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

Simulation of Immune Cell Deficiencies in a State-Based Virtual Infection Model of Human Whole-Blood Assays for *Candida albicans*

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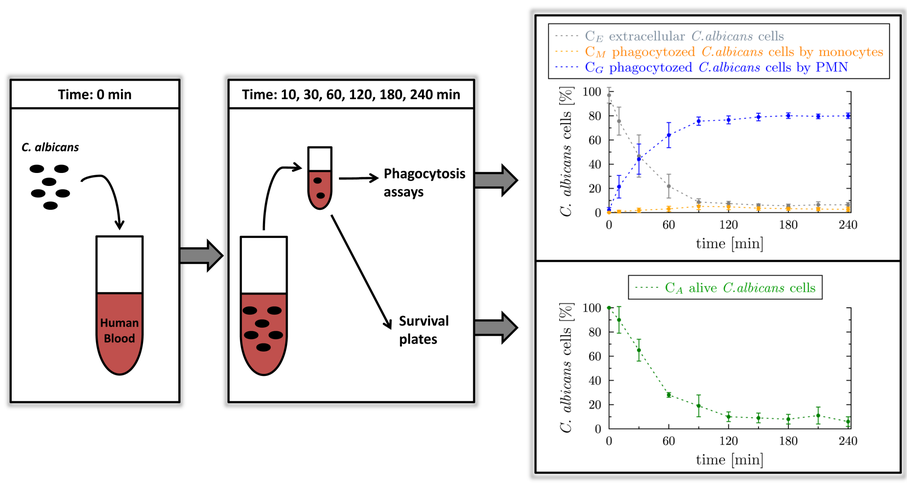
Human Whole-Blood Infection Assay

The opportunistic human fungal pathogen *Candida albicans* can enter the blood stream and causes severe systemic infections such as sepsis. Whole-blood infection assays with *C. albicans* yield time resolved data that were used to generate a non-spatial state-based virtual infection model and to estimate the model parameters [1]. Finally, we can quantify different non-spatial properties of the immune response against *C. albicans* in human blood.

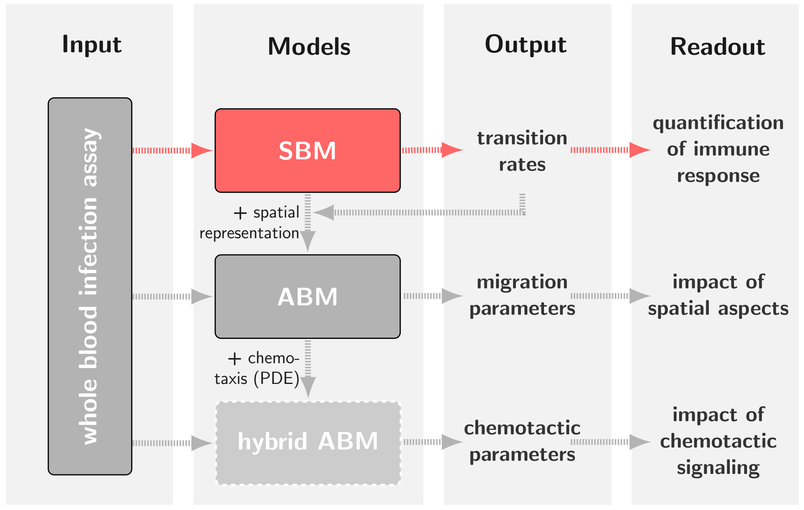
[1] Hünniger and Lehnert *et al.* (2014), *PLOS Comp. Biol.* 10(2), e1003479.



Bottom-up Modeling Approach

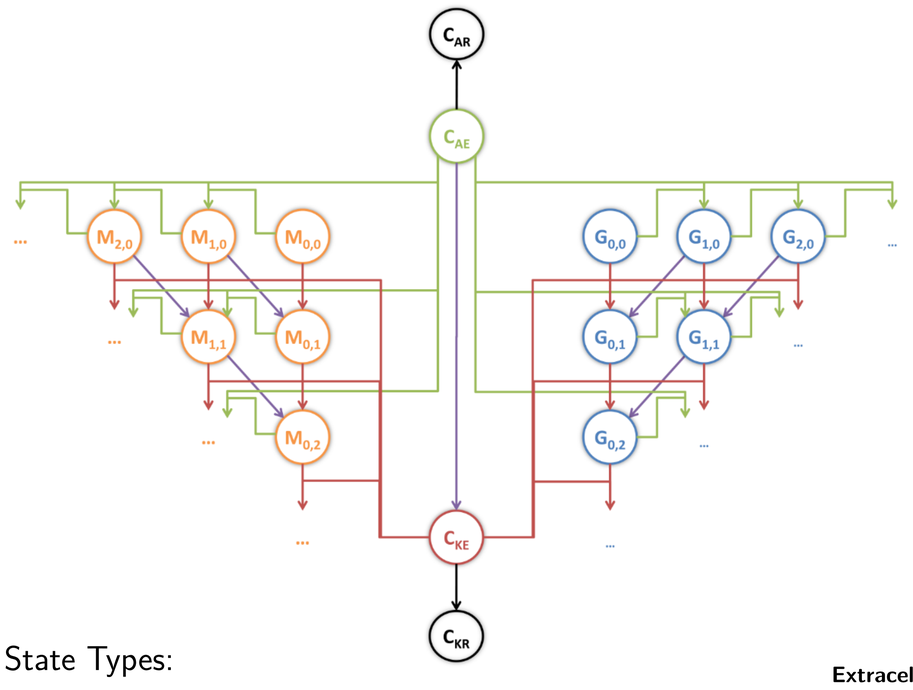
The non-spatial state-based model (SBM) is part of a bottom-up modeling approach that comprises the generation of different mathematical models and the estimation of model parameters [2]. The models focus on different properties of the immune response during *C. albicans* infection in human blood.

[2] Lehnert and Timme *et al.* (2015), *Frontiers in Microbiology* 6(608).



State-Based Virtual Infection Model

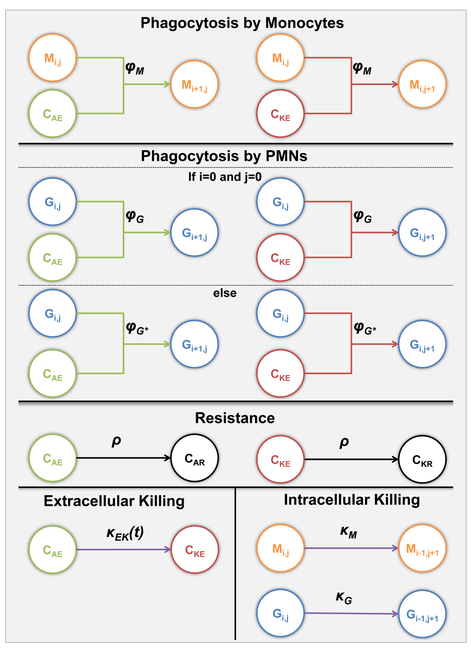
States and Transitions



State Types:

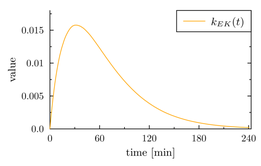
- C_{AE} = **extracellular, alive yeast cells**
- C_{KE} = **extracellularly killed yeast cells**
- C_{AR} = **alive yeast cells that became resistant**
- C_{KR} = **killed yeast cells that became resistant**
- $G_{i,j}$ = granulocytes with i alive and j killed yeast cells
- $M_{i,j}$ = monocytes with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

Transition Rates:



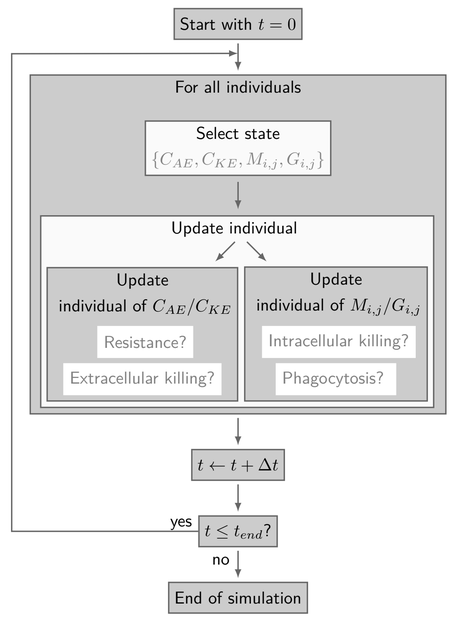
Extracellular Killing

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



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

Simulation Algorithm



Flow Chart of SBM Simulation Algorithm:

In each time-step Δt, all individuals are tested for possible state transitions. Individuals of extracellular alive and killed *C. albicans* states, *i.e.* C_{AE} and C_{KE}, respectively, are tested for becoming resistant and for extracellular killing. Individuals of immune cell states ($M_{i,j}$ or $G_{i,j}$) are tested for phagocytosis and for intracellular killing of *C. albicans* cells.

Parameter Estimation

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	2.83 $\cdot 10^{-2}$ min^{-1}	1.7	κ_M	3.59 $\cdot 10^{-2}$ min^{-1}	10.4
$\phi_{G^\star}$	4.75 $\cdot 10^{-2}$ min^{-1}	8.1	κ_G	4.69 $\cdot 10^{-2}$ min^{-1}	9.1
ϕ_M	1.25$\cdot 10^{-2}$ min^{-1}	5.9	ρ	0.45 $\cdot 10^{-2}$ min^{-1}	4.2
γ	1.93 $\cdot 10^{-2}$ min^{-1}	14.3	$\kappa_{\bar{EK}}$	26.07 $\cdot 10^{-2}$ min^{-1}	8.7

Prediction of Immune Cell Dynamics

Quantification of Immune Response

Predictions on Immune Cell Deficiencies

→ phagocytosis by PMN occurs with higher rate than by monocytes

→ killing of *C. albicans* in human blood is mainly mediated by PMN
PMN kill fungal cells intracellularly (C_{GKG}) and extracellularly (C_{EKG})

→ monocytopenia: lack of monocytes is completely compensated by PMN

→ neutropenia: lack of PMN can be compensated up to $5 \times 10^5 PMN/ml$
→ confirms threshold for severe clinical neutropenia

Outlook

- application to patient blood
- application to whole-blood infection with other pathogens and in other organisms

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