Computer Aided Modeling in Pharmacokinetics

Dr. Michael Wulkow, Dr. Regina Telgmann, CiT GmbH

© 2017 CIT GmbH, Rastede

Graphics on pages 5,6,8 by Prof. Dr. Wilhelm Huisinga, Uni Potsdam, Dr. Max v. Kleist, FU Berlin
PBPK modeling: supporting the stages of development

- Early drug discovery
  - prioritize drug candidates
  - indicate critical pharmacokinetic properties
- Preclinical drug design
  - analyse in vivo data from animal studies
  - predict the PK in other species and in man
  - support dose finding for first-time-in-man studies
- Clinical phases
  - use modeling to understand and interpret clinical data
  - extrapolate to different scenarios like dosing schemes
- Seems to be difficult for several reasons
Remarks
- In technical chemistry (TC) some models “live” (from simple ideas to full process models) for more than 10 years and across research areas
  - “CFD-people” use kinetics developed by other teams
  - “Kinetic people” add complex thermodynamics
- In TC many problems are induced by very complex mathematics
- In PBPK we also have to solve a major software design problem

Aims of this project:
- Provide a software environment make possible an ongoing modeling process
- Find a reasonable mix of fixed model approach and purely equation-based solutions
PBPK – the whole body model

- Compartment model
- Compartments represent anatomical volumes (organs, tissues)
- Compartments may be divided into sub-compartments (“phases”: blood cells, interstitial, etc.)
- Compartments are connected in an anatomically meaningful way
- Very often, only two (or a few) compartments are used, but here we have to aim at a general solution
  - It is easy to **reduce** a general model to a few compartments
  - The other way round is much more difficult and destroys structure and insights
A multi-compartment PK-structure

- Open list of organ types
- Body template defining the connection/interaction of organs
In organs we consider two or four sub-compartments (BC, Plasma, Interstitial, Cell/Tissue).

There are several basic processes ("phenomena") in each sub-compartment:
- Distribution
- Protein binding
- Metabolism
- Dosing
Physiological processes in PK-model

- Distribution (equations for one substance in one organ)

\[ V^e \frac{d}{dt} C^e = Q(C_{in}^e - C^e) - D^{e,p}(C_u^e - C_u^p) \]

\[ V^p \frac{d}{dt} C^p = Q(C_{in}^p - C^p) + D^{e,p}(C_u^e - C_u^p) - D^{p,i}(C_u^p - C_u^i) \]

\[ V^i \frac{d}{dt} C^i = D^{p,i}(C_u^p - C_u^i) - D^{i,c}(C_u^i - C_u^c) \]

\[ V^c \frac{d}{dt} C^c = D^{i,c}(C_u^i - C_u^c) \]
Physiological processes in PK-model

- Protein binding
  - Early model
    \[ C_u = f_u^{pr} \cdot C \]
  - Refined model: consider the process of protein binding (complex formation) between the neutral compound C and the protein PR given by
    \[ C + PR \xrightleftharpoons[k_d]{k_a} C : PR \]
- Generalization
  \[ C + PR_1 \xrightleftharpoons[k_{d1}]{k_{a1}} C : PR_1 \]
  \[ C + PR_2 \xrightleftharpoons[k_{d2}]{k_{a2}} C : PR_2 \]

*Processes collected by M. v. Kleist and W. Huisinga

Figure 5: Tissue decomposition and additional processes underlying the a priori partition coefficient models for moderate to strong bases by Rodgers et al. (left), and for neutrals and acids by Rodgers and Rowland (right). For details, see the text.
Physiological processes in PK-model

- Metabolism (here: in liver)

\[
V_{\text{liv}} \frac{d}{dt} C_{\text{liv}}^c = D_{\text{liv}}^{i.e} \left( C_{\text{u,liv}}^i - C_{\text{u,liv}}^c \right) - V_{\text{meta}}
\]

\[
V_{\text{meta}} = - \left( \frac{V_{\text{max}}}{K_m / f_u + C} \right) \cdot C
\]

\[
V_{\text{meta}} = - \left( \frac{V_{\text{max}}}{K_m} \right) \cdot C_u = -CL_{\text{int}} \cdot C_u
\]

\[
V_{\text{meta}} = -CL_{\text{int}} \cdot \left( 1 - \frac{C_u}{K_m + C_u} \right) \cdot C_u
\]

- More complex, but very important: drug-drug-interaction

\[
V_{\text{liv}} \frac{d}{dt} C_{1,\text{liv}}^c = D_{1,\text{liv}}^{i.e} \left( C_{1,\text{u,liv}}^i - C_{1,\text{u,liv}}^c \right) - V_{\text{meta}}
\]

\[
V_{\text{liv}} \frac{d}{dt} C_{2,\text{liv}}^c = D_{2,\text{liv}}^{i.e} \left( C_{2,\text{u,liv}}^i - C_{2,\text{u,liv}}^c \right) - V_{\text{meta}}
\]

\[
V_{\text{meta}} = -K \cdot C_{1,u} \cdot C_{2,u}
\]
Model equations – balances for compounds

- Equations for
  - each compound
  - in each organ
  - in sub compartments
  - additional equations for enzymes or proteins
  - addition of system biology models (SBML) in single (or all!) compartments

- Parameter often are **sets** of values (e.g. organ-dependent)

- Typical models easily add up to more than 100 equations with many terms and parameters

- It is error-prone to set up *one* system, but it is much more challenging to change and administrate model variations, incorporation of new ideas, etc.

- **Remark:** at a first glance PBPK models looks like bio-kinetics in a cascade with multiple-phase reactors, but the structure of parameters and the requirements are quite different!
Special difficulty – structure of model parameters

- There are some general parameters
- Many parameter may depend on
  - compound
  - individual
  - organ
  - compound + individual
  - organ + individual
  - compound + organ
  - compound + individual + organ
Typical modeling scenarios

- Basis: Compartment model with organ topology and transfer, binding and metabolism processes
- Run model
  - for different individuals
  - for different compounds (also mixed in one model)
  - with different parameter sets
  - with variations of process (e.g. simple, complex, old and new binding kinetics)
  - with different dosing strategies
  - with additional local systems biology
- Typical question: What happens, if we exchange the binding model in cell by a new promising approach from literature
  - We have to exchange all terms related to the new binding model, possibly in certain compartments only
  - We have to add and correctly assign all related parameters
- This requires a modular problem setup and a mainly automatic equation generation
- Otherwise new ideas are often suppressed ...
Modular structure of MEDICI-PK

**Model definition**

- Organs (o) + Phases
- Topology templates
- Physiological process library
  - type (binding, metabolisms, etc.)
  - description, formulas
  - general parameter dependencies (o,c,i)
- Full body model:
  - topology
  - selected processes

**Parameter definition**

- Compounds (c):
  - definitions
  - parameters (o)
- Individuals (i):
  - definitions
  - parameters (o)
- Mix parameters (c+i)

**Simulation scenario**

- full body model
- individual
- compounds
- dosing strategies

**Simulation results**
Model set-up: compounds, individuals and model database
# Model set-up: compounds, individuals and model database

## Available Models

<table>
<thead>
<tr>
<th>No.</th>
<th>m...</th>
<th>Name</th>
<th>Type</th>
<th>Unit type</th>
<th>Unit</th>
<th>No used compound</th>
<th>System biology</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>c</td>
<td>Poulin-Theil refined (non-adipose)</td>
<td>Binding model</td>
<td>mole flow</td>
<td>micro...</td>
<td>1-compound model</td>
<td>Comp1_bound, logPow, fVnl, fVph, fVw, f...</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>[+]</td>
<td>Poulin-Theil (non-adipose)</td>
<td>Binding model</td>
<td>mole flow</td>
<td>micro...</td>
<td>1-compound model</td>
<td>Comp1_bound, logPow, fVnl, fVph, fVw, f...</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(e)</td>
<td>linear binding + ionization</td>
<td>Binding model</td>
<td>mole flow</td>
<td>micro...</td>
<td>1-compound model</td>
<td>Comp1_bound, Hct, B:P, fast_rate, V, fuP,</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(e)</td>
<td>linear binding</td>
<td>Binding model</td>
<td>mole flow</td>
<td>micro...</td>
<td>1-compound model</td>
<td>Comp1_bound, Hct, B:P, fast_rate, V, fuP,</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>[+]</td>
<td>Poulin-Theil (adipose)</td>
<td>Binding model</td>
<td>mole flow</td>
<td>micro...</td>
<td>1-compound model</td>
<td>Comp1_bound, fVnl, fVph, fVw, fVnP, fVp,</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(p)</td>
<td>binding to albumin</td>
<td>Binding model</td>
<td>mole flow</td>
<td>micro...</td>
<td>1-compound model</td>
<td>Comp1_bound, fast_rate, V, noBindingSit,</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>(c)</td>
<td>Poulin-Theil refined (non-adipose)</td>
<td>Binding model</td>
<td>mole flow</td>
<td>micro...</td>
<td>1-compound model</td>
<td>Comp1_bound, fast_rate, V, Kd_albumin,</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>(c)</td>
<td>experimental values + ionization</td>
<td>Binding model</td>
<td>mole flow</td>
<td>micro...</td>
<td>1-compound model</td>
<td>Comp1_bound, fast_rate, V, Kd_albumin,</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>(c)</td>
<td>experimental values</td>
<td>Binding model</td>
<td>mole flow</td>
<td>micro...</td>
<td>1-compound model</td>
<td>Comp1_bound, fast_rate, V, Kd_albumin,</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>(i)</td>
<td>binding to albumin</td>
<td>Binding model</td>
<td>mole flow</td>
<td>micro...</td>
<td>1-compound model</td>
<td>Comp1_bound, fast_rate, V, Kd_albumin,</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>(p)</td>
<td>linear binding</td>
<td>Binding model</td>
<td>mole flow</td>
<td>micro...</td>
<td>1-compound model</td>
<td>Comp1_bound, fast_rate, V, fuP,</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>no binding</td>
<td>Binding model</td>
<td>mass flow</td>
<td>mg/min</td>
<td>1-compound model</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>oral inverse gaussian distr.</td>
<td>Dosing model</td>
<td>mass flow</td>
<td>mg/min</td>
<td>1-compound model</td>
<td>-</td>
<td>MAT, tbio, CV2,</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>bolus i.v. 3 sec</td>
<td>Dosing model</td>
<td>mass flow</td>
<td>mg/min</td>
<td>1-compound model</td>
<td>-</td>
<td>dose (per weight), body w...</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>Insulin-Glucose (Maki Keizer)</td>
<td>Metabolism</td>
<td>mole flow</td>
<td>micro...</td>
<td>1-compound model</td>
<td>G_i, G_c, l_i, J. Vmax1, K1, Vmax2, K2, K...</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>no metabolism</td>
<td>Metabolism</td>
<td>mass flow</td>
<td>mg/min</td>
<td>1-compound model</td>
<td>-</td>
<td>V, K1, Vmax1, K2, K...</td>
</tr>
</tbody>
</table>
Model set-up: organ topology and full body template
Model set-up: simulation scenario

- Requirement by cooperation partner: make all used equations and parameters transparent
Simulation based on selected parameter set
How can proper software and administration help?

- Store parameters separately, assigned to equations by some “intelligent” device
- Model your system in terms of phenomena rather than in terms of equations
- Start simple, but not too simple:
  - In compartment models try to separate the “residence time behaviour” from the “kinetics” → better 10 compartments with identical models but realistic volumes and streams than only 1 or 2 compartments mixing all effects
- If you work with an equation-based solver
  - consolidate your project regularly
  - separate dosing and initial values
  - use subroutines for sub-models
- Think of future usage of your model
- Believe in rough parameter estimates as a source for identifying sensitivities
- Use sensitivity analysis, e.g. the simple sigma-point method