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Virtual Infection Models of Candida albicans in Whole Blood

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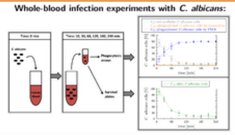
Immune Defense against *Candida albicans* in Human Whole-blood

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_{AF} – free, alive yeast cells
C_{EF} – extracellularly killed yeast cells
C_{AR} – alive yeast cells that became resistant
C_{ER} – killed yeast cells that became resistant
$G_{i,j}$ – granulocyte with i alive and j killed yeast cells
$M_{i,j}$ – monocyte with i alive and j killed yeast cells

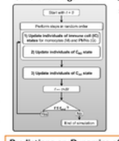
Transition rates:

Extracellular killing

$$\kappa_{EF}(t) = \kappa_{EF} \cdot \frac{N_{GM}(t) - n\Delta G}{G_{tot}(0)} \cdot \exp(-\gamma \Delta t (n-m))$$

κ_{EF} constant transition rate
$N_{GM}(t)$ 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:

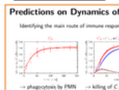
- explore parameter space
- compare simulated and experimental data
- always accept parameter values that improve fitting
- accept parameter values that impair fitting based on Boltzmann distribution

Resulting transition rates:

rate	SD [1]	rate	SD [1]
ϕ_G 2.69·10^{-2} min^{-1}	1.24	κ_{EF} 6.08·10^{-2} min^{-1}	6.64
ϕ_G 3.58·10^{-2} min^{-1}	5.24	κ_G 4.26·10^{-2} min^{-1}	4.76
ϕ_M 0.63·10^{-2} min^{-1}	5.25	μ 0.41·10^{-2} min^{-1}	3.25
γ 3.16·10^{-2} min^{-1}	6.8	κ_{EK} 29.13·10^{-2} min^{-1}	4.93

Predictions on Dynamics of Host-pathogens Interaction

Identifying the main route of immune response



→ phagocytosis by PMN is 3 times more than by monocytes

Determining the distribution of *C. albicans* in PMN

→ killing of *C. albicans* in PMN is 2 times higher mediated by PMN

Quantifying the immune escape of *C. albicans*

→ majority of PMN bear one fungus during infection time

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

Agent-based Virtual Infection Model

Environment

- spatio-temporal modeling

Structure:

Boundary Condition:

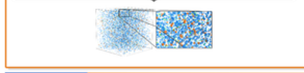
Agents

single entities → cells

Interactions:
Rule-based approach
Emergent system behaviour

Candida albicans PMN Monocyte

Movement:
e.g. Random Walk
Investigation of cell dynamics



Transformation of transition rates

Uniform Rates:

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

$$\tau_{SBM} = \tau_{ABM}$$

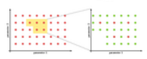
Space-dependent Rates:

- rates of space-dependent events
- $\theta_G, \psi_G, \psi_M \rightarrow$ phagocytosis depends on cell contacts
- space-dependent event should occur with **equal probability** in SBM and ABM

$$P_{ABM} = P_{SBM} \rightarrow \tau_{ABM} = \frac{P_{ABM}}{\Delta t_{ABM}}$$

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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