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

Virtual Infection Models of *Candida albicans* in Whole Blood

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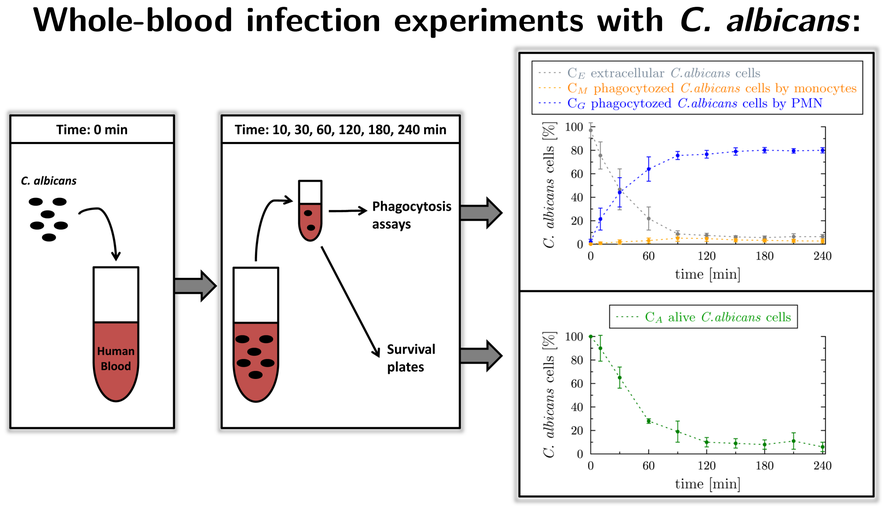
Immune Defense against *Candida albicans* in Human Whole-blood

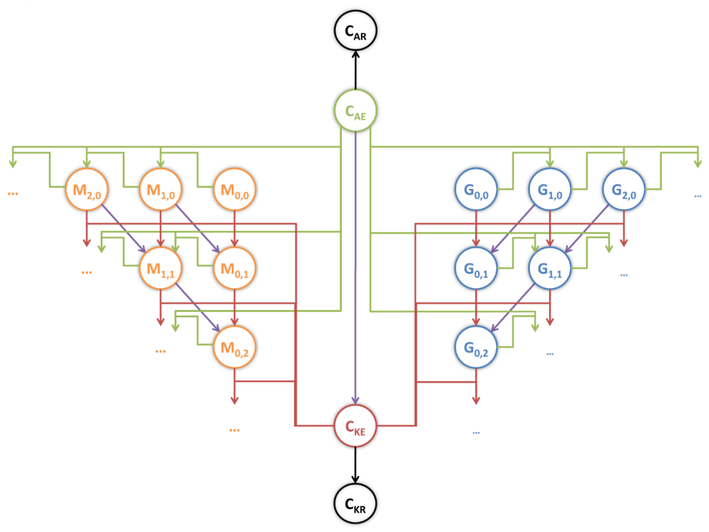
The opportunistic human fungal pathogen *Candida albicans* causes severe systemic infections such as bloodstream infections and is becoming an increasing clinical problem associated with a high mortality rate.
We quantified the different routes of immune response to *C. albicans* in human blood by developing a state-based virtual infection model that simulates the host-pathogen interaction using time resolved data of whole-blood infection assays.
Furthermore, we generated a spatial agent-based model that enables to investigate the migration behaviour of the host immune cells that respond to *C. albicans* in human whole-blood. This close-to-reality model yield predictions on currently not experimental accessible spatial motility parameter and enables further investigation of spatial dependent *C. albicans* killing mechanisms in human blood.

Whole-blood infection experiments with *C. albicans*:



State-based Virtual Infection Model

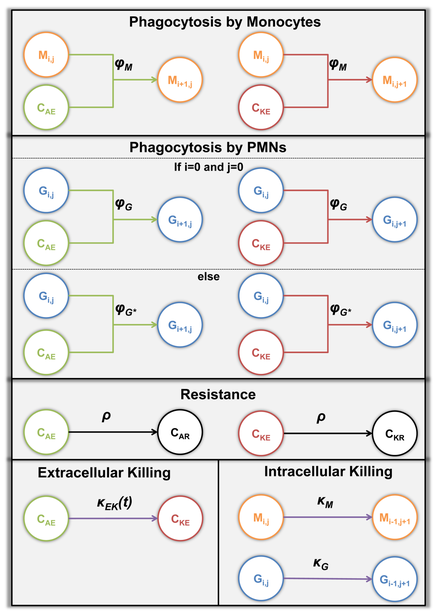
States and transitions



State types:

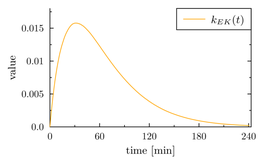
- C_{AE} .. free, alive yeast cells
- C_{KE} .. extracellularly killed yeast cells
- C_{AR} .. alive yeast cells that became resistant
- C_{KR} .. killed yeast cells that became resistant
- $G_{i,j}$ .. granulocytes with i alive and j killed yeast cells
- $M_{i,j}$ .. monocytes with i alive and j killed yeast cells

Transition rates:



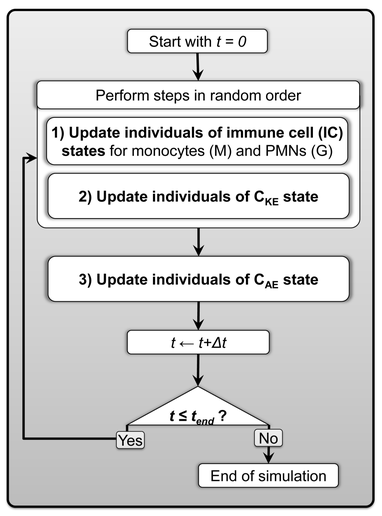
Extracellular killing

$$\kappa_{EK}(t = n\Delta t) = \bar{\kappa}_{EK} \sum_{m=0}^{n} \frac{N_{GP}(t = m\Delta t)}{G_{0,0}(0)} \exp(-\gamma \Delta t(n - m))$$



- $\bar{\kappa}_{EK}$ constant transition rate
- $N_{GP}(t)$ number of first-time phagocytosis events
- γ half-life time of the effect of antimicrobial factors

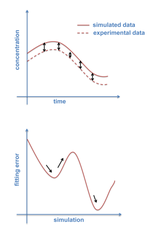
Simulation algorithm



Estimation of transition rate values

Simulated annealing based on Metropolis Monte-Carlo:

- explore parameter space
- compare simulated and experimental data
- always accept parameter values that improve fitting
- accept parameter values that impair fitting based on Boltzmann distribution

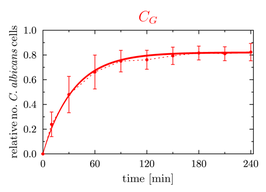


Resulting transition rates:

	rate	SD [%]		rate	SD [%]
ϕ_G	2.69 $\cdot 10^{-2}$ min^{-1}	1.24	κ_M	6.08 $\cdot 10^{-2}$ min^{-1}	6.64
ϕ_{G^*}	3.58 $\cdot 10^{-2}$ min^{-1}	5.24	κ_G	4.26 $\cdot 10^{-2}$ min^{-1}	4.76
ϕ_M	0.63$\cdot 10^{-2}$ min^{-1}	5.25	ρ	0.41 $\cdot 10^{-2}$ min^{-1}	3.25
γ	3.16 $\cdot 10^{-2}$ min^{-1}	6.8	$\bar{\kappa_{EK}}$	29.13 $\cdot 10^{-2}$ min^{-1}	4.93

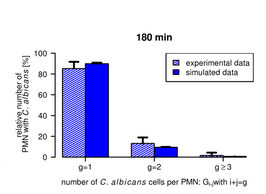
Predictions on Dynamics of Host-pathogens Interaction

Identifying the main route of immune response



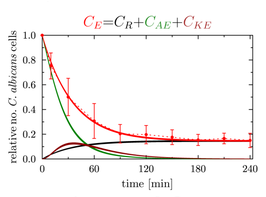
→ phagocytosis by PMN more probable than by monocytes

Determining the distribution of *C. albicans* in PMN



→ majority of PMN bear one fungus during infection time

Quantifying the immune escape of *C. albicans*



→ killing of *C. albicans* in human blood mainly mediated by PMN

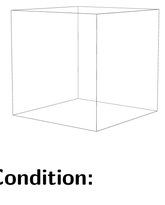
→ mechanism of *C. albicans* escape still under investigation

Agent-based Virtual Infection Model

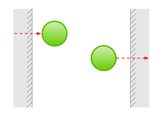
Environment

- spatio-temporal modeling

Structure:



Boundary Condition:



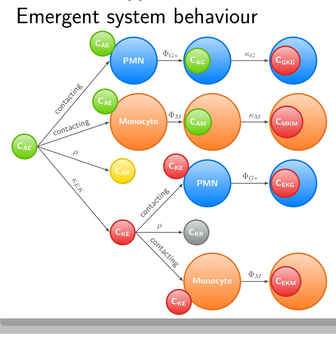
Agents

single entities = cells

Candida albicans: alive non-resistant, dead non-resistant, alive resistant, dead resistant; PMN; Monocyte

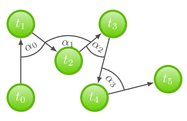
Interactions:

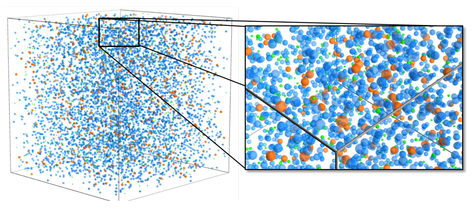
Rule-based approach
Emergent system behaviour



Movement:

e.g. Random Walk
Investigation of cell dynamics





Transformation of transition rates

Uniform Rates:

- rates of space-independent events
- $\rho, \kappa_G, \kappa_M, \kappa_{EK}$
- space-independent events should occur with **equal rate** in SBM and ABM

$$r_{ABM} \stackrel{!}{=} r_{SBM}$$

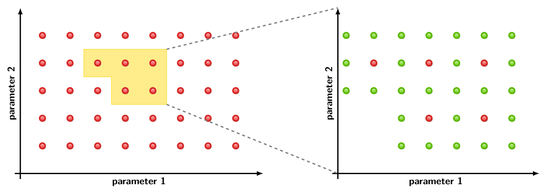
Space-dependent Rates:

- rates of space-dependent events
- $\Phi_G, \Phi_{G*}, \Phi_M \rightarrow$ phagocytosis depends on cell contacts
- space-dependent event should occur with **equal probability** in SBM and ABM

$$P_{ABM} \stackrel{!}{=} P_{SBM} \longrightarrow r_{ABM} = \frac{P_{SBM}}{\Delta t_{ABM}}$$

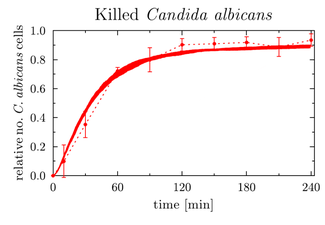
Estimation of movement rates

- ABM computational very expensive
- sparse approaches for parameter estimation
- Grid search approach with refinement levels



Results

- Transformation of transition rates and estimation movement rates enable an accurate fit to experimental data.
- Comparison of immune cell migration behaviour reveals that PMN are faster than monocytes.



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Outlook

In the future, we will investigate the spatial diffusion of antimicrobial factors in the agent-based model, by implementation of diffusing molecules that are released by immune cells. Furthermore, we are very interested in the identification of the escape mechanism of *C. albicans* in human as well as murine blood.

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