


The biophysics of malaria-infected red blood cells

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Collaborative Research Center 1129: Quantitative Analysis of Pathogen Replication and Spread

<http://www.sfb1129.de>



SFB 1129 - introduction
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Dept. of Infectious Diseases - Virology

SFB 1129 plans to obtain an integrative perspective on the mutual interplay of pathogen and host factors determining the outcome of an infection for individual events in systems of different complexity and at high spatial and temporal resolution.

Integration on several levels: scales, complexities, disciplines.

SFB 1129 will...

- ...comprehensively analyse replication and spread of human pathogens in a quantitative manner at high temporal and spatial resolution and at the level of stochastic events.
- ...determine the influence of physical parameters and extracellular matrix on pathogen success and control.
- ...directly determine the course of individual pathogens and host countermeasures in culture systems of increasing complexity.

NEWS

- > 25.07.2019 | HIV Spreads Through Direct Cell-To-Cell Contact: HIV-Ausbreitung über direkte Zell-Zell-Kontakte
- > "Nacht der Forschung" in Heidelberg on Sept. 27th, 2019
- > SFB scientists modeled the spread of HIV in tissue culture (Project 8, Fackler group)
- > New publication: Frischknecht group investigated the role of microtubules in malaria parasites
- > 2nd Mechanobiology Meeting in Vietnam: When Physics meets Biology, July 2019








Our experimental collaborators



Michael Lanzer
parasitology



Motomu Tanaka
physical chemistry

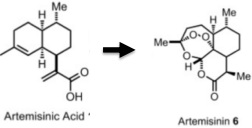
Some basic facts on malaria

- The disease malaria is caused by a unicellular eukaryotic parasite from the genus *Plasmodium*.
- There are several *Plasmodium* species infecting humans and *P. falciparum* is the most dangerous one.
- According to the World Health Organization (WHO), there are more than 200 million new cases per year and each year there are around 500.000 deaths, with the main victims being children in Africa.
- There is still no effective vaccine for malaria. It can be treated well with drugs, but they are expensive. The standard choice is artemisinin, like quinine a herbal drug (Nobel Prize 2015), but resistance is increasing.
- No other disease has left a stronger imprint on our genome than malaria.
- Several genetic diseases related to blood disorders (e.g. sickle cell anemia resulting from hemoglobinopathies) provide some protection from malaria.

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Artemisinin

- Herbal drug isolated from the plant *Artemisia annua* („sweet wormwood“), used in combination therapy, is produced botanically or synthetically; a molecular precursor (artemisinic acid) can be produced by genetically-engineered yeast
- Discovered in 1972 by Tu Youyou, Nobel Prize for Medicine 2015
- Exact mechanism of action not known, leads to formation of free radicals when in contact with hemoglobin in the RBC

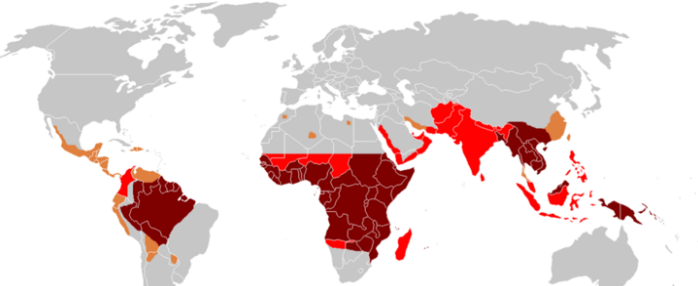


Artemisinic Acid → Artemisinin 6

[Levesque and Seeburger, Continuous-Flow Synthesis of the Anti-Malaria Drug Artemisinin, Angew. Chem. Int. Ed. 51:1706-1709 (2012)]

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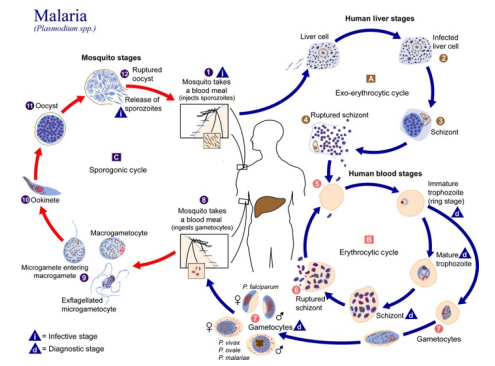
Geographical distribution of malaria



Mainly equatorial regions are affected (mosquitos need water puddles to lay their eggs). Example for the growing problem of drug resistance: chloroquine can now only be used in the orange regions. [Wikipedia]

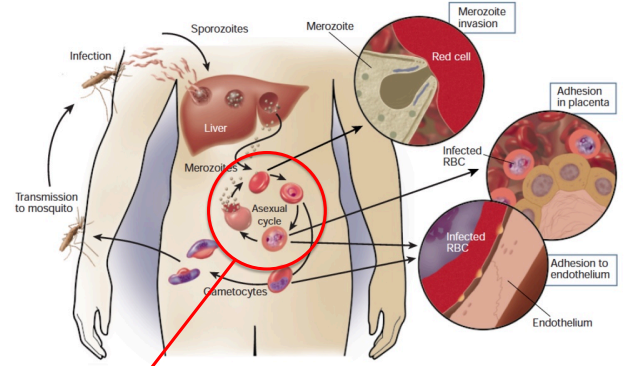
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Malaria (*Plasmodium* spp.)



The FEBS Journal
 Volume 284, Issue 16, pages 2556-2559, 21 AUG 2017 DOI: 10.1111/febs.14160
<http://onlinelibrary.wiley.com/doi/10.1111/febs.14160/full#febs14160-fig-0001>


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blood stage


[Miller+ Nature 2002]

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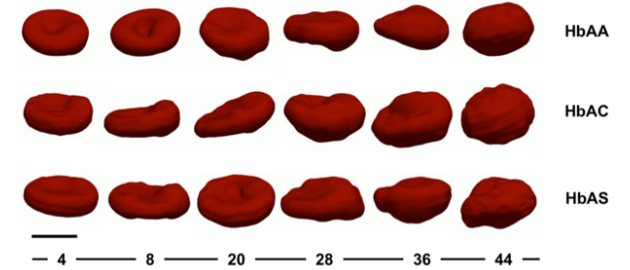
Malaria blood stage

- The blood stage of the infection can be divided into three stages:
 - Ring stage (0-24 hpi)
 - Trophozoite stage (24-36 hpi)
 - Schizont stage (40-48 hpi)
- At 15 hpi, iRBC starts developing adhesive knobs on its surface.
- Cytoadherence of iRBC avoids clearance by spleen and leads to capillary obstruction.



[Anal. Chem., 2014, 86 (9), pp 4379–4386]


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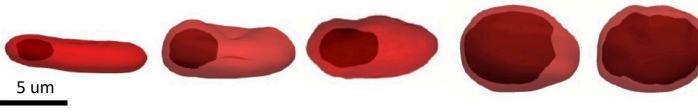
Reconstructed shapes of normal and haemoglobinopathic cells

[Waldecker et al. Cellular Microbiology. 2017;19:e12650]

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Time course over 48 hours



5 μ m

4 16 28 40 44


ring stage 0-20 hpi trophozoite 24-36 hpi schizont 40-48 hpi

$V = 100 \mu\text{m}^3$
 $A = 140 \mu\text{m}^2$
 $v = 0.63$

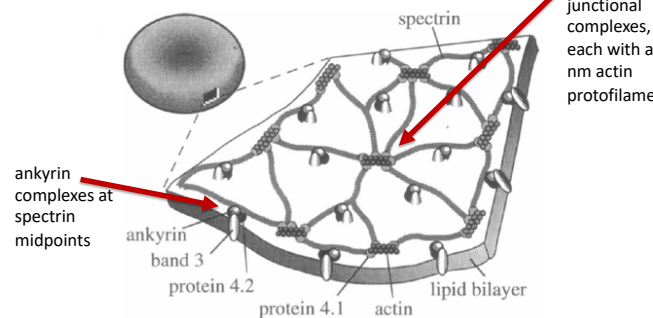
$V = 160 \mu\text{m}^3$
 $A = 140 \mu\text{m}^2$
 $v = 1.0$

reduced volume $v = V / V_0 = \frac{6\sqrt{\pi V}}{A^{3/2}}$

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RBC-cytoskeleton

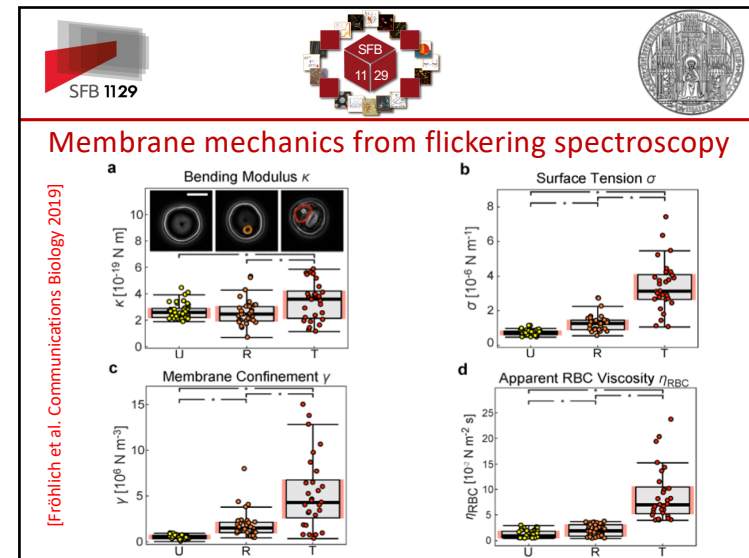
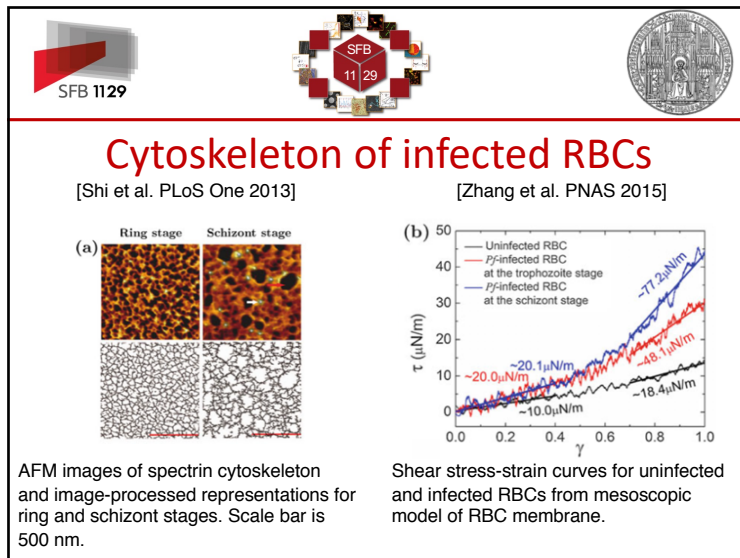
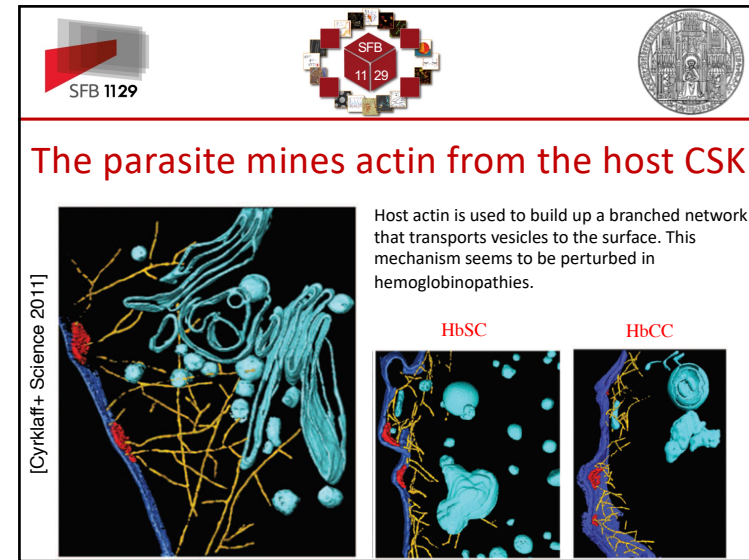
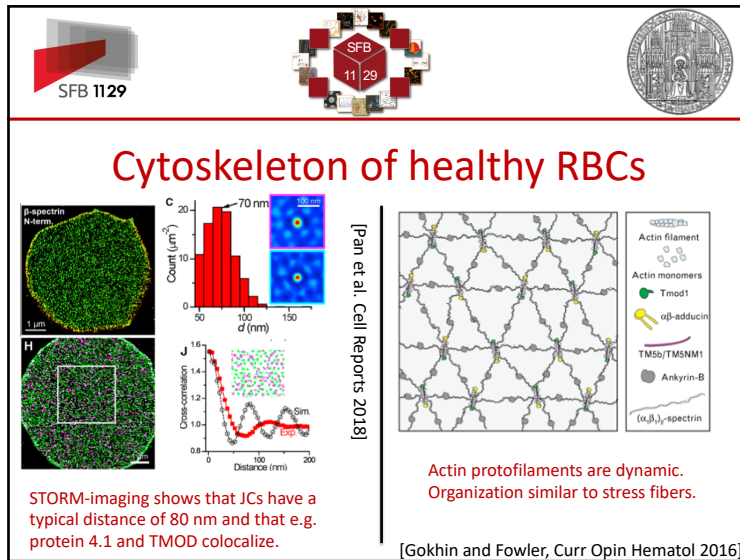


30-40.000 junctional complexes, each with a 37 nm actin protofilament


ankyrin complexes at spectrin midpoints

ankyrin, band 3, protein 4.2, protein 4.1, actin, lipid bilayer

[Hansen+ BPJ 1997]

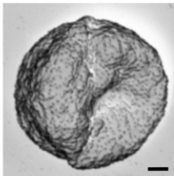


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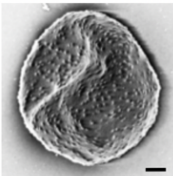


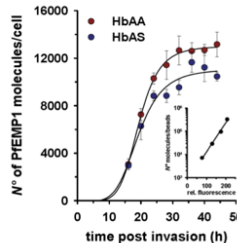
Adhesive knob dynamics

HbAA



HbAS






N° of PfEMP1 molecules/cell

time post invasion (h)

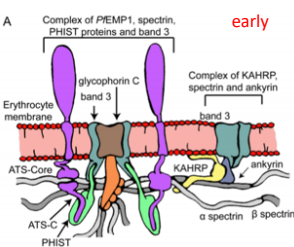
Cytoadhesion avoids clearance by the spleen.
Adhesion receptors PfEMP1 are localized to knobs and start to appear 15 hpi.
[Sanchez et al. Communications Biology 2019]

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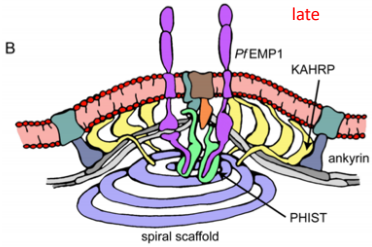
Suggested molecular architecture of knobs

A



early

B




late

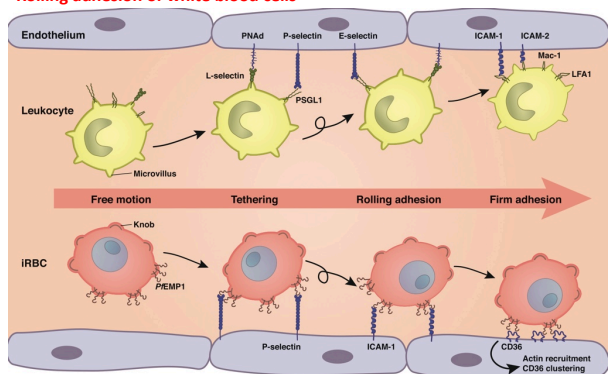
[Cutts et al. PLOS Pathogens 2017]

With super-resolution microscopy (STED), image processing and KAHRP-mutations, we are currently exploring the localization of the different components. The cellular effects will be checked in flow chamber experiments.

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Rolling adhesion of white blood cells

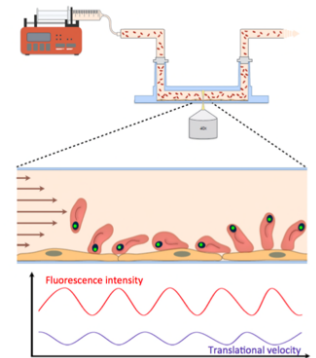


Rolling adhesion of iRBCs [Helms+ FEBS Lett 2016]

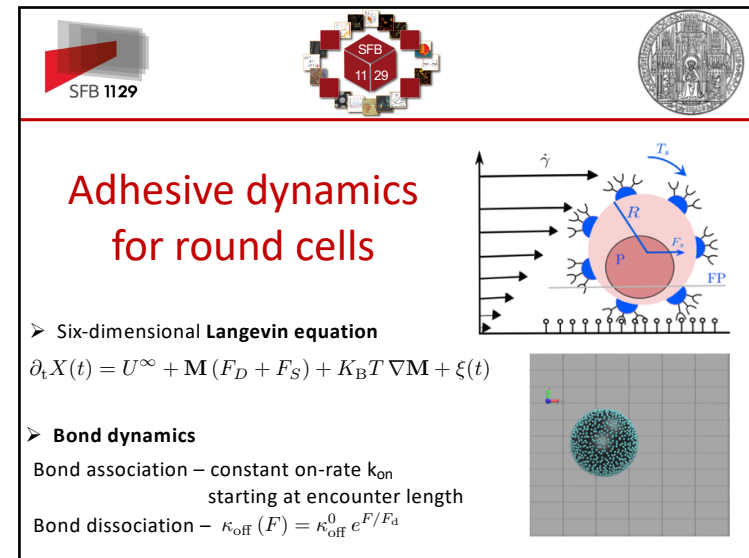
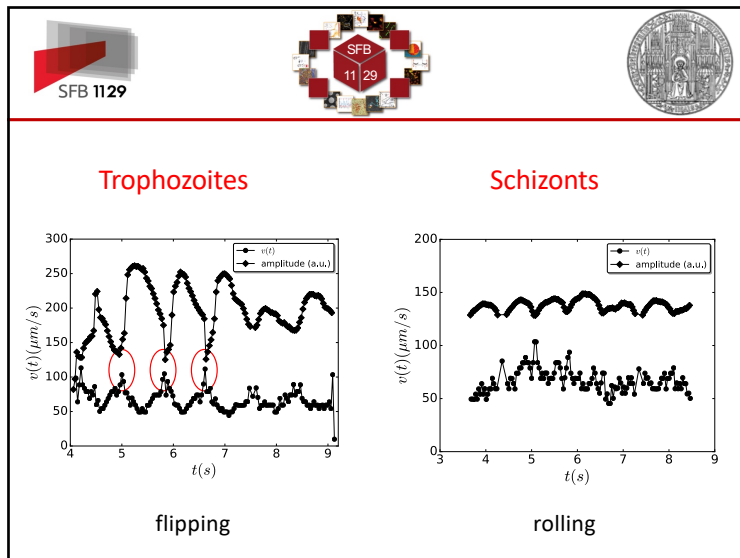
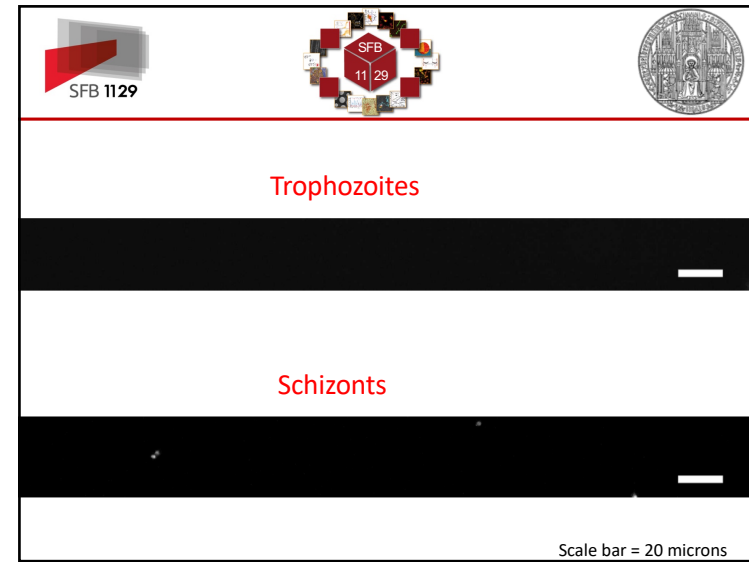
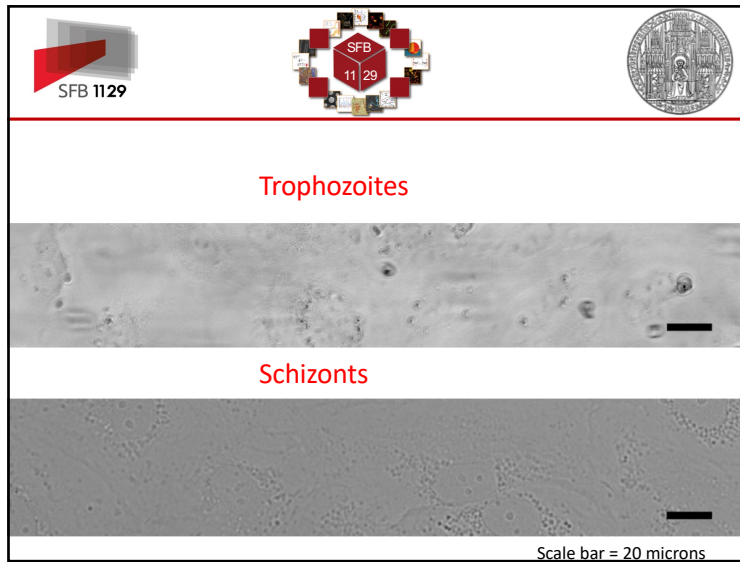
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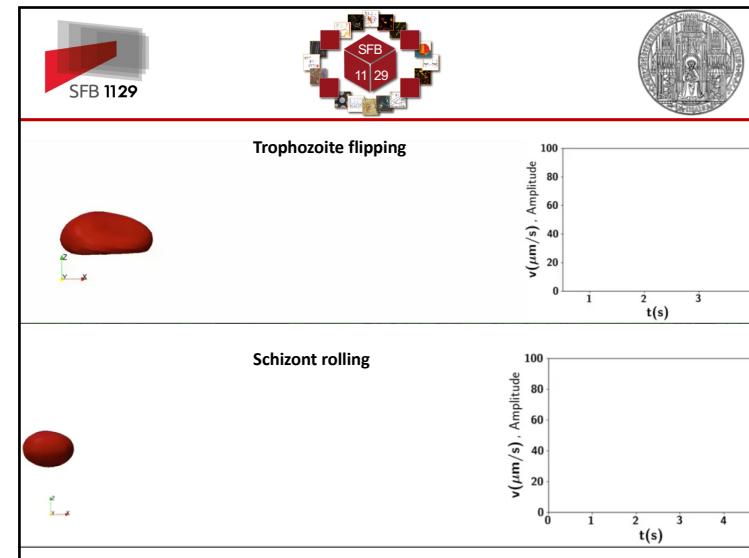
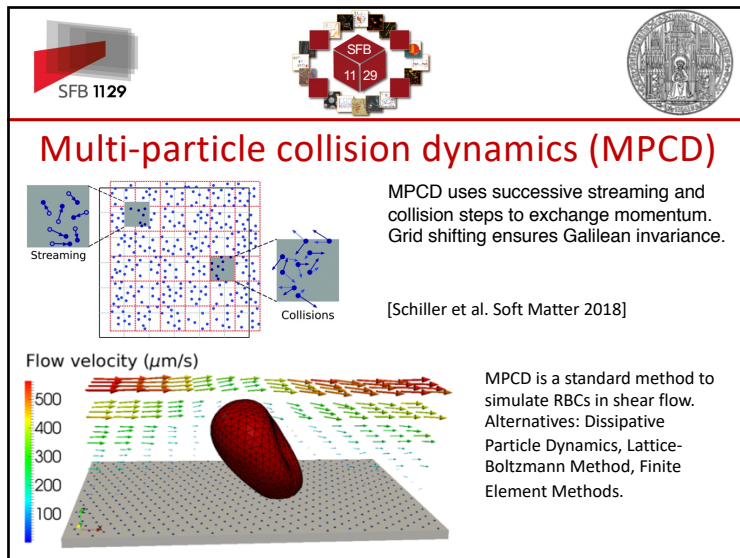
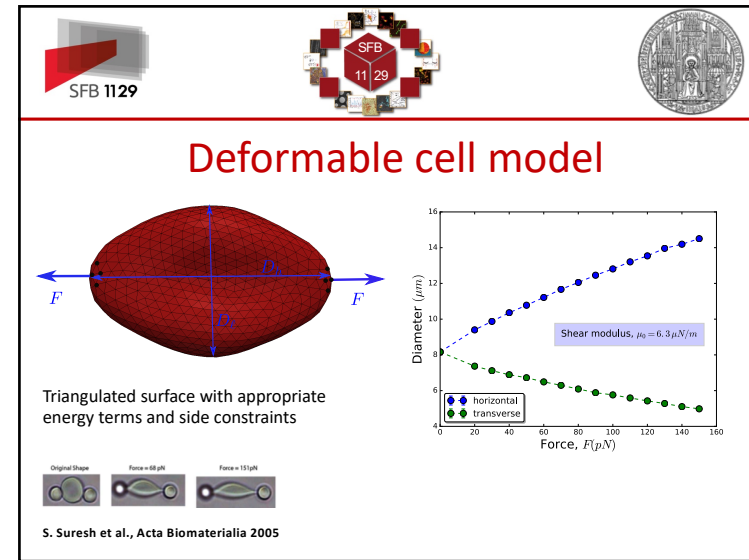
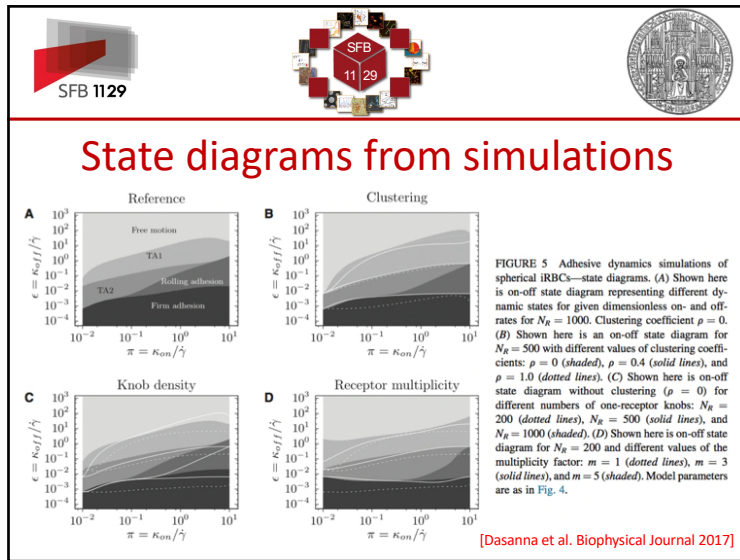


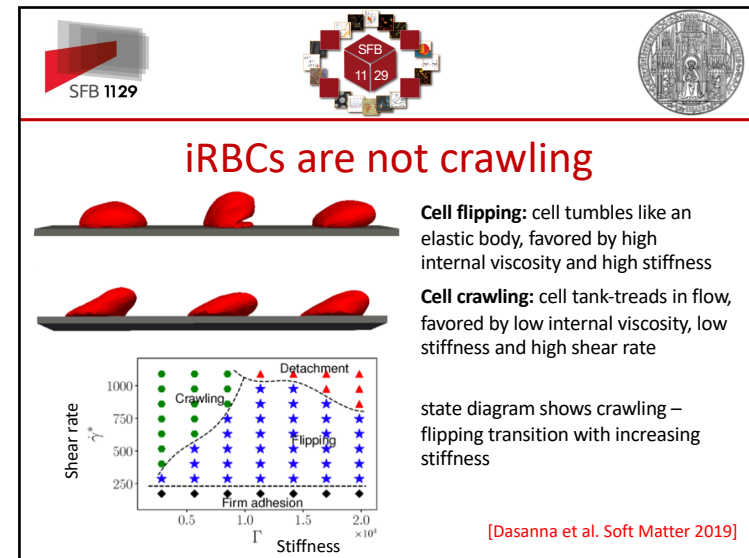
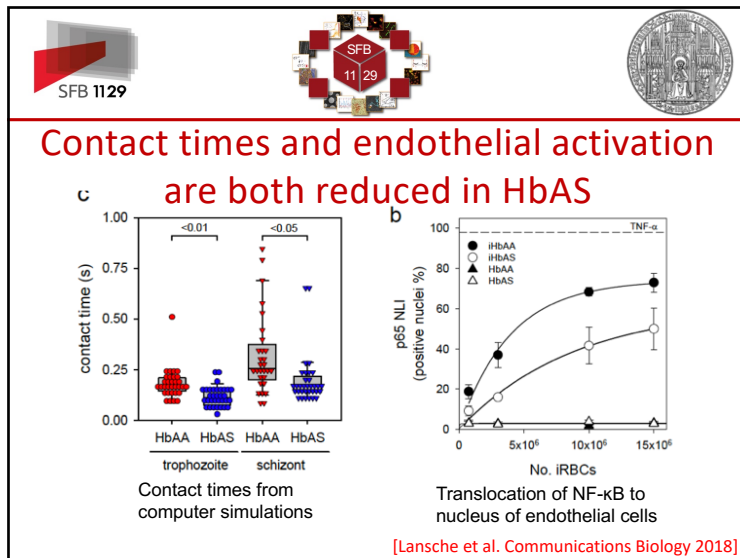
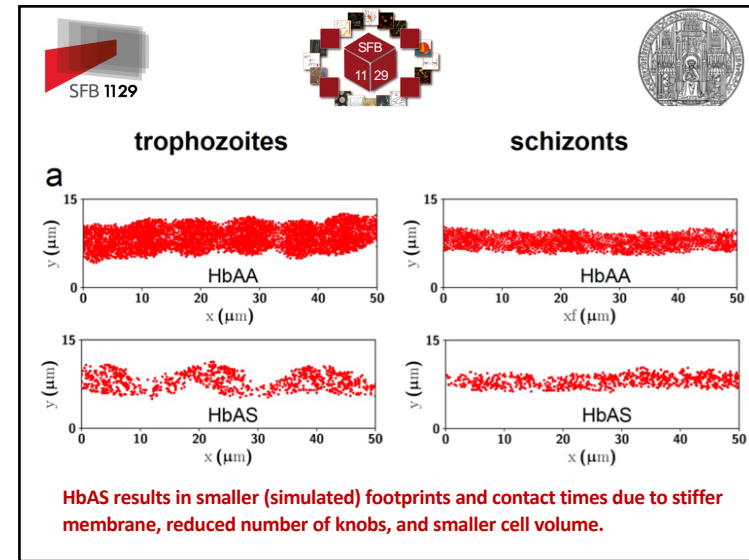
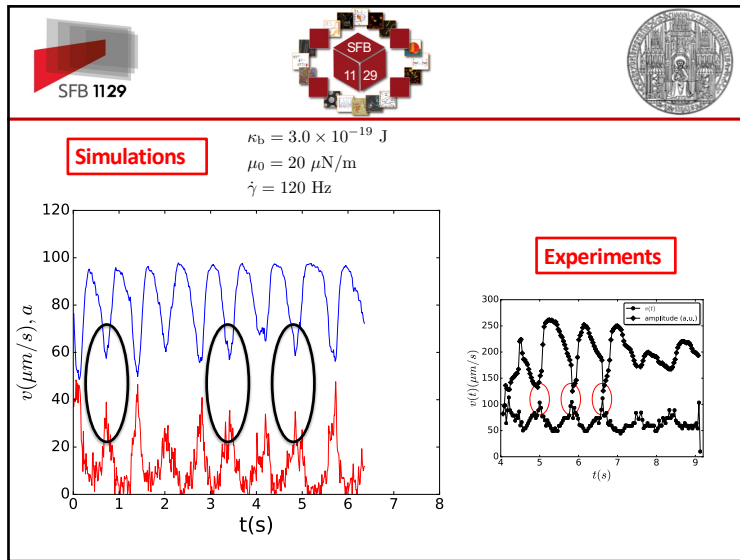
Flow chamber experiments





- Rolling adhesion of trophozoite and schizonts at different shear stresses on endothelial surface.
- Different dynamical states such as non-rolling, firm adhesion and rolling adhesion are observed.
- Both translational velocity and fluorescence intensity of parasite (nucleus) with focus close to membrane are measured.








Two reviews on computational aspects

F 5 Physics of the malaria parasite
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Multiscale Modeling of Malaria-Infected Red Blood Cells
Anil K. Dasanna, Ulrich S. Schwarz, Gerhard Gompper, and Dmitry A. Fedosov

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