

Pulmonary absorption, elimination and dissolution of an orally inhaled drug

A size- and location-structured partial differential equation model



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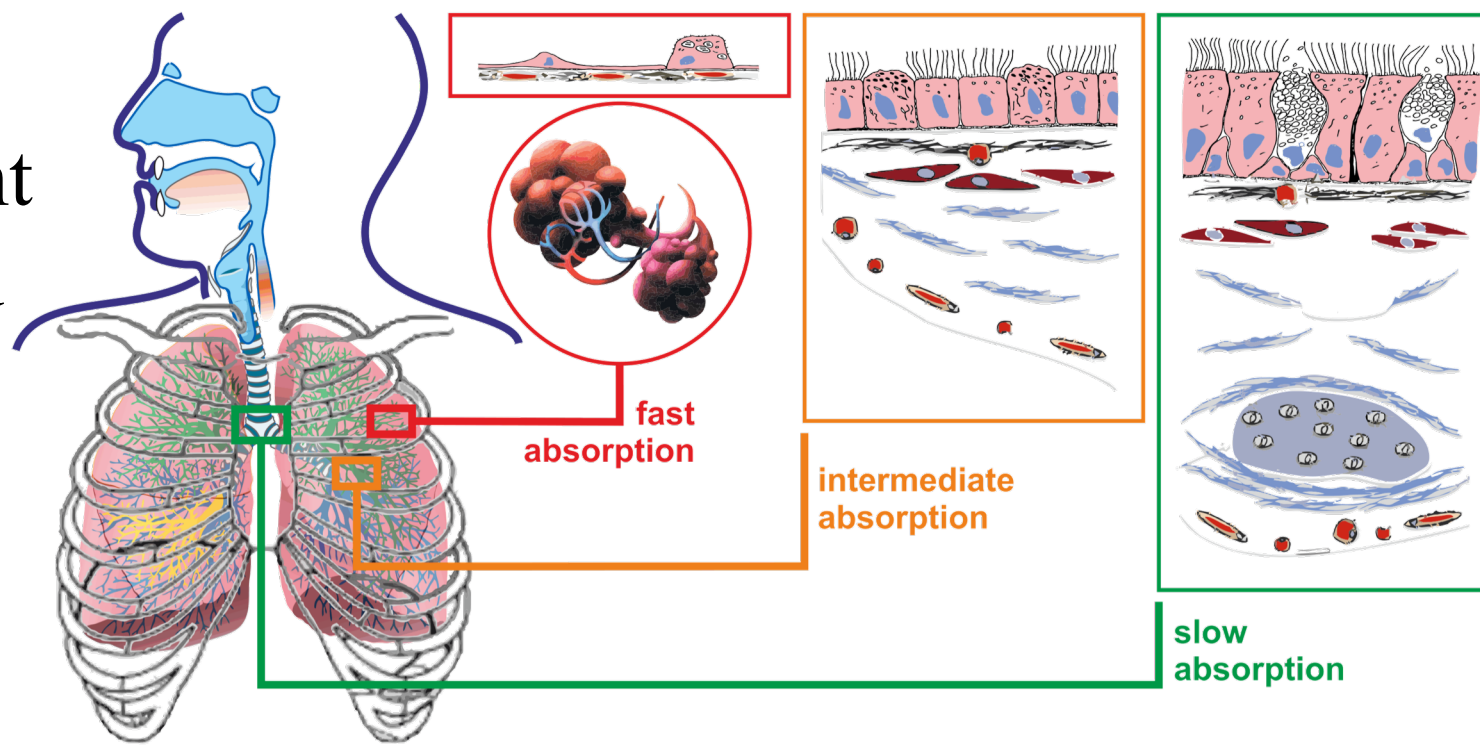


Absorption after inhalation

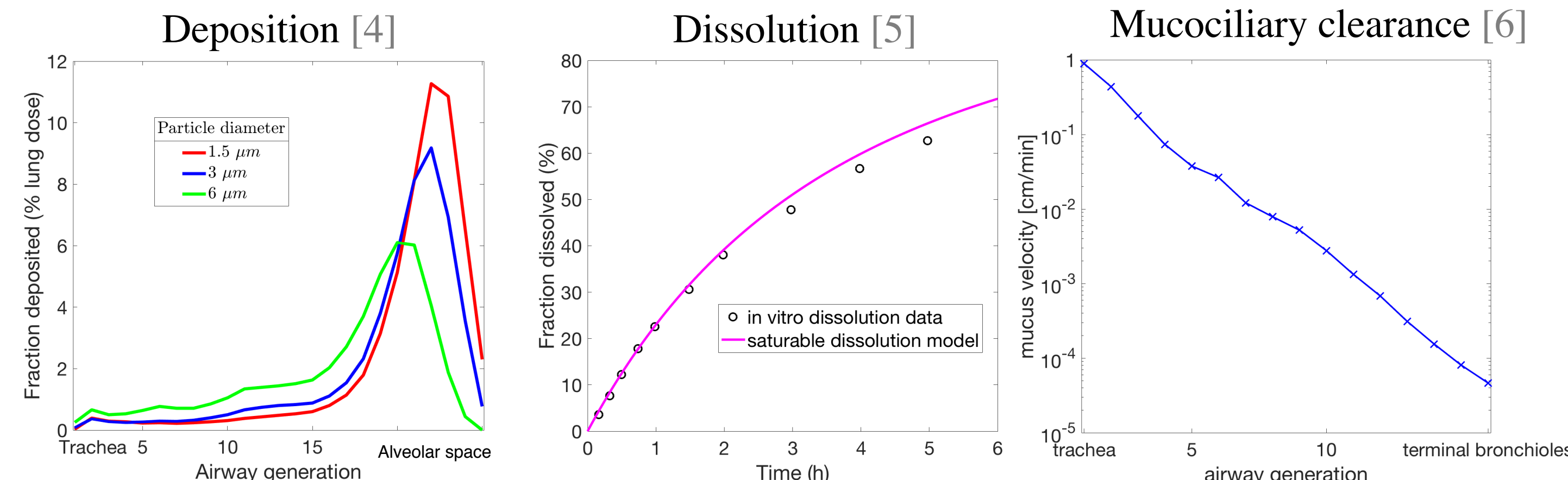
Clinical observation

Nonlinear dose- / particle size-dependent absorption for slowly dissolving inhaled drugs [1-2], which cannot be explained by applied standard (PB)PK models [3].

Schematic overview



Key processes



ODE modelling used in literature

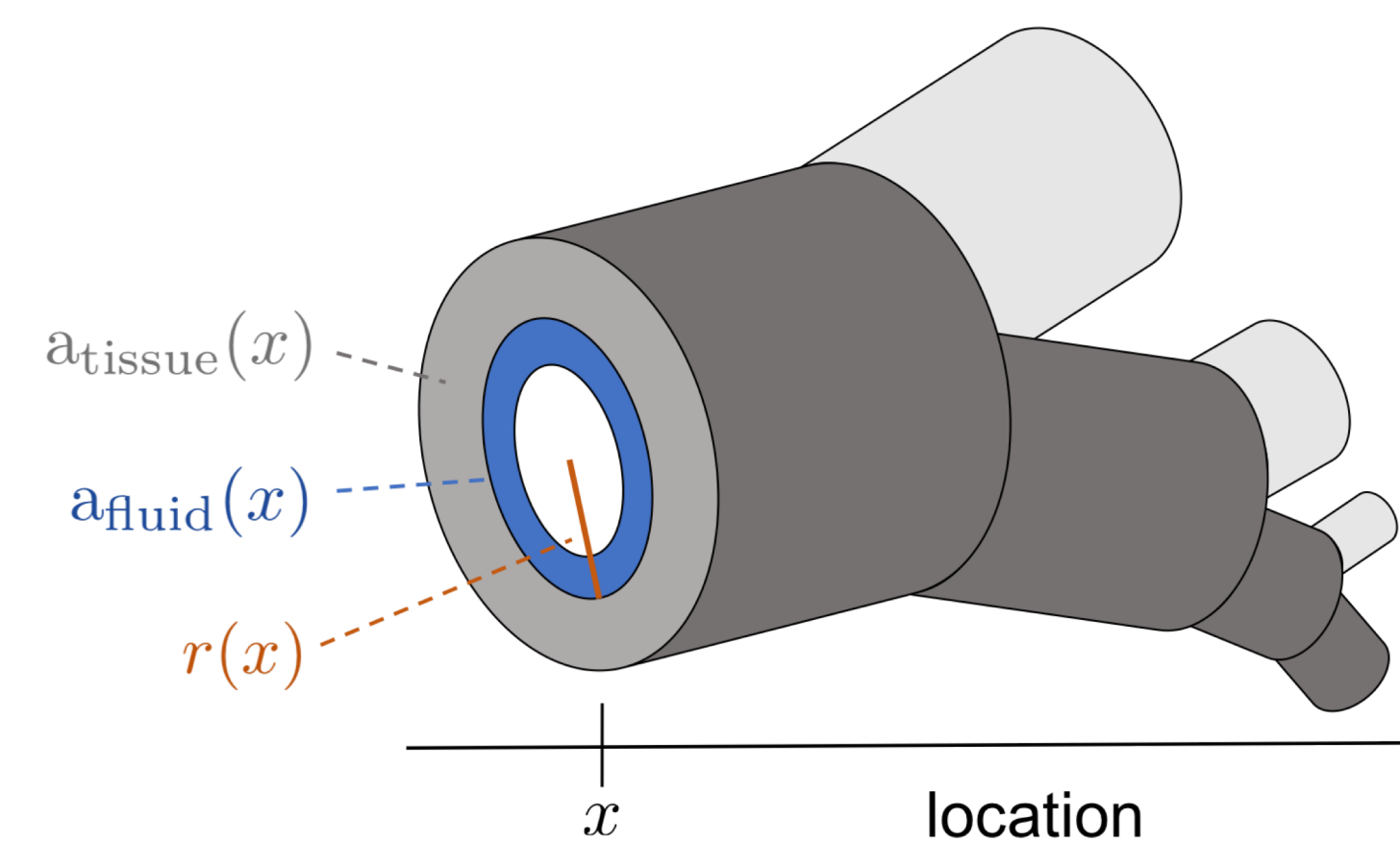
1 ODE per particle size Nernst-Brunner equation Transit compartments

But how to model the combined effect of these processes?

Objectives

- to develop and implement a mechanistic **partial differential equation** framework for pulmonary dissolution, mucociliary clearance and pulmonary absorption
- to confront PDE model predictions to clinical data
- to evaluate suitability for predicting the pulmonary bioavailable fraction

Mathematical model



Symbol	Parameter meaning
s	particle volume
x	location along typical airway
$\rho(t, x, s)$	size-/location-structured density
$d(C_{\text{fluid}}, S)$	saturable dissolution model
$\lambda_{\text{mc}}(x)$	mucociliary clearance
R	blood-to-plasma ratio
$K_{\text{p,tissue}}$	(unbound) plasma/lung tissue partition coefficient
k_p	permeability
$r(x)$	airway radius (including mucus)
a_{fluid}	cross-sectional area of lining fluid
a_{tissue}	cross-sectional area of lung tissue
$q(x)$	location-resolved blood flow

Physiological parameters mainly from [6,7]

Undissolved drug

$$\partial_t \rho(t, x, s) + \partial_x [\lambda_{\text{mc}}(x) \rho(t, x, s)] - \partial_s [d(C_{\text{fluid}}(t, x, s) \rho(t, x, s))] = 0$$

Mucociliary clearance Saturable dissolution

Drug in lining fluid

$$a_{\text{fluid}}(x) \partial_t C_{\text{fluid}}(t, x) = \int_0^{s_{\text{max}}} d(C_{\text{fluid}}(t, x, s) \rho(t, x, s)) ds - k_p 2\pi r(x) \left(C_{\text{fluid}}(t, x) - \frac{C_{\text{tissue}}(t, x)}{K_{\text{p,tissue}}} \right)$$

Dissolved drug Absorption to tissue

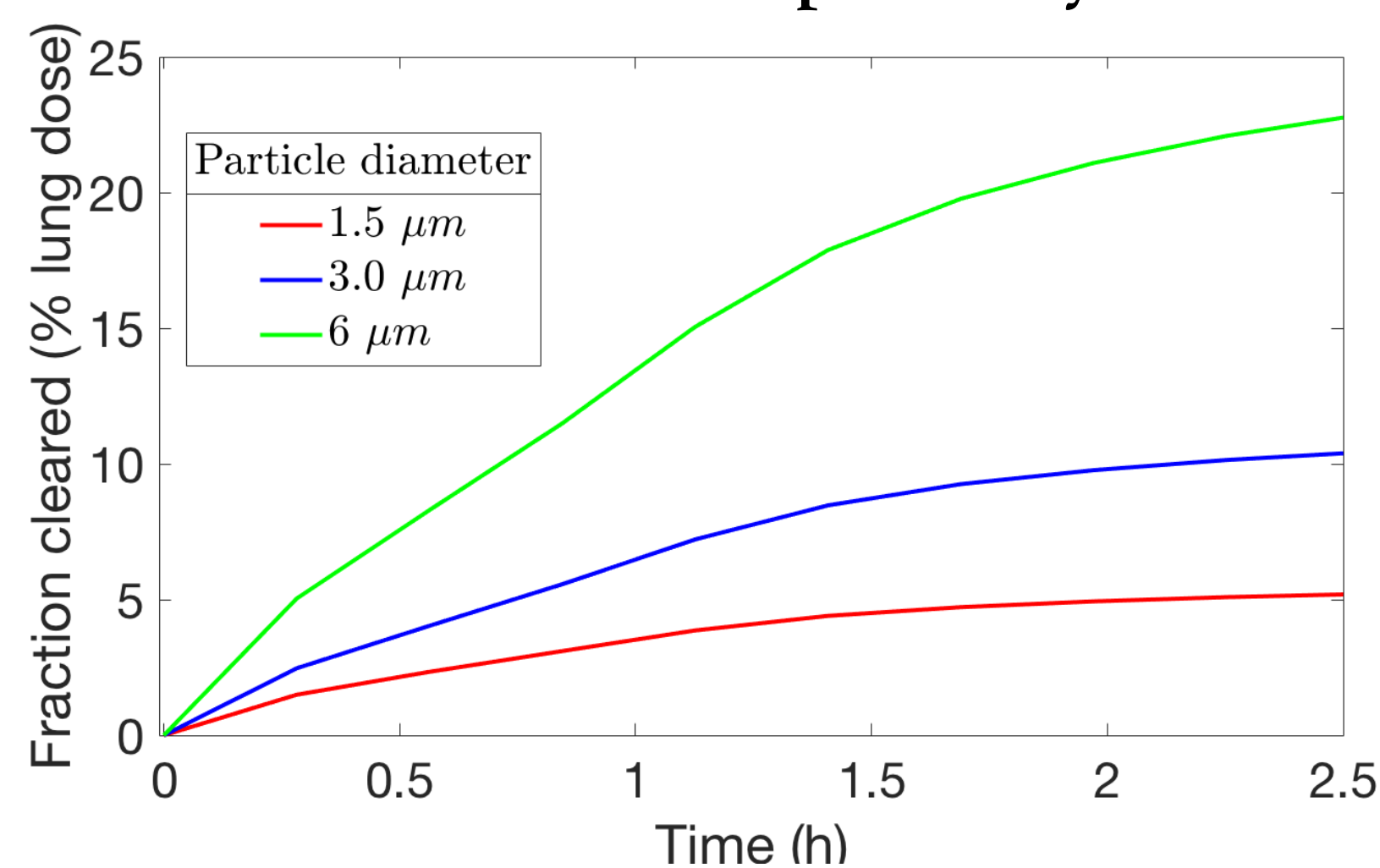
Drug in lung tissue

$$a_{\text{tissue}}(x) \partial_t C_{\text{tissue}}(t, x) = k_p 2\pi r(x) \left(C_{\text{fluid}}(t, x) - \frac{C_{\text{tissue}}(t, x)}{K_{\text{p,tissue}}} \right) - q \frac{R C_{\text{tissue}}(t, x)}{K_{\text{p,tissue}}}$$

Distribution to plasma

Results: Fluticasone propionate inhalation

Particle size-dependency



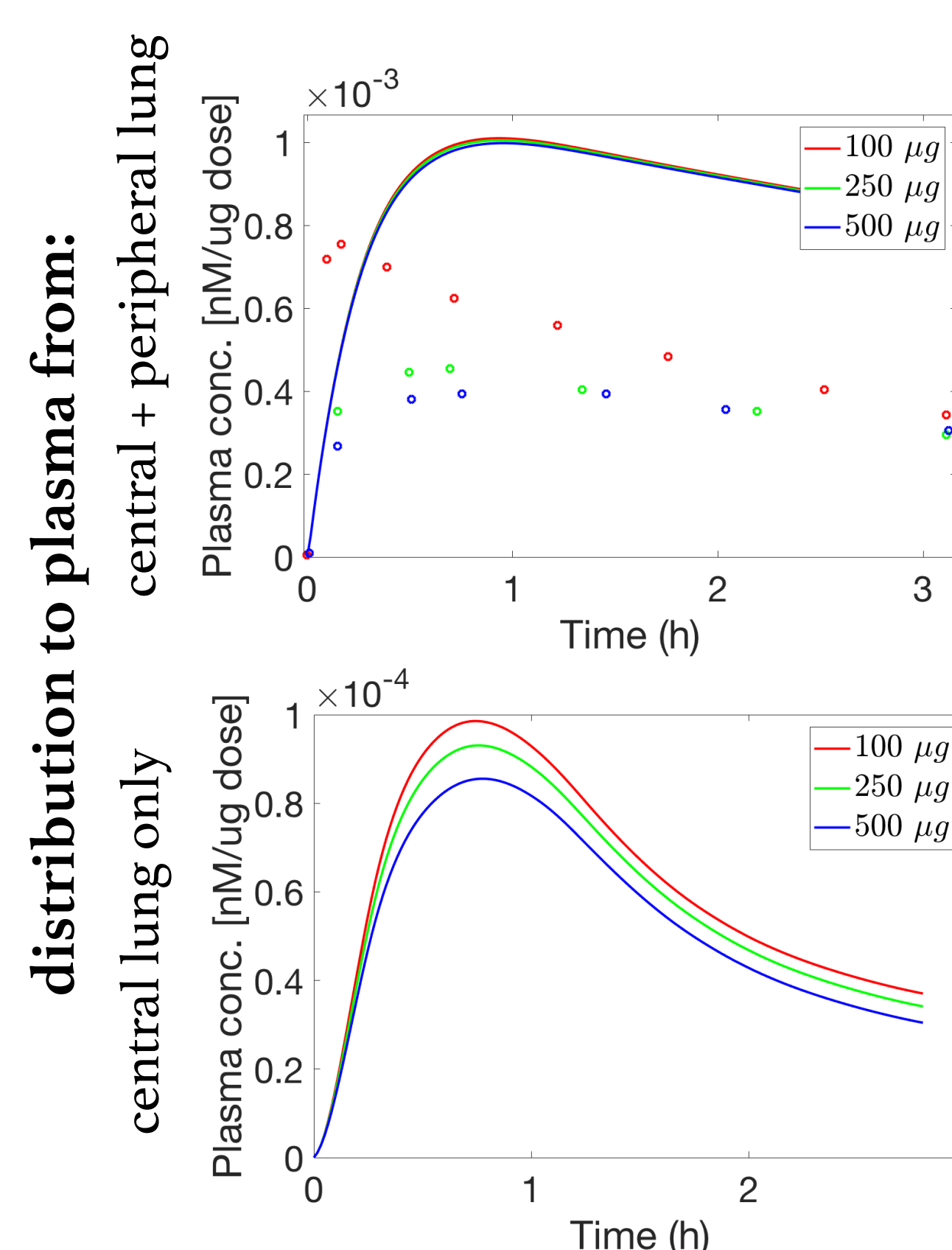
- identical doses, different inhaled particle sizes
- size-dependent deposition patterns + dissolution
- location-dependent mucociliary clearance

aerodynamic diameter	AUC Usmani [pg h/mL]	AUC PDE model [pg h/mL]
1.5 μm	923.28	355.6
3 μm	891.15	291.55
6 μm	222.08	211.6

qualitative agreement

Dose-dependency [2]

- identical particle sizes, different inhaled doses



in principle:
nonlinear effect possible;
not with current parametrisation

Discussion

Overall agreement between PDE system and clinical PK observations; but extent of nonlinearity underpredicted (no fitting).

Potential reasons:

- lower saturation solubility *in vivo* compared to available *in vitro* data.
- differing saturation solubility between conducting airways (mucus) and alveolar space (surfactant-containing alveolar lining fluid)
- thinner airway lining fluids than reported in literature
- more central deposition in asthma patients compared to healthy volunteers
- heterogeneous particle distribution within airway generation (“deposition hot spots”)

Conclusions

PDE model developed to predict the complex interaction between

- dissolution (particle size-dependent, saturable),
- mucociliary clearance (location-dependent),
- pulmonary absorption (location-dependent).

qualitative description of nonlinearities

Perspectives

- confront model predictions to other drugs (e.g. inhaled budesonide) / insoluble particles
- account for airway heterogeneity and refine dissolution / clearance models
- long-term: assess local uptake profiles for different formulations / schedules; evaluate pulmonary selectivity for model compounds / development candidates

References

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