Computer Modeling of Aerosol Diffusion through Lung Mucosa

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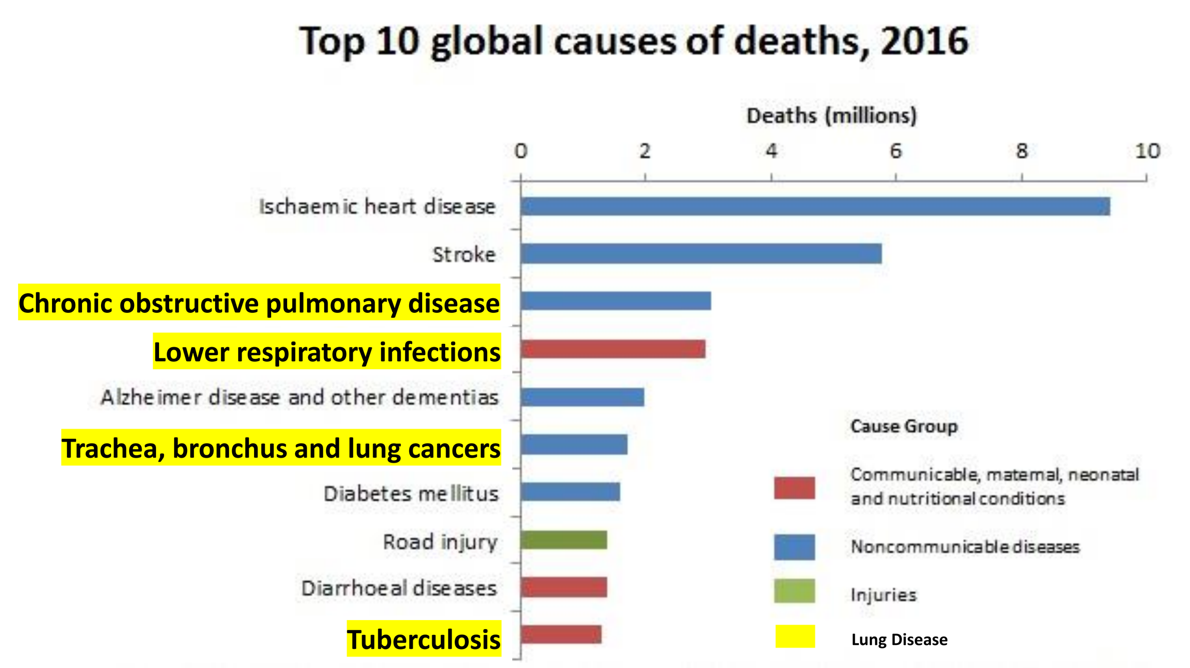
Objectives

- Create a physics-based computer model of the lung's inner mucus layer
- Include the mucociliary effect and the rheology of mucus
- Simulate the convection of aerosolized drug particles across that layer

Lung Diseases

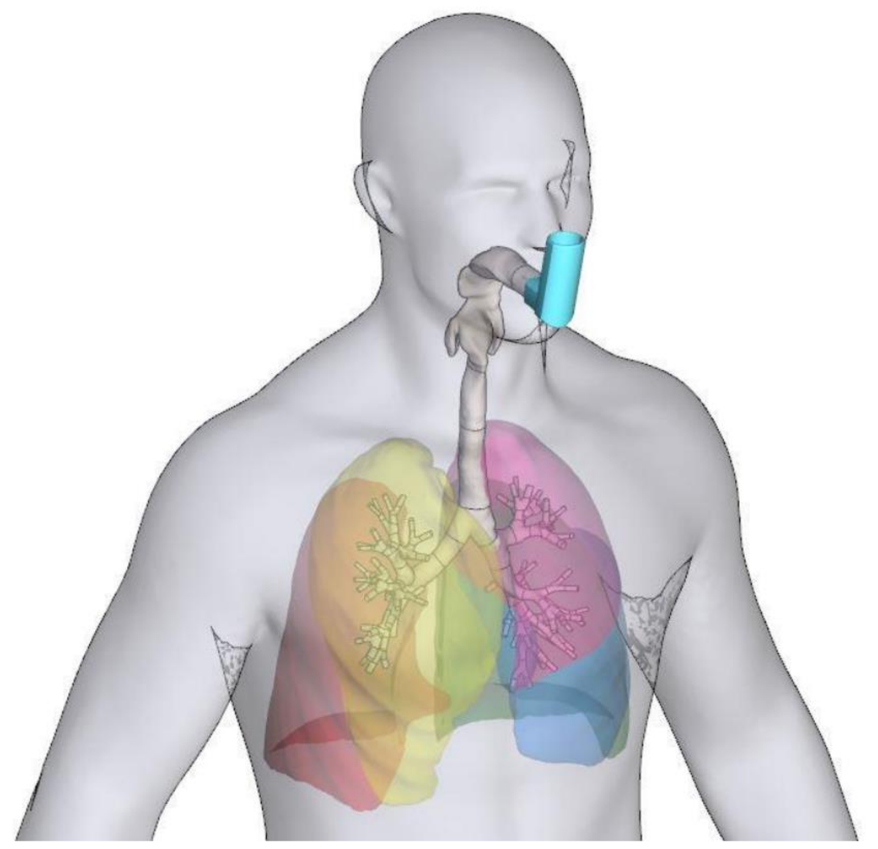


https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

Non-aerosol Treatment Challenges

- Few treatments exist
- Tend to be invasive and extremely rigorous
- Poor bioavailability

Aerosol Treatment Potential

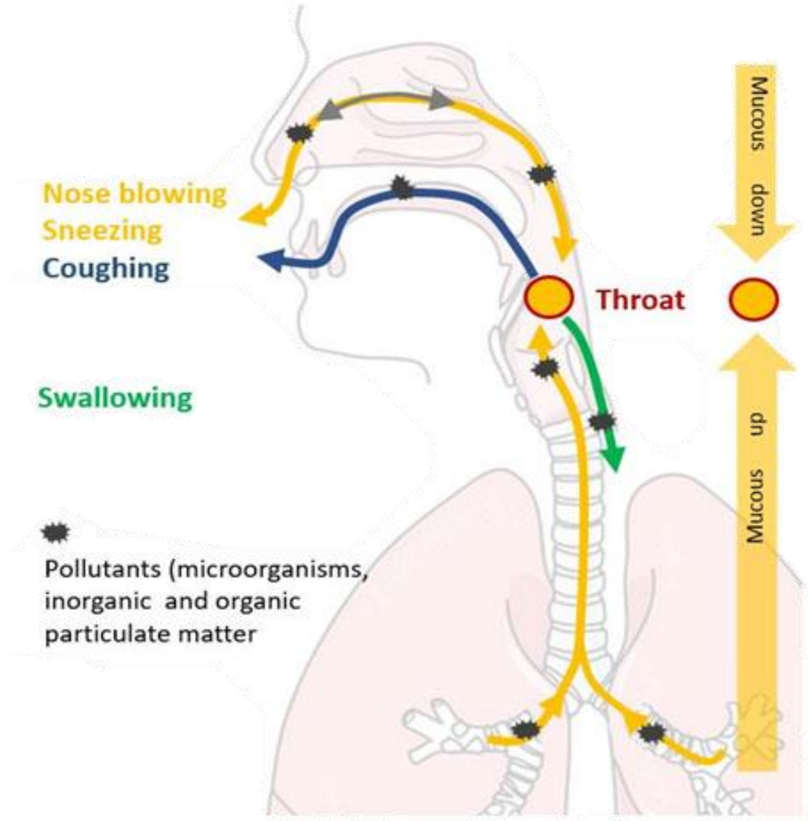


Localized Treatment of Lung

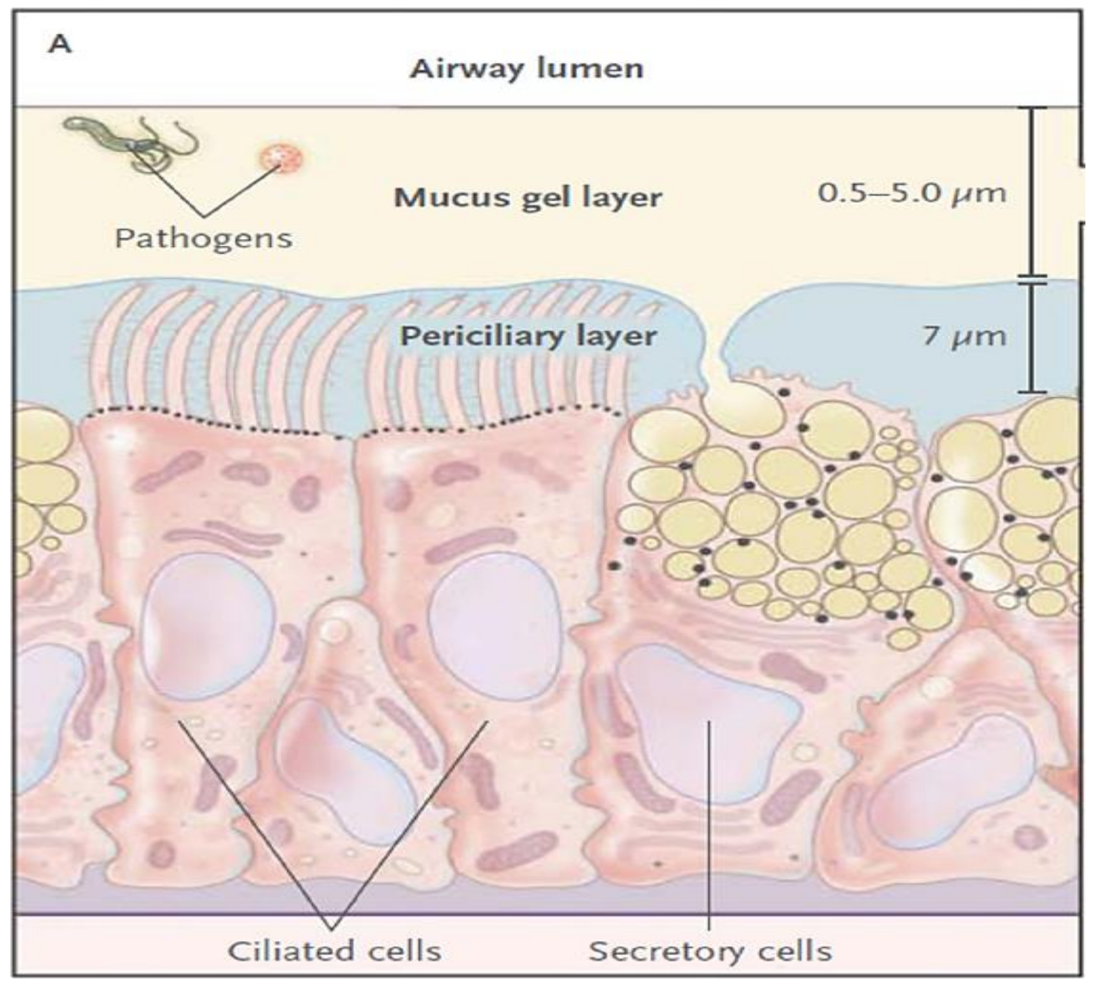
- Maximize the amount of drug that reaches the diseased portion of the lung
- Reduce off-target side effects
- Take advantage of large lung surface area
- Minimize administration inconveniences

Lung Mucosa

Lung Mucus and Mucociliary Clearance



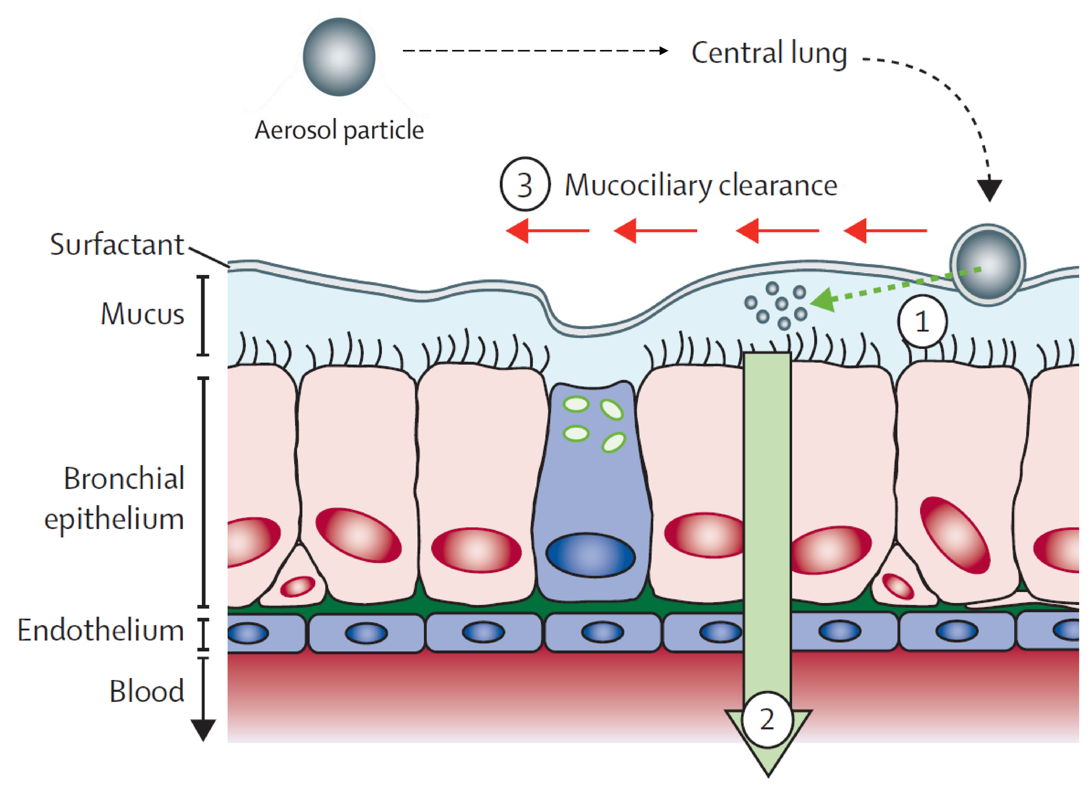
https://www.condair-group.com/humidity-health-wellbeing/how-dry-air-affects-our-immune-system



Fahy & Dickey, N Engl J Med, 2011

Particle Impaction and Clearance

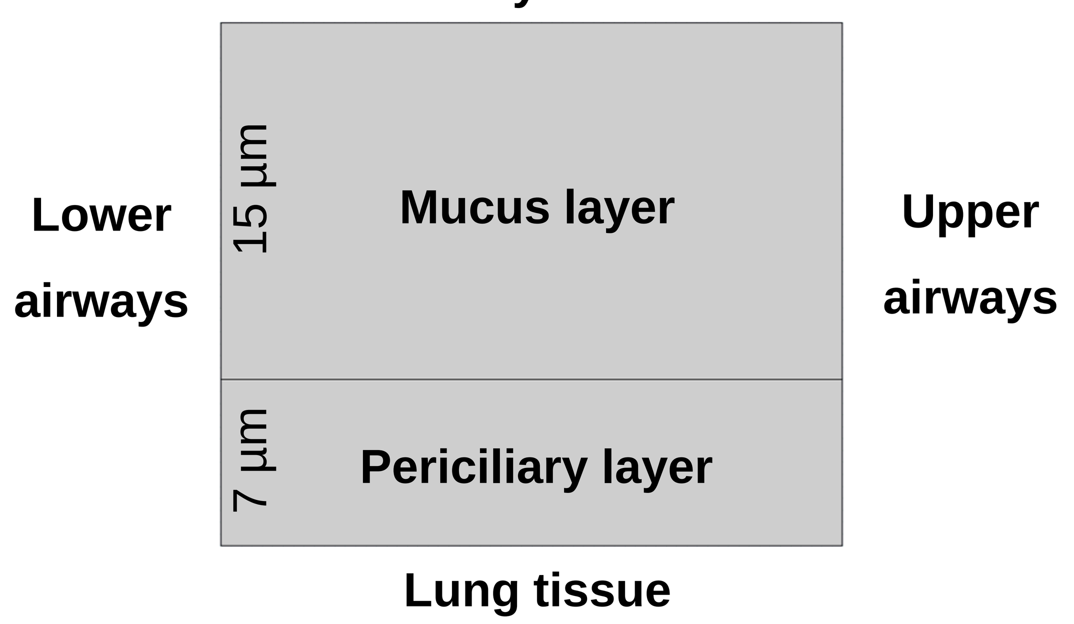
1. Particle contact with the mucus
2. Transport of the particle across the epithelium to target tissue
3. Mucociliary clearance of particle



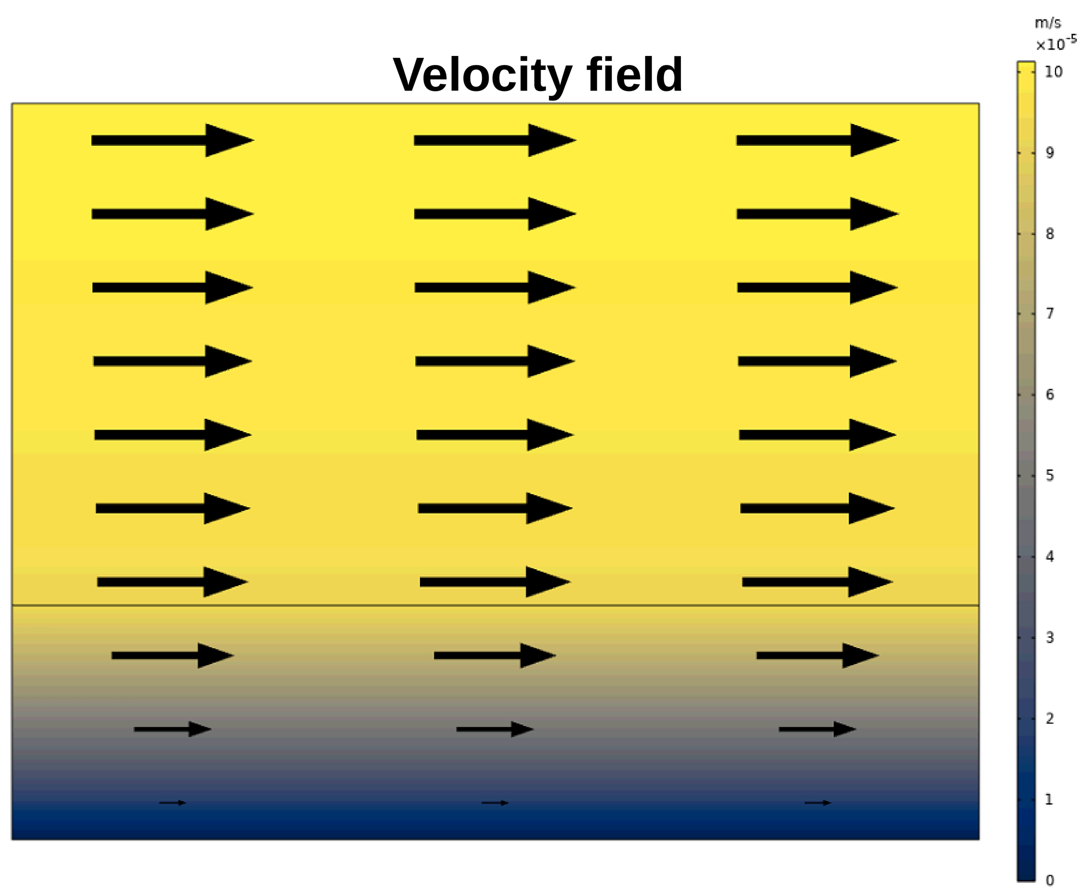
Adapted from Ruge et al., Lancet Respir Med, 2013

Computer Model

Simulation Domain



Velocity field



Laminar flow

$$\rho(u \cdot \nabla)u = \nabla \cdot [-pI + K]$$
$$\rho \nabla \cdot (u) = 0$$
$$K = \mu(\nabla u + (\nabla u)^T)$$

Transport of a dilute species

$$\nabla \cdot J_i + u \cdot \nabla c_i = 0$$
$$J_i = -D_i \nabla c_i$$

Bulk diffusivity

$$D_{i,\infty} = \frac{k_B T}{6\pi\mu r_i}$$

Effective diffusivity

$$\frac{D_i}{D_{i,\infty}} = \exp\left[-\left(\frac{1}{\lambda}+1\right)\sqrt{\phi}\right]$$

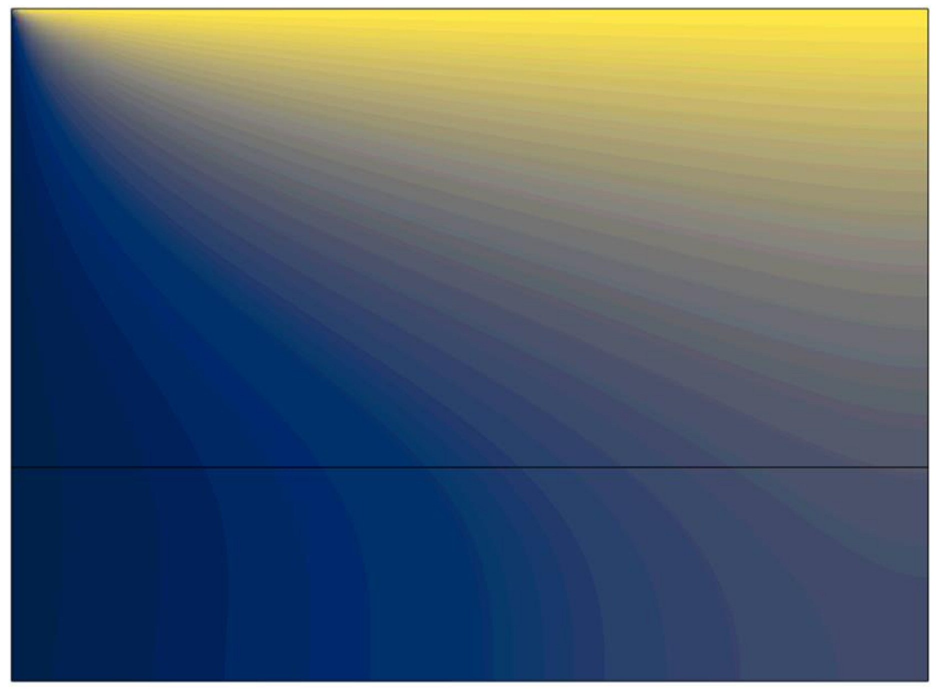
Notation

k_B = Boltzmann's constant; T = Temperature
μ = Viscosity of fluid; r_i = Stokes radius of i
λ = Fiber radius/r_i; ϕ = Fiber volume fraction
ρ = Density of fluid; p = Fluid pressure
u = Fluid velocity = 5 mm/min at inlet

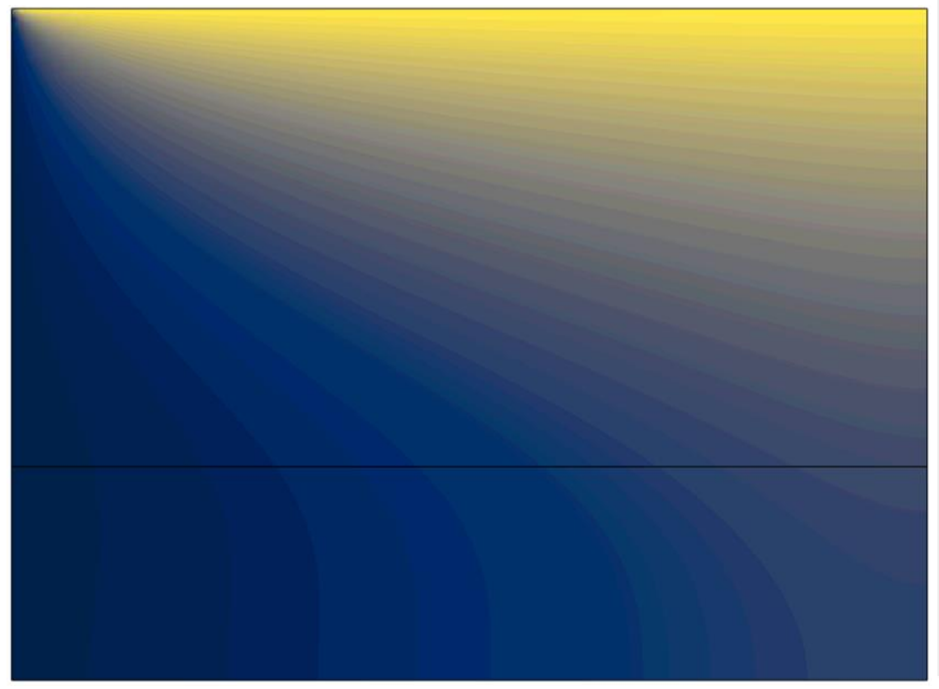
Results

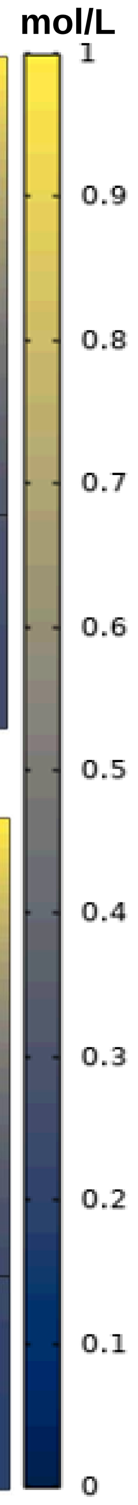
Diffusion of particle with radius r_i through the mucosa with fiber volume fraction ϕ

ϕ = 0.01, r_i = 1 nm

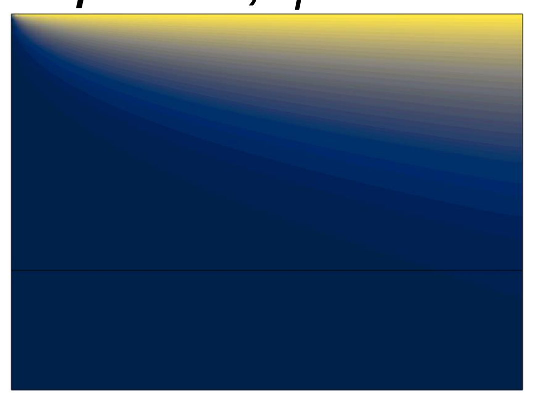


ϕ = 0.09, r_i = 1 nm

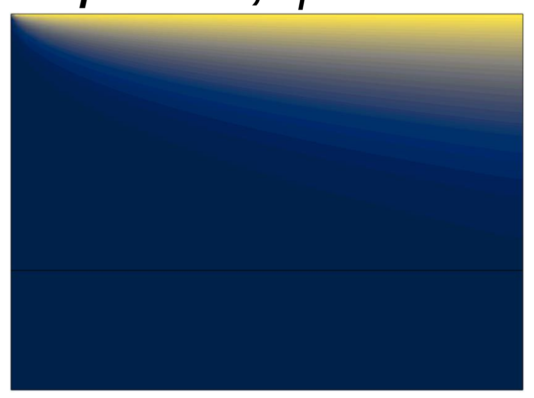




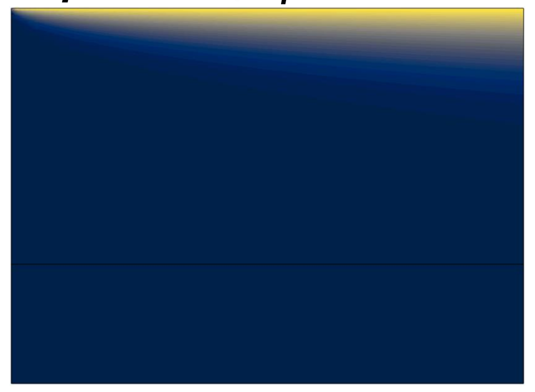
ϕ = 0.01, r_i = 5 nm



ϕ = 0.09, r_i = 5 nm



ϕ = 0.01, r_i = 20 nm



ϕ = 0.09, r_i = 20 nm

Summary

- Smaller particles diffuse faster
- Particles diffuse slower through more fibrous mucus (high fiber volume fraction)
  - Relevant to cystic fibrosis conditions
- More of the dosage reaches the tissue downstream of the dosage site