Computer Modeling of Aerosol Particle Transport through Lung Mucosa

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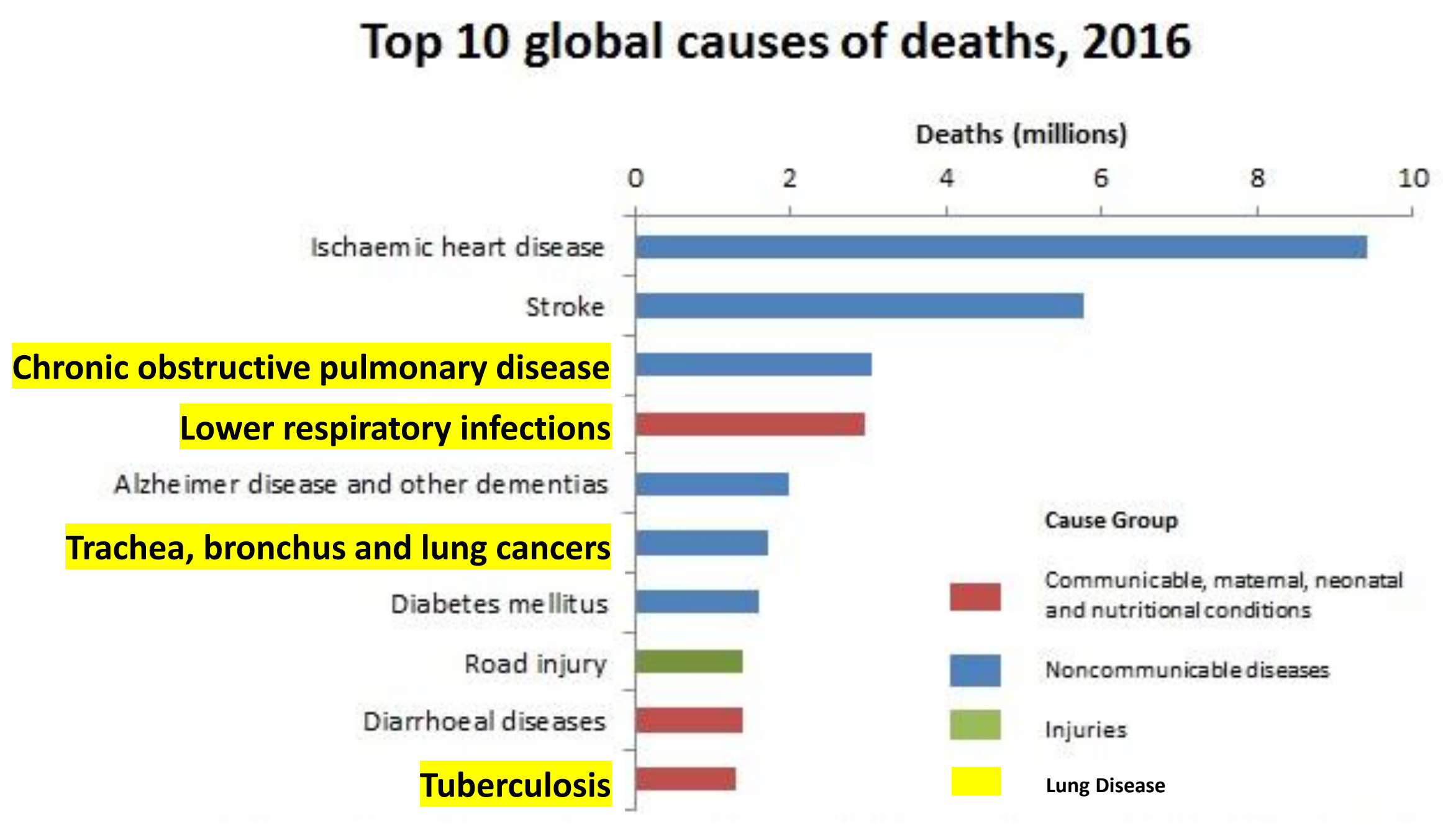
Objectives

- **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

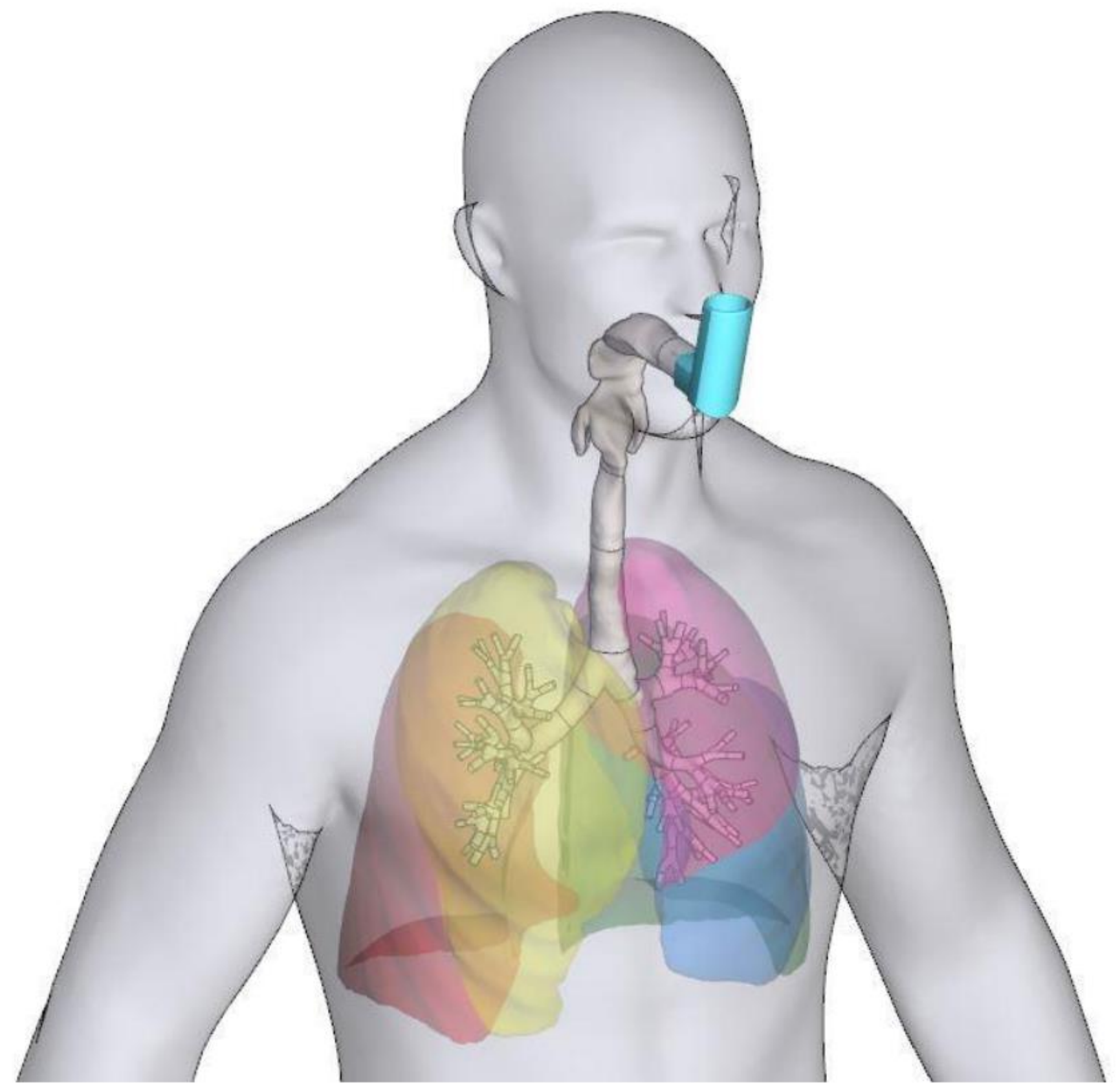


https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

Non-aerosol Treatment Challenges

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

Aerosol Treatment Potential

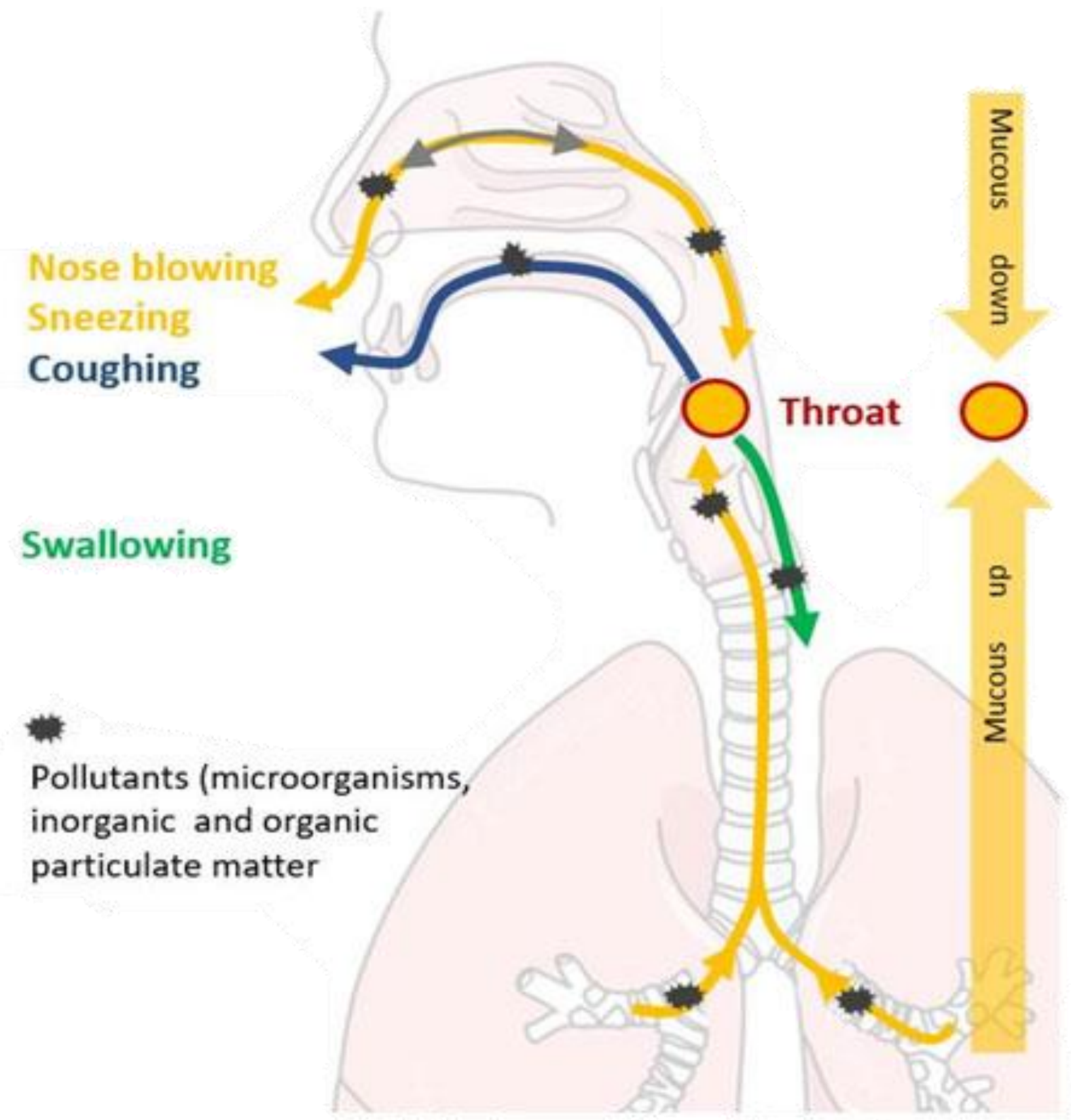


Localized Treatment of Lung

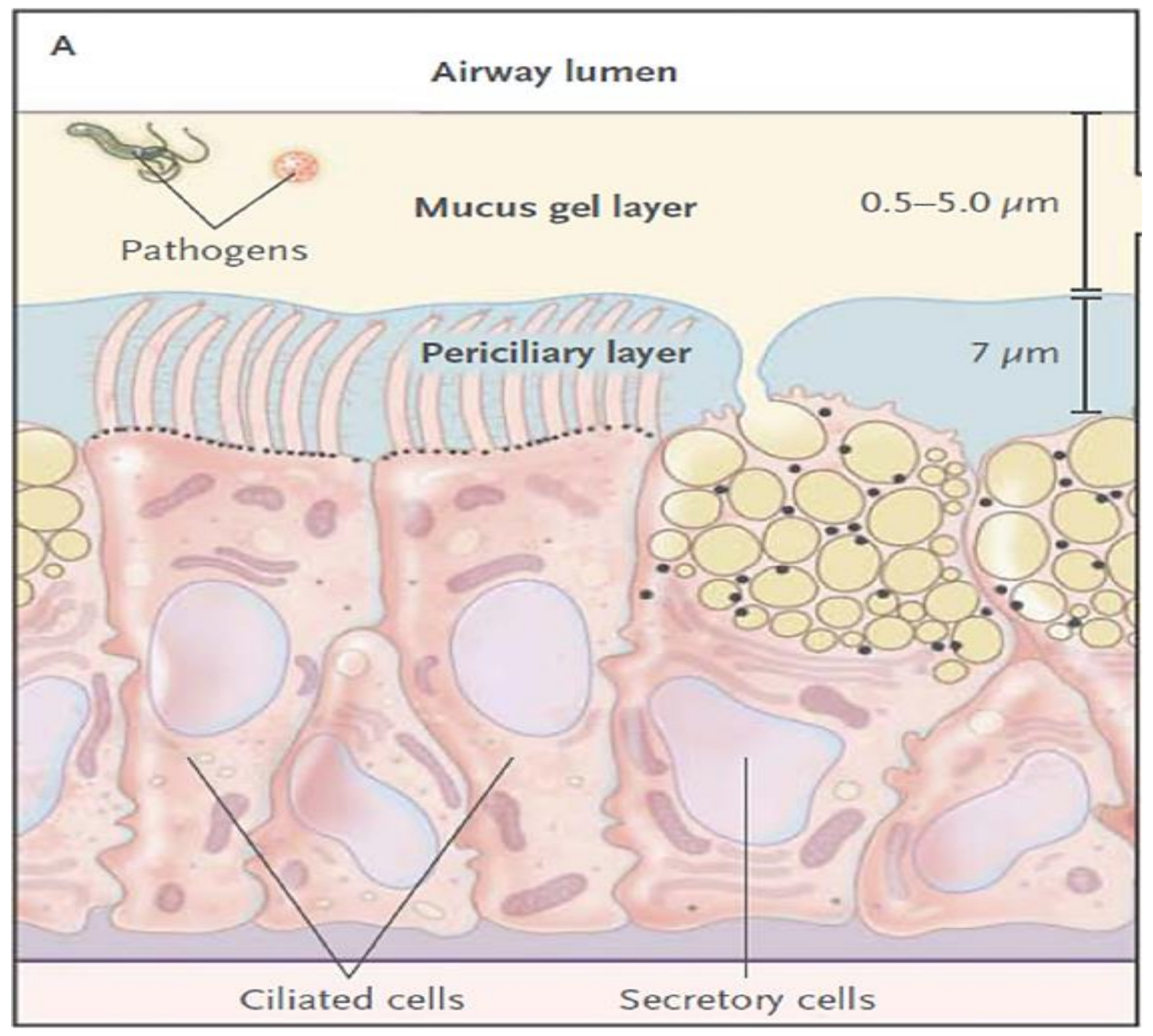
- **Maximize the amount of drug that reaches the diseased portion of the lung**
- **Reduce off-target side effects**
- **Take advantage of large lung surface area**
- **Minimize administration inconveniences**

Lung Mucosa

Lung Mucus and Mucociliary Clearance



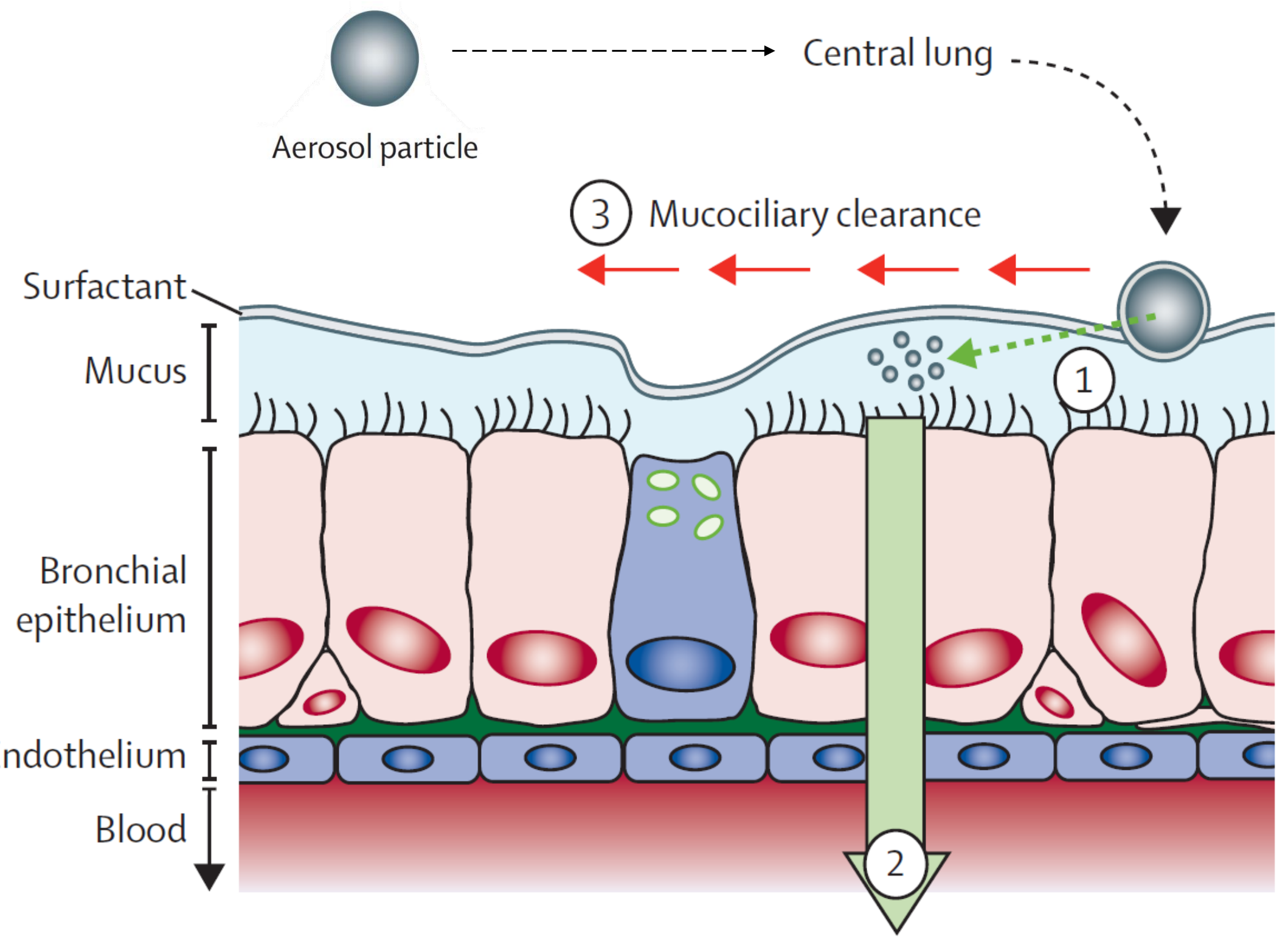
https://www.condair-group.com/humidity-health-wellbeing/how-dry-air-affects-our-immune-system



Fahy & Dickey, N Engl J Med, 2011

Particle Impaction and Clearance

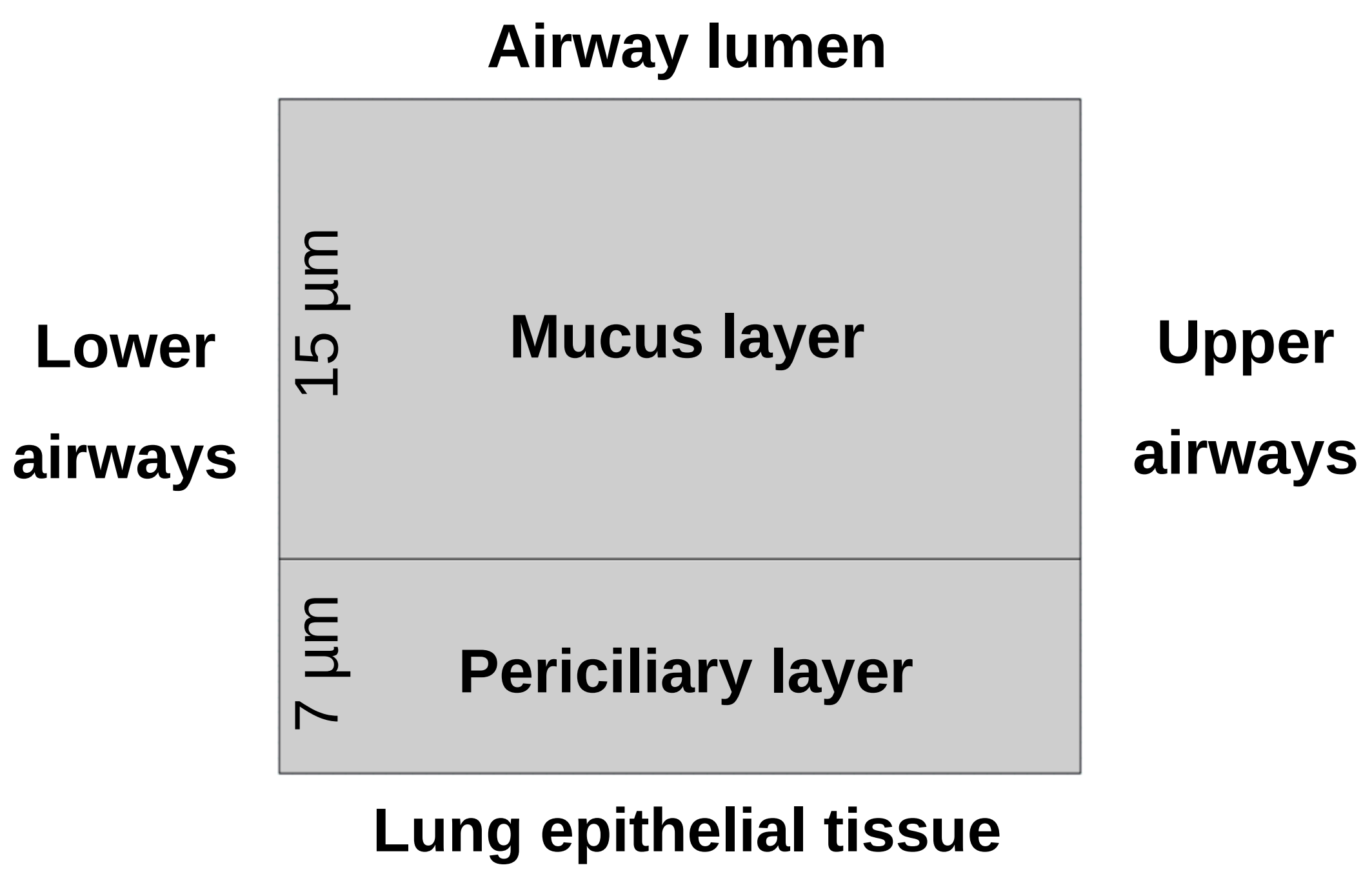
1. **Particle contact with the mucus**
2. **Transport of the particle across the epithelium to target tissue**
3. **Mucociliary clearance of particle**



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

Computer Model

Simulation Domain



Airway lumen

Lower airways

15 μm

Mucus layer

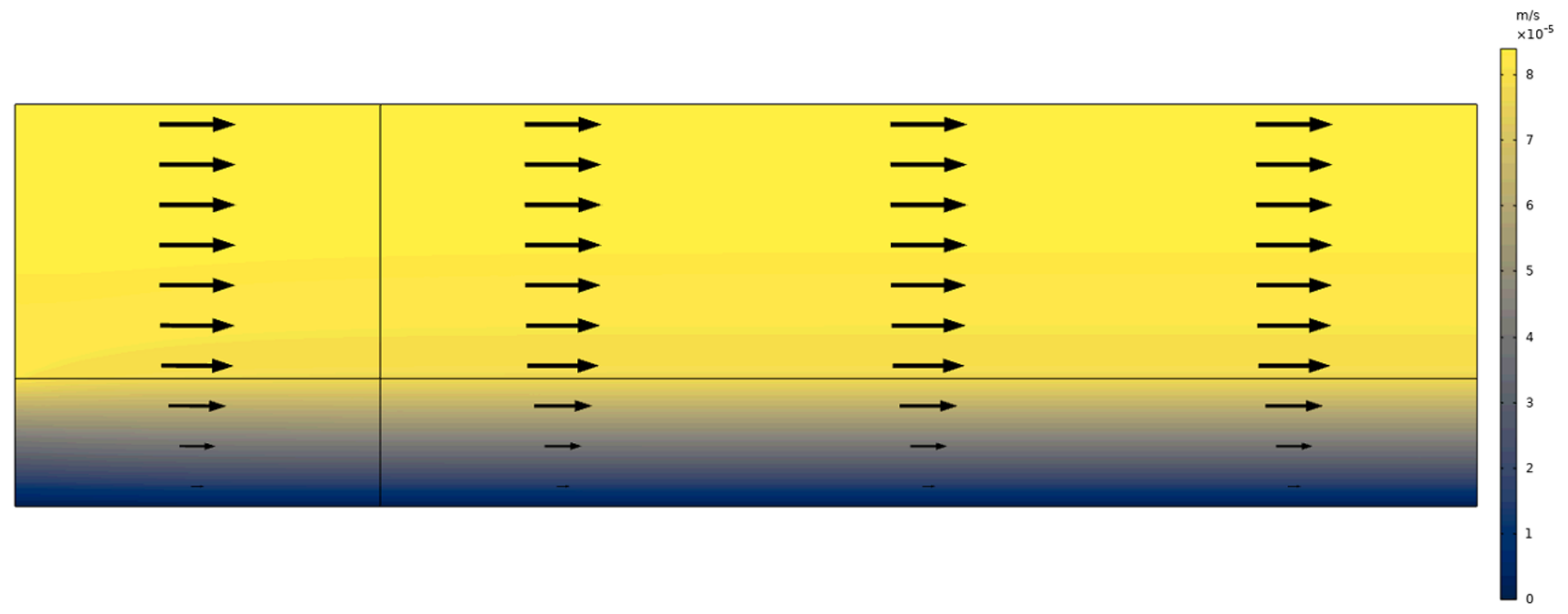
Upper airways

7 μm

Periciliary layer

Lung epithelial tissue

Velocity field



Equations

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

$$D_0 = \frac{k_B T}{6\pi\mu r_i}$$

Effective diffusivity

$$\frac{D}{D_0} = \exp(-0.84 f^{1.09})\exp(-a\phi^b)$$

Carreau fluid

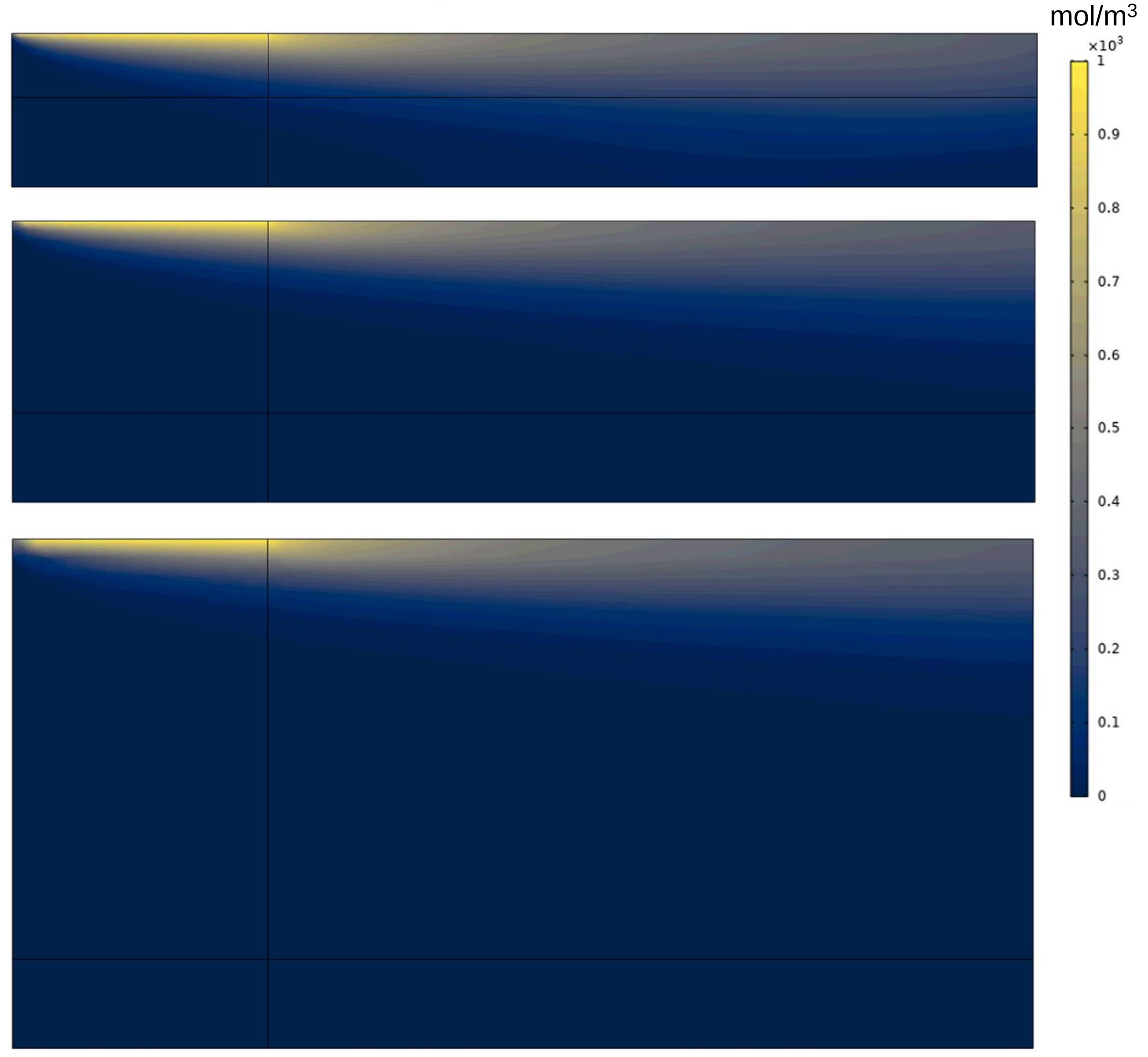
$$\mu_{eff}(\dot{\gamma}) = \mu_{inf} + (\mu_0 - \mu_{inf})(1 + (\tau\dot{\gamma})^2)^{\frac{n-1}{2}}$$

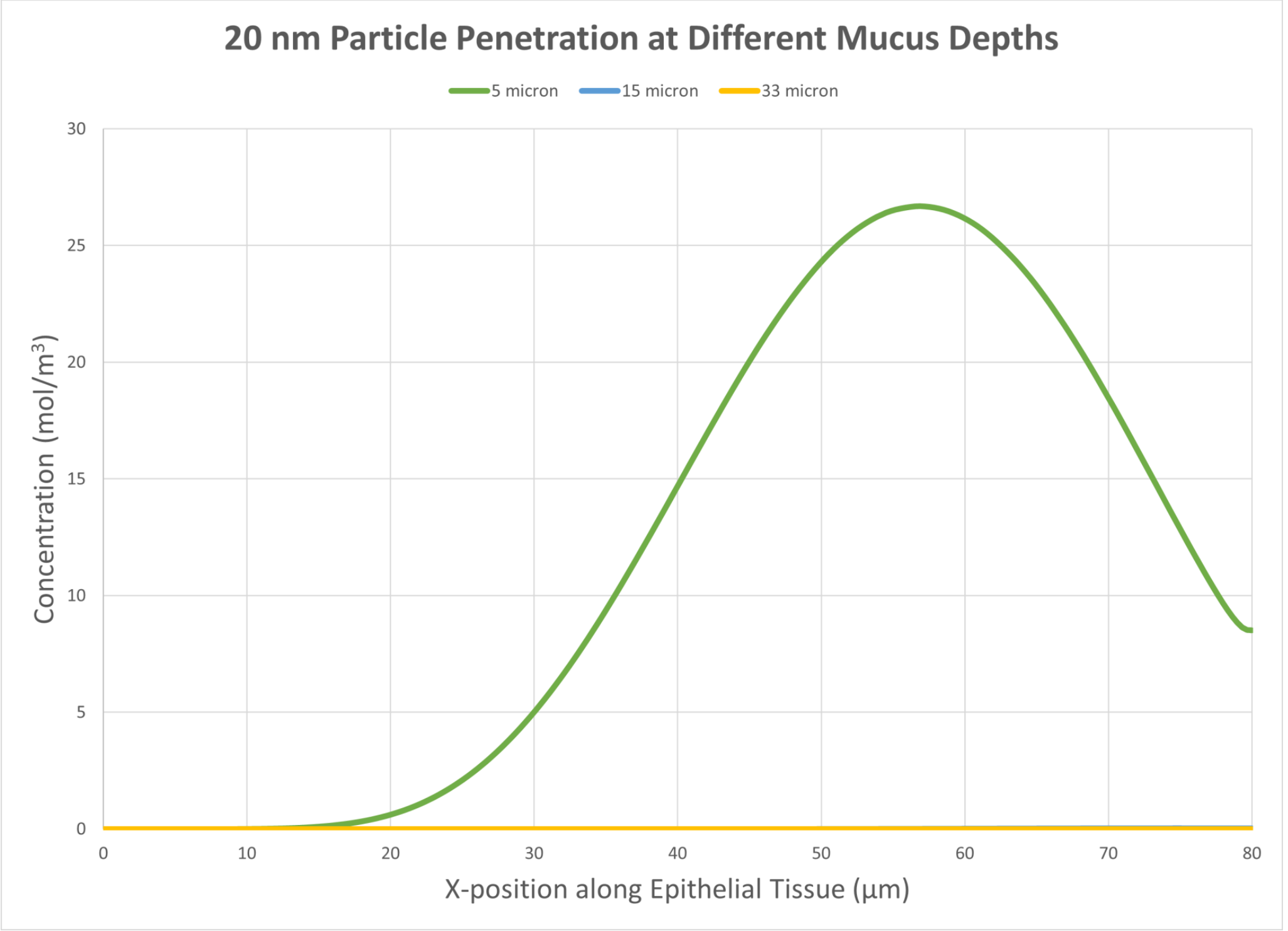
Relevant parameters

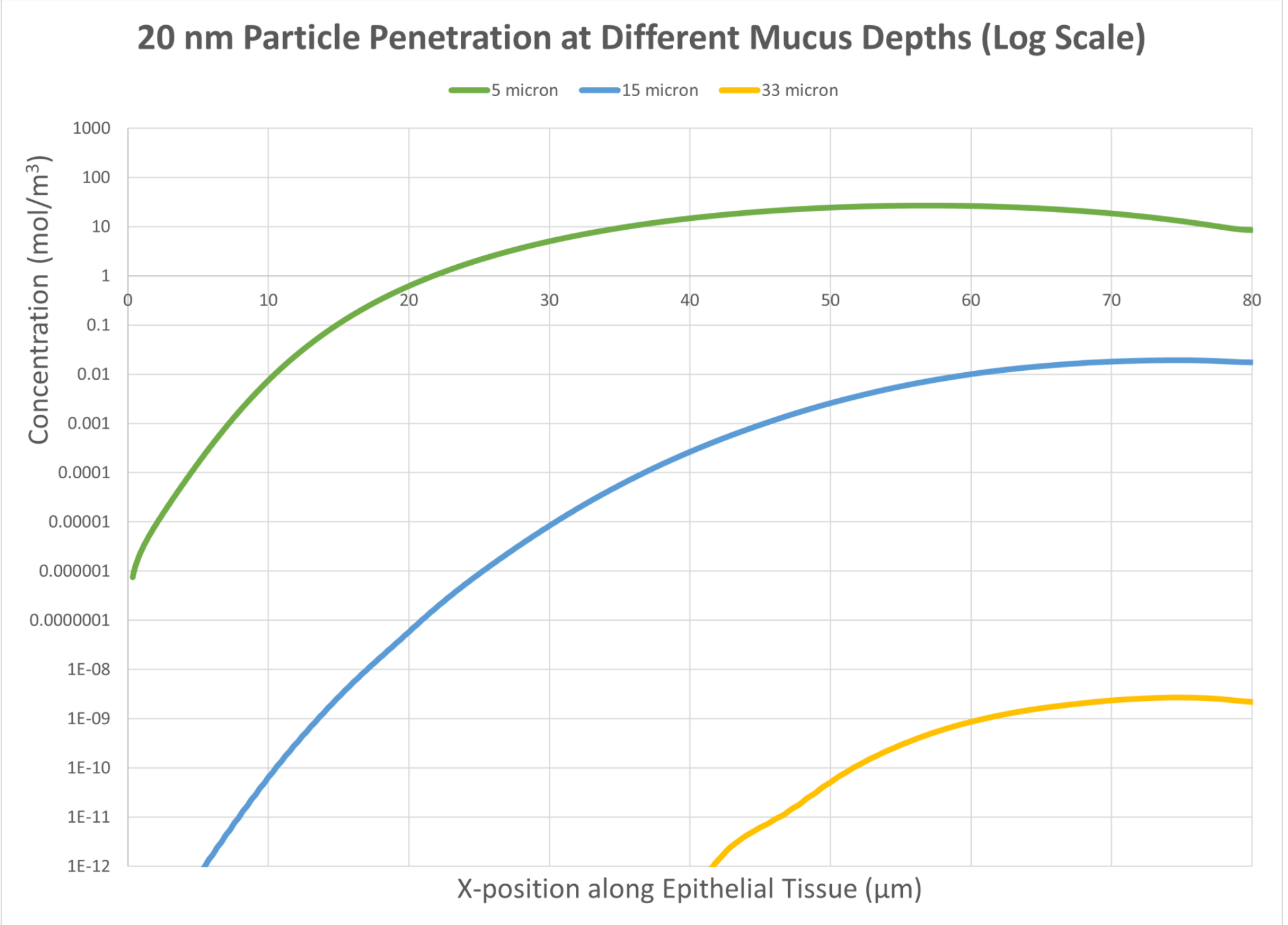
k_B = Boltzmann's constant T = Temperature
μ = Viscosity of fluid r_i = Stokes radius of i
λ = Fiber radius/r_i ϕ = Fiber volume fraction
ρ = Density of fluid p = Fluid pressure
u = Fluid velocity = 5 mm/min at inlet

Results

Particle Diffusion as a Function of Mucus Depth







Summary

- **Smaller particles diffuse faster**
- **Thinner mucus is crossed faster and at higher concentrations**
- **At some point upstream of the dosage site there is a maximum delivered dosage**
  - **Can be used in the development of disease treatments**