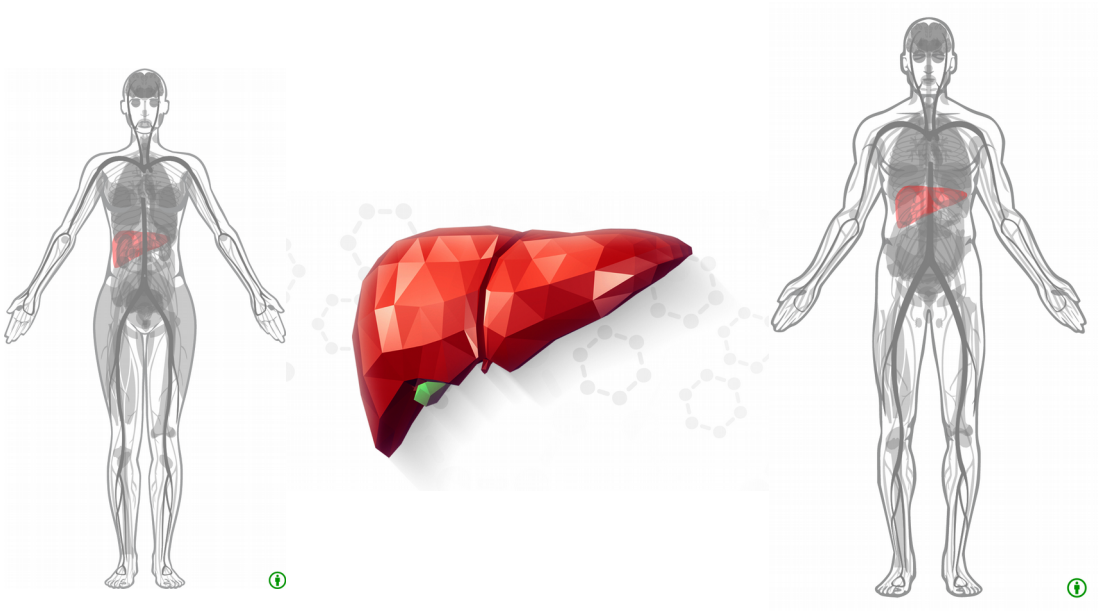
LiSyM
Liver Systems Medicine

Bundesministerium
für Bildung
und Forschung



Physiological based pharmacokinetics models for analysis of liver function

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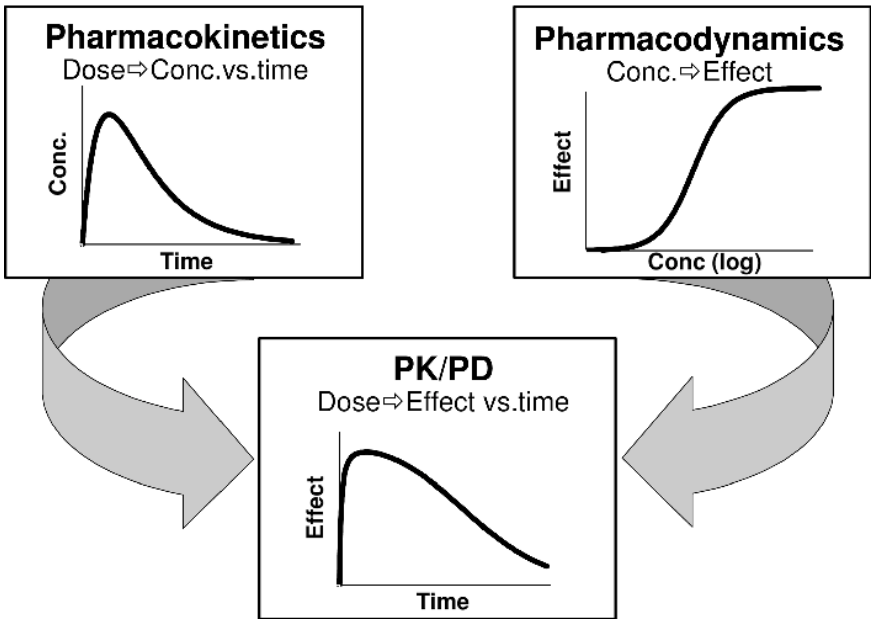
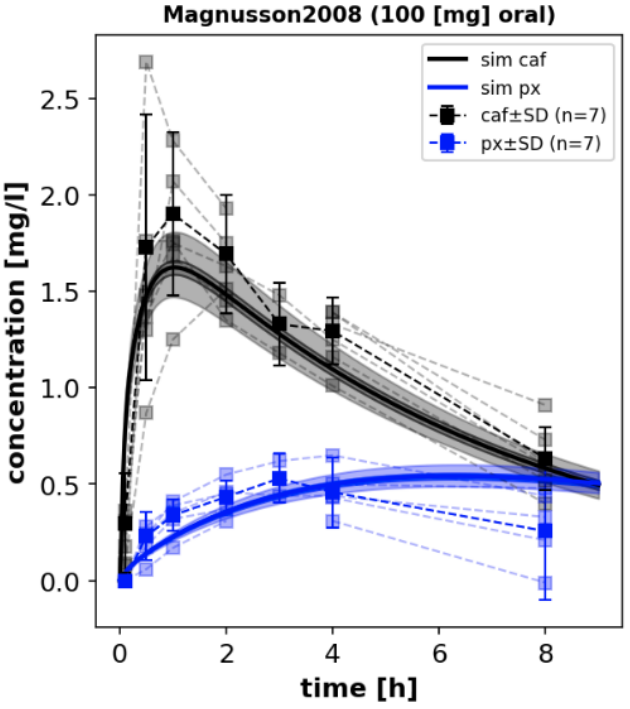
GERMAN NETWORK FOR BIOINFORMATICS INFRASTRUCTURE

Pharmacokinetics & pharmacodynamics

- **Pharmacokinetics** is **what the body does to the drug**, i.e., how the drug is absorbed, distributed, metabolized & excreted (**drug disposition**)
- **Pharmacodynamics** is what the drug does to the body (**therapeutic effects**)





100 mg oral caffeine

Pharmacokinetic parameters

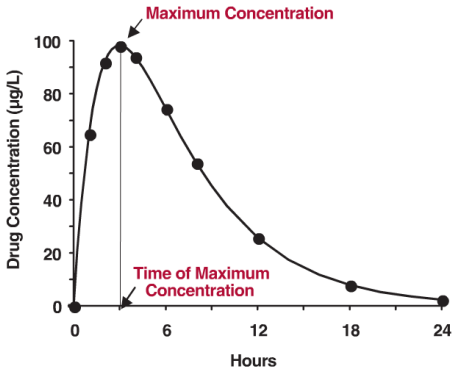


FIGURE 2-1. Drug concentration–time curve following a single oral dose showing the maximum systemic exposure (C_{max}) and the time of its occurrence (t_{max}). The concentration could represent drug in whole blood, plasma, or serum.

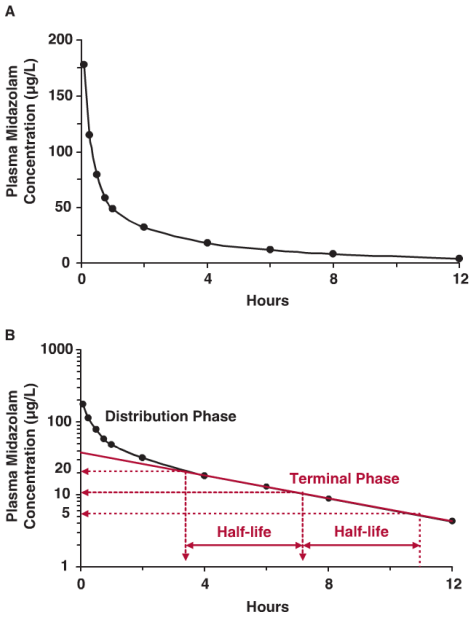


FIGURE 3-4. **A.** Plasma concentration of midazolam with time in an individual after an 8.35-mg i.v. bolus dose of midazolam hydrochloride (7.5 mg of the base) in a healthy adult. **B.** The data in A are redisplayed as a semilogarithmic plot. Note the short distribution phase. (From: Pentikäinen PJ, Välisalmi L, Himberg JJ, Crevoisier C. Pharmacokinetics of midazolam following i.v. and oral administration in patients with chronic liver disease and in healthy subjects. J Clin Pharmacol 1989;29: 272–277.)

- **C_{max}** : Maximal concentration
- **T_{max}** : time of maximal concentration
- **AUC** : area under the curve
- **k_{el}**: elimination rate
  fitting linear part of terminal phase (log)
- **$t_{1/2}$** : half-life (= $\ln 2/k_{el}$)
  time for concentration to fall to half
- **Vd**: volume of distribution
  (= CL/k), dilution space
- **CL**: clearance (=Dose/AUC, $=\text{Dose}/C(0)_{extrapolated}$)

Compartment models

- Pharmacokinetics can be modeled via simple compartment models
- Main processes (**ADME**)
  - **A**bsorption
  - **D**istribution
  - **M**etabolization
  - **E**limination

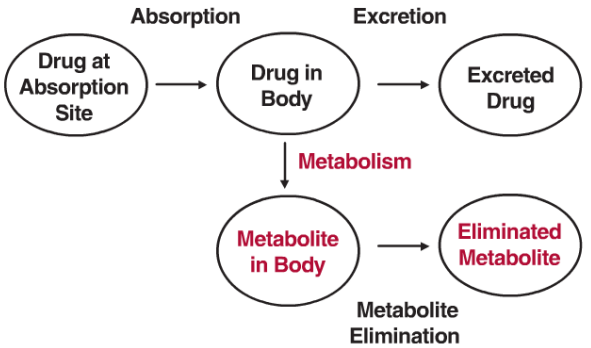


FIGURE 2-5. A drug is simultaneously absorbed into the body and eliminated from it, by excretion and metabolism. The processes of absorption, excretion, and metabolism are indicated with arrows and the compartments with ovals. The compartments represent different locations and different chemical species (color = metabolite). Metabolite elimination may occur by further metabolism or excretion.

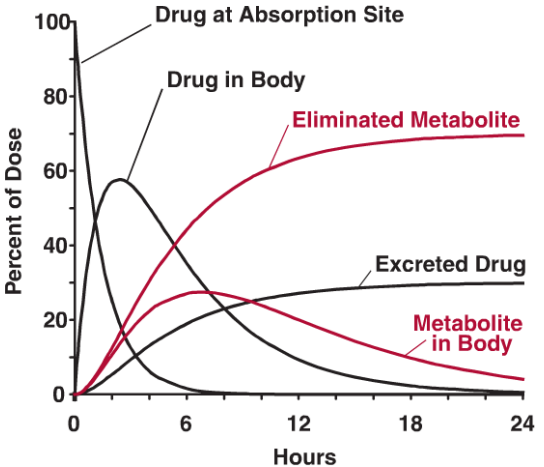
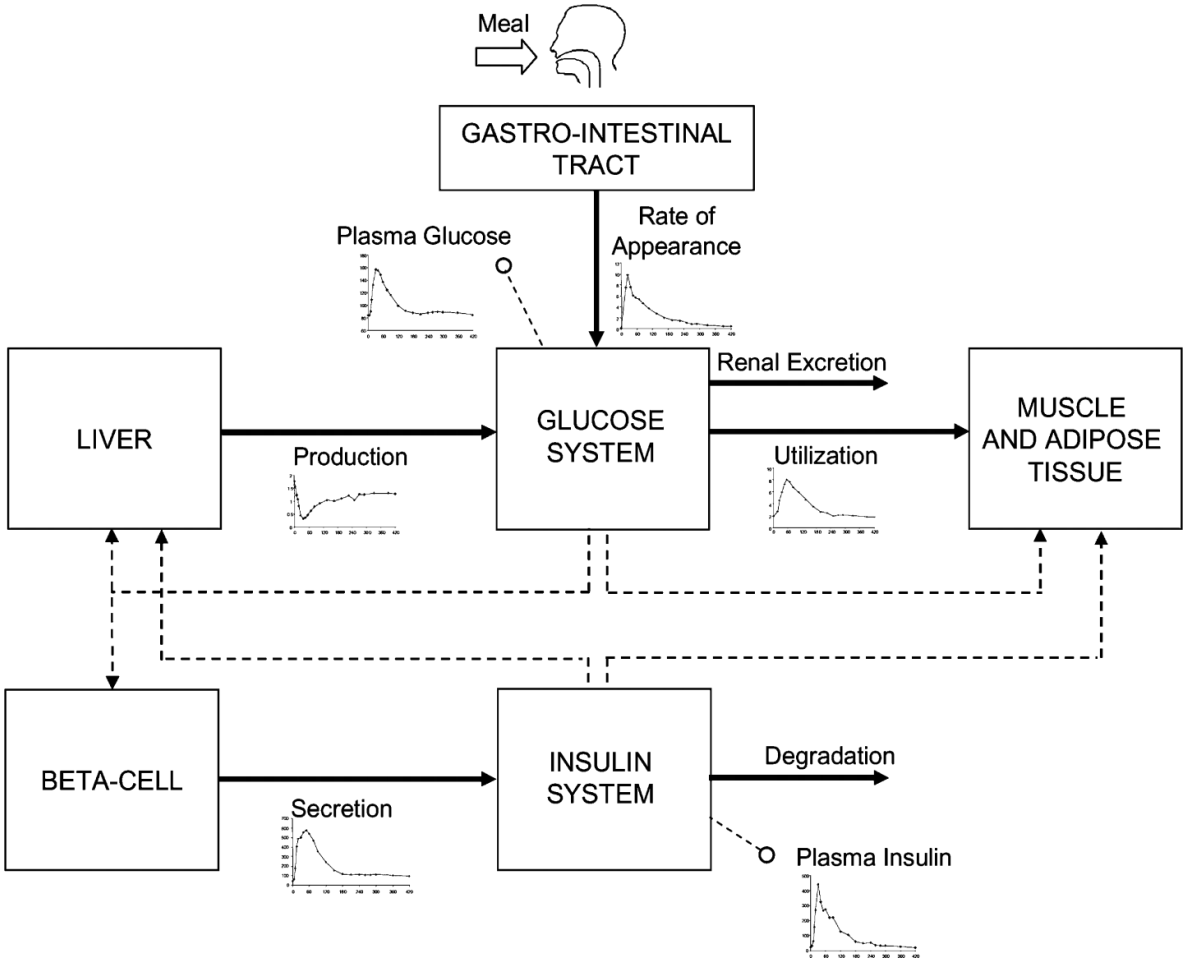
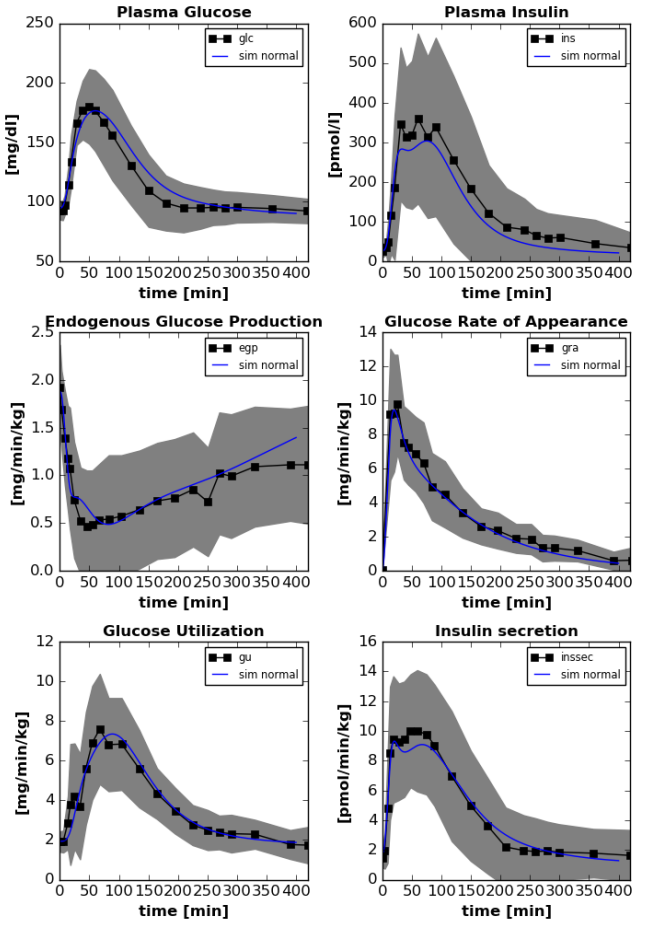


FIGURE 2-6. Time course of drug and metabolite in each of the compartments shown in Fig. 2-5. The amount in each compartment is expressed as a percentage of the dose administered. In this example, all the dose is absorbed. At any time, the sum of the molar amounts in the five compartments equals the dose.

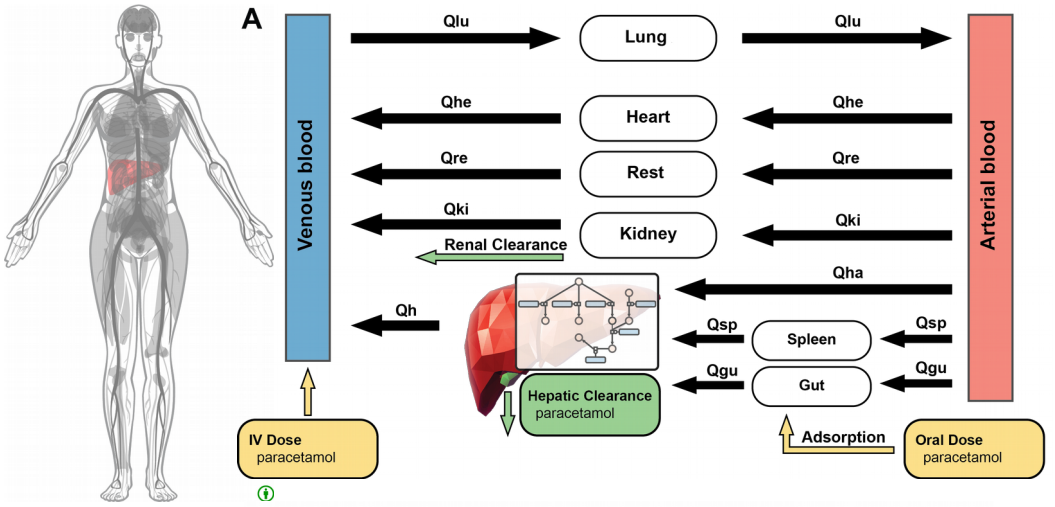
Example: Glucose Insulin system

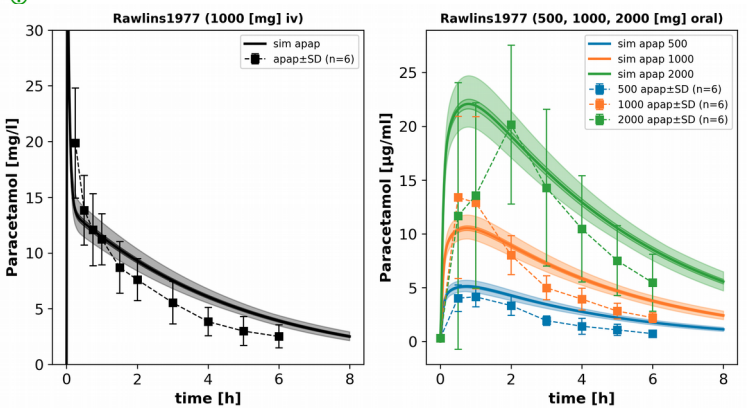




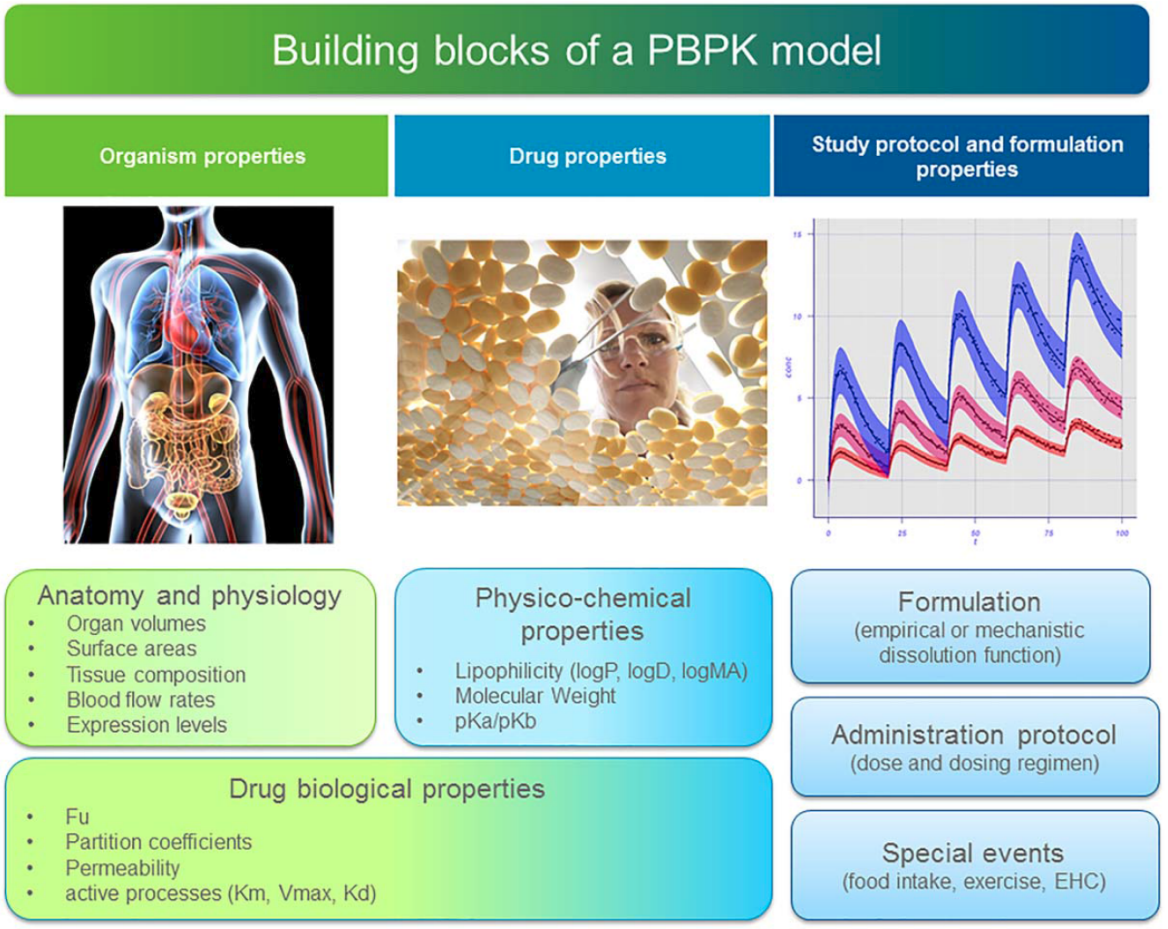
Physiological-based pharmacokinetics models (PBPK)

- Human (animal) physiology *in silico*
- **Tissues are linked by arterial and venous blood compartments** characterized by associated blood flow rates, tissue-partition coefficient , and permeability
- combines information on the drug with knowledge on the physiology and biology at organism level
- **Time dependent concentrations of substances/drugs in organs, blood & urine**
- High pharmacological relevance since it enables the estimation of drug exposure not only in plasma but also at the site of action





PBPK Models



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Compartments

- organs

State variables:

- drug & metabolite amounts

Ordinary Differential equations (ODE) & rules

- Blood flows, Transport, Disposition
- Metabolism, Elimination
- Absorption

Parameters

- Tissue partition coefficients
- Protein binding
- Kinetic parameter (transport & elimination)
- Blood flows, organ volumes, …

PBPK Applications

Cross-Species Extrapolation

PBPK models can be used to facilitate the extrapolation of knowledge generated in various preclinical species to humans

Drug Drug Interactions (DDI)

Thanks of the explicit inclusion of enzymatic processes, the combination of two or more models allow the prediction of interaction between drugs

Individual Dosing

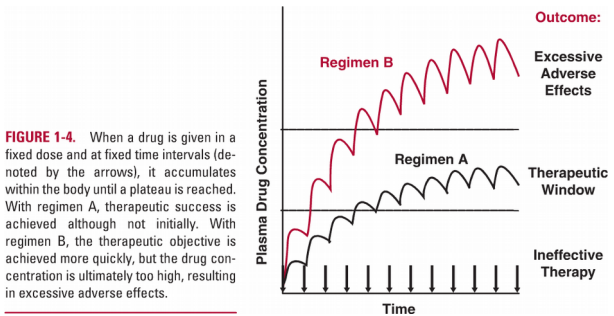
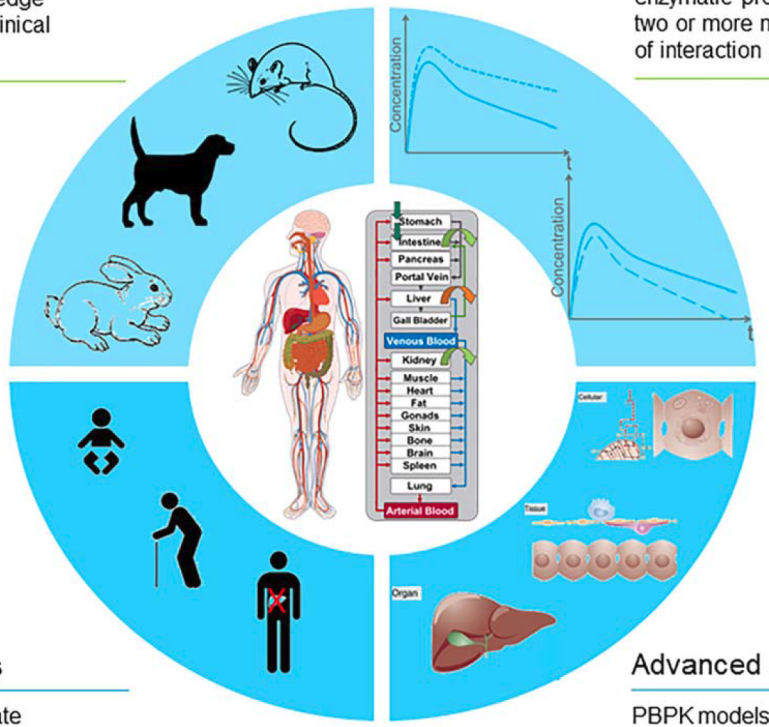


FIGURE 1-4. When a drug is given in a fixed dose and at fixed time intervals (denoted by the arrows), it accumulates within the body until a plateau is reached. With regimen A, therapeutic success is achieved although not initially. With regimen B, the therapeutic objective is achieved more quickly, but the drug concentration is ultimately too high, resulting in excessive adverse effects.

In silico drug trials



Special Populations

By including the appropriate physiological information, PBPK models can be used to make predictions in special populations

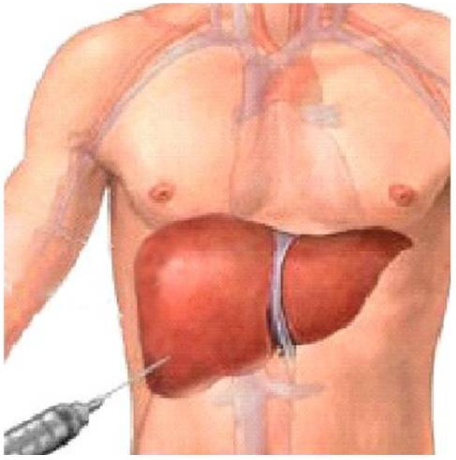
Advanced Applications

PBPK models can also be integrated in more complex models such as multiscale modelling or statistical modelling, using methods such as Bayesian approaches

Figure 3 Schematic representation of the most common applications of PBPK modeling.

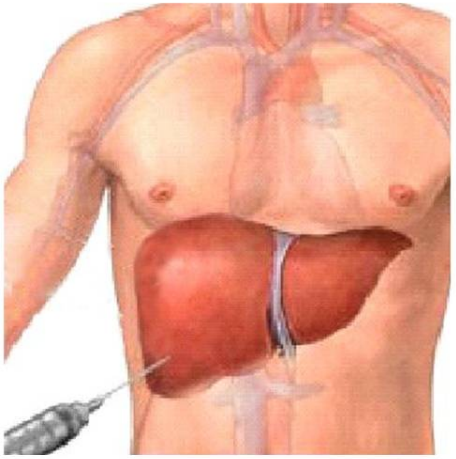
What is the functional status of the liver of a patient?

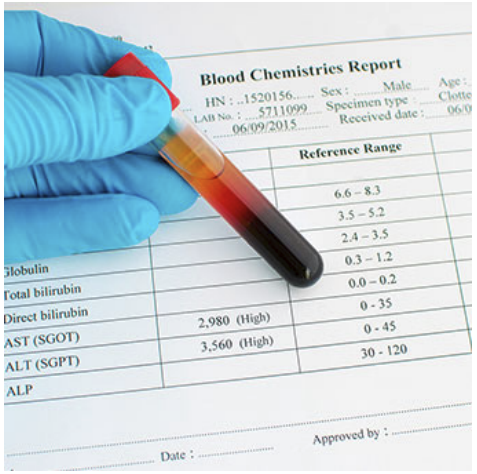
- Diagnostics
- Monitoring disease progression & interventions
- Functional capacity (transplantation & resection)



Liver biopsy
“gold standard”

- histology not function
- highly invasive
- sampling & interobserver variability





Liver biopsy “gold standard”

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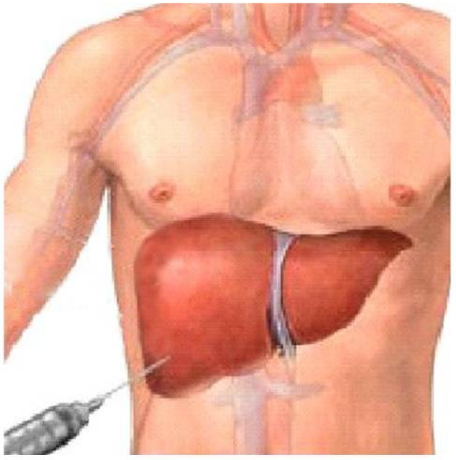
- highly invasive
- sampling & interobserver variability

Liver function tests

- static biochemical parameters
- AST, ALT, ALP, GGT, ...
- prothrombin, albumin, ...
- no reliable marker to quantify liver function (or functional reserve)



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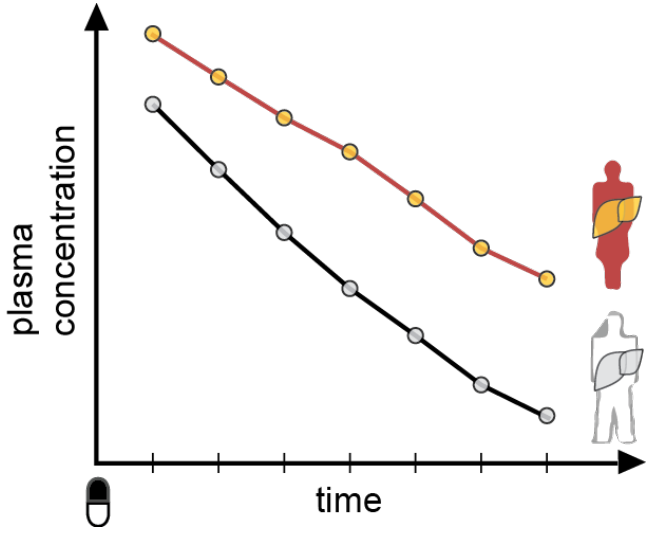


Dynamical liver function tests

Liver specific clearance of test substance

- Rate of (dis-)appearance as proxy for liver function (**pharmacokinetics**)
- Caffeine, LiMAx, galactose (GEC)

Challenges

- Large interindividual variability
- Dose dependency

Large inter-individual variability

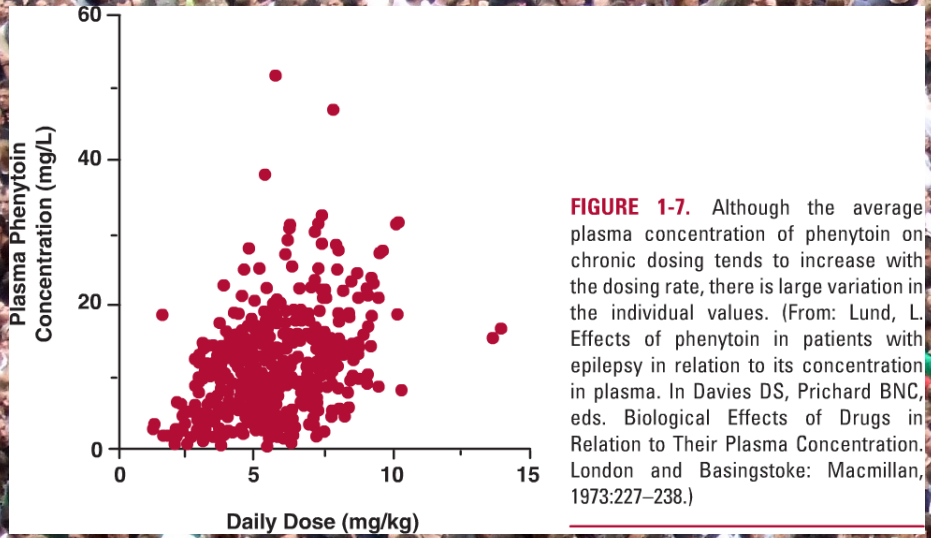


FIGURE 1-7. Although the average plasma concentration of phenytoin on chronic dosing tends to increase with the dosing rate, there is large variation in the individual values. (From: Lund, L. Effects of phenytoin in patients with epilepsy in relation to its concentration in plasma. In Davies DS, Prichard BNC, eds. Biological Effects of Drugs in Relation to Their Plasma Concentration. London and Basingstoke: Macmillan, 1973:227–238.)

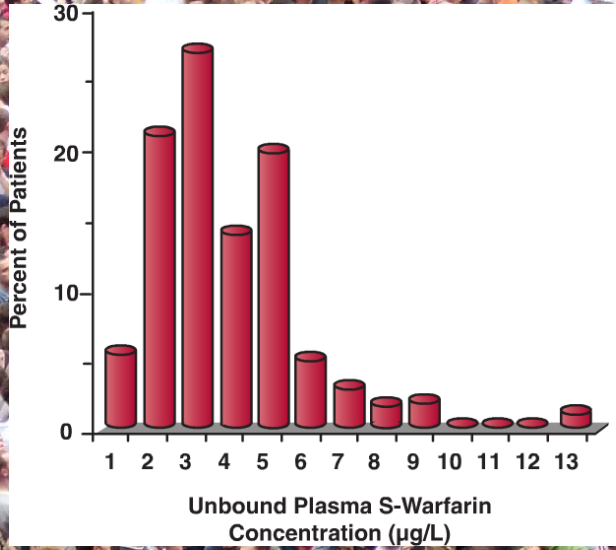


FIGURE 1-8. There is considerable interindividual pharmacodynamic variability in response to the oral anticoagulant warfarin as demonstrated by the substantial spread in the unbound concentration of the active S-isomer associated with a similar degree of anticoagulation in a group of 97 patients on maintenance therapy. (From: Scordo MG, Pengo V, Spina E, et al. Influence of CYP2C9 and CYP2C19 genetic polymorphisms of warfarin maintenance dose and metabolic clearance. Clin Pharmacol Ther 2002;72:702–710.)

Pharmacogenomics

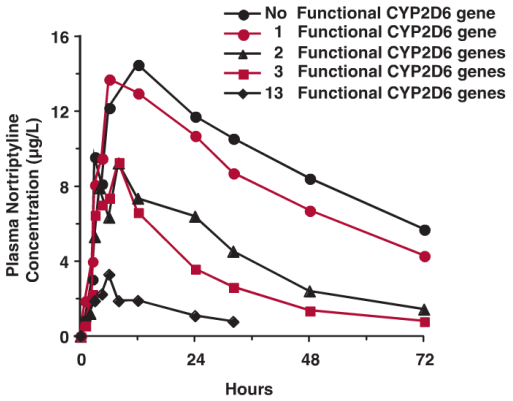


FIGURE 13-2. Strong genetic influence in the pharmacokinetics of nortriptyline is clearly demonstrated by the high correlation between the plasma concentration–time profile and the number of functional CYP2D6 genes possessed by an individual; the larger the number of functional genes, the higher is the clearance and the lower is the exposure profile following a single 25-mg dose of nortriptyline. (From: Dalén P, Dahl ML, Bernal Ruiz ML, et al. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. Clin Pharmacol Ther 1998;63:444–452.)

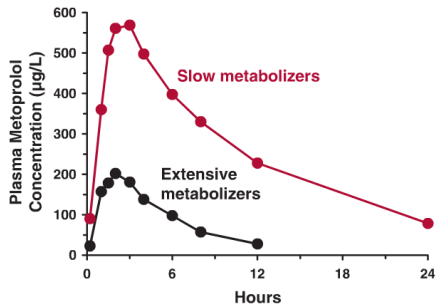


FIGURE 13-3. Plasma metoprolol concentrations after a single oral dose of 200-mg metoprolol tartrate were much higher in poor (*colored line*) than in extensive (*black line*) CYP2D6 metabolizers. Because metoprolol is a drug of high hepatic clearance, the difference between poor and extensive metabolizers is expressed in the large difference in oral bioavailability, because of differences in first-pass hepatic loss. (From: Lennard MS, Silas JH, Freestone S, et al. Oxidative phenotype—a major determinant of metoprolol metabolism and response. Reprinted by permission of New Eng J Med 1982;307:1558–1560.)

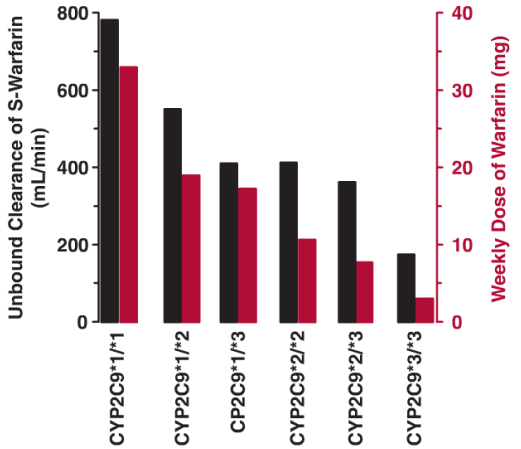


FIGURE 13-4. Genetics plays a significant role in the maintenance dose requirement of warfarin used in the treatment of various cardiovascular diseases. Shown are the unbound clearance of S-warfarin (*black*) in groups of patients with different CYP2C9 genotypes, all titrated and stabilized to a narrow target INR (International Normalization Ratio) range, a measure of anticoagulation, of between 2 and 3, and the mean weekly maintenance dose (obtained by summing the daily dose over 1 week, *in color*). Warfarin is administered as the racemate, with most of the therapeutic effect associated with the more active S-isomer, which is primarily eliminated by CYP2C9-catalyzed metabolism. Homozygous patients with two wild-type alleles (denoted by CYP2C9*1/*1) have the highest S-warfarin clearance and require the highest maintenance dose, and those with two of the most deficient alleles (CYP2C9*3/*3) have the lowest clearance and need the smallest maintenance dose. Heterozygous patients have intermediate clearance. However, as noted in Fig. 12-4 (Chapter 12, *Variability*), in addition to pharmacokinetic variability, there is also considerable interindividual variability in pharmacodynamics of this compound. (From: Scordo MG, Pengo V, Spina E, et al. Influence of CYP2C9 and CYP2C19 genetic polymorphisms of warfarin maintenance dose and metabolic clearance. Clin Pharmacol Ther 2002;72:702–710.)

Variability in Liver Enzymes

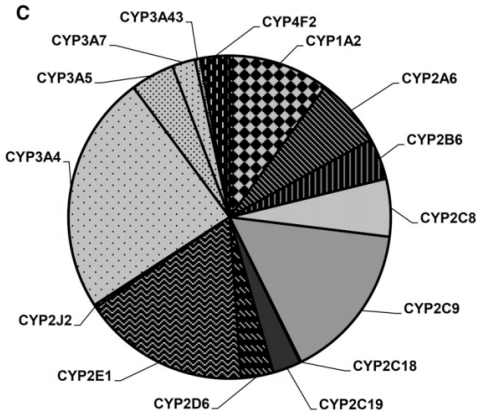


Fig. 1. Bar graph (A and B) and pie chart (C) of weighted mean abundances of cytochrome P450 enzymes in livers from adult Caucasians. Error bars represent weighted standard deviation values. *n*, the number of livers.

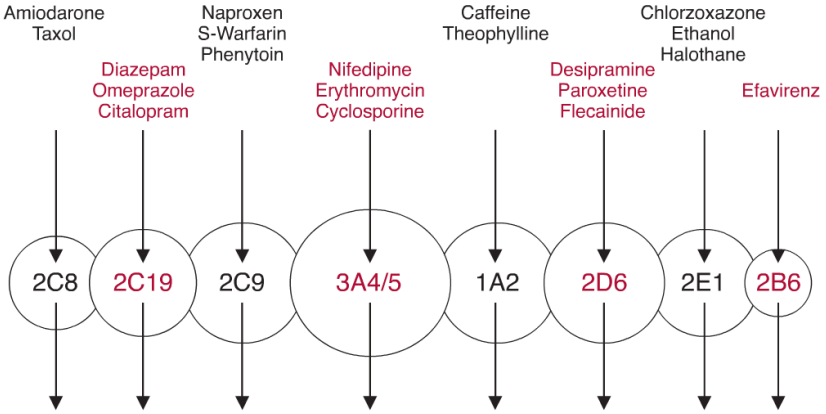


FIGURE 5-3. Graphic representation of the different forms of human cytochrome-P450 enzyme (*circles*) with different but often overlapping substrate specificities. The arrows indicate the single metabolic pathways. Representative substrates are listed above each enzyme.

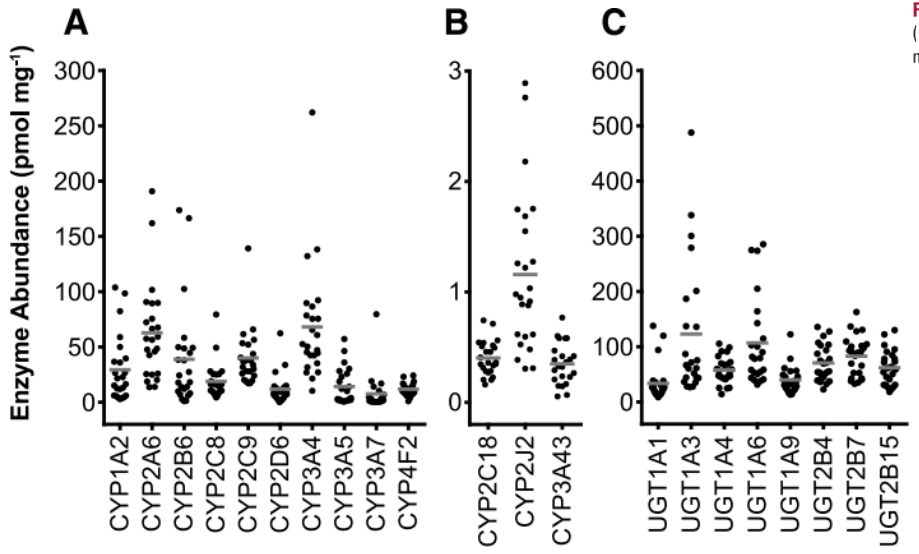
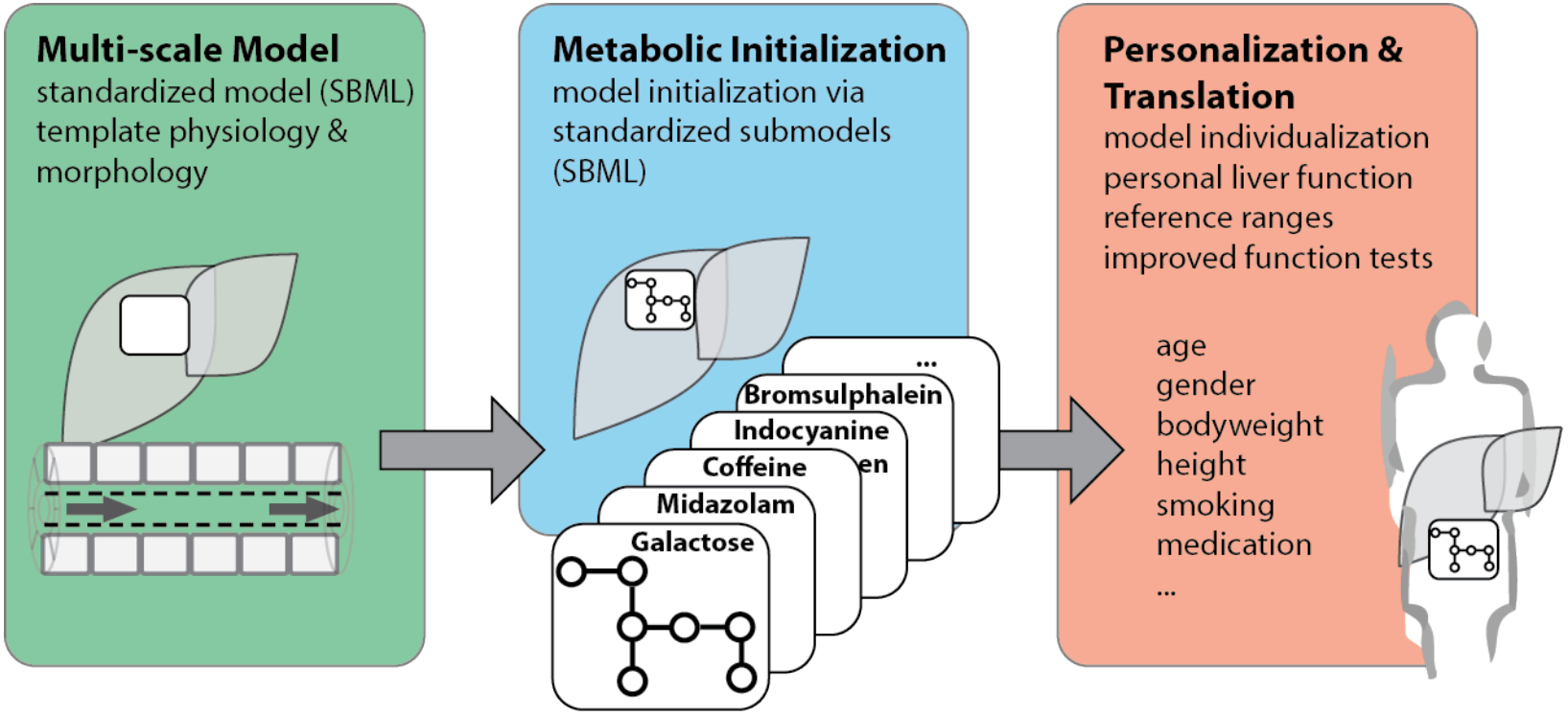
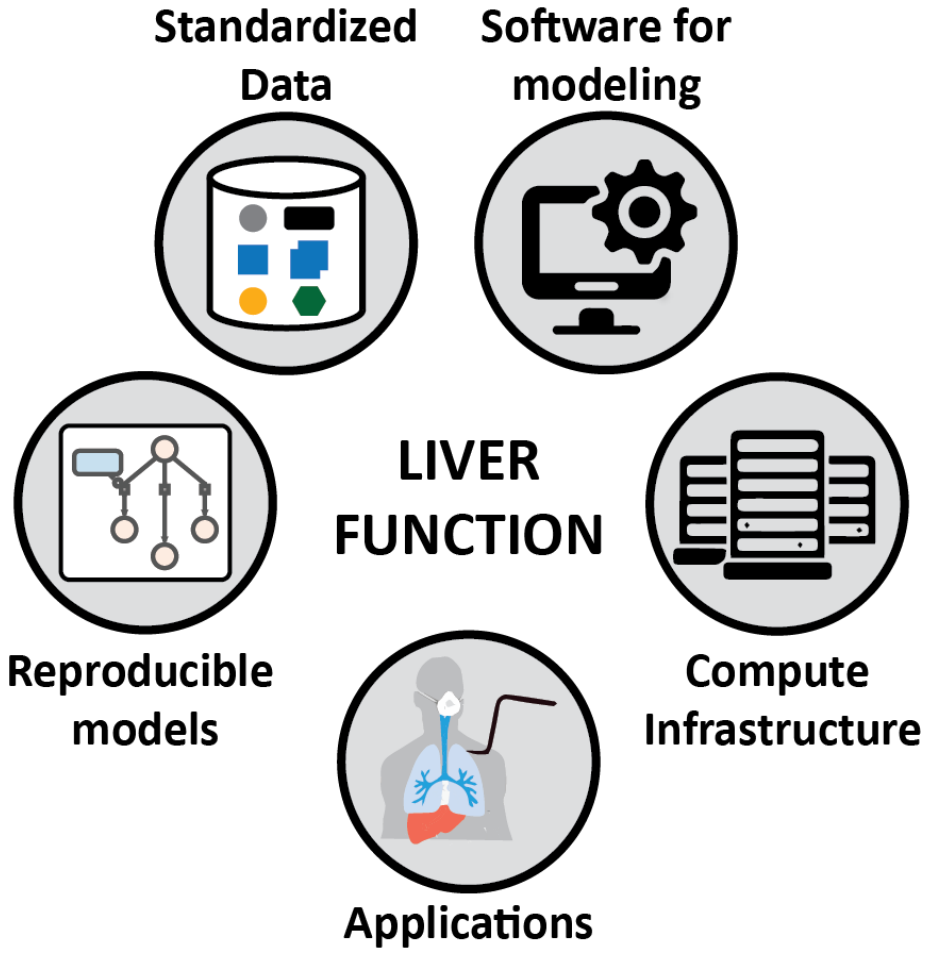
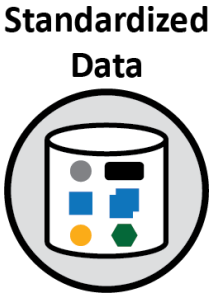


Fig. 2. A scatter plot of the measured abundance values of P450 (A and B) and UGT (C) enzymes. The number of samples is 24 for each enzyme except CYP2C9, CYP3A5, CYP3A7, CYP3A43, UGT1A3, UGT1A4, and UGT1A6 (n = 23). Lines indicate population means of the sets of data.

Modeling dynamical liver function tests

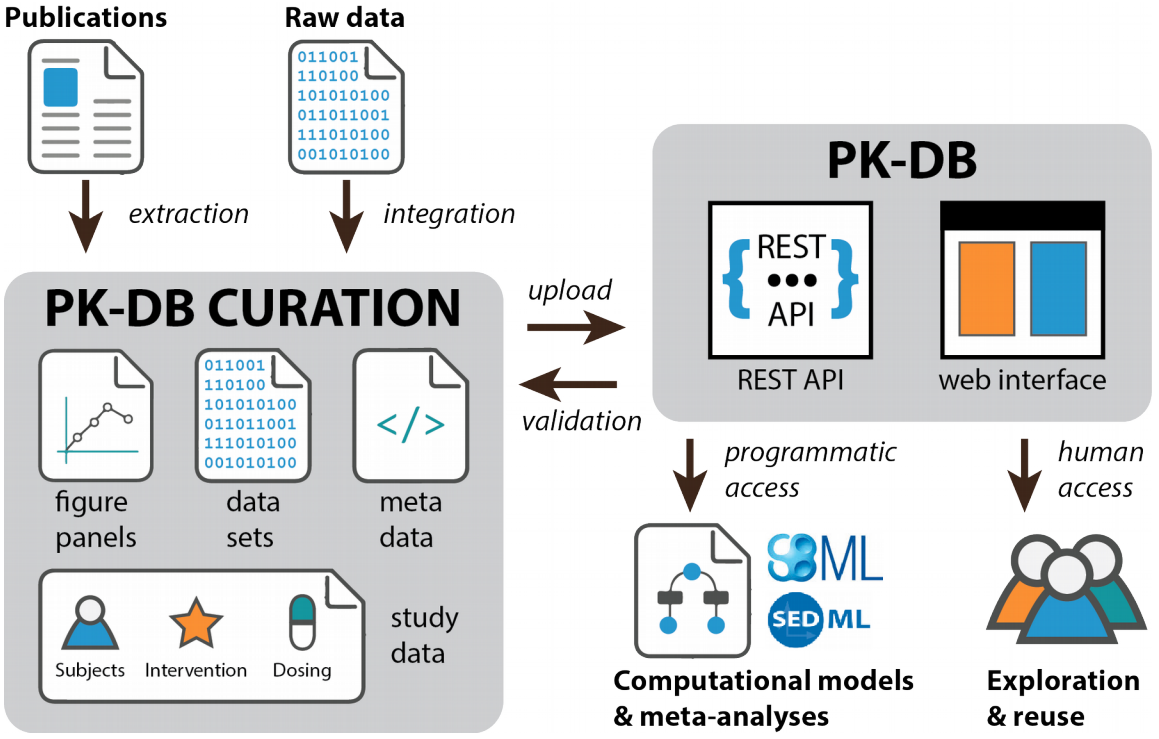



Standardized Data
Software for modeling
LIVER FUNCTION
Reproducible models
Compute Infrastructure
Applications

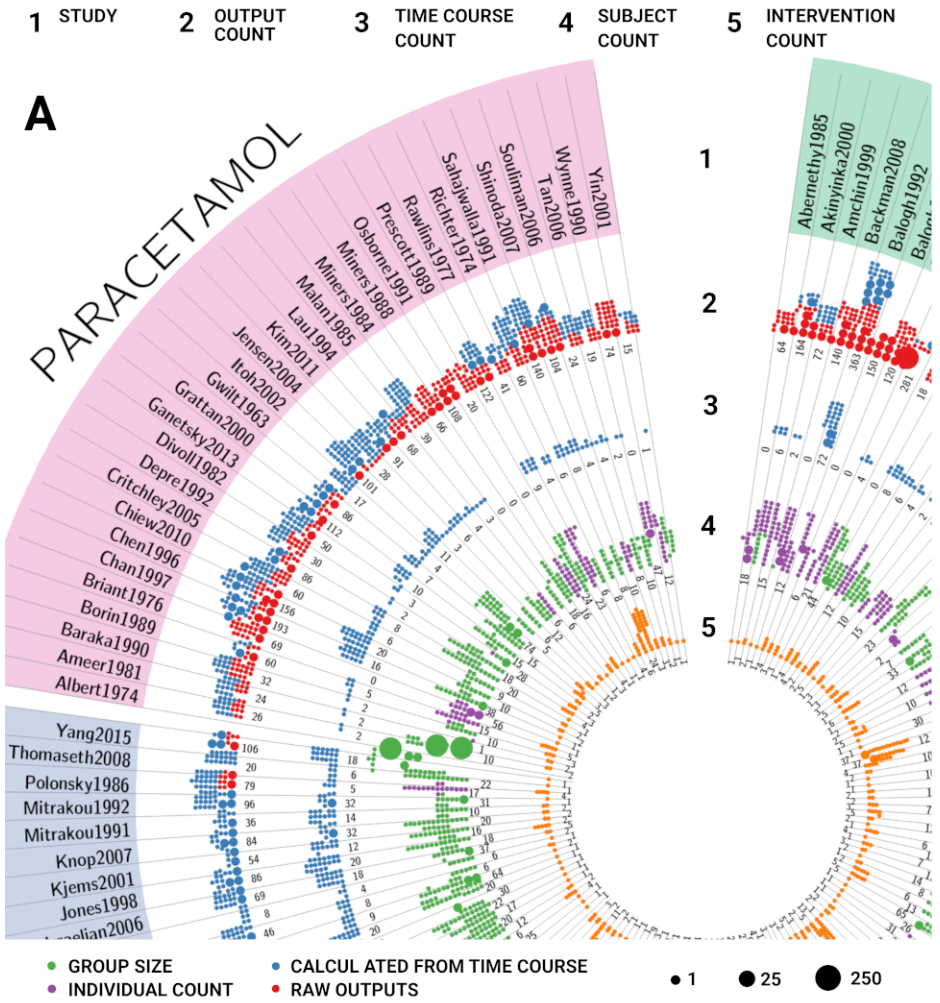


Pharmacokinetics database (PK-DB)

- Standardized representation of pharmacokinetics data
- Meta-information for stratification & individualization
- https://pk-db.com



PK-DB - Studies

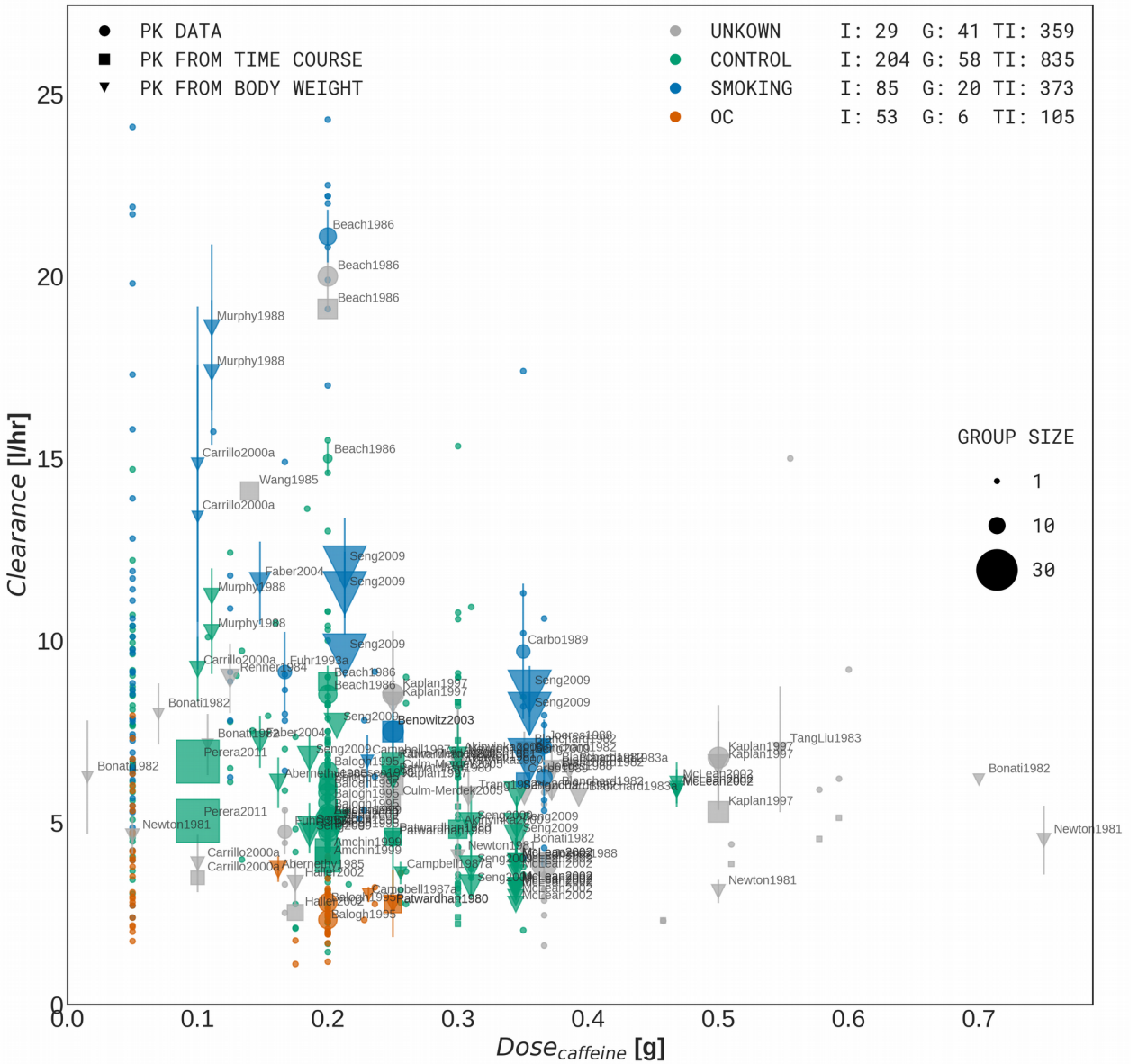


329	Studies
871	Groups
3831	Individuals
992	Interventions
28210	Outputs
2174	Timecourses
329	References

Jan Grzegorzewski & Matthias König. (2019, May).
matthiaskoenig/pkdb: PKDB - pharmacokinetics database (Version v0.5.2).
Zenodo. http://doi.org/10.5281/zenodo.2670026
Manuscript in preparation

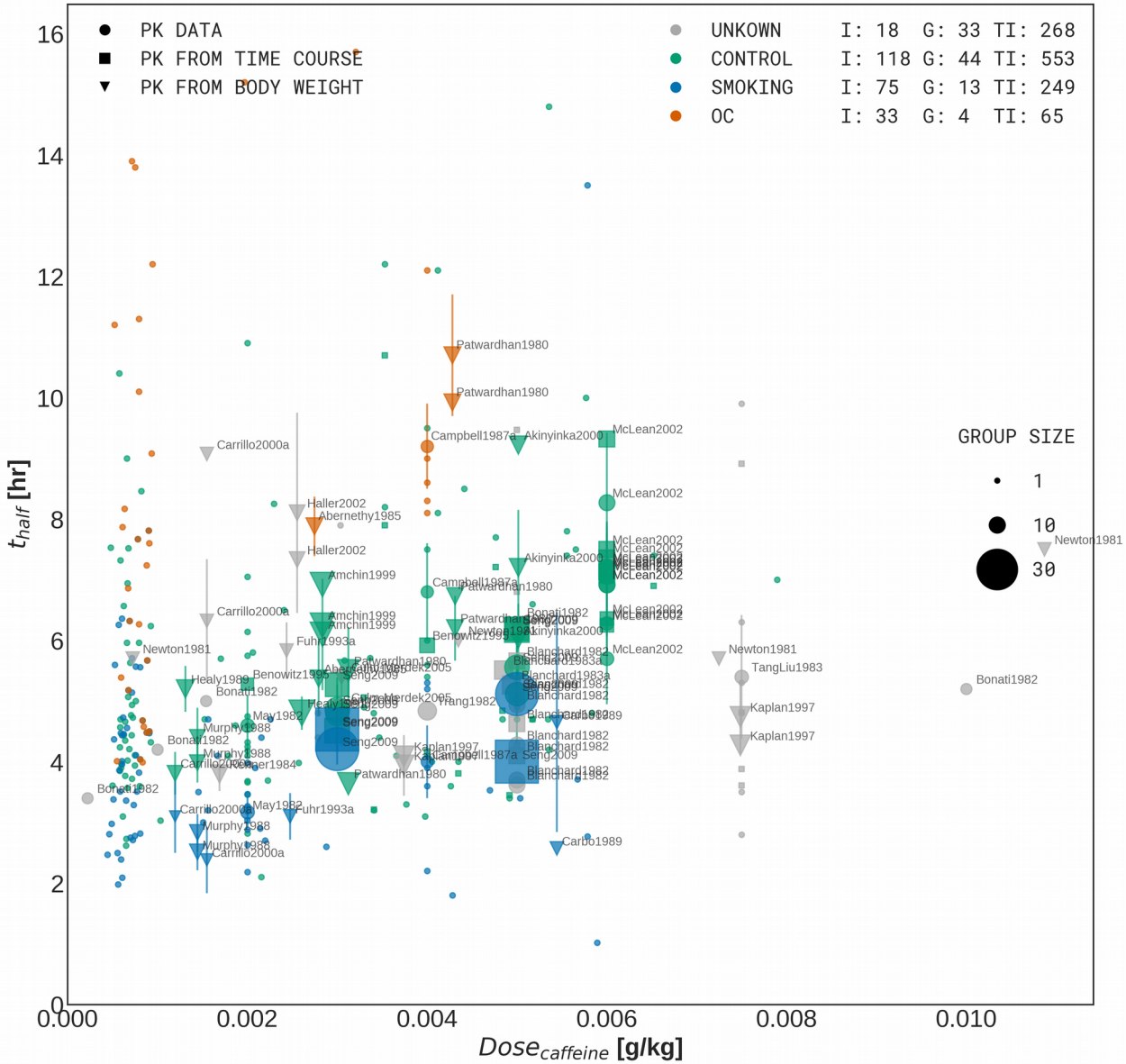
Meta-analysis

- **Caffeine clearance**
- **Stratification into subgroups** depending on smoking and/or oral contraceptive use



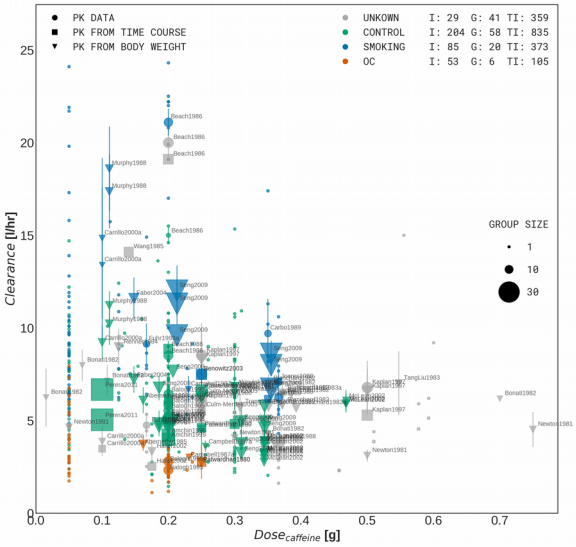
Jan Grzegorzewski & Matthias König. (2019, May). matthiaskoenig/pkdb: PKDB Zenodo. http://doi.org/10.5281/zenodo.2670026
Manuscript in preparation

- Dose-dependent half-lifes
- Pooling of data allows for more robust and translatable results
- But: missing characteristica, individual data & timecourses



Jan Grzegorzewski & Matthias König. (2019, May). matthiaskoenig/pkdb: PKDB Zenodo. http://doi.org/10.5281/zenodo.2670026
Manuscript in preparation

Applications



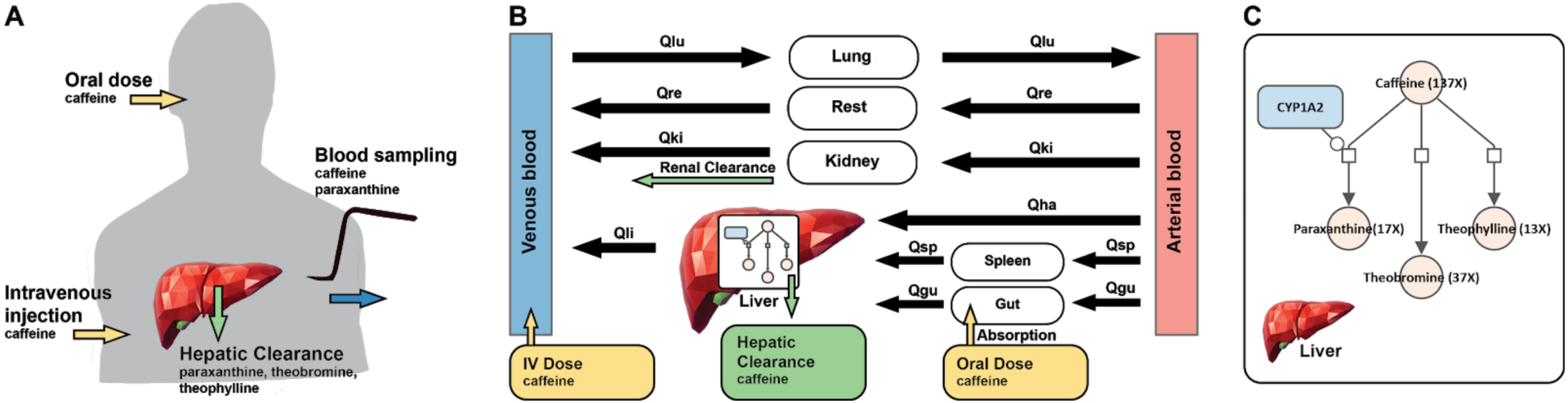
Caffeine

Stratified/personalized predictions by accounting for lifestyle & medication

Cooperation Partners

- Clinical partners; Dr. Hofmann & Prof. Schwab

Physiologically based caffeine model

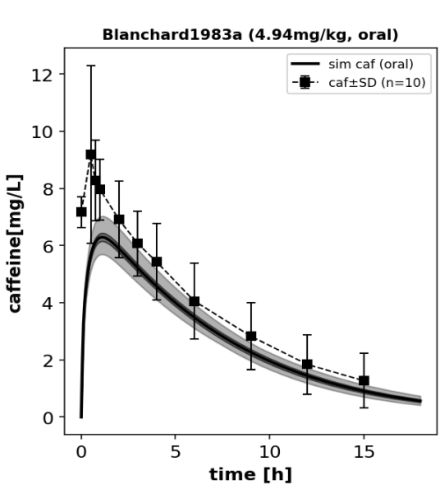


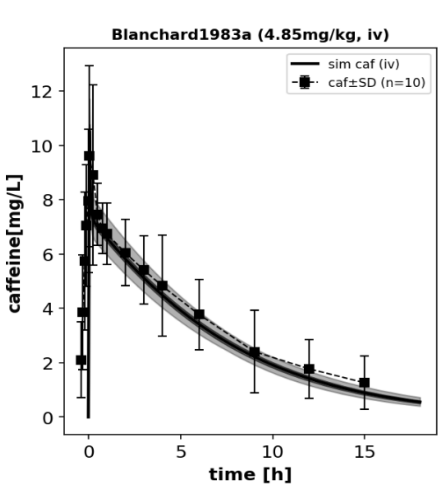
- Caffeine metabolized by **CYP1A2** to paraxanthine,
- Classical liver function test
  - Time course of caffeine
  - Caffeine/paraxanthine ratio

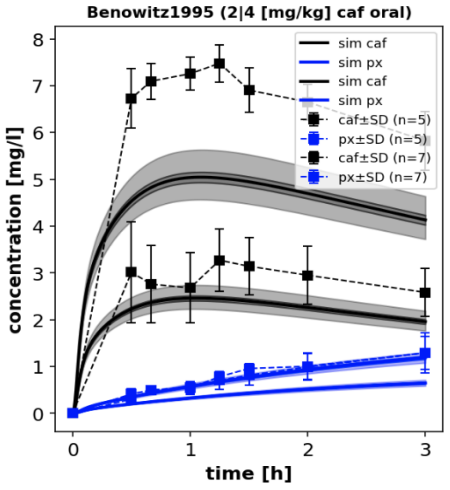
Challenges

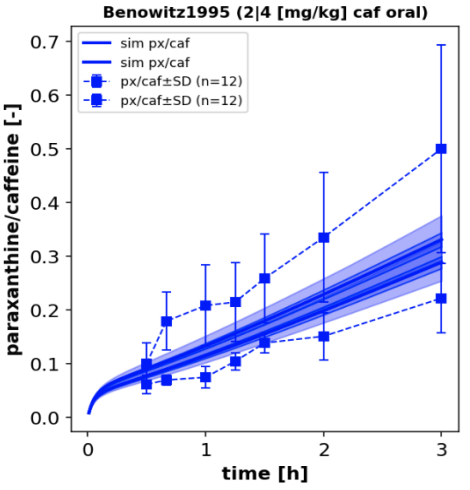
- Large inter-subject variability
  - Effects of lifestyle on expression (induction smoking)
  - Effects of medication (oral contraceptives)
- Dose dependency

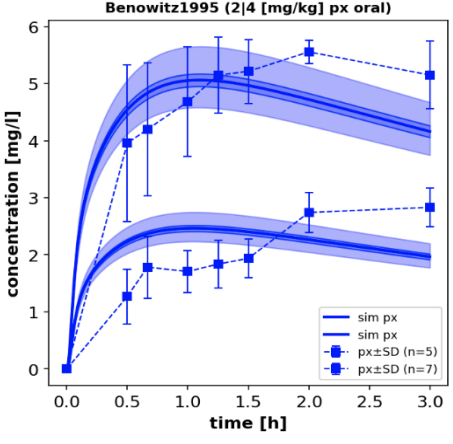
Model performance (training)

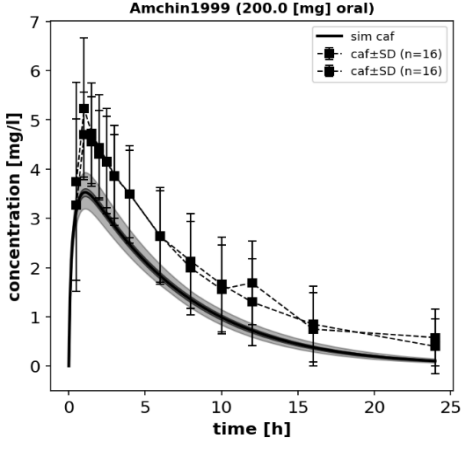


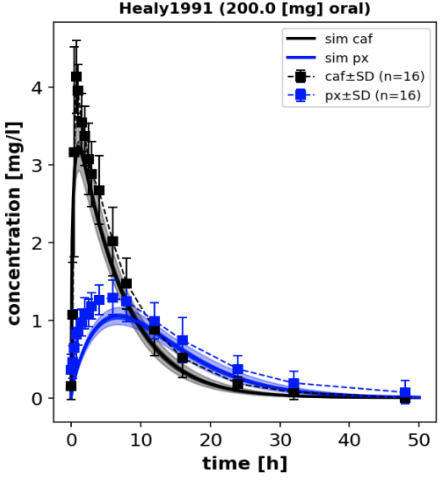


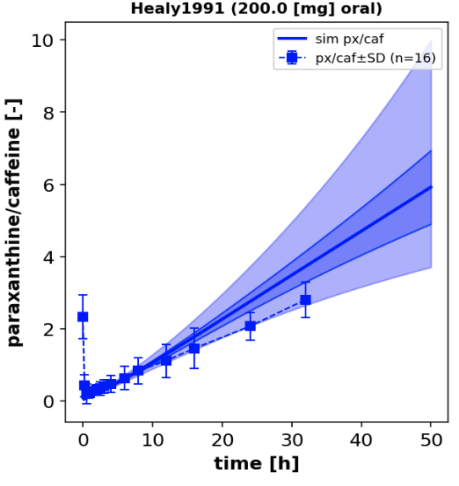




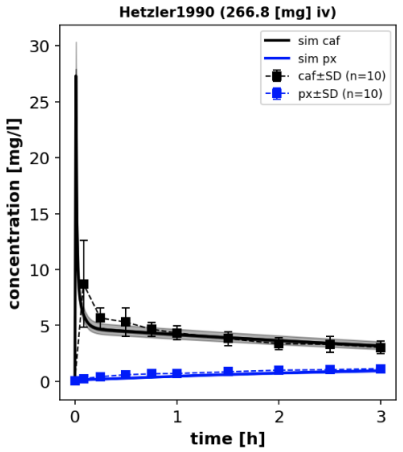


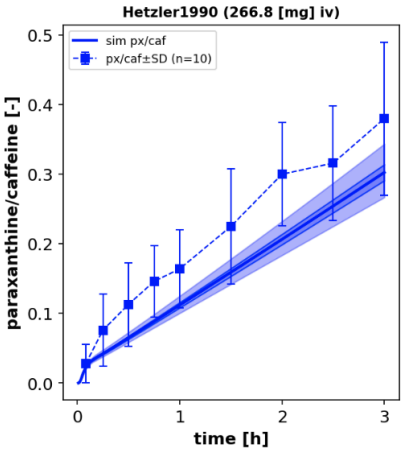


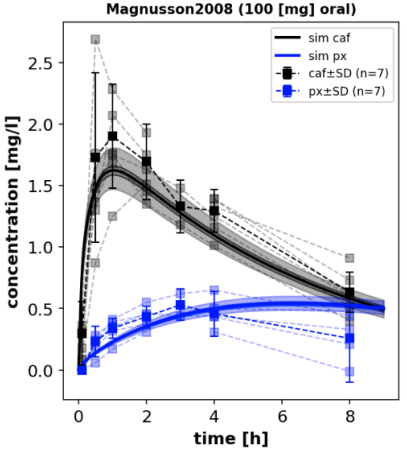


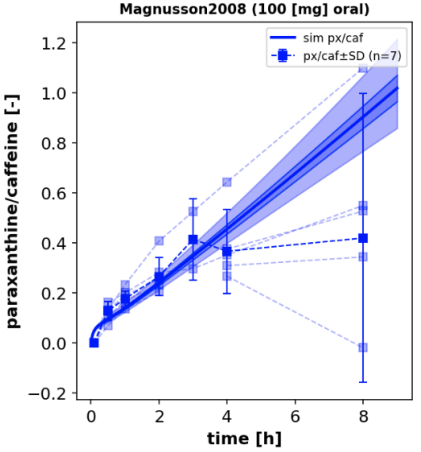


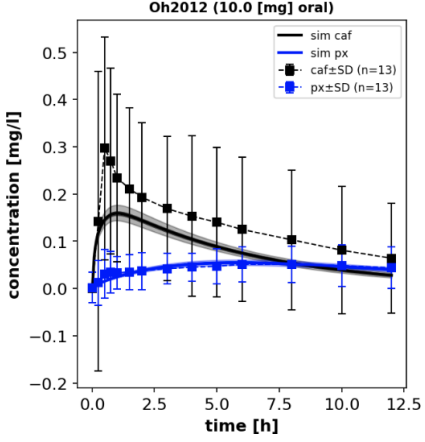
Model performance II (training)

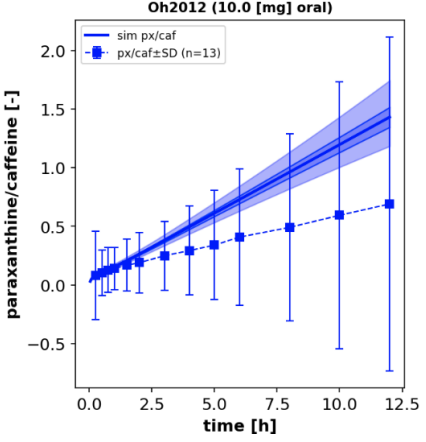


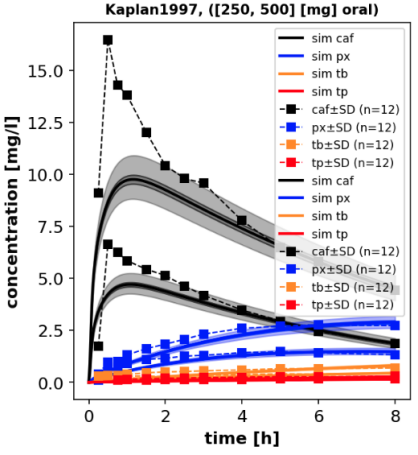


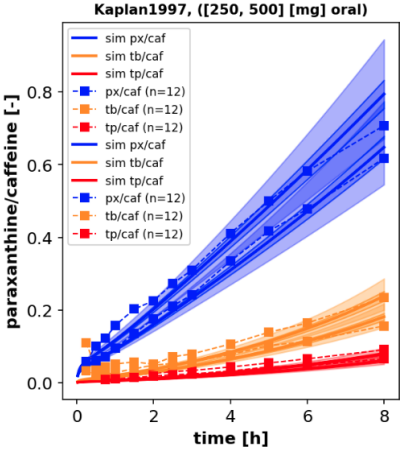




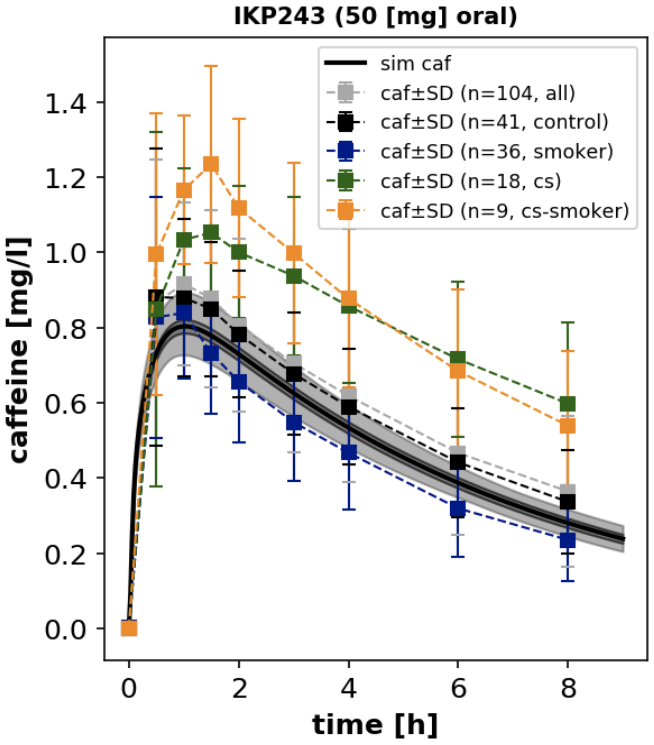


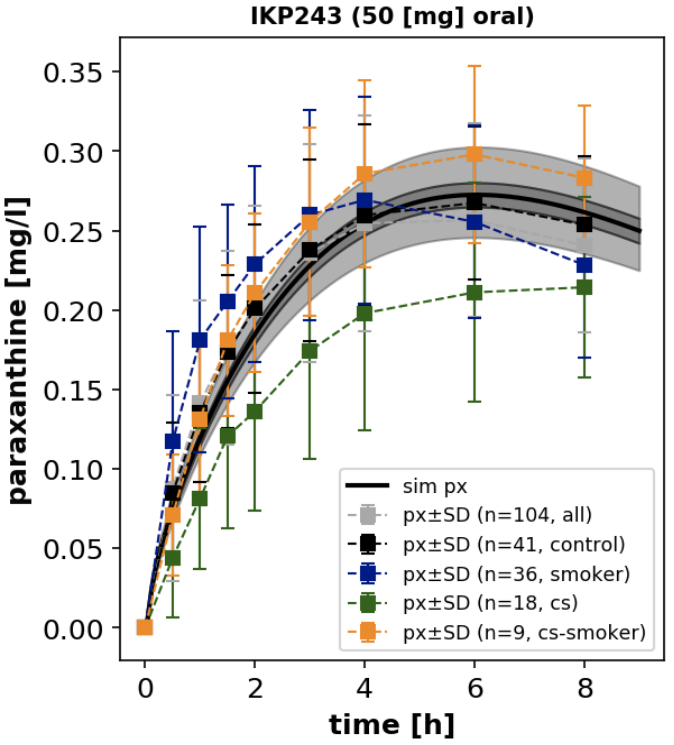


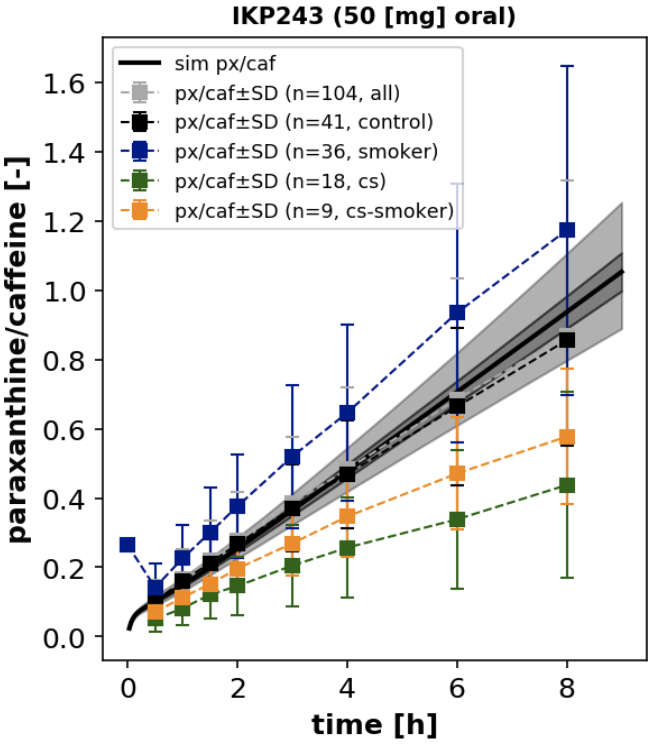




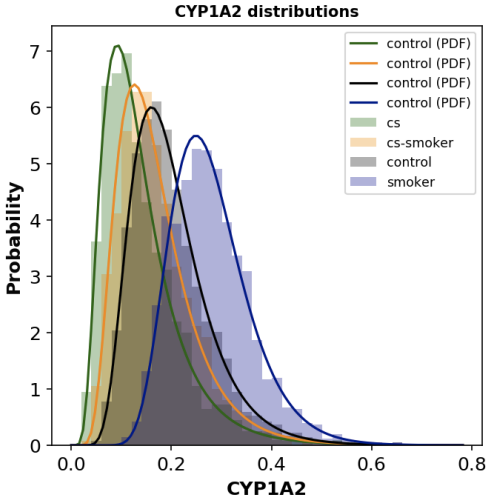
Stratification by smoking & contraceptives





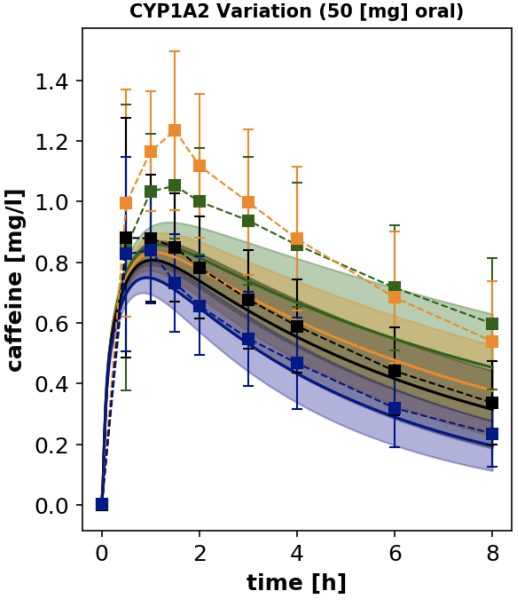


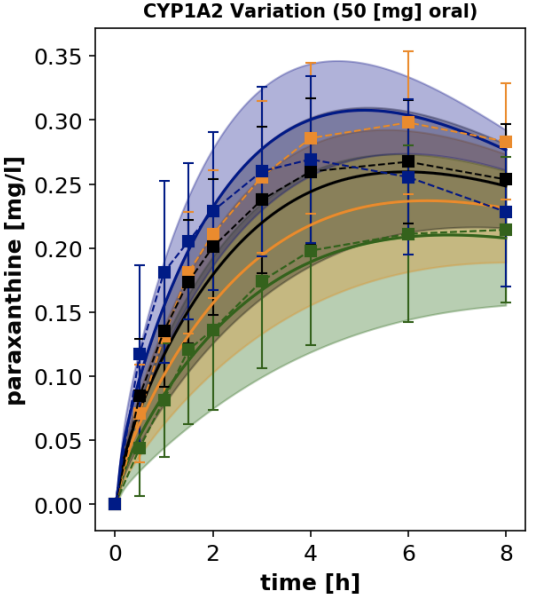
contraceptives (cs)
contraceptives-smoker (cs-smoker)
control
smoker

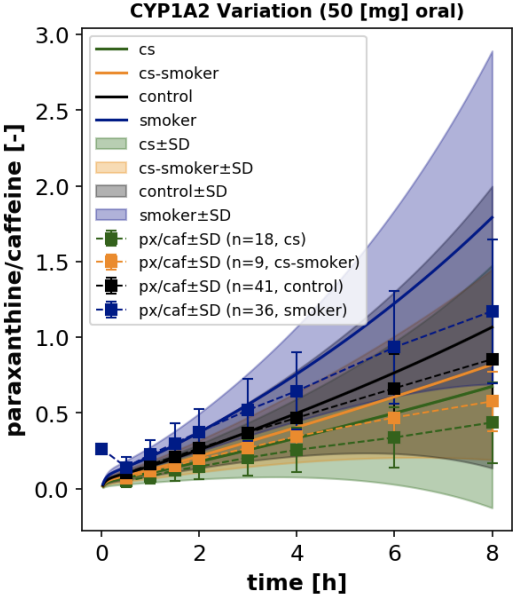


CYP1A2 distributions

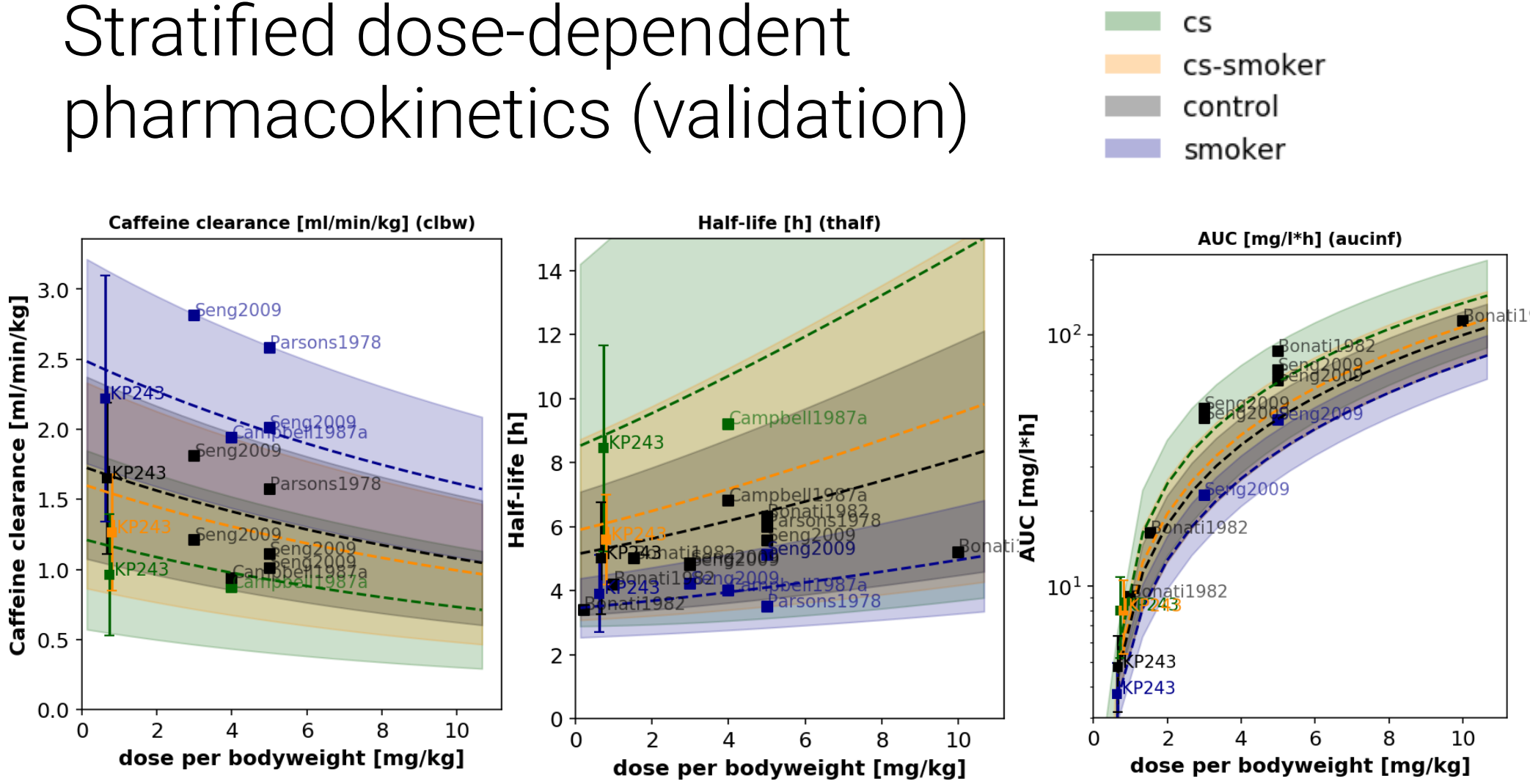
- contraceptives (cs)
- contraceptives-smoker (cs-smoker)
- control
- smoker







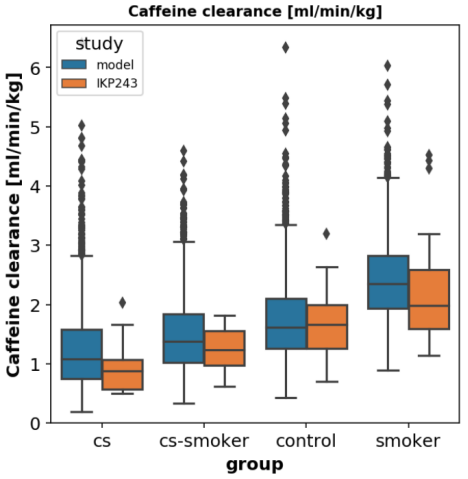
Stratified dose-dependent pharmacokinetics (validation)

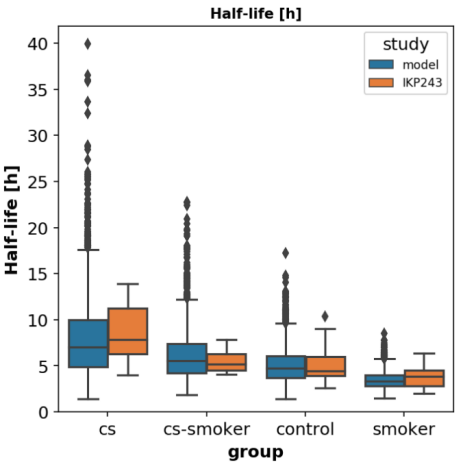


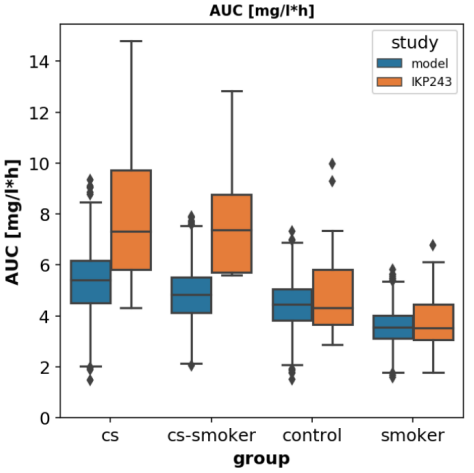
Stratified pharmacokinetic parameters

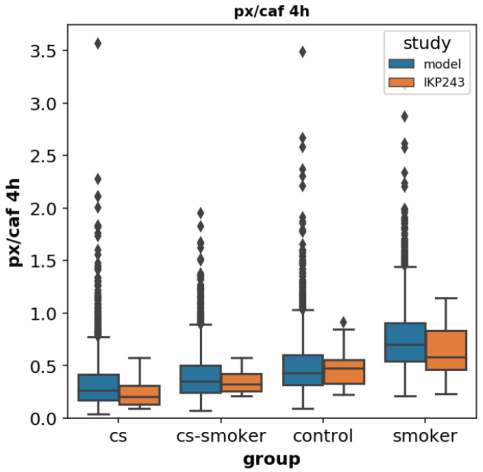
model predictions

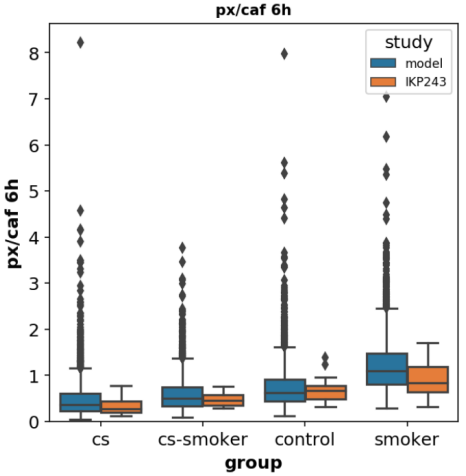
clinical data

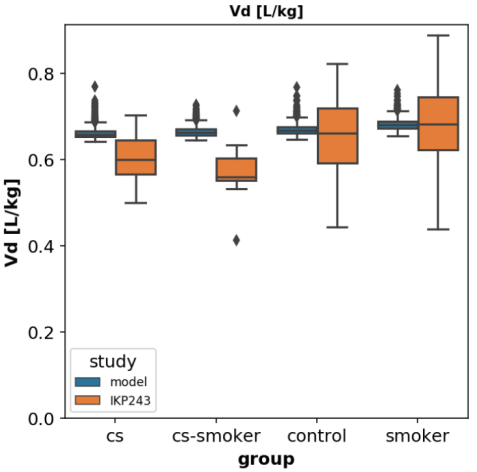






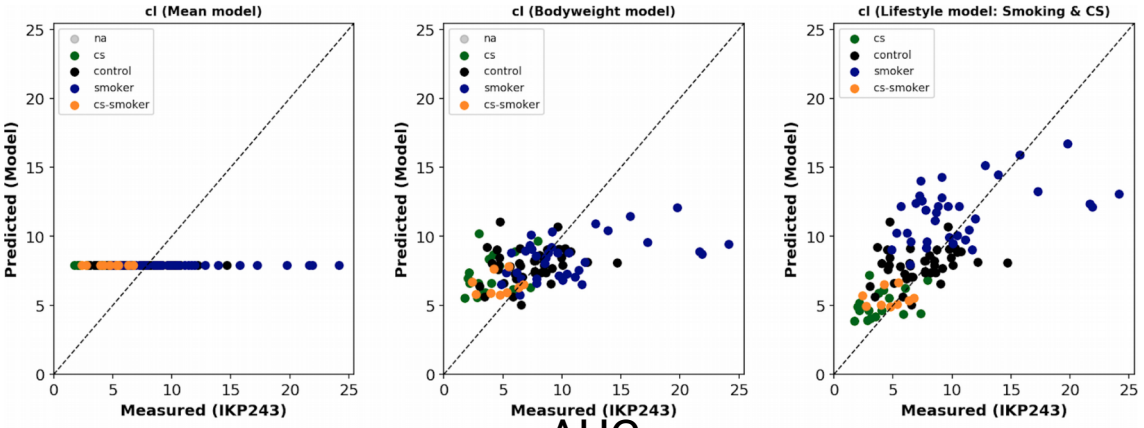






Individualized predictions

Clearance



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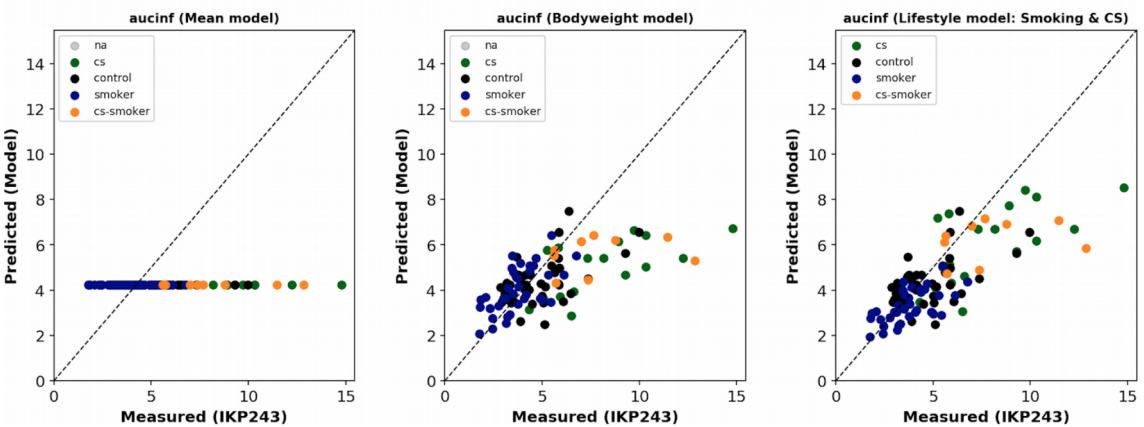


mean anthropometric lifestyle

contraceptives (cs)
contraceptives-smoker (cs-smoker)
control
smoker

- Improved predictions of pharmacokinetic parameters by account for individual lifestyle factors (smoking)
- Results directly transfer to all drugs metabolized via CYP1A2

CYP1A2 & caffeine pharmacokinetics

- CYP1A2 expression altered by many lifestyle factors
- Strong effect: **Smoking**
- Altered function test results

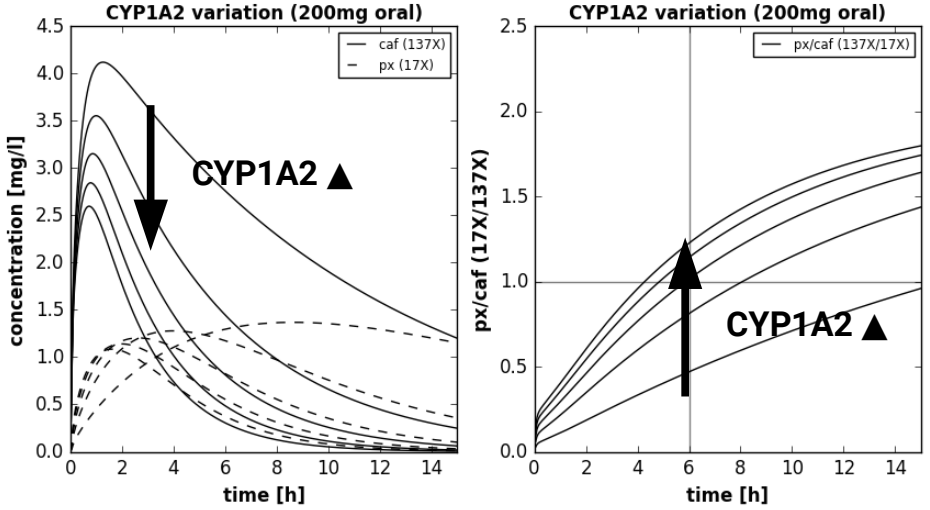


Table 4. Parameter estimates of covariates obtained for logarithmic clearance values using the paraxanthine/caffeine ratio method (equation 1)

Covariate	Symbol used in equation 5	Estimate	95% Confidence interval		Mean resulting change of clearance (factor)
			Lower bound	Upper bound	
–	Intercept	0.264	–0.015	0.542	–
Coffee intake (litre day^{-1})	$Slope_{coffee}$	0.368	0.287	0.449	1.445
Body mass index (kg m^{-2})	$Slope_{BMI}$	–0.010	–0.018	–0.002	0.990
Cigarettes/day					
Non-smokers	$V_{smoking\ habit\ index}$	0	–	–	Reference
1–5		0.195	0.065	0.324	1.215
6–10		0.383	0.253	0.509	1.467
11–20		0.504	0.386	0.621	1.655
>20		0.543	0.430	0.655	1.721
Oral contraceptives					
No	$V_{oral\ contraceptive\ index}$	0	–	–	Reference
Yes		–0.332	–0.236	–0.428	0.717
Country					
Germany	$V_{country\ of\ residence\ index}$	0	–	–	Reference
Bulgaria		–0.209	–0.356	–0.061	0.811
Slovakia		–0.303	–0.450	–0.156	0.739
Sex					
Male		0	–	–	Reference
Female	$V_{sex\ index}$	–0.111	–0.178	–0.044	0.895

CYP1A2 induction ▲

- Clearance ▲
- kel ▲
- T1/2 ▼
- Tmax ▼
- px(17X)/caf(137X) ▲

Modelling Tools, Software, Workflows & Standardization

Version control

GitHub is a code hosting platform for version control and collaboration. It lets you and others work together on projects from anywhere.

Version control

- Diffs & Branches

Collaborative editing

- Pull requests

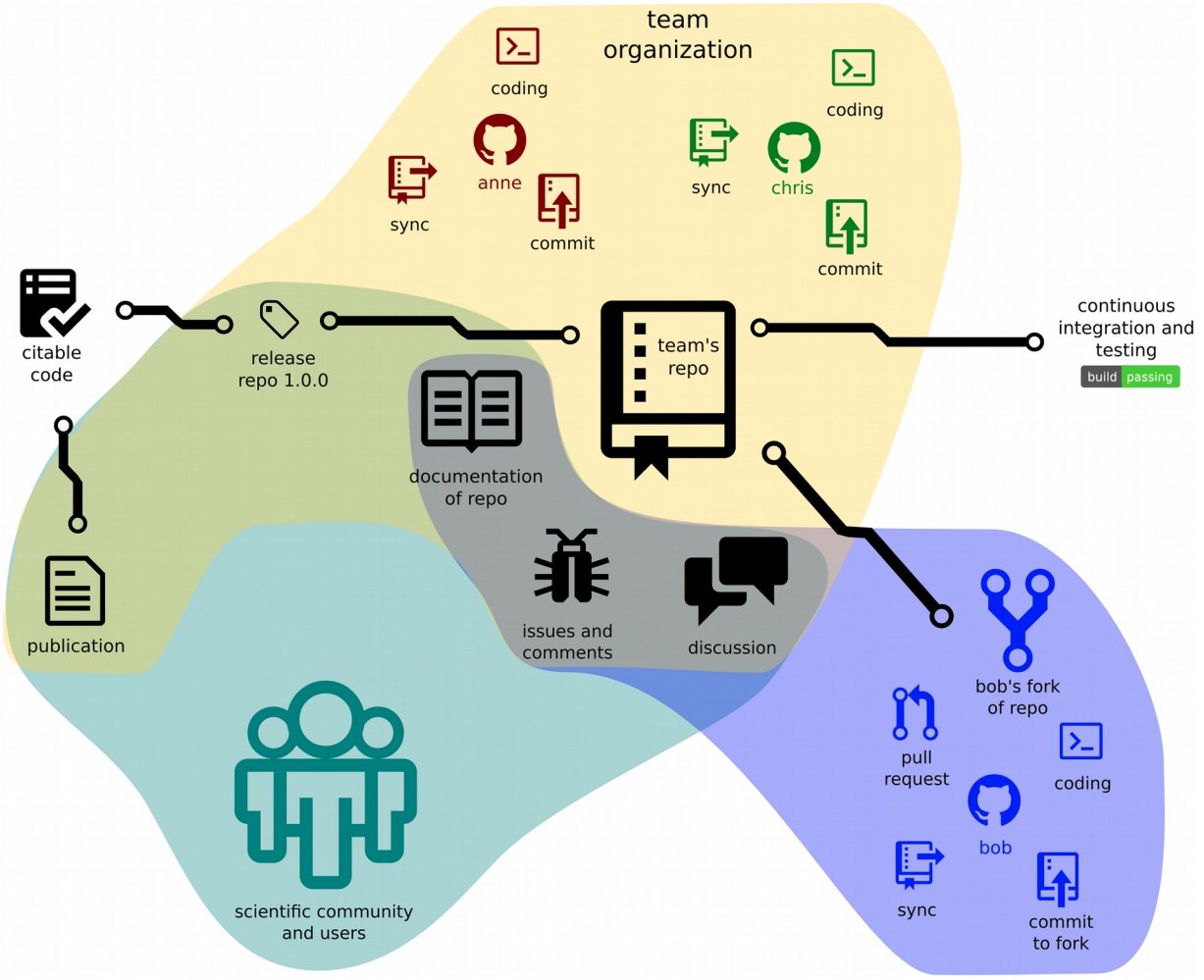
Continuous integration

- unit tests
- Commit hooks

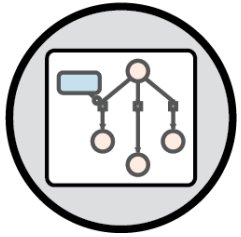
Releases & snapshots (citable code)

Issue tracker

Work anywhere & offline

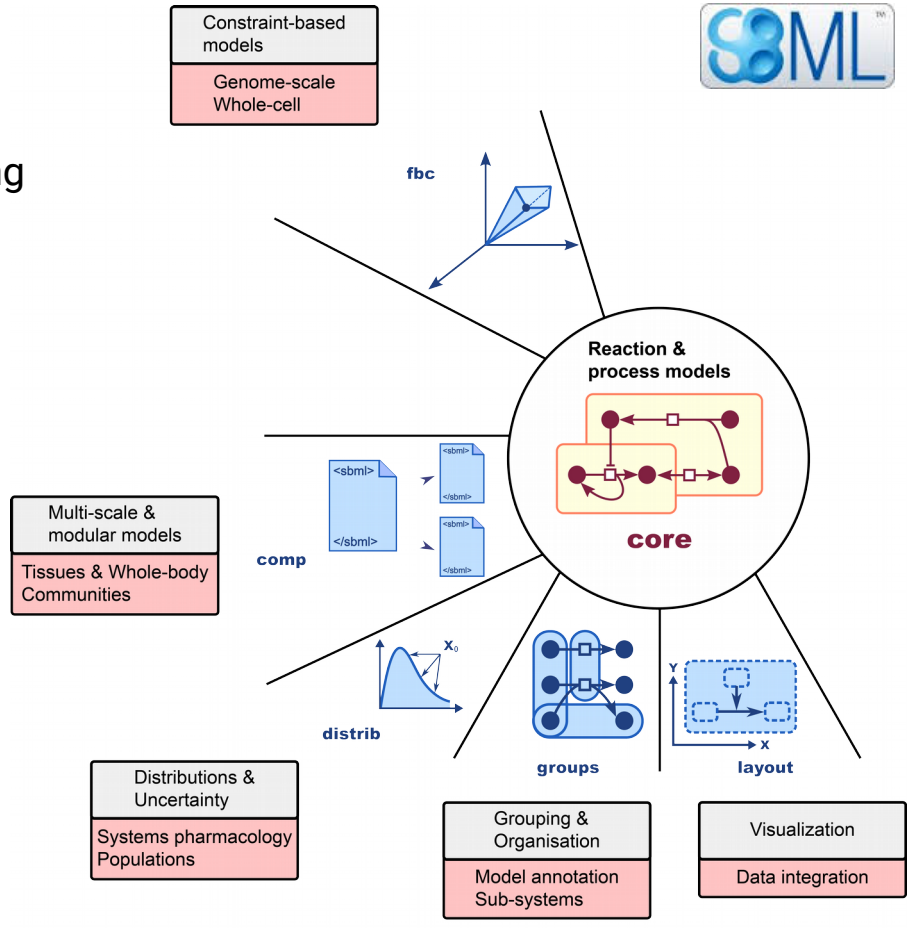


Reproducible models



Standardization

- Reproducible & exchangeable model encoding (**SBML**)
- Annotations to modelling, biological and medical ontologies (**SBML core**)
- Hierarchical models/multi-scale models (**SBML comp**)
- Automatic unit validation
- Distributions in models & uncertainty in data and parameters (**SBML distrib**)
- Mass- & charge balance (**SBML fbc**)
- **Use wide range of tools** (visualization, parameter fitting, simulation, ...)

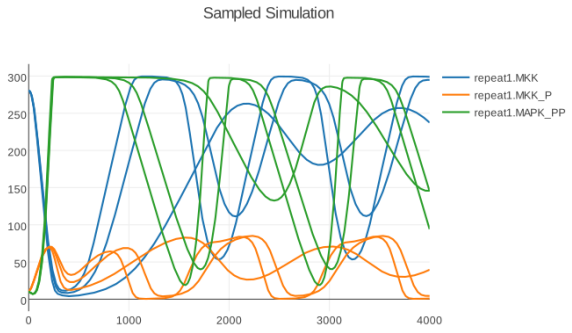


The Systems Biology Markup Language (SBML): Language Specification for Level 3 Version 2 Core
M. Hucka, F. Bergmann, C. Chaouiya, A. Dräger, S. Hoops, S. Keating, **M. König**, N Le Novere, C. Myers, B. Olivier, S. Sahle, J. Schaff, R. Sheriff, L. Smith, D. Waltemath, D. Wilkinson, F. Zhang, **J Integr Bioinform. 2019 [accepted]**

Simulation experiment description markup language (SED-ML) level 1 version 3 (L1V3).
Bergmann FT., Cooper J, **König M**, Ion Moraru I., Nickerson D., Le Novère N., Olivier BG., Sahle S, Smith L., and Waltemath D, **J Integr Bioinform 2018, 3**

Harmonizing semantic annotations for computational models in biology
Neal, **König**, Nickerson, Mısırlı, Kalbasi, Dräger, ..., Waltemath
Brief Bioinform. 2018 Nov 21. doi: 10.1093/bib/bby087

```
[3]
// -- Begin Antimony block converted from MAPKcascade.xml
// Created by libAntimony v2.9.3
model *MAPKcascade()
  ...
  // Reactions:
  J0: MKKK => MKKK_P; J0_V1*MKKK/((1 + (MAPK_PP/J0_Ki)^J0_n)*(J0_K1 + MKKK));
  J1: MKKK_P => MKKK; J1_V2*MKKK_P/(J1_KK2 + MKKK_P);
  J2: MKK => MKK_P; J2_k3*MKKK_P*MKK/(J2_KK3 + MKK);
  J3: MKK_P => MKK_PP; J3_k4*MKKK_P*MKK_P/(J3_KK4 + MKK_P);
  J4: MKK_PP => MKK_P; J4_V5*MKK_PP/(J4_KK5 + MKK_PP);
  J5: MKK_P => MKK; J5_V6*MKK_P/(J5_KK6 + MKK_P);
  J6: MAPK => MAPK_P; J6_k7*MKK_PP*MAPK/(J6_KK7 + MAPK);
  J7: MAPK_P => MAPK_PP; J7_k8*MKK_PP*MAPK_P/(J7_KK8 + MAPK_P);
  J8: MAPK_PP => MAPK_P; J8_V9*MAPK_PP/(J8_KK9 + MAPK_PP);
  J9: MAPK_P => MAPK; J9_V10*MAPK_P/(J9_KK10 + MAPK_P);
  ...
end
// -- End Antimony block

// -- Begin PhraSEDML block converted from main.xml
// Created by libphrasedml v1.0.7
// Models
model1 = model "MAPKcascade"

// Simulations
sim1 = simulate uniform(0, 4000, 1000)

// Tasks
task1 = run sim1 on model1

// Repeated Tasks
repeat1 = repeat task1 for model1.J1_KK2 in [1, 10, 40], reset=true

// Outputs
plot "Sampled Simulation" repeat1.time vs repeat1.MKK, repeat1.MKK_P, repeat1.MAPK_PP
// -- End PhraSEDML block
```

Simulation & Analysis

Software for modeling

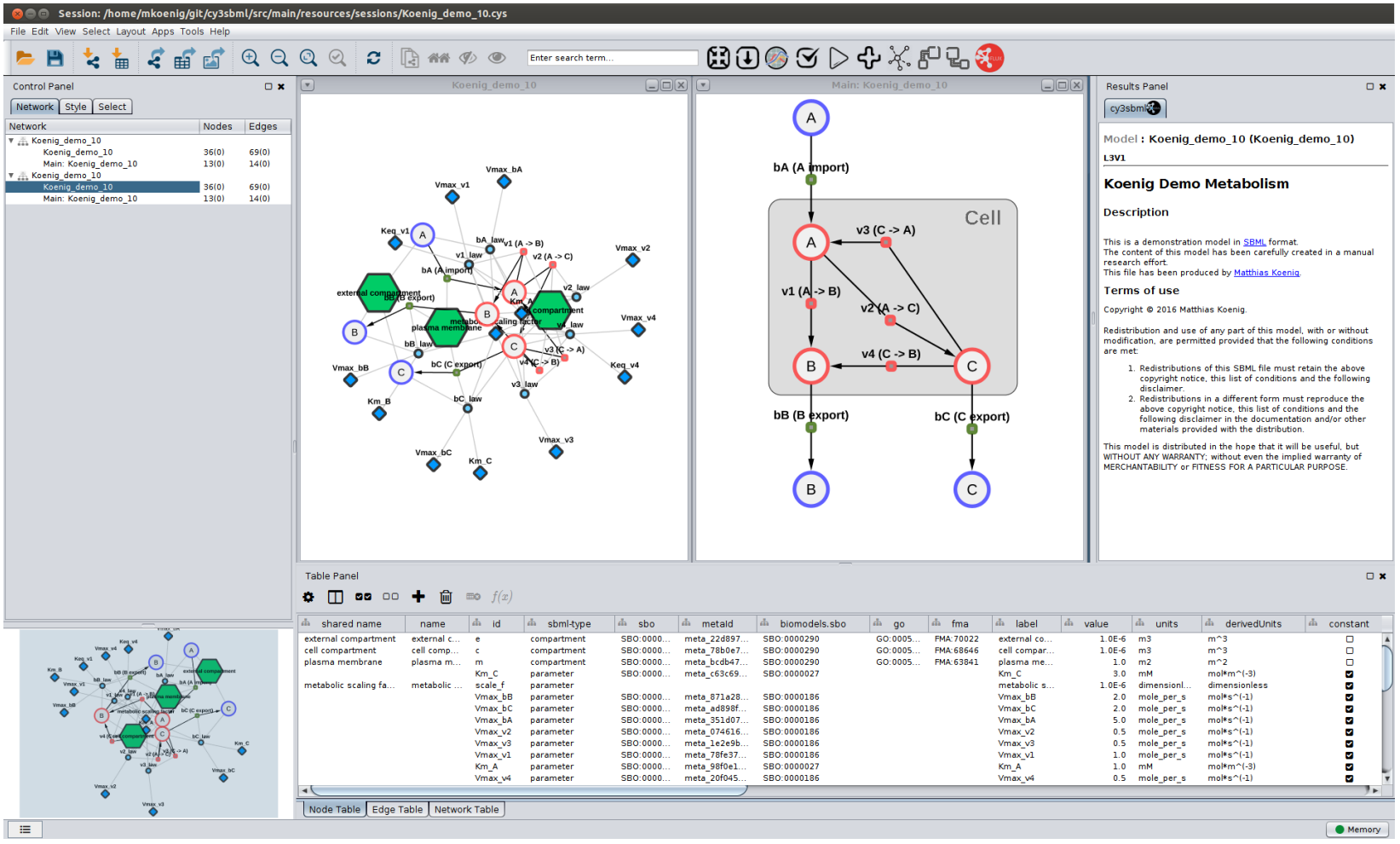
- **roadrunner**: high performance SBML simulator
  - Compile to machine code, cluster-ready
- **tellurium**: python based modeling environment for SBML models

libRoadRunner: a high performance SBML simulation and analysis library.
Somogyi, Bouteiller, Glazier, **König**, Medley, Swat, Sauro.
Bioinformatics. 2015

Tellurium Notebooks - An Environment for Dynamical Model Development, Reproducibility, and Reuse
Medley K, Choi K, **König M**; Smith L, Gu S, Joseph Hellerstein, Sealfon S., Sauro HM.
PLoS, Comp. Bio. 2018

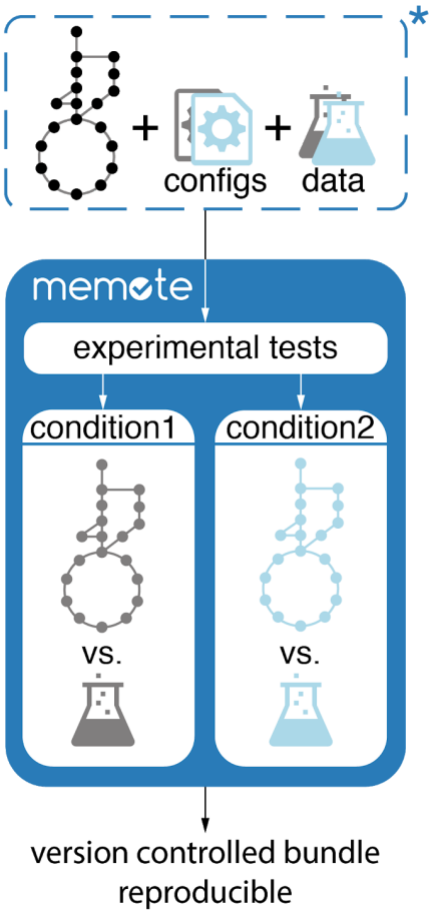
Tellurium: An Extensible Python-based Modeling Environment for Systems and Synthetic Biology
K Choi, JK Medley, **M König**, K Stocking, L Smith, S Gua, HM Sauro
Biosystems. 2018 Jul 24. pii: S0303-2647(18)30125-4.

Visualization



Model building, quality checks & visualization

- **sbmlutils –** model building, annotation, reports
- **memote -** integrated testing for models and model checks
- **Cy3SBML** – model visualization (data integration)

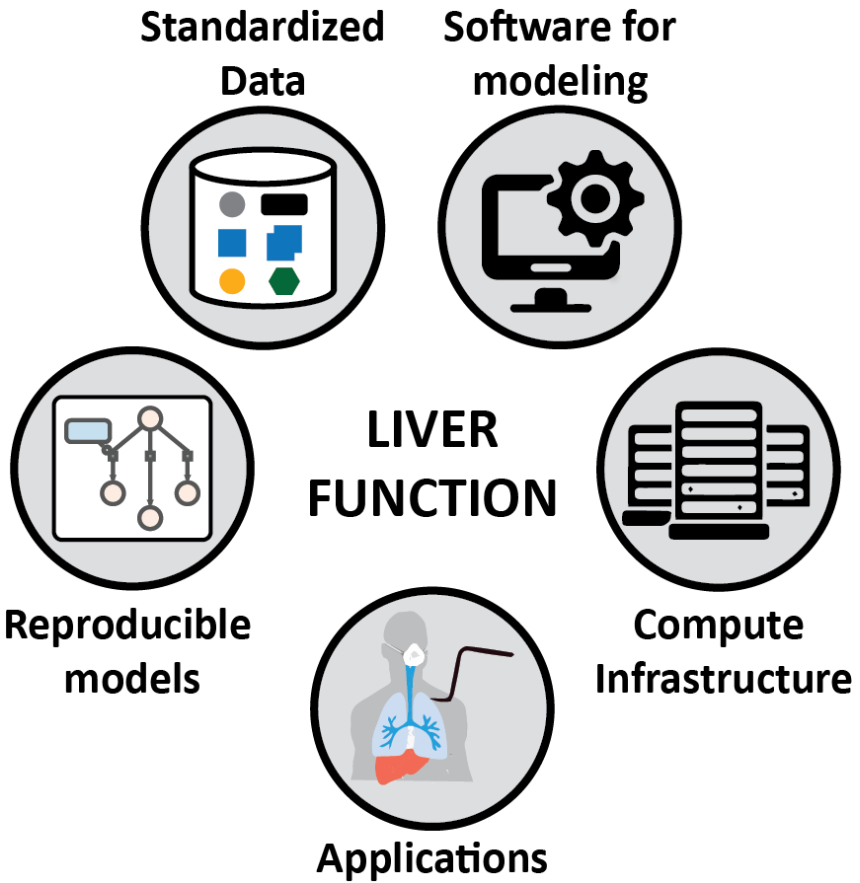


matthiaskoenig/sbmlutils: sbmlutils-v0.3.3 (Version v0.3.3)
M. König. (2019, April 29). Zenodo. http://doi.org/10.5281/zenodo.2653495

Memote: A community-driven effort towards a standardized genome-scale metabolic model test suite
C Lieven, M Beber, B Olivier, F Bergmann, M Ataman, P Babaei, J Bartell, L Blank, S Chauhan, K Correia, C Diener, A Dräger, B ..., **M König**, S Klamt, E Klipp, ..., J Wodke, J Xavier, Q Yuan, M Zakhartsev, C Zhang
bioRxiv 350991; doi: 10.1101/350991 Nature Biotechnology [in revision]

matthiaskoenig/cy3sbml: cy3sbml-v0.2.7 (Version v0.2.7)
M. König, N. Rodriguez, A. Dräger (2017, November 12). Zenodo. http://doi.org/10.5281/zenodo.1045487

Summary & outlook



Interactive personalized pharmacokinetics models

Pharmacokinetics database

- pharmacokinetics data in standard format
- open source, open access, open data & FAIR
- integration in workflow via REST web services
- annotation to ontologies

PK database

- Study information
- Subject & groups
- Dosing
- Time courses
- Pharmacokinetic parameters

REST API (web services)

- Pharmacokinetics data for subgroups
- Pharmacokinetics data for individual subjects
- Workflow for data curation

Physiological based pharmacokinetics models

Standard medications, substances & drugs
- caffeine
- paracetamol
- omeprazole
- codeine
- liver function tests (LiMax, galactose)

SBML

- Curated and validated models for caffeine, paracetamol, galactose & methacetine
- Stratification & individualization of models
- Standardization (SBML)
- Tools for model building

Frontend

- Interactive computational models (web interface)
- Stratified & individualized simulations
- Integration of clinical data
- Providing view to different stakeholders

pharmML
SED ML

- High-performance SBML simulator (libroadrunner)
- Web simulation (tellurium-web)
- Simulation setups (SED-ML)
- Proof-of-principle for stratification & personalization

Patients
- Interactive exploration
- Introduction to pharmacokinetics
- Education (dose, timing, drug-drug interaction, halflife)

Health-care Professionals
- Risk predictions
- Senitivities & Specificieties, cutoffs
- drug-drug interactions
- Reports

Research
- testing of hypotheses
- sensitivity analysis
- export of models, simulation setups, data sets in standard formats
- improved liver function tests

Tutorial

1. Install `libroadrunner` as python library

```
pip install libroadrunner
```

or

```
conda install libroadrunner
```

2. Download & extract tutorial Data

http://bit.ly/pkpd-tutorial-data

3. Open tutorial notebook (jupyter or jupyter lab)

```
pkpd-tutorial.ipynb
```

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