Predicting Regional Lung Deposition of Pharmaceutical Aerosols with CFD

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Deposition Modeling Approaches

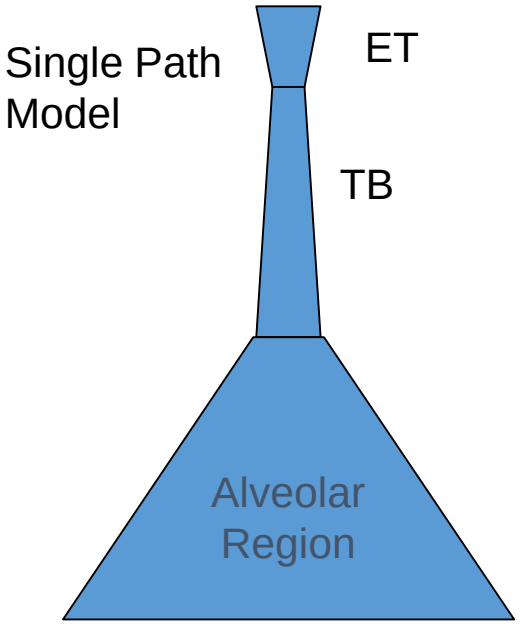
Complexity

Algebraic Whole-Lung

- Strength: easy to implement
- Weakness: accuracy of regional predictions

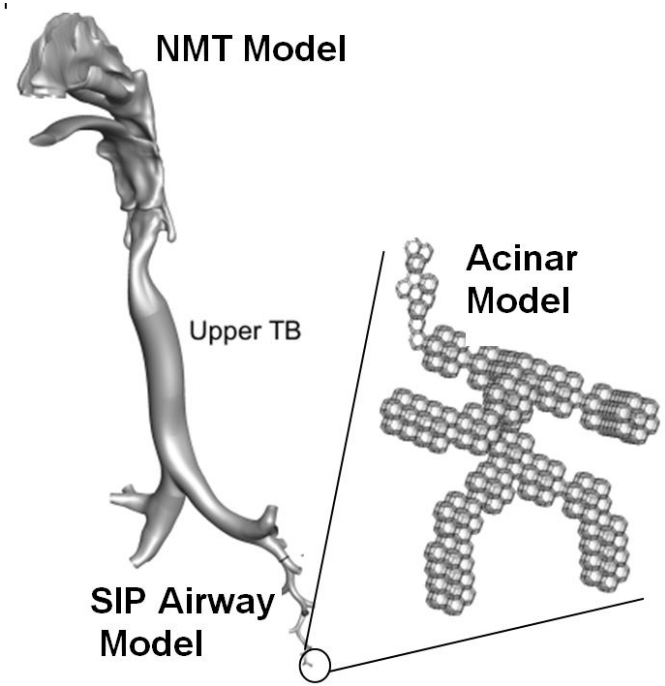
Complete Airway CFD

- Strength: 1st principles approach
- Weakness: Difficult to implement and validate



3D/1D Hybrid Models

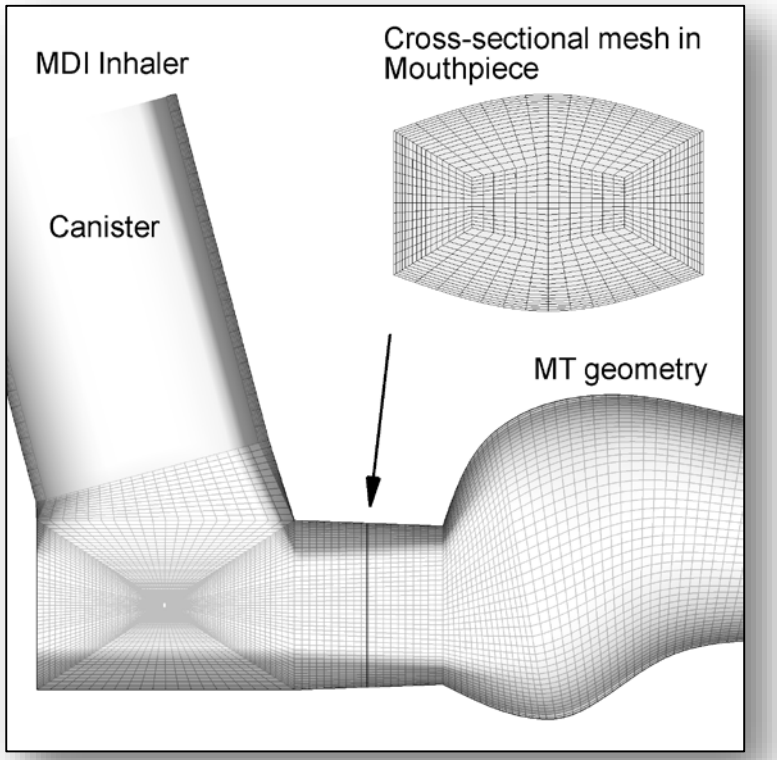
- Strength: potential to leverage strengths of each approach
- Weakness: subject to weaknesses of each approach



Longest et al. (2019) Expert Opinion in Drug Delivery 16: 7-26

Regional CFD Predictions

- Transport equations are solved in realistic 3D geometries
  - Geometries are constructed from medical scans and literature data
  - CFD process subdivides geometry into small discrete volumes
  - These control volumes make up the grid or mesh
- As with experiments, “best practices” should be followed
  - Use of accurate control volume styles (hex or poly)
  - Validation with experimental results
- First principles approach allows for the inclusion of:
  - Jet and spray momentum
  - Turbulent dispersion
  - Multicomponent evaporation and hygroscopic growth
  - Moving airway walls; particle charge; transient effects



Longest and Holbrook (2012) *Advanced Drug Delivery Reviews* 64: 296-311

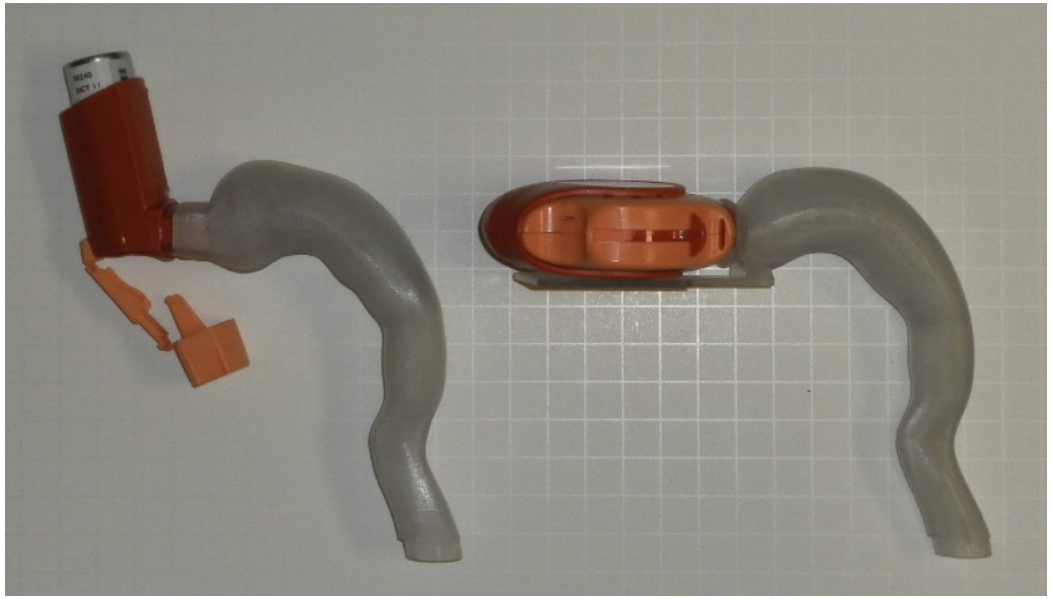
Concurrent *In Vitro*–CFD Analysis

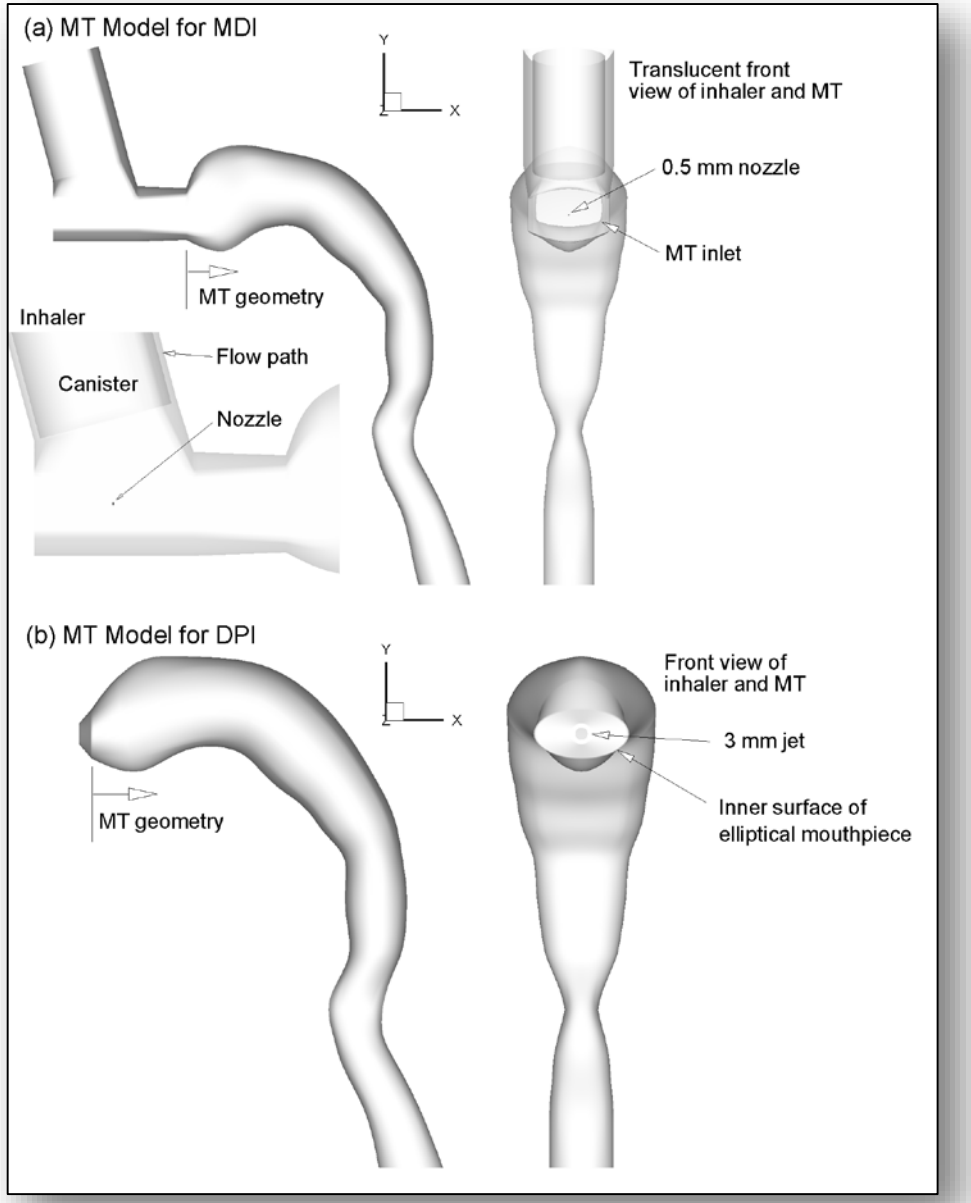
- Simultaneous testing using both *in vitro* experiments and CFD simulations
- Concurrent analysis seeks to leverage the strengths of each method
  - *In vitro* testing
    - Provide initial size distribution and spray characterization of the aerosol
    - Benchmark deposition within the model
    - Validate CFD results
  - CFD modeling
    - Analyze experimentally difficult systems (entire TB or alveolar airways) and provide additional resolution of deposition
    - Modify and optimize device performance

Hindle and Longest (2013) *J Aerosol Med* 26: 237-247

CFD Simulations of Inhaler Usage

- Mouth-Throat (MT) geometry connected to characteristic MDI and DPI models
  - MDI: Flovent with HFA (GSK) delivering a 250 µg of fluticasone propionate (FP) as a suspension
  - DPI: Flovent Diskus (GSK) delivering 250 µg of FP

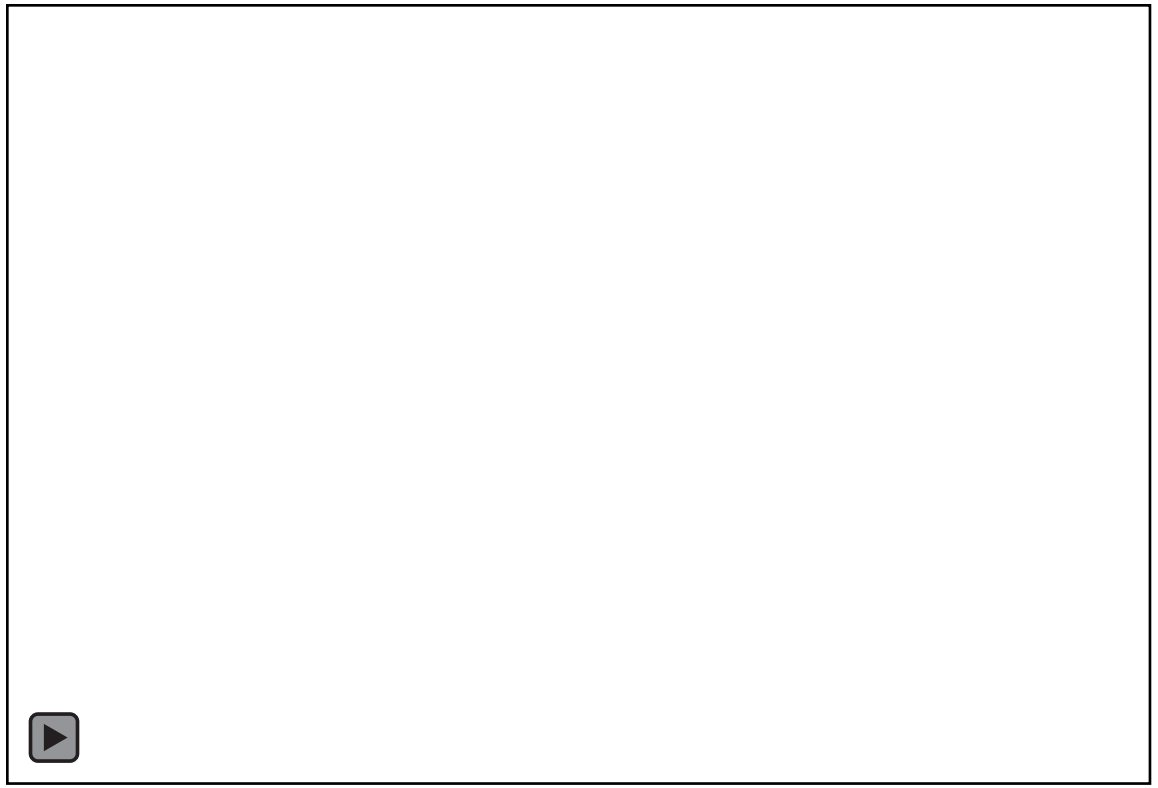




Longest et al. (2012) *Pharm Res* 29: 1670-1688

MDI Usage

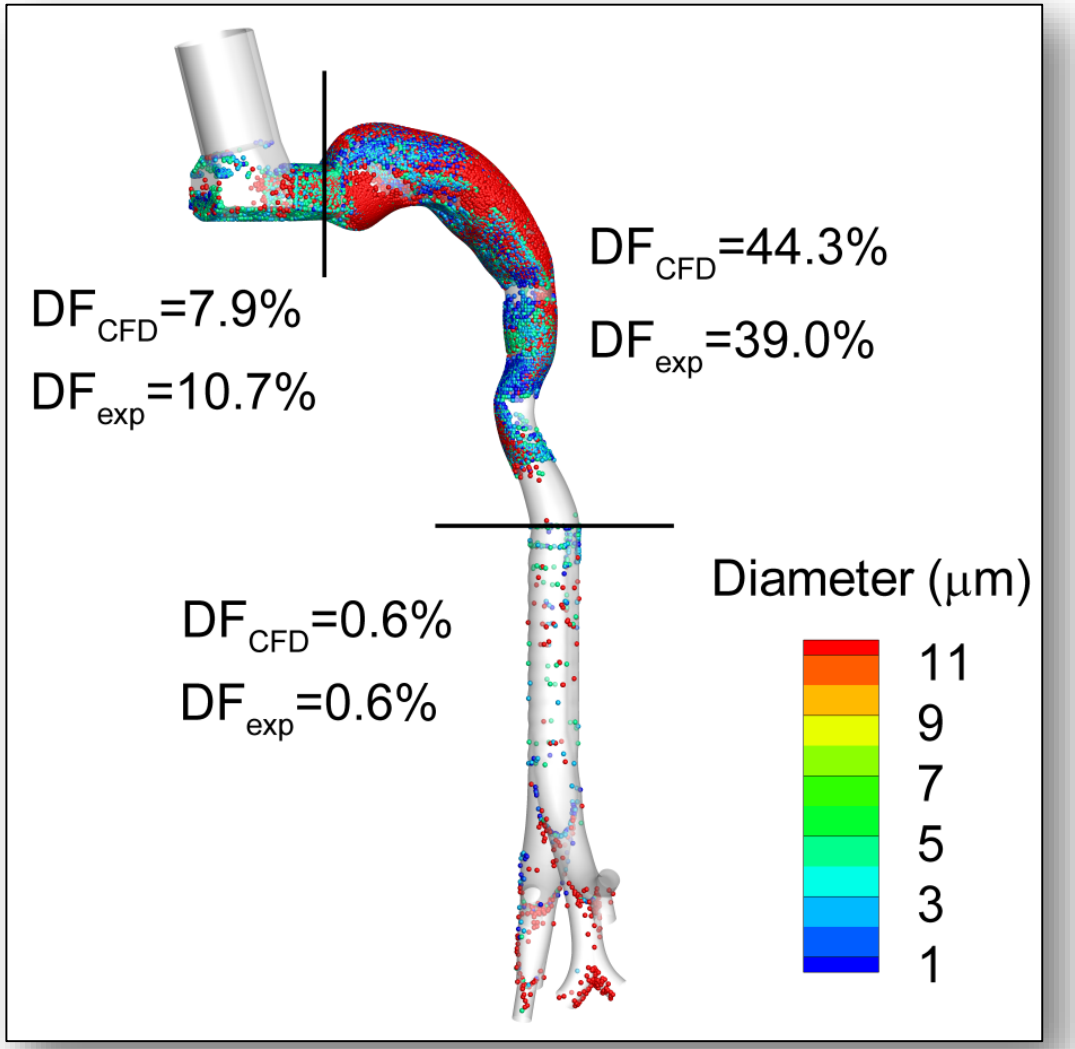
- MDI velocity field (MDI actuated at t = 0.2 s)



For Video:
https://sites.google.com/vcu.edu/longest-lab/videos

In Vitro Validations

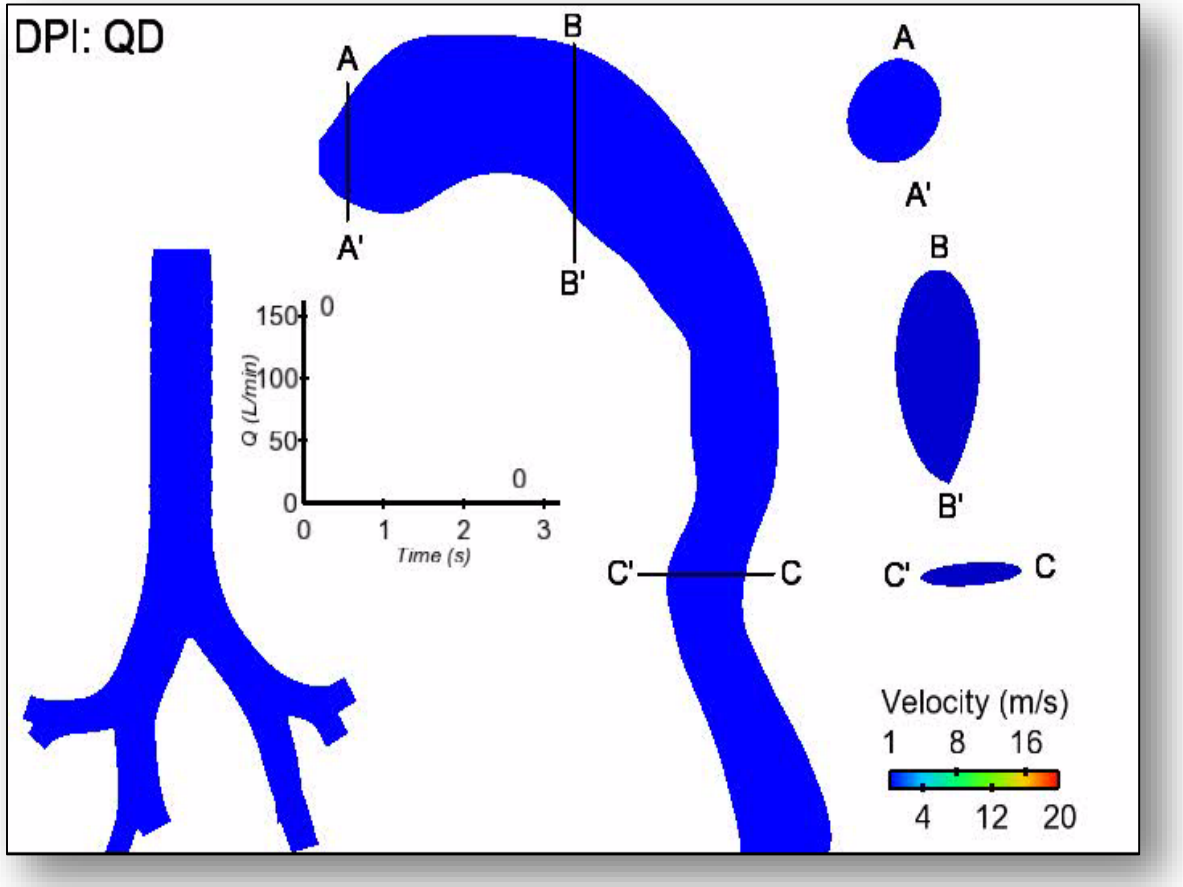
- Comparison of *in vitro* results of drug deposition with CFD model predictions for an MDI
  - Flovent HFA MDI (GSK) delivering 250 µg of fluticasone propionate
  - First study to report good agreement between CFD predictions and deposition results in a MT-TB model with an MDI



Longest et al. (2012) *Pharmaceutical Research* 29: 1670-1688

DPI Usage

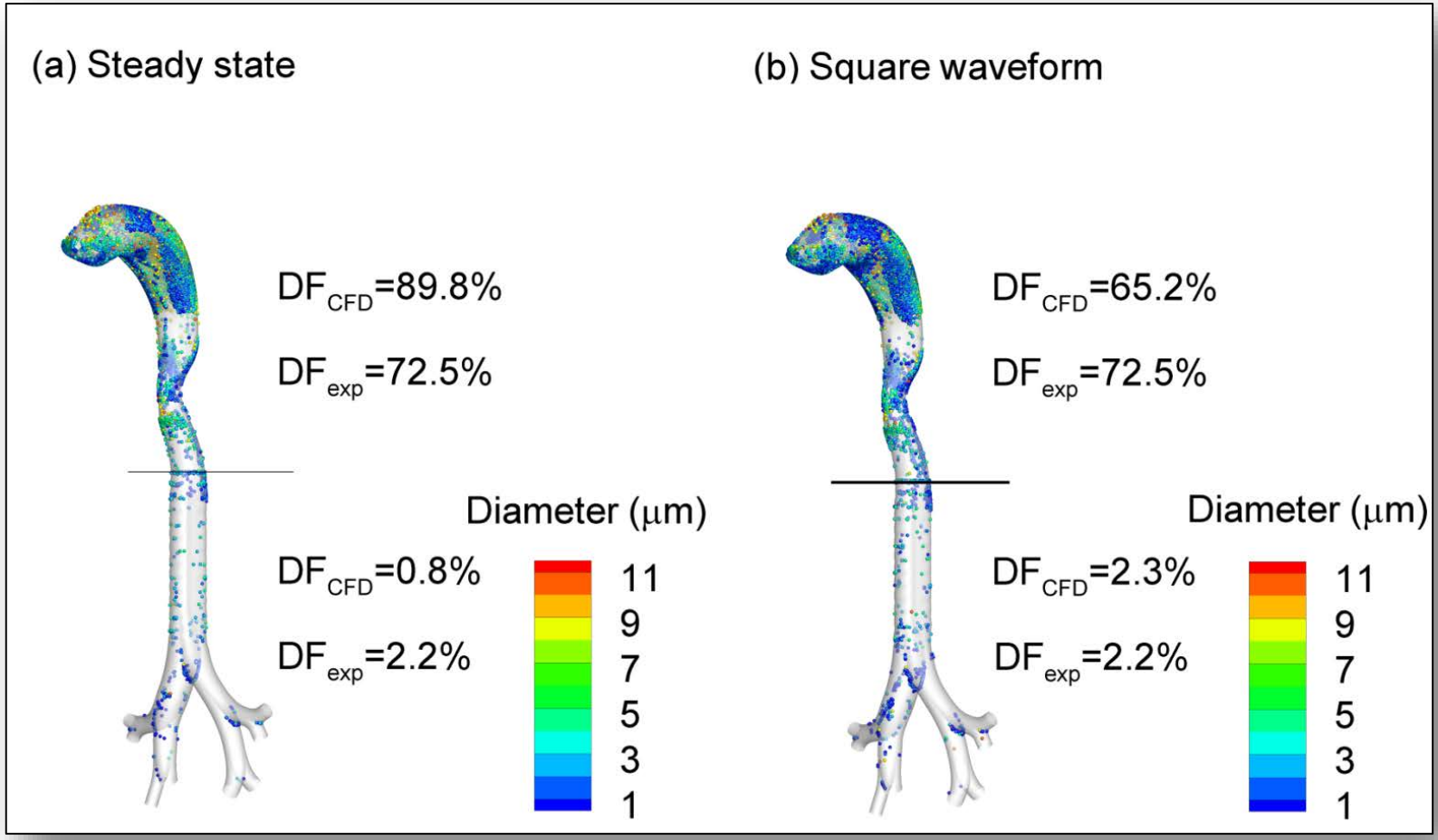
- DPI velocity field in the MT-TB model with Quick / Deep (QD) inhalation



For Video:
https://sites.google.com/vcu.edu/longest-lab/videos

In Vitro Validations

- Comparison of *in vitro* results of drug deposition with CFD model predictions for a DPI
  - Flovent Diskus DPI (GSK) delivering 250 µg of fluticasone propionate

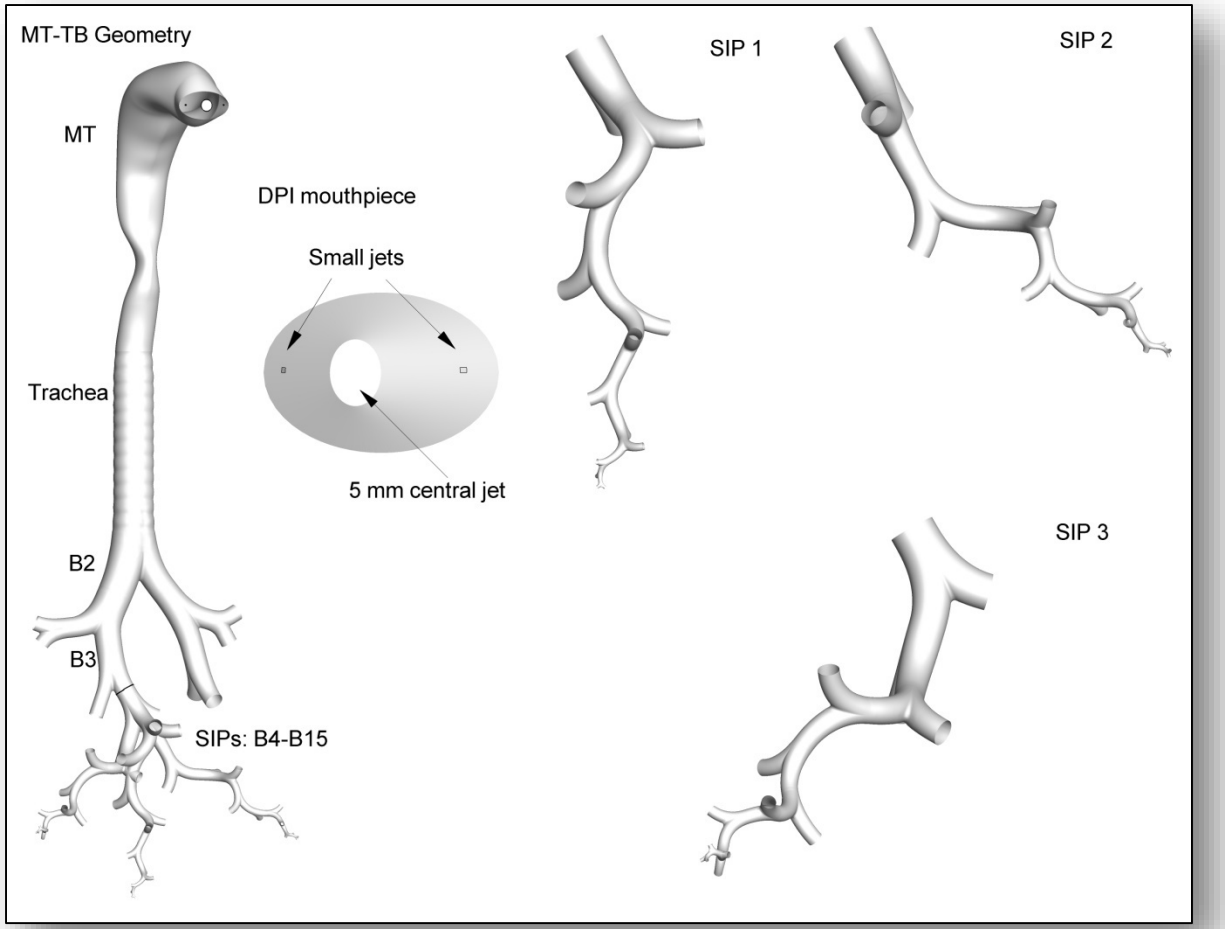


Tian et al. (2012) *Journal of Aerosol Science* 42: 781-799

Development of a Complete-Airway CFD Model

Stochastic Individual Pathways

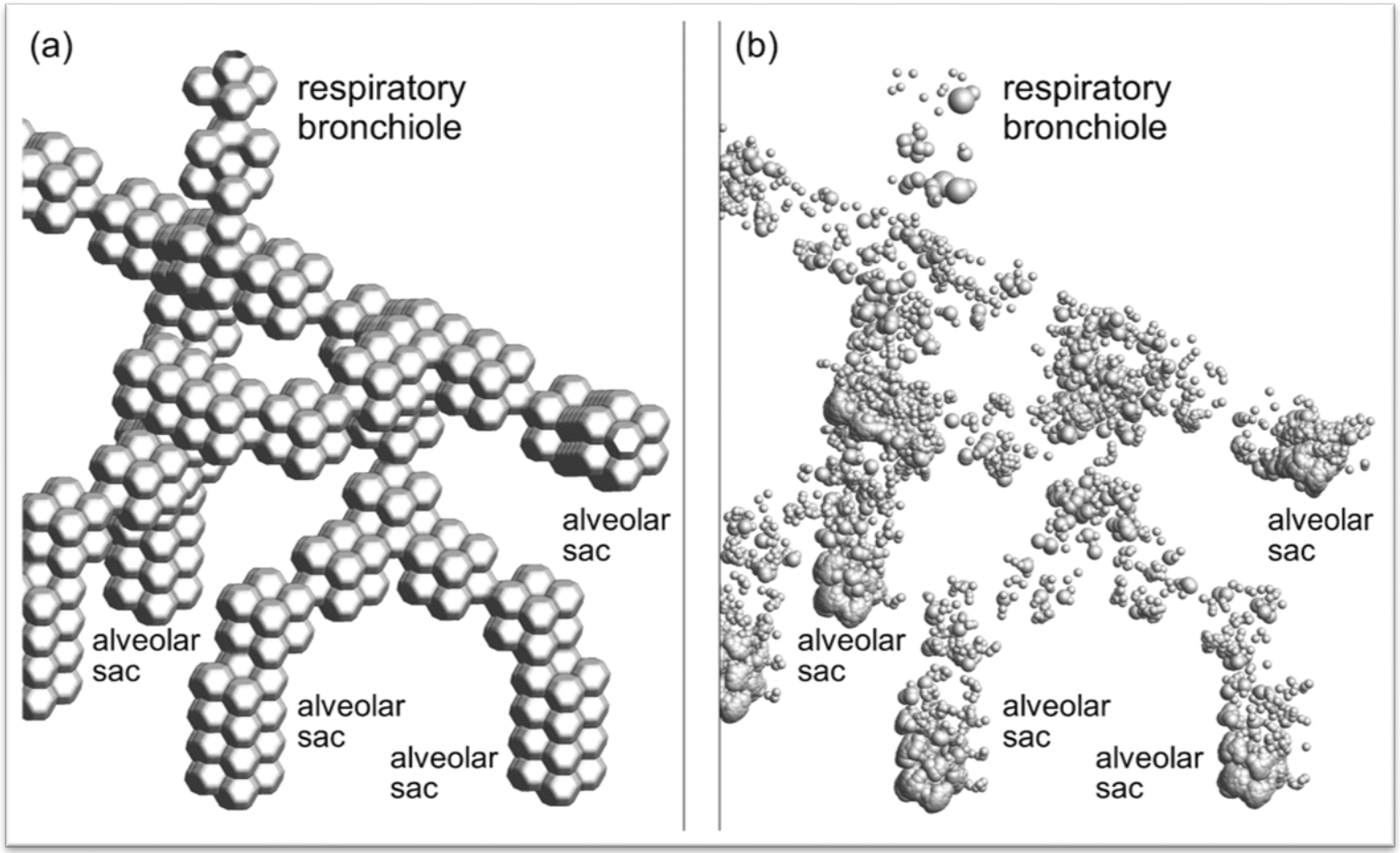
- Development of the SIP modeling approach
  - How many SIP paths are required in each lobe to resolve local deposition?
  - Are fully transient simulations required or can a steady state approximation be made?



Tian et al. (2012) *Journal of Aerosol Science* 42: 781-799

Alveolar Model Development

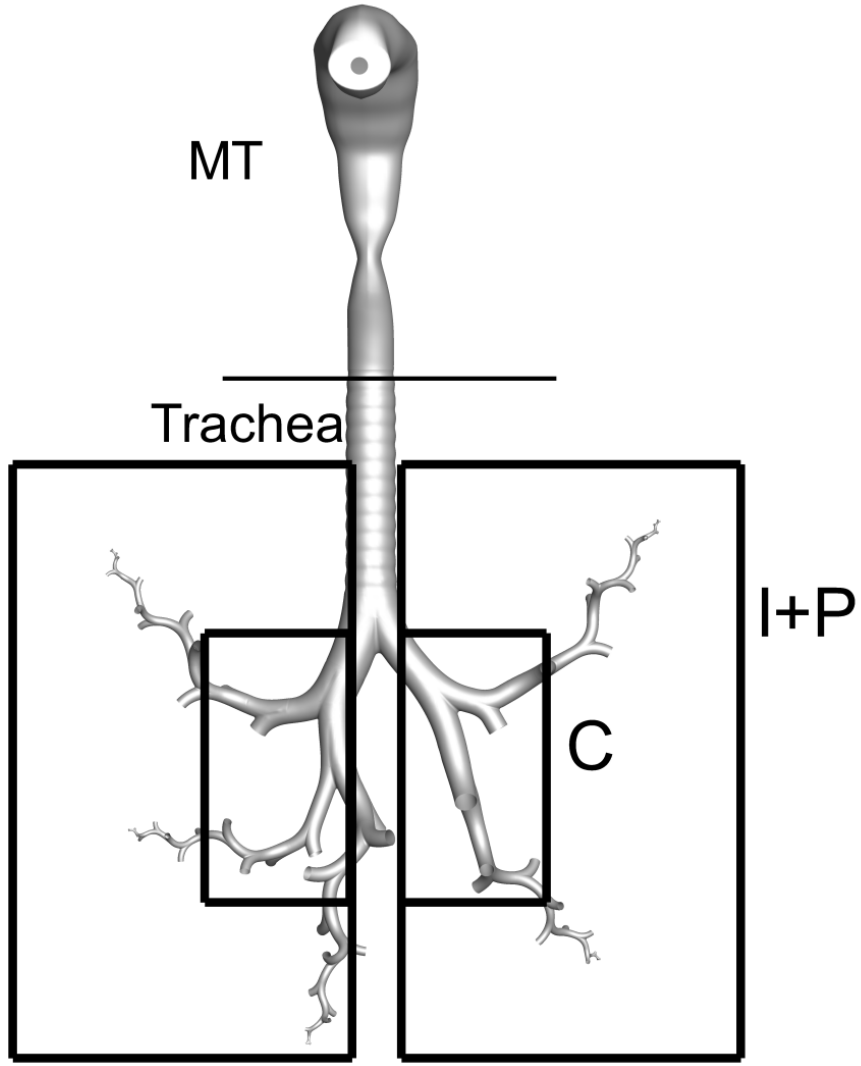
- Developed accurate model of a complete acinus (extending from the terminal bronchioles)
- Wall motion drives airflow
  - Slow and deep (SD) inhalation (3L)
  - Quick and deep (QD) inhalation (3 L)



Khajeh-Hosseini-Dalasm et al. (2015) *Journal of Aerosol Science* 79: 15-30

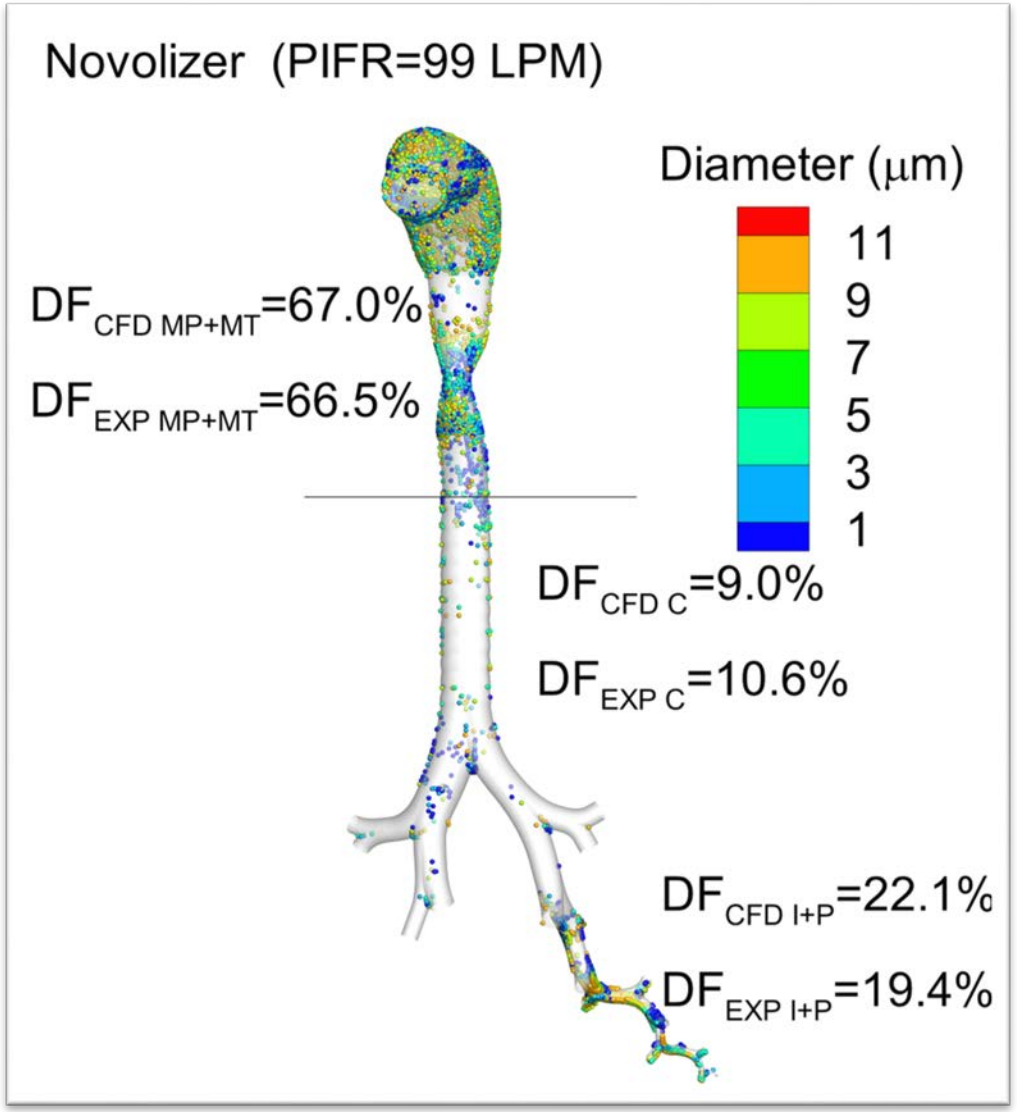
In Vivo Validations

- 2D gamma scintigraphy is frequently used to evaluate pharmaceutical aerosol delivery *in vivo*
  - Lungs are divided into central, intermediate, and peripheral airways
  - Comparisons with 2D gamma scintigraphy provides a challenging method to validate the SIP model



In Vivo Validations

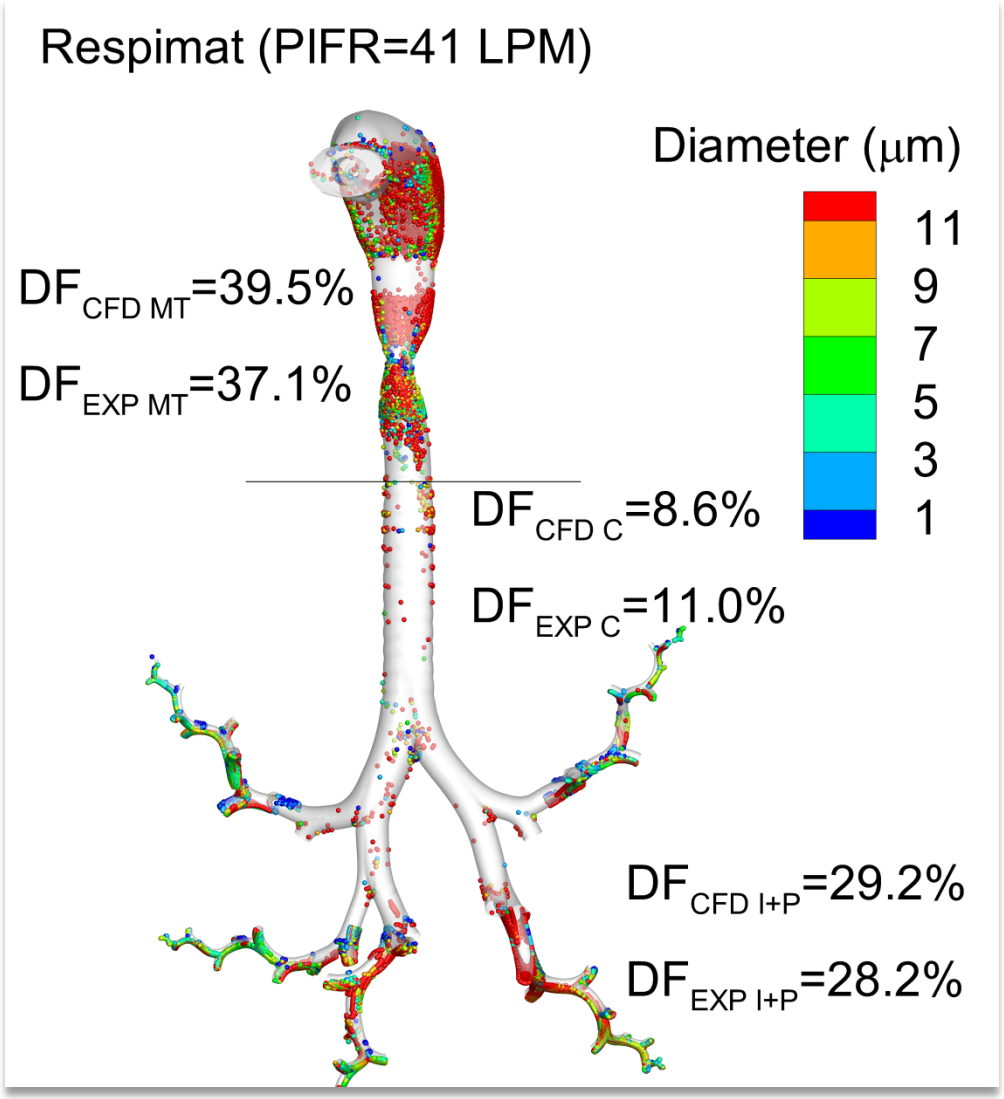
- Novolizer DPI with budesonide and QD inhalation
  - *In vivo* gamma scintigraphy data of Newman et al. (2000) (EXP)
  - CFD predictions using the SIP approach (CFD)
  - Alveolar predictions based on a new space filling model



Tian et al. (2015) *Pharm. Res.* *32*: 3170-3187

In Vivo Validations

- Respimat soft mist inhaler with fenoterol and SD inhalation
  - *In vivo* gamma scintigraphy data of Newman et al. (1998) (EXP)
  - CFD predictions using the SIP approach (CFD)
  - Alveolar predictions based on a new space filling model

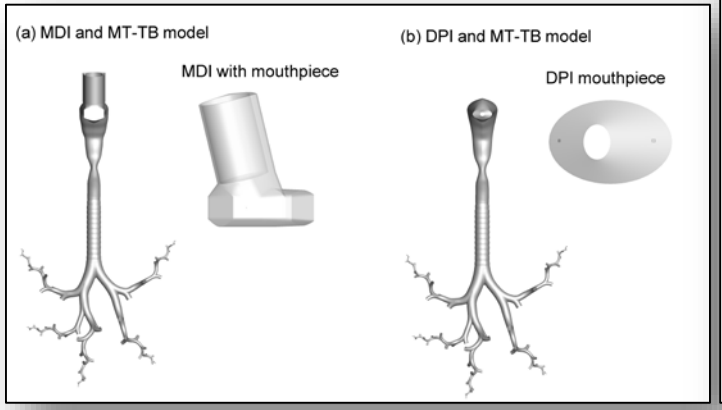


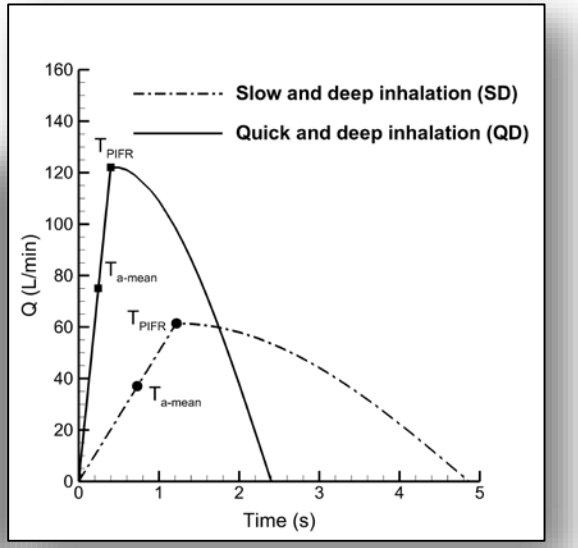
Tian et al. (2015) *Pharm. Res.* *32*: 3170-3187

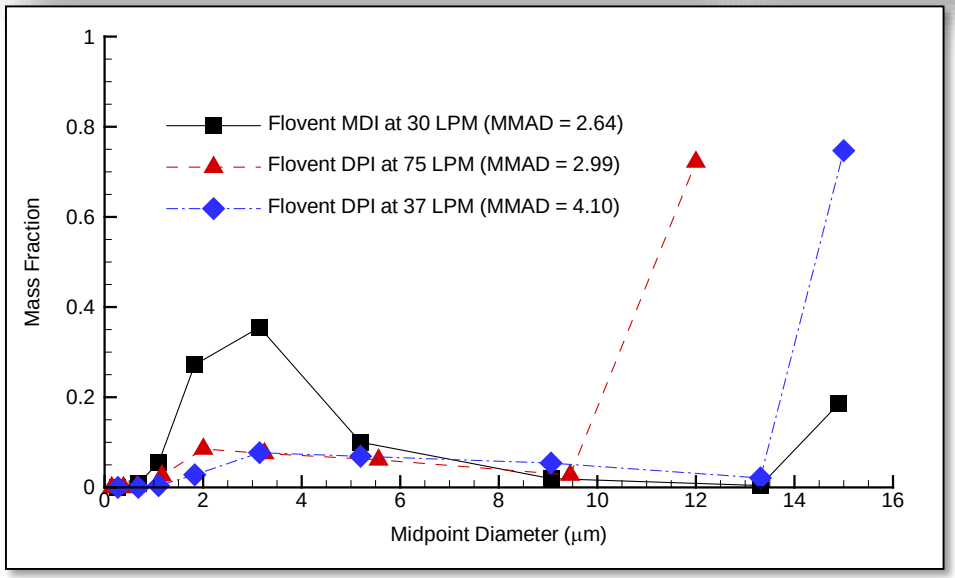
Case Study: Comparison of MDI and DPI Deposition

Case Study: MDI vs. DPI

- How similar is regional airway deposition for a common MDI and DPI?
  - Flovent HFA MDI (GSK)
  - Flovent Diskus DPI (GSK)
    - Both deliver fluticasone propionate at 250 µg
- Considered correct and incorrect inhalation profiles with each inhaler
- Experimentally measured inlet particle size distributions
- CFD validations with *in vitro* data
- **Conducted a CFD-based complete-airway simulation reporting regional initial deposition of drug**



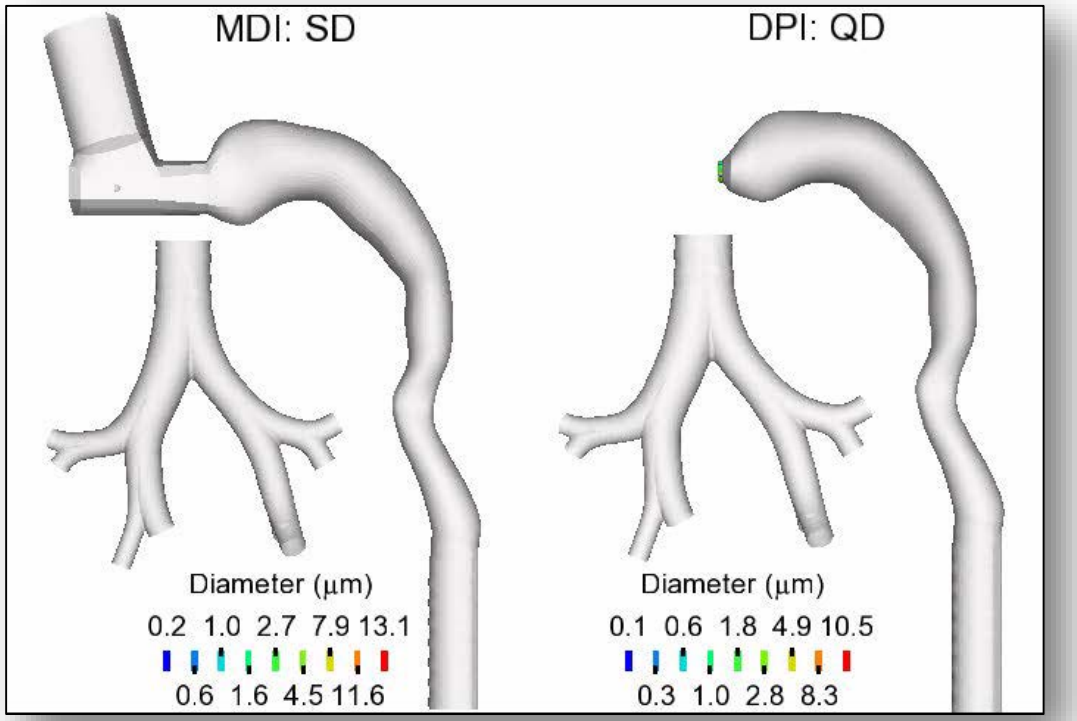




Longest et al. (2012) *Pharm Res* 29: 1670-1688

Case Study: MDI vs. DPI

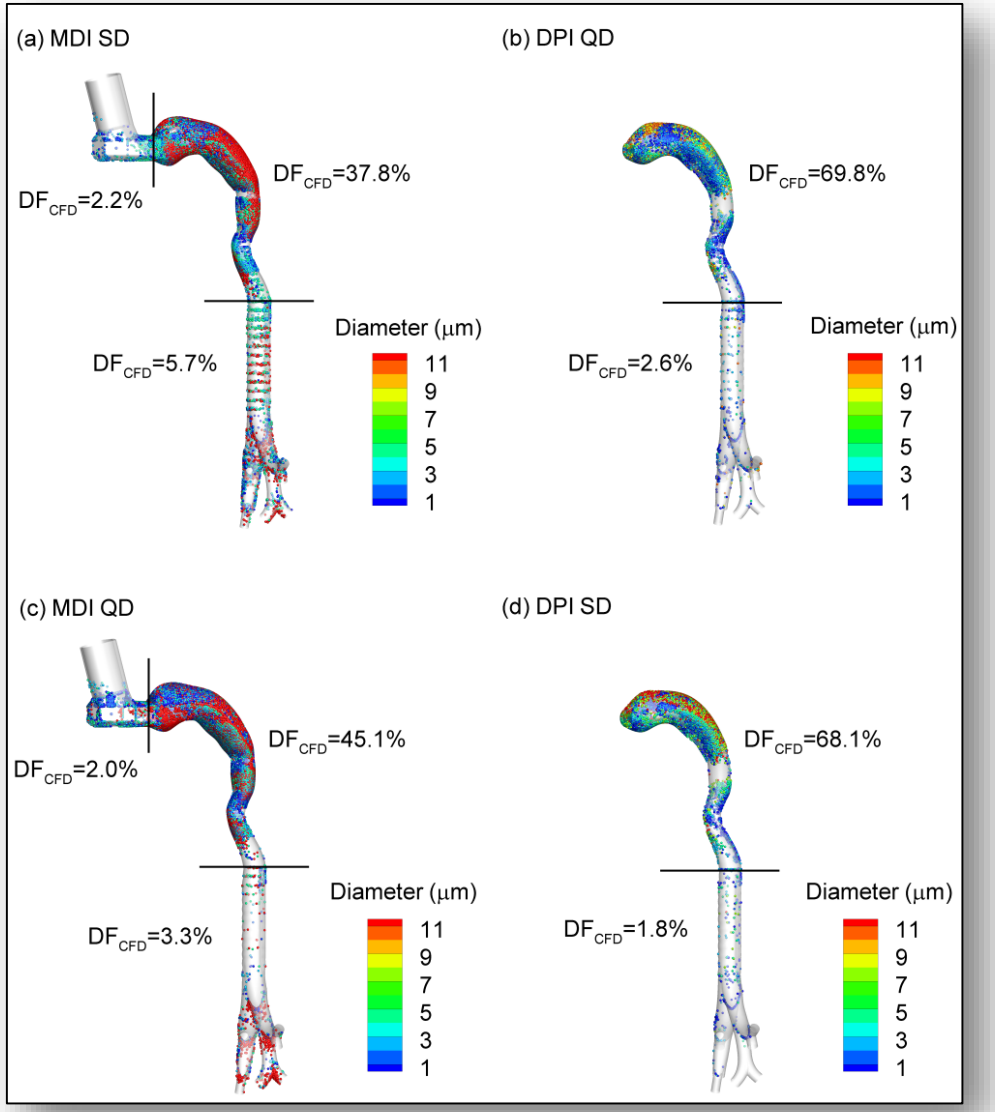
- MDI vs. DPI aerosol delivery with correct inhalation waveforms



For Video:
https://sites.google.com/vcu.edu/longest-lab/videos

Case Study: MDI vs. DPI

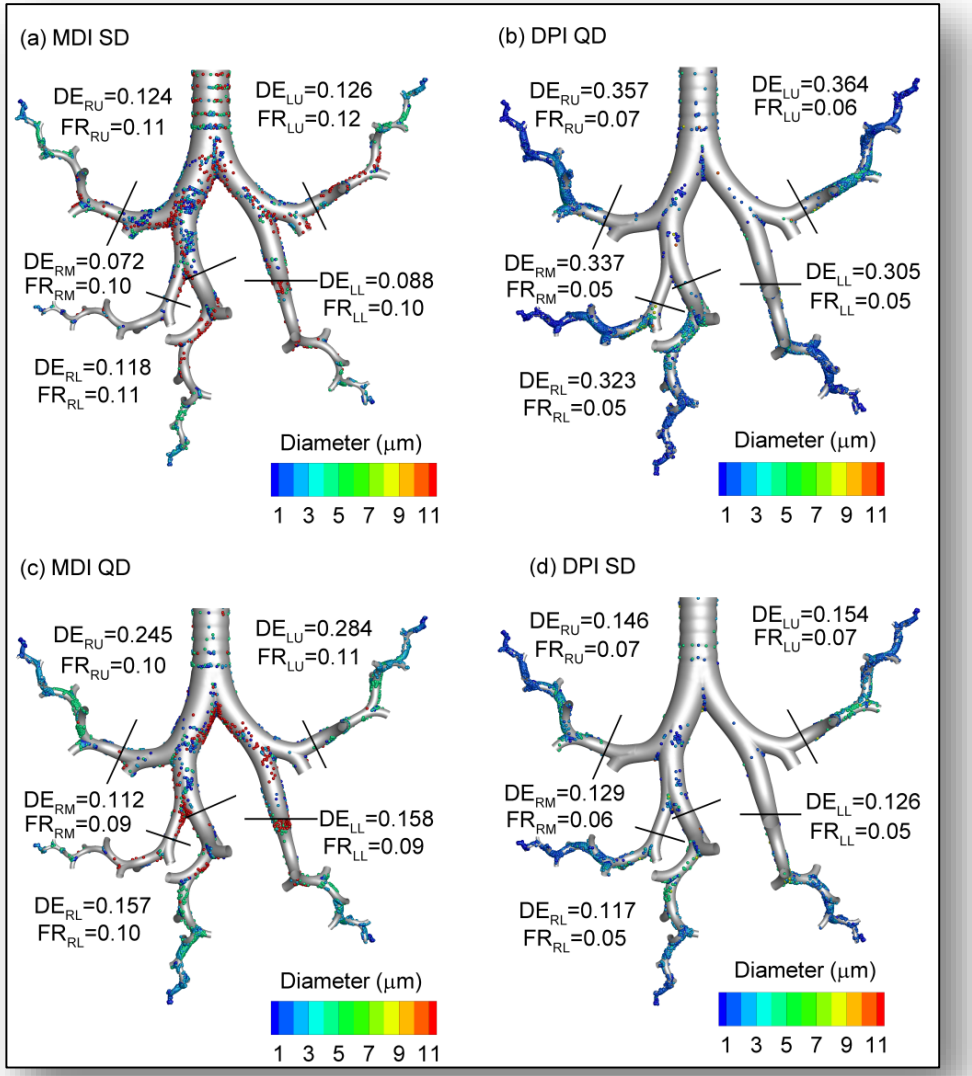
- MT and upper TB deposition with correct (top row) and incorrect (bottom row) inhalation profiles
  - With correct inhalation, MDI delivers 2x dose to the upper TB with ½ the loss in the MT
  - With incorrect inhalation, MDI still performs better than the DPI



Longest et al. (2012) *Pharm Res* 29: 1670-1688

Case Study: MDI vs. DPI

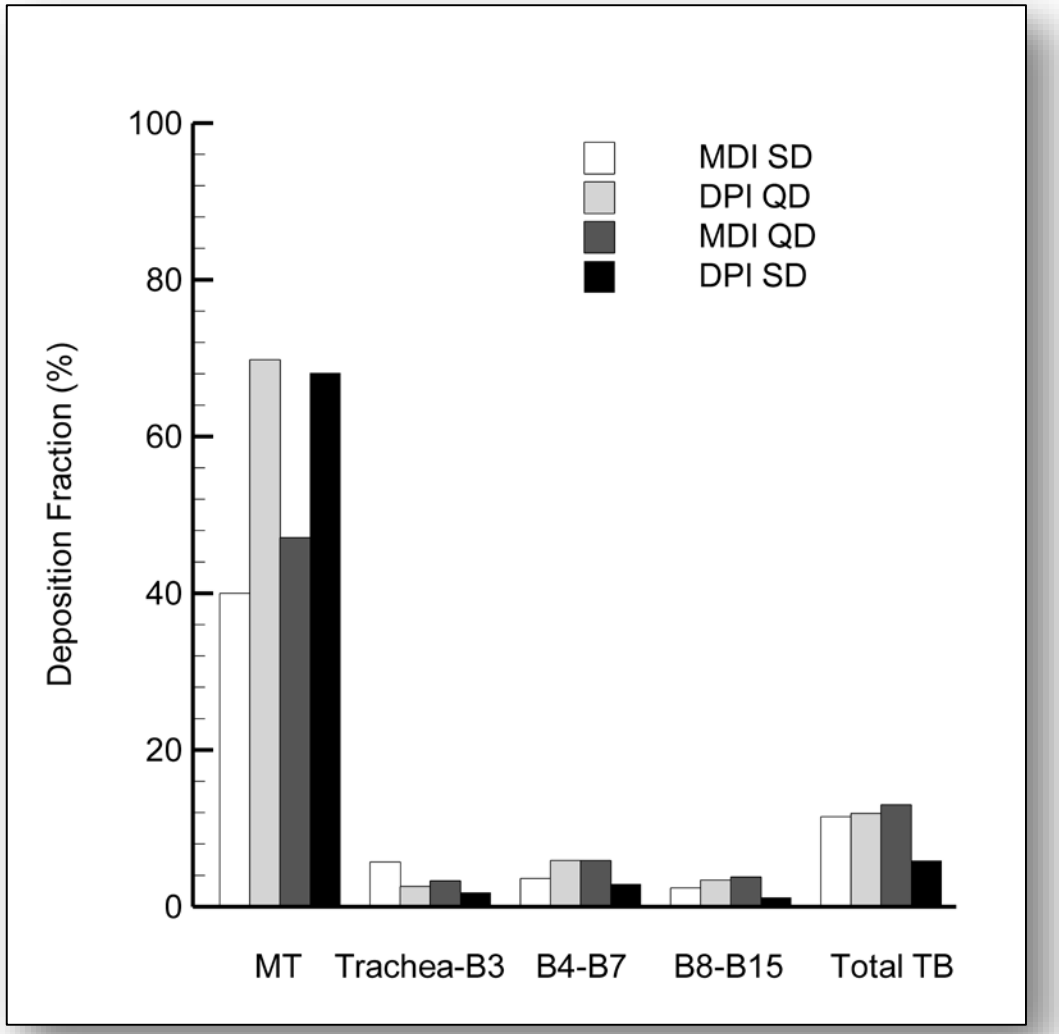
- Lower TB deposition with correct (top row) and incorrect (bottom row) inhalation profiles
  - Delivery is a function of deposition efficiency (DE) and fraction remaining (FR) entering each lobe
  - DPI has higher DE, but lower FR in each lung lobe using the correct technique



Longest et al. (2012) *Pharm Res* 29: 1670-1688

Case Study: MDI vs. DPI

- Regional deposition fraction of drug mass with the MDI and DPI
  - MDI delivers 2x drug to Trachea-B3 (correct usage)
  - DPI delivers 2x drug to B4-B7 (correct usage)
  - Total TB deposition is nearly identical between MDI and DPI with correct inhalation
  - With incorrect inhalation, DPI TB dose decreases by 2x



Longest et al. (2012) *Pharm Res* 29: 1670-1688

Case Study: MDI vs. DPI

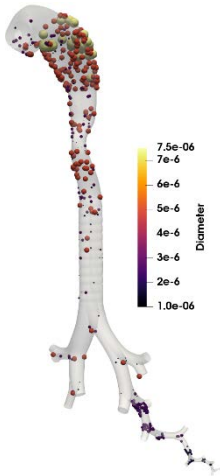
Deposition fractions (DF) and penetration fractions (PF) at the outlet of individual airway regions with correct inhalation

	Deposition Fraction (DF)			Penetration Fraction (PF)		
Region	MDI	DPI	**Relative Difference (%)**	MDI	DPI	**Relative Difference (%)**
MT	0.400	0.698	**54%**	0.600	0.302	**66%**
Trachea-B3	0.057	0.026	**75%**	0.543	0.276	**65%**
B4-B7	0.035	0.059	**51%**	0.508	0.217	**80%**
B8-B15	0.023	0.034	**39%**	0.485	0.183	**90%**
Total TB	0.115	0.119	**3.4%**	0.485	0.183	**90%**

- Including a range of input factors like different inhalation waveforms and subject characteristics will enable variance analysis
- Mean and variance of deposition within each region will enable a more statistical approach to equivalence determination

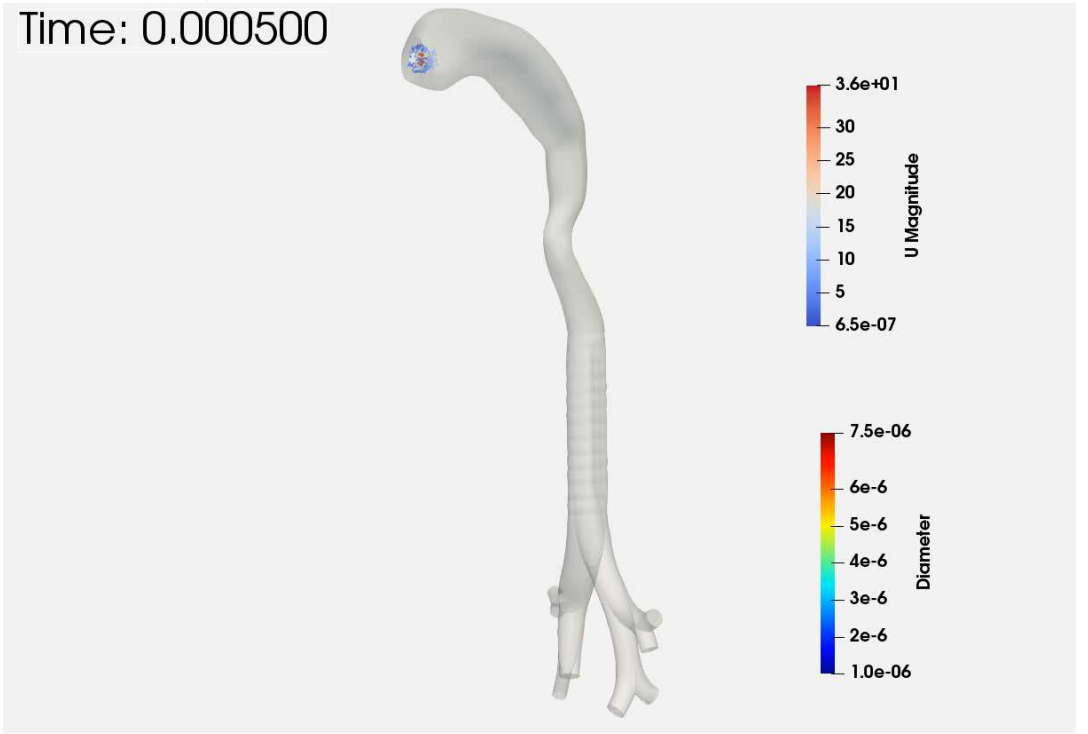
Shift to Open Source Software

- Advancements with New Project:
  - Focus on open source CFD: OpenFOAM
    - Freely available and modifiable source code
    - Provides a common sharable base among users within government, industry and academia
  - Extend complete-airway modeling efforts
    - Improve modeling approach to better capture lung physiology and exhalation
    - Comparisons with 2D and 3D regional *in vivo* data
  - Emphasis on the use of *in vitro* characterization data
    - Spray physics
    - Upper airway deposition in characteristics models
  - Creation of a website for code and mesh geometry dissemination



Initial OpenFOAM results for Novolizer DPI

	MT DF (%)	Central DF (%)	I+P DF (%)
In Vivo	64.9	12.1	22.1
CFD	71.3	8.7	21.3

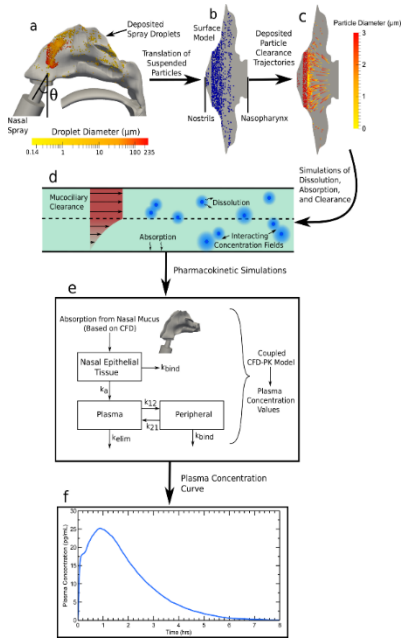


Alternative Bioequivalence Approaches

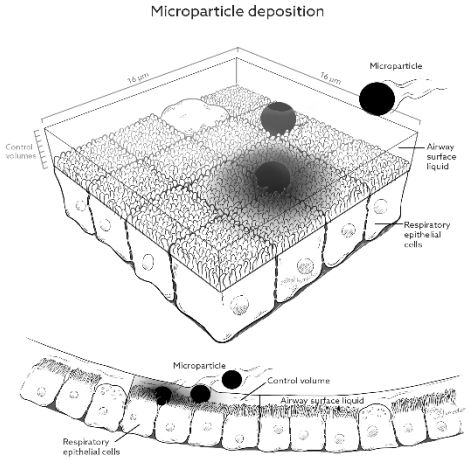
Ways CFD-Predicted Regional Lung Deposition May Be Useful

Regional Deposition

- **Accurate PBPK Inputs**



- **Combine with DAC Modeling for Tissue Dose Predictions**



- **Stand-Alone Metric**

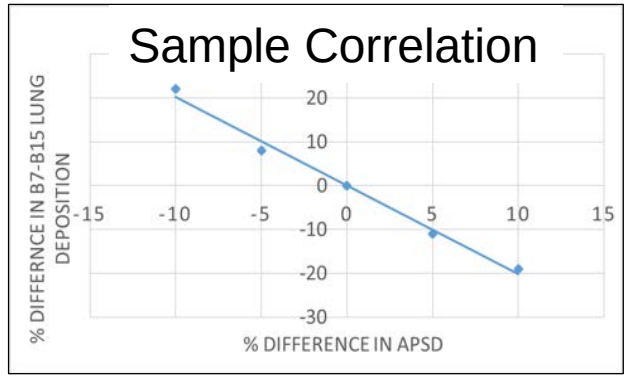
+

- **Dissolution**

+

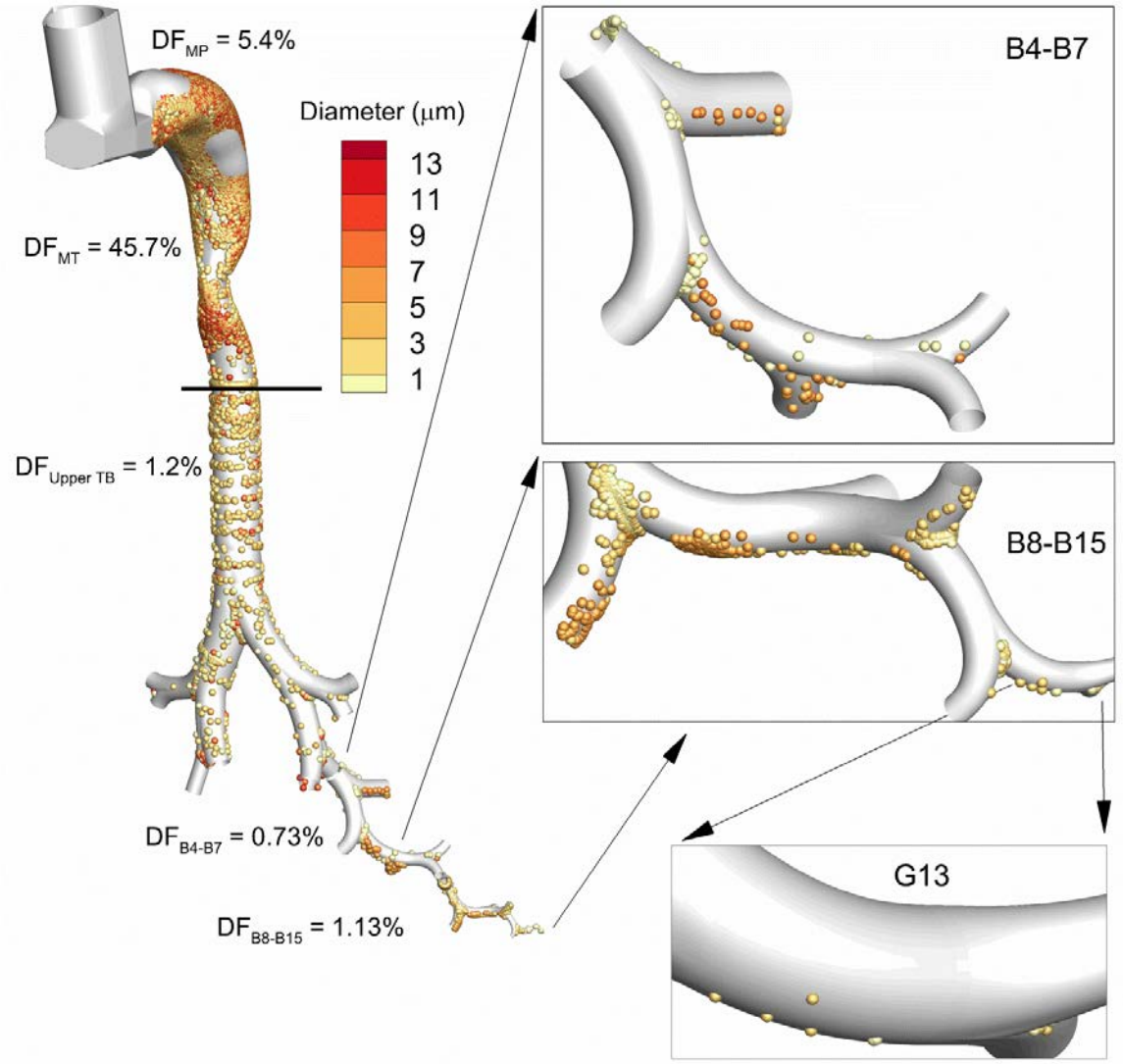
- **Absorption**

- **Correlation Development with Current FDA In Vitro Test Metrics**



Dissolution, Absorption and Clearance (DAC) Modeling

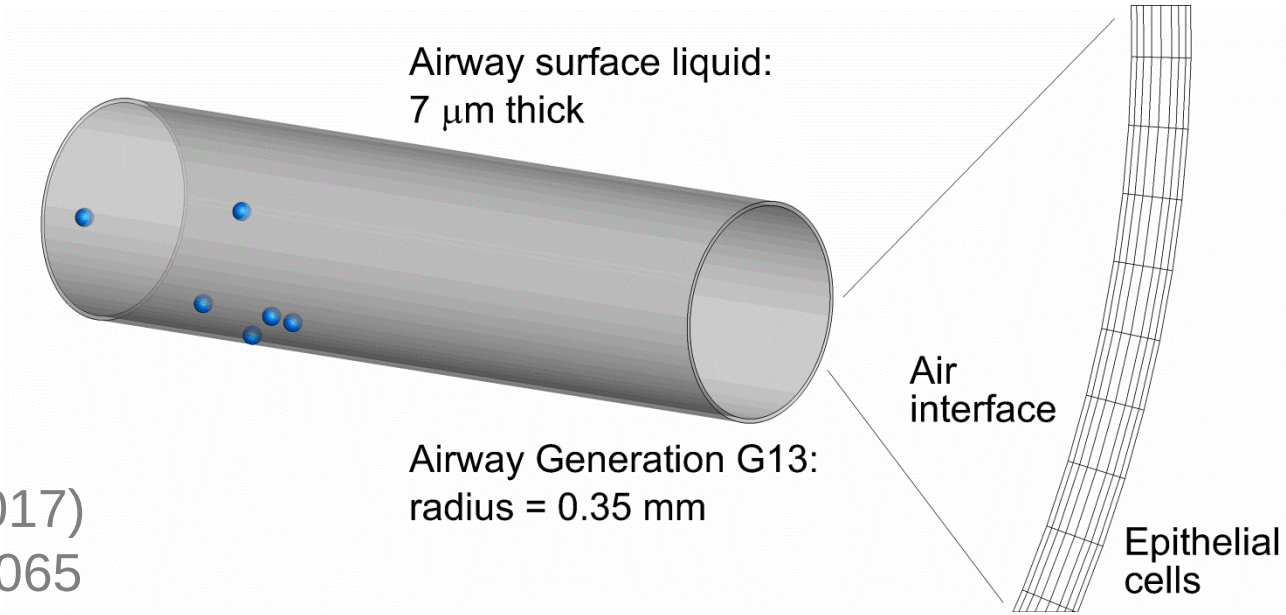
- Flovent HFA MDI
- Fluticasone propionate (250 µg)
- Slow and deep inhalation



Longest and Hindle (2017)
Pharm Res 34: 2049-2065

Dissolution, Absorption and Clearance Modeling

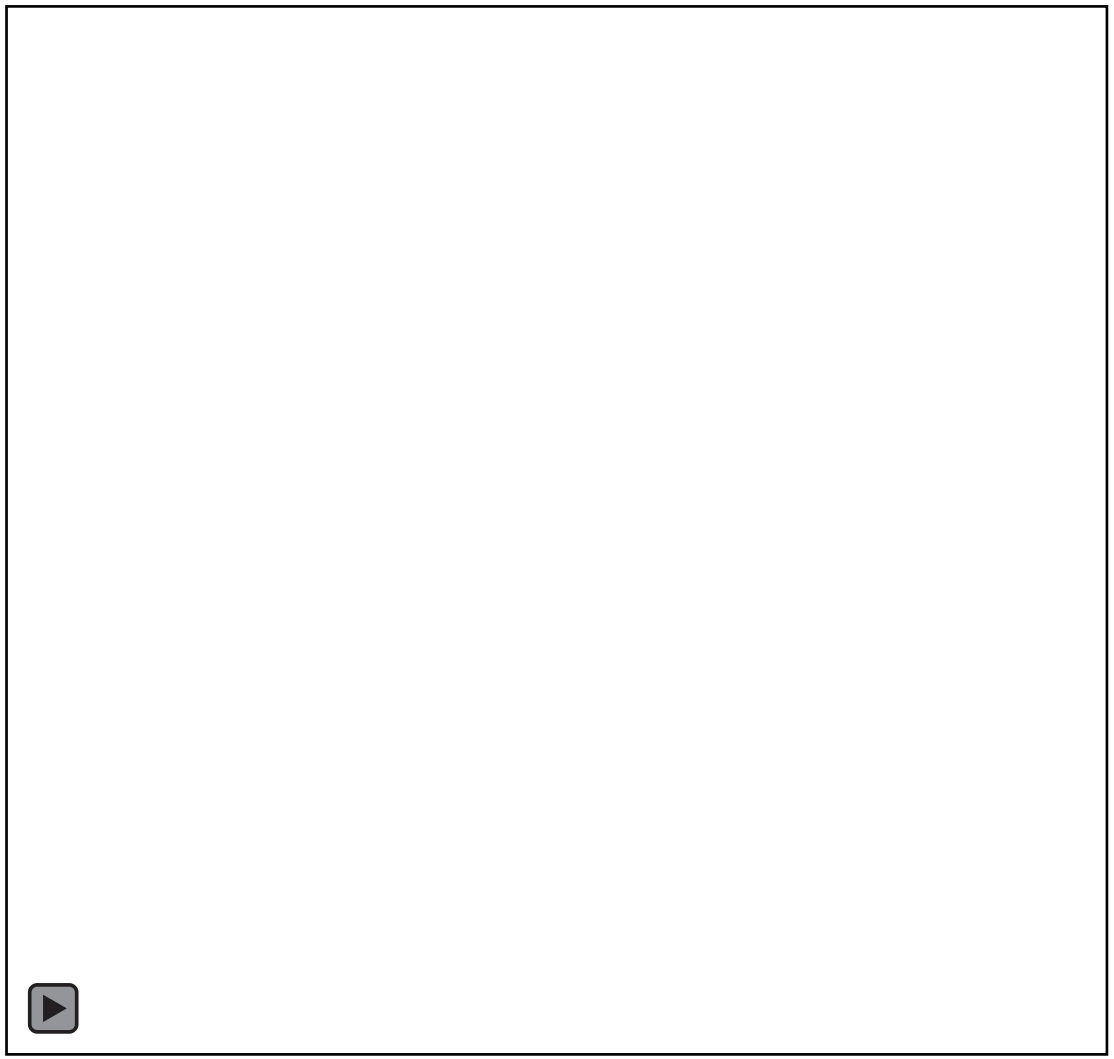
- Assume cyclic breathing over 300 s and a healthy mucus clearance velocity
- CFD used to simulate dissolution, absorption, and clearance of deposited particles
  - Similar to



Longest and Hindle (2017)
Pharm Res 34: 2049-2065

Dissolution, Absorption and Clearance Modeling

- Budesonide; 2.6 µm particles; Fast clearance
  - Dissolution and absorption over 300 s during respiration with fast clearance



Longest and Hindle (2017)
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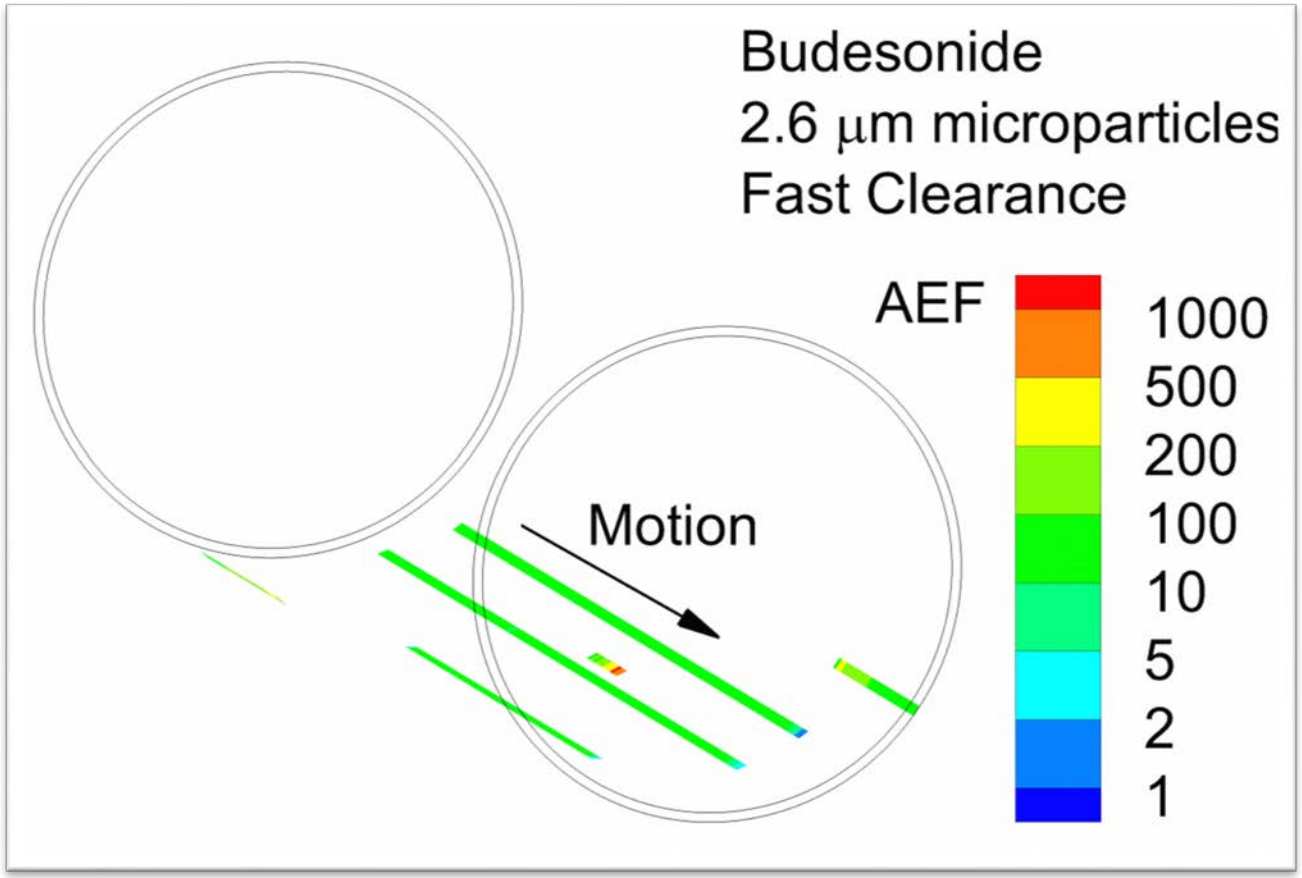
Dissolution, Absorption and Clearance Modeling

- Contours of cellular-level absorption fraction
  - Particles dissolve completely over time period of 300 s
- Distribution of cellular-level dose

1.7% of cells receive 99% of dose



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Pharm Res 34: 2049-2065

Conclusions

- Efficient use of CFD to determine regional whole-lung deposition requires a concurrent approach with good *in vitro* data
  - Initial particle size distribution
  - Benchmark deposition data in realistic airway models
- Current agreement with regional *in vivo* data for pharmaceutical aerosols (2D gamma scintigraphy) is reasonable
- Current complete-airway focus at VCU:
  - Improved model realism with comparisons to 3D SPECT-CT
  - Move to open source CFD
- Ways regional deposition data may be used in assisting with bioequivalence determination
  1. More accurate PBPK inputs
  2. Combination with DAC modeling to determine tissue dose (local *site of action*)
  3. Stand alone metric (with other tests to determine factors like dissolution and uptake)
  4. Establish correlations between current *in vitro* test metrics and regional deposition

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