



Translational physiologically based pharmacokinetic modeling to predict human pulmonary kinetics after lung delivery

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1. Introduction

Oral inhalation is an attractive approach for drug delivery, especially when targeting respiratory diseases.¹ However, accurately assessing and predicting the exposure of orally inhaled drugs in the human lung poses a significant challenge in drug development.

The translational ability to bridge between animals and humans has generally not been well addressed and is hampered by the limited availability of pulmonary concentrations in human.²

2. Aim

We aimed to develop a comprehensive physiologically based pharmacokinetic (PBPK) framework tailored for the pulmonary pharmacokinetic (PK) behavior in both humans and rats, in order to bridge the translational gap.

3. Software

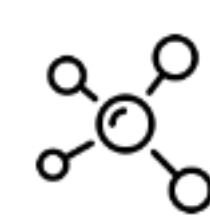
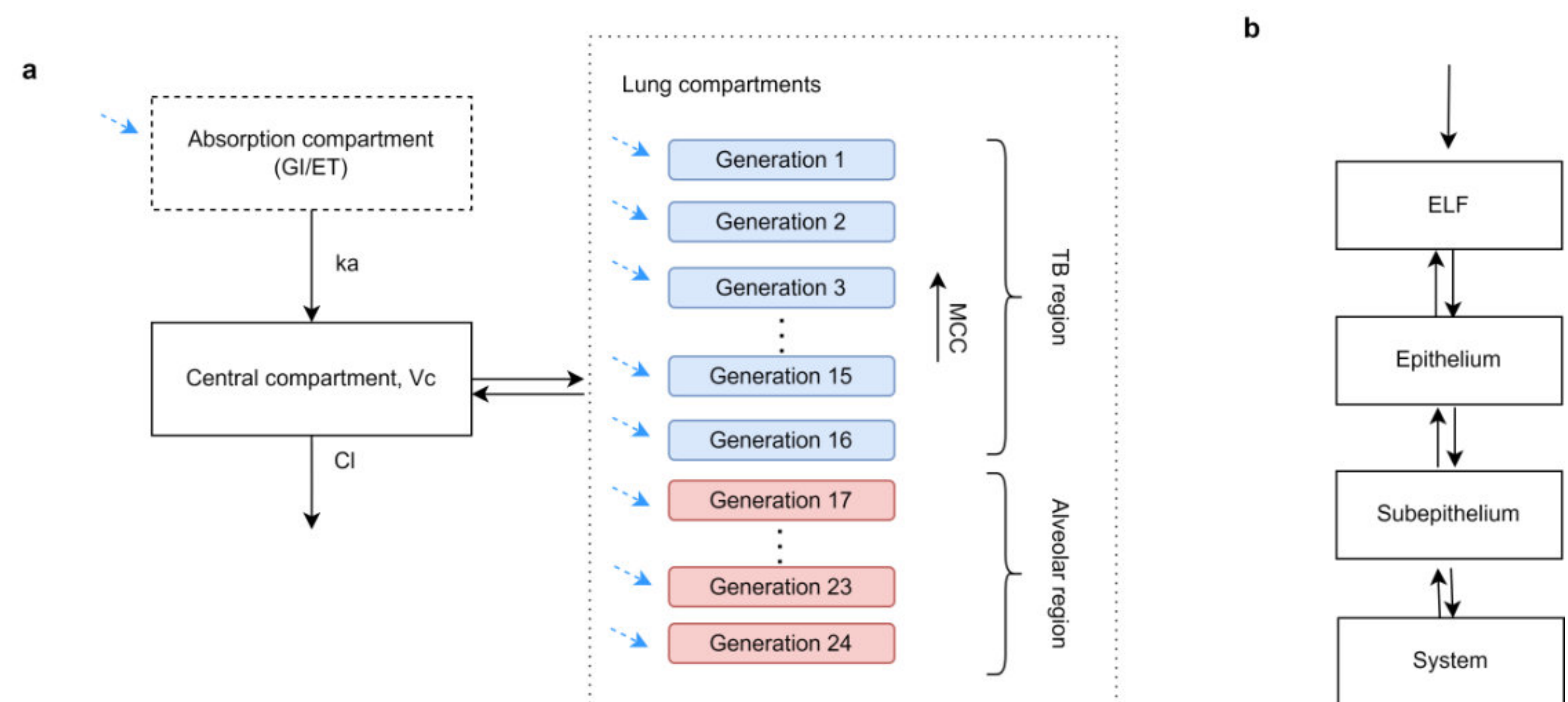
Model implementation was done in MoBi[®] and PK-Sim[®] Version 11.2, starting from a Mobi file shared by Pellowe.³

5. Results

4. Methods



A mechanistic pulmonary PBPK model was developed to extend existing models^{4,5} by more comprehensively integrating key pulmonary kinetic processes. The model adopts a 24-generation airway structure (a) and incorporates drug deposition, dissolution, mucociliary clearance (MCC), and mass transfer in lung tissues (b).



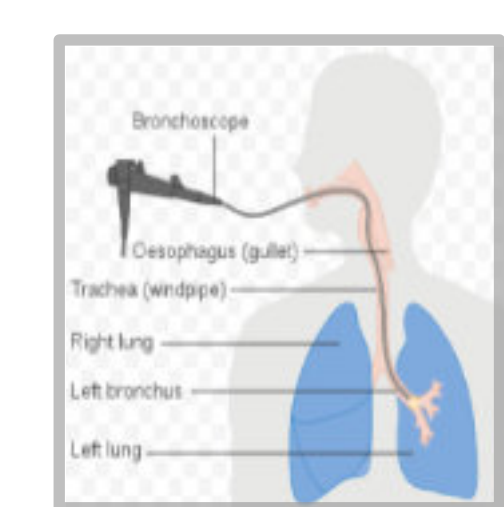
Drug physiochemical properties of salbutamol and fluticasone propionate (FP) were collected from literature.



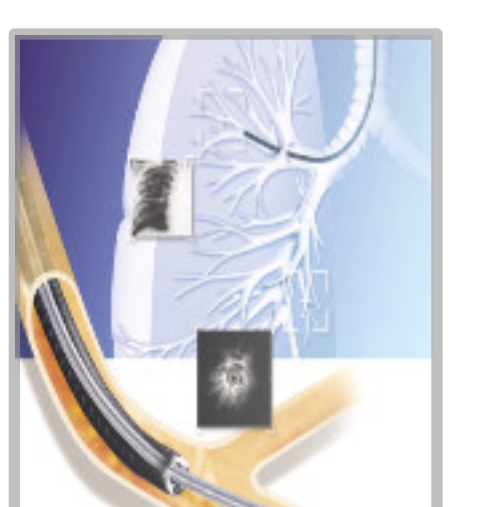
Rat lung PK data were digitized from literature. Model performance was compared when permeabilities were estimated with default PK-Sim[®] method (base model), with IVIVC method, or with rat PK data (est parameters).



Human pulmonary PK was predicted with an equivalent model structure featured with human physiological characteristics, and the parameters estimated (est) with rat data. Model performance was validated with ELF PK obtained with both BAL (mean ELF), and bronchosorption (bronchial ELF), as well as plasma PK.

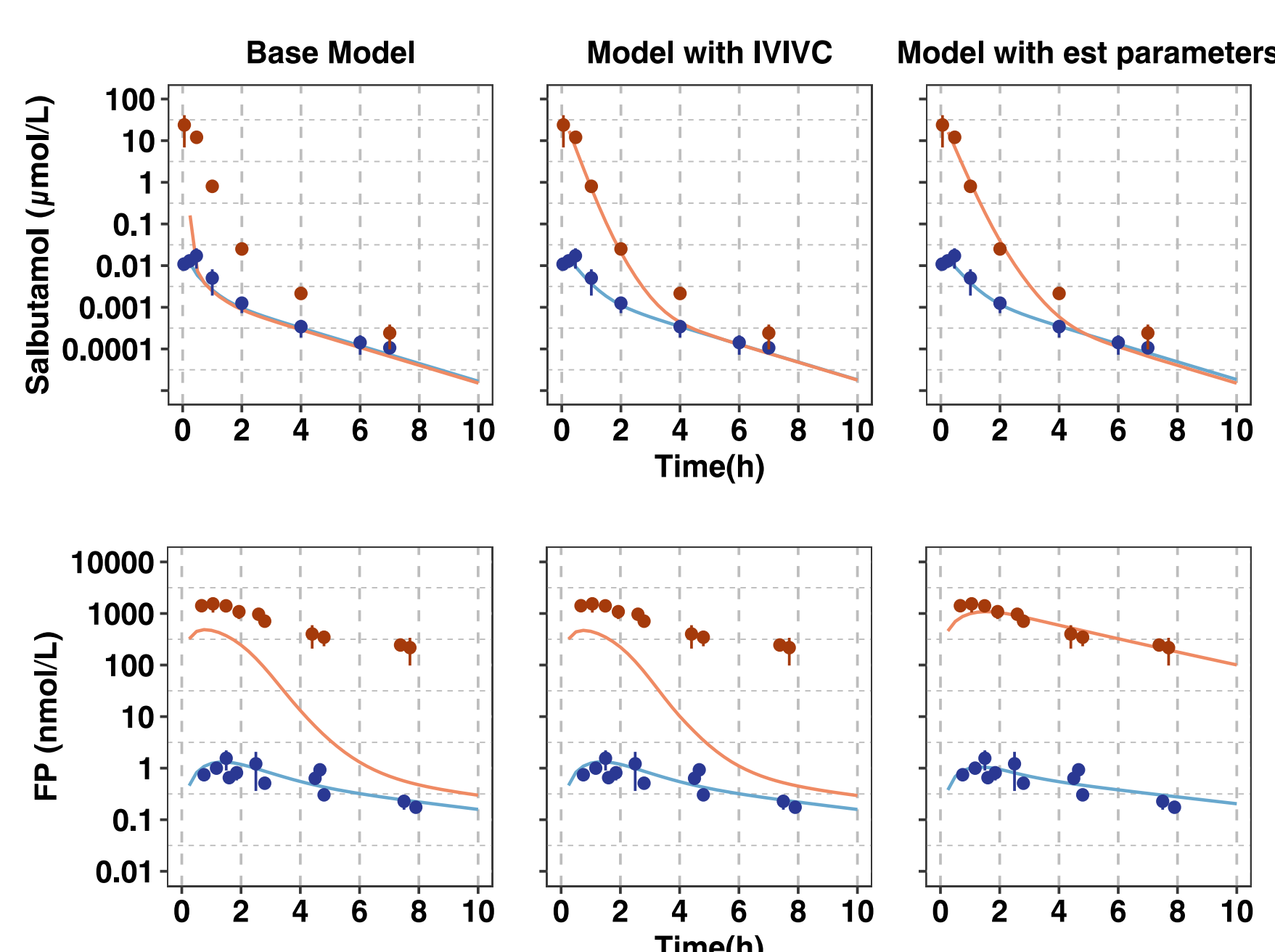


Broncho-alveolar lavage (BAL)

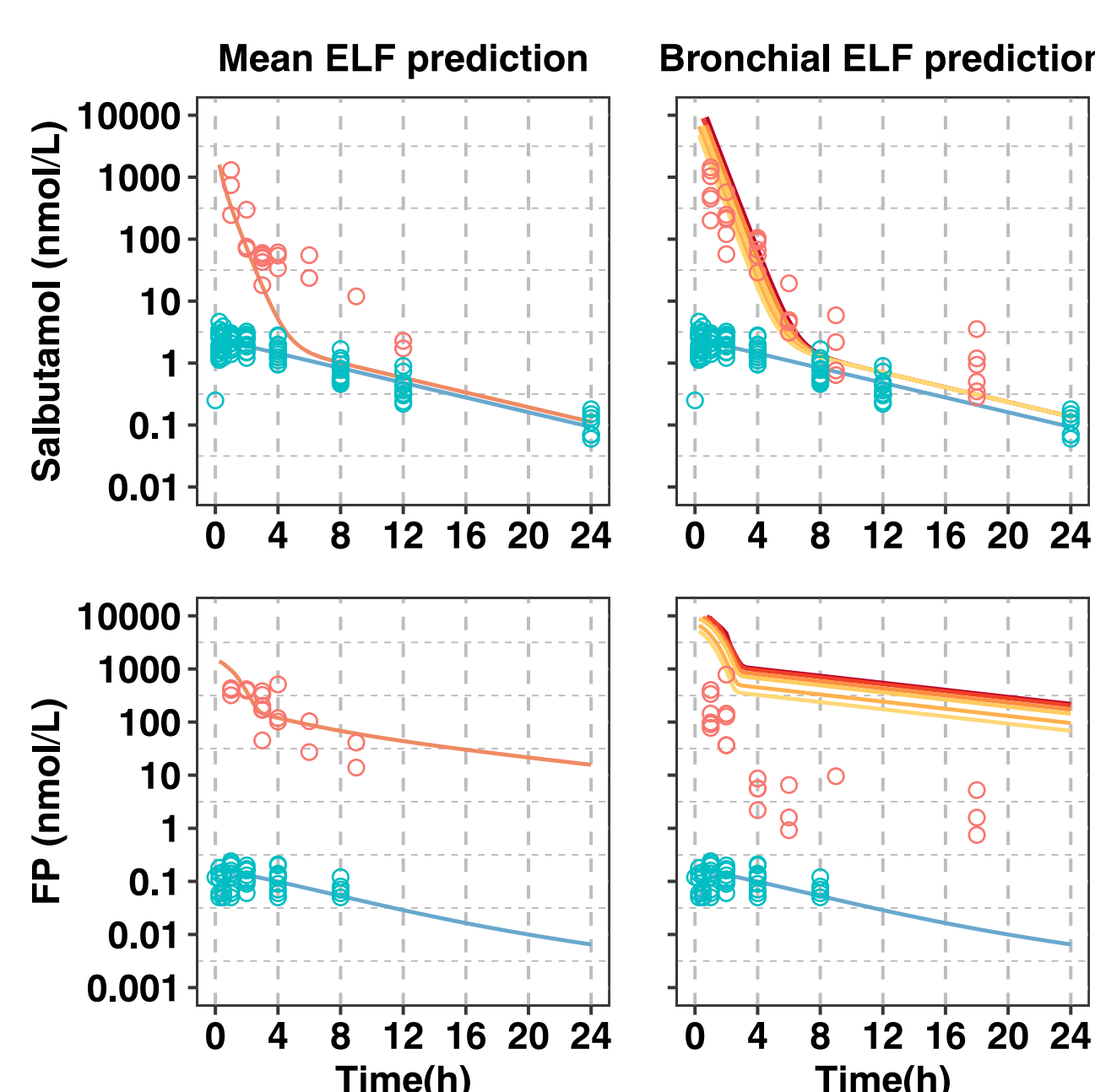


Bronchosorption (BAL)

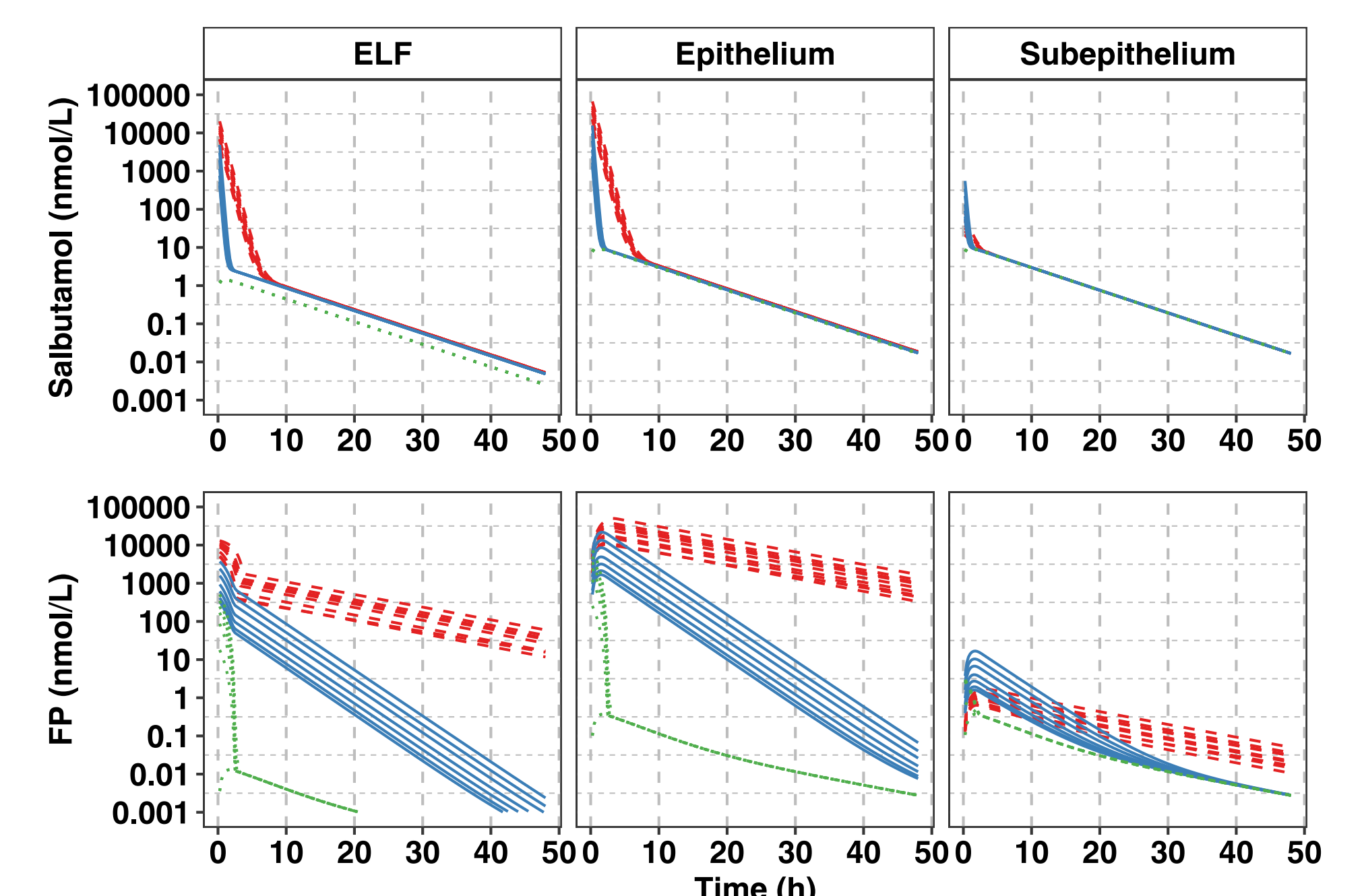
5.1 Predictive performance of salbutamol and fluticasone propionate (FP) in rats



5.2 Translational predictive performance for salbutamol and fluticasone propionate (FP) in humans



5.3 Model predictions of drug concentrations in different lung tissues and regions in humans



6. Limitations

- The framework was only validated with salbutamol and FP due to data availabilities
- Translation from healthy subjects to a diseased population is not addressed in the current model

7. Take home message

- IVIVC method can well predict pulmonary PK of salbutamol but not FP
- The model framework allowed accurate prediction of salbutamol and FP plasma and mean ELF PK profiles following oral inhalation by human subjects
- The model predicts heterogeneous pulmonary PK in different lung tissues and regions

ABBREVIATIONS

BAL, broncho-alveolar lavage; ELF, epithelium lining fluid; est, estimated; FP, fluticasone propionate; TB, tracheobronchial; IVIVC, in vitro in vivo correlation