

Bottom-up modeling approach for the quantitative estimation of parameters in pathogen-host interactions.

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Abstract

Opportunistic fungal pathogens can cause bloodstream infection and severe sepsis upon entering the blood stream of the host. The early immune response in human blood comprises the elimination of pathogens by antimicrobial peptides and innate immune cells, such as neutrophils or monocytes. Mathematical modeling is a predictive method to examine these complex processes and to quantify the dynamics of pathogen-host interactions. Since model parameters are often not directly accessible from experiment, their estimation is required by calibrating model predictions with experimental data. Depending on the complexity of the mathematical model, parameter estimation can be associated with excessively high computational costs in terms of run time and memory. We apply a strategy for reliable parameter estimation where different modeling

approaches with increasing complexity are used that build on one another. This bottom-up modeling approach is applied to an experimental human whole-blood infection assay for *Candida albicans*. Aiming for the quantification of the relative impact of different routes of the immune response against this human-pathogenic fungus, we start from a non-spatial state-based model (SBM), because this level of model complexity allows estimating *a priori* unknown transition rates between various system states by the global optimization method simulated annealing. Building on the non-spatial SBM, an agent-based model (ABM) is implemented that incorporates the migration of interacting cells in three-dimensional space. The ABM takes advantage of estimated parameters from the non-spatial SBM, leading to a decreased dimensionality of the parameter space. This space can be scanned using a local optimization approach, i.e. least-squares error estimation based on an adaptive regular grid search, to predict cell migration parameters that are not accessible in experiment.

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Topics

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