

Bayesian workflow for minimal PBPK modeling: a case study with dapagliflozin

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Introduction

- Dapagliflozin is a sodium-glucose cotransporter-2 inhibitor originally developed for the treatment of type 2 diabetes mellitus and subsequently approved in several other indications, including heart failure and chronic kidney disease [1]. More than 300 clinical trials have been conducted and multiple PK models were published with various degrees of mechanistic complexity.
- Integration of the accumulated prior knowledge into a single quantitative mathematical system may serve as a powerful tool for decision-making in post-approval activities (e.g., local registration or life cycle management).

Aim

The aim of this research is to create an integrative Bayesian workflow for the development of minimal physiologically-based pharmacokinetic (PBPK) models based on the open-source aggregated clinical data and previously developed mathematical models and benchmark it in three different software packages using dapagliflozin PK as a case example.

Methods

Systematic Literature Review

A systematic literature search was conducted following the best practices described in [2] across PubMed and ClinicalTrials.gov databases. Two search queries were formed to identify all available dapagliflozin PK data and existing PK models. Renal filtration model was adopted from the Sokolov et al. [3].

Model Calibration and Diagnostics

- Data from parallel-group clinical trials were used for model calibration.
- Parameters were estimated using three Bayesian modeling packages: Nimble (v1.1.0) with R_xODE2 (v2.1.2), MCSim (v6.2.0), and Stan (v2.32.6) with Torsten (v0.89.0).
- Numerical criteria used for model diagnostics and program comparison:

Convergence Check	Sampling Efficacy
$\hat{R} = \sqrt{\frac{\text{Dispersion across chains}}{\text{Mean dispersion in one chain}}}$ $\hat{R} > 1.05$ – bad convergence	$N_{eff} = \frac{N}{1 + 2 \sum_{t=1}^{inf} \rho_t}$ $\hat{E} \sim N\left(E, \frac{\sigma}{\sqrt{N_{eff}}}\right)$ ρ_t – autocorrelation with offset t $\hat{R} < 100$ per chain – bad efficacy
Fit to Data	
$WAIC = -2(lppd - pWAIC)$ $lppd$ – logarithm of posterior predictive posterior density in the observed datapoints $pWAIC$ – effective number of model parameters	$mKS = \frac{1}{n} \sum_{i=1}^n \sup_x F_o(x_i) - F(x_i) $ F_o – cumulative probability function of the observed data, F – cumulative probability function of the posterior predictive

Model Validation and Evaluation

- The model was validated using dapagliflozin urine recovery and PK data from clinical trials with a cross-over design.
- Local sensitivity analysis was conducted using the one-at-a-time method.

Results

Structural Model Development

- Dapagliflozin PK data were collected and digitized from 18 clinical trials (38 study arms, 8 dosing levels, 578 participants in total).
- A two-compartment PK model with transit compartments was selected for the analysis based on the evaluation of 10 dapagliflozin PK models identified through systematic literature review.

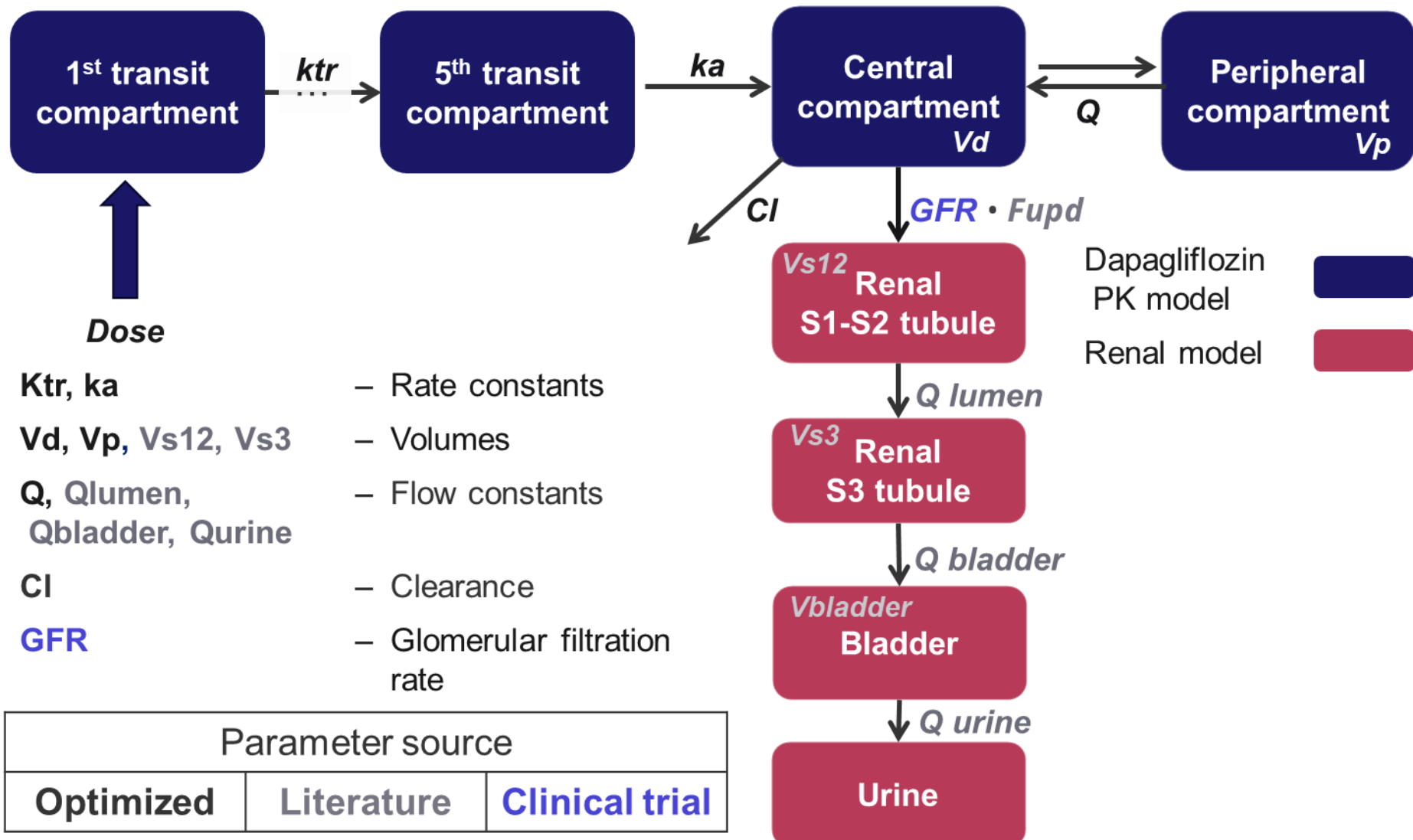


FIGURE 1. Schematic representation of the minimal physiologically-based dapagliflozin PK model structure

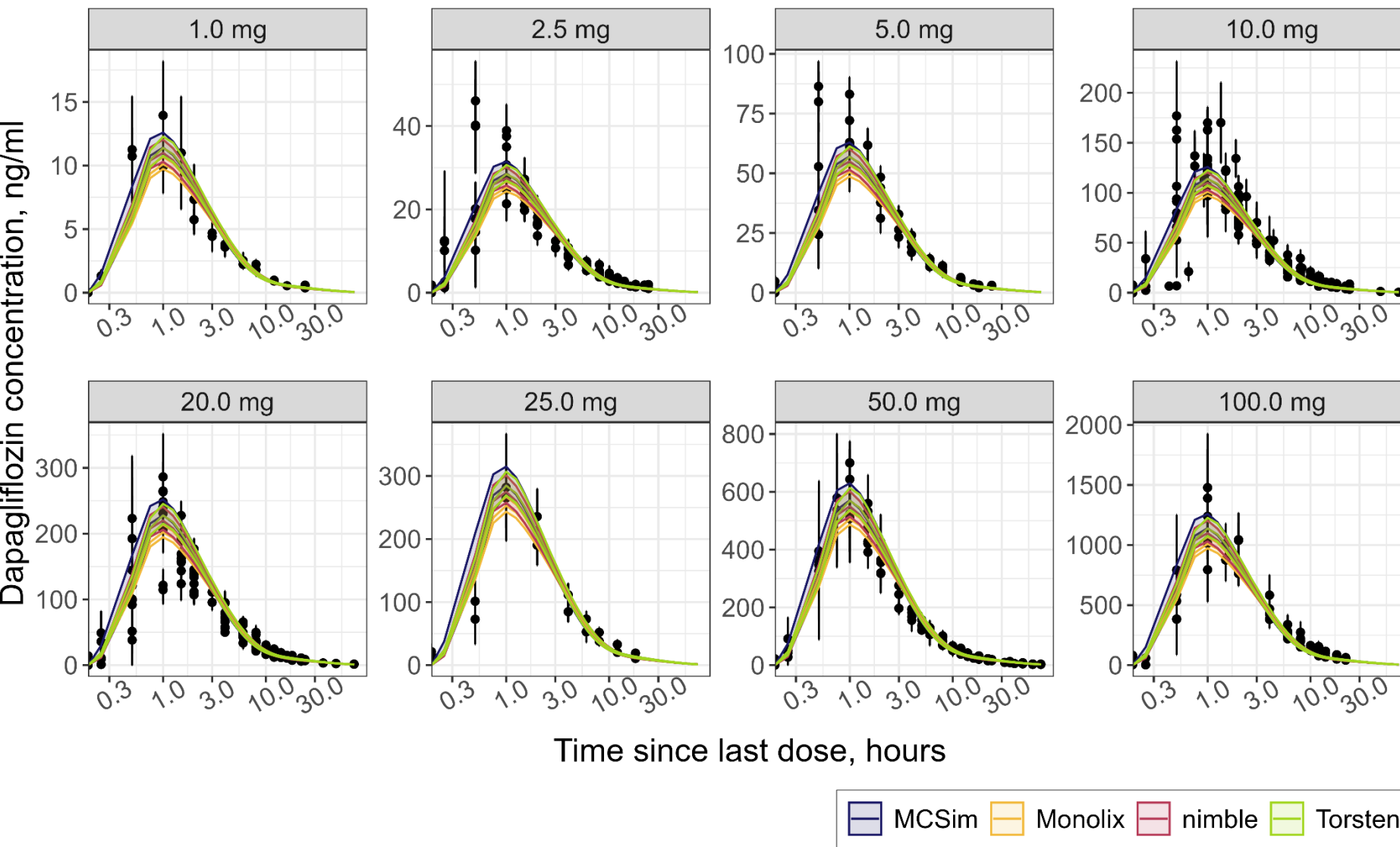
- For all parameters, except residual error variance, prior distributions were set to lognormal, with mean and deviance calculated by the following formula:

$$\bar{\theta}_j' = \log\left(\frac{\bar{\theta}_j^2}{\bar{\theta}_j^2 + \sigma_j^2}\right), \quad \sigma_j^2 = \log\left(1 + \frac{\sigma_j^2}{\bar{\theta}_j^2}\right)$$

$j \in \overline{1..K}$, K – number of parameters in the model,
 $\bar{\theta}_j$ is the weighted average of j^{th} model parameter,
 σ_j^2 – the weighed variance of j^{th} parameter,
 $\bar{\theta}_j$ – mean value of the prior distribution of model parameters.

For residual error variance, a uniform prior distribution within the (0, 100] range was set.

Model Calibration and Diagnostics



Black dots with error bars – observed mean (95% CI) PK stratified by study and dose; solid lines with shaded area – median (95% CrI) of predicted posterior distribution.

FIGURE 2. Observed and predicted change over time in plasma dapagliflozin concentration

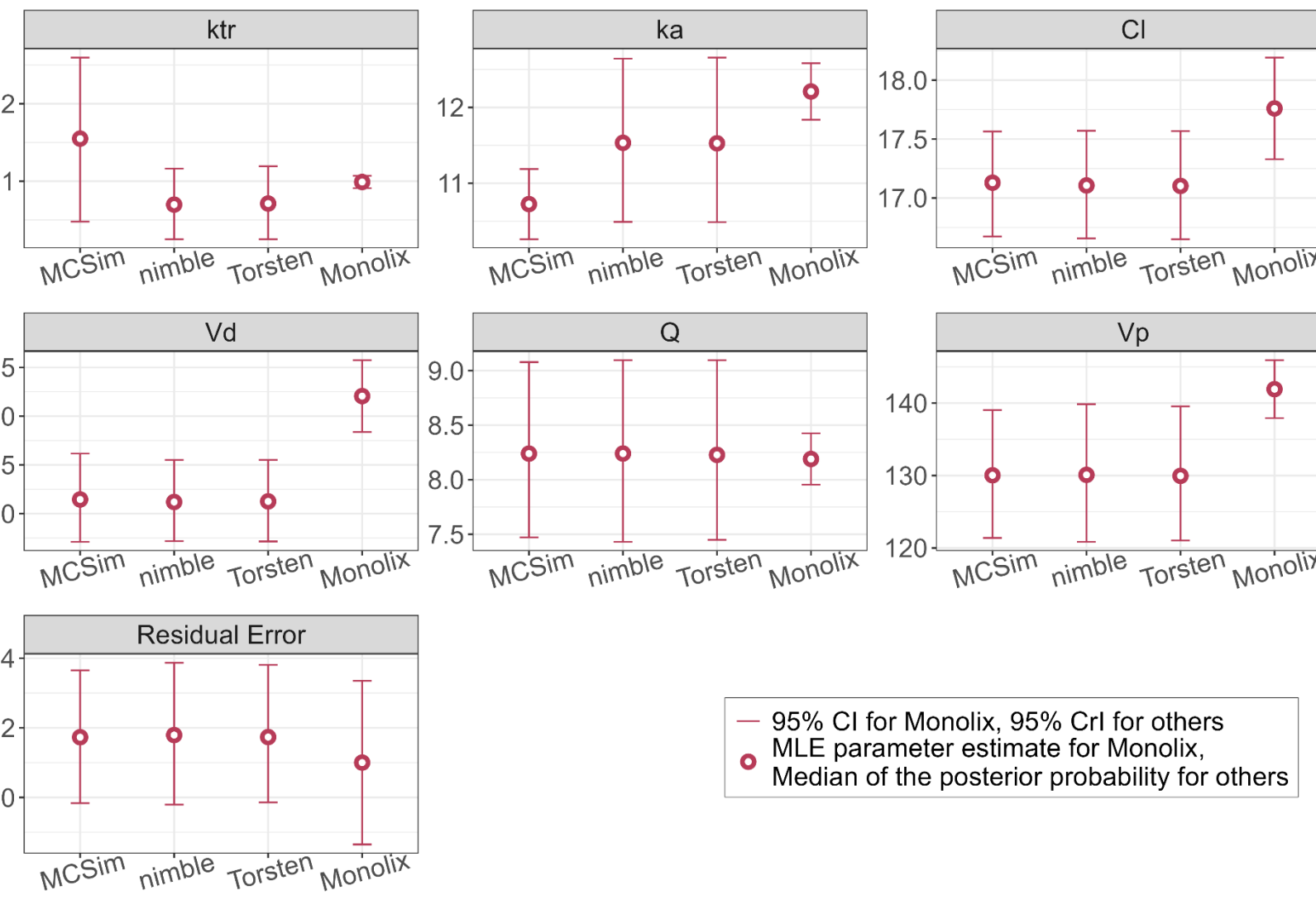


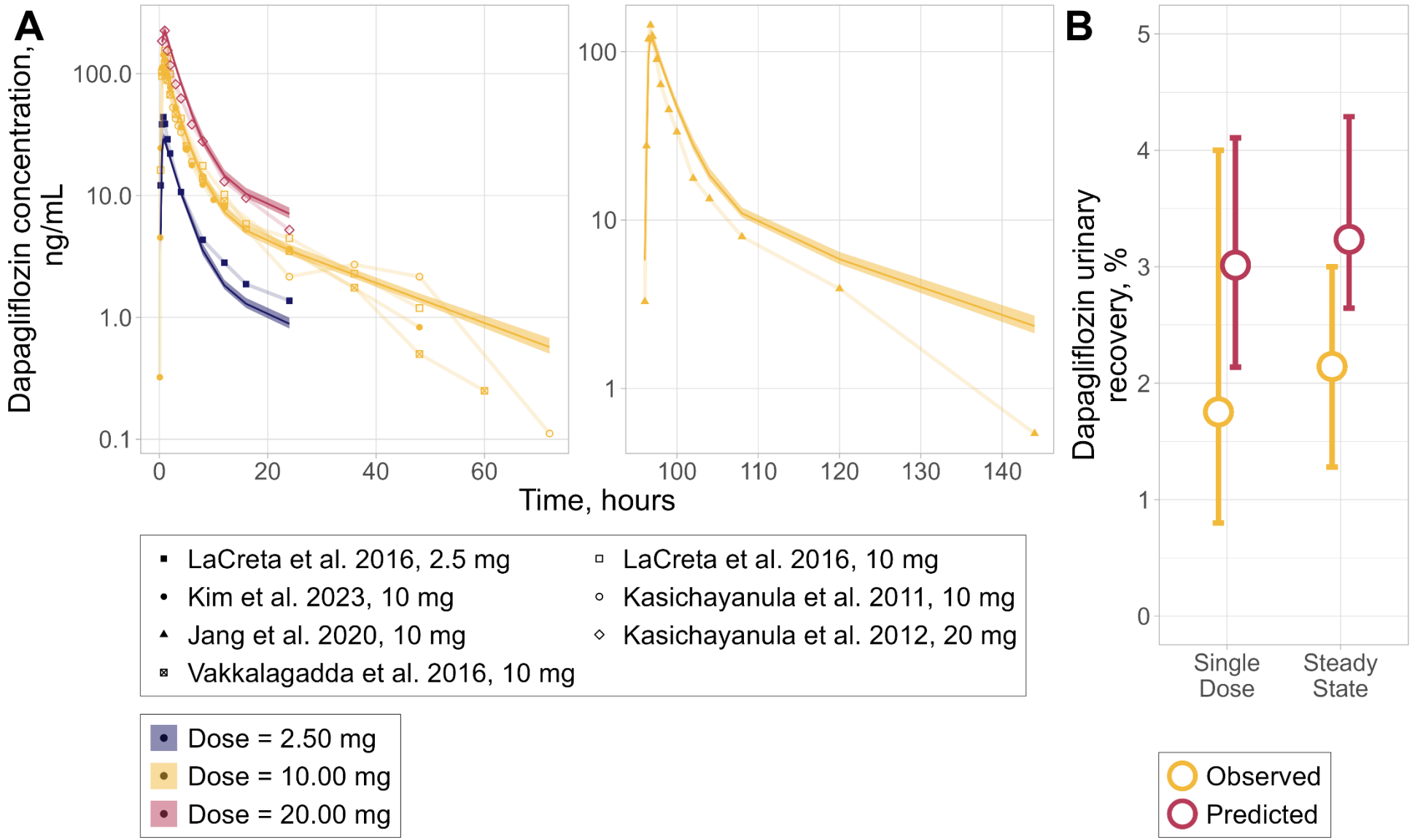
FIGURE 3. Posterior distributions of the estimated parameters obtained by different software

	WAIC	mKS	Mean Tail-ESS	Mean bulk-ESS	One chain of 5000 nodes calculation time, h
MCSim	4713.2	0.6615	1605.7	1226.8	0.22
Nimble	4721.6	0.6742	2070.1	1338.3	0.52
Torsten	4721.5	0.6738	9261.5	10944.6	1.75

Table 1. Performance of different software solutions

- 95% credible intervals (CrI), obtained by MCSim and Nimble, overlapped with the Torsten derived intervals.
- Posterior predictive distributions generated by different programs exhibited comparable descriptive performances: 95% CI of these distributions overlapped; WAIC metrics differed by less than 1%.
- Stan exhibited superior sampling efficacy compared to Nimble and MCSim – demonstrating a 5.1-fold increase in efficiency in the central posterior region and a 8.5-fold increase in the tails. However, this efficiency came at a cost, with Torsten requiring an average 5.7 times longer runtime.

Model Validation and Diagnostics



A – validation of the model based on the plasma PK data from the trials with crossover design. Dots – observed mean; solid lines with shaded area – median (95% CrI) of predicted posterior distribution, B – validation based on urinary recovery data (Dapagliflozin amount in urine / Dose * 100 %). Points with error bars – observed or predicted weighted mean (range).

FIGURE 4. Model validation using plasma PK and urinary recovery data

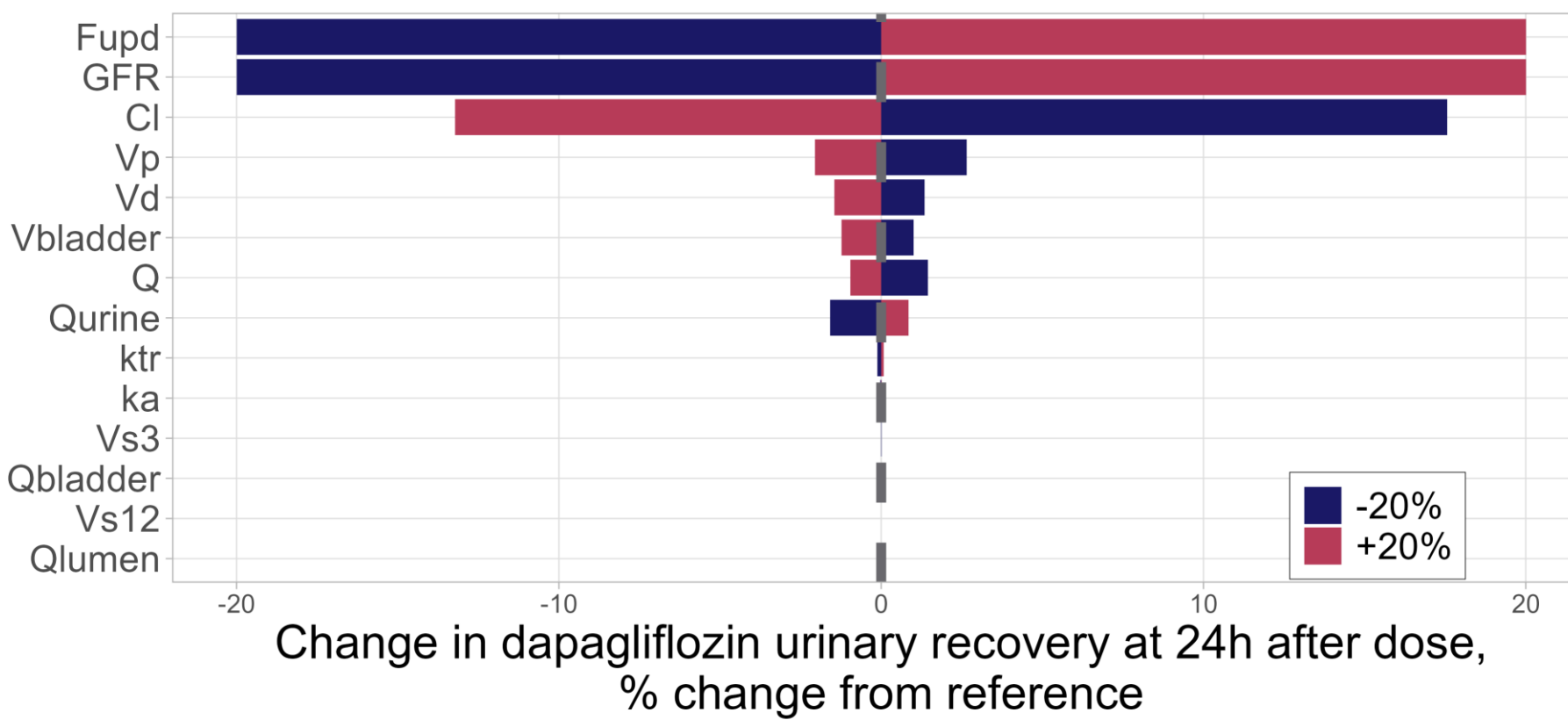


FIGURE 5. Local sensitivity analysis of model parameter influence on the UR

- The model describes dapagliflozin plasma PK data but overpredicts mean urinary recovery, which is most sensitive to the changes in Cl, GFR and the fraction unbound parameters.

Conclusions

In this work, we have created an integrative Bayesian workflow for the development of mPBPK models and implemented it in 3 different software solutions (Nimble, MCSim, Torsten), using dapagliflozin PK data and prior models as a case example. The packages provided identical posteriors for the estimated parameter, with Torsten exhibiting ~5 fold increased sampling efficiency compensated by ~5-fold slower calculation times. The workflow established in this research can be adapted for other types of mechanistic models, such as full PBPK or quantitative systems pharmacology models.

