

BACKGROUND:

- Alveolar epithelial lining fluid (ELF) has been suggested as an important site of lower respiratory tract infections caused by extracellular pathogens. Therefore, the drug concentrations in ELF has been demonstrated more relevant than the concentrations in plasma. Most of the fluoroquinolones have been studied for determining the degree of lung penetration, and the overall results showed that they could achieve the higher ELF concentrations than in serum or plasma [1, 2]. However, there are still limited data of drug penetration in critically ill patients.
- Oral sitafloracin was rapidly absorbed and widely distributed into various tissues. Pharmacokinetics of sitafloracin were demonstrated with linear plasma pharmacokinetics that maximum plasma concentration (C_{max}) and area under concentration-time curve (AUC) were increased in dose proportion ranging from 25 mg to 500 mg [3-5].
- The objective of this study was to develop physiologically based pharmacokinetic (PBPK) modeling approach to predict concentrations of sitafloracin in ELF.

RESULTS:

- The concentrations in ELF had variation with different sampling times. The mean $\pm$ SD of C_{max} was $1.07 \pm 0.93 \mu\text{g/mL}$.
- The PBPK model can be used to predict the pharmacokinetic behavior of sitafloracin in agreement with observed data (RMSE of 0.54).
- From the modelling and simulation, sitafloracin penetrated into ELF and accumulated with the dose proportion at steady state.
- Stimulation with the dose of 200 mg, 300 mg, 400, mg, and 500 mg q 12 h, the C_{max} of sitafloracin in ELF at steady state were 0.8 $\mu\text{g/mL}$, 1.20 $\mu\text{g/mL}$, 1.61 $\mu\text{g/mL}$, and 2.01 $\mu\text{g/mL}$, respectively.

Figure 2: Concentration-time profiles of sitafloracin in ELF simulated from dose 200 mg, 300 mg, 400 mg, and 500 mg q 12 h.

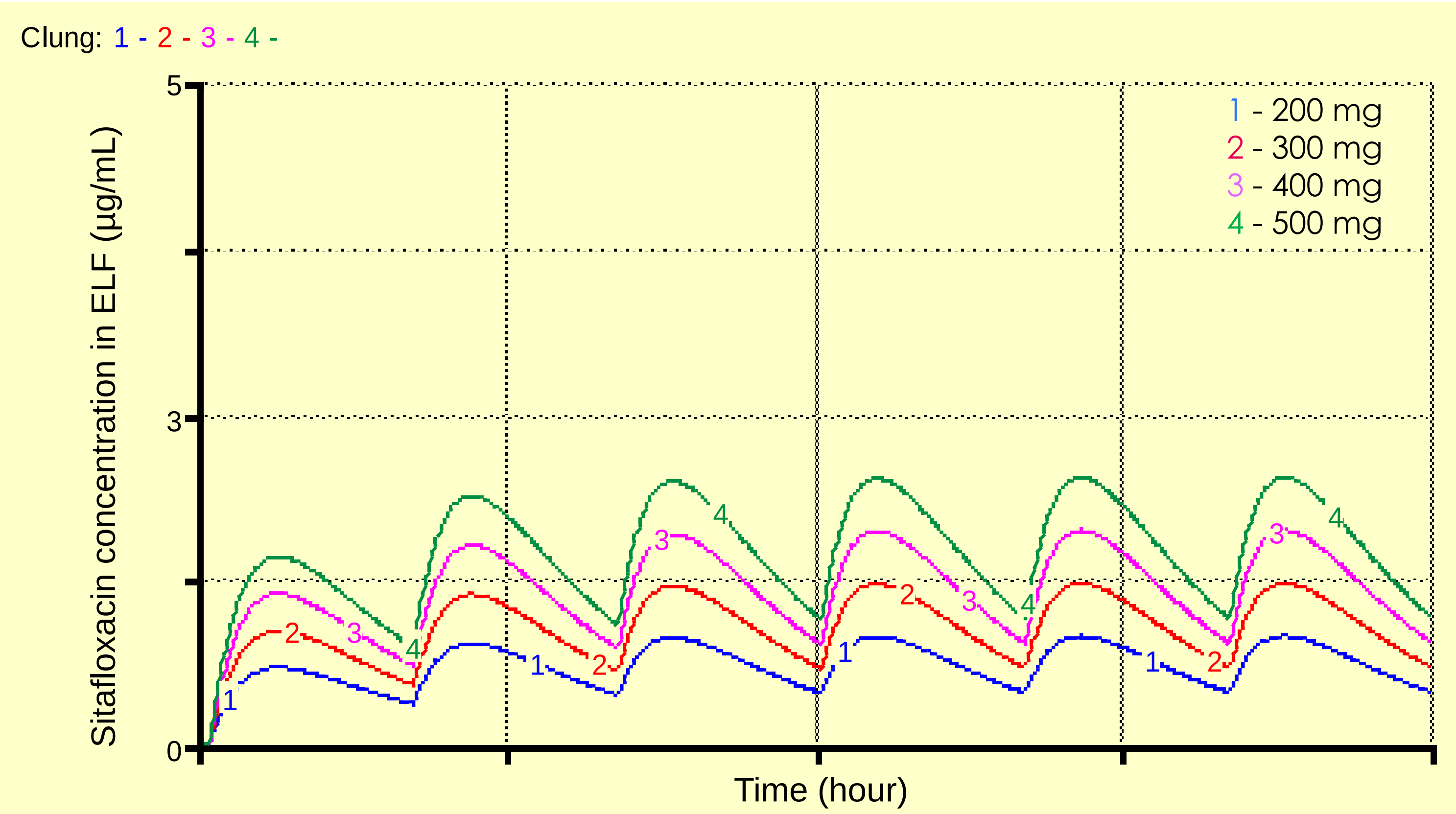


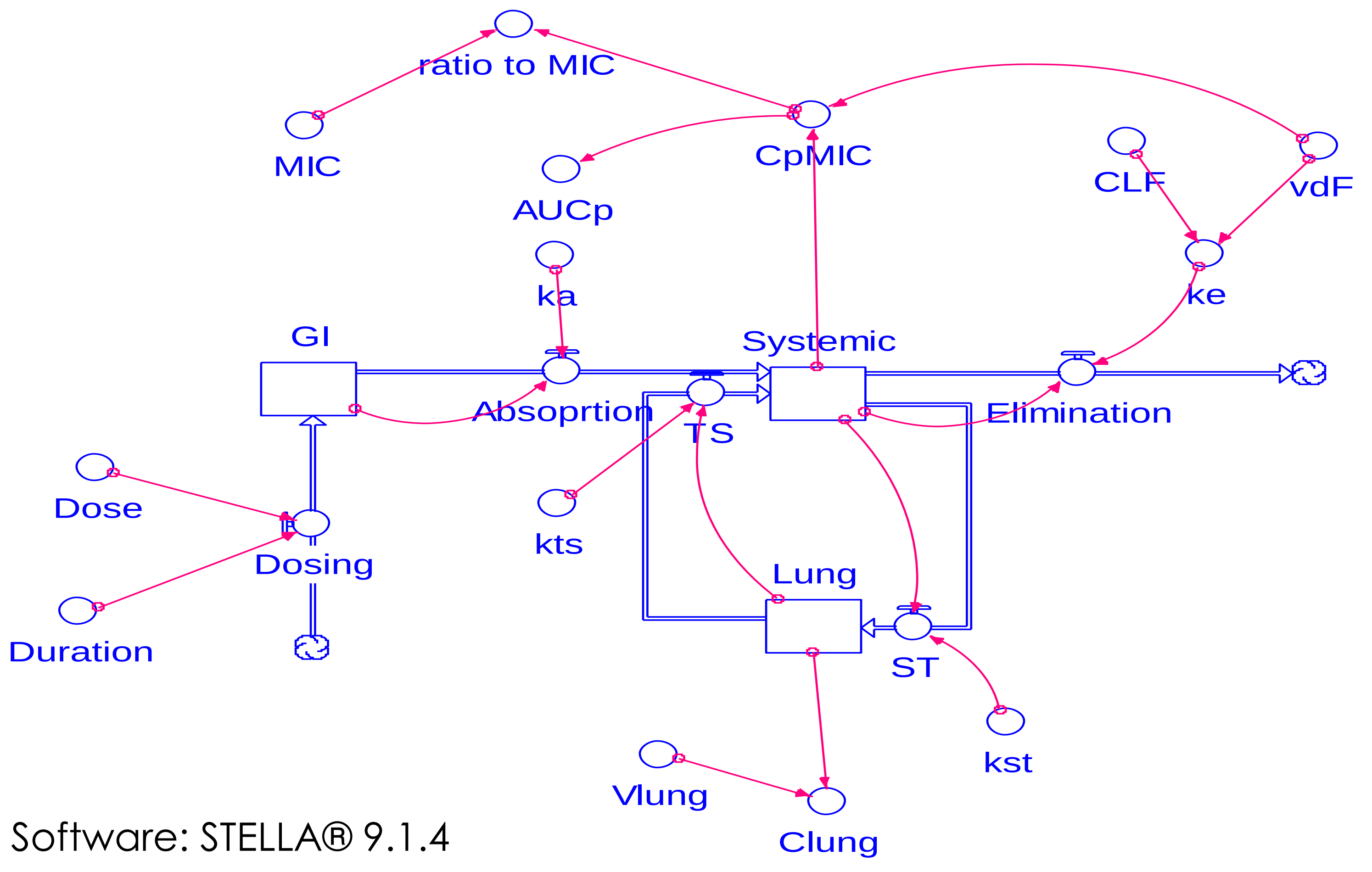
Table 2: Model evaluation using ELF concentration data

Number	C observed	C predicted	Residual	Squared Residual
1	0.11	0.24	-0.127	0.016
2	0.41	0.41	0	0
3	0.73	0.73	0	0
4	0.17	0.61	-0.443	0.196
5	0.11	0.74	-0.632	0.399
6	1.12	0.78	0.340	0.116
7	0.55	0.73	-0.178	0.032
8	1.50	0.66	0.840	0.706
9	1.97	0.82	1.149	1.320
10	0.16	0.63	-0.475	0.226
11	0.04	0.59	-0.554	0.307
12	0.15	0.63	-0.478	0.228
			RMSE	0.544

METHODS:

- The PBPK model was constructed and evaluated using plasma and ELF concentrations obtained from 12 critically ill patients with pneumonia after oral sitafloracin single dose 200 mg administration during 0.5-2, 3-4, 5-6, and 7-9 h. Sitafloracin concentrations were determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS).
- The concentrations in ELF were calculated using plasma concentration * fraction unbound in plasma calculated from albumin level in each subject. The concentrations in ELF were assumed to be free drug.
- The plasma PK parameters described by one-compartment model with first-order absorption were used in conjunction with lung compartment for developing simple PBPK model
- Blood flow (Q) and volume of lung compartment (V_{lung}) were inputted into the model.

Figure 1: Schematic representation of the PBPK model



- Tissue to plasma distribution coefficients (K_p) were determined from the ratio of ELF and plasma concentrations.
- The PBPK model was evaluated by root-mean-square error (RMSE) between concentrations predicted by the model and the concentrations actually observed in ELF.
- The different dosage regimens were simulated to create sitafloracin concentration-time profiles in ELF.

$$K_p = \frac{C_{ELF}}{C_{Plasma}}$$

$$\text{The amount of drug} = C_{ELF} * V_{lung} = K_p * C_{plasma} * V_{lung}$$

CONCLUSIONS:

The PBPK modeling of sitafloracin are acceptable to predict sitafloracin concentrations in ELF in critically ill patients with pneumonia. This findings provided the useful information for further development of population PK/PD modelling to predict the optimal dosage regimen of sitafloracin

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