In silico Experiments of Fungal and Bacterial Infections in Virtual Neutropenic Patients suggest Optimal Treatment Strategies

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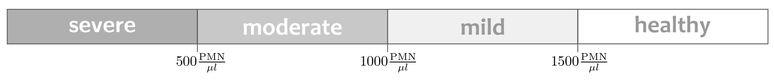
Motivation

With over 70 %, neutrophils represent the highest fraction of blood leukocytes. Since they can migrate to sites of infection and clear the organism from pathogens they constitute an important part of the immune system .

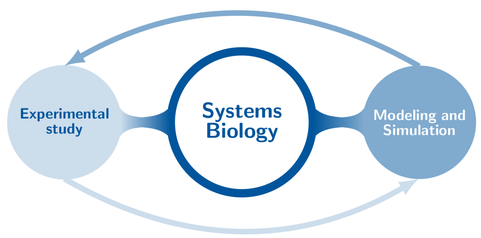
However, diseases or medical treatments can result in a reduction in the absolute neutrophil count (ANC) in blood called neutropenia. Neutropenia can be due to a disturbed development of neutrophils in the bone marrow, a disturbed migration to the blood stream or a rapid consumption due to an infection.

The severity and the duration of neutropenia directly correlates with a higher risk for infections. Such infections are primarily caused by bacteria like Staphylocoocus spp. and Streptococcus spp. but also by fungal pathogens like Candida spp. and Aspergillus spp.

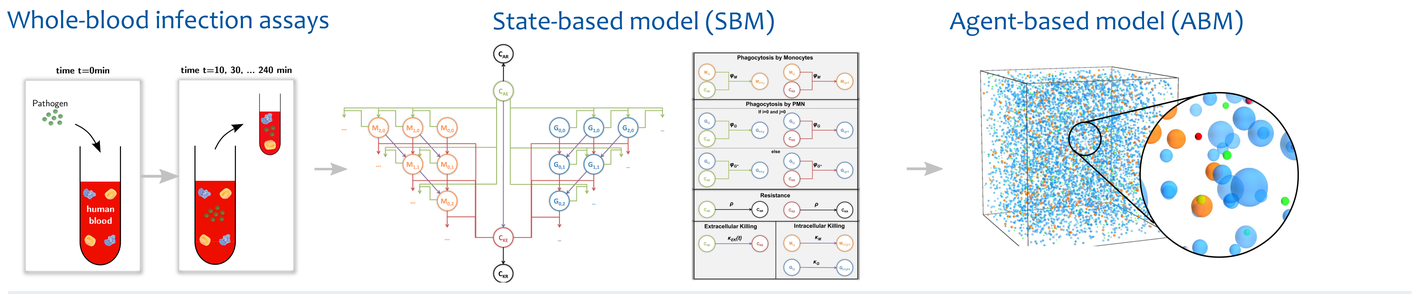
Degrees of Severety of Neutropenia:

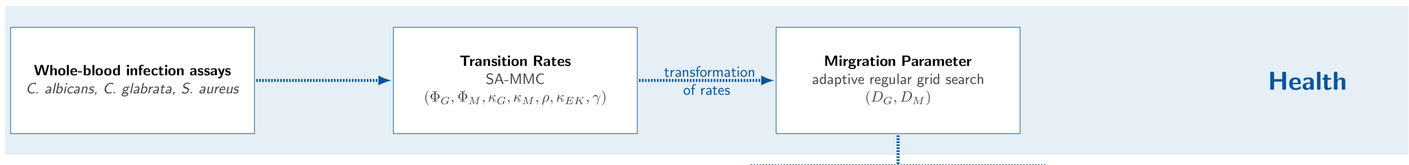


We investigate the infection with *Candida albicans*, *Candida glabrata* and *Staphylococcus aureus* in human whole blood. Therefore we apply a systems biology approach that makes use of wet-lab as well as dry-lab studies that complement each other:



Bottom-up Model





We performed whole blood infection assays, where blood from healthy donors is infected with cell of *C. albicans*, *C. glabrata* or *S. aureus*. With phagocytosis assays and survival plates, pathogen populations of alive, killed, extracellular and phagocytosed cells by monocytes and neutrophils are determined.

The SBM consists of states and transitions between these states that resemble the biological system. Fitting the SBM to the experimental data allowed quantification of immune reaction rates, such as phagocytosis and killing rates.

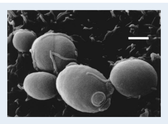
To investigate also spatial aspects of the biological system we build an ABM, where single cells are simulated in a continous three-dimensional environment. Based on the experimental data and the previously fitted rates we could determine diffusion coefficients of immune cells.

In the current study we use this bottom-up approach to simulate virtual neutropenic patients. Thereby, we investigate whole-blood infections with different bacterial and fungal pathogens and test possible treatment strategies *in silico*.

Results

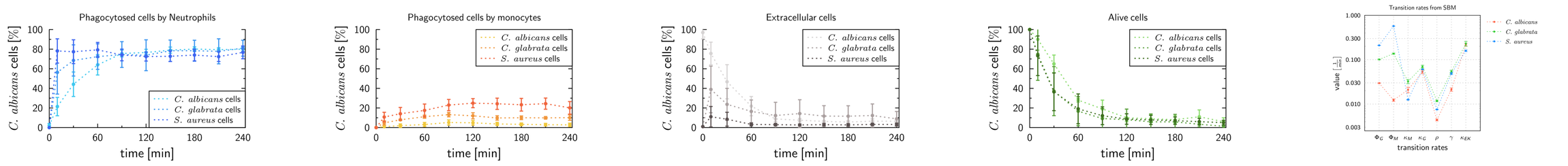
C. albicans

C. glabrata

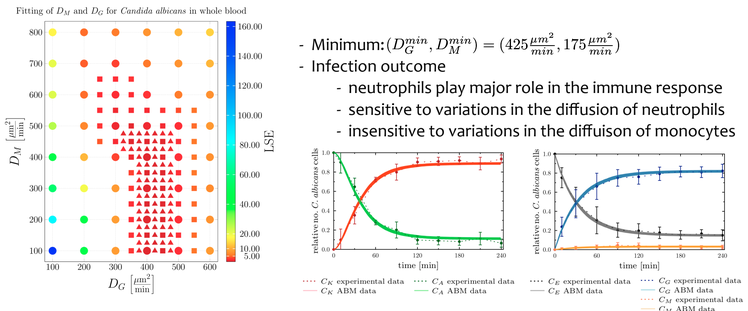


S. aureus

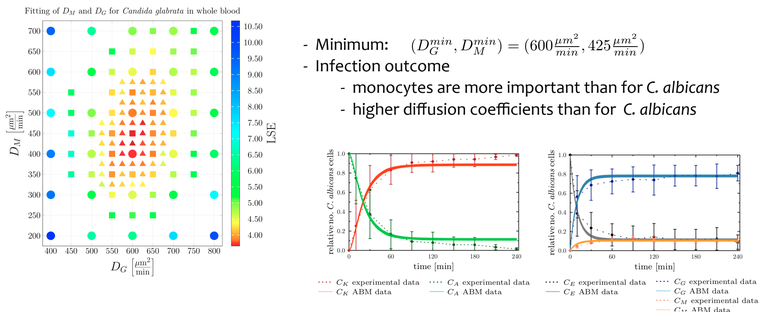
Experimental Data and Transition Rates



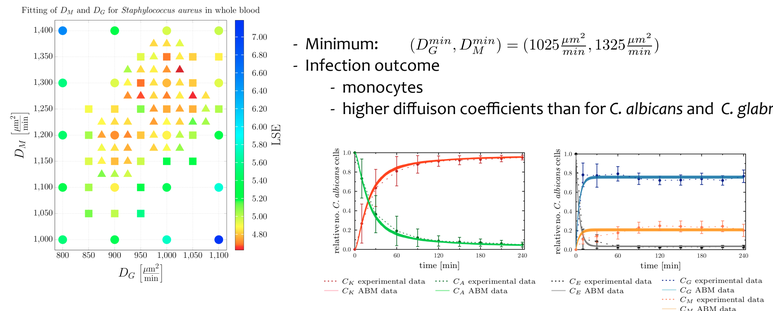
Fitting of Diffision constants



- Minimum: $(D_G^{min}, D_M^{min}) = (425\frac{\mu m^2}{min}, 175\frac{\mu m^2}{min})$
- Infection outcome
  - neutrophils play major role in the immune response
  - sensitive to variations in the diffusion of neutrophils
  - insensitive to variations in the diffuison of monocytes

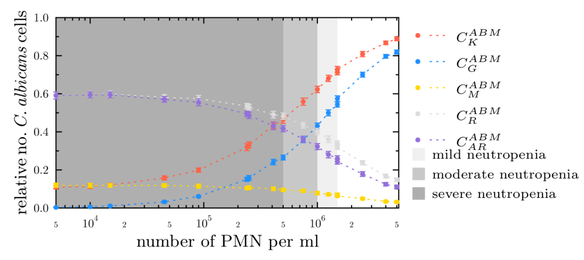


- Minimum: $(D_G^{min}, D_M^{min}) = (600\frac{\mu m^2}{min}, 425\frac{\mu m^2}{min})$
- Infection outcome
  - monocytes are more important than for *C. albicans*
  - higher diffusion coefficients than for *C. albicans*

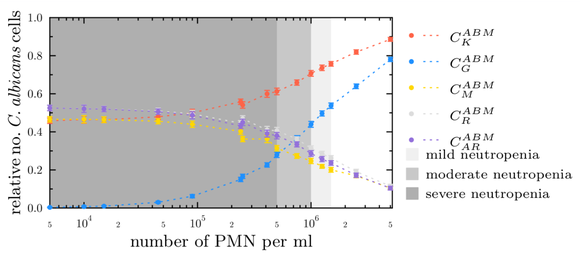


- Minimum: $(D_G^{min}, D_M^{min}) = (1025\frac{\mu m^2}{min}, 1325\frac{\mu m^2}{min})$
- Infection outcome
  - monocytes
  - higher diffuison coefficients than for *C. albicans* and *C. glabrata*

Virtual Neutropenic Patients

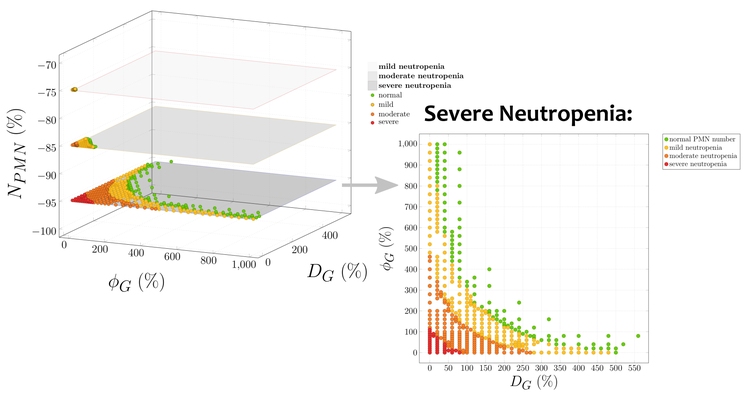


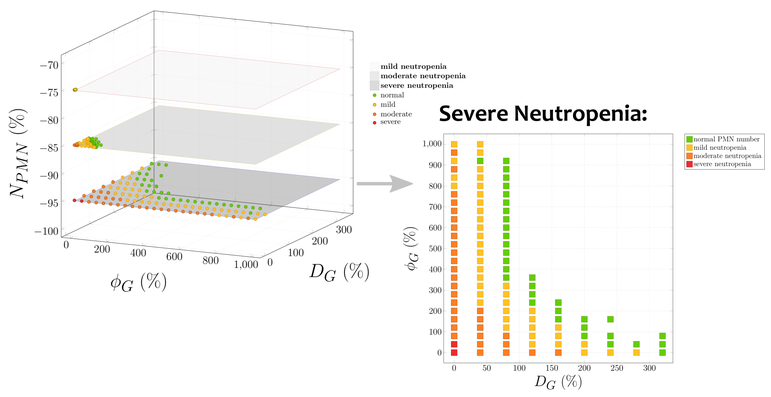
- increasing number of resistant and alive cells (up to 60 %)
- decreasing number of killed cells (down to 10 %)
- monocytes can compensate only in very limited amounts



- increasing number of resistant and alive cells (up to 50 %)
- decrease of killed cells not so strong as for *C. albicans* (down to 45 %)
- monocytes can compensate the reduction of neutrophils much better

Treatment





Summary:

- experimental data can be fitted with the SBM and ABM
- virtual neutropenic patients can be simulated:
  - strong decrease of killed *C. albicans* cells in severe neutropenia
  - for *C. glabrata* monocytes can partially compensate the low number of neutropenia
- infection outcome in neutropenic virtual patients can be compensated by increasing phagocytosis rata and/or diffusion coefficients

Outlook:

- simulations of neutropenic virtual patients and medical treatment for *S. aureus*
- quatitative comparative analysis of whole-blood infections with *C. albicans*, *C. glabrata* and *S. aureus*

References:

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