

PURPOSE

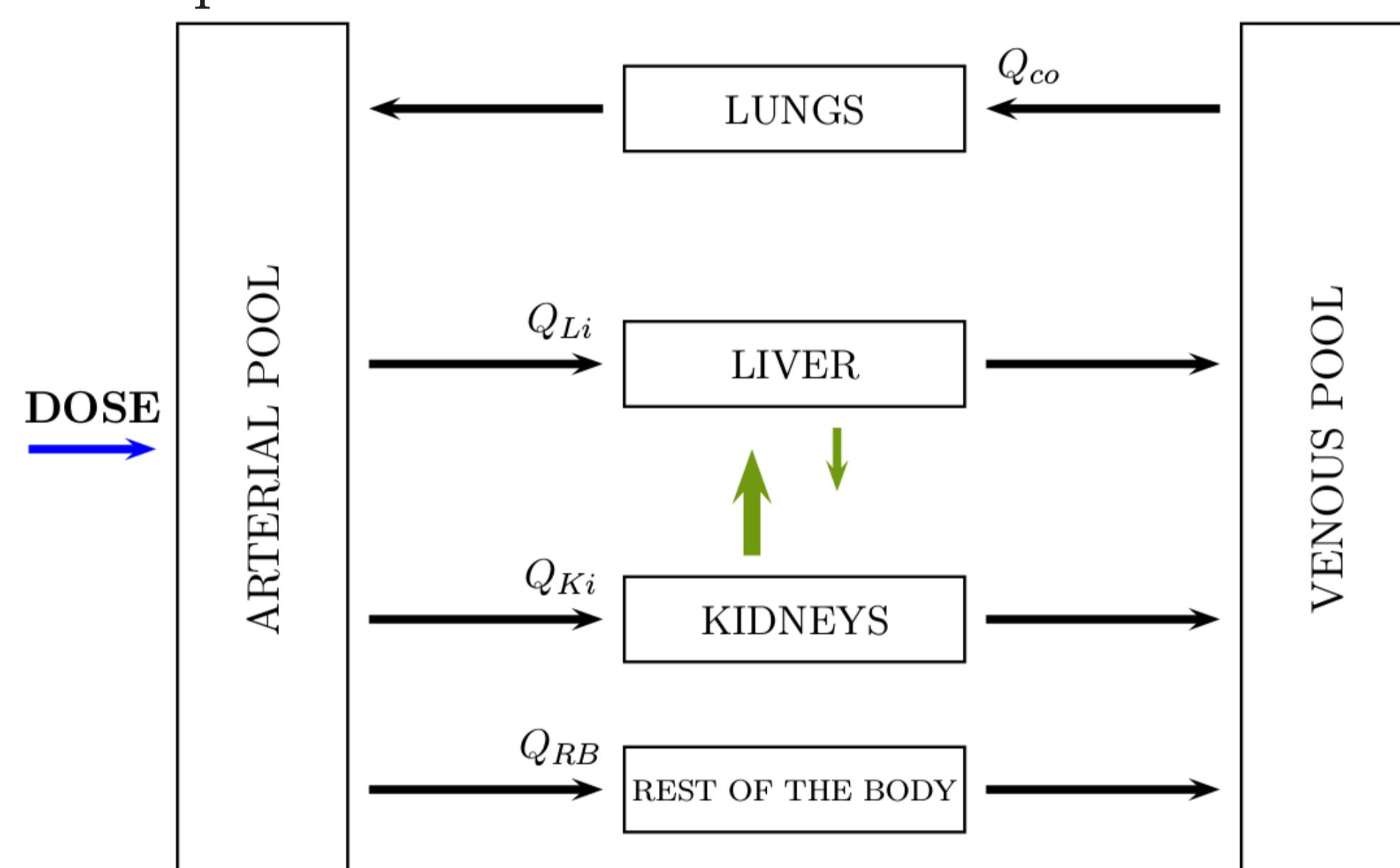
To develop a reduced physiologically based pharmacokinetic (PBPK) model using a top-down approach in patients with severe nosocomial pneumonia

PHYSIOLOGICALLY BASED PHARMACOKINETIC ANALYSIS

Based on a previous compartmental PK analysis and real values taken from the literature [1], total clearance and tissue-to-blood partition coefficients were estimated to describe the meropenem disposition in pneumonic patients. Patient data used are from the clinical trial PROMESSE (PROtocol MERopenem Steady State Evaluation)^[2].

Structural model

A PBPK model is built on physiological and anatomical considerations. The mathematical description consists in mass balance equation for each compartment, using real values^[1] for compartment volumes and blood flow rates.



Real volume and blood flow rates were expressed as a fraction of total bodyweight and cardiac output, respectively.

Statistical model

- Interindividual variability was included on clearance only and described by an exponential model:

$$CL_i = TVCL \cdot \exp(\eta_i)$$

- Residual error model is proportional and additive for plasma concentrations, $Y_{ij} = F_{ij}(1 + \epsilon_{ij}^p) + \epsilon_{ij}^a$, and proportional for ELF concentrations, $Y_{ij} = F_{ij}(1 + \epsilon_{ij}^p)$.

Covariate model

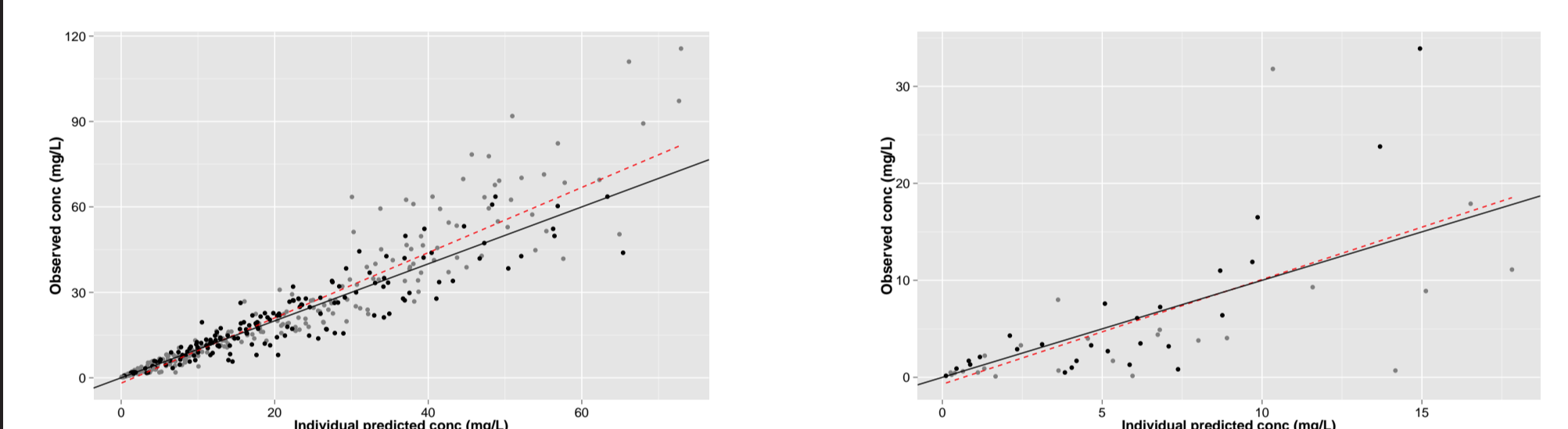
In the previous compartmental analysis, glomerular filtration rate (*GFR*) was determined to be a covariate related to elimination:

$$TVCL = \theta_{CL} \left(\frac{GFR}{65} \right)^{0.722}$$

Parameter estimates

Param.	Estimate	Bootstrap CI
θ_{CL}	8.174	7.684 - 8.940
K_{pLu}	0.2629	0.219 - 0.314
$K_{pLi} = K_{pKi}$	0.1946	0.141 - 0.201
K_{pRB}	0.2525	0.238 - 0.288
ω_{CL}^2 (%CV)	0.109 (32.98)	0.093 - 0.161
Arterial pool:		
σ_p^2 (%)	0.086 (29.37)	0.076 - 0.112
σ_a^2 (mg/L)	0.036 (0.19)	0.032 - 0.049
Lungs:		
σ_p^E (%)	0.482 (69.43)	0.422 - 0.650

Goodness of fit plots



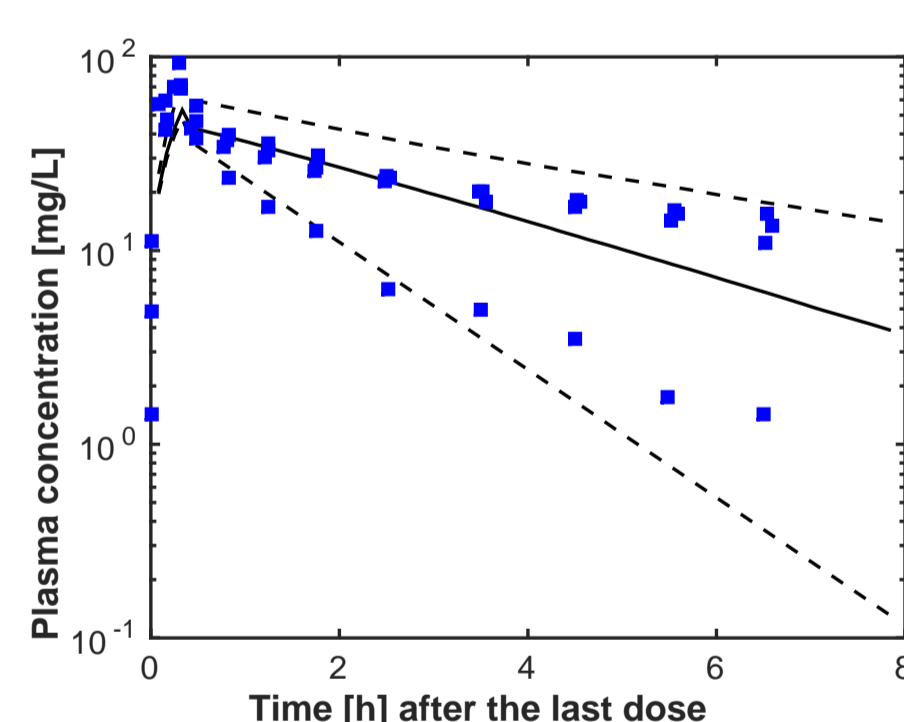
(a) plasma concentrations

(b) ELF concentrations

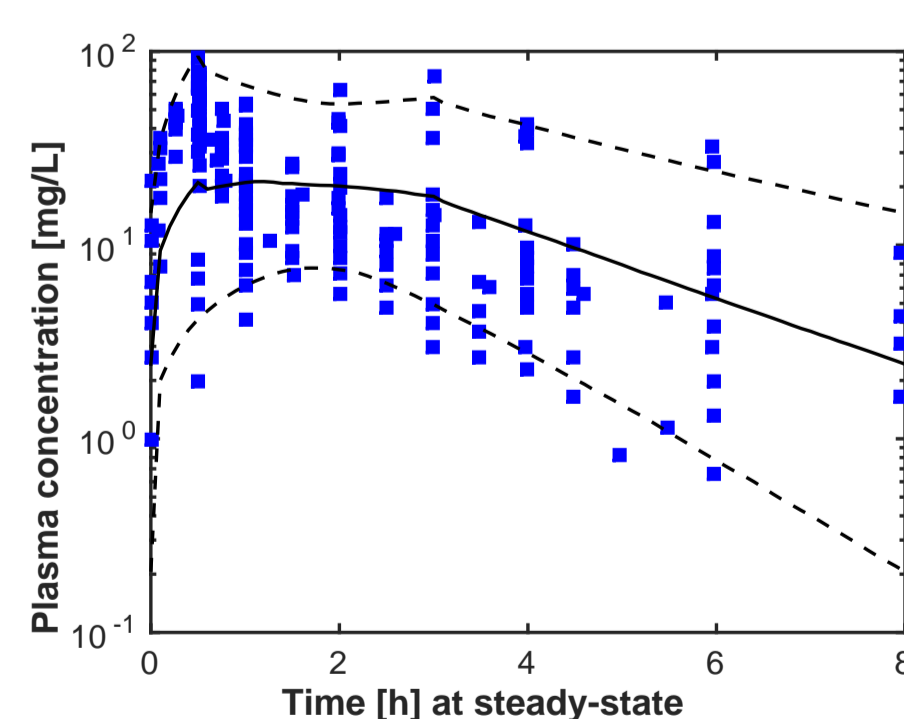
EXTERNAL VALIDATION & EXTRAPOLATION IN OTHER POPULATIONS

External validation consisted in comparing model predictions (90 % prediction interval) with independent measured concentrations (digitized data).

Other pneumonic populations

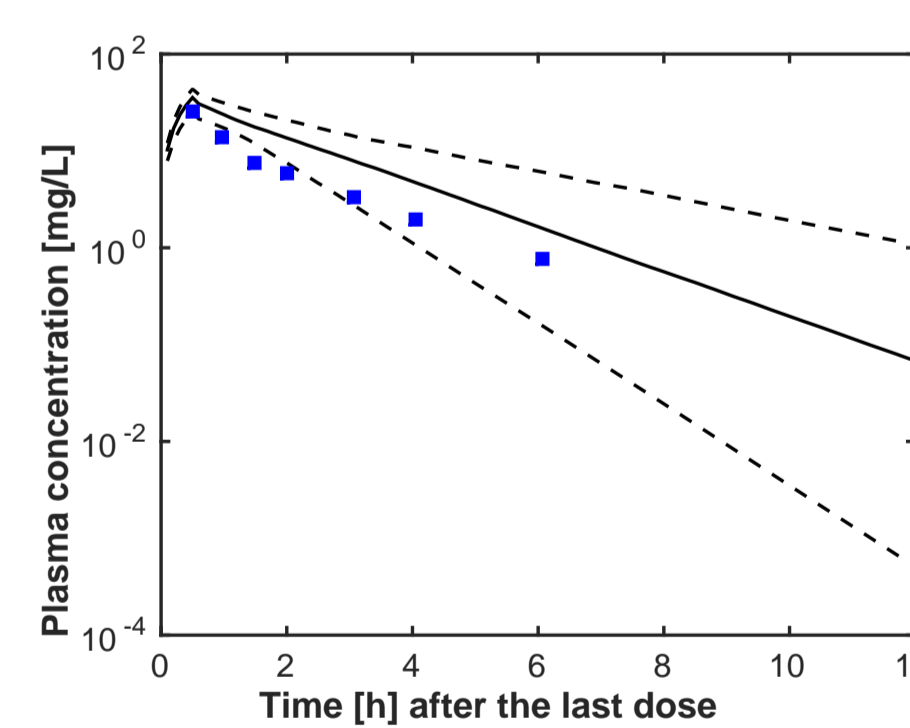


Observed concentrations from [3]: 4 patients with severe peritonitis associated with septic shock



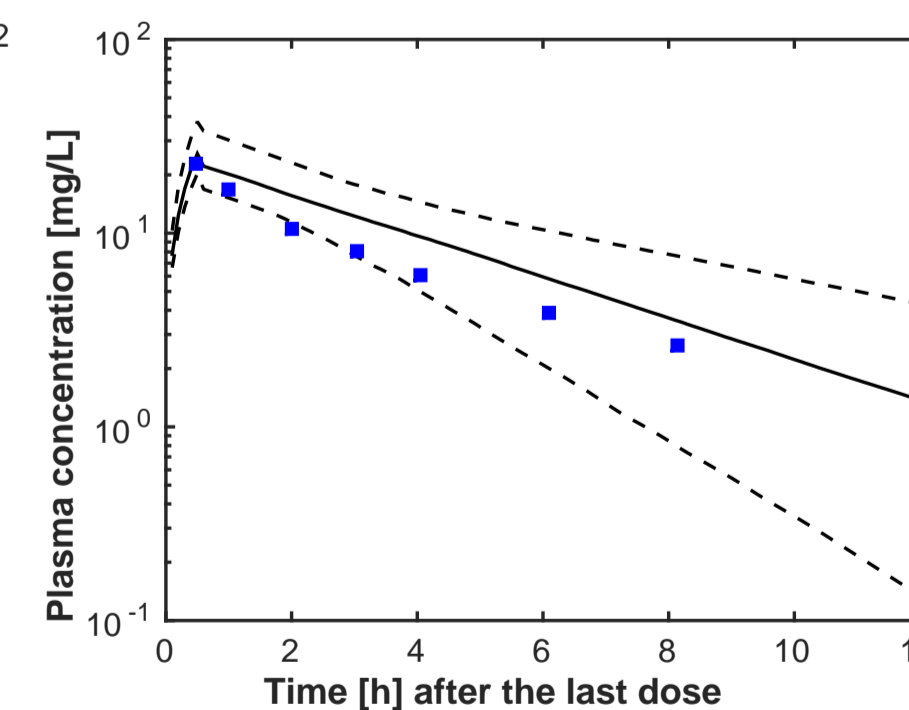
Observed concentrations from [6]: 79 pneumonic patients obtained from 3 previously conducted clinical trials

Patients with various degrees of renal function [4]

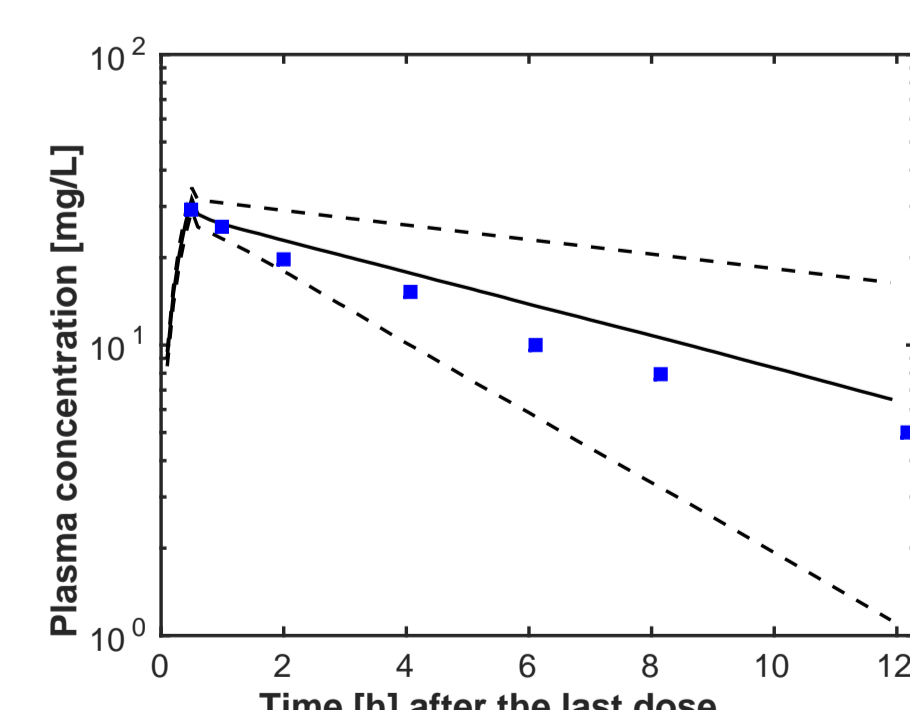


Group 1:
 $CL_{CR} \geq 50 \text{ mL/min}$

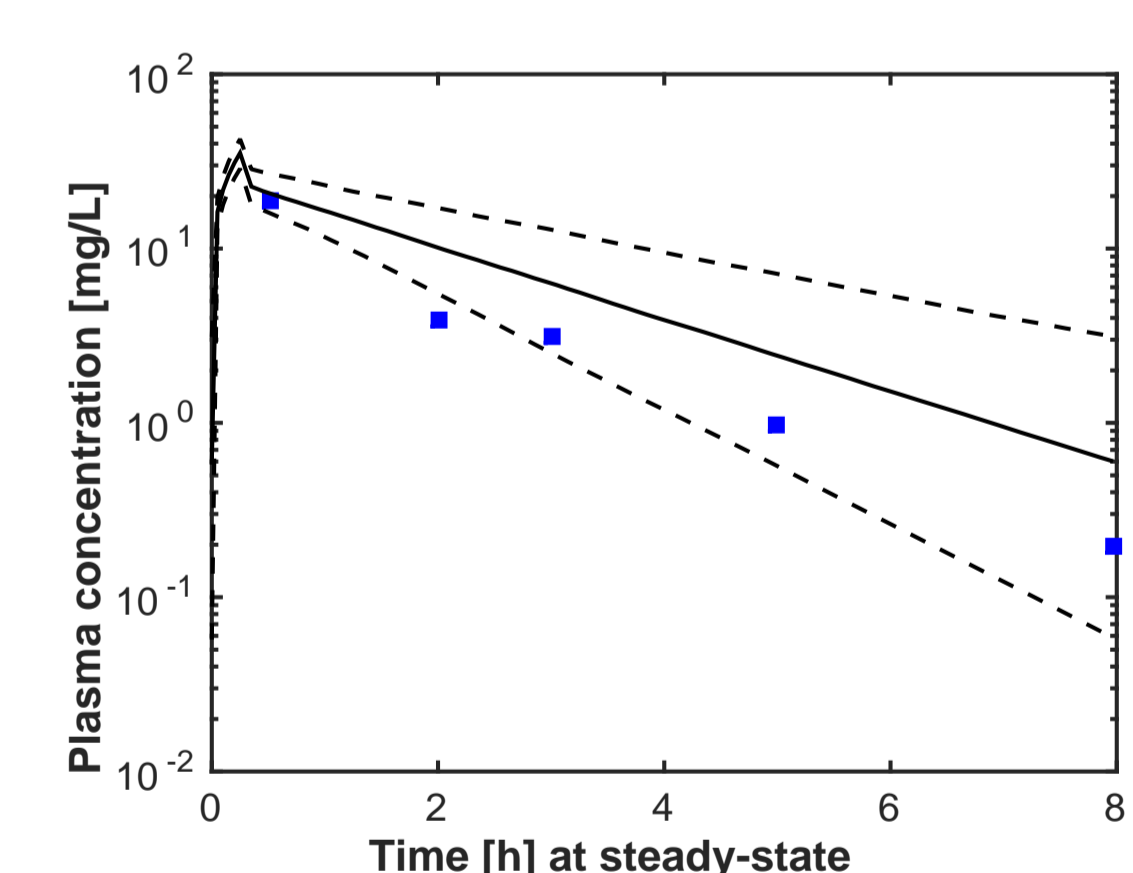
Group 2:
 $30 \leq CL_{CR} \leq 50$



Group 3:
 $CL_{CR} \leq 30 \text{ mL/min}$



Morbidly obese patients [5]



Simulated dataset generated using the population tab of Simcyp

	Range Wittau pop	Range virtual simcyp pop
Weight (kg)	116 - 203	89 - 191
S_{CR} ($\mu\text{mol/L}$)	64.0 - 80.0	19.7 - 119.4
Age (years)	31 - 49	30 - 50
BSA (m^2)	2.23 - 3.19	1.82 - 3.07

Conclusion : All internal and external validation steps gave satisfactory results.

- H. Jones et al. A novel strategy for physiologically based predictions of human pharmacokinetics. *Clinical pharmacokinetics*, 45(5):511–542, 2006.
- F. Fripiat, F. T. Musuamba, et al. Modelled target attainment after meropenem infusion in patients with severe nosocomial pneumonia: The promesse study. *Journal of Antimicrobial Chemotherapy*, 70(1):207–216, Sep 2015.
- J. Karjagin et al. Pharmacokinetics of meropenem determined by microdialysis in the peritoneal fluid of patients with severe peritonitis associated with septic shock. *Clinical Pharmacology & Therapeutics*, 83(3):452–459, 2008.
- M. Chimata et al. Pharmacokinetics of meropenem in patients with various degrees of renal function, including patients with end-stage renal disease. *Antimicrobial agents and chemotherapy*, 37(2):229–233, 1993.
- M. Wittau et al. Population pharmacokinetics and target attainment of meropenem in plasma and tissue of morbidly obese patients after laparoscopic intraperitoneal surgery. *Antimicrobial agents and chemotherapy*, 59(10):6241–6247, 2015.
- C. Li et al. Population pharmacokinetic analysis and dosing regimen optimization of meropenem in adult patients. *The Journal of Clinical Pharmacology*, 46(10):1171–1178, 2006.