AI for Augmenting and Accelerating Computational Fluid Dynamics Predictions of Regional Lung Deposition

Modeling and Artificial Intelligence (AI) in Generic Drug Development and Product Lifecycle Management: Regulatory Insights and Future Trends

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Orally Inhaled Drug Products (OIDPs)

- Indicated for a variety of diseases, including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and influenza, among others.
    - Regional lung drug delivery is typically important for products that treat pulmonary diseases.
- Device types include metered dose inhalers (MDIs), dry powder inhalers (DPIs), and inhalation sprays.

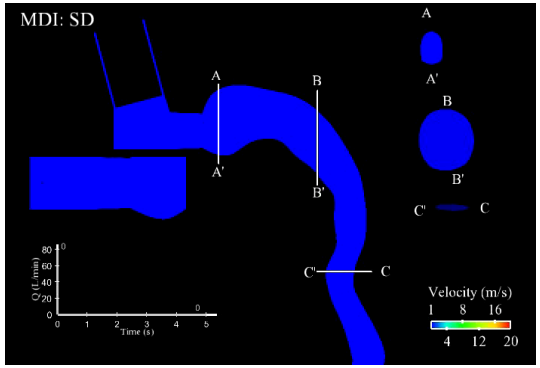
Figure from Inhalexpert website[1]

Purposes for OIDP Modeling

- Regional deposition models, using computational fluid dynamics (CFD) or semi-empirical methods, can predict the impact of device or formulation changes prior to in vivo or in vitro testing.
  - May accelerate product development by avoiding unnecessary testing.
  - For generic OIDPs, modeling may be used to justify biorelevant bioequivalence (BE) limits for relevant in vitro studies.[2]
- Physiologically based pharmacokinetic (PBPK) models can examine relationships between in vivo plasma concentration pharmacokinetics (PK) data and regional absorption.
  - May be used to make decisions about product development based on PK data.
  - May be used to assess need for a PK study with a charcoal block or to identify alternatives.

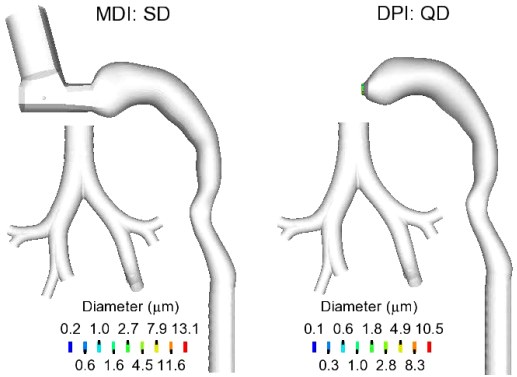
Computational Fluid Dynamics (CFD) Modeling

- Prediction of fluid and particle transport
- Allows for consideration of realistic geometries
- Validated with in vitro or in vivo data



MDI

Simulations from Longest et al.[3]



DPI

Carrier-API Particle Interactions

- CFD typically considers particles as point masses
  - Cannot consider complex carrier-active pharmaceutical ingredient (API) particle interactions for DPIs
- DEM modeling can consider complex particle interactions
- May be paired with CFD

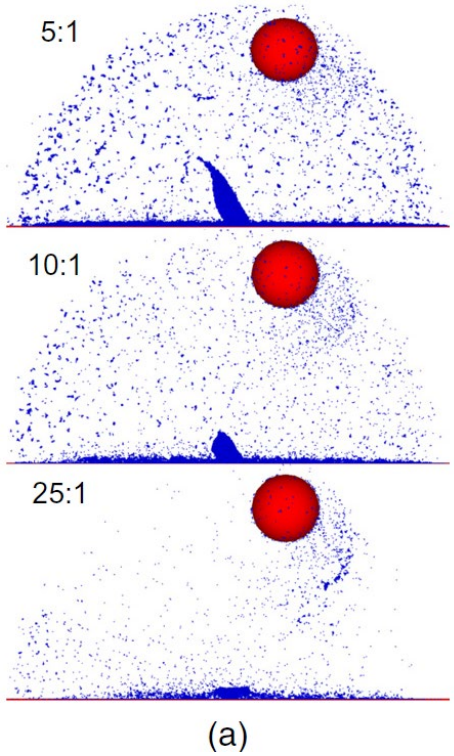


Figure 4a from Tong et al.[4]

CFD-DEM Modeling for DPIs – GDUFA Research

- **Building capabilities**
  - Grant U01FD006514 (Princeton University): 2018 – 2022
    - *Modeling Complex Particle Interactions in Dry Powder Inhaler Based Drug Delivery* (PIs: Jari Kolehmainen and Sankaran Sunderesan)
  - Grant U01FD006525 (University of Sydney): 2018 – 2021
    - *Development of Computational Models to Predict Delivery of Inhalation Drug Powders: From Deagglomeration in Devices to Deposition in Airways* (PI: Kim Chan)
- **Enhance practicality**
  - Grant U01FD008379 (Oklahoma State University): 2024 – 2026
    - *ML-CFD-DEM Based Reduced Order Models (ROM) to Quantify Variability in Inhalers, Drugs, and Users for Evaluating Comparability of Generic OIDP Complex Products* (PI: Yu Feng)

Tracking Carrier and API Particle Interactions

- Grants U01FD006514 and U01FD006525 developed models that consider surface and electrostatic forces between carrier and API particles as well as between particles and surfaces.
- Simulations only included limited numbers of particles and only used one representative size for each of the carrier and API particles.

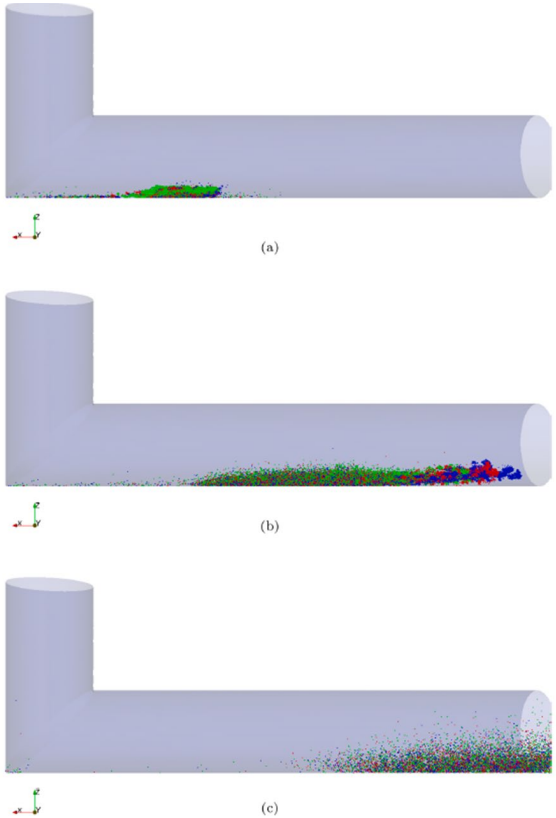


Figure 4 from Sulaiman et al. (2021):[5] Motion of carrier particles in an idealized device at times (a) 0.01 s, (b) 0.02 s, and (c) 0.03 s. The particles are colored blue, red, or green to correspond to the initial shape of the pile of powder on the surface (sphere, cylinder, or cone).

Evaluating Impacts of Device Changes on Aerosolization (part I)

- A CFD-DEM model for umeclidinium bromide; vilanterol trifenatate inhalation powder (brand name: Anoro Ellipta), which uses a blister-based design, was created for Grant U01FD006514.
- A variety of cases were considered by varying numbers and masses of carrier and API particles, as well as the use of one or two blisters.
- Results showed that the inclusion of a second blister, even with the same API, tended to increase fine particle fraction.

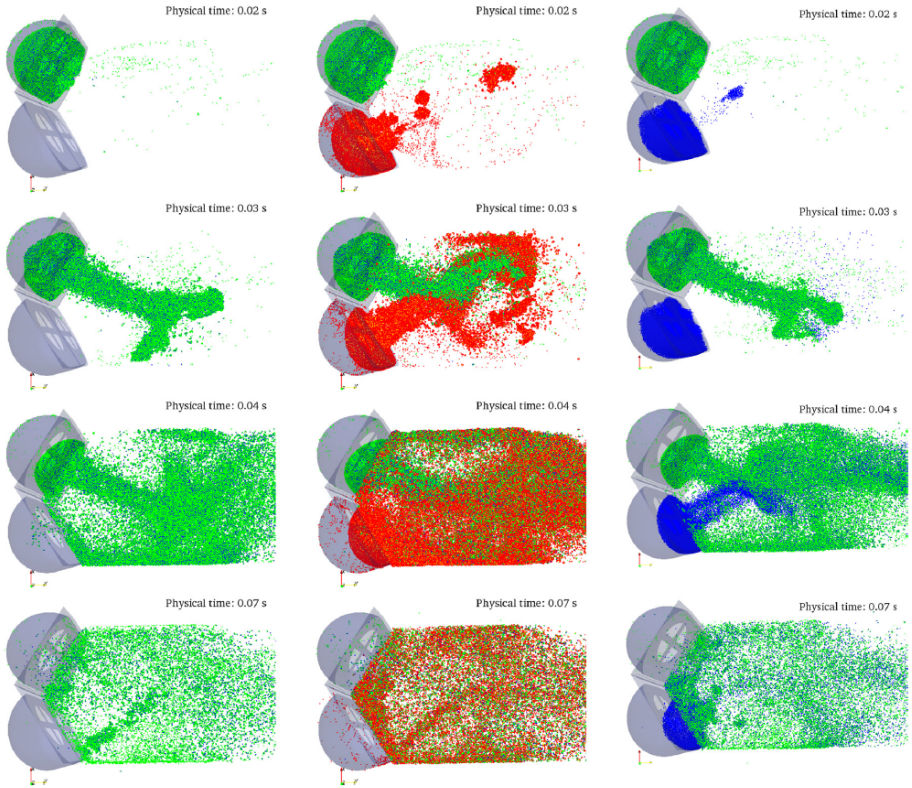


Figure 6 from Sulaiman et al. (2022):[6] Different formulation combinations where carrier particles are blue and yellow for Formulations A and B and API particles are green and red, correspondingly.

Evaluating Impacts of Device Changes on Aerosolization (part II)

- A CFD-DEM model for tiotropium bromide inhalation powder (brand name: Spiriva HandiHaler), which uses a capsule-based design, was created for Grant U01FD006525.
- The impact of differences in capsule aperture diameter were predicted for particle-particle and particle-wall collisions as well as for particle dispersion. Results showed a plateau for each effect when the aperture diameter was > 1.3 mm.

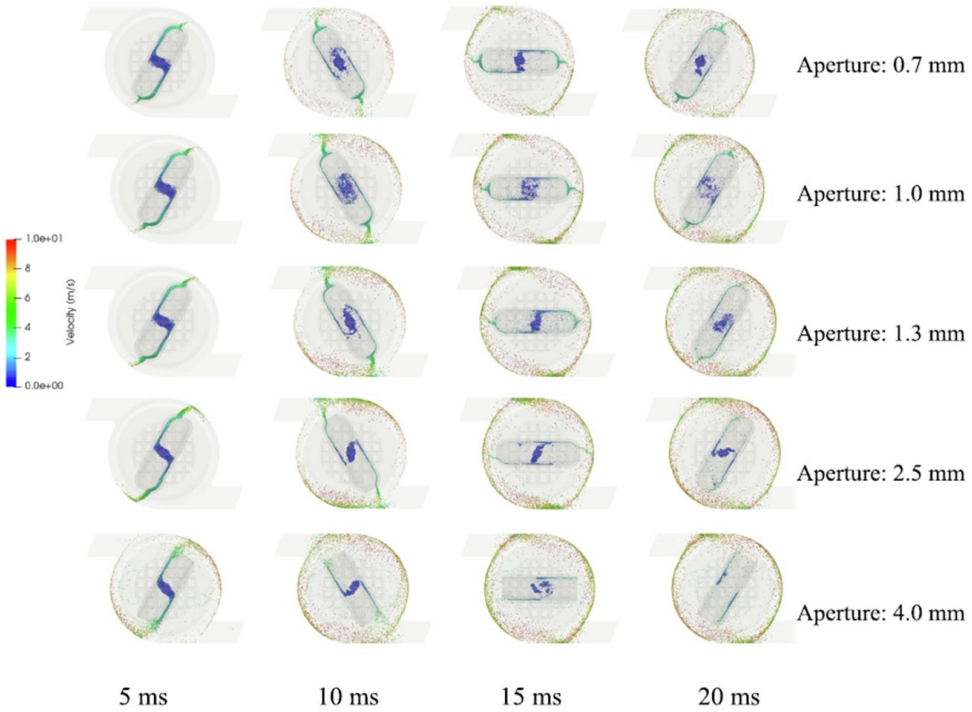


Figure 4 from Zhu et al. (2023):[7] Visualization of particle evacuation at different times from capsules with different aperture diameters. Particles are colored according to velocity magnitude.

Challenges of CFD-DEM Modeling

- Long simulation times (on the order of days or weeks):[8]
  - Slow down model development and execution
  - Require significant resources, and thereby limit access
  - Reduce number of particles that may be injected
  - Reduce capacity to conduct parameter sensitivity analyses
- Model parameterization and validation
  - Particle size distributions of both carrier and API particles
  - Surface energy

Machine Learning (ML) to Accelerate Aerosol Characterization Predictions

- Grant U01FD008379 “focuses on alleviating some of the challenges with using computational fluid dynamics (CFD), including computational time, limited grid resolution, pre- and post-processing of large simulation datasets, model parameter estimations, and uncertainty quantifications.”[9]
- Machine learning (ML), a form of artificial intelligence (AI), will be used to develop reduced order models (ROMs) that can predict particle size distribution of powder emitted from DPI, using CFD-DEM predictions as training data sets.

Improving Numerical Solver Efficiency for CFD

- A key bottleneck to CFD is the size of the computational mesh.
- Direct numerical simulation (DNS) is a computational technique that accurately predicts turbulent eddies.
- A learned interpolation model, aided by a convolutional neural network technique, enabled an approximately 80-fold decrease in computational time by decreasing mesh size without significantly sacrificing accuracy.[10]

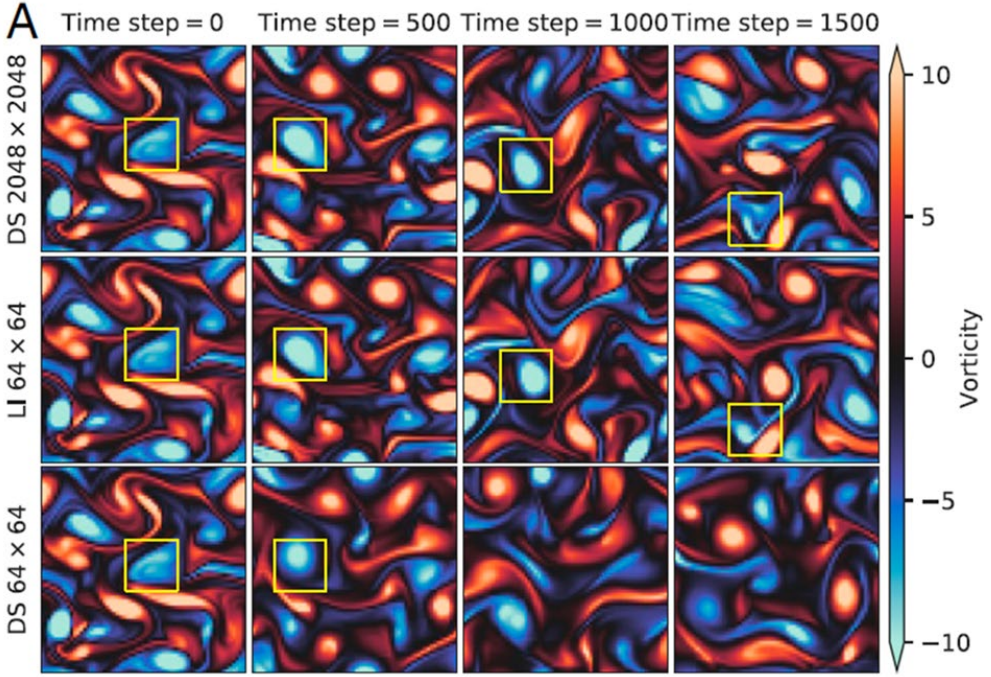


Figure 4 from Kochhov et al. (2021):[10] Visualization of a) direct numerical simulation (DNS) using 2,048 x 2,048 cell mesh, b) learned interpolation (LI) simulation using 64 x 64 cell mesh, and c) DNS using 64 x 64 cell mesh.

CFD Modeling Accounting for Asthma Intersubject Variability – GDUFA Research

- Grant U01FD005837 (University of Iowa): 2016 – 2022
  - *A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways* (PI: Ching-Long Lin)

Cluster Analysis to Account for Intersubject Variability

- Principal component analysis and k-means clustering analysis (an ML technique) were applied using 248 computed tomography (CT) scans from asthmatic patients.
- Functional and structural variables
- Identified four clusters associated with biomarker variables, demographics, and other characteristics.

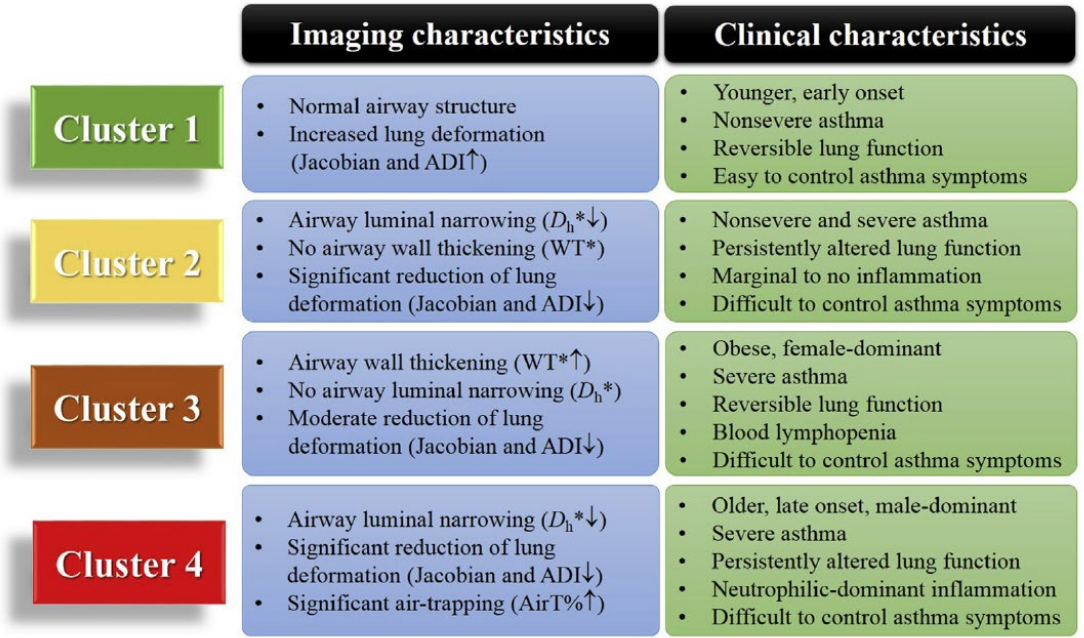


Figure 2 from Choi et al. (2017):[11] four asthma clusters identified via principal component analysis and k-means clustering analysis.

Deposition Prediction Variability

- Predictions of lobar deposition values using CFD models representing two healthy and eight (two for each of four clusters as defined in Choi et al.[11]) subjects
- Models did not include mouth-throat regions
- One-dimensional (1D) airway tree extended based on volume filling technique from previous publications
- Subject specific flow rates
- Monodisperse particle injections

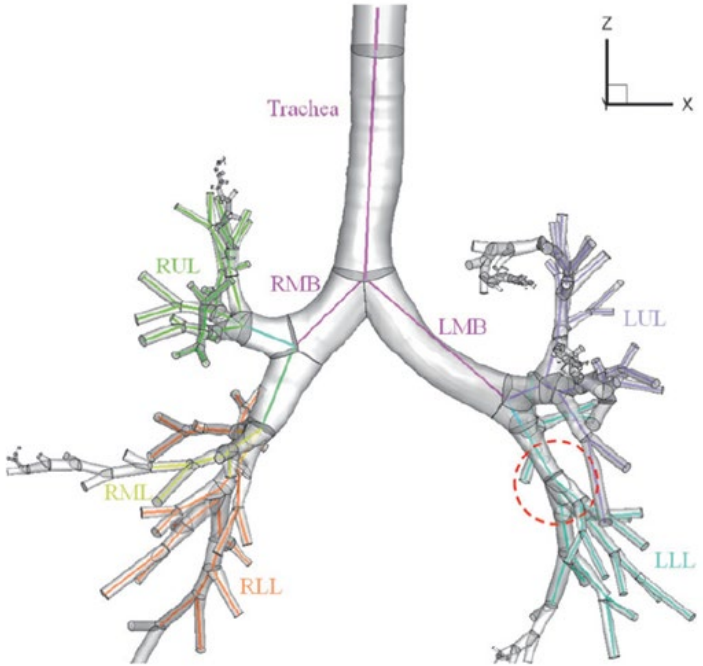


Figure 1 from Choi et al.[12]: healthy male lung geometry based on CT scan data from Choi et al.[11] LMB, left main bronchus; LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RMB, right main bronchus; RML, right middle lobe; RUL, right upper lobe.

Deposition Prediction Variability - Results

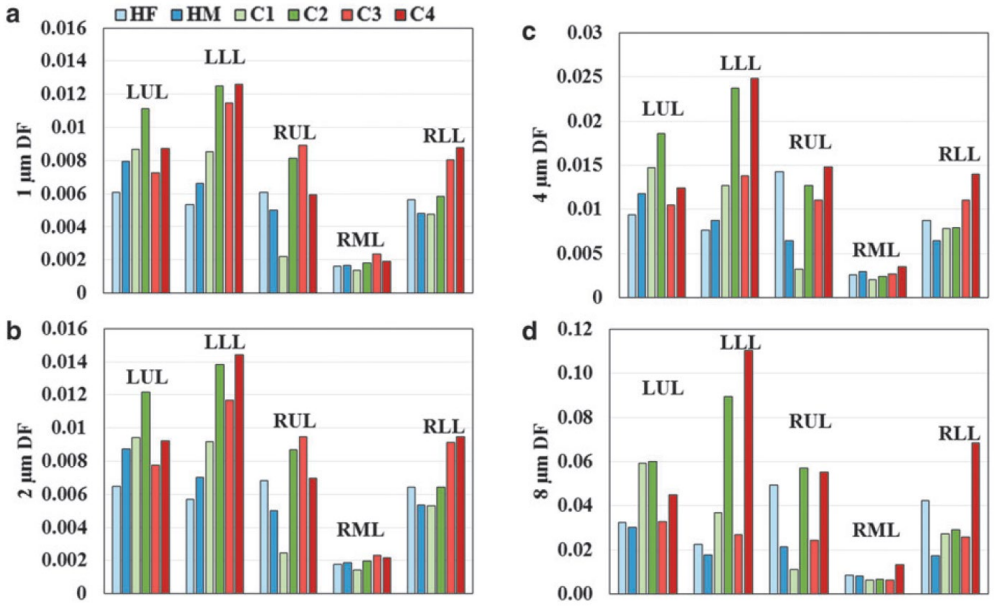


Figure 2 from Choi et al.[12]: regional DF values for four particle sizes (1 μm, 2 μm, 4 μm, and 8 μm)

- Deposition fraction (DF) in five lung lobes
  - Left upper lobe (LUL)
  - Left lower lobe (LLL)
  - Right upper lobe (RUL)
  - Right middle lobe (RML)
  - Right lower lobe (RLL)
- Healthy female (HF), healthy male (HM), and four clusters (C1, C2, C3, and C4)

Conclusions

1. Mechanistic modeling for OIDPs is used to accelerate product development and facilitate approval.
2. CFD and CFD-DEM modeling techniques are used to predict regional deposition for OIDPs.
3. AI/ML techniques may be used to reduce the number of CFD or CFD-DEM simulations needed, improve numerical solver efficiency, and characterize intersubject variability.

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We Are OGD

Ask me why...

"I make sure that the **generic** drug and the **brand** drug work **the same**."

"The first time I was able to buy my son's inhaler as a generic and realized that my out of pocket dropped, I cried and was able to breathe a sigh of relief."

www.fda.gov

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