2018 ATS International Conference
ISAM/ATS Pre-Conference Session
"Current Practice and Future Developments in Aerosol Medicine"

Characteristics of Inhaled Particle Deposition in the Lungs of Imaging-based Asthma Clusters: a Numerical Study

May 19, 2018, 2:45pm

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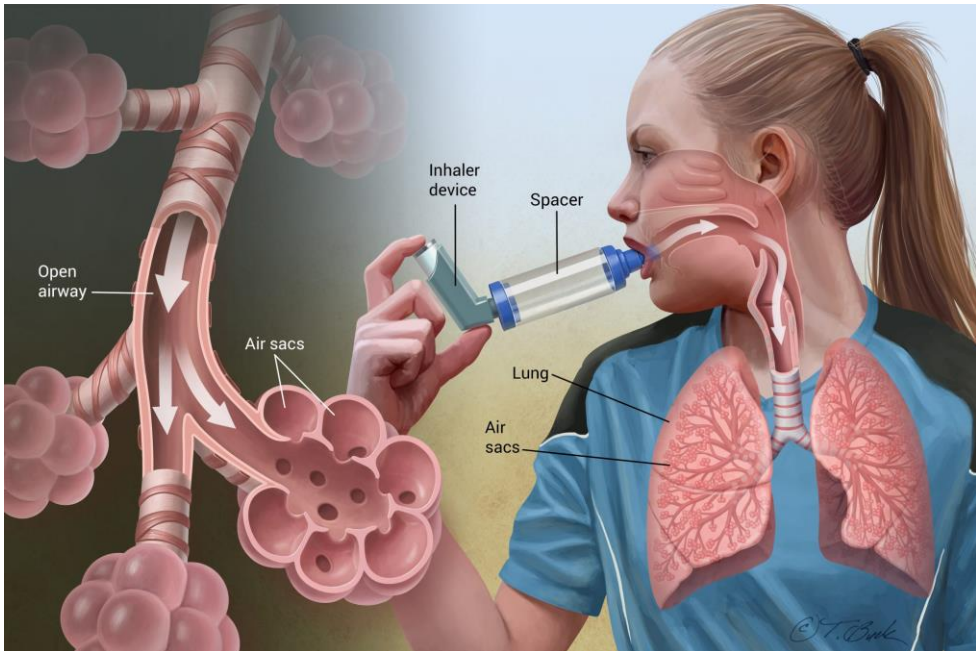
Disclosures: Eric A. Hoffman is a shareholder in VIDA diagnostics, a company that is commercializing lung image analysis software derived by the University of Iowa lung imaging group. He is also a member of the Siemens CT advisory board.

Particle inhalation in asthma

- Inhalation of medication (aerosolized bronchodilators and corticosteroids) is a major treatment for asthma,
- to relax airway smooth muscle and reduce airway wall inflammation, respectively.
- Current delivery methods are limited by low deposition in the peripheral lung regions,
- attributable to
  - structural and functional variability of lung,
  - aerosol size,
  - inspiration patterns, and
  - device misuse.



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

Objectives

- A recent study (Choi et al. J Allergy Clin Immunol 2017;S0091-6749(17):30146-X)
  - 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 cluster-specific characteristics in inhaled particle deposition patterns, using
- computational fluid dynamics (CFD) simulations of subject-specific air flow and particle transport.

Imaging-based asthma clusters

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
Imaging Features	• Reversible lung function • $J \uparrow$	• $J \downarrow$ • Airway constriction ($D_h^* \downarrow$ in LLL, RMB, & bronchus intermedius) • $\vartheta_{RMB} \downarrow$	• Moderate reduction in J • Airway wall thickening • Reversible lung function	• $J \downarrow\downarrow$ • Airway constriction ($D_h^* \downarrow$) • $\vartheta_{RMB} \downarrow$ • Significant air trapping
Clinical Features	• Non-severe asthma • Similar to healthy subjects • Easy to control symptoms	• Mix of non-severe & severe subjects • Little inflammation • Difficult to control symptoms	• Severe asthma • Female dominant • Difficult to control symptoms	• Severe asthma • Male dominant • Difficult to control symptoms

J, Local Jacobian determinant indicating local lung volume change.

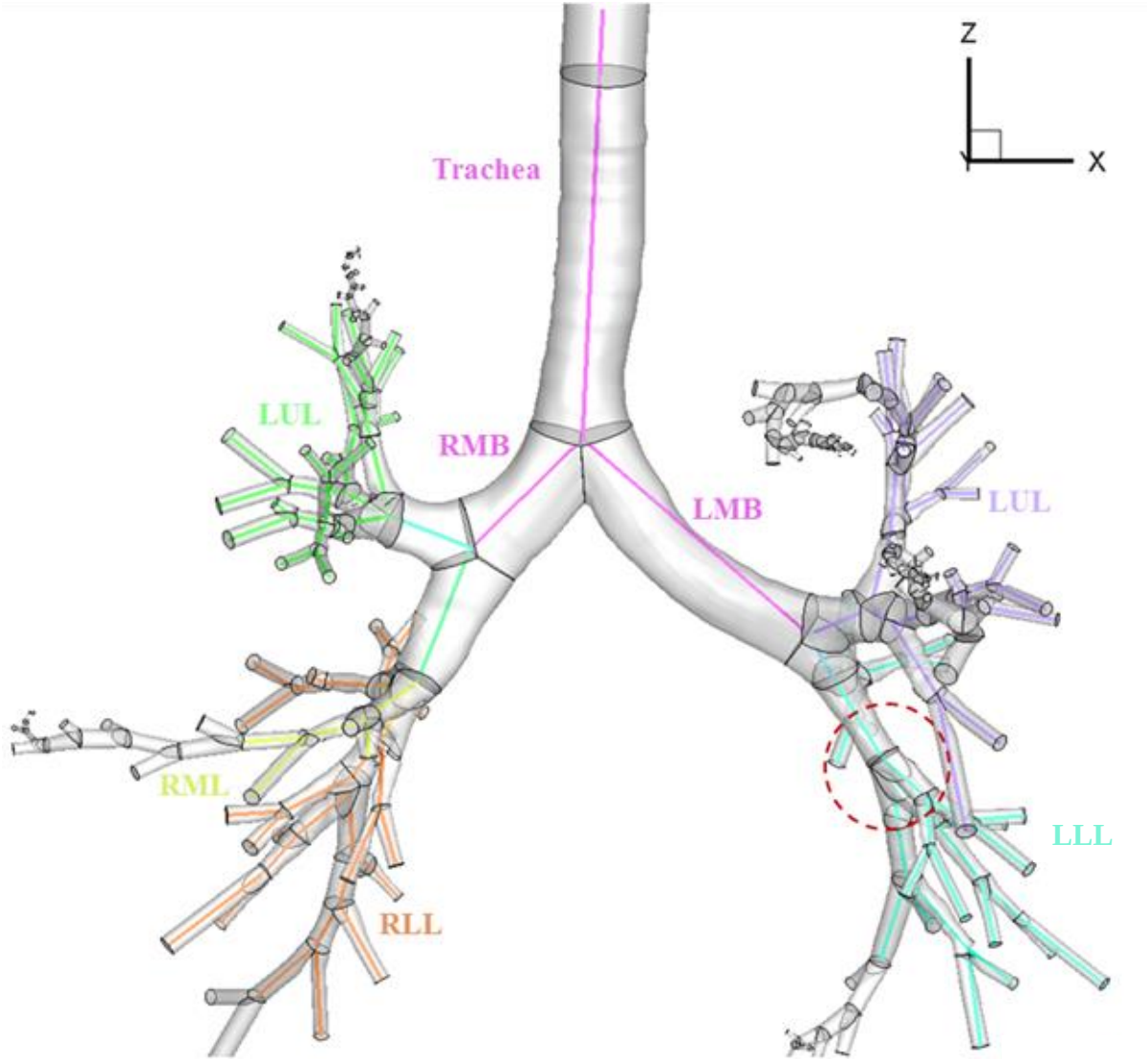
D_h^*, Hydraulic diameter of airway branch, normalized by healthy predicted diameter of the trachea.

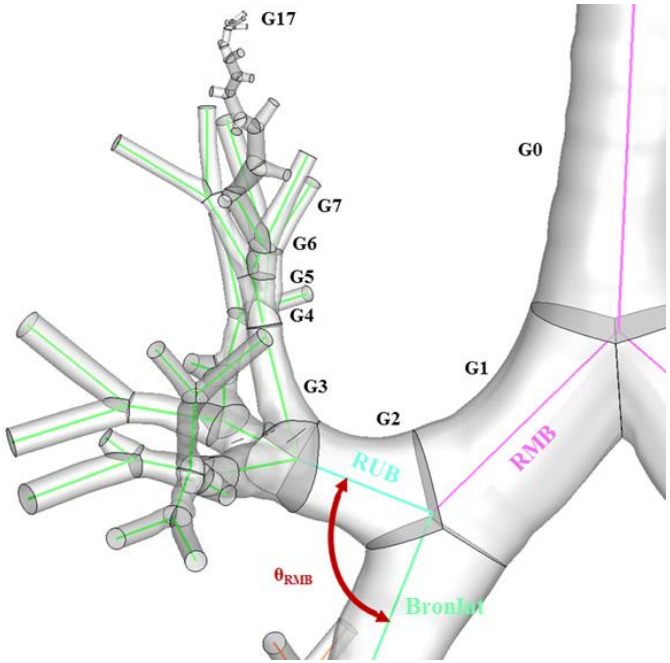
ϑ_{RMB}, Branching angle at the right main bronchus (RMB)

Choi et al. J Allergy Clin Immunol 2017;140(3):690-700.e8

Airway geometry and ROIs

CT-resolved large airways + 6 paths to terminal bronchioles





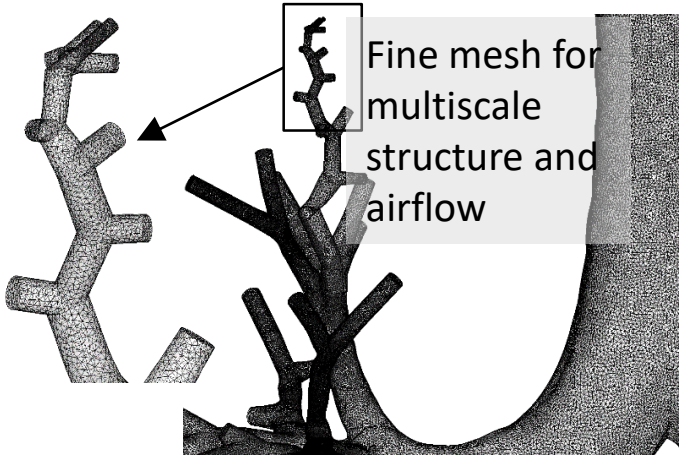
Structural alteration of interest

1. Airway narrowing (LLL)
2. Smaller branching angle (RMB)

Key features for subject selection, analysis, and CFD

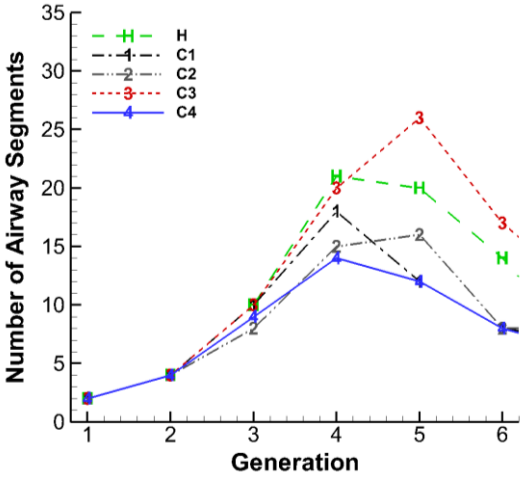
	Healthy Female, HF	Healthy Male, HM	Cluster 1, C1	Cluster 2, C2	Cluster 3, C3	Cluster 4, C4
Demography						
Gender	Female	Male	Female	Male	Female	Male
Age (yrs.)	29	28	20	52	49	51
Weight (kg.)	61.5	99.0	58.6	111.8	85.1	103.0
Asthma Severity	N/A	N/A	Non-severe	Non-severe	Severe	Severe
Features for Presented Subject (Sub-population Average)						
D_h^* (sLLL)	0.35 (0.34)	0.38 (0.33)	0.37 (0.34)	0.24 (0.27)	0.43 (0.34)	0.23 (0.28)
J	2.0 (2.0)	2.4 (2.1)	3.3 (2.5)	1.8 (1.7)	1.9 (1.9)	1.4 (1.5)
IC (Liters)	2.5 (2.2)	3.4 (3.1)	3.0 (3.2)	2.5 (1.8)	2.7 (2.0)	1.8 (2.1)
ϑ_{RMB} (º)	90.0	90.0	94.8	74.8	91.3	67.9
CFD Flow Inlet Conditions at Peak Inspiration (PI)						
Q_{PI} (L/min)	50.2	66.7	60.2	50.5	53.3	35.8
D_h^* (Trachea)	1.17	0.99	0.88	0.94	1.23	0.97
Re	4364	5364	6647	3905	3894	2742

Subject specific multiscale CFD simulations



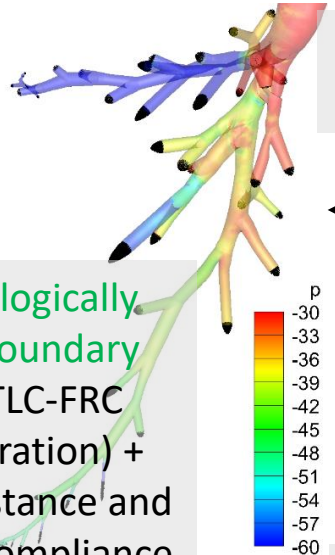
Fine mesh for multiscale structure and airflow

Slow and deep inhalation
(CT-based inspiratory capacity)

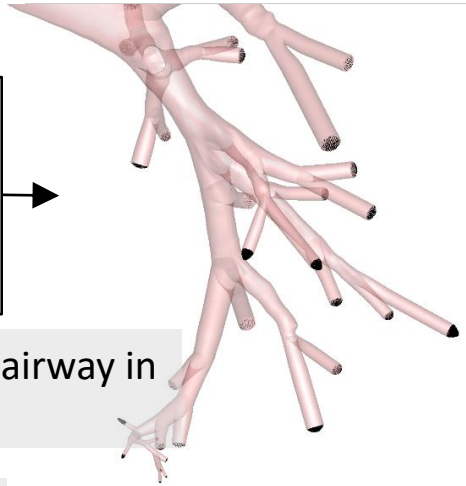


200,000 particles
1, 2, 4, & 8 µm

3D-1D coupling



Pathophysiologically consistent boundary condition. (TLC-FRC image registration) + (airway resistance and peripheral compliance model)

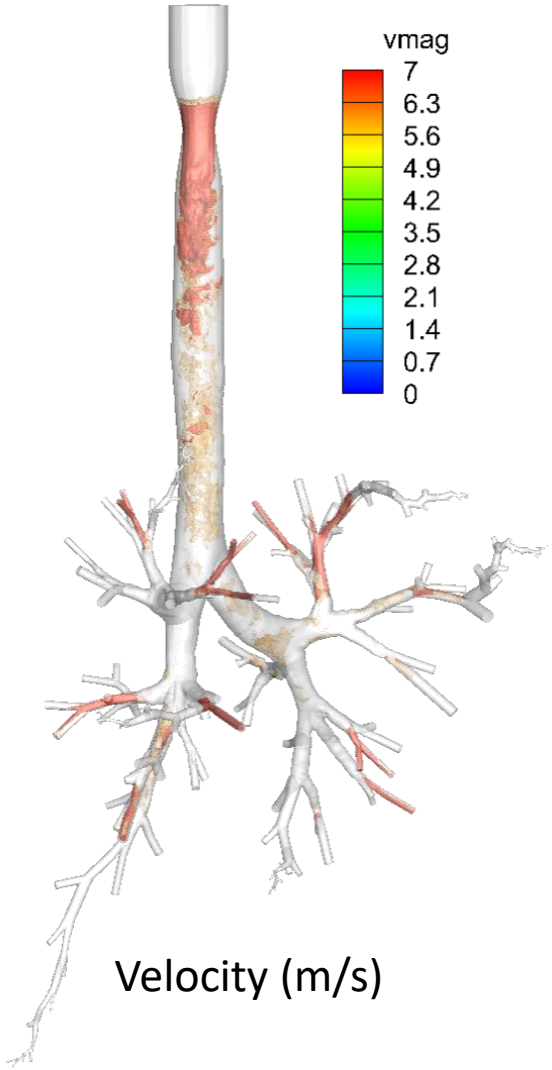


Entire conducting airway in 6 regional paths

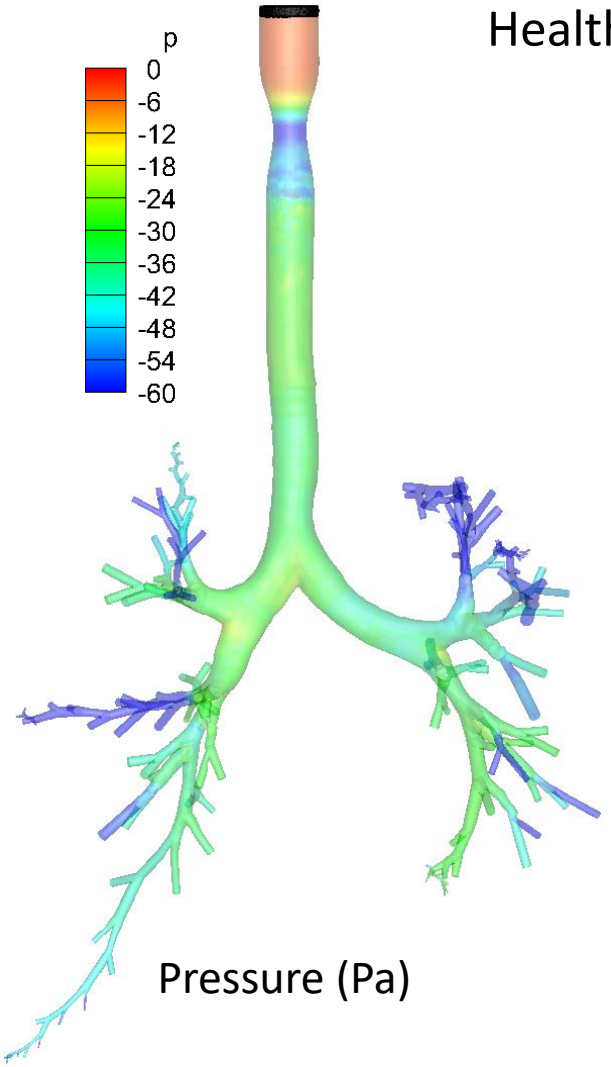
Large eddy simulations on a MPI-based finite element framework (160-320 CPU cores)

Choi et al. 2009 PoF 21 (10), 101901; Yin et al. 2010 J Biomech 43 (11), 2159-2163; Lin et al. 2013 WIREs Syst Biol Med 5:643–655

Airflow and particle transport

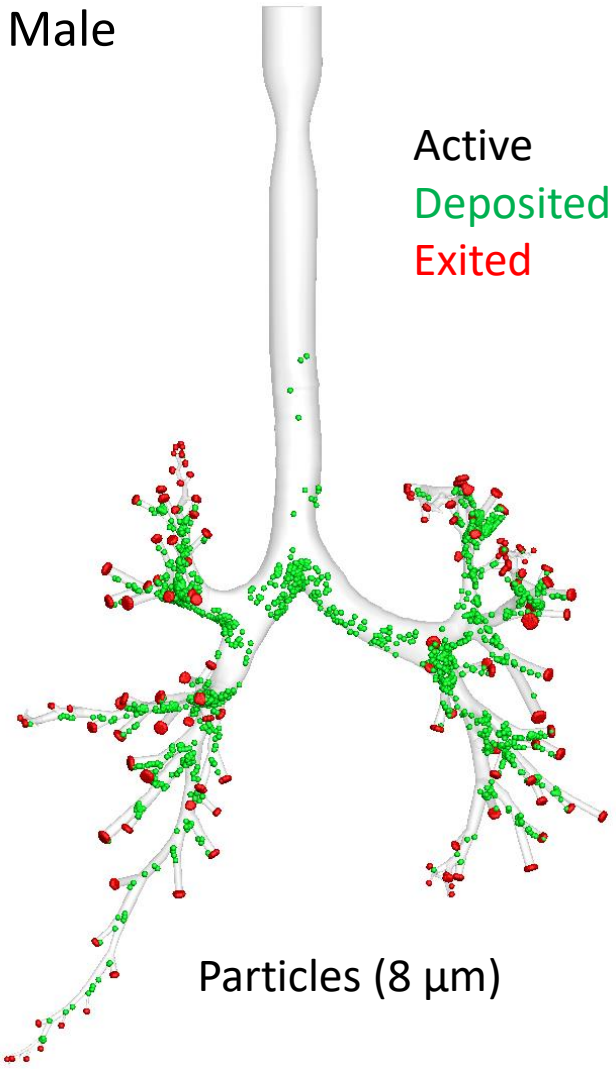


Velocity (m/s)



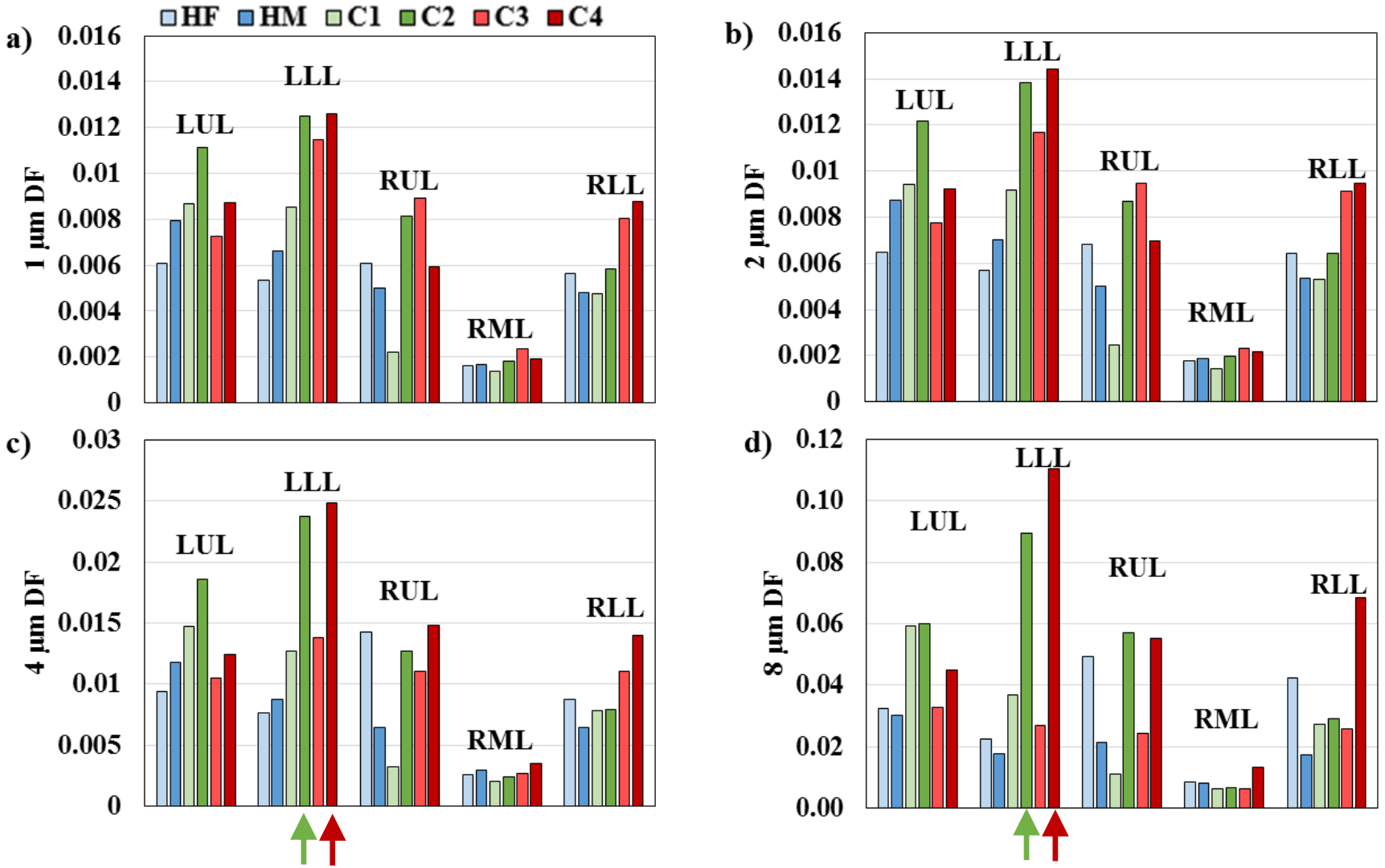
Pressure (Pa)

Healthy Male



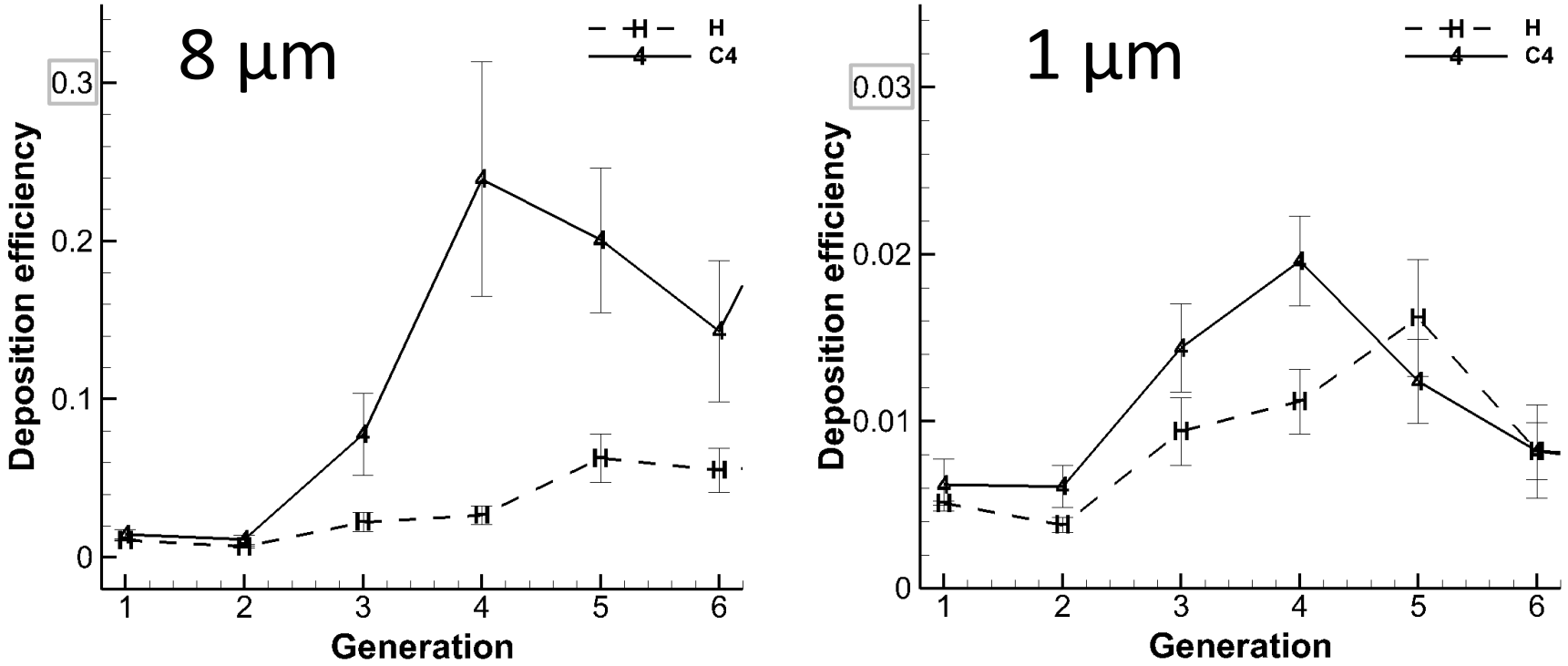
Particles (8 µm)

Lobar particle deposition fractions (Deposited/Inhaled)



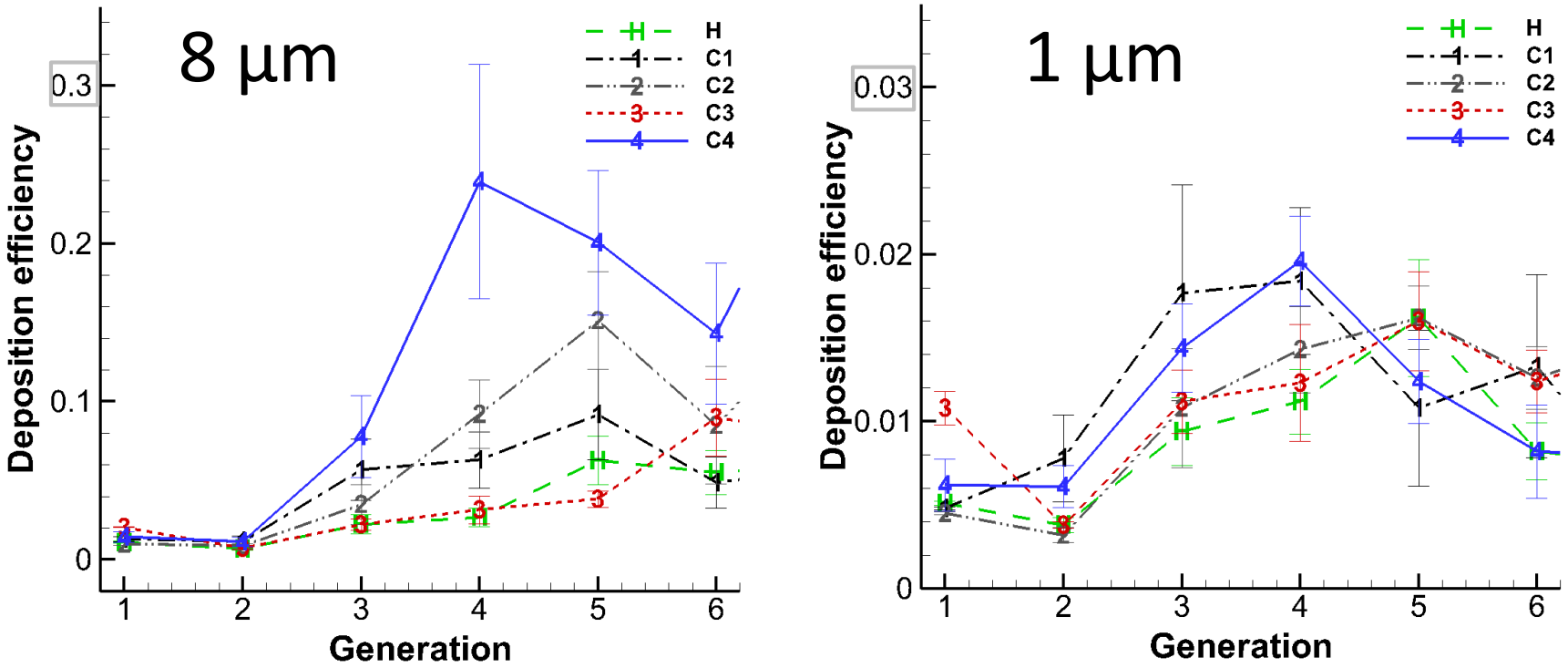
Lobar deposition fraction (DF) in LLL is greater in the C2 and C4 subjects than in the others. The relative difference increases as the particle size increases, as indicated by arrows.

Deposition efficiency by generation
(Deposited / Entered the branch)



- For 8 µm particles, Cluster 4 subject (C4) had greater deposition efficiency than the healthy subject (H). Generations 3-6 includes lobar, segmental, and sub-segmental airways.
- For 1 µm particles, difference is smaller. However, C4 had higher deposition efficiency in generations 2-4, which correspond to lobar and segmental airways.

Deposition efficiency by generation
(Deposited / Entered the branch)



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Deposition efficiency by generation
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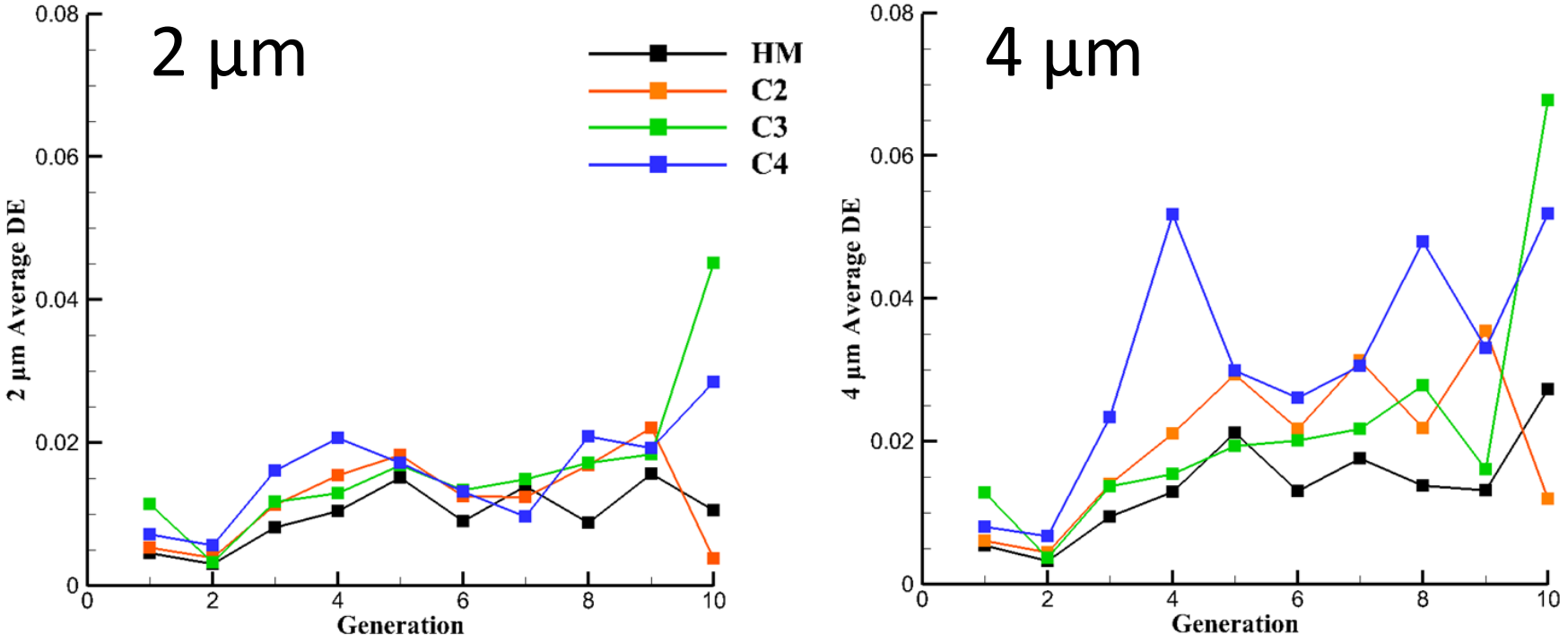
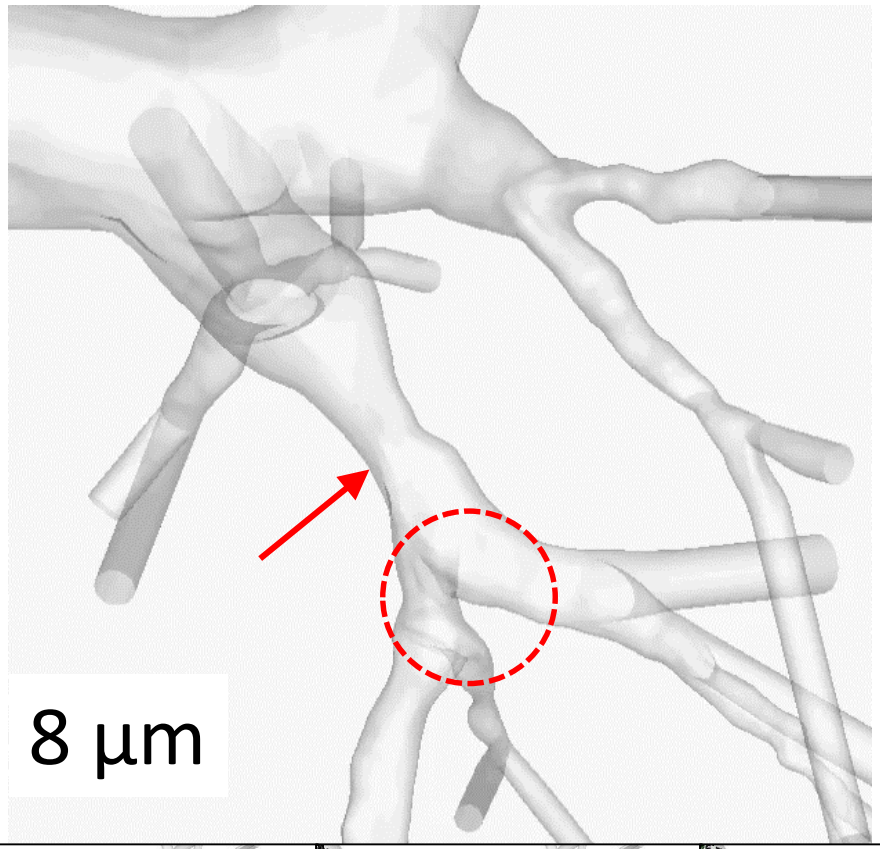
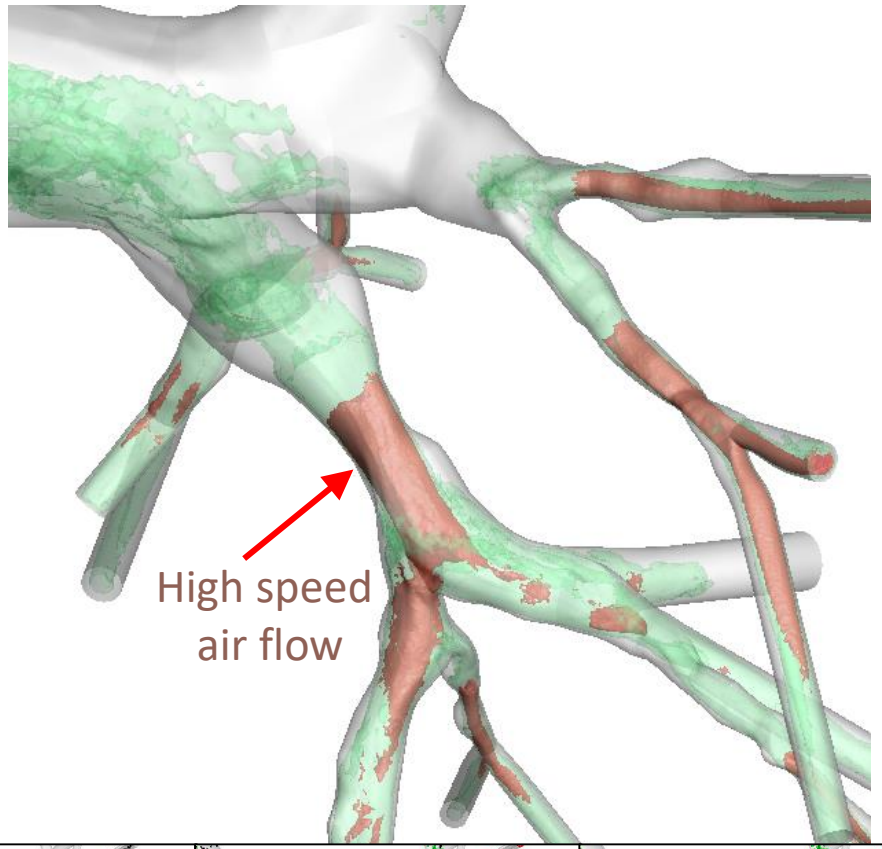


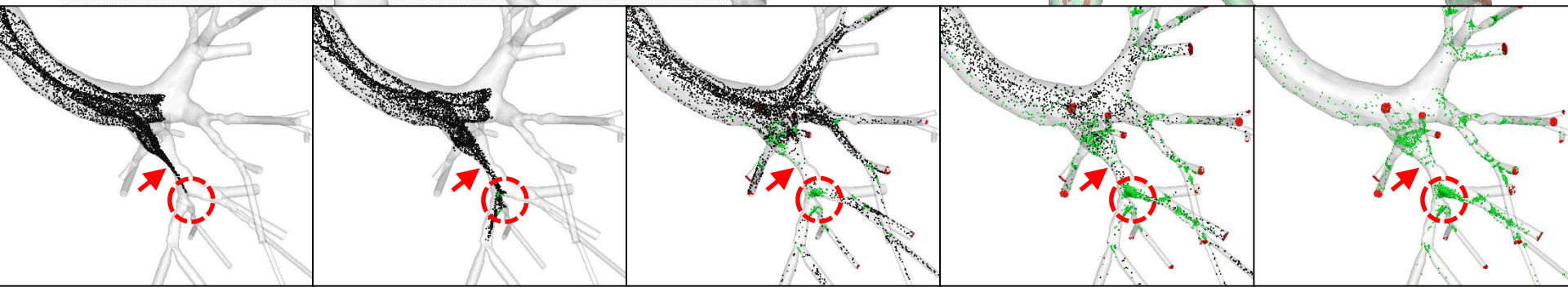
Particle deposition fraction and efficiency both increased in one severe (C4) and one non-severe (C2) asthmatic cluster subjects characterized by segmental airway constriction, as compared with the other two cluster subjects (one non-severe and one severe asthmatics) without airway constriction.

Airway constriction in LLL

Cluster 4

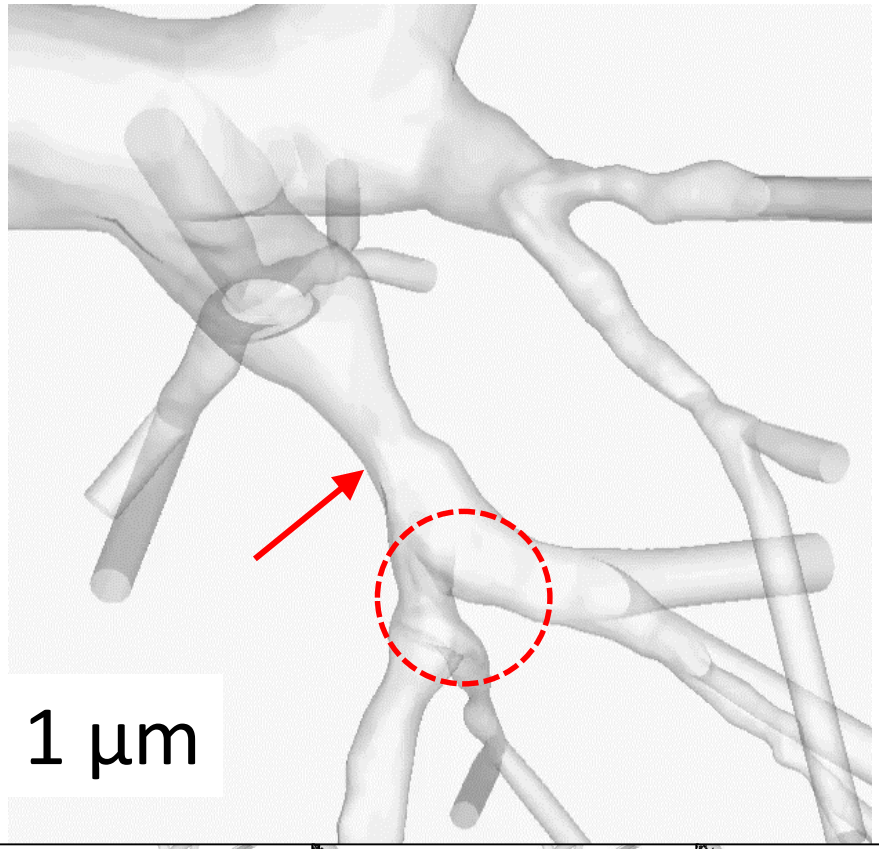




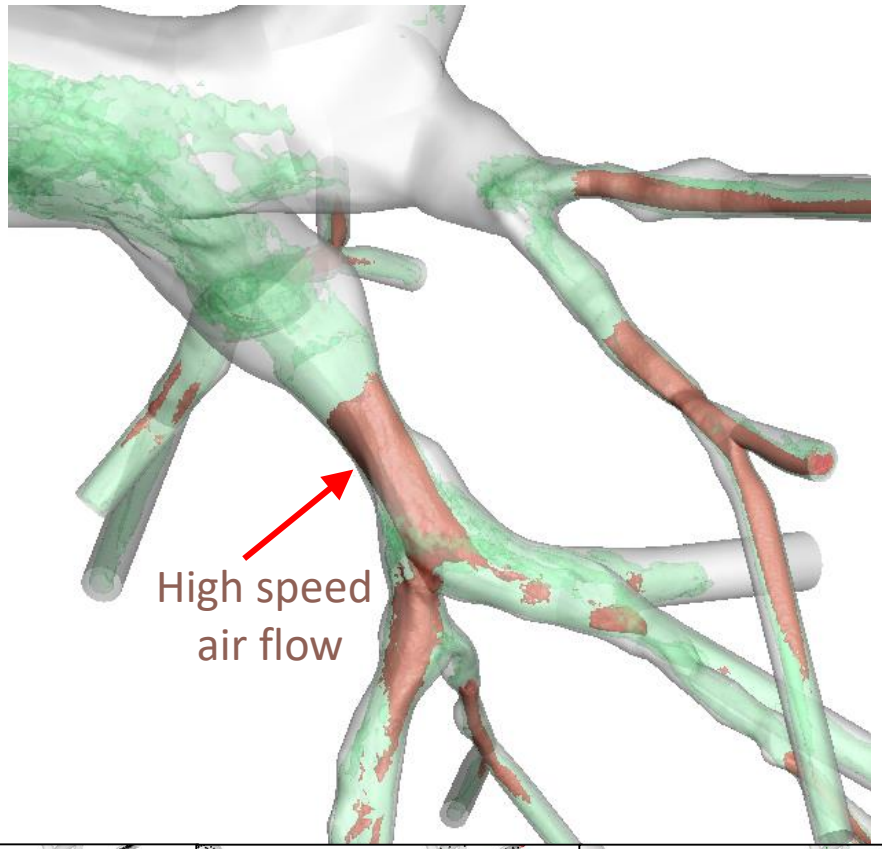


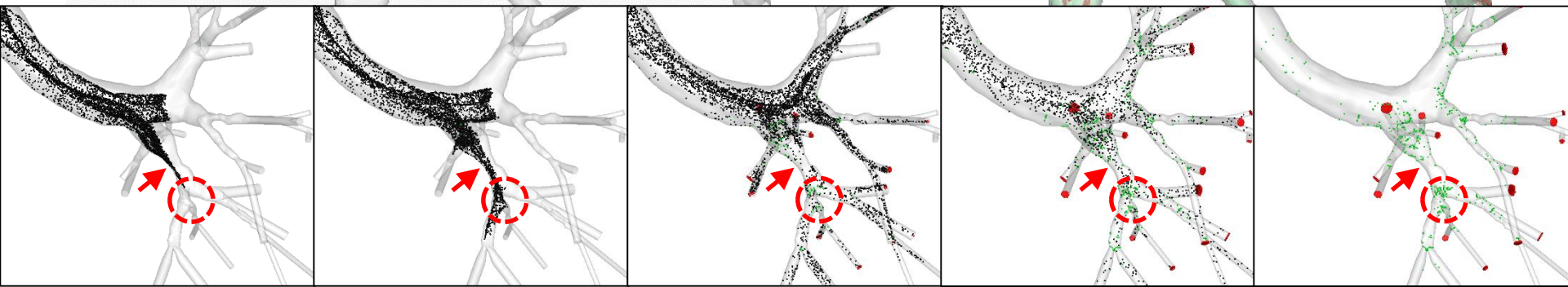
Airway constriction in LLL

Cluster 4



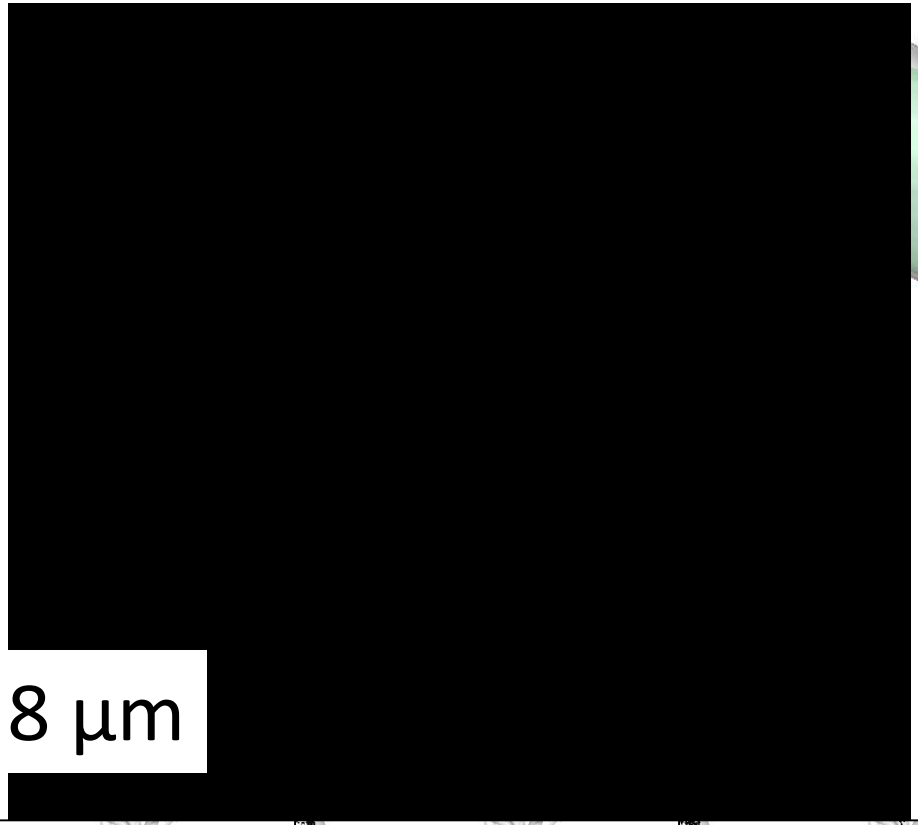
1 µm

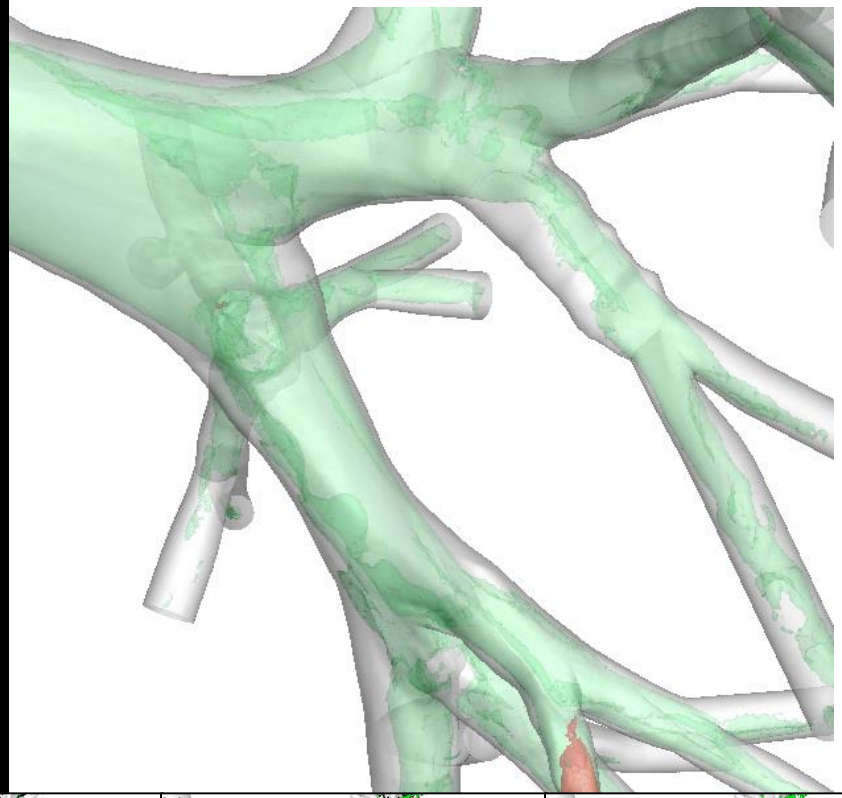


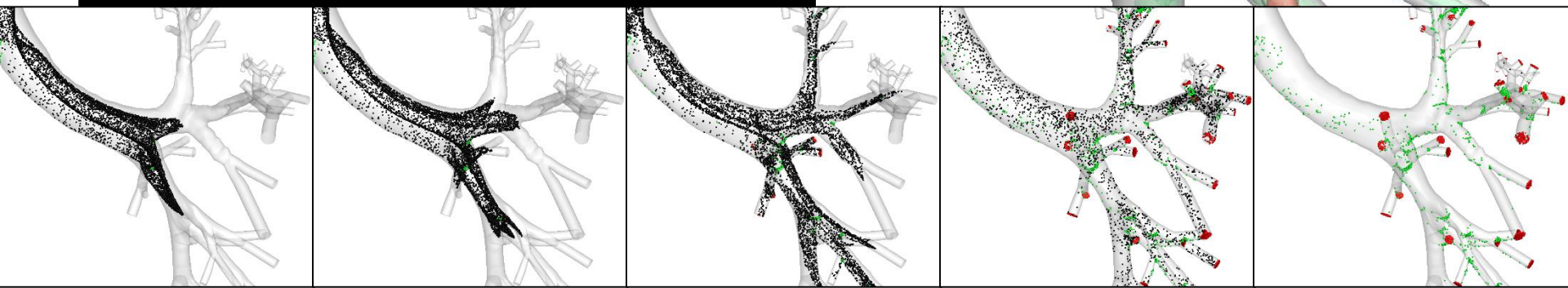


Airway constriction in LLL

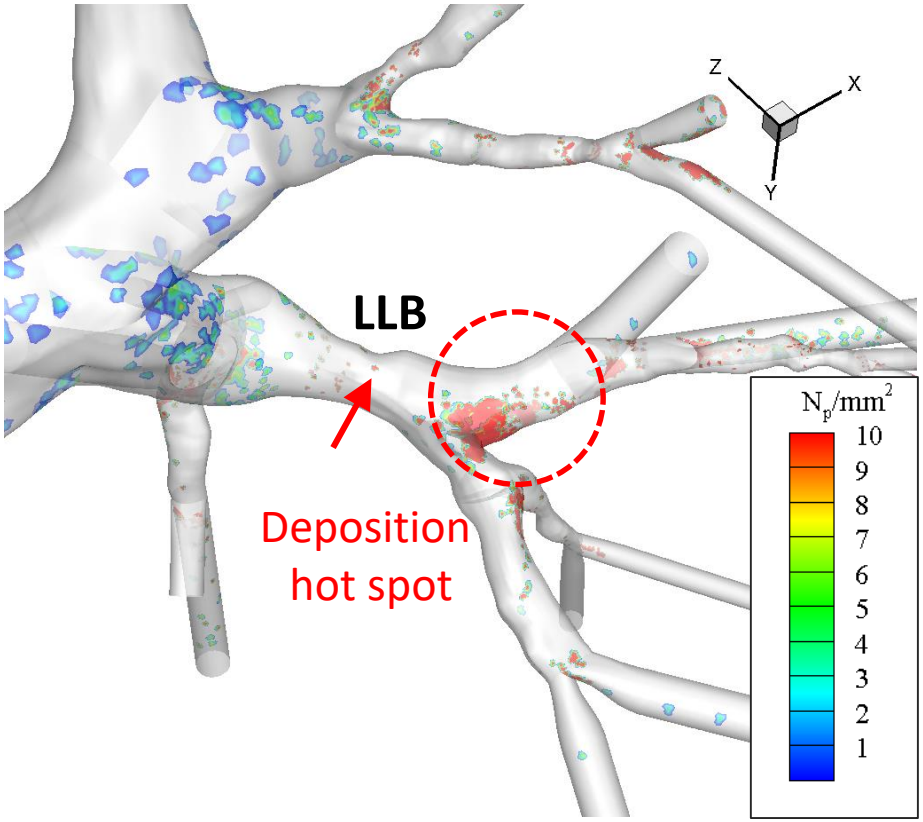
Healthy

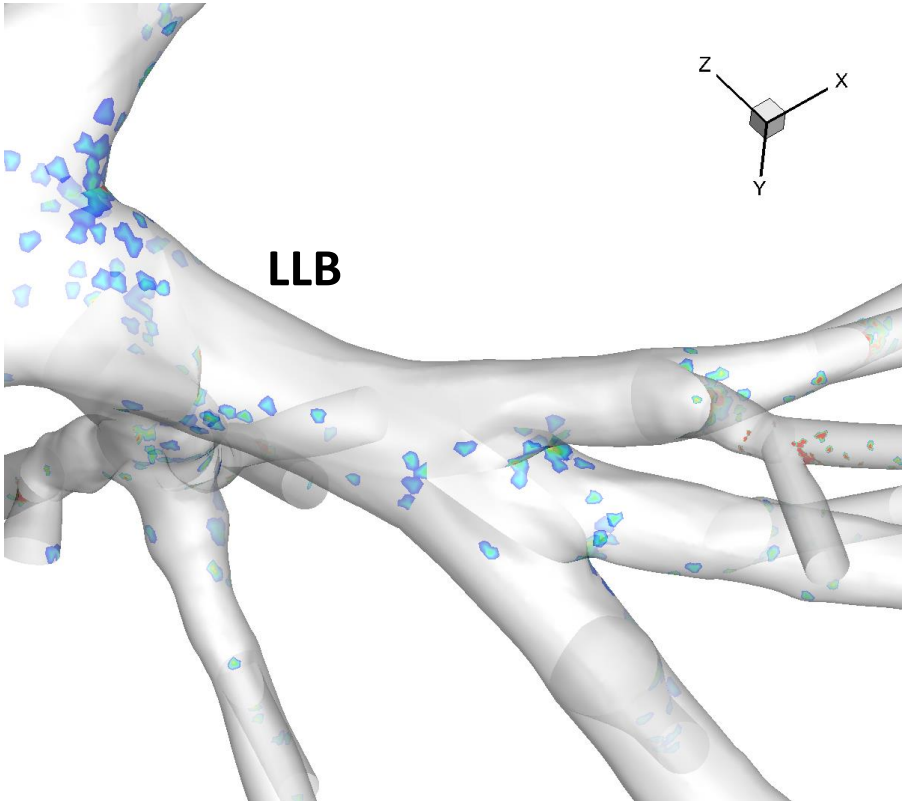






Airway constriction in LLL

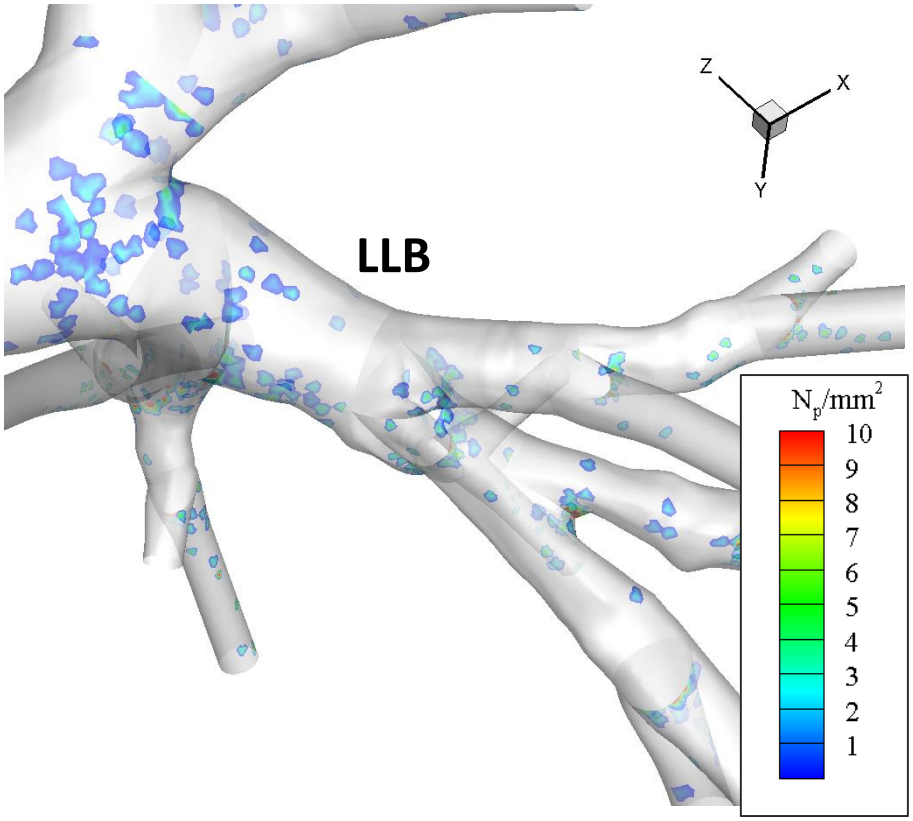


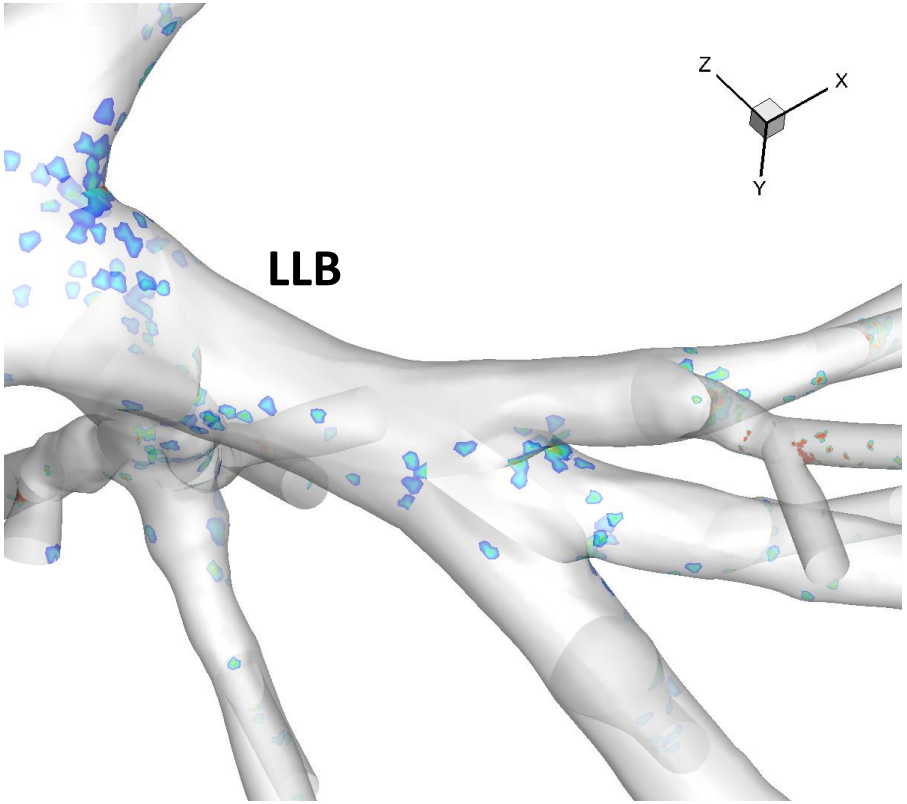


Cluster 4, D_h^* = 0.226

Healthy Male, D_h^* = 0.380

Airway constriction in LLL

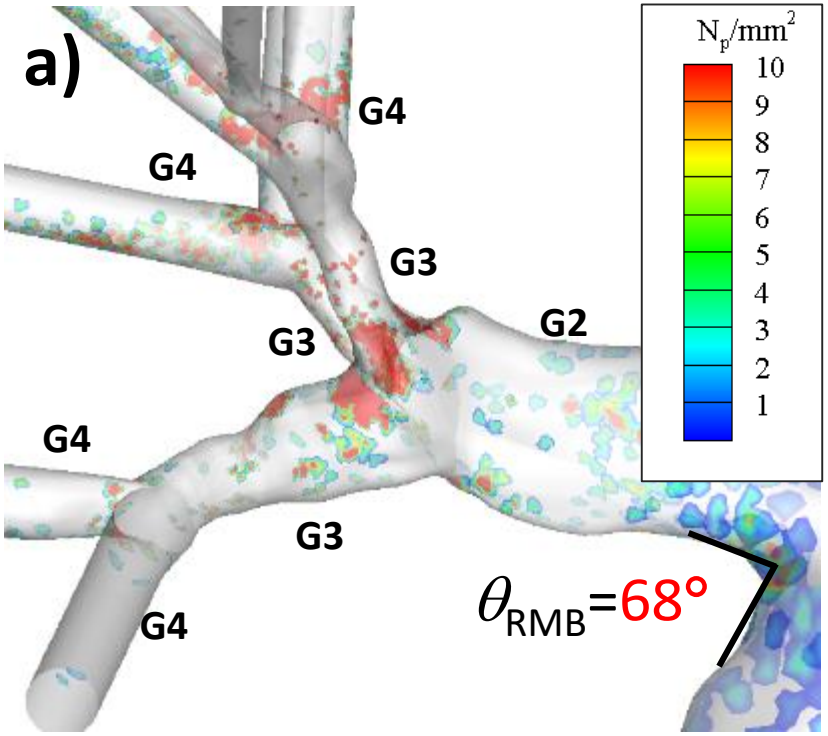


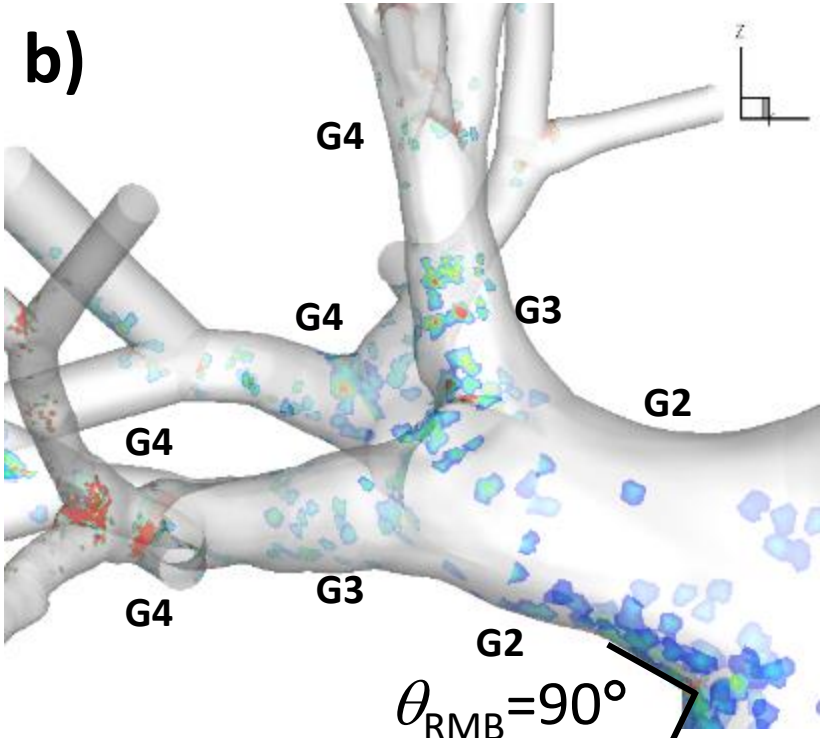


Cluster 3: D_h* = 0.428

Healthy Male, D_h* = 0.380

Small RMB branching angel, θ, & RUL airway constriction



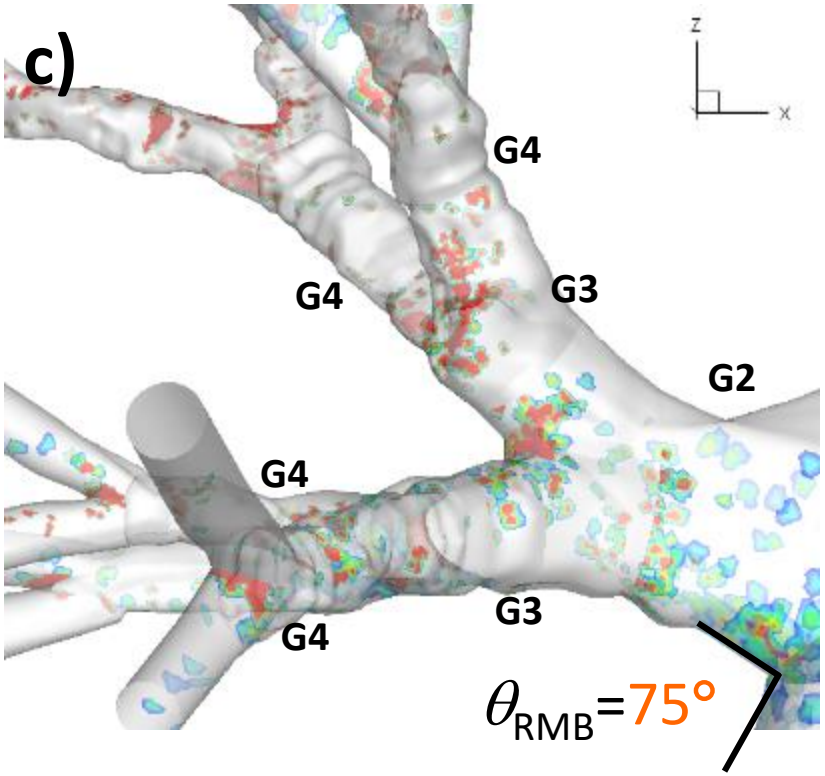


Cluster 4

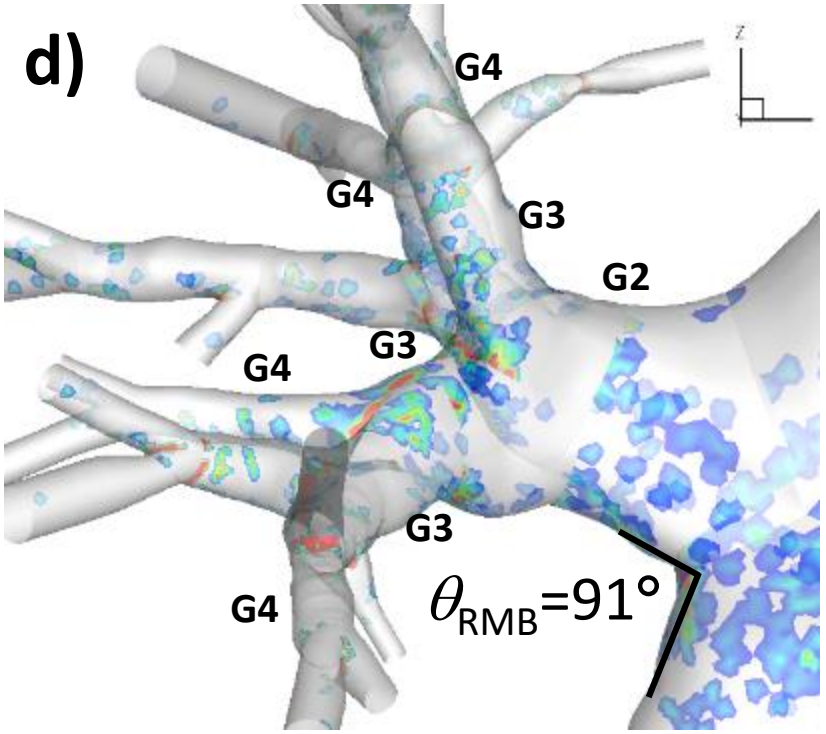
Healthy male

DD of 4-µm particles in RUL of (a) cluster 4 and (b) healthy male. Airway constriction and small branching angle at RMB induced deposition hot spots in C4 (↑↑) and C2 (↑).

Small RMB branching angel, θ, & RUL airway constriction



Cluster 2



Cluster 3

DD of 4-µm particles in RUL of (c) cluster 2, and (d) cluster (3). Airway constriction and small branching angle at RMB induced deposition hot spots in C4 (↑↑) and C2 (↑).

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
Clinical Features	• Similar to healthy subjects • Non-severe asthma • Easy to control symptoms	• Mix of non-severe & severe subjects • Little inflammation • Difficult to control symptoms	• Severe asthma • Female dominant • Difficult to control symptoms	• Severe asthma • Male dominant • Difficult to control symptoms
Imaging Features	• Reversible lung function • J ↑	• J ↓ • Airway constriction (D_h* ↓ in LLL, RMB & BronInt) • ϑ_{RMB} ↓	• Moderate reduction in J • Airway wall thickening • Reversible lung function	• J ↓↓ • Airway constriction (D_h* ↓) • ϑ_{RMB} ↓ • Significant air trapping
CFD Features	• Re ↓ • Stk ↑ • Similar to healthy subjects	• Re ↓ • Stk ↑ • LLL DF ↑ • DE ↑ in segmental and sub-segmental airways • DE ↑ distal to ϑ_{RMB}	• Re ↓ • Stk ↑ • Generational DE similar to healthy subjects • Particle FF ↑ in RUL	• Re ↓ • Stk ↑ • LLL DF ↑ • DE ↑ in segmental and sub-segmental airways • DE ↑ distal to ϑ_{RMB}

Concluding remarks

- We utilized imaging-based cluster membership in conjunction with lung CFD to assess the effects of cluster-specific, imaging-based variables on air flow and particle deposition characteristics.
- Structural metrics such as proximal airway narrowing in C2 and C4 clusters contributed to higher deposition in lobar, segmental, and selective sub-segmental airways.
- Characterization of inter-cluster variability with respect to particle transport could potentially help improve inhalation drug delivery in asthma sub-populations.
- Results demonstrated the power of understanding MICA features, and using them as a means of exploring the asthma drug treatment implications of structural and functional differences within an asthmatic population, and assessing the efficacy of orally-inhaled drugs.