Applying Sampling Importance Resampling to Improve Simcyp PBPK Models Predictions Performance

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Sampling Importance Resampling allows for integration of clinical data into PBPK model-based Simcyp simulations and performing predictive simulations

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Background and Objectives

Physiologically based pharmacokinetic (PBPK) modeling integrates in vitro and in vivo data to predict drug behavior. A key challenge is the model parameters uncertainty from limited or variable observed data; often addressed using clinical observations such as plasma concentrations. Sampling Importance Resampling (SIR) [1], a Bayesian method, is well suited for population PBPK models because it captures uncertainty while preserving inter-individual variability. Here, SIR was used to refine the prediction performance of a theophylline PBPK model in Simcyp Simulator, and the resulting model was applied to drug–drug interaction (DDI) simulations.

PREDICTION OF THEOPHYLLINE DDI

- SIR-derived weights were then used to predict theophylline pharmacokinetics under CYP1A2 inhibition by ciprofloxacin.
- A clinically relevant dosing regimen was applied [4].

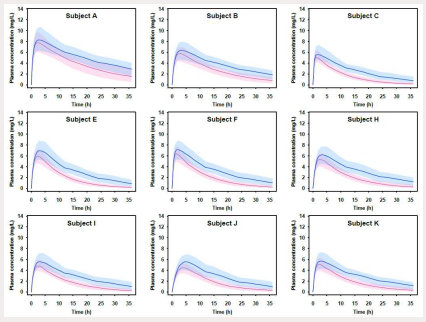

Figure 4: SIR-filtered theophylline plasma concentration profiles with (blue) and without (pink) inhibitor

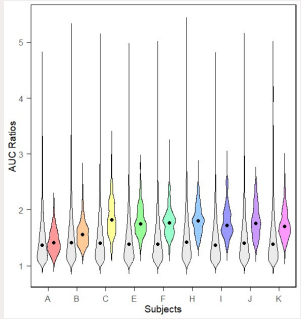

Figure 5: Prior (grey) and SIR-filtered (color) distribution of the AUC ratios for the 9 subjects

SAMPLING IMPORTANCE RESAMPLING

1. SAMPLING

- A minimal PBPK model for theophylline in healthy volunteers in Simcyp V24.
- Clinical data for 9 men [2].
- Prior distributions:
  - Default Simcyp distributions for the physiological parameters.
  - For drug parameters, lognormal distributions with means equal to initial values (literature or variability analysis) and a 30% coefficient of variation for all drug parameters except 3 uncertain parameters for which a CV of 100% was used [3].
- Sampling: 10,000 prior PBPK simulations generated per subject.

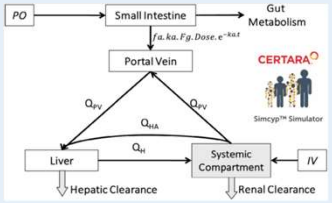

Figure 1: a minimal PBPK model for theophylline

2. WEIGHT

- The weights are proportional to the likelihood of observed clinical data given model predictions.
- Data likelihood: a normal measurement error model with both constant and concentration-dependent components.
- Importance weights calculated for each simulation.

3. RESAMPLING

1,000 posterior samples drawn from the prior distributions according to the normalized weights.

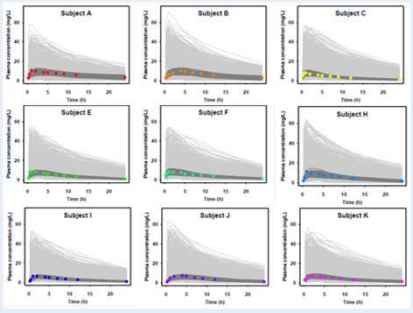

Figure 2: Prior (light grey) and SIR-filtered (dark grey) theophylline plasma concentration profiles with the clinical data (color dots)

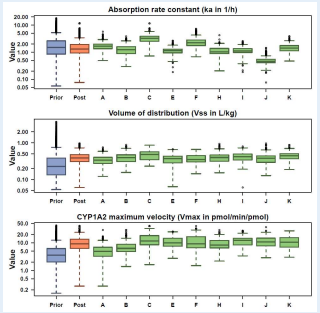

Figure 3: Prior distribution, the population mean posterior distribution and the individual distributions for 3 PBPK model parameters

Key takeaways

SIR offers a robust and scalable approach to integrate clinical data into population based PBPK models. By updating joint parameter distributions while **preserving inter-individual variability and covariate relationships**, SIR enhances predictive model accuracy, supporting individualized dose optimization and rational design of clinical pharmacology studies.

Using the theophylline case study, we showed that:

- Predictive simulations using SIR shows better performance compared to the prior simulations (Figure 2).
- The distributions of the most uncertain drug parameters were updated to realistic values, similar to those obtained with other population fitting methods (Figure 3).
- Predicted AUC ratios for DDI with a CYP1A2 inhibitor showed narrower distributions than with the prior simulations and better matched published clinical observations (Figure 5).

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[1] Rubin DB Using the SIR algorithm to simulate posterior distributions. Bayesian Statistics 3. Oxford University Press, Oxford, 1988, pp 395–402
[2] Trembath PW, Boobois SW. Pharmacokinetics of a sustained-release theophylline formulation. Br J Clin Pharmacol. 1980;9(4):365–9.
[3] Wedagedera et al. Population PBPK modeling using parametric and nonparametric methods of the Simcyp Simulator, and Bayesian samplers. CPT Pharmacometrics Syst Pharmacol. 2022;11(6):755–65.
[4] Batty KT et al. The effect of ciprofloxacin on theophylline pharmacokinetics in healthy subjects. Br J Clin Pharmacol. 1995;39(3):305–11.