Simulation of virtual phagocytosis assays with alveolar macrophages and *Aspergillus fumigatus* conidia reveals immune reaction rates

Claudia Sichting[1,2], Sandra Timme[1,2], Marc Thilo Figge[1,2]

1) Applied Systems Biology, Leibniz Institute for Natural Product Research and Infection Biology – Hans-Knöll-Institute (HKI), Jena, Germany
2) Friedrich Schiller University Jena, Jena, Germany

Motivation

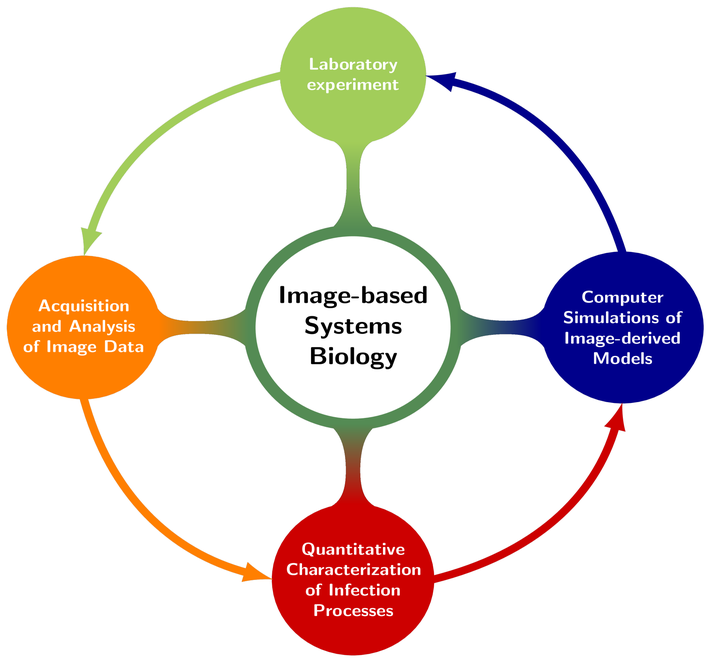
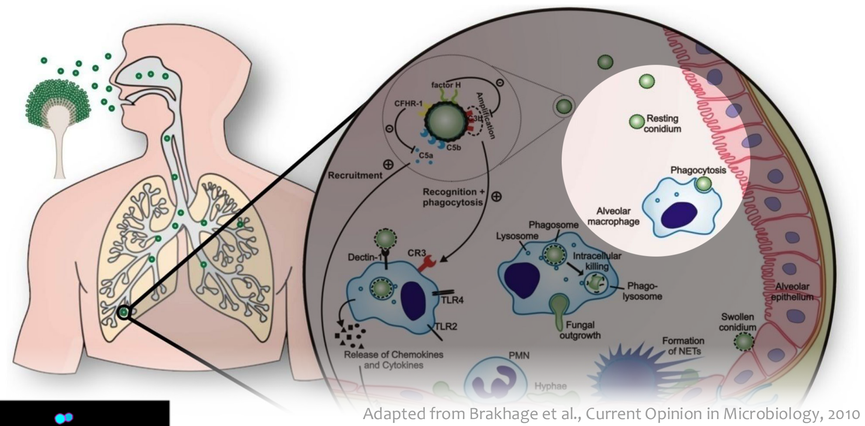


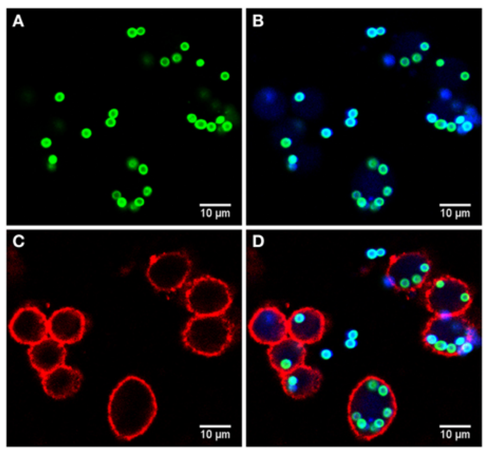
Image-based systems biology deploys the cycle of experiment, analysis and modeling onto microscopy images and can be applied to investigate host-pathogen interactions of the human immune system and pathogens.

Biological Background

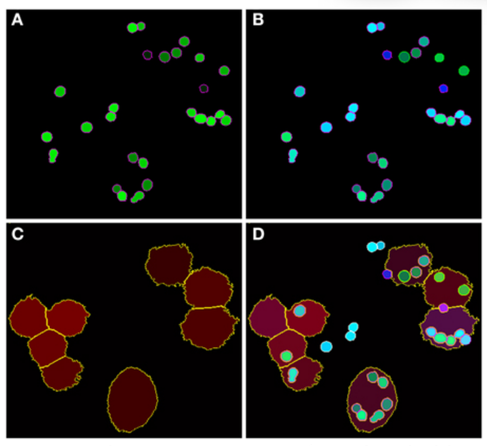
Several hundred airborne conidia of the fungus *A. fumigatus* are inhaled by every human every day. If not cleared by the resident immune cells, alveolar macrophages (AM), they can cause severe pulmonary infections in immunocompromised patients with high mortality rates. To investigate the interaction of the two wild-type strains ATCC 46645 and CEA10 of *A. fumigatus* with AM, fluorescent microscopy images of phagocytosis assays have been conducted, where differential staining allowed to distinguish phagocytosed, adherent and non-associated conidia.



Adapted from Brakhage et al., Current Opinion in Microbiology, 2010



A) all conidia B) differential staining
C) macrophages, D) all together



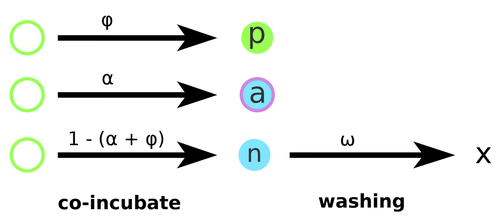
Automated Image Processing (e.g. thresholding, watershed segmentation, classification)

Adapted from Kraibooj et al., Frontiers in Microbiology, 2010

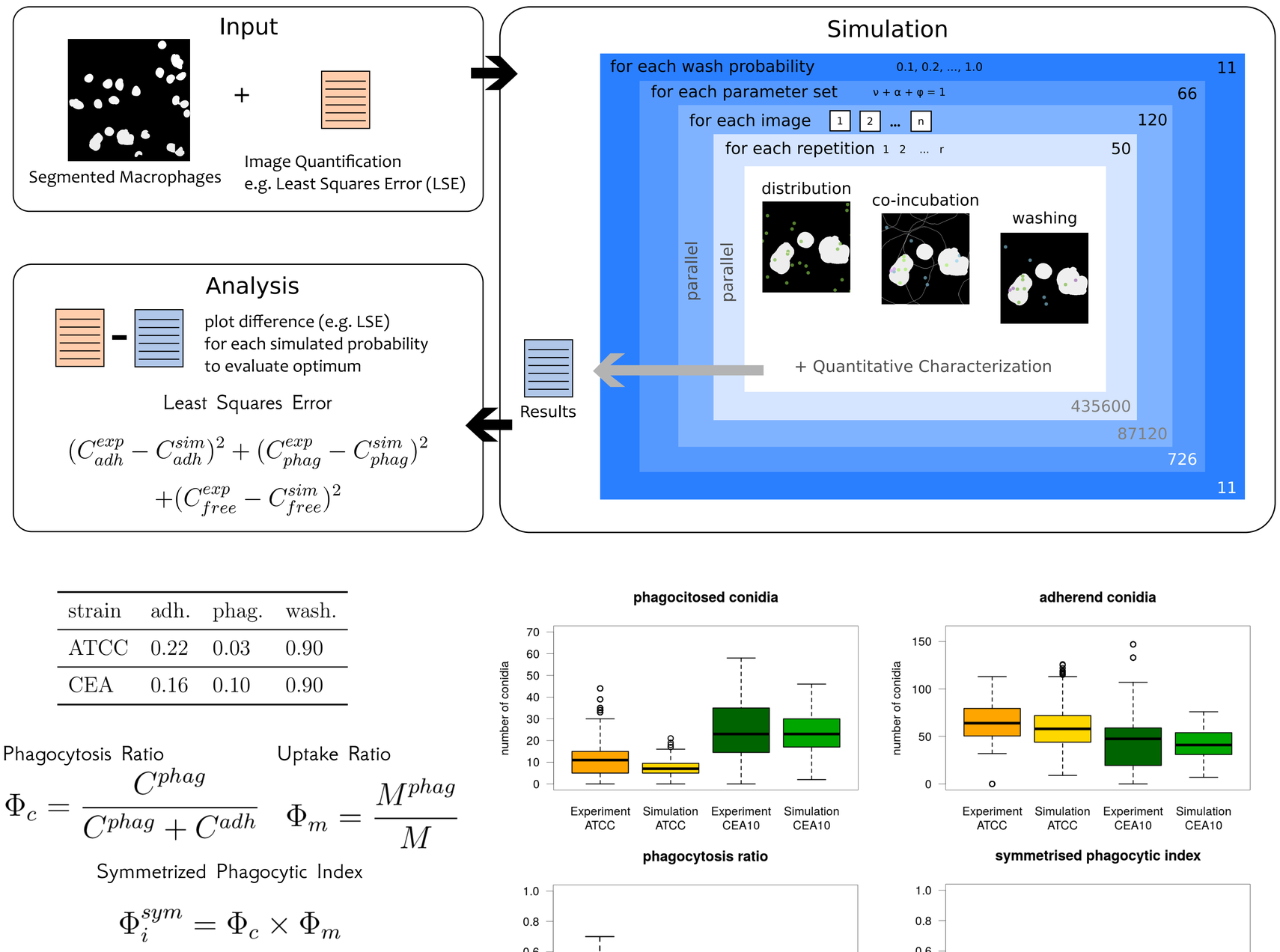
To investigate the interaction of the two wild-type strains ATCC 46645 and CEA10 of *A. fumigatus* with AM, fluorescent microscopy images of phagocytosis assays have been conducted, where differential staining allowed to distinguish phagocytosed, adherent and non-associated conidia.

We constructed a simulation framework CellRain for image-derived modeling to investigate immune reaction rates and to simulate phagocytosis assays.

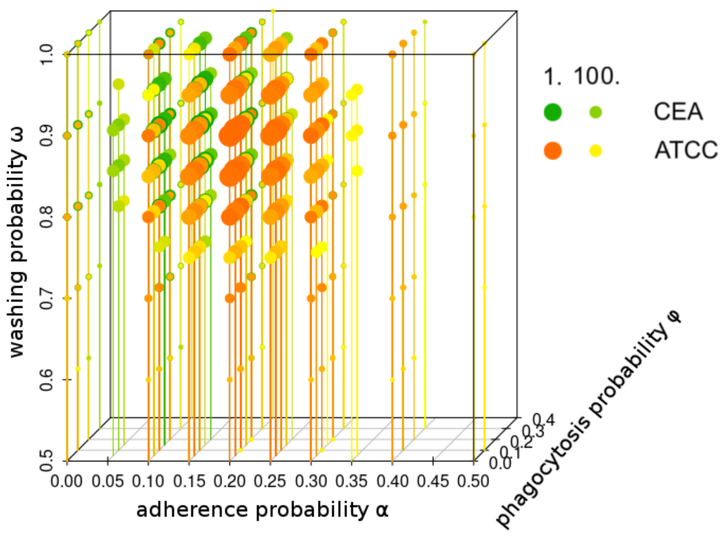
Modelling Framework CellRain



First, virtual conidia were distributed randomly on images with segmented alveolar macrophages. Subsequently, co-incubation and washing were simulated. If the conidia are located in the proximity of a macrophage, they can become adherent or phagocytosed with certain rates during co-incubation, which entails a position change of the conidia.
Finally, washing is simulated in which non-associated cells are removed with a certain rate. For parameter estimation we performed a grid-based screening of the immune reaction rates.



Results



strain	adh.	phag.	wash.
ATCC	0.22	0.03	0.90
CEA	0.16	0.10	0.90

Phagocytosis Ratio

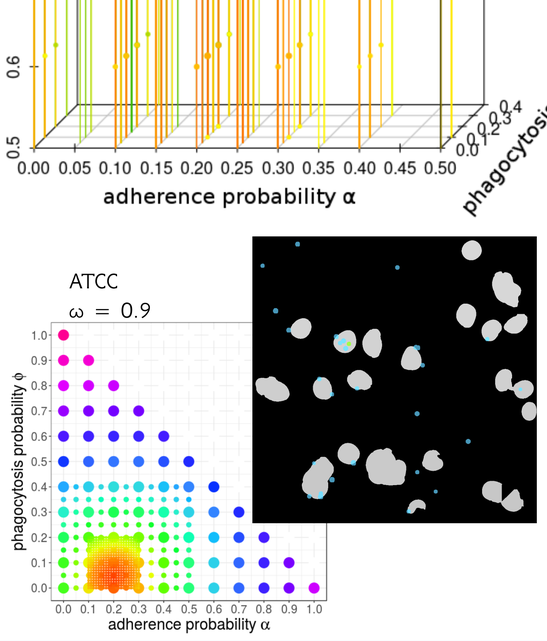
$$\Phi_c = \frac{C^{phag}}{C^{phag} + C^{adh}}$$

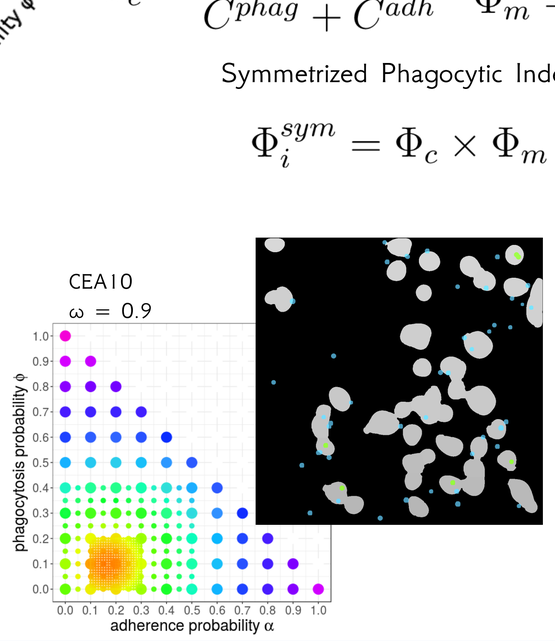
Uptake Ratio

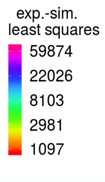
$$\Phi_m = \frac{M^{phag}}{M}$$

Symmetrized Phagocytic Index

$$\Phi_i^{sym} = \Phi_c \times \Phi_m$$







Outlook

- in silico confrontation assays for various immune-cells and pathogens to compare co-localization and/or random distibutions with experimental image data
- extension for 3D-images

References:

[1] Kraibooj, K., Schoeler H., Svensson, C., Brakhage, A. A., and Figge, M. T. (2015). Automated quantification of the phagocytosis of aspergillus fumigatus conidia by a novel image analysis algorithm. Frontiers in Microbiology, 6:549.

[2] Cseresnyes, Z. et al. (2018), Hessian-based quantitative image analysis of host-pathogen confrontation assays. Cytometry, 93: 346-356.

Contact:

Claudia Sichting
claudia.sichting@hki-jena.de
Research Group:
Applied Systems Biology