

Physiologically Realistic Simulation of DEHP Penetration in the Human Airways

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This presentation will cover

1 Background

2 Mathematical Modeling

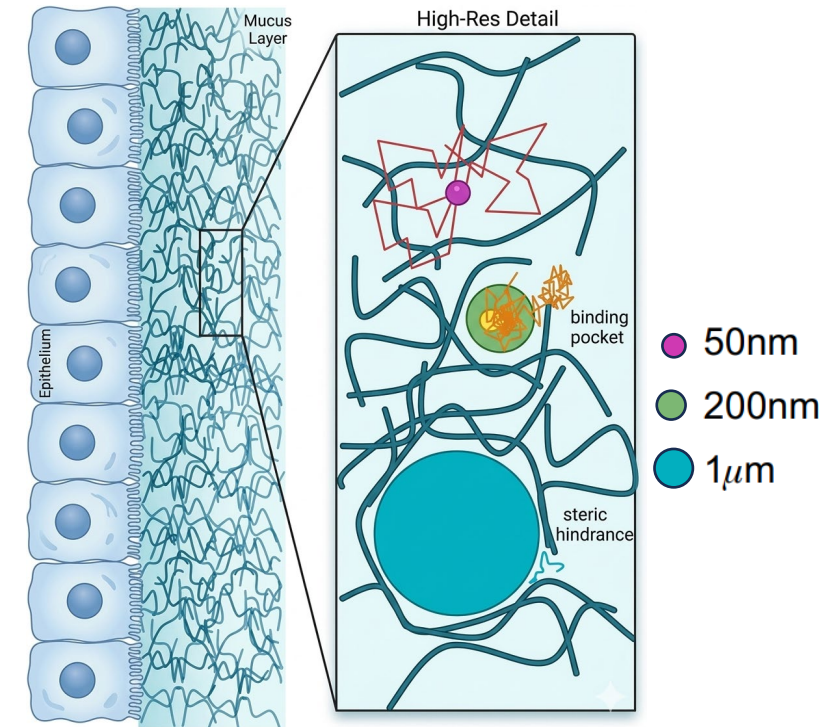
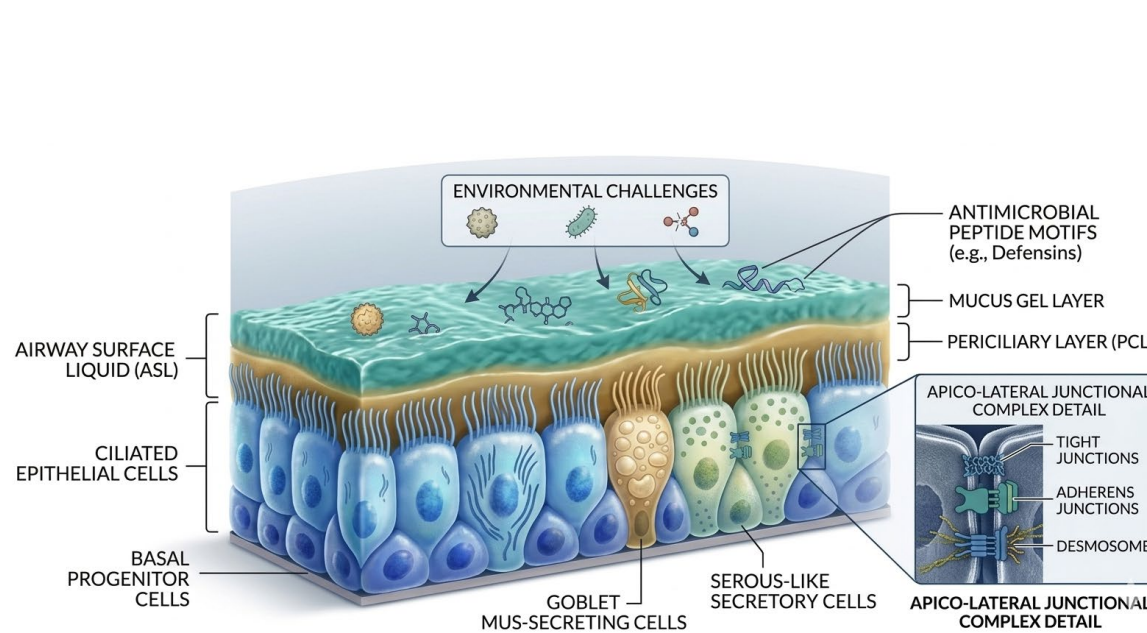
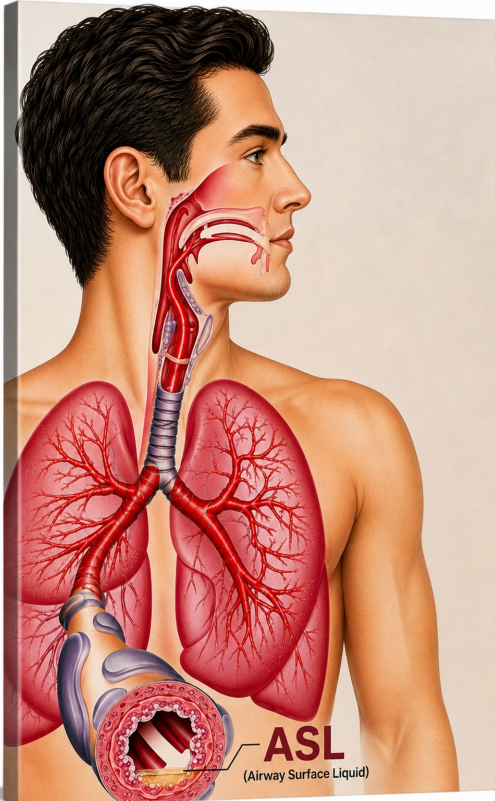
3 Simulation of Mucociliary Clearance

4 DEHP Absorption Modeling in ASL

5 Conclusions & Key Findings

6 Future Research

Airway Surface Liquid (ASL)



Adapted from: Newby et al., *Advanced drug delivery reviews* 124 (2018): 64-81.

❖ Composition of the ASL

- **Mucus Layer:** A sticky, viscoelastic fluid that traps inhaled particles
- **PCL:** A low-viscosity, Newtonian watery fluid that bathes the cell surface
- **Ciliary Apparatus:** A dense mat of coordinated cilia exhibiting cyclic motion within the PCL to propel the mucus.

❖ Main Functions of ASL

- Lubrication of the epithelia
- Maintenance of a hydrated layer
- Exchange of gases and nutrients with the epithelium
- Acting as a barrier to pathogens and foreign substances

DEHP: Di(2-ethylhexyl) Phthalate

An Important Semi-Volatile Plasticizer

❖ What is DEHP?

- Di(2-ethylhexyl) phthalate (CAS 117-81-7)
- Man-made colorless and odorless liquid
- Most widely used phthalate plasticizer worldwide
- Added to PVC plastics to increase flexibility
- Ubiquitous in indoor environments

(flooring, cables, medical devices, packaging)

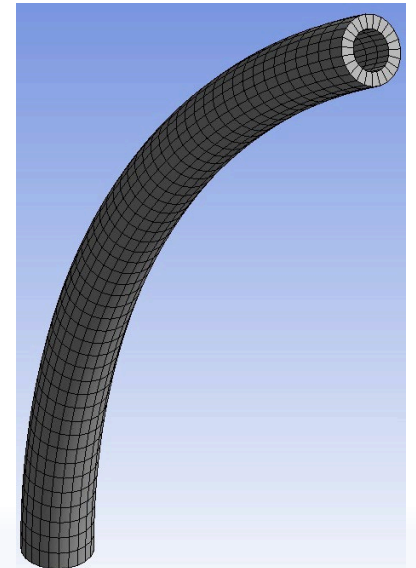
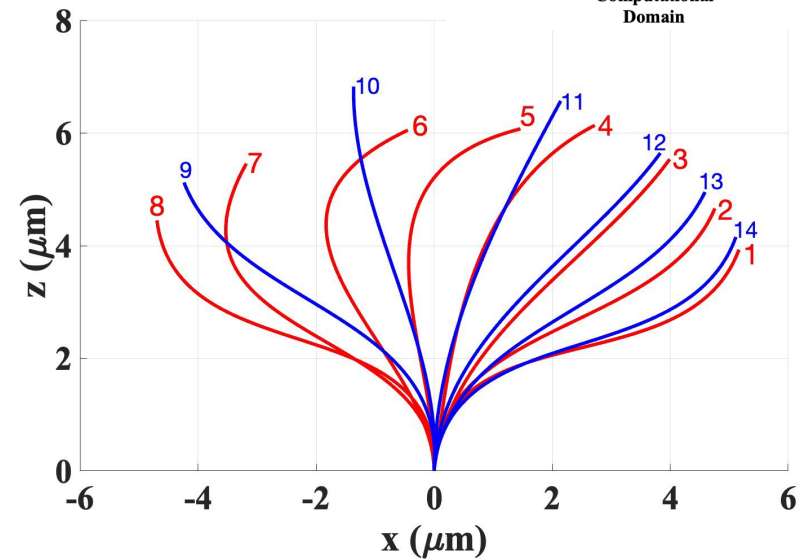
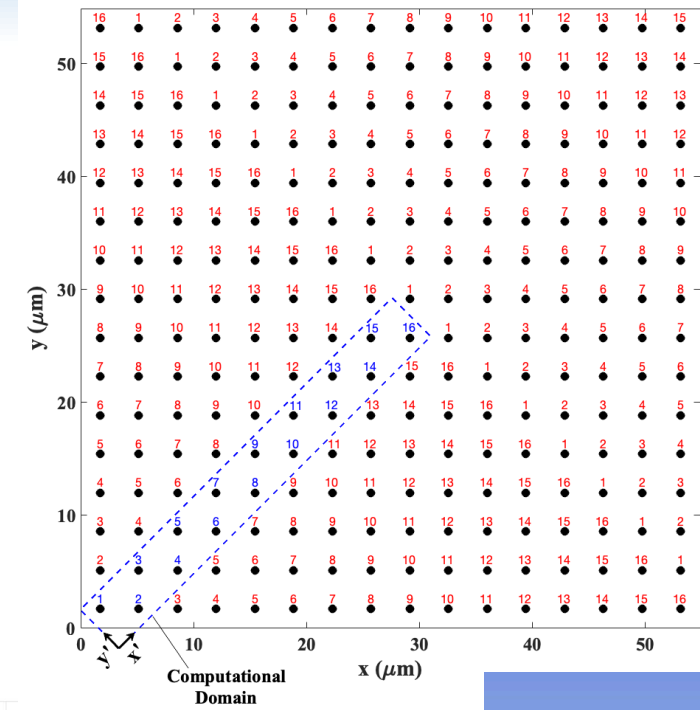
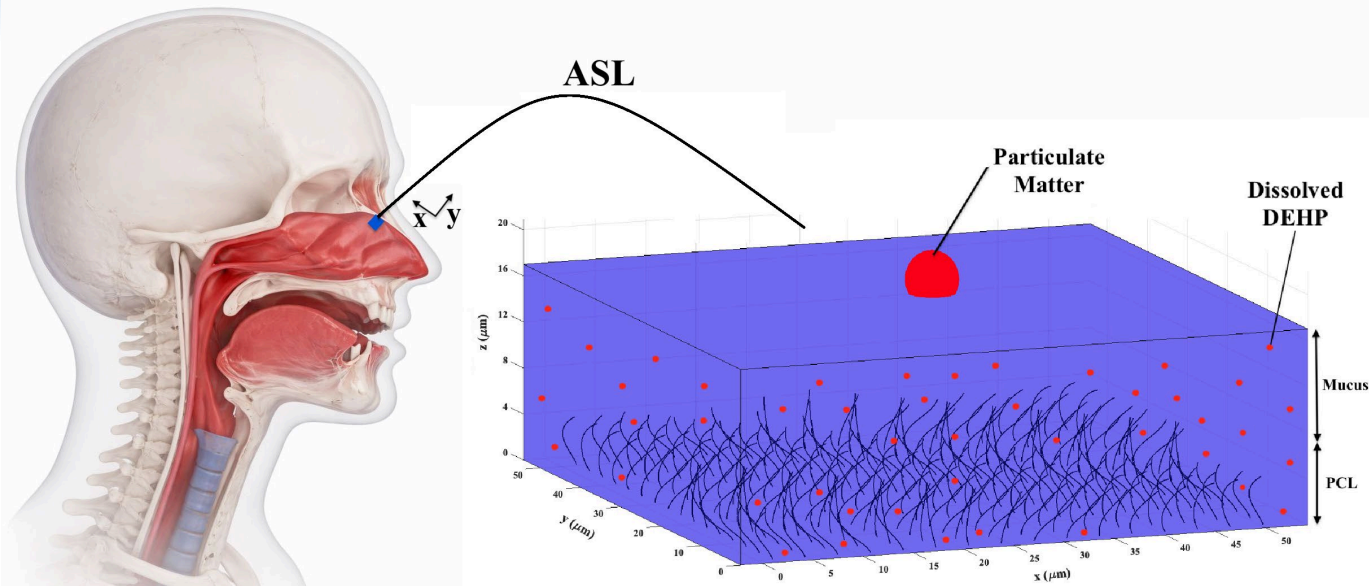
❖ Key Physicochemical Properties

Property	Value	Implication
Molecular Formula	$C_{24}H_{38}O_4$	—
Molar Mass	390.56 g/mol	—
Density	0.986 g/cm ³ (liquid)	—
Water Solubility	~2–3 µg/L (extremely low)	Highly hydrophobic
Log K _{ow}	~7.5	Strong partitioning to particles & lipids
Vapor Pressure	Very low (3.4×10^{-8} kPa)	>90% exists in particle phase

❖ Environmental & Exposure Relevance

- Predominantly **particle-bound** in air (>90%)
- Commonly adsorbed on fine & ultrafine PM (especially 0.1–0.5 µm)
- Major route of exposure: **Inhalation of DEHP-laden particulate matter**
- Slow dissolution into airway surface liquid (ASL) after deposition
- DEHP makes up only ~0.01% (or less) of the particle's total mass.

3D Simulation of MCC and DEHP Absorption in ASL



ASL Flow:

□ Continuity & Momentum Equations

$$\nabla \cdot \mathbf{u} = 0$$

$$\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} = -\frac{1}{\rho} \nabla p + v_s \nabla^2 \mathbf{u} + \frac{1}{\rho} \nabla \cdot \boldsymbol{\tau} + \mathbf{f},$$

□ Cilia Forces (IBM)

$$\mathbf{f}(\mathbf{x}, t) = \int_{\Gamma} \mathbf{F}(\mathbf{X}, t) \delta_d(\mathbf{x} - \mathbf{X}) dV,$$

□ Mucus Constitutive Equation

$$\boldsymbol{\tau} = \sum_i \boldsymbol{\tau}_i$$

$$\boldsymbol{\tau}_i + \lambda_i \nabla \boldsymbol{\tau}_i + \frac{\alpha_i \lambda_i}{\eta_i^p} \boldsymbol{\tau}_i \cdot \boldsymbol{\tau}_i = 2\eta_i^p \mathbf{D}$$

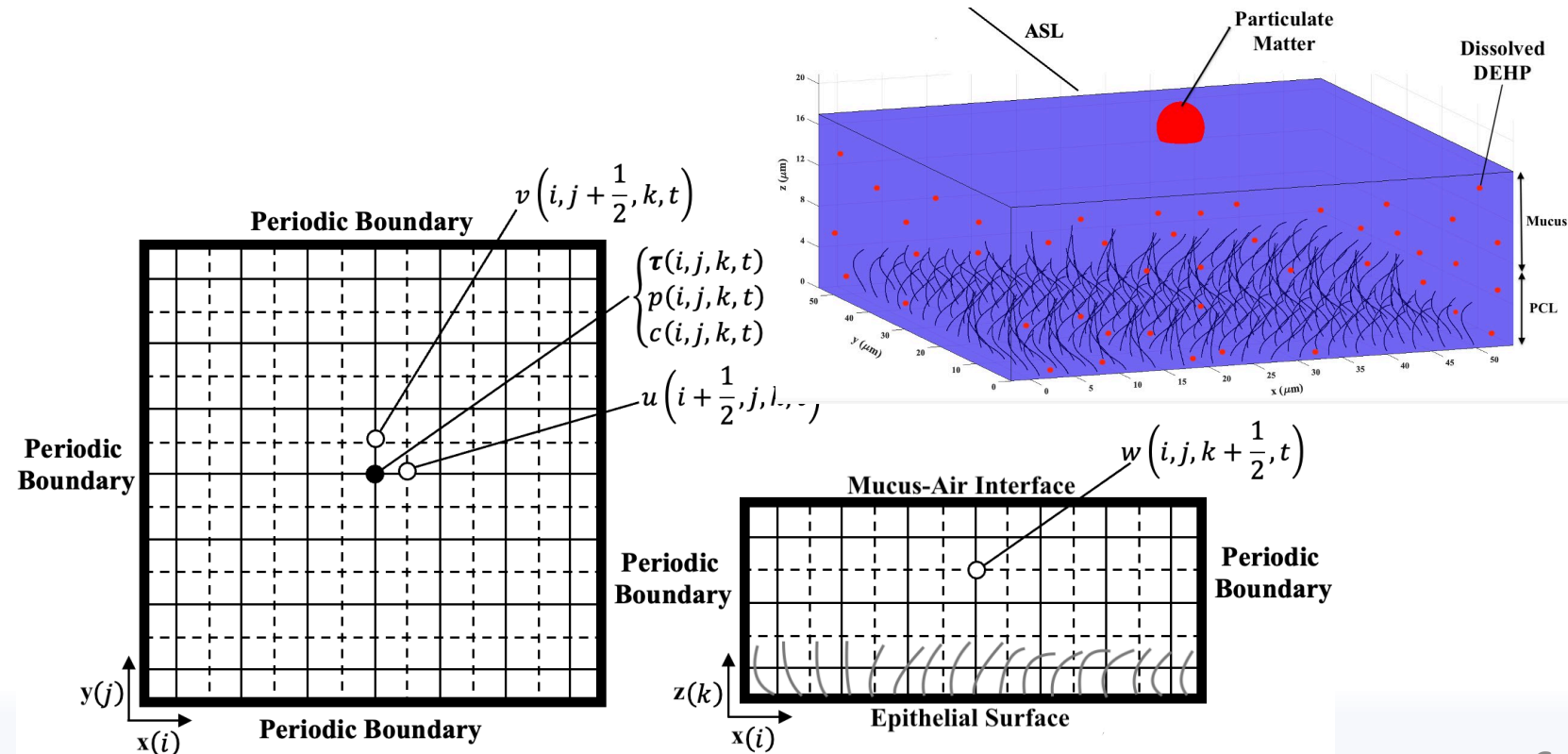
$$\nabla \boldsymbol{\tau} = \frac{\partial \boldsymbol{\tau}}{\partial t} + \mathbf{u} \cdot \nabla \boldsymbol{\tau} - \boldsymbol{\tau} \cdot \nabla \mathbf{u} - \nabla \mathbf{u}^T \cdot \boldsymbol{\tau}$$

$$\mathbf{D} = \frac{1}{2} (\nabla \mathbf{u} + \nabla \mathbf{u}^T)$$

Particle Absorption in ASL:

$$\frac{\partial c}{\partial t} + c \cdot \nabla \mathbf{u} = D_{ASL} \nabla^2 c$$

$$\frac{D_M}{D_0} = e^{\frac{-\pi(r_p+r_f)^2}{4(r_g+r_f)^2}} \quad D_0 = \frac{K_B T}{6\pi\mu_0 r_p}$$

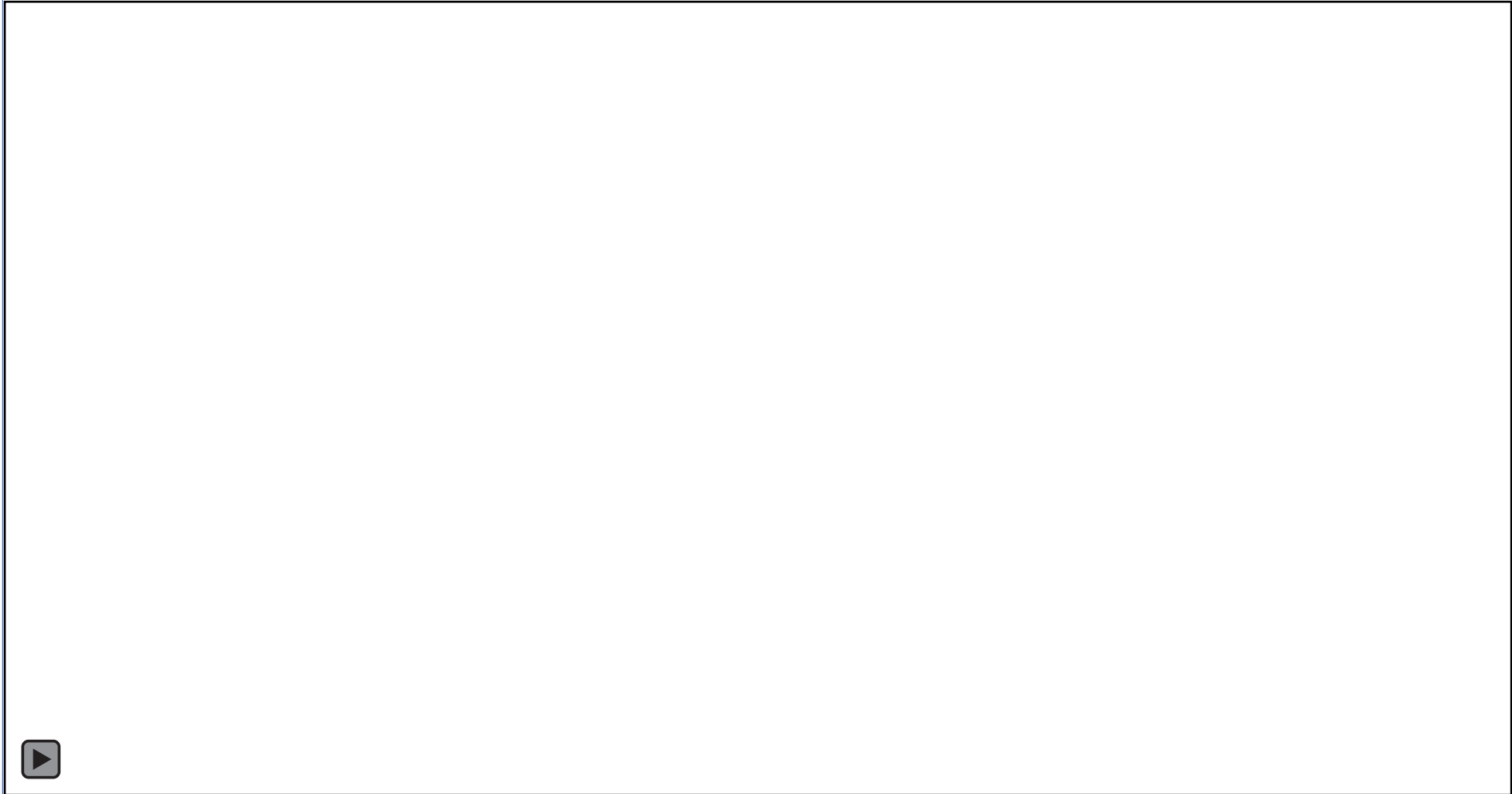


Simulation of Mucociliary Clearance

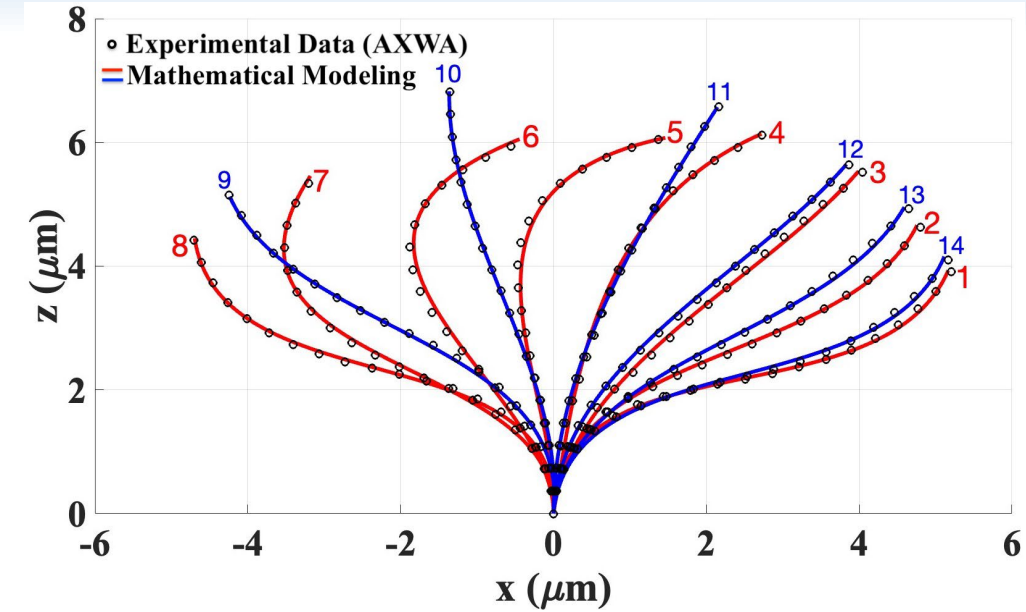
Study	Type	Cilia Force	Mucus Constitutive Model
Fulford and Blake (1986)	2D-Analytical	Fourier series	Newtonian
Smith et al. (2007)	2D-Analytical	Fourier series	Viscoelastic (Linear Maxwell)
Lee et al. (2011)	2D-Numerical	IBM	Newtonian
Jayathilake et al. (2012)	3D-Numerical	IBM	-
Chatelin and Poncet (2016)	3D-Numerical	FSI	Non-Newtonian (Shear thinning)
Manolidis et al. (2016)	3D-Numerical	Moving wall boundary	Newtonian
Sedaghat et al. (2016)	2D-Numerical	IBM	Viscoelastic (semi- linear-Oldroyd-B)
Vasquez et al. (2016)	2D-Numerical	Sinusoidal Function	Viscoelastic (5-mode nonlinear Giesekus)
Guo and Kanso (2017)	2D-Numerical	IBM	Viscoelastic (Oldroyd-B)
Vanaki et al. (2020)	3D-Numerical	IBM	-
Sedaghat et al. (2021)	2D-Numerical	IBM	Viscoelastic (5-mode nonlinear Giesekus)
Choudhury et al. (2023)	2D- Numerical	Navier-slip moving-carpet	Viscoelastic (semi- linear-Oldroyd-B)
Sedaghat et al. (2021, 2022, 2023,2025,2026)	3D-Numerical	IBM	Viscoelastic (5-mode nonlinear Giesekus)

2 Extracting Healthy Ciliary Motion from Video Microscopy

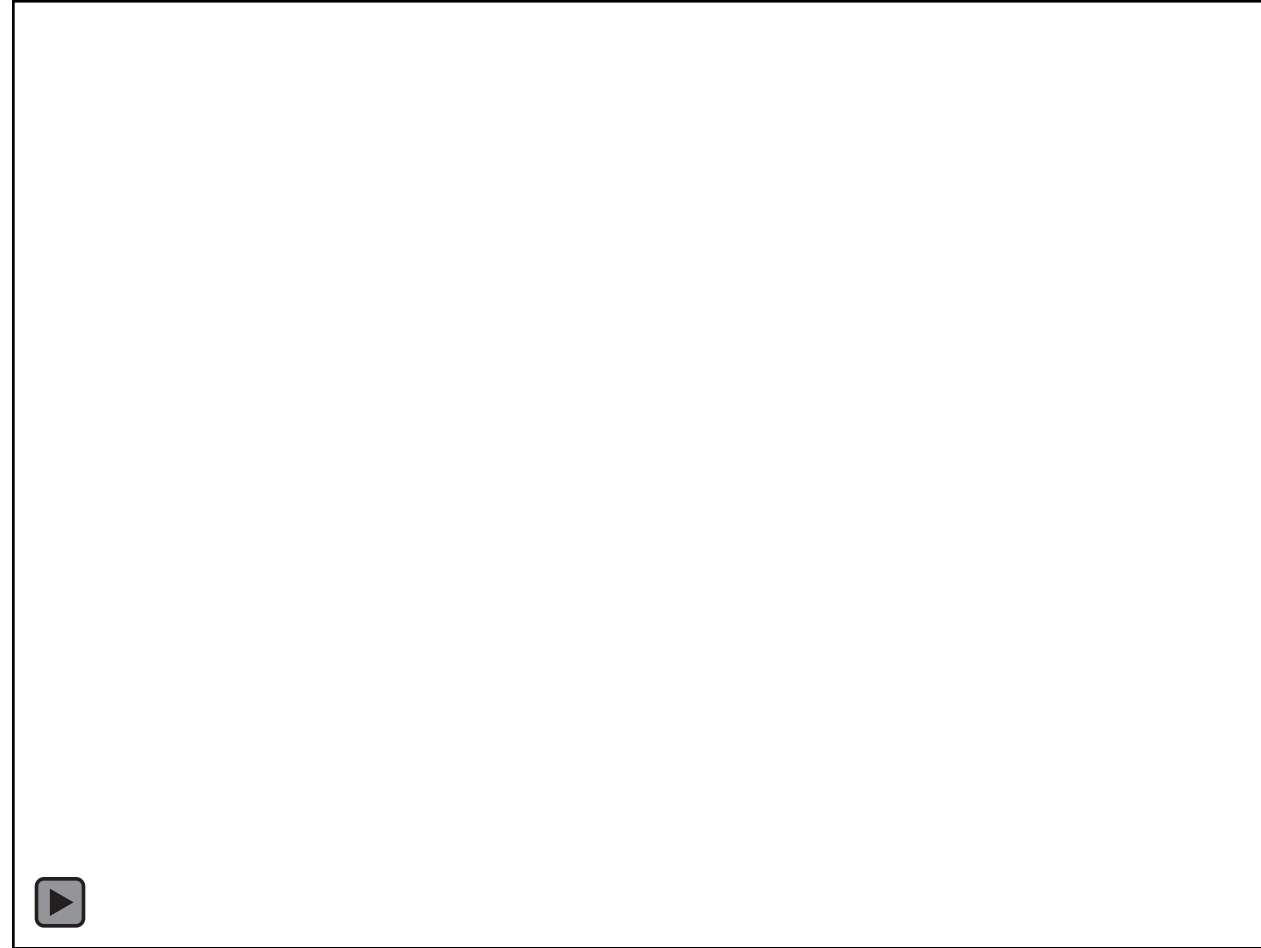
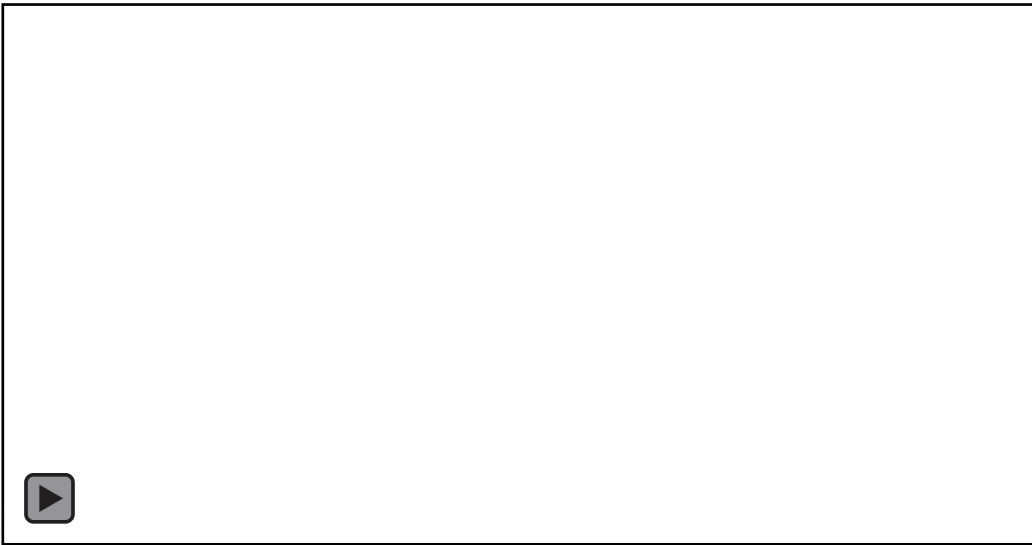
AXWA Software- Sears et al. (2013)



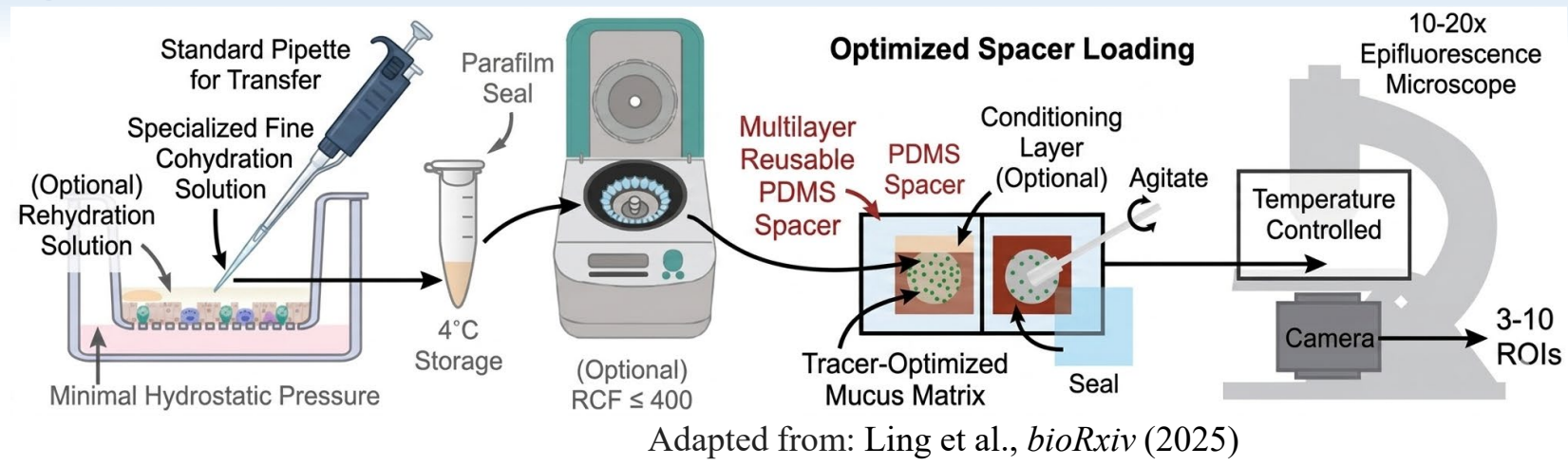
3D Mathematical Modeling of Ciliary Motion



$$X_C(s, t) = L_C \sum_{n=0}^6 \sum_{m=1}^3 \left(A_{nm} \cos \frac{2n\pi t}{T_C} + B_{nm} \sin \frac{2n\pi t}{T_C} \right) s^m$$

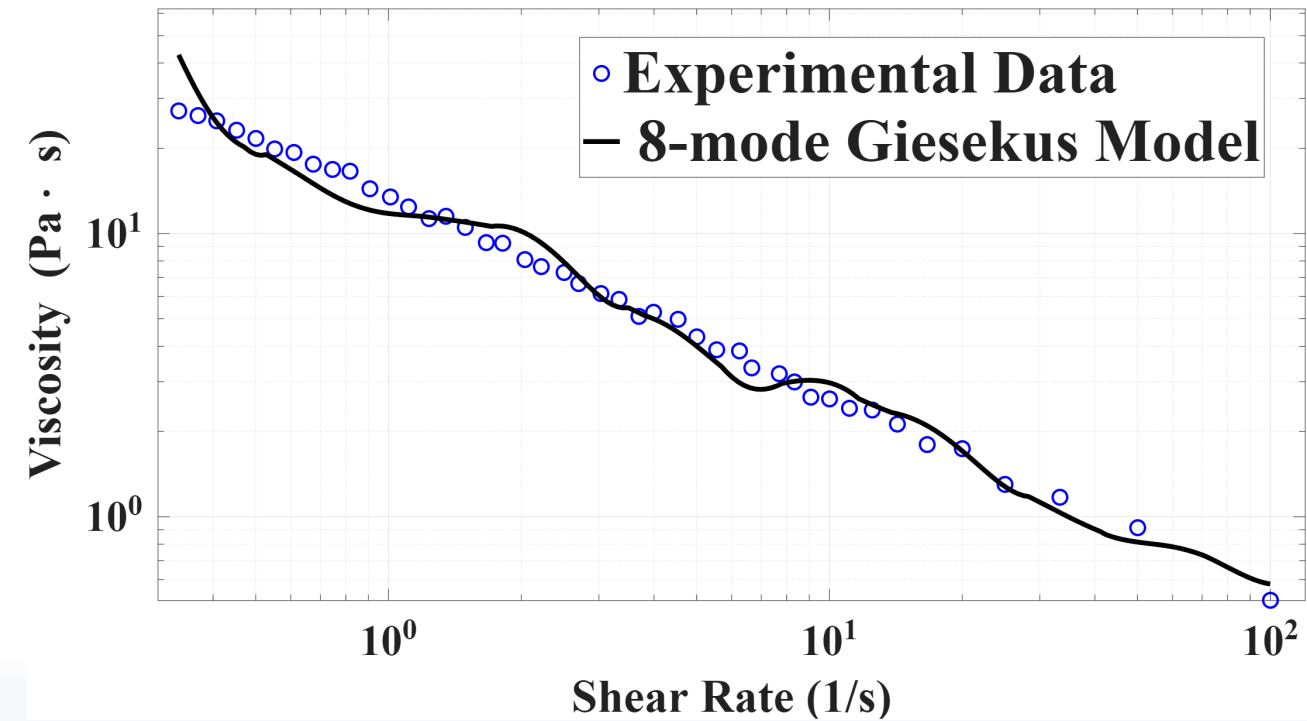
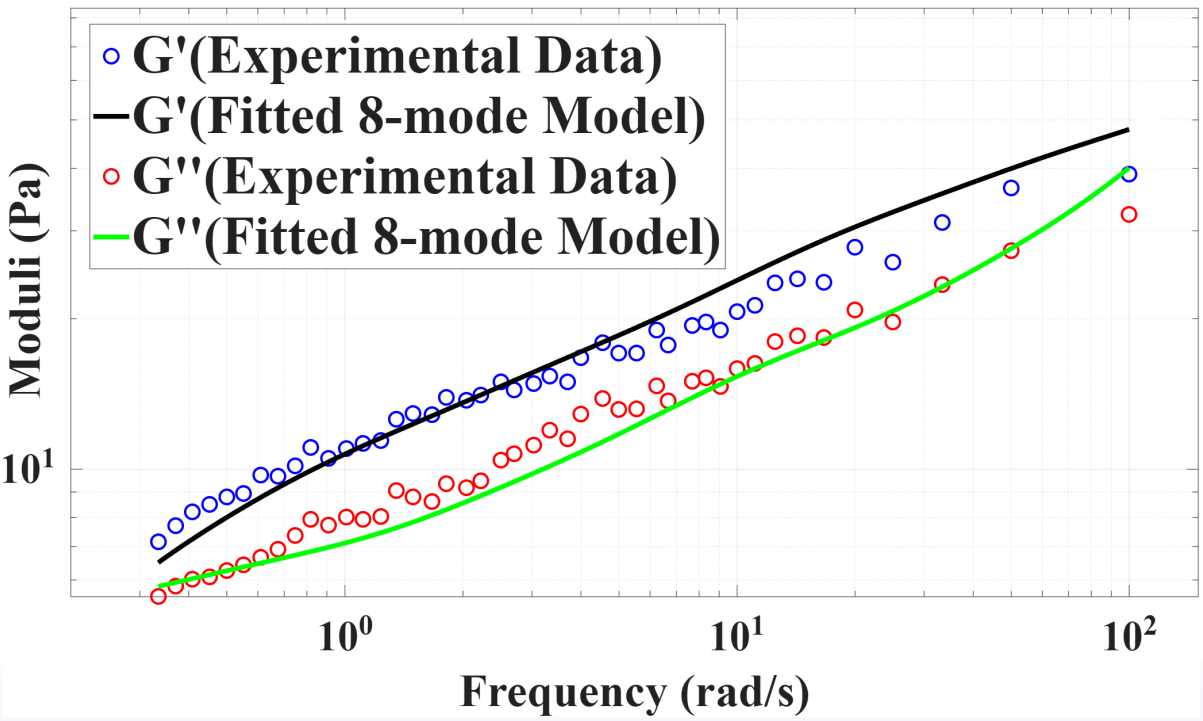


2 Modeling Mucus Rheology as a Nonlinear Viscoelastic System

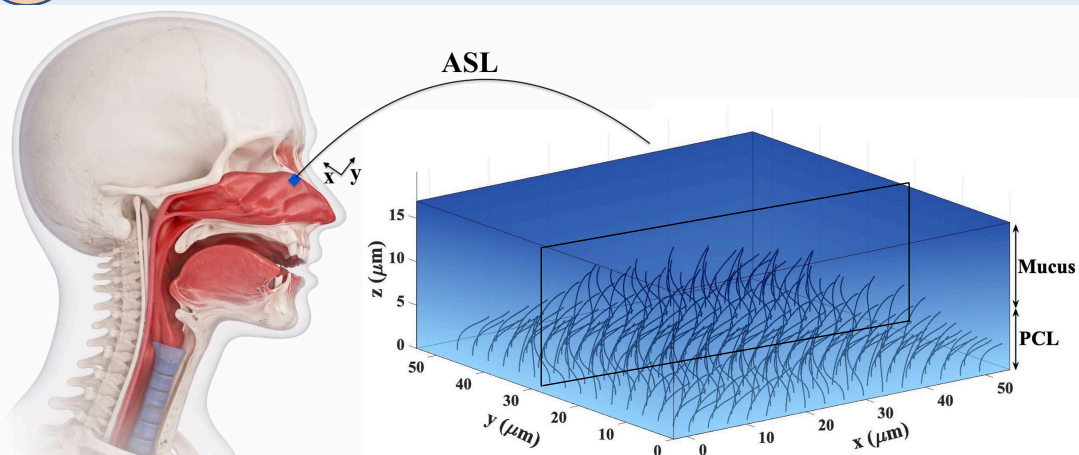


$$\tau_i + \lambda_i \nabla \tau_i + \frac{\alpha_i \lambda_i}{\eta_i^p} \tau_i \cdot \tau_i = 2\eta_i^p D$$

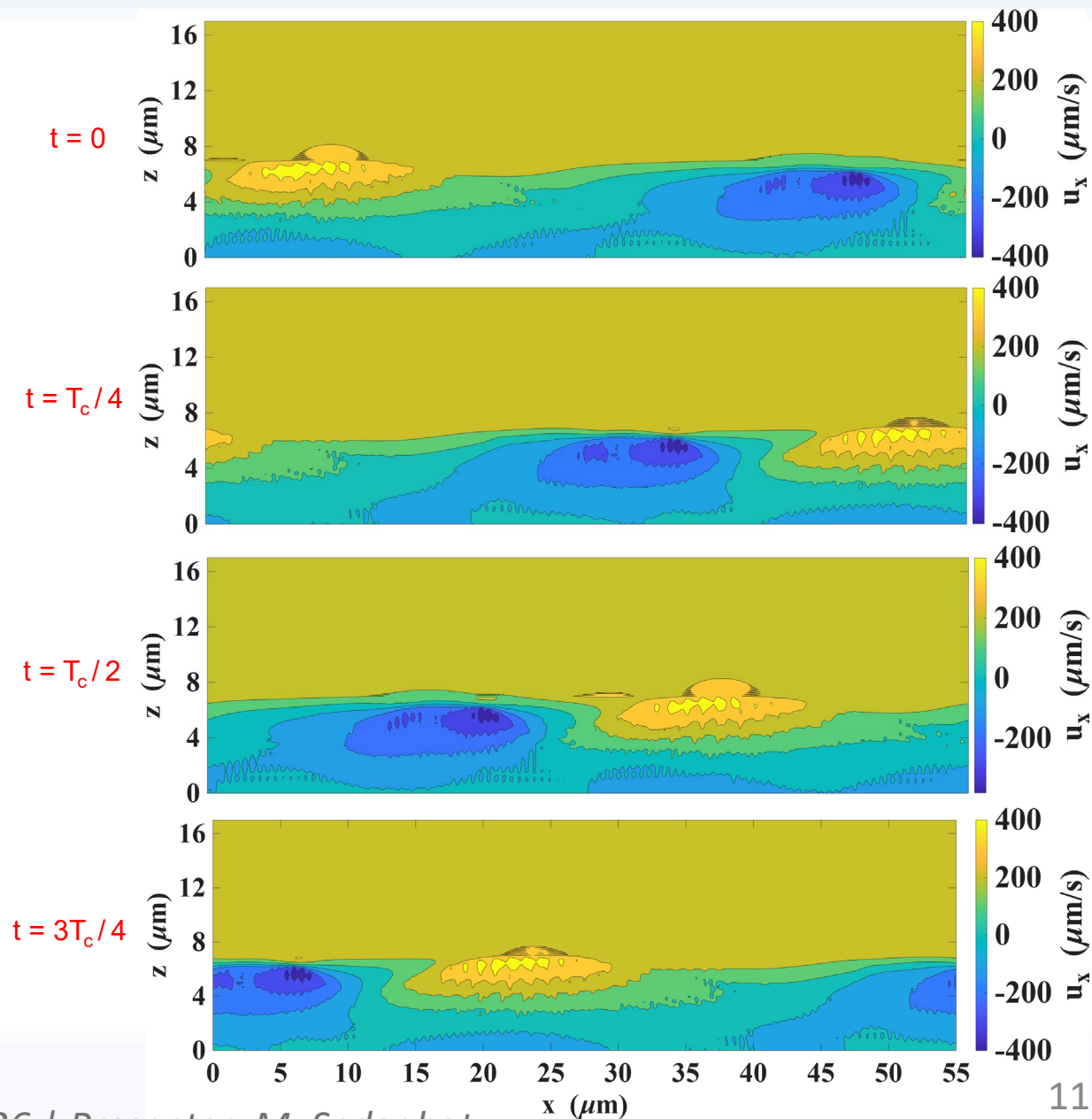
$$\tau = \sum_i \tau_i$$



3D Simulation of MCC in a Healthy Nasal Airway



Parameter	Value	Explored Range
Cilia beat frequency (Hz)	8.6	7-16
Cilia length (μm)	7	5-7
Cilia diameter (μm)	0.15	0.15 - 0.3
Cilia spacing in x and y directions (μm)	0.4	0.3-0.4
Number of cilia in x and y directions	100	100
Metachronal wavelength (μm)	55	37-60
Metachronal wave Metachronism	Antilaeoplectic	Antilaeoplectic
PCL depth (μm)	7	5-10
Mucus depth (μm)	10	5-15
Mucus and PCL density ($\text{kg} \cdot \text{m}^{-3}$)	1000	1000
PCL viscosity ($\text{Pa} \cdot \text{s}$)	0.001	0.001
Newtonian part of mucus Viscosity ($\text{Pa} \cdot \text{s}$)	0.001	0.001
Mean Mucus Velocity ($\mu\text{m} \cdot \text{s}^{-1}$)	248.29	83-217



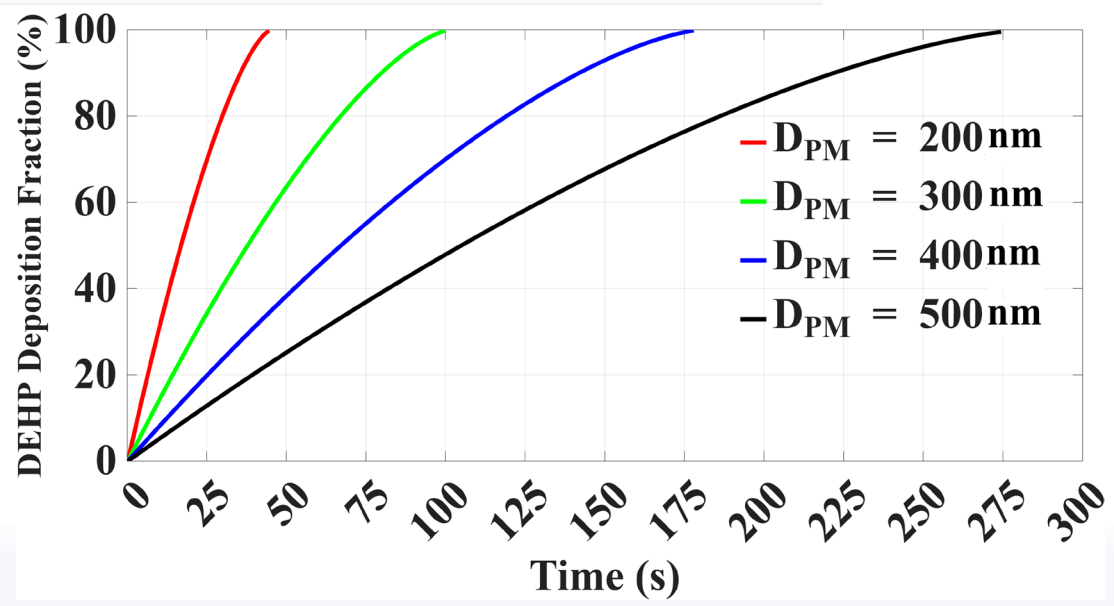
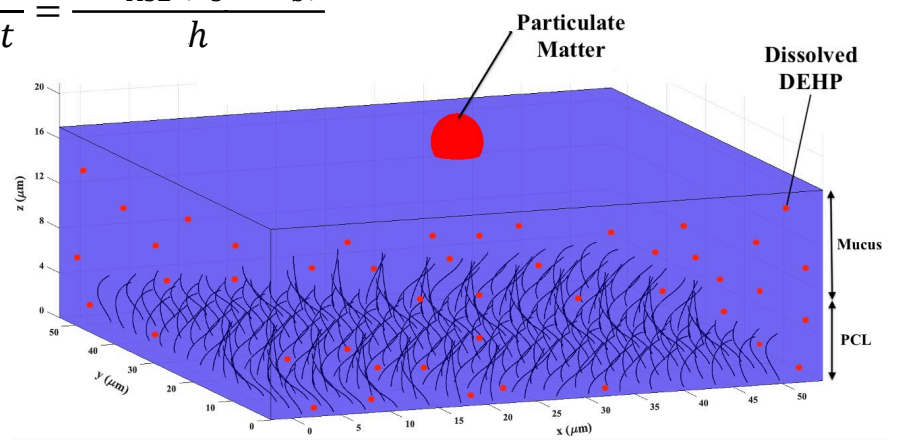
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Simulation of PM Dissolution and DEHP Absorption in ASL

$$\frac{\partial c}{\partial t} + c \cdot \nabla u = D_{ASL} \nabla^2 c$$

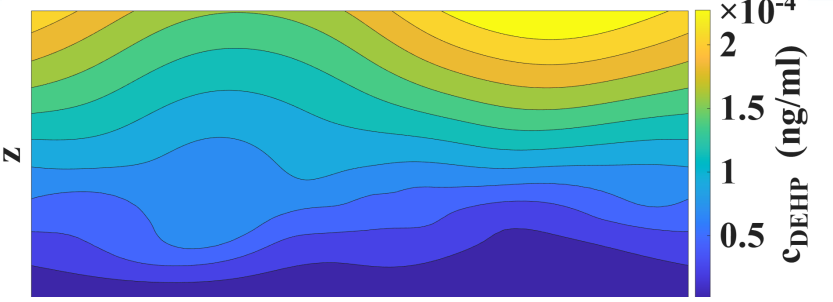
$$\frac{dm}{dt} = \frac{A D_{ASL} (C_s - C_b)}{h}$$

$$M_{DEHP} = 0.01\% M_{PM}$$

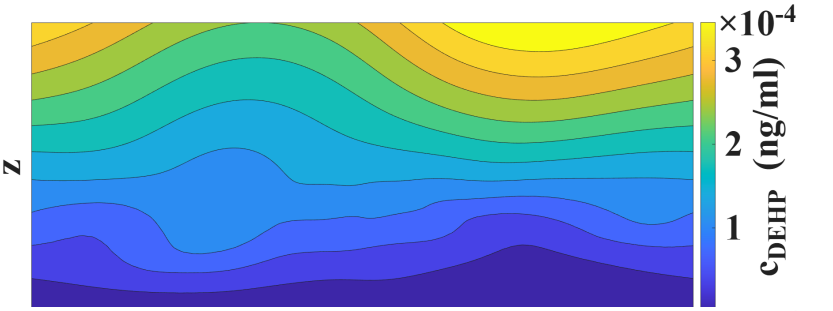


$t = 3 s$

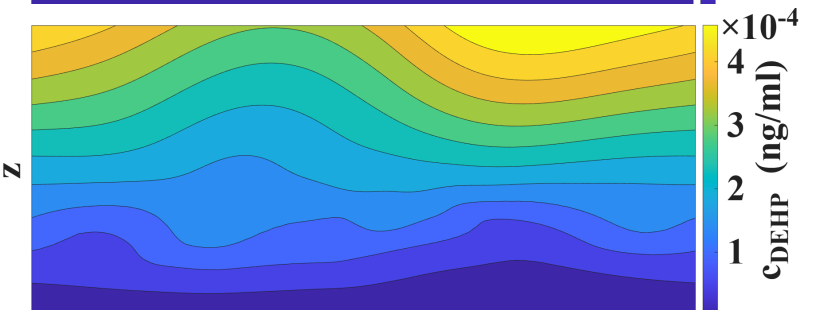
D_{PM}
(200 nm)



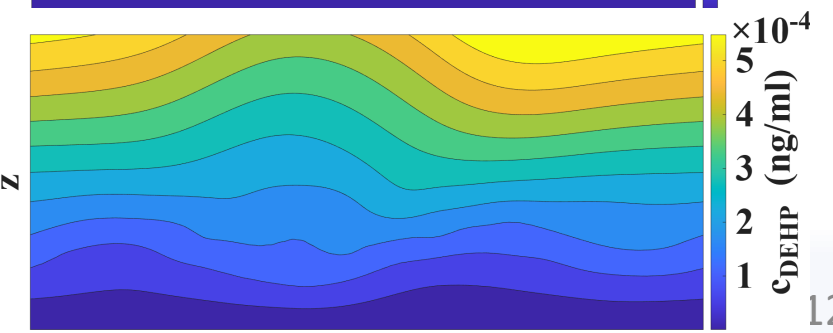
D_{PM}
(300 nm)



D_{PM}
(400 nm)

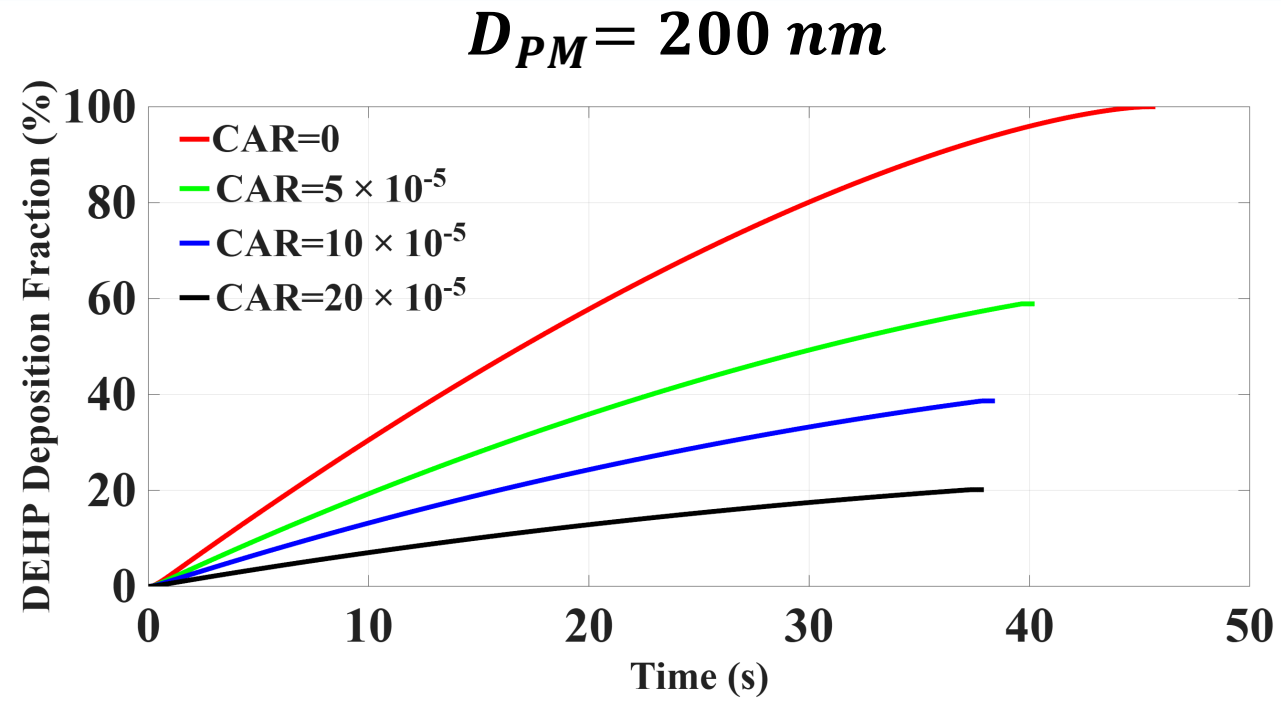
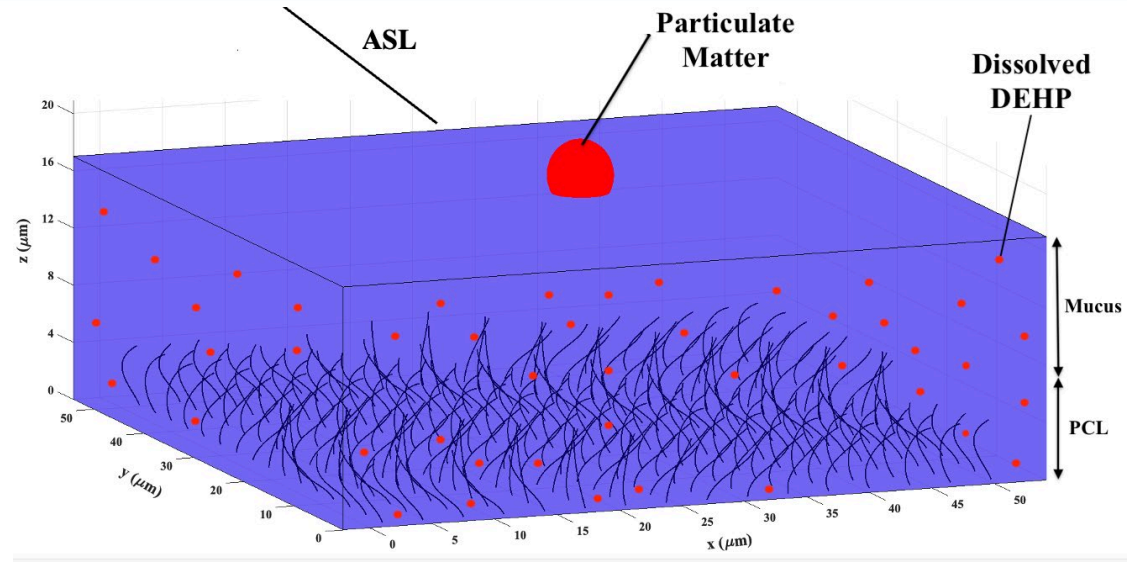


D_{PM}
(500 nm)



4

Simulation of PM Dissolution and DEHP Absorption in ASL



Ciliary Attachment Ratio (CAR)

$$CAR = \frac{m_{adh}(t)}{m_{max}(t)}$$

m_{adh} : mass of DEHP adhered to an individual cilium

m_{max} : maximum available mass of DEHP in the vicinity of that cilium

CAR	Total DEHP Deposition Fraction on Epithelium
0	100%
5×10^{-5}	58 %
10×10^{-5}	38%
20×10^{-5}	20%

Conclusions & Key Findings

Defensive Shielding

Established the first fully-resolved 3D multiphysics modeling approach for DEHP, pairing multi-mode Giesekus viscoelastic rheology with the Immersed Boundary Method (IBM) for accurate ciliary kinetics.

Ciliary Sponge Effect

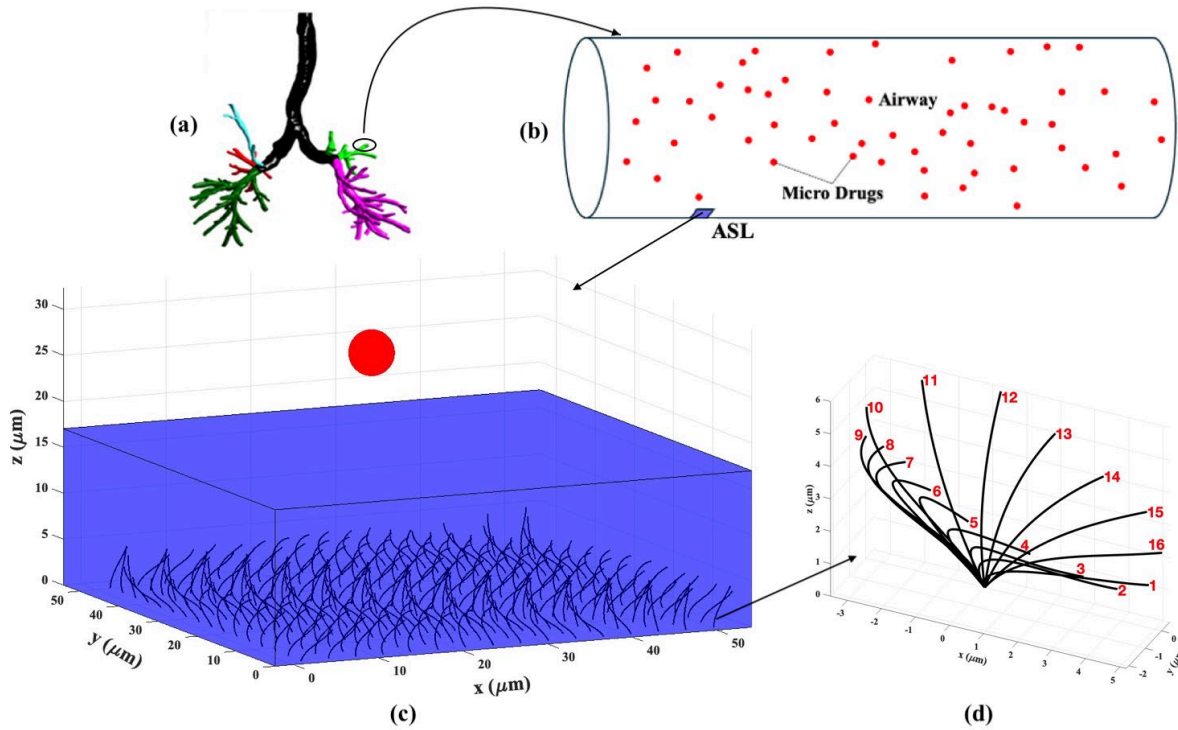
Quantified the ciliary attachment ratio (CAR). Increasing ciliary attachment parameters dramatically reduces the net fraction of dissolved DEHP reaching the baseline epithelium, highlighting cilia's active scavenging role.

Retention Kinetics

Hydrophobic plasticizers like DEHP ($\log K_{ow} \approx 7.5$) showcase exceptionally slow dissolution rates in aqueous ASL, suggesting clearance dominates over immediate tissue penetration.

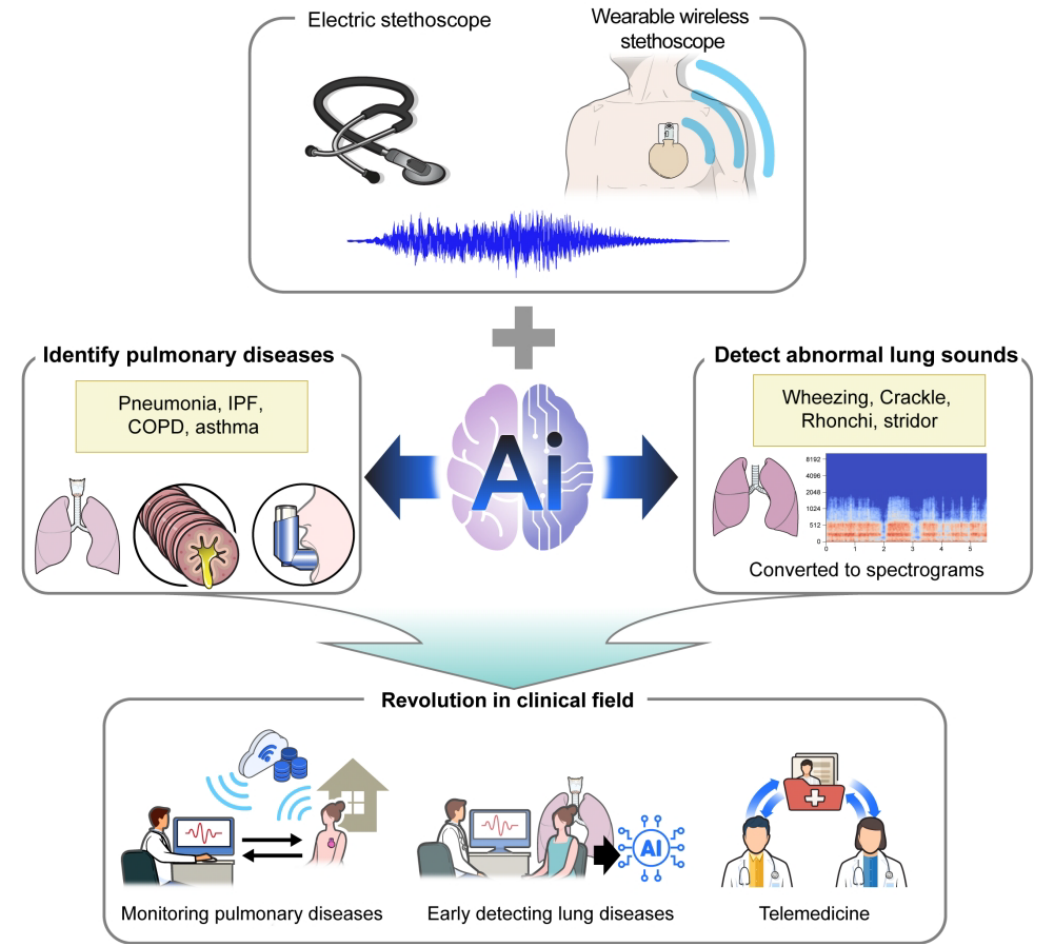
Future Research Outlook

Scaling to Diseased States



- Cystic Fibrosis
- Bronchiectasis
- COPD
- Asthma

Aerosol & Drug Delivery Optimization



Thank you for your Patience

Questions & Scientific Discussion

Presenter: MohammadHadi Sedaghat

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