Predictive Virtual Infection Modeling of Fungal Immune Evasion in Human Whole Blood

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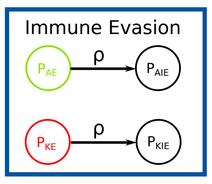
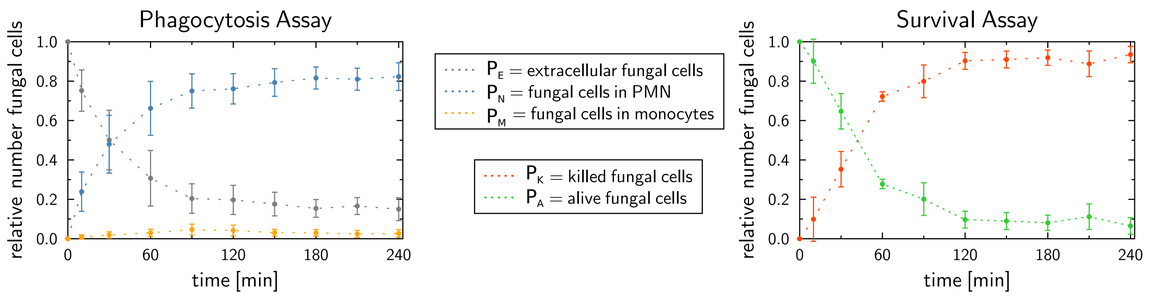
Introduction: the State-based Model of Whole-blood Infection

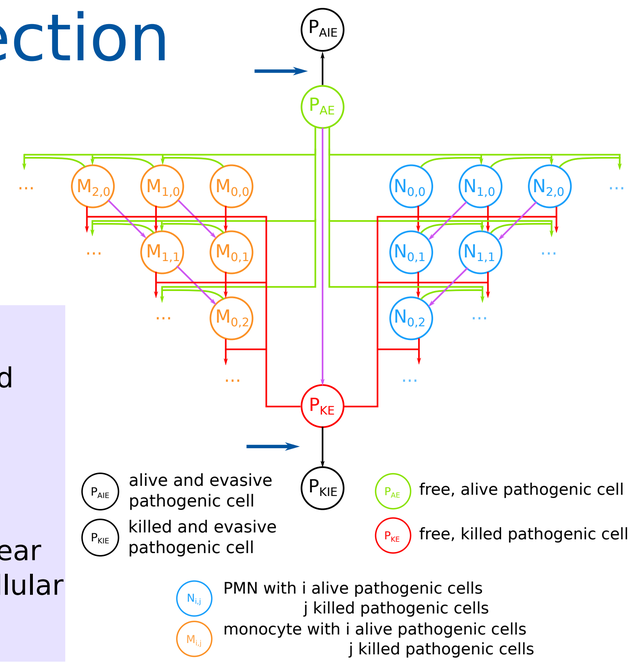
- rising incidence of microbial infections, *e.g.* by *Candida albicans* and *Candida glabrata*
- data collected from whole-blood infection assays to investigate innate immune response
- a fraction of pathogenic cells exhibit immune evasion (IE), *i.e.* remain extracellular
- mathematical modeling allows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





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



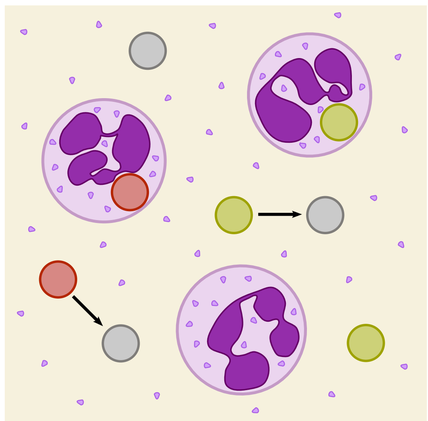
Modification of the SBM

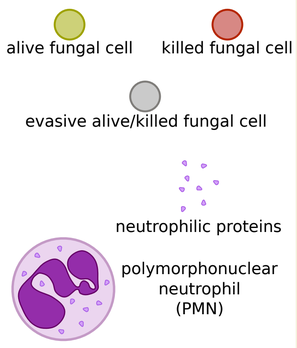
- it is unknown why pathogenic cells are able to evade the immune response
- possible reason are polymorphonuclear neutrophils which secrete proteins into extracellular space
- proteins could mask pathogenic cells or shave certain PAMPs
- spontaneous IE mechanism changed to a PMN-mediated IE mechanism

$$\rho = constant \text{ changed to } \rho(t = n\Delta t) = \bar{\rho} \sum_{m=0}^{n} \frac{N_{NP}(t' = m\Delta t)}{PMN_{(0,0)}(0)} \exp(-\gamma_R \Delta t(n-m))$$

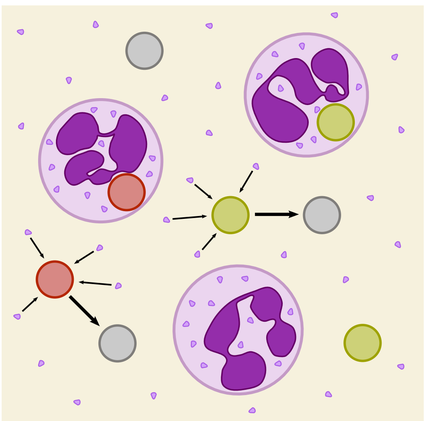
$\rho(t = n\Delta t)$ = time-dependent immune evasion rate
$\bar{\rho}$ = constant rate of immune evasion
$-\gamma_R$ = half-life time of evasion-inducing proteins
$\sum_{m=0}^{n}$ = sum from time point 0 to n
$N_{NP}(t' = m\Delta t)$ = number of first-time phagocytosis events
$PMN_{(0,0)}(0)$ = number of neutrophils/PMN in the system

Spontaneous IE



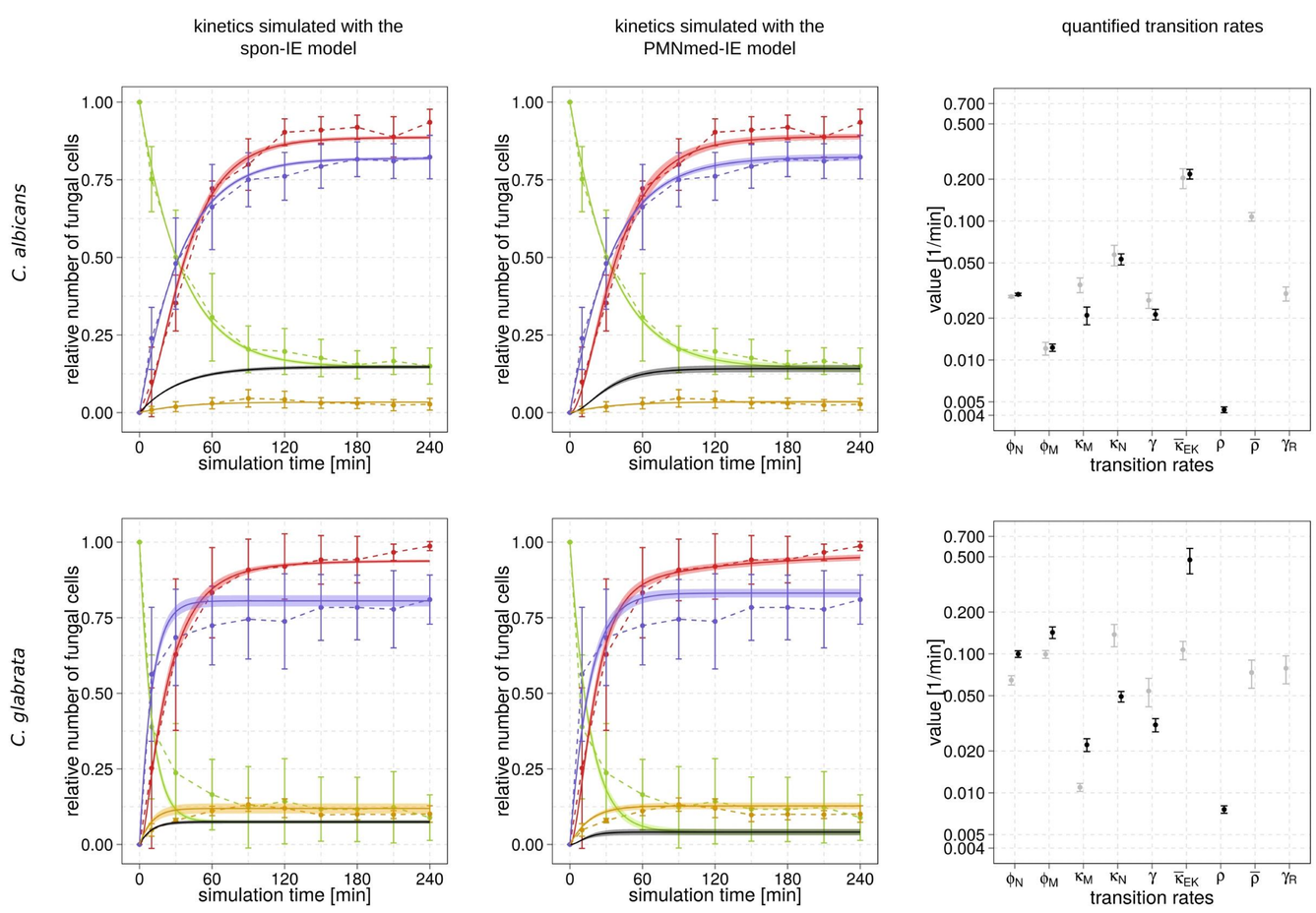


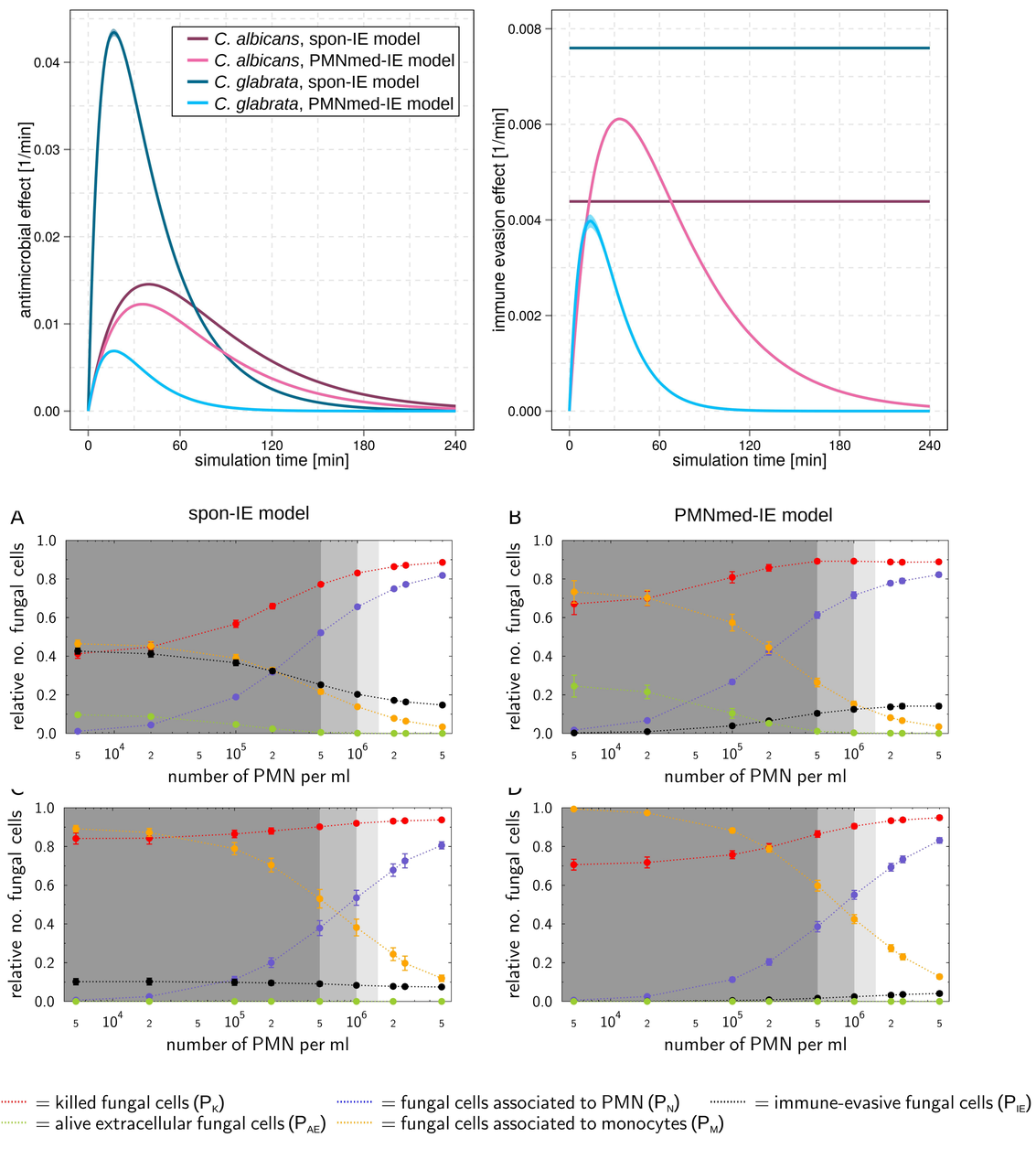
PMN-mediated IE



Results

- both models in agreement with experimental data for both pathogens
- transition rate values for *C. glabrata* are significantly different for extracellular killing
- antimicrobial effect peaks at a 3 times higher value for *C. glabrata* than for *C. albicans* in the spon-IE model
- simulations of neutropenic whole-blood indicates a strong decrease of immune-evasive cells for *C. albicans*





- proposal of future experiments for validation or rejection of any of the two 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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