

Hybrid agent-based modeling framework to simulate *A. fumigatus* infection scenario in the lung

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01/10/2021

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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 hour
- Hyphal invasion into blood stream
- Life-threatening invasive aspergillosis

Route of invasion [1]: Sporulation → Inhalation of airborne conidia → Conidium enters alveolus → Germination within hour → Hyphal growth → Hyphae → Lumen → Epithelial cells → Membrane

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:

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 $l(t) < f(t)$

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	Inflammation	Infection
Game II	Alveolar Macrophage	Inflammation	Infection
Game III	Polymorphous Neutrophils	Inflammation	Infection

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)

References:
[1] Degener and Keller. 2009. Curr Microbiol Rev. 22:447-65.
[2] Polmischer et al. 2019. Sci Rep. 9:27097.
[3] Polmischer and Figge. 2014. PLoS ONE. 9(10).
[4] Polmischer and Figge. 2015. Front Microbiol. 6:154.

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