

MuMoSim: Machine Learning Supported Multi-Model Simulator for Infection Research

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Abstract

- Novel quantitative and predictive simulation tool in infection research modeling
- Multi-model approach: combination of different modeling techniques of increasing complexity within a single framework
- Integration of different experimental data types: flow cytometric analyses, pathogen survival assay, proteomics data, microscopy data
- Application to difficult-to-treat infections for predicting efficient treatment strategies

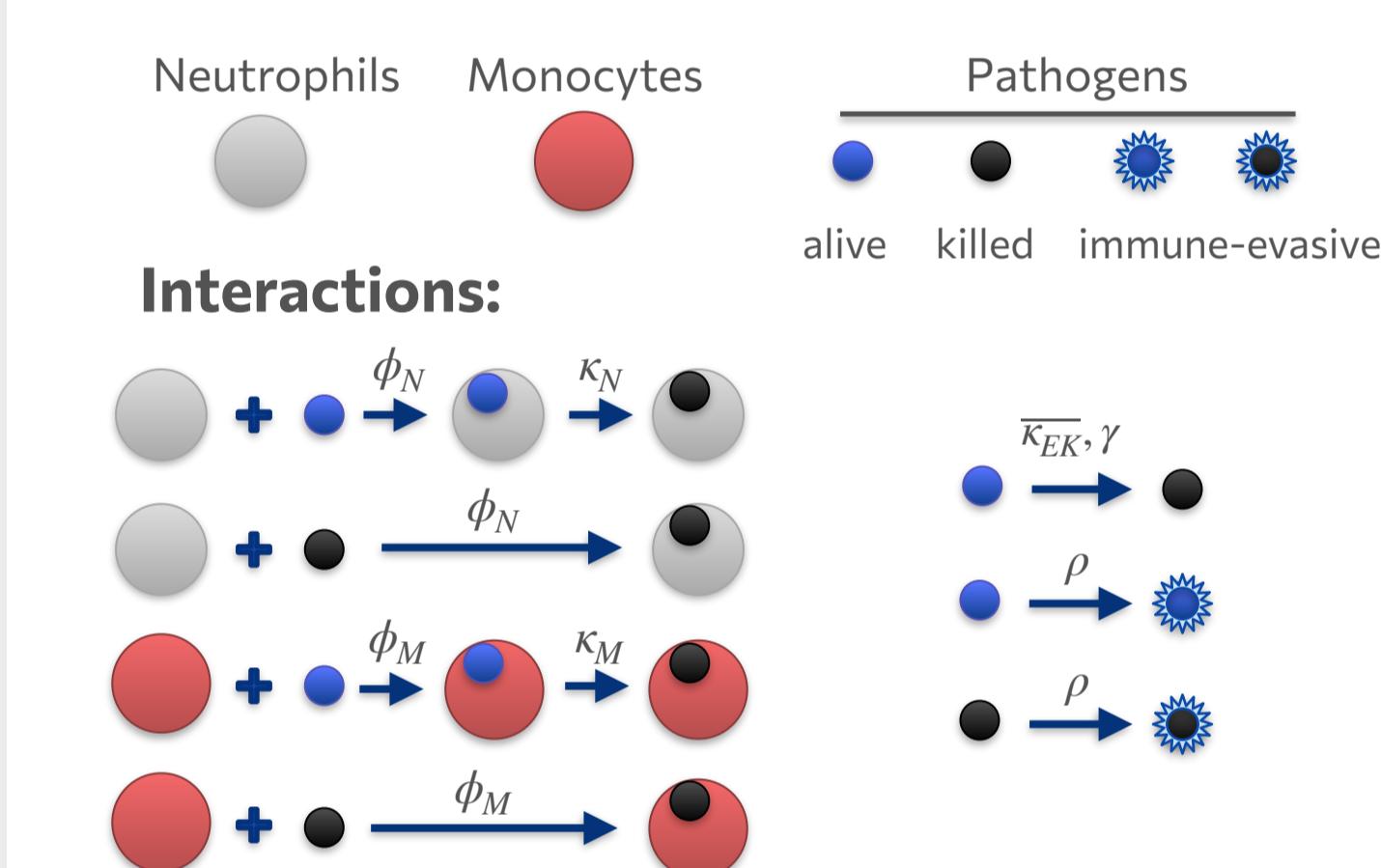
Systemic fungal infections

- *Candida albicans* is a major cause of nosocomial systemic infections
- Patients with neutropenia and under immunosuppressive therapy are at high risk for an infection
- Two main routes to enter the bloodstream:

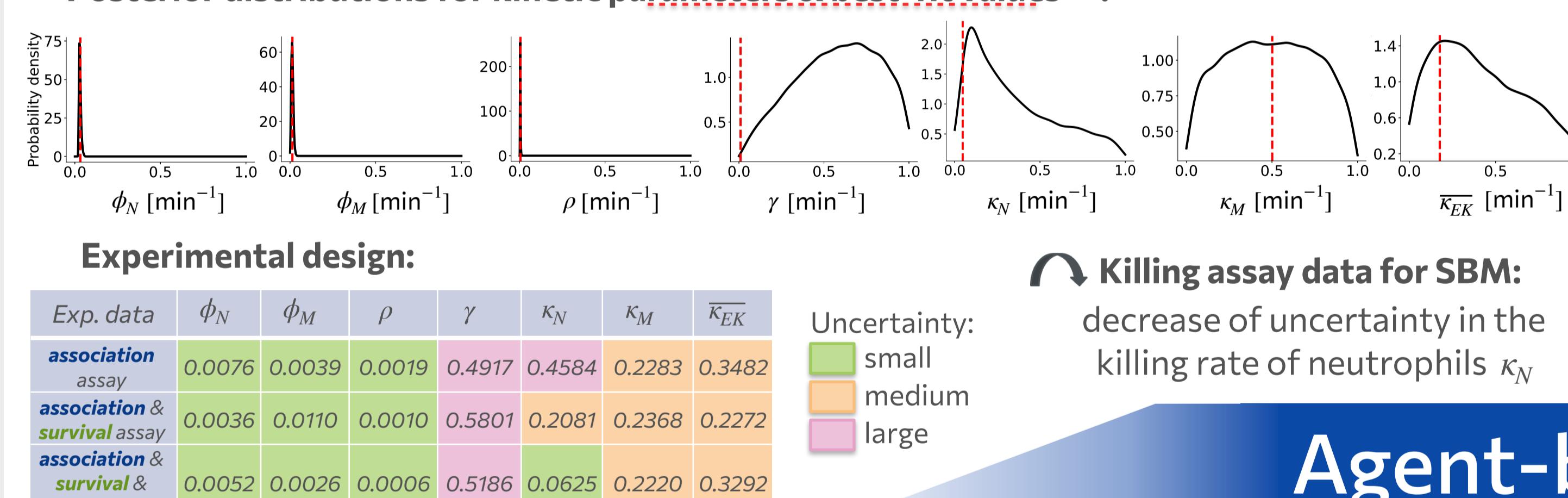


State-based model

- Stochastic temporal model
- Well-mixed environment



Posterior distributions for kinetic parameters & best-fit values^[3]:



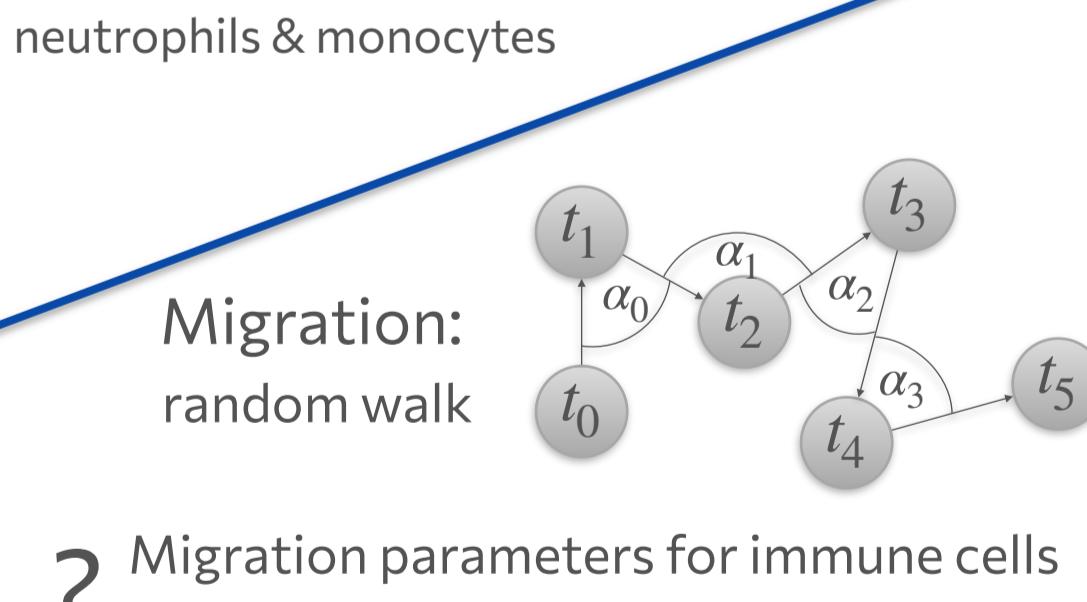
Experimental design:

Exp. data	ϕ_N	ϕ_M	ρ	γ	κ_N	κ_M	κ_EK
association assay	0.0076	0.0039	0.0079	0.4917	0.4584	0.2283	0.3482
association & survival assay	0.0036	0.0110	0.0010	0.5801	0.2081	0.2368	0.2272
association & survival & killing assay	0.0052	0.0026	0.0006	0.5186	0.0625	0.2220	0.3292

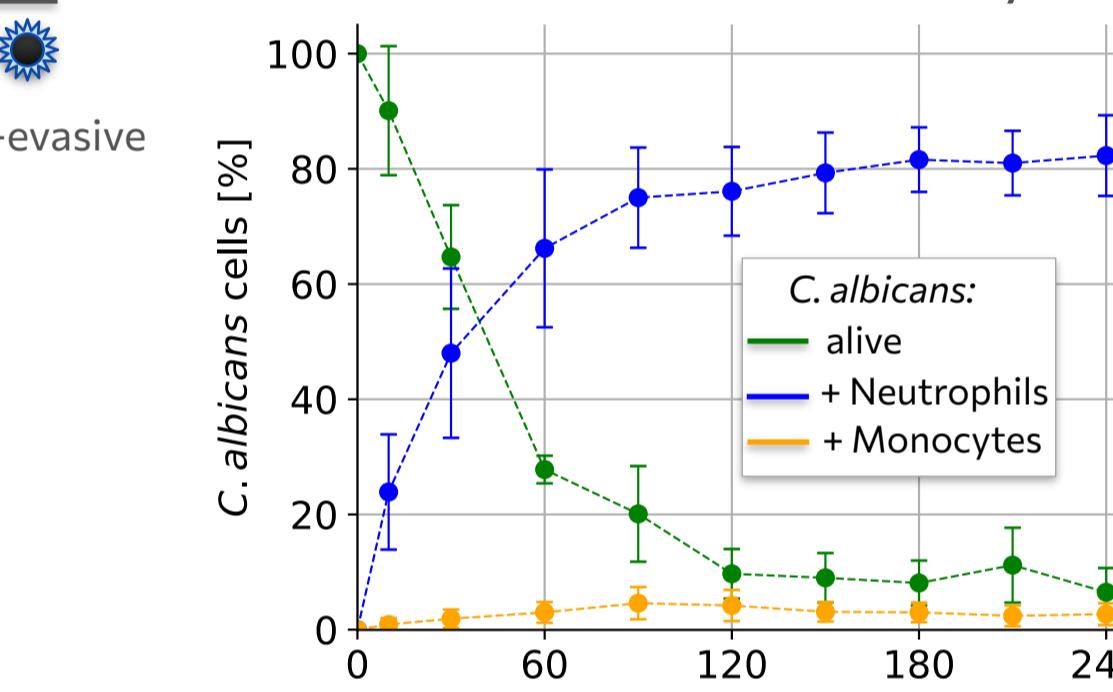
• Posterior distributions vs. the ground truth

• Wasserstein distance used as a metric

Killing assay: % pathogens killed by neutrophils & monocytes

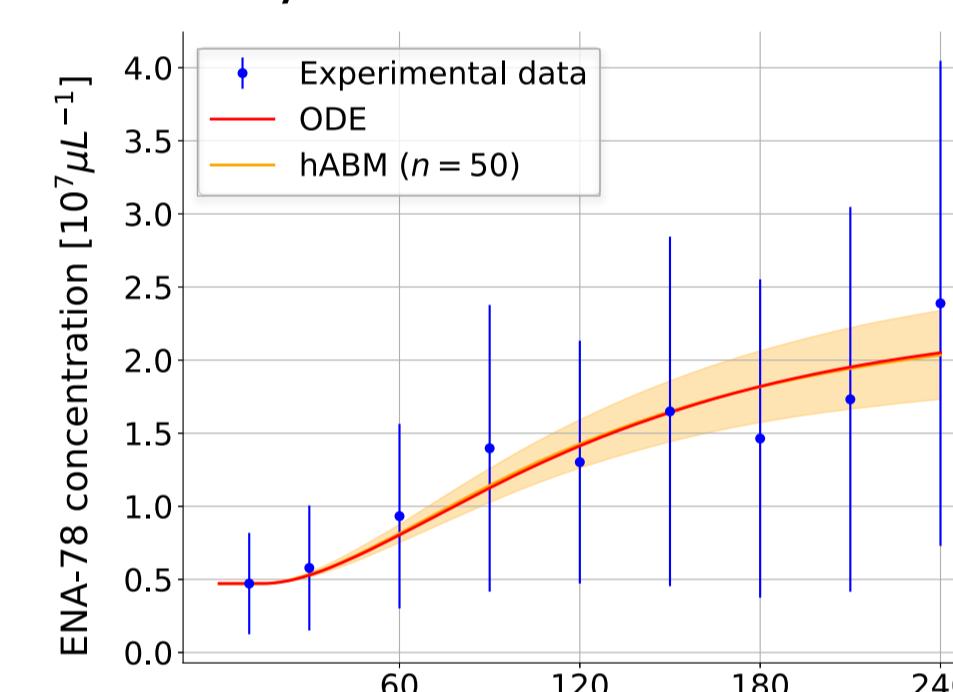


Experimental data: association & survival assay

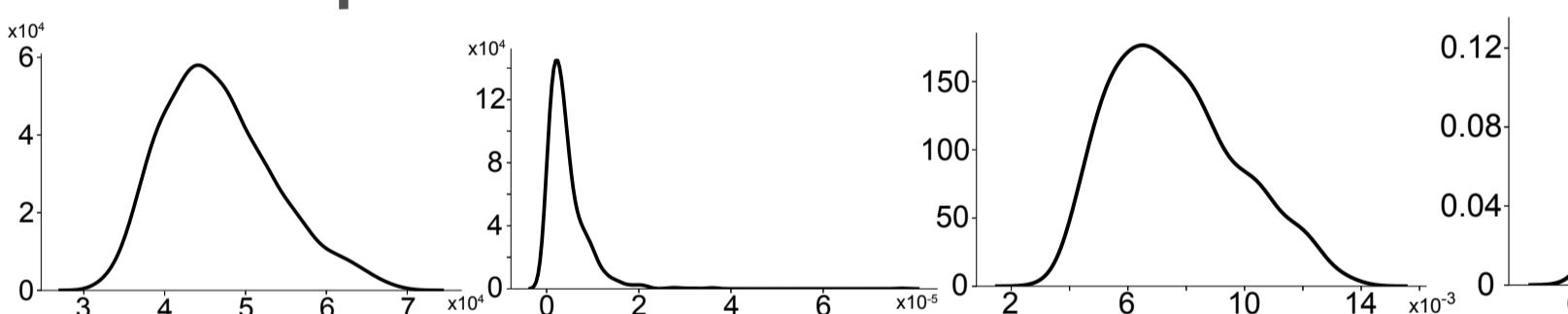


Experimental data: cytokines concentration

Experimental data: cytokines concentration



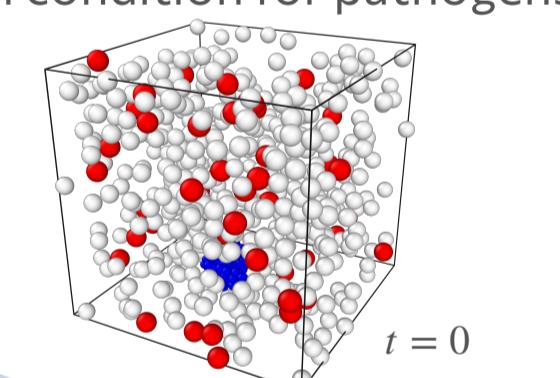
Posterior parameter distributions for the ODE model:



Killing assay data for SBM:

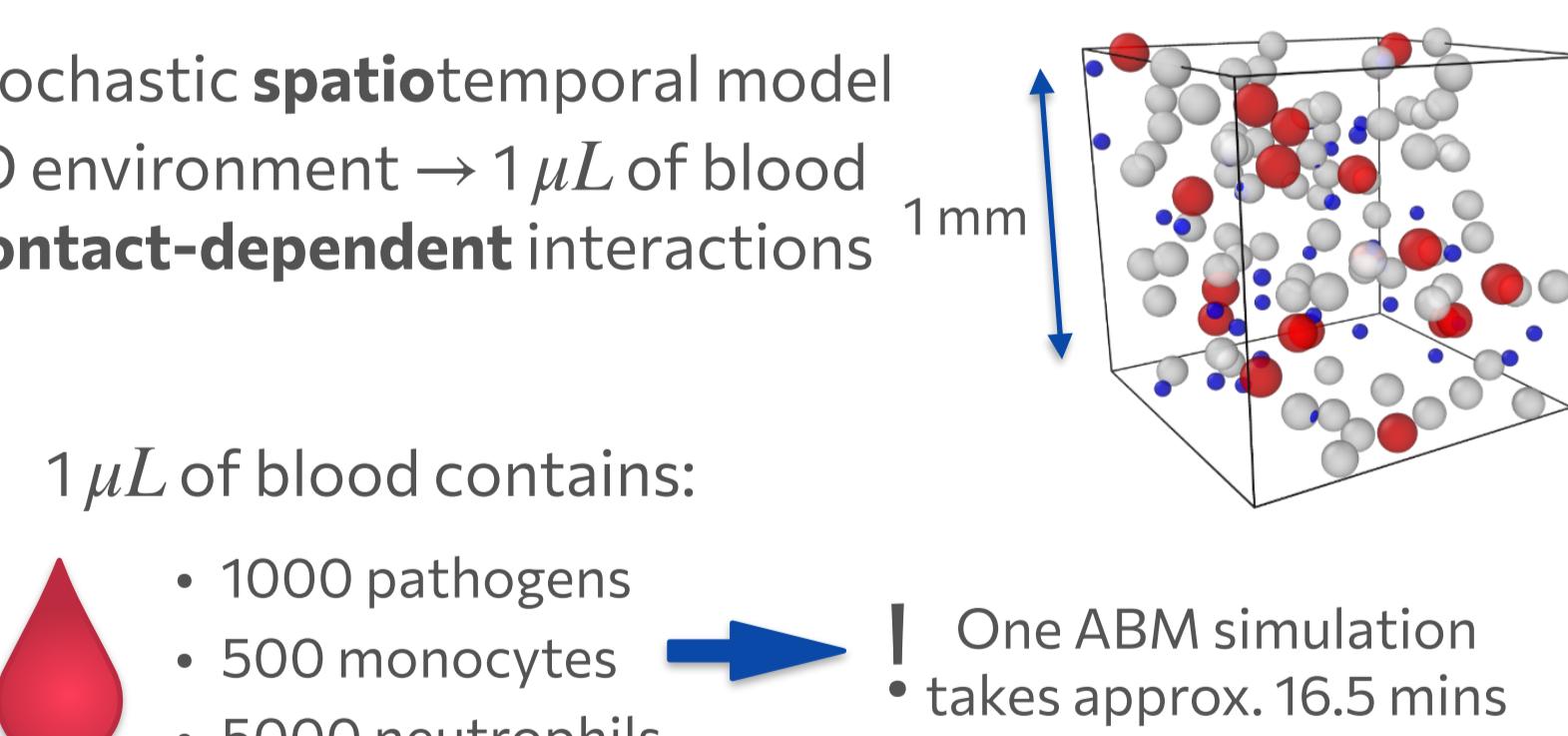
decrease of uncertainty in the killing rate of neutrophils κ_N

Initial condition for pathogens:

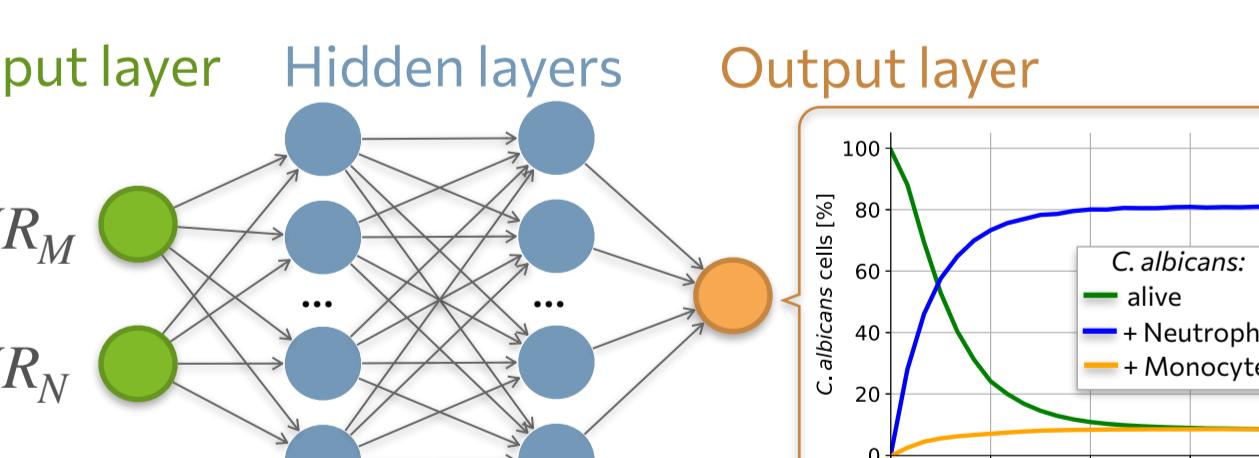


Agent-based model

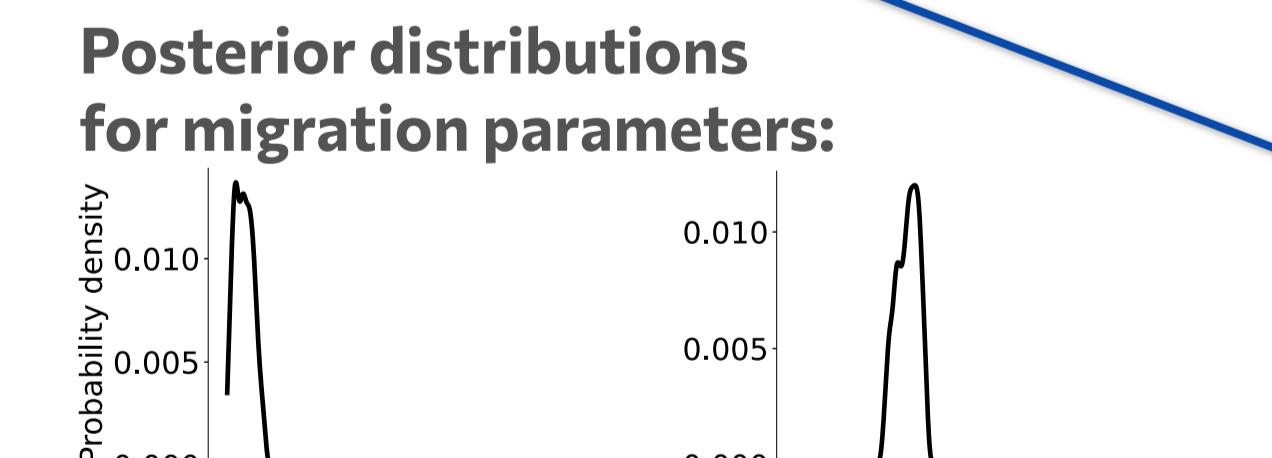
- Stochastic spatiotemporal model
- 3D environment $\rightarrow 1 \mu L$ of blood
- Contact-dependent interactions



- ML surrogate model for parameter inference
- Multilayer perceptron^[4] as a surrogate model
- Optuna^[5] used to tune the hyper-parameters



Posterior distributions for migration parameters:



Conclusions and outlook

- The gradual increase of model complexity from SBM to hABM enables us to describe chemokine-induced guidance of cells to sites of infection.
- The parameter inference for the SBM module allows prediction for experimental design.
- Surrogate modeling enables parameter inference for computationally expensive ABM simulation.
- MuMoSim is a general framework that aims to quantify host-pathogen interactions for various conditions (bacterial/fungal infections in patients cohorts) and to predict treatment strategies.

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References

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