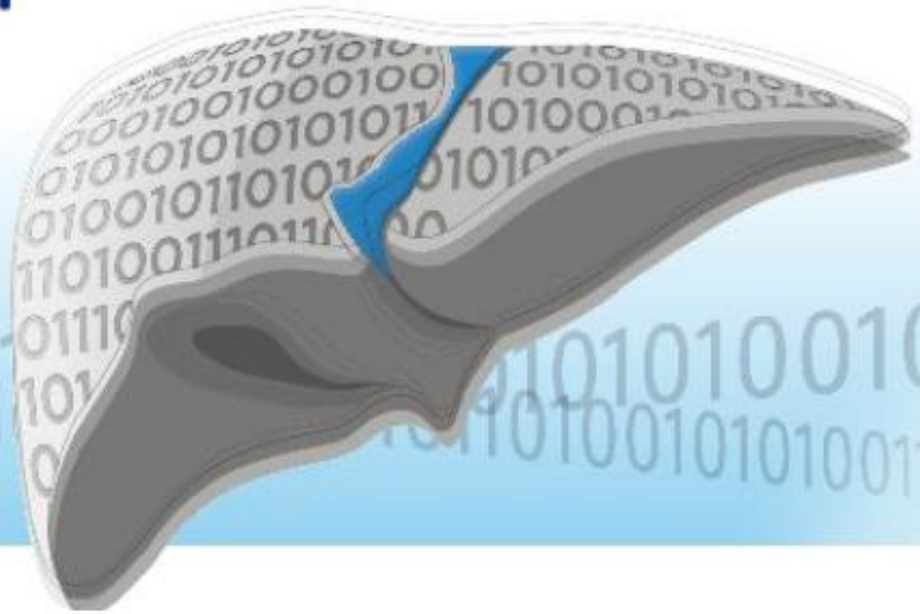
virtual liver network



The Virtual Liver: a Multiscale Systems Biology Platform to Study Liver Function, Dysfunction & Injury

Adriano Henney, Programme Director
Lars Kuepfer, Bayer Technology Services GmbH

GEFÖRDERT VOM
Bundesministerium für Bildung und Forschung

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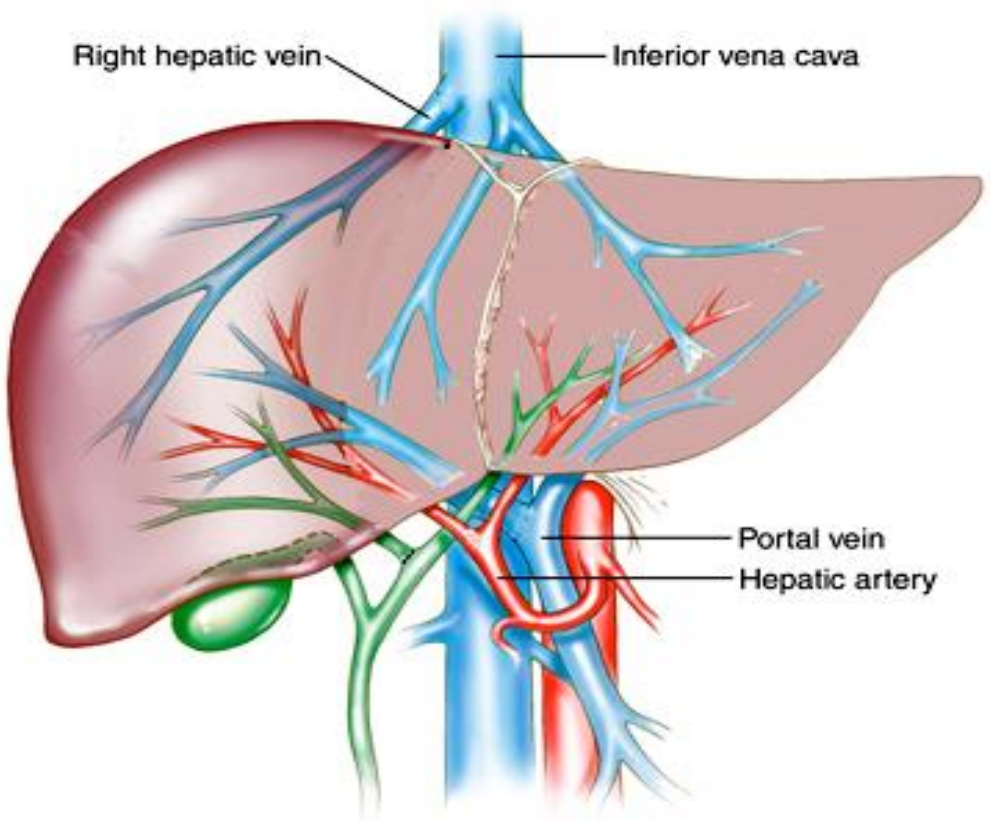
Why Focus on the Liver?

- Major organ of homeostasis
  - Innate immunity
  - Acute phase response mediators
- Critical role in detoxification
- Dysfunction -> significant burden on health care budgets
- Dysfunction associated with modern lifestyle
- Toxicity: major hurdle to delivering novel medicines
- Access to data at all level of organisation



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Objectives

- Move from the study at the cellular level to consider the whole organ
  - Building on successes of HepatoSys and learning from the Virtual Heart
- Deliver a true multi-scale representation of liver physiology
  - Modular, flexible and modifiable
- Deliver novel tools, processes, technologies and know-how
  - Understanding of dynamics of liver function in normal & diseased states
  - Informed decision making based on network interactions rather than reductionist data
- Deliver tangible evidence of impact on unmet medical needs, through specific, defined objectives aligned to diseases:
  - Non alcoholic fatty liver disease
  - Regeneration
  - Inflammation

virtual liver network

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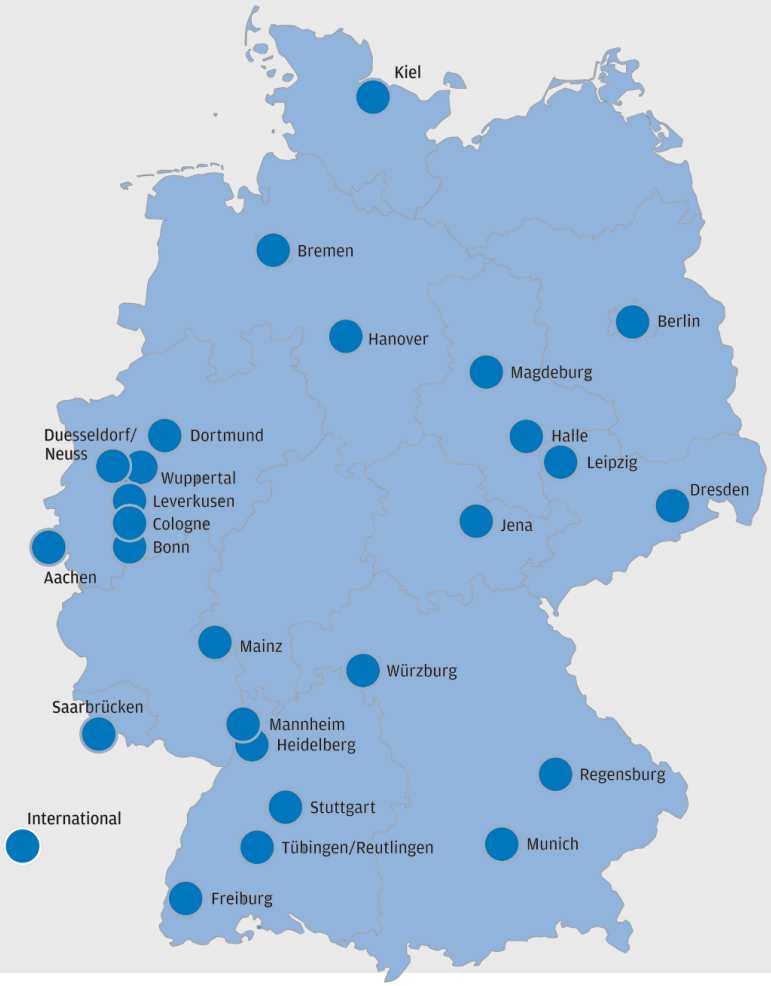
The Virtual Liver Network



- Complex Organisation:
  - 9 Work Packages
  - 69 Principal Investigators
  - 44 Projects
  - >200 contributing Scientists
  - 36 Independent Institutions
  - Mix of academics & industry
- Geographically Dispersed
- €50M distributed budget

virtual liver network

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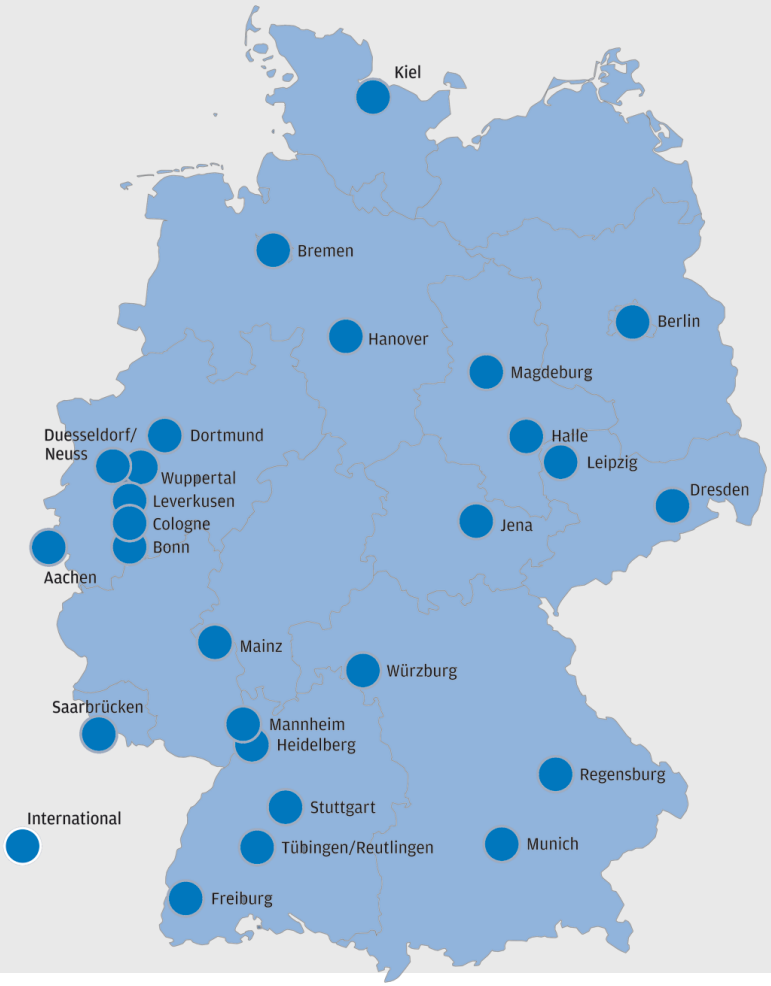
The Virtual Liver Network



To create:

- A dynamic mathematical model that represents human liver physiology, morphology and function
- A model that integrates quantitative data from all levels of organisation, from sub-cellular levels to the whole organ
- A model that has a specific focus on application to address the needs of the patient and clinician.
- A platform that can be modified, supplemented and improved over time

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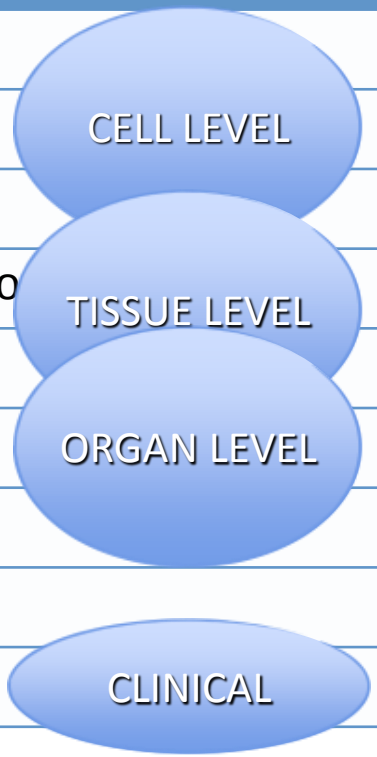
Structure

Work Package	Subject	Projects
A1	Cellular Metabolism	3
A2	Cellular Signalling	5
A3	Cross Linking	6
B	Cell-Cell Communicatio	9
C	Liver Lobule	6
D	Whole Organ	4
E	**Integrated Model**	4
F	**Data Management**	3
G	Clinical Translation	4



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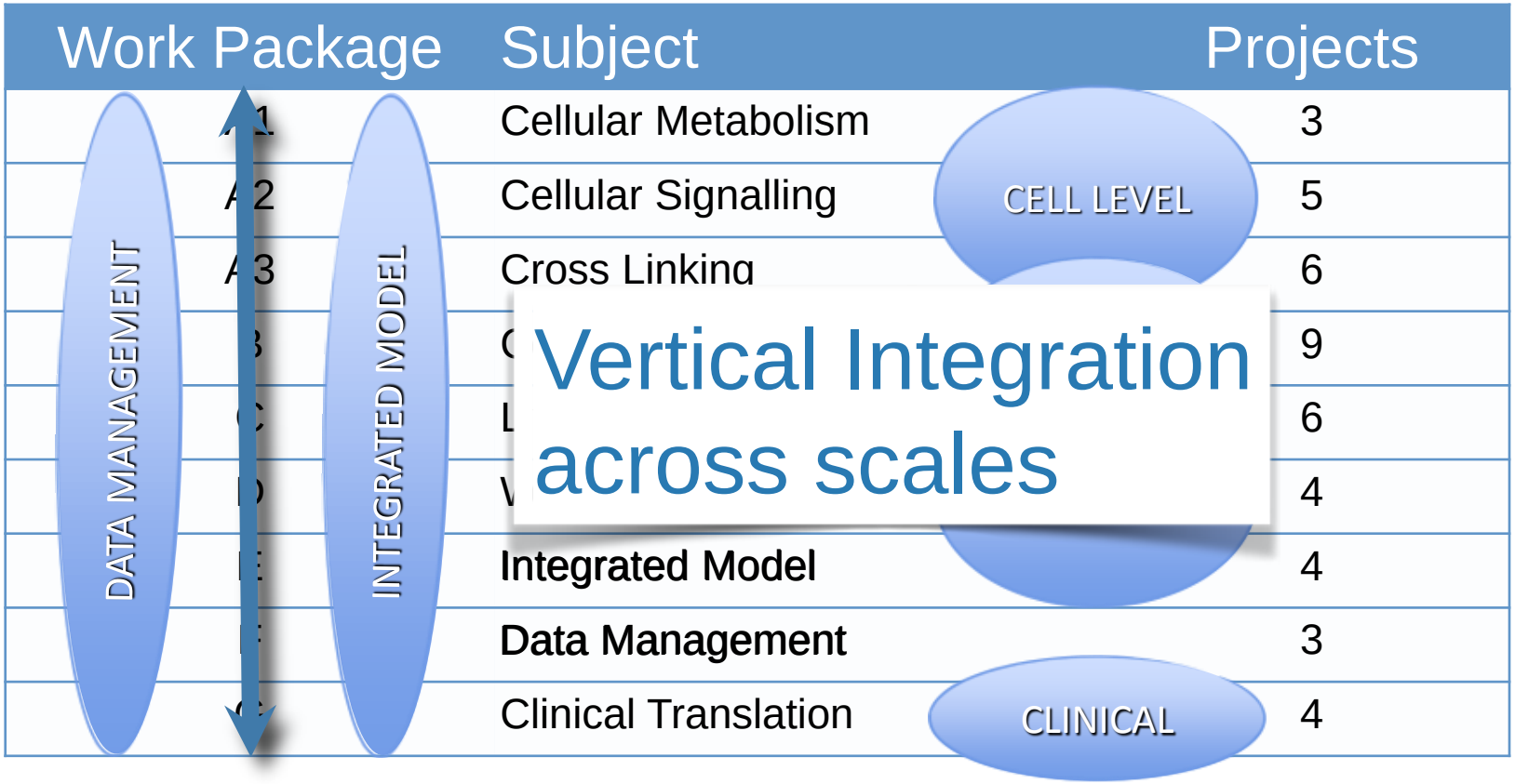
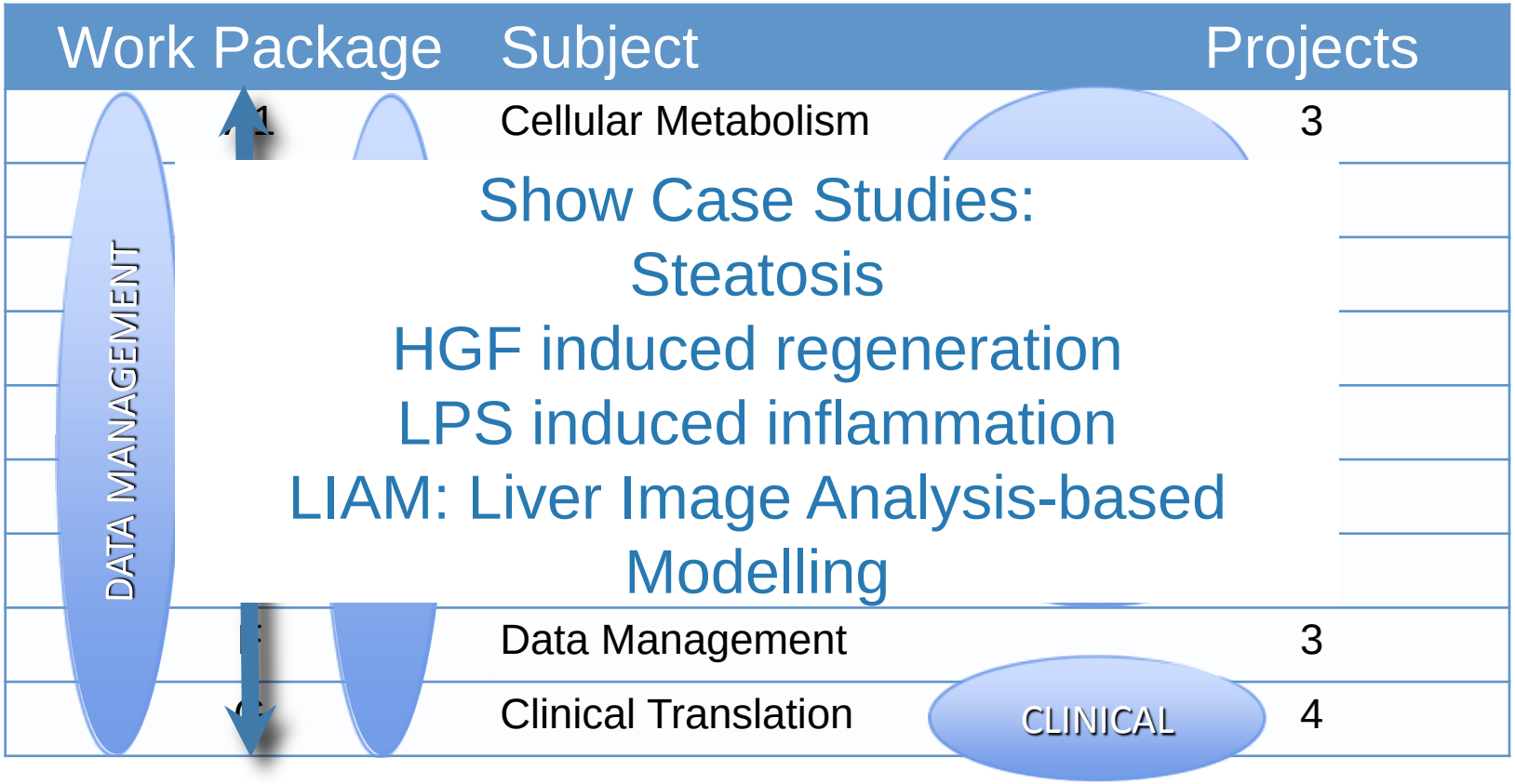
Structure



Structure



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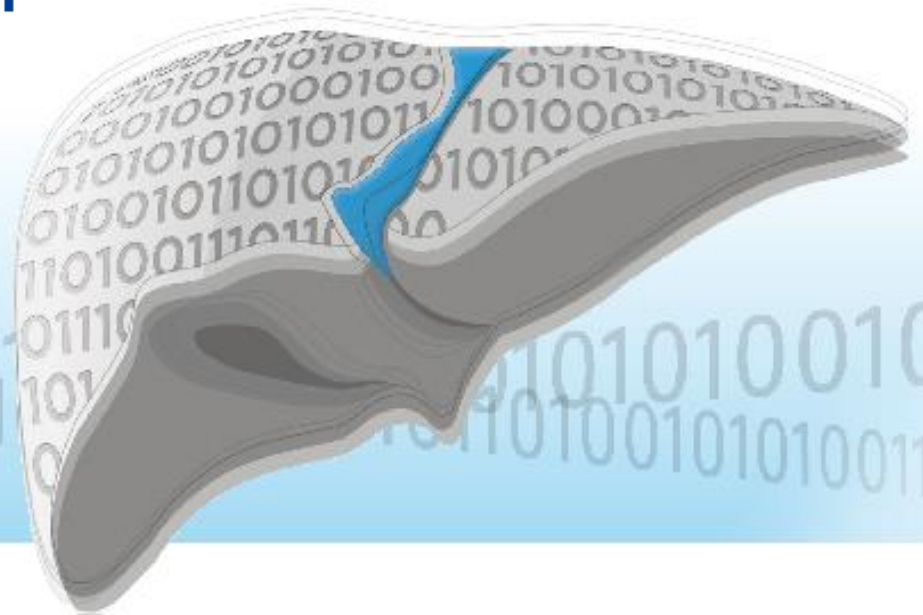
virtual liver
network



Show Cases

Leadership Team & Work Package Leaders

Steven Dooley
Mannheim

Dirk Drasdo
INRIA Paris/
Leipzig

Rolf Gebhardt
Leipzig

Jan Hengstler
Dortmund

Hergo Holzhütter
Charité, Berlin

Ursula
Klingmüller
DKFZ, Heidelberg

Ursula Kummer
BioQuant,
Heidelberg

Lars Küpfer
Bayer Technical
Services

Wolfgang Müller
HITS, Heidelberg

Tobias Preusser
Fraunhofer
MEVIS, Bremen

Jens Timmer
Freiburg

Marino Zerial
Max-Planck CBG,
Dresden

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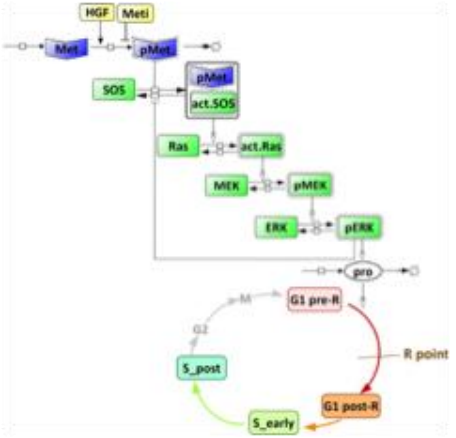
HGF-Induced Regeneration (Klingmüller & Drasdo)

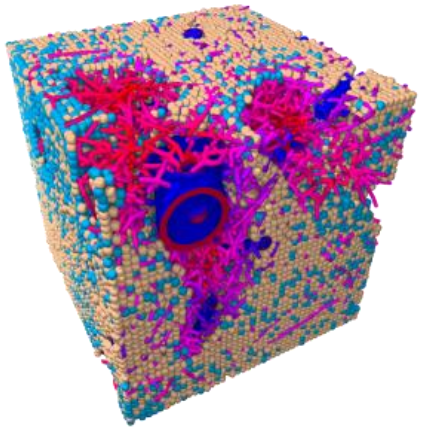
Overview

Addresses how proliferation patterns during liver regeneration are controlled by multi-scale spatio-temporal modelling describing events from intracellular to tissue level.



Objectives

- To link activation of signalling pathways to hepatocyte proliferation by ODE modelling.
- To integrate intracellular and tissue models developed based on proliferation in CCl_4 treated mice
- To Link the multi-scale model to a compartmental pharmacokinetic model of HGF for the whole-body taking into account recirculation of proteins via the blood.
- To provide an integrative multi-scale model to gain insights into mechanisms that could promote drug induced liver injury or liver failure after resection.



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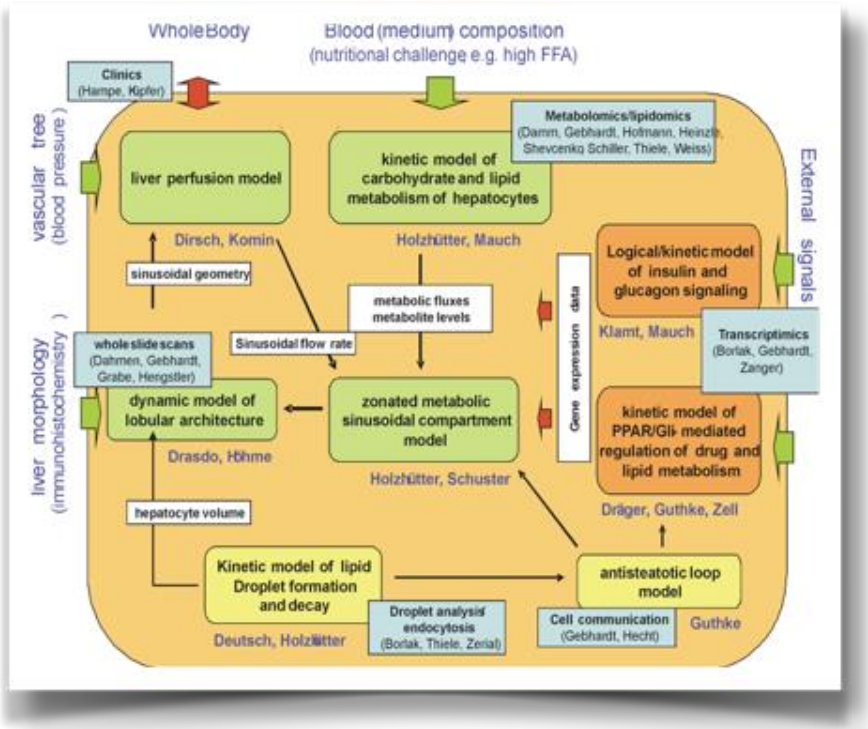
Steatosis (Holzhütter & Gebhardt)

- Development and validation of a multi-scale organ model to simulate hepatic lipid accumulation, export & degradation
- Dynamic models of metabolism and tissue structure models of liver lobule (Drasdo & Höhme PNAS 2010)
  - a modular backbone of models of the steatotic process bridging spatial and temporal scales.
- Application of the modular backbone:
  - Quantification & Impact of pro- & anti-steatotic factors
  - Propose novel clinical tests to assess individual risk for hepatic steatosis
  - Develop novel dietary & pharmacological strategies for prevention and reversion
  - Impact of steatosis on drug metabolism.



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Inflammation (Dooley & Timmer)

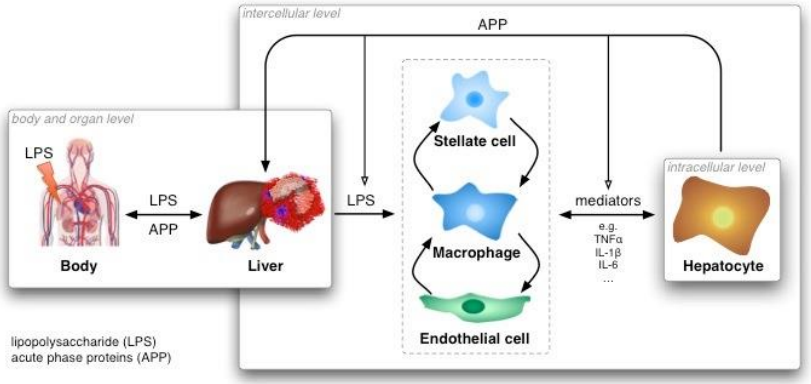
Aim

To identify and mathematically model the complex interplay of the different cell types and the most relevant mechanisms that control the inflammatory response of the liver to LPS.

Objectives

A multi-scale understanding of the role of liver and hepatocyte derived factors in the LPS response of the organism to:

- bridge intra- to intercellular to whole-body scale
- integrate experimental data into a mathematical model, which relies on models within several submodules
- test the hypothesis that response of the liver predominantly includes communication between hepatocytes, Kupffer cells, sinusoidal endothelial cells & hepatic stellate cells.



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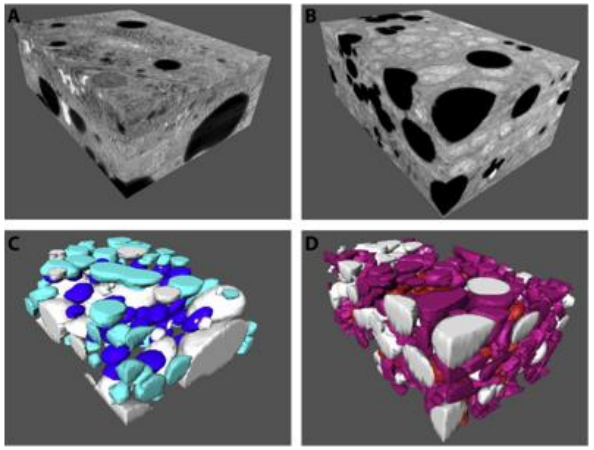
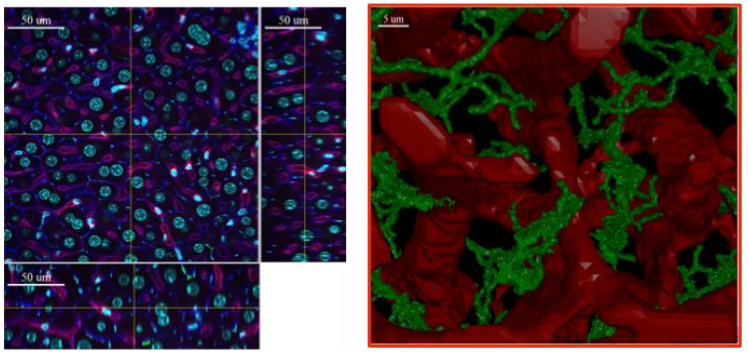
LIAM (Zerial & Drasdo)

- Regulation and control of bile flow in normal and diseased liver based on detailed study of liver micro-architecture
- Flow, zonation & osmotic gradients control cellular uptake
- Interplay of factors controlling flow integrated in a multi-scale model reflecting physical constraints involved in function.
- IMAGING
  - 3D-structure of liver tissue and its dynamics in vivo.
  - high- & super-resolution light & electron microscopy, intra-vital imaging
  - multi-scale quantitative understanding of tissue organisation
- MODELLING:
  - A tissue structure model based on 3D organisation
  - A fluid mechanics model: blood flow, bile flux and processes important in flow control.
- VALIDATION:
  - Intra-vital imaging, Genetic perturbations, Pharmacological perturbations



3D tissue architecture after serial block-face EM



reconstruction of bile canaliculi & sinusoidal networks

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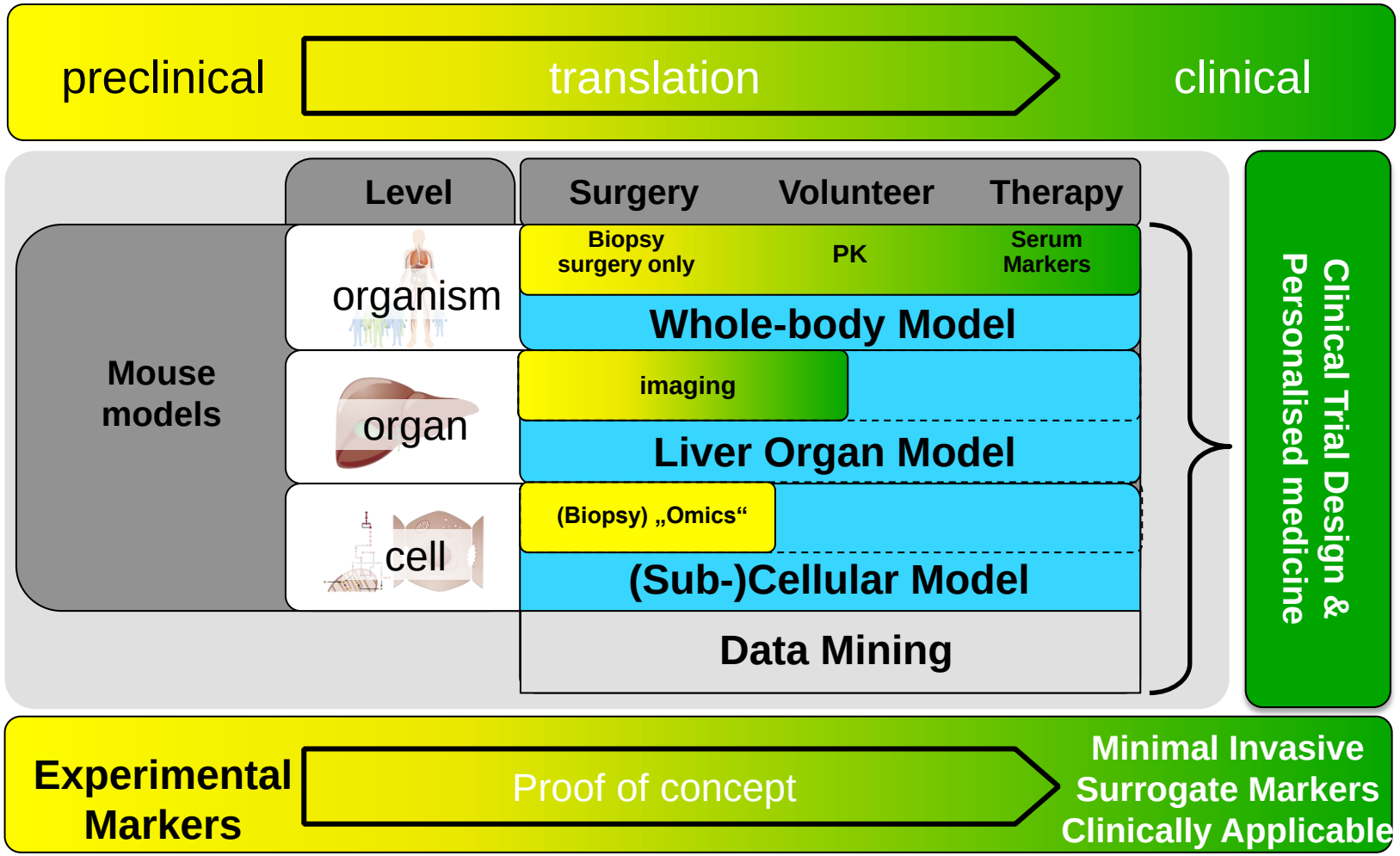
In Vivo Translation (Küpfer, Hengstler, Kerb)



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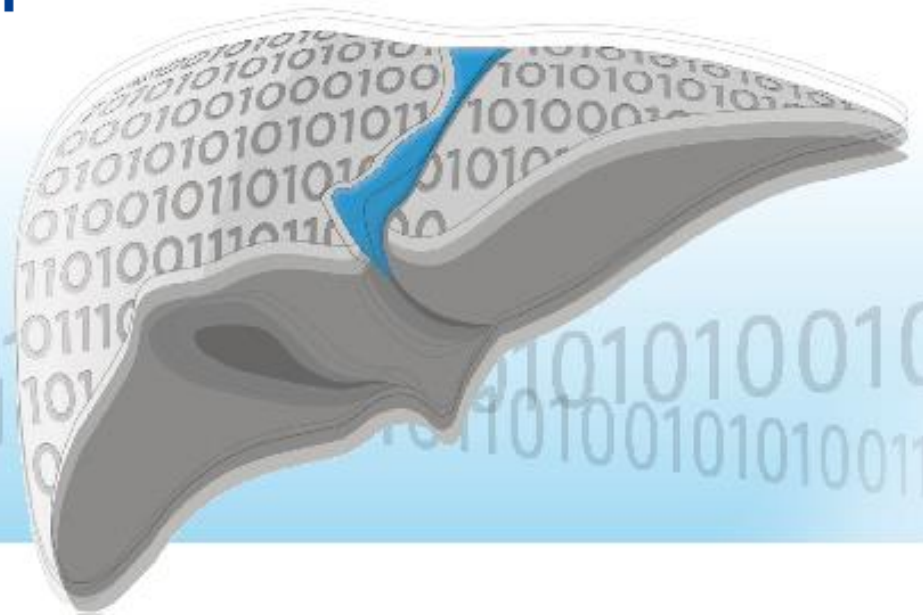
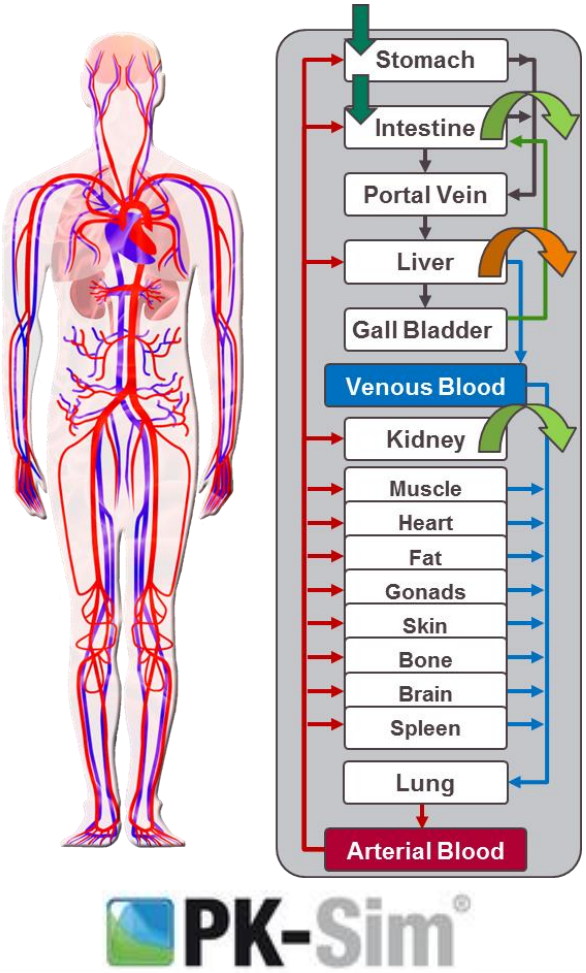


Physiology-based pharmacokinetic (PBPK) modelling

Physiology-based pharmacokinetic (PBPK) modelling



Physiology-based pharmacokinetic (PBPK) models

- organs are structurally included
- distribution models for generic description of mass transfer (passive and active processes)
- substance specific model-parameters are calculated from few physicochemical data
- extensive data collections of prior biological and physiological data included
- comprehensive representation of experimental data from different scales of biological organization

A unified model representation of prior physiological and (pre-)clinical knowledge.

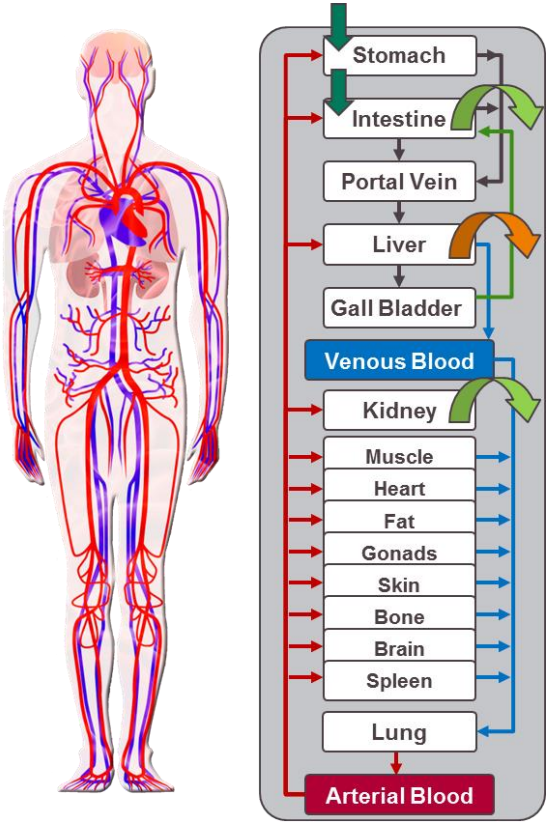
Using gene expression data as a surrogate for tissue-specific protein abundance

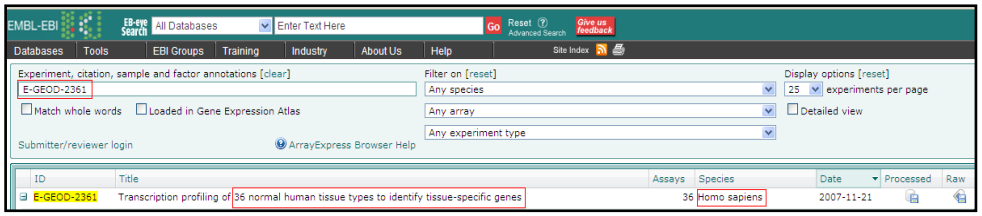
PK-Sim® Express-Expression Database:

ArrayExpress

UniGene

Literature





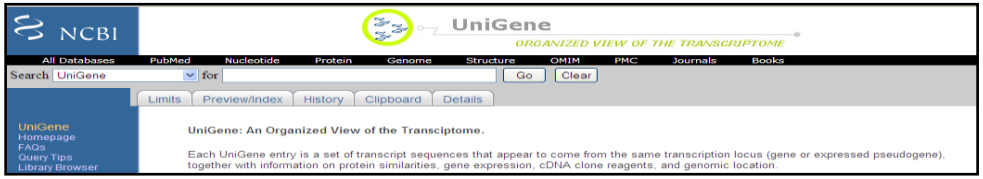
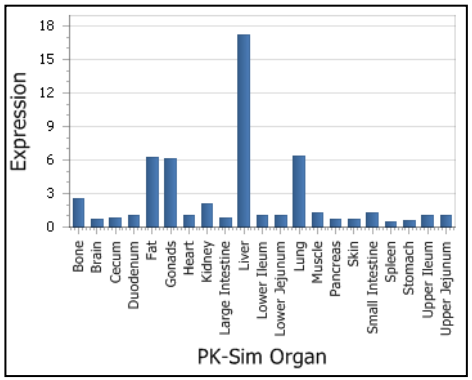


Table 1. Total RNA Source Information and Values for Human β-Actin and P450 mRNAs in Various Tissues

CYP	liver	Fetal liver	Small intestine	Kidney	Adrenal gland	Lung	Brain	Prostate	Testis	Uterus	Placenta
CYP1A1	0.0594	0.000272	0.00176	0.000239	0.00677	0.0679	0.000388	0.00465	0.00215	0.0201	0.00101
CYP1A2	4.77	BLQ	BLQ	0.000021	0.00113	0.000119	BLQ	0.000740	0.00141	0.00193	BLQ
CYP1B1	0.00578	0.000622	0.0128	0.0139	0.0144	0.0167	0.00174	0.104	0.0197	0.0413	0.00490
CYP2A6/7	27.8	0.199	0.00193	0.00188	0.0105	0.0622	0.00867	0.00809	0.0187	0.0390	0.0231



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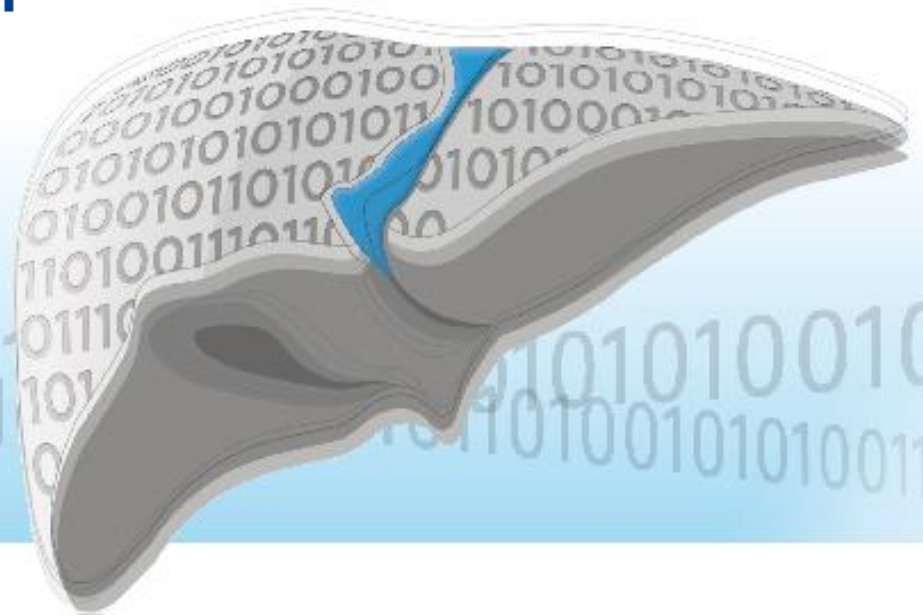
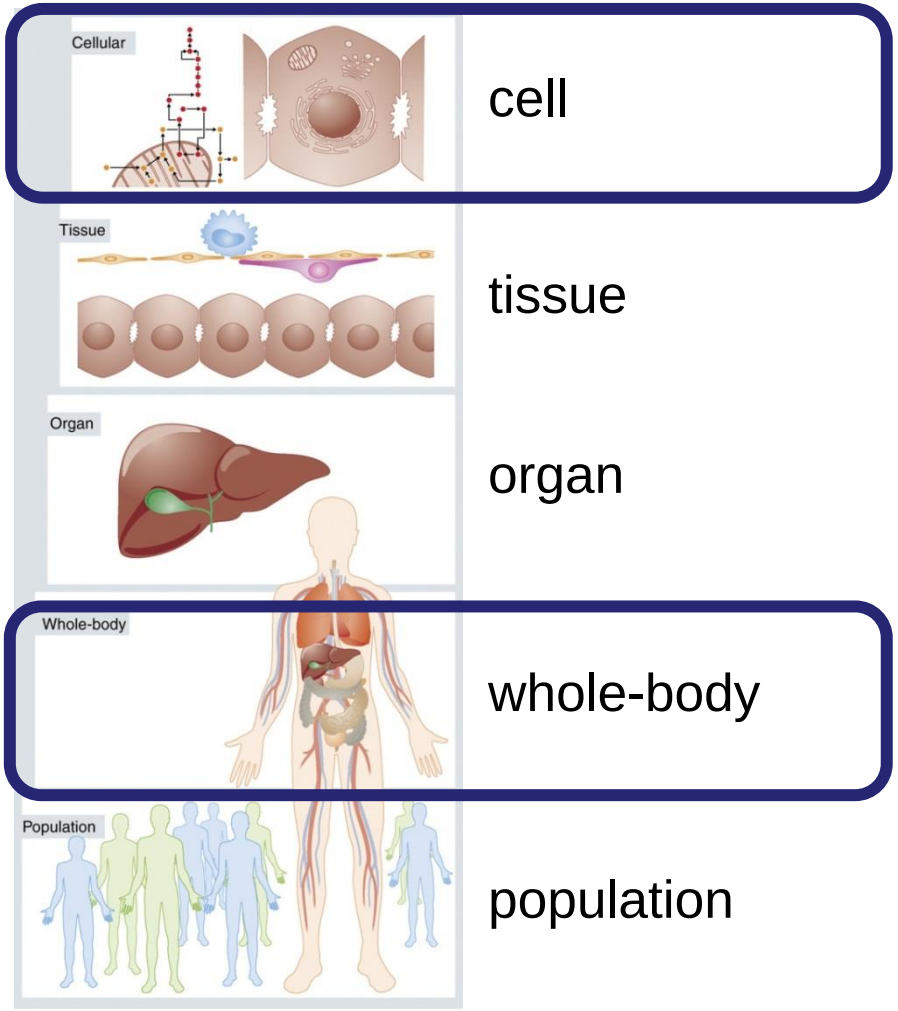


Vertical model integration

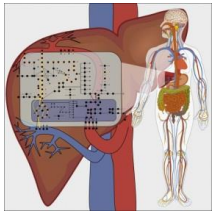
Vertical model integration



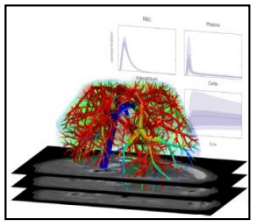
Kuepfer, *MSB*, 2010

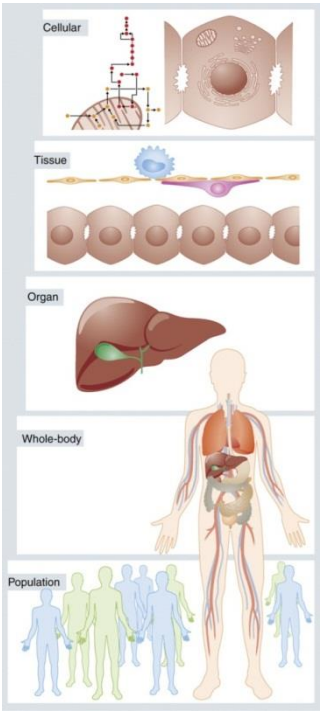
Vertical model integration

Integrating hepatic metabolism into a whole-body model



first-pass perfusion of the liver





cell

tissue

organ

body

population

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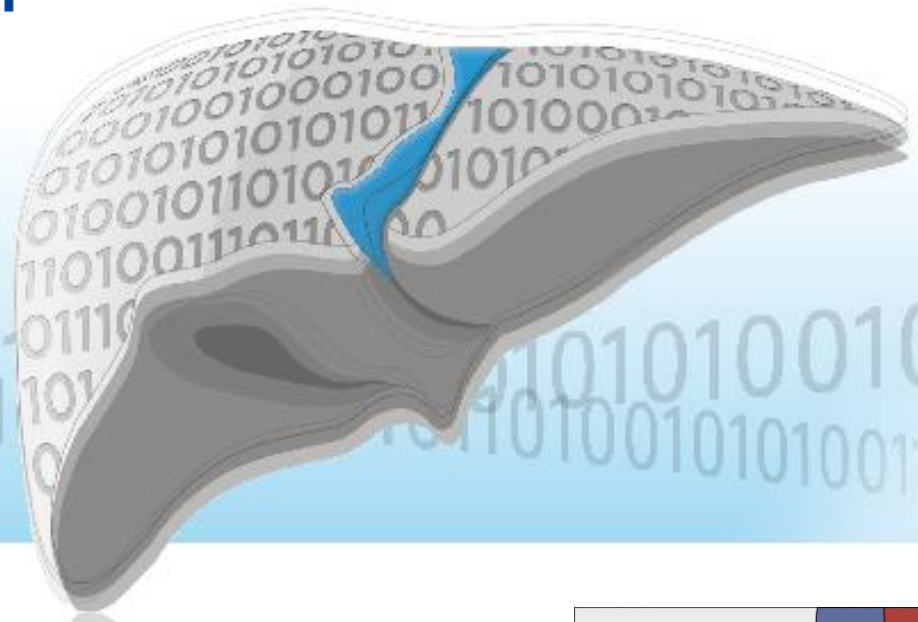
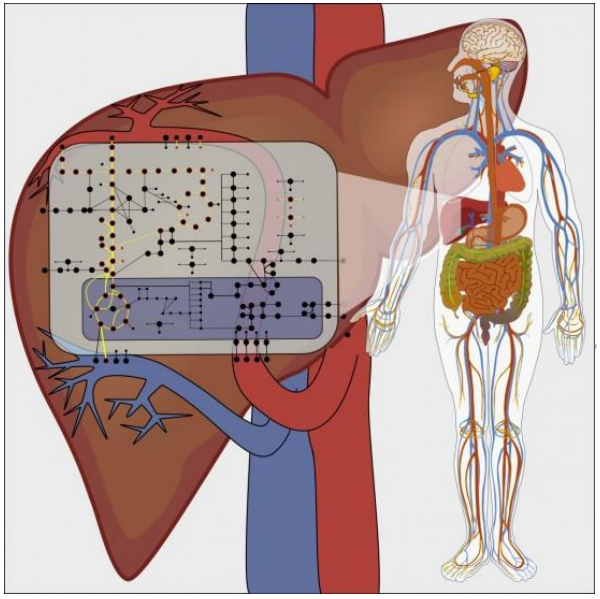
virtual liver
network



Integrating hepatic metabolism into a whole-body model



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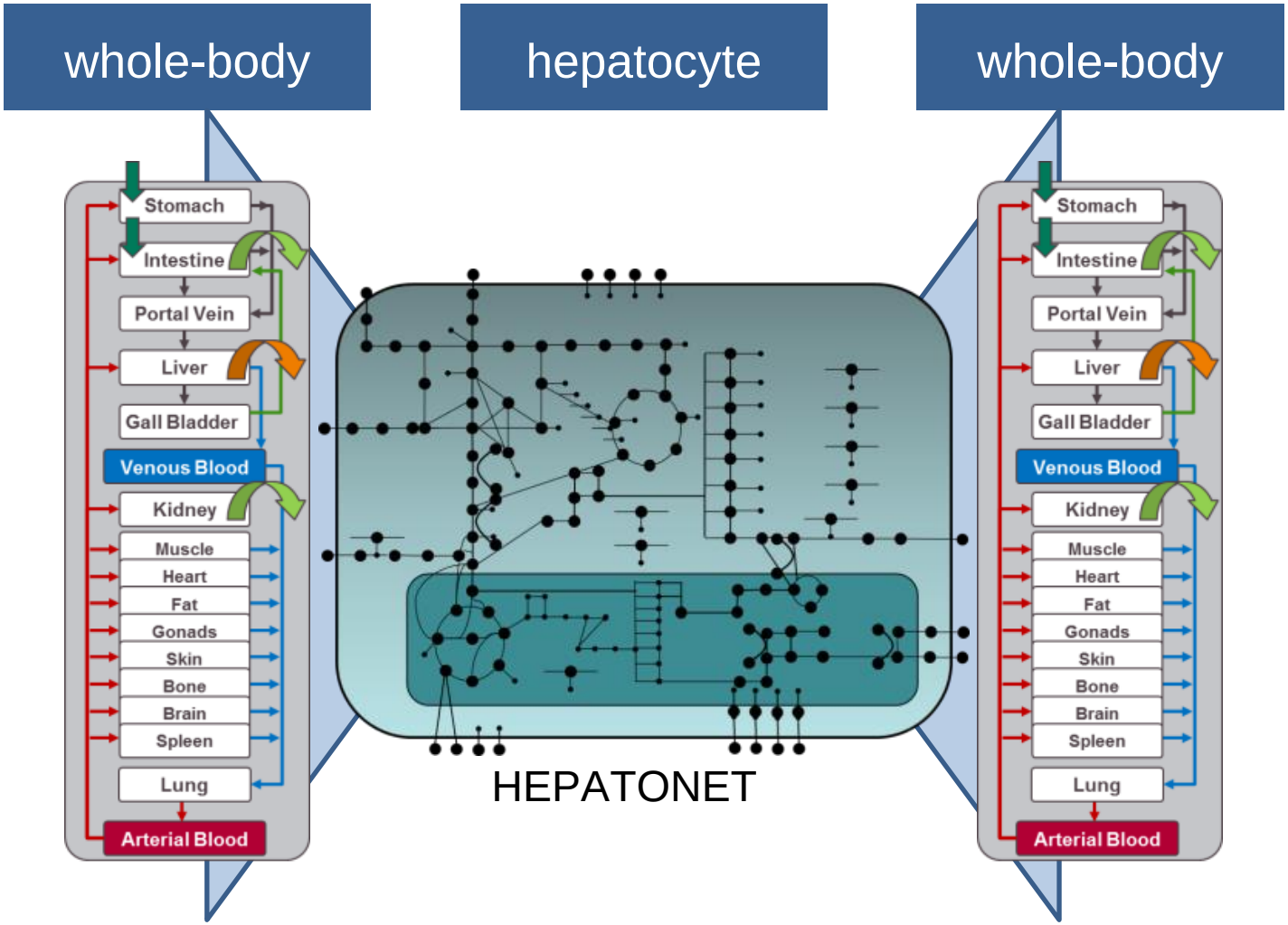

Gille et al., *MSB*, 2009

Krauss et al., *PLoS Comp Biol*, 2012

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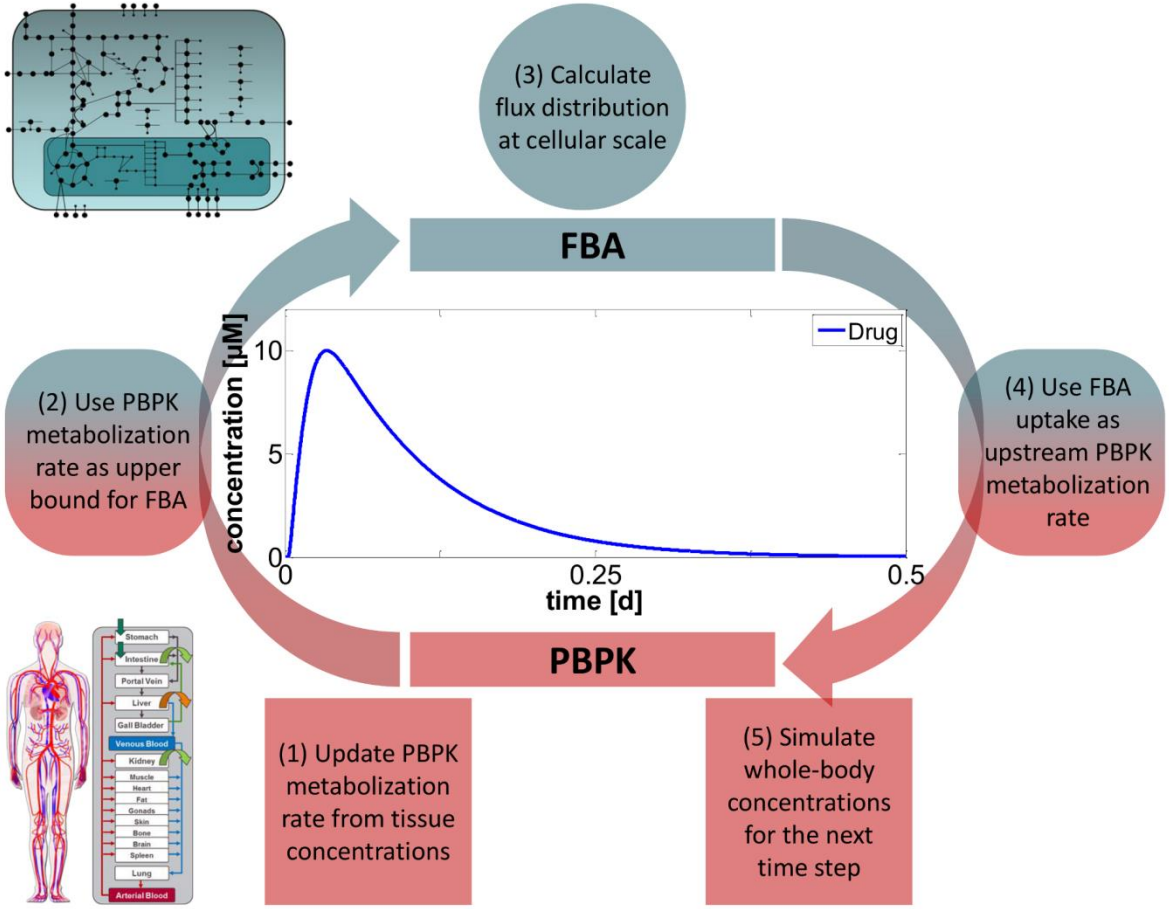
Integrating hepatic metabolism into a whole-body model



Krauss et al., *PLoS Comp Biol*, 2012

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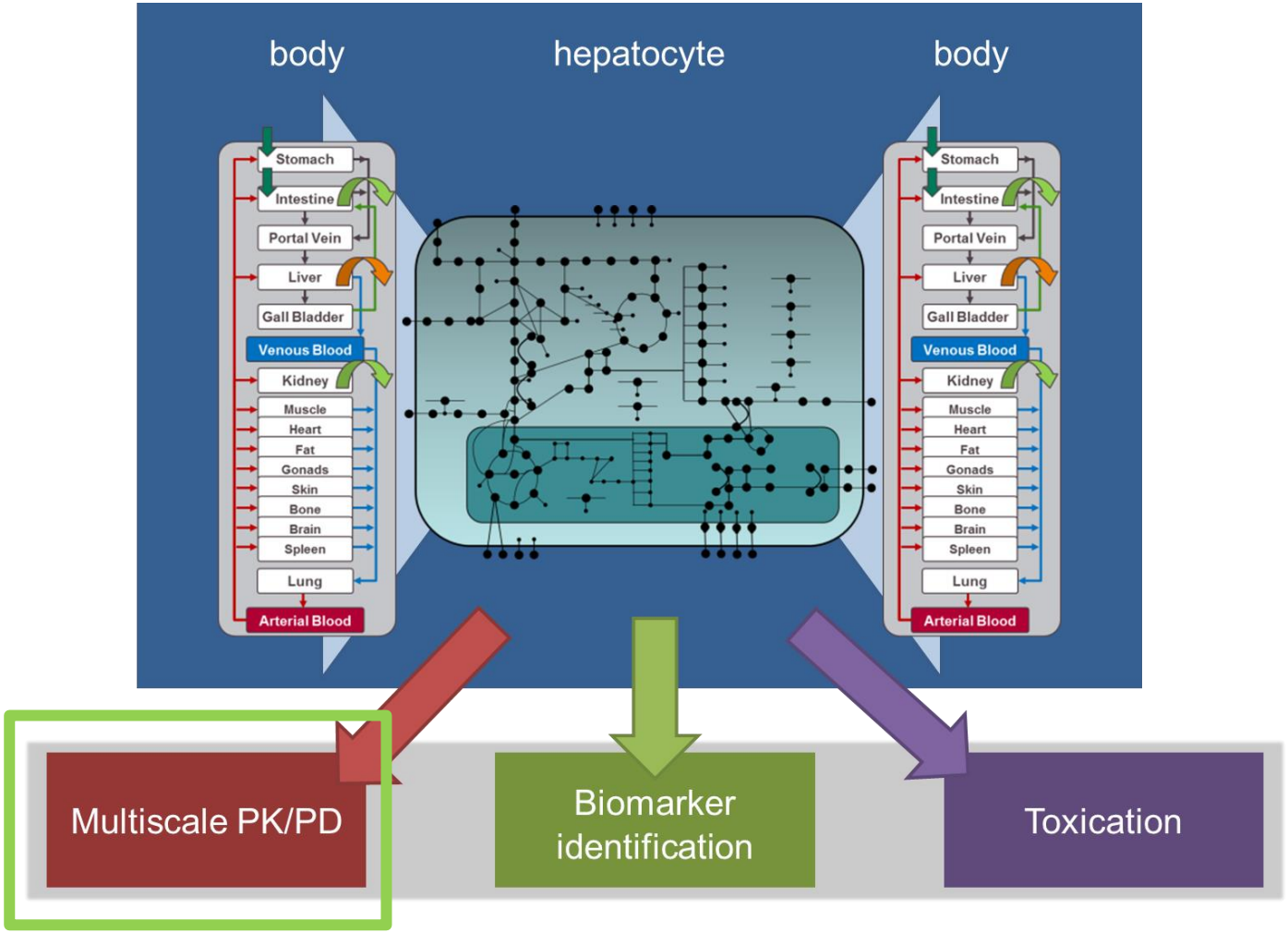
Integrating hepatic metabolism into a whole-body model



Krauss et al., *PLoS Comp Biol*, 2012

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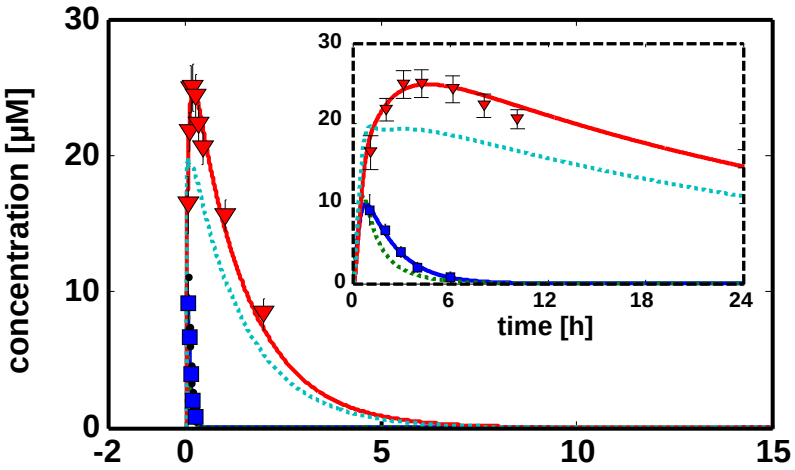
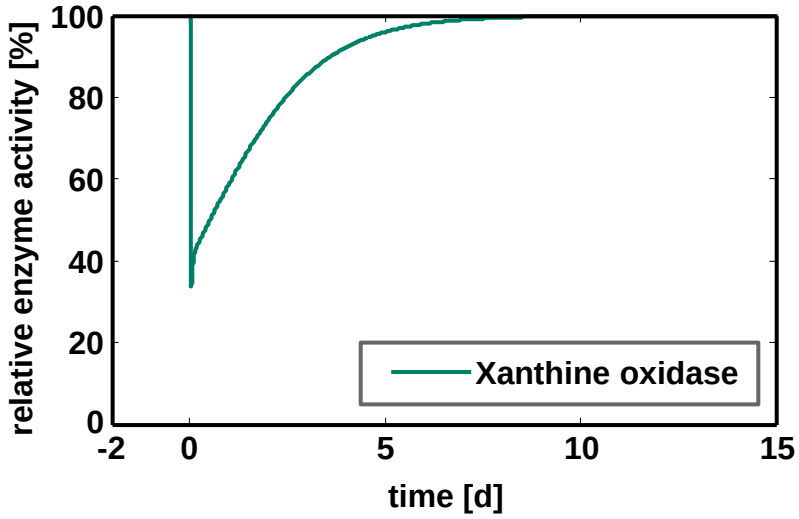
Allopurinol treatment of hyperuricemia

whole-body PK

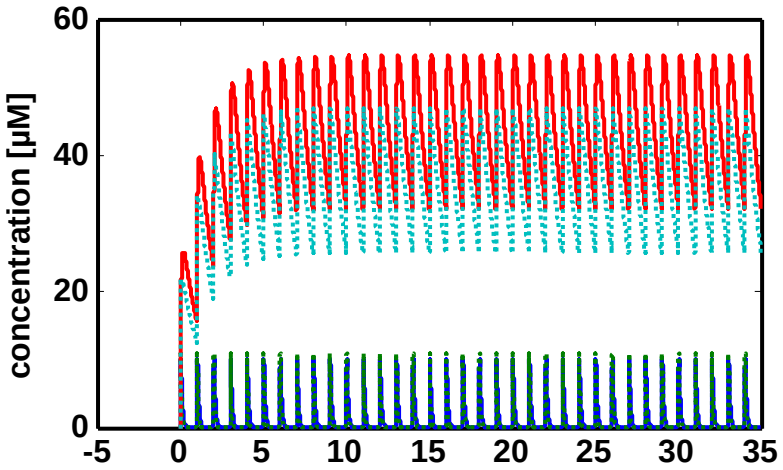
cellular response

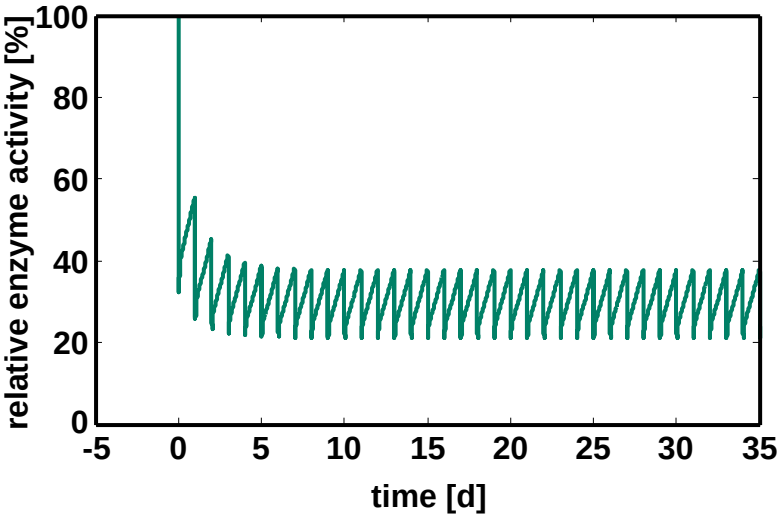
Single dose





Multiple dose

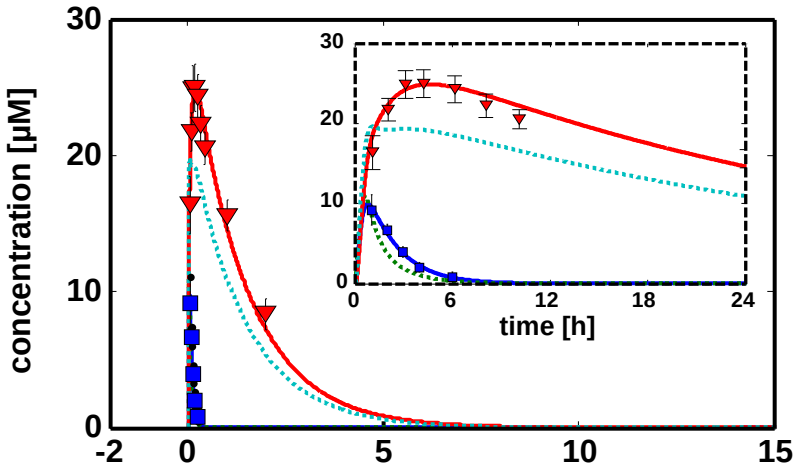


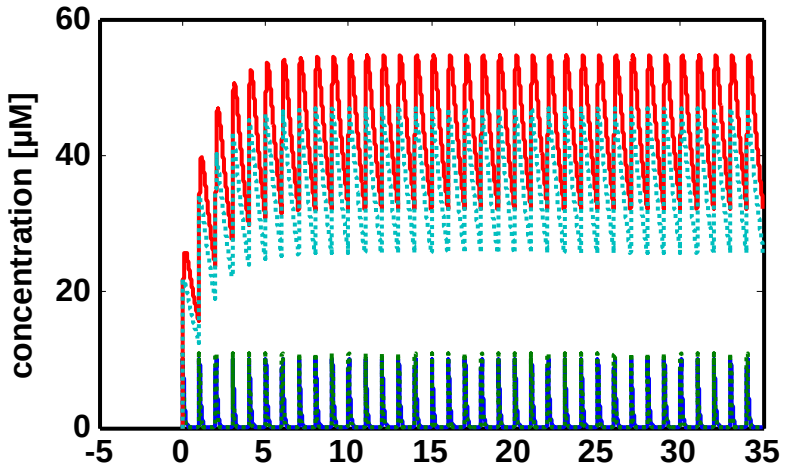


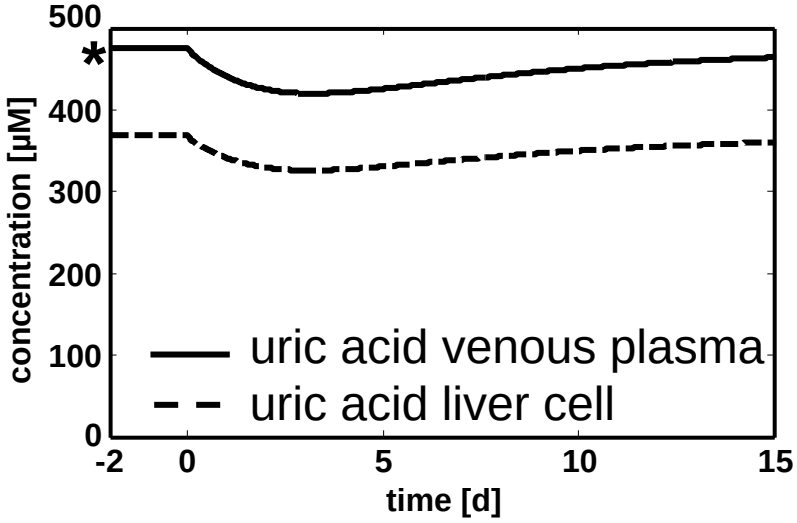
Allopurinol treatment of hyperuricemia

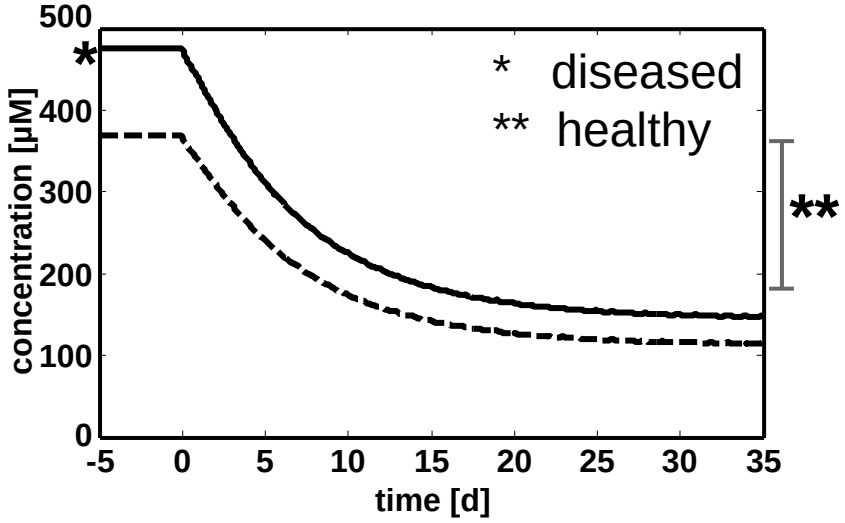
Single dose

Multiple dose

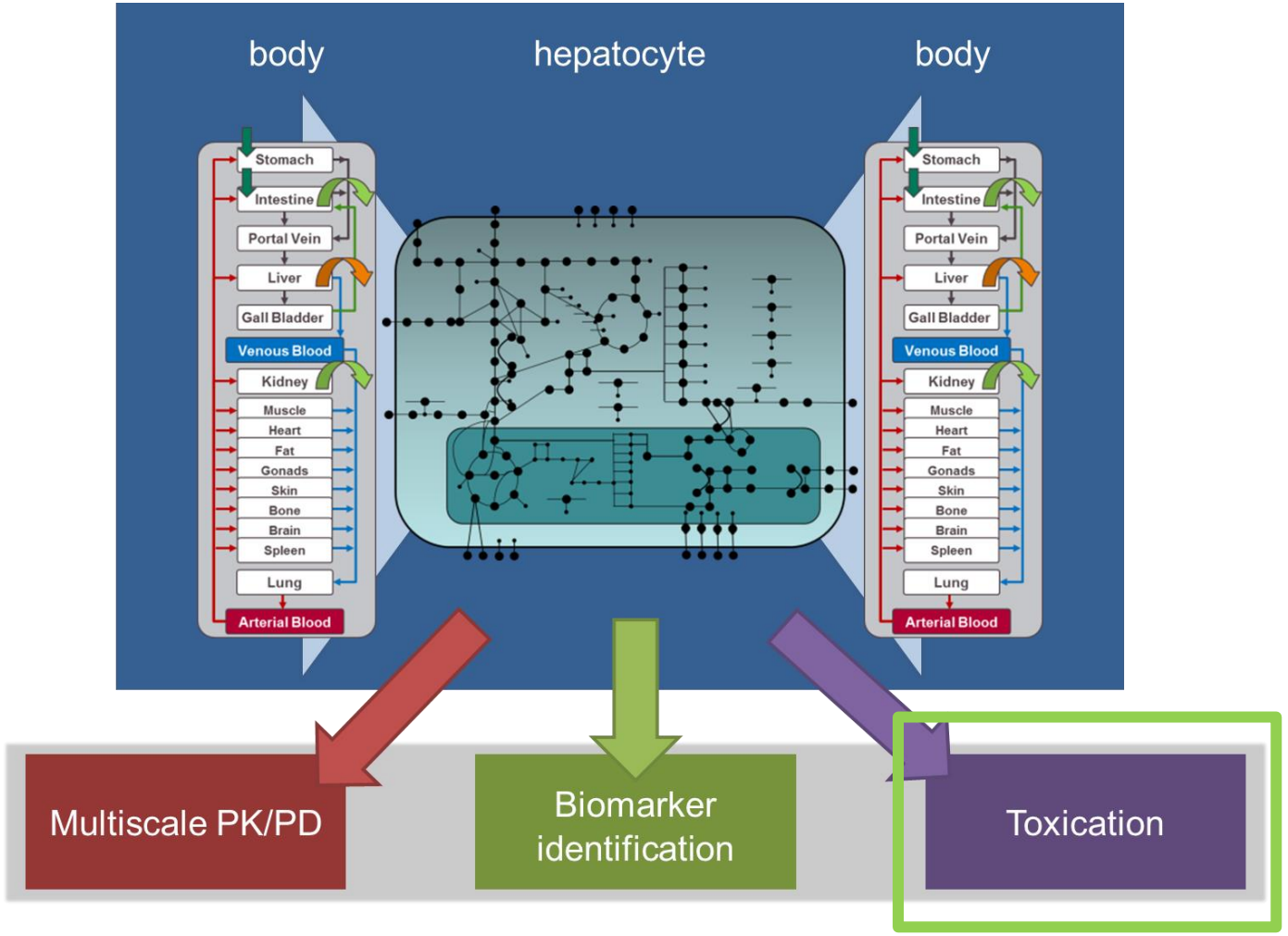








Integrating hepatic metabolism into a whole-body model



Krauss et al., *PLoS Comp Biol*, 2012

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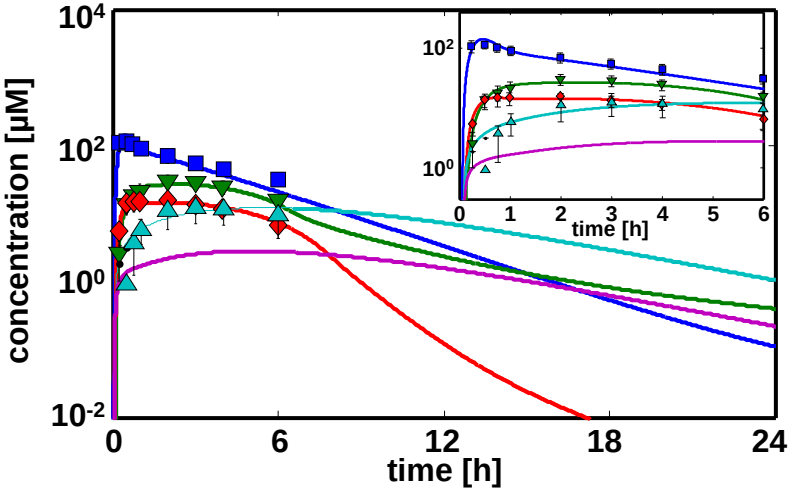
Paracetamol intoxication

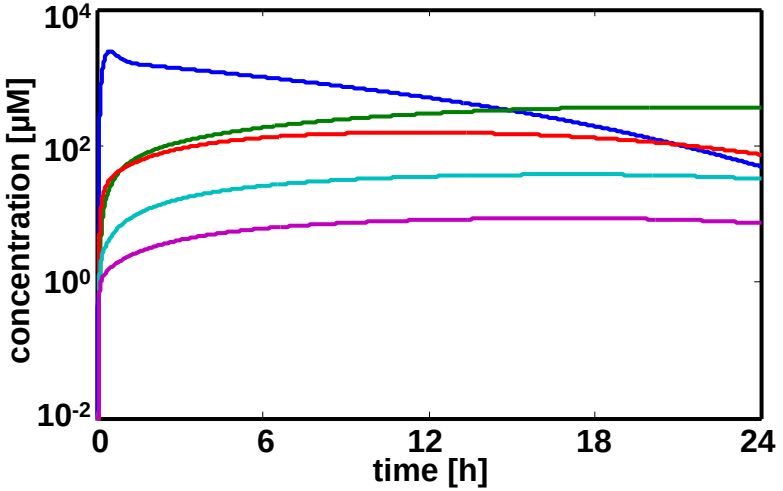
whole-body PK

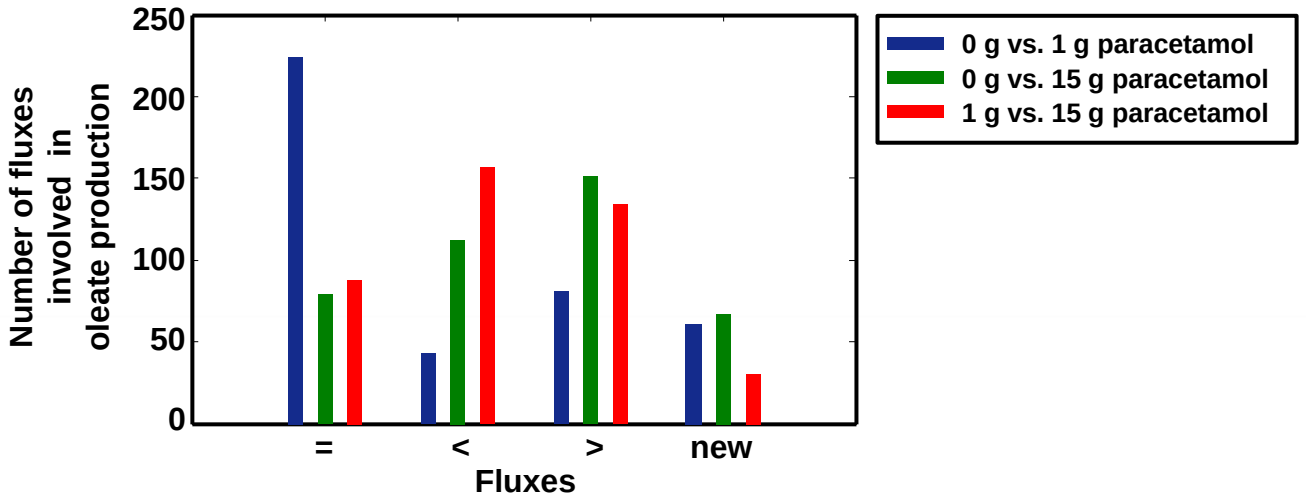
cellular response

1 g paracetamol



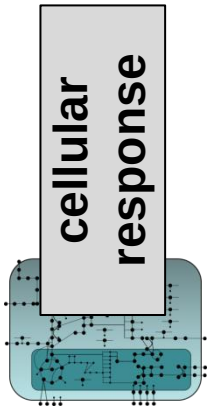
15 g paracetamol

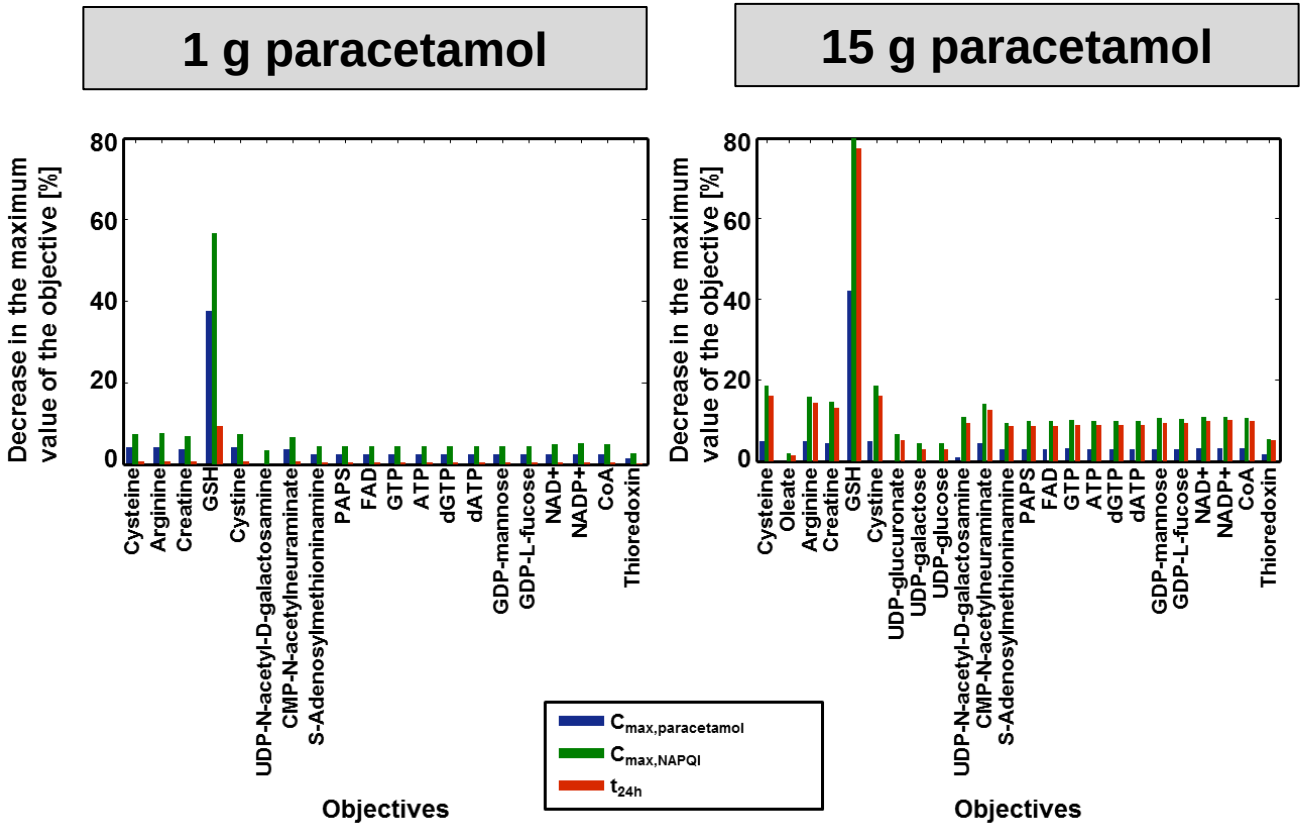




Krauss et al., *PLoS Comp Biol*, 2012

Paracetamol intoxication

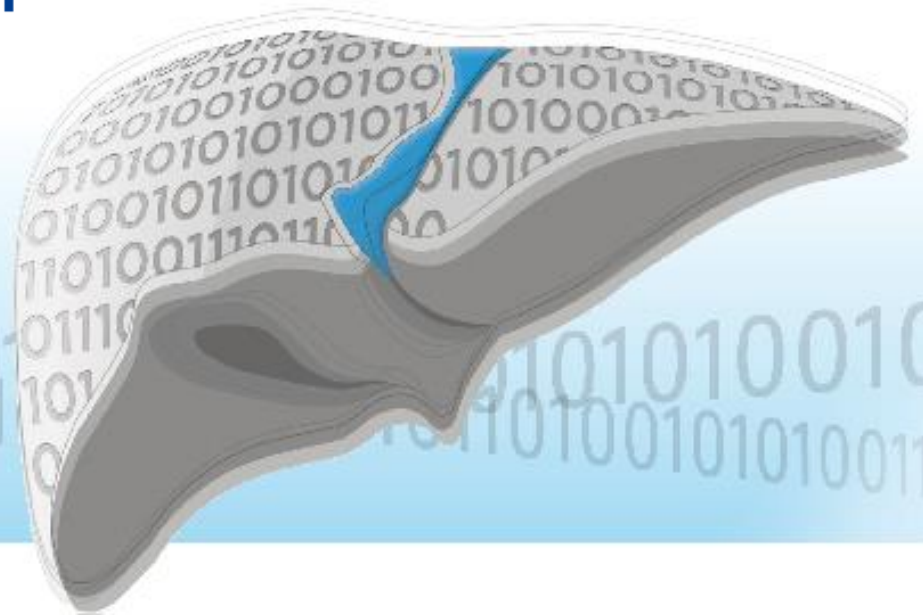




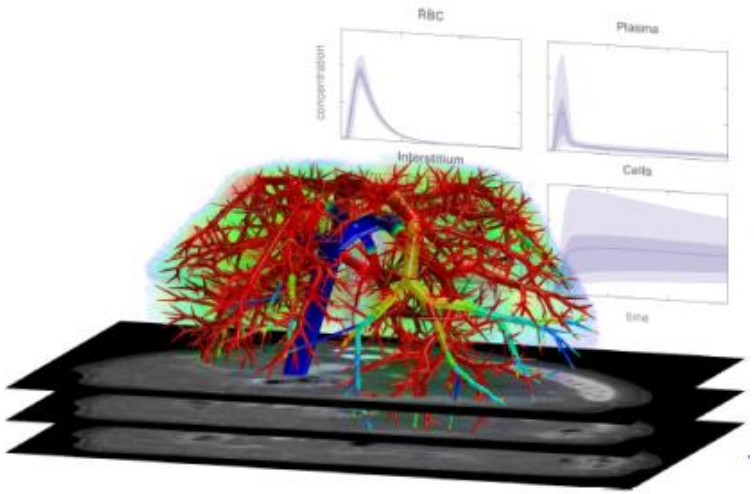
Krauss et al., *PLoS Comp Biol*, 2012

A toxic dose of paracetamol significantly affects the correct execution of metabolic functions of the hepatocyte

virtual liver
network

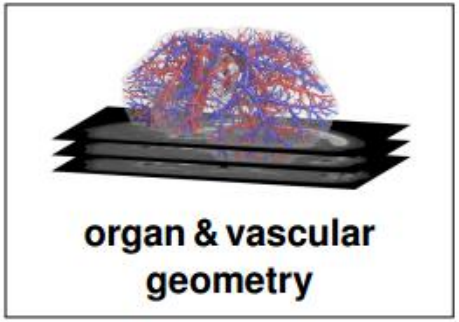


Spatio-Temporal Simulation of First Pass Drug Perfusion in the Liver

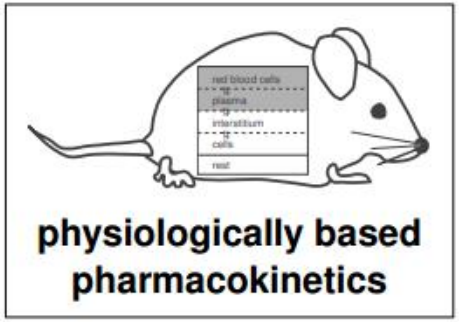


A spatio-temporal model of the liver

geometry of the organ and the vascular tree

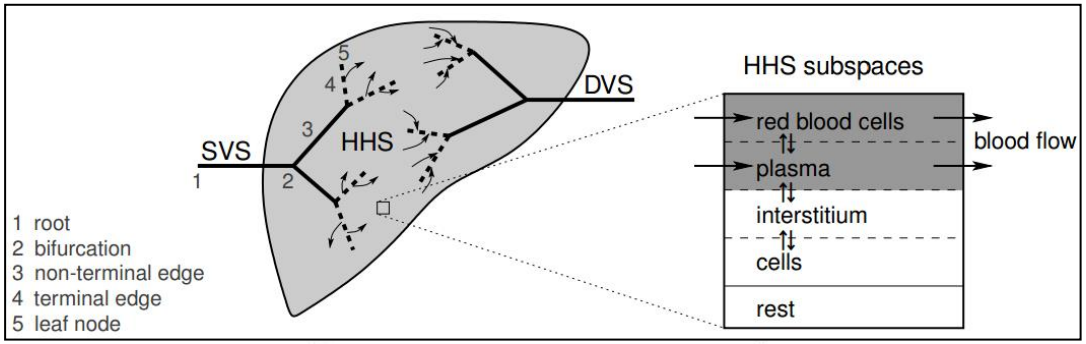


organ & vascular geometry



physiologically based pharmacokinetics

mass transfer within hepatic tissue



a spatially-resolved model of the liver

Schwen et al., *PLoS Comp Biol, 2014*

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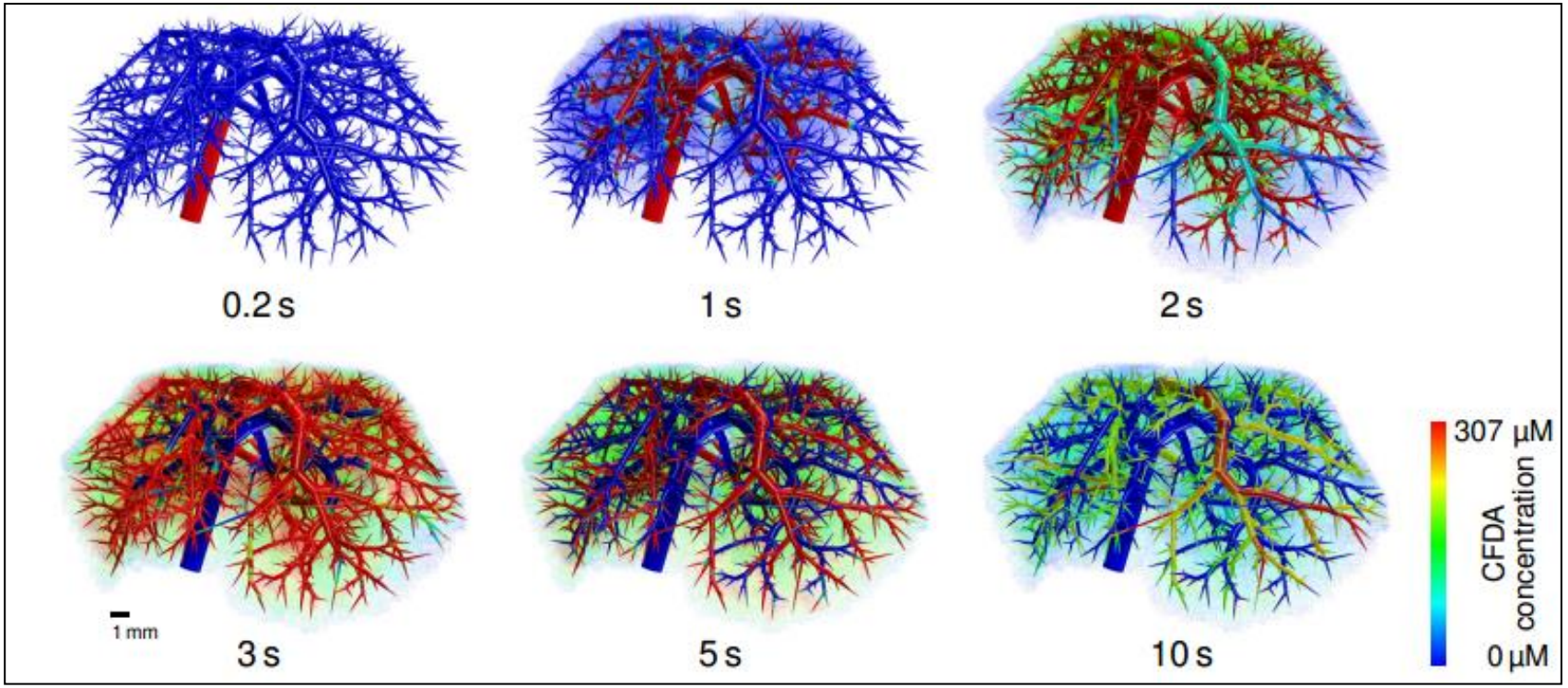
Spatio-temporal distribution within the liver

Visualization of a 2 second pulse of carboxyfluorescein diacetate succinimidyl ester (CFDA SE) within the liver



Schwen et al., *PLoS Comp Biol, 2014*

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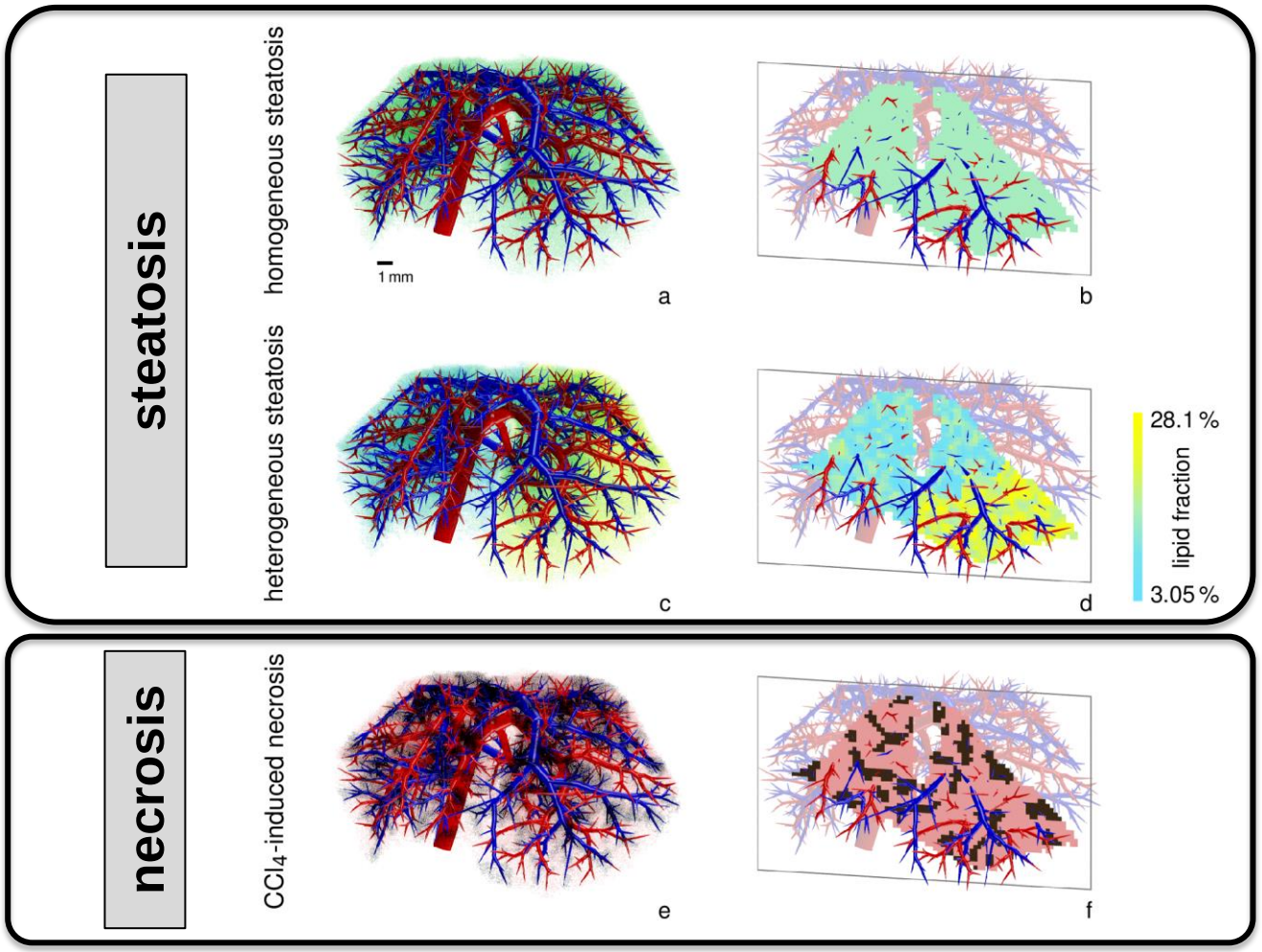
Visualization of pathophysiological states in the spatially resolved liver model



Schwen et al., *PLoS Comp Biol, 2014*

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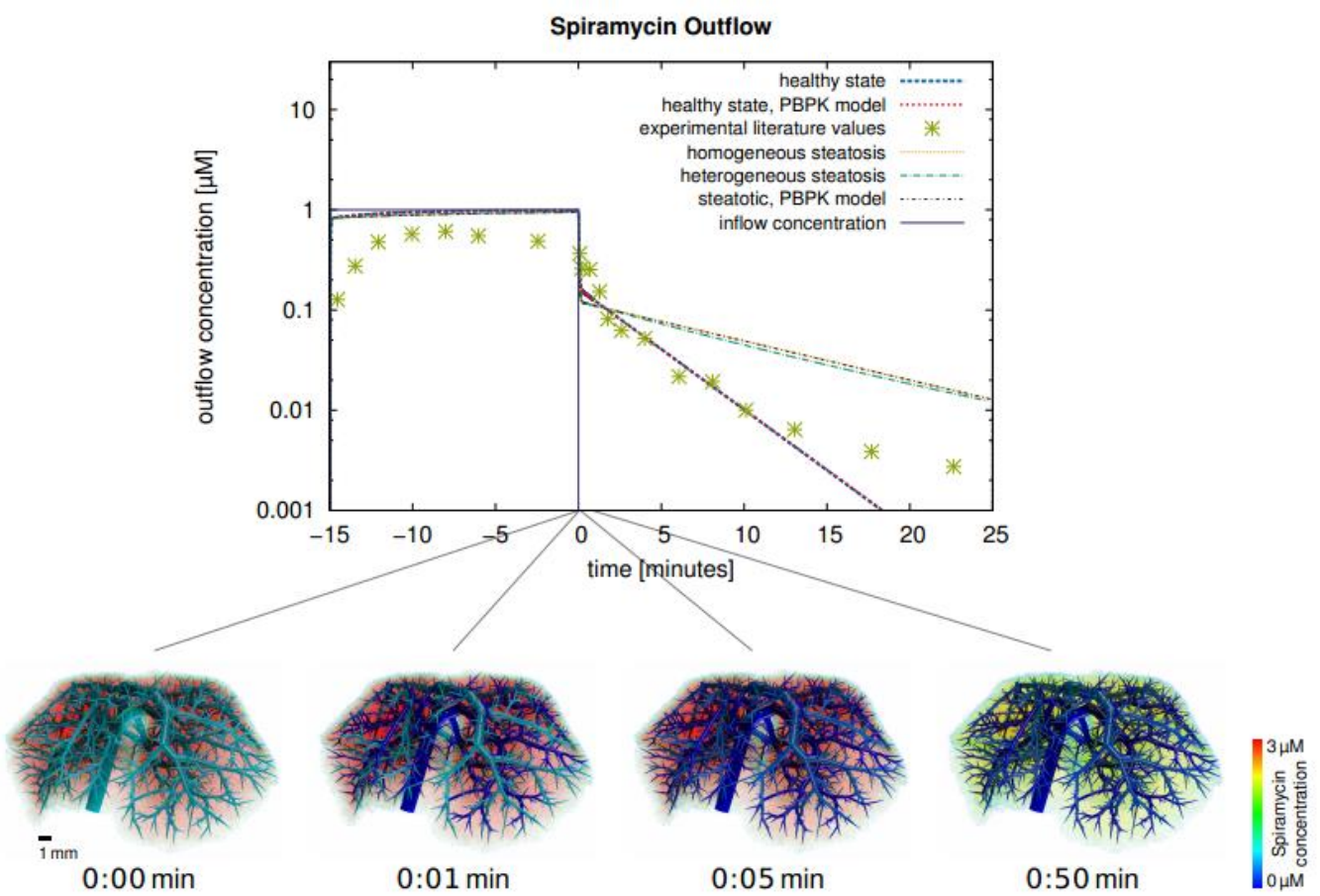
Simulation of an isolated perfused liver

Spatio-temporal concentration profiles in an isolated perfused liver



Schwen et al., *PLoS Comp Biol, 2014*

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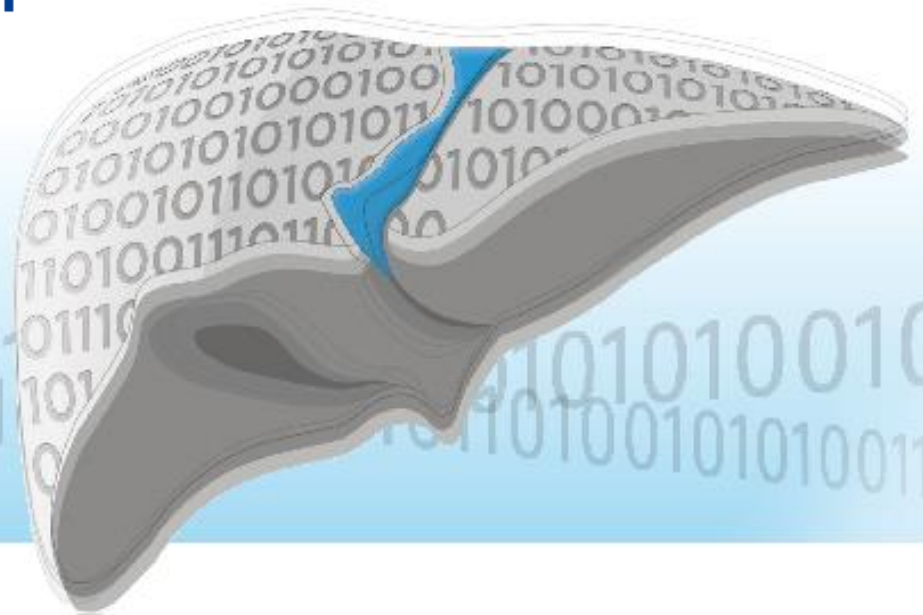
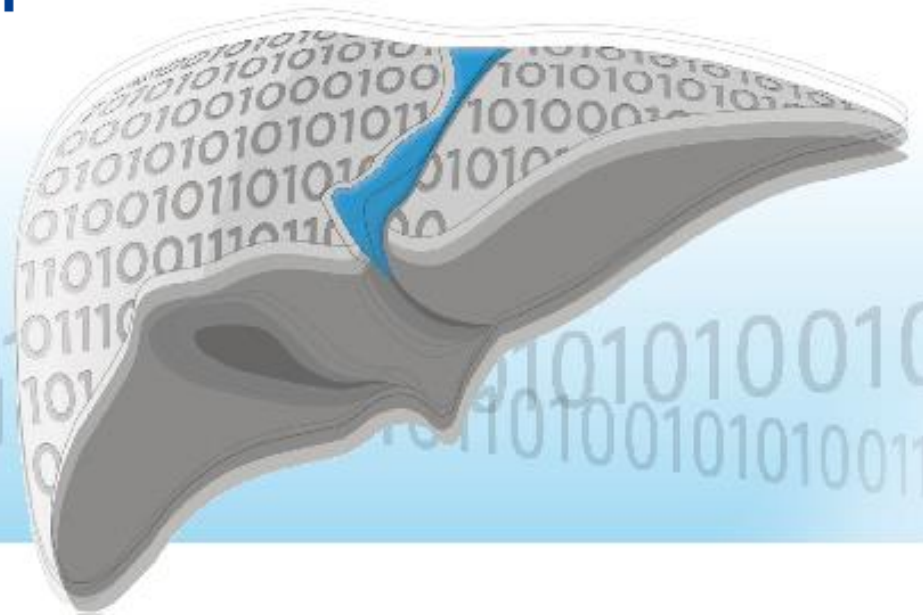
network

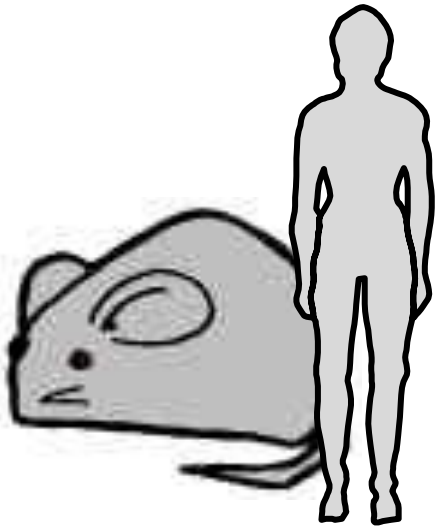


Translational Studies

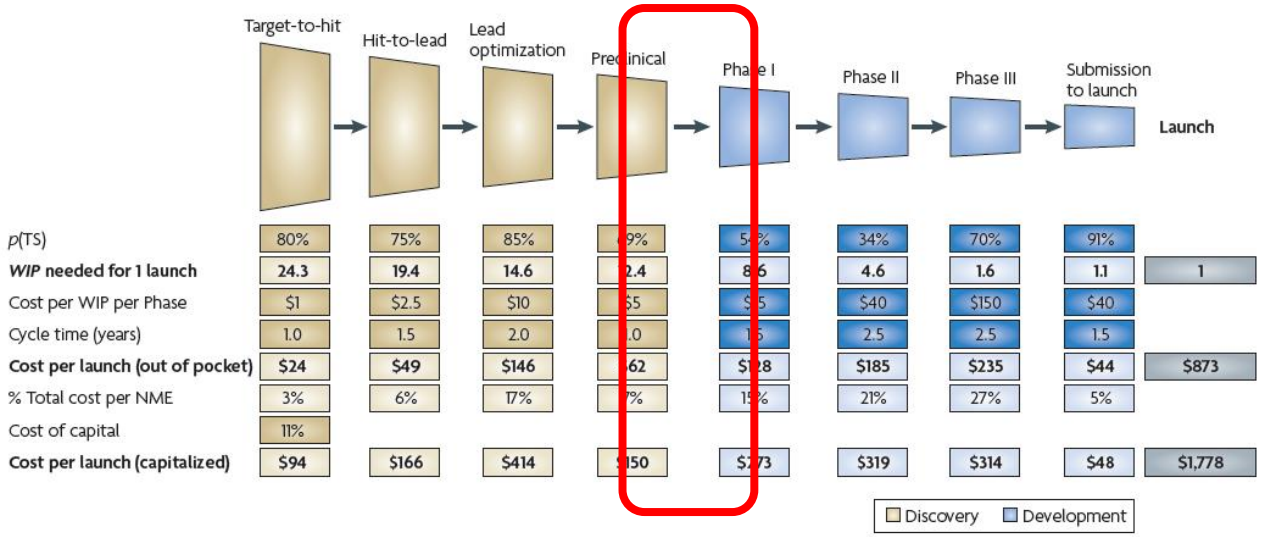
virtual liver
network



PBPK-based Cross-Species Extrapolation



Cross-species extrapolation in clinical development



First in man studies are a critical step in drug development:

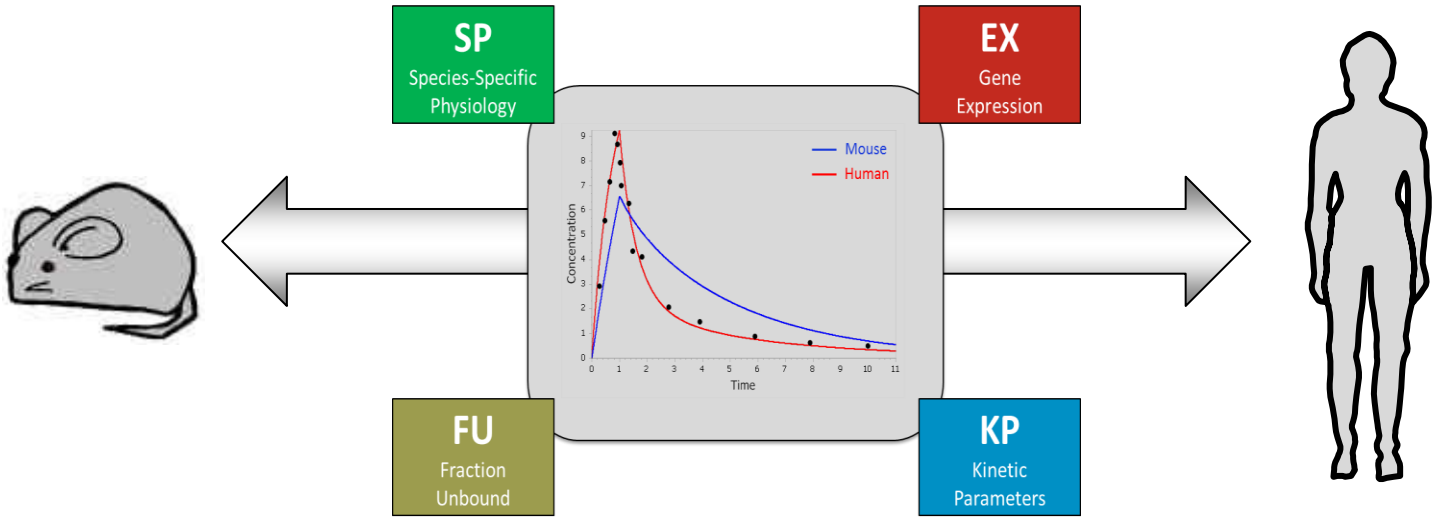
- limited physiological comparability of different species
- different genetic/enzymatic setup of different species
- caution needed in terms of patient safety

Cross-species extrapolation

Which information in PBPK models is the most important?

Consideration of four PBPK parameter domains:

- Species specific physiology (SP)
- Gene expression, i.e. tissue-specific protein abundance (EX)
- Kinetic paramers (KP)
- Fraction unbound (FU)



Thiel *et al.*, *J. Phar. Sci. 2014*

Consideration of 10 exemplary drugs

Exemplary consideration of ten different drugs (*i.v.*)

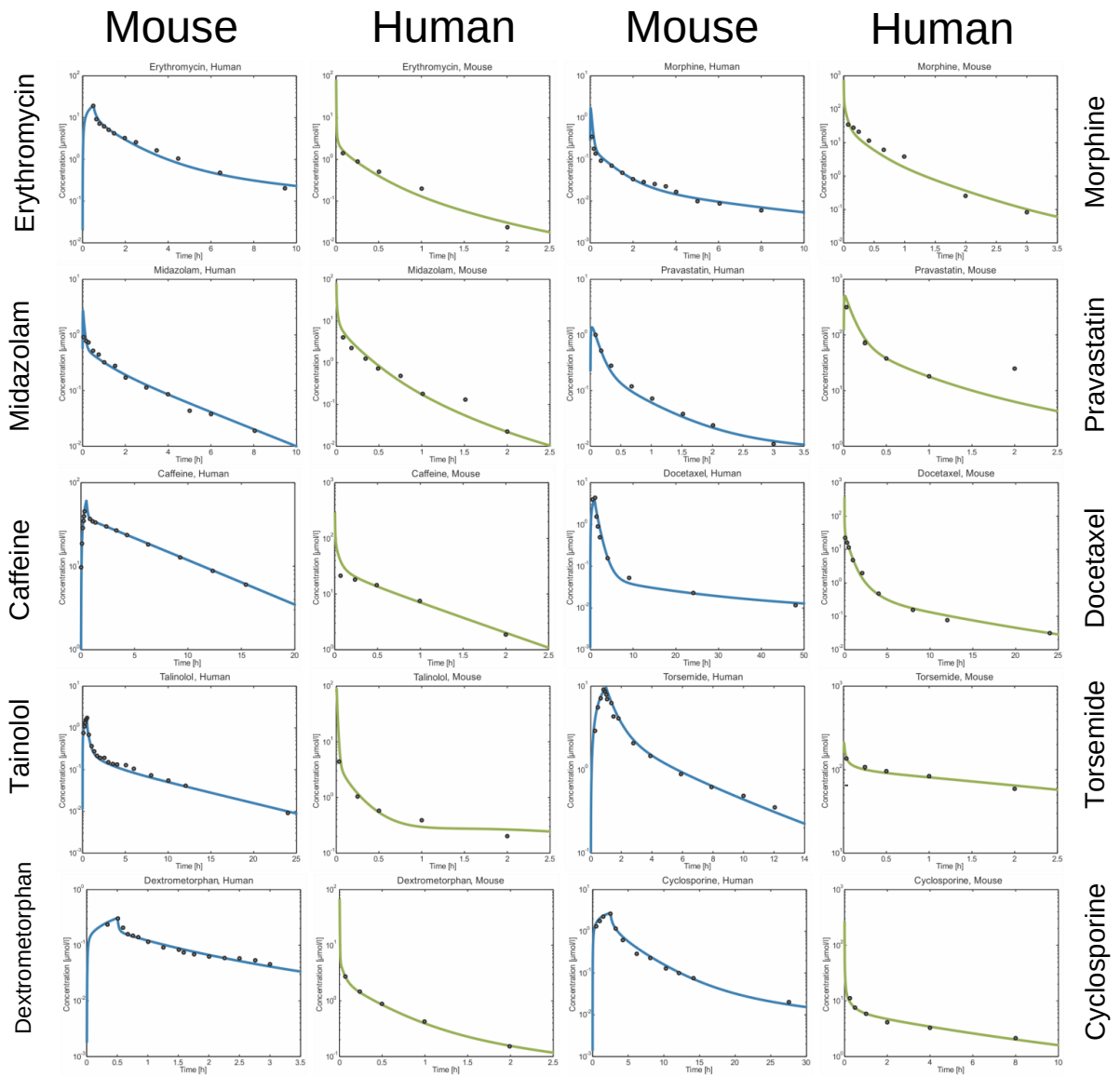
Drug	Log *P*	MW (g/mol)	p*K*a
Torsemide[21]	0.57[22]	348.40[22]	7.10[22]
Talinolol[23]	2.30[24]	363.50[25]	9.43[25]
Midazolam[26]	2.70[27]	325.77[28]	6.04[28]
Caffeine[29]	−0.07[28]	194.20[28]	10.40[28]
Morphine[30]	0.89[28]	285.30[28]	8.20[28]
Docetaxel[31]	2.92[28]	807.88[28]	10.96[28]
Dextromethorphan[32]	3.60[28]	271.39[28]	9.85[28]
Cyclosporine[33]	3.64[28]	1202.60[28]	11.83[28]
Erythromycin[34]	3.06[28]	733.92[28]	8.88[28]
Pravastatin[35]	1.65[28]	424.53[28]	4.56[28]

Route of degradation is governed by a single reaction

Drug	Primary Route of Degradation	Species	Log *P*	F_U	Enzyme/ Transporter	K_M (μmol/L)	v_{max}[a] (μmol/(L*min))
Torsemide	Metabolic[28]	Human	0.57	0.024[36]	CYP2C9	11.20[63]	12.22
		Mouse	0.57	0.050[64]	Cyp2c55	5.20[b]	2.71
Talinolol	Renal[65]	Human	2.27	0.300[25]	ABCB1	0.69[a]	2.13
		Mouse	2.73	0.650[34]	Abcb1a	100.00[66]	44234.00
Midazolam	Metabolic[28]	Human	2.89	0.024[28]	CYP3A4	2.20[67]	23.54
		Mouse	2.95	0.057[68]	Cyp3a[c]	1.35[b]	19.30
Caffeine	Metabolic[28]	Human	0.07	0.700[28]	CYP1A2	400.00[69]	30.40
		Mouse	0.07	0.850[70]	Cyp1a2	452.00[b]	167.10
Morphine	Metabolic[28]	Human	1.45	0.700[28]	UGT2B7	420.00[71]	15910.00
		Mouse	1.45	0.820[71]	Ugt2b[c]	28.70[b]	115.30
Docetaxel	Metabolic[72]	Human	2.92	0.050[73]	CYP3A4	1.10[74]	144.40
		Mouse	2.92	0.100[75]	Cyp3a[a]	10.30[74]	31.50
Dextromethorphan	Metabolic[28]	Human	3.15	0.295[76]	CYP2D6	3.70[77]	7.00
		Mouse	3.20	0.200[76]	Cyp2d22	250.00[78]	1885.00
Cyclosporine	Metabolic[37]	Human	3.71	0.127[79]	CYP3A4	2.10[80]	45.30
		Mouse	3.69	0.062[81]	Cyp3a[c]	5.90[80]	4.10
Erythromycin	Metabolic[28]	Human	3.06	0.145[82]	CYP3A4	44.00[83]	42.05
		Mouse	3.06	0.464[82,84]	Cyp3a[c]	7.50[85]	79.30
Pravastatin	Biliary, renal[28]	Human	1.65	0.500[86]	ABCC2	223.00[87]	495.20
					OATP1B1	11.50[88]	5.50
		Mouse	1.65	0.730[89]	Abcc2	223.00[87]	405.90
					Oatp1b2	11.50[88]	2.50

Thiel *et al.*, *J. Phar. Sci. 2014*

PBPK models of 10 different drugs for both mouse and humans

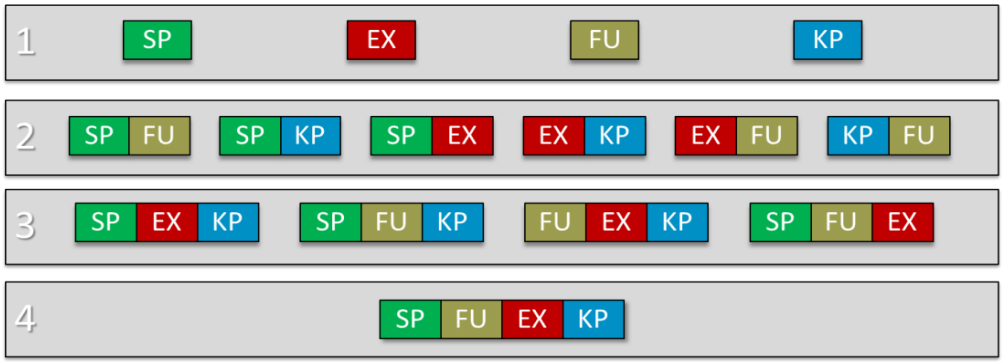


Thiel *et al.*, *J. Phar. Sci. 2014*

Cross-species extrapolation

Consideration of four PBPK parameter domains:

- Species specific physiology (SP)
- Gene expression, i.e. tissue-specific protein abundance (EX)
- Kinetic paramers (KP)
- Fraction unbound (FU)



Thiel *et al.*, *J. Phar. Sci. 2014*

15 combinations × 10 drugs × 2 directions (m2h, h2m) = **300 cases considered**

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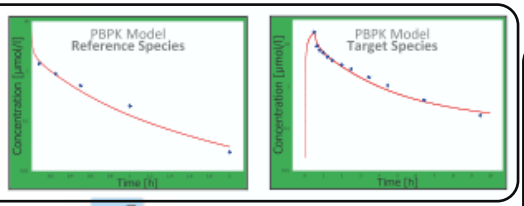
Benchmarking the benefit of using different combinations of parameter domains

PBPK models of reference & target species

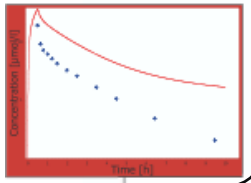


1. Naïve Extrapolation

Integration

SP FU KP EX

Naïve Model

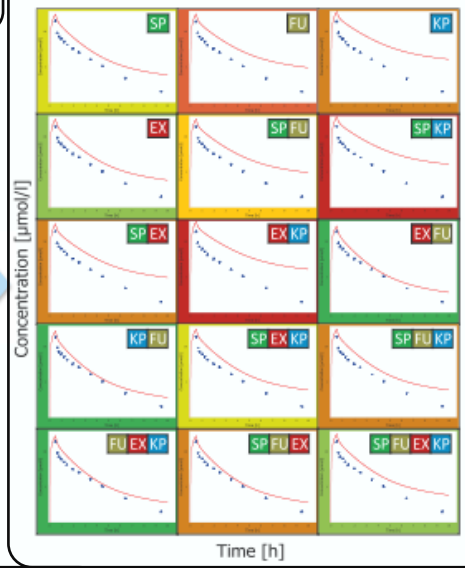


Naive extrapolation (benchmark): dose/(BW weight)

2. Knowledge-Driven Extrapolations

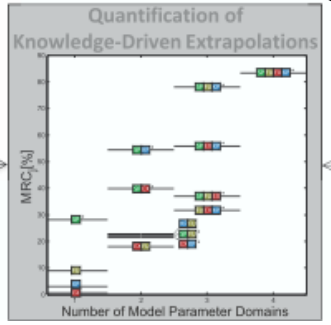
Model Error

Knowledge-Driven Models



15 combinations of parameter domains

Quantification of Knowledge-Driven Extrapolations



Statistical analysis

Thiel *et al.*, *J. Phar. Sci. 2014*

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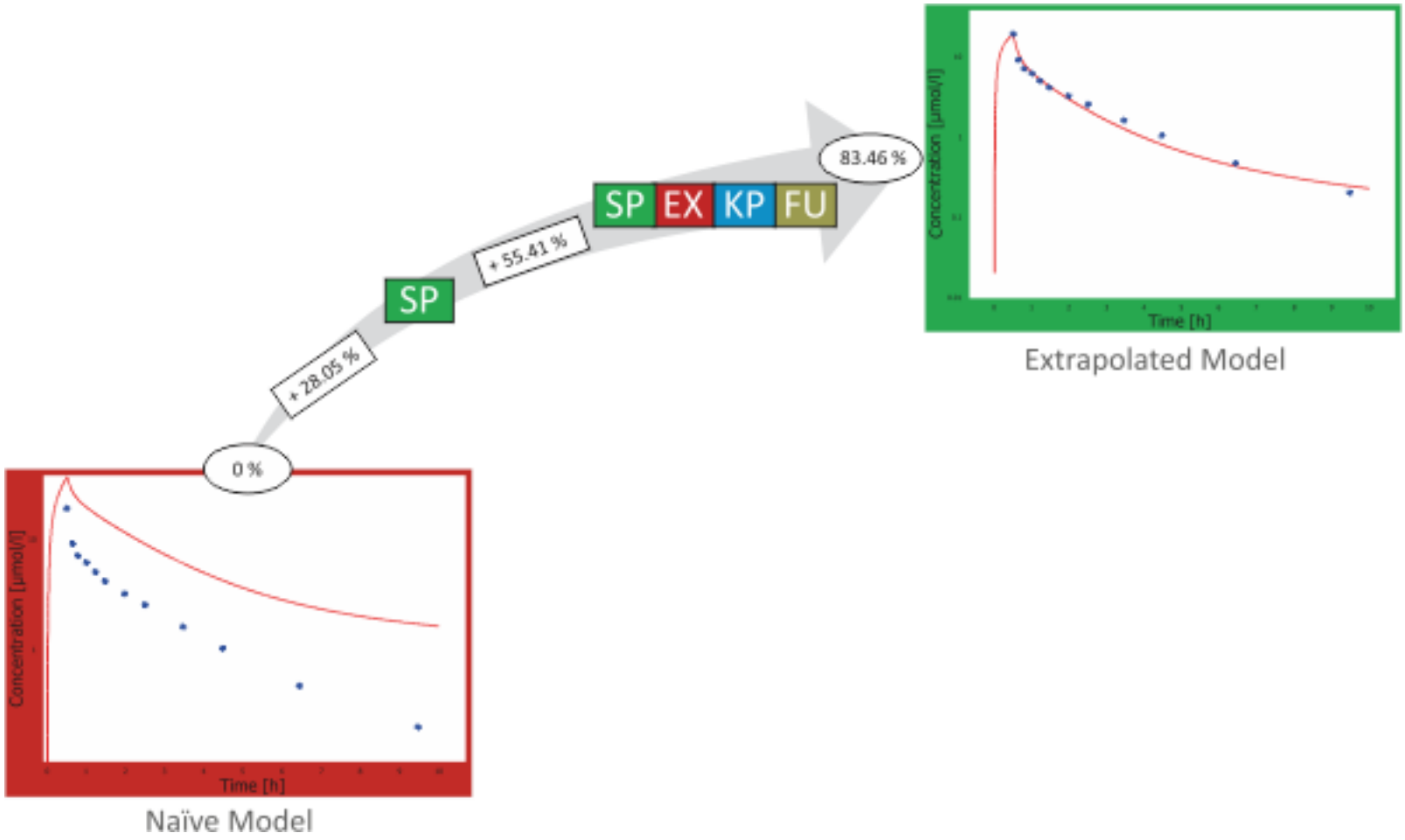
Evaluating the benefit of using additional degree of prior information (i.e. PBPK parameter domains)



Thiel *et al., J. Phar. Sci. 2014*

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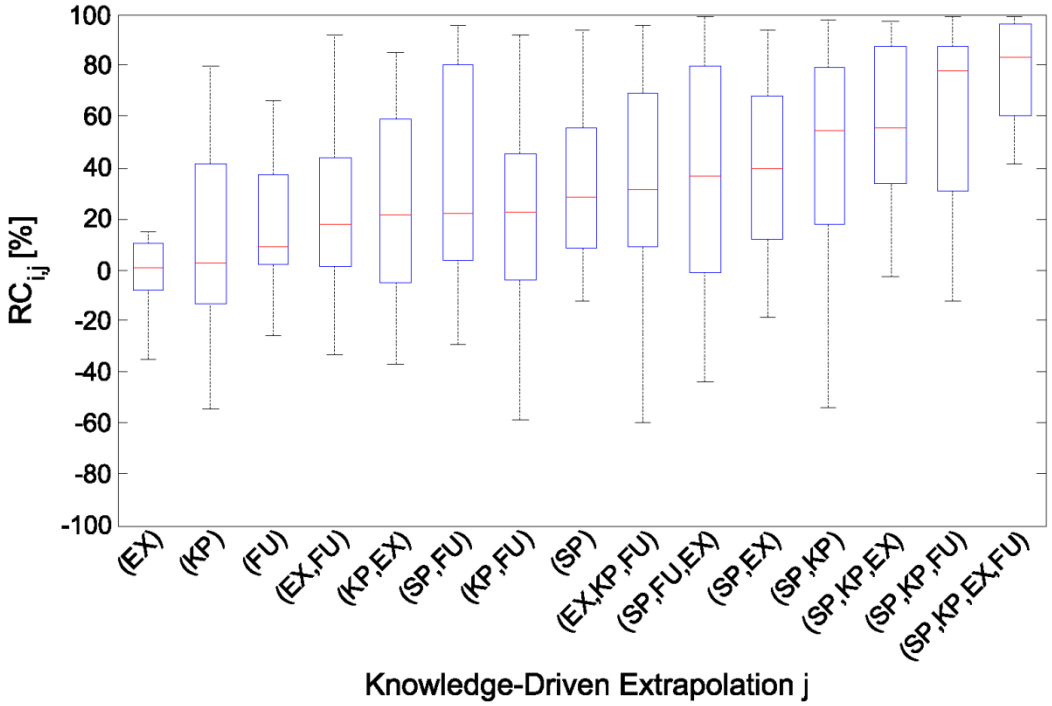
Cross-species extrapolation in clinical development



The relative change (RC) of using different combinations of parameter domains relative to using the naive approach (benchmark) shows significant variability for the ten drugs, yet obvious trends.

Thiel *et al., J. Phar. Sci. 2014*

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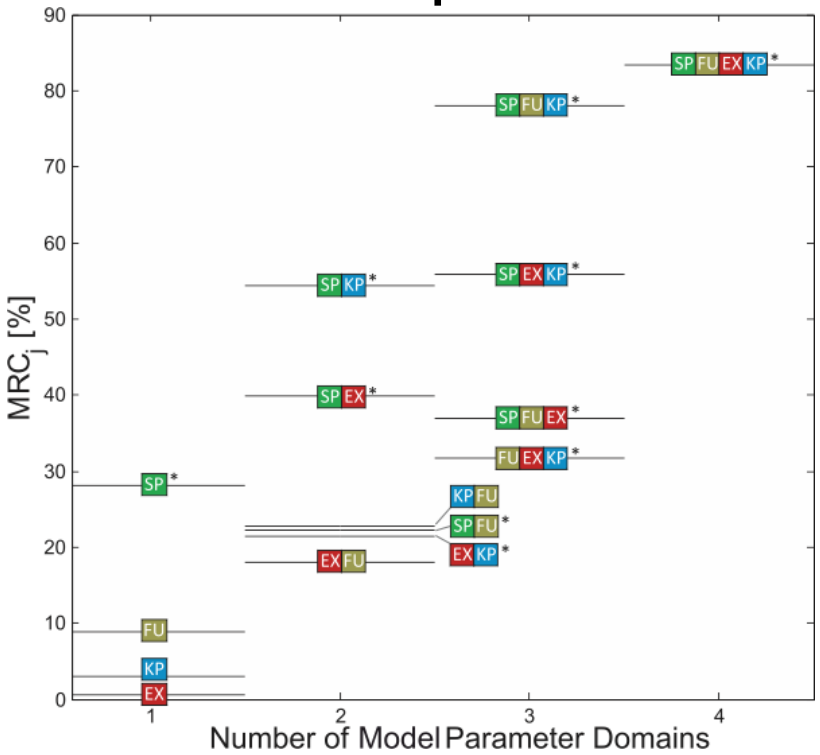
Statistical analysis of 300 cross-species extrapolations



Thiel *et al.*, *J. Phar. Sci. 2014*

Statistical analysis of the results identifies the following key results

1. Species-specific physiology is of major relevance
2. If using all available information, 83.5% of model agreement can be reached
3. Expression data must only be used together with corr. kinetic parameters.

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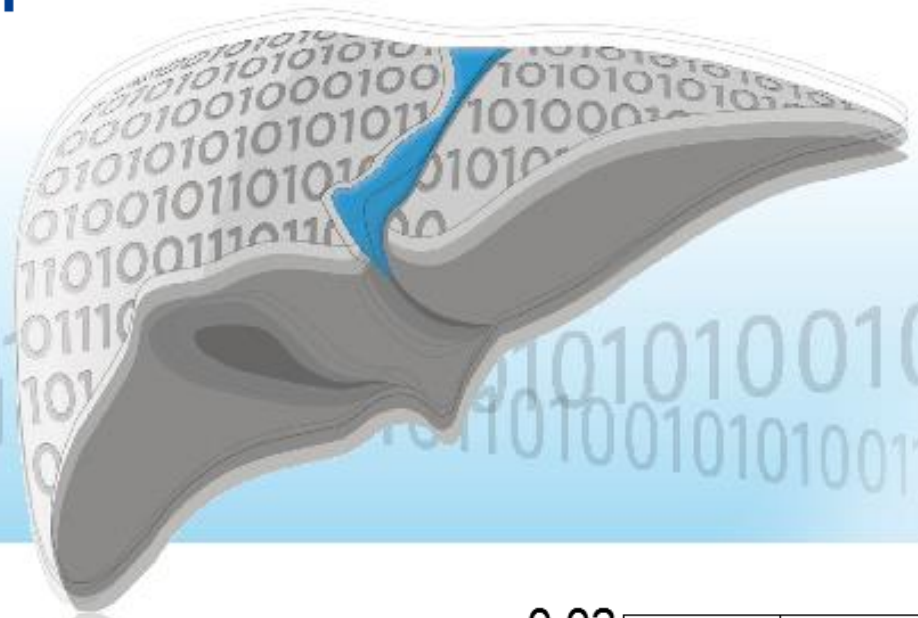
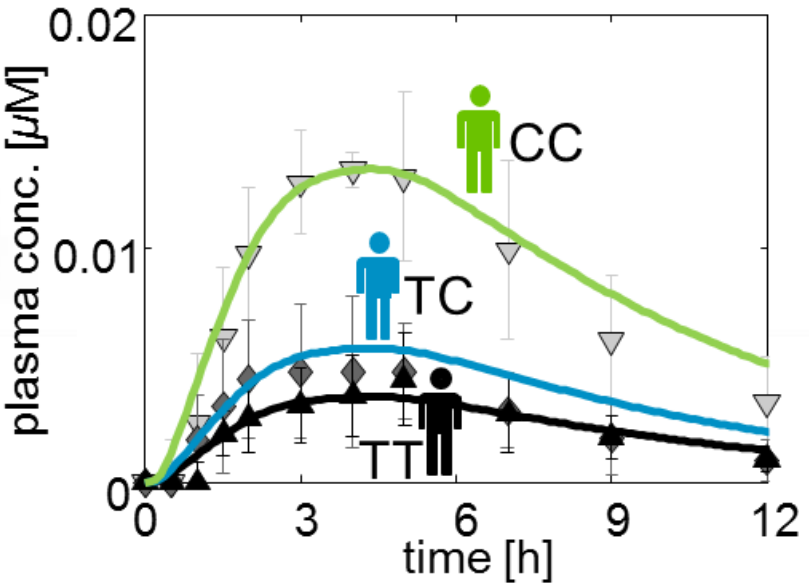
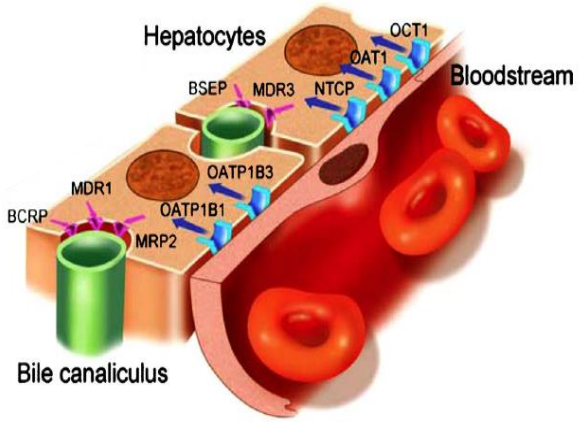


Translational Studies

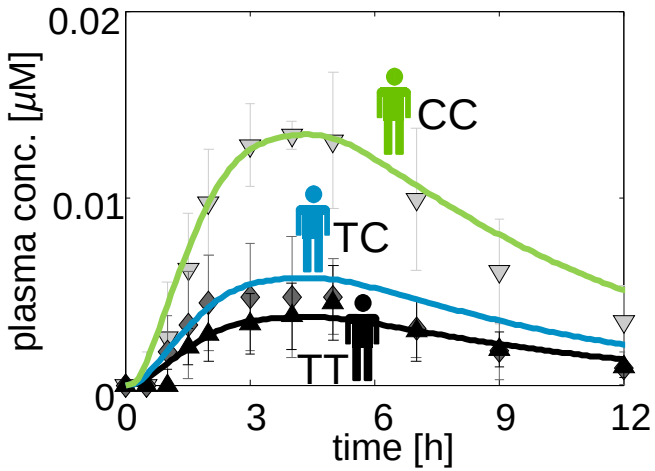


Statin pharmacogenomics

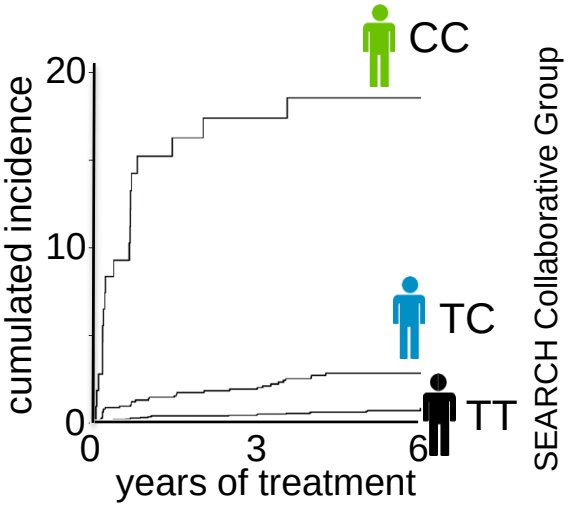
Physiology



Statin PK



GWAS of myopathy



Hepatic uptake by OATP1B1

Genotype-phenotype correlation (c.521T>C SNP)

A mechanistic explanation, however, is lacking as of now

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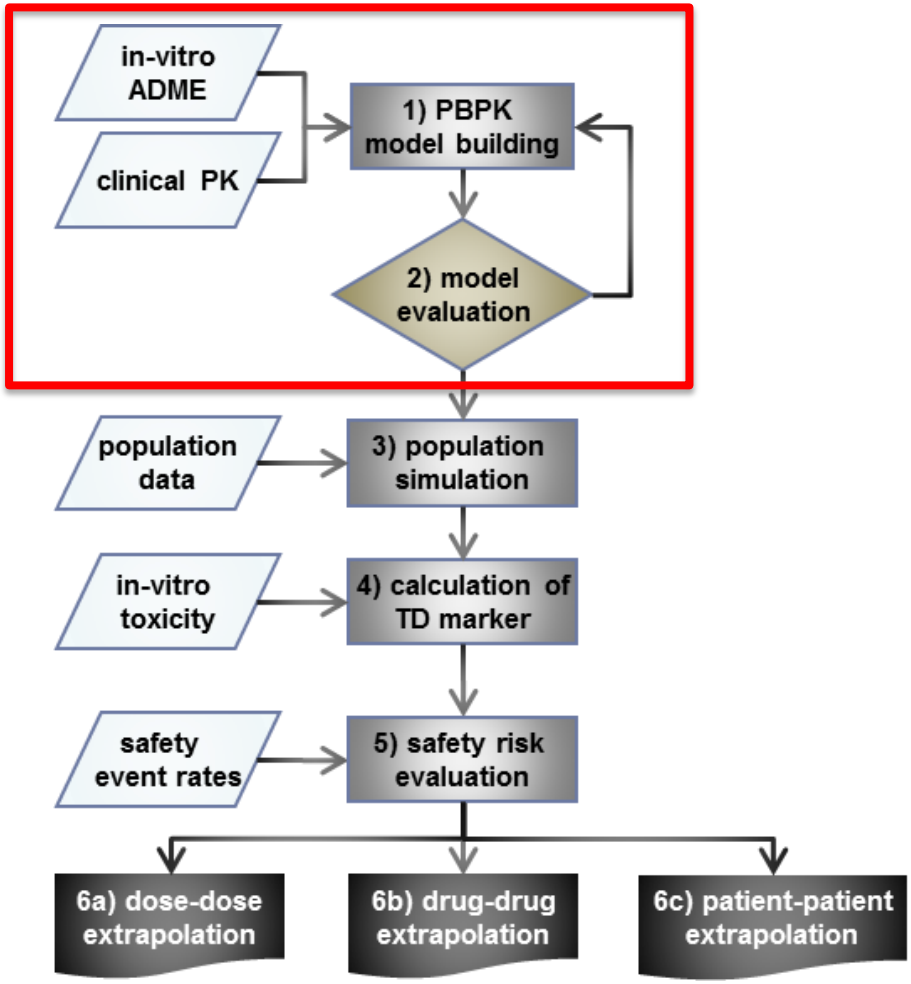
Model-based risk assessment in pharmaceutical R&D



Lippert et al., *CPT:PSP*, *2012*

1. establishment of reference PBPK models
2. model evaluation at relevant scales
3. simulation of virtual populations and model evaluation
4. calculation of toxicodynamic (TD) markers
5. evaluation of the safety risk
6. prediction of drug safety
   a. dose to dose
   b. drug to drug
   c. patient to patient extrapolation

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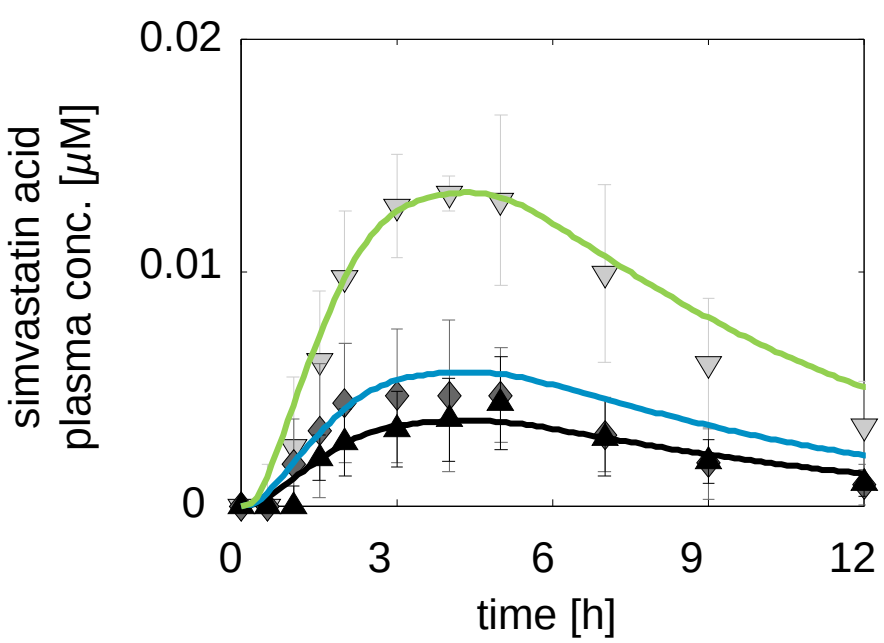
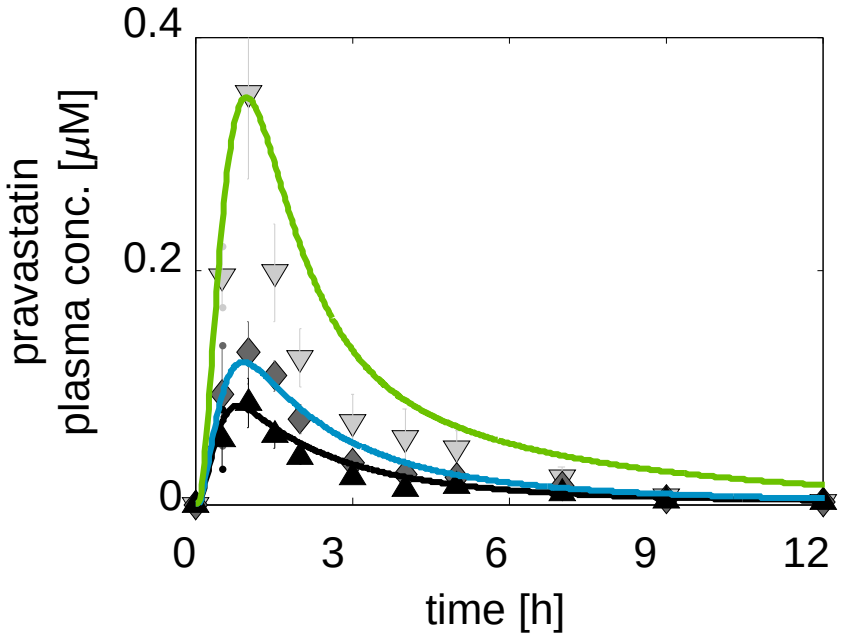
Validating the predictive power for PK genotypes





TT genotype

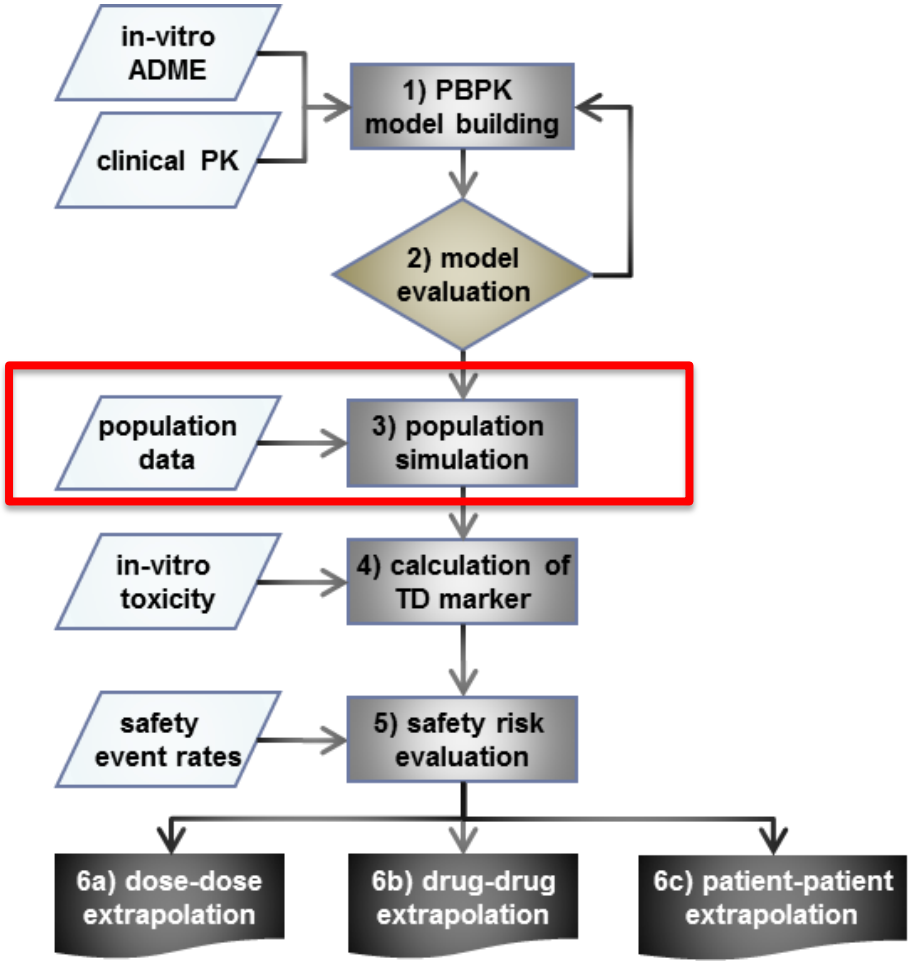
CC genotype

TC genotype

Model is predictive for pharmacokinetic phenotypes

Niemi et al., 2006; Pasanen et al., 2006

Model-based risk assessment in pharmaceutical R&D



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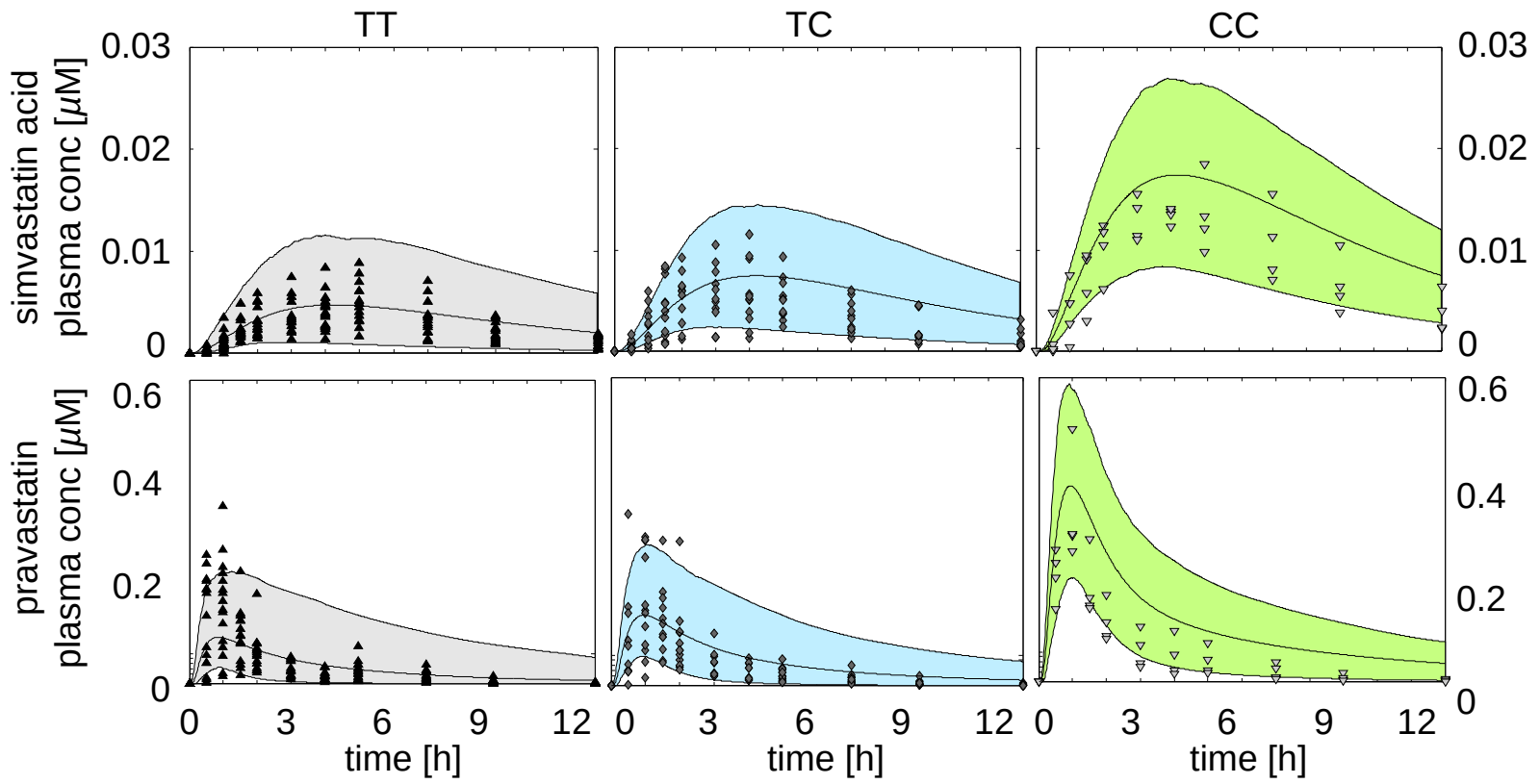
Population simulations

Genotype-specific virtual patient populations (n=1000 individuals).



Lippert et al., *CPT:PSP*, 2012

Pasanen et al., *Pharmacogenet Genomics*, 2006

Niemi et al., *Clin Pharmacol Ther,* 2006

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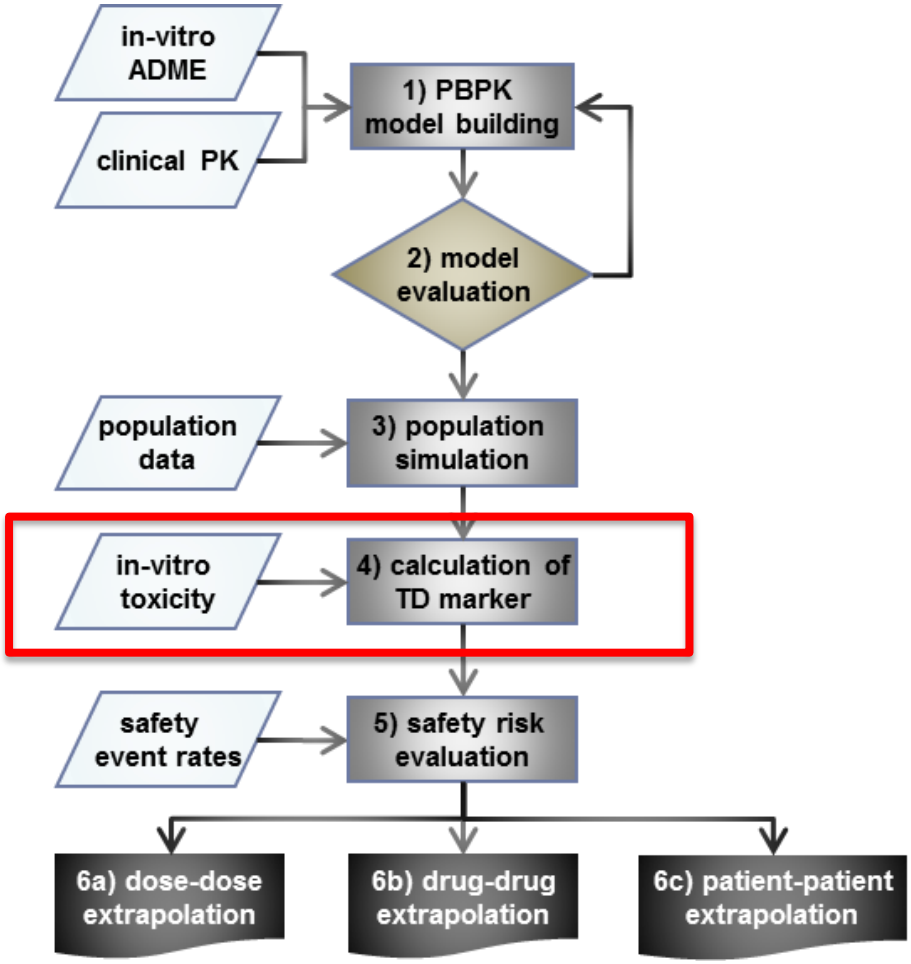
Model-based risk assessment in pharmaceutical R&D



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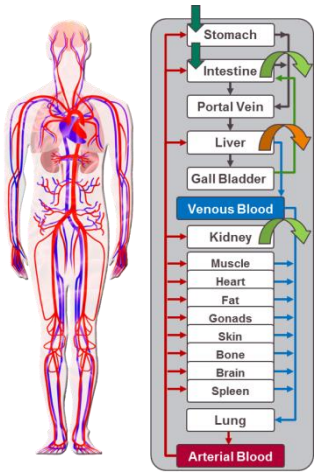
Calculation of a toxicodynamic (TD) marker for statin toxicity

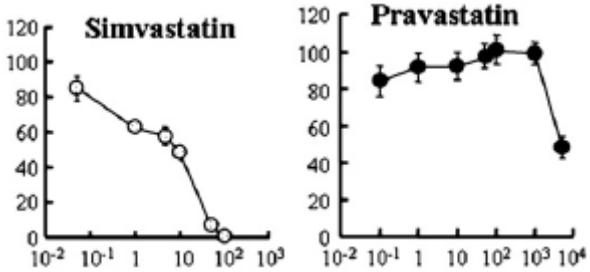


Model-based estimation of drug exposure in the target tissue

$$TD = \frac{C_{max}}{IC50}$$

$IC50_{Simvastatin}$=3.99µM

$IC50_{Pravastatin}$=4890µM



In vitro toxicity (IC50 values) in *embryonal rhabdomyosarcoma* cells

Kobayashiet al., *Life Sciences*, 2008

An *in vivo* marker for statin toxicity

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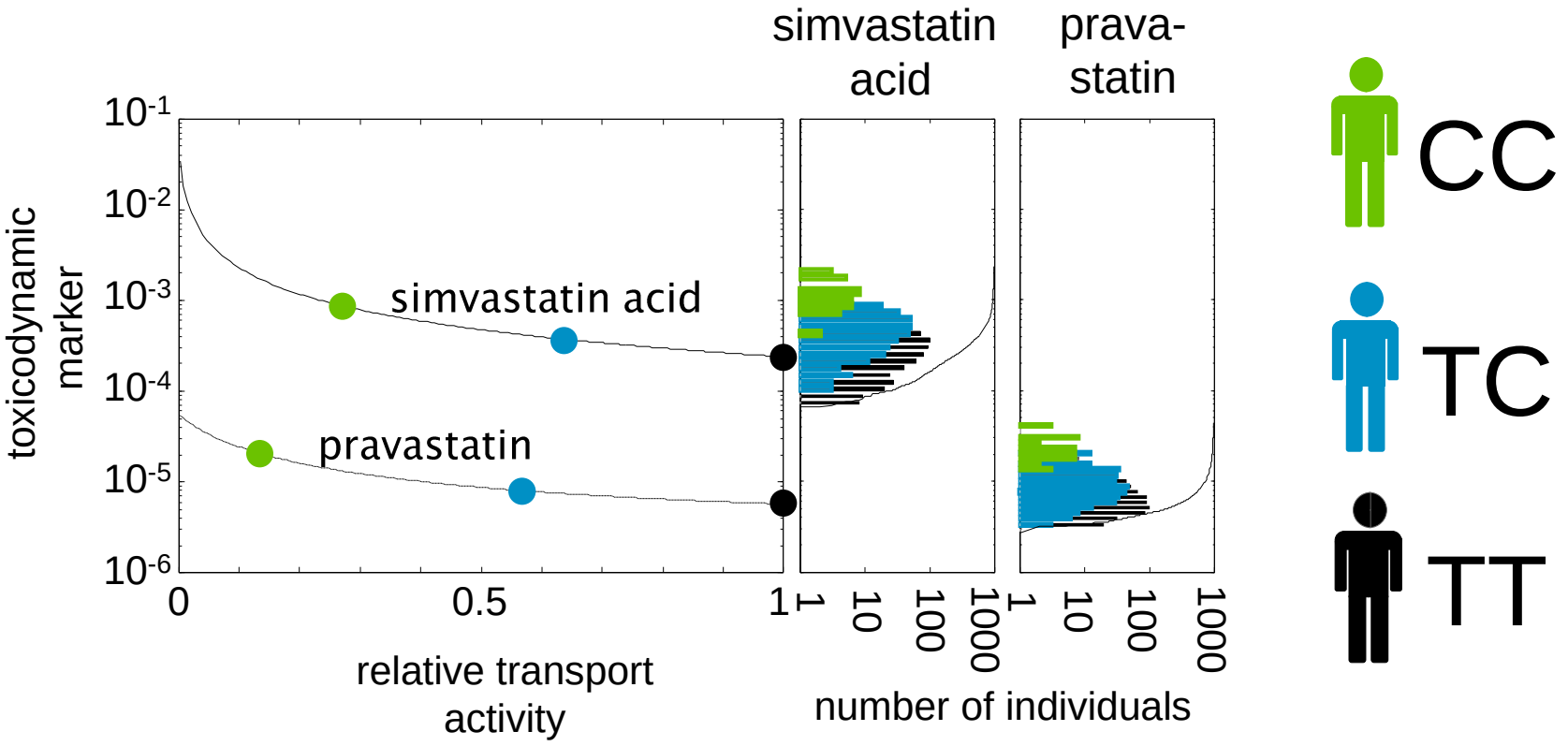
Cumulated distributions of the toxico-dynamic marker for different genotypes



Lippert et al., *CPT:PSP*, 2012

The toxicodynamic marker is considerably higher for simvastatin, which is in agreement with observations in clinical practice.

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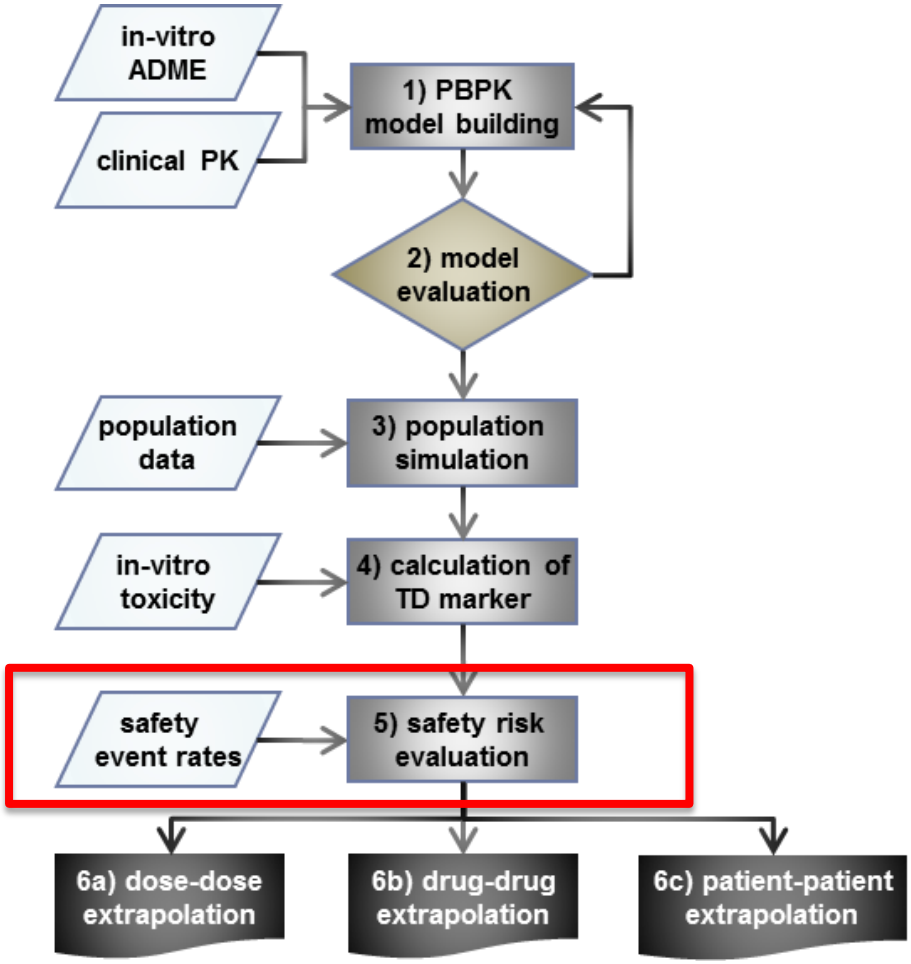
Model-based risk assessment in pharmaceutical R&D



Lippert et al., *CPT:PSP*, *2012*

1. establishment of reference PBPK models
2. model evaluation at relevant scales
3. simulation of virtual populations and model evaluation
4. calculation of toxicodynamic (TD) markers
5. evaluation of the safety risk
6. prediction of drug safety
   a. dose to dose
   b. drug to drug
   c. patient to patient extrapolation

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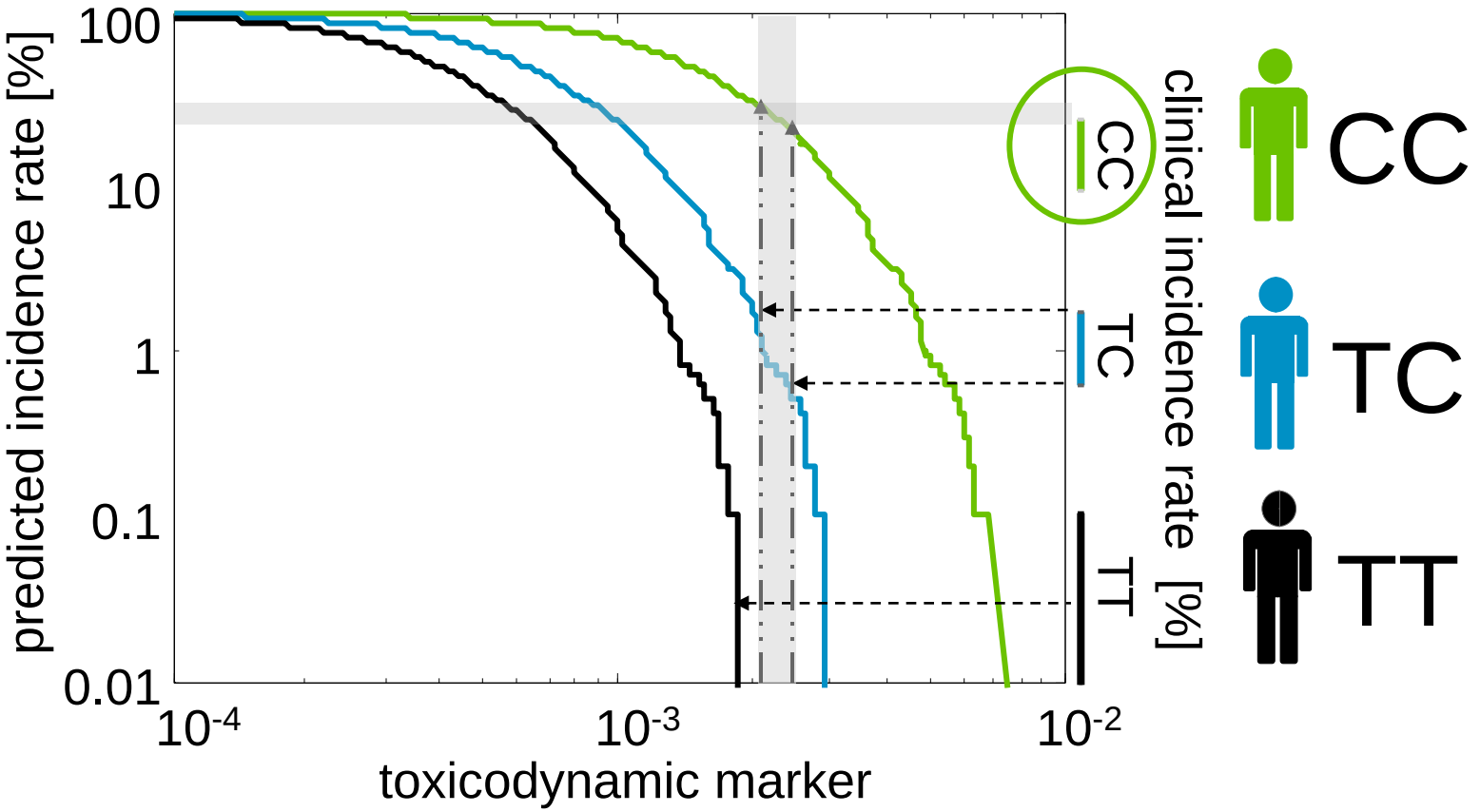
Prediction of clinical incidence rates for the rare CC-subpopulations.



Lippert et al., *CPT:PSP*, *2012*
SEARCH Collaborative Group, *NEJM*, 2010

A model-based approach to safety assessment in clinical development

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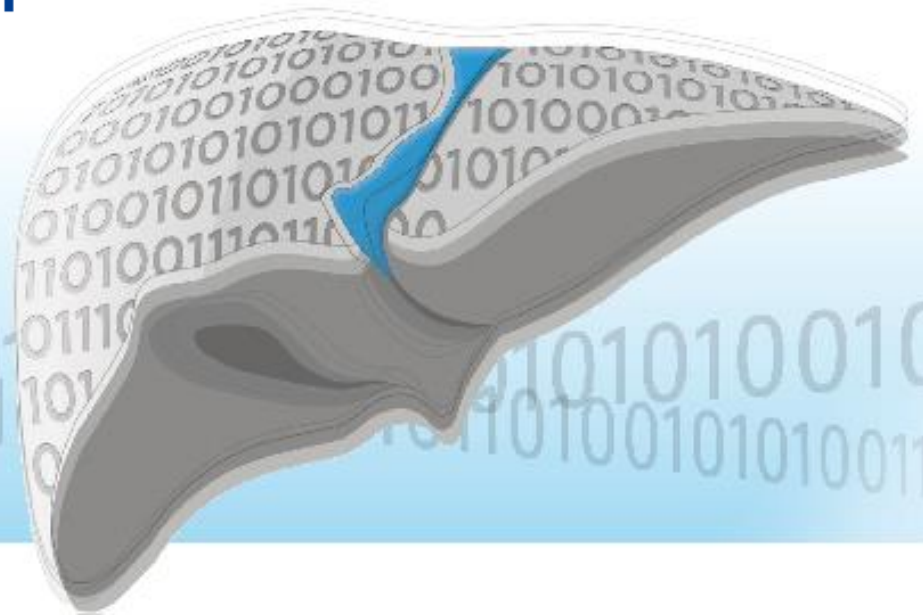
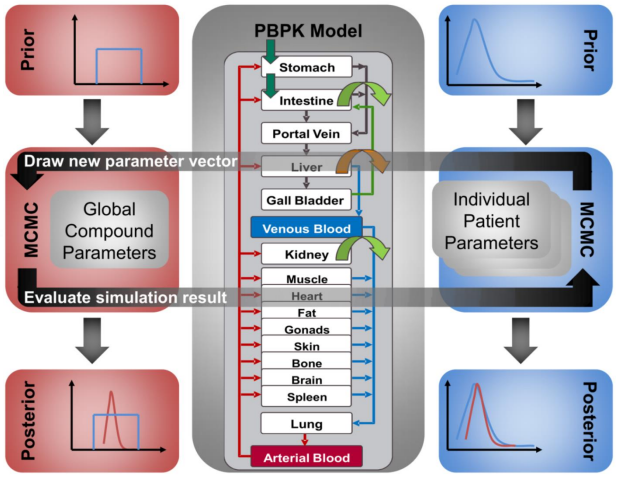
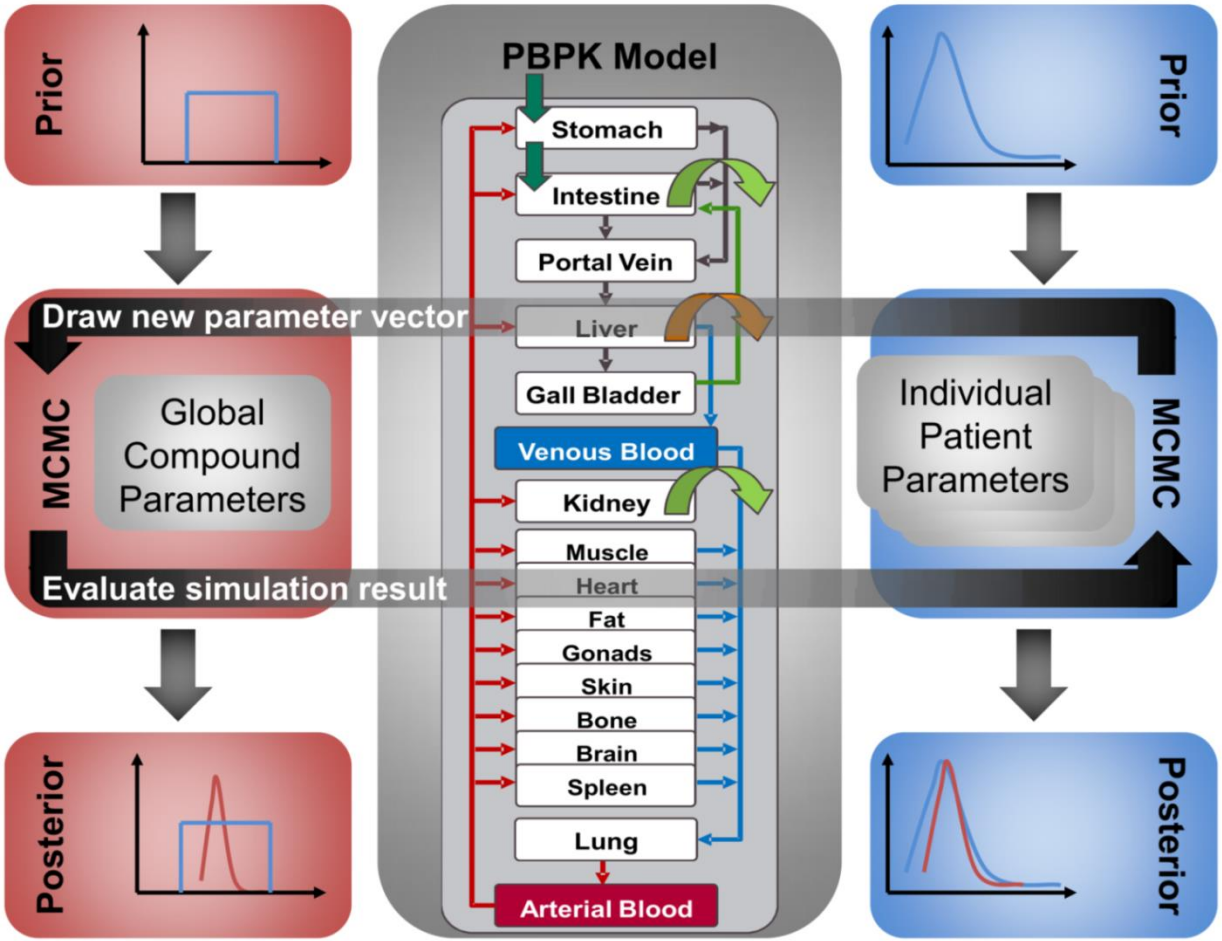


Bayesian PBPK



Bayesian PBPK



Krauss et al., *In silico pharmacol*, 2013

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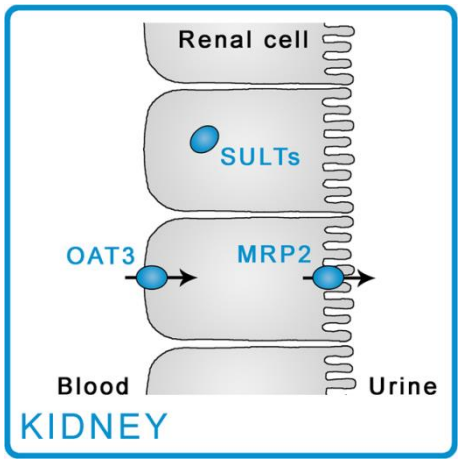
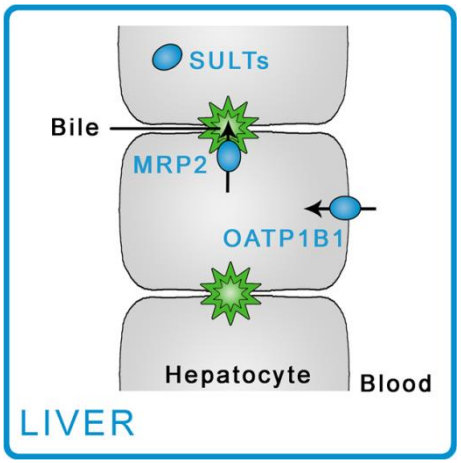
PBPK model for pravastatin

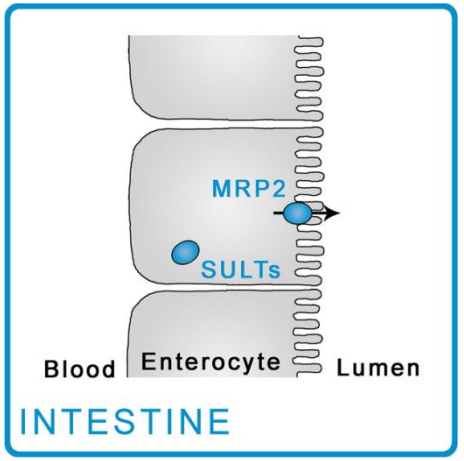
Pravastatin:

- low lipophilicity
- degradation by sulfotransferases in various tissues
- uptake and secretion by active transport processes in various tissues: OATP1B1, OAT3, MRP2

➔ protein abundance was estimated by using tissue-specific gene expression levels a surrogate







Krauss et al., *In silico pharmacol*, 2013

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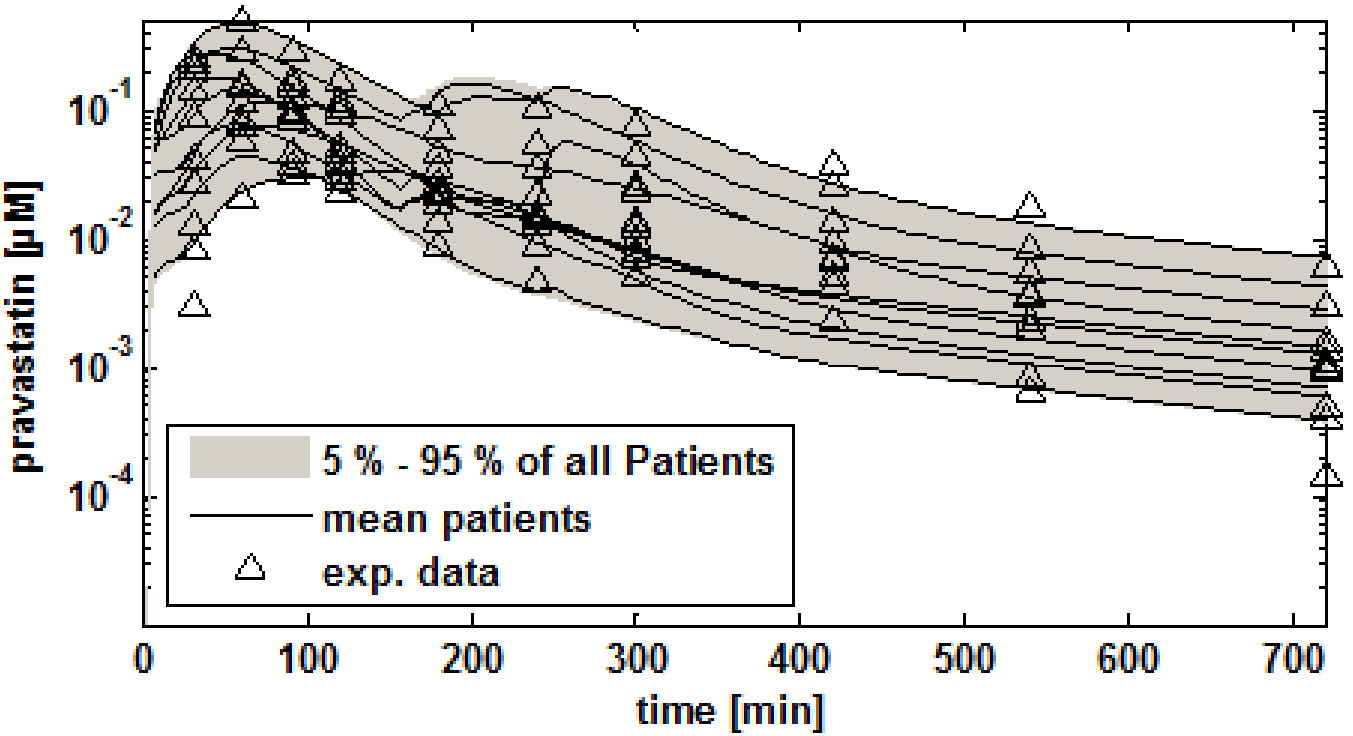
Variability of pravastatin pharmacokinetics

200 parameter vectors from the posterior distribution obtained with Bayesian PBPK were used to perform population PK simulations

➔ **Quantification of inter-individual variability**



Niemi et al., *Clin Pharmacol Ther*, 2006
Krauss et al., *In silico pharmacol*, 2013

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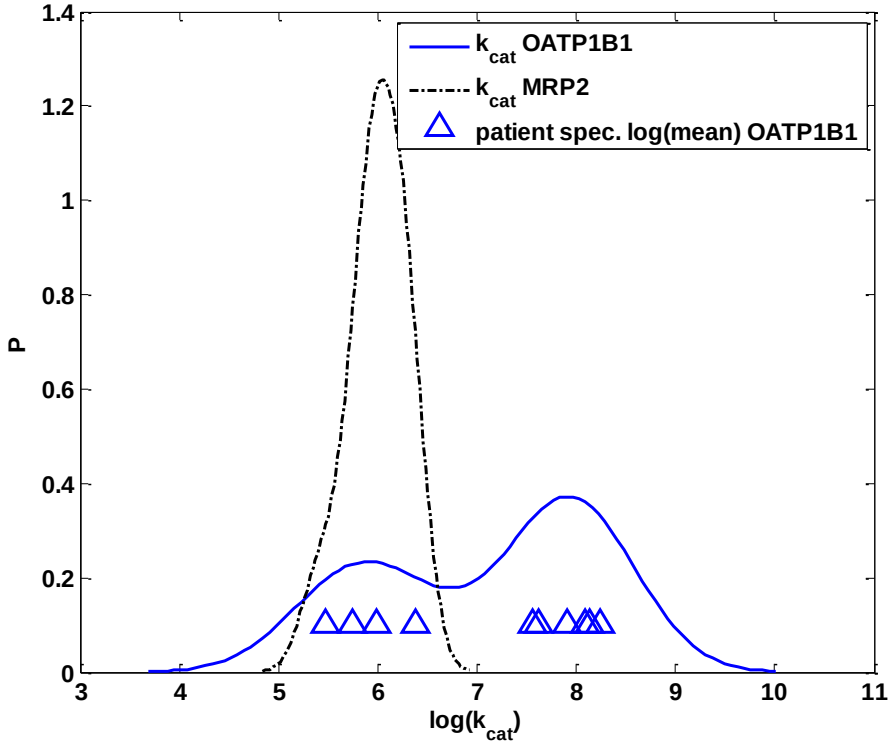
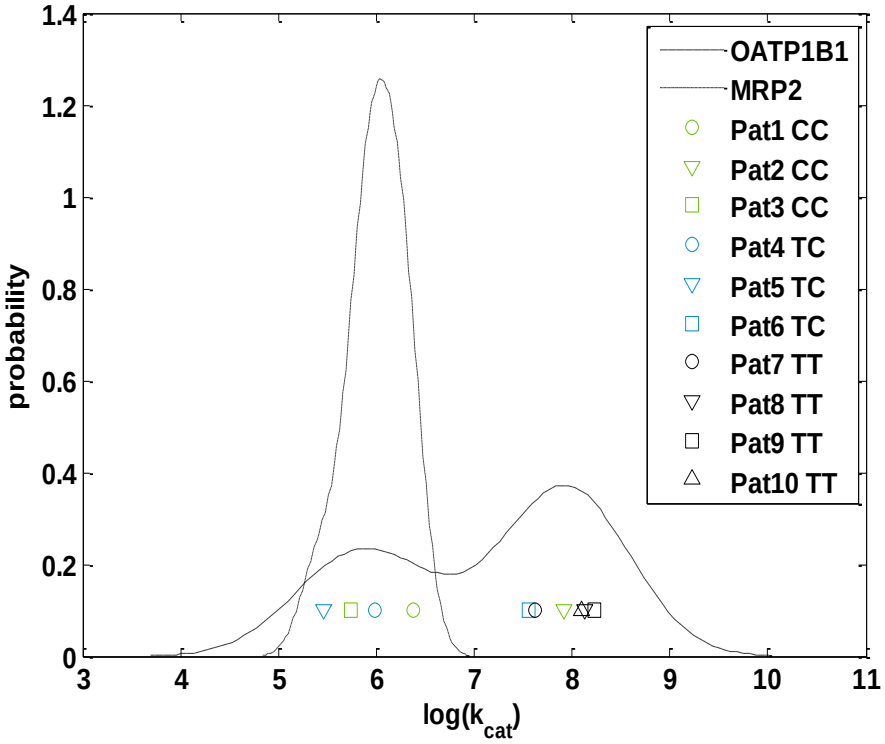
Identification of subgroups

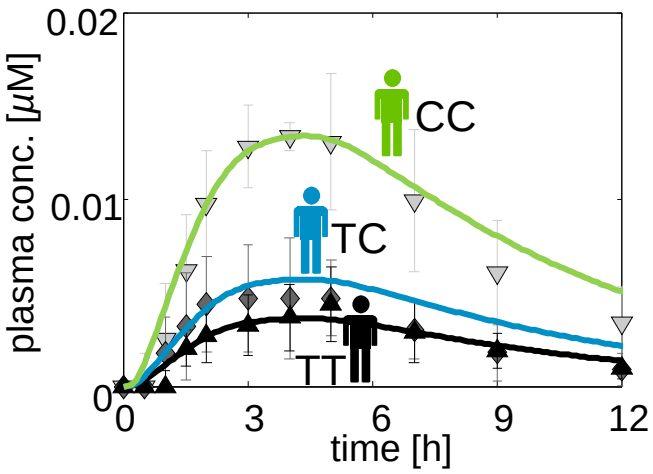


The distribution of OATP1B1 transporter efficacy (k_{cat}) shows a bi-modal behavior indicating the existence of specifc patient subgroups!

Krauss et al., *In silico pharmacol*, 2013

Pravastatin pharmacogenomics





Krauss et al., *In silico pharmacol*, 2013

Plotting OATP1B1 transporter efficacies for patients with known OATP1B1 genotype can be assigned to the two different subgroups

➔ **Huge potential for (early) clinical development**

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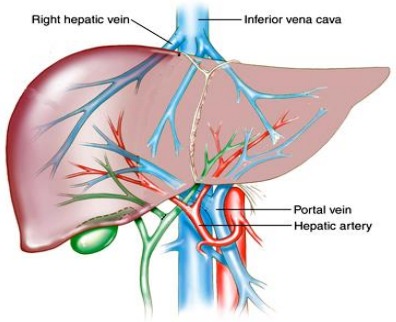
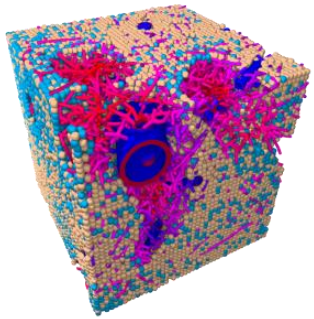
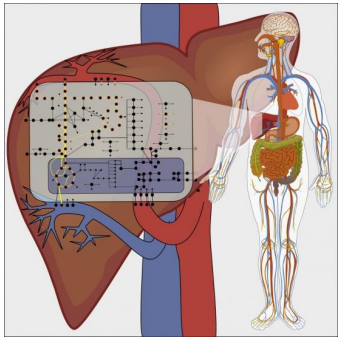
Summary

- models of the liver as the key detoxification organ in the human body

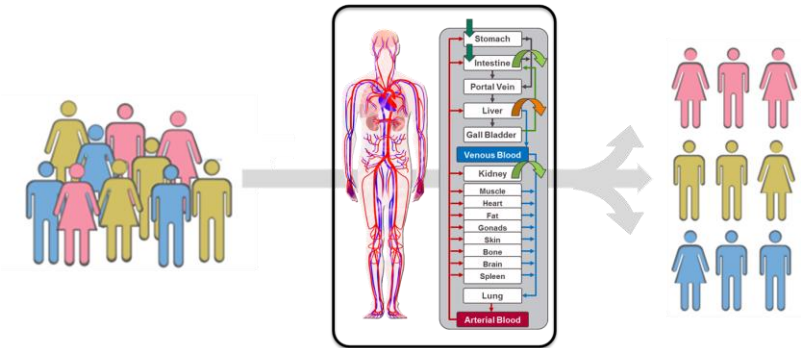




- representation of the liver within the context of the organism



- clinical translation



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