

CIT

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Computer Aided Modeling in Pharmacokinetics

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Graphics on pages 5,6,8 by Prof. Dr. Wilhelm Huisinga, Uni Potsdam, Dr. Max v. Kleist, FU Berlin

- ▶ 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

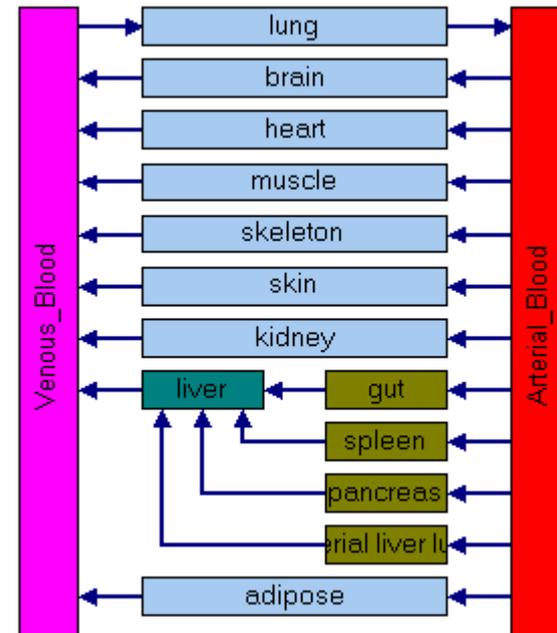
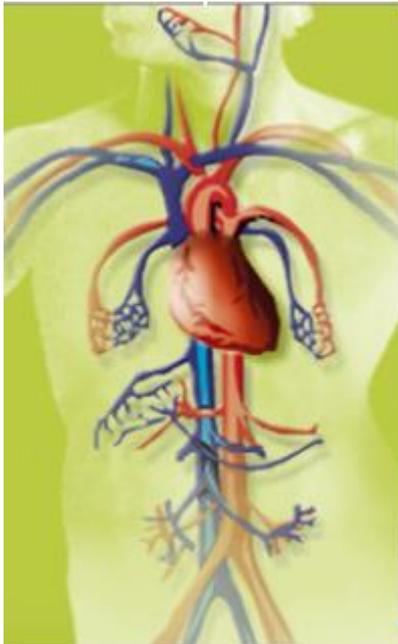
- ▶ **Remarks**
 - ▶ In technical chemistry (TC) some models “live” (from simple ideas to full process models) for more than 10 years and across research areas
 - ▶ “CFD-people” use kinetics developed by other teams
 - ▶ “Kinetic people” add complex thermodynamics
 - ▶ In TC many problems are induced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

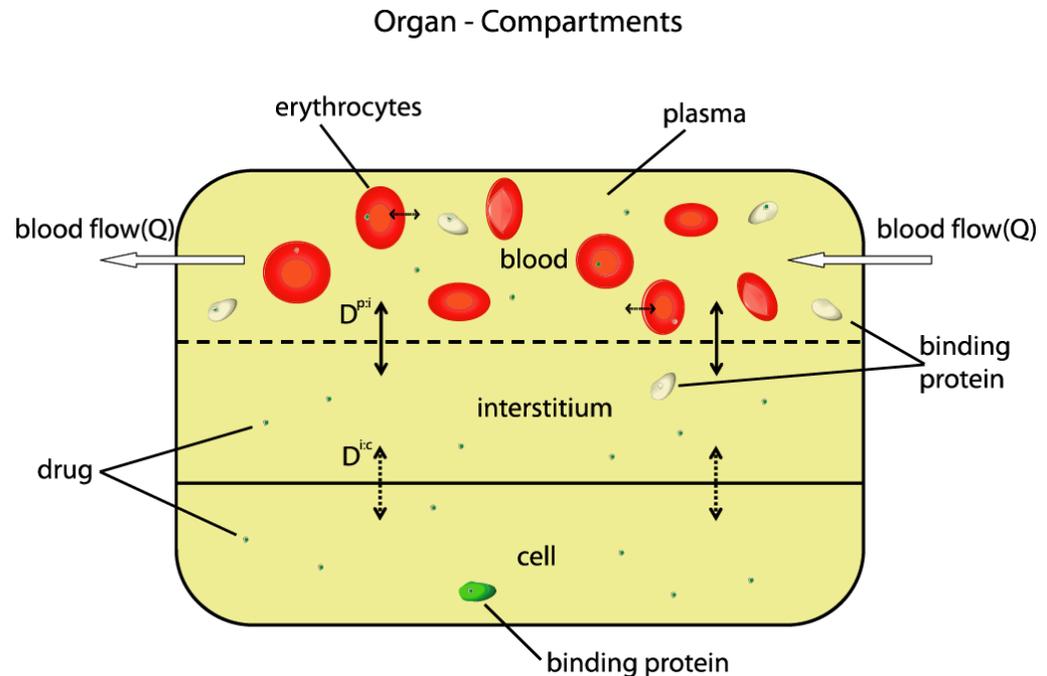
A multi-compartment PK-structure

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



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



- Distribution (equations for one substance in one organ)

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

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

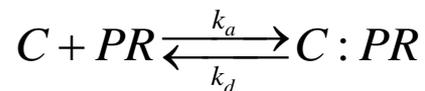
$$V^i \frac{d}{dt} C^i = D^{p:i} (C_u^p - C_u^i) - D^{i:c} (C_u^i - C_u^c)$$

$$V^c \frac{d}{dt} C^c = D^{i:c} (C_u^i - C_u^c)$$

- ▶ 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



- ▶ Generalization

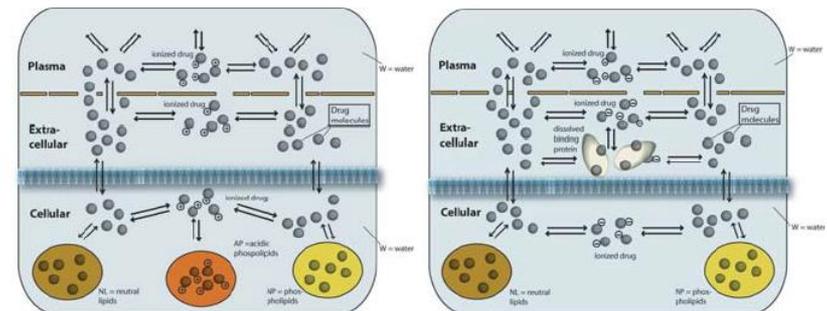
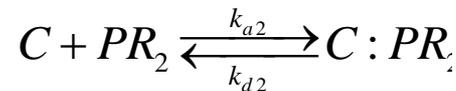
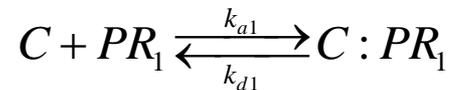


Figure 5: Tissue decomposition and additional processes underlying the *a priori* partition coefficient models for moderate to strong bases by Rodgers et al. (left), and for neutrals and acids by Rodgers and Rowland (right). For details, see the text.

- ▶ Metabolism (here: in liver)

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

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

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

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

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

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

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

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

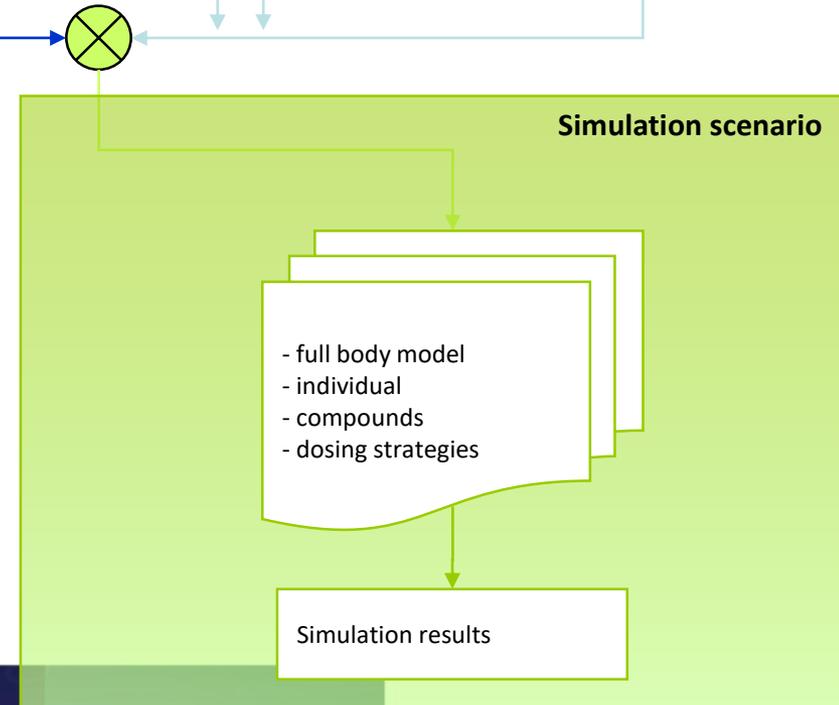
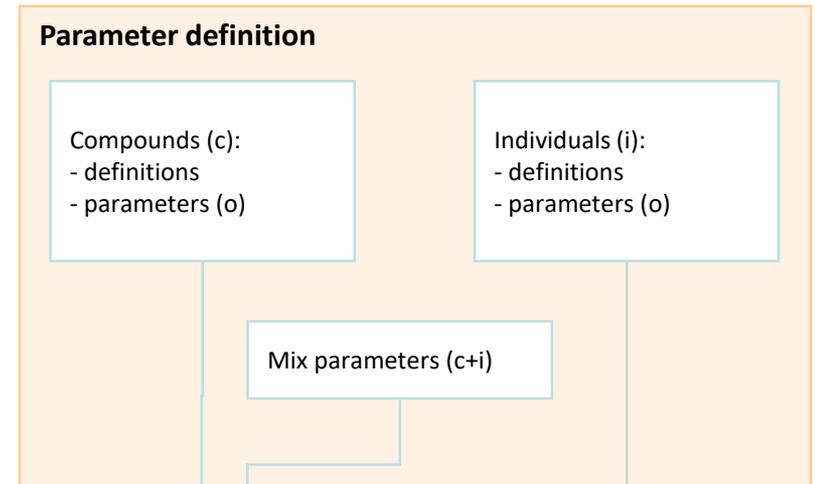
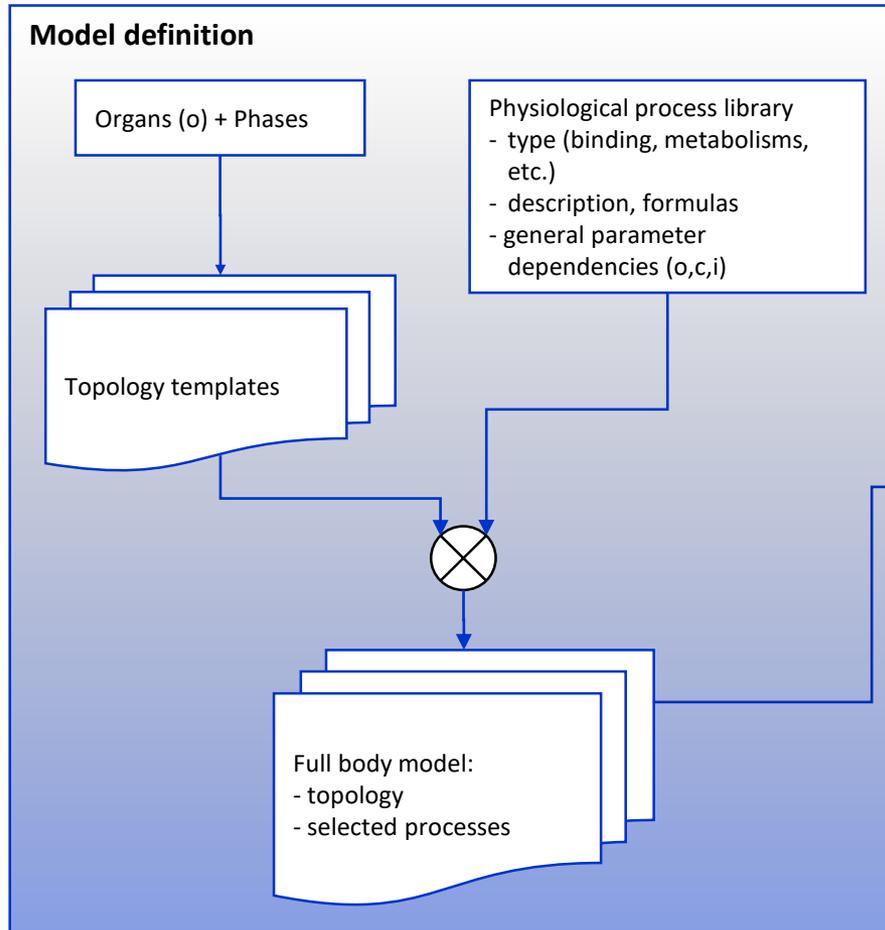
- ▼ Equations for
 - ▶ each compound
 - ▶ in each organ
 - ▶ in sub compartments
 - ▶ additional equations for enzymes or proteins
 - ▶ addition of system biology models (SBML) in single (or all!) compartments
- ▶ Parameter often are **sets** of values (e.g. organ-dependent)
- ▶ Typical models easily 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

- ▶ 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

3	Trimethoprim	C14H18N4...	000738-70-5	290.32 g/mol
4	Triazolam	C17H12Cl2...	028911-01-5	343.21 g/mol
5	Toluene	C7H8	000108-88-3	92.138 g/mol
6	Tolbutamide			
7	Timolol-S			
8	Thiopeta			
9	Thiopental			
10	Theophylline			
11	Tetrahydrocannabinol			
12	Tetracycline			
13	Tenoxicam			
14	t-Butyl alcohol			
15	Sulpiride			
16	Sotalol			
17	Sildenafil			
18	Sematilide			
19	Salicylic acid			
20	Ropivacaine			
21	Remoxipride			
22	Quinidine			

Compound

Tolbutamide

Property	Value
Name	Tolbutamide
Alias	
IUPAC name	
Formula	C12H18N2O3S
CAS-NO	000064-77-7
Molweight	270.35
Molweight unit	g/mol

Parameter + data

General constants

No.	m...	Name	Actual value	Unit
1		pKa1	5.3000e+00	1
2		log P (o:w)	2.4000e+00	1

attributes:
type A
literature "Rodgers and Rowland (2005) J Pharm Sci"

Individual

healthy male human

Property	Value
Name	healthy male human
Alias	SWH
Age	25
Height	180
Weight	80
Gender	1
Race	1

Parameter + data

General constants

No.	m...	Name	Actual value	Unit
1		Hct	4.5000e-01	value betwe...
2		albumin (plasma)	6.4000e+02	micro M
3		body weight	8.0000e+01	kg
4		fWp	9.4500e-01	value betwe...
5		fVpH	2.2500e-03	value betwe...
6		fVnIP	3.5000e-03	value betwe...
7		pHp	7.4000e+00	1
8		pHe	7.0000e+00	1

Model set-up: compounds, individuals and model database

Available Models								
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, fVnIP, 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

Body Topology organ topology incl. art liver buffer

Key	Value
Name	organ topology incl. art liver buffer
Image	

Automatic graph | Image

Do for all | lung | Arterial_Blood | Venous_Blood | brain | heart | muscle | gut | spleen | skeleton | skin | kidney | liver | pancreas | ar

Volume treatment by model

Subcompartments description

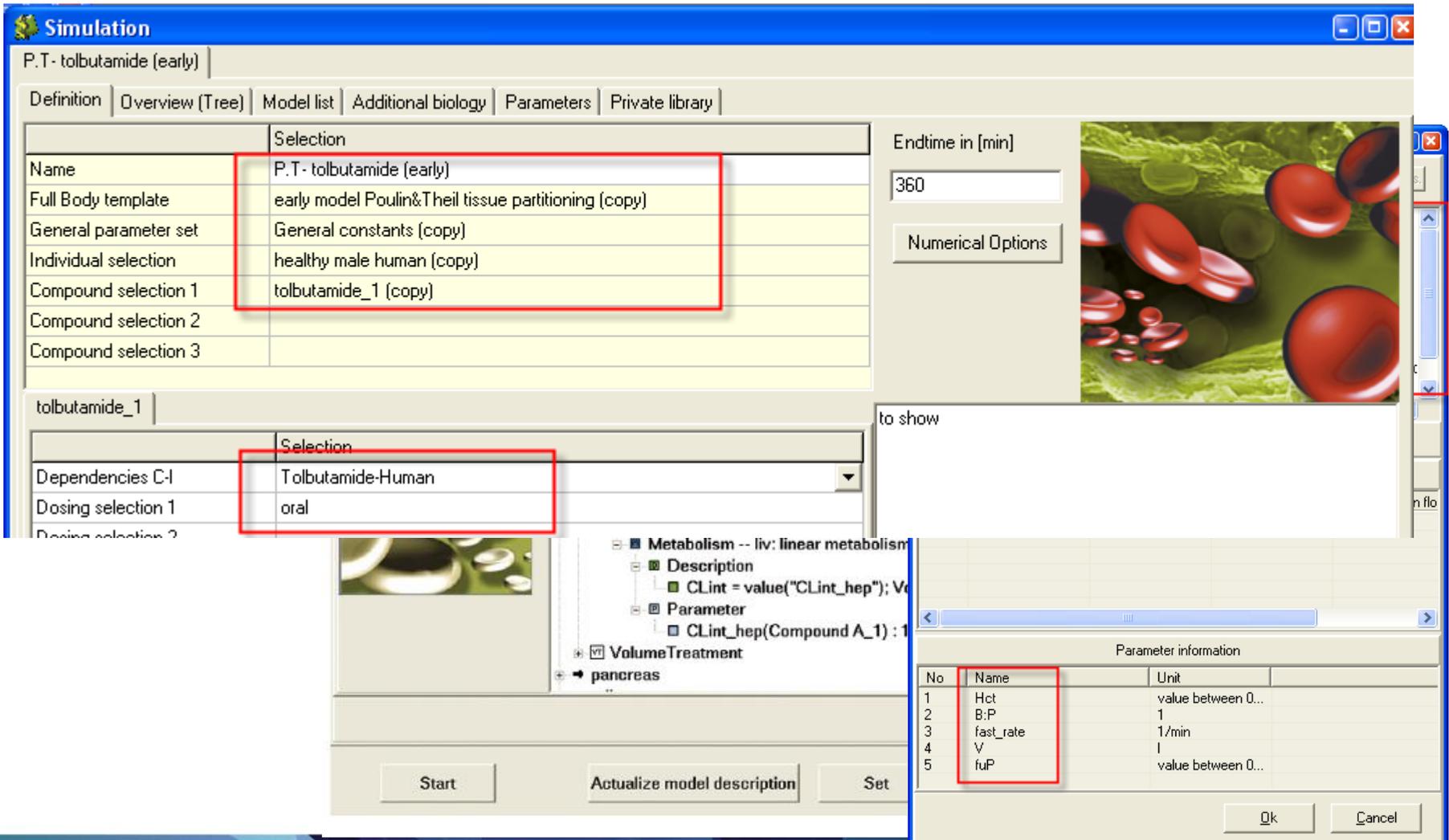
Phase/Model	Binding	Transfer	Metabolism
Blood Cell	(e) linear binding		no metabolism
		fast passive diffusion	
Plasma	(p) linear binding		no metabolism
		fast passive diffusion	
Interstitial	(i+c) Poulin-Theil (non-adipose)		no metabolism
		fast passive diffusion	
Cellular	(i+c) Poulin-Theil (non-adipose)		linear hepatic clearance

Collapsed tree

?

Model set-up: simulation scenario

- ▶ Requirement by cooperation partner: make all used equations and parameters transparent



Simulation
P.T. - tolbutamide (early)

Definition | Overview (Tree) | Model list | Additional biology | Parameters | Private library

	Selection
Name	P.T. - tolbutamide (early)
Full Body template	early model Poulin&Theil tissue partitioning (copy)
General parameter set	General constants (copy)
Individual selection	healthy male human (copy)
Compound selection 1	tolbutamide_1 (copy)
Compound selection 2	
Compound selection 3	

Endtime in [min]
360
Numerical Options

tolbutamide_1

	Selection
Dependencies C-1	Tolbutamide-Human
Dosing selection 1	oral
Dosing selection 2	

to show

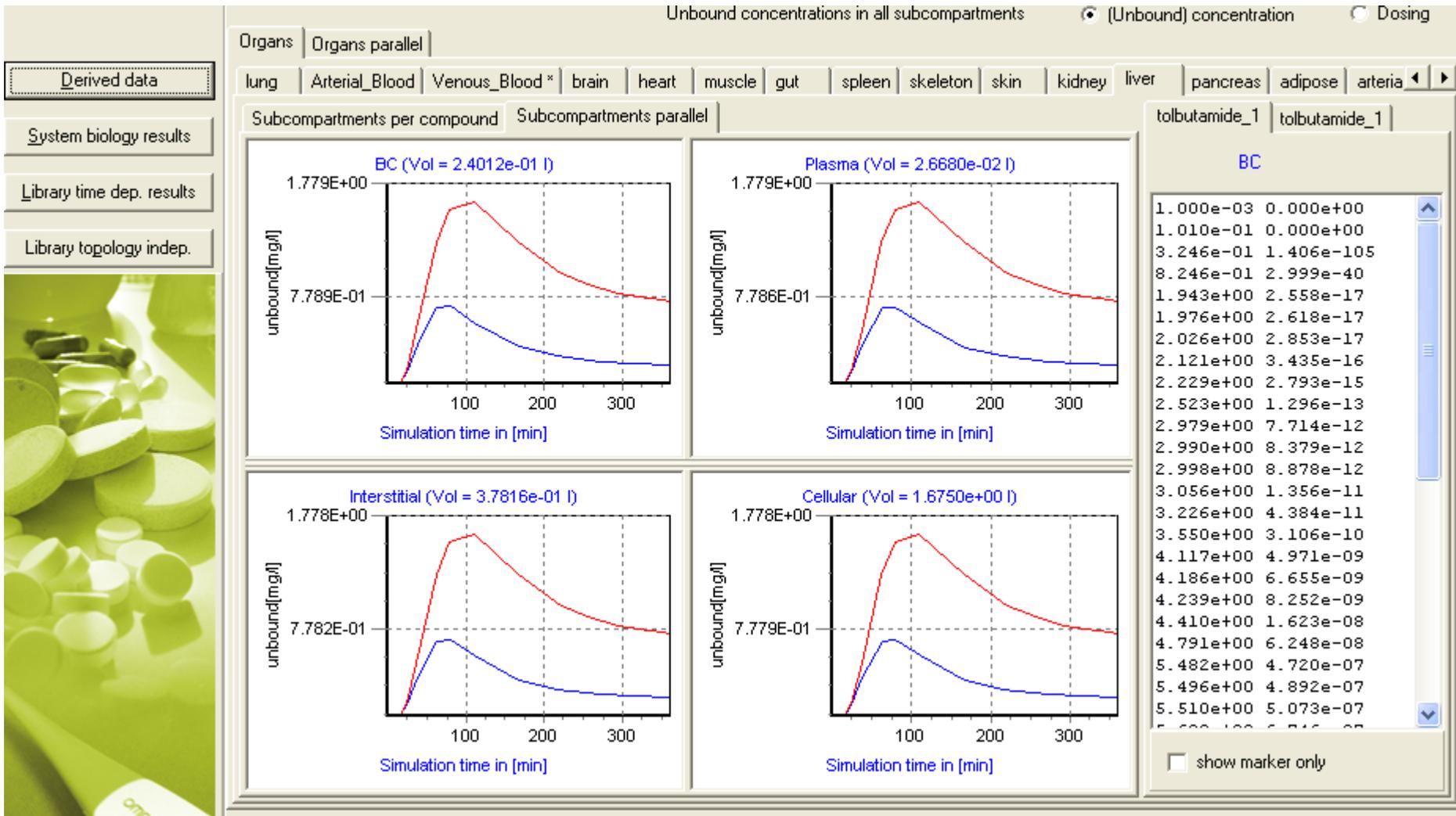
- Metabolism -- liv: linear metabolism
 - Description
 - CLint = value("CLint_hep"); V
 - Parameter
 - CLint_hep(Compound A_1) : 1
- Volume Treatment
 - pancreas

Parameter information

No	Name	Unit
1	Hct	value between 0...
2	B:P	1
3	fast_rate	1/min
4	V	l
5	fuP	value between 0...

Start Actualize model description Set

Simulation based on selected parameter set



- ▶ 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

