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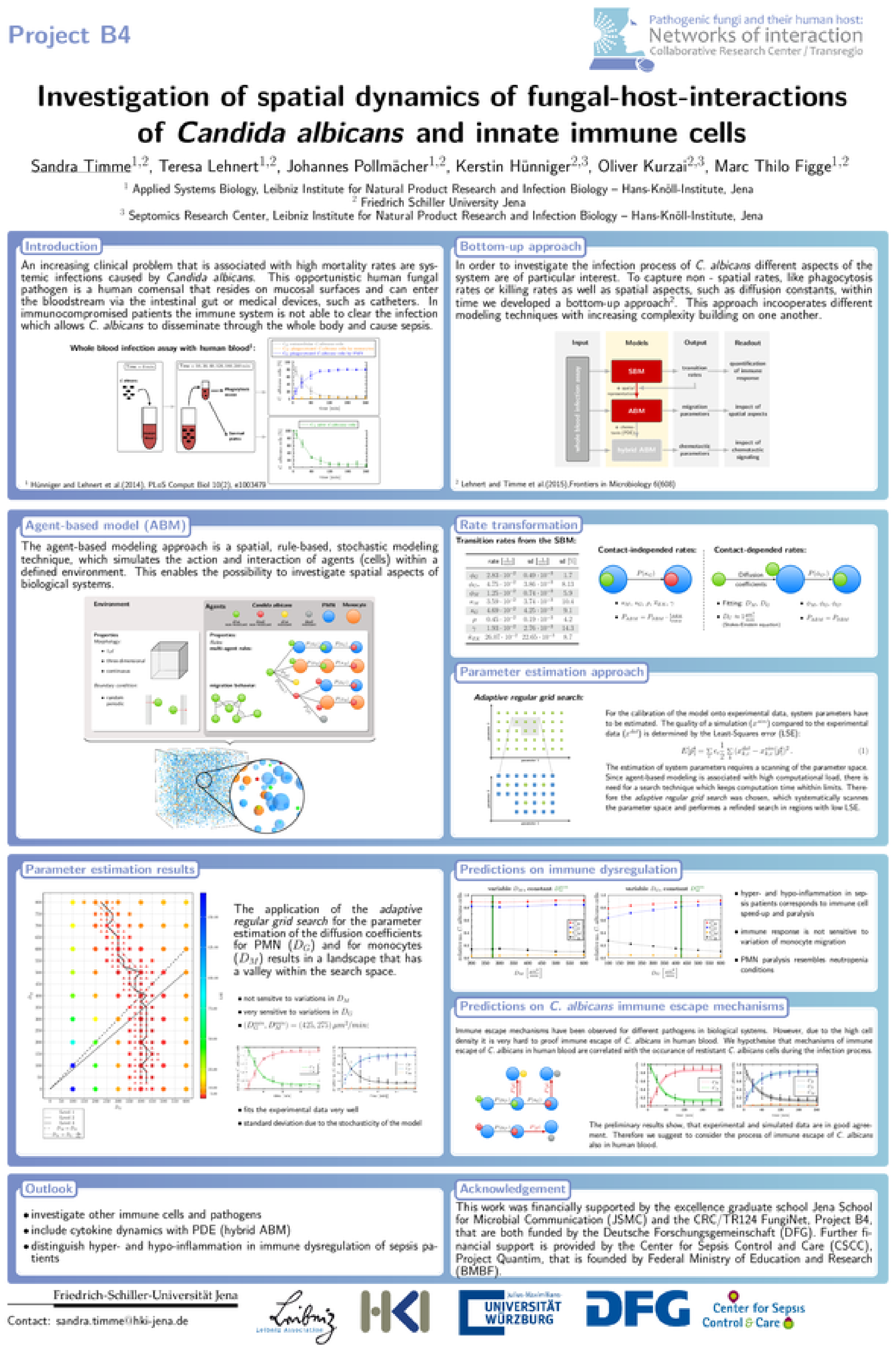

Project B4

Pathogenic fungi and their human host: Networks of interaction
Collaborative Research Center / Transregio

Investigation of spatial dynamics of fungal-host-interactions of *Candida albicans* and innate immune cells

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Introduction

An increasing clinical problem that is associated with high mortality rates are systemic infections caused by *Candida albicans*. This opportunistic human fungal pathogen is a human comensal that resides on mucosal surfaces and can enter the bloodstream via the intestinal gut or medical devices, such as catheters. In immunocompromised patients the immune system is not able to clear the infection which allows *C. albicans* to disseminate through the whole body and cause sepsis.

Whole blood infection assay with human blood[1]:

[1] Hünniger and Lehnert et al.(2014), PLoS Comput Biol 10(2), e1003479

Bottom-up approach

In order to investigate the infection process of *C. albicans* different aspects of the system are of particular interest. To capture non - spatial rates, like phagocytosis rates or killing rates as well as spatial aspects, such as diffusion constants, within time we developed a bottom-up approach[2]. This approach incooperates different modeling techniques with increasing complexity building on one another.

[2] Lehnert and Timme et al.(2015),Frontiers in Microbiology 6(608)

Agent-based model (ABM)

The agent-based modeling approach is a spatial, rule-based, stochastic modeling technique, which simulates the action and interaction of agents (cells) within a defined environment. This enables the possibility to investigate spatial aspects of biological systems.

Rate transformation

Transition rates from the SBM:

Contact-independed rates:

Contact-depended rates:

Parameter estimation approach

Adaptive regular grid search:

For the calibration of the model onto experimental data, system parameters have to be estimated. The quality of a simulation compared to the experimental data is determined by the Least-Squares error (LSE):

The estimation of system parameters requires a scanning of the parameter space. Since agent-based modeling is associated with high computational load, there is need for a search technique which keeps computation time whithin limits. Therefore the *adaptive regular grid search* was chosen, which systematically scannes the parameter space and performes a refinded search in regions with low LSE.

Parameter estimation results

The application of the *adaptive regular grid search* for the parameter estimation of the diffusion coefficients for PMN (D_G) and for monocytes (D_M) results in a landscape that has a valley within the search space.

- not sensitive to variations in D_M
- very sensitive to variations in D_G

- fits the experimental data very well
- standard deviation due to the stochasticity of the model

Predictions on immune dysregulation

- hyper- and hypo-inflammation in sepsis patients corresponds to immune cell speed-up and paralysis
- immune response is not sensitive to variation of monocyte migration
- PMN paralysis resembles neutropenia conditions

Predictions on *C. albicans* immune escape mechanisms

Immune escape mechanisms have been observed for different pathogens in biological systems. However, due to the high cell density it is very hard to proof immune escape of *C. albicans* in human blood. We hypothesise that mechanisms of immune escape of *C. albicans* in human blood are correlated with the occurance of restistant *C. albicans* cells during the infection process.

The preliminary results show, that experimental and simulated data are in good agreement. Therefore we suggest to consider the process of immune escape of *C. albicans* also in human blood.

Outlook

- investigate other immune cells and pathogens
- include cytokine dynamics with PDE (hybrid ABM)
- distinguish hyper- and hypo-inflammation in immune dysregulation of sepsis patients

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