Verifying Hypotheses on Immune Evasion by Pathogens in Human Whole Blood by State-based Virtual Infection Models

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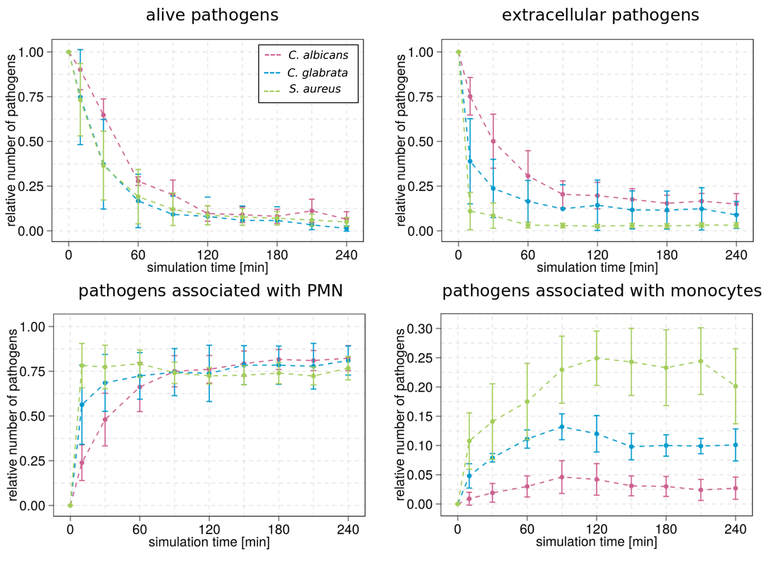
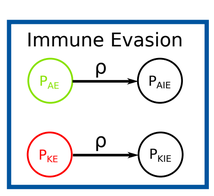
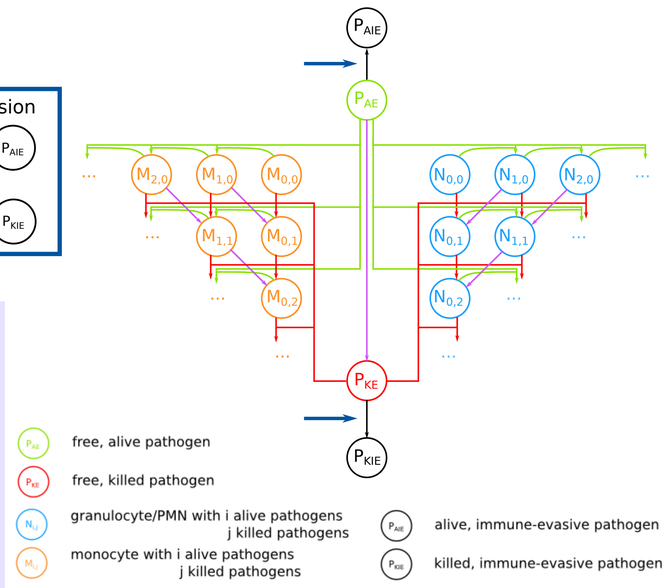
Introduction: the State-based Model of Whole-blood Infection



- rising incidence of microbial infections *e.g.*
  Candida albicans, Candida glabrata, Staphylococcos aureus
- data collected from whole-blood infection assays
- fraction of pathogenic cells exhibit immune evasion (IE)
- mathematical modeling allows for hypothesis testing



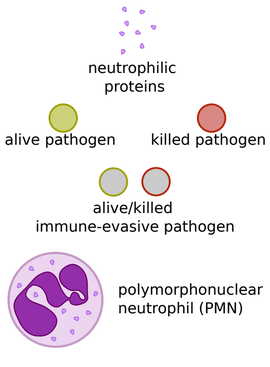
- modeling of biological processes observed
  in experiments with a state-based model (SBM) [1,2]
- usage of states and transition rates to represent
  biological processes virtually
- transitions comprise phagocytosis and
  intracellular killing by polymorphonuclear neutrophils (PMN)
  and monocytes, extracellular killing and immune evasion (ρ)
- new model: calibration of start population of alive
  imme-evasive pathogens (P_{AIE})

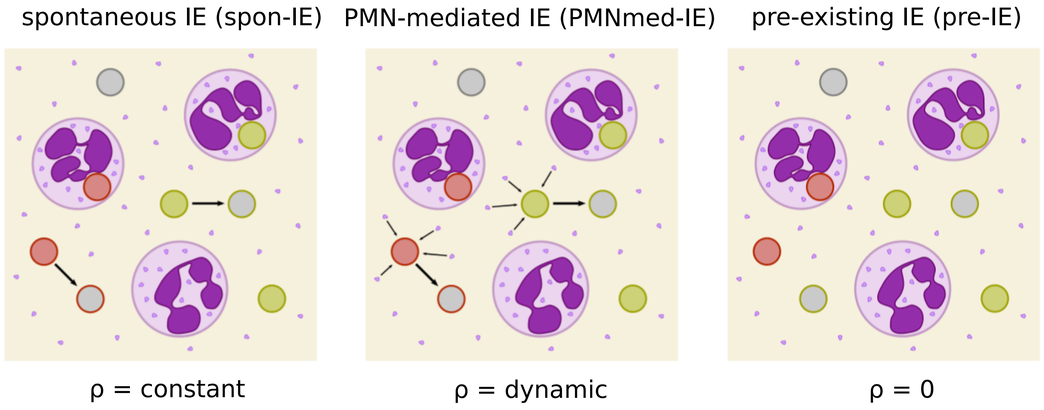


Modification of the SBM

- unknown why pathogenic cells are able to evade the immune response
- alternative IE mechanisms investigated: PMN-mediated IE or pre-existing IE
- possible reasons:
  - polymorphonuclear neutrophils secrete proteins into extracellular space [3]
  - immune-evasive state was acquired before infection
- all combinations tested for agreement with data

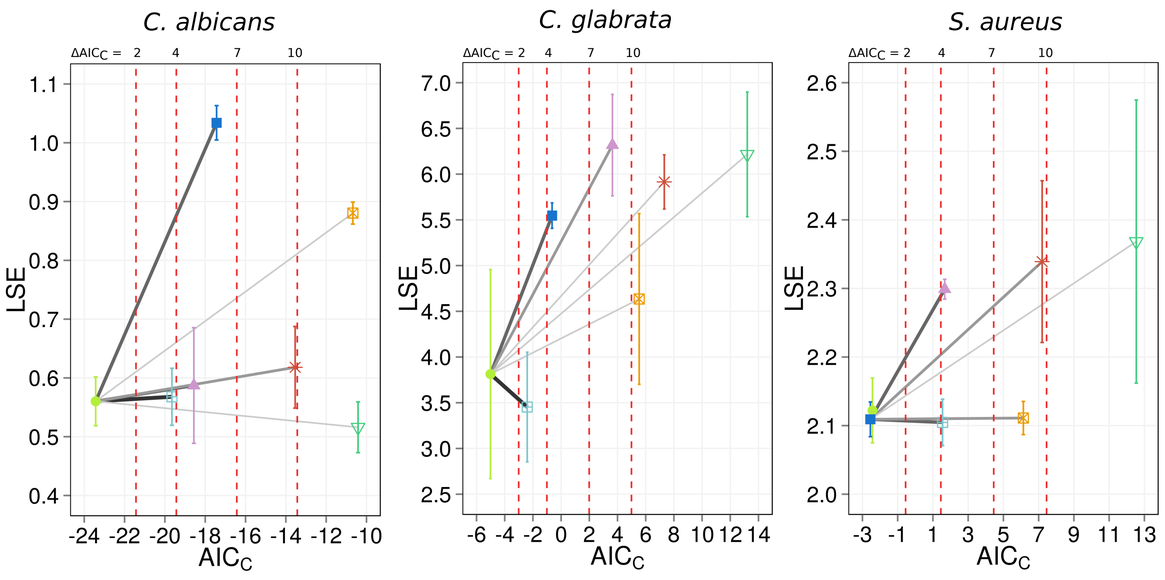
single mechanism: spon-IE, PMNmed-IE, pre-IE (base models)
two mechanisms: pre-spon-IE, pre-PMNmed-IE, spon-PMNmed-IE (combined models)
three mechanisms: pre-spon-PMNmed-IE (combined models)

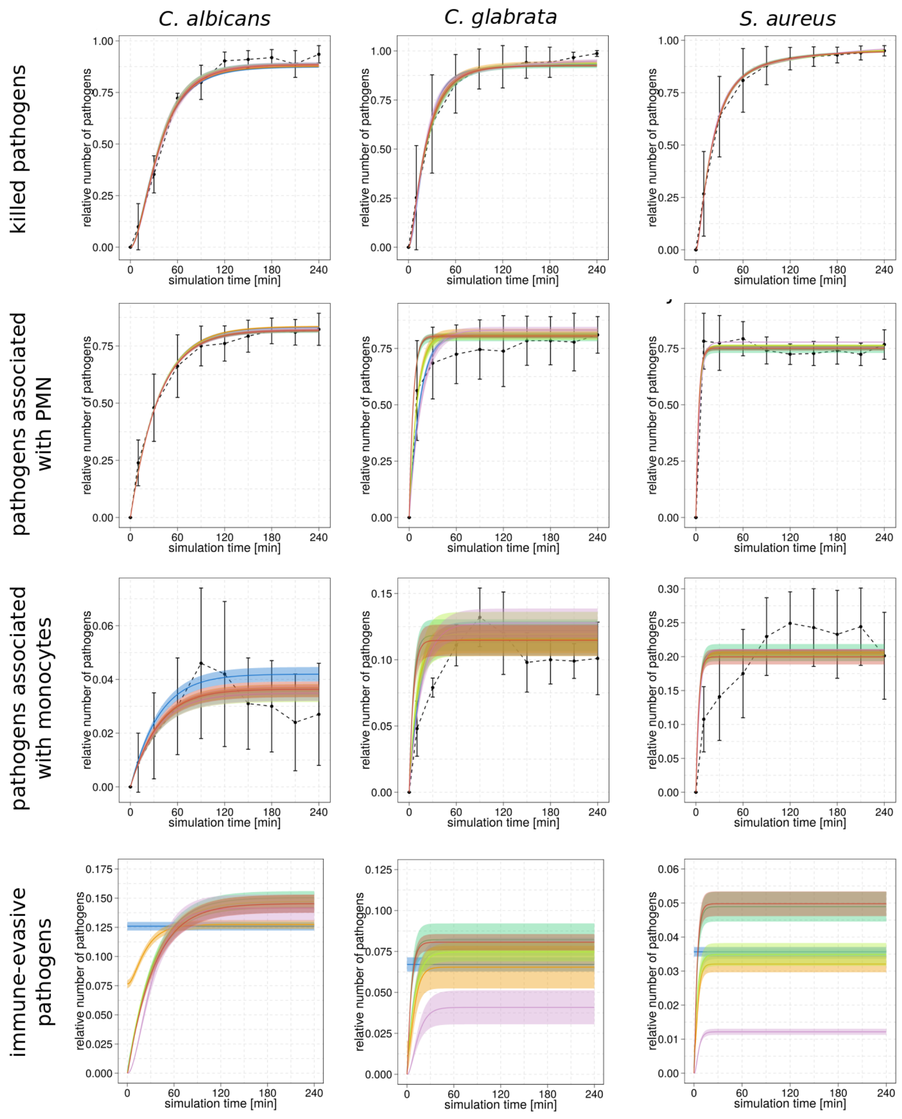




Results

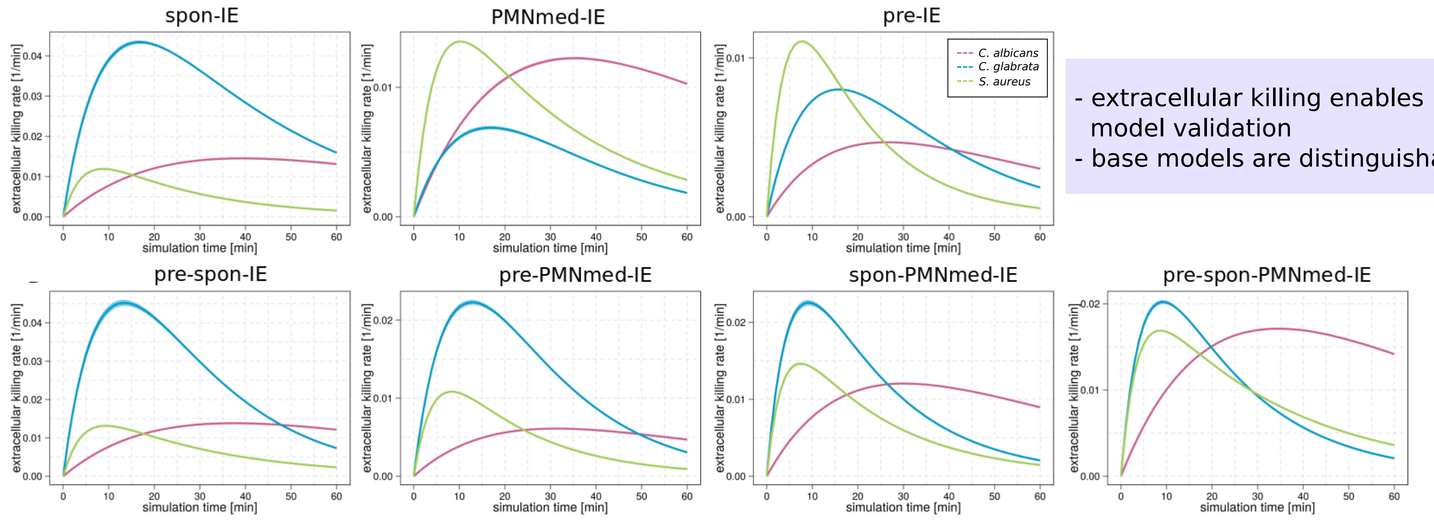
- all base and combined models in agreement with experimental data for the pathogens
- often minor differences in predicted fraction of immune-evasive cells
- evaluation with the help of the Akaike Information Criterion (AIC_C)
  - takes into account: number of parameters and least-squared error (LSE)
  - spon-IE and pre-IE model favored, closely followed by pre-spon-IE model





models
colors and symbols
- spon-IE
- PMNmed-IE
- pre-IE
- pre-spon-IE
- pre-PMNmed-IE
- spon-PMNmed-IE
- pre-spon-PMNmed-IE

model support granted by AIC_C
- $\Delta AICC \leq 2$ substantial support
- $2 < \Delta AIC_C < 4$ good support
- $4 \leq \Delta AIC_C \leq 7$ considerably less support
- $7 < \Delta AIC_C < 10$ little support
- $\Delta AIC_C > 10$ essentially no support



- extracellular killing enables
  model validation
- base models are distinguishable

- prediction of immune evasion rate shows differences between models
- future experiments for model validation
  - measuring antimicrobial proteins for comparison with simulated results

References
[1] Hünniger and Lehnert *et al.* (2014), PLOS comp Biol. 10(2), e1003479
[2] Lehnert and Timme *et al.* (2015), Front Microbiol. 6
[3] Prauße *et al.* (2018), Frontiers in Immunology.

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