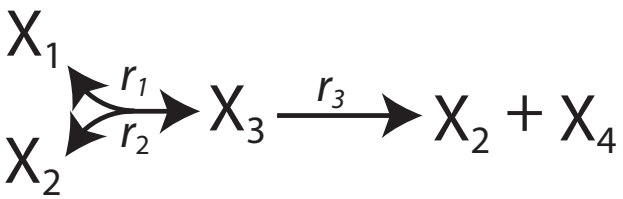
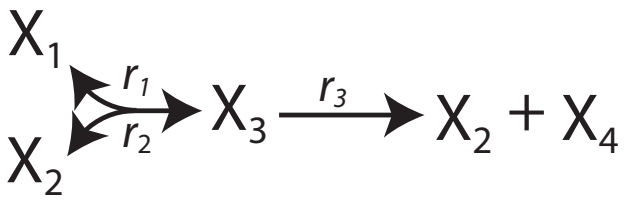





```
1 % Reaction volumes of each species in units [L]
2 V = zeros(NrSpecies,1);
3 V(1) = 1e2;% reaction volume of X1
4 V(2) = 1e2;% reaction volume of X2
5 V(3) = 1e1;% reaction volume of X3
6 V(4) = 1e3;% reaction volume of X4
```

Example: Matlab:Initial Conditions




```
1 X0 = zeros(NrSpecies,1);
2 % Initial conditions
3 % in [mole]
4 X0(1) = 1e3;% X1 Substrate
5 X0(2) = 30;  % X2 Enzyme
6 X0(3) = 0;  % X3 Complex
7 X0(4) = 0;  % X4 Product
8
9 x0 = X0./V;
```

Example: Matlab: Reaction Network

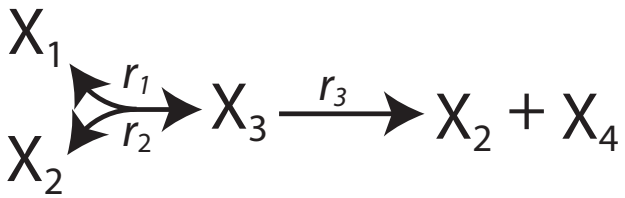
```
% Stoichiometric Matrix
% unit: # of molecules/moles changed by reaction
global S
S = zeros(NrSpecies,NrReactions);
%            X1   X2      X3      X4
S(:,1) = [-1;   -1;     1;      0]; %r1
S(:,2) = [1;    1;      -1;     0]; %r2
S(:,3) = [0;    1;      -1;     1]; %r3
```

```
% reaction parameters
global k
k = ones(NrReactions,1);
k(1) = 3e2; %kon; unit [L^2/mole*min]
k(2) = 5e-0; %koff; unit [L/min]
k(3) = 5e0;%kcat; unit [L/min]
```

Example: Matlab: RHS

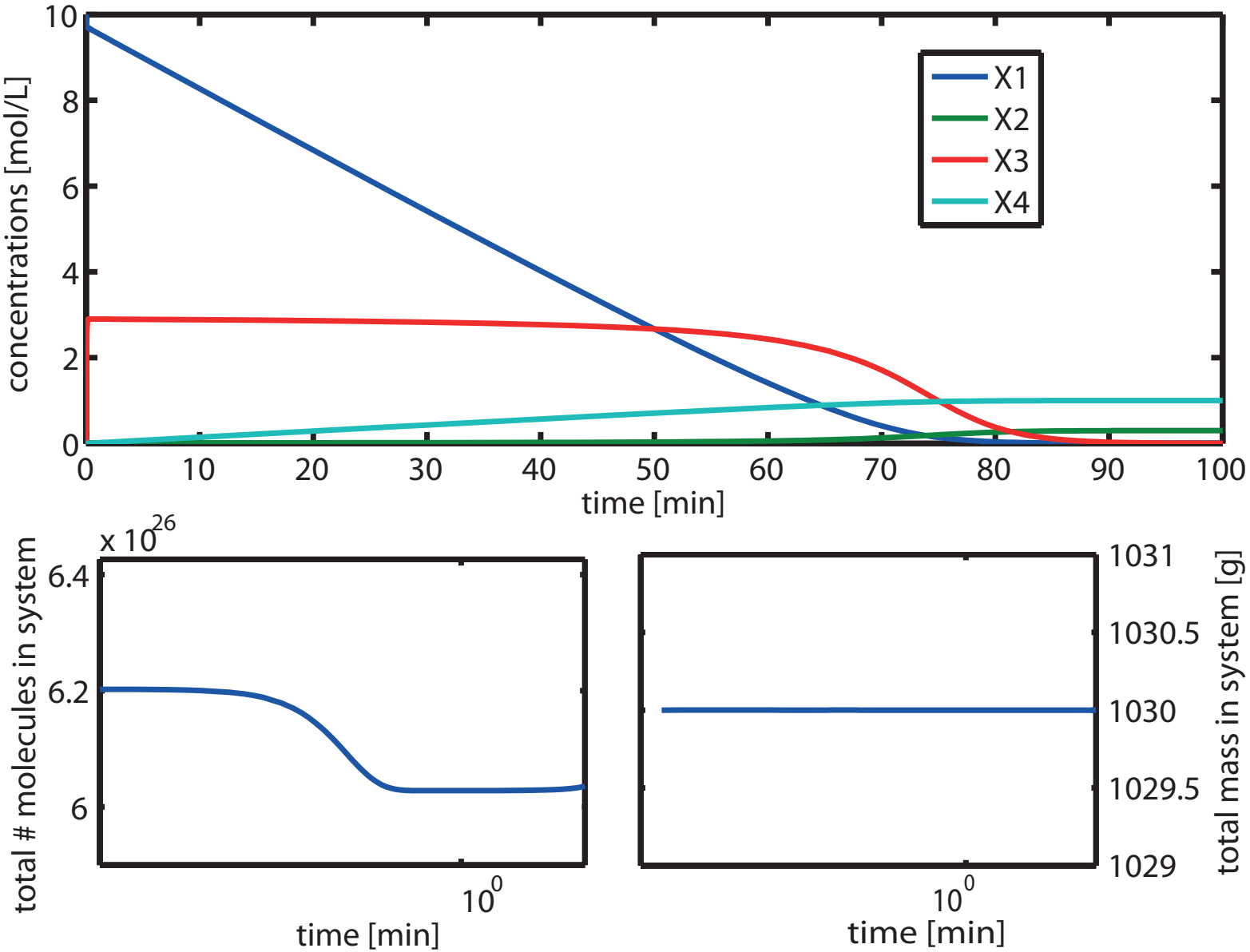
```
1  function dx = RHS(¬,x)
2
3  % import constants
4  global S k NrReactions
5  % import (time-dependent) reaction rates
6  r = ReactionFunctions(x,k,NrReactions);
7  % compute derivative unit: [mole/min]
8  dx = S*r;
9
10 %compute reaction rates
11 function r = ReactionFunctions(x,k,NrReactions)
12 r = zeros(NrReactions,1);
13 r(1) = x(1)*x(2)*k(1); % second order reaction
14 r(2) = x(3)*k(2);% first order reaction
15 r(3) = x(3)*k(3);% first order reaction
```

Example: Matlab: Simulate




```
1 %% Simulate
2 %settings of the ODE solver (mass balance ...
      equations, accuracy (relative, absolute))
3 options = ...
      odeset('Mass',diag(V),'RelTol',RTol,'AbsTol',ATol);
4 [t,x] = ode15s(@RHS,[0 Simtime],x0,options);
```

Example: Illustration

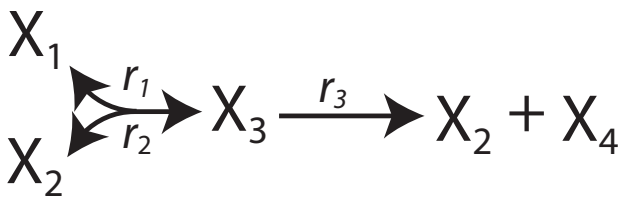


Exemplary files

to be found at:
`http://page.mi.fu-berlin.de/vkleist/`
$\rightarrow$ Teaching $\rightarrow$ "Modelling and Simulation in Systems Pharmacology" $\rightarrow$ "Codes".
Main Script:
BasicScript.m
RHS & dynamical update of reaction functions:
RHS.m
Utility:
PlotNicely.m

ODE Model $\Rightarrow$ Model Constituents

Decomposing a Model...



$$
\begin{aligned}
V_1 \frac{\mathrm{d}}{\mathrm{d}t} x_1 &= -k_1 \cdot x_1 \cdot x_2 + k_2 \cdot x_3 \\
V_2 \frac{\mathrm{d}}{\mathrm{d}t} x_2 &= -k_1 \cdot x_1 \cdot x_2 + k_2 \cdot x_3 \\
V_3 \frac{\mathrm{d}}{\mathrm{d}t} x_3 &= k_1 \cdot x_1 \cdot x_2 - k_2 \cdot x_3 - k_3 \cdot x_3 \\
V_4 \frac{\mathrm{d}}{\mathrm{d}t} x_4 &= k_3 \cdot x_3
\end{aligned}
$$

Decomposing a Model...

$$
\begin{aligned}
V_1 \frac{\mathrm{d}}{\mathrm{d}t} x_1 &= -k_1 \cdot x_1 \cdot x_2 \quad +k_2 \cdot x_3 \\
V_2 \frac{\mathrm{d}}{\mathrm{d}t} x_2 &= -k_1 \cdot x_1 \cdot x_2 \quad +k_2 \cdot x_3 \\
V_3 \frac{\mathrm{d}}{\mathrm{d}t} x_3 &= \quad k_1 \cdot x_1 \cdot x_2 \quad -k_2 \cdot x_3 - k_3 \cdot x_3 \\
V_4 \frac{\mathrm{d}}{\mathrm{d}t} x_4 &= \quad\quad k_3 \cdot x_3
\end{aligned}
$$

$$
\begin{aligned}
V_1 \frac{\mathrm{d}}{\mathrm{d}t} x_1 &= -r_1(x_1, x_2, k_1) + r_2(x_3, k_2) \\
V_2 \frac{\mathrm{d}}{\mathrm{d}t} x_2 &= -r_1(x_1, x_2, k_1) + r_2(x_3, k_2) \\
V_3 \frac{\mathrm{d}}{\mathrm{d}t} x_3 &= r_1(x_1, x_2, k_1) - r_2(x_3, k_2) - r_3(x_3, k_3) \\
V_4 \frac{\mathrm{d}}{\mathrm{d}t} x_4 &= r_3(x_3, k_3)
\end{aligned}
$$

with

$$
\begin{aligned}
r_1(x_1, x_2, k_1) &= k_1 \cdot x_1 \cdot x_2 \\
r_2(x_3, k_2) &= k_2 \cdot x_3 \\
r_3(x_3, k_3) &= k_3 \cdot x_3
\end{aligned}
$$

$$\boxed{\mathbf{V}\frac{\mathrm{d}}{\mathrm{d}t}\mathbf{x}(t) = S \cdot R_V(t, \mathbf{x}, k)}$$

with $R_V(t, \mathbf{x}, k) = \{r_1(t, \mathbf{x}, k)\}$.

$$\begin{aligned} r_1(x_1, x_2, k_1) &= k_1 \cdot x_1 \cdot x_2 \\ r_2(x_3, k_2) &= k_2 \cdot x_3 \\ r_3(x_3, k_3) &= k_3 \cdot x_3 \end{aligned}$$

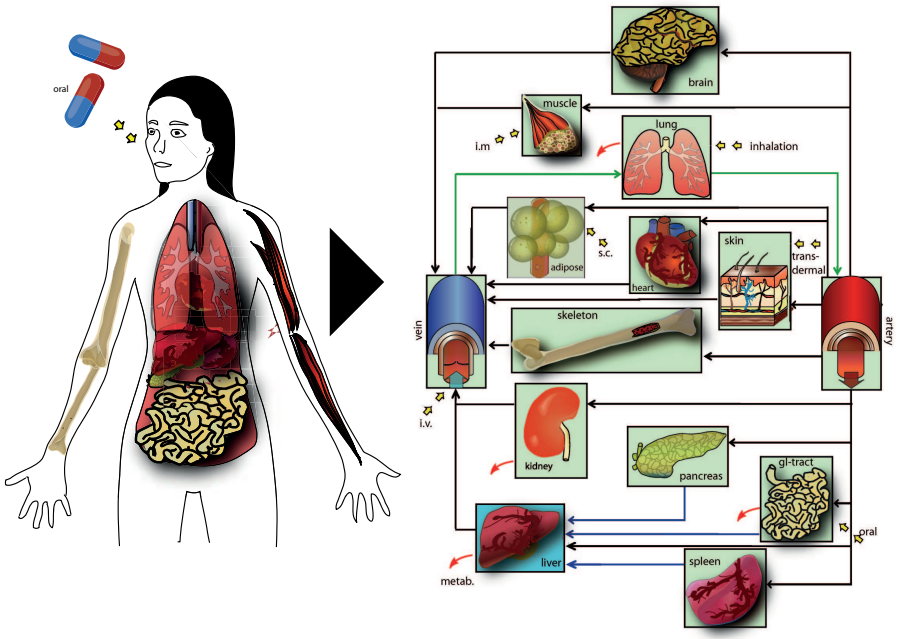
and ...

$$S = \begin{pmatrix} -1 & 1 & 0 \\ -1 & 1 & 0 \\ 1 & -1 & -1 \\ 0 & 0 & 1 \end{pmatrix} \tag{4}$$

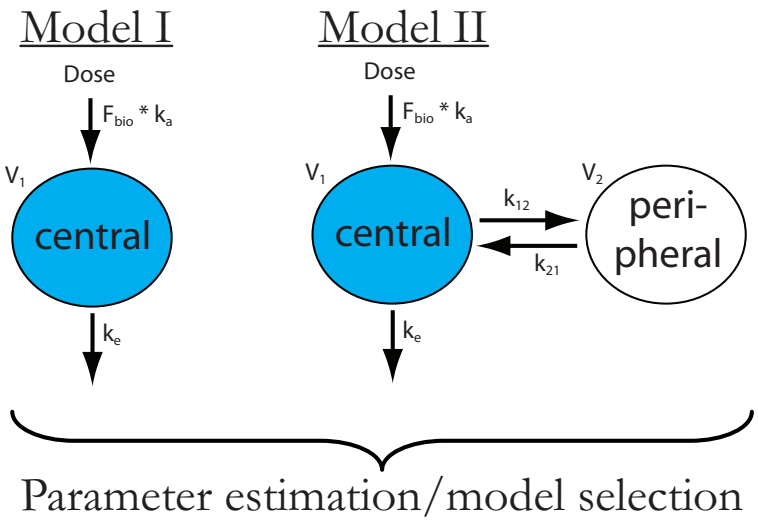
Pharmacokinetic Models

Modeling philosophies

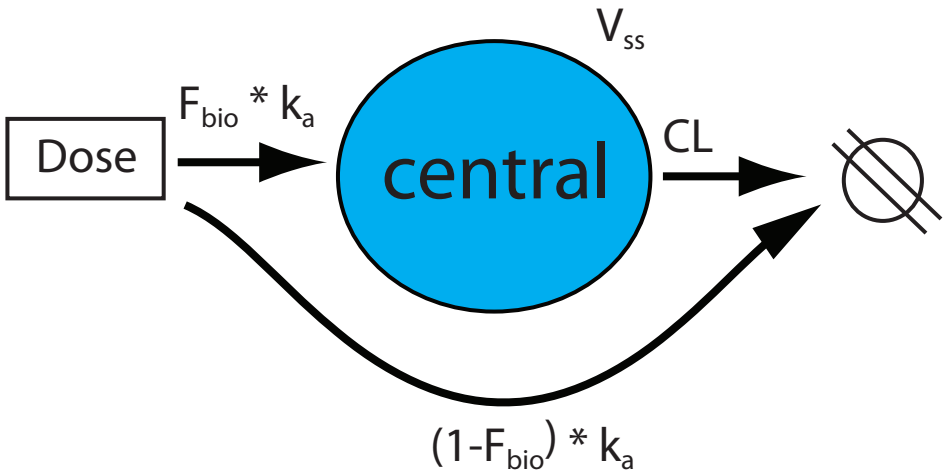
Mechanistic



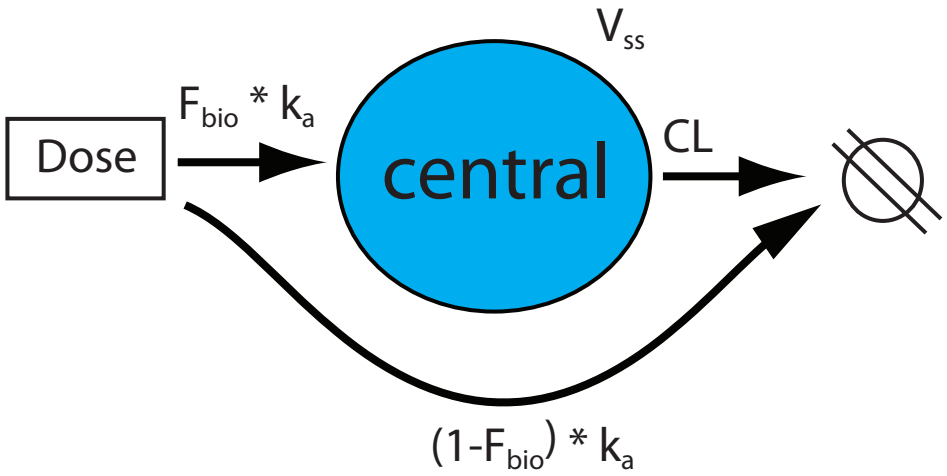
Descriptive



PK Example

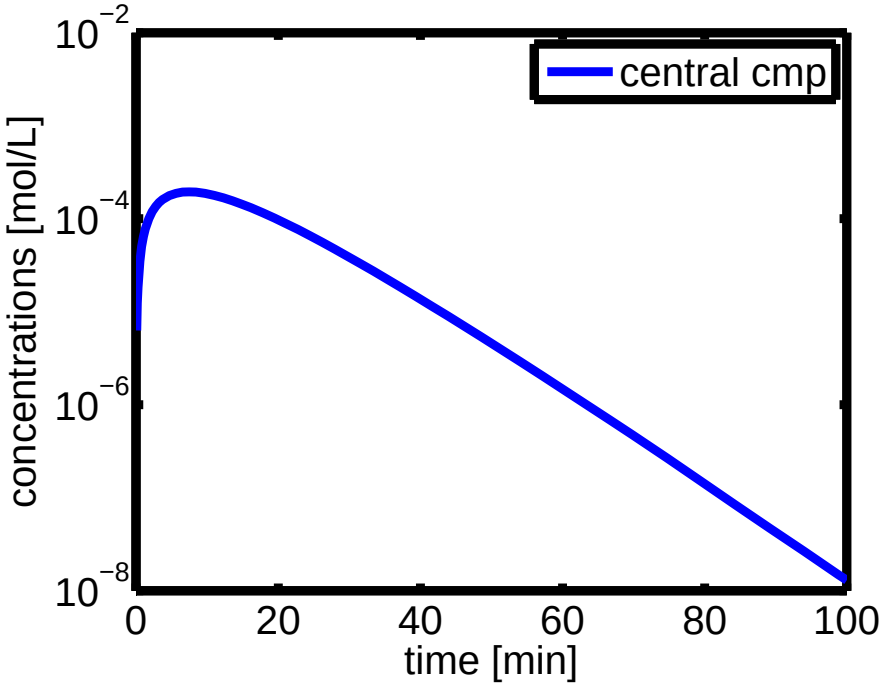


PK Example



$$
\begin{aligned}
r_1 &= F_{\text{bio}} \cdot k_a \cdot x_1 \\
r_2 &= (1 - F_{\text{bio}}) k_a \cdot x_1 \\
r_3 &= k_e \cdot x_2
\end{aligned}
$$

$$
S = \begin{pmatrix} -1 & -1 & 0 \\ 1 & 0 & -1 \\ 0 & 1 & 1 \end{pmatrix} \quad , \quad \mathbf{v} = \begin{pmatrix} 1 \\ V_{ss} \\ 1 \end{pmatrix}
$$



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Main Script:

BasicScriptPK.m

RHS & dynamical update of reaction functions:

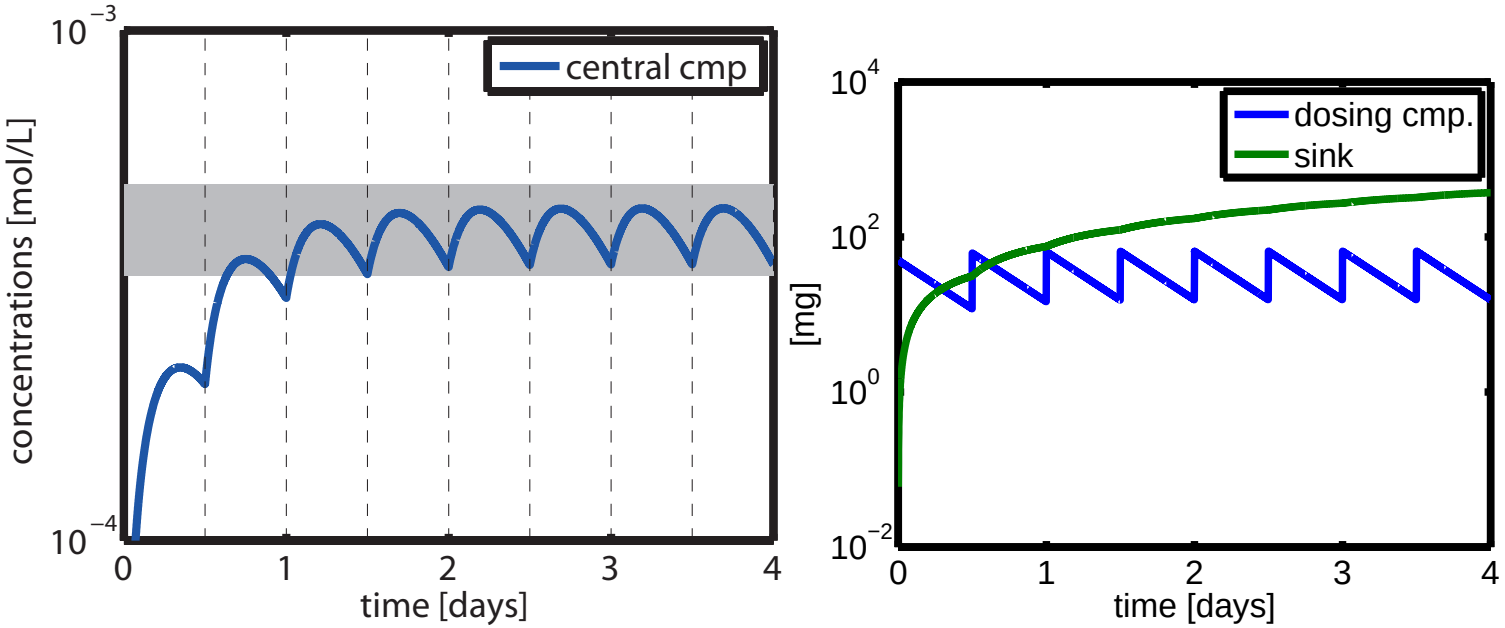
Multiple Dosing

```
1 OutInt = 1;%output interval; written every ... min
2 tOutput = 0:OutInt:Simtime;%time points
3 %initialize Trajectory
4 xOutput = zeros(length(tOutput),NrSpecies);
5 DosingInterval = 12*60; %every ... minutes
6
7 actualtime = 0;%actual runtimne
8 Dose = 1;%Dosing event number ...
9 RunIdxStart = 1;%running start index for storage
```

Multiple Dosing

```
while actualtime < Simtime %break condition
    %output time points of interest
    tspan = actualtime:OutInt:Dose*DosingInterval;
    %running end index for storage
    RunIdxEnd = RunIdxStart + length(tspan) - 1;
    %simulation over one dosing interval
    [t,x] = ode15s(@RHSPK,tspan,x0,options);
    %store trajectory
    xOutput(RunIdxStart:RunIdxEnd,:) = x;
    %update running index for storage
    RunIdxStart = RunIdxEnd;
    %re-initialize
    x0 = x(end,:)'; %update intial condition
    x0(1) = x0(1) + dose;%add dose
    Dose = Dose +1;
    actualtime = t(end); %update 'intial' time
end
```

Multiple Dosing



to be found at:

`http://page.mi.fu-berlin.de/vkleist/`

$\rightarrow$ Teaching $\rightarrow$ "Modelling and Simulation in Systems Pharmacology" $\rightarrow$ "Codes"

Main Script:

BasicScriptPKMultiDosing.m

Organization of this seminar

every thursday 12:00-14:00 (2x45min)

"Topics and schedule"

date	topic		date	topic	
17.04.	~~Overview~~	~~M.v.K.~~	12.06.	proj. feedback	stud. + superv.
24.04.	**Modelling & PK**	M.v.K.	19.06.	proj. feedback	stud. + superv.
08.05.	Parameter Estimation	M.v.K.	**26.06.**	Drug Absorption PBPK	Marco Johanna
15.05.	proj. feedback	stud. + superv.	**03.07.**	Part. coeff. Parameter estimation	Benjamin ?
25.05.	proj. feedback	stud. + superv.	**10.07.**	Dis. Modelling I Dis. Modelling II	? ?
05.06.	proj. feedback	stud. + superv.	**17.07.**	ODE vs. stoch. sim.	Ivo