

Systematic evaluation of personalized physiologically based pharmacokinetic simulations

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Objective

Physiologically based pharmacokinetic (PBPK) models typically rely on parameter values that represent the mean of the study cohort or population. In reality, persons that have the same properties as average individuals hardly exist. The goal of this study was to build personalized PBPK models and evaluate their predictive performance. Caffeine was chosen as an example because the compound is a probe drug for CYP1A2 and the compound's disposition is well investigated.

Methods

Drug cocktail study [1]

Study population: 48 healthy volunteers (29 males, 19 females),

Drugs: caffeine, codeine, midazolam, pravastatin, talinolol and torsemide

Administration: Oral administration of single, subtherapeutic doses (50 mg caffeine)

PBPK models were simulated with PK-Sim, which is part of the open systems pharmacology suite [2]. Personalization was carried out in MATLAB with the OSP toolbox.

Workflow

Before model personalization, a base caffeine PBPK model was established that simulated caffeine pharmacokinetics for a reference individual (1.76 m, 73 kg, male, 30 years) and fitted the mean caffeine plasma concentration of the study cohort. The base model served as a benchmark for the evaluation of PBPK model personalization.

In the first step, the caffeine PBPK model simulations were personalized with demographic data. In the second step, physiologic data was included in addition to the demographic data. In the third step, CYP1A2 activity was informed with the paraxanthine/caffeine concentration ratio (PXC_{F_{ratio}}) at 4h (Equation 1 & 2).

Equation 1: Calculation of the scale factor for the ith individual.

$$scaleFactor_i = \frac{PXC_{F_{ratio},i}}{PXC_{F_{ratio},mean}}$$

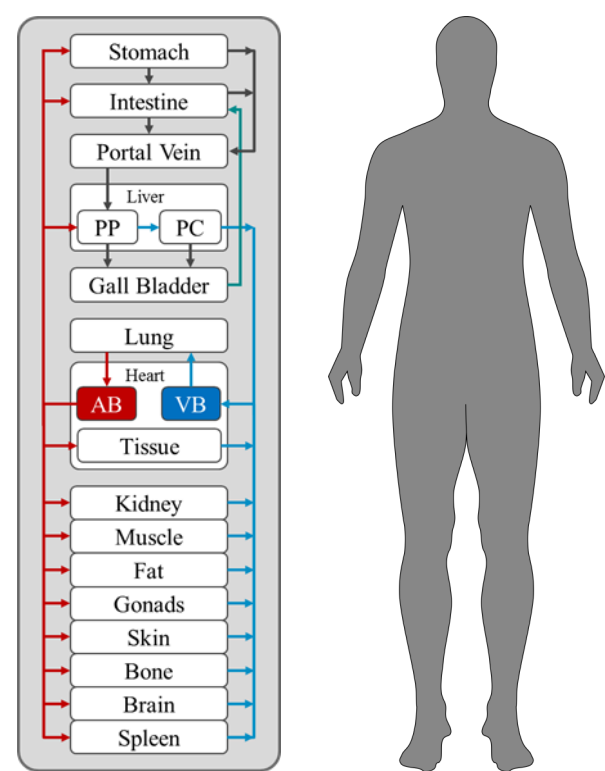
Equation 2: Scaling of the specific CYP1A2 clearance Cl_{spec}

$$Cl_{spec,i} = Cl_{spec,baseModel} * scaleFactor_i$$

Evaluation of model performance

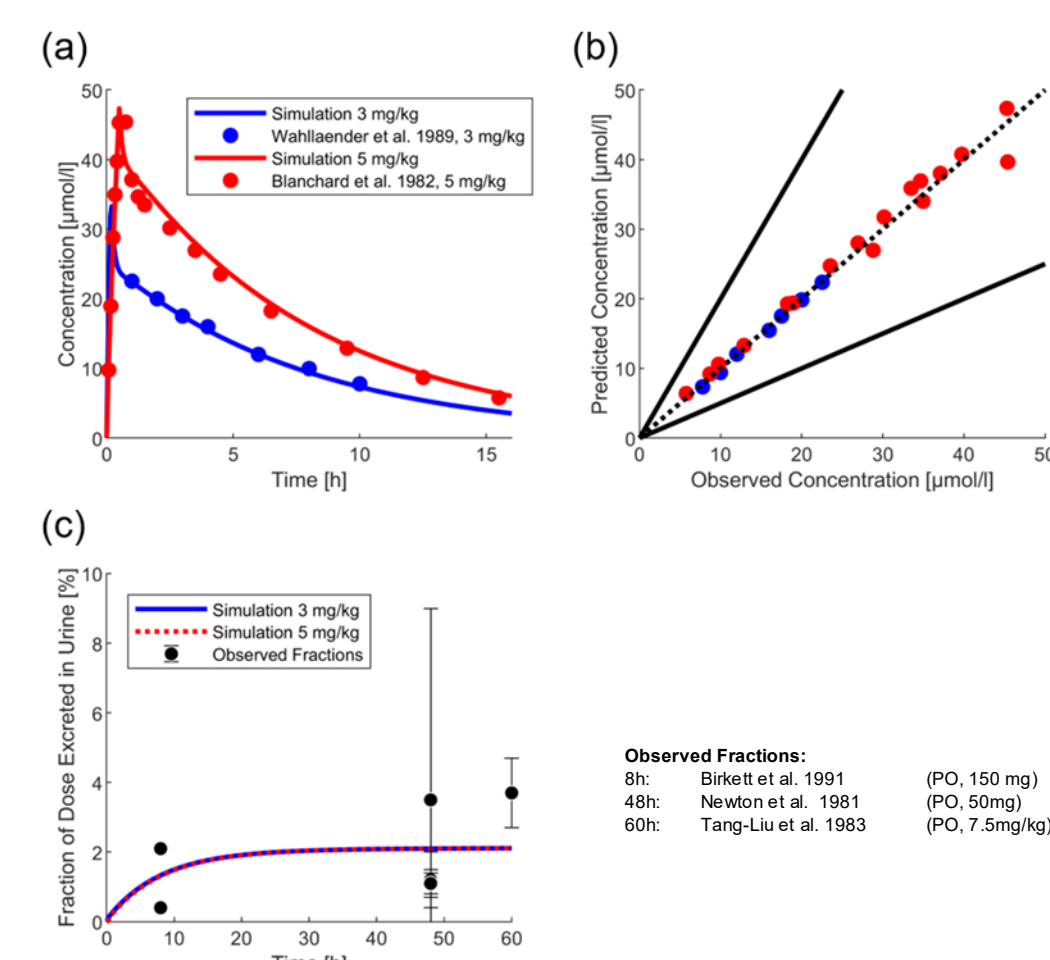
The following model metrics were calculated to evaluate model performance:

The root-mean-square error (RMSE), the geometric mean fold error (GMFE) of pharmacokinetic parameters and the percentage of predicted concentrations that fell within the 1.25– and the 2-fold range of the observed data.



Reference Individual
1.76 m, 73 kg , male, 30 years

IV fit
intestinal permeability and CYP1A2 activity
fitted to literature data



PO fit
intestinal permeability and CYP1A2 activity
fitted to mean of the study population

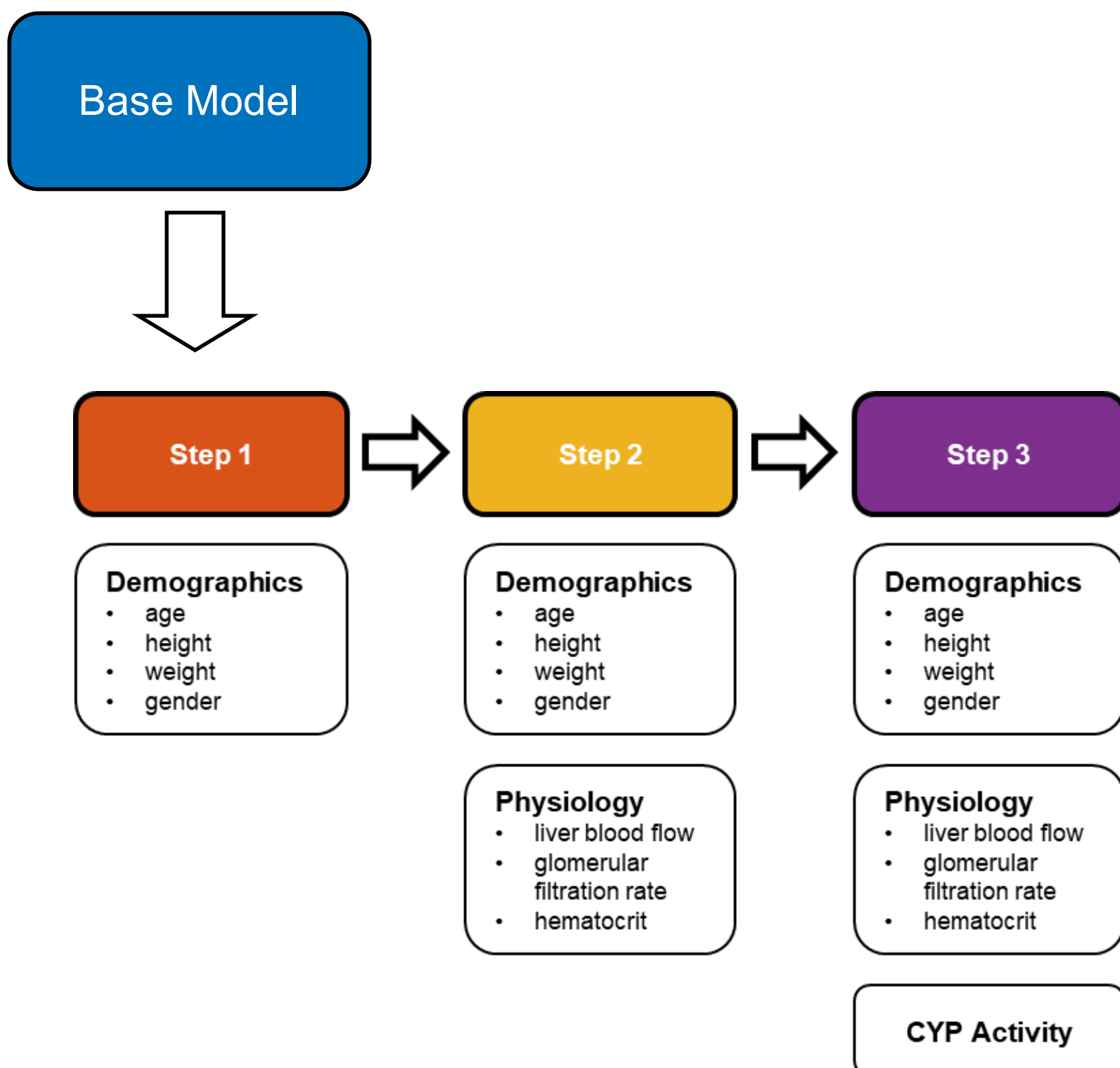


Figure 1: Base model establishment and PBPK model personalization workflow.

Results

Base Model

Step 1

Step 2

Step 3

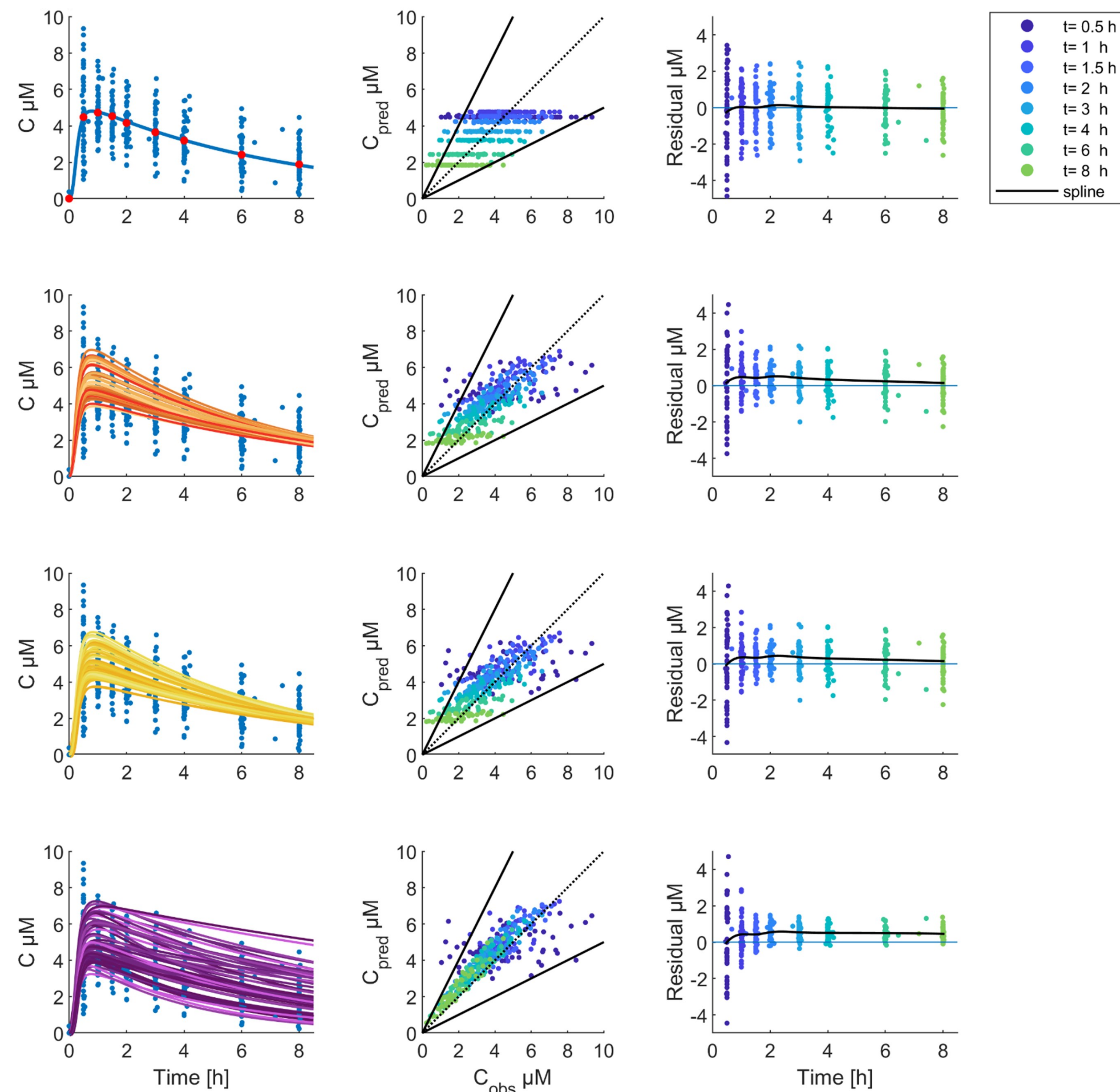


Figure 2: Goodness of fit plots. Visual predictive check (left column), predicted vs observed concentrations (middle column), residuals vs time (right column).

Conclusions

We systematically analyzed the impact of biometric, physiologic and CYP1A2 phenotype data on personalized caffeine PBPK model simulations. Informing the caffeine PBPK model with of biometric data (height, weight, age, sex) of study individuals improved the performance of model simulations, inclusion of physiologic information (glomerular filtration rate, liver blood flow, hematocrit) did not. CYP1A2 phenotyping by the paraxanthine/caffeine ratio in plasma also improved the model performance.

Furthermore, we concluded that the drug's pharmacology determines which parameters are relevant for model personalization. Caffeine clearance is enzyme-limited and renal clearance is low, therefore the low impact of personalized liver blood flows and glomerular filtration rates on the model simulation was expected.

The presented approach demonstrates that personalized PBPK models can predict individual pharmacokinetic profiles more accurately and that they could be applied for model informed precision dosing in the future.

Table: Caffeine PBPK model evaluation metrics.

Crosses (X) indicate whether the information was used in the respective step or additional analysis

	Biometry	Physiology	CYP activity	% in 1.25-fold range	% in 2-fold range	GMFE AUC	GMFE V _d	RMSE
Benchmark								
Base Model				45.83	92.71	1.31	1.21	1.28
Workflow								
Step 1	X			57.81	93.75	1.24	1.14	1.08
Step 2	X	X		59.11	93.49	1.24	1.12	1.07
Step 3	X	X	X	66.15	97.40	1.16	1.12	0.97

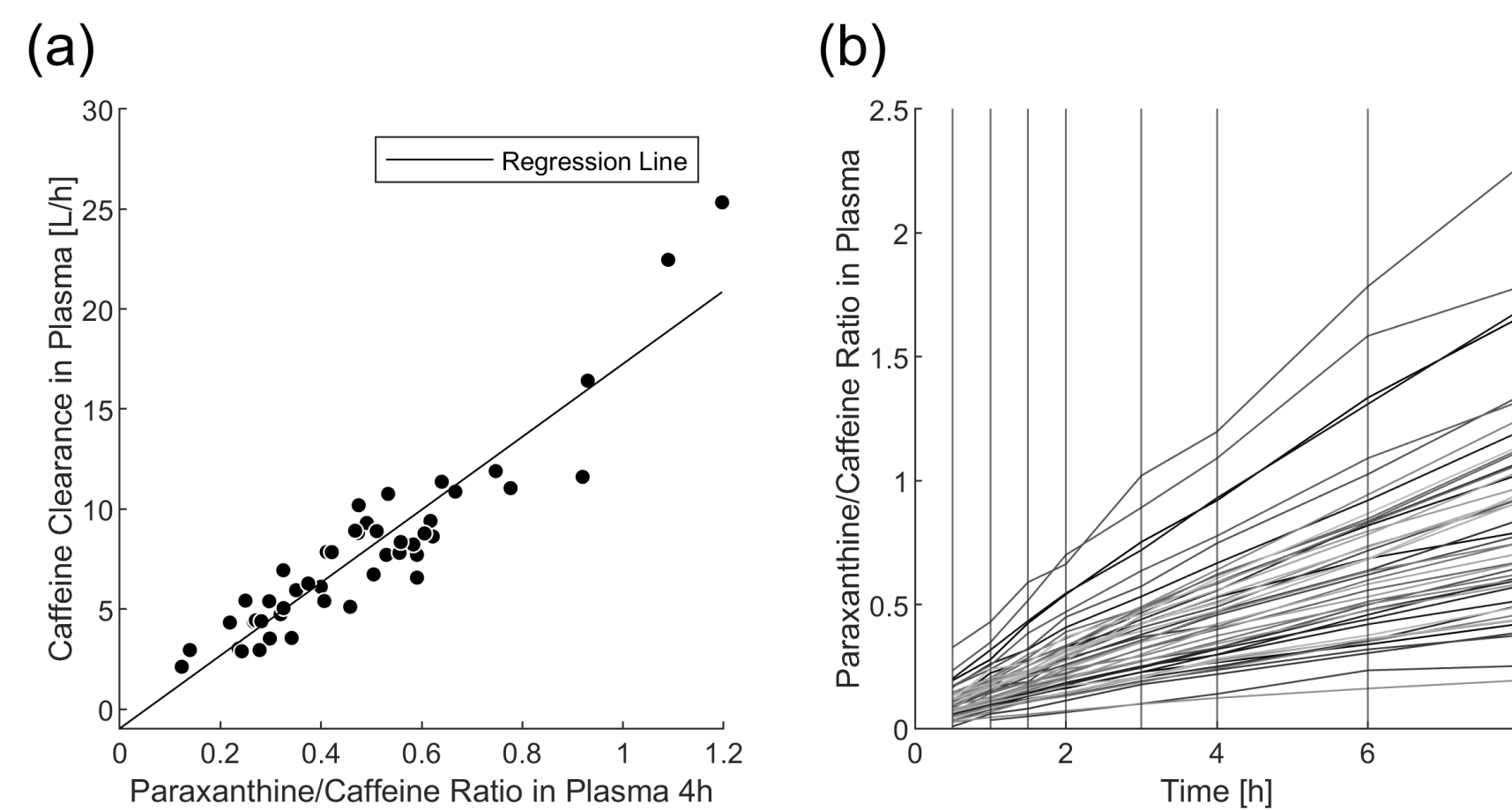


Figure 3: Correlation of observed clearances and paraxanthine/caffeine ratio. (a) Linear regression model with the paraxanthine/caffeine ratio in plasma at 4h as the explanatory variable and the observed caffeine clearance in plasma as the response variable. (R²=0.86) (b) Individual time courses of paraxanthine/caffeine ratios in plasma.

References

- [1] Kuepfer, L., R. Kerb, et al. (2014). "Clinical Translation in the Virtual Liver Network." CPT Pharmacometrics Syst. Pharmacol. 3(7): e127.
[2] <http://www.open-systems-pharmacology.org>

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