Hybrid agent-based modeling framework to simulate *Aspergillus fumigatus* infection scenarios in the lung

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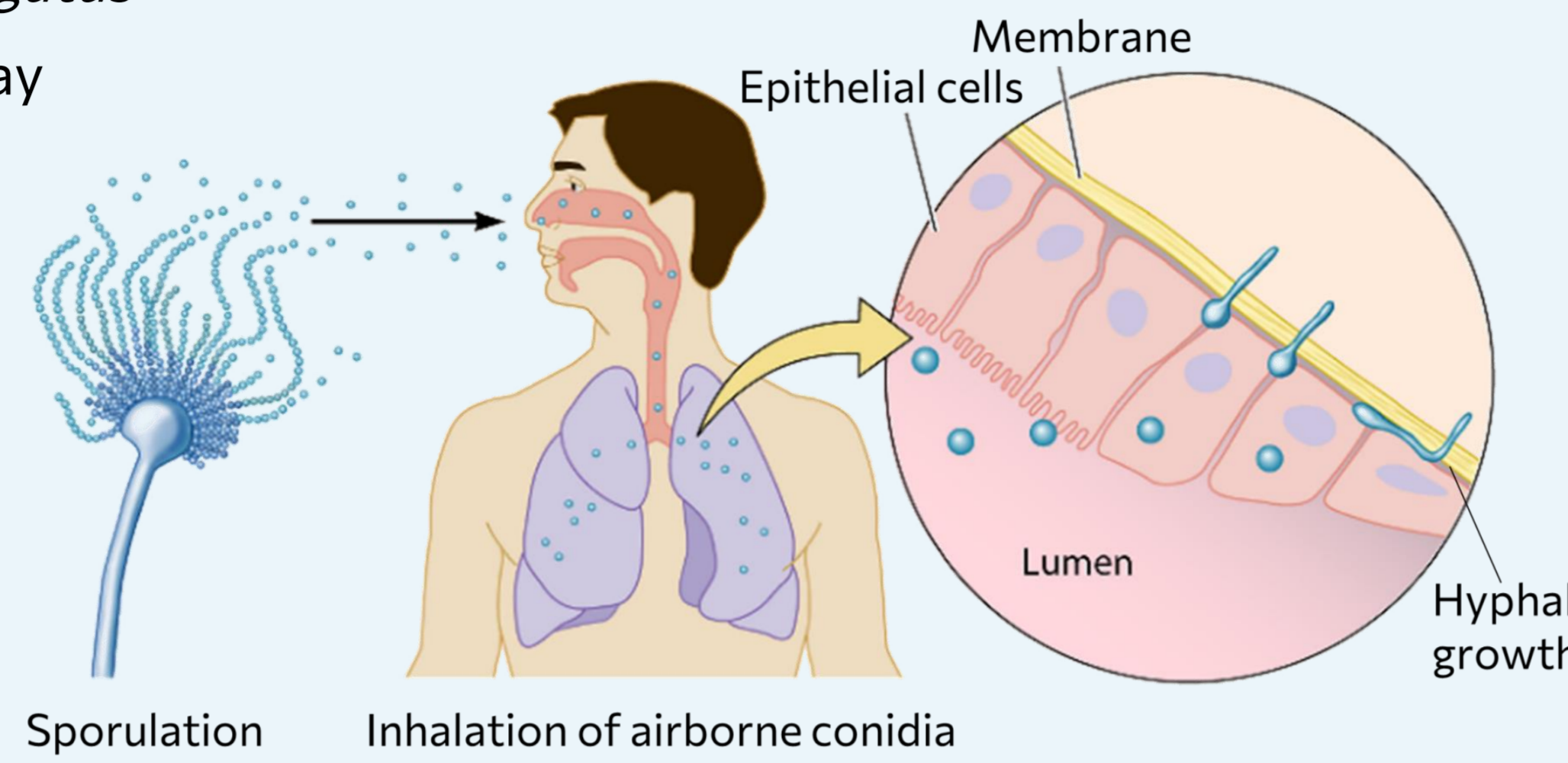
Motivation

- Opportunistic pathogen *Aspergillus fumigatus*
- Inhalation of hundreds of conidia every day
- Germination within hours
- Hyphal invasion into blood stream
- Life-threatening invasive aspergillosis

→ Route of invasion [1]:

Sporulation   Inhalation of airborne conidia

Membrane
Epithelial cells
Lumen
Hyphal growth

Infection scenario events

- Conidium enters alveolus
- Chemokine secretion by conidium –associated AEC
- AM perform chemotactic walk along chemokine gradient
- AM enter and leave system through boundaries
- Chemokine concentration reaches equilibrium
- Potential detection and clearance of conidium
- If not cleared: conidium swells and grows hyphae
- Simulation ends at t_{max}

Hybrid agent-based model

Modeling infection dynamics of *A. fumigatus* is realized using an agent-based modeling approach [3] combined with partial and ordinary differential equations for modeling the dynamics of chemokines:

- Cells correspond to interacting agents
- Molecules are represented as concentrations distributed over the inner alveolar surface

Chemokine dynamics

Spatio-temporal dynamics of chemokine concentration $c(\vec{r}, t)$ at position $\vec{r}$ and time t is described by the reaction diffusion equation [4]:

$$\frac{\partial c(\vec{r}, t)}{\partial t} = D \, \Delta c(\vec{r}, t) - \lambda c(\vec{r}, t) + S(\vec{r}, t) - Q(\vec{r}, t)$$
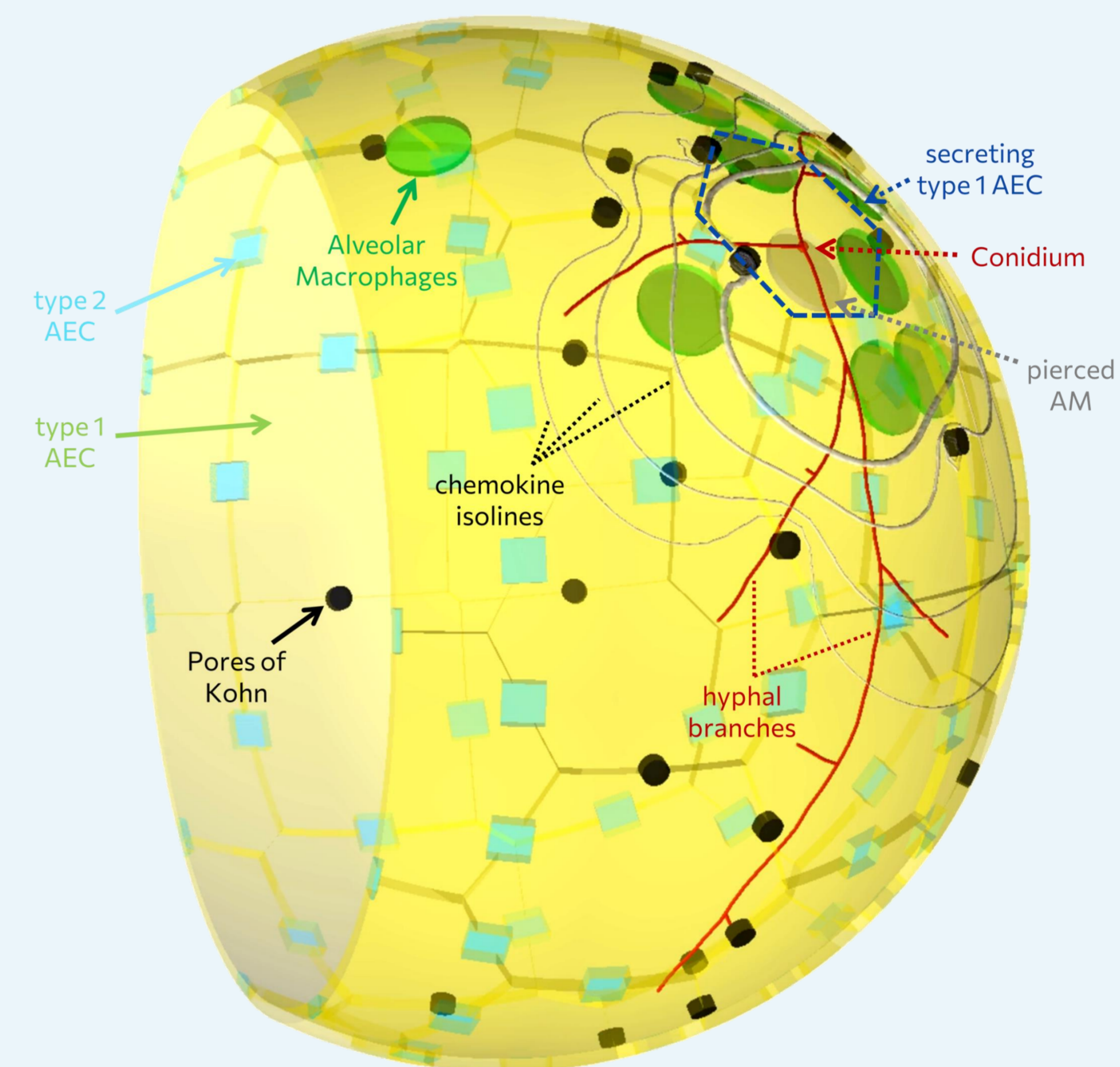
- D isotropic diffusion coefficient
- λ chemokine decay
- $S(\vec{r}, t)$ source associated with the secreting AEC
- $Q(\vec{r}, t)$ uptake of chemokines by AM

- Application of Euler method on Delaunay triangulated surface (5000 grid points)
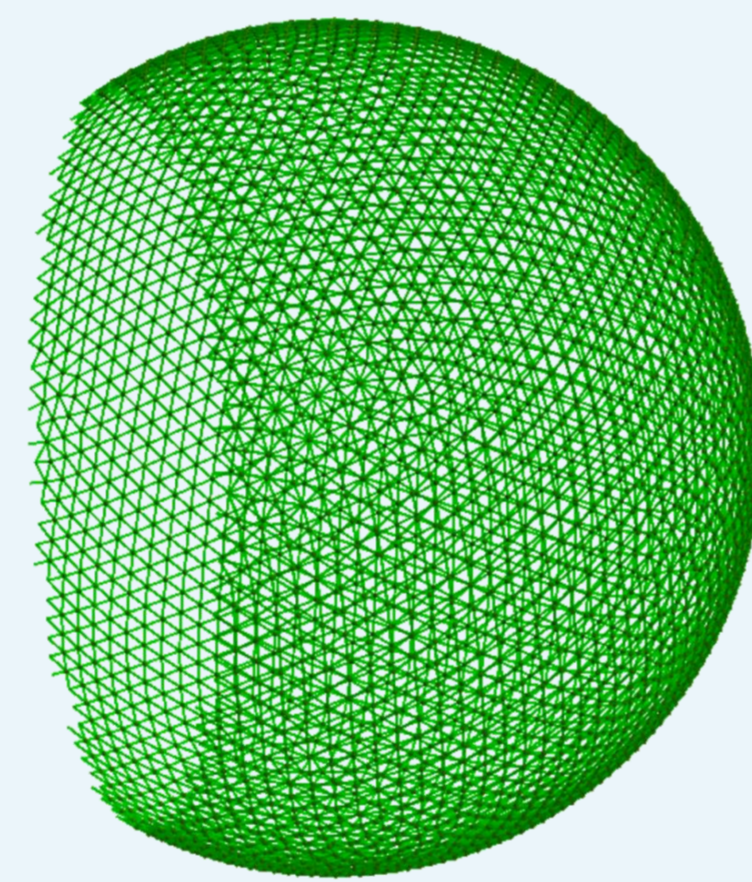

Model environment and entities

The to-scale approach involves a 3D representation of the human alveolus as the environment and the entities as shown below:

secreting type 1 AEC
Conidium
pierced AM
type 2 AEC
type 1 AEC
Alveolar Macrophages
chemokine isolines
Pores of Kohn
hyphal branches

Modeling hyphal growth

- Highly generic implementation
- Depends on growth rate, branching degree, curvature, etc.
- Piercing branch through membrane orthogonal to surface
- Approximation of hyphae by spheres
- Growth according to logistic function $f(t)$
- At time t, a new sphere is added to the hypha, if length of hypha $l(t) < f(t)$

Conidium
Piercing
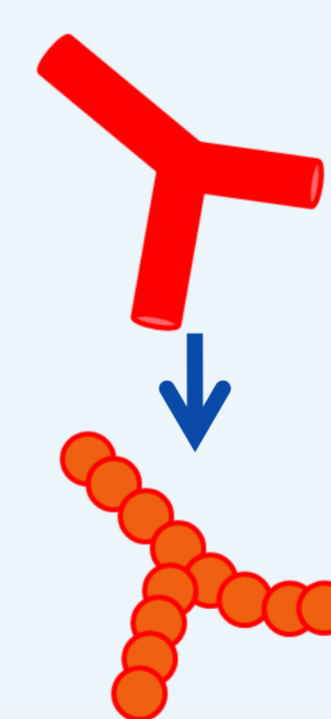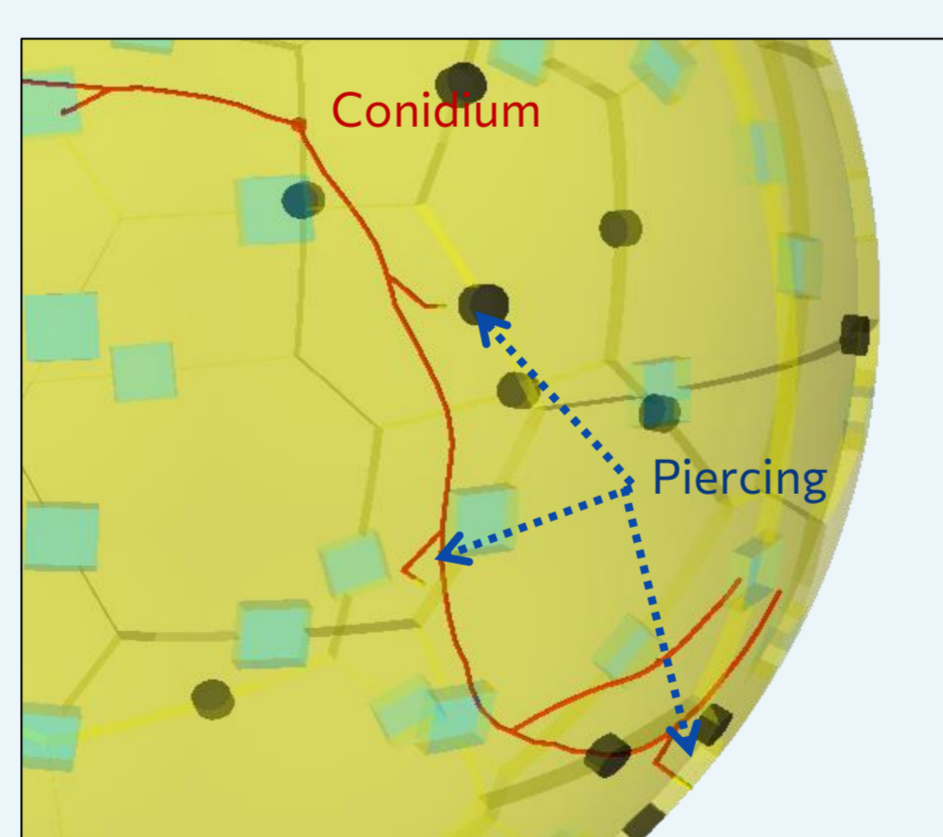
Extension to alveolar sac

- Next higher structural unit in the lung
- Generation of a set of points and their associated Delaunay triangulated alveolar surface
- Single alveolus is represented as multiple truncated spheres
- Individual alveoli are connected by a central alveolar airway (cylinder)
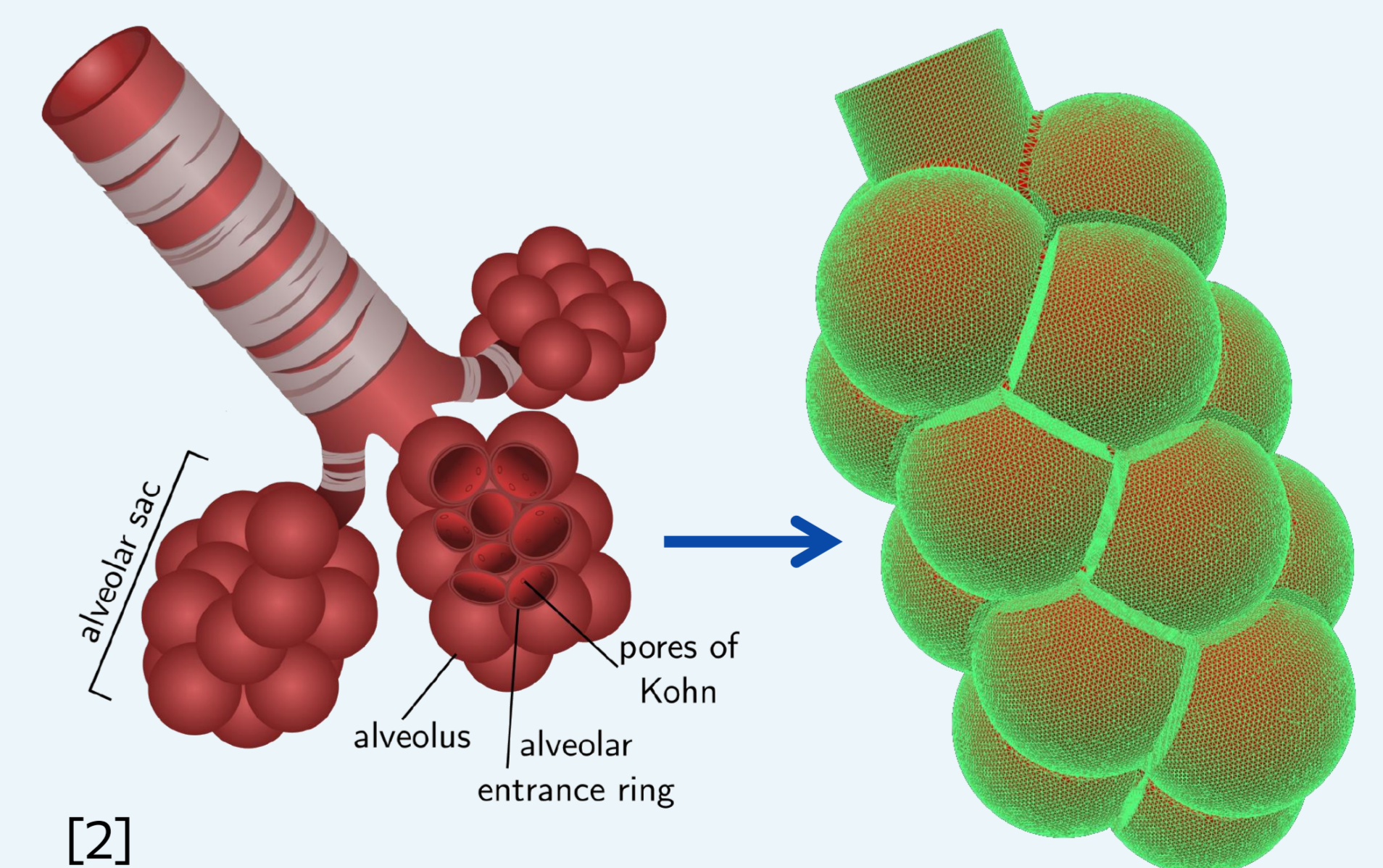
Game Theory

- Simulation of infection-inflammation counterplay: of *A. fumigatus* and innate immunity for:
  - Immunocompromised patients
  - Different infection-doses
- Reconcile contradictory view on alveolar macrophages in literature

Game I Complement System	Game II Alveolar Macrophages	Game III Polymorphonuclear Neutrophils
Inflammation / minutes / Infection	Inflammation / minutes / Infection	Inflammation / hours / Infection

alveolar sac
pores of Kohn
alveolus
alveolar entrance ring

[2]

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[4] Pollmächer and Figge. 2015. *Front Microbiol.* 6:1-14

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