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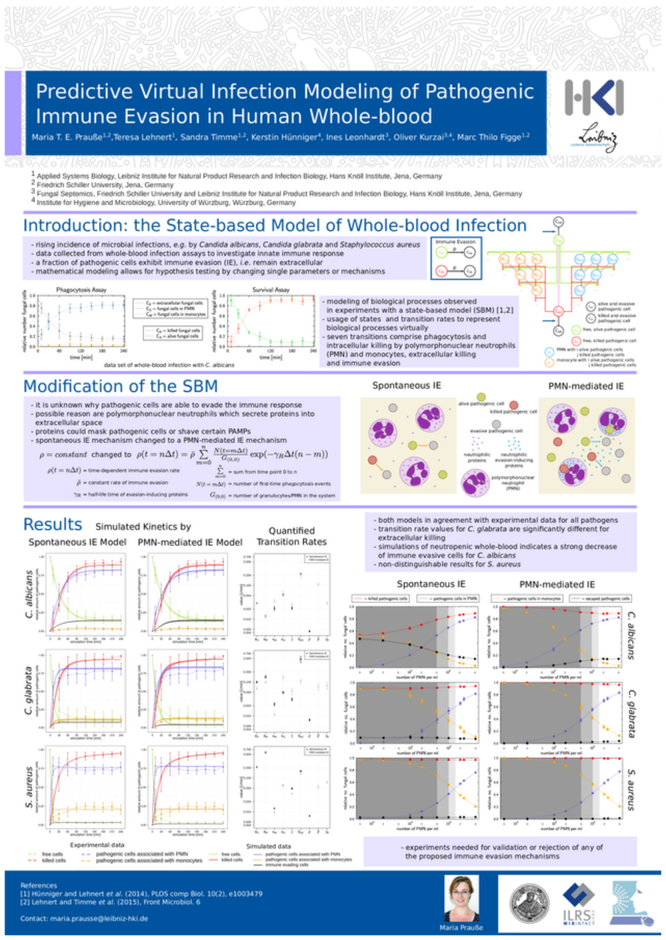

Predictive Virtual Infection Modeling of Pathogenic Immune Evasion in Human Whole-blood

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Introduction: the State-based Model of Whole-blood Infection

- rising incidence of microbial infections, *e.g.* by *Candida albicans*, *Candida glabrata* and *Staphylococcus aureus*
- data collected from whole-blood infection assays to investigate innate immune response
- a fraction of pathogenic cells exhibit immune evasion (IE), *i.e.* remain extracellular
- mathematical modeling allows for hypothesis testing by changing single parameters or mechanisms

Immune Evasion

Phagocytosis Assay

Survival Assay

data set of whole-blood infection with *C. albicans*

- modeling of biological processes observed in experiments with a state-based model (SBM) [1,2]
- usage of states and transition rates to represent biological processes virtually
- seven transitions comprise phagocytosis and intracellular killing by polymorphonuclear neutrophils (PMN) and monocytes, extracellular killing and immune evasion

Modification of the SBM

- it is unknown why pathogenic cells are able to evade the immune response
- possible reason are polymorphonuclear neutrophils which secrete proteins into extracellular space
- proteins could mask pathogenic cells or shave certain PAMPs
- spontaneous IE mechanism changed to a PMN-mediated IE mechanism

$\rho = constant$ changed to $\rho(t = n\Delta t) = \bar{\rho} \cdot \sum_{m=0}^{n} \frac{N(t=m\Delta t)}{G_{(0,0)}} \exp(-\gamma_R \Delta t(n-m))$

$\rho(t = n\Delta t)$ = time-dependent immune evasion rate
$\bar{\rho}$ = constant rate of immune evasion
γ_R = half-life time of evasion-inducing proteins
$\sum_{m=0}^{n}$ = sum from time point 0 to n
$N(t = m\Delta t)$ = number of first-time phagocytosis events
$G_{(0,0)}$ = number of granulocytes/PMN in the system

Spontaneous IE

PMN-mediated IE

Results

Simulated Kinetics by

Spontaneous IE Model | PMN-mediated IE Model | Quantified Transition Rates

C. albicans, *C. glabrata*, *S. aureus*

Experimental data | Simulated data

- both models in agreement with experimental data for all pathogens
- transition rate values for *C. glabrata* are significantly different for extracellular killing
- simulations of neutropenic whole-blood indicates a strong decrease of immune evasive cells for *C. albicans*
- non-distinguishable results for *S. aureus*

Spontaneous IE | PMN-mediated IE

- experiments needed for validation or rejection of any of the proposed immune evasion mechanisms

References
[1] Hünniger and Lehnert *et al.* (2014), PLOS comp Biol. 10(2), e1003479
[2] Lehnert and Timme *et al.* (2015), Front Microbiol. 6

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