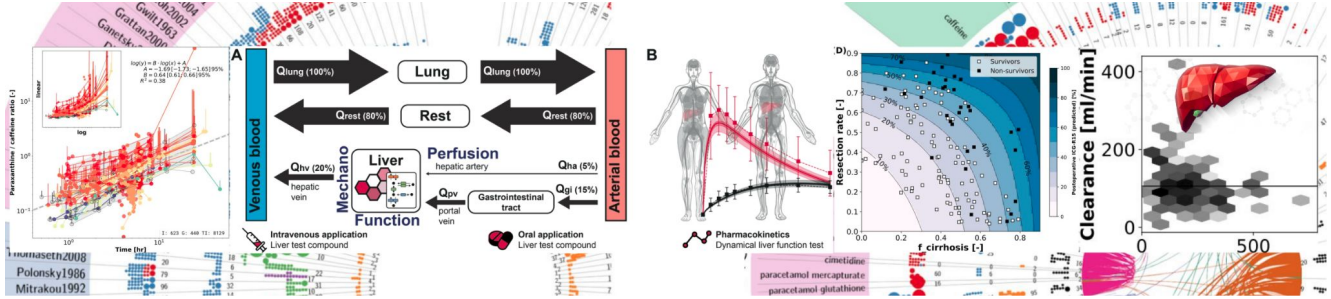
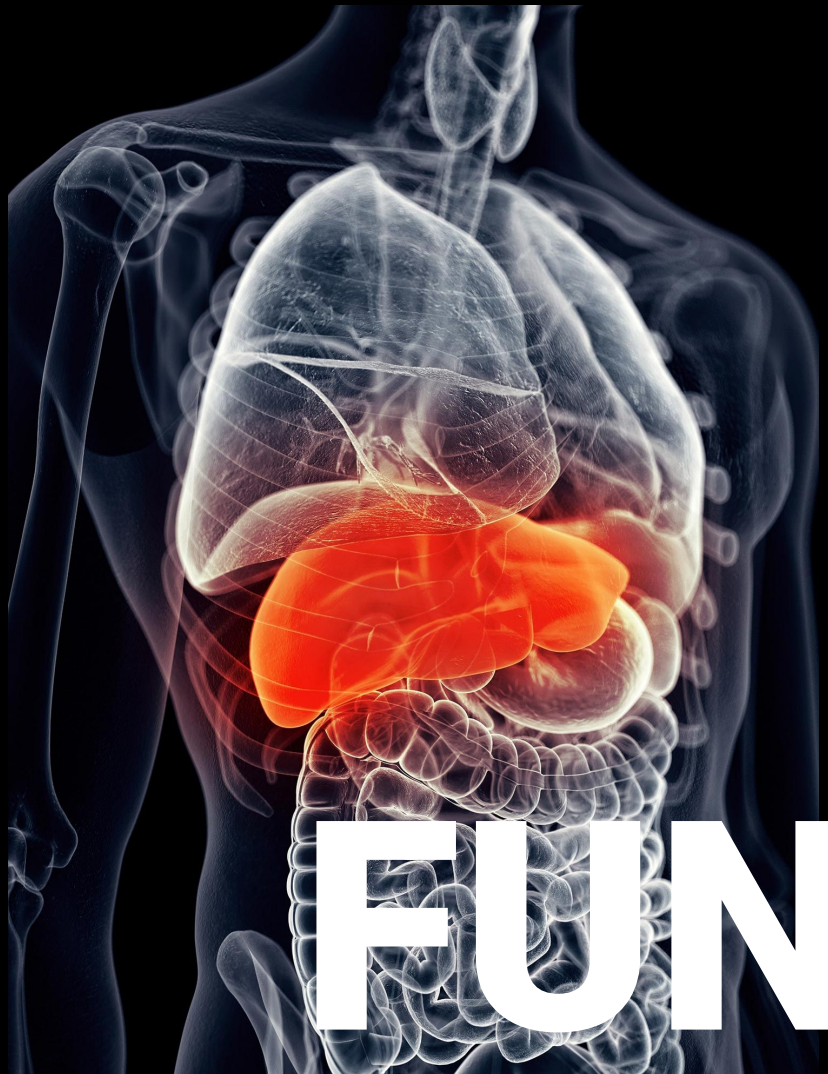


Advancing Liver Function Assessment: Personalized and Stratified Approaches with Standardized Computational Models and Data

Matthias König
Workshop Computation Models in Biology and Medicine, Stuttgart, 2023-06-15
Humboldt-University Berlin, Systems Medicine of the Liver Lab
https://livermetabolism.com
konigmatt

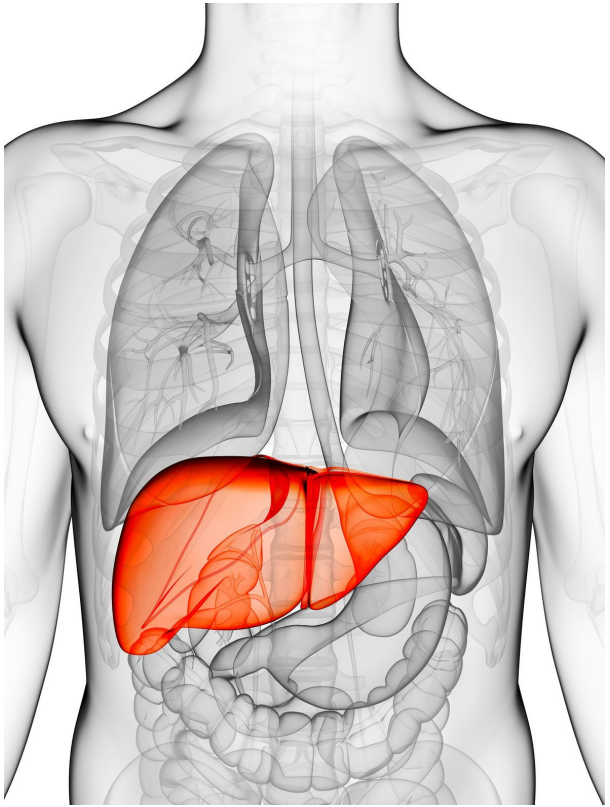
BMBF, ATLAS (AI and Simulation for Tumor Liver ASessment), grant number **031L0304B**. **DFG**, Research Unit Programme FOR 5151 "QuaLiPerF (Quantifying Liver Perfusion-Function Relationship in Complex Resection - A Systems Medicine Approach)" grant number **436883643** and by Priority Programme SPP 2311, Subproject SimLivA - Simulation supported liver assessment for donor organs- grant number **465194077**.



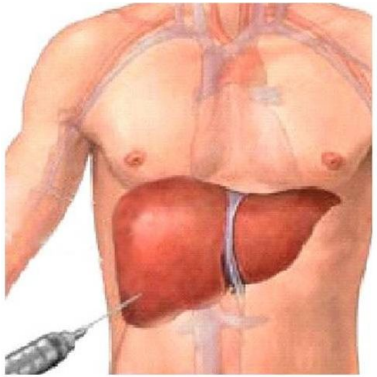
LIVER FUNCTION

Liver function

- Diagnostics
- Monitoring disease progression & interventions
- Functional capacity
  - hepatectomy
  - transplantation

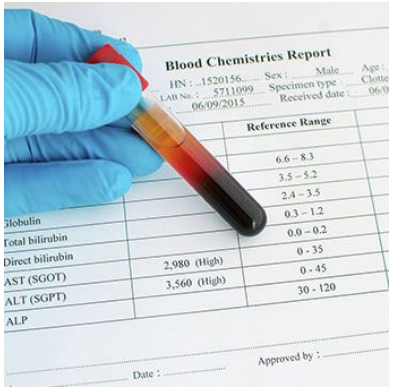


How to measure liver function?



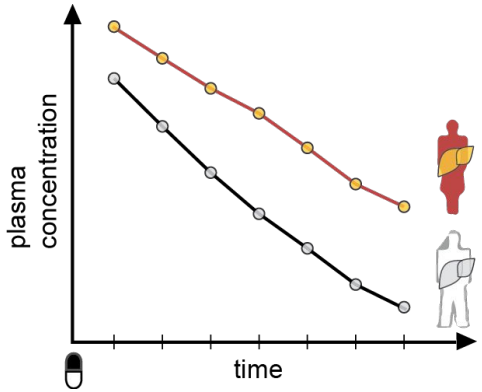
Liver biopsy
“gold standard”

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



Static liver function tests

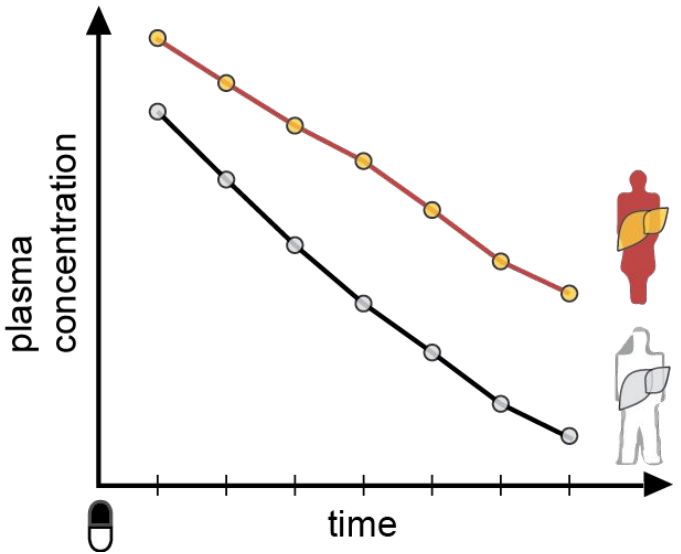
- single point biochemical parameter
- AST, ALT, prothrombin, albumin
- no reliable marker to quantify liver function



Dynamic liver function tests

Dynamic liver function tests

- **Liver specific elimination** of test substance *in vivo*
- **Rate of disappearance** as proxy for liver function
- **Metabolic phenotyping** of pathways/enzymes
  - caffeine (CYP1A2)
  - indocyanine green (OATP1B3, excretion)
  - dextromethorphan (CYP2D6)
  - chlorzoxazone (CYP2E1)
  - …
- **Challenge**
  - large interindividual variability



Pharmacokinetic models

- Elimination of drugs can be studied via compartmental models
- Main processes
  - absorption
  - distribution
  - metabolization
  - elimination
- Ordinary differential equations (ODE)

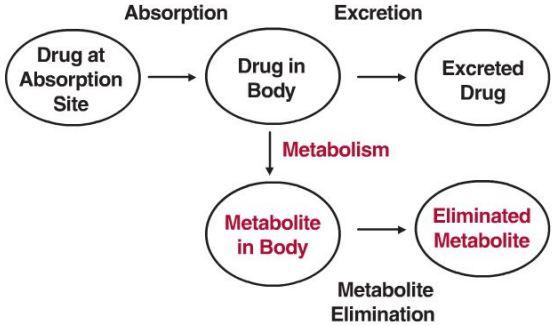


FIGURE 2-5. A drug is simultaneously absorbed into the body and eliminated from it, by excretion and metabolism. The processes of absorption, excretion, and metabolism are indicated with arrows and the compartments with ovals. The compartments represent different locations and different chemical species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

Pharmacokinetic models

- Elimination of drugs can be studied via compartmental models
- Main processes (ADME)
  - absorption
  - distribution
  - metabolization
  - elimination
- Ordinary differential equations (ODE)

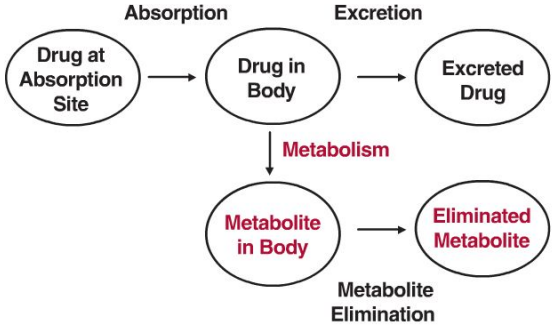


FIGURE 2-5. A drug is simultaneously absorbed into the body and eliminated from it, by excretion and metabolism. The processes of absorption, excretion, and metabolism are indicated with arrows and the compartments with ovals. The compartments represent different locations and different chemical species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

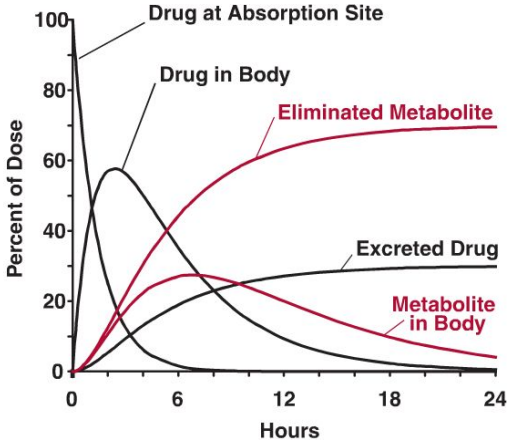
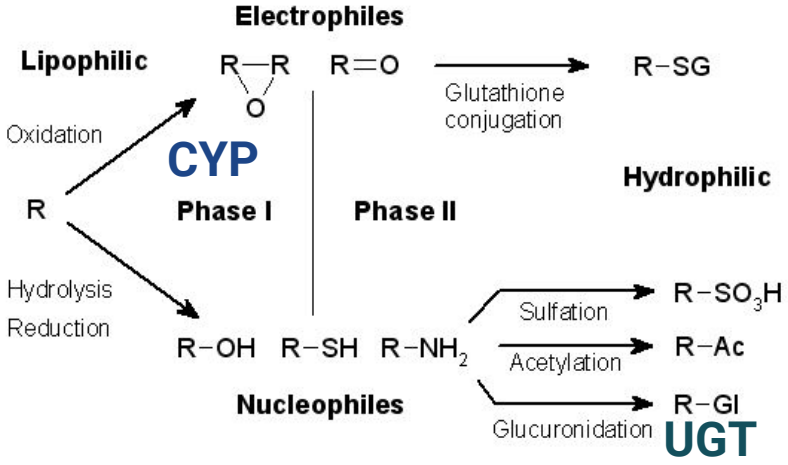
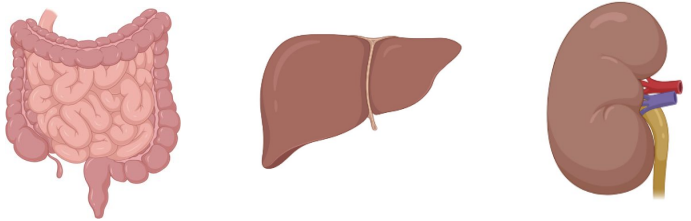


FIGURE 2-6. Time course of drug and metabolite in each of the compartments shown in Fig. 2-5. The amount in each compartment is expressed as a percentage of the dose administered. In this example, all the dose is absorbed. At any time, the sum of the molar amounts in the five compartments equals the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

Drug metabolism in a nutshell

- metabolism of xenobiotics is often divided into 3 phases: **modification, conjugation, and excretion**.
- **Cytochrome P450 (CYP)** main players in phase I (modification)
- **UDP-glucuronosyltransferases (UGT)** main players phase II (conjugation)
- **ATP-binding cassette (ABC)** and **Solute Carrier (SLC)** transporters are main drug transporters
- **Multiple isoforms** of CYP, UGT, ABC and SLC with different substrate specificity
- **Multiple organs**
  - **Intestine**: often metabolization during absorption
  - **Liver**: main organ of **drug metabolism**
  - **Kidneys:** minor metabolism & **excretion** of (modified) compounds in the urine





https://en.wikipedia.org/wiki/Drug_metabolism

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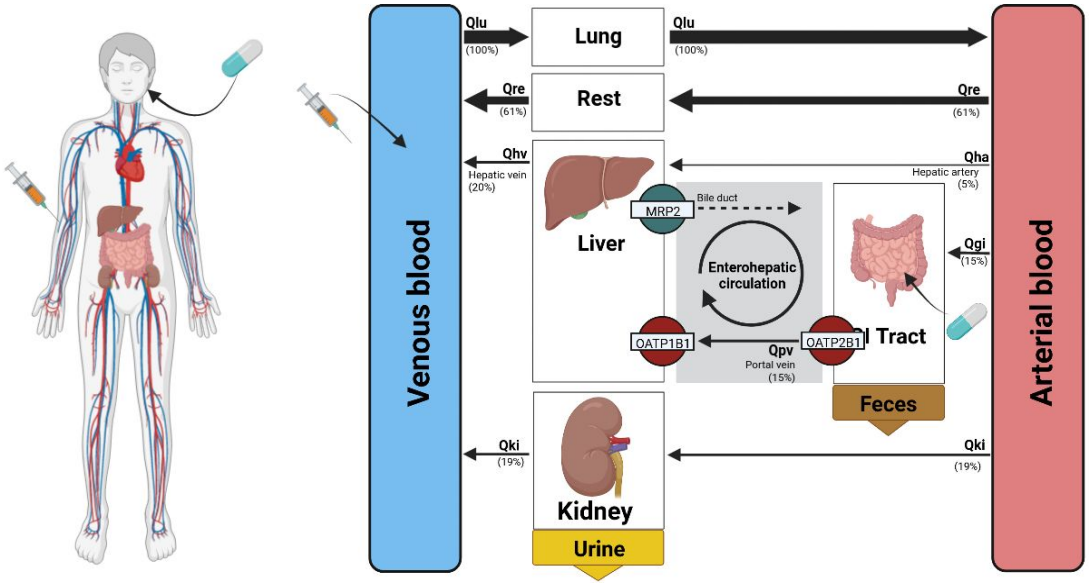
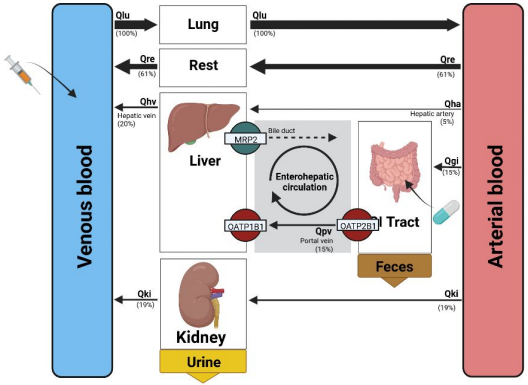
Physiologically based pharmacokinetics (PBPK) models

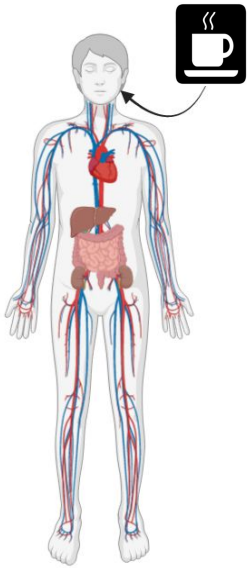
- **Human physiology *in silico* - Digital Twin**
- **Multi-scale**
  Body-Organs-Cells
- **High pharmacological & clinical relevance**
  - Individualization & Stratification
  - Pathophysiology

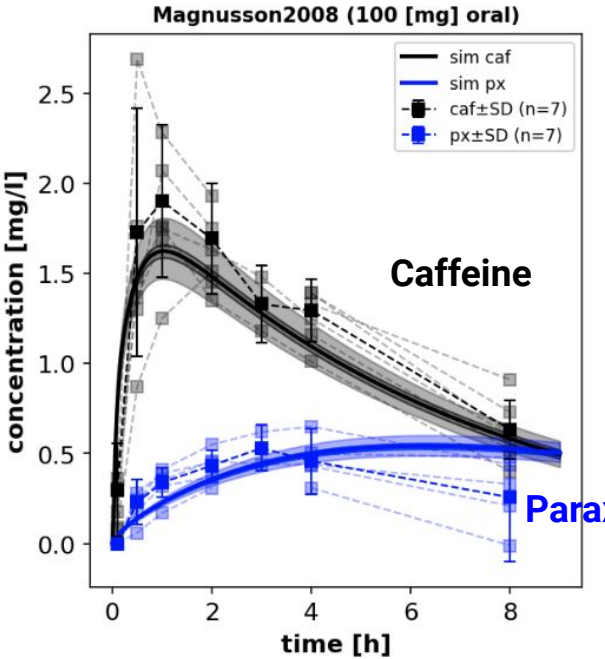


Physiologically based pharmacokinetics (PBPK) models

- **Metabolite time courses**
  blood, urine, tissues







Large interindividual variability

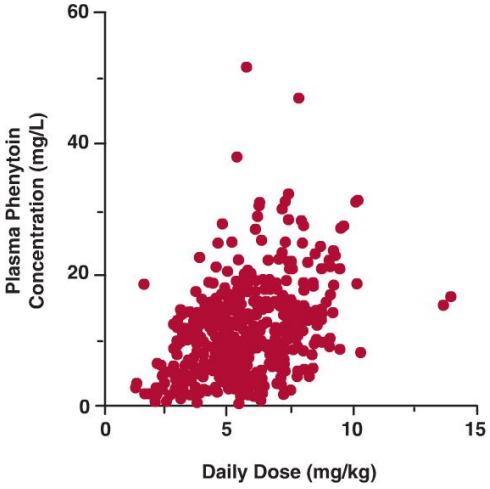


FIGURE 1-7. Although the average plasma concentration of phenytoin on chronic dosing tends to increase with the dosing rate, there is large variation in the individual values. (From: Lund, L. Effects of phenytoin in patients with epilepsy in relation to its concentration in plasma. In Davies DS, Prichard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

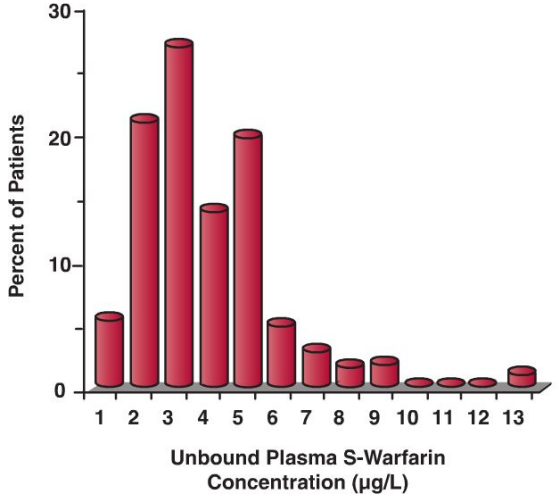
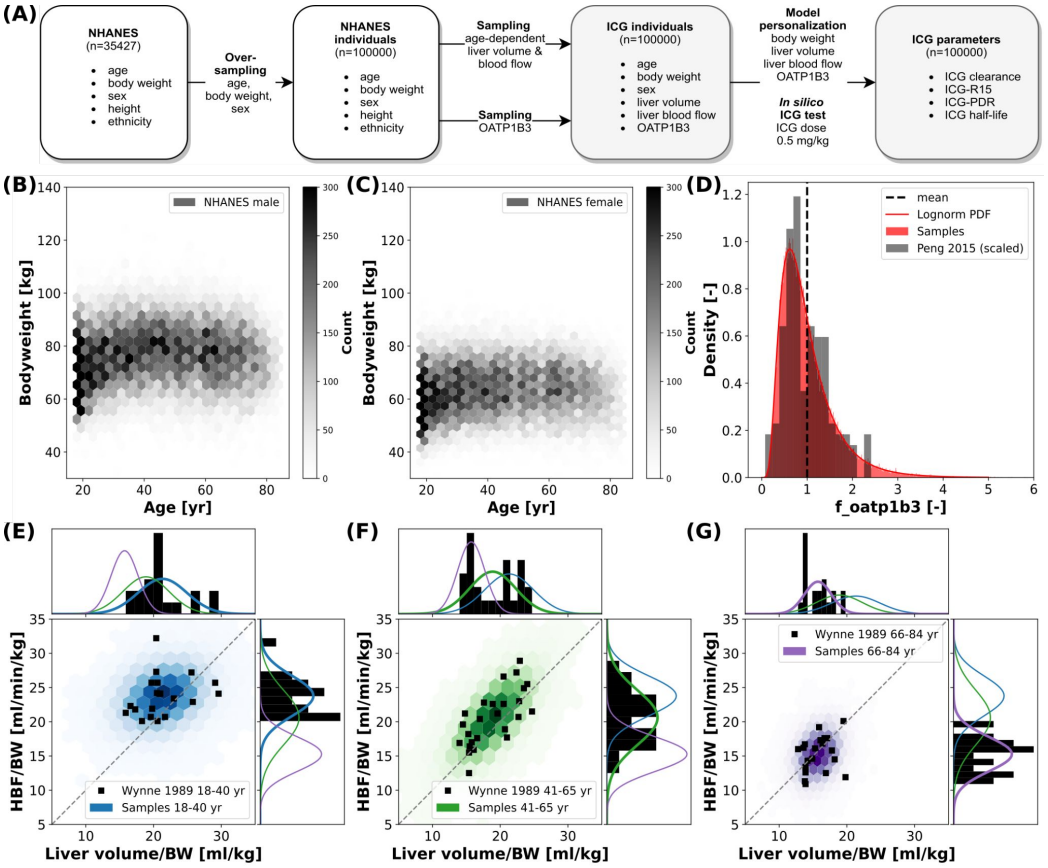


FIGURE 1-8. There is considerable interindividual pharmacodynamic variability in response to the oral anticoagulant warfarin as demonstrated by the substantial spread in the unbound concentration of the active S-isomer associated with a similar degree of anticoagulation in a group of 97 patients on maintenance 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.)

Variability in physiology

- large differences in body weight, organ volumes, perfusion
- age & sex dependencies
- changes in disease



Variability in protein amounts

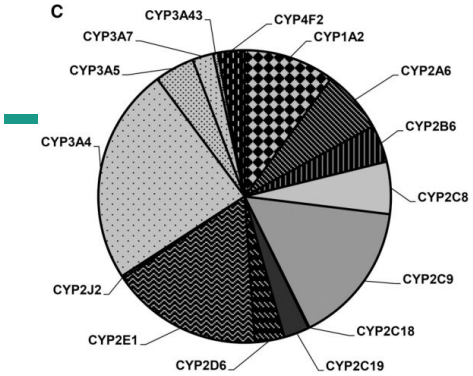


Fig. 1. Bar graph (A and B) and pie chart (C) of weighted mean abundances of cytochrome P450 enzymes in livers from adult Caucasians. Error bars represent weighted standard deviation values. *n*, the number of livers.

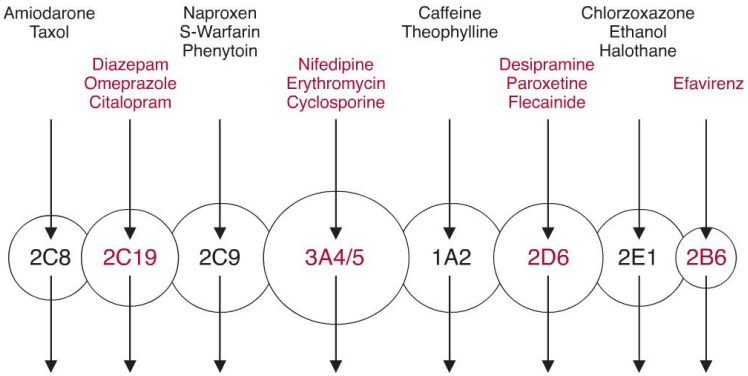


FIGURE 5-3. Graphic representation of the different forms of human cytochrome-P450 enzyme (*circles*) with different but often overlapping substrate specificities. The arrows indicate the single metabolic pathways. Representative substrates are listed above each enzyme.

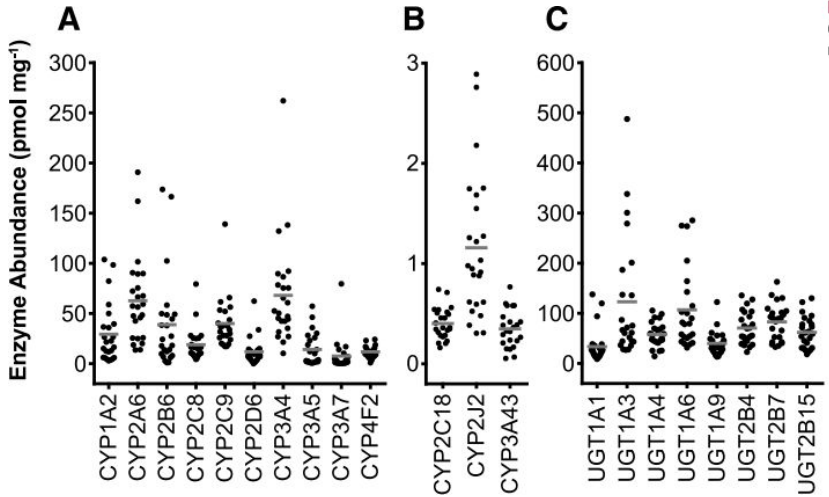


Fig. 2. A scatter plot of the measured abundance values of P450 (A and B) and UGT (C) enzymes. The number of samples is 24 for each enzyme except CYP2C9, CYP3A5, CYP3A7, CYP3A43, UGT1A3, UGT1A4, and UGT1A6 (n = 23). Lines indicate population means of the sets of data.

Pharmacogenomics

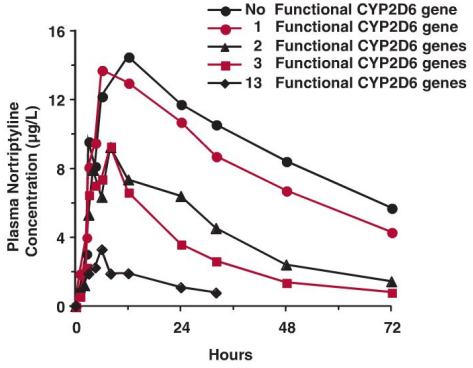


FIGURE 13-2. Strong genetic influence in the pharmacokinetics of nortriptyline is clearly demonstrated by the high correlation between the plasma concentration–time profile and the number of functional CYP2D6 genes possessed by an individual; the larger the number of functional genes, the higher is the 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.)

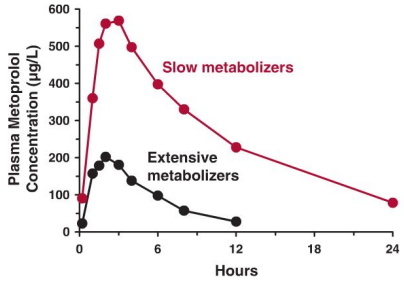


FIGURE 13-3. Plasma metoprolol concentrations after a single oral dose of 200-mg metoprolol tartrate were much higher in poor (*colored line*) than in extensive (*black line*) CYP2D6 metabolizers. Because metoprolol is a drug of high hepatic clearance, the difference between poor and extensive metabolizers 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.)

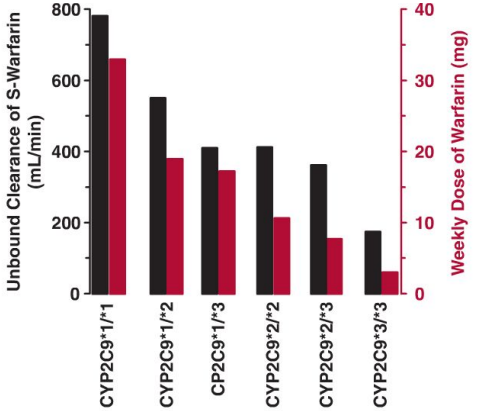


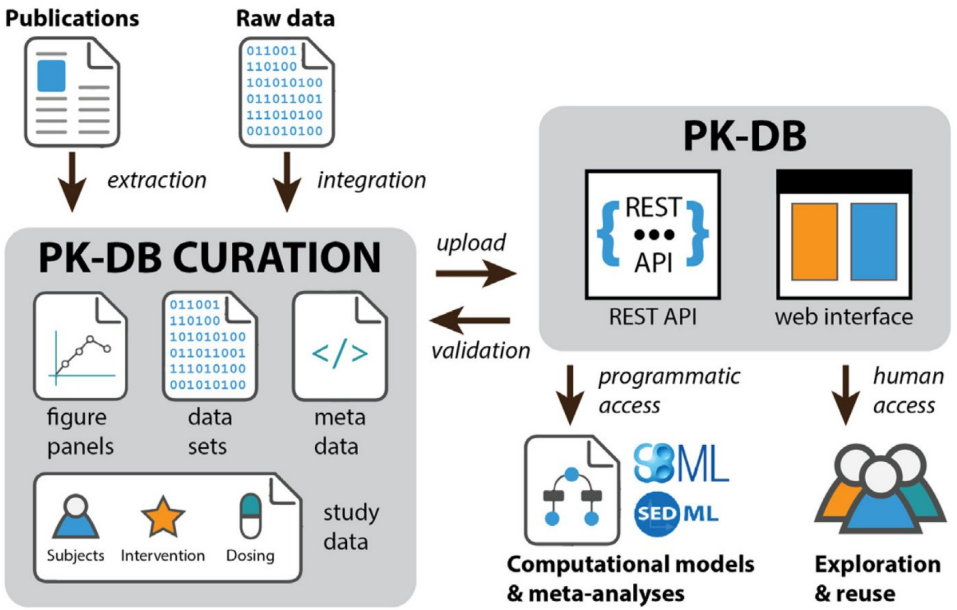
FIGURE 13-4. Genetics plays a significant role in the maintenance dose requirement of warfarin used in the treatment of various cardiovascular diseases. Shown are the unbound clearance of S-warfarin (*black*) in groups of patients with different CYP2C9 genotypes, all titrated and stabilized to a narrow 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.)


DATA

Pharmacokinetics Database (https://pk-db.com)

- **Database of pharmacokinetic time courses** and parameters

- **liver function tests**
  - icg, caffeine, LiMAx, galactose, Gd-EOB-DTPA
- **metabolic phenotyping**
  - dextrometorphan, chlorzoxazone, talinolol
- **important drugs**
  - paracetamol, omeprazol, pravastatin, simvastatin, metoprolol, midazolam, diazepam, sorafenib, ramipril, …



Grzegorzewski J, Brandhorst J, Green K, Eleftheriadou D, Duport Y, Barthorscht F, Köller A, Ke DYJ, De Angelis S, **König M.** ***PK-DB: pharmacokinetics database for individualized and stratified computational modeling*** Nucleic Acids Res. 2020 Nov 5:gkaa990. doi: 10.1093/nar/gkaa990.

Groups

Individuals

Intervention

Our subjects were 13 normal males (age range 18 to 71 years; mean weight ± S.D. 80.0 ± 12.18 kg), nine normal females not taking OCS (age range 22 to 33 years; mean weight ± S.D. 58.0 ± 5.9 kg), and nine healthy females (age range 22 to 33 years; mean weight ± S.D. 58.4 ± 9.6 kg) who had been on OCS for more than 6 months. Five of the 9 normal women not taking OCS were studied during the second half of their menstrual cycle and 4 during the first half. All subjects studied had a normal clinical history, physical examination, and sequential multiple analyzer of 12 vital determinations (SMA_{12}) profiles and, apart from oral contraceptives as indicated above, had taken no drugs or alcohol for at least 2 weeks prior to the study. Smokers were not included in this study.

After an overnight fast the subjects received 250 mg of caffeine (approximately equivalent to 3 cups of coffee) in a capsule with 150 ml of water.

Time courses

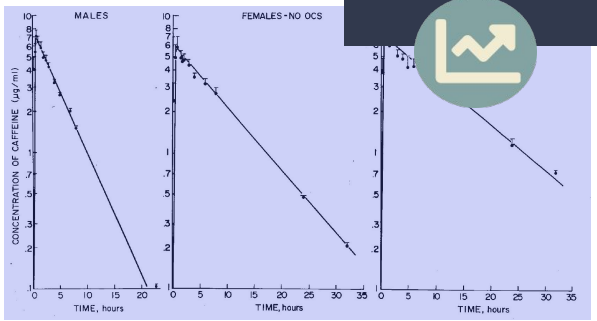


Fig. 1. Comparison of caffeine plasma concentration/time profiles in 13 healthy male subjects (left panel), nine healthy females taking no OCS (center panel), and nine healthy females on OCS (right panel) (mean ± S.E.).

Outputs

Table I. Pharmacokinetic parameters of caffeine (250 mg) in males, females, and females on OCS

	Normal males (n = 13)	*Normal females taking no OCS* (n = 9)	*Normal females on OCS* (n = 9)
$t½_{(\beta)}$ (hr)	5.5 ± 2.6	6.2 ± 1.6	10.7 ± 3.0†
$Vd_{(\beta)}$ (L/kg)	0.54 ± 0.18	0.69 ± 0.16*	0.72 ± 0.24
$Vd_{(extrap)}$ (L/kg)	0.54 ± 0.13	0.70 ± 0.14*	0.75 ± 0.28
Plasma clearance (ml/min/kg)	1.3 ± 0.42	1.3 ± 0.35	0.79 ± 0.21†
Plasma binding (%)	31.4 ± 1.9	31.5 ± 4.5	29.35 ± 2.17
Plasma clearance of unbound drug (ml/min/kg)	1.8 ± 0.6	1.97 ± 0.57	1.12 ± 0.28†

Values are mean ± S.D.
*$p < 0.05$ for normal males vs females taking no OCS.
†$p < 0.001$ for females taking no OCS vs. females on OCS.

PK-DB content

		DATA
758	**Studies**	Clinical or experimental study measuring data in groups and/or individuals.
2439	**Groups**	Group of individuals for which data was reported, e.g., the control group and the group which received an intervention. A group is described by certain characteristica, e.g., bodyweight, health status, smoking status or medication.
17050	**Individuals**	A single subject in the study. A subject is characterized by the group it belongs to as well as individual characteristica like age, body weight or sex. Individuals are only created if outputs or timecourses have been reported on the subject level (not group level).
2163	**Interventions**	Intervention which was performed in the study. Often interventions consist of application of a substance, e.g. caffeine or codeine. Other examples are changes in lifestyle like smoking cessation.
136330	**Outputs**	Clinical or experimental output. These can be single parameters or variables, e.g. pharmacokinetic parameters like AUC, clearance or half-life of the applied substances. An output is always linked to the respective intervention and group or individual.
6662	**Timecourses**	Clinical or experimental time course measurements. Often timecourses are concentration measurements. A timecourse is always linked to the respective intervention and group or individual.
150	**Scatters**	Correlations between outputs are often provided as scatter plots (e.g. age ~ clearance).

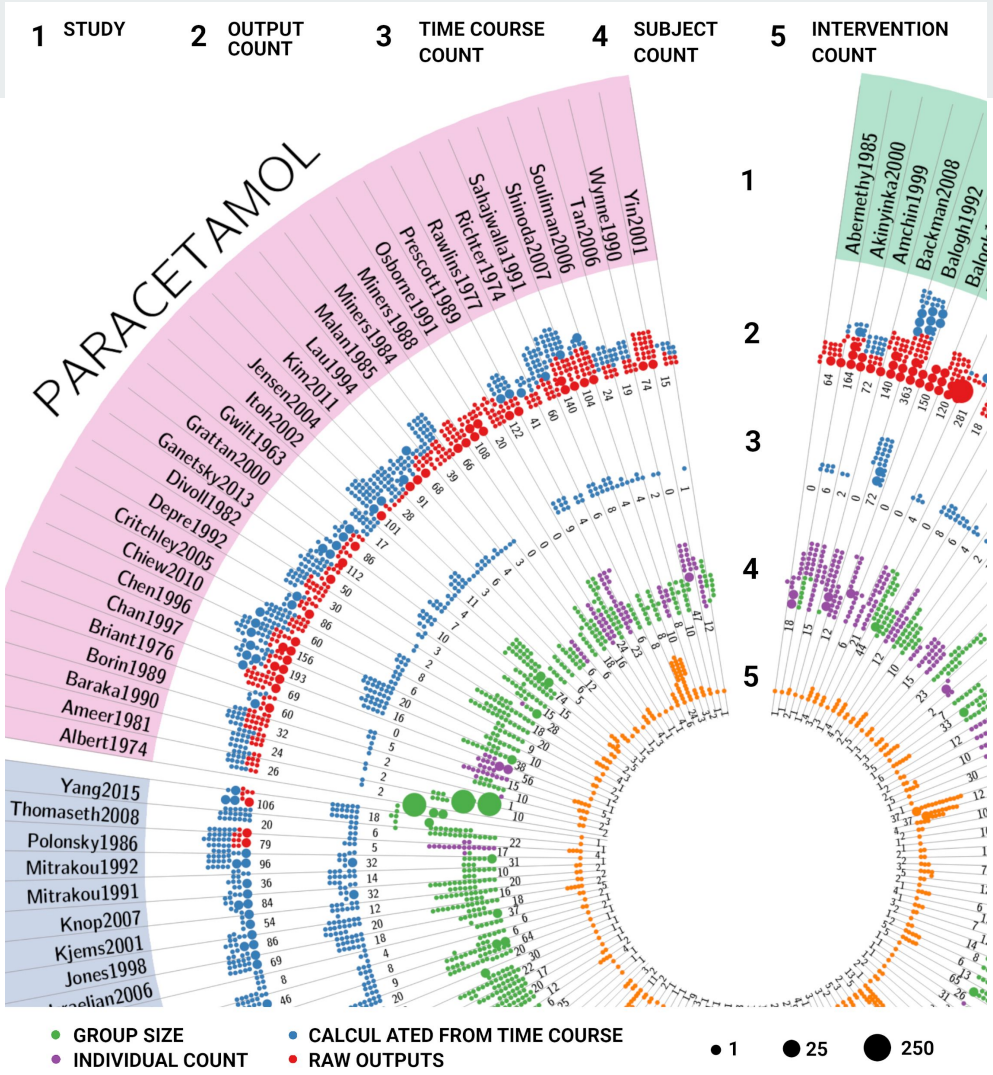
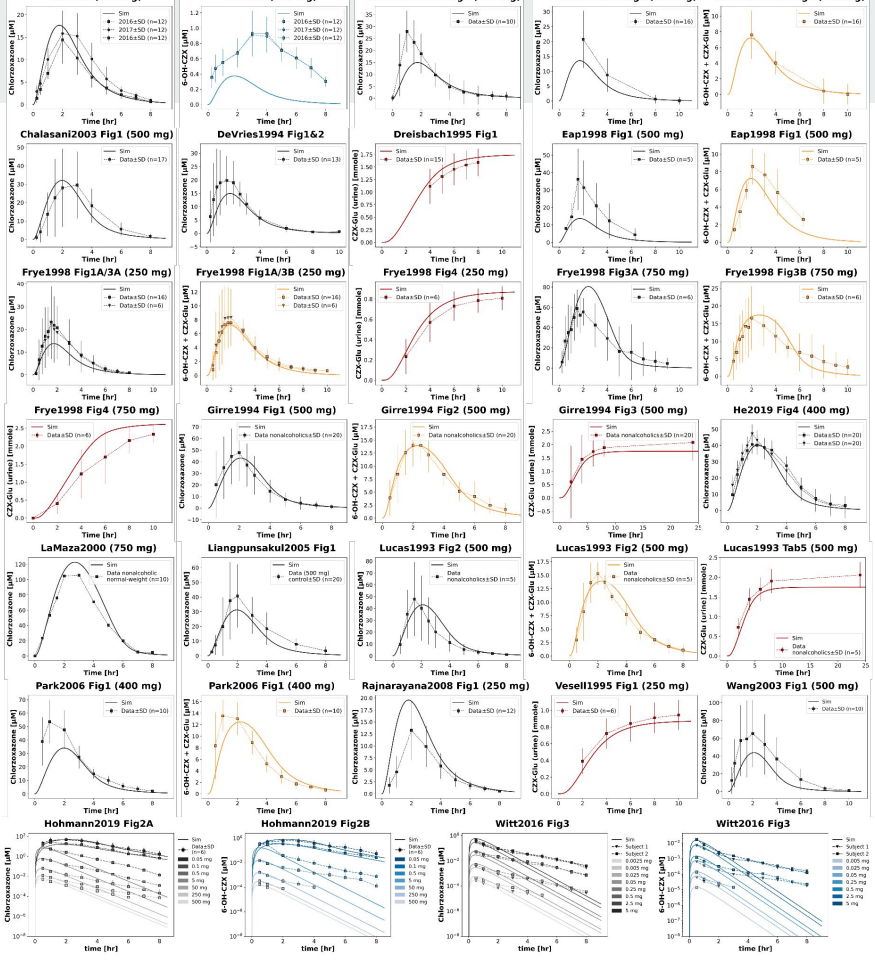


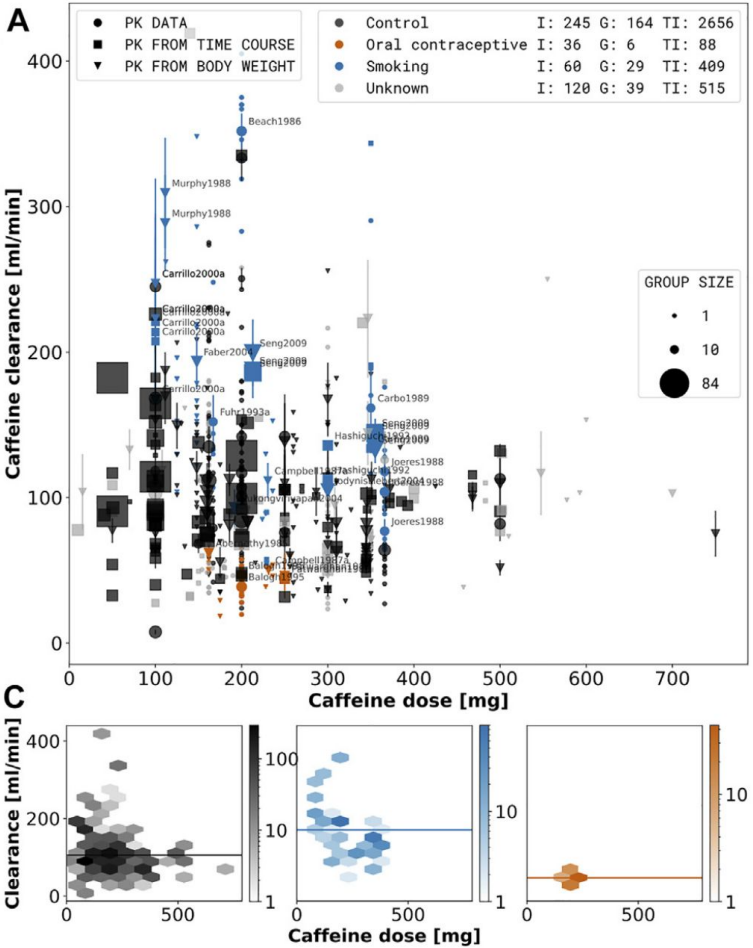
Table 1: Overview of curated clinical studies.

References	PK-DB	PMID	Dosing protocol	Health status	Data	Fit	Validation
Bedada and Neerati (2016)	PKDB00621	26680654	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX*)	✓*	
Bedada and Boga (2017)	PKDB00622	27670974	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX*)	✓*	
Bedada and Neerati (2018)	PKDB00623	28983678	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX*)	✓*	
Benowitz et al. (2003)	PKDB00623	14586387	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urinary recovery	✓	
Chalasani et al. (2003)	PKDB00623	12601351	500 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urinary recovery	✓	
Burckart et al. (1998)	PKDB00624	9542473	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX), urinary recovery	✓	
de Vries et al. (1994)	PKDB00626	7849234	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urinary recovery	✓	
Dreisbach et al. (1995)	PKDB00627	12534643	500 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX), urine time-course (6-OH-CZX)	✓	
Ernstgard et al. (2004)	PKDB00699	15255802	250, 500, 750 mg, oral, multiple dose, tablet	healthy	metabolic ratios, urinary recovery		✓
Frye et al. (1998)	PKDB00629	9597564	250, 750 mg, oral, multiple dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX), urine time-course (6-OH-CZX)	✓	
Girre et al. (1994)	PKDB00631	7910460	500 mg, oral, single dose, tablet	healthy, alcoholics	plasma time-course (CZX,6-OH-CZX), urine time-course (6-OH-CZX)	✓	✓
He et al. (2019)	PKDB00632	31363741	400 mg, oral, single dose, tablet	healthy	plasma time-course (CZX)	✓	
Hohmann et al. (2019)	PKDB00633	31222796	0.005, 0.01, 0.05, 0.5, 5, 50 mg as solution, 250, 500 mg as tablet, oral, multiple dose	healthy	plasma time-course (CZX, 6-OH-CZX*)	✓	
Hukkanen et al. (2010)	PKDB00698	20233178	250 mg, oral, single dose, tablet	healthy	urinary recovery	✓	
Kharasch et al. (1993)	PKDB00623	8513656	750 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urinary recovery	✓	
de la Maza et al. (2000)	PKDB00634	10832901	750 mg, oral, single dose, tablet	healthy	plasma time-course (CZX)	✓	
Liangpunsakul et al. (2005)	PKDB00636	15841467	500 mg, single dose, tablet	healthy	plasma time-course (CZX)	✓	
Lucas et al. (1993)	PKDB00637	8120116	500 mg oral, single dose, tablet	healthy, alcoholics	plasma time-course (CZX, 6-OH-CZX), urine time course (6-OH-CZX)	✓	✓
Lucas et al. (1995)	PKDB00688	7625570	500 mg oral, single dose, tablet	alcoholics	metabolic ratios		✓
Mishin et al. (1998)	PKDB00638	9820389	750 mg, oral, single dose, tablet	alcoholics	plasma time-course (CZX, 6-OH-CZX)		✓
Oneta et al. (2002)	PKDB00689	7955797	500 mg, 250 mg, oral, multiple dose, tablet	alcoholics	metabolic ratios		✓
Orellana et al. (2006)		16321567	500 mg, oral, single dose, tablet	healthy, steatosis, steatohepatitis	metabolic ratios		✓
O'Shea et al. (1994)	PKDB00697	11804663	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX), urinary recovery	✓	
Park et al. (2006)	PKDB00641	16397290	400 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX)	✓	
Rajnarayana et al. (2008)	PKDB00643	19326774	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX)	✓	
Vesell et al. (1995)	PKDB00644	7773304	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urine time-course (6-OH-CZX)	✓	
Wang et al. (2003)	PKDB00639	12534643	500 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urinary recovery	✓	
Witt et al. (2016)	PKDB00640	27300008	5, 2.5, 0.5, 0.25, 0.05, 0.025, 0.005, 0.0025mg, oral, single dose, solution	healthy	plasma time-course (CZX, 6-OH-CZX*)	✓	
Wilkinson et al. (1977)	PKDB00700	881642	ethanol: 11.2, 22.5, 33.7, 45.0 g, oral, single dose, solution	healthy	plasma time-course (ethanol)	✓	

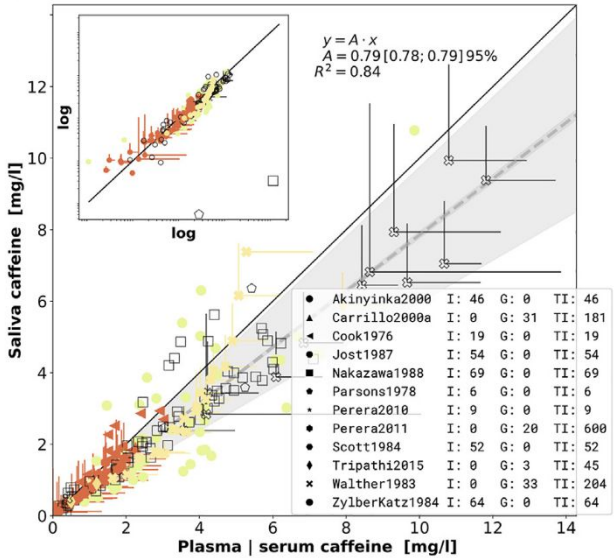
* 6-OH-CZX was measured without the chlorzoxazone-O-glucuronide.



Caffeine meta-analysis



control
smoking
oral
contraceptives

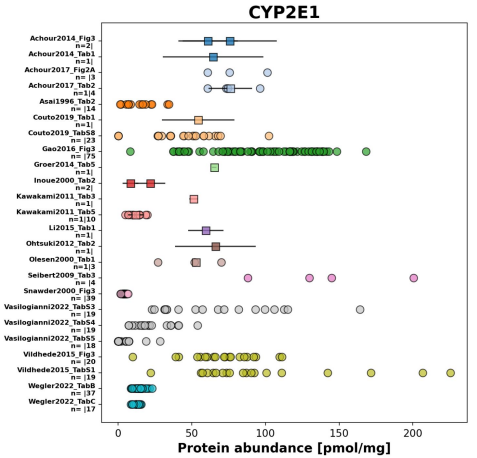


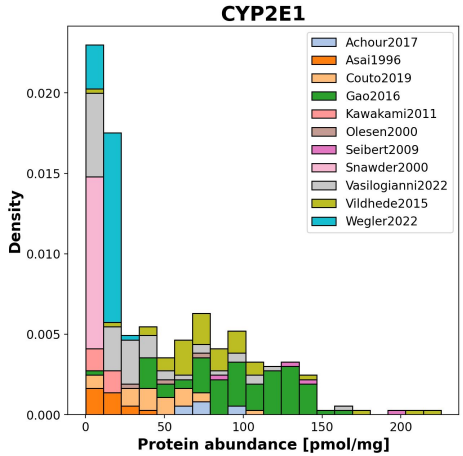
J.Grzegorzewski, F.Bartsch, A.Köller, and **M.König** ***Pharmacokinetics of caffeine: A systematic analysis of reported data for application in metabolic phenotyping and liver function testing***
Frontiers in Pharmacology 2022, Vol12; doi: 10.3389/fphar.2021.752826

Grzegorzewski J, Brandhorst J, Green K, Eleftheriadou D, Duport Y, Barthorscht F, Köller A, Ke DYJ, De Angelis S, **König M.** ***PK-DB: pharmacokinetics database for individualized and stratified computational modeling***
Nucleic Acids Res. 2020 Nov 5:gkaa990. doi: 10.1093/nar/gkaa990.

METDETOX - METabolization and DETOXification protein database

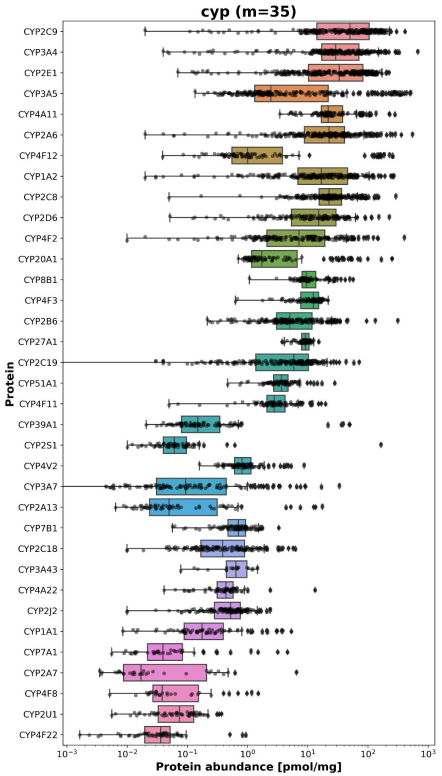
- **Protein distributions** (interindividual variability) are key to understand variability in drug metabolism and hepatic function
- **Cytochrome P450 (CYP, n=35)**
  UDP-glucuronosyltransferases (UGT, n=16)
  ATP-binding cassette transporter (ABC, n=24)
  Solute carrier organic anion transport (SLC, n=102)
- **Objective:** Determine distributions and correlations in protein abundance of CYP, UGT, ABC and SLC isoforms



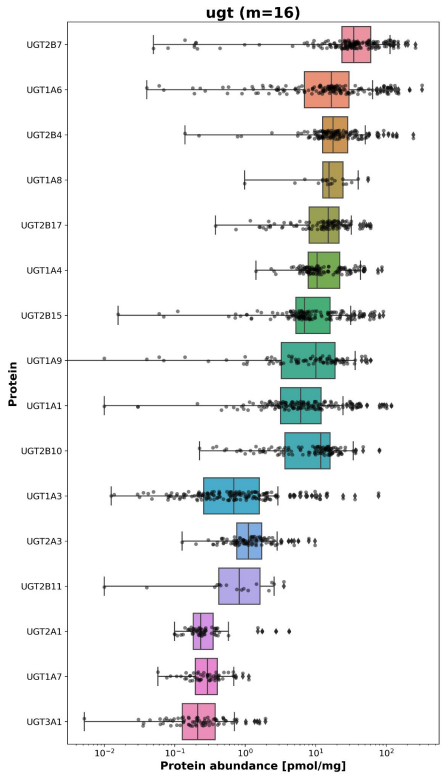


Large variability & multitude of isoforms (Human Liver)

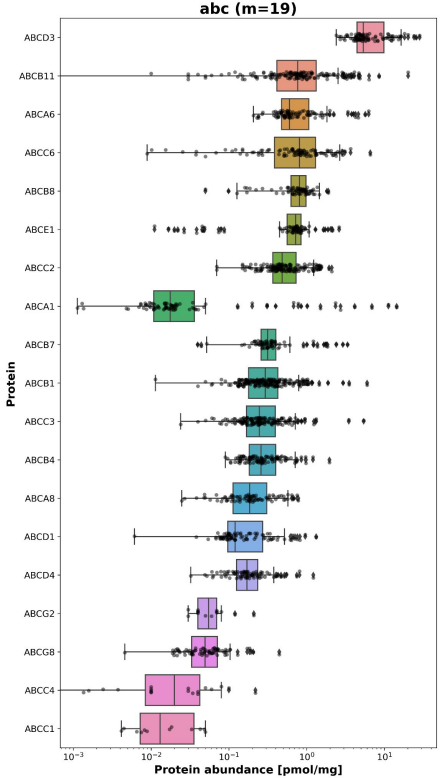
Cytochrome P450 (CYP)



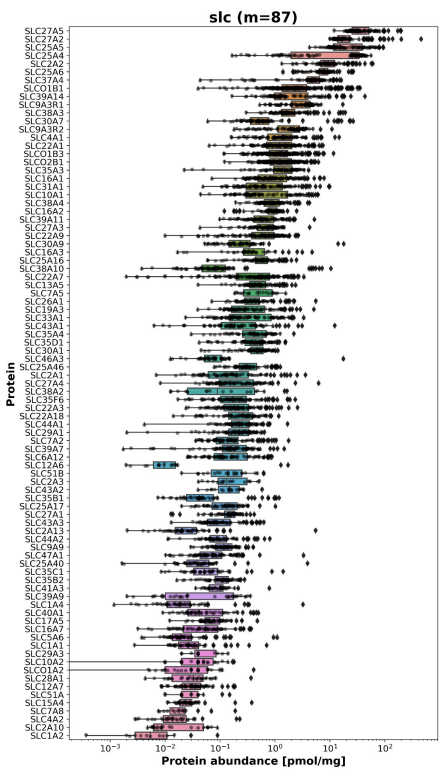
UDP-glucuronosyltransferases (UGT)



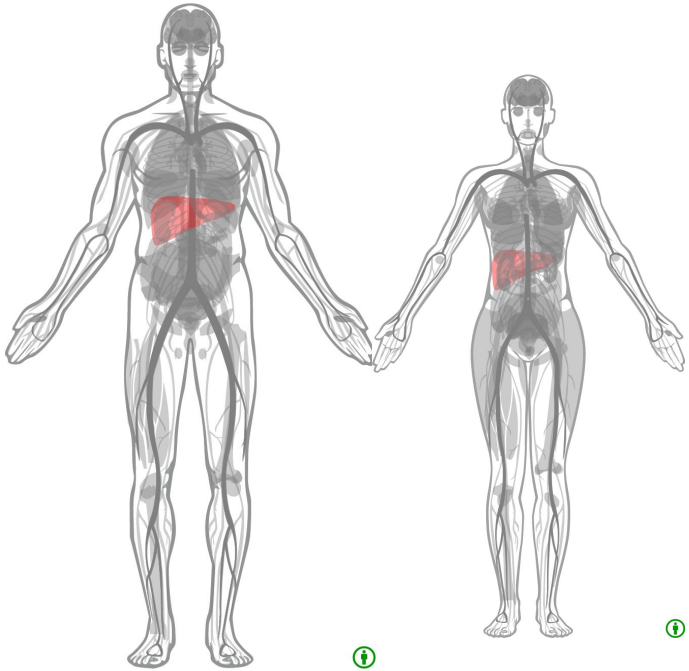
ATP-binding cassette (ABC)



Solute Carrier (SLC)



A. Hossain, S. Silberhorn, M. König. **Protein distributions of drug metabolizing and transporting enzymes in the human Liver.** In preparation.

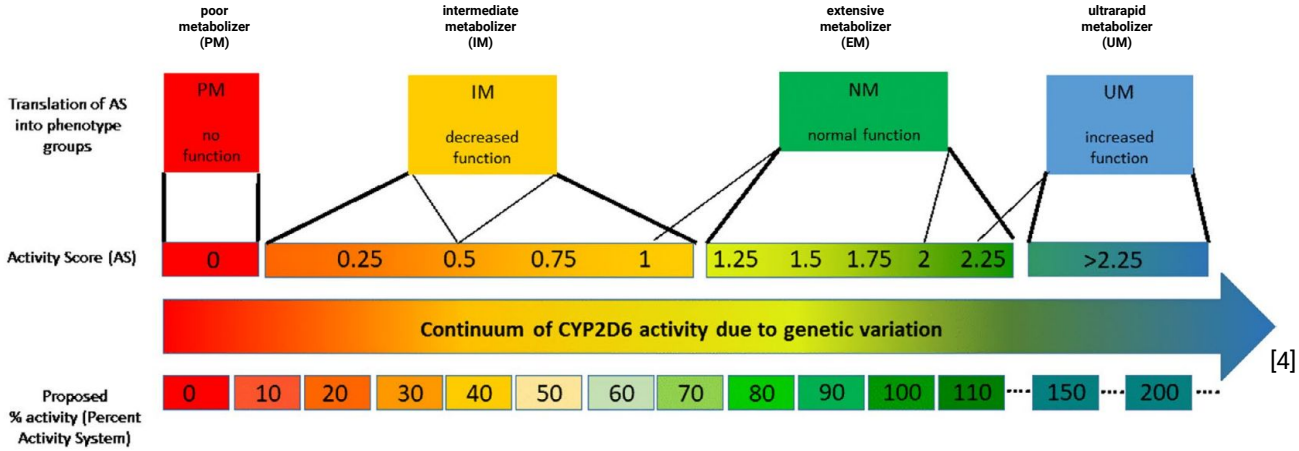


Models

1. dextromethorphan

CYP2D6 Polymorphism

- genetic variants have different activity values
- subjects carry combinations of these variants
- sum of individual activity values is the activity score (AS)



[4]

Activity Score (AS): $AS = \sum ActivityValue$

	Activity Value	Allele
	0	*3,*4, *5, *6, *7, *8,*11,*12,*13,*15,*42,*44, …
	0.25	*10
	0.5	*9,*10x2,*14,*17,*29,*41,*49,*50,*54,*55,*59
	1	*1,*2,*9x2, *17x2, *33,*34,*35,*45,*46,*53,
	>1	*1x2, *1x>2, *2x2, *1x>3, …

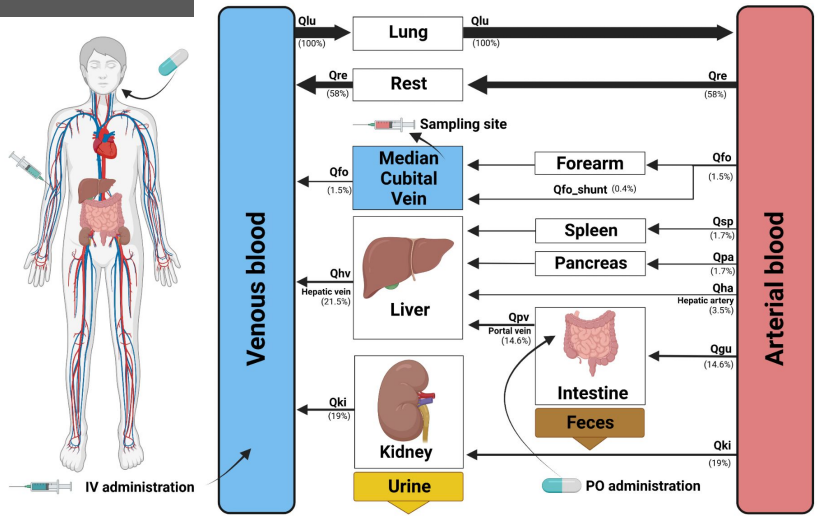
[5]

[4] K. E. Caudle et al., "Standardizing CYP 2D6 Genotype to Phenotype Translation: Consensus Recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group," Clin Transl Sci, vol. 13, no. 1, pp. 116–124, Jan. 2020, doi: 10.1111/cts.12692.

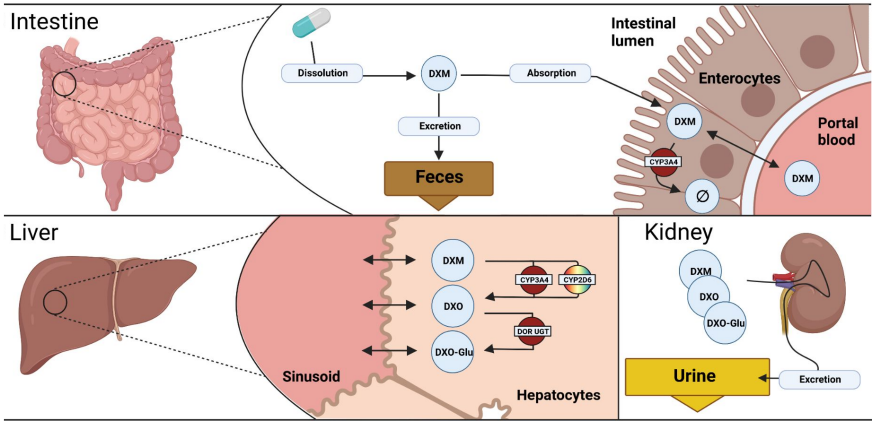
[5] M. Whirl-Carrillo[1], R. Huddart[1], L. Gong, K. Sangkuhl, C.F. Thorn, R. Whaley and T.E. Klein. "An evidence-based framework for evaluating pharmacogenomics knowledge for personalized medicine" *Clinical Pharmacology & Therapeutics* (2021) online ahead of print.

Dextromethorphan - Genetic polymorphisms CYP2D6

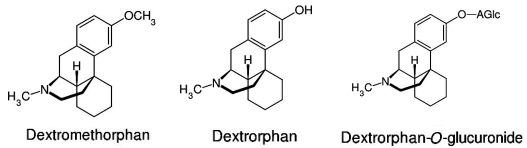
Whole-body model



Tissue models



Substance/Metabolites



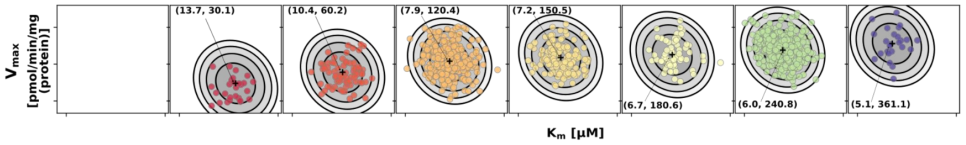
J.Grzegorzewski, J.Brandhorst, **M.König**
Physiologically based pharmacokinetic (PBPK) modeling of the role of CYP2D6 polymorphism for metabolic phenotyping with dextromethorphan
https://doi.org/10.1101/2022.08.23.504981 [in print, Frontiers in Pharmacology]

Model of CYP2D6 polymorphism and variability

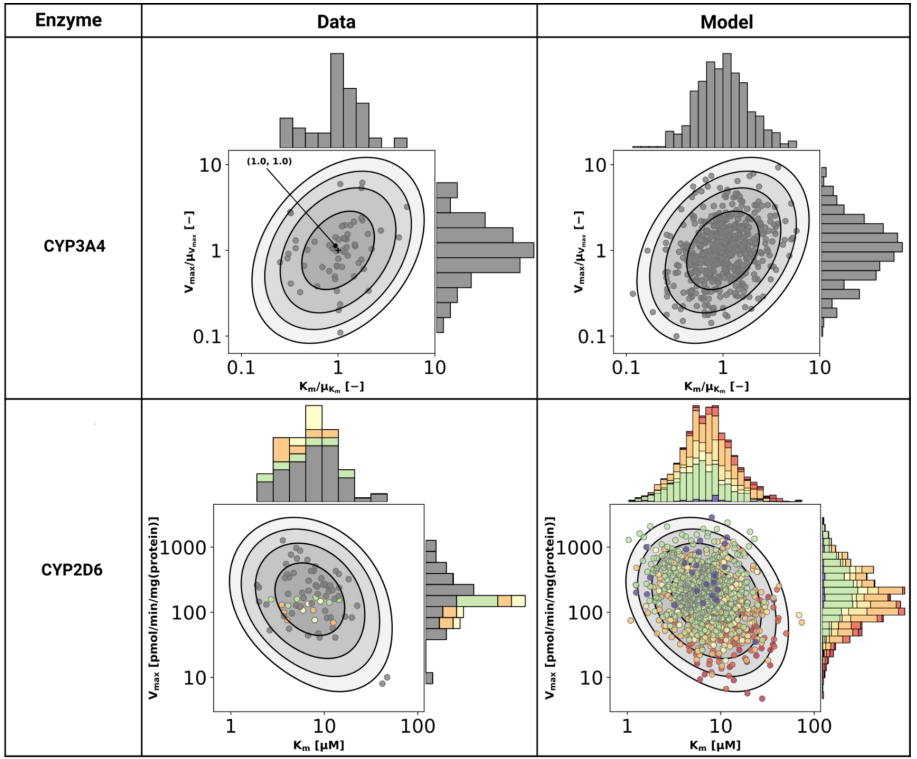
Activity Value	Allele
0	*3,*4, *5, *6, *7, *8,*11,*12,*13,*15,*42,*44, …
0.25	*10
0.5	*9,*10x2,*14,*17,*29,*41,*49,*50,*54,*55,*59
1	*1,*2,*9x2, *17x2, *33,*34,*35,*45,*46,*53,
>1	*1x2, *1x>2, *2x2, *1x>3, …

Michaelis Menten: $v = \frac{V_{\max}[S]}{K_M + [S]}$

Activity Score (AS): $AS = \sum ActivityValue$

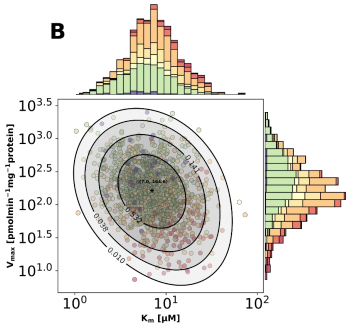


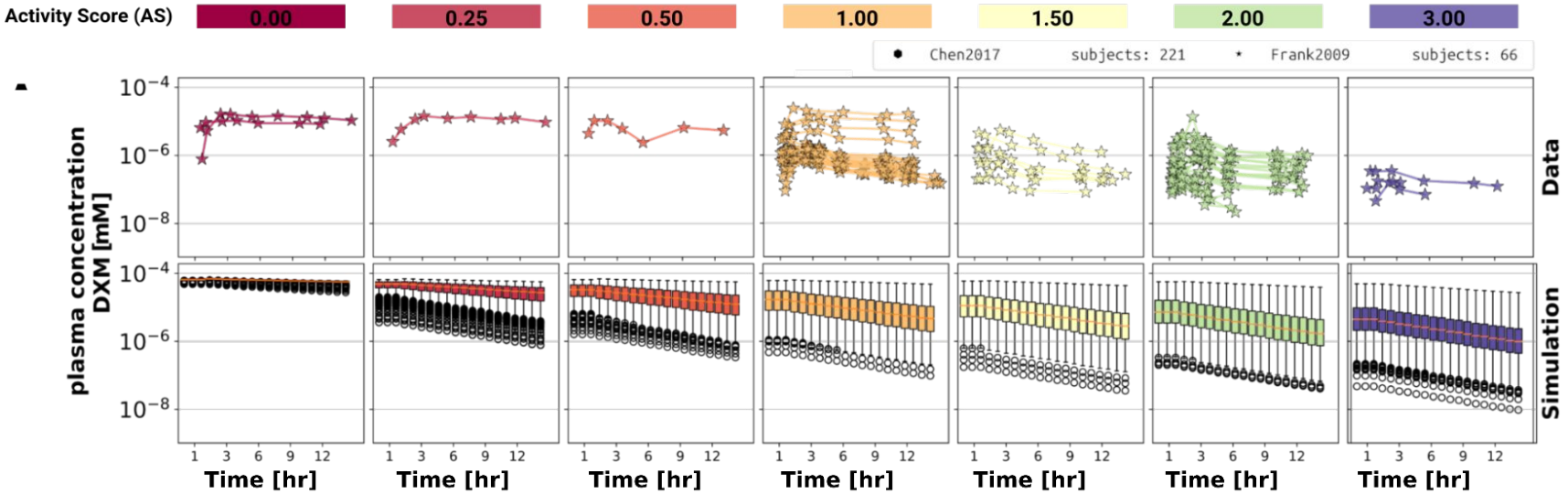
AS	0.00	0.25	0.50	1.00	1.25	1.50	2.00	3.00
gPT	gPM	gIM	gIM	gIM	gEM	gEM	gEM	gUM
μ_{Vmax}	0.00	30.1	60.2	120.4	150.5	180.6	240.8	361.1
μ_{Km}	0.00	13.7	10.4	7.9	7.2	6.7	6.0	5.1
P(AS)	0.06	0.02	0.07	0.29	0.13	0.06	0.33	0.02



Effect of polymorphism on pharmacokinetics

- **Prediction of effect of genetic variants**
- Time course of dextromethorphan (DXM) and metabolites

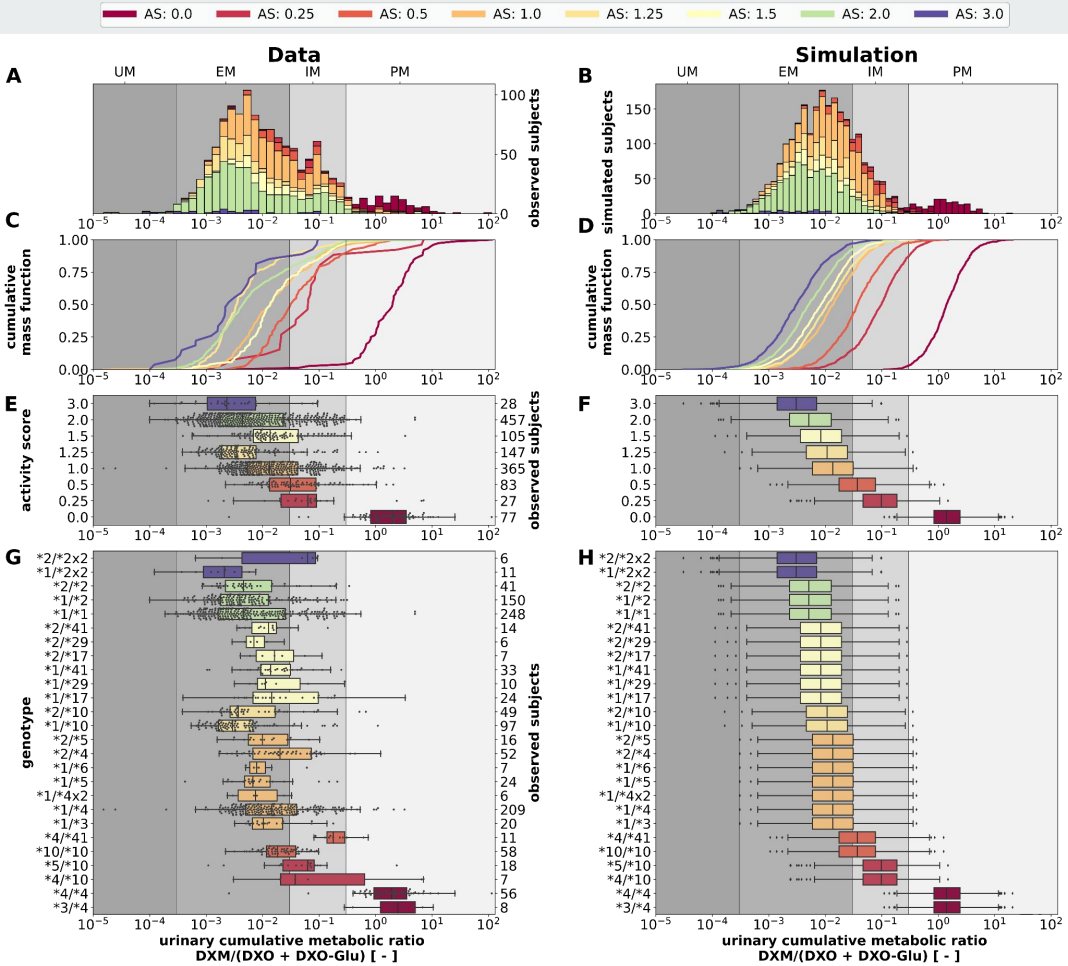




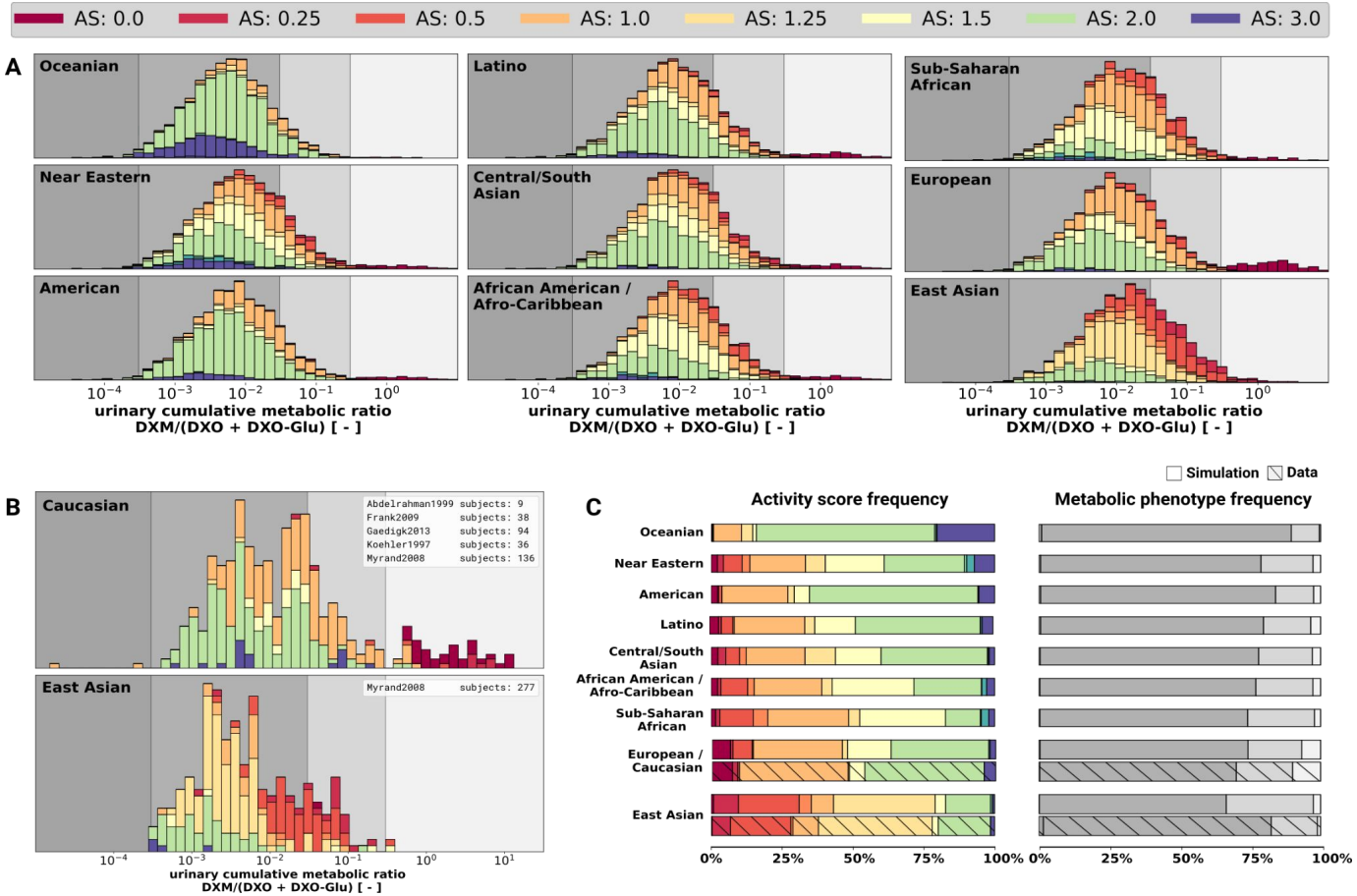
Metabolic phenotyping

- Model predicts effect of CYP2D6 activity and genetic polymorphisms
- Urinary cumulative metabolic ratio (UCMR) for metabolic phenotyping

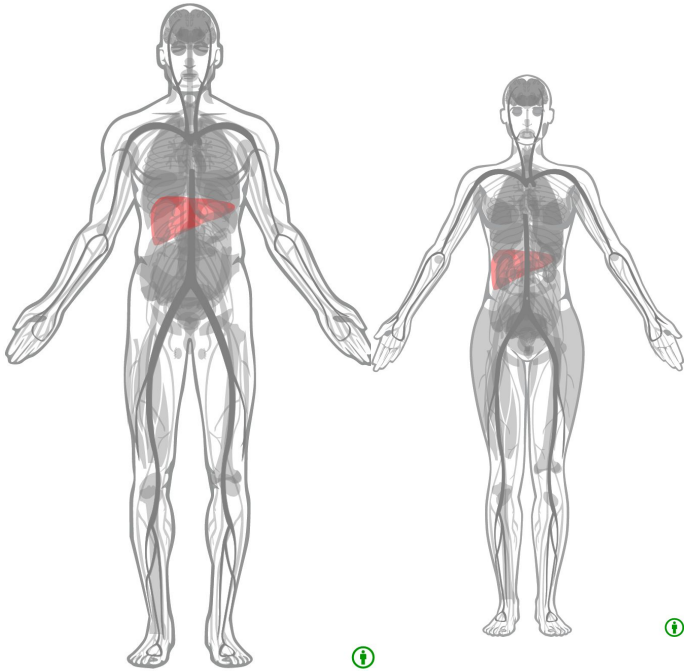
J.Grzegorzewski, J.Brandhorst, **M.König** ***Physiologically based pharmacokinetic (PBPK) modeling of the role of CYP2D6 polymorphism for metabolic phenotyping with dextromethorphan*** https://doi.org/10.1101/2022.08.23.504981
In print, Frontiers in Pharmacology



Dextromethorphan - CYP2D6 populations



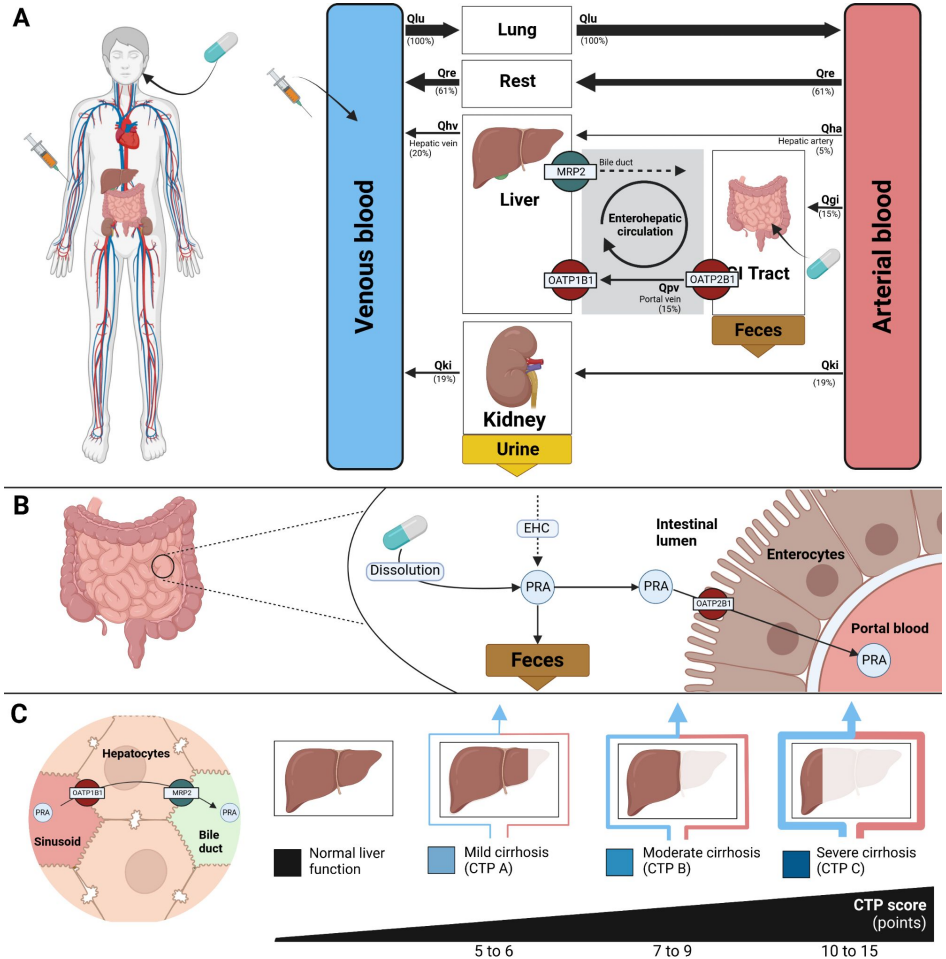
J.Grzegorzewski, J.Brandhorst, **M.König** ***Physiologically based pharmacokinetic (PBPK) modeling of the role of CYP2D6 polymorphism for metabolic phenotyping with dextromethorphan*** https://doi.org/10.1101/2022.08.23.504981
In print, Frontiers in Pharmacology



Models

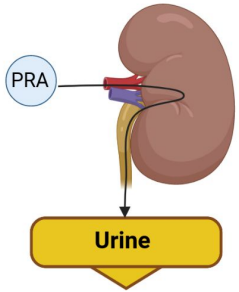
2. pravastatin

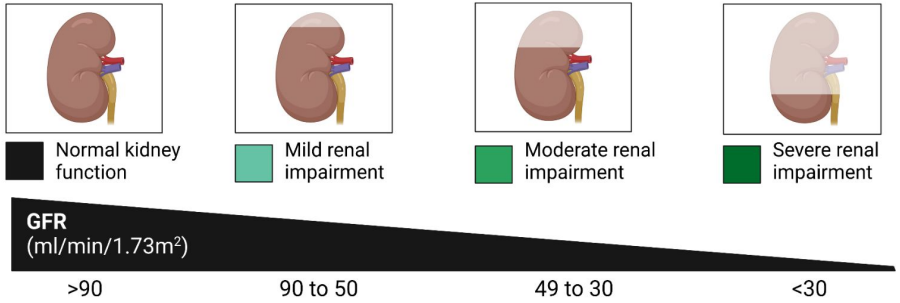
Pravastatin - Hepatorenal impairment

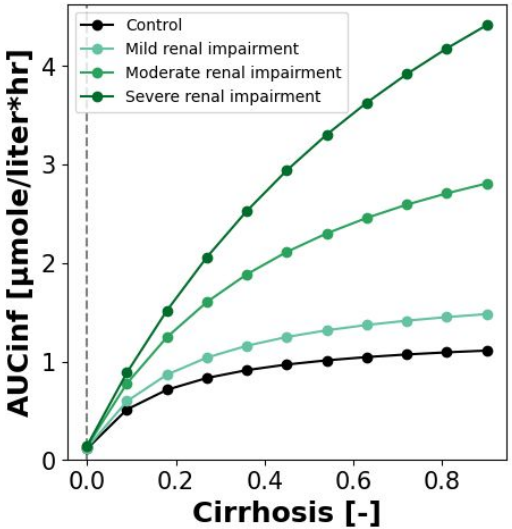


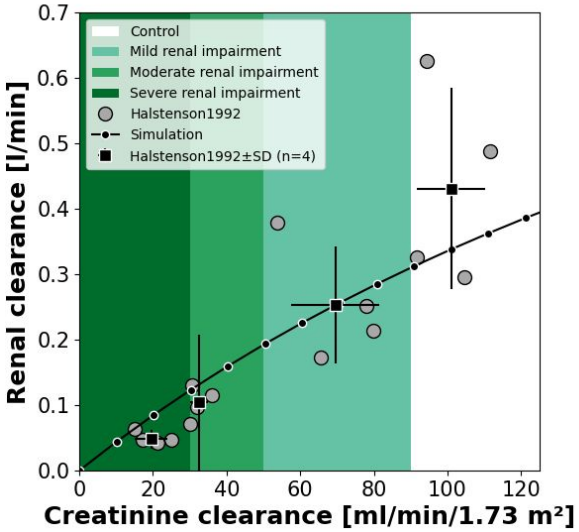
HL Pujol, J Grzegorzewski, F Bartsch, HM Tautenhahn, **M.König**
A physiologically based pharmacokinetic (PBPK) model of pravastatin: Impact of hepatorenal impairment and genetic polymorphisms of OATP1B1, OATP2B1 and MRP2 *[submitted]*
https://www.youtube.com/watch?v=ddQYx4fGqRE

Pravastatin - Renal impairment





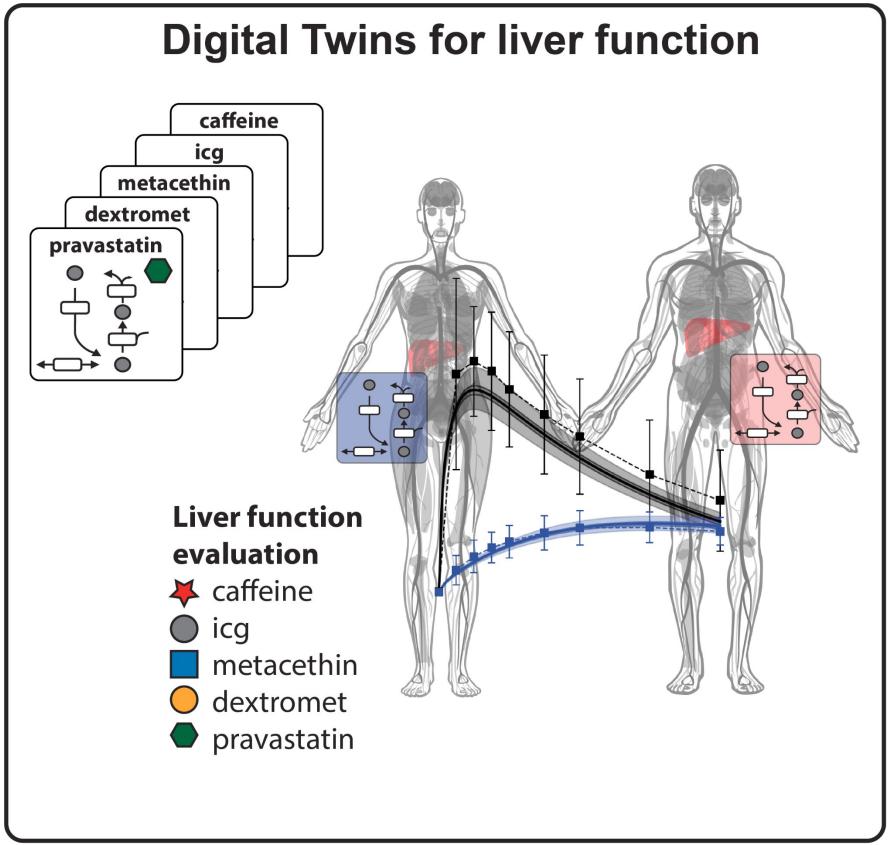




HL Pujol, J Grzegorzewski, F Bartsch, HM Tautenhahn, **M.König** ***A physiologically based pharmacokinetic (PBPK) model of pravastatin: Impact of hepatorenal impairment and genetic polymorphisms of OATP1B1, OATP2B1 and MRP2*** *[submitted]*
https://www.youtube.com/watch?v=ddQYx4fGqRE

Other models/data

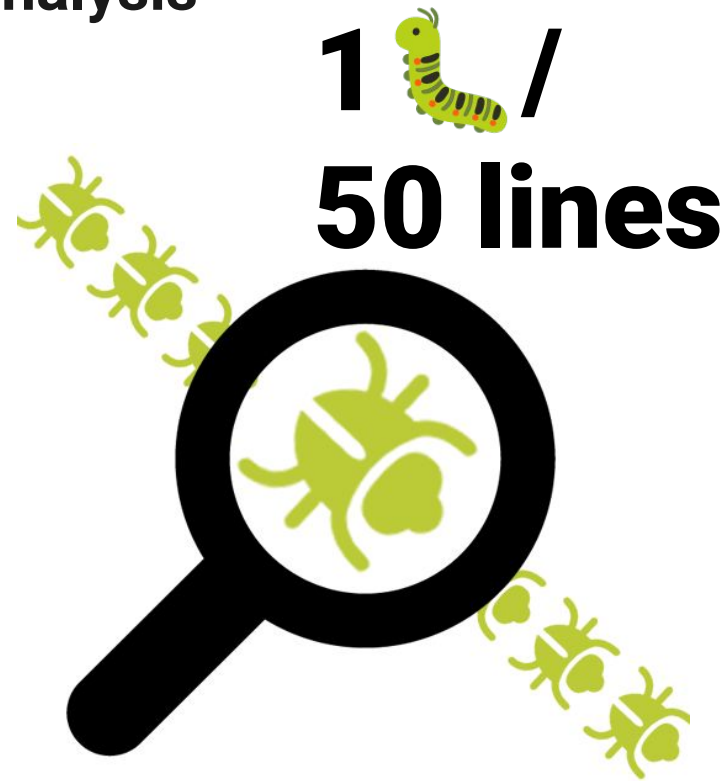
- Omeprazol (CYP2C19)
- Indocyanine green (OATP1B3)
- Pravastatin (OATP1B1)
- Metacetin (LiMAx, CYP1A2)
- Talinolol (P-Glycoprotein)
- Chlorzoxazone (CYP2E1)
- Paracetamol
- Caffeine (CYP1A2)
- Metoprolol (CYP2D6)
- Simvastatin (OATP1B1)
- Midazolam (CYP3A4)
- Galactose
- Codeine/Morphine
- Glucose
  - Glucose, Insulin, C-Peptide, Glucagon, FFA, GIP, GLP-1, ...
- Ramipril




REPRO-
DUCIBILITY

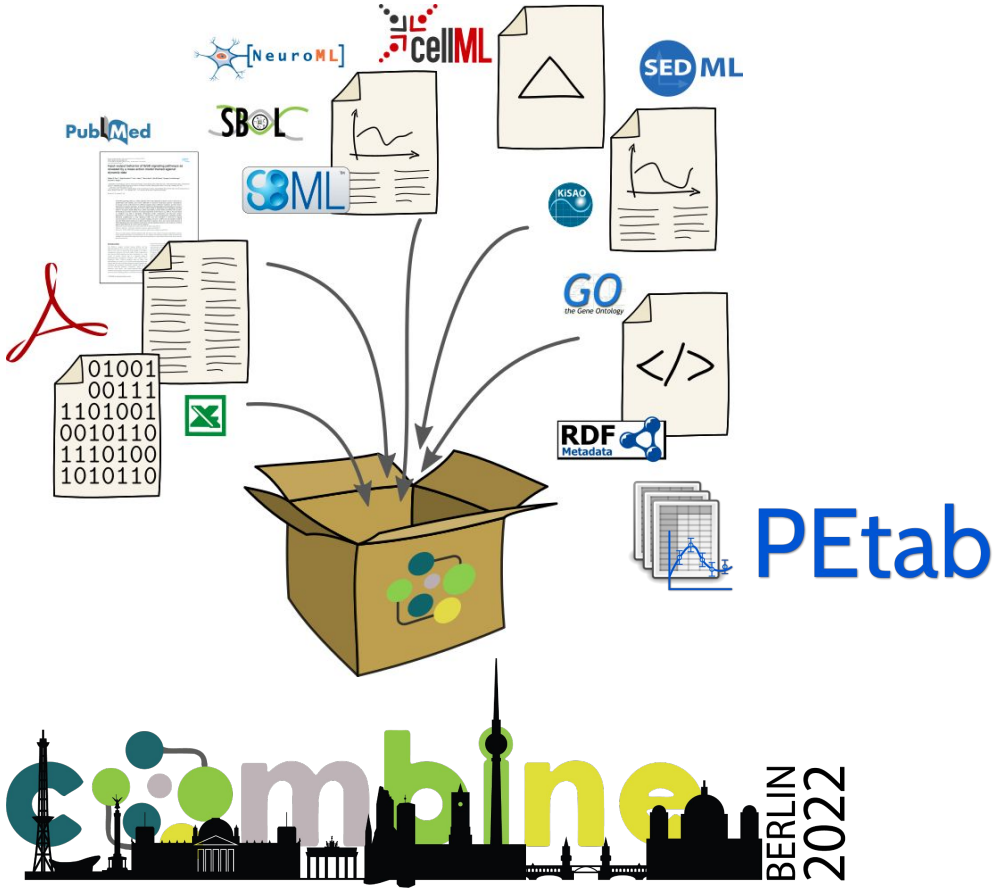
You have bugs in your model & analysis

- On average 85% of bugs introduced in design and development are caught before the code is released
- **~ 1 bug per 50 lines of code**
- **~ 25% will be severity 1 show stoppers** – real production problems that cause something significant to break



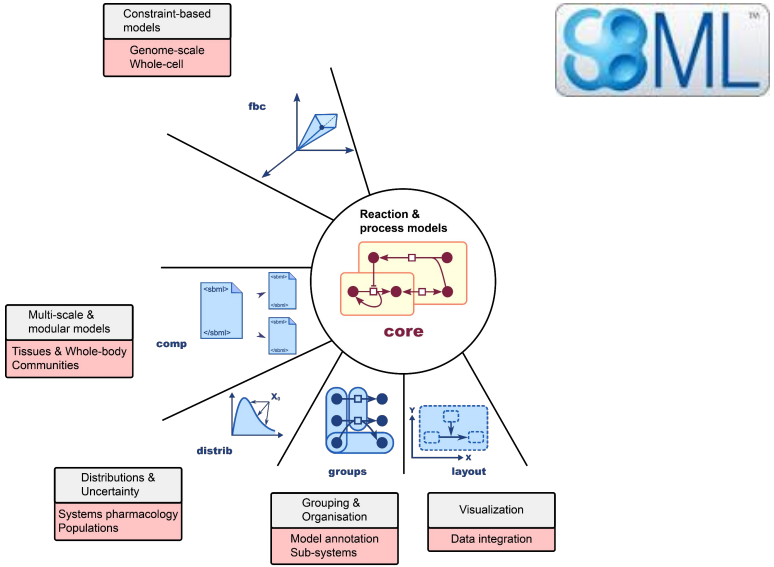
COMBINE Standards

- **SBML**
  - reproducible models
- **COMBINE archive**
  - packaging & distribution
- **SED-ML**
  - simulation experiments
- **OMEX metadata**
  - annotation
- **PETab**
  - parameter fitting



Systems Biology Markup Language (SBML)

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

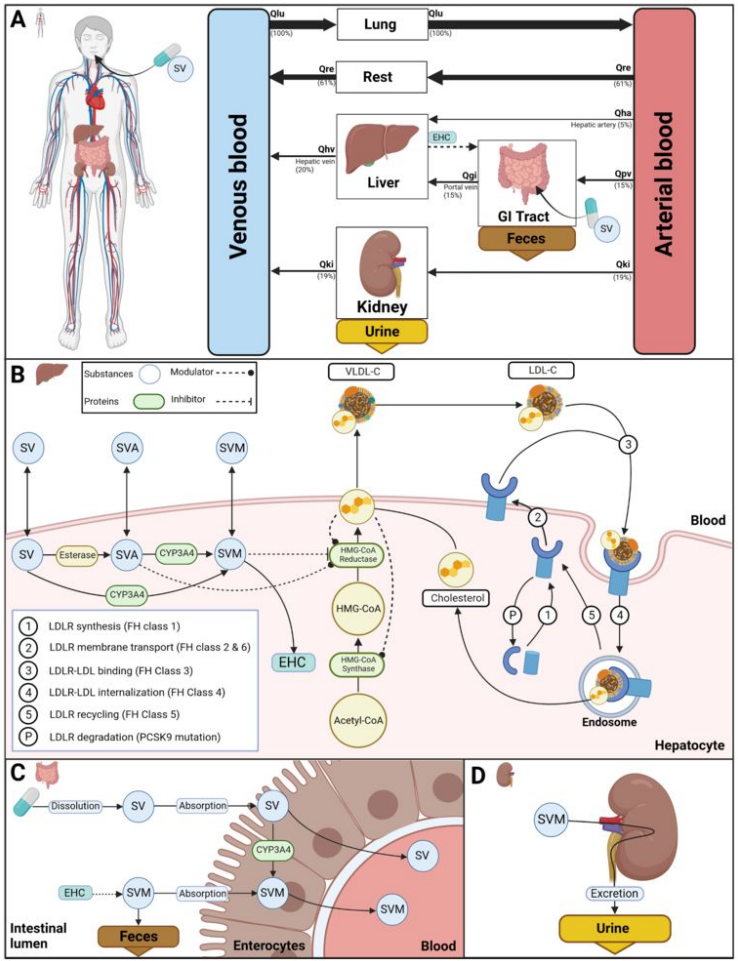


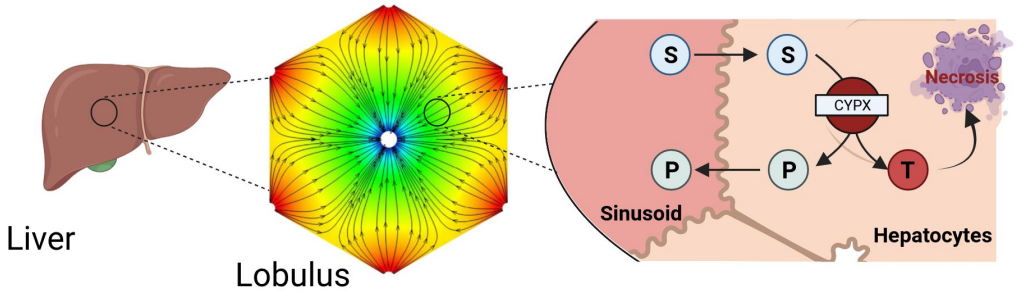
SM Keating, D Waltemath, **M König**, F Zhang, A Dräger, C Chaouiya, FT Bergmann, A Finney, CS Gillespie, T Helikar, S Hoops, RS Malik-Sheriff, SL Moodie, II Moraru, CJ Myers, A Naldi, BG Olivier, S Sahle, JC Schaff, LP Smith, MJ Swat, DT, L Watanabe, DJ Wilkinson, ML Blinov, K Begley, JR Faeder, HF Gómez, TM Hamm, Y Inagaki, W Liebermeister, AL Lister, D Lucio, E Mjolsness, CJ Proctor, K Raman, N Rodriguez, CA Shaffer, BE Shapiro, J Stelling, N Swainston, N Tanimura, J Wagner, M Meier-Schellersheim, HM Sauro, B Palsson, H Bolouri, H Kitano, Akira Funahashi, H Hermjakob, JC Doyle M Hucka, and SBML Community members
SBML Level 3: an extensible format for the exchange and reuse of biological models
Mol Syst Biol. 2020;16(8):e9110. doi:10.15252/msb.20199110

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
The Systems Biology Markup Language (SBML): Language Specification for Level 3 Version 2 Core
J Integr Bioinform. 2019 Jun 20;16(2); 10.1515/jib-2019-0021

L Smith, S Moodie, F Bergmann, C Gillespie, S Keating, **M. König**, C Myers, M Swat, D Wilkinson, M Hucka
The Distributions Package for SBML Level 3
J Integr Bioinform. 2020 Aug 4; doi: 10.1515/jib-2020-0018

SBML enabling model coupling & exchange & reuse





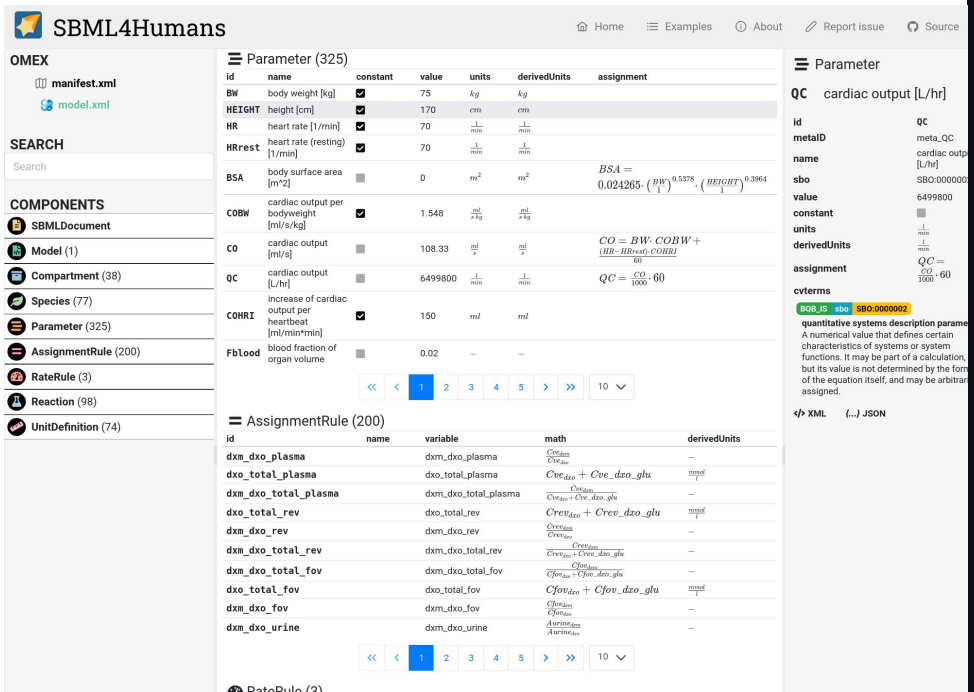
- coupling of submodels
  - **scales**: cells/organs/body
  - **function:** pharmacokinetics/pharmacodynamics
- coupling between frameworks
  - ODE/PDE (porous media)
  - ODE/FBA (dynamic FBA)
  - ODE/Bayes (uncertainty)
- model composition
  - uncertainty models

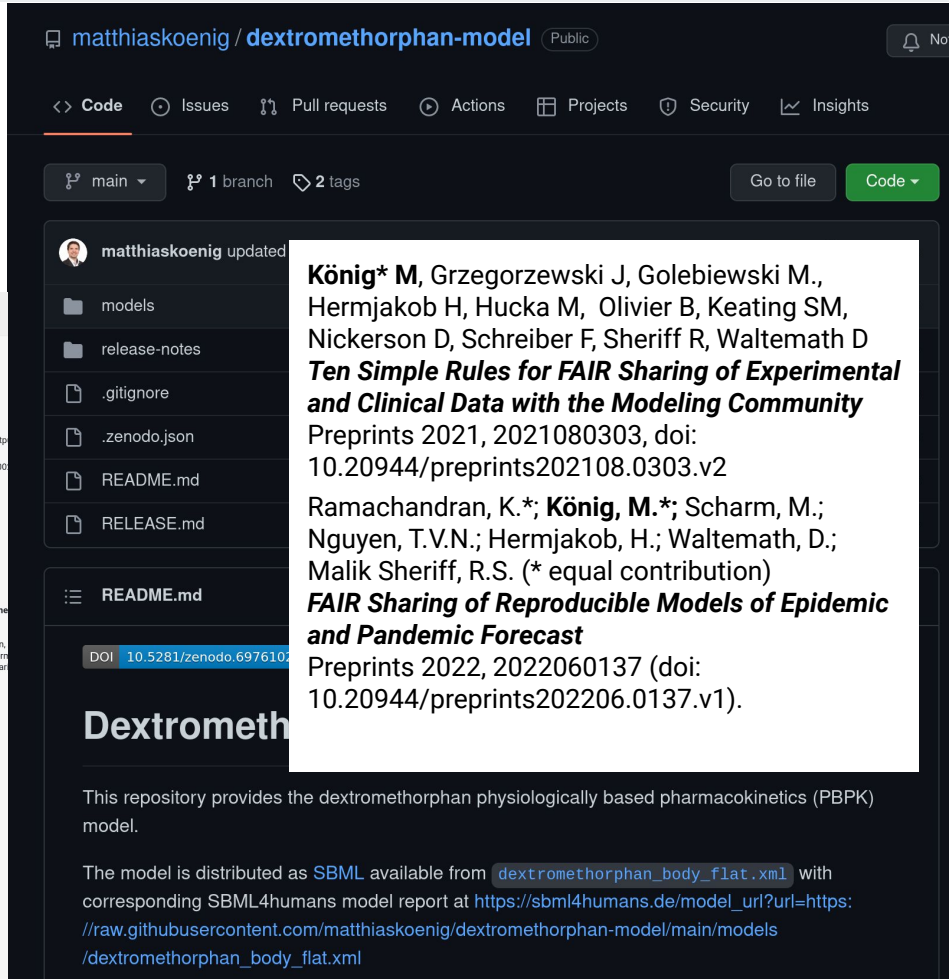
Key challenges:

- interfaces
- units
- deletions/adaptations

FAIR Models & Data (CC-BY)

https://github.com/matthiaskoenig/dextromethorphan-model





König* M, Grzegorzewski J, Golebiewski M., Hermjakob H, Hucka M, Olivier B, Keating SM, Nickerson D, Schreiber F, Sheriff R, Waltemath D
Ten Simple Rules for FAIR Sharing of Experimental and Clinical Data with the Modeling Community
Preprints 2021, 2021080303, doi: 10.20944/preprints202108.0303.v2

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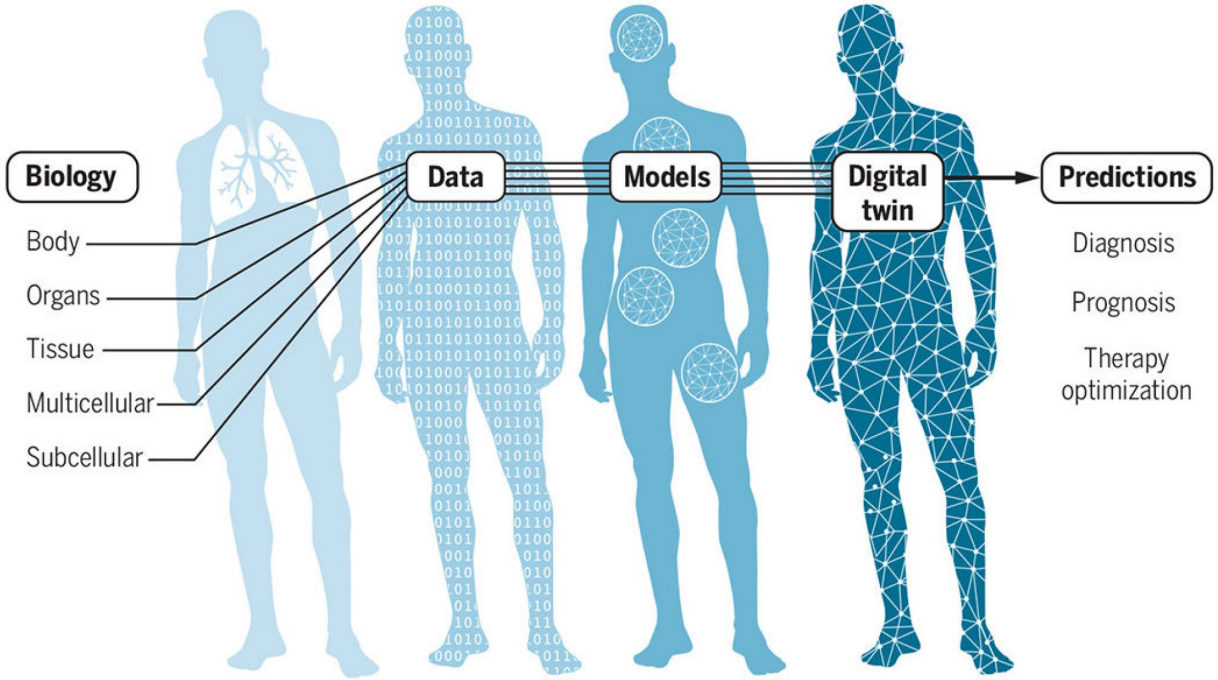
FAIR Sharing of Reproducible Models of Epidemic and Pandemic Forecast
Preprints 2022, 2022060137 (doi: 10.20944/preprints202206.0137.v1).


FUTURE

Digital twins

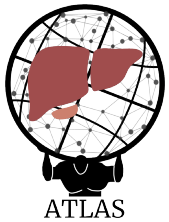
- **personalized digital twin models based on patient data**
  - improved diagnostics
  - improved decision support
- **model & data integration**



Laubenbacher R, Sluka JP, Glazier JA. **Using digital twins in viral infection.** Science. 2021 Mar 12;371(6534):1105-1106. doi: 10.1126/science.abf3370.

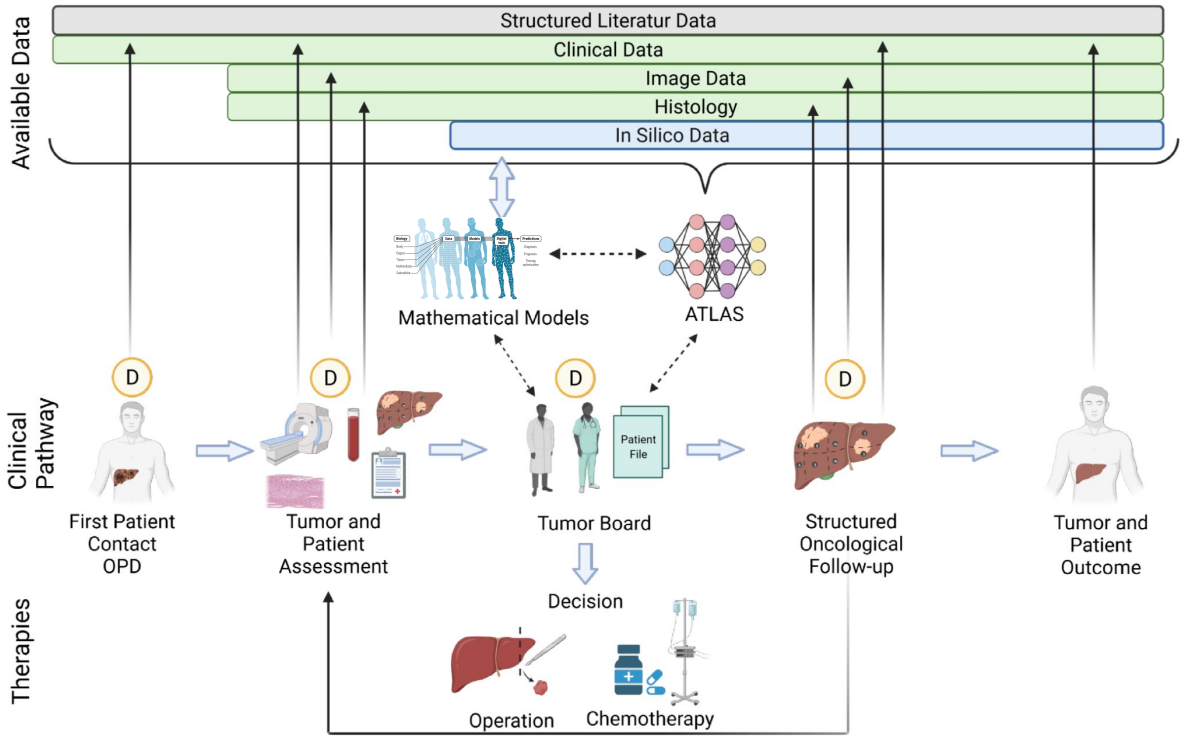
Digital twins + artificial intelligence (AI)

- **AI** and Simulation for **T**umor **L**iver **AS**sessment (ATLAS)



- Combining computational models with AI
  - feature generation
  - capture expert & domain knowledge

- Open position (PhD)



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sbmlutils

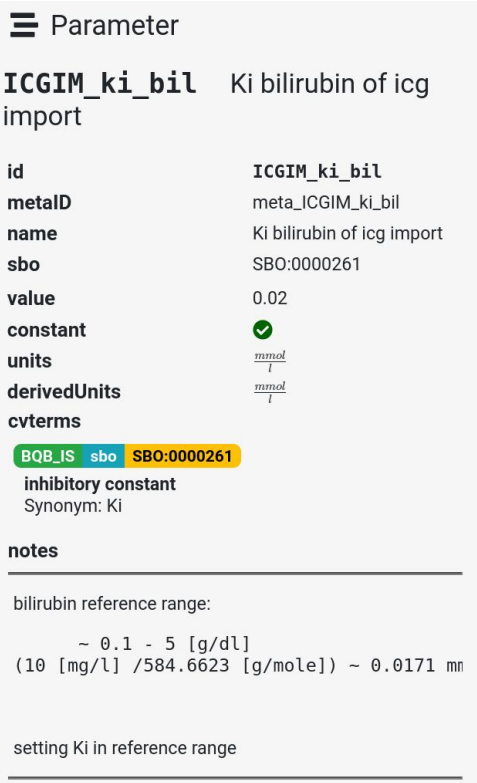
Python utilities for working with SBML models
https://github.com/matthiaskoenig/sbmlutils

Packages
- core, fbc, comp, distrib, layout

Features
- model creation, manipulation & merging
- unit support
- model annotation
- file converters (XPP)
- cy3sbml integration

```
Parameter(
    "ICGIM_ki_bil",
    0.02,
    unit=U.mM,
    name="Ki bilirubin of icg import",
    sboTerm=SBO.INHIBITORY_CONSTANT,
    notes="""
    bilirubin reference range:
    ```
    ~ 0.1 - 5 [g/dl]
    (10 [mg/l] /584.6623 [g/mole]) ~ 0.0171 mmole/l`
    ```


    setting Ki in reference range
    """,
),
```



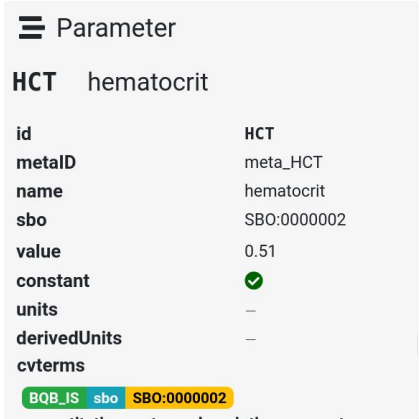
CI-CD passing | pypi v0.5.8 | python 3.7 | 3.8 | 3.9 | license LGPL-3.0 | codecov 63% | docs passing
DOI 10.5281/zenodo.5559603 | code style black | mypy checked

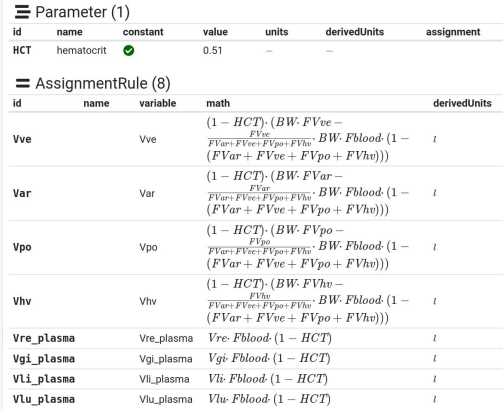
SBML4Humans

https://sbml4humans.de

- **interactive SBML report** with navigation between SBML objects
- **web application** (no setup)
- **search** and filter functionality
- **resolve/render metadata**
- **hierarchical models** (SBML comp)
- **distributions and uncertainties** (SBML distrib)
- **flux balance** (SBML fbc)
- **COMBINE archives** (multiple models)
- **URL endpoint** for integration in tools/ workflows/ webpages/ presentations

https://sbml4humans.de/model_url?url=https://www.ebi.ac.uk/biomodels/model/download/BIOMD0000000001.2?filename=BIOMD0000000001_url.xml





cy3sbml

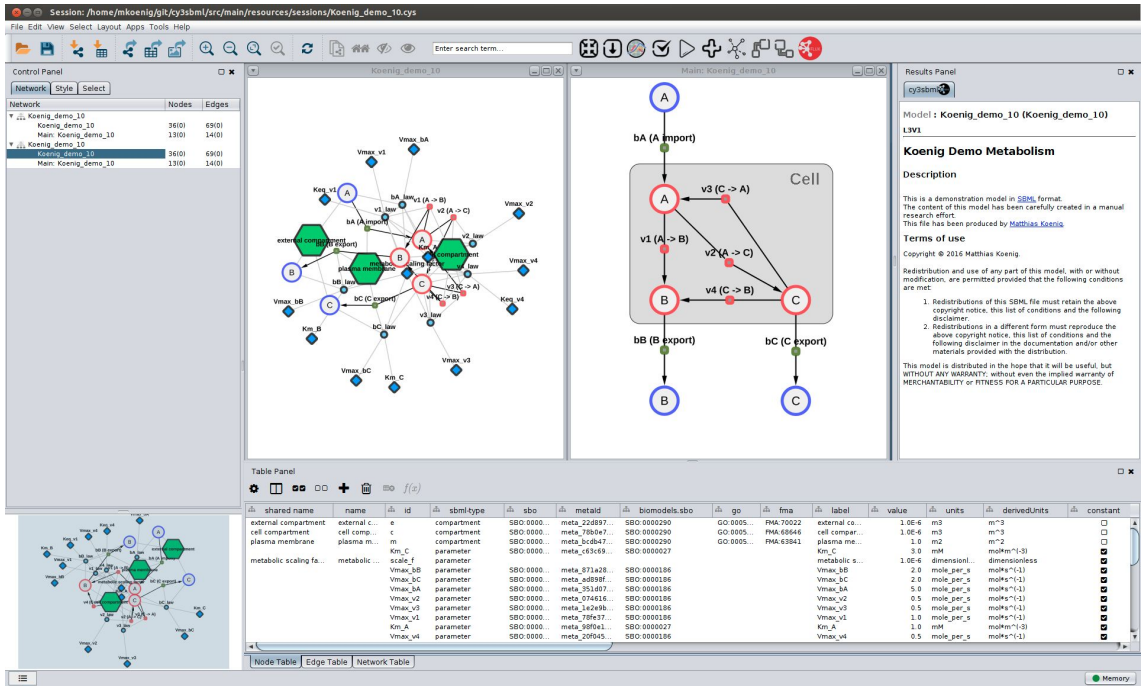
Cytoscape app for visualizing SBML models
https://github.com/matthiaskoenig/cy3sbml

Features

- kinetic & reaction-species view
- subgraphs & filtering
- annotation support
- works for large scale networks (genome-scale)

New

- sbmlutils integration (py2cytoscape)



König M., Dräger A. and Holzhütter HG.
CySBML: a Cytoscape plugin for SBML
Bioinformatics. 2012 Jul 5.