CFD Research Corporation

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A Multiscale framework for Computational Inhalation Pharmacology

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CFD Research Corporation: Divisions

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- **Biomedical & Life Sciences (BLS)**
- **Computational Medicine & Bio (CMB)**
- **Energy & Materials**

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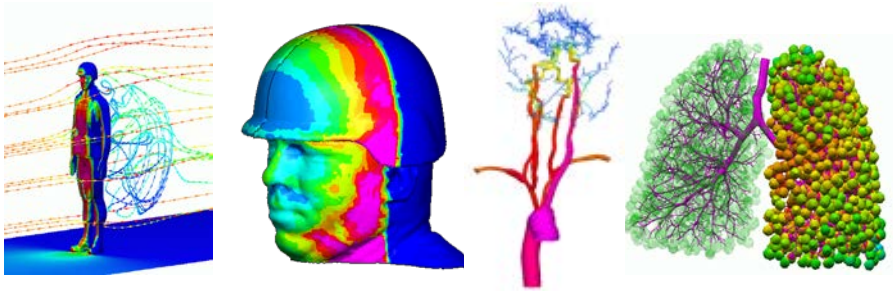
Designs, Prototypes, Simulation Tools & Analysis, 55^{+} Patents, …

Supporting Government and Industry since 1987

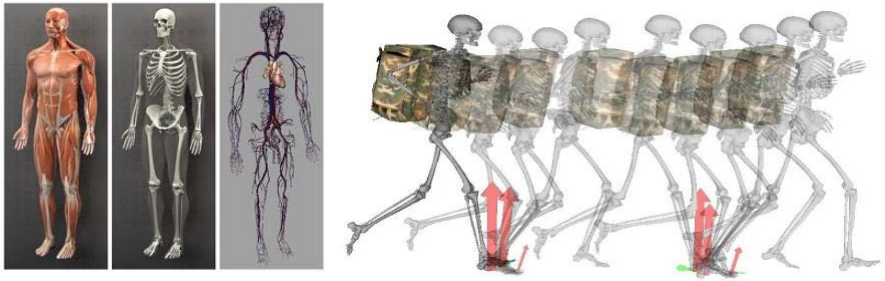
CMB Division Overview

Technologies that Improve Healthcare & Warfighter Performance

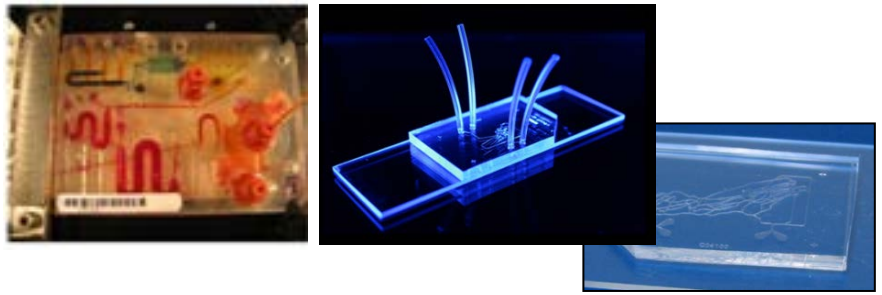
Computational Medicine & Biology



- **Warfighter Protection:** Traumatic Brain Injury, Improved Helmets/Pads/PPE, Vehicle Crew Injury, Noise Induced Hearing Loss
- **Warfighter Performance:** Lightening the Load, Spinal/Shoulder/Neck injury, Exoskeleton support systems, Pain & Fatigue
- **Personalized Health:** Metabolism, Diabetes
- **Drug Delivery, PK/PD, Toxicity Modeling**



Lab- & Organ-on-a-Chip Devices



- **Microfluidic biochips** for sample preparation and environmental, biological and clinical diagnostics
- **Synthetic Microvascular Networks (SynVivo)** for Drug Discovery

SYNVIVO

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The Scientist TOP TEN INNOVATIONS 2013

The Scientist Magazine
Top 10 Innovations 2013

CMB Core: Respiratory Physiology & Pharmacology

CoBi Models

CoBi Inhalation Pharmacology Environment

Patient End-user
Reduced order models

Human body

Lung anatomy mesh

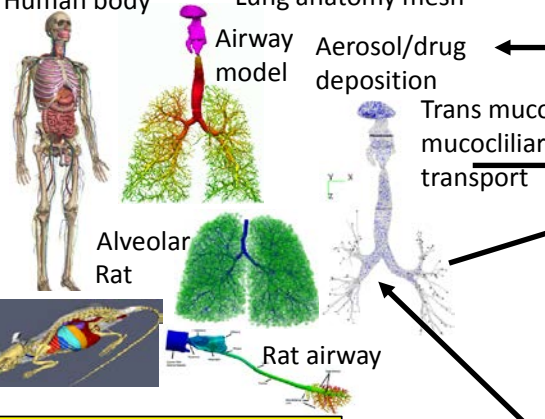
Airway model

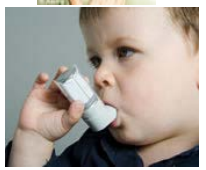
Aerosol/drug deposition

Personalized Model

Trans mucosal mucocliliary transport

Pharmacokinetics





Alveolar Rat

Rat airway

Population

Age, gender, Anthropometry

Airway mechanics & disease

Asthma airway

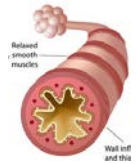
wall mechanics

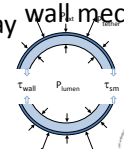
ASM cell

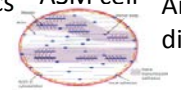
Airway dimensions

Biomarkers & diagnostics

Lung disease model
Disease progression







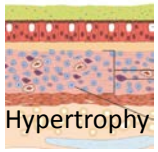
mucosal folding

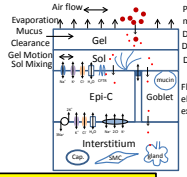
Contractile model

SpitoSmart
FEC, FEV1

Mucosal barrier model

Pharmacodynamics





Hypertrophy

CoBi lung mucosal model

CoBi-PharmaLab
PBPK/PD tools
on Android Tablet

SYK inhibitor

In vitro device/mode;

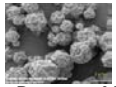
Wyss Lung on chip

Pharma End-user
High fidelity models

Drug/vehicle properties

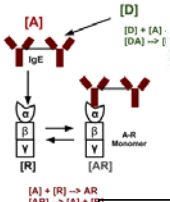
Budesonide

QSAR

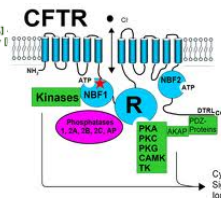


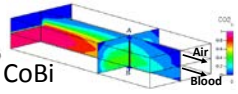
Porous NP

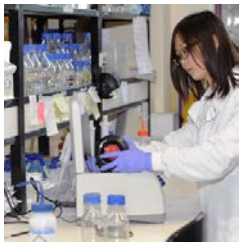
Micelle, PEG,..
Contr. release



CFTR modulator







Turbuhaler

Turbuhaler model

Nebulizer
MDI,....

Systems Biology

CoBi
Lung on chip model

Current Respiratory Projects

FDA

- PBPK modeling and simulation of lung absorption via oral inhalation.
  Goal is to aid generic drug development.

Pharma

- Computational tools for modeling asthma pathophysiology and pharmacology.
  Goal is to evaluate inhaled corticosteroids in asthma.

NIH

- Develop computational tools to optimize the efficacy of pulmonary drug delivery process.

Others

- **DTRA**: Multiscale computational framework for respiratory aerosol pathogenesis, protection and countermeasures (RAPP)
- **CBD**: Aflatoxin pharmacokinetics and liver biotransformation
- **FDA**: PBPK for ocular drug development

Current methods for predicting fate of OIDPs

- **Experiment/Cast data** for the drug deposition in various airway sections (TB, Central, Pulmonary, Alveolar)
- **Empirical Models** (e.g., Typical Path Lung model) to predict the drug deposition, as a function of the drug particle diameter and the inhalation velocity
- **0D compartmental models** to model the subsequent dissolution, transport across the lung wall and mucosal clearance, systemic circulation and clearance

Limitations of the current methods

- **Limited predictability** of regional pulmonary drug deposition
- Drug deposition is **not spatially resolved**
- Modeling monodisperse instead of **actual poly-dispersed** drug particles
- **Empirical models may not account for** flow physics, particle-flow interaction, and the local effects (vorticity near the ridges, turbulence effects)
- **Unavailability of spatial distribution** of the drug in molecular (dissolved) form:
  - Limited knowledge of the bio-availability of the drug in required targets
  - Extension to diseased states (including locally constricted airways, blocked airways, thickened surface lining liquid) may be challenging

Our multiscale solution

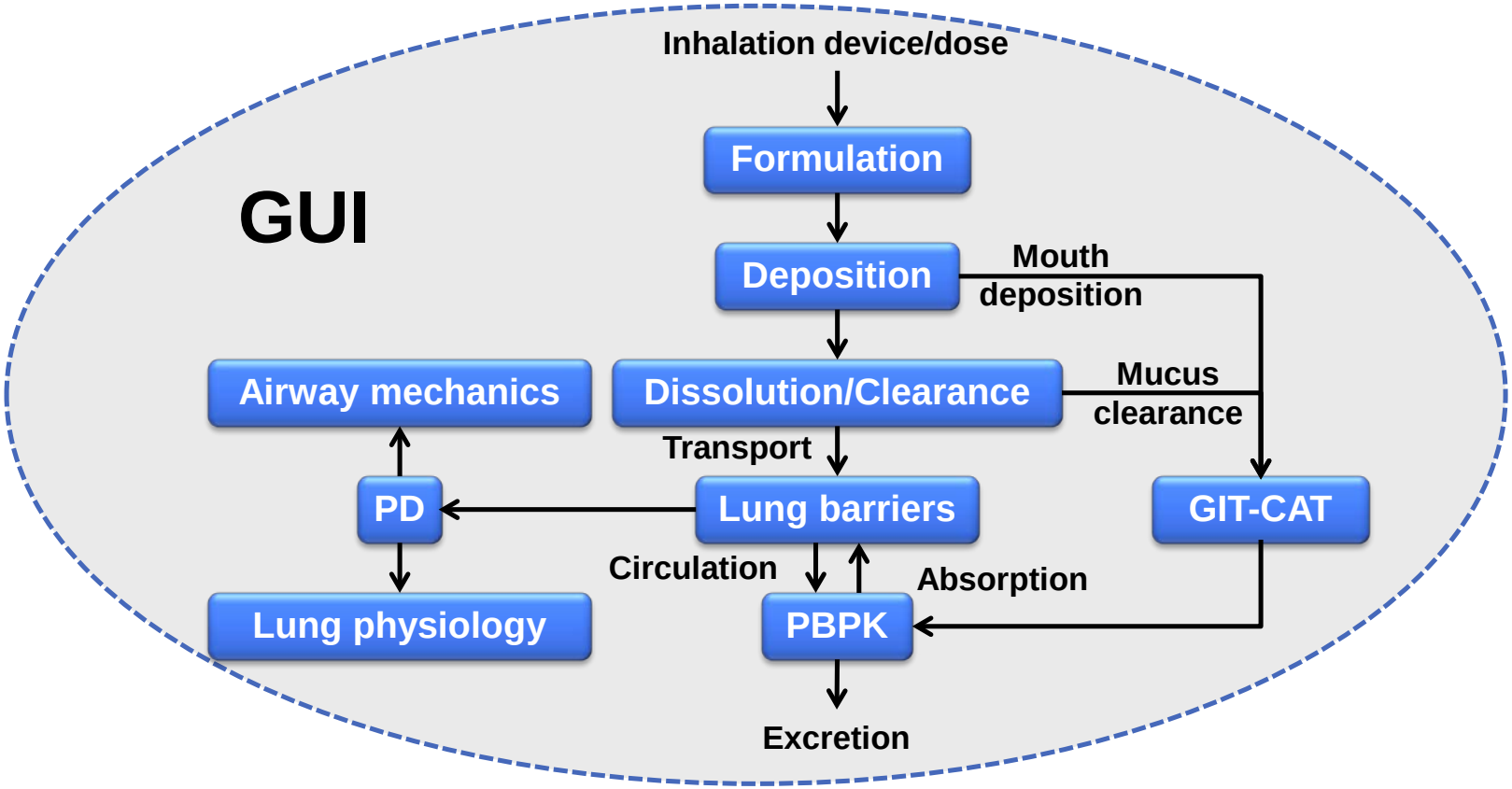
CFDRC's computational multiscale framework for predicting Pulmonary Drug Delivery

- **Computational Fluid Dynamics** (CFD) to obtain the flow physics:
  - Captures localized phenomena (vorticity at the ridges, wall stress turbulence
  - Serial/Parallel simulations
- **Euler-Lagrangian particle transport** for spatially resolved drug deposition:
  - Handles poly-dispersed sizes
  - Captures the inertial, flow and geometry effects
  - Can run concurrently with the flow module or using the saved flow velocities
- **Quasi 3D (Q3D) formulation** to model the dissolution, transport, and mucosal clearance for the upper airways
  - Faster than traditional CFD: 3-25K times faster!
  - Ideal for studying O(days) time scales
  - Obtain the dissolution effects in a spatially distributed manner
  - Obtain the spatio-temporal drug concentration levels in the airways!
- **Integrated 0D compartmental models** for dissolution, transport across the lung walls in the lower airways

CFDRC-FDA: Goals and framework

- Develop, evaluate, and improve physiologically-based absorption and pharmacokinetic models of pulmonary (inhaled) drugs.
- Support the development of generic OIDPs.

Integrated view of the computational framework for pulmonary drug delivery and PBPK-PD simulation



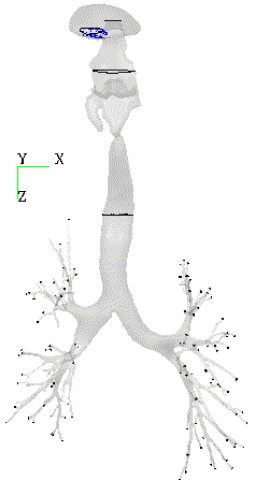
Framework: Drug deposition

3 different modeling approaches to simulate drug particle deposition from air to the ‘sticky’ lung mucosa (deposition)

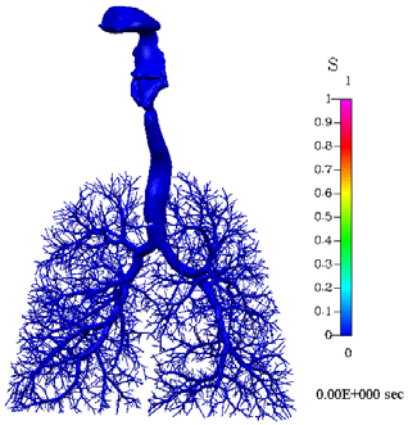
CFD Model Geometry & mesh generation; Inhalation profile; Airflow; Size-based monodisperse and polydisperse particle motion, transport and deposition. Represent multiple generations.

Hybrid-CFD Wire Model Mesh is represented as tubes in 3D space where simulation along the radial direction is greatly simplified - resulting in faster simulations. Represent full lung.

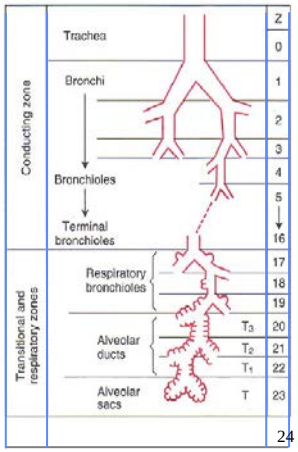
Empirical TPL Model Typical Path Lung (TPL) model is capable of predicting the formulation property based particle depositions in the mouth/NOPL, TB, and pulmonary (P) region for all generations of lung.

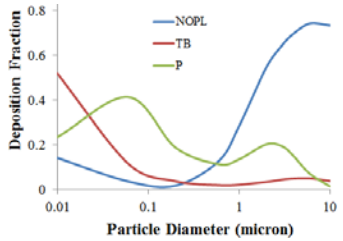


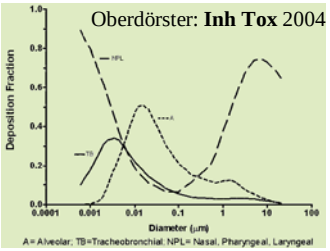
CFD particle motion (10µm dia)
Free vs Stuck



Hybrid: CFD (NOPL and trachea)+ Wire (rest)







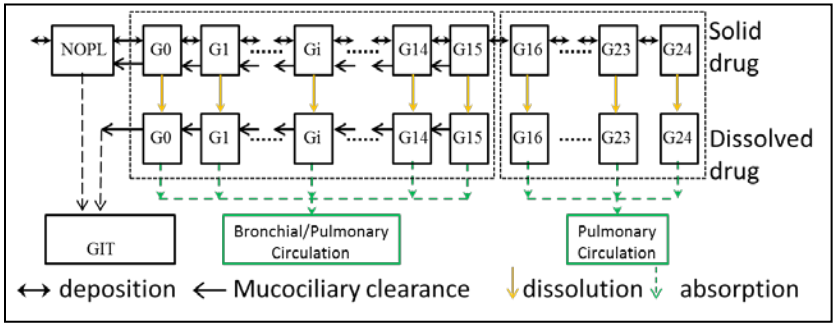
TPL model: Predict deposition in NOPL, TB, & P of all 23+1 Gen.

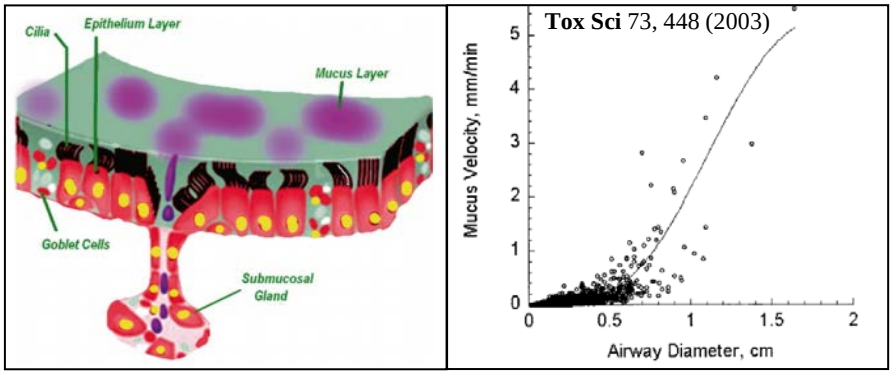
Framework: Mucous-to-blood transport

Multi-compartmental model for drug dissolution, transport, absorption, and clearance from respiratory mucus to blood crossing multiple lung barriers

Dissolution & Clearance

- Modified Noyes-Whitney type equation to evaluate drug dissolution in any compartment based on dose, solubility, diffusivity, size, and mono/poly-dispersability.
- Experimental data-based mucociliary transport equation to account for loss of dissolved drug when mucous moves from lung branches (only airways) → Mouth → Gut.





Mucociliary escalator

$$\frac{dM_S}{dt} = -\frac{3M_S}{\tau}\left(1-\frac{M_d}{C_S V}\right)$$

Dissolution eq

$$m_V = 5.5(1-\exp(-0.4962D^{2.2694}))$$

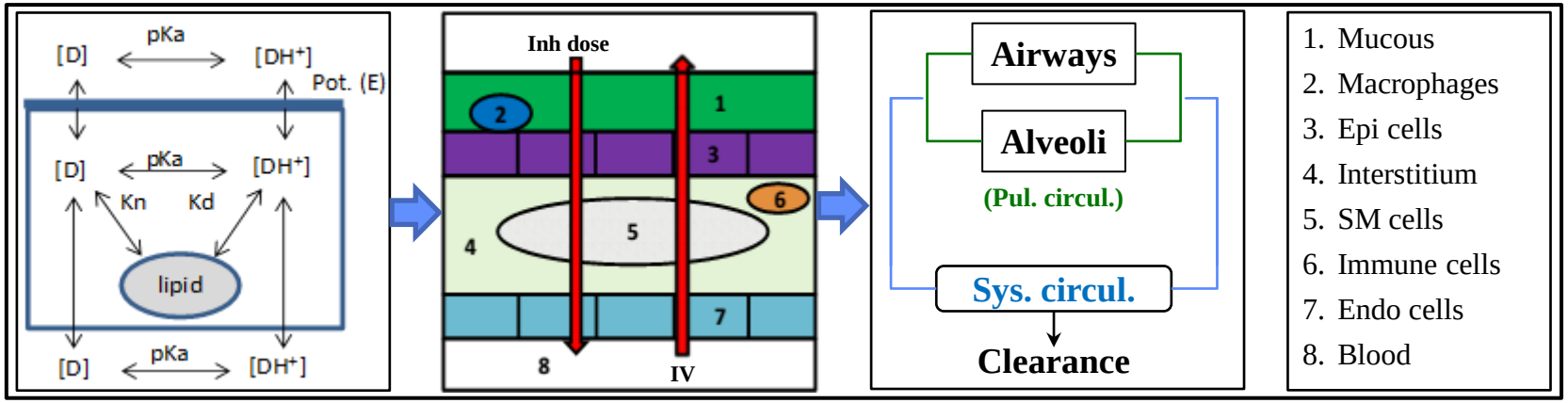
Mucociliary clearance eq

Framework: Lung barrier transport

Multi-compartmental model for drug dissolution, transport, absorption, and clearance from respiratory mucus to blood crossing multiple lung barriers

Barrier transport /absorption

- Modified from Yu *et al*. **Pharm Res.** (2010). Predict drug retention/transport across lung tissue



- Model considers drug ionization, partition into lipid components, and passive diffusion across the air-plasma barrier

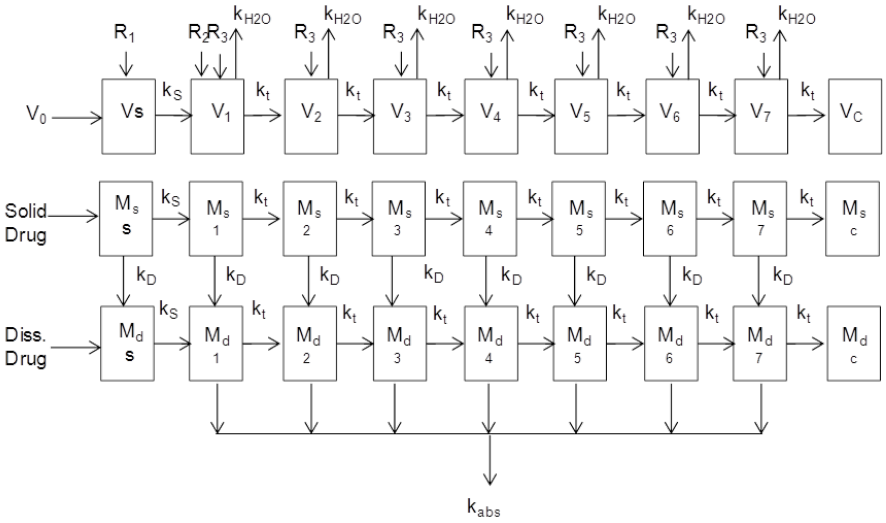
- Processes are determined by drug physicochemical properties such as logP and pK_a as well as tissue anatomy and physiological/pathological properties (barrier thickness).

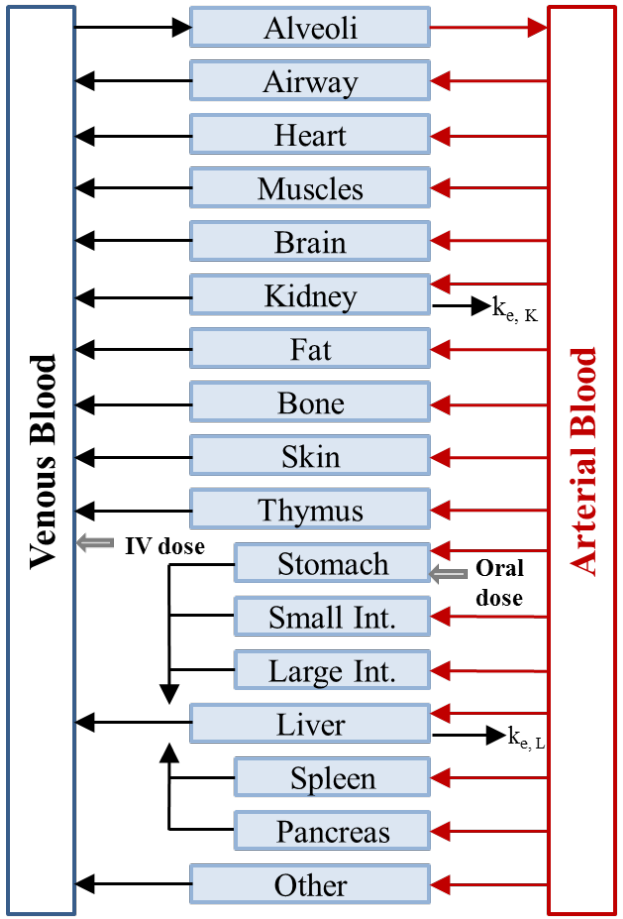
Framework: Whole-body PBPK

Whole-body PBPK model for drug dissolution, transport, absorption, and clearance from respiratory mucus to blood crossing multiple lung barriers

Whole-body human PBPK

- Central component of drug ADME
- Connect lung barrier model (through blood compartment) and gut models
- 19 compartments that can test multiple delivery route
- **Gut model (CAT)**: Important component since the swallowed drug contributes to drug PK
- 9 segments connecting ‘stomach(1)-intestine(7)-colon(1)’

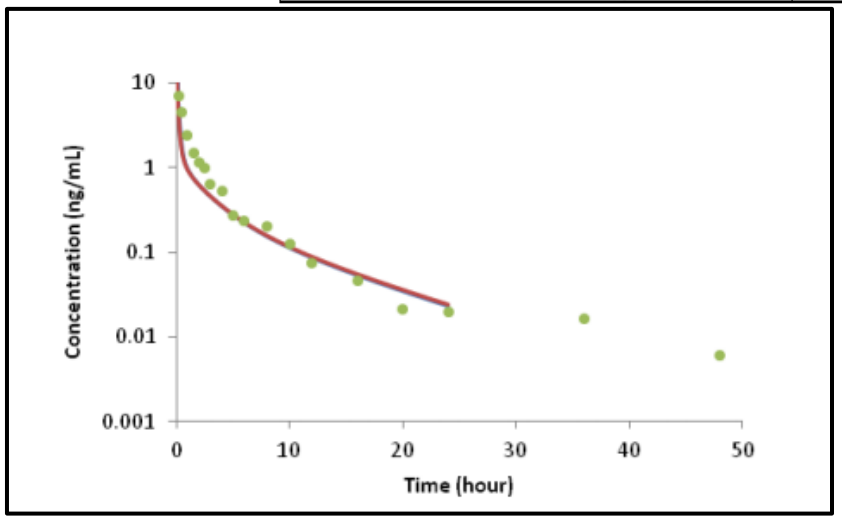




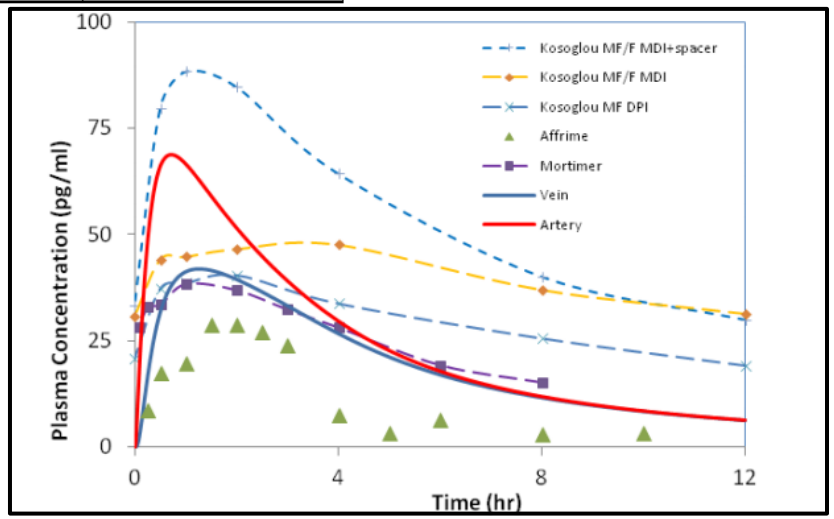
Framework: Selected results - MF

Parameters values for inhaled Mometasone Furoate (MF) & Budesonide

Parameters	MF	Budesonide
Particle density (g/cm^3)	1.23	-
MMAD of particles (µm)	2.2	-
Molecular weight	427.4	430.5
Intestinal permeability(cm/hour)	0.11	-
Solubility (µg/mL)	5.23	-
B2P	0.55	0.90
Protein Binding	98-99%	85-90%
fu	1.5%	12.5%
Liver extraction rate	99%	80%
Half-life time after IV (hour)	4.5	2.0-3.6
First Pass Effect	99%	10-20%
Clearance rate after IV (ml/min)	892	



MF plasma concentration after 400 µg **IV** dose. Plotted (solid circles) are the experimental data after IV administration of 400 µg from Affrime et al., 2000.



MF plasma concentration after 400 µg **inhalation** dose. Plotted (solid circles) are the experimental data from Mortimer et al. (2007), Affrime et al. (2000) and Kosoglou et al. (2013).

Affrime, *JCP, 40(11), 2000;* **Mortimer**, *BJCP, 64(4), 2007;* **Kosoglou**, *IJCOPD, 8, 2013*

Framework: Selected results - Budesonide

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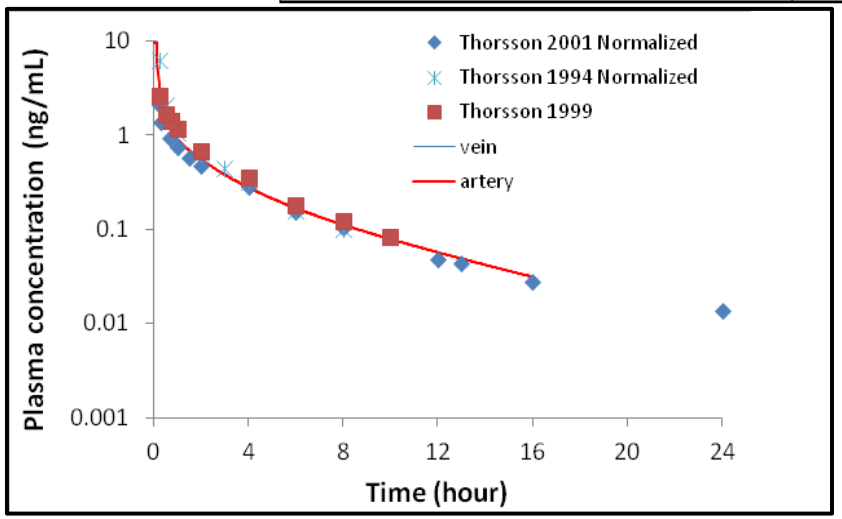
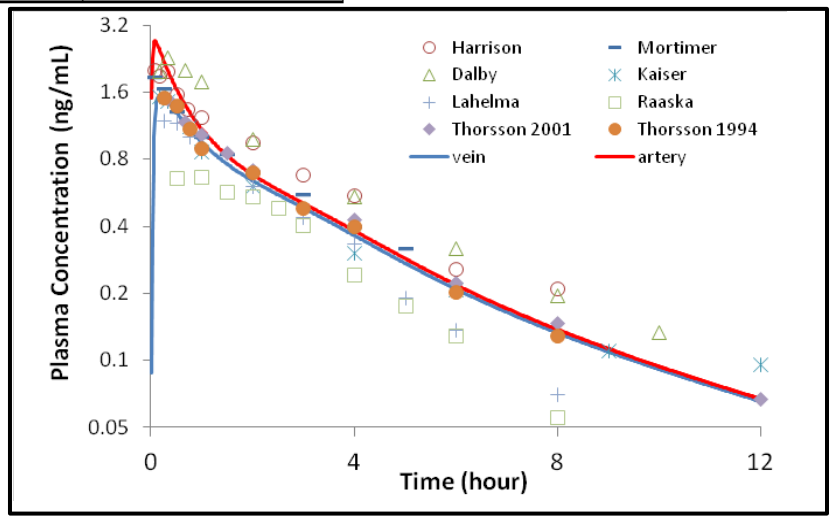


Budesonide plasma concentration after 400 µg **IV** dose. Plotted are the experimental data from Thorsson et al. All experimental data is normalized to dose of 400 µg.



Budesonide plasma concentration after 1000 µg **inhalation** dose. Plotted are the various experimental data normalized (for some) to dose of 1000 µg.

Thorsson, *BJP, 52(5), 2001;* **Thorsson**, *ERJ, 7(10), 1994;* **Thorsson**, BJCP, 47(6): 1999; **Affrime**, *JCP, 40(11), 2000;* **Harrison**, *Thorax, 58(3), 2003;* **Dalby**, *RR, 10(1), 2009;* **Lahema**, *BJCP, 59(2), 2005;* **Mortimer**, *BJCP, 64(4), 2007;* **Kaiser**, *BJCP, 48(3), 1999;* **Raaska**, *CPT, 72(4), 2002*

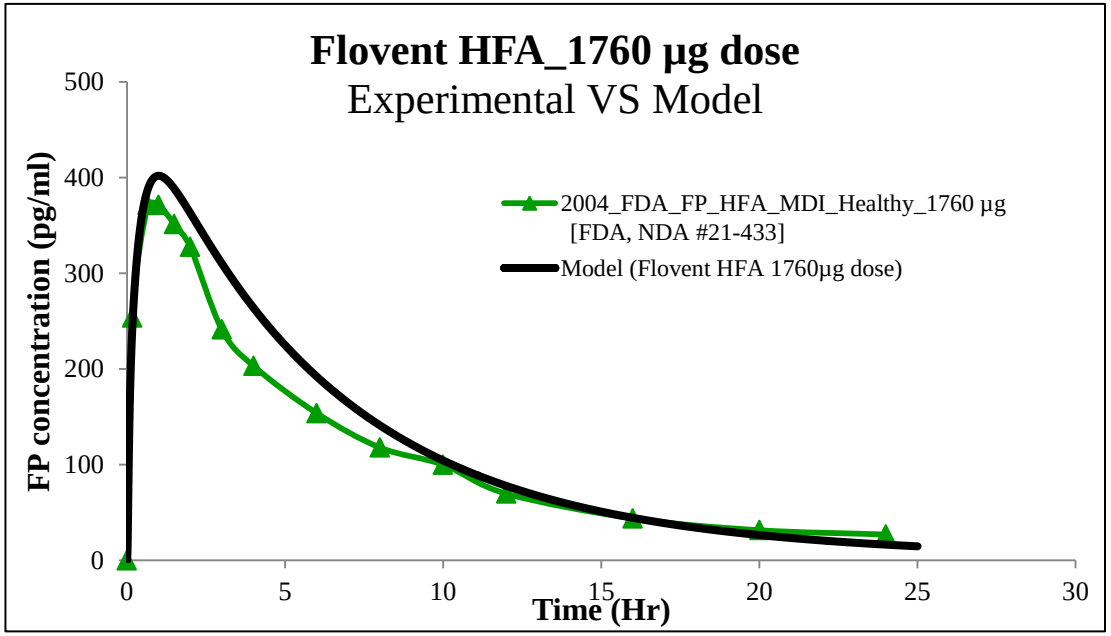
Framework: Selected results - FP

Flovent HFA with Fluticasone propionate (FP) simulation results

Plot shows the PK profile from FDA 2004 document (1760 µg dose)

Comparison is shown with Model output at 1760 µg dose

The PK properties are compared in the table below



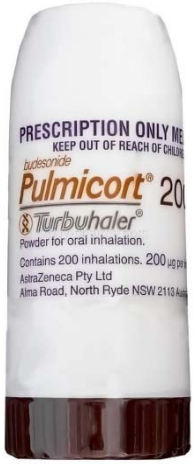
		Experimental_FDA 2004	Model
AUClast (pg*hr/ml)	Min-(**Mean**)-Max	1945-(**2495**)-3200	3000
C_{max} (pg/ml)	Min-(**Mean**)-Max	338-(**420**)-524	402
T_{max} (hr)	Min-(**Mean**)-Max	0.33-(**1**)-2.05	1
$t_{1/2}$ (hr)	Min-(**Mean**)-Max	5.92-(**6.63**)-7.42	5.7

[**FDA, NDA #21-433**; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021433s000_Flovent%20HFA_biopharmr.PDF]

FDA Framework (selected results - devices)

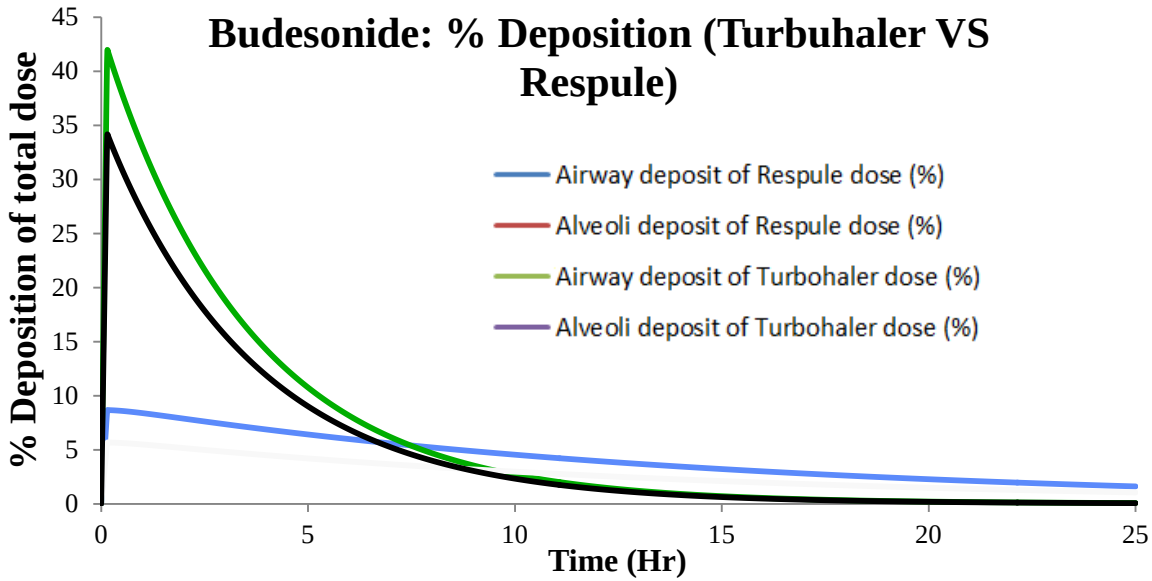
Device Comparison: Budesonide Turbohaler vs Respule

- Budesonide % deposition of two devices at different doses (500 µg for Respule and 1000 µg for Turbuhaler) shows that within 20 minutes of inhalation 43% (in alveoli) and 9% (in airways) of the total drug gets deposited in Respule inhalation while these numbers are 34% and 6% in Turbuhaler inhalation.
- Overall the drug amount drops quickly due to transport into plasma.
- Validation data for these devices is not yet available



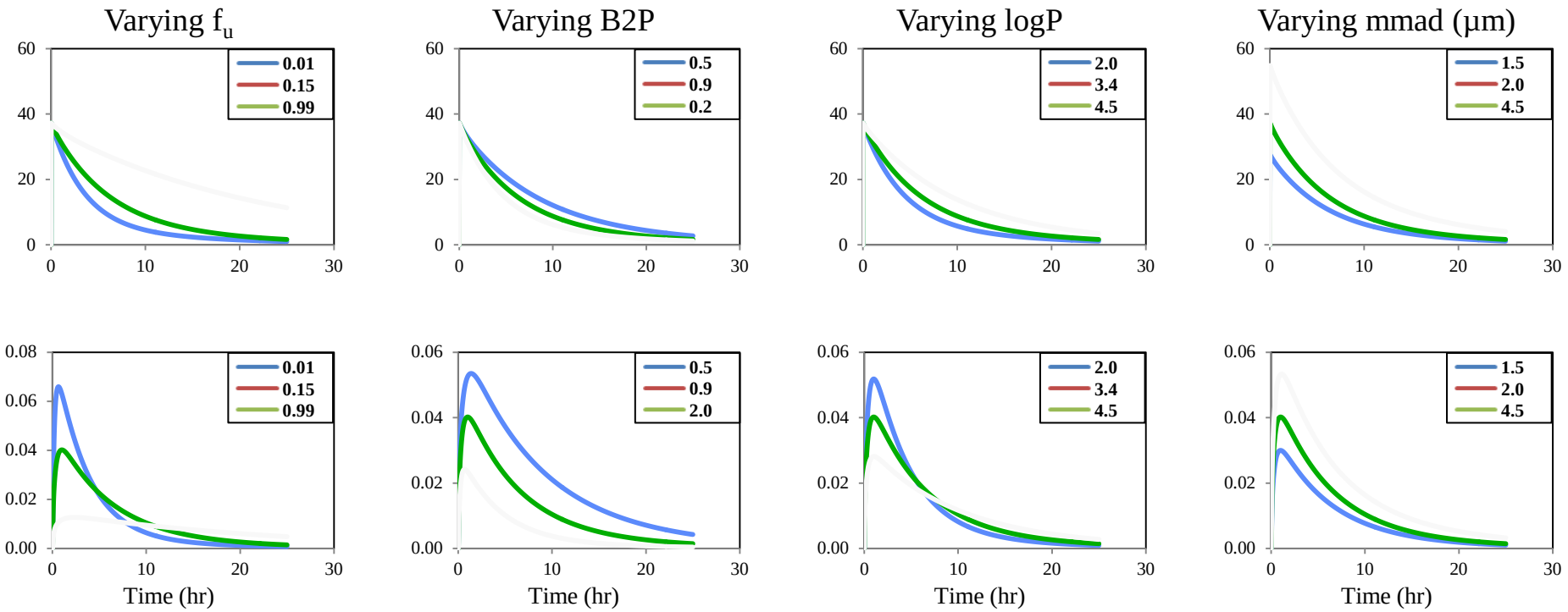
Turbuhaler

Respule



FDA Framework (selected results - property effects)

Model sensitivity:
Systematically varying key physicochemical properties to analyze
Pulmonary Vs Systemic (plasma) PK

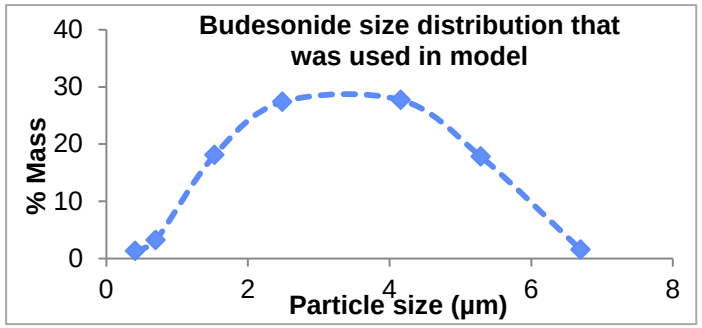


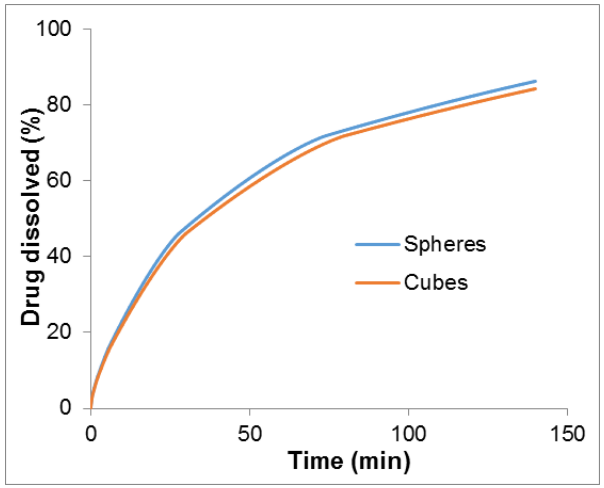
Upper row: **Pulmonary** concentration (µg/ml); Lower row: **Systemic** concentration (µg/ml)

FDA Framework (selected results - formulation)

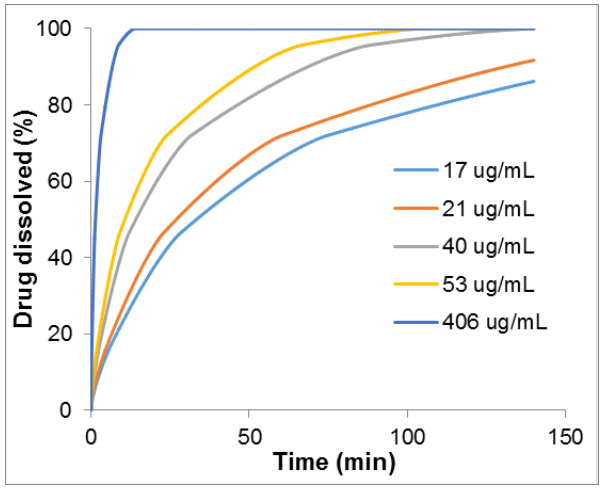
Formulation effects of pulmonary drugs on drug particle dissolution

- As FPF from devices are polydisperse, different fractions of drug size distribution is used
- A modified Nernst-Brunner eq.
- Validation: **Test drug Budesonide**
  - Polydisperse aerosol of dose = 200 µg
  - Solubility = 17 µg/ml
  - Diffusion coeff. = 6.2e-6 cm^2/min
  - Dissolution vol. = 1 L

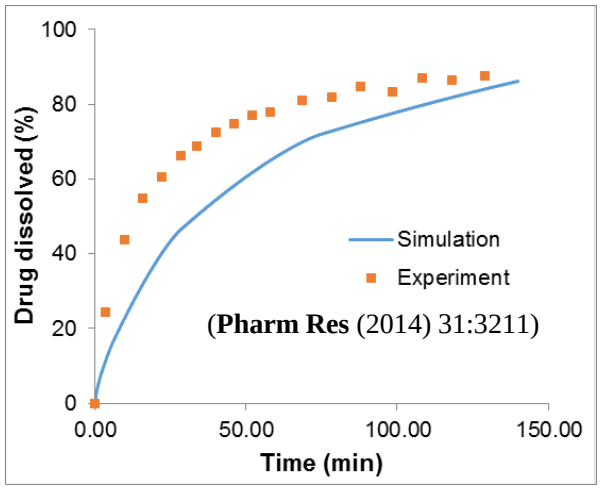




Effect of drug shape
(Faster for spheres)



Effect of solubility
(Faster dissolution=higher solubility)

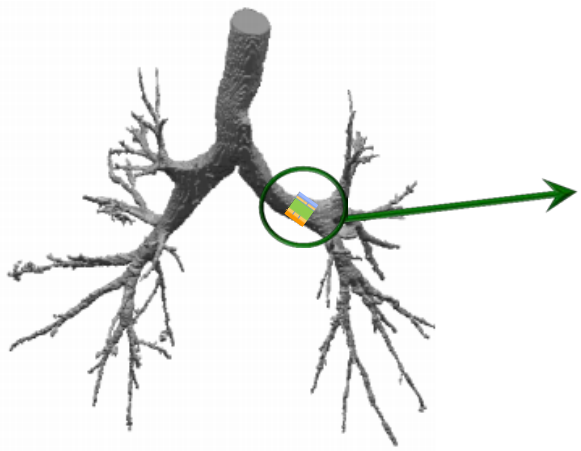


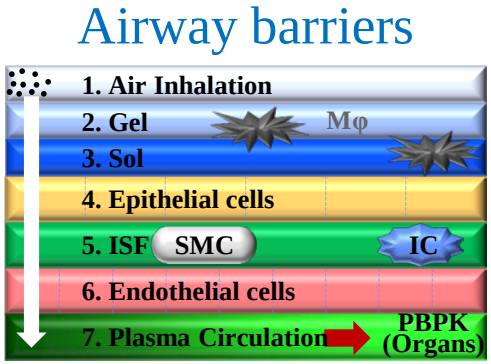
Experimental validation
(Overall good trend)

Framework: Review and assumptions

- **<u>Quick Review</u>:** Our compartmental model with embedded Rosania's model for the drug transport across the lung airway walls has been tested previously, its main features are

  - Module involves deposition on the lung walls using a TPL method
  - Dissolution on the surface lining liquid
  - Transport across the lung walls into the blood
  - Mucosal transport along the trachea to drain into the stomach





Schematic of the Rosania model

- **<u>Broad Assumptions:</u>**
  - TPL model for the deposition
  - Averaged concentrations from 1 (trachea) to 15th generation: airway zone
  - Averaged concentrations from 16-24th generations: alveoli zone
  - Limited to mono-dispersed drug particles

Framework: 2nd generation of modeling

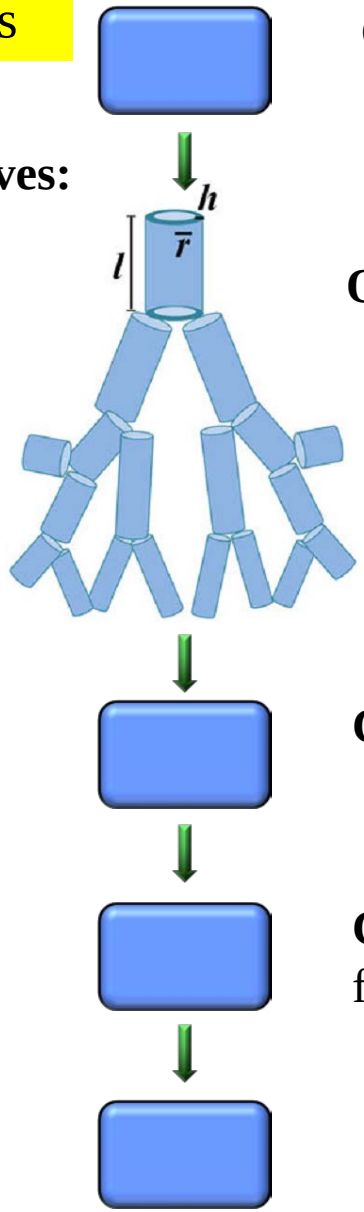
Rosania model implementation in Quasi-3D wires

- **Converting the Rosania model to the Quasi-3D format has following advantages:**
  - Not lumped: Individual concentrations at each lung airway (i.e., the concentrations of the drug can be made available at any location)
  - Thus, a valuable indicator to predict the spatial efficacy of the treatment (for instance, the deposition is more on the bifurcations than on the trachea)
  - Use of our CFD/particle-transport modules to obtain the depositions.
  - These will be used as the starting point for the quasi-3D model
  - Can also use the deposition data from other sources (e.g., from Tian *et al*)
  - NOTE: This can't be done in Compartmental due its lack of 3D coordinate space
  - Needs some pre-processing to get the cell-id in the wire coordinates
  - Dissolution is spatially resolved in Q3D
  - However, the Q3D takes ~20 mins for 1 day worth of simulation, compared to few minutes for Compartmental model

Framework: 2nd generation of modeling

Rosania model implementation in Quasi-3D wires

- **The major physics/architecture of Q3D model involves:**
  - zygote Q3D spatially resolved section,
  - lower airway section,
  - alveolar section,
  - mucosal effect from #15 to the gut,
  - NOPL deposition, transported/convected to the GUT by cilia motion
  - Rosania model in the lung,
  - dissolution in the GUT and transport to the liver,
  - clearance in the liver and then drain to the vein,
  - drug diffusion from the airways to the vein,
  - drug diffusion from the alveoli to the artery,
  - drug convection from artery to the organs and from the organs to the vein,
  - additional clearance at the kidneys.



CFD deposition input

Q3D from trachea till G8 (Rosania+ MCL+ Dissolution)

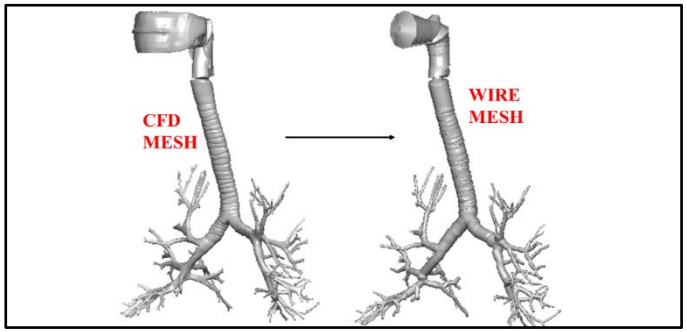
Compartmental from G9-G15

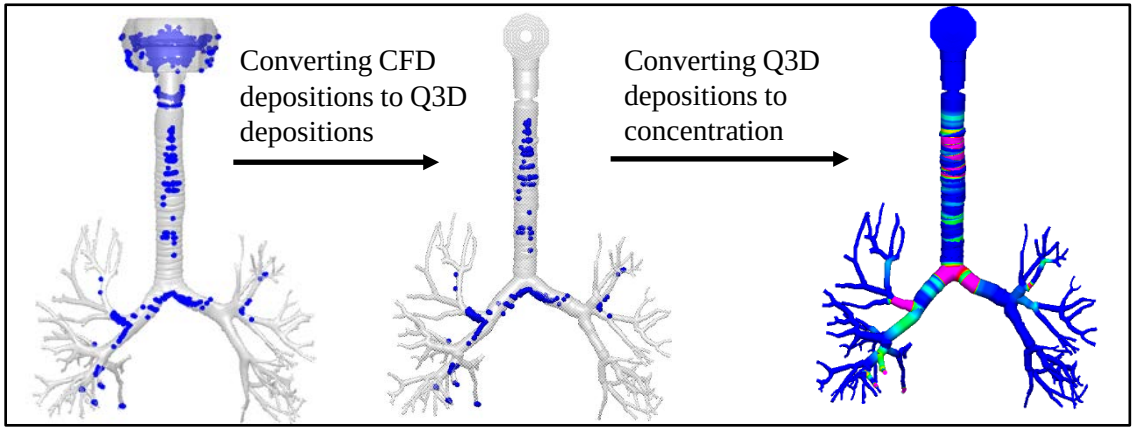
Compartmental from G16-plasma

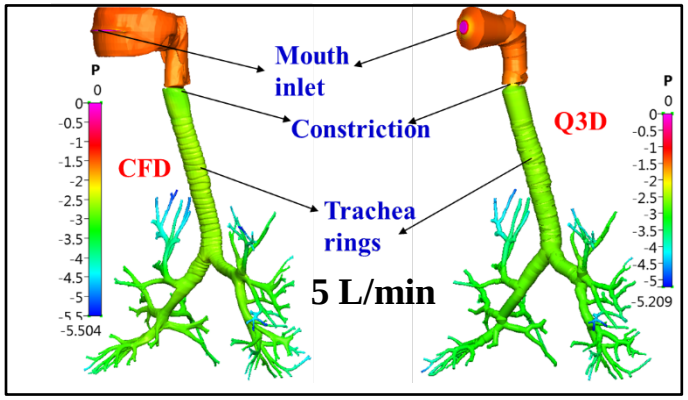
PBPK

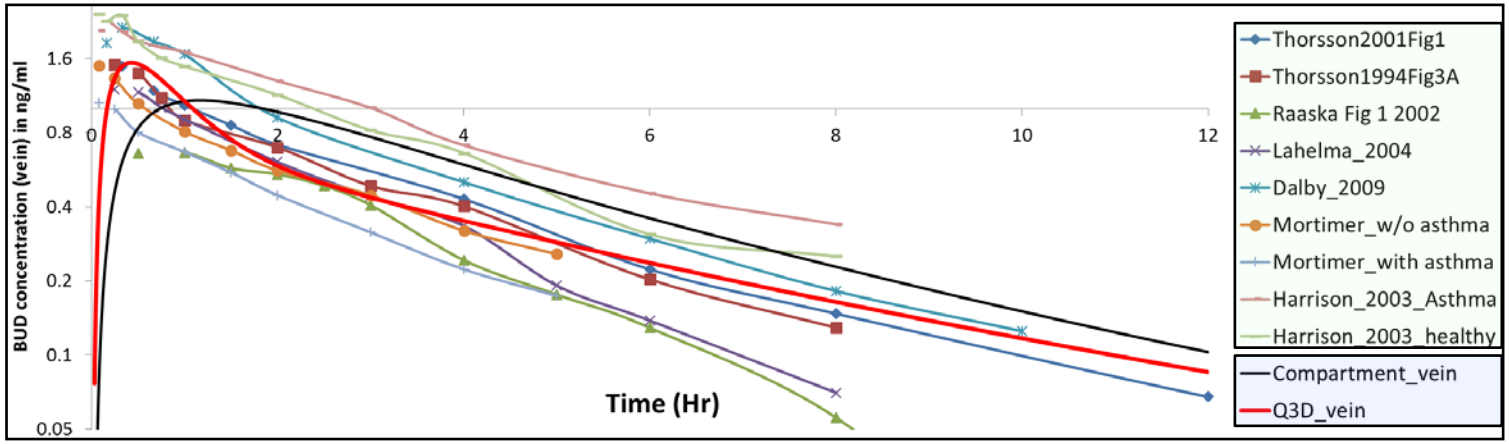
PK Transport Model in Spatial Quasi-3D (Q3D) mode

- **Q3D** (wire) versus **CFD** versus **Compartmental** PK models
- 3D CFD model (and mesh) has around 5-6 generations (200+ outlets!) : O(1.5M) cells
- CFDRC team was able to generate a quasi-3D wire mesh using the above mesh: O(1500) cells
- Used this Q3D for solving the PK equations spatially







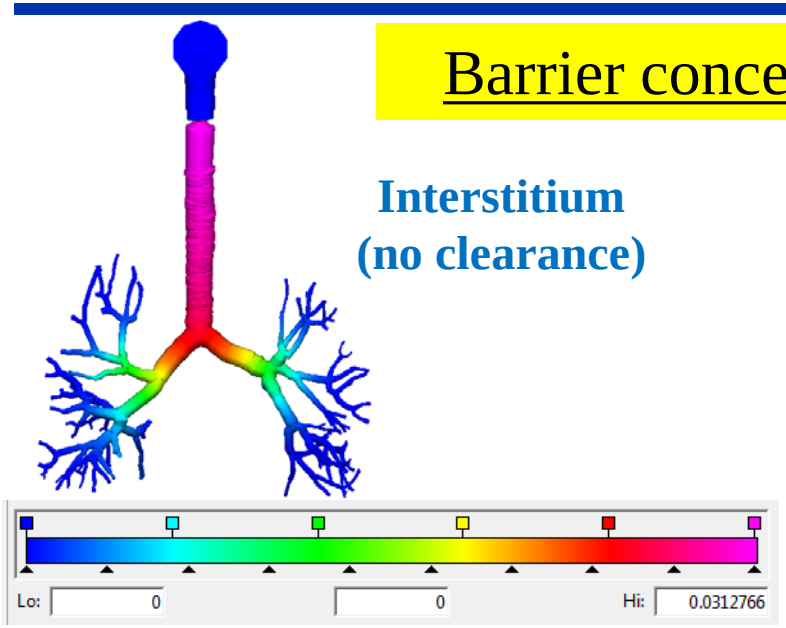


Predicted **Budesonide**(Inhalation, 1000 µg) vein PK compared to available experimental data. Predicted plots are for Q3D output (red) compared to compartmental output (black) [References are same as in Slide # 13-14]

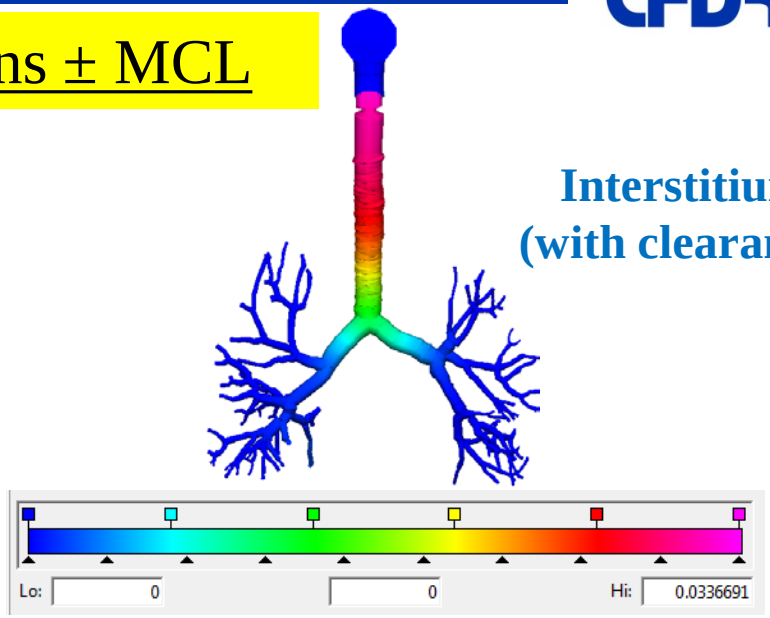
Multi-scale scenario (250 min): Budesonide (1mg Inh. dose)

Barrier concentrations ± MCL

Interstitium (no clearance)

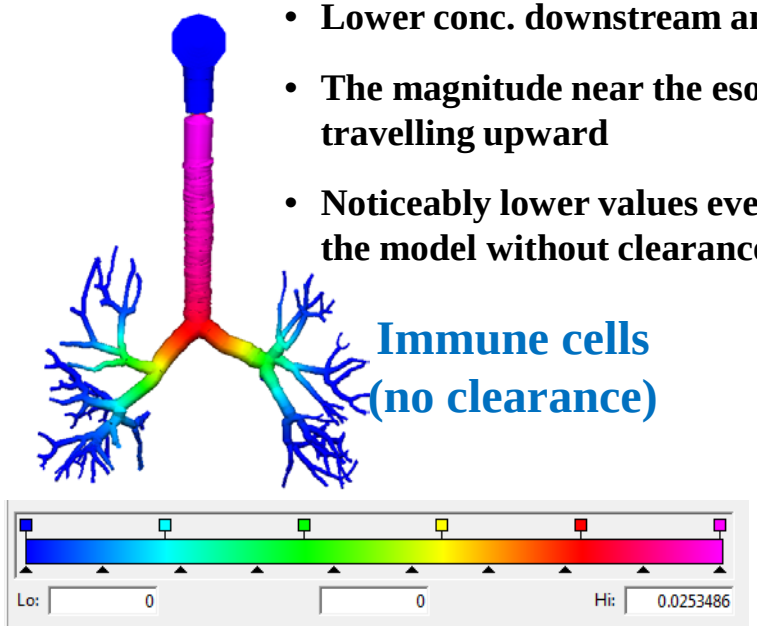


Interstitium (with clearance)

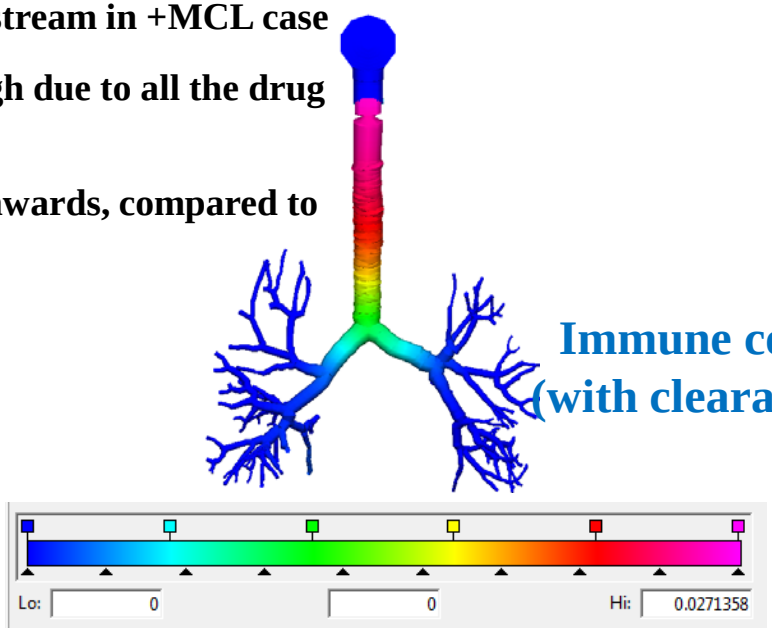


- **Lower conc. downstream and higher upstream in +MCL case**
- **The magnitude near the esophagus is high due to all the drug travelling upward**
- **Noticeably lower values even from B2 onwards, compared to the model without clearance**

Immune cells (no clearance)

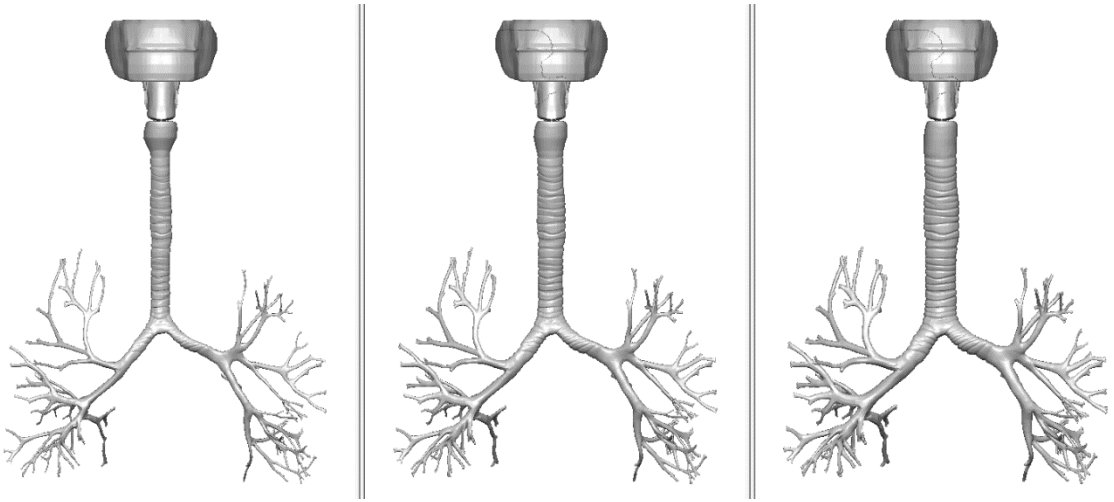


Immune cells (with clearance)

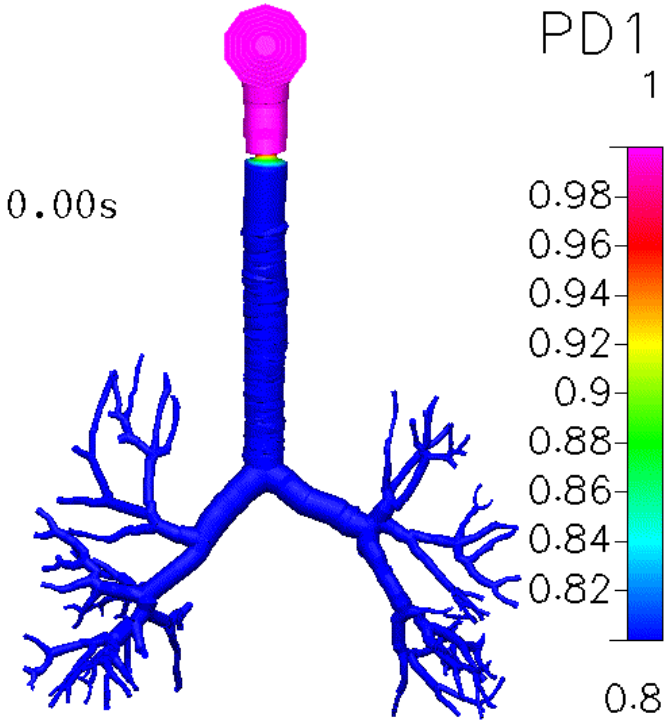


Ongoing work

- **Constricted lung scenarios:**
  - Different levels of constriction
  - Will affect the deposition, dissolution and the PK effects spatially



- **PD effects:**
  - Compute the (non-dimensional) diameter
  - 2 days worth of simulation
  - Lower airways have the least amount of the dissolved drug concentration (immune cell region)
  - Consequently, difficult to maintain the “relaxed” diameter levels at these locations.



Conclusion and Review

- **A multiscale combination of CFD modelling, Euler Lagrangian particle transport, Q3D model is developed for dissolution, mucosal transport, radial species transport in the upper airways**
- **Compartmental model in the lower airways & alveoli can yield a time and space resolved concentration profiles in the lung**
- **A good measure of the bioavailability at the intended target**

References:

1. Ravishekar Kannan et al, "Particle transport in the human respiratory tract: formulation of a nodal inverse distance weighted Eulerian–Lagrangian transport and implementation of the Wind–Kessel algorithm for an oral delivery ", International Journal for numerical methods in biomedical engineering, DOI: 10.1002/cnm.2746
2. Ravishekar Kannan et al, “A Quasi-3D wire approach to model pulmonary airflow in human airways”, International Journal for numerical methods in biomedical engineering (after revision round)
3. Ravishekar Kannan et al, “Pharmaceutical aerosols deposition patterns from a Dry Powder Inhaler: Euler Lagrangian prediction and validation”, Medical Engineering & Physics Journal (submitted)
4. Geng Tian et al, “Validating CFD Predictions of Pharmaceutical Aerosol Deposition with In Vivo Data”, Pharm Res (2015) 32:3170–3187 DOI 10.1007/s11095-015-1695-1

Thank You