ASCPT 2019
ASCPT/FDA Pre-Conference
"PBPK Modeling for the Development and Approval of Locally Acting Products"

CFD Lung Models for Drug Delivery

March 13, 2019, 8:40am

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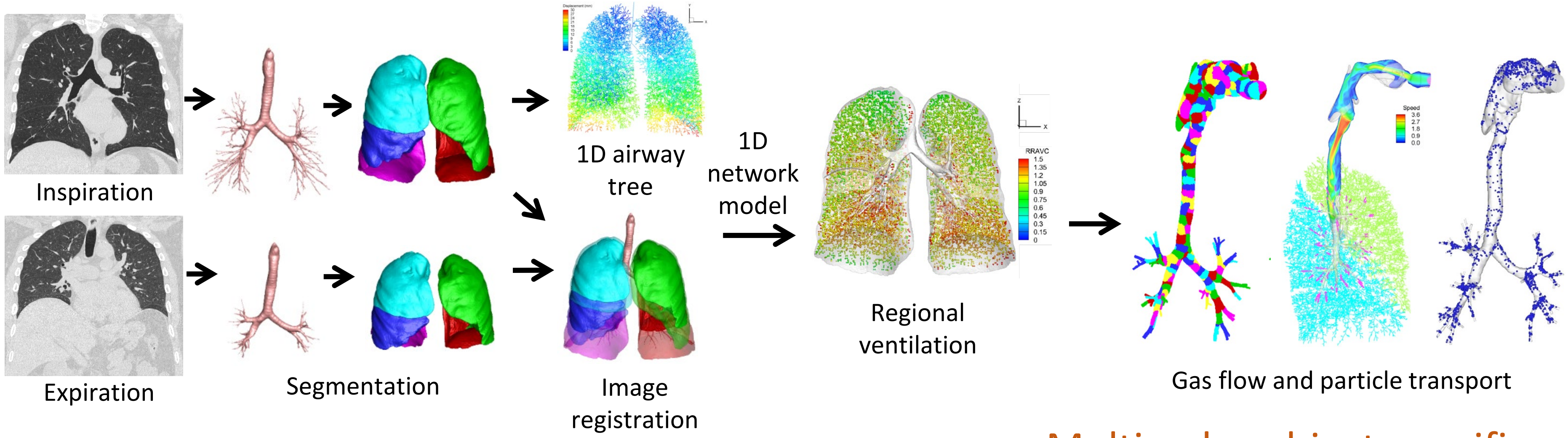
CT-based computational fluid dynamics (CFD) lung model

CT Imaging & Reconstruction	Individual Image Processing & Analysis	Comprehensive Image Processing, Computational Modeling, Visualization, Gas Flow and Particle Transport Simulations



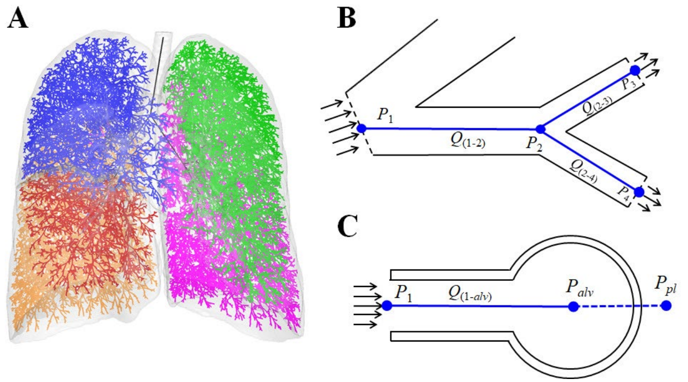
- Anatomically accurate airway structure geometry
- Physiologically consistent regional lung function

➔ Multiscale subject-specific imaging, air flow, and particle transport features

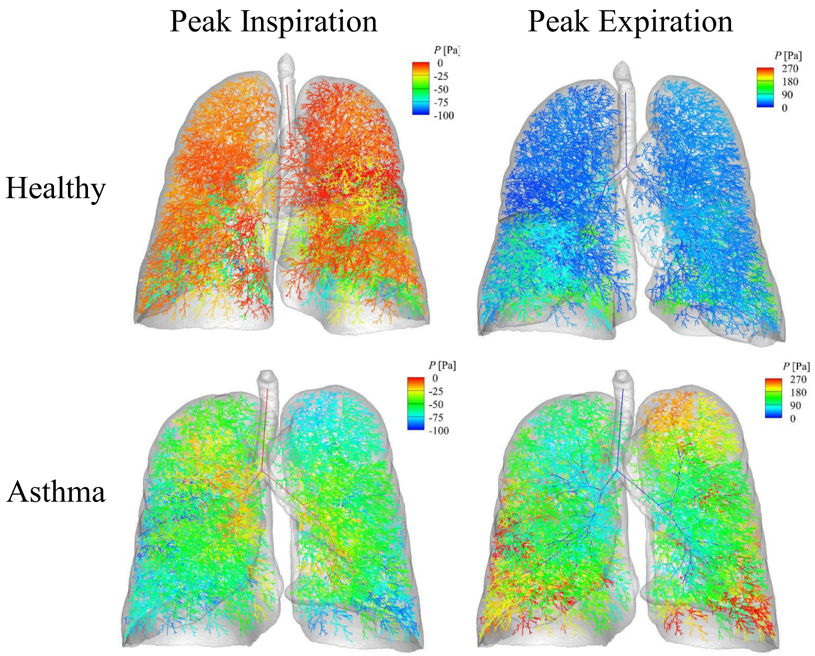
1D network model

- Population-based airway constriction model
- Integrated unsteady incompressible isothermal energy balanced 1D solver
- 1D airflow resistance & lung compliance model

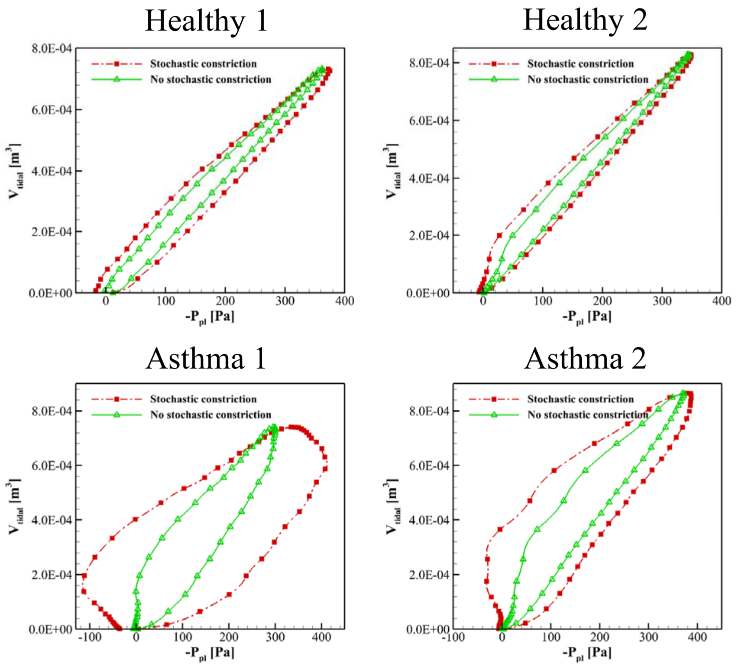
Model description



Pressure distribution

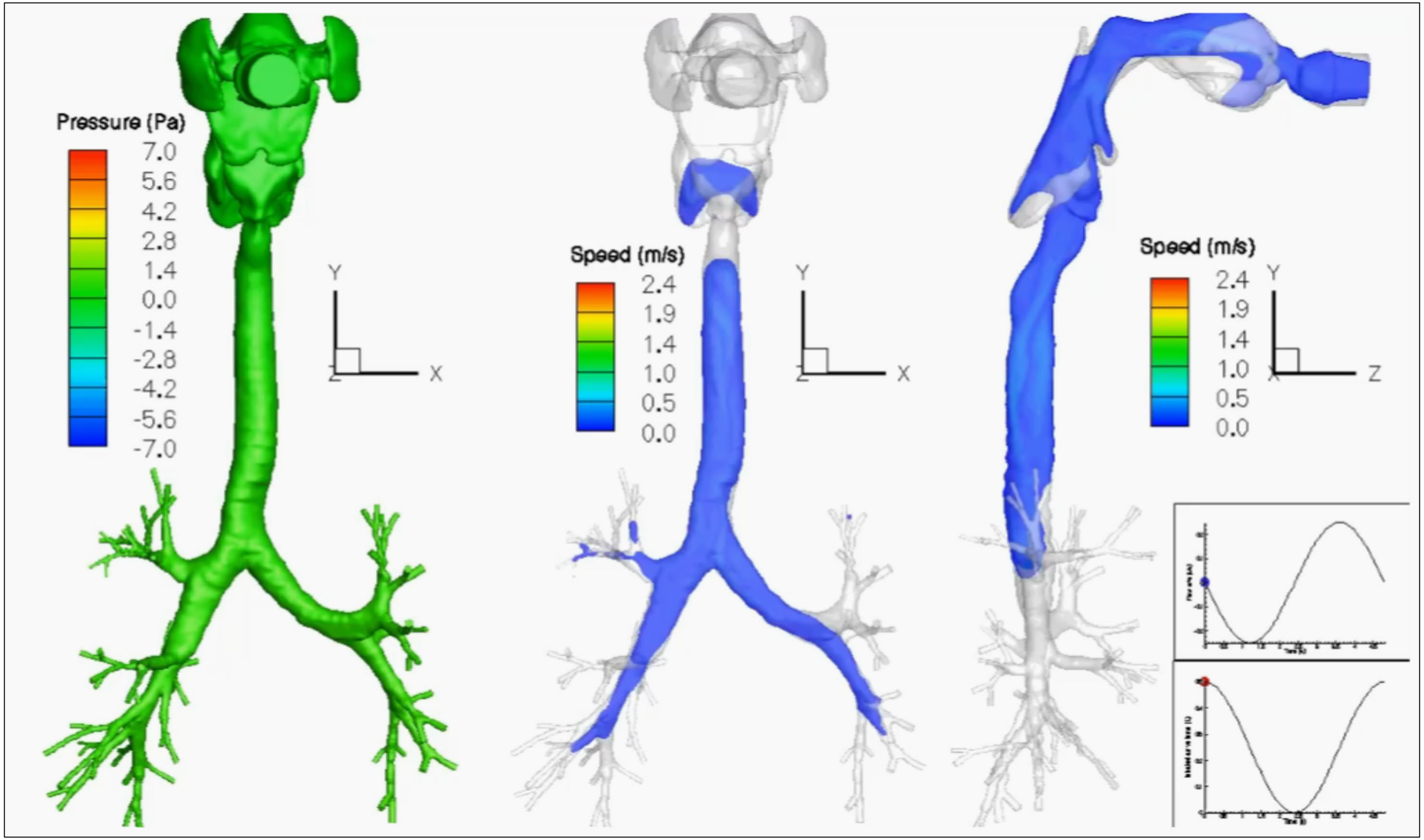


Pressure-volume hysteresis



CFD for air flows in breathing human lung

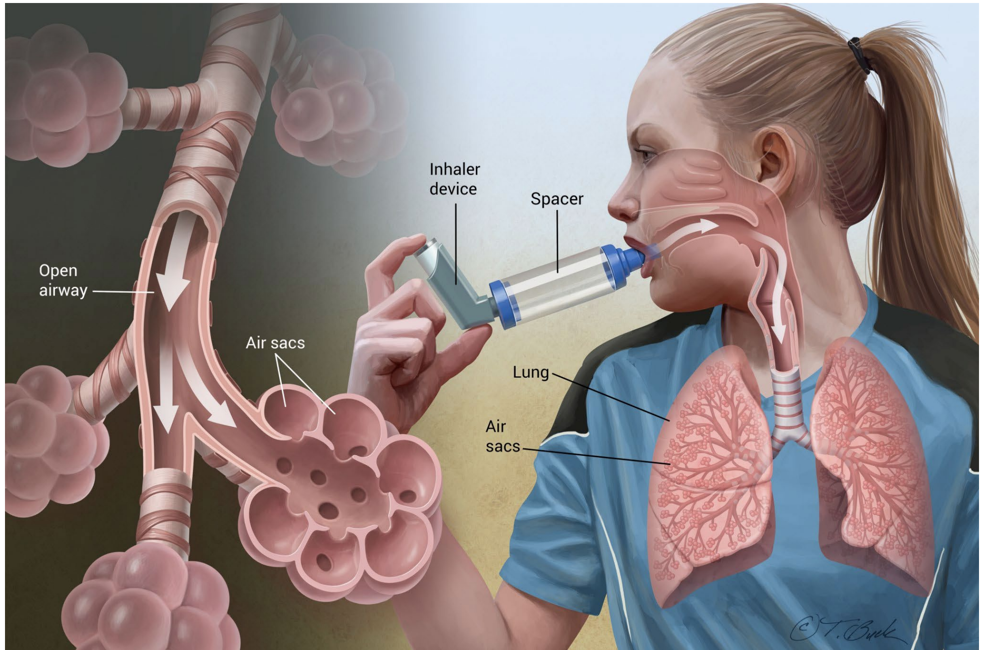
Choi et al. 2013 APS DFD Gallery of Fluid Motion



Pressure Velocity

Drug aerosol inhalation in asthma

- Inhalation of medication is a major treatment for asthma.
- Aerosolized bronchodilators relax airway smooth muscle and corticosteroids reduce airway wall inflammation.
- A limitation of current delivery methods is low deposition in the peripheral lung regions, being attributable to
  - structural and functional variability of lung,
  - aerosol size,
  - inspiration patterns, and
  - device misuse.



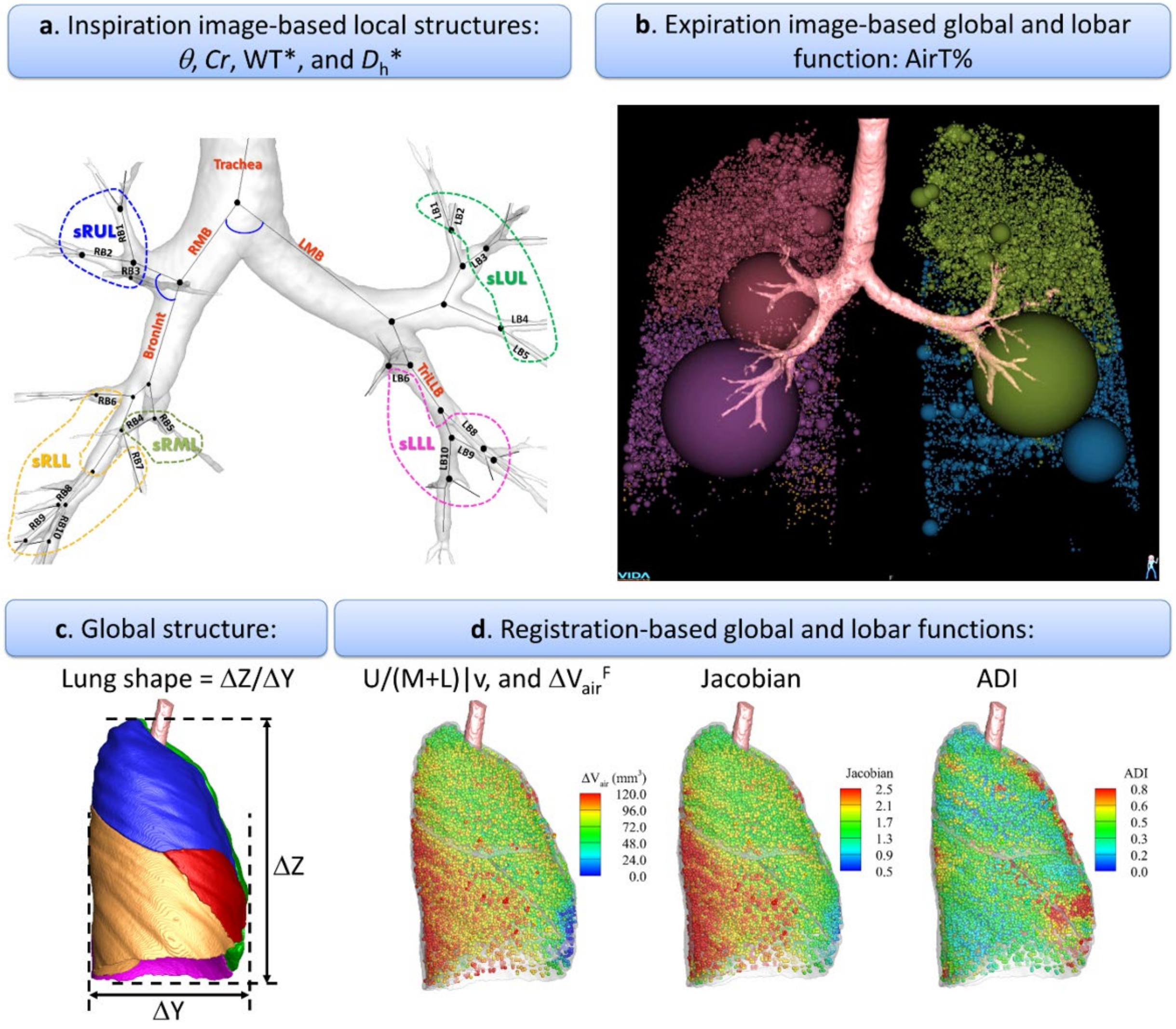
https://foundation.chestnet.org/patient-education-resources/asthma/

Cluster-guided CFD analysis for aerosol particle delivery in asthma

- A recent study [1]
  - performed multiscale imaging-based cluster analysis (MICA) using local/global structural and functional variables, and
  - established four distinctive clusters that are correlated with clinical phenotypes and demographic features from Severe Asthma Research Program (SARP) cohort.
- We have sought to identify cluster-specific characteristics in inhaled aerosol particle deposition patterns, using CFD simulations of subject-specific air flow and 1-8 µm particle transport [2].

[1] Choi S et al. *J Allergy Clin Immunol* (JACI) 2017;140(3):690-700.
[2] Choi J et al. *J Aerosol Med Pulm Drug Deliv* (JAMPDD) 2019, *accepted for publication.*

Multiscale Imaging-based Cluster Analysis (MICA) in Asthmatics



248 asthmatics

Major Features of 4 Asthma Clusters

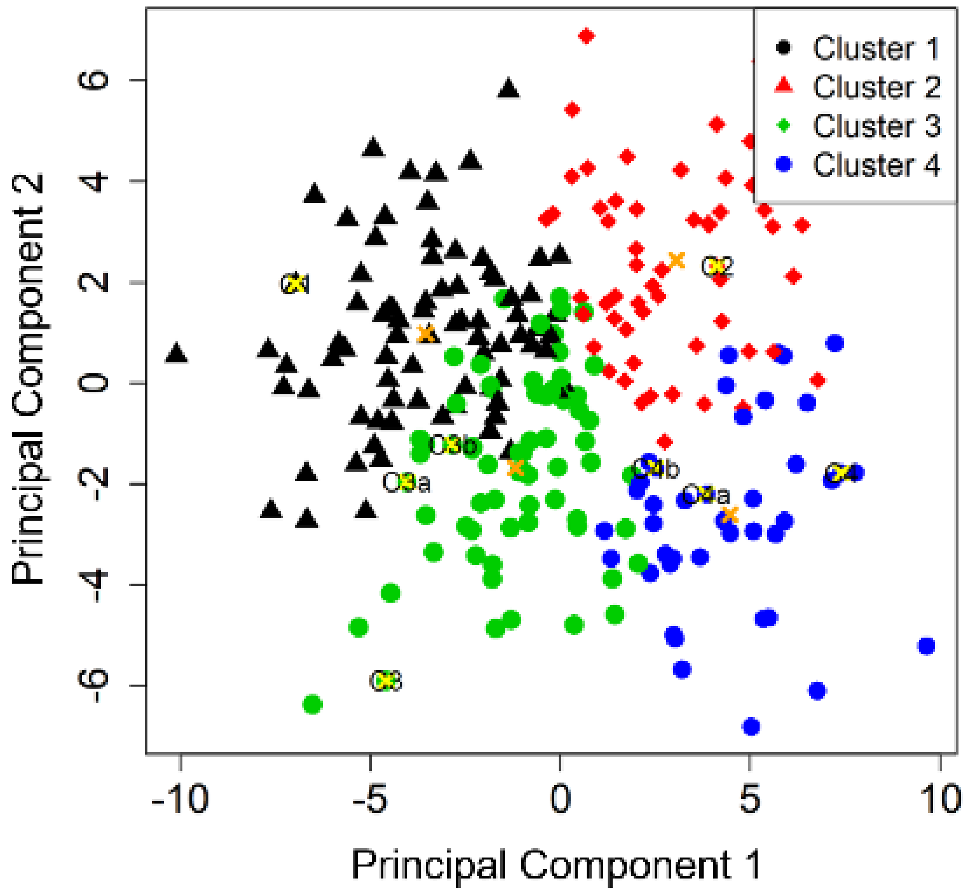
	Imaging characteristics	Clinical characteristics
Cluster 1	• Normal airway structure • Increased lung deformation (Jacobian and ADI↑)	• Younger, early onset • Nonsevere asthma • Reversible lung function • Easy to control asthma symptoms
Cluster 2	• Airway luminal narrowing (D_h*↓) • No airway wall thickening (WT*) • Significant reduction of lung deformation (Jacobian and ADI↓)	• Nonsevere and severe asthma • Persistently altered lung function • Marginal to no inflammation • Difficult to control asthma symptoms
Cluster 3	• Airway wall thickening (WT*↑) • No airway luminal narrowing (D_h*) • Moderate reduction of lung deformation (Jacobian and ADI↓)	• Obese, female-dominant • Severe asthma • Reversible lung function • Blood lymphopenia • Difficult to control asthma symptoms
Cluster 4	• Airway luminal narrowing (D_h*↓) • Significant reduction of lung deformation (Jacobian and ADI↓) • Significant air-trapping (AirT%↑)	• Older, late onset, male-dominant • Severe asthma • Persistently altered lung function • Neutrophilic-dominant inflammation • Difficult to control asthma symptoms

Cluster-representative subjects

10 subjects were selected for CFD simulations of air flow and particle transport.

First, a representative subject was selected from each cluster. Then, two subjects were added from severe asthma clusters (cluster 3 and cluster 4) for further comparison.

One healthy male and one healthy female subjects were also selected from healthy controls.

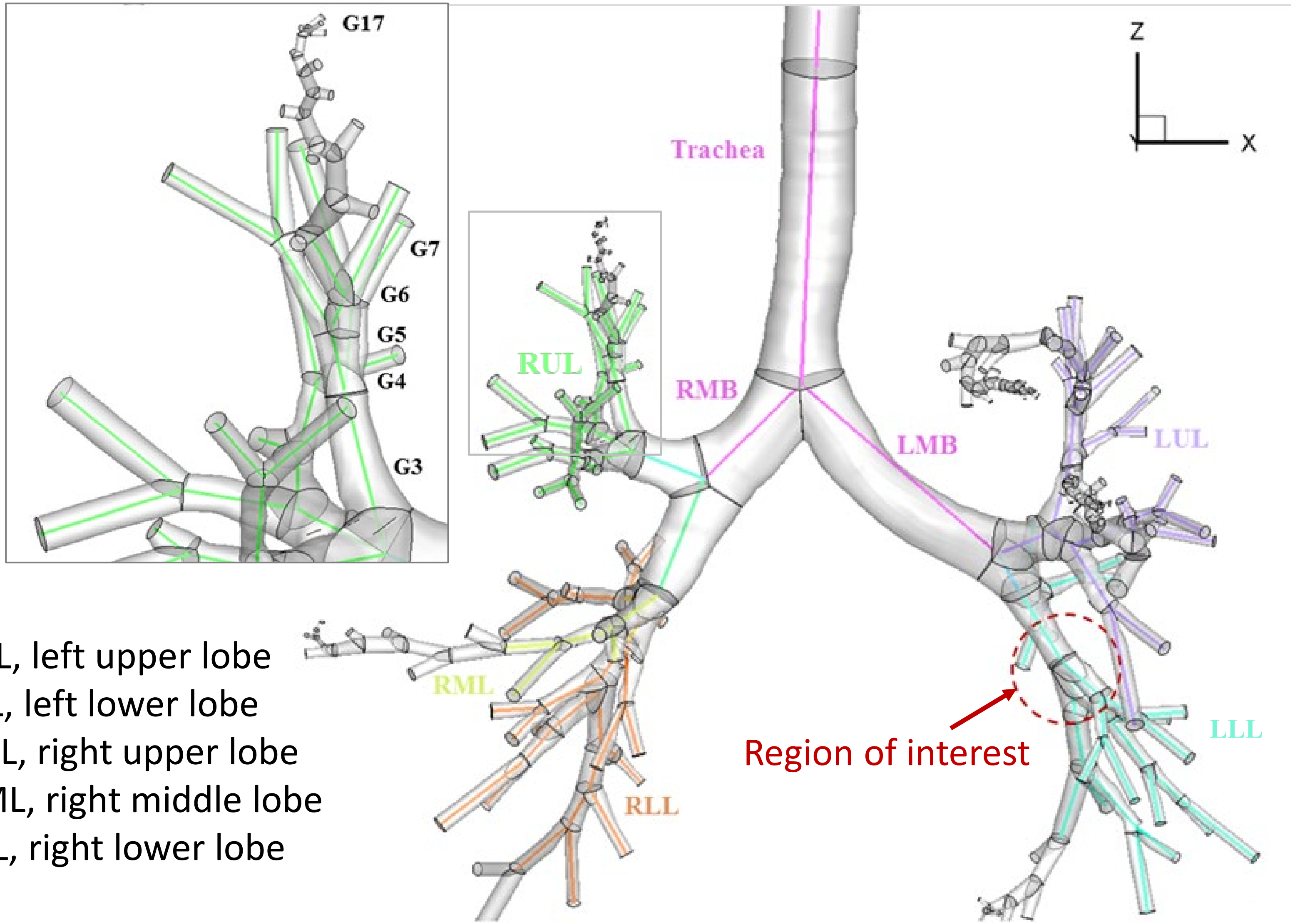


Projection of the four color-coded cluster subjects and their respective cluster means ("x") on principal component (PC) 1 and PC 2 coordinates

Choi et al. *JAMPDD* 2019

Airway geometry model

CT-resolved large airways + 6 paths to terminal bronchioles

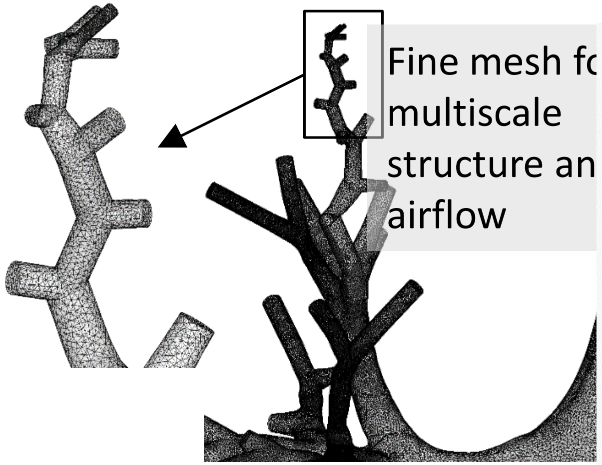


LUL, left upper lobe
LLL, left lower lobe
RUL, right upper lobe
RML, right middle lobe
RLL, right lower lobe

Subject specific multiscale CFD simulations

~10M tetrahedral elements

Slow and deep inhalation with synthetic eddy



Fine mesh fo
multiscale
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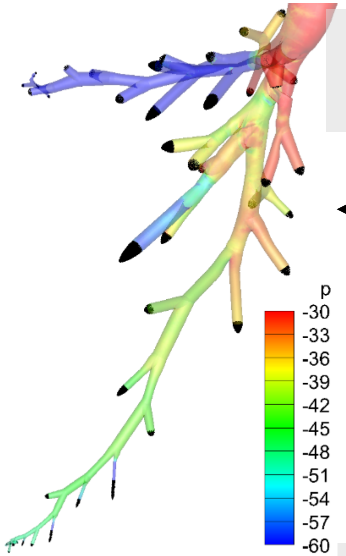
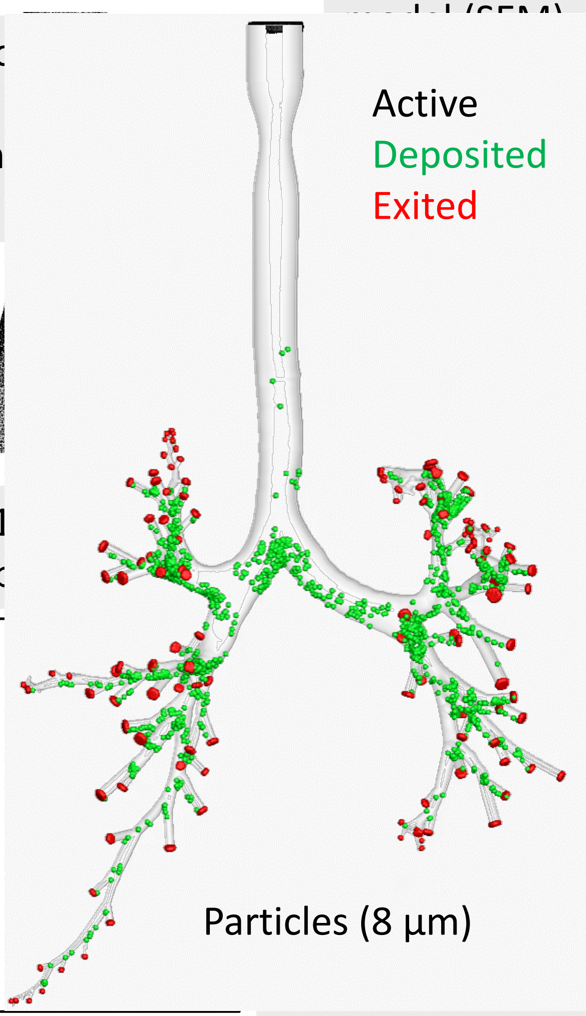
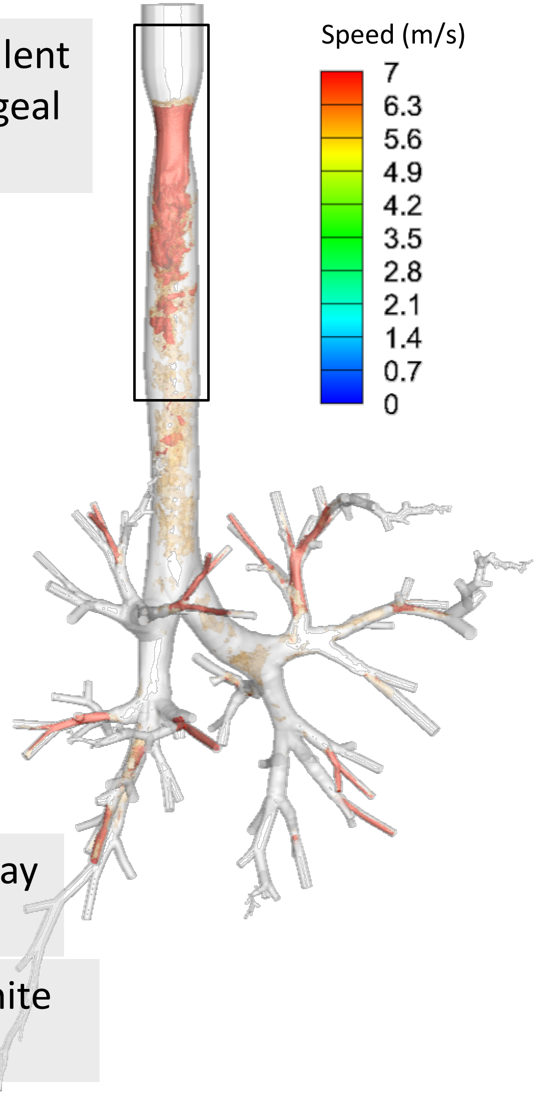


3D-1
coup



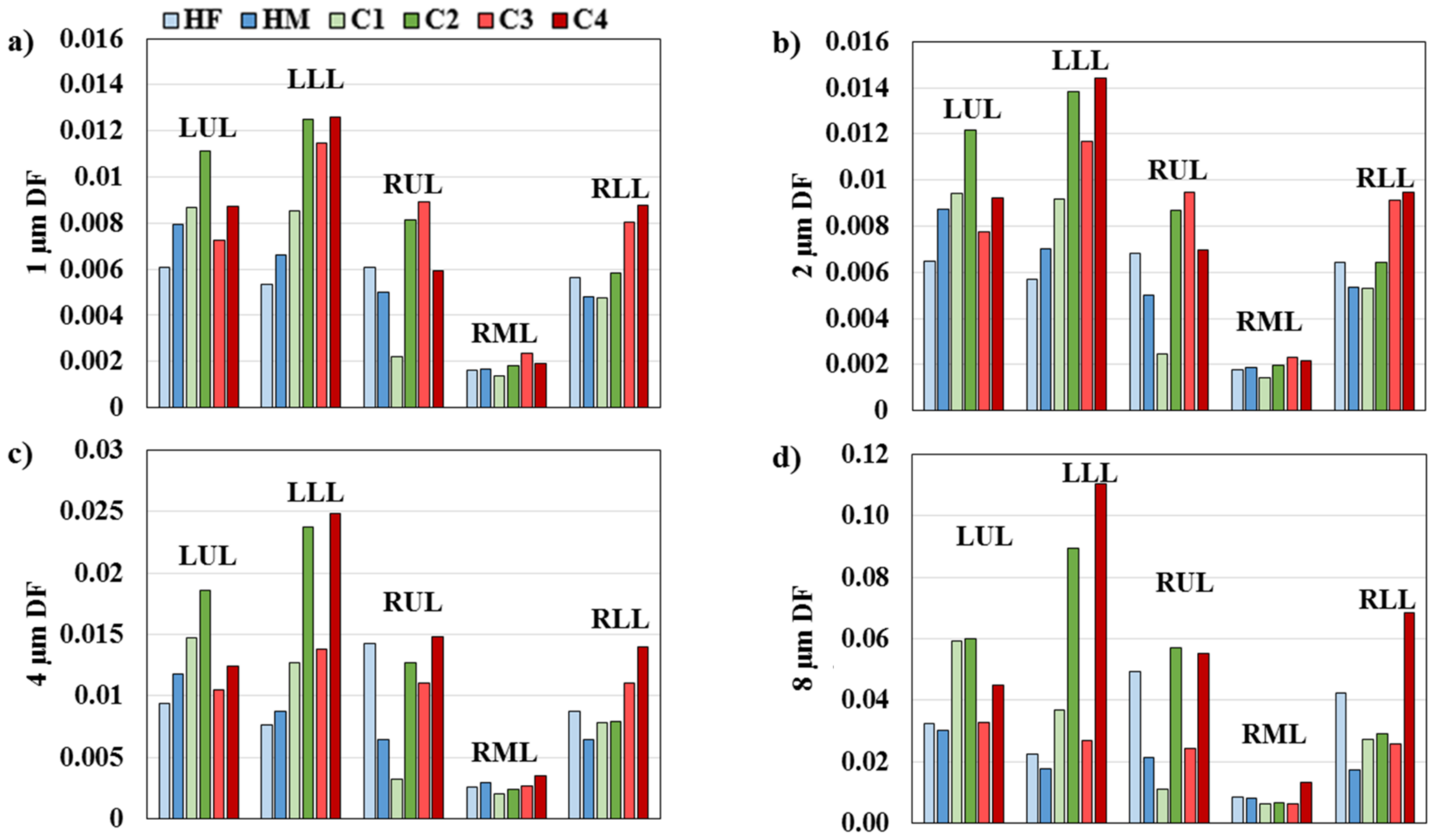


airway
s

Large eddy simulations on a MPI-based finite element framework (160-320 CPU cores)

Lin et al. 2013 WIREs Syst Biol Med 5:643–655

Lobar deposition fractions (DF)



- Cluster 2 and cluster 4 characterized with airway constriction showed large deposition of inhaled aerosol particles, most noticeably in LLL.
- LLL constriction is a key variable found in the cluster analysis.

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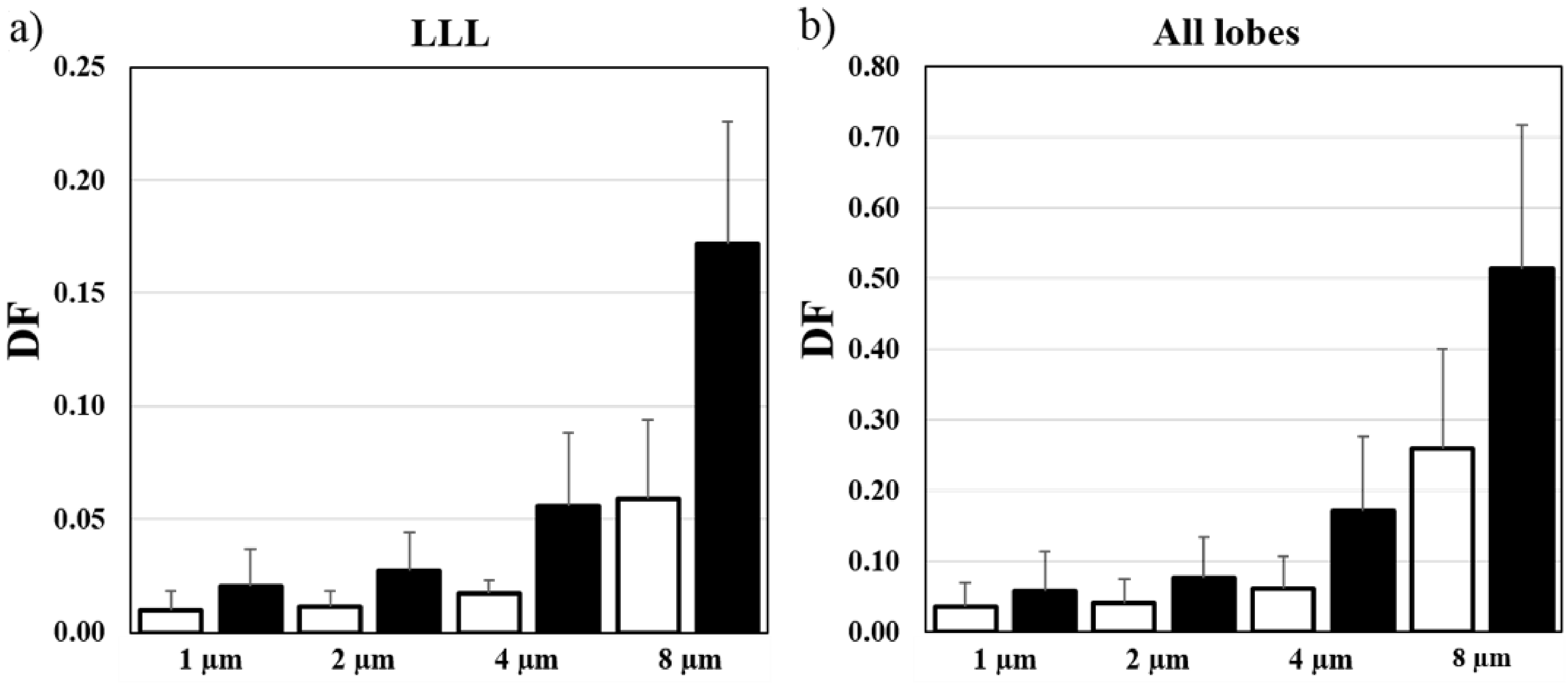
Mean DFs in cluster 3 and cluster 4 subjects



- DFs of 1, 2, 4, and 8 µm particles are compared in (a) LLL and (b) all the lobes for the three cluster 3 (blank) and cluster 4 (filled) subjects, respectively.
- DF is greater in cluster 4 than cluster 3.
- The difference is greater for larger particles.

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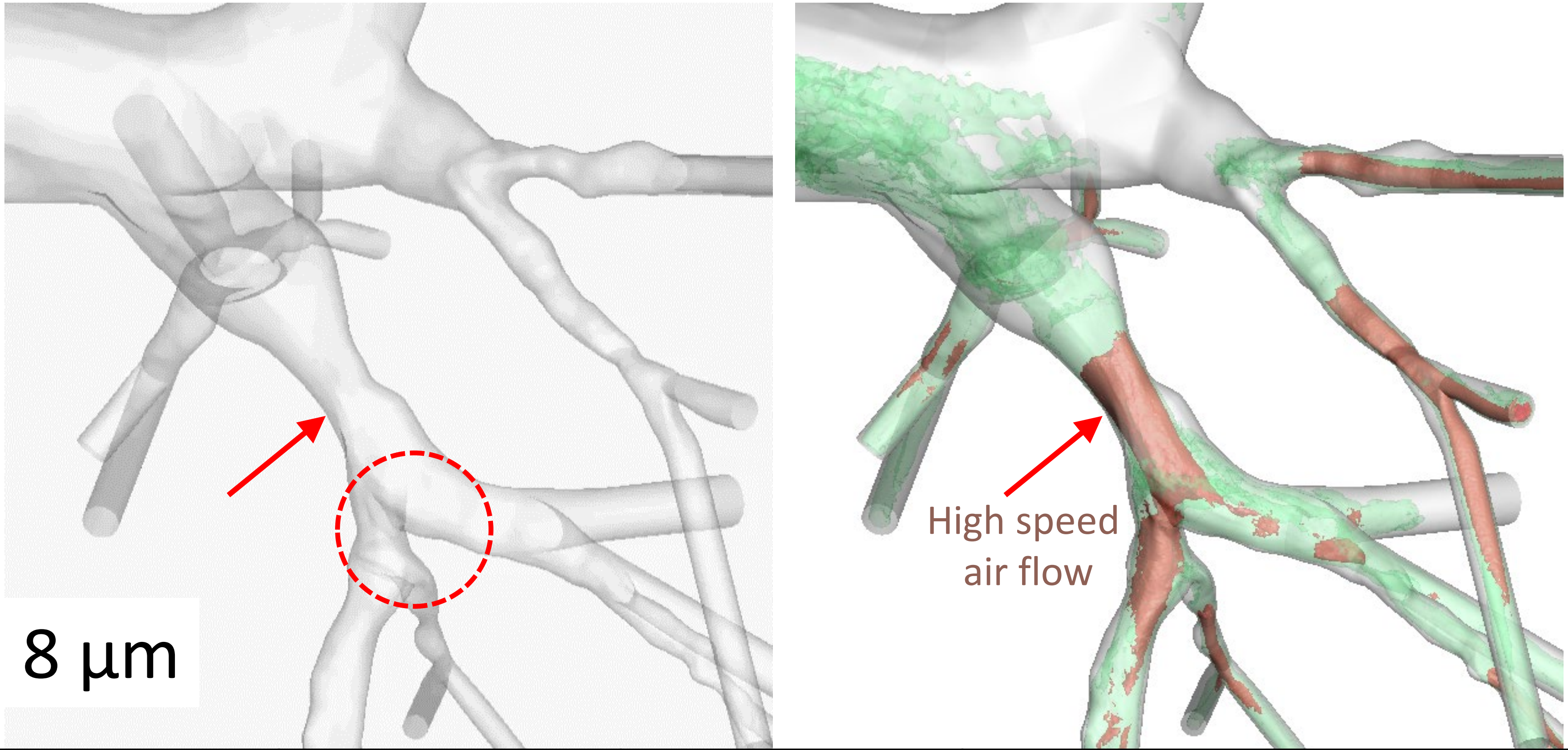
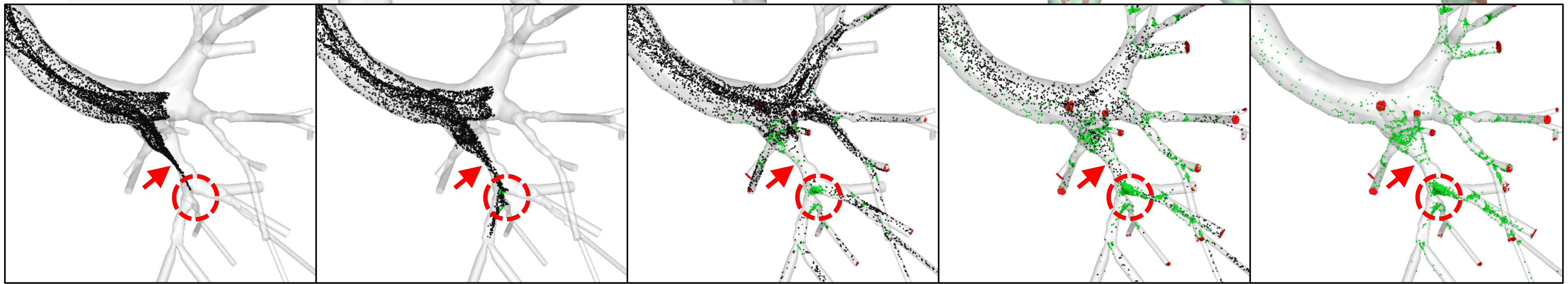
Airway constriction in LLL

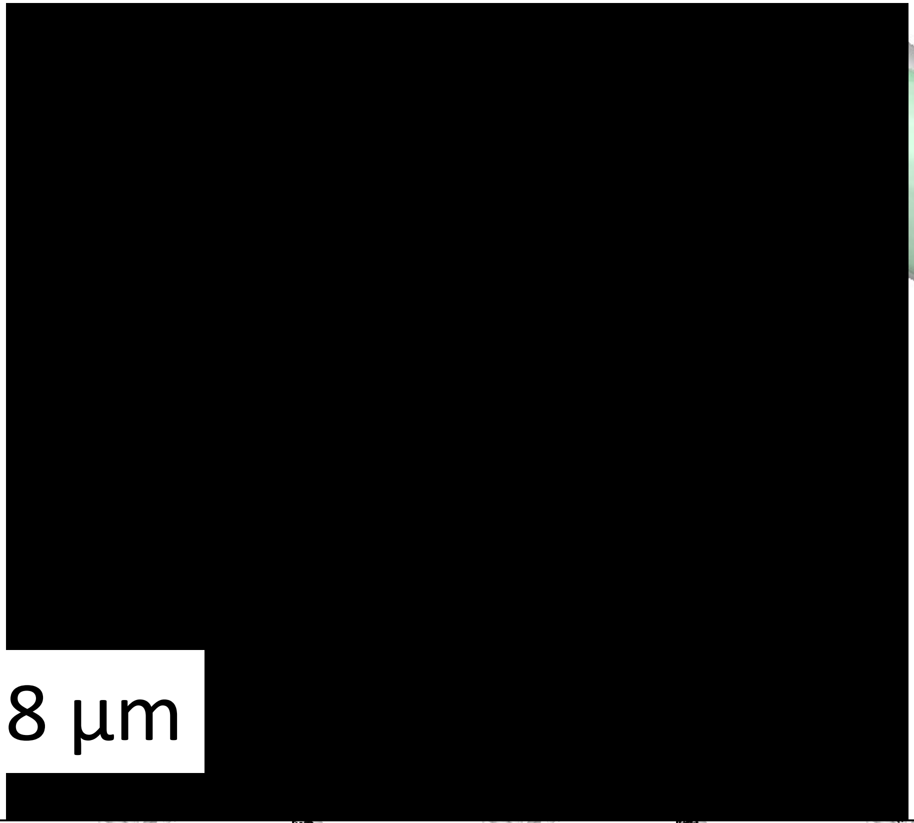
Cluster 4

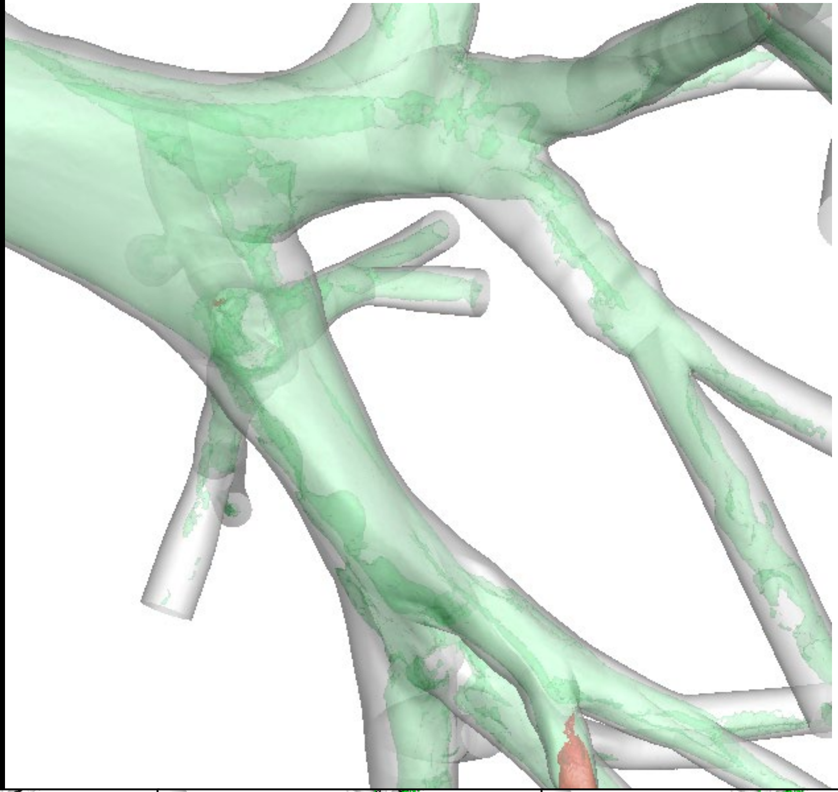


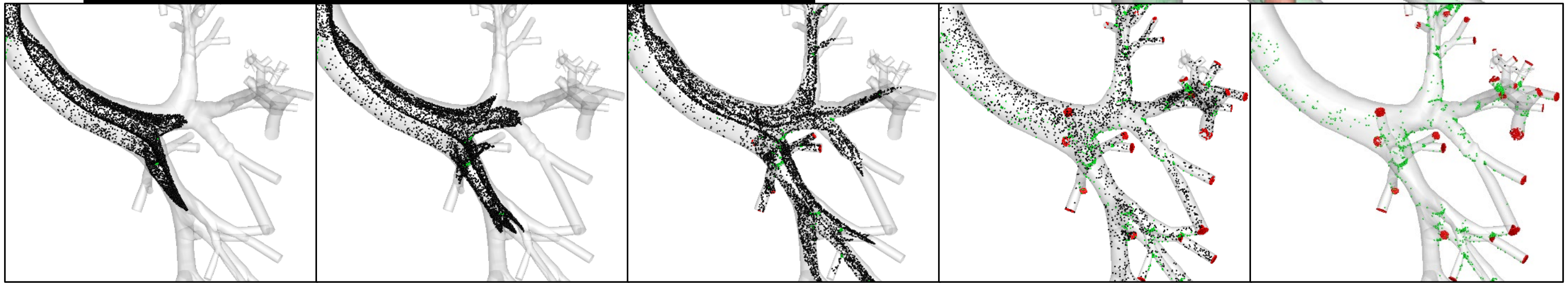


Airway constriction in LLL

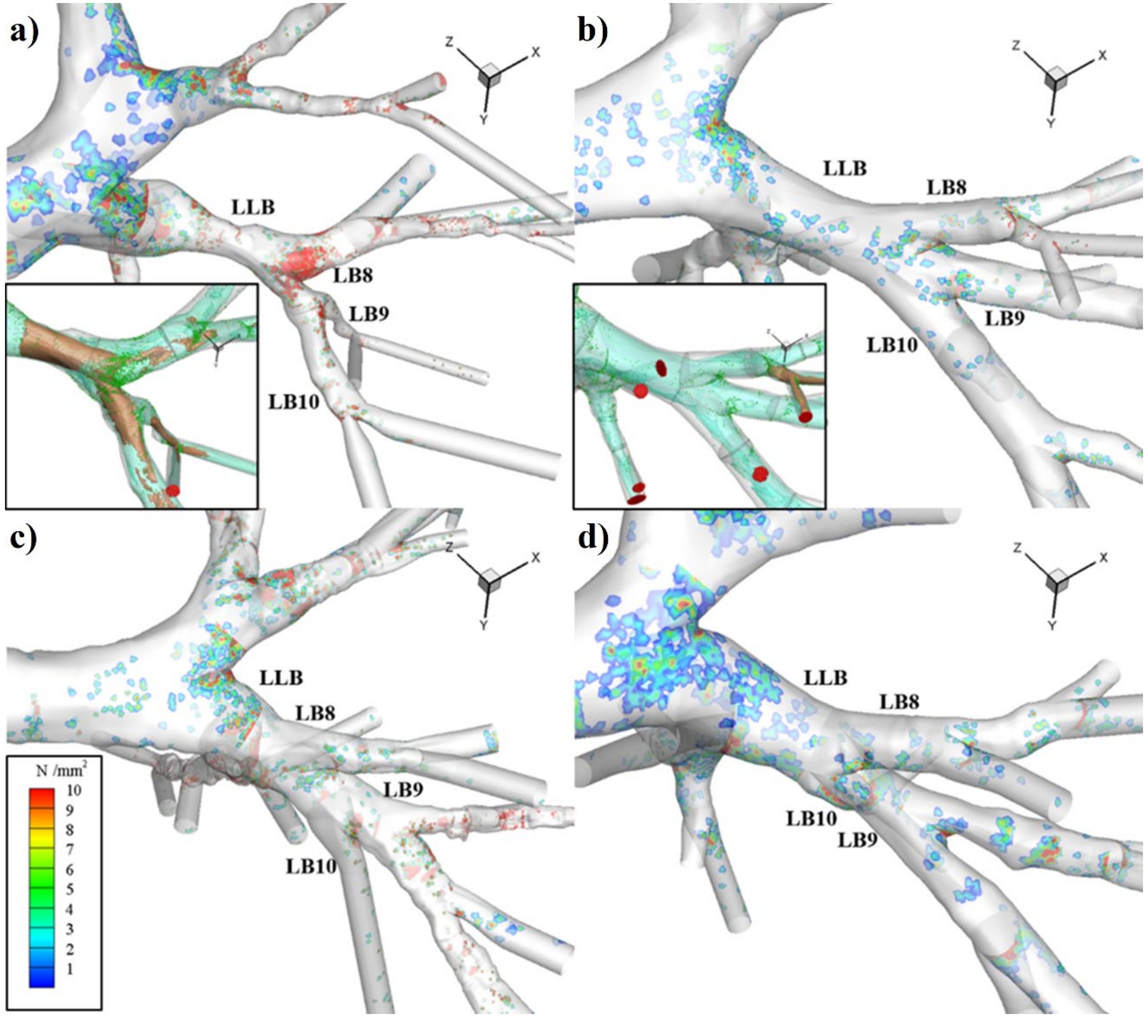
Healthy







Constriction induced particle deposition hot spot in cluster 4



In the cluster 4 subject (a), high-speed air jet through the local constriction impinges on the downstream bifurcation (brown, insert figure).

Consequently, particle deposition density is high in the cluster 4 subject (a), forming a hot spot (red) downstream to the local constriction, compared with healthy (b), cluster 2 (c) and cluster 3 (d) subjects.

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Summary

- We demonstrated the effects of cluster-specific imaging-based features on particle deposition.
- Airway narrowing, which characterizes only one of the two severe asthmatic clusters, induces greater particle deposition in the proximal airways, and hence reduces the particle delivery into the small peripheral airways, which may be the primary target sites.
- The above effect was augmented for the large particles.
- The ability to differentiate severe asthmatics into sub-groups by imaging-based features may help devise strategies for improved inhalational drug delivery.

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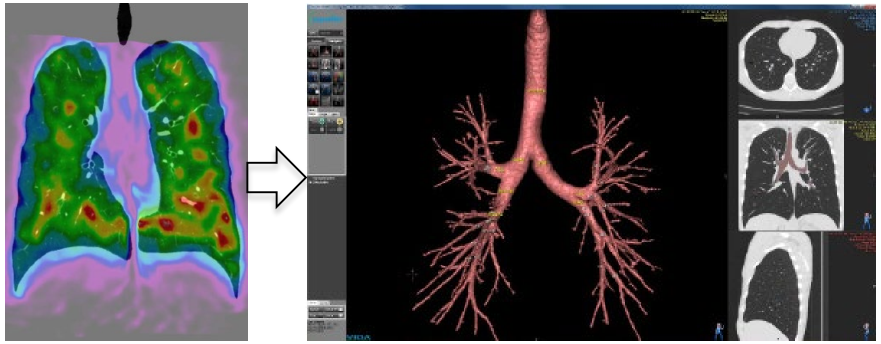
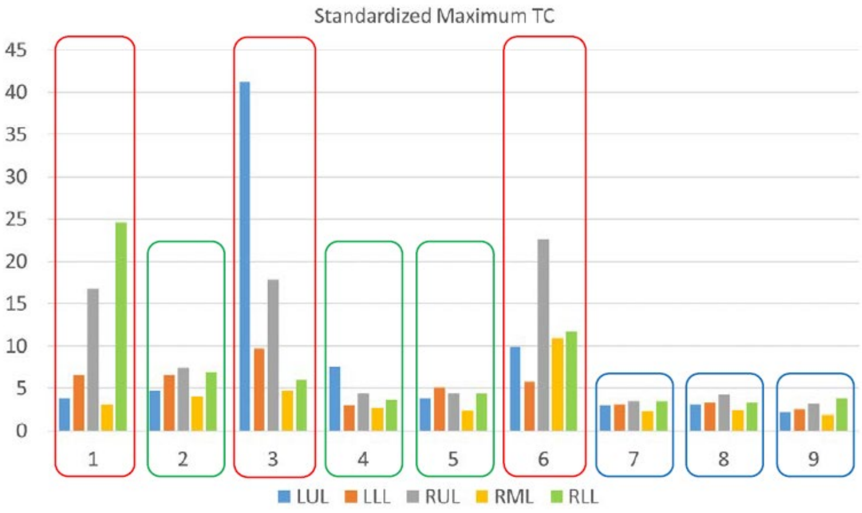
Work in Progress

CT/SPECT human subject study

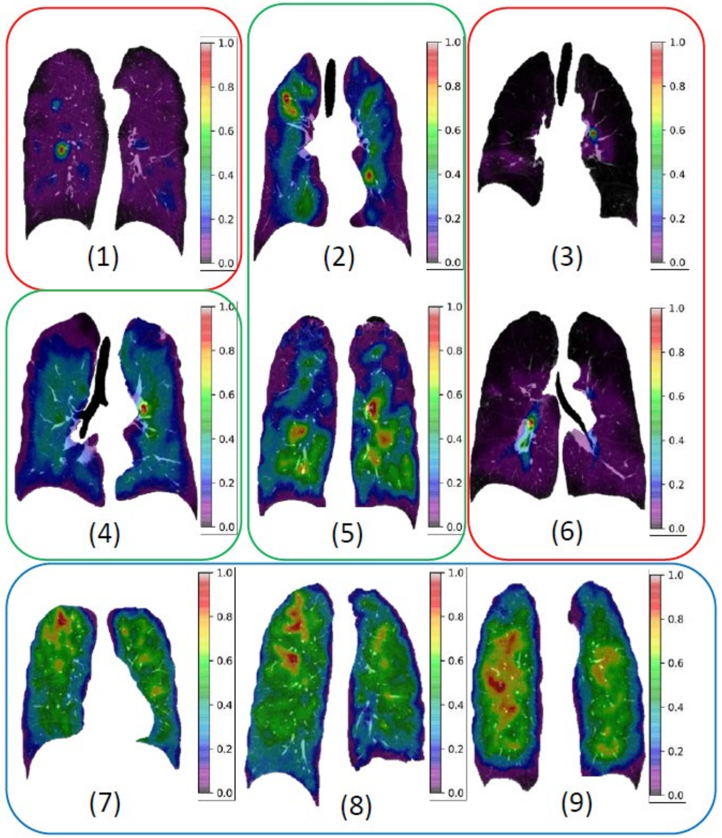
(a)



(b)



(c)

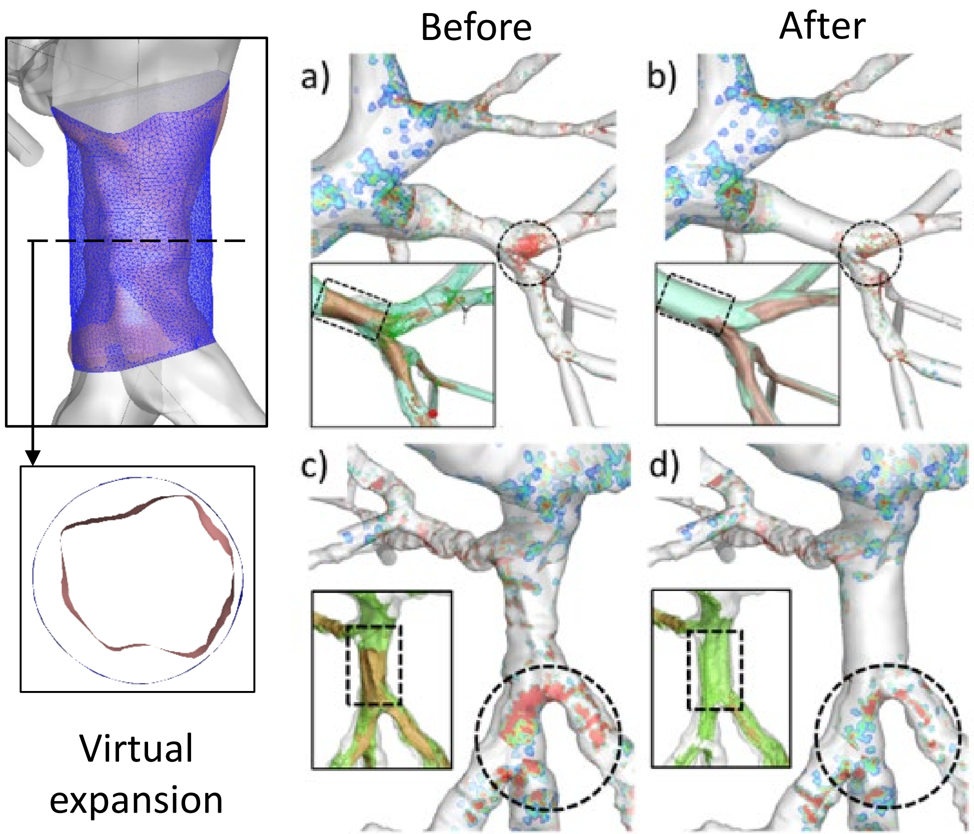


(a) SPECT images of inhaled tracers were co-registered with CT images at full inspiration.
(b) High concentrations were found in severe COPD cluster subjects 1, 3, and 6.

Work in Progress

Bronchial thermoplasty response

CFD demonstrated the luminal expansion effect on constricted proximal airways in severe asthmatics (cluster 4).

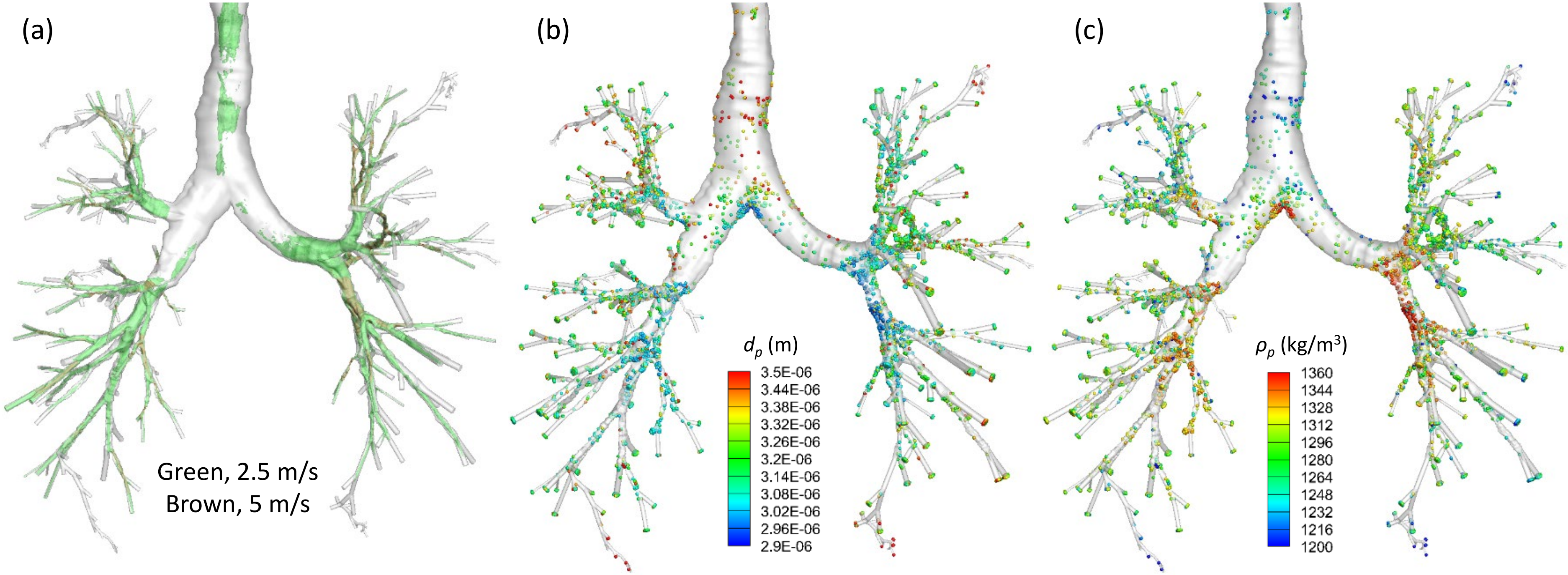


- High-speed jet as well as hot spots disappeared.
- Proximal deposition of inhaled particles deceased, resulting in an increase of particle transport to distal small airways.

Work in Progress

Particle growth: evaporation model

Air speed | Particle diameter | Particle density



- Results of initially 2μm particles with a density of 2165 kg/m^3 in a representative cluster 4 subject are presented.
- Particles in the high speed stream deposited early on the airway wall, growing relatively less (blue).
- Less grown particles have relatively larger densities (red).

Acknowledgments

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- Views expressed in this work do not necessarily reflect the official policies of the Department of Health and Human Services and may not be quoted as being made on behalf of a reflecting the position of the US Food and Drug Administration; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.
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Disclosures: Eric A. Hoffman is a shareholder in VIDA diagnostics, a company that is commercializing lung image analysis software derived by the University of Iowa lung imaging group. He is also a member of the Siemens CT advisory board.

Thank You!