Leibniz Institute for Natural Product Research and Infection Biology - Hans Knöll Institute

Agent-based Modeling on Cellular and Molecular Scales

Sandra Timme[1,4], Johannes Pollmächer[1,4], Teresa Lehnert[1,4], Anna Medyukhina[1], Sören Totzauer[1,4], Kerstin Hünniger[2,4], Denise Buhlmann[3,4], Christine Skerka[3,4], Oliver Kurzai[2,4] and Marc Thilo Figge[1,4]

[1]Applied Systems Biology, Leibniz Institute for Natural Product Research and Infection Biology - Hans Knöll Institute
[2]Fungal Septomics, Leibniz Institute for Natural Product Research and Infection Biology - Hans Knöll Institute
[3]Infection Biology, Leibniz Institute for Natural Product Research and Infection Biology - Hans Knöll Institute
[4]Friedrich Schiller University Jena, Jena, Germany

Agent-based Modeling

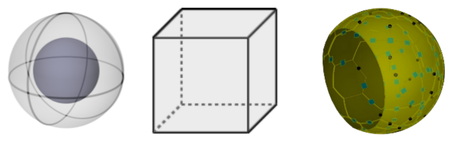
Biological systems typically show stochastic behavior as a consequence of single entities, like cells and molecules, acting and interacting individually. Their behavior depends mainly on their lifetime, position in space and activation status. Agent-based modeling allows for realistic simulation of such systems. Here, each entity (e.g. molecule or cell) is represented by one virtual object in the computer. Although this approach is memory intensive and computationally demanding it has the advantages of a low abstraction level and emergent bottom-up system behaviour in contrast, e.g. to differential equation models. We use agent-based modeling to model distinct interactions of human immune cells with different molecules and cellular species, such as the pathogenic fungi *Aspergillus fumigatus* and *Candida albicans*. Our predictions yield starting points for biological experiments in the interative cycle of systems biology.

Environment

- represents a defined space of the model

Properties

Morphology:

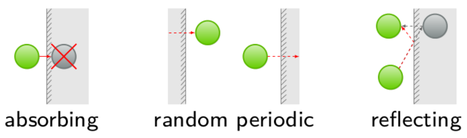


Medium:

isotropic diffusion equation with sources/sinks:

$$\frac{\partial c(\vec{r},t)}{\partial t} = D\Delta c(\vec{r},t) + Q(\vec{r},t)$$

Boundary condition:



Computational realisation:

- continuous space (off-lattice) method
- agent interaction detection by neighbor-lists within environment

Agents

- single entities (e.g. cells and molecules)
- present in the simulation environment
- act according to specific rules

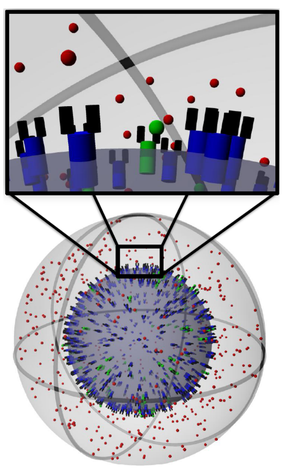
Properties	Molecular level (agent = molecule)	Cellular level (agent = cell)
Morphology	aggregated morphologies	spheric morphologies
Migration behavior	random walk	migration based on distributions of speed and direction
Behavioral rules: • single agent rules (action event) • multi-agent rules (interaction events)	binding, dissociation	killing, phagocytosis, chemokine uptake
Computational realisation:		
Simulation dynamics	next-reaction dynamics random selection dynamics	random selection dynamics

Receptor-Ligand Model

Introduction:

Molecular interactions between cellular receptors and soluble ligands lead to activating pattern formation on immune cells, e.g. immunological synapse on B and T-cells. The role of binding kinetics, spatial aspects of binding sites and multiple binding sites are important aspects in the formation of specific molecular patterns.

Model:



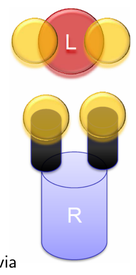
Input:

- receptor and ligand sizes, concentrations, diffusion constants (from literature)
- 2D-RL binding kinetics

Output:

- binding dynamics (time-evolution of complex and cluster formation)
- molecule distribution (cluster size and location)

Agents:



Ligands L
(spherical morphology)

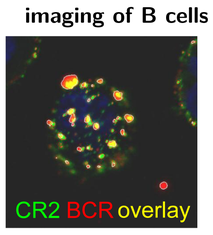
Receptors R
(two-arm morphology)

Complexes LR
(combined morphology)

Interactions:

Binding and dissociation via multiple binding domains on receptors and ligands

Automated image analysis of fluorescence microscopy imaging of B cells



Readout:

(1) Detecting size and area of

- B cell receptor (BCR) cluster (red)
- Complement Receptor Type 2 (CR2) cluster (green)
- overlay (yellow) of BCR and CR2

(2) Calculating the number of co-localization of CR2 and BCR

Aim:

- investigation of multiple binding sites
- investigation of BCR pattern formation mechanism during treatment of B cell inhibitory ligand
- image analysis results are used for model validation

A. fumigatus Infection Model in Human Alveoli

Introduction:

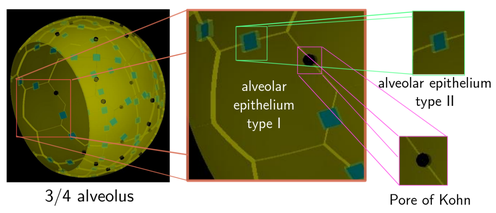
Alveoli are small gas-exchange units of the lung. They are the portal for environmental threats like the opportunistic human pathogenic fungus *A. fumigatus*. We model and simulate the early stages of *A. fumigatus* infection in human alveoli under physiological conditions.

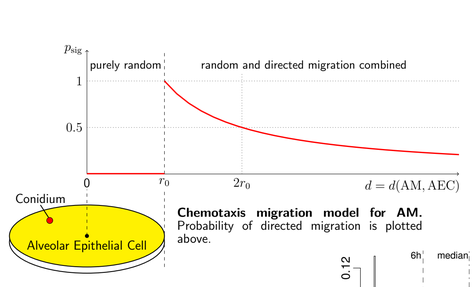
Model:

Agents:

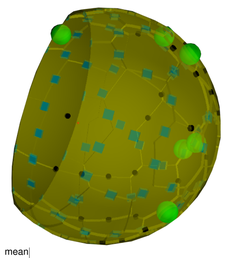
A. fumigatus

alveolar macrophage (AM)





Chemotaxis migration model for AM. Probability of directed migration is plotted above.

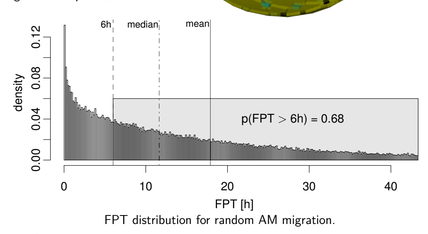


Simulation scenarios:

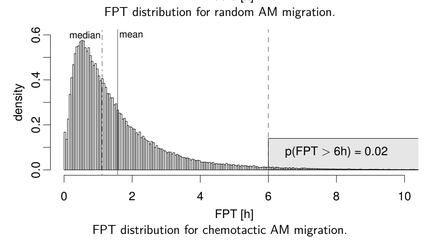
- random AM migration
- chemotactic AM migration

Readout:

- first-passage-time (FPT) distributions



FPT distribution for random AM migration.



FPT distribution for chemotactic AM migration.

Results:

- randomly migrating AM can not clear the infection before germination ($\sim$ 6 hrs)
- AM require chemotactic cues to find the pathogen before germination
- respiration induces only small changes in the FPT

3D Virtual Infection Model with *C. albicans*

Introduction:

Cellular interaction between the opportunistic fungal pathogen *C. albicans* and human immune cells is simulated using current insights from experimental and *in silico* whole-blood infection assays [1]. The spatial resolution enables to simulate and predict the unknown cellular migration behavior.

Model:

Agents:

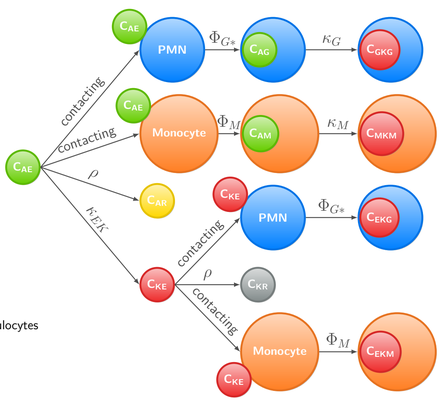
Candida albicans

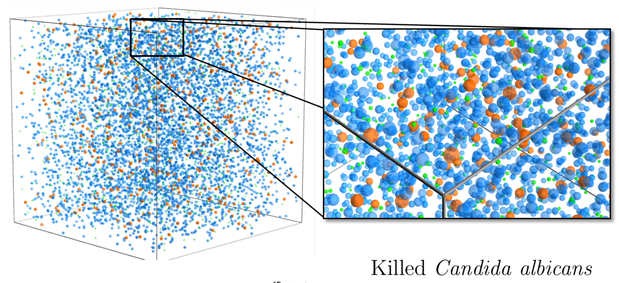
PMN

Monocyte

PMN = polymophonucleare neutrophilic granulocytes

Interactions:

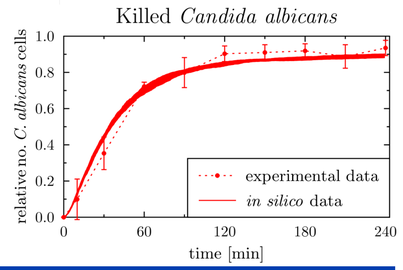




Input:

- experimentally determined cell sizes and cell amounts
- rates from a non-spatial virtual infection model [1]

Killed *Candida albicans*



Aim:

- investigation of cell migration/movement
- integration of molecule diffusion to investigate intercellular signalling

References

[1] Hünniger and Lehnert *et al.* *PLOS Comp. Biol.* **10**(2): e1003479 ,2014

Contact:
sandra.timme@hki-jena.de
johannes.pollmaecher@hki-jena.de
teresa.lehnert@hki-jena.de

Acknowledgements

This work was financially supported by the excellence graduate school Jena School for Microbial Communication (JSMC) and the CRC/TR124 FungiNet, Project B4, that are both funded by the Deutsche Forschungsgemeinschaft (DFG).

– FungiNet –

JSMC

Leibniz Association