

How should target-mediated drug disposition (TMDD) model be used for predicting receptor occupancy?

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Introduction

Assessing target engagement is important for understanding drug action and selecting dosing regimens. Full TMDD models and its approximations – quasi-steady state/quasi-equilibrium (QSS/QE) and Michaelis-Menten (MM) models – have often been used to describe drug-target interactions, and, at times, receptor occupancy (RO) e.g. via MM model parameter K_M based only on drug concentration data.¹⁻⁵ However, there is still a lack of understanding about how TMDD model should be used for predicting RO accurately. We used simulations based on a model from literature⁶ to investigate the issue.

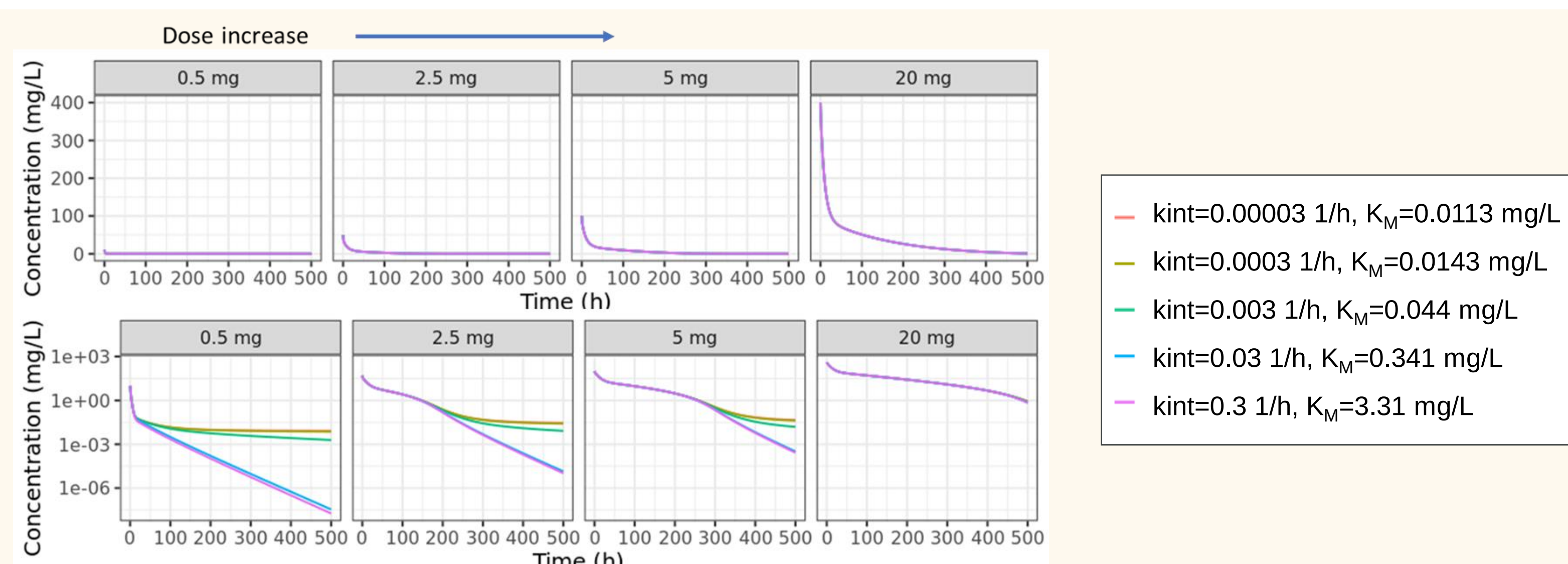
Objectives

To investigate if RO can be predicted using only drug concentration data and test if incorrect assumption of binding locations – central or peripheral – would influence the prediction of RO.

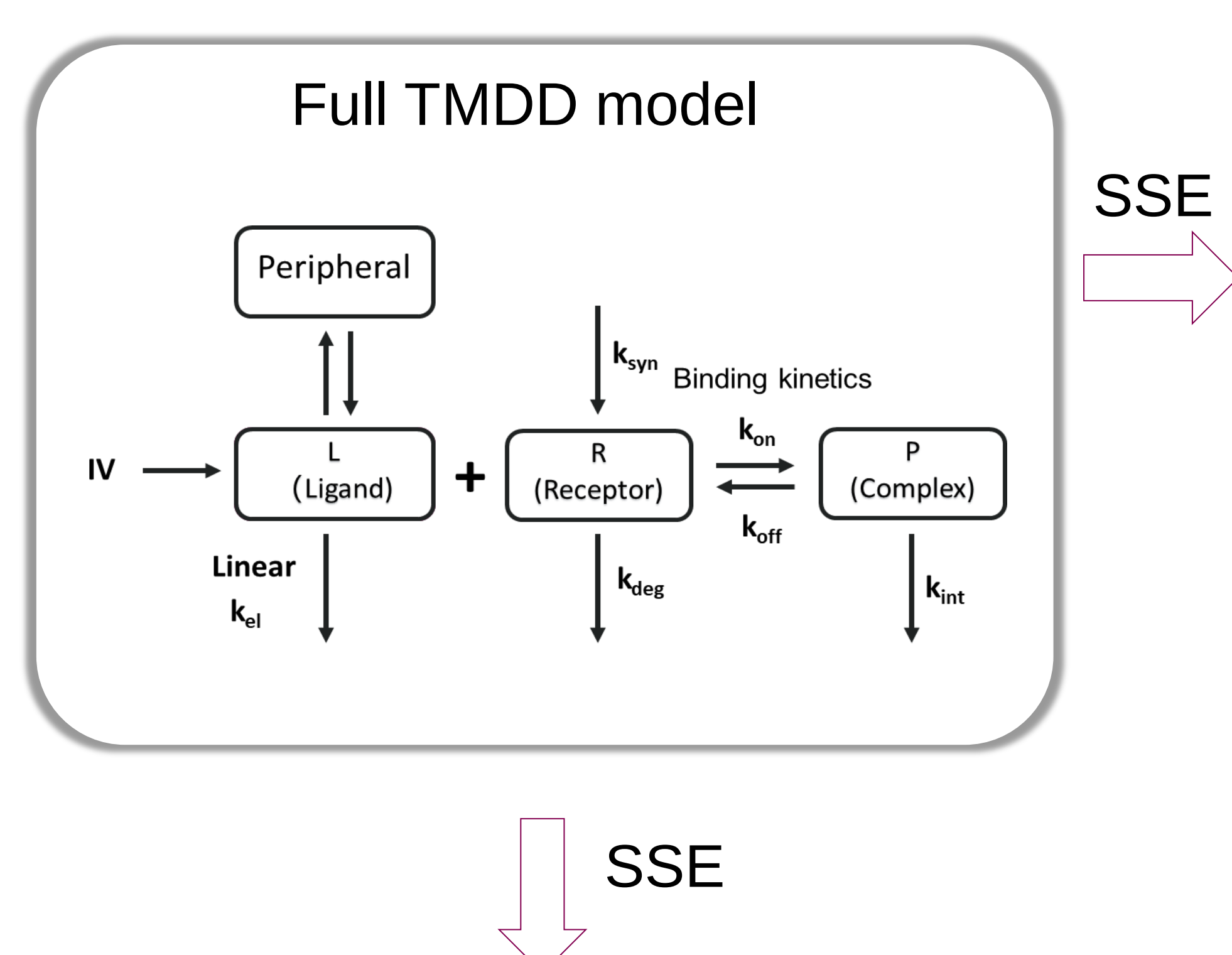
Sensitivity to K_M

The receptor-ligand complex internalization rate k_{int} was varied 10000 folds, which resulted in K_M changes of ~300 folds.

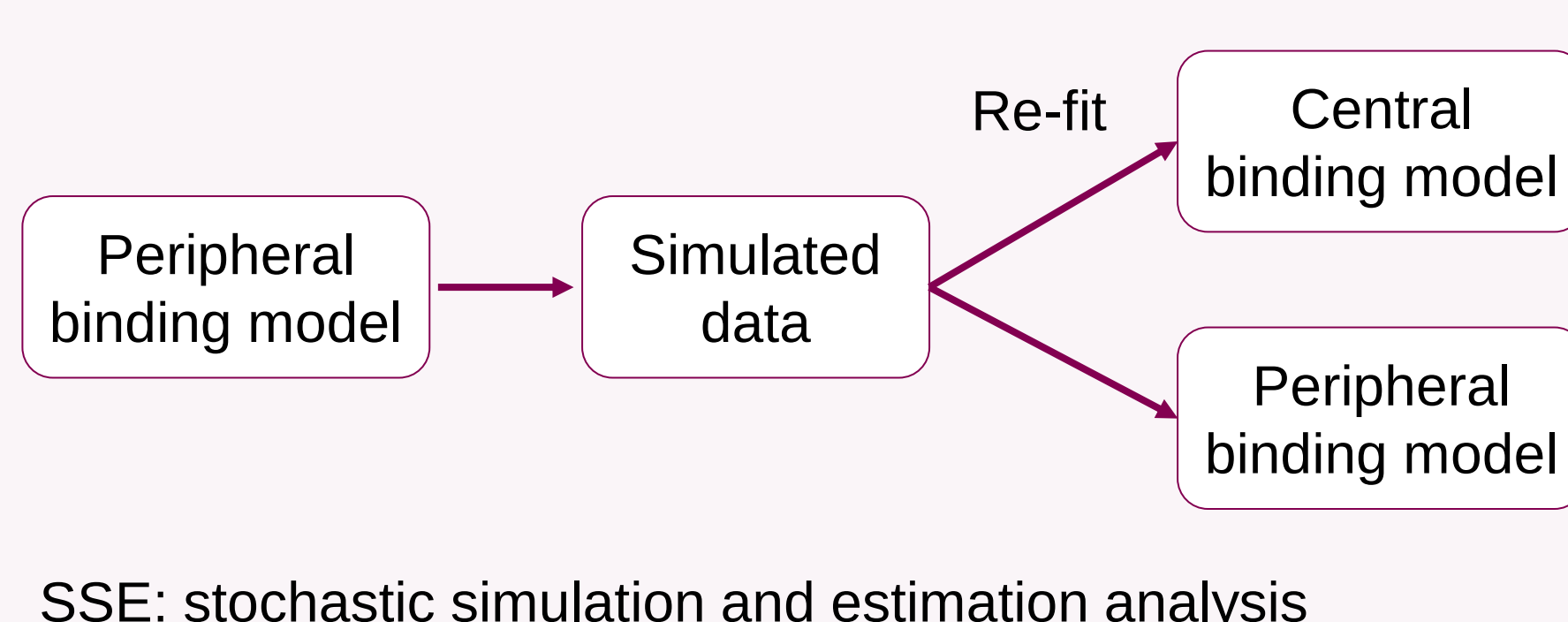
Concentration profiles are indistinguishable in the raw scale with different magnitudes of K_M , showing that K_M cannot be accurately estimated based only on drug concentration data.



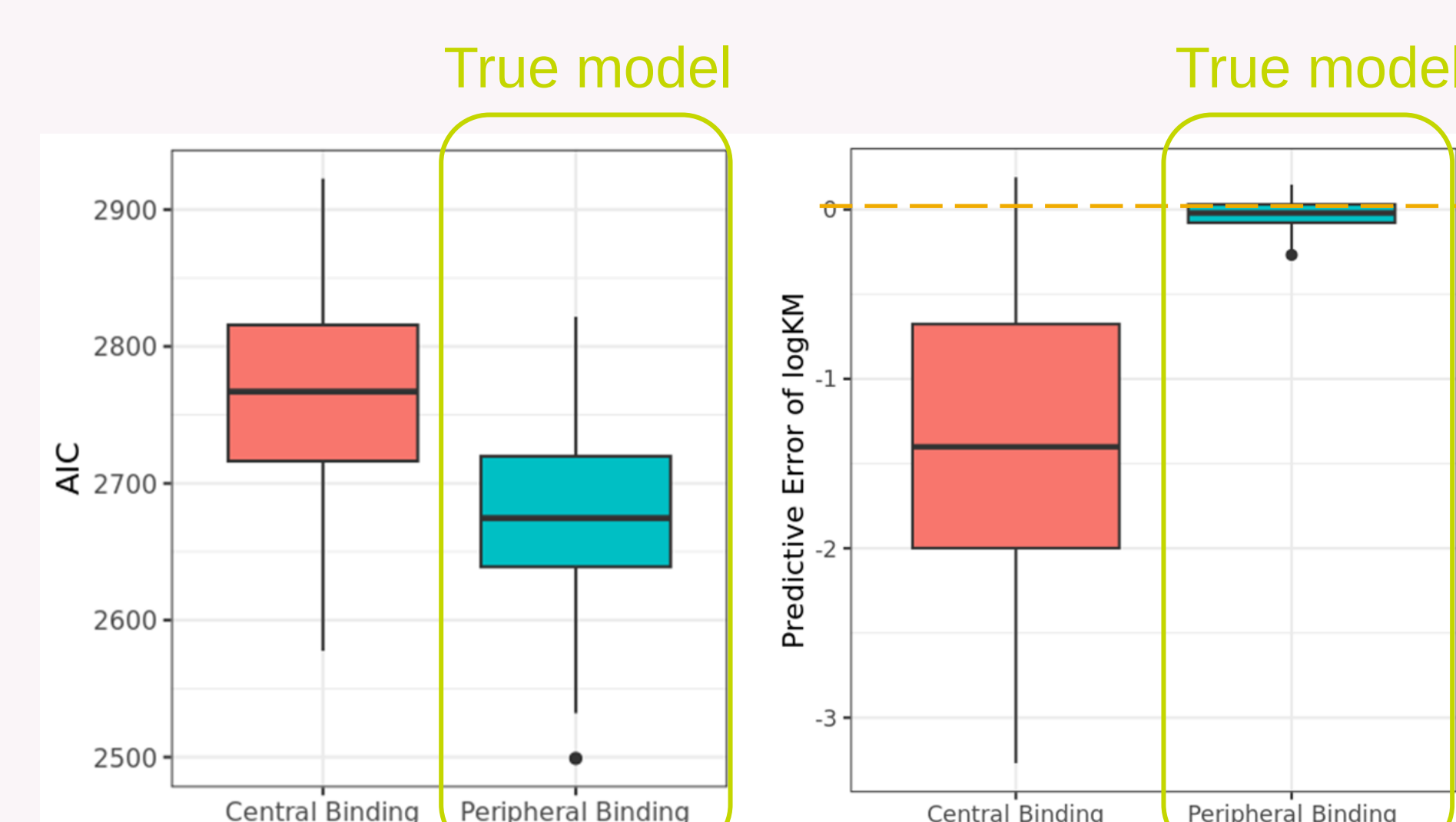
Simulation



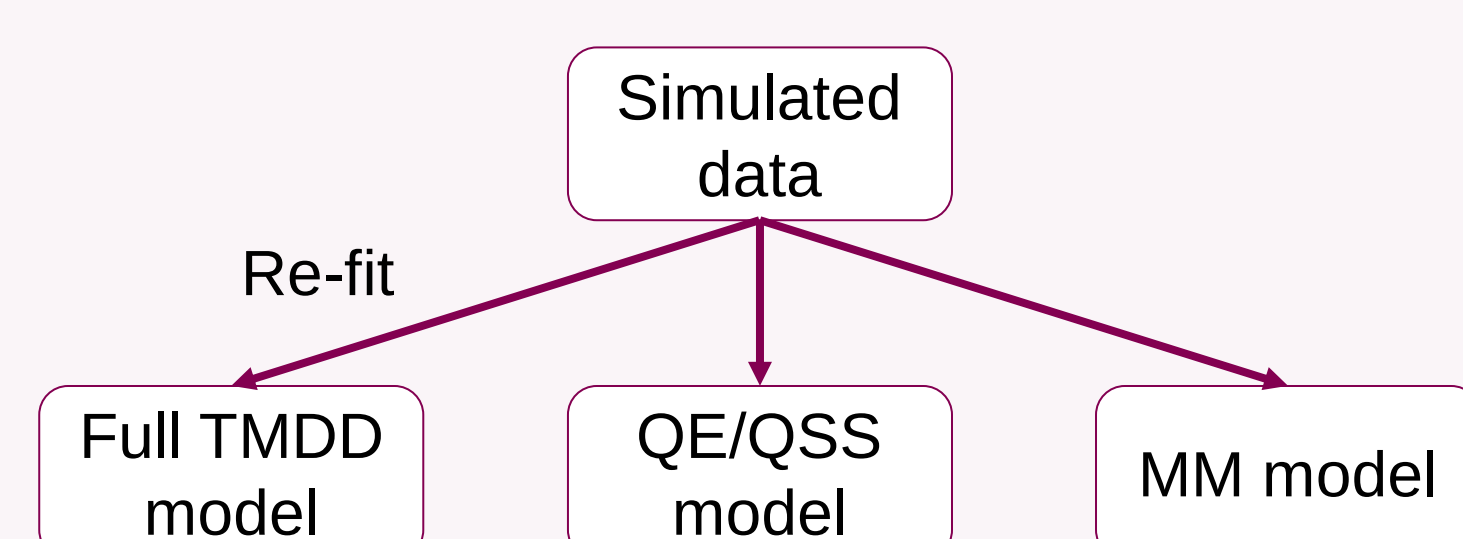
Assessment of the impact of receptor-ligand binding location on K_M



Wrong assumption of the binding compartment could lead to increased AIC and worse accuracy/precision of the K_M parameter



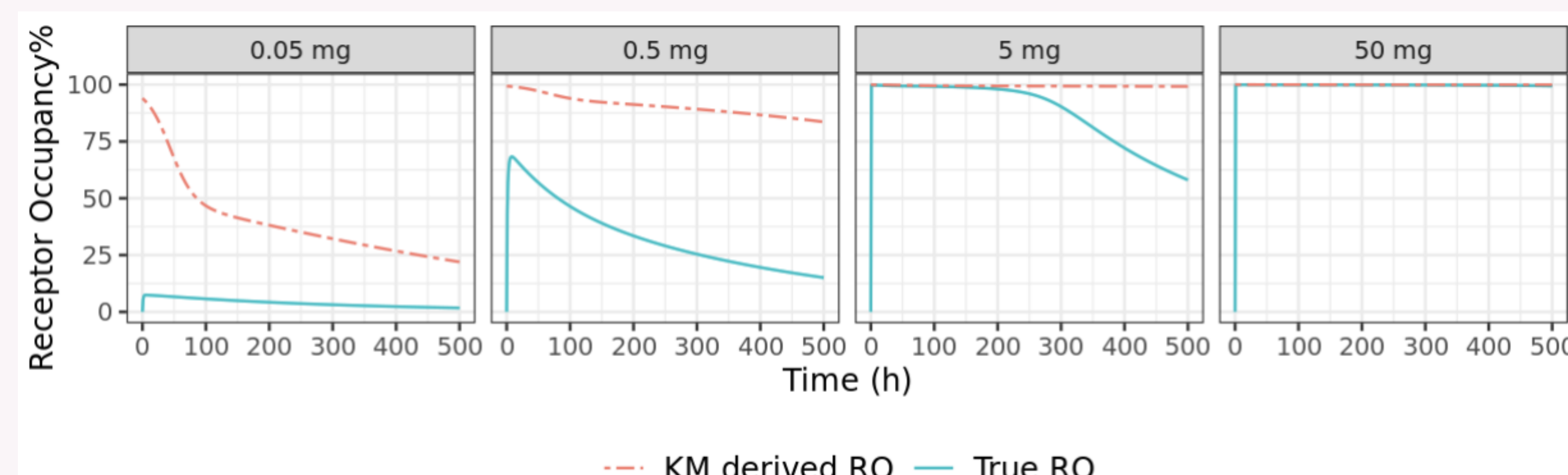
Evaluation of the estimation performance of K_M using different TMDD models



$$K_M \text{ derived RO: } RO\% = \frac{C}{K_M + C} \cdot 100\%$$

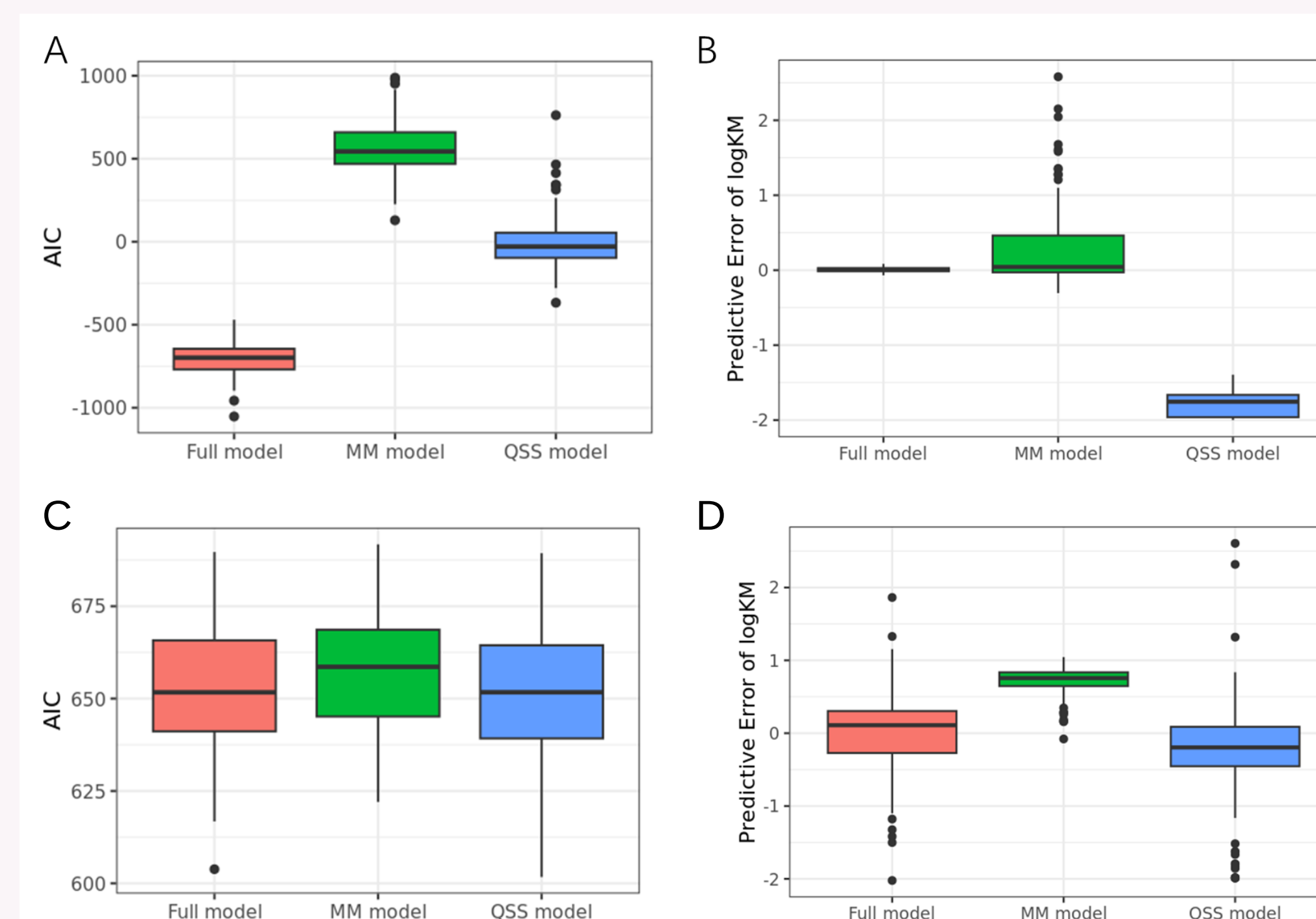
$$\text{True RO: } RO\% = \frac{RC}{R_{total}} \cdot 100\%$$

Time-dependent RO profiles are at times different using K_M -derived RO in MM model and the true RO in full TMDD model. Therefore, RO calculated using K_M in MM model could be inaccurate.



Using intensive PK data (A and B): full model performed the best, as expected

Using sparse PK data (C and D): MM model showed a similar AIC as the full TMDD model, but the estimated K_M had over 5-fold bias



Conclusions

- K_M from an MM model may not be a suitable parameter for RO calculation with only drug concentration data.
- Model performance (AIC) does not guarantee parameter accuracy.
- Full TMDD models, if not overparameterized, should be considered initially.
- Incorrect assumption of binding locations could result in inaccurate prediction of RO.