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Virtual infection model of the immune response against Candida albicans in human whole-blood assay

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Virtual infection model of the immune response against *Candida albicans* in human whole-blood assays

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Motivation

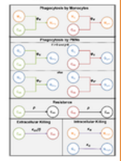
The opportunistic human fungal pathogen *Candida albicans* causes severe systemic infections such as bloodstream infections and is becoming an increasing clinical problem associated with a high mortality rate.
We quantified the different routes of immune response to *C. albicans* in human blood by developing a virtual infection model that simulates the host-pathogen interaction using time resolved data of whole-blood infection assays.

Virtual Infection Model

Virtual infection model defined as a state based model

States and transitions:

Transition rates:



State types:

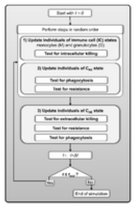
C_{ff} – free, alive yeast cells
C_{fd} – extracellularly killed yeast cells
C_{rf} – alive yeast cells that became resistant
C_{rd} – killed yeast cells that became resistant
$G_{i,j}$ – granulocyte with i alive and j killed yeast cells
$M_{i,j}$ – monocytes with i alive and j killed yeast cells

Extracellular killing

$$\kappa_{EK}(t) = n\Delta t(1-\kappa_{EK}\sum_{m=0}^{\frac{t}{\Delta t}}\frac{N_{ff}(t-m\Delta t)}{N_{ff}(0)}\exp(-\gamma\Delta t(n-m)))$$

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

Simulation algorithm



Estimation of transition rate values

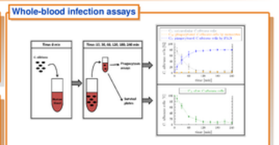
Simulated annealing based on Metropolis Monte-Carlo:

- 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:

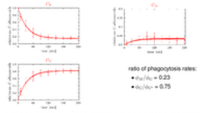
rate	standard deviation [%]
ϕ_{Ki} 2.69 $\cdot 10^{-2}$ min^{-1}	1.24
ϕ_{Kd} 3.58 $\cdot 10^{-2}$ min^{-1}	5.24
ϕ_{rf} 0.63 $\cdot 10^{-2}$ min^{-1}	5.25
κ_{EK} 6.08 $\cdot 10^{-2}$ min^{-1}	6.64
κ_{IK} 4.26 $\cdot 10^{-2}$ min^{-1}	4.76
ρ 0.41 $\cdot 10^{-2}$ min^{-1}	3.25
γ 3.16 $\cdot 10^{-2}$ min^{-1}	6.8
κ_{EK} 29.13 $\cdot 10^{-2}$ min^{-1}	4.93

Whole-blood infection assays



Predictions on Dynamics of Host-pathogen Interaction

Identifying the main route of immune response



ratio of phagocytosis rates:
- ϕ_{Ki}/ϕ_{Kd} = 0.23
- ϕ_{ri}/ϕ_{rf} = 0.75

→ phagocytosis by PMN more probable than by monocytes

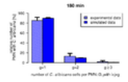
killing of *C. albicans*:
- 67.3% in PMN
- 30.0% in extracellular space
- 2.7% in monocytes

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

Determining the distribution of *C. albicans* in PMN

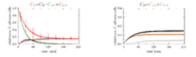
Manual evaluation of microscopy images

C. albicans in PMN



→ majority of PMN bear one fungus during infection time

Quantifying the immune escape of *C. albicans*



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

Outlook

In the future, we will simulate neutropenia for comparison to experiments with blood of neutropenia patients. Furthermore, we are very interested in the identification of the escape mechanism of *C. albicans* in human blood.

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