

Towards pharmacokinetic profile predictions for small molecules using machine learning derived parameters and compartmental modeling

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INTRODUCTION

The prediction of *in vivo* plasma pharmacokinetic (PK) profiles for new small molecules is a large challenge in drug discovery. Several model-based (hybrid) PK prediction approaches were published which differ in their complexity and combination of machine learning (ML) and mechanistic modeling. Prediction models are trained on noncompartmental analysis (NCA) parameters as clearance (CL) and volume of distribution (Vss) predicting a monophasic PK curve [1]. Another approach uses a physiologically based PK (PBPK) model which is parameterized with ML predicted physicochemical parameters, see [1] and references therein. Approaches without mechanistic models make use of PK profiles as input and predict the PK profile using trained neural networks [2-3]. Our proposed hybrid approach based on empiric PK models and ML predicted parameters is embedded between approaches using NCA and mechanistic PBPK models. A similar approach was recently published lacking the consideration of a classifier selecting the best empirical PK model for a molecule [4].

Objective

- Development of a PK prediction approach to support compound selection in drug discovery
- PK-prediction-guided compound selection for *in vivo* testing
- Replacement of *in vivo* studies with PK prediction workflow

PK prediction workflow



RESULTS

1. NCA

Figure 1: Goodness of fit plot.

One compartment PK simulations with Vss and CL from NCA for every compound and study.

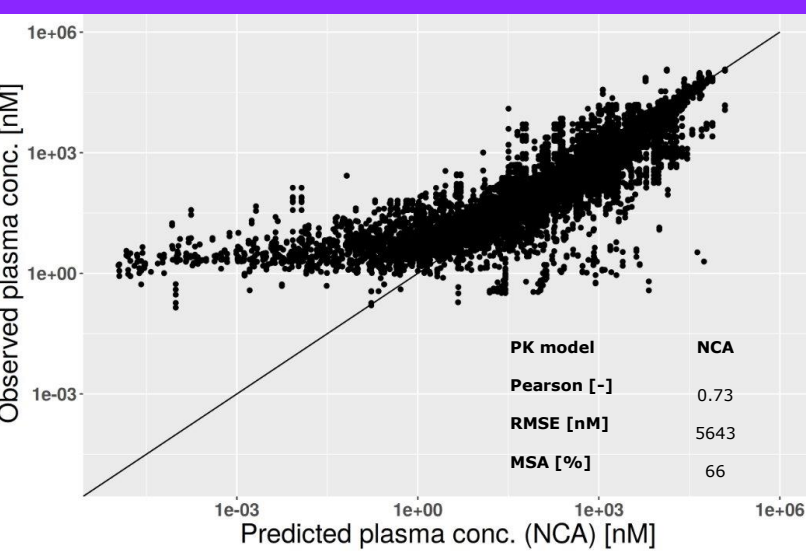


Table 1: Summary statistics of parameters Vss and CL from automated NCA.

	1 st Qu	Median	Mean	3 rd Qu
Vss [L/kg]	0.744	1.94	6.27	5.94
CL [L/(h kg)]	0.477	1.20	2.54	2.50

PK simulations with one compartment PK model parametrized by Vss and CL from NCA adequately describe PK profiles besides trough concentrations from non-monophasic PK profiles.

2. PK model fitting & 3. Selection of best model

Table 2: Distribution of compartmental models depending on CV% and based on lowest RMSE.

CV [%]	10	20	30	40	50	60	70	80	90	100
One	183	257	280	271	253	245	233	219	205	192
Two	18	45	76	129	161	197	219	247	270	290
Three	120	253	315	360	392	402	411	410	412	408
Sum	321	555	671	760	806	844	863	876	887	890

Figure 2: Boxplot of ratio between observed vs. predicted AUC, C_{max} and C_{last}. Predicted values were derived from PK simulations with best PK model and estimated parameters.

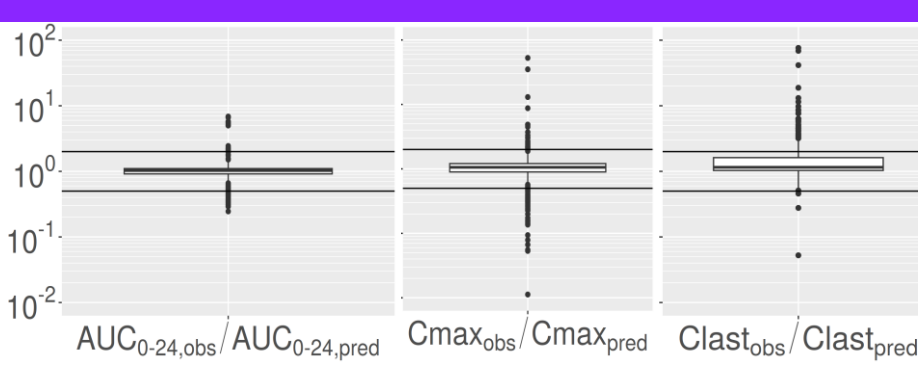
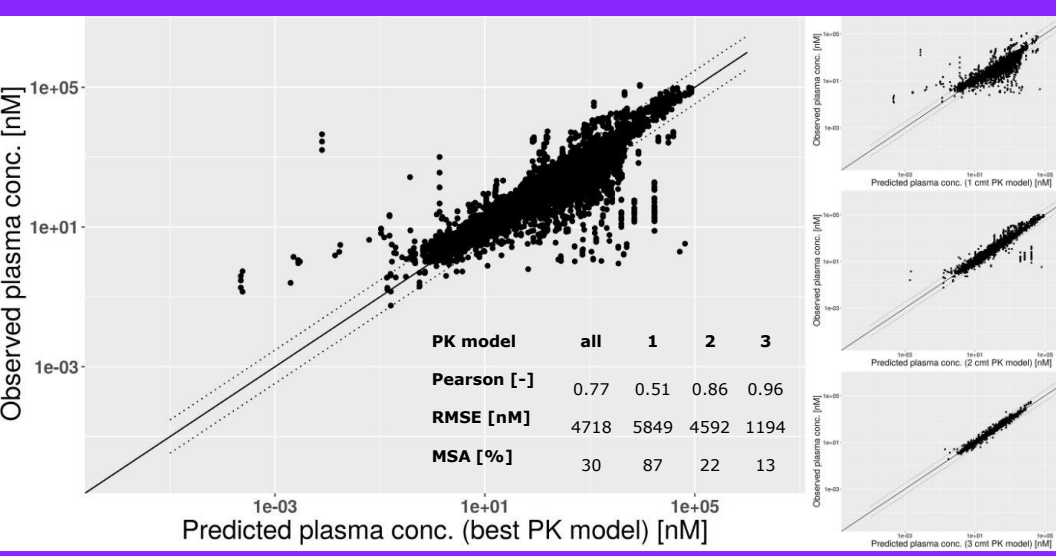


Figure 3: Goodness of fit plot using best PK model.

PK simulations with best PK model and estimated parameters for every compound and study.



PK simulations with best PK model and estimated parameters adequately describe PK profiles and outperform NCA simulations regarding the description of non-monophasic profiles.

PK model classifier

Table 3: Accuracy of three different classifier for 1 vs. 2 compartment model.

Algorithm	Train	Test	Validate
Logistic Regression	0.69	0.66	0.63
K-nearest neighbors	0.71	0.70	0.63
Gradient boosting	0.70	0.66	0.62

Table 4: Accuracy of three different classifier for 1 vs. 2 vs. 3 compartment model.

Algorithm	Train	Test	Validate
Logistic Regression	0.81	0.46	0.55
K-nearest neighbors	0.61	0.44	0.45
Gradient boosting	0.73	0.39	0.52

Classifier have a low validation accuracy.

Graph convolutional networks to predict PK parameters

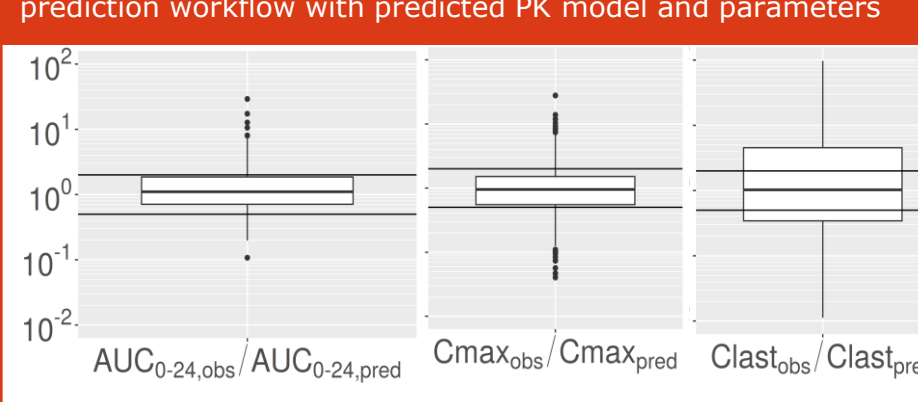
Table 5: Three metrics separated into training, test and validation set for predicted PK parameters.

	Mean pearson r2 score	Mean squared error	Mean absolute error
Dataset	Train Test Validate	Train Test Validate	Train Test Validate
Vss = V1+V2+V3	0.77 0.63 0.75	0.08 0.11 0.11	0.22 0.25 0.25
V1	0.75 0.56 0.65	0.11 0.23 0.21	0.26 0.37 0.38
V2	0.75 0.71 0.76	0.15 0.16 0.14	0.30 0.28 0.30
V3	0.51 0.78 0.71	0.28 0.24 0.30	0.42 0.42 0.43
CL	0.78 0.40 0.59	0.08 0.23 0.17	0.21 0.37 0.28
CL2	0.90 0.77 0.67	0.08 0.23 0.27	0.22 0.37 0.40
CL3	0.30 0.76 0.36	0.36 0.26 0.39	0.50 0.45 0.45

Prediction models have an overall acceptable validation accuracy.

PK prediction workflow

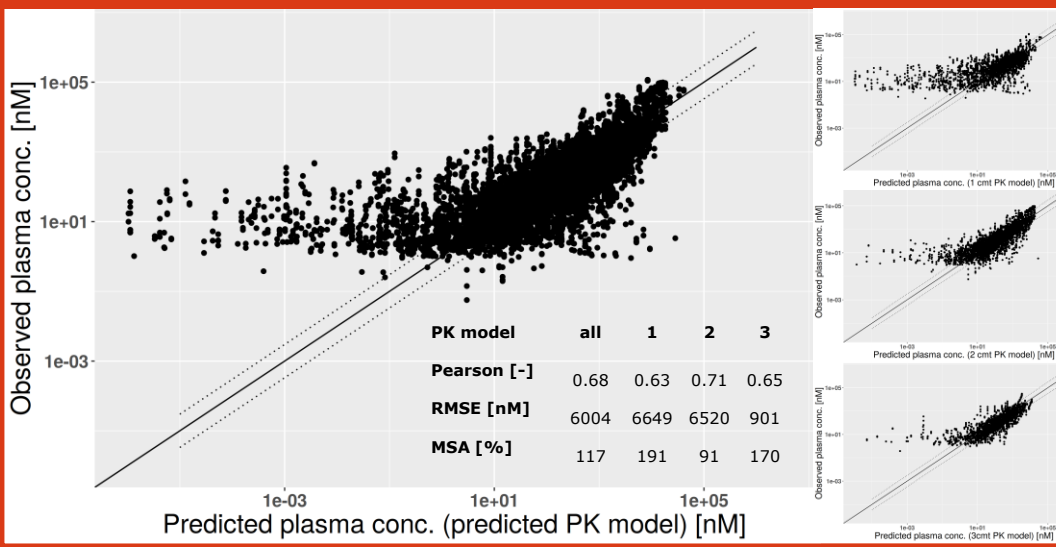
Figure 4: Boxplot of ratio between observed vs. predicted AUC, C_{max} and C_{last}. Predicted values were derived from PK prediction workflow with predicted PK model and parameters



PK predictions with PK models from logistic regression classifier and PK parameters from GCNs adequately describe PK profiles with predicted AUC and C_{max} values within a 2-fold error. C_{last} predictions range between ~ 3-5 fold errors.

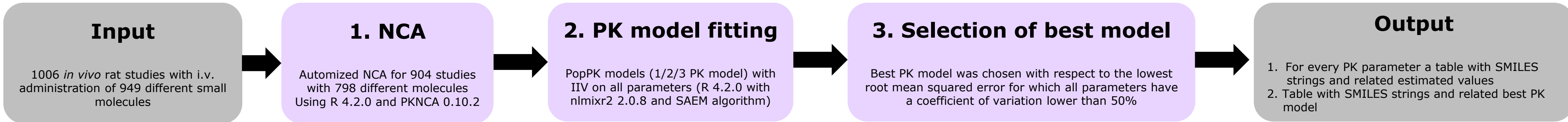
Figure 5: Goodness of fit plot for PK prediction workflow.

PK simulations were performed with predicted PK model and predicted parameters for every compound and study.



METHODS

Noncompartmental analysis & PK modeling



Machine learning

Development of PK model classifier

3 different classifiers were tested

- Logistic regression / K-nearest neighbors / Gradient boosting

Dataset with best PK model for each SMILES string was splitted into training and test sets with a split of 85% and 15%. Training set is further splitted into training and validation sets with a split of 85% and 15%. Stratified 20-folds cross-validation was used and hyperparameter optimization.

Development of 6 separate graph convolutional networks to predict PK parameters

For every PK parameter a separate graph convolutional network was trained with the estimated values from the parameter estimation as input. The datasets were divided into training, validation and test sets with a split of 80%, 10%, 10%, respectively. Here, splitting was done using a chemical diversity-based algorithm (Min-Max-Picking as implemented in RDkit). Models were optimized by monitoring the Pearson correlation score (PCS) for the test dataset. For tuning the hyperparameters, several models with different hyperparameter combinations were build and tested [5]. The best performing method was used for further calculations. Training was stopped if the loss of PCS did not improve for 20 subsequent steps (early-stopping).

Conclusion & Challenges

- Our work presents a **workflow to predict PK profiles** of small molecules **using predicted PK models via a classifier** together with **predicted PK parameters via GCNs**. The workflow was developed and tested on rat PK data and provides **predicted AUC and C_{max} values within a 2-fold error. C_{last} predictions range between ~ 3-5 fold errors**.
- Challenges, which impact the prediction accuracy and are part of future research to improve overall PK prediction accuracy and particularly prediction of trough concentration are a relatively small dataset, an un-even distribution of best PK models, the prediction of best PK model and the separation of PK parameters of second and third compartment into four categories (small vs. large volume and fast vs. slow intercompartmental clearance).

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