

Physiological based Models for the Analysis of Liver Function

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Physiological compartment models

- Absorption, Distribution, Metabolism, Elimination (ADME)

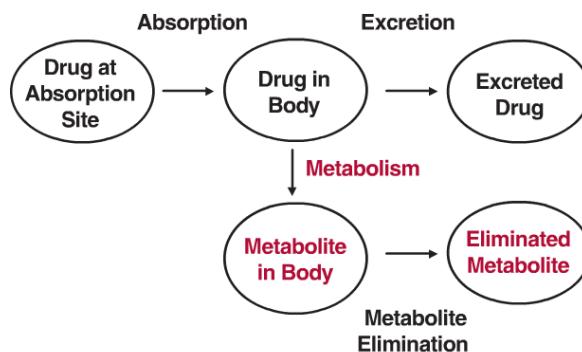


FIGURE 2-5. A drug is simultaneously absorbed into the body and eliminated from it, by excretion and metabolism. The processes of absorption, excretion, and metabolism are indicated with arrows and the compartments with ovals. The compartments represent different locations and different chemical species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

$$\text{Dose} = \frac{\text{Amount at}}{\text{Absorption Site}} + \frac{\text{Amount}}{\text{in Body}} + \frac{\text{Amount}}{\text{Excreted}} + \frac{\text{Amount}}{\text{Metabolized}}$$
$$\text{Rate of Change of Drug in Body} = \frac{\text{Rate of}}{\text{Absorption}} - \left[\frac{\text{Rate of}}{\text{Excretion}} + \frac{\text{Rate of}}{\text{Metabolism}} \right]$$

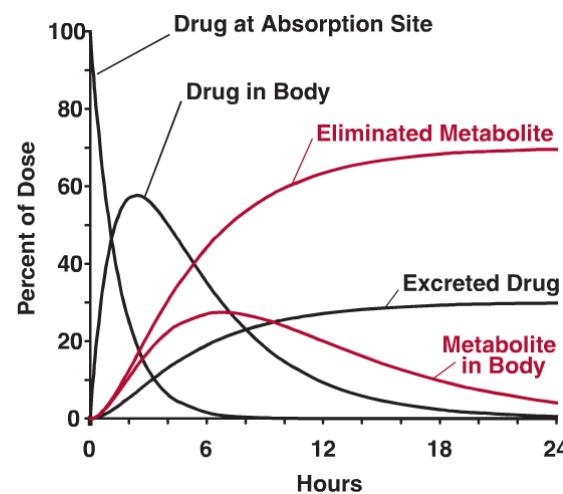
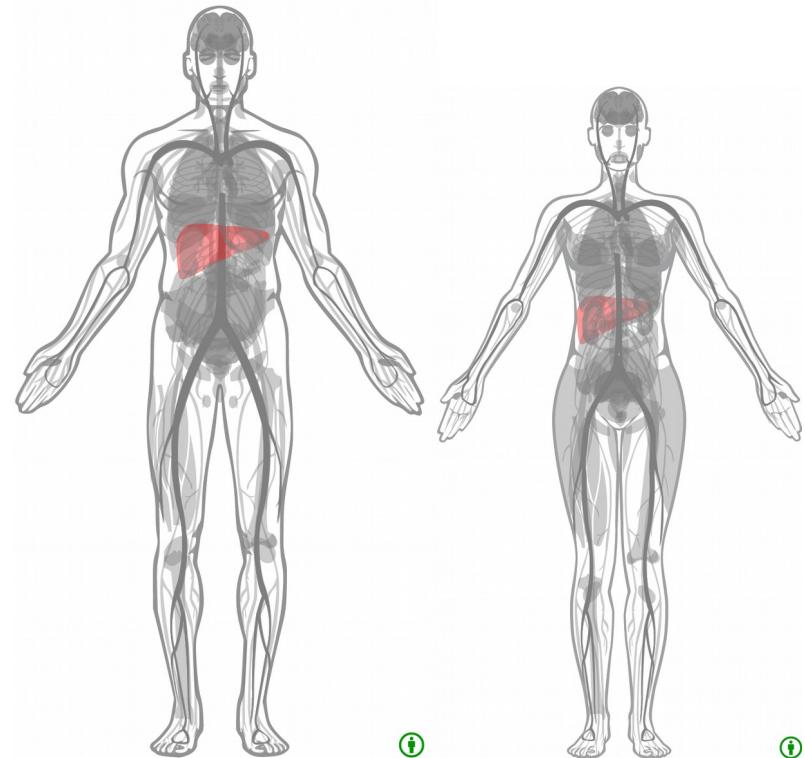
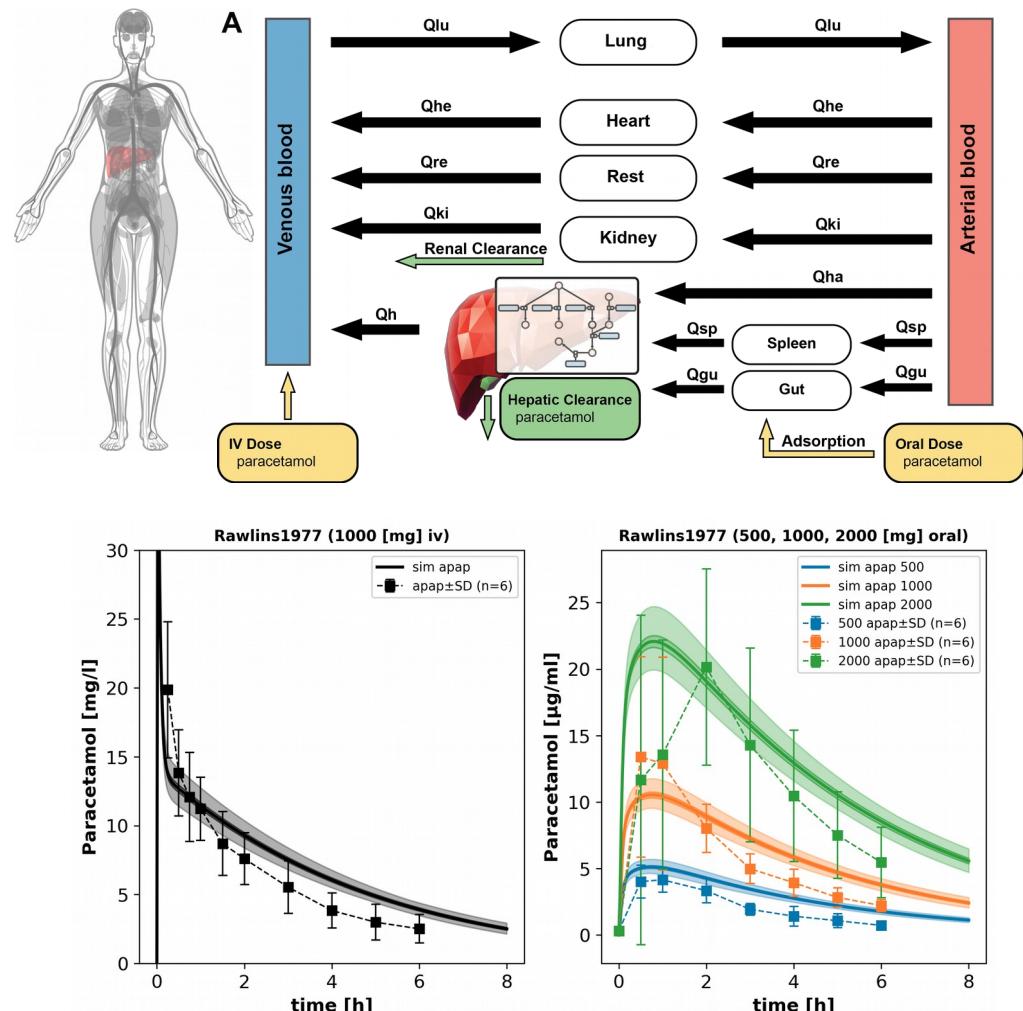


FIGURE 2-6. Time course of drug and metabolite in each of the compartments shown in Fig. 2-5. The amount in each compartment is expressed as a percentage of the dose administered. In this example, all the dose is absorbed. At any time, the sum of the molar amounts in the five compartments equals the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



Physiological-based pharmacokinetics models (PBPK)

- pharmacokinetics: determines fate of substances administered to organism
- combines information on the drug with knowledge on the physiology and biology at organism level
- human/animal physiology in the computer
- **Tissues are linked by arterial and venous blood compartments** characterized by associated blood flow rates, tissue-partition coefficient , and permeability
- Specific models for certain drugs & substances
- Result: 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



Example: Glucose-Insulin system

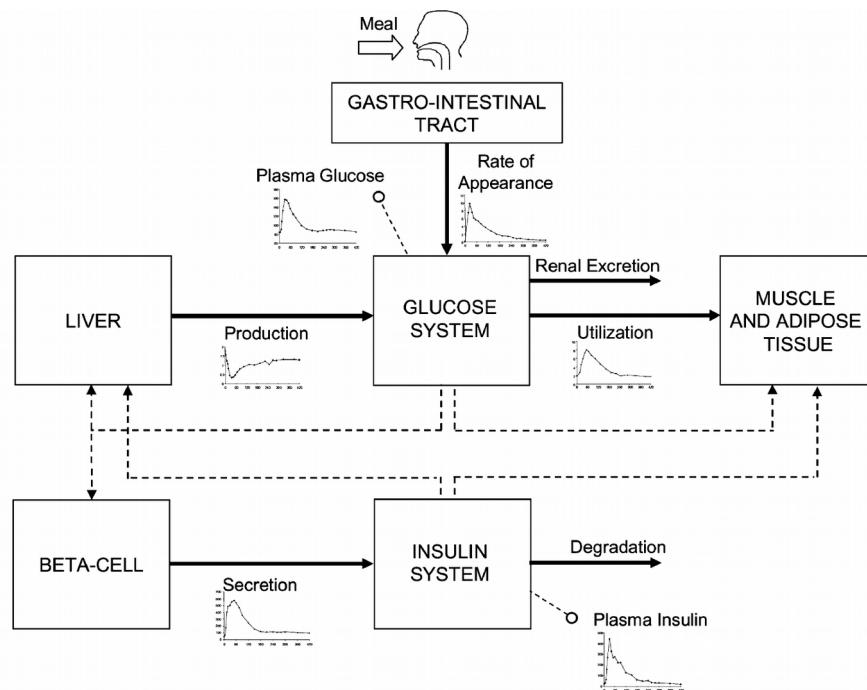
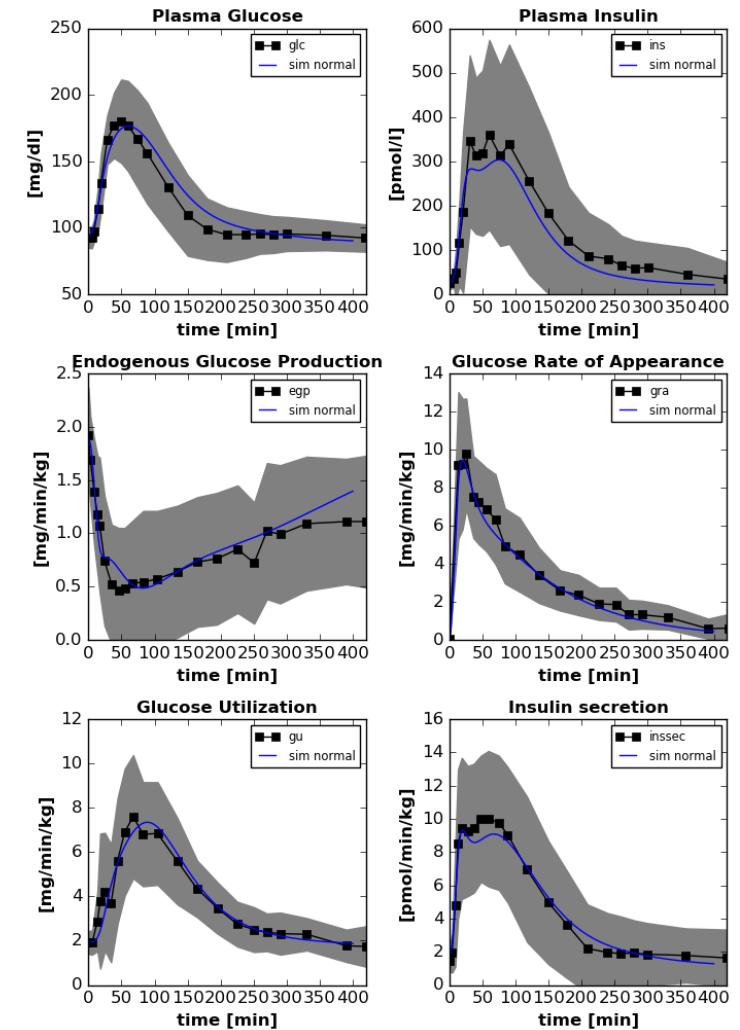


Fig. 2. Scheme of the glucose-insulin control system which puts in relation the measured plasma concentrations, i.e., glucose G , and insulin I , to glucose fluxes, i.e., rate of appearance R_a , production EGP , utilization U , renal extraction E , and insulin fluxes, i.e., secretion S , and degradation D .



Pharmacokinetic Parameters

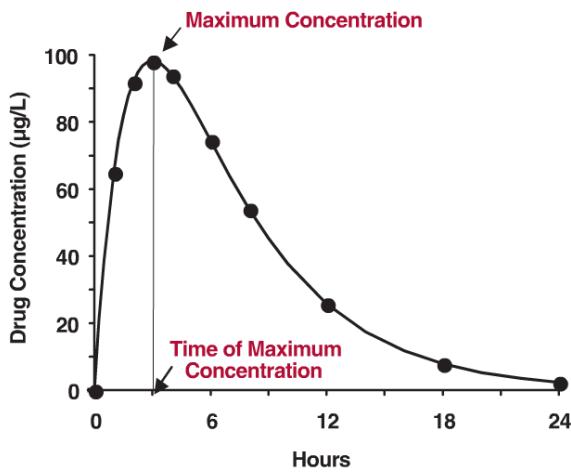


FIGURE 2-1. Drug concentration-time curve following a single oral dose showing the maximum systemic exposure (C_{max}) and the time of its occurrence (t_{max}). The concentration could represent drug in whole blood, plasma, or serum.

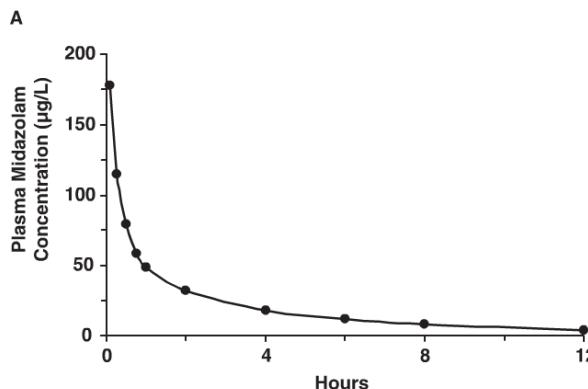
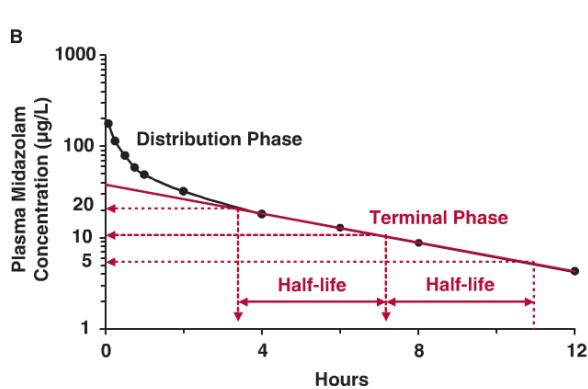
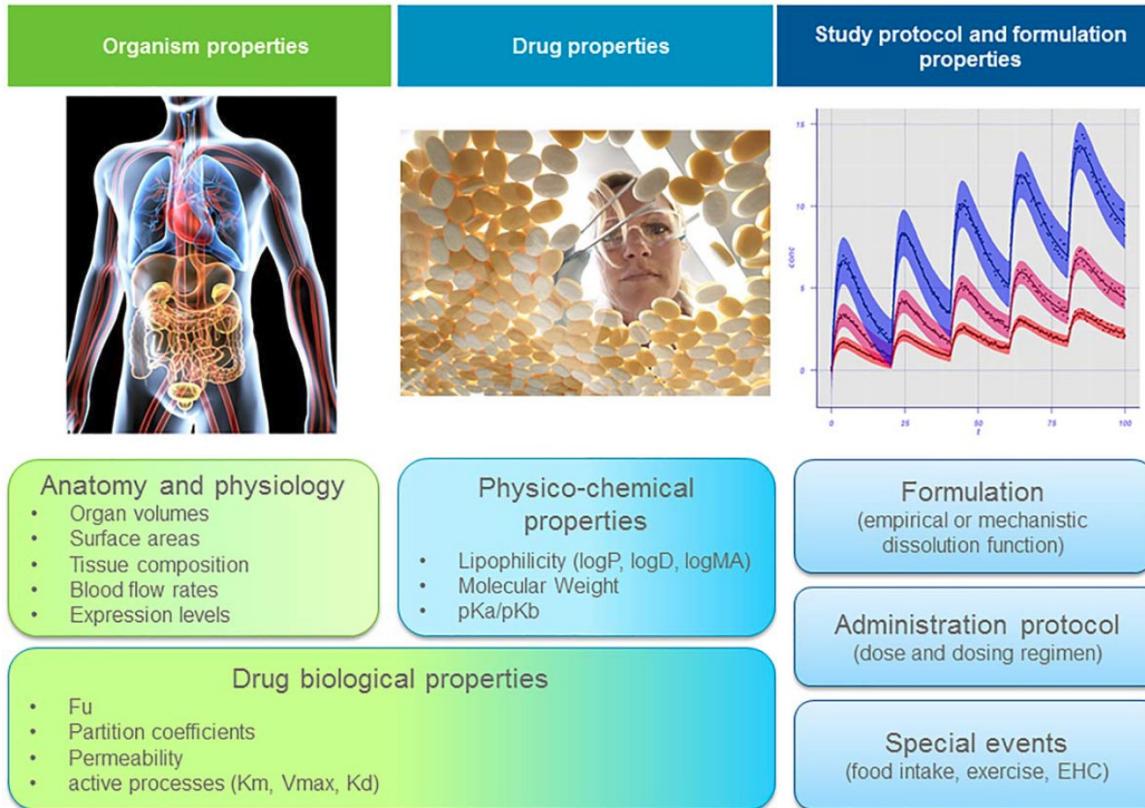


FIGURE 3-4. A. Plasma concentration of midazolam with time in an individual after an 8.35-mg i.v. bolus dose of midazolam hydrochloride (7.5 mg of the base) in a healthy adult. B. The data in A are redisplayed as a semilogarithmic plot. Note the short distribution phase. (From: Pentikäinen PJ, Välijoki 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 ($= \text{Dose}/\text{AUC}$, $= \text{Dose}/C(0)_{\text{extrapolated}}$)

Building blocks of a PBPK model



Kuepfer2016

Differential equations

- **Compartments**
 - organs
 - **State variables:**
 - drug & metabolite amounts
 - **ODEs & rules**
 - Blood flows, Transport, Disposition
 - Metabolism, Elimination
 - Absorption
 - **Parameters**
 - Tissue partition coefficients
 - Protein binding
 - Kinetic parameter (transport & elimination)
 - Blood flows, organ volumes,
- ...

PBPK Applications

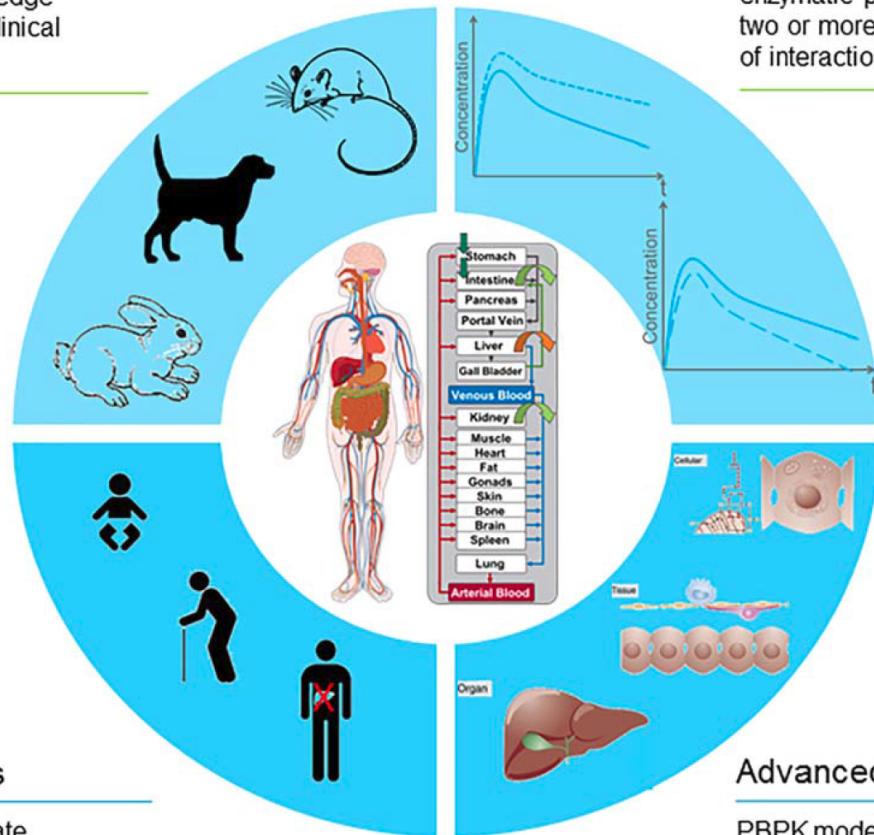
Cross-Species Extrapolation

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



Special Populations

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



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

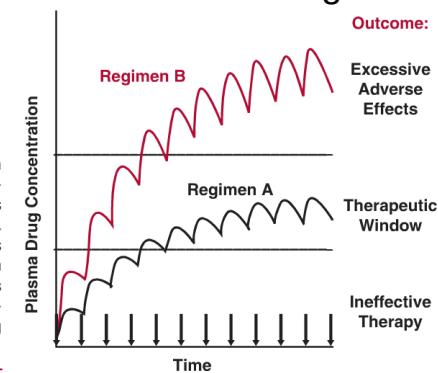


FIGURE 1-4. When a drug is given in a fixed dose and at fixed time intervals (denoted by the arrows), it accumulates within the body until a plateau is reached. With regimen A, therapeutic success is achieved although not initially. With regimen B, the therapeutic objective is achieved more quickly,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

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.

Large inter-individual variability

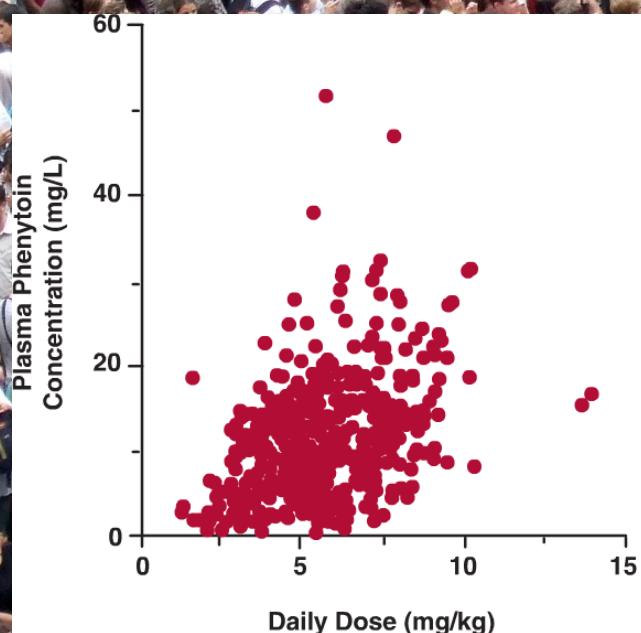


FIGURE 1-7. Although the average plasma concentration of phenytoin on chronic dosing tends to increase with the dosing rate, there is large variation in the individual values. (From: Lund, L. Effects of phenytoin in patients with epilepsy in relation to its concentration in plasma. In Davies DS, Prichard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

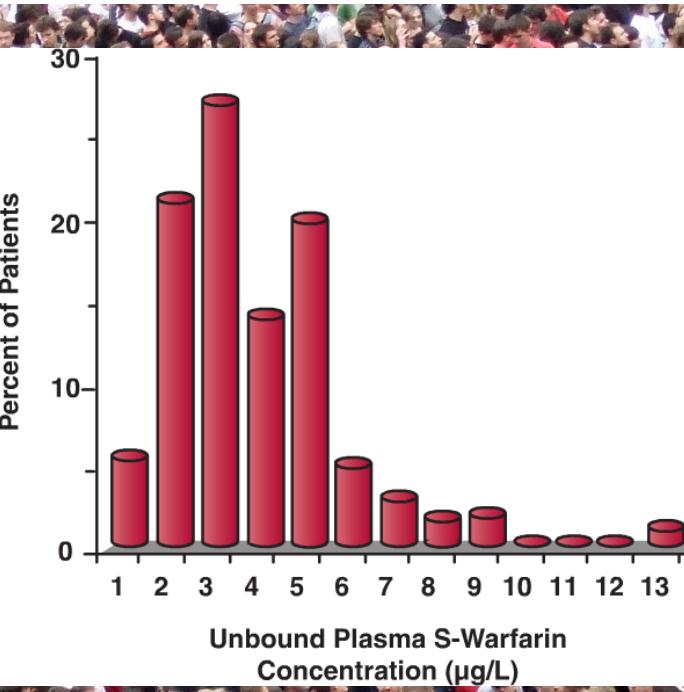


FIGURE 1-8. There is considerable interindividual pharmacodynamic variability in response to the oral anticoagulant warfarin as demonstrated by the substantial spread in the unbound concentration of the active S-isomer associated with a similar degree of anticoagulation in a group of 97 patients on maintenance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

Variability Liver Enzymes

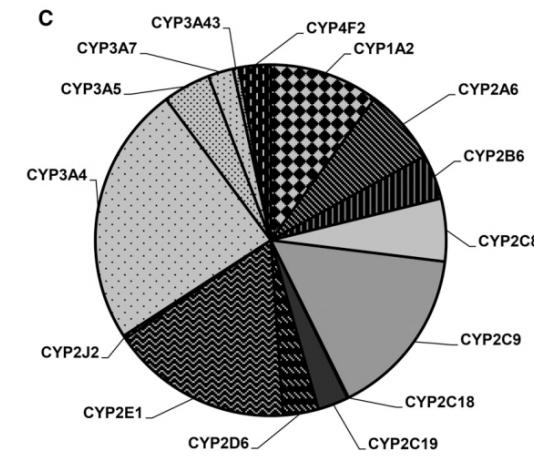
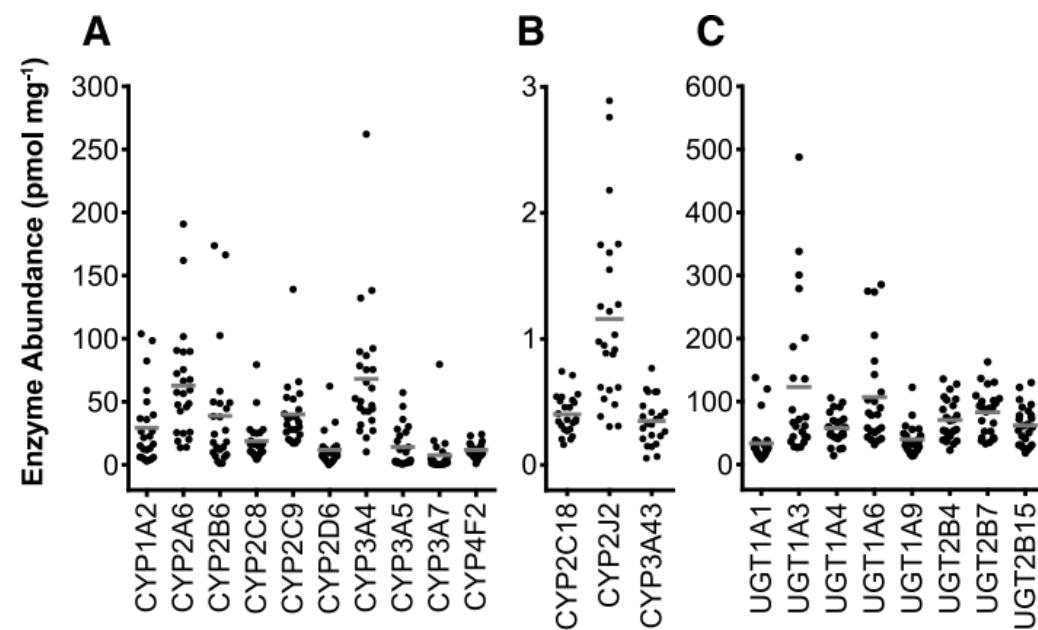


Fig. 1. Bar graph (A and B) and pie chart (C) of weighted mean abundances of cytochrome P450 enzymes in livers from adult Caucasians. Error bars represent weighted standard deviation values. n , the number of livers.



Archour2014b

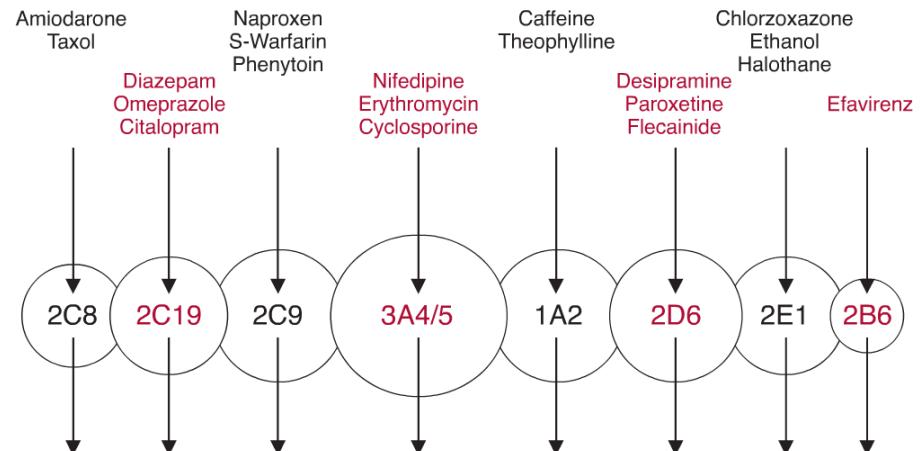


FIGURE 5-3. Graphic representation of the different forms of human cytochrome-P450 enzyme (circles) with different but often overlapping substrate specificities. The arrows indicate the single metabolic pathways. Representative substrates are listed above each enzyme.

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

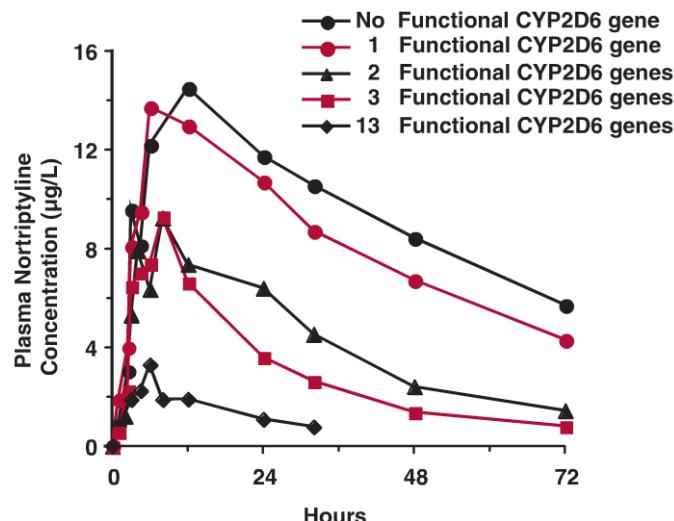


FIGURE 13-2. Strong genetic influence in the pharmacokinetics of nortriptyline is clearly demonstrated by the high correlation between the plasma concentration–time profile and the number of functional CYP2D6 genes possessed by an individual; the larger the number of functional genes, the higher is the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

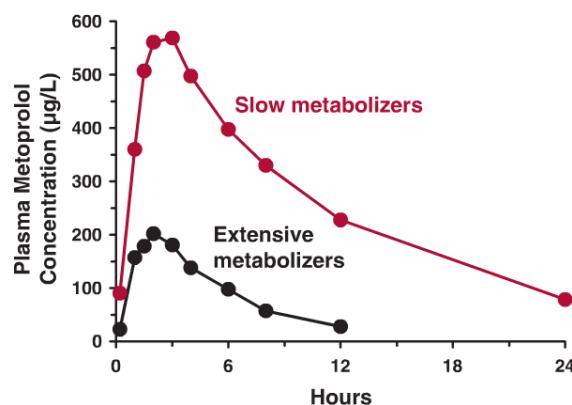


FIGURE 13-3. Plasma metoprolol concentrations after a single oral dose of 200-mg metoprolol tartrate were much higher in poor (colored line) than in extensive (black line) CYP2D6 metabolizers. Because metoprolol is a drug of high hepatic clearance, the difference between poor and extensive metabolizers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

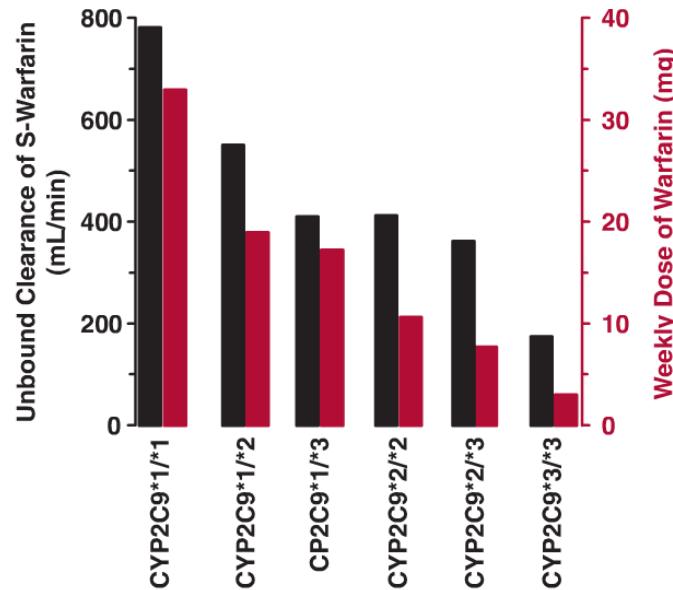
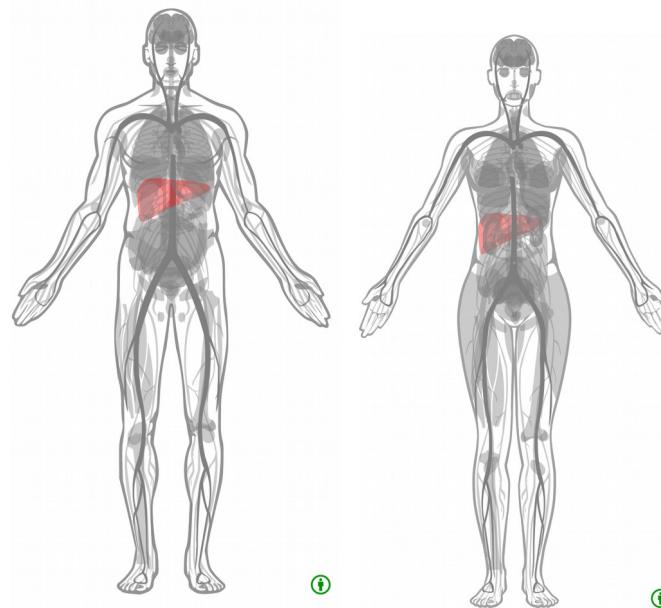


FIGURE 13-4. Genetics plays a significant role in the maintenance dose requirement of warfarin used in the treatment of various cardiovascular diseases. Shown are the unbound clearance of S-warfarin (black) in groups of patients with different CYP2C9 genotypes, all titrated and stabilized to a narrow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

Liver Function Tests



Liver Function Tests

Liver central organ of metabolism

- Metabolic homeostasis (glucose, amino acids, ...)
- Detoxification & clearance of most drugs

Liver specific clearance of substance

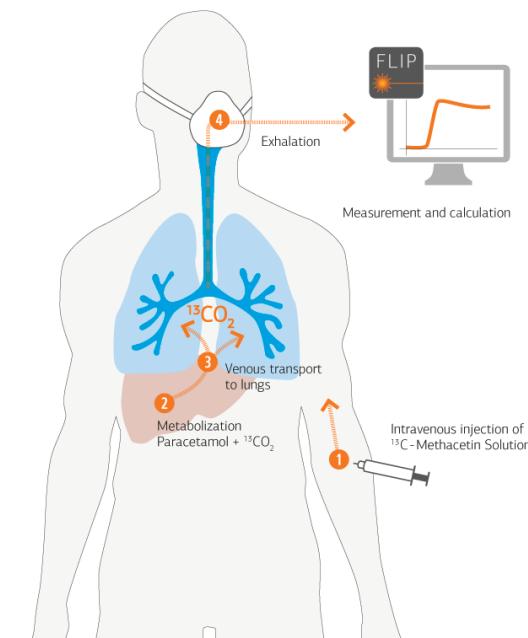
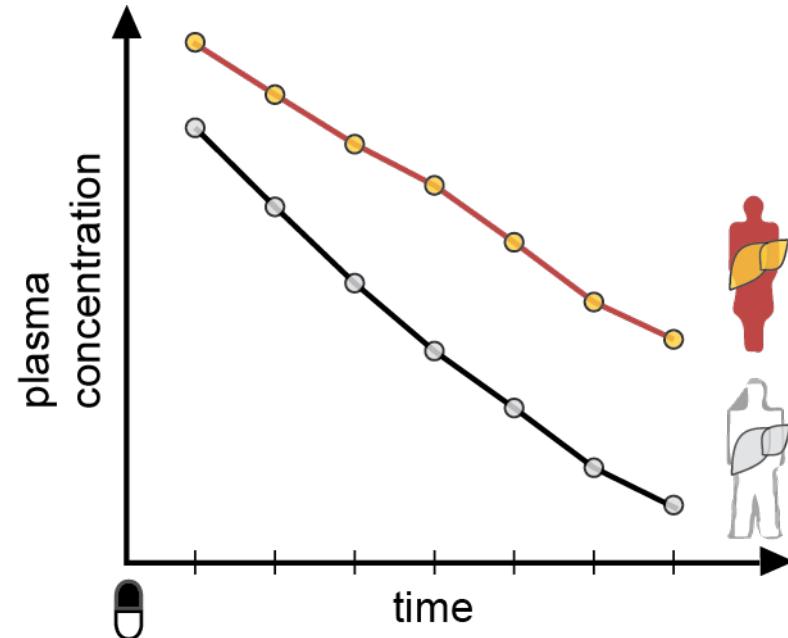
- Galactose elimination capacity (GEC)
- LiMAX Test (Methacetin)
- Caffeine clearance

Detection of product

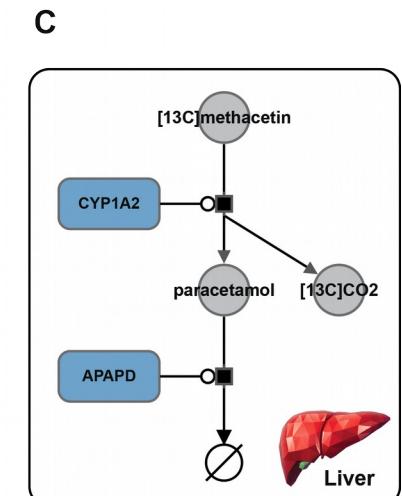
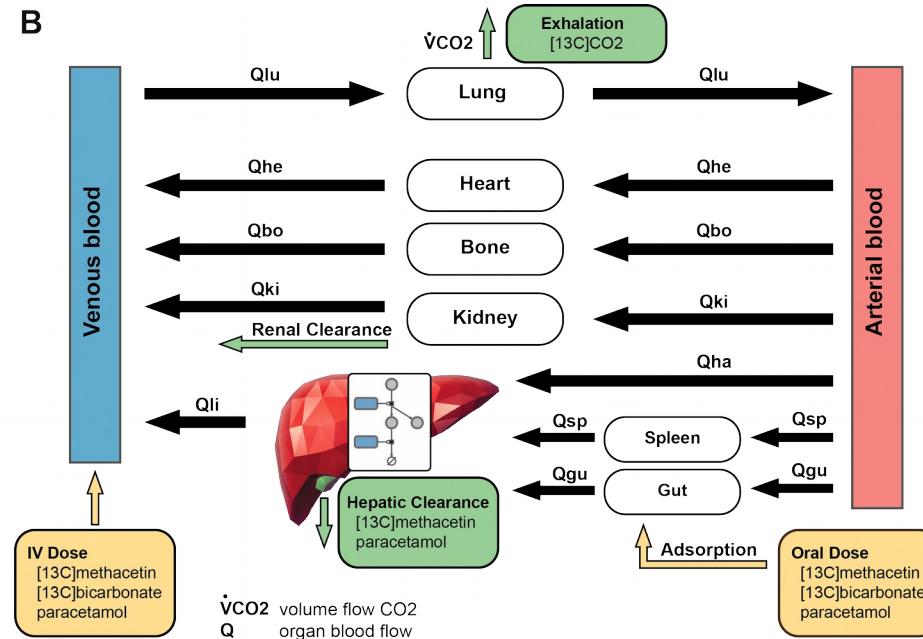
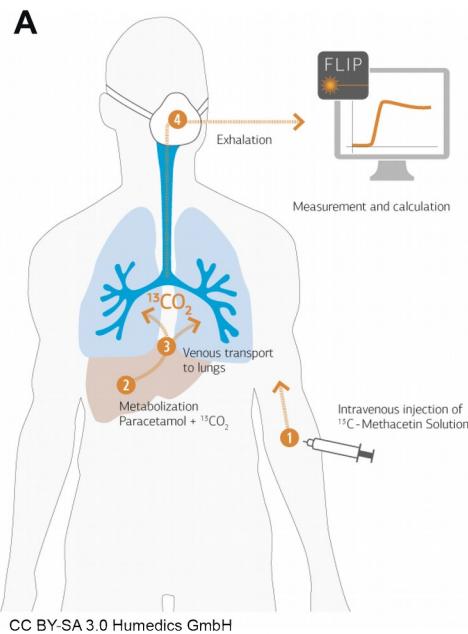
- plasma, urine, breath

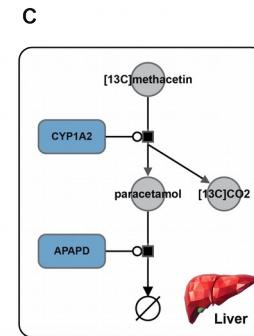
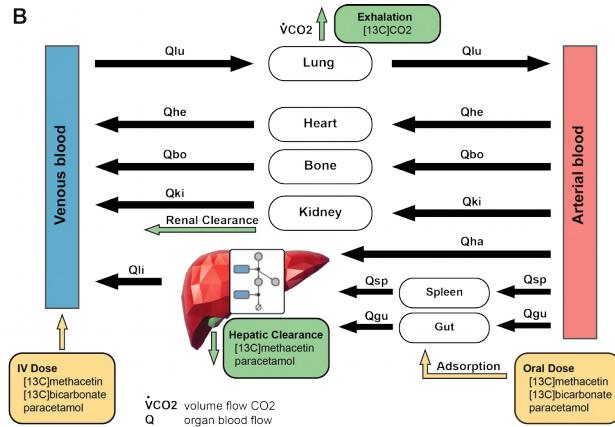
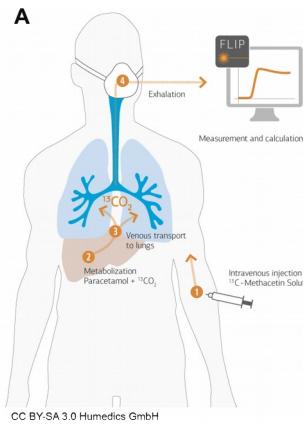
Non-invasive evaluation of liver function

- Transplantation & Hepatectomy
- Liver disease

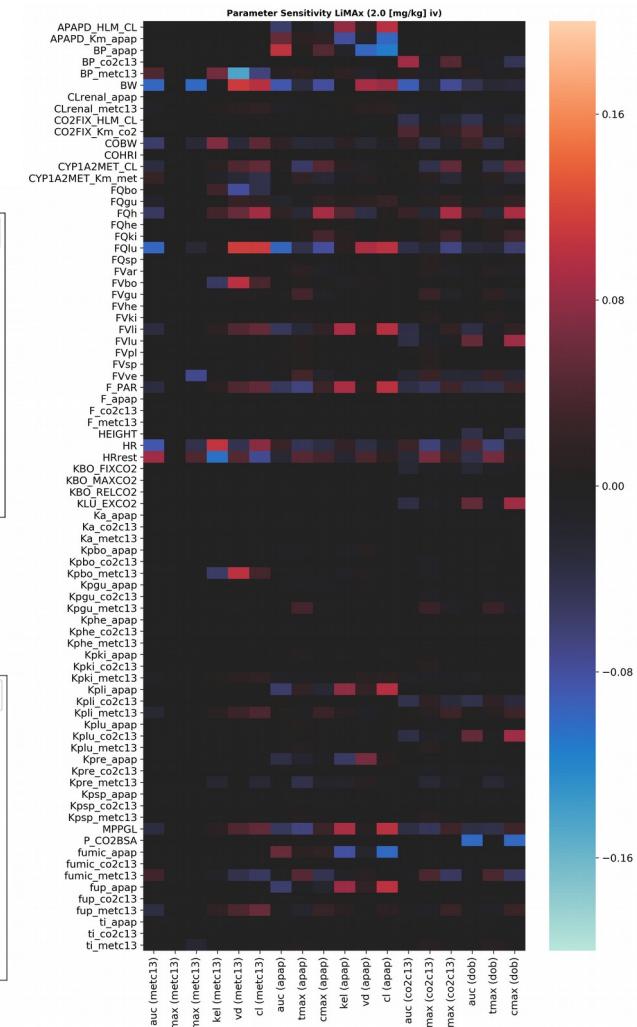


LiMAX (metacethin)

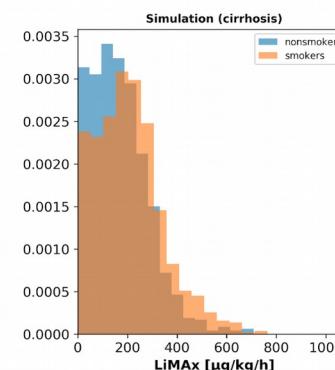
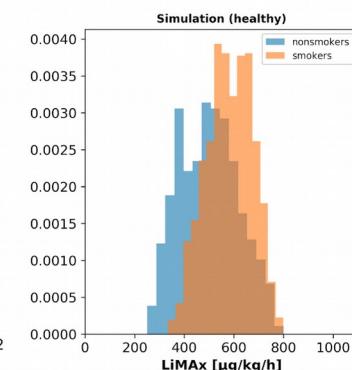
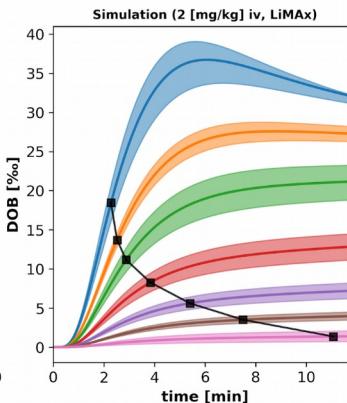
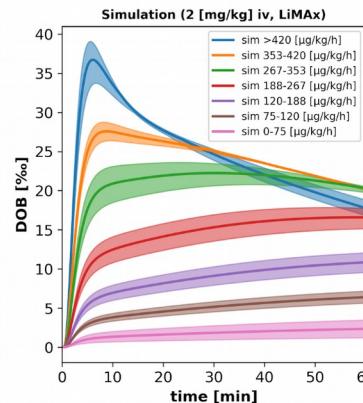
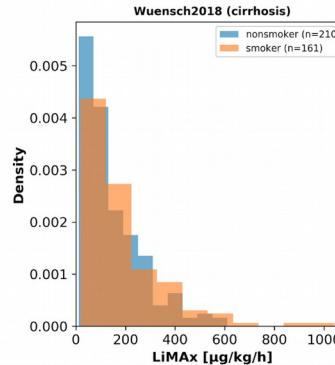
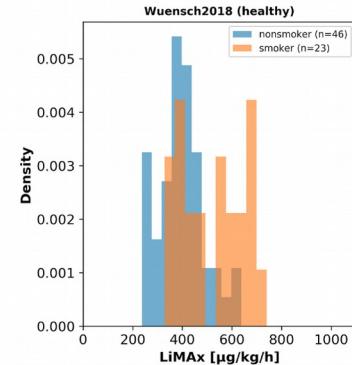
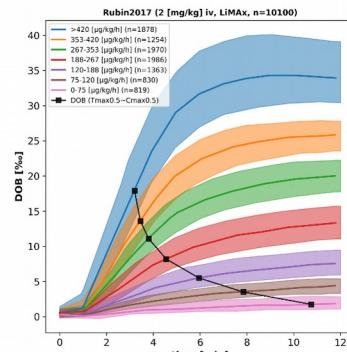
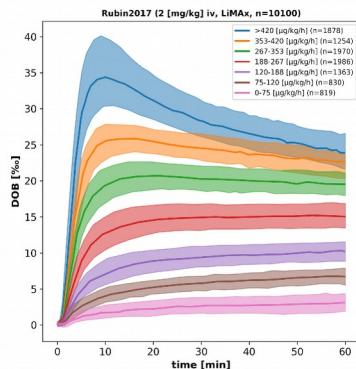




Sensitivity Analysis



Reduced liver function



Caffeine PBPK

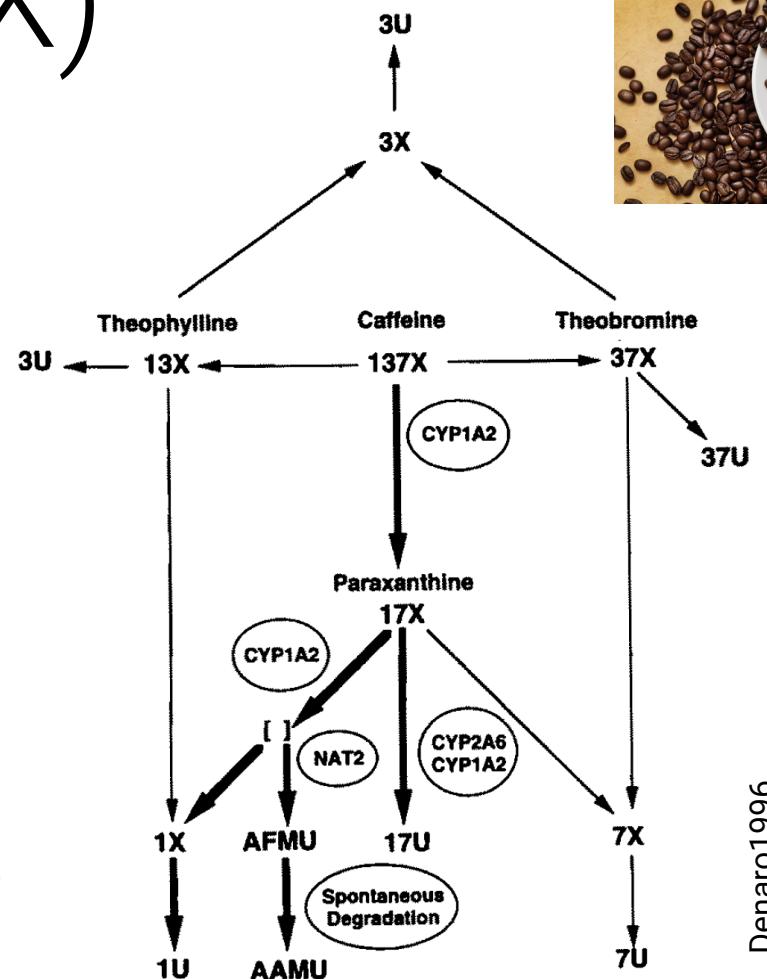


Caffeine & smoking



Caffeine (137X)

- world's most widely consumed psychoactive drug
- Metabolized in liver by **CYP1A2**
 - to **paraxanthine (17X)**, theobromine & theophylline
- Classical liver function test
 - Time course of caffeine
 - urinary ratios of methyl-xanthines
 - Caffeine/paraxanthine ratio
- Large Variability
 - Effects of lifestyle on expression
 - Smoking is one of such lifestyle factors



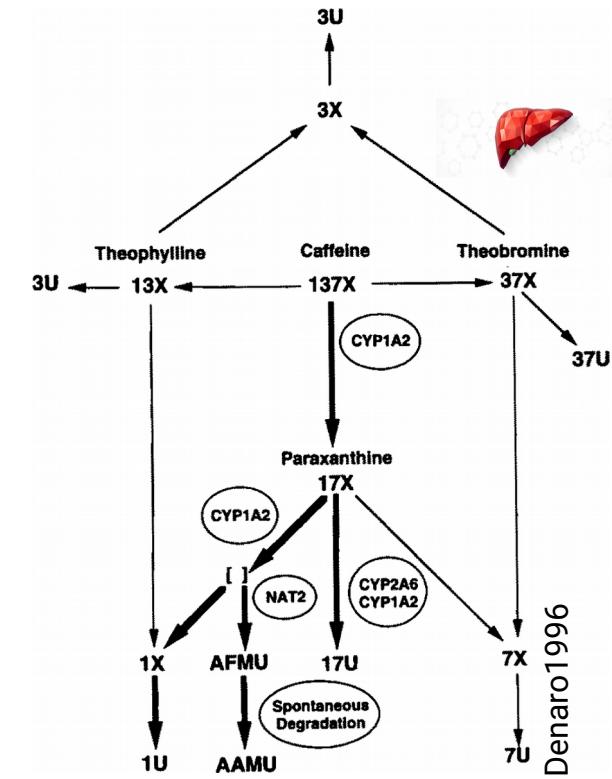
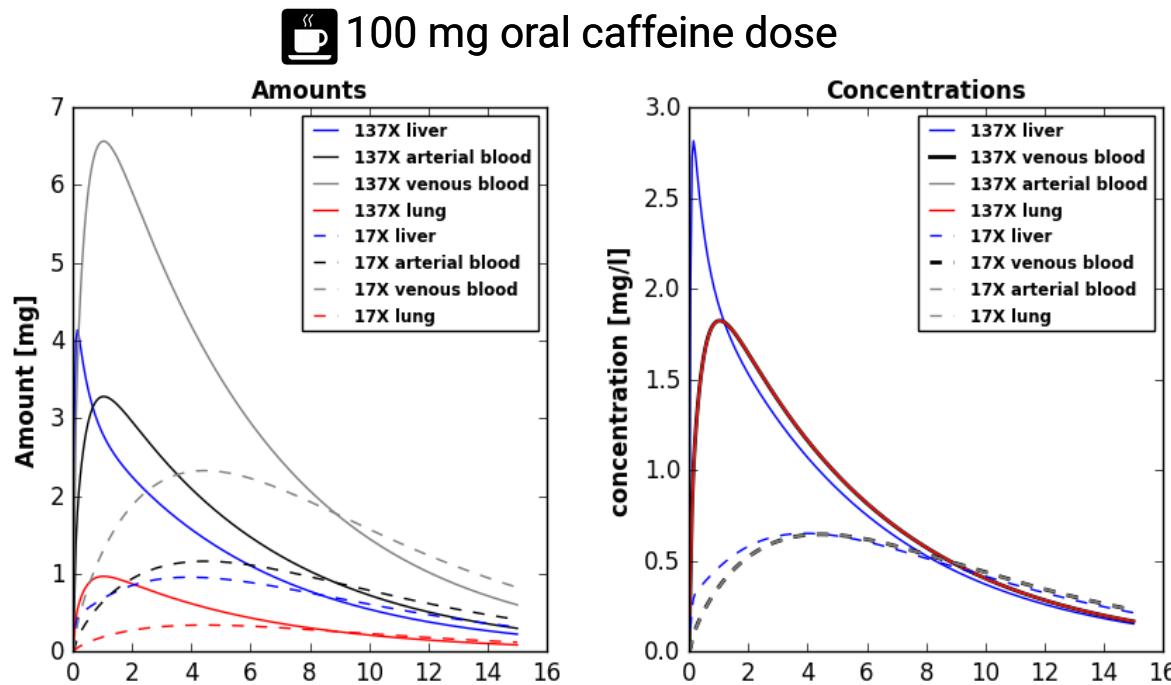
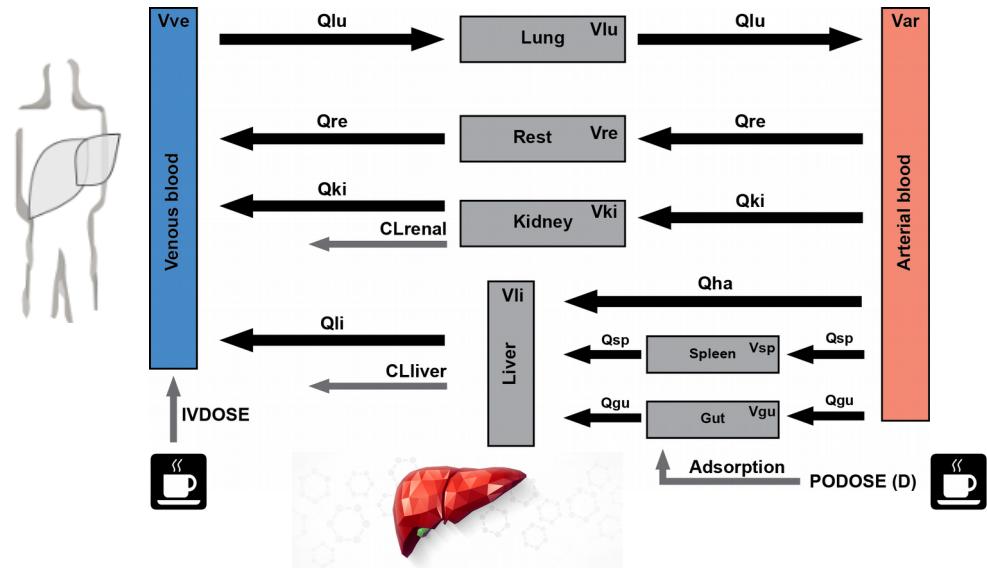
Denaro1996

- How is smoking affecting the clearance of caffeine ?

$$\text{Cup of Coffee} + \text{Smoking} = ?$$

PKPD

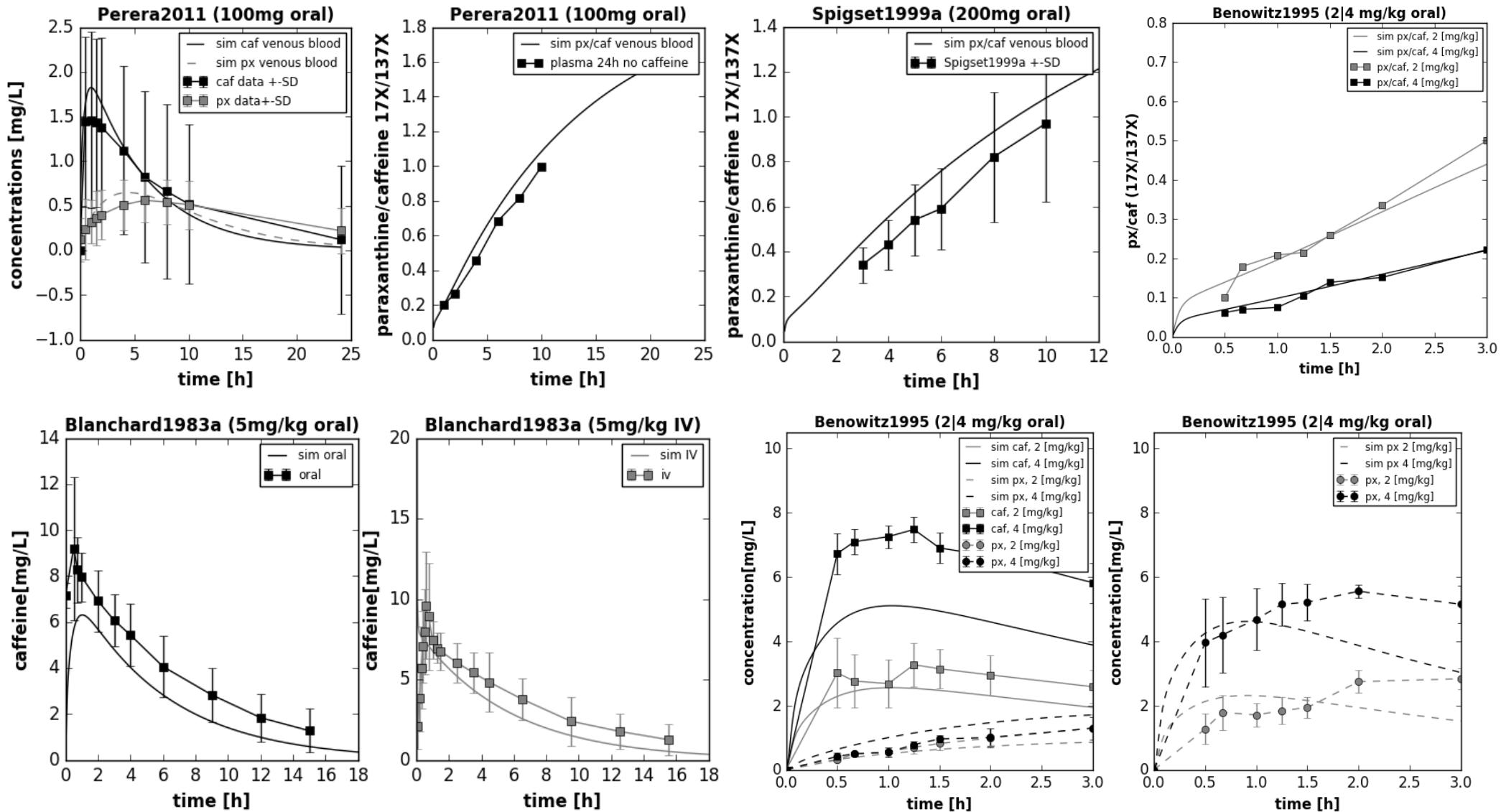
- Kinetic model of caffeine liver metabolism
- Renal clearance
- Whole-body distribution kinetics



Mean model



human (70kg, male),
mean microsomal CYP1A2 content,
non-smoker

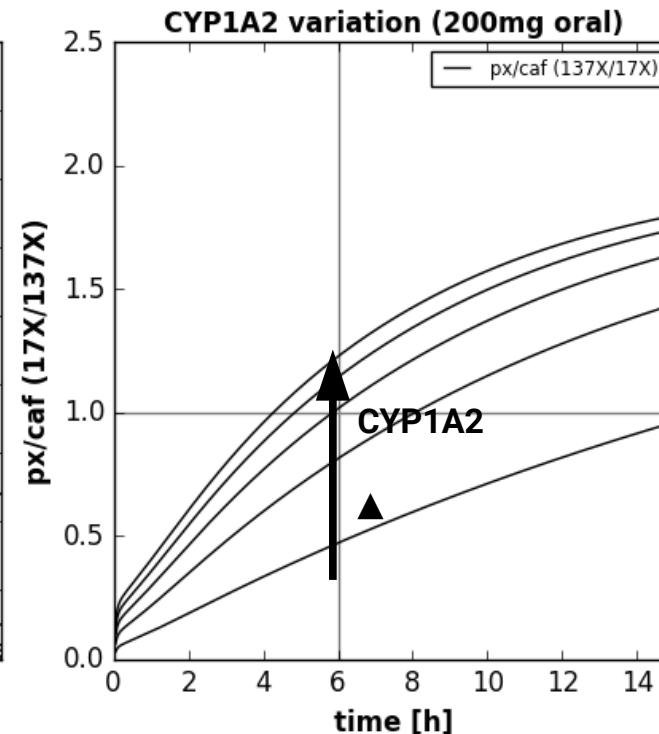
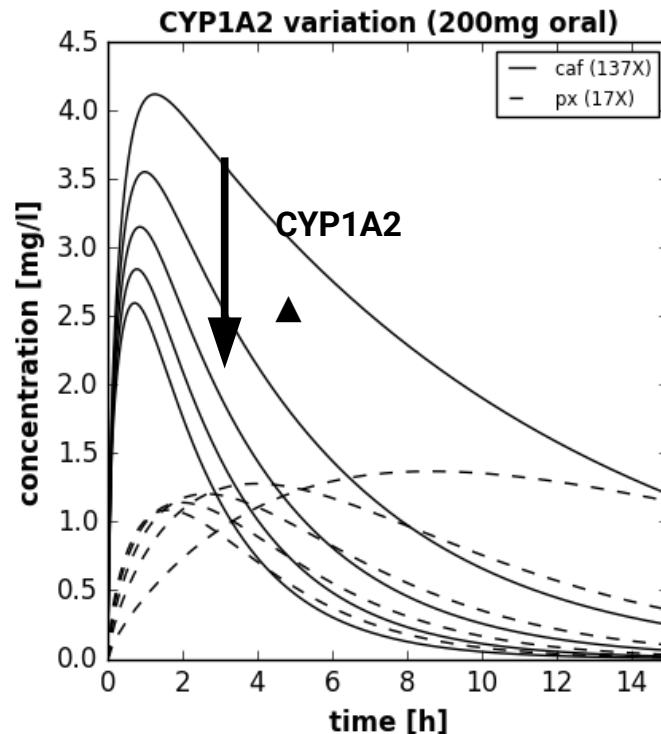


CYP1A2

- CYP1A2 expression altered by many lifestyle factors
 - Strong effect: **Smoking**
- Altered function test results
 - clearance, half-life, kel, max value, metabolic ratios

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	$V_{\text{smoking habit index}}$	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	$V_{\text{oral contraceptive index}}$	0	-	-	Reference
Yes		-0.332	-0.236	-0.428	0.717
Country					
Germany	$V_{\text{country of residence index}}$	0	-	-	Reference
Bulgaria		-0.209	-0.356	-0.061	0.811
Slovakia		-0.303	-0.450	-0.156	0.739
Sex					
Male	$V_{\text{sex index}}$	0	-	-	Reference
Female		-0.111	-0.178	-0.044	0.895

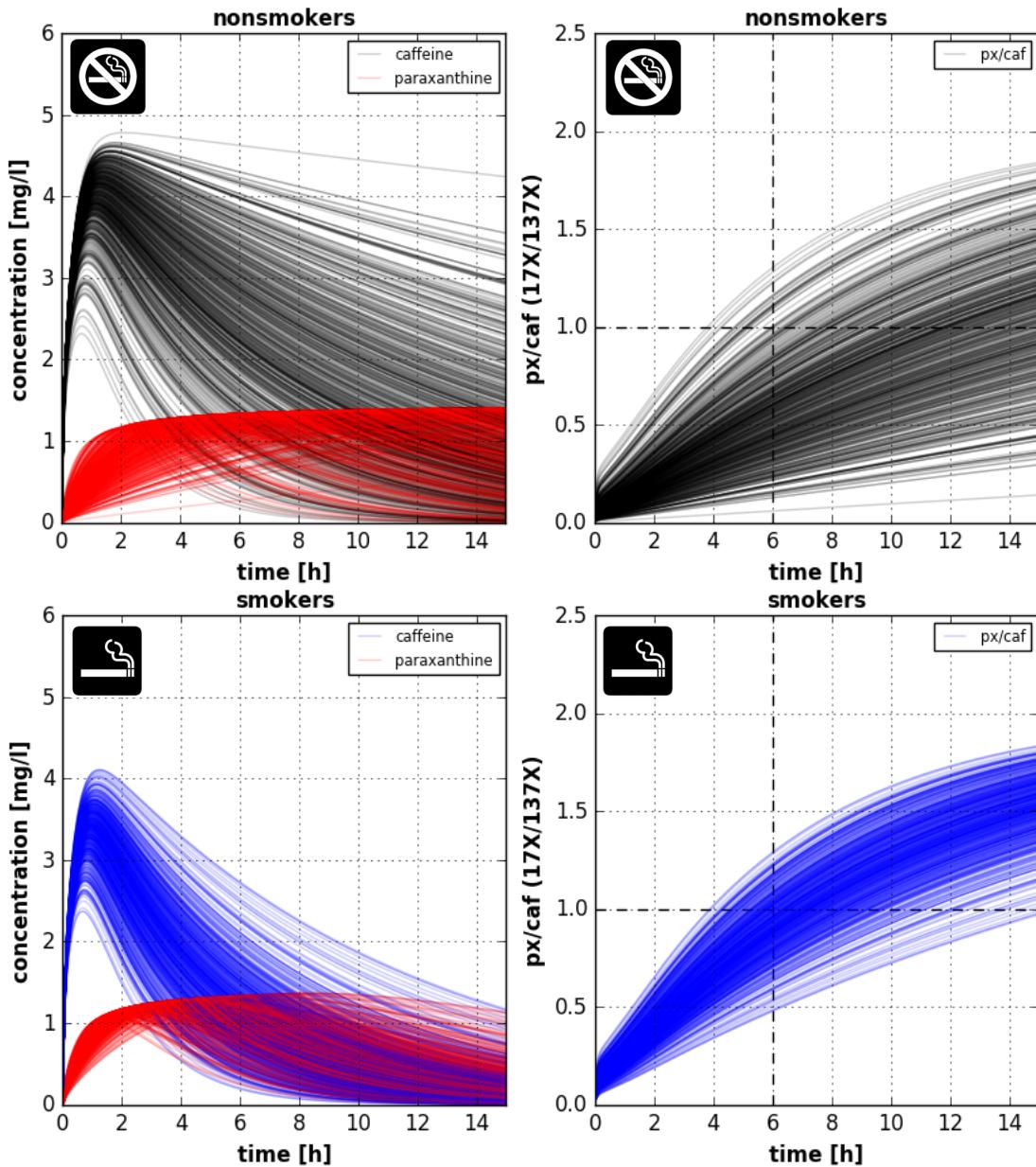
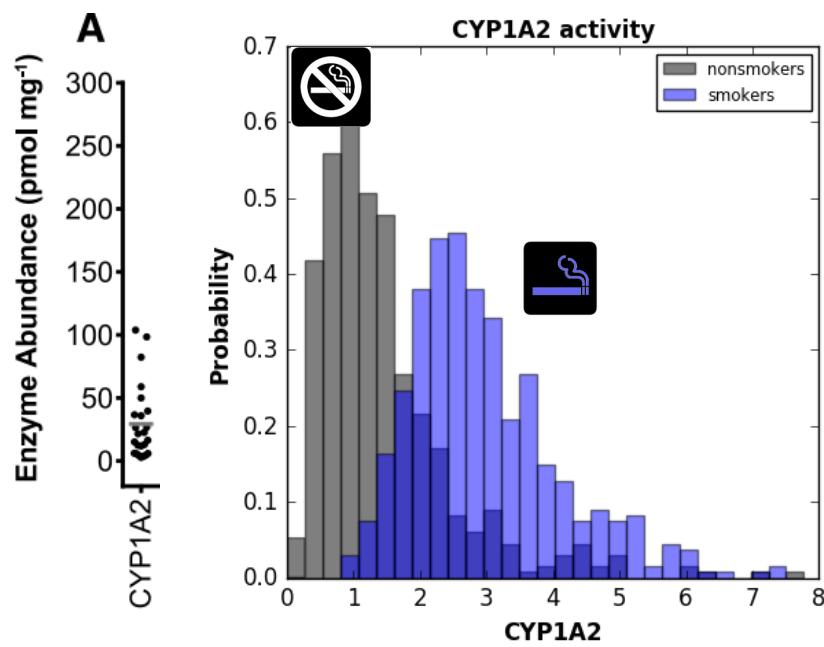


CYP1A2 induction ▲

- Clearance ▲
- kel ▲
- T_{1/2} ▼
- T_{max} ▼
- px(17X)/caf(137X) ▲

Smoking

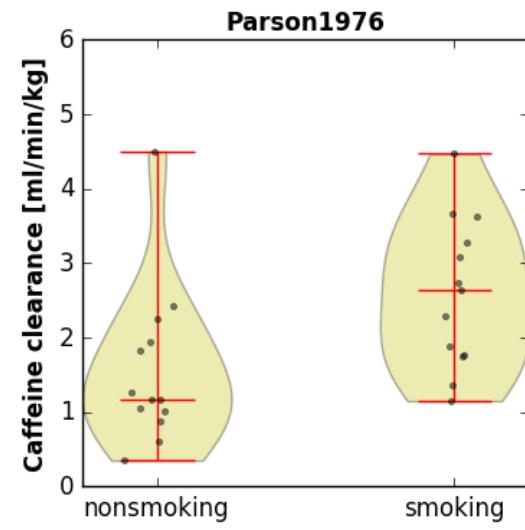
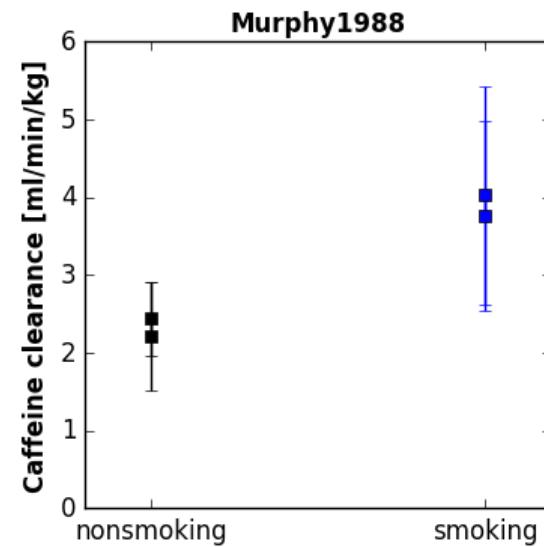
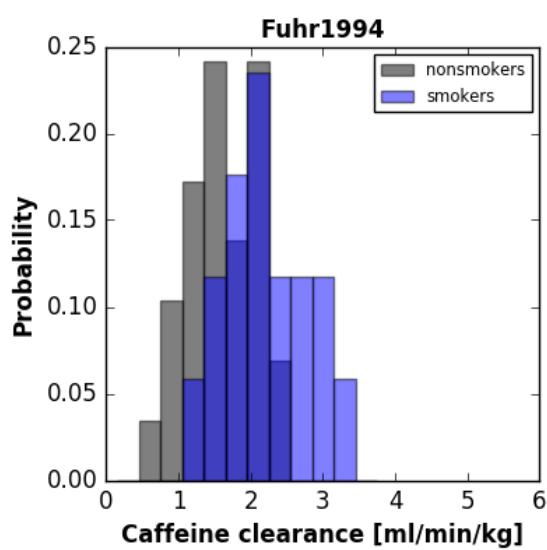
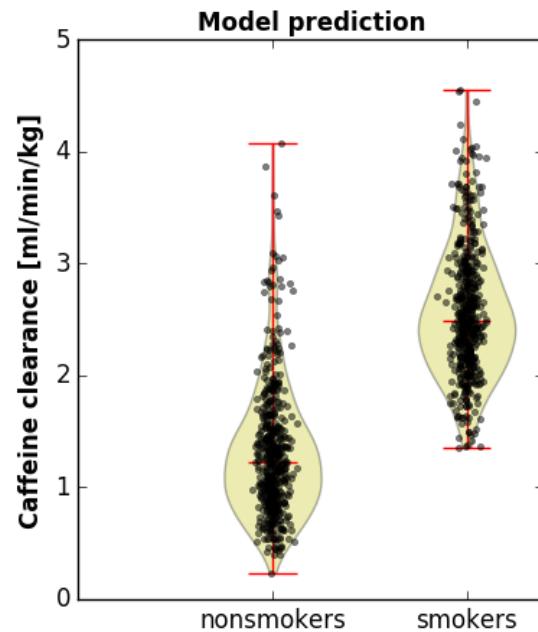
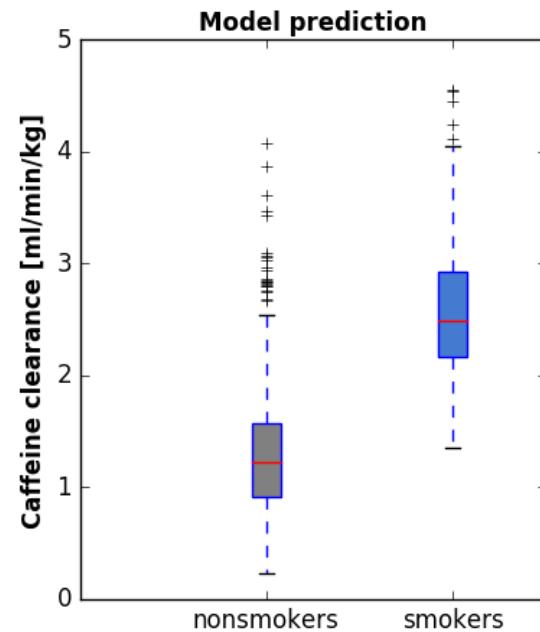
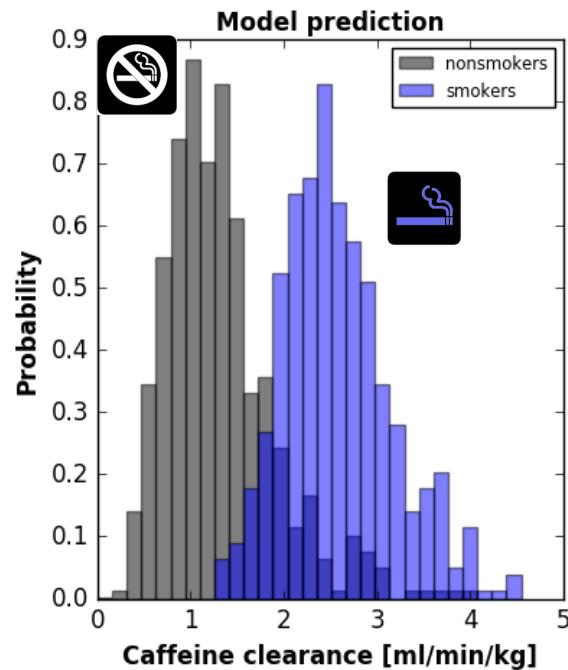
- CYP1A2 smoking effect
 - Distribution of liver microsome activity (log-normal) for non-smokers and smokers
 - Simulation of moderate smoking effect (6-10 cigarettes, ~40% increase)



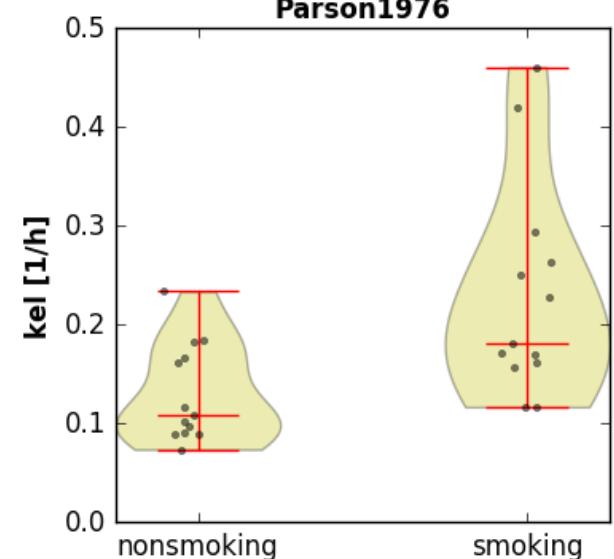
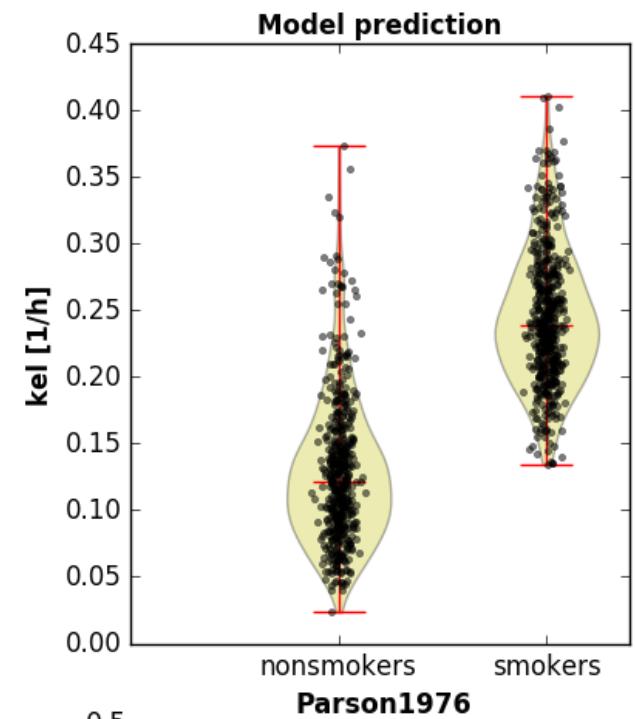
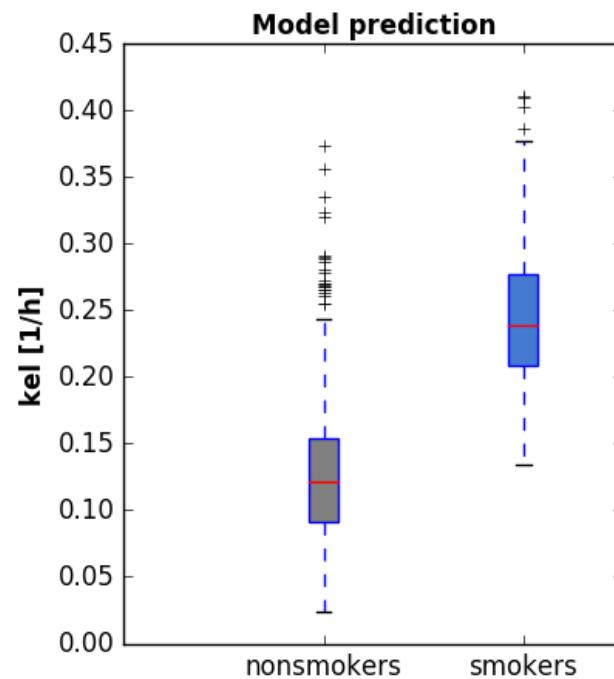
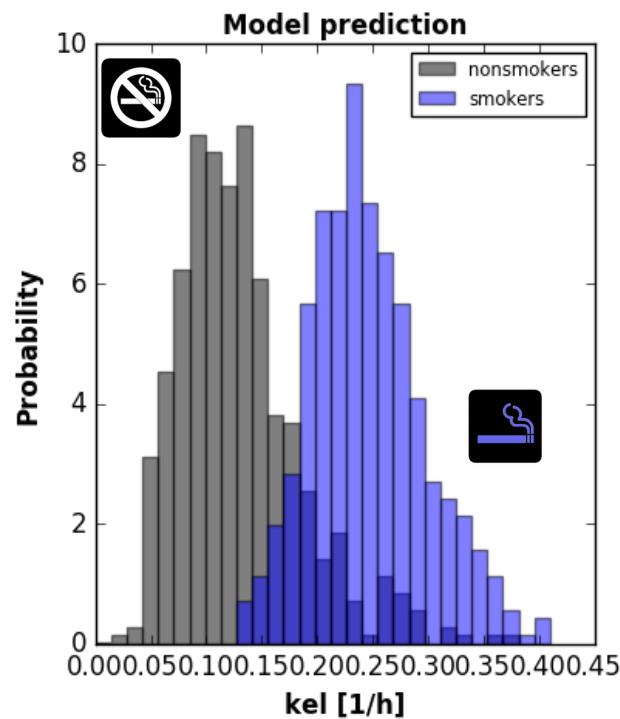
The weighted means, coefficients of variation (CV), ranges, and heterogeneity analysis of the analyzed hepatic cytochrome P450 enzyme abundance data from 50 studies

Enzyme	Mean	CV (%)	Range*	No. of Livers	Q	I^2	Heterogeneity	Studies ^a
CYP1A2	39	78	1-263	148	19.54	54	% Medium	[1-10]

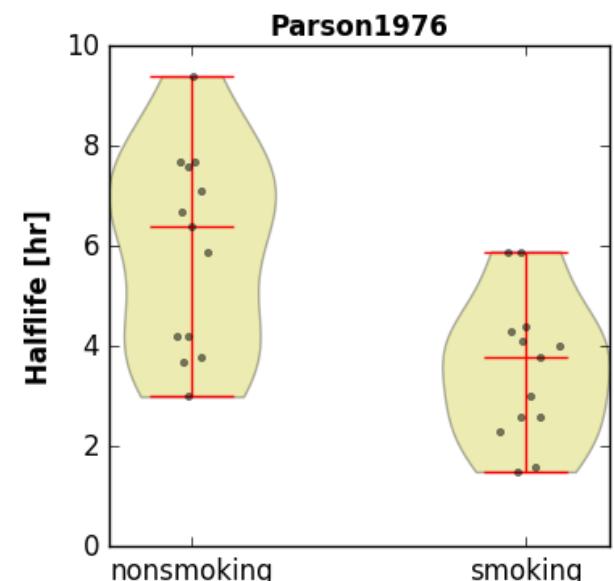
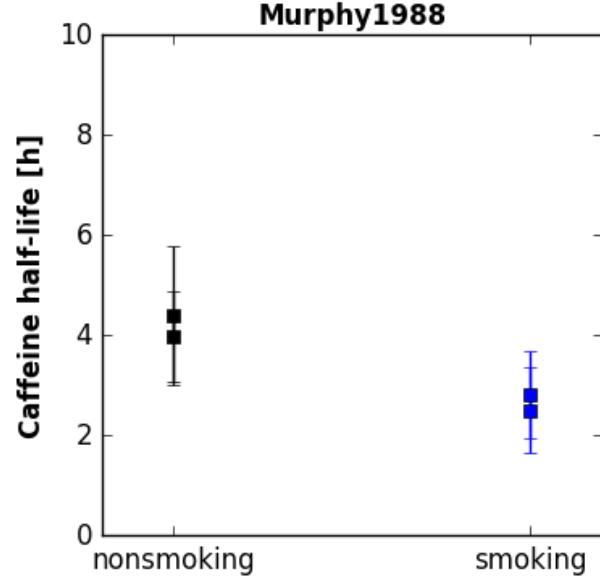
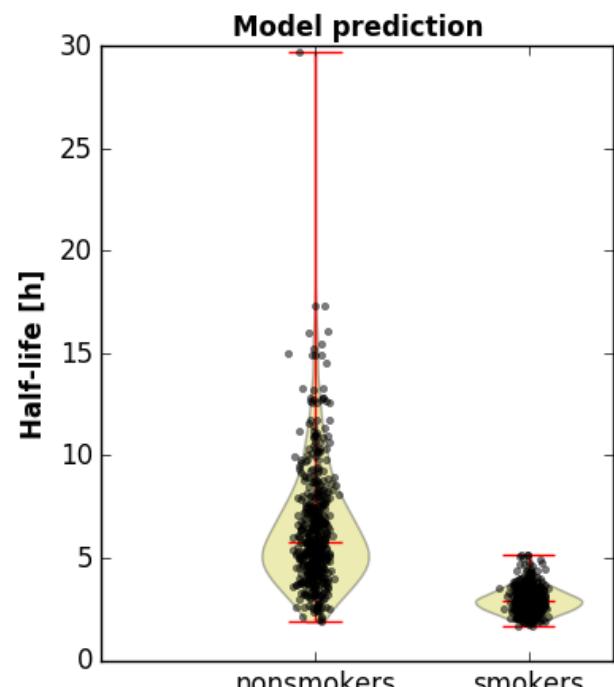
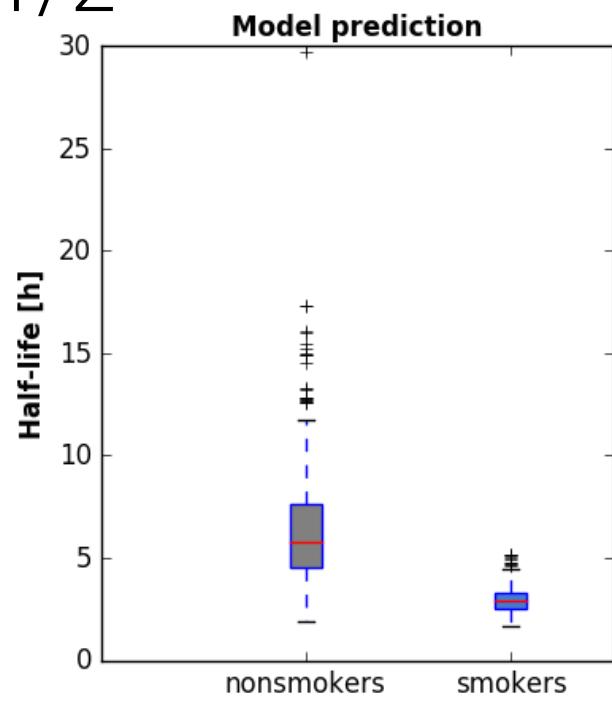
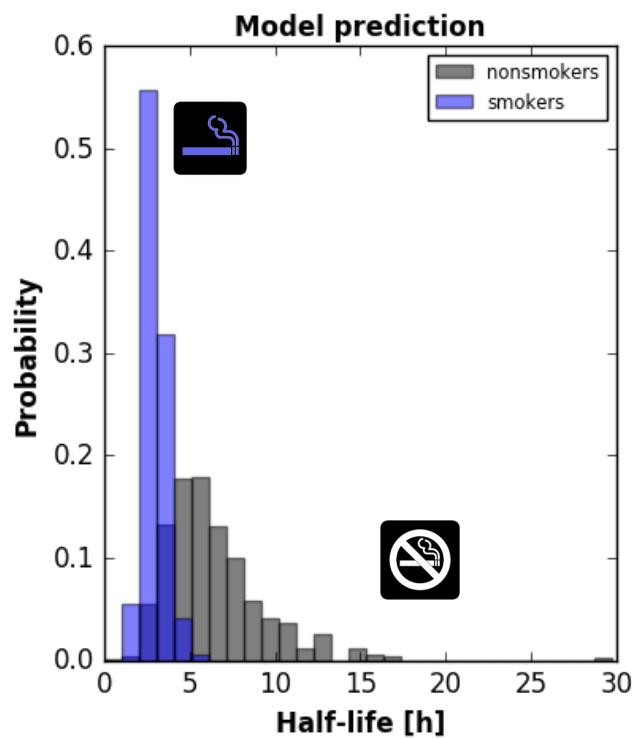
CL: Clearance



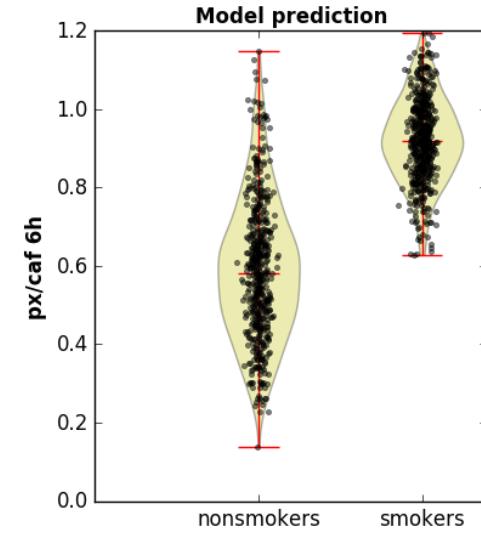
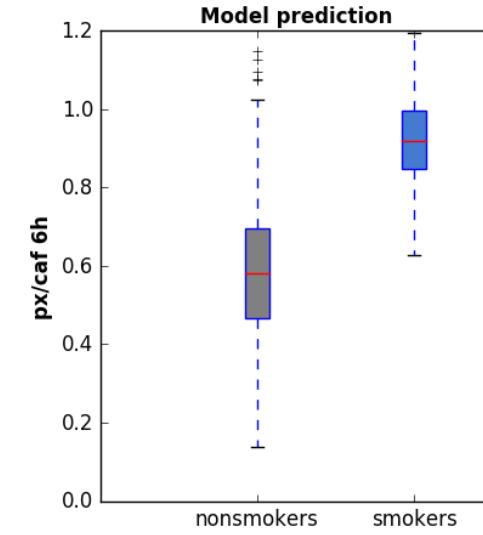
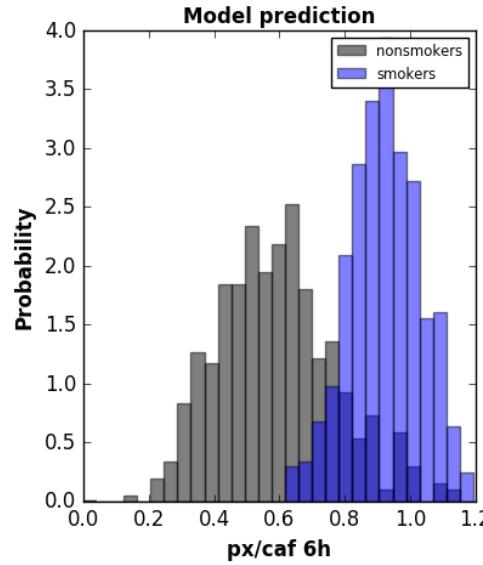
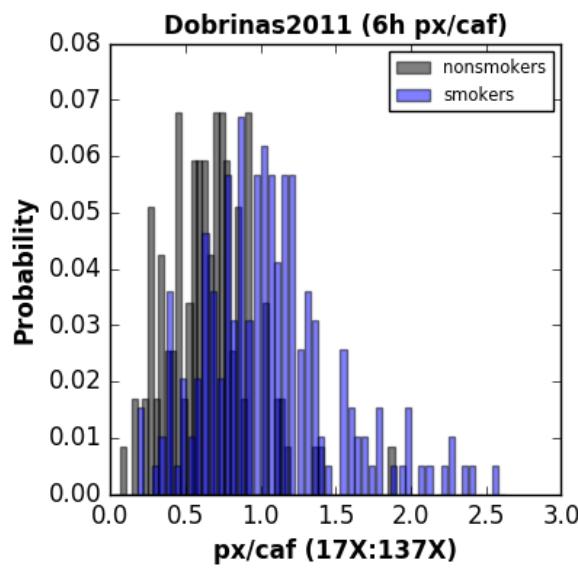
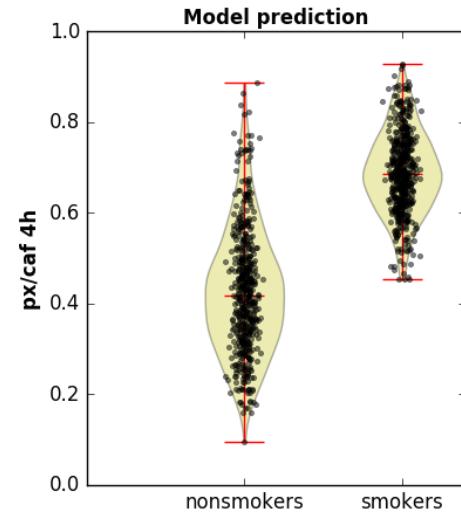
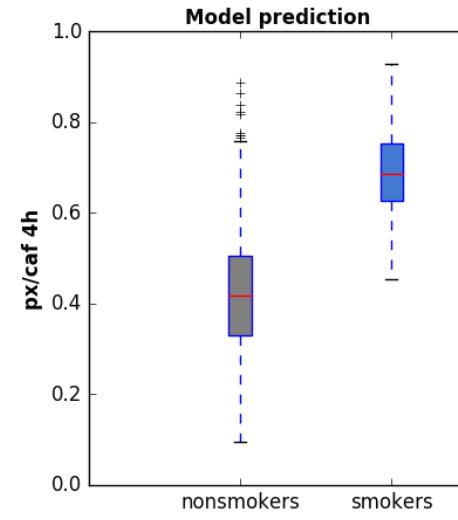
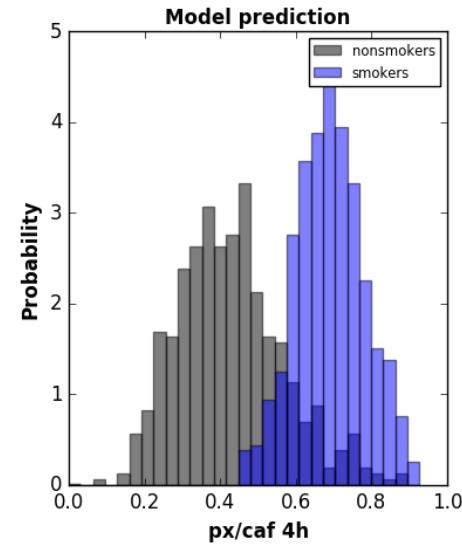
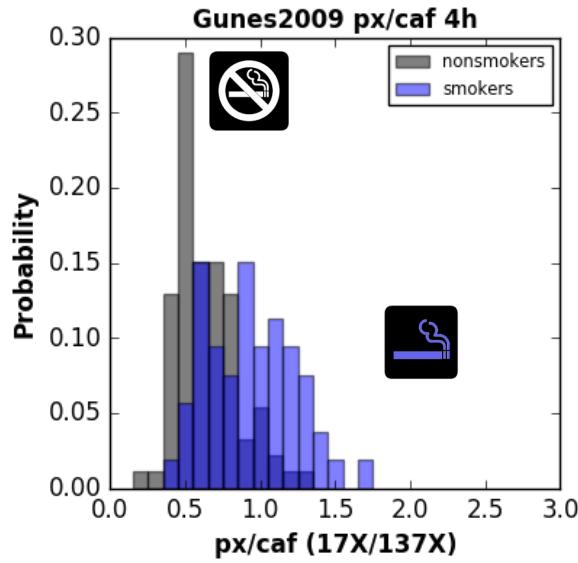
k_{el} : elimination rate



$t_{1/2}$: half-life

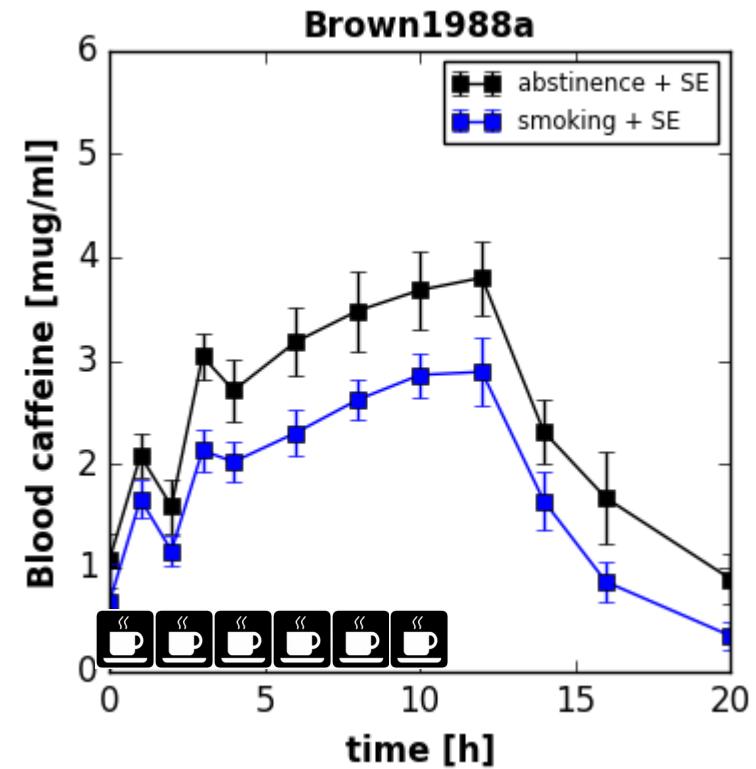
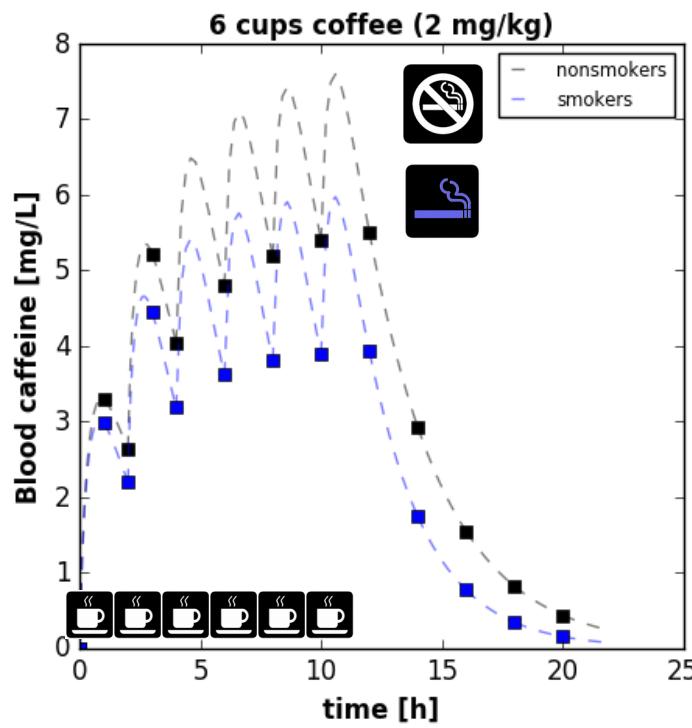


px/caf ratio (4h, 6h)



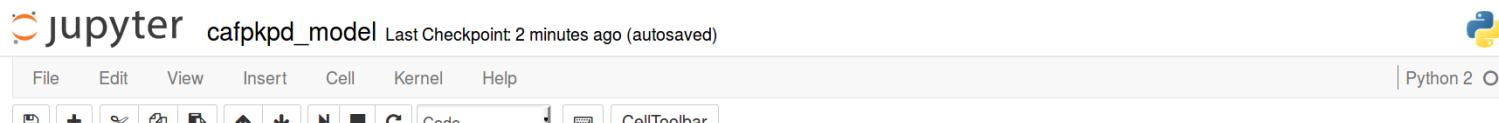
Prediction: coffee consume

- Multiple dosing
- Adaption to smoking status, i.e.
high smokers, via dose response
curve (CYP1A2 ~ smoking)



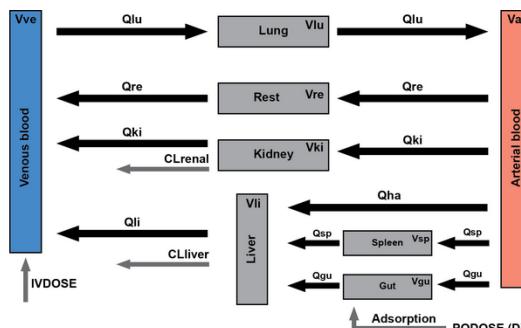
Caffeine Notebook

http://localhost:8888/notebooks/caffeine_pkpd/cafpkpd_model.ipynb



PKPD model

PKPD model for clearance of caffeine by the human liver.



Caffeine and the primary metabolite paraxanthine are removed from the blood stream by hepatic or renal clearance. Caffeine can be given either as intra-venous injection or by oral dose.

TODO: create picture programmatically

```
In [1]: %matplotlib inline
from __future__ import print_function, division
import tellurium as te
from matplotlib import pyplot as plt
import pandas as pd
import numpy as np

# global settings for plots
plt.rcParams.update({
    'axes.labelsize': 'large',
    'axes.labelweight': 'bold',
    'axes.titlesize': 'large',
    'axes.titleweight': 'bold',
    'legend.fontsize': 'small',
    'xtick.labelsize': 'large',
    'ytick.labelsize': 'large',
})
```

Modeling Tools, Software, Workflows

git repositories

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



&



CODE

DATA

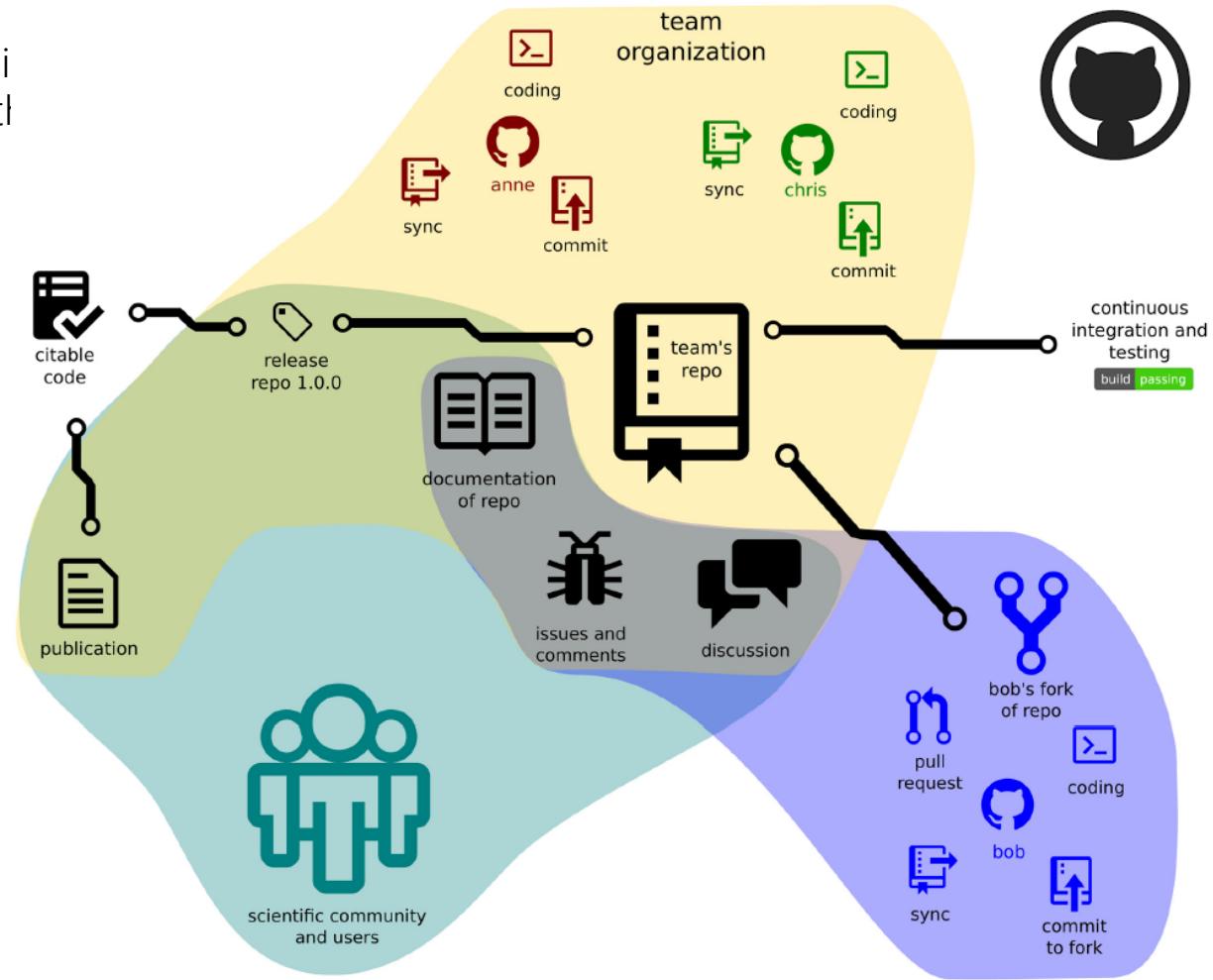


Fig 1. The structure of a GitHub-based project illustrating project structure and interactions with the community.

doi:10.1371/journal.pcbi.1004947.g001

Perez.Riverol2016

<https://github.com/matthiaskoenig/cy3sbml/>

<https://github.com/matthiaskoenig/cy3sbml/commit/986ebbdd5e77d403cf031ff0a5230de4d28fc284>

Reproducible Analyses

Dynamic report generation !

Jupyter notebooks

- Web application that allows to create and share documents that contain live code, equations, visualizations and explanatory text.
- Open source, interactive data science and scientific computing across over 40 programming languages.
- Complete analysis, examples, test cases
<http://tellurium.readthedocs.io/en/latest/notebooks.html#feedback-oscillations>
http://localhost:8888/notebooks/feedback_oscillations.ipynb



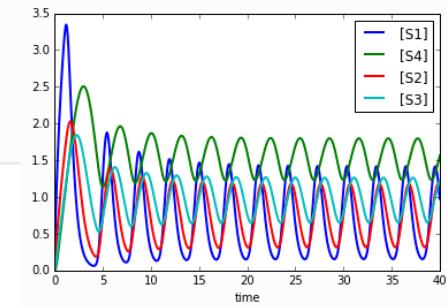
R: Knitr

- Elegant, flexible and fast dynamic report generation with R
- BDL example
<https://github.com/matthiaskoenig/bdl-analysis>



Feedback oscillations

Model oscillations via feedback



```
import tellurium as te

r = te.loada '''
model feedback()
// Reactions:
J0: $X0 -> S1; (VM1 * (X0 - S1/Keq1))/(1 + X0 + S1 + S4^h);
J1: S1 -> S2; (10 * S1 - 2 * S2) / (1 + S1 + S2);
J2: S2 -> S3; (10 * S2 - 2 * S3) / (1 + S2 + S3);
J3: S3 -> S4; (10 * S3 - 2 * S4) / (1 + S3 + S4);
J4: S4 -> $X1; (V4 * S4) / (KS4 + S4);

// Species initializations:
S1 = 0; S2 = 0; S3 = 0;
S4 = 0; X0 = 10; X1 = 0;

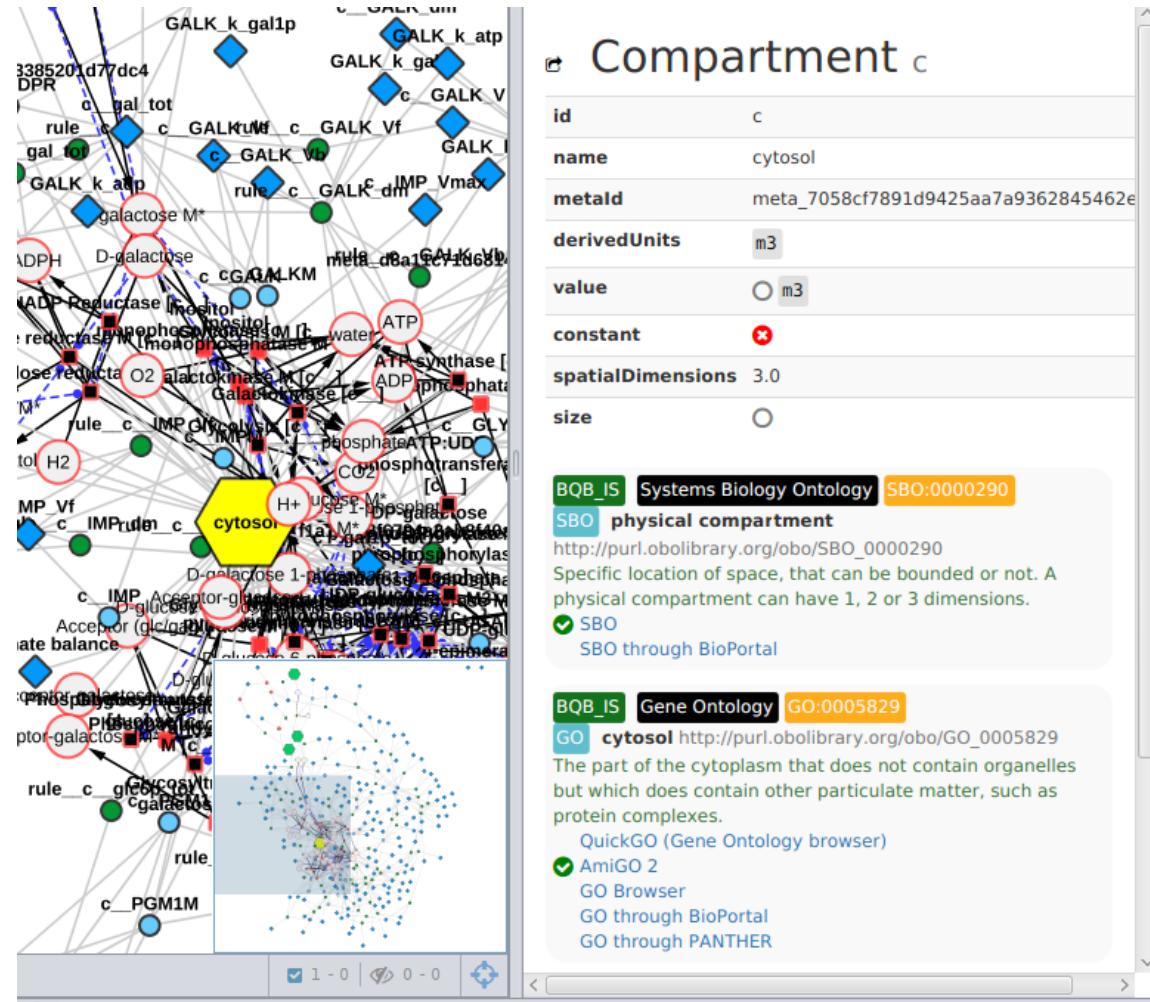
// Variable initialization:
VM1 = 10; Keq1 = 10; h = 10; V4 = 2.5; KS4 = 0.5;
end'''

res = r.simulate(0, 40, 500)
r.plot()

import matplotlib.pyplot as plt
plt.plot(res["[S1]"], res["[S2]"], 'o-', color="black")
plt.xlabel("[S1]")
plt.ylabel("[S2]");
```

Standard Formats

- Encoding of information in standard formats where possible
 - Models in SBML (core, comp, fbc)
 - Simulations in SED-ML
 - Minimal Information for models and simulation (MIRIAM, MIASE)
- Annotations to ontologies
 - Knowledge integration
 - Documentation
- Reproducibility
 - Reproducibility of results (roadrunner, COPASI, JWS)
- Model quality
 - Passes library tests (e.g., module unit tests, ...)
- Visualization
 - Iterative model cycle



König, Rodriguez, and Dräger
cy3sbml: A Cytoscape app for SBML
2017, manuscript in preparation
<https://github.com/matthiaskoenig/cy3sbml>

```

// -- Begin Antimony block converted from MAPKcascade.xml
// Created by libAntimony v2.9.3
model *MAPKcascade()
...
// Reactions:
J0: MKKK_P => 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

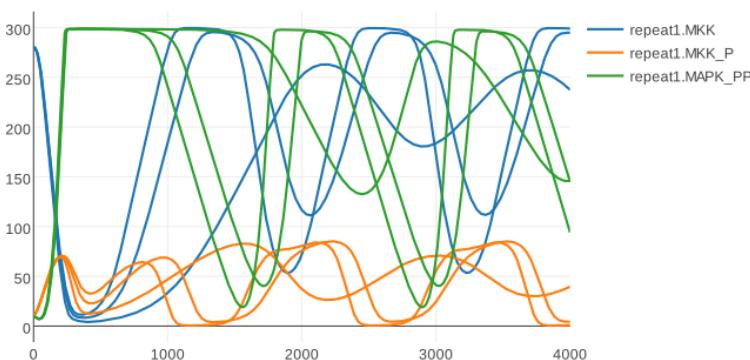
// Repeated Tasks
repeat1 = repeat task1 for model1.J1_KK2 in [1, 10, 40], reset=true

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

```



Sampled Simulation

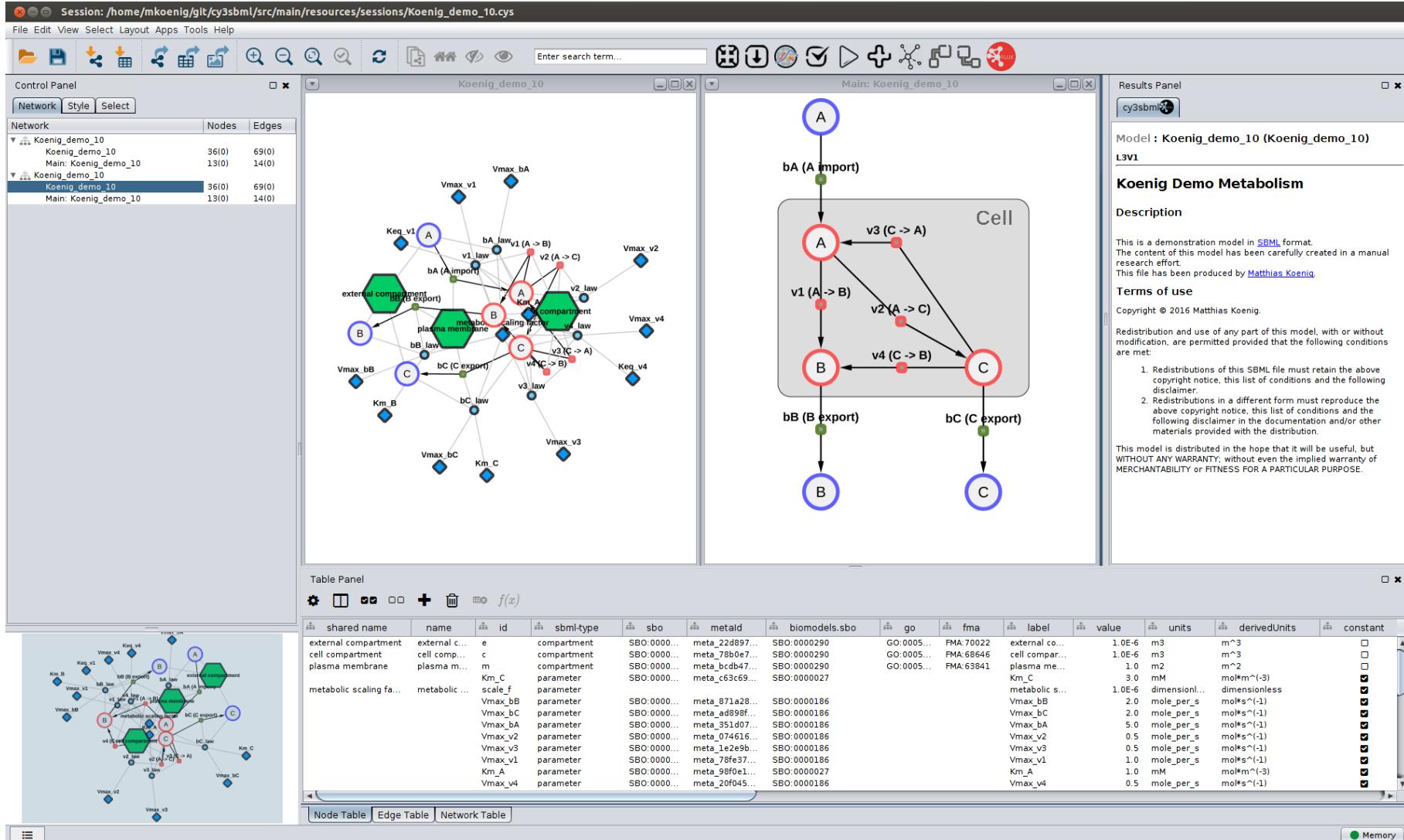


Modeling Tools

- **libRoadRunner**: High performance SBML simulator
- **tellurium**: Python based modeling environment (library & notebook)

Medley K, Choi K, **König M**; Smith L, Gu S, Joseph Hellerstein, Sealfon S., Sauro HM.
Tellurium Notebooks - An Environment for Dynamical Model Development, Reproducibility, and Reuse
[submitted, 2017]
 Somogyi, Bouteiller, Glazier, **König**, Medley, Swat, Sauro.
libRoadRunner: a high performance SBML simulation and analysis library.
 Bioinformatics. **2015**

Visualization & Data Integration



König

cy3sabiork: A Cytoscape app for visualizing kinetic data from SABIO-RK

2016 [version 1; referees: 2 approved with reservations]

<http://f1000research.com/articles/5-1736/v1>

<https://github.com/matthiaskoenig/cy3sabiork>

König, Rodriguez, and Dräger

cy3sbml: A Cytoscape app for SBML

2017, manuscript in preparation

<https://github.com/matthiaskoenig/cy3sbml>

Tutorial

<http://bit.ly/pkpd-tutorial>

