

## Background

One of the key advantages of physiologically based pharmacokinetic (PBPK) models is the ability to predict drug concentrations in different tissues. However, the validation of these predictions is challenging due to the difficulty of measuring drug concentrations in tissues. The predicted outcome can vary significantly depending on the choice of the distribution model (i.e., the method to predict the tissue-to-plasma partition coefficient) [1], and there is a need to improve such predictions [2,3], particularly when there is variability in the clinical condition affecting physiological factors relevant for drug distribution and elimination. In our opinion, one important limitation of current PBPK models is not considering that molecules return to blood from the tissues by a constant intrinsic clearance that depends on the organ size instead of the supplied blood flow [4]. The aim of this work is to propose an approach that enhances the predictive accuracy of PBPK models for drug distribution in tissues by accounting for the impact of the relative distribution of blood flow to each organ.

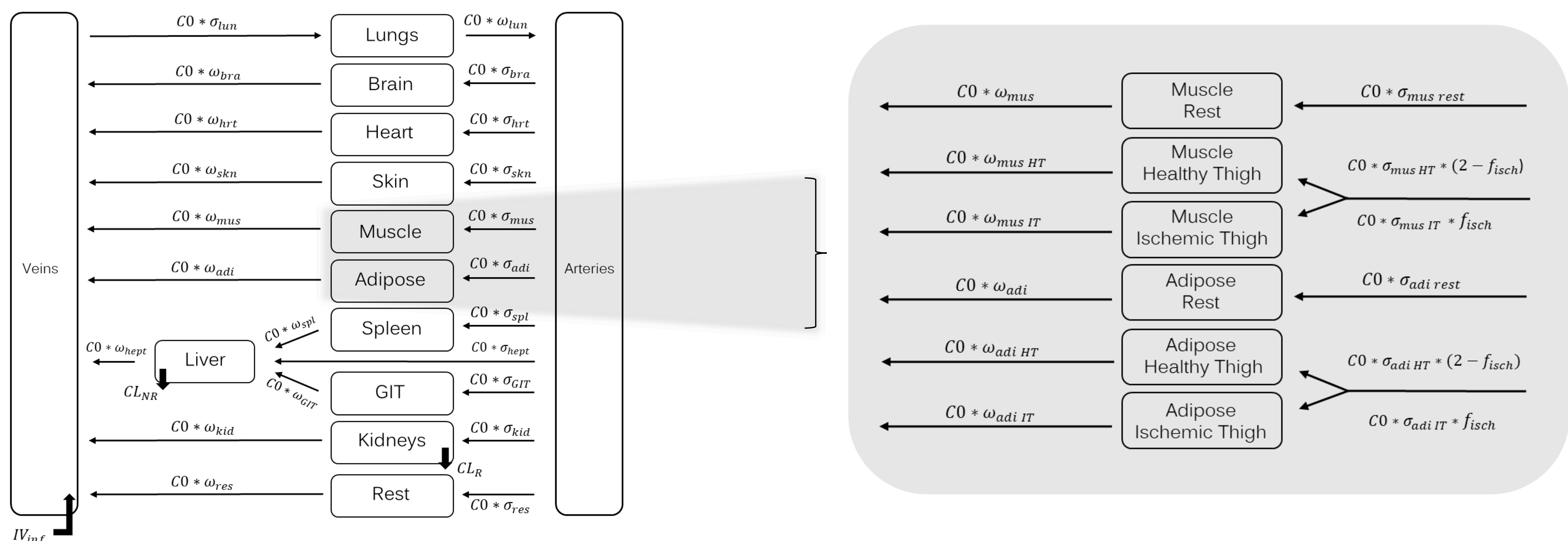
## Methods

Sadiq MW et al. [7], reported a ciprofloxacin whole-PBPK model which was adapted and implemented in NONMEM 7.5 (ICON plc) in order to simulate the data from Joukhadar et al. [6], who observed changes in the ciprofloxacin tissue-to-plasma AUC ratio (T/P) in the adipose tissue of thigh before and after angioplasty in patients with peripheral arterial occlusive disease. Creatinine clearance, sex, and body weight were included as covariates.

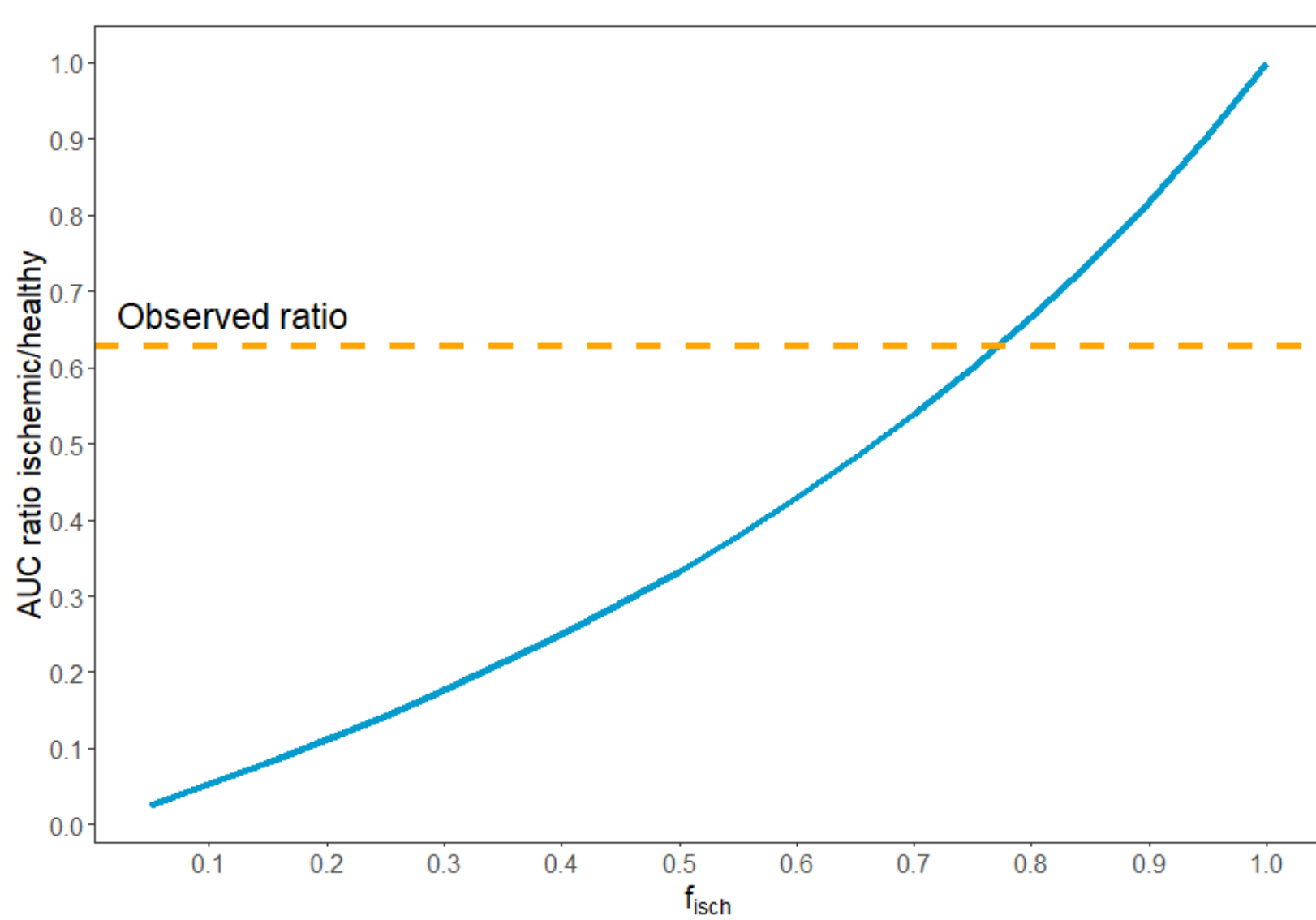
The adaptation of the model included the following changes:

- Division of muscle and adipose tissue to simulate healthy and ischemic thigh considering the relative thigh weight to body weight in men and women

- Adjustment of the drug distribution model now defined by the equation:  $V_T * \frac{dC_T}{dt} = CO * \sigma_T * C_A - CO * \omega_T * \frac{f_{u,T}}{f_{u,V}} * C_T$



## Results

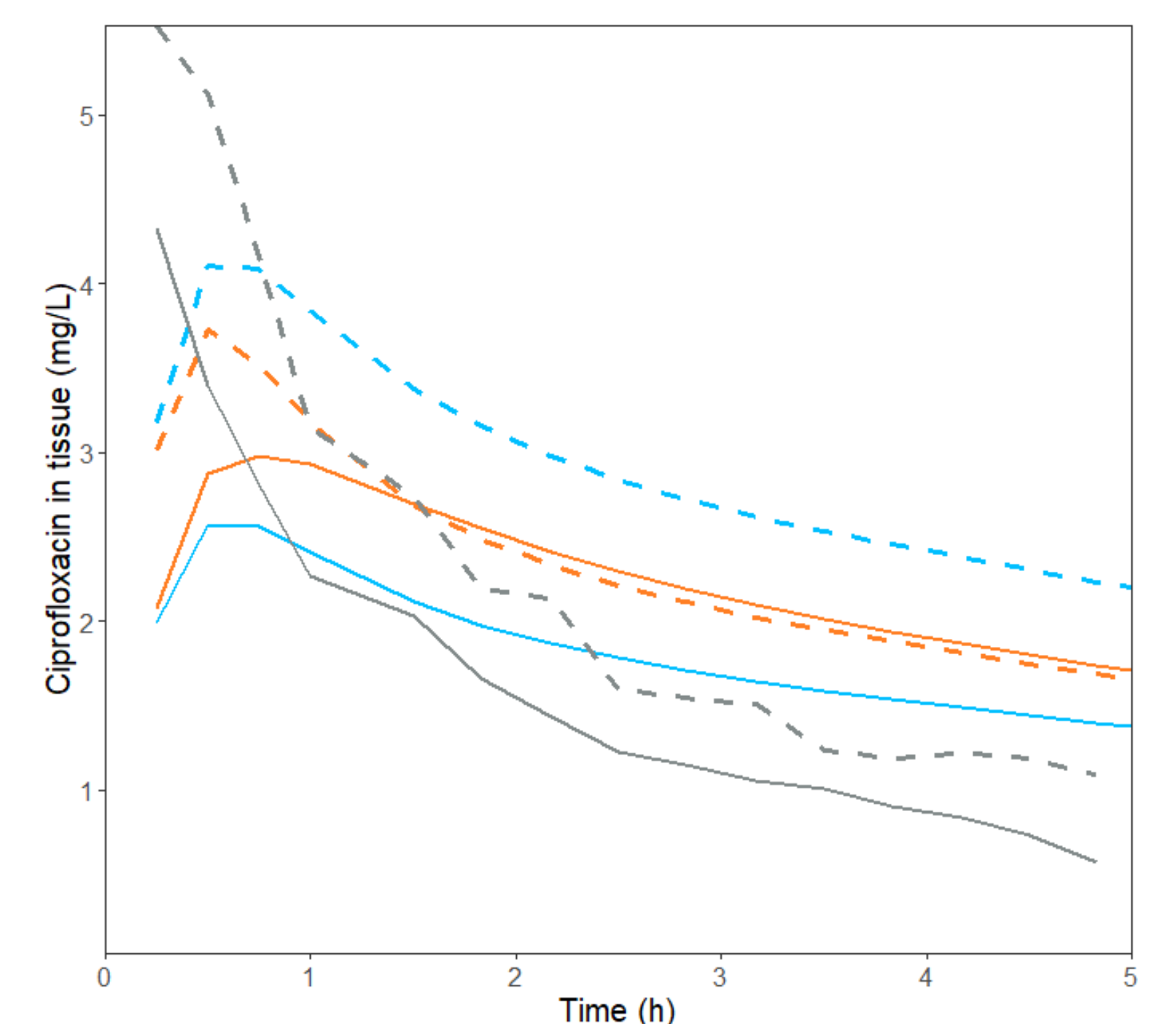


Inference of blood flow reduction to ischemic tissue ( $f_{isch}$ ) using the adapted PBPK model

	Observed [6]		Traditional PBPK [7]		Adapted PBPK	
AUC <sub>0-300</sub> plasma (mg.h/L)	16.4	14.5	15.76	(8.45-28.3)	16.16	(8.37-28.3)
Cmax <sub>0-300</sub> plasma (mg/L)	8.2	7.3	11.65	(8.18 - 16.43)	11.63	(8.18-16.3)
AUC <sub>0-300</sub> Ischemic adipose (mg.h/L)	7.1	8.0	4.60	(2.66-6.18)	4.68	(2.67-6.38)
AUC <sub>0-300</sub> Healthy adipose (mg.h/L)	11.3	8.5	4.73	(2.68-6.53)	4.68	(2.67-6.38)
AUC ratio ischemic/healthy adipose	0.628	0.94	0.97	1	0.62	1
AUC <sub>0-300</sub> Ischemic muscle (mg.h/L)	---	---	10.9	(6.52-14.2)	11.2	(5.26-11.7)
AUC <sub>0-300</sub> healthy muscle (mg.h/L)	---	---	11.4	(6.60-15.4)	11.2	(6.54-14.9)
AUC ratio ischemic/healthy muscle	---	---	0.96	1	0.62	1

Before revascularization  
 Blood flow to ischemic tissue reduced to 77%

After revascularization  
 Blood flow normalized



Observed (adipose, grey) and predicted (muscle) ciprofloxacin concentrations in ischemic (dotted) and healthy (solid) tissue before revascularization. Predictions shown for traditional (orange) and adapted (light blue) PBPK models.

## Conclusions

The proposed approach was successfully implemented to describe the reported changes for ciprofloxacin T/P in adipose tissue before and after angioplasty. The equation allows to further evaluate the impact of changes in blood flow distribution on T/P in the context of PBPK models.

References:  
 [1] Utsey K et al. Quantification of the Impact of Partition Coefficient Prediction Methods on Physiologically Based Pharmacokinetic Model Output Using a Standardized Tissue Composition Drug Metabolism and Disposition (2020) 48(10): 903-916. [2] De Sutter PJ et al. Predictive Performance of Physiologically Based Pharmacokinetic Modelling of Beta-Lactam Antibiotic Concentrations in Adipose, Bone and Muscle Tissues. Drug Metab Dispos (2023). [3] Muladitan M et al. Prediction of lung exposure to drugs using plasma pharmacokinetic data: Implications for dose selection. European Journal of Pharmaceutical Sciences (2022) 173, 106163. [4] Ibarra M et al. Current PBPK Models: Are They Predicting Tissue Drug Concentration Correctly? Drugs (2020) 20:295-299. [5] Lenz T. The effects of high physical activity on pharmacokinetic drug interactions. Expert Opinion on Drug Metabolism and Toxicology (2011) 7(3):257-266. [6] Joukhadar C et al. Angioplasty increases target site concentrations of ciprofloxacin in patients with peripheral arterial occlusive disease. Clinical Pharmacology and Therapeutics (2001) 70(6): 532-539. [7] Sadiq MW et al. A whole-body physiologically based pharmacokinetic (WB-PBPK) model of ciprofloxacin: a step towards predicting bacterial killing at sites of infection. Journal of Pharmacokinetics and Pharmacodynamics (2017) 44:69-79.