# M-9

## Simulation of Immune Cell Deficiencies in a State-based Virtual Infectin Model of Human Whole-blood Assays for Candida albicans

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

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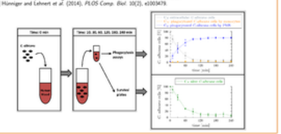
## Human Whole-Blood Infection Assay

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.



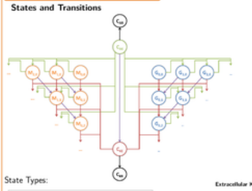

## Bottom-up Modeling Approach

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

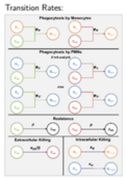
### States and Transitions



State Types:

- $C_{ai}$ = extracellular, alive yeast cells
- $C_{ki}$ = extracellularly killed yeast cells
- $C_{iai}$ = alive yeast cells that became resistant
- $C_{iki}$ = killed yeast cells that became resistant
- $G_{ij}$ = granulocytes with $i$ alive and $j$ killed yeast cells
- $M_{ij}$ = monocytes with $i$ alive and $j$ killed yeast cells

Transition Rates:

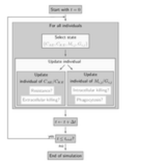



Extracellular Killing

$$\nu_{\mathbf{EK}}(t + n\Delta t) = \kappa_{EK} \frac{\sum_{m=0}^{n} N_{ai}(t + m\Delta t)}{C_{ai0}(0)} \exp(-\gamma \Delta t (n - m))$$

- $\kappa_{EK}$ constant transition rate
- $N_{ai}(t)$ number of first-time phagocytosis events
- half-life time of the effect of antimicrobial factors

### Simulation Algorithm




Flow Chart of SBM Simulation Algorithm:

In each time-step $\Delta t$, all individuals are tested for possible state transitions. Individuals of extracellular alive and killed *C. albicans* states, i.e. $C_{ai}$ and $C_{ki}$, respectively, are tested for becoming resistant and for extracellular killing. Individuals of immune cell states ($M_{ij}$ or $G_{ij}$) 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:**

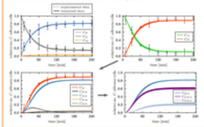
- explore parameter space
- compare simulated and experimental data
- always accept parameter values that improve fitting
- accept parameter values that impair fitting based on Boltzmann distribution

**Resulting Transition Rates:**

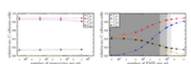
| | rate | SD [%] | | rate | SD [%] |
|---|---|---|---|---|---|
| $\phi_{ki}$ | $2.83 \cdot 10^{-2}\ min^{-1}$ | 1.7 | $\kappa_{iki}$ | $3.59 \cdot 10^{-2}\ min^{-1}$ | 10.4 |
| $\phi_{iki}$ | $4.75 \cdot 10^{-2}\ min^{-1}$ | 8.1 | $\kappa_{EK}$ | $4.69 \cdot 10^{-2}\ min^{-1}$ | 9.1 |
| $\phi_{iki}$ | $1.25 \cdot 10^{-2}\ min^{-1}$ | 5.9 | $\mu$ | $0.45 \cdot 10^{-2}\ min^{-1}$ | 4.2 |
| $\gamma$ | $1.93 \cdot 10^{-2}\ min^{-1}$ | 14.3 | $\kappa_{IEK}$ | $26.07 \cdot 10^{-2}\ min^{-1}$ | 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 ($C_{iki}$) and extracellularly ($C_{ki}$)
→ monocytopenia: lack of monocytes is completely compensated by PMN
→ neutropenia: lack of PMN can be compensated up to $5 \times 10^3 PMN/ml$
→ 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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