Evaluating the benefit of individual patient data for physiologically based pharmacokinetic simulations

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Introduction

In this work, personalized physiologically-based pharmacokinetic (PBPK) models for midazolam and caffeine were built based on information from a clinical study in healthy volunteers. The mechanistic nature of PBPK models allowed incorporating knowledge about the studied healthy volunteers such as biometrics (height, weight, age, sex) or physiological data (hematocrit, glomerular filtration rate, liver blood flow). The goal of the study was to evaluate whether incorporation of this individual information improves the agreement of personalized pharmacokinetic simulations with pharmacokinetic measurements.

Drug Cocktail Study

- **Study population:** 103 healthy volunters (49 females, 54 males)
- **Oral administration** of a single dose
- **Drug cocktail**: caffeine, codeine, midazolam, pravastatin, talinolol and torsemide
- **Probe drugs** for CYP Enzyme or drug transporter activity
  - Caffeine metabolized by CYP1A2
  - Midazolam metabolized by CYP3A4
- **Subtherapeutic doses** (e.g. 50 mg for Caffeine and 1 mg Midazolam)
- **PK data:** blood plasma concentrations (8h) of parent drugs and metabolites

Relevant data for PBPK model personalization collected additionally:

- **Biometric data** (height, weight, age, sex)
- **Physiological data** (e.g. glomerular filtration rate, liver blood flow)
- **Pharmacogenetic data** (e.g. CYP2D6, CYP3A4, PXR, OATP1B1)
- **Lifestyle** (smoking, medication, nutrition)

Reference: Kuepfer et al., CPT:PSP 2014

Modeling

Software: PK-Sim (open systems pharmacology suite, version 7.3)
MATLAB (version 2015b)

Workflow:

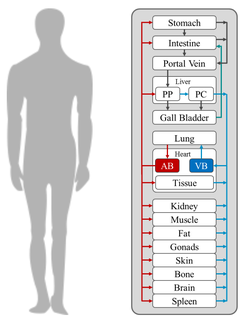
Base model: CYP expression was fitted to the mean of the plasma concentration
Step 1: base model compared to observed data
Step 2: personalized PBPK models were simulated with base model CYP expression
Step 3: CYP expression was fitted using the reference individual
Step 4: CYP expression was fitted using personalized PBPK models

Model evaluation:

- Concordance correlation coefficient (describes the degree to which observed and simulated data pairs fall on the line of unity)
- Percentage of data in the 2-fold range

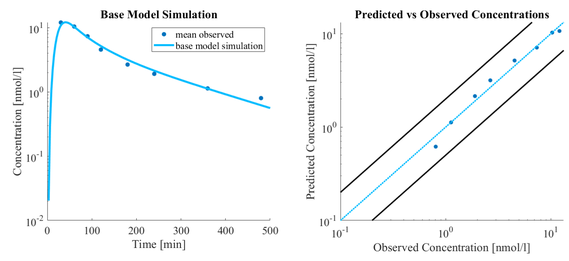
Midazolam Model Personalization

1) Base Model Construction

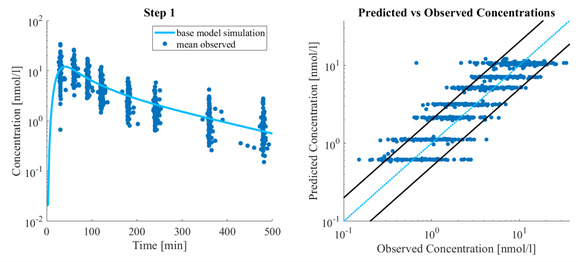
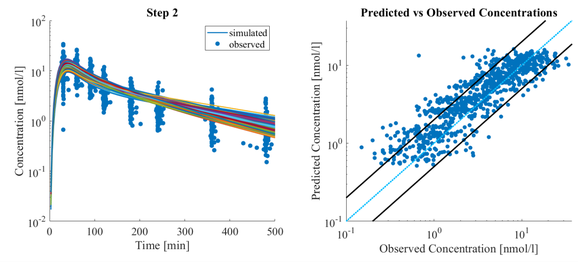
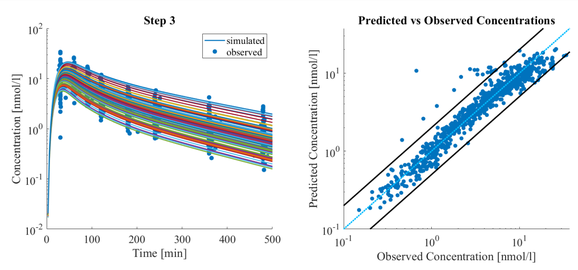
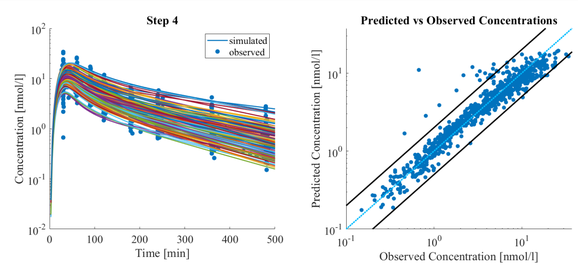


Reference Individual

Fit CYP3A4 Expression

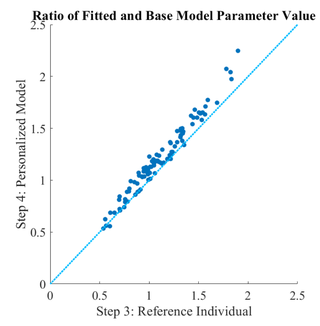


2) Simulation Results

	Reference Individual 1.76 m, 73 kg , male, 30 years	Personalized Models height, body weight, sex, age
Base model CYP3A4 expression		
Fitted CYP3A4 expression		

	Reference Individual	Personalized Models
Base Model Expression	0.75 80.1 %	0.74 76.1 %
Fitted Expression	0.88 97.0 %	0.87 97.2 %

Concordance correlation coefficient
% of the Data in 2-fold range



Caffeine Model Personalization

The same workflow as for midazolam was executed with a caffeine PBPK model to test PBPK model personalization for a compound with different properties.
Compared to midazolam, caffeine binds less to plasma proteins and distributes equally into all tissues. Known covariates on CYP1A2 activity and thus caffeine plasma clearance are smoking, coffee consumption and oral contraception.

Therefore the CYP1A2 turnover number kcat was optimized during the model fitting. Caffeine model personalization slightly improved the PK profile prediction.

Compound	caffeine	midazolam
Dose	50 mg	1 mg
Substrate of	CYP1A2	CYP3A4
Metabolite Measured	paraxanthine	1-hydroxymidazolam
Fraction Unbound	70%	1.6%
Lipophilicity	-0.07	3.13
Molecular Weight	194.2 g/mol	325.77 g/mol

	Reference Individual	Personalized Models
Base Model Expression	0.40 90.8 %	0.62 92.8 %
Fitted Expression	0.72 97.0 %	0.78 97.0 %

Concordance correlation coefficient
% of the Data in 2-fold range

Conclusion & Outlook

PBPK model personalization with biometric features was systematically evaluated for two compounds, midazolam and caffeine. The prediction accuracy for midazolam slightly decreased upon incorporation of biometric features, but slightly improved for caffeine. Caffeine distributes very well to all tissues. It can be assumed that its pharmacokinetics is more closely related to body weight than that of midazolam. Therefore it seems reasonable that prediction accuracy increased when body weight was considered in the simulation.

Both PBPK models are very sensitive to CYP activities and expression. CYP activites are variable between subjects but cannot be readily measured. Simulation of the base model, that uses a mean CYP activity or expression, described the observed PK profiles reasonably well (with at least 75% of the data within the 2-fold range). Parameter fitting strongly improved the prediction accuracy. Fitted parameter values for CYP3A4 expression tended to be slightly higher for the personalized models.

Acknowledgements

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