Computer Aided Modeling in Pharmacokinetics

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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

PBPK modeling: supporting the stages of development

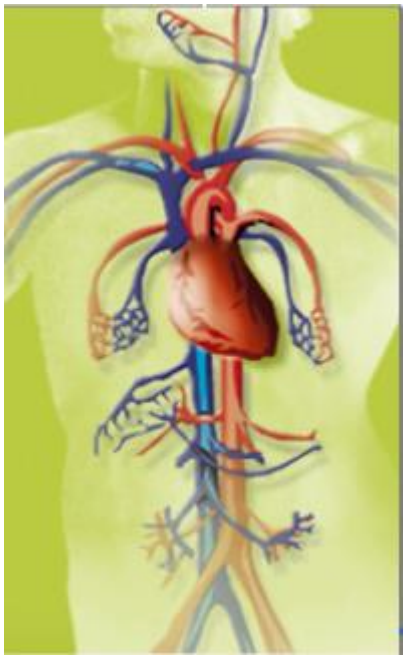
- Remarks
  - In technical chemistry (TC) some models “live” (from simple ideas to full process models) for more than 10 years and across research areas
    - “CFD-people” use kinetics developed by other teams
    - “Kinetic people” add complex thermodynamics
  - In TC many problems are induced by very 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

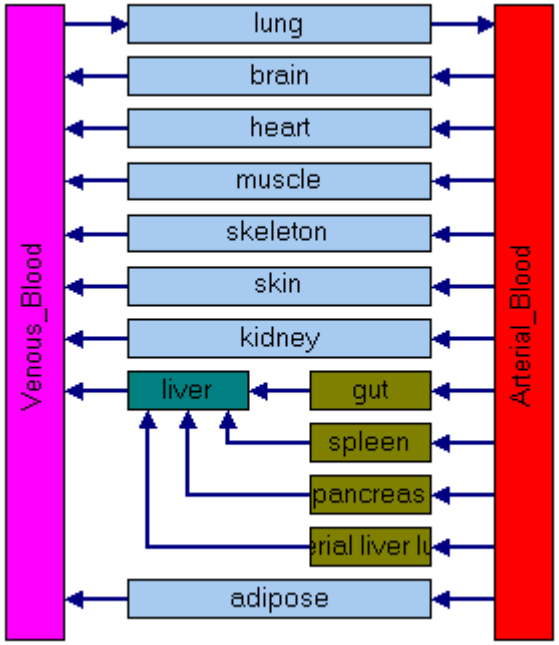
PBPK – the whole body model

- 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

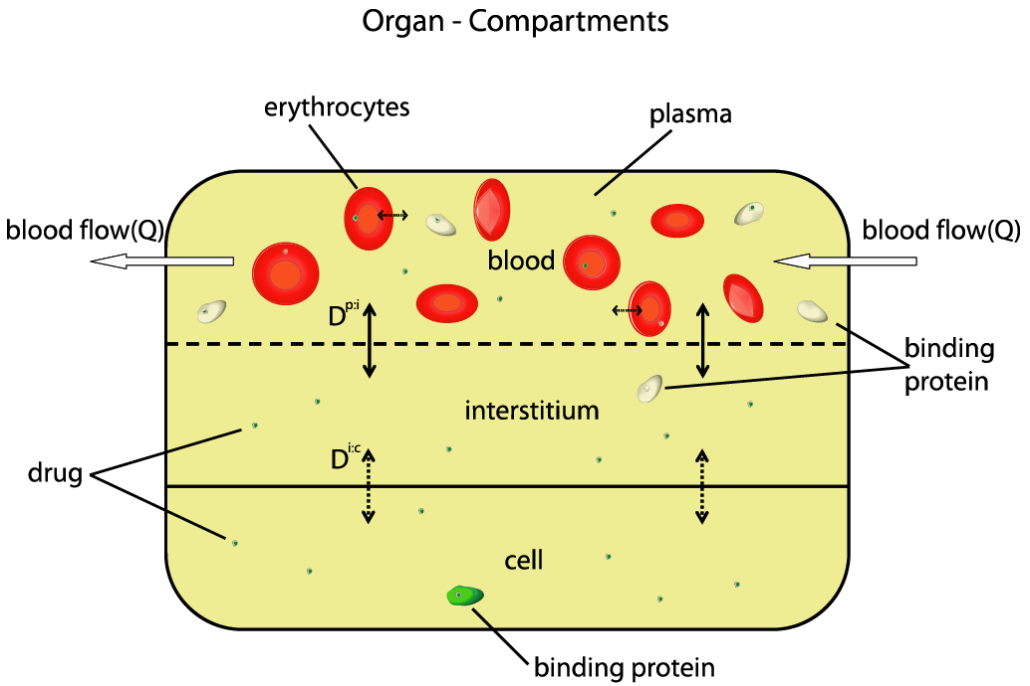
- **Open** list of organ **types**
- Body **template** defining the connection/interaction of organs





Organs and sub-compartments

- 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

$$C + PR \underset{k_d}{\overset{k_a}{\rightleftarrows}} C:PR$$

  - Generalization

$$C + PR_1 \underset{k_{d1}}{\overset{k_{a1}}{\rightleftarrows}} C:PR_1$$

$$C + PR_2 \underset{k_{d2}}{\overset{k_{a2}}{\rightleftarrows}} C:PR_2$$

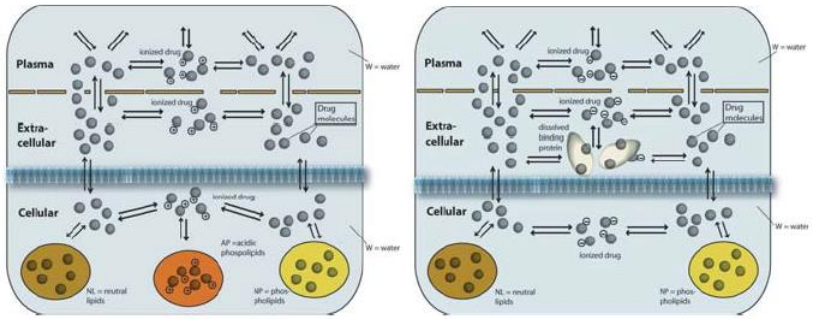


Figure 5: Tissue decomposition and additional processes underlying the *a priori* partition coefficient models for moderate to strong bases by Rodgers et al. (left), and for neutrals and acids by Rodgers and Rowland (right). For details, see the text.

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

Physiological processes in PK-model

- Metabolism (here: in liver)

$$V_{liv}^{c}\frac{d}{dt}C_{liv}^{c} = D_{liv}^{i:e}(C_{u.liv}^{i} - C_{u.liv}^{c}) - v_{meta}$$

$$v_{meta} = -\left(\frac{V_{\max}}{(K_m / f_u) + C}\right)\cdot C$$

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

$$v_{meta} = -CL_{\text{int}}\cdot\left(1 - \frac{C_u}{K_m + C_u}\right)\cdot C_u$$

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

$$V_{liv}^{c}\frac{d}{dt}C_{1,liv}^{c} = D_{1,liv}^{i:e}(C_{1,u.liv}^{i} - C_{1,u.liv}^{c}) - v_{meta}$$

$$V_{liv}^{c}\frac{d}{dt}C_{2,liv}^{c} = D_{2,liv}^{i:e}(C_{2,u.liv}^{i} - C_{2,u.liv}^{c}) - v_{meta}$$

$$v_{meta} = -K\cdot C_{1,u}\cdot C_{2,u}$$

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!

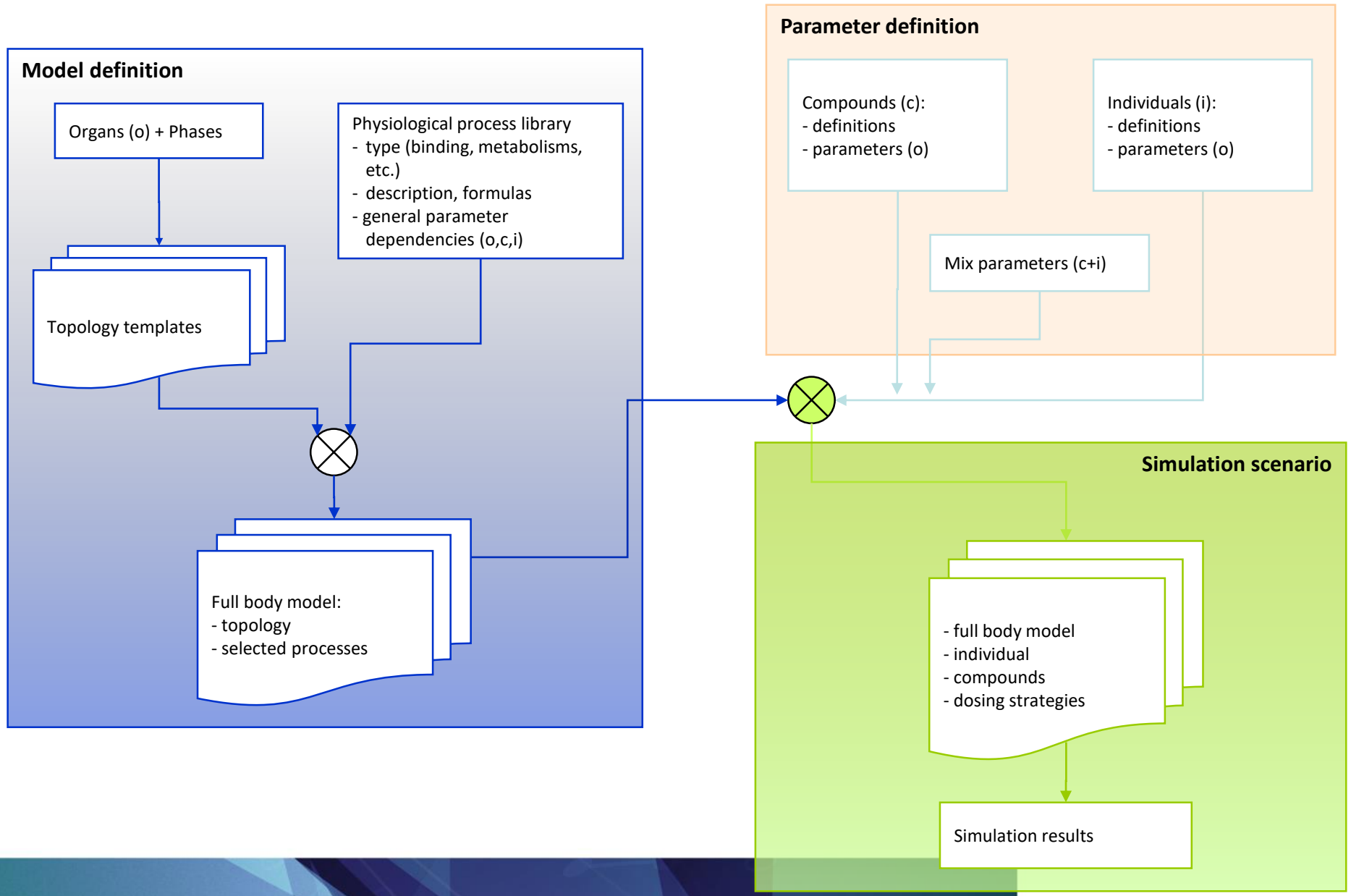
Special difficulty – structure of model parameters

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

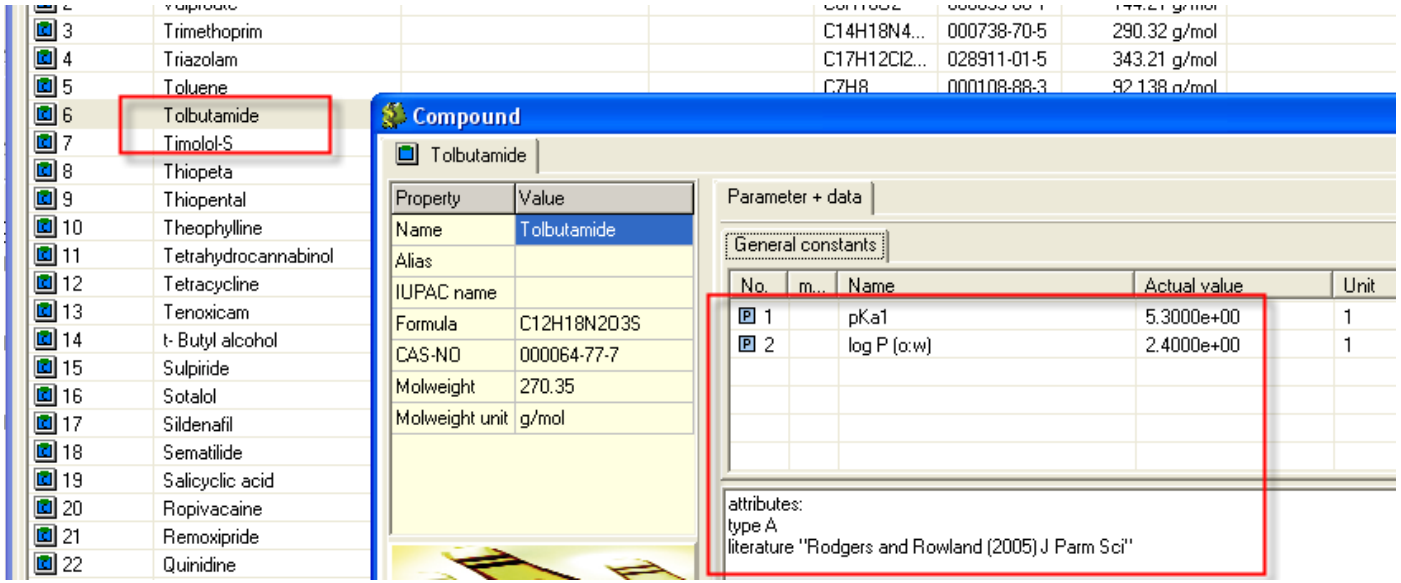
Typical modeling scenarios

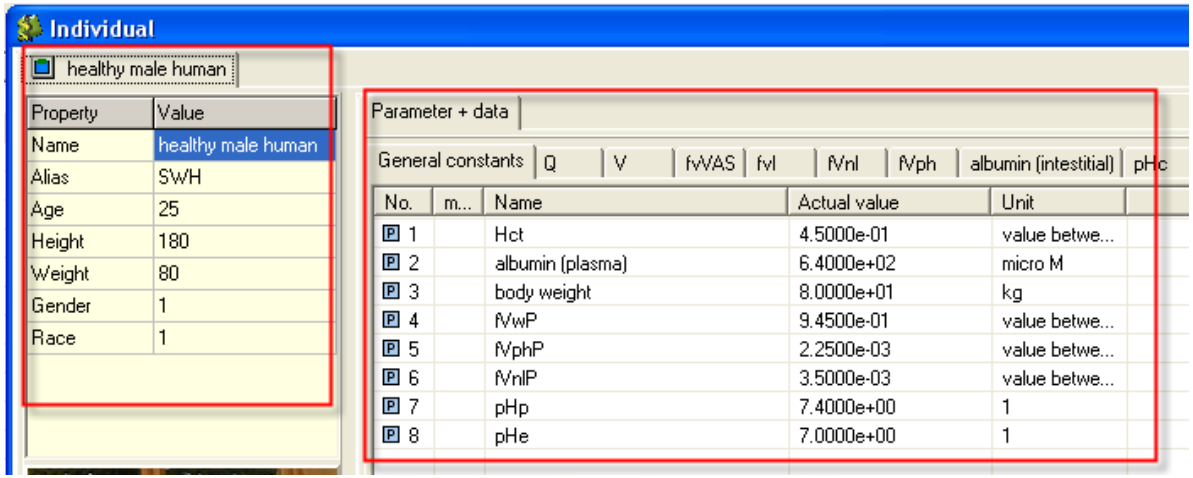
- Basis: Compartment model with organ topology and transfer, binding and metabolism processes
- Run model
  - for different individuals
  - for different compounds (also mixed in one model)
  - with different parameter sets
  - with variations of process (e.g. simple, complex, old and new binding kinetics)
  - 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 set-up: compounds, individuals and model database





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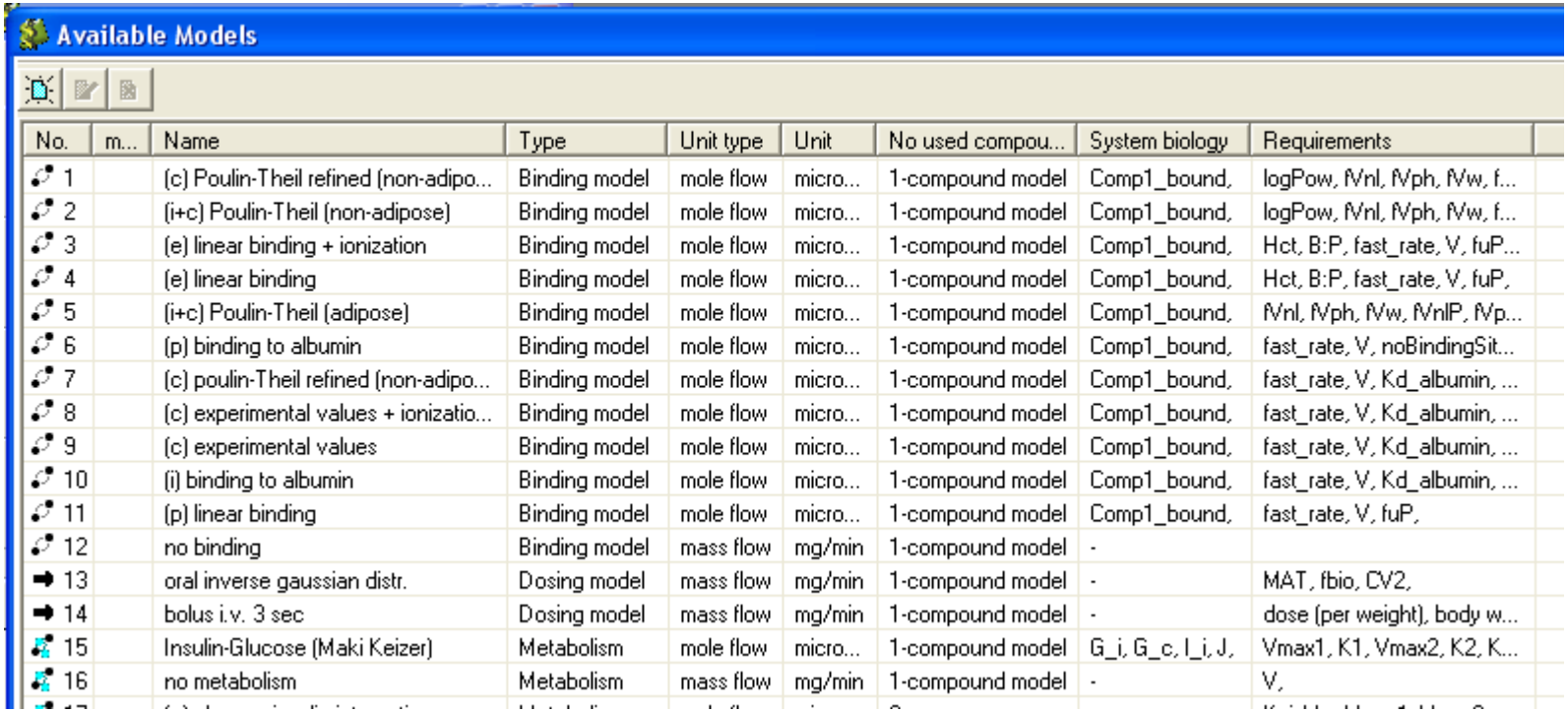
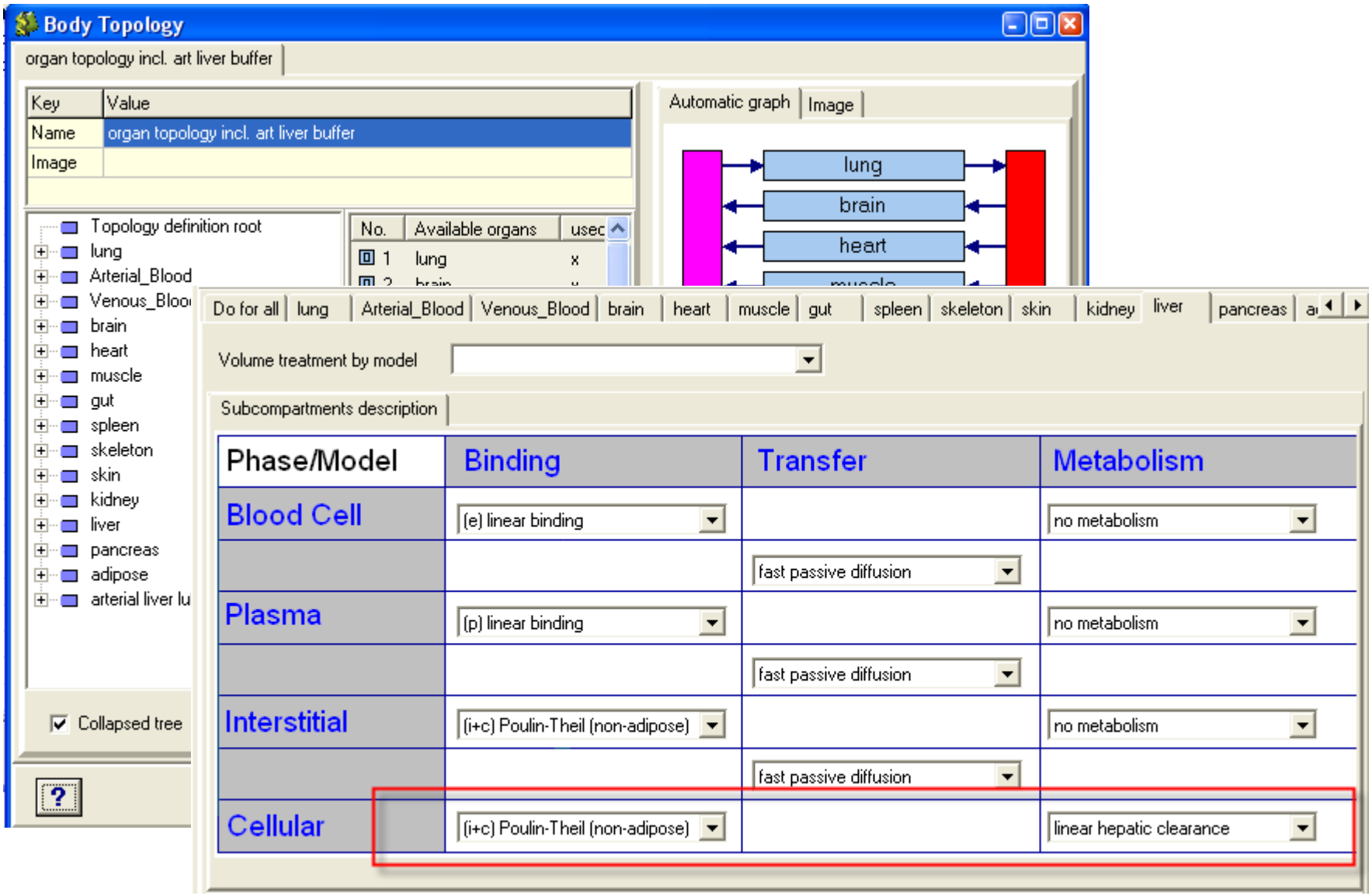


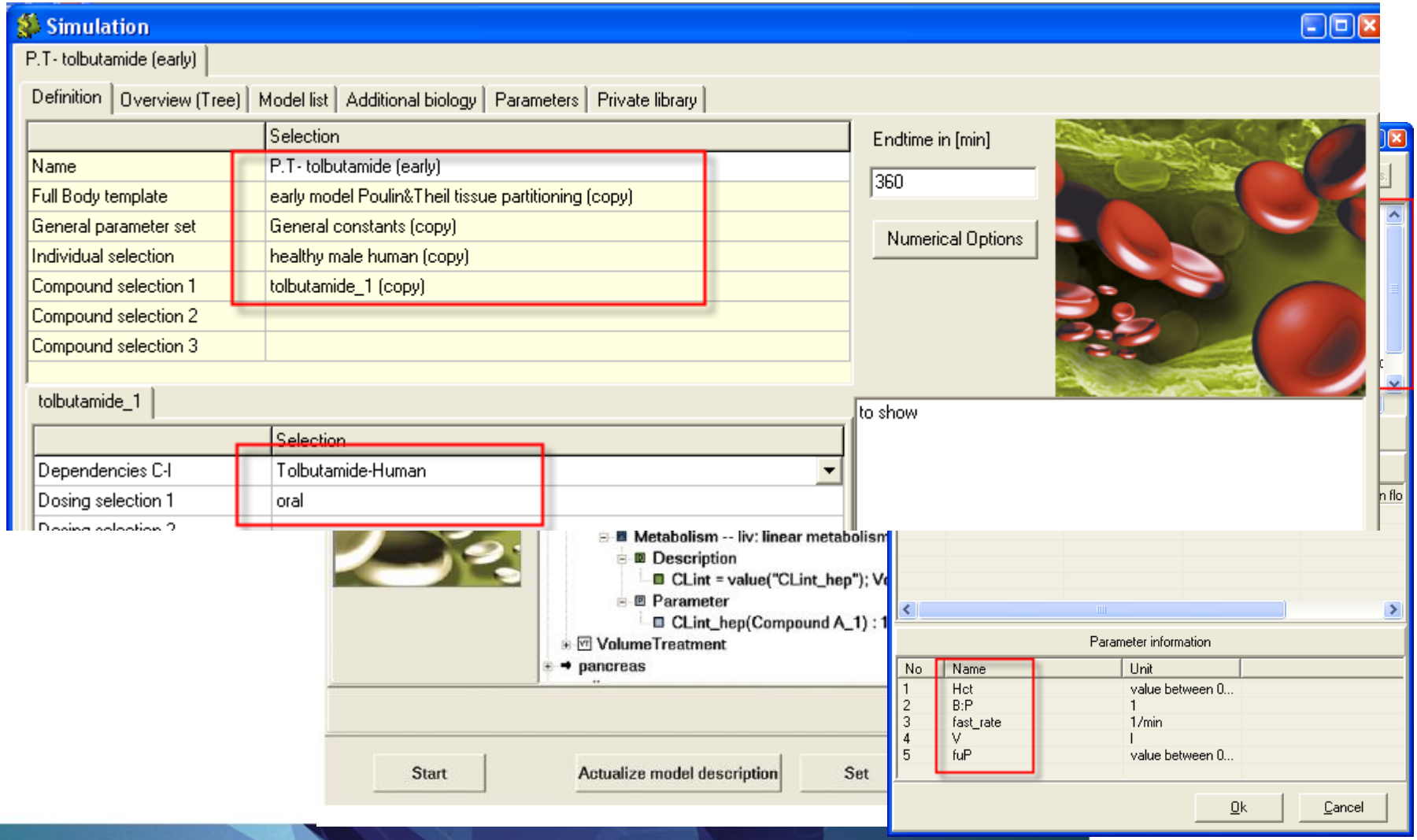
No.	m...	Name	Type	Unit type	Unit	No used compou...	System biology	Requirements
1		(c) Poulin-Theil refined (non-adipo...	Binding model	mole flow	micro...	1-compound model	Comp1_bound,	logPow, fVnl, fVph, fVw, f...
2		(i+c) Poulin-Theil (non-adipose)	Binding model	mole flow	micro...	1-compound model	Comp1_bound,	logPow, fVnl, fVph, fVw, f...
3		(e) linear binding + ionization	Binding model	mole flow	micro...	1-compound model	Comp1_bound,	Hct, B:P, fast_rate, V, fuP...
4		(e) linear binding	Binding model	mole flow	micro...	1-compound model	Comp1_bound,	Hct, B:P, fast_rate, V, fuP,
5		(i+c) Poulin-Theil (adipose)	Binding model	mole flow	micro...	1-compound model	Comp1_bound,	fVnl, fVph, fVw, fVnlP, fVp...
6		(p) binding to albumin	Binding model	mole flow	micro...	1-compound model	Comp1_bound,	fast_rate, V, noBindingSit...
7		(c) poulin-Theil refined (non-adipo...	Binding model	mole flow	micro...	1-compound model	Comp1_bound,	fast_rate, V, Kd_albumin, ...
8		(c) experimental values + ionizatio...	Binding model	mole flow	micro...	1-compound model	Comp1_bound,	fast_rate, V, Kd_albumin, ...
9		(c) experimental values	Binding model	mole flow	micro...	1-compound model	Comp1_bound,	fast_rate, V, Kd_albumin, ...
10		(i) binding to albumin	Binding model	mole flow	micro...	1-compound model	Comp1_bound,	fast_rate, V, Kd_albumin, ...
11		(p) linear binding	Binding model	mole flow	micro...	1-compound model	Comp1_bound,	fast_rate, V, fuP,
12		no binding	Binding model	mass flow	mg/min	1-compound model	-	
13		oral inverse gaussian distr.	Dosing model	mass flow	mg/min	1-compound model	-	MAT, fbio, CV2,
14		bolus i.v. 3 sec	Dosing model	mass flow	mg/min	1-compound model	-	dose (per weight), body w...
15		Insulin-Glucose (Maki Keizer)	Metabolism	mole flow	micro...	1-compound model	G_i, G_c, I_i, J,	Vmax1, K1, Vmax2, K2, K...
16		no metabolism	Metabolism	mass flow	mg/min	1-compound model	-	V,

Model set-up: organ topology and full body template

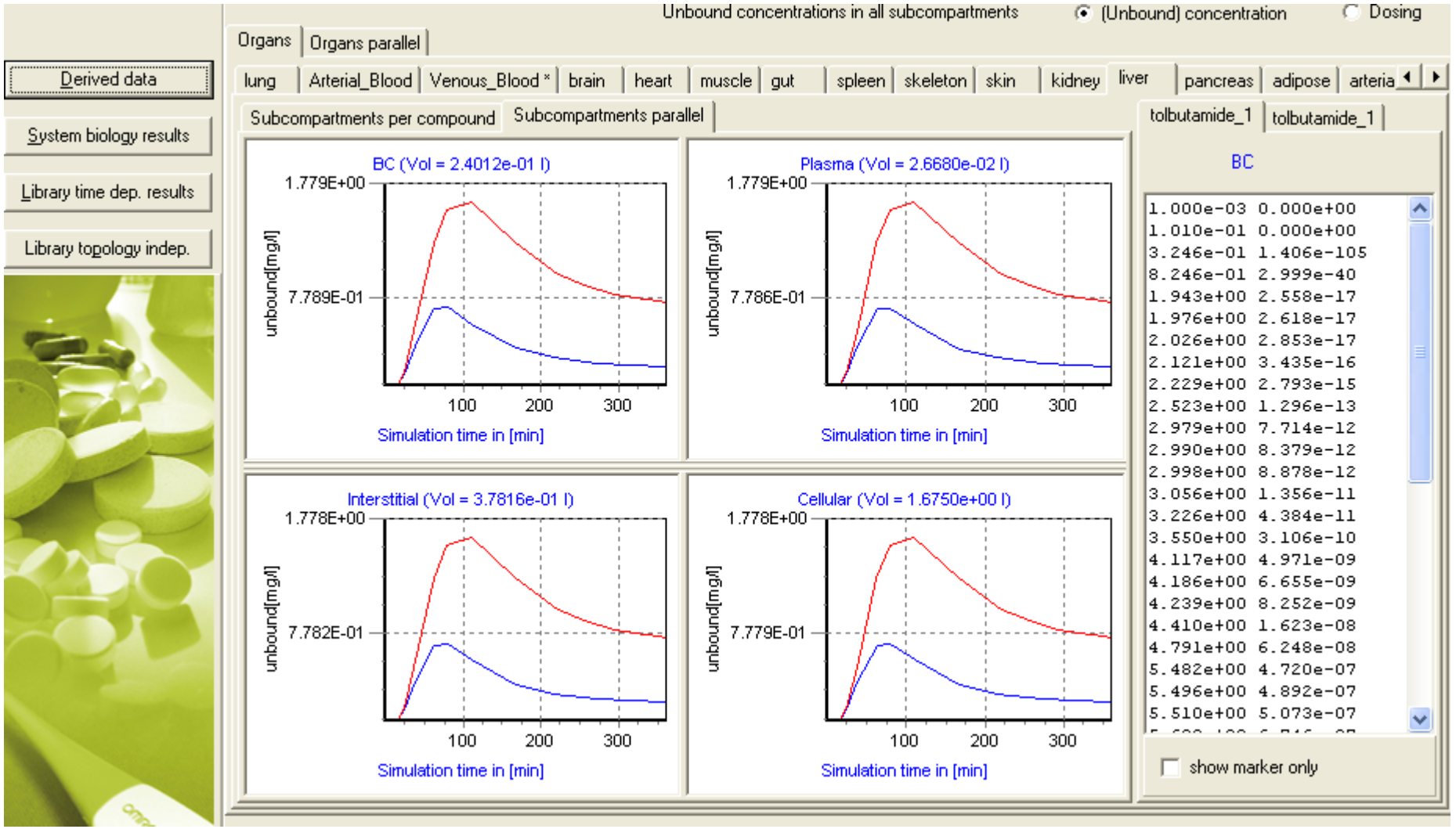


Model set-up: simulation scenario

- 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