Predictions of antimicrobial treatment strategies based on *in silico* experiments of virtual neutropenic patients

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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 Staphylococcus spp. and Streptococcus spp. but also by fungal pathogens like Candida spp. and Aspergillus spp.

Aim:

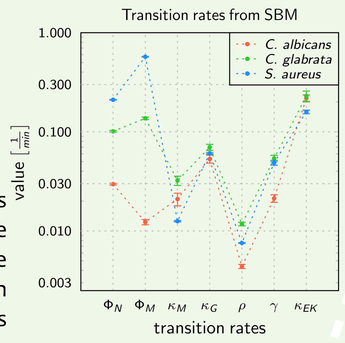
In the current study we use a prevously established bottom-up approach to simulate virtual neutropenic patients. Thereby, we investigate whole-blood infections with different bacterial and fungal pathogens and test possible treatment strategies *in silico*.

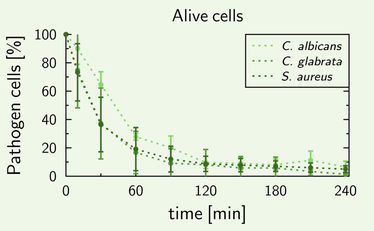
Legend: Health | Desease | Treatment | Outlook

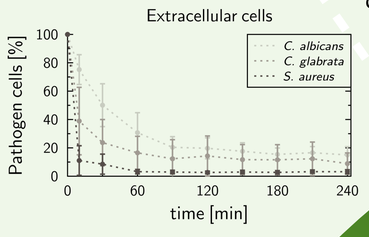
We performed whole blood infection assays, where blood from healthy donors is infected with cell of *C. albicans*, *C. glabrata* or *S. aureus*. With phagocytosis assays and survival plates we determined pathogen populations of alive, killed, extracellular and phagocytosed cells by monocytes and neutrophils.

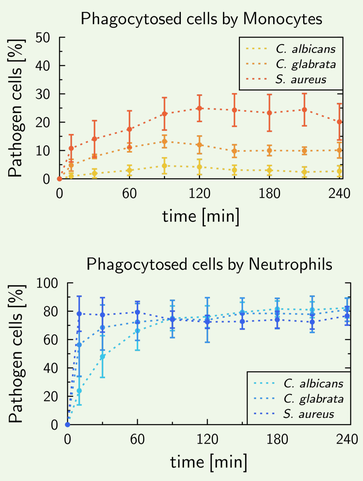
Rate		Description
Φ_N	...	phagocytosis rate of neutrophils
Φ_M	...	phagocytosis rate of monocytes
κ_N	...	killing rate of neutrophils
κ_M	...	killing rate of monocytes
ρ	...	pathogen immune evasion
κ_{EK}	...	secretion of anti-microbial peptides by neutrophils upon first phagocytosis
γ	...	half-life time of anti-microbial peptides

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.

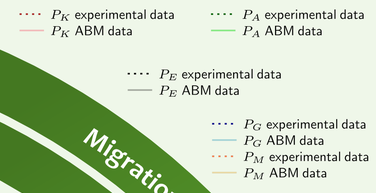


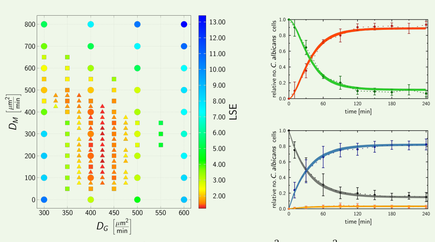




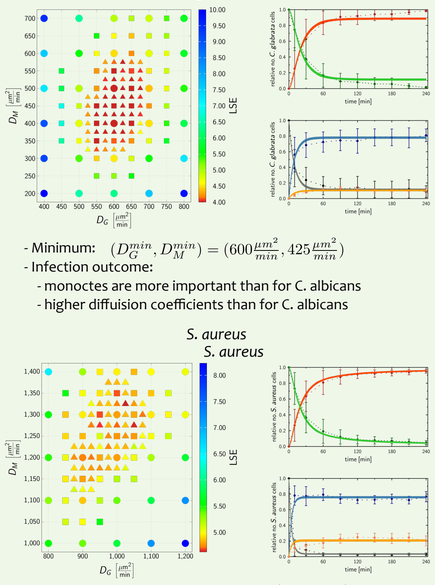


To investigate also spatial aspects of the biological system we build an ABM, where single cells are simulated in a continous three-dimensional environment. Based on the experimental data and the previously fitted rates we could determine diffusion coefficients of immune cells.





- 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 in the diffusion of monocytes



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

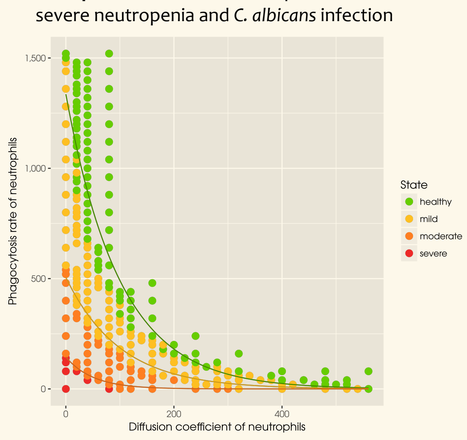
- Minimum: $(D_G^{min}, D_M^{min}) = (1025\frac{\mu m^2}{min}, 1325\frac{\mu m^2}{min})$
- Infection outcome:
  - monoctes are more important than for both Candida species
  - higher diffuision coefficients than for both Candida species

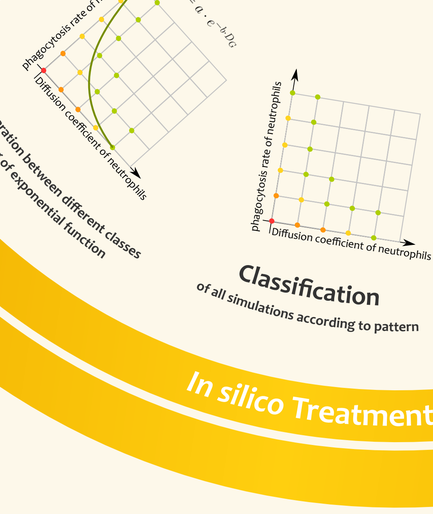
Summary:
- experimental data can be fitted with the SBM and ABM
- virtual neutropenic patients can be simulated:
  - strong decrease of killed *C. albicans* cells in severe neutropenia
  - for *C. glabrata* and *S. aureus* monocytes can partially compensate the low number of neutropenia
- virtual neutropenic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

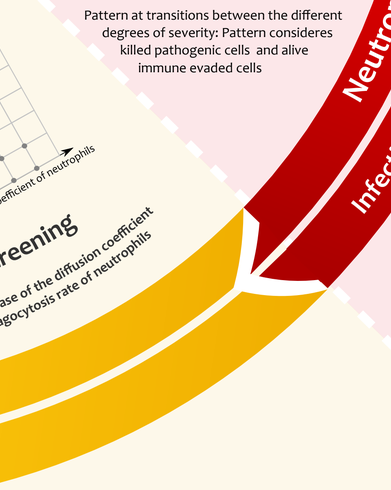
Outlook:
- *in silico* supplementation of donor neutrophils
- clarify the mechanism for pathogen immune evasion

We simulated the treatment for all three pathogens at different degrees of severity. Therefore, we considererd ANCs of 1250 neutrophils/µl (mild, -75%), 1000 neutrophils/µl (-80%), 750 neutrophils/µl (moderate, -85%), 500 neutrophils/µl (-90%) and 250 neutrophils/µl (severe, -95%).

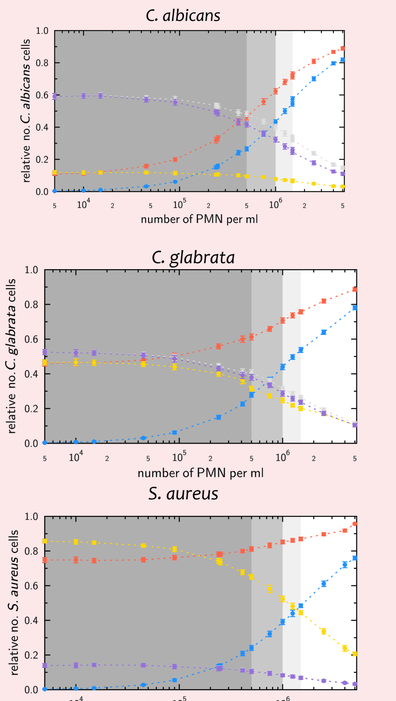
Example: Treatment of virtual patient with severe neutropenia and *C. albicans* infection



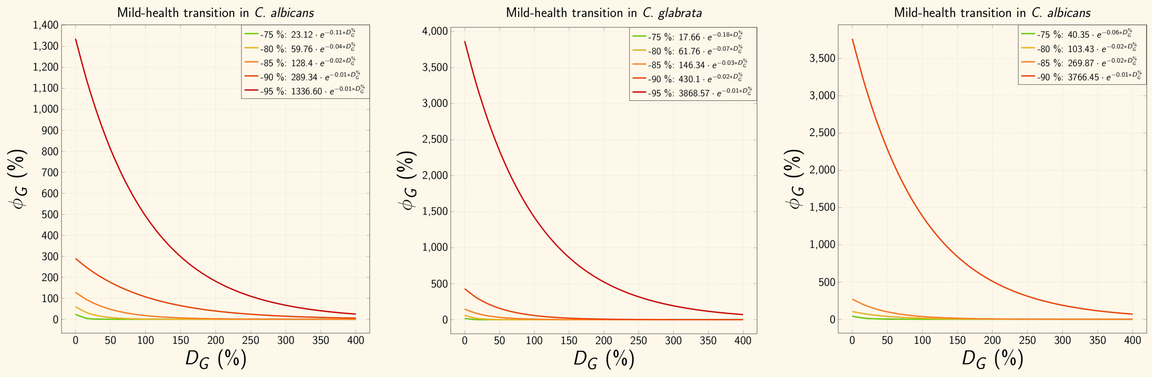




Pattern at transitions between the different degrees of severity: Pattern consideres killed pathogenic cells and alive immune evaded cells



- killed pathogenic cells
- pathogenic cells phagocytosed by granulocytes
- pathogenic cells phagocytosed by monocytes
- immune evaded pathogenic cells
- alive immune evaded pathogenic cells



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Pathogenic fungi and their human host: Networks of interaction
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