

Understanding what influences small-molecule drug distribution: a systematic sensitivity assessment of the Rodgers-Rowland equations

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Introduction and objectives

- Physiologically-based pharmacokinetic (PBPK) models allow prediction of a drug's pharmacokinetics (PK) and are extensively used for optimising early candidate drugs, extrapolating dosing regimens in special population, predicting drug-drug interaction, developing oral formulations etc. [1]
- The large number of input parameters and outputs in PBPK models hinders simultaneous estimation of uncertain and/or unknown parameters.
- Heterogeneous and subjective approaches for parameter estimation using PBPK models have been proposed in the literature.
- Combining PBPK models with Bayesian methods could provide a more formal parameter estimation process [2]. However, before initiating parameter estimation procedures, parameter sensitivity analysis (SA) is generally recommended [3,4].
- In this work, a comprehensive sensitivity analysis was conducted to identify key parameters influencing the prediction of tissue-to-plasma partition coefficients (Kp) reflecting the drug distribution in tissues in a whole-body PBPK model. This was carried out to potentially reduce the dimensionality by excluding less influential parameters.

Methods

Global sensitivity analysis (GSA) and uncertainty analysis were performed on the Rodgers-Rowland mechanistic equations for tissue-to-unbound plasma partition coefficient ($K_{pu}=K_p/f_{up}$) predictions [5,6]

1. The partial rank correlation coefficient (PRCC) method [7,8] was used to identify influential drug parameters after simulating prototypical drugs (N=10000 per drug class) with relevant sets of drug parameters using Latin hypercube sampling (LHS) (Table 1)
2. Impact of variability/uncertainty in physiological parameters (tissue composition data) was explored by incorporating 30% biological variability/uncertainty [9]

Rodgers-Rowland mechanistic equations [5,6] to predict K_{pu} for :

➤ moderate to strong bases

$$K_{pu} = \left(\frac{X \cdot f_{IW}}{Y} \right) + f_{EW} + \left(\frac{P \cdot f_{NL} + (0.3P + 0.7) \cdot f_{IW}}{Y} \right) + \left[\left(\frac{Ht - 1 + BP}{f_{up} \cdot Ht} - \left(\frac{1 + 10^{pKa - pH_{RBC}}}{Y} \cdot f_{IW,RBC} \right) - \left(\frac{P \cdot f_{NL,RBC} + (0.3P + 0.7) \cdot f_{NP,RBC}}{Y} \right) \right) \cdot \left(\frac{[AP^-]_T \cdot X}{[AP^-]_{RBC} \cdot 10^{pKa - pH_{RBC}}} \right) \right]$$

➤ weak bases, acids and neutrals

$$K_{pu} = \frac{X \cdot f_{IW}}{Y} + f_{EW} + \left(\frac{P \cdot f_{NL} + (0.3P + 0.7) \cdot f_{NP}}{Y} \right) + \left[\left(\frac{1}{f_{up}} - 1 - \left(\frac{P \cdot f_{NL_p} + (0.3P + 0.7) \cdot f_{NP_p}}{Y} \right) \right) \cdot \frac{[PR]_T}{[PR]_p} \right]$$

physiological parameters, drug-dependent parameters, physiological and drug-dependent parameters

X and Y account for degree of ionisation

	Neutral	Acid	Weak Base	Strong Base
pKa	-	[2:8]	[3:7]	[7:11]
logP	[-3:6]	[-3:6]	[-3:6]	[-3:6]
fup	[0.001:1]	[0.001:1]	[0.001:1]	[0.001:1]
BP	[0.55:2.4]	[0.55:2.4]	[0.55:2.4]	[0.55:2.4]

Table 1: Constrained bounds of drug parameters (uniform distribution) for prototypical drugs (n= 10000 per drug class)

Results and discussion

1. Global sensitivity analysis of drug specific parameters

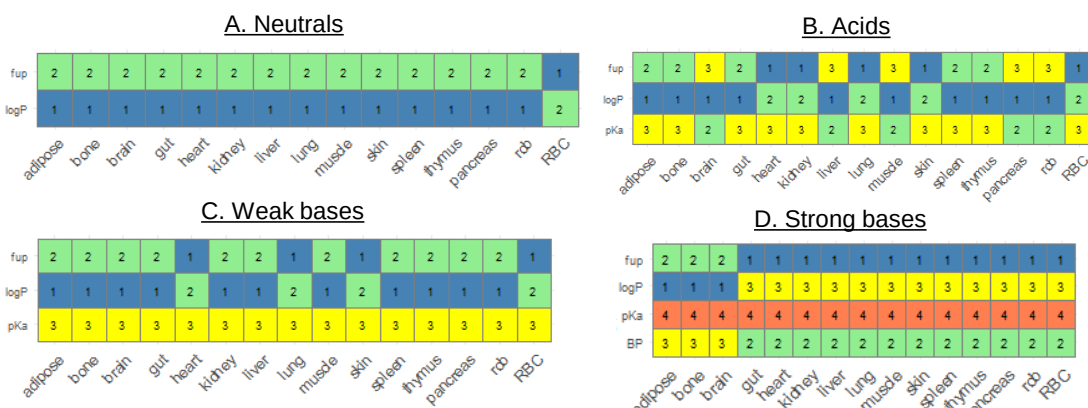
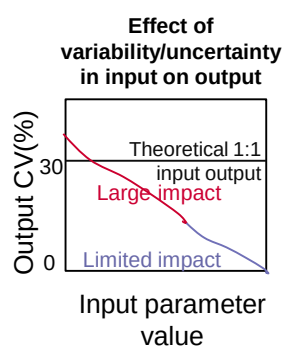


Figure 1: Parameter sensitivity ranking (1 as most important) based on PRCC of tissue K_{pu} and parameter sensitivity ranking for each drug class with independently sampled LogP and fup following LHS

2. Uncertainty analysis of physiological parameters

- Based on the assessment of a prototypical drug per class, variability/ uncertainty in tissue composition data (30% CV of inputs) can have a large impact on K_{pu} predictions (0 to 43% CV on output) for all classes (Fig.2) especially for strong bases with low fup (<0.1) (purple line, Fig. 2A, 2B, 2C)
- Changes in K_{pu} output values were especially caused by changes in the tissue acid phospholipid concentration and extracellular protein tissue:plasma ratio values (dotted line, Fig. 2)



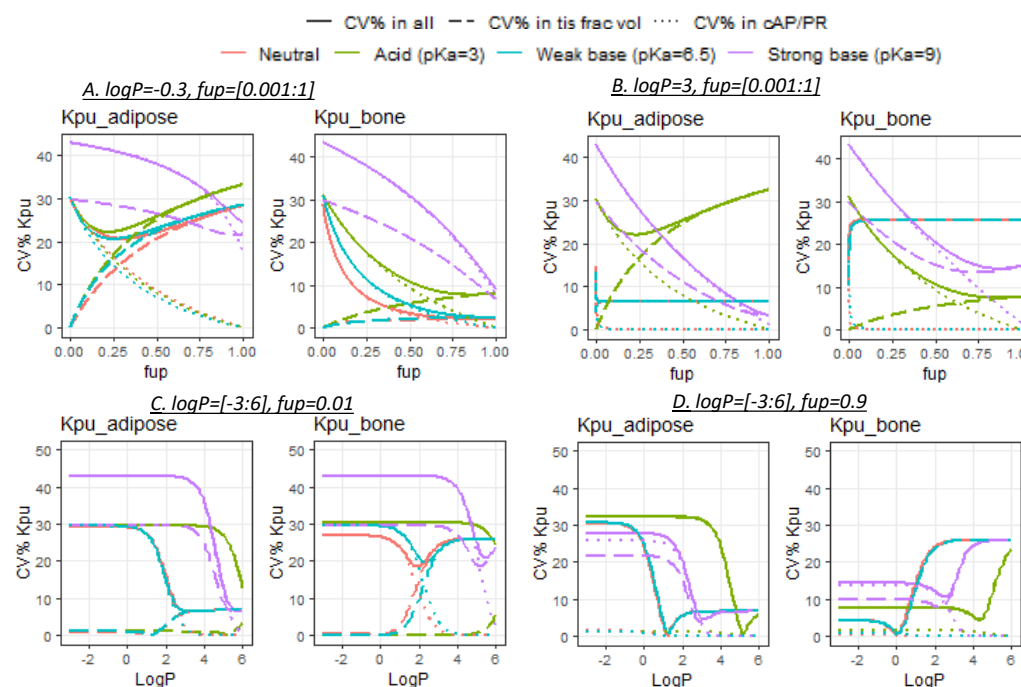
The variability/uncertainty in tissue composition data showed similar results on Vss as output (0 to 32% CV on output) (results not presented).

Figure 2: Effect of CV 30% in fractional tissue volumes and/or in all tissue acid phospholipids concentrations and extracellular protein tissue:plasma ratios (cAP/PR), simultaneously or individually, on adipose and bone K_{pu} when varying fup or LogP for a hypothetical neutral, acidic, weakly basic and strongly basic compound.

Given the explored parameter space (Table 1):

- For neutrals and weak bases, all tissues showed comparable sensitivity rankings (Fig.1A, 1C) while for acids and strong bases some tissues showed sensitivity differences (Fig.1B, 1D)
- LogP and fraction of unbound drug in plasma (fup) were generally the most influential parameters on K_{pu} predictions for most drug classes (Fig. 1A, 1B, 1C). For strong bases, blood:plasma ratio (BP) became more influential than LogP in a number of tissues (Fig. 1D)
- pKa (Fig. 1B, 1C, D) for ionisable compounds and fup for neutrals (Fig.1A) were the least influential parameters

A local SA of volume of distribution at steady state (Vss) showed that the least influential parameters identified from the GSA can have an influence on the Vss predictions in certain parameter space, especially between pKa of 5 and 9, and fup less than 0.1 (results not presented).



References

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Conclusions

- Based on the GSA, the most influential parameters on K_{pu} predictions in each drug class were generally LogP and fup
- Variability/uncertainty in tissue composition especially acid phospholipid concentrations and extracellular protein tissue:plasma ratios can be influential when predicting K_{pu} and Vss for all classes and especially for strong bases with low fup (<0.1)
- For parameter estimation for PBPK models and dimensionality reduction purposes, less influential parameters might be assigned fixed values depending on the sensitivity of the parameter space while influential parameters would be fitted in a Bayesian context using priors and uncertainty associated with experimental methods and data