

Berfin Gülave¹, Luke van Boven¹, Helle W van Maagdenberg¹, Elizabeth CM de Lange¹, JG Coen van Hasselt¹

¹Division of Systems Pharmacology and Pharmacy, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands;

LACDR

Introduction

- The **rate** and **extent** of blood-brain barrier (BBB) transport are **critical parameters** for central nervous system (CNS) drug distribution.
- The unbound drug partition coefficient $K_{p,uu,BBB}$ is an **essential-parameter** required for generating predictions for CNS drug disposition using PBPK modelling approaches.
- Quantitative structure-property relationship (QSPR) models can be used to **predict** $K_{p,uu,BBB}$ values for novel compounds¹⁻³.

Aims

- To **develop** a QSPR model to predict $K_{p,uu,BBB}$ values.
- To **integrate the developed QSPR** model in a previously established CNS PBPK model (**LeiCNS-PK3.0**)⁴.

Methods

QSPR model development

- Rat $K_{p,uu,BBB}$ values were collected for 98 compounds by an extensive literature search.
- 2D and 3D physico-chemical and structural properties of the drugs were calculated using the Molecular Operating Software (MOE).
- The dataset containing $K_{p,uu,BBB}$ and 2D and 3D properties was split randomly in 80% train set and 20% test set.
- Multiple machine learning algorithms, such as random forest, support vector machines, K-nearest neighbors, and (sparse-) partial least were trained on the train dataset.

Integration of the QSPR model predicted $K_{p,uu,BBB}$ into the LeiCNS-PK3.0

- CNS PBPK model was demonstrated for 6 drugs.

Results

QSPR model – Random forest

- A random forest model showed the best fit with a prediction error (R^2) of 0.511 and root mean square error (RMSE) of 0.542 (**Fig 1**).
- Prediction errors were 72.5% and 88.8% for 2-fold and 3-fold errors compared to the observed data.
- Ionization potential, electronegativity and molecule energy were identified as most important drug properties.

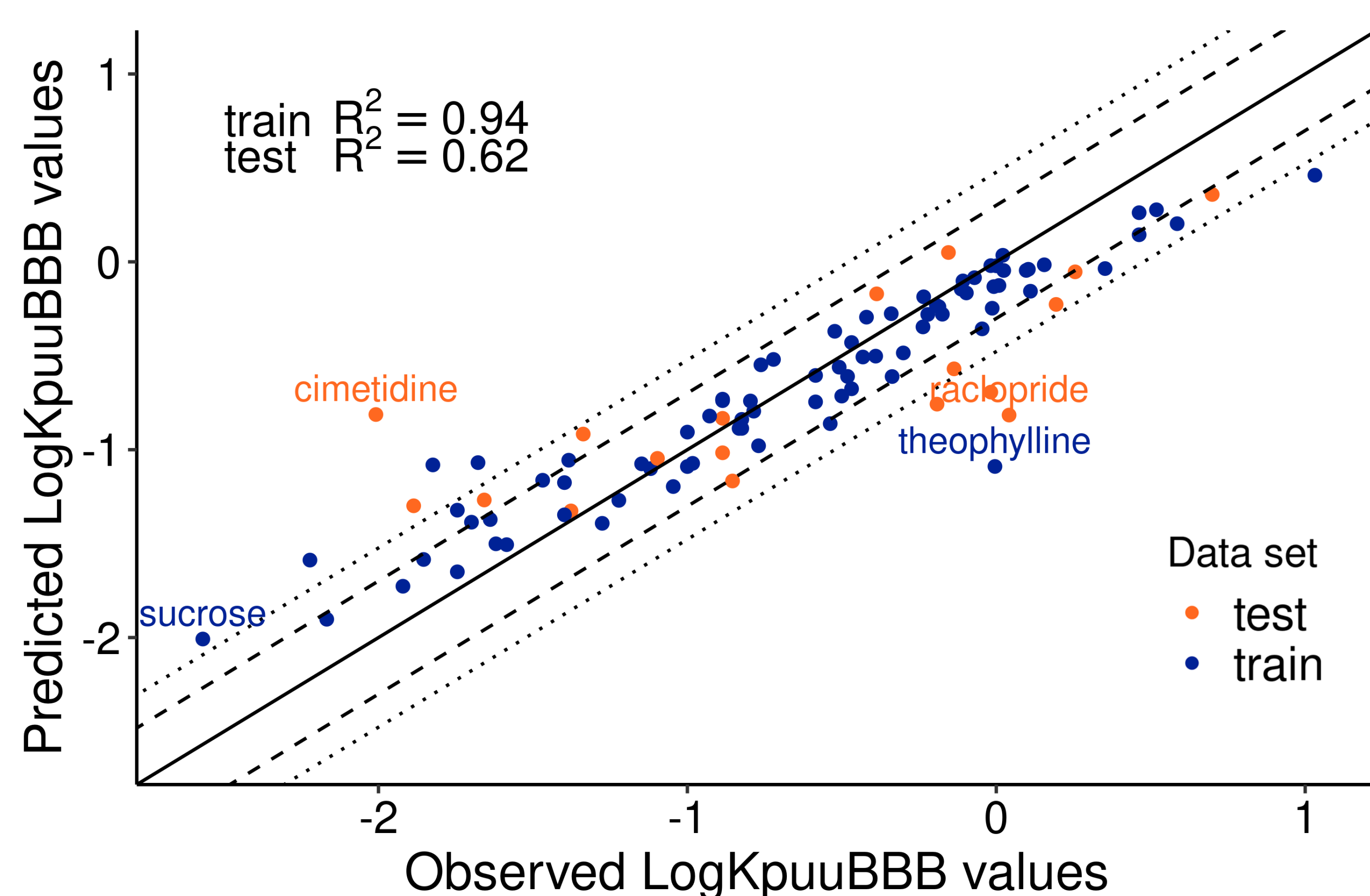


Figure 1. Observed versus predicted with Random Forest model $\log K_{p,uu,BBB}$ values for train and test data. The prediction error (R^2) of both datasets is given in the left top corner. The dataset was 98 compounds were randomly split in 80% train set and 20% test set.

Integration of predicted $K_{p,uu,BBB}$ values in LeiCNS-PK3.0

Most of the drugs had overlapping predictions with observed measured datapoints using the LeiCNS-PK3.0, raclopride is an exception (**Fig 2**).

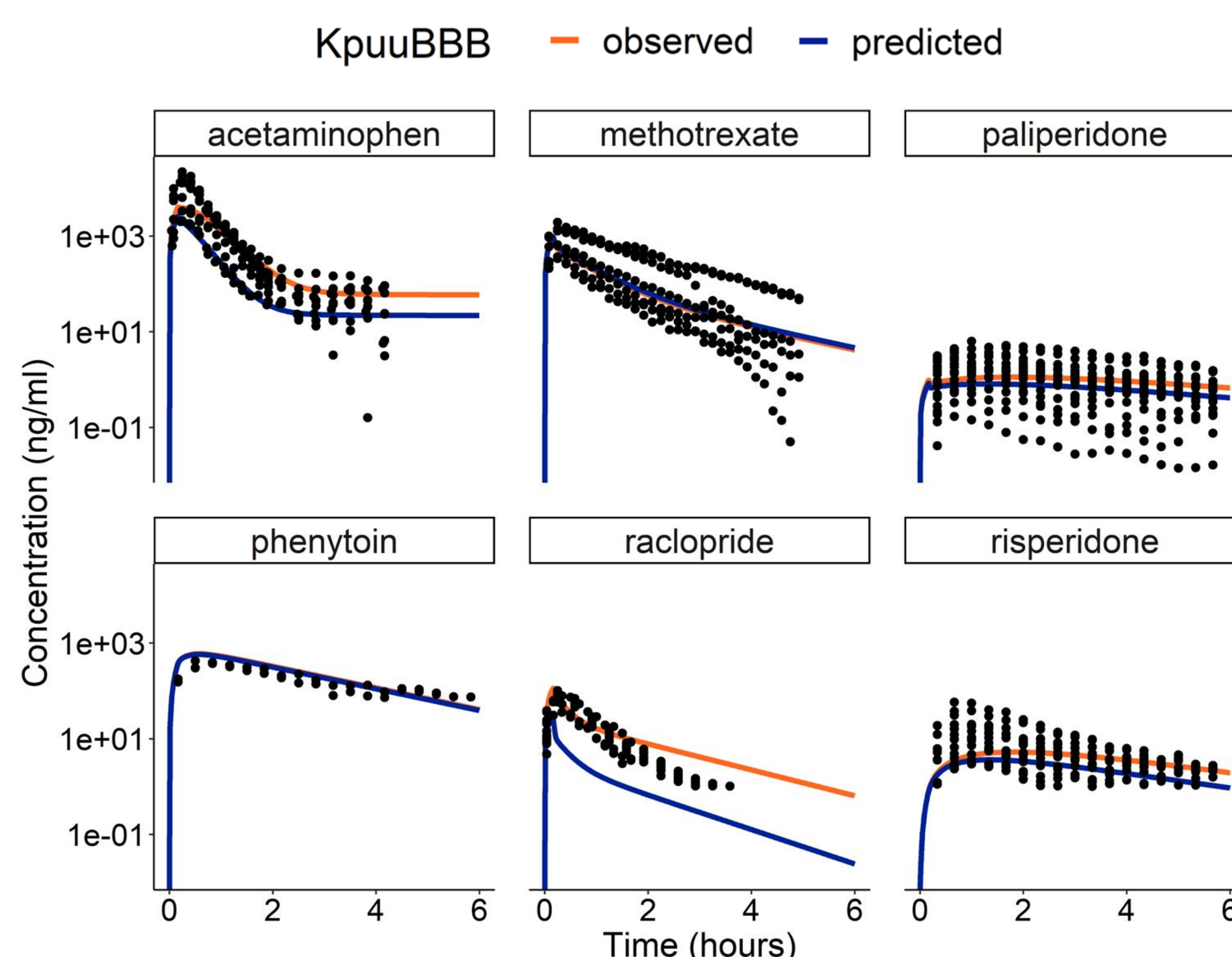


Figure 2. Concentration-time profiles of six drugs at the rat brain extracellular fluid (brain_{ECF}). Simulations were performed with the observed and predicted $K_{p,uu,BBB}$ value for acetaminophen, methotrexate, paliperidone, phenytoin, raclopride and risperidone.

Conclusions

- The developed QSPR model for prediction of $K_{p,uu,BBB}$, **adequate** predictive performance was demonstrated.
- The in silico $K_{p,uu,BBB}$ predictions can be used in CNS PBPK models, such as **LeiCNS-PK3.0**, **reducing animal experimentation**.
- For 5 out of 6 drugs evaluated, the random forest QSPR model shows **adequate performance** on $K_{p,uu,BBB}$ prediction.
- The QSPR model can be further **used for support** in drug discovery and development.

References

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