Cell Physics

9.–11. Oktober 2019

Welcome...

...to the conference "Cell Physics 2019" at the Saarland University in Saarbrücken, Germany, 9.-11.10.2019. The conference is organized and financed by the Collaborative Research Center SFB 1027 "Physical modeling of non-equilibrium processes in biological systems".

It is intended to be an interdisciplinary platform for scientific exchange between participants from cell biology and biophysics, both represented in roughly equal numbers, and focusses centrally on theoretical concepts in conjunction with cell biological experiments. Topics include

- Cell mechanics
- Cytoskeleton
- Cellular self-organization
- Cell adhesion
- Cell membrane & membrane proteins
- Cancer & immune system

The conference will start Wednesday 9.10.2019 at 8:30 a.m. and finish Friday 11.10.2019 at 5:00 pm. It consists of invited talks, contributed oral presentations and poster sessions.

Heiko Rieger, Ludger Santen
(Saarland University, Germany)

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UNIVERSITÄT DES SAARLANDES

SFB 1027

Cell Physics 2019

9. - 11. Oktober | Saarbrücken

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Cytoskeleton
Cellular Self-Organization
Cell Adhesion
Cell Membrane & Membrane Proteins
Cancer & Immune Response

INVITED SPEAKERS

Patricia Bassereau (Inst. Curie Paris)
Anne Bernheim (Ben Gurion Univ.)
Alexander Bershadsky (NU Singapore)
Timo Betz (Univ. Münster)
Laurent Blanchoin (CEA Grenoble)
Guillaume Charras (UCL London)
Dennis Discher (Univ. Pennsylvania)
Thierry Emonet (Yale Univ.)
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Rhoda Hawkins (Univ. Sheffield)
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Gijsje Koenderink (AMOLF Amsterdam)
Ana-Maria Lennon-Duménil (Inst. Curie Paris)
Martin Lenz (Univ. Paris-Sud Orsay)
Ilya Levental (Univ. Texas, Houston)
Rudolf Merkel (FZ Jülich)
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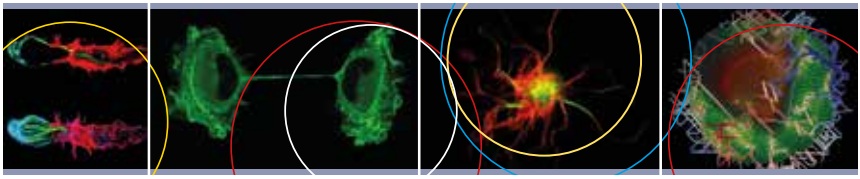

ORGANIZERS (UdS)

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Ludger Santen

http://www.cell-physics.uni-saarland.de

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Conference Program

Wednesday 10.9.2019

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9:30–10:00	Andreas Janshoff	Viscoelastic properties of cells and cellular cortices **I.15**
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Wednesday 10.9.2019

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19:00	Social Dinner (Marquee)			

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Abstracts of Invited Talks

I.1 Linkers at the membrane-cortical actin interface: only linkers?

Julien Pernier[1], Feng-Chin Tsai[1], Remy Kusters[1], Yosuke Senju[2], Hugo Bousquet[3], Jean-François Joanny[1], Pekka Lappalainen[2], Evelyne Coudrier[3], **Patricia Bassereau**[1]

[1] *Physico-Chimie Curie , Institut CurieParis, France*

[2] *Institute of Biotechnology, University of Helsinki, Finland*

[3] *Cell Biology and Cancer, Institut Curie, Paris, France*

The cortical actin cytoskeleton is a dynamic and polarized network that grows from the plasma membrane. It is dynamically coupled to the plasma membrane by different types of linkers: type 1 myosin motors, BAR-domains proteins with an intrinsically curved shape and ERM (Ezrin-Radixin-Moesin) proteins that play different roles at the membrane-cortex interface. Using in vitro biomimetic assays, we have evidenced that these linkers influence both the cytoskeleton organization and the localization of cytoskeletal forces on the membrane, thus the cell membrane shape. First, we have shown that the non-processive Myosin 1b has a direct effect on actin dynamics and architecture: it depolymerizes actin at the plus-end, which is due to its catch-bond property (i.e. actin-myosin interaction lifetime is increased by 2 orders of magnitude under load) [1] and it also transforms branched actin network in parallel actin bundles (Pernier, in preparation). The I-BAR domain protein IRSp53 that is a curvature sensor (Prevost et al., 2015), spontaneously forms clusters on membranes, which allows local recruitment of actin nucleators and actin polymerization for the initiation of cellular protrusions such as filopodia (Tsai, in preparation). In contrast, ezrin, the most abundant actin-membrane linker, binds to actin in a phosphorylation-dependent manner and is often found enriched in curved cellular protrusions (for instance microvilli, filopodia). Our in vitro experiments evidence that ezrin is not a curvature-sensor protein but is recruited in protrusions through a direct interaction with the curvature-sensor IRSp53, where it reinforces the interaction between actin filaments and the cell membrane.

[1] Pernier, J., Kusters, R., Bousquet, H., Lagny, T., Morchain, A., Joanny, J.-F., Bassereau, P., and Coudrier, E. (2019). A new actin depolymerase: a catch bond Myosin 1 motor. bioRxiv, 375923.

[2] Prevost, C., Zhao, H., Manzi, J., Lemichez, E., Lappalainen, P., Callan-Jones, A., and Bassereau, P. (2015). IRSp53 senses negative membrane curvature and phase separates along membrane tubules. Nat Commun 6, 8529.

I.2 Spontaneous shape transitions of active contractile sheets

Anne Bernheim-Groswasser[1] and Yaron Ideses[1], Vitaly Erukhimovitch[1], Ron R. Brand[1], Samuel Safran[2], Karsten Kruse[3]

[1]*Department of Chemical Engineering, Ilse Kats Institute for Nanoscale Science and Technology, Ben Gurion University of the Negev, Beer-Sheva, Israel*

[2]*Department of Chemical and Biological Physic, Weizmann Institute of Science, Rehovot, Israel.*

[3]*Departments of Biochemistry and Theoretical Physics, University of Geneva, Geneva, Switzerland*

Shape transitions in developing organisms can be driven by active stresses, notably, active contractility generated by myosin motors. The mechanisms generating tissue folding are typically studied in epithelia. There, the interaction between cells is also coupled to an elastic substrate, presenting a major difficulty for studying contraction induced folding. Here we study the contraction and buckling of active, initially homogeneous, thin elastic actomyosin networks isolated from bounding surfaces. The network behaves as a poroelastic material, where a flow of fluid is generated during contraction. Contraction starts at the system boundaries, proceeds into the bulk, and eventually leads to spontaneous buckling of the sheet at the periphery. The buckling instability resulted from system self-organization and from the spontaneous emergence of density gradients driven by the active contractility. Our system offers a well-controlled way to study mechanically induced, spontaneous shape transitions in active matter [1].

[1] Ideses Y. et al., Nat. Comm, 9, 2461 (2018).

I.3 Crosstalk between myosin IIA filaments, integrin-mediated cell-matrix adhesions, and microtubules

Alexander D. Bershadsky[1,2]

[1]*Mechanobiology Institute, National University of Singapore, Singapore 117411, Singapore, and* [2]*Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot 7610001, Israel*

Actomyosin cytoskeleton and cell-matrix adhesions are the key elements determining cell morphogenesis. Transmembrane integrin receptors trigger the assembly of various types of actin filament-based adhesion structures, such as focal adhesions, filopodia, and podosomes. These structures are all myosin-IIA-dependent but their dynamics and function are controlled by myosin-IIA-filaments in a differential manner. In particular, assembly of myosin-IIA-filaments promotes growth of focal adhesions but disrupts podosomes. A feedback response from the integrin adhesions to the myosin IIA filaments is in part mediated by another essential cytoskeletal system, microtubules. Guanine nucleotide exchange factor GEF-H1 is trapped and inactivated by microtubules when they are coupled with integrin adhesions via KANK family proteins. Uncoupling microtubules from the integrin adhesions allows the release and activation of GEF-H1 followed by triggering Rho/Rho kinase (ROCK) pathway, and thereby the assembly of myosin IIA filaments, which in turn remodel the adhesions. These regulatory processes may play a role in cell migration and angiogenesis.

[1] S. Hu et al., Nat Cell Biol. 19, 133 (2017).
[2] N.B.M. Rafiq et al., Nature Materials 18, 638 (2019).
[3] N.B.M. Rafiq et al., Phil. Trans. R. Soc. B 374, 20180228 (2019).

I.4 Walk my way: Collective migration in development and cancer

Timo Betz[1]

[1]*University Münster, Institute of Cell Biology*

Understanding tissue dynamics is a key element for new insights into cancer cell invasion, development and wound healing. Tissues mechanics is commonly described in analogy to liquids, sharing many properties like relaxation of shear forces and collective flows as response to mechanical stress. However, the fact that active forces are generated on the single cell level increases complexity of the description considerably. While individual cells are the source of active forces, they couple to each other in a collective fashion, thus leading to global effects on the tissue level which eventually drives tissue flow and morphogenesis. Here we study to which extend hydrodynamics approaches and simple wetting ideas can be used to explain the early collective migration in zebrafish epiboly. In a second direction we present a new collective bursting growth mechanism found as a striking, invasion like phenotype of cancer cell spheroids.

I.5 Reconstitution of the dynamic steady state of actin networks

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The dynamic assembly and turnover of actin networks in cells control shape changes, migration and organelle function, as well as communication with extracellular substrates or neighbors. The intracellular actin cytoskeleton forms such complex intricate networks in cells that it is difficult to identify the principles of their dynamic self-organization. We have developed reconstituted systems in vitro as simplified models for the study of the cytoskeleton. Using this approach, we have established general principles on how the dynamic steady state of actin network emerges from biochemical and structural feedbacks.

I.6 Dissecting the intercellular forces shaping tissues

Guillaume Charras[1,2] and Jonathan Fouchard[1], Kazunori Yamamoto[1], Alexandre Kabla[3], Hervé Turlier[4], Amsha Proag[5], Magali Suzanne[5]

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During embryonic morphogenesis, tissue shape arises from interactions between cells. In tissues, the spatial patterning of cellular surface stresses generated by myosins interplays with intercellular adhesion to yield complex shapes. Here, I will present recent work examining interactions between cells in vivo and in vitro in small and large cell aggregates.

To study the interplay between cortical tension and intercellular adhesion, we examine the early C Elegans embryo, in which clear mechanical differences exist between the different cell lineages that arise from asymmetric division in the one cell embryo. We explore how dynamic changes in cell arrangement arise from dynamic mechanical and adhesive changes occurring during development.

While in plane stresses acting during development have received considerable interest, little is known about out-of-plane mechanics in planar tissues. Yet, epithelial monolayers are thought to generate active torques due to the polarized distribution of myosin molecular motors along their apico-basal axis. However, the amplitude of those torques and the bending modulus of monolayers have never been measured, making the contribution of out-of-plane forces to morphogenesis impossible to evaluate. We identify tissues in vivo and in vitro that curl when a free surface is created and use epithelial curling as a model phenomenon to investigate active torques.

I.7 Nuclear rupture at high curvature & high rates causes defects in DNA repair, affecting cell cycle, differentiation, & genome variation

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The nucleus links physically to cytoskeleton, adhesions, and extracellular matrix – all of which are subject to forces. We find nuclear rupture in tumors [1], embryonic organs [2], and various *in vitro* models results from high nuclear curvature and leads to cytoplasmic mis-localization of multiple DNA repair factors and transcription factors. Curvature is imposed by an external probe [1], by migrating quickly (not slowly) through small constricting pores [3,4], or simply by cell attachment to either aligned collagen fibers or stiff matrix [1], and theory indicates rupture pores from by a heterogeneous nucleation mechanism [5]. Mis-localization of nuclear factors is greatly enhanced by depleting lamin-A, requires many hours for nuclear re-entry, and correlates with pan-nucleoplasmic foci of the DNA damage marker γH2AX and with electrophoretic breaks. Excess DNA damage is rescued in ruptured nuclei by co-overexpression of multiple DNA repair factors as well as by soft matrix or inhibition of either actomyosin tension or oxidative stress – with combination treatments needed to rescue cell cycle suppression [4]. Increased contractility has the opposite effect, and stiff tumors with low lamin A indeed exhibit increased nuclear curvature, more frequent nuclear rupture, and excess DNA damage. Normal differentiation processes of myogenesis and ostoegenesis are also affected by migration through constricting pores, suggesting general effects on cell fates [6]. Mis-repair of DNA is further suggested by two cancer lines that, after constricted migration, exhibit greater genome variation [1,3].

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[2] S Cho ... Discher DE. Mechanosensing by the lamina protects against nuclear rupture, DNA damage, and cell cycle arrest. *Developmental Cell* (2019).
[3] J Irianto ... DE Discher. DNA damage follows repair factor depletion and portends genome variation in cancer cells after pore migration. *Current Biology* (2017).
[4] Y Xia ... Discher DE. Rescue of DNA damage after constricted migration reveals bimodal mechano-regulation of cell cycle. *Journal of Cell Biology* (2019).
[5] D Deviri ... Discher DE, Safran SA. Scaling laws indicate distinct nucleation mechanisms of holes in the nuclear lamina. *Nature Physics* (2019).
[6] LR Smith ... Discher DE. Constricted migration modulates stem cell differentiation. *Molecular Biology of the Cell* (2019).

I.8 Molecular simulations of protein-membrane interactions during membrane fusion

Jochen Hub[1]

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Viral fusion proteins catalyze the fusion of the viral envelope with the host membrane, thereby allowing the virus to deliver its genome into the cytoplasm of the host cell. In this talk, a combined crystallographic and simulation study on the interactions of a class II fusion protein of rift valley fever virus is presented, which presents a major thread to humans and life stock throughout Africa. Both in the crystal and in MD simulations, we observe a specific recognition pocket for phosphatidylcholine (PC) lipids. Notably, the pocket is conserved throughout class II fusion proteins, suggesting that viruses do not merely anchor themselves into the hydrophobic membrane core, but that they may also sense the lipid composition of their host. Further. The simulations provide a atomic-level rationale for cholesterol-dependent membrane binding of the protein.[1]

The opening of the fusion pore has been suggested as the rate-limiting step during fusion. To rationalize such findings in energetic terms, and presented in the second part of the talk, we develop rigorous methods for computing the free-energy landscape of the opening and closing of membrane pores, so far with a focus on flat membranes. With these methods, we recently confirmed a 40-year old hypothesis on metastability (ability to live long) of membrane pores.[2,3]

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I.9 Jamming transitions of cancer cells during tissue invasion

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Cancer cell migration is a plastic and adaptive process which depends on molecular and physical properties of the microenvironment. When monitored in vivo using intravital multiphoton microscopy, tissue microniches provide invasion-promoting tracks that enable collective migration along tracks of least resistance. In regions of tissue confinement, invading cancer cells undergo a jamming transition towards collective migration and circulate as both individual cells and multicellular clusters for collective organ colonization. Using targeted interference with cadherin adhesion systems, conversion from collective invasion to single-cell dissemination was obtained only in zones of low tissue confinement, whereas at high tissue density multicellular migration was enforced. The data suggest that metastatic cancer cells can undergo physicochemical reprogramming in response to physical determinants of the encountered tissue, and thereby balance cell-intrinsic adhesion and mechanocoupling with encountered cues.

I.10 Molecular mechanisms of extreme mechanostability in microbial adhesion

Hermann E. Gaub[1]

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Life is based on interactions between molecules. A large number of these molecular complexes are optimized for adequate resilience to mechanical stress e.g. to allow for adhesion, motility, and structural integrity in cells and tissues. In prokaryotic cells or in tissue of higher organisms the typical forces stabilizing these protein complexes peak in the range of tens of piconewtons. However, certain prokaryotic adhesion complexes were recently found to provide significantly higher mechanical stability beyond nanonewton values, reaching the limit of covalent bonds. We combined AFM-based SMFS with all-atom steered MD simulations to investigate the molecular mechanisms governing this extraordinary stability. This hybrid *in-vivo* and *in-silico* single molecule force spectroscopy reveals details of the force propagation paths and the delicate balance of unbinding and unfolding processes of the protein complexes under load. In this talk, an overview on recent discoveries on the high resilience complexes of cellulosomal constituents of different cellulolytic microbes and on the adhesion complexes of various staphylococcus strains will be given.

[1] Molecular mechanism of extreme mechanostability in a pathogen adhesinLukas F. Milles, Klaus Schulten, Hermann E. Gaub, Rafael C. BernardiScience, March 2018, DOI: 10.1126/science.aar2094.

[2] Direction matters: Monovalent Streptavidin/Biotin complex under load
Steffen M. Sedlak, Leonard C. Schendel, Marcelo C. R. Melo, Diana A. Pippig, Zaida Luthey-Schulten, Hermann E. Gaub, and Rafael C. Bernardi, Nano Lett., October 2018, doi:10.1021/acs.nanolett.8b04045

[3] Calcium stabilizes the strongest protein fold
Lukas F. Milles, Eduard M. Unterauer, Thomas Nicolaus, Hermann E. GaubNature Communications, November 2018, DOI: 10.1038/s41467-018-07145-6

I.11 Force exertion on the cell nucleus

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Cells actively generate force on the cell nucleus. In this talk I will focus on force exerted on the nucleus during cell migration. Active gel theory has proved a useful paradigm for modelling the cell cytoskeleton and applications to cell migration. Given that the cytoskeleton is connected to the nucleus via LINC complex proteins, how does this affect the nucleus? Here I will treat the nucleus as a passive mechanical object and describe how it is moved by an active gel model of the cytoskeleton.

I will then consider the deformation of nuclei during cell migration through constrictions. Starting from experimental images and a simple elastic model of the nucleus I will describe the forces required to deform the nucleus to pass it through constrictions smaller than its usual size.

I.12 Dynamics of cell state transitions – theory & single-cell transcriptomics

Sui Huang[1]

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The 'cell state' can be operationally defined by the configuration of activities of all gene loci in the genome and is approximately measured by the transcriptome. Since gene loci interact, transcriptomes change in a highly constraint manner (only certain configurations are possible), generating the characteristic dynamics of cell states: existence of stable attractors (which map to 'cell types') and instabilities. The ensuing phenotype plasticity is essential in development. But it is also at the core of tumor progression, where new phenotypes are still explained by genetic mutations while non-genetic plasticity is ignored [1]. Enters single-cell transcriptomics which affords the capacity to measure the state of individual cells in a population traditionally thought to be uniform, and to explore cell states dynamics predicted by theory: attractor dynamics and critical transitions with macroscopic consequences [2]. This talk deviates from the conference topic 'CELL PHYSICS', where 'physics' refers to the material aspect of cells, but suits the Collaborative Research Center's focus around "non-equilibrium processes in biological systems". After an introduction to theoretical principles of cell state dynamics that shall be of general utility, I will present experimental data on critical transitions in development and cancer and associated counterintuitive phenomena.

[1] Brock, A. & Huang, *S. Cancer Res 77*, 6473-647 (2017).
[2] Mojtahedi,M., et. al. (2016). *PLoS Biol* 14, e2000640 (2016).

I.13 Remodeling and destruction of biological membranes

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Living cells have developed elaborate machineries to create, shape, and maintain lipid membranes. Conversely, pathogens have developed equally elaborate machineries to attack, invade, and destroy the lipid membranes of their hosts. In my talk I will show how molecular simulations give us a detailed understanding of the physico-chemical principles underlying key membrane remodeling and destruction processes in normal cellular functions and in disease. I will concentrate on the action of the membrane receptor FAM134B in the autophagy of the ER and on membrane perforation by bacterial cytolysins.

I.14 The tubulin code – a mechanism to control microtubule properties

Carsten Janke[1], Satish Bodakuntla[1], A.S. Jijumon[1], Maria M. Magiera[1]

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The tubulin code is a concept predicting that functions of the microtubule cytoskeleton are regulated, or even determined, by a variety of biochemically complex tubulin posttranslational modifications [1,2]. While this concept looks at the first glimpse like a straight-forward regulatory system, only few functions could so far be attributed to specific tubulin modifications.

We use a combination of in-vitro and in-vivo approaches to determine how microtubule properties and functions are controlled in neurons. Neurons are particularly dependent on the microtubule cytoskeleton, which is essential for a multitude of their physiological functions. We have shown that deregulation of one posttranslational modification of tubulin, polyglutamylation, leads to neurodegeneration due to slight perturbations of organelle transport [3], indicating that this modification might only subtly, but significantly alter microtubule functions. We developed novel approaches to directly measure the molecular mechanisms that are controlled by polyglutamylation, which will be presented here.

The concept that arises from our work is that fine-tuning mechanisms might be key for understanding how physiological processes are kept in balance over longer periods of time and changing environmental conditions. Their perturbation might be a so-far underestimated trigger for late-onset diseases such as neurodegeneration and cancer.

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I.15 Viscoelastic properties of cells and cellular cortices

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The mechanical properties of cells influence their shape and cellular functions, including cell adhesion, migration, growth, and differentiation. Cellular elasticity and cortex structure are found to be inherently interwoven and largely responsible for the cells' response to external mechanical stimuli.

We propose a shell-based tension-model to describe the mechanical response of cells to external probing and examined the impact of cell-size, cortex integrity, cortex attachment to the plasma membrane, cell-substrate adhesion, cell-cell-contacts and motor activity on the viscoelastic properties of cells.

In order to unequivocally relate the viscoelastic properties found for living cells to the mechanics of the cellular cortex we devised a top-down strategy to measure the viscoelasticity of isolated cortices. We found that the mechanical properties of isolated cortices resemble those of living cells, however, with a stiffening effect that can be resolved by invoking motor activity externally.

I.16 From mechanical resilience to active material properties in biopolymer networks

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The cells and tissues that make up our body juggle contradictory mechanical demands. It is crucial for their survival to be able to withstand large mechanical loads, but it is equally crucial for them to produce forces and actively reconfigure during biological processes such as tissue growth and repair. The mechanics of cell and tissues is determined by fibrous protein scaffolds known as the cytoskeleton and the extracellular matrix, respectively [1]. Fibrous networks have many advantageous mechanical properties: fibers can form space-filling elastic networks at low volume fractions and they reversibly stress-stiffen, which provides protection from damage. It is still poorly understood how biopolymer networks can combine these features with the ability to dynamically adapt their structure and mechanics. I will summarize recent insights in this question obtained via quantitative measurements on reconstituted biopolymer networks across molecular to network scales. I will focus on the cytoskeleton, which combines mechanical strength with the ability to generate forces by means of active filament (de)polymerization and the action of motor proteins, and on the extracellular matrix, which is adaptive due to mechanochemical activity of resident cells.

[1] F. Burla, Y. Mulla, B.E. Vos, A. Aufderhorst-Roberts, G.H. Koenderink, Nature Physics Reviews 1, 249 (2019).

I.17 Impact of mechanical stress on the immune-surveillance function of dendritic cells

Dr. Ana-Maria Lennon-Duménil[1]

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Dendritic cells (DCs) exert their immune-surveillance function by sampling tissues and migrating to lymph nodes where they transmit the information to T cells. In homeostasis, only few DCs migrate to lymph nodes, this being nonetheless essential to maintain T cell tolerance. Upon inflammation, the number of migratory DCs increases and they now activate T cells that initiate the adaptive immune response. The microenvironment of DCs in peripheral tissues therefore determines the information transmitted to T lymphocytes and type of immune response these cells ultimately develop.

The DC microenvironment in tissues consists not only of biochemical cues (cytokines, chemokines, microbial products...) but also of physical ones (geometry, pressure, stiffness...). The latter result from the materials tissues are made of -cells, matrix and fluid- and from their 3-D organization. How physical signals impact the immune-surveillance function of DCs is unknown. This question becomes highly relevant when considering the tremendous physical changes that peripheral tissues undergo upon inflammation/infection.

During my talk, I will discuss how the mechanical stress that DCs experience in peripheral tissues shapes their migration and immune-surveillance functions.

I.18 Elasticity from entanglements in branched actin

Martin Lenz[1,2] and Mehdi Bouzid[1], Cesar Valencia-Gallardo[2], Lara Koehler[1], Julien Heuvingh[2], Olivia du Roure[2]

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The biologically crucial elasticity of actin networks is usually understood as an interplay between the bending and stretching of its filaments. This point of view however fails when applied to the weakly coordinated branched actin networks found throughout the cell. Through experiments and theory, we show that their elasticity crucially involves reversible entanglements between their filaments. These entanglements can in turn be controlled during network growth to regulate the final properties of the network. These properties could be key to understanding how moving cells dynamically adapt their cytoskeleton to their environment.

I.19 Cyclic stretch is a potent cue for animal cells

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Throughout the organism, all tissue cells experience mechanical strain, e.g. due to the pulsating blood flow. Cells recognize, process, and act upon this signal. To study this mechanoresponse we applied well-defined mechanical strain cyclically to cultivated cells [1]. Cellular mechanoresponses were quantified via reorientation of cytoskeletal fibers. In cultivated endothelial cells we compared responses of actin, microtubules, and vimentin [2, 3] using a correlation-based algorithm that enabled quantification of cytoskeletal order. We observed distinctly different ordering dynamics and amplitudes [3].

Even though the rigid skull protects the brain, it experiences intense mechanical deformations. Therefore we studied mechanoresponses of primary neurons from cortices of rat embryos. We observed a pronounced reorientation of neuronal dendrites upon cyclic strain and found a surprising mechanical resilience of these cells that survived even several days of uniaxial, cyclic stretching at an amplitude of 28% and a frequency of 300 mHz [4].

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[2] A. Zielinski et al., Cytoskeleton 75, 385 (2018).
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I.20 Dynamics and heterogeneity of inflammatory signaling in cells and tissues

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Immune cells must accurately decode changing environmental signals to make fate decisions and coordinate tissue-level responses. Here we use a suite of single cell biology approaches including mathematical modelling, live-cell time-lapse microscopy and transcriptomics to understand signaling of the Nuclear Factor kappa B (NF-κB) system, a master regulator of inflammatory and immune responses. We show that this presumably noisy system, uses oscillatory „deterministic" refractory states to encode closely timed inflammatory cues [1], and operates in the cytokine consumption regime to restrict out-od-control propagation of the inflammation in the tissue [2]. We also demonstrate, that downstream of NF-κB activation, the stochastic expression of NF-κB-dependent genes is constrained by transcriptional bursting. Our analyses suggest that seemingly stochastic immune cells responses are defined by functional constrains.

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I.21 Morphodynamics and mechanosensitivity of spreading T cells

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The ability of a T cell to explore environmental mechanical cues, through bonds formed by its special receptors called T cell receptors (TCRs), is crucial for the first steps of immune recognition. While the mechanobiology of the TCR at the molecular level is increasingly well documented, its link to cell-scale response is poorly understood. We show that the response of T cells, quantified in terms of their spreading behaviour, is biphasic with substrate stiffness when mediated through TCRs [1]. However, when the ligands of the T cell integrins are additionally involved, the cellular response becomes monotonic [1]. This ligand-specific mechanosensing is effected through an actin-polymerization–dependent mechanism [2]. Based on a mesoscale model, this unusual response can be attributed to differences in force sensitivity and effective stiffness of the link formed between the ligand/receptor pairs and the actin cytoskeleton [1,2]. This may provide a general mechanism for immune cells to discriminate mechanosensitive bonds.

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I.22 Physical effects catalyzing cell adhesion: from mimetic systems to tissues

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A number of cell functions rely on the formation of macromolecular platforms in the plasma membrane. While the functional role of these assemblies has been intensively investigated over the years, little is known about the mechanisms underlying their formation. In this presentation, several possible physical pathways will be explored by studying adhesion of mimetic vesicles, cells and epithelial tissue. Focusing on the formation of adhesion domains, the role of membrane elasticity, composition fluctuations, and the interactions with the cytoskeleton will be discussed. Furthermore, cooperative attachments of proteins with different length, flexibility and affinities will be analyzed, allowing the development of a hypothesis regarding the simultaneous repellent and catalytic roles of the glycocalyx in adhesion. In the closing, the relation between cell adhesion and mechanoresponse in cellular aggregates will be examined.

I.23 The architecture and mechanics of ezrin-linked minimal actin cortices

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The actin cortex is a thin cross-linked network attached to the plasma membrane, being responsible for the cell's shape during migration, division and growth. Direct linkage between the plasma membrane and the actin cortex is controlled by ezrin, a member of the ezrin-radixin-moesin protein family. To become fully functional, ezrin switches from a "dormant" to an active state controlled by binding to the lipid PI(4,5)P_2 and phosphorylation of a conserved threonine residue [1,2]. In a reductionist approach, we have created minimal actin cortices on a supported 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC) bilayer doped with the receptor lipid phosphatidylinositol(4,5)-bisphosphate (PtdIns(4,5)P_2) to which a constitutively active mutant of ezrin was bound. With this approach, we can modulate the individual components of the membrane, its linkage as well as the actin network including cross-linkers and myosin. By means of fluorescence microscopy, we were able to relate the F-actin architecture to the number of PIP_2/ezrin binding sites at the membrane interface [3] and could resolve the impact of cross-linkers such as fascin and α-actinin on the F-actin structure [4]. Dynamic changes of the network were observed in the presence of myosin motors. Bead tracking microrheology on the membrane attached actin network provided further information about the viscoelastic properties [3]. Our results demonstrate that ezrin serves as a dynamic cross-linker for the actin cortex attached to a lipid bilayer.

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I.24 How microtubules induce local membrane protrusion

Tatyana Svitkina[1], Nadia Efimova[1], Changsong Yang[1], Jonathan Chia[1], and Kristi Neufeld[2]

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Microtubules play key roles in directional cell migration and neuron navigation, but the underlying mechanisms are extremely complex and poorly understood. We show that microtubules can regulate these processes by inducing assembly of branched actin networks at their tips and thereby driving local membrane protrusion. The key role in this mechanism in growth cones of cultured rat hippocampal neurons belongs to adenomatous polyposis coli (APC), a protein with both tumor suppressor and cytoskeletal functions. APC is localized at the interface between the microtubule and associated branched actin filaments. APC knockdown leads to severe depletion of branched actin filaments in growth cones and abrogates growth cone recovery after repellent-induced collapse. Overexpression of APC in non-neuronal cells induces elongated processes by a mechanism that depends on the N-terminus of APC. When dynamic APC-positive microtubule tips hit the cell edge in these cells, they often induce local actin- and cortactin-rich protrusions. Together, our data suggest a novel mechanism by which microtubules can navigate growth cone guidance and cell migration.

I.25 Directed migration of lymphocytes by integrins

Olivier Theodoly[1], Marie-Pierre Valignat[1], Alexander Hornung[1], Thomas Sbarrato[1], Nicolas Garcia-Seyda[1], Laurene Aoun, Xuan Luo[1], Martine Biarnes-Pelicot[1]

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Upon recruitment from blood to inflamed zones, leukocytes cross blood vessels endothelium at transmigration portals enriched in integrins ligands[1] and then migrate in inflamed tissues with an arguable integrin-dependent manner[2,3]during inflammation, changes to the extracellular matrix (ECM. These observations suggest that integrins play a direct or indirect role in leukocyte guided migration in vivo. In vitro, crawling lymphocytes orient either with or against a flow on substrates coated by ligands of integrins[4–6] T lymphocytes are captured by the endothelium and migrate along the vascular wall to permissive sites of transmigration. These processes take place under the influence of hemodynamic shear stress; therefore, we investigated how migrational speed and directionality are influenced by variations in shear stress. We examined human effector T lymphocytes on intercellular adhesion molecule 1 (ICAM-1. In absence of flow, their orientation is further biased towards increasing or decreasing gradients of integrins ligands density[7]. These rheo- and hapto-taxis phenotypes reveal original and robust capacities of integrins to direct leukocytes migration with mechanisms involving integrins spatio-temporal activation and cross-talk.

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I.26 Cell growth rate dictates the onset of glass to fluid-like transition and long time super-diffusion in an evolving cell colony

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Collective migration dominates many phenomena, from cell movement in living systems to abiotic self-propelling particles. By focusing on the early stages of tumor evolution, I hope to enunciate the principles involved in cell dynamics and highlight their implications in understanding similar behavior in seemingly unrelated soft glassy materials and possibly chemokine-induced migration of CD8+ T cells. Using simulations and theory I will show that tumor cells at the periphery move with higher velocity perpendicular to the tumor boundary, while motion of interior cells is slower and isotropic. The mean square displacement, of cells exhibits glassy behavior at times comparable to the cell cycle time, while exhibiting super-diffusive behavior at longer times. A sketch of the theory for these characteristics motion will be given. In the process we establish the universality of super-diffusion in a class of seemingly unrelated non-equilibrium systems. Our findings for the collective migration, which also suggests that tumor evolution occurs in a polarized manner, are in quantitative agreement with in vitro experiments. Although set in the context of tumor invasion the findings should also hold in describing collective motion in growing cells and in active systems where creation and annihilation of particles play a role.

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I.27 Torques and forces in the mitotic spindle

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The mitotic spindle is a fascinating and complex micro-machine made of microtubules and the accompanying proteins. Spindle microtubules attach to chromosomes via protein complexes called kinetochores. We have recently shown that a bundle of antiparallel microtubules, termed "bridging fiber", connects sister kinetochore fibers [1, 2]. Bridging microtubules are linked together by the protein regulator of cytokinesis 1 (PRC1). To explore the role of bridging fibers, we developed an optogenetic approach to remove PRC1 from the spindle in a fast and reversible manner. PRC1 removal during metaphase reduced bridging fibers, changed spindle shape, decreased interkinetochore distance, and resulted in misaligned chromosomes. Thus, our optogenetic experiments show that PRC1, by crosslinking bridging microtubules and kinetochore fibers, regulates spindle mechanics and forces acting on kinetochores in metaphase, promoting chromosome alignment. In addition to linear forces, rotational forces (torques) may also exist in the spindle. We have shown that the spindle is chiral, based on our finding that microtubule bundles follow a left-handed helical path [3]. Our theoretical model predicts that bending and twisting moments generate curved shapes of the bundles. We conclude that torques, in addition to linear forces, exist in the spindle and determine its chiral architecture.

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Abstracts of Contributed Talks

C.1 A simple model of keratocyte interface dynamics

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The cell interface dynamics is studied analytically in the framework of the nonlocal phase field model suggested in [1]. That model includes an equation for the order parameter coupled with an equation for the two-dimensional vector field, which describes the actine network polarization. A close evolutionary integro-differential equation governing the interface shape is derived. That equation provides the dependence of the normal velocity of the membrane on the interface curvature and some other relevant parameters. In a certain limit, the governing equation is reduced to a Burgers-like equation. The criteria for the existence of a stationary shape is obtained.

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C.2 Biochemical and electrophysiological approaches for studying the stoichiometry of ORAI channels

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The dynamics of intracellular Ca^{2+} signals govern a wide variety of cellular functions. Especially for long lasting processes cells rely on the so-called store-operated Ca^{2+} entry pathway. STIM1 proteins in the endoplasmic reticulum (ER) sense a decrease of the Ca^{2+} concentration, then react by clustering and trapping of ORAI1 proteins, located in the plasma membrane, to form functional Ca^{2+} channels in close apposition to the ER. ORAI channel stoichiometry may thus change during different functional states (i.e. at rest, and during channel activation). The assembly and stoichiometry of ORAI channels remains controversial with dimeric, tetrameric as well as hexameric assemblies being reported. To address these possibilities we generated cells lacking endogenous ORAI1-3 channels using CRISPR-Cas9 mediated gene deletion. We used these cells to express monomeric *ORAI1* channels or ORAI1 concatenated to a second ORAI1 or an ORAI2 subunit. We expressed ORAI1 with a genetically encoded HA tag and treated cells with cell membrane (im)-permeable cross linkers. Our results showed that the stoichiometry of the ORAI1 multimers did not change upon activation of cells. Furthermore, blue native gel analysis showed that ORAI1 exists mainly as a multimeric complex of an estimated molecular weight of at least a hexameric channel. Electrophysiological and fura-2 based Ca^{2+} imaging analyses of heterodimeric ORAI1-ORAI2 channels with varied concatenation sequence, indicate that the biophysical properties of the channel are mainly determined by the channel occupying the second subunit position.

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C.3 Mechanical phenotyping of single cells using shear and inertial microfluidics

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Disease can alter the biological constituents of cells and as such, whole cell deformability can be a marker of disease state. Microfluidics is an appealing technique for mechano-phenotyping due to being high-throughput. Cell viscoelasticity results in a mechano-response dependent on stress, strain-rate and technique. Typically, microfluidics hydrodynamically deforms cells under inertia or shear-dominant stress. Where inertia-dominant regimes show sensitivity to cytoplasmic and nuclear changes [1], shear regimes show more sensitivity to cytoskeletal changes [2]. Here, cells were deformed in a microfluidic extensional flow using both inertial and shear flows, measuring their maximum stretch at a stagnation point. HL60 cells showed different mechano-responses dependent on flow regime [3]. Microfilaments were disrupted using LatA, which showed cell softening in a low-strain shear-dominant regime. Assays were also done using the microtubule disruptor CA4 and chromatin decondenser TSA. Overall, actin had a larger effect on deformability, and nuclear changes were only detectable in a high-strain and inertia-dominant regime. Colorectal cancer cell lines: SW480, HT29 and SW620, were studied as a model for disease progression. Multiparameter analysis was used to classify cells by tracking deformation and recovery, with elastic moduli found using the Kelvin-Voigt model. Results showed that the cells become softer with disease progression. HT29 and SW620 showed incomplete shape recovery, indicating increased plasticity.

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C.4 Blood platelet formation - a biological rayleigh-plateau instability

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Blood platelets form out of long protrusions, which are established by stem cells into blood vessels of the bone marrow. After extension these protrusions fragment into the blood platelets. Despite experimental identification of cytoskeletal dynamics, a biophysical understanding of this fragmentation into platelets and of its connection to blood flow is at present absent.

We use a newly developed 3D Lattice-Boltzmann/Immersed-Boundary method for active elastic cell membranes in presence of fluid flow [1] to investigate this fragmentation process and provide a biophysical explanation: cytoskeletal active stress triggers a pearling instability, which fragments the protrusion into platelets. This instability can be understood as a biological Rayleigh-Plateau instability with the active stress playing the same role as the surface tension of a liquid jet. Rather than to a biochemical regulation of platelet size, this points to a pure physical regulation, namely by the dominant wavelength of the instability. The presence of external blood flow accelerates the dynamics of the instability strongly in agreement with experimental observations.

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C.5 ESCRT-III helical polymers deform membranes into helical tubes

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ESCRT-III proteins assemble into membrane-remodeling polymers during many cellular processes, ranging from HIV budding to cytokinesis [1]. Despite their biological importance, the mechanism by which ESCRT-III polymers deform membranes is still unclear. In our recent experiments, we have looked at how ESCRT-III helical polymers deform spherical vesicles, in vitro. Surprisingly, we have observed that ESCRT-III helical polymers reshape vesicles into stable helical tubes [2]. A helical tube is an unusual shape for a membrane because of its high local curvature, which should make it energetically more expensive than, for example, a straight tube. Helical polymers could, in principle, generate straight tubes and wind around them. However, we can only observe helical tubes in the experiments, which raises the question of what makes them so energetically favorable. We have addressed this question combining theoretical models, based on the elasticity and mutual interactions of membranes and polymers, with cryoelectron tomography [2]. Our results suggest that the secret behind the stability of helical tubes is an anisotropy in the architecture of ESCRT-III polymers, which makes straight tubular configurations geometrically frustrated.

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C.6 Onset of 3D tissue morphogenesis near integer topological defects

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Distortions or imperfections of ideal patterns, often called defects, are responsible for the selection and steady-state evolution of patterns. Defects are found in several biological systems and they participate in key processes for tissue homeostasis, such as cell extrusion. However, our understanding of the role of defects in biological systems remains still in its infancy [1,2]. Here, we built on a physical description for defects in active polar fluids [3] to study the onset of 3D reshaping of cell monolayers under strong 2D confinement. Our physical approach adds two types of active forces, corresponding to nematic-like cell-cell interactions (active stresses) and polar-like cell-substrate interactions (active traction forces). For sufficiently small confinements, we find a second-order bifurcation between unmoving aster defects to spinning spiral defects. Asters and spirals result in distinct mechanical environments, depending on the confinement geometry and material characteristics. The experimental cell velocity and cell orientation maps fixed the sign of both active forces, and the shape of spirals provided a direct way to measure the flow-alignment coefficient in cell monolayers, which currently remains unknown. Based on these results, asters render compressive stresses at the defect core, resulting in 2D density accumulation and conditioning 3D migration.

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C.7 Tissue competition: coexistence and tumor heterogeneity

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Cells grow and divide, i.e. they change their volume. The conjugate force to a change in volume is pressure. Thus, growing cells exert a mechanical pressure onto their surroundings. Vice versa, mechanical forces feed back onto growth. This leads to a mechanical contribution when tissues compete for space. Typically, the tissue with the higher homeostatic pressure, the pressure at which cell division and death balance, overwhelms the weaker one [1,2,3].

Computer simulations reveal that homeostatic pressure is not the only determining quantity, but that adhesive properties play an important role in tissue competition as well. Small adhesion between the competing tissues leads to coexistence between them in a variety of segregated structures, even when one tissue has a lower homeostatic pressure [4]. These structures break apart when the adhesion between the tissues increases, but coexistence can still be found, given the right adhesive properties of the individual tissues.

Starting from there, we employ a dynamic setup in which cells can mutate and change their mechanical properties dynamically. The obtained results yield a mechanical explanation how intra-tumor heterogeneity may arise.

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C.8 Morphology and mechanics of membrane nanotubes interacting with reconstituted actin networks

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Inside living cells, the remodeling of membrane nanotubes by the dynamics of acto-myosin networks is crucial for processes such as intracellular traffic or endocytosis. However, the mechanisms by which acto-myosin dynamics affect nanotube morphology are largely unknown. To address this question, we perform *in vitro* experiments to decipher the physics of nanotube remodeling in biochemically controlled assays recapitulating key aspects of cellular membranes and actin dynamics. We use two complementary techniques to form membrane nanotubes on which we reconstitute actin networks from purified proteins. By using optical tweezers, we show that actin stabilizes tubes but, depending on the actin actin amount on the tube, transient heterogeneities in the tube radius can appear upon tube elongation.

In parallel, we develop a novel assay to image and study the mechanics of supported nanotubes at the nanometric scale by using Atomic Force Microscopy. A theoretical description of the AFM tip-membrane interaction allows us to relate AFM measurements of the nanotubes' morphology to the membrane mechanical parameters. In addition, we use AFM to assess the induced changes in nanotube physical properties when actin polymerizes at their surface.

C.9 A bottom-up approach to study the interplay between signaling and mechanics in early mammalian embryogenesis

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During early mouse embryonic development, as the blastocyst cavity begins to form and expand, the inner cell mass (ICM) undergoes lineage and spatial segregation to form the primitive endoderm (PrE) facing the blastocyst cavity, and the epiblast (EPI) enclosed between the PrE and the outer trophectoderm. However, the mechanisms driving such cell sorting behavior remain unknown. Furthermore, it remains unclear whether cell position determines their fate, or that the cells are pre-specified in a random manner before sorting out their positions. Here, using a combination of embryological and biophysical approach, we revealed a fluid-to-solid transition that underlies the ICM morphogenesis, which is characterized by a pronounced increase in tissue stiffness and viscosity during ICM maturation. We further showed that increased tissue fluidity correlates with dynamic cellular rearrangements and extensive nuclear shape fluctuations during the sorting phase, while the solid-like phase at the mature stage is accompanied by PrE epithelialization. Notably, cell sorting behavior correlates with changes in nuclear deformability and FGF-mediated actomyosin contractility in the two cell types. Overall, this bottom-up approach allows us to dissect the interplay between cell sorting and fate specification and to establish the mechanochemical feedback loops regulating ICM morphogenesis.

C.10 Microtubule search-and-capture mechanism orchestrates MTOC clustering and nuclear division via proper spindle positioning in yeast

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In budding yeast C. neoformans, the spindle pole body (SPB) formation requires timely clustering of MTOCs, embedded on the outer nuclear envelope. Our *in silico* model for search and capture via cytoplasmic microtubules (cMT), for the first time, identifies redundant mechanisms of MTOC clustering mediated by inter cMT coupling at the nuclear envelope and cMT-cell cortex interactions within the experimentally observed timescale [1, 2]. During early stages of spindle formation, nuclear microtubules (nMTs) form many low tension syntelic and stable high tension amphitelic attachments. Syntelic attachments are degraded and amphitelic attachments are stabilized in presence of Ipl1-mediated phosphorylation gradient, preventing aneuploidy and promoting equal division. Our experimental results suggest that greater amount of nuclear mass is retained by the mother bud in Ipl1-depleted cells [1]. Computer simulations explain that the asymmetric division might stem from the differential functionality of the two SPBs. Delayed/impaired MT nucleation from the SPB settling into the daughter bud accounts for the unequal division.

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C.11 Association of signaling active ErbB2 homodimers with actin-rich membrane structures of cancer cells revealed by liquid phase electron microscopy

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Growth factor receptor 2 (ErbB2) is found overexpressed in many cancers such as gastric or breast cancer and acts as therapeutic target [1]. ErbB2 plays a central role in cancer cell invasiveness and is, as such, closely linked to cytoskeletal reorganization [2]. In order to study the spatial correlation of single ErbB2 proteins and actin filaments, we applied correlative fluorescence microscopy (FM) and high resolution scanning transmission electron microscopy (STEM) on specifically labeled breast cancer cells as described before [3]. For this purpose SKBR3 cells were grown on microchips and transformed with BacMam-GFP-Actin in order to label the actin cytoskeleton. Before prospected to STEM imaging, the cells were labeled with quantum dot (QD) nanoparticles attached to specific anti-ErbB2 Affibodies and covered with graphene. Spatial distribution patterns of ErbB2 in the membrane was studied on actin-rich structures and compared to adjacent flat regions of the same cell, revealing an association of ErbB2 homodimers with actin-rich regions which were not found in flat parts. Next, we treated the cells with 2 µM of Cytochalasin D, disrupting the actin network and inducing ErbB2 distribution patterns similar to that of flat regions. This links signaling active ErbB2 homodimers to actin-rich membrane structures in cancer cells, pointing to a role during cancer cell invasion.

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C.12 Nanomechanical sub-surface mapping of living biological cells by force microscopy

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Mapping force versus distance curves with an atomic force microscope and the local evaluation of soft samples allows the operator to "see" beneath the sample surface and to capture the local mechanical properties [1]. In this work, we combine atomic force microscopy with fluorescence microscopy to investigate cancerous epithelial breast cells in culture medium. With unprecedented spatial resolution, we provide tomographic images for the local elasticity of confluent layers of cells. For these particular samples, a layer of higher elastic modulus located directly beneath the cell membrane in comparison with the average elastic properties was observed. Strikingly, this layer appears to be perforated at unique locations of the sample surface of weakest mechanical properties where distinct features were visible permitting the tip to indent farthest into the cell's volume. We interpret this layer as cell membrane mechanically supported by the components of the cytoskeleton that is populated with sites of integral membrane proteins. These proteins act as breaking points for the indenter and thus explaining the mechanical weakness at these locations. Contrarily, the highest mechanical strength of the cell was found at locations of the cell cores as cross-checked by fluorescence microscopy images of staining experiments, in particular at nucleoli sites as the cumulative elastic modulus of the cell membrane comprising cytoskeletal features and the tight packing ribosomal DNA of the cell [2].

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C.13 Curvature induced rupture of nuclei

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The nucleus is physically linked to the cytoskeleton, adhesions, and extracellular matrix—all of which sustain forces, but the physical consequences of linkage to nuclear integrity and their relationships to DNA damage are obscure. We show that nuclear rupture with cytoplasmic mis-localization of multiple nuclear proteins including DNA repair factors correlates with high nuclear curvature imposed by an external probe or by cell attachment to either aligned collagen fibers or stiff matrix [1,2]. Mis-localization is greatly enhanced by depletion of a main nuclear structure protein lamin-A, and it requires hours for nuclear reentry while also correlating with an increase in pan-nucleoplasmic foci of the DNA damage marker γH2AX. Excess DNA damage is rescued in ruptured nuclei by co-overexpression of multiple DNA repair factors as well as by soft matrix or inhibition of actomyosin tension. Increased contractility has the opposite effect, and stiff tumors with low lamin-A indeed exhibit increased nuclear curvature, more frequent nuclear rupture, and excess DNA damage. Additional stresses likely play a role, but the data indicate high curvature promotes nuclear rupture, which compromises retention of DNA repair factors and favors sustained damage. Further studies underscore roles for heterogeneous nucleation of rupture pores [3] and for rate-dependent curvature effects in migration through a wide range of small, circular pores [4]

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C.13 Mechanotransduction of axonal growth: novel perspectives in mechanobiologyfield

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Axonal growth has always been considered an interesting and enigmatic phenomenon. Historically, the scientific community has considered fundamental the role played by the growth cone, which provides an axonal guidance mechanism, influencing the direction and orientation of the movement, in response to chemical signals [1]. However, recent discoveries have shown that mechanical signalling is just as critical as biochemical signalling for axonal growth [2]. Currently, it is widely accepted that neurites elongate, when mechanical tension is applied, the process being referred as "stretch-growth" [3]. Recently, we developed a methodology to stretch axons by applying extremely low mechanical forces, similar to those generated endogenously [4]. Specifically, magnetic nanoparticles (MNPs) have been used to label axons and to stretch them by using the dragging force generated by a permanent magnet. MNP- mediated stretching has been found to strongly increase the spontaneous elongation rate and the sprouting of primary neurons in culture. Experimental data suggest that local mechanisms, including local translation and local transports, may be involved. These novel perspectives open new horizons in the understanding of the mechanisms that govern axonal growth and, more generally, in the knowledge of what is behind cell response to external mechanical forces.

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C.14 Interplay between membrane elasticity and active cytoskeleton forces regulates the aggregation dynamics of the immunological synapse

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Adhesion between a T cell and an antigen presenting cell is achieved by TCR–pMHC and LFA1–ICAM1 protein complexes. These segregate to form a special pattern, known as the immunological synapse (IS), consisting of a central quasi-circular domain of TCR–pMHC bonds surrounded by a peripheral domain of LFA1–ICAM1 complexes. Insights gained from imaging studies had led to the conclusion that the formation of the central adhesion domain in the IS is driven by active (ATP-driven) mechanisms. Recent studies, however, suggested that passive (thermodynamic) mechanisms may also play an important role in this process. In the talk, I will present our recent study of a simple lattice model which is capable of following the evolution of the system on length scales of several micrometers and time scales of minutes. The model takes into account the membrane-mediated thermodynamic attraction between the TCR–pMHC bonds and the effective forces that they experience due to ATP-driven actin retrograde flow and transport by dynein motor proteins. Monte Carlo simulations exhibit a very good spatio-temporal agreement with the experimentally observed pattern formation of the TCR–pMHC microclusters. The agreement is lost when one of the aggregation mechanisms is ''muted'', which helps to identify their respective roles in the process. We conclude that actin retrograde flow drives the centripetal motion of TCR–pMHC bonds, while the membrane-mediated interactions facilitate microcluster formation and growth. The interplay between the passive and active mechanisms regulates the rate of the accumulation process, which in the absence of one them proceeds either too quickly or slowly

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C.15 Structural analysis of the actin cortex and its correlation to cell mechanics in adhered and suspended states

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The cellular cortex plays an important role in biological processes such as cell migration and division. This 200nm thick network beneath the cell membrane is mainly composed of actin filaments, associated with motor proteins and linkers. Its mechanical properties act as the main contributor to the mechanics of cells and their shape. During cell adhesion the cortex is expected to be altered [1]. In order to test how such alterations influence the cellular mechanics during adhesion, we compared the mechanical properties of RPE1 cells in adhered and suspended states by AFM. The results were correlated to the local structure of the actin network using scanning electron microscopy. We found differences in the cell mechanics and structures depending on the state of adhesion. Altering the activity of the motor protein myosinII allowed us to further asses the contribution of this protein to the mechanical properties of the cells in both states. Structural changes were analyzed using a home-made vectorial tracing software.

Hence, we describe here a quantitative correlation between the structure of the actin cortex and the mechanical properties of cells both in the frame of adhesion state and by chemical alteration. These results are promising in understanding the mechanical plasticity of cells in processes like e.g. cell differentiation or metastasis.

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C.16 Relating surface structure to function in cell membrane penetrating nanoparticles

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Previous work has shown that the shape and surface structure of nanoparticles plays a key role in their uptake by the cell membrane[1,2]. Despite this, a complete understanding of the structural features that govern uptake remains incomplete. In this study, the effect of spatial distribution of ligands on the nanoparticle surface on vesicle formation was investigated. Coarse grain simulations of the cellular membrane, and of a model nanoparticle were used in the context of an evolutionary algorithm to explore ligand placement. By seeking optimal ligand patterning to enable cell entry across various ligand population sizes, robust nanoparticle designs across a range of binding energies were generated. Designs of the resulting populations were transposed into pairwise ligand distance matrices and used to build networks describing the surface structure. Analysis of these ligand distance networks suggest that arrangements of ligands into low density but connected strings, forming long belts across the particle surface is optimal at low ligand numbers, while at large ligand numbers surface structure plays a less important role. That is, ligands with long lines of ligands perform much better than their evenly spaced counterparts, a novel result which builds upon the models developed in previous studies[1].

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[2] Loverde, S. M., Klein, M. L. & Discher, D. E. Nanoparticle Shape Improves Delivery: Rational Coarse Grain Molecular Dynamics (rCG-MD) of Taxol in Worm-Like PEG-PCL Micelles. *Advanced Materials* **24**, 3823–3830(2012).

C.17 Fine-grained simulation of the microenvironment of vascularized tumors

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One of many important features of the tumor microenvironment is that it is a place of active Darwinian selection where different tumor clones become adapted to the variety of ecological niches that make up the microenvironment. These evolutionary processes turn the microenvironment into a powerful source of tumor heterogeneity and contribute to the development of drug resistance in cancer. We developed a computational tool to study the ecology of the microenvironment by combining a lattice- free simulation of tumor cells (VBL) with a lattice based blood vessel dynamic simulation (Tumorcode) to mimic vascularized solid tumors at the tissue scale. The simulation of the partial oxygen pressure (P_{O2}) and the pH in a virtual setup, similar to the experimental setup used by Jain et al., produced remarkably similar data. In addition to the experimental setup, our approach allows a time resolved study of the tumor microenvironment at the angiogenetic switch. We observed the formation of ecological niches at a very early stage of tumor growth and conjecture that the high evolutionary pressure (Darwinian dynamics) is one reason for tumorheterogeneity.

C.18 Dynamic real-time deformability cytometry: High-throughput single cell rheology in complex samples

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In life sciences, the material properties of suspended cells have attained significance close to that of fluorescent markers but with the advantage of label-free and unbiased sample characterization. Until recently, cell rheological measurements were either limited by acquisition throughput, excessive post processing, or low-throughput real-time analysis. Real-time deformability cytometry [1] expanded the application of mechanical cell assays to fast on-the-fly phenotyping of large sample sizes, but has been restricted to single material parameters as the Young's modulus.

For comprehensive cell rheological measurements of elasticity and viscosity on a millisecond time-scale we developed dynamic real-time deformability cytometry (dRT-DC) [2]. Utilizing Fourier decomposition, dRT-DC is capable to disentangle cell response to complex hydrodynamic stress distributions found in almost all microfluidic systems.

We demonstrate that reconstruction of cell deformation from odd Fourier components only, provides a measure that is governed by the steady state flow inside the channel but not by entrance or exit effects.

This system is capable to determine viscoelastic properties of suspended cells at a rate of up to 100 cells/s. As a first application we show a rheological characterization of all major blood cell types including the label-free discrimination of B- and CD4+ T-lymphocytes.

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C.19 Restricting desmosomal assembly in interfollicular stem cells (IFSCs) via desmosomal protein nanopatterns

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Adhesion between intra follicular stem cells (IFSCs) is established by the formation of specific cellular junctional complexes, desmosomes. Such junctions are specialized for strong adhesion and their failure can result in various diseases [1]. Regarding the dynamic structure of desmosomal junctions, this type of cell-cell adhesion may also play the role of signaling centers [2]. Desmosomes are composed of two types of cadherins, desmocollins (Dsc) and desmogleins (Dsg), but their combinatorial roles in desmosome assembly and cell behaviors are not understood well in IFSCs.

In this work, nanopatterns of desmoglein 2 are created as mimics of the cellular interface and used to study the formation of desmosomal assemblies for adherent IFSC cells. Nanoscale engineering was used to create a chemical pattern which was used to assemble oriented Dsg2Fc into created arrays of circular nanopatterns of the Dsg2Fc protein with size 100, 300, 500 nm. Between the protein nanopatterns, cell adhesion studies show that IFSCs adhere to the Dsg2Fc patterns and start expression of intra- and extra-cellular domains of the Dsg2 protein after 2 hr in high Ca^{2+} media while cells in low Ca^{2+} media just express a small number of intracellular domain of Dsg2 proteins even after 6 hr post incubation. The preliminary results show that the size of nanopatterned and Ca^{2+} concentration alter desmosomal formation.

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P.24 Linking chemokine receptor dynamics with neutrophil migration behaviour *in vivo* through image analysis

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Guided cell migration is essential in immune responses [1]. Neutrophils are the first immune cells to reach a site of inflammation (infection or tissue damage lesion), guided by chemoattractants [2]. The sub- cellular protein movements that dictate neutrophil migration *in vivo* involve highly complex dynamics which lack a quantitative framework. In this study, we employed the zebrafish model and we used quantitative imaging to study the trafficking of neutrophil chemokine receptors (Cxcr1 and Cxcr2) and their effect on neutrophil behaviour towards and away from sites of acute tissue damage. While several algorithms have been developed to quantify neutrophil directed migration, automated methods to quantify dispersal (or so-called 'reverse migration') from these sites are lacking. In addition, quantification of receptor dynamics in moving leukocytes *in vivo* is challenging due to the complex shape changes in these migrating cells. Here we have developed a tracking analysis approach to quantify neutrophil forward and reverse migration traffic to wounds and link this to chemoattractant receptor redistribution during this process. Together with a series of genetic manipulations, these analyses revealed that chemokine receptor persistence at the plasma membrane is important for neutrophil reverse migration from wounds [3]. These quantitative tools can be further used in other cell systems to link molecular dynamics with cell-movements.

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C.20 Integer topological defects steer cell flows during tissue morphogenesis

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Morphogenesis, involving tissue growth and reshaping, is directed by cellular collective flows and forces, which can respond to orientation cues. In vitro, anisometric cells have been found to align with each other giving rise to macroscopic (multicellular) nematically-oriented domains, at the interface of which topological defects are located [1-3]. Although they have a clear effect on the morphology and dynamics of cell monolayers, the functionality of topological defects in morphogenesis remains hypothetical [1,2]. Here, we study the organization of muscle cells (myoblasts) under circular confinement, which enforces a total topological charge S=+1 [3], to investigate the influence of topological defects on the formation of muscle-like structures. Under strong confinement, we find that a single integer topological defect is formed at the geometrical center, around which muscle cells self-assemble giving rise to two different phases: rotating spiral-like arrangements or quasi-static aster-like arrangements. Cells around defects feature well-defined orientations that facilitate the generation of center-symmetric flows and compressive cell-cell stresses at the defect core. The resulting biomechanical stimulation, which is known to play a critical role in the regulation of myogenesis [4,5], triggers early differentiation of myoblasts, predominantly where the defect core resides. Alternatively, non-fusion-competent cells are extruded and accumulated at the center of the cellular domains, leading to the growth of 3D cellular structures. Using a hydrodynamic description of active polar gels with suitable boundary conditions [6], we describe the link between the cellular flows and the director field and predict the cell-cell forces and cell density for both topological configurations, in agreement with experimental observations.

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[3] G. Duclos, et al., *Nat. Phys.*, **13**, 58 (2017).
[4] H. Vandenburgh, et al., *Science*, **203**, 265 (1979).
[5] R. Chandran, et al., Am J Physiol *Cell Physiol*, **293**, 267 (2007).
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C.21 Hydrophobins: Model proteins and building blocks for lipid-free membranes and vesicles

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Hydrophobins are small proteins whose unique feature is a pronounced amphiphilicity rendering them naturally occurring Janus particles. This feature allows them to cover rapidly any hydrophilic-hydrophobic interface. One class of hydrophobins produced by filamentous fungi builds interfacial monolayers that exhibit a highly ordered two-dimensional structure as well as very high lateral cohesion. Moreover, these proteins possess an extremely stable conformation making them ideal candidates also for theoretical investigations.

Studying the temporal evolution of hydrophobin films from the fungus Trichoderma reesei revealed an unusual assembly behavior which was shown experimentally and in simulation to be caused by crystallization at the interface and the interplay of protein-protein interactions [1]. In an attempt to measure the interactions between the proteins directly in a microfluidic setup, stable pure protein bilayers have been created, either between two aqueous or two oily phases. Studying the properties of these artificial membranes led then also to the production of vesicles made from these membranes [2]. These vesicles are the first example of liposomes with a membrane composed solely of natural proteins.

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[2] Hähl, H. *et al.,* Adv Mater 29, 1602888 (2017).

C.22 Physical modelling of ESCRT-III mediated cell division in archaea

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Studying the mechanism of cell division in evolutionary simpler cells can teach us about the mechanistic principles that have been conserved as life evolves into more complex cells. The archaeon Sulfolobus acidocaldarius possesses a cell division cycle similar in structure and logic to that of many eukaryotes. While the archaeal ESCRT-III homologues CdvB and CdvB1/B2 are essential for the final stage of cell division, their exact function in the timely remodelling of the cell membrane is elusive. Based on experimental findings, we suggest a mechanistic model of ESCRT-III mediated division in archaea [1]: As cells prepare to divide, they assemble a non-contractile CdvB ring of a fixed diameter at the cell midzone. The CdvB ring acts as a template for the assembly of a CdvB1/B2 polymer which, like force-generating ESCRT-III polymers in other systems, has a small preferred curvature. As a result, the loss of the CdvB scaffold drives rapid contraction of the CdvB1/B2 ring towards its preferred curvature, constricting the membrane as it does so. In order to test the proposed model, we perform coarse-grained molecular dynamics simulations of a large spherical membrane coupled to an elastic filament that can both change its curvature and disassemble. We map the cell division phase space as a function of the CdvB degradation procedure (i.e. instantaneous, sequential, randomised), as well as the intrinsic curvature and the disassembly rate of the ESCRT-III filament [2]. Our results show that cell division is not achieved by contraction of the ESCRT-III filament alone; disassembly is also required. Furthermore, we analyse the furrow constriction in time and find a good qualitative agreement between simulation and experiment. We thereby determine a molecular mechanism by which the timely degradation of one protein, CdvB, triggers the division of a single archaeal cell into two daughtercells.

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C.23 Optoregulated force application to individual cellular receptors using molecular motors

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Mechanical force is a driving factor in guiding cell shape, migration and even gene regulation. Several methods have been developed to apply mechanical forces to cells, including micropipettes, magnetic tweezers and magnetic actuation of nanoparticles. Optical strategies for manipulating biological systems have experienced a great development in recent years, such as photoswitches and optogenetic constructs. Methods that allow for precise light-induced physical inputs to biological systems could impact studies in mechanotransduction. However, it is still challenging to develop molecular systems that can transfer light into mechanical force with molecular specificity and high spatiotemporal resolution.

We present a novel approach for applying forces to cells with molecular specificity and at molecular resolution using a light-driven synthetic molecular motor. The motor is modified with two orthogonal sets of polymer chains in its upper and bottom parts. It is immobilized on a biomaterial and contains adhesive ligands at two free ends. Upon light exposure, the molecular motor rotates and twists the entangled polymer chains, thereby applying a mechanical load to receptor-ligand complexes on the cell surface. Using Flow Force Microscopy we show that the motors are able to induce picoNewton forces. We further demonstrate the motor-induced mechanical activation of integrins in fibroblasts, leading to Focal Adhesion growth, as well as T-cell receptor activation as measured through calcium signaling.

C.24 Morphogenesis is stressful – elasticity and mechanics of folding cell sheets

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Living tissues are intelligent materials that can change their mechanical properties while they develop. In spite of extensive studies in multiple model organisms we are only just beginning to understand these dynamic properties and their role in tissue development. Although many tissues are known to exhibit visco-elastic properties, it is unclear which properties dominate three-dimensional shape changes of cellular monolayers, such as epithelia.

The embryonic inversion process in the micro-algal family Volvocales is uniquely suited for comparative studies on epithelial morphogenesis. Volvocalean embryos consist of cup-shaped or spherical cellular monolayers which invert their curvature in order to expose their flagella. These inversion processes involve a range of species-dependant complexity in terms of both the local cell shape changes and the resulting deformations of the cell sheet. Volvox globator exhibits one of the most striking processes of cell sheet folding: The initially spherical embryonic cell sheet adopts a mushroom shape through invagination at the equator, the posterior moves into the anterior hemisphere and the embryo eventually turns itself inside-out through an anterior opening [1]. A combination of time-lapse fluorescence imaging and computational analyses is used to correlate local cellular changes with global topological changes [2, 3]. Laser ablation experiments are used to determine local stresses and the role of the cell sheets' elastic properties during its deformation [4]. Our results indicate that the cell sheet retains its elasticity throughout a period of over an hour while undergoing slow deformations.

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C.25 Interpretation of SAXS data using MD simulations: Detergent micelles and ion cloud of charged proteins

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Small-angle X-ray scattering (SAXS) is an experimental technique used to study biomolecules under near-native conditions. As the information content of the experimental data is low, methods that integrate the data with accurate computational models are urgently required. In recent years, all-atom molecular dynamics (MD) simulations have developed to a increasingly popular and reliable tool for interpreting SAXS experiments and and, more general, for gaining atomic-level insights into biomolecules. [1]

Detergent micelles are often employed as a membrane mimics to solubilize membrane proteins. Accurate information about the size and shape of micelles is important for the stability of protein- detergent complex. We show how MD can be combined with the SAXS data to derive temperature- dependent atomic models of monodisperse micelles. [2]

The ion cloud around charged proteins influence the radius of gyration (Rg) of the protein, complicating the interpretation of experimental SAXS data. In order to quantify this effect, we compared SAXS curves calculated from all-atom MD simulations with the experimental data. Furthermore, we developed a tool for a fast and accurate prediction of the ion cloud effect on Rg. [3]

Our current work is focusing on using multiple-replica MD coupled to SAXS data, following the maximal entropy principle, in attempts to study polidisperse micelles. In addition, we aim to expand available analytic models for the prediction of SAXS curves of micelles and to understand the influence of micelle shape fluctuations on SAXS curves.

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C.26 Exercising mesenchymal stem cells through nomadic culture on heterogeneous field of matrix elasticity

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Recently, it has been established that mesenchymal stem cells (MSCs) memorize the history of mechanical dose from culture environment, which essentially affect the lineage specifications [1]. To ensure stemness of MSCs in maintaining subculture, accumulation of such mechanical dose should be avoided in order to inhibit the lineage bias. For this issue, we have tried to develop cell culture hydrogels whose surface has heterogeneous distribution of elasticity, and to make MSCs move nomadically among different region of elasticity in a certain short duration. In this report, we have established complete design of the microelastically-patterned gels to realize the nomadic movement of MSCs and quasi-oscillatory input of mechanosignals to the MSCs so as to eliminate the history of mechanical dose (we termed such MSC as in frustrated differentiation [2, 3]). After culture of MSCs on the gels for 4days, transcriptome analysis revealed that many genes relating to cellular growth, cell death and survival as well as cellular movement were strongly up-regulated, which means the cells after nomadic culture become more vigorous like an effect of physical exercise for the cells. We will discuss mechanobiology of this phenomenon from the views of chromatin mechanics.

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C.27 Role of oxidative stress on the cell mechanical properties of suspended and adherent cells

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Increase in oxidative stress has been linked to many haematological and neurological disorders. Reactive oxygen species (ROS) are one of the primary sources of oxidative stress which are associated with essential alterations in cell physiology[1]. Mechanical properties have long been established as a label-free biomarker, but their interplay with alternating levels of ROS has not been thoroughly investigated. This study focusses on understanding the impact of oxidative stress on the mechanical properties of the human leukaemia cell line (HL-60) and immortalized rat brain C6 glioma cells. In an *in-vitro* assay, mitochondrial superoxide was generated by exposing cells to varying concentrations of hydrogen peroxide. Using real-time fluorescence deformability cytometry[2], we link for the first time the molecular phenotype of ROS using MitoSOX-red a fluorescent marker to changes in the mechanical phenotype which is a label-free biomarker. We show for micromolar concentrations of H_2O_2 that an increase in ROS induces alterations in cell mechanical properties. For adherent cells, we find a decrease in the Young's modulus, which is in contrast to previous results for concentrations in the millimolar range[3]. For suspended cells, we observe a different cell response to oxidative stress of increased elastic modulus.

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C.28 Recovery behavior of single vimentin filaments

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Intermediate filaments (IFs) are believed to have an important impact on determining the mechanical properties of cells. Together with microfilaments and microtubules they form dense networks, which compose the cytoskeleton. In order to determine the impact of individual IFs on the overall network, we perform stretching experiments on the single filament level. Optical tweezers, combined with microfluidics and fluorescence microscopy, are used to directly probe the stress-strain behavior of single IFs.

Previous experiments showed that under strain, α-helices in IFs uncoil to ß-sheet like structures. Here, we stretch single vimentin IFs up to the plateau region where the uncoiling takes place and relax them again. The relaxation shows no plastic deformation and therefore it is suggested to be a reversible process even though the energy barrier between these two states is comperatively high. To investigate the filament recovery after the uncoiling, a second cycle of stretching and relaxation is performed after waiting times of different duration. Our results show that the initial tensile behavior can not be recovered. However, treatment of the filaments with chemical crosslinkers restores full reversibility.

C.29 Entropic chromatin swelling drives complex cellular behavior

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Neutrophilic granulocytes are able to release their own DNA as neutrophil extracellular traps (NETs) to capture and eliminate pathogens. DNA expulsion (NETosis) has also been documented for other cells and organisms, thus highlighting the evolutionary conservation of this process. Moreover, dysregulated NETosis has been implicated in many diseases, including cancer and inflammatory disorders. During NETosis, neutrophils undergo dynamic and dramatic alterations of their cellular as well as sub-cellular morphology whose biophysical basis is poorly understood. Here, we investigate NETosis in real-time on the single-cell level using fluorescence and atomic force microscopy[1]. Our results show that NETosis is highly organized into three distinct phases with a clear point of no return defined by chromatin status. Entropic chromatin swelling is the major physical driving force that causes cell morphology changes and the rupture of both nuclear envelope and plasma membrane. Through its material properties, chromatin thus directly orchestrates this complex biological process.

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C.30 Entropic origins of substrate-guided cell morphology and alignment

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The organization of cells in tissues is critical for all physiological functions of tissues and organs. It is widely known that cellular organization—such as spreading, elongation, and alignment—can be sensitively influenced by the physical features of the microenvironment. The underlying mechanisms behind this response is still debated, especially as the length scale of the cues becomes comparable to cell sizes. To explore cellular response to this range of cues, we systematically monitored and quantified cell adhesion and morphology on micropatterned substrates over a large range of feature sizes, from μm to mm. Together with a new statistical thermodynamics model of living cells, the experimental results reveal that alignment of cells to large features (hundreds of μm scale) is associated with the cells' tendency to maximize morphological entropy through shape fluctuations [1]. Looking further at the μm scales, alignment of focal adhesions and actin fibers were surprisingly found to be dispensable for whole-cell orientation, contrary to proposed theories. Comparison with the model reveals that cell alignment emerges as an energetic consequence of cell elasticity and adhesion on the non-adhesive gaps. Our finding therefore offers a scale-free, physical mechanism for cell morphology and alignment that does not necessitate specific molecular pathway or biochemical regulation.

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C.31 Vimentin provides the mechanical resilience required for amoeboid migration and protection of the nucleus

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Dendritic cells employ amoeboid migration through constricted passages to reach the lymph nodes, a crucial homing function for immune responses. Amoeboid migration requires mechanical resilience but the underlying molecular mechanisms remain unknown. As vimentin intermediate filaments (IFs) and microfilaments bidirectionally regulate adhesion-dependent migration, we analyzed whether analogous interactions could be engaged also in amoeboid migration. Vimentin was required for cellular resilience, resulting from a joint interaction between vimentin IFs and F-actin. Reduced actin mobility in the cell cortex of vimentin-reduced cells demonstrated that vimentin promotes subunit exchange and F-actin dynamics. These mechano-dynamic alterations in vimentin-deficient dendritic cells resulted in a striking impairment of amoeboid migration in confined environments in vitro and blocked lymph node homing in vivo in mouse experiments. As nuclear positioning is involved in confined amoeboid migration, vimentin–deficiency resulted in DNA double-strand breaks and cell death in compressed cells. These observations show that vimentin IF-microfilament interactions provide the specific mechano-dynamics required for dendritic cell migration, at the same time protecting the genome againstdeformation.

C.32 Confining cancer cells in 3D tumor-like microcapsules: A new strategy to induce tumor heterogeneity *in vitro*, and to enhance extravasation capabilities *invivo*

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Traditionally, established methods to test of cancer pathogenicity and drug sensitivity *in vitro* are standardized using cell lines, commonly pre-cultured (*i.e.* expanded) on 2D flat surfaces, such as petri dishes, cell culture flasks or several types of well-plates.

However, these culture conditions do not address the microarchitecture and/or composition found in the neoplastic milieu, characterized by being three-dimensional, hardly degradable, stiff and weakly permeable, forcing the entrapped population to support solid and metabolic stress, restricting their proliferation, migration and further release from confinement.[(1)] Based on these facts, in this work we developed a new kind of semi- degradable tumor-like microcapsules, used to immobilize healthy (MCF10A, EA.hy926) and malignant cell lines (MCF7). Our scaffolds mimic values of elasticities (around 25 kPa in the shell and 20 kPa in the internal core) as well as biological composition of breast tumors.

Our results are showing that our tumor-like microcapsules allow cancer cells to migrate, proliferate and be released (*i.e.* intravasation-like), hindering however, all these processes on healthy-like cells.

Interestingly, cancer cells growing/released inside/from the capsules showed the existence of tumor heterogeneity, the apparition of different morphological phenotypes (*i.e.* non-adherent; small, adherent and highly proliferative cells; and large, adherent and highly motile cells), as well as

the presence of poly-nucleated cells, phenomena not observed on same cells pre-cultured on 2D.

With the purpose to characterize detected phenotypes at biophysical level, we performed single-cell traction force measurements and *in vivo* extravasation assays (*i.e.* zebrafish model).

Our results show that cells pre-cultured in 3D matrices exert a wider range of biomechanical forces *in vitro,* and are likely undergoing to extravasation *in vivo,* compared to cells pre-cultured on 2D.

Furthermore, qPCR assays showed that cells isolated from tumor-like scaffolds, those freely released from these matrices and control cells exhibited a different molecularprofile.

These outcomes are remarking the relevance of performing invasiveness assays and biophysical test in three- dimensional milieus, instead of continuing studying the behavior of cancer cells on hard and flat 2D surfaces.

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C.33 Mechanical interaction between cells in fibrous environments

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Tissues are made up of cells and an extracellular matrix (ECM), a cross-linked network of biopolymers with complex mechanics. Cells actively alter the extracellular matrix (ECM) structure and mechanics by applying contractile forces. These forces can propagate to far distances and allow for remote sensing. We study experimentally and computationally how cell- induced forces are transmitted in fibrous environments, the underline physical mechanisms [1], and the ability of the propagated forces to support mechanical interaction between distant cells. We also demonstrate how the changes in ECM isotropy and density can lead to improve transport of molecules traveling between the cells, facilitating mechano-biochemical feedback interactions [2]. Such long-range interactions through the matrix can drive large-scale cooperative biological processes, such that occur during wound healing and morphogenesis. Our work can also provide design parameters for biomaterials used in tissue engineering.

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C.34 Lateral subunit coupling determines intermediate filament mechanics

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The cytoskeleton is vital for cell motility, cell division and mechanical stability of the cell. These tasks are distributed among three different protein classes, microfilaments (MFs), microtubules (MTs) and intermediate filaments (IFs). Unlike MFs and MTs, IFs are expressed in a cell-type specific manner [1–3] giving the cell a tool to adapt to different mechanical requirements. So far, the mechanical properties of different IFs on a single filament level have not been probed. Therefore, we study the stress-strain behavior of two IFs, vimentin and keratin filaments, by optical trapping in combination with fluorescence microscopy and microfluidics [4-6]. In comparison to keratin IFs, vimentin IFs are stiffer [6] and dissipate more energy, which predestines vimentin to act as a cellular "safety belt" [4-6]. Monte-Carlo simulations based on theoretical modelling allow the decoupling of different IF-type depending parameters like the monomer interaction and the number of monomers per cross-section of the IF. The obtained parameter distributions show that more energy is required to extend vimentin IFs than keratin IFs [6]. This behavior can possibly be explained by a compaction step of vimentin during IF assembly which is not observed for keratin IFs.

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C.35 Cell competition in mouse embryo

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Cell competition is a biological process whereby cells eliminate their less fitted neighbours [1] [2]. It has myriad positive roles in the organism: it selects against mutant cells in developing tissues, prevents the propagation of oncogenic cells and eliminates damaged cells during ageing. While it was first characterized in drosophila [3], it is currently unclear what are the transcriptional features of cells eliminated through competition and what are the roles of cell competition during mammalian development. We analysed single-cell transcriptomic data from mouse embryos around the time gastrulation starts (stage E6.5) where apoptosis was inhibited. We show that in these embryos a new population of epiblast cells emerges, expressing markers of cell competition previously characterized [4]. Our analysis also identifies additional features of eliminated cells, including disrupted mitochondrial activity that we validate in vivo. Moreover, by using physical modelling, we show that cell competition might play a role in the regulation of embryo size, which could be particularly important around gastrulation [5].

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C.36 Stokes' law in complex liquids and inside cell cytoplasm

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The 'viscosity' experienced by a small tracer particle in complex liquids depends both on its size and on the structure of the liquid, which itself may contain different length scales. Thus, in a microrheological experiment the complex liquid may best be described by wave-vector-dependent viscosity η(k). Here we derive Stokes' law in complex liquids and formulate a method to determine the wave-vector-dependent viscosity from microrheological experimental data. We initiate our approach by determining the wave-vector-dependent viscosities η(k) of HeLa and Escherichia Coli cell cytoplasm from the experimental data on diffusion of macromolecules in these systems. Determination of this quantity opens an avenue for computer simulations of motion and biochemical reactions inside living cells.

C.37 The narrow escape problem in a circular domain with radial piecewise constant diffusivity

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The stochastic motion of particles in living cells is often spatially inhomogeneous with a higher effective diffusivity in a region close to the cell boundary due to active transport along actin filaments [1]. As a first step to understand the consequence of the existence of two compartments with different diffusion constant for stochastic search problems we consider a Brownian particle in a circular domain with different diffusion constants in the inner and the outer shell. We focus on the narrow escape problem and compute the mean first passage time (MFPT) for Brownian particles starting at some predefined position to find a small region on the outer reflecting boundary. The asymptotic expression of the MFPT are obtained following [2].

For the annulus geometry we find that the MFPT can be minimized for a specific value of the width of the outer shell. In contrast for the two-shell geometry we show that the MFPT depends monotonously on the outer shell width. Then, the MFPT can be optimized only when a mechanism enforce the particle to stay close to the surface (e. g. [1,3]). Moreover we find that the distance between the starting point and the narrow escape region which maximizes the MFPT depends discontinuously on the ratio between inner and outer diffusivity.

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C.38 Subcellular transfer of nanoparticles and targeting of organelles

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Probing and perturbing the function of specific molecules inside cells is an essential prerequisite to widen our understanding of the subcellular organization. However, little means are hitherto capable of monitoring and manipulating biomolecules on nanometric scales. Nanoparticles in the form of quantum dots or magnetic nanoparticles constitute exquisitely sensitive tools to explore how molecules are dynamically orchestrated in cells. In recent years, these nanoprobes have led to fundamentally new insights about the viscoelastic nature of the cytoplasm, they enabled spatial localization of cytosolic molecules, as well as demonstrated the actuation of cell signaling processes [1,2]. Of particular challenge in undertaking these studies is the transfer of nanoprobes to the cytoplasm while maintaining their stealth property, monodispersity, and without compromising the cell integrity. Here, we present different mechanisms of subcellular nanoparticle transfer and summarize their (dis-)advantages. We characterize the nanoparticle mobility and stability after the transfer using FCS and single particle tracking, as well as present strategies to target nanoparticles to particular organelles [3]. Our results demonstrate how the subcellular environment influences particle behaviour and how these strategies may be used to probe cell mechanics, intracellular transport or membrane dynamics.

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C.39 Flagellar number governs bacterial spreading and transport efficiency

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Peritrichous bacteria synchronize and bundle their flagella to actively swim while disruption of the bundle leads to a slow motility phase with a weak propulsion. It is still not known whether the number of flagella represents an evolutionary adaptation towards optimizing bacterial navigation. Here, we study the swimming dynamics of differentially flagellated *Bacillus subtilis* strains in a quasi-two-dimensional system. We find that decreasing the number of flagella Nf reduces the average turning angle between two successive run phases and enhances the run time and the directional persistence of the run phase. As a result, having less flagella is beneficial for long-distance transport and fast spreading, while having a lot of flagella is advantageous for the processes which require a slower spreading, such as biofilm formation. We develop a two-state random walk model that incorporates spontaneous switchings between the states and yields exact analytical expressions for transport properties, in remarkable agreement with experiments. The results of numerical simulations based on our two-state model suggest that the global effciency of searching and exploring the environment is optimized at intermediate values of N_f . The optimal choice of Nf, for which the search time is minimized, decreases with increasing the size of the environment in which the bacteria swim [1]. We stained flagella to investigate the bacterial motility in more detail and find out bacillus can make several bundles during run phase. Number of bundles are independent of the flagellar number and formation of three bundles is always the most probable case. The projected angle between bundles on the observation plane widens with the number of flagella which leads to a slight modification of the effective cell aspect ratio while there is no significant trend in the other bundle properties.

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C.40 Geometry and mechanics of growing bacterial suspensions

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Densely packed colonies of growing, non-motile bacteria interact through physical contact, pushing each other out of the way as they grow. Due to the rod shaped geometry of a bacterium, short ranged nematic alignment is observed. We study the development of the nematic director in a growing colony of bacteria by modelling them as growing, inflexible rods. This allows us to identify a characteristic length scale in the director associated with highly aligned 'patches' that form within the colony. We then frame this in the context of an active nematic, observing that the growth of the bacteria plays the role of an active stress [1]. This can further be used to understand the process by which bacteria form multi-layered colonies in the early stages of biofilm development [2].

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C.41 Soft cell confiner development to decipher the impact of mechanical stimuli on cancer cells

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During tumor progression, many changes in the physical properties of the microenvironment can occur such as the apparition of compressive stresses due to proliferation burst or increase in the microenvironment stiffness. While the effect of matrix stiffness has been extensively studied in the context of tumor progression and resistance to treatment, limited studies have focused on the role of solid stresses. Indeed, the field is lacking standard in vitro test reproducing this long-term compression, without affecting cells behavior by other means.

We designed a hydrogel-based microsystem with rigidity close to physiological conditions and enabling efficient medium renewal. We challenged our so-called "Soft confiner" with different cell lines for several days (both epithelial and mesenchymal cell types, as well as non-adhesive immature hematopoietic cell lines) and found no major impact on cell proliferation. This set up is compatible with time-lapse microscopy, in-situ immunostaining, as well as classical molecular analysis (qPCR, Western Blot)

Our soft-cell confiner appears thus as a powerful tool that could be used in different biological contexts to decipher the impact of long-term mechanical stimulation on cell behavior.

C.42 Stilbene derivative as a photosensitive compound to control the excitability of neonatal rat cardiomyocytes

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The aim of the present work is to study the effect of stilbene derivative c-TAB (2-{4-[(E)-2-(4-ethoxyphenyl) vinyl] phenoxy} ethyl) trimethylammonium bromide) [1] on the voltage-gated ion channels in cardiac cells. C-TAB is a structural analogue to AzoTAB [2], reported as a photoswitch for cardiac and neural cells. However, while AzoTAB reversibly enables the tuning of cardiomyocyte excitability to the desired degree [3], it seems to be toxic to the cells due to azobenzene group.

A replacement of the azobenzene moiety by a stilbene grouping makes c-TAB less toxic to living cells. C-TAB successfully inhibits excitation in cardiac cells in both trans- and *cis*- forms. It was shown that the nature of the excitability blockage on membrane is in the modulation of voltage-gated ion channels. Under the action of c-TAB, the fast sodium and calcium currents are suppressed, while the slow potassium currents and Ito increase. The inhibition under *trans*- c-TAB is reversible and can be overturned easily by washing out. The irradiation with near-UV, when we get the *cis*- form, changes reversible inhibition to a permanent one that cannot be overturned by a washout.

C-TAB as a photosensitizer can be very helpful in modeling excitation in membrane or a cardiac tissue culture and may have prospective use in the temporary and permanent ablation of unwanted excitation sources in the heart.

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C.43 Multiscale modeling of tumor development

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The temporal and spatial resolution in the microscopy of tissues has increased significantly within the last years, yielding new insights into the dynamics of tissue development and the role of the single cell within it. A thorough theoretical description of the connection of single cell processes to macroscopic tissue reorganizations is still lacking. Especially in tumor development single cells play a key role in the advance of tumor properties.

We introduce a scale-bridging method that is able to model tissue development up to the centimeter scale with micrometer resolution of single cells. Through parallelization it enables the efficient use of HPC systems, therefore facilitating detailed simulations on a large scale. We developed a generalized tumor model that respects adhesion driven cell migration, cell-to-cell signaling and mutation driven tumor heterogeneity. We scan the response of the tumor development and composition in dependence of different treatment plans using chemotherapy as well as radiation therapy. We then investigate how the presence of tumor stem cells changes tumor evolution, composition and treatment response. With this model, we enable in *silico* medicine to deepen the theoretical understanding of the interplay of tissue and single cells and therefore moving towards to computational personalized medicine.

C.44 Intracellular transport by molecular motors: the effect of number of binding sites

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Intracellular transport carries a large variety of cargos in many cellular processes. Molecular motors bound to the cargo usually work together in teams. The tails of motors are strictly bound to the cargo whereas the head of motors stepping along the track can bind and unbind from the filament. Interestingly, when rebinding, how far the motors can bind beyond of the width of cargo is unknown. We introduce a latticed based stochastic model to study the effect of the number of accessible binding sites on the filament, on the collective behaviour of molecular motors. We extended the analytical solution for force-velocity relations of a cluster of motors bound on a cargo from [1] by including attachment and detachment and theoretical probability distributions of bound motors with limited and unlimited number of binding sites along the filament. We present analytical and simulation results of probability distributions of bound motors. Moreover, the position or the sequence of motors on the filament can be swapped or preserved during unbinding and rebinding. We show and compare differences between swapping and preserving the the sequence of motor binding on the filament.

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C.45 Bacterial confinement in hydrogels to develop living therapeutic materials

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"Living therapeutics" refers to the use of engineered bacteria in the human body to produce drugs on-site. In spite of expected advantages for targeted delivery and cost savings in drug synthesis/isolation/encapsulation, clinical applicability of living therapeutics has not been realized yet. Many important issues are associated with the delivery of engineered bacteria into the body, which remain to be solved. "Living materials", where active bacteria are encapsulated in a synthetic matrix that sustains their activity, regulates proliferation and prevents bacterial escape, might overcome many problems associated with the use of bacteria in a biomedical context. Similar to natural biofilms, the mechanical properties and geometry of the synthetic matrix play crucial roles in modulating bacterial behavior. Likewise, depending on the bacterial strain, matrix modifications and drug production traits can vary. I will present my work in developing optogenetically-engineered bacterial hydrogels capable of producing and releasing proteins[1] or metabolically synthesized drugs[2] regulated by light. The effects of chemical and physical cross-linking of the synthetic matrix on bacterial growth, division and drug production will be discussed. The behavior of two very different bacterial strains, Escherichia coli and Streptomyces albus within these environments will also be described.

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C.46 Tuning the mechanics of single intermediate filaments

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Intermediate filaments (IFs), together with microfilaments (MFs) and microtubulues (MTs), give cells specific and unique mechanical properties as part of the cytoskeleton. Whereas MFs and MTs are conserved between cell types, IFs are expressed in a cell type specific manner. Vimentin IFs, found in cells of mesenchymal origin, have a remarkable potential for elongation and high stability [1,2]. To understand the mechanisms within IFs that determine the mechanical response to stress, single IFs are investigated in vitro using a setup that combines optical tweezers, fluorescence microscopy and microfluidics. By changing the environment (pH, buffer, ion valency and ion concentration) different force-strain behaviours of single vimentin IFs are observed in stretching experiments. IFs show a remarkable dependence on the buffer pH and presence of cations while the cation valency seems to be negligible. With these experimental results and Monte-Carlo simulations [3], we can link changes of the molecular architecture of vimentin IFs to their mechanical response.

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C.47 Dynamics, correlations, and search optimization in active processes with distinct motility states

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Despite the broad range of stochastic transport processes with distinct motility states in nature (examples are active biological processes such as swimming of bacteria, migration of cells, and transport of motor proteins, or passive processes like chromatography and transport in amorphous materials), a comprehensive theoretical framework to identify their universal transport properties is lacking. To capture some of the specific features of these systems often simple mixtures of stochastic processes has been employed (e.g. run-and-tumble models for bacterial dynamics) but in general an arbitrary combination of two stochastic active processes with different activities is required, which is technically very challenging.

We develop a general theoretical framework to combine multi-state active processes with arbitrary self-propulsions and velocity distributions. This enables us to provide a quantitative link between the characteristics of particle dynamics to macroscopically observable transport properties. We derive exact analytical expressions for the time evolution of the transport quantities of interest, such as the velocity autocorrelation function, and identify several timescales for orientational correlations, set by the self-propulsions and the transition probabilities between the states. The variations of the correlation length by several orders of magnitude dramatically affects the ability of the active particle to efficiently explore the environment. Using Monte Carlo simulations we clarify how the sets of parameters that lead to the same mean-first-passage time are distributed in the phase space of the control parameters.

C.48 Towards understanding the role of BAR domain proteins in membrane tension sensing

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Membrane tension has been shown to have a critical role as a physical regulator of cell migration, polarization, and the balance between endocytosis and exocytosis. Despite its importance, it remains unclear how cells sense this mechanical property. We hypothesize that cells sense it by monitoring surface deformations, also referred to as membrane curvature. A group of proteins that is of particular interest in the context of membrane curvature binding is BAR domain family.

Membrane tension affects the landscape of membrane deformations which, in turn, could alter the binding of BAR domain proteins. Following RNAseq we identified BAR domain proteins with upregulated expression in differentiated (migratory) vs undifferentiated (non-migratory) HL-60 cells. Next, we used live TIRF imaging to capture the localization of GFP-tagged BAR domain proteins on the plasma membrane and assessed if their binding is affected by plasma membrane tension. Moreover, we prepared CRISPR/Cas9 knockout cell lines with chosen candidates and performed membrane tension measurements using Atomic Force Microscopy. We observe an increase in membrane tension in some knockout cell lines and are looking into its origin, focusing on structure and polymerization dynamics of actin.

C.49 Single-cell force spectroscopy to study bacterial adhesion: fundamental mechanisms and effect of substrate nano-topography

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Biofilms formed by pathogenic bacteria at solid surfaces are a nuisance in a wide area of healthcare applications. We present single cell force spectroscopy [1] experiments to reveal fundamental mechanisms of bacterial adhesion to various materials.

Since bacterial adhesion is mediated by thermally fluctuating cell wall molecules [2], comparing the shapes of force-distance curves on different surfaces provides information on the physical/chemical interactions between the bacterial cell wall molecules and the underlying material. In addition, the number of molecules involved and their average lengths during fluctuations can be determined. With this knowledge the adhesion of S. aureus to nano-structured surfaces can be quantified [3]: Thereto, etched silicon substrates with nano-structures in the same size range as the bacterial cell wall molecules (7 nm < RMS < 35 nm) were used for adhesion measurements. Their surface morphology was analyzed in great detail by Minkowski functionals showing that all surfaces are morphologically equivalent with only differences in their physical dimensions. It shows that as the surface nano-structures increase in size, adhesion forces decrease in a way that is directly correlated with the proportion of the surface area available for tethering cell wall molecules.

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C.50 Dynamics of immune cell morphology and motility on a topographical surface with controlled elasticity

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In this presentation, we experimentally show the spatiotemporally correlated parameters which determine the surface-adhered cell shape change during migratory processes. Guided crawling of a single immune cell (neutrophil), activated by chemoattractant concentration fluctuation, is demonstrated by adopting cell-attachable elastic micrograting and real-time optical live cell imaging techniques. After cell spreading on the micrograting surface, the pattern anisotropy and elastic modulus of the substrate induce significant changes in the cell morphology-motility interaction characteristics. Time-resolved interaction dynamics is quantitatively analysed, revealing the relation between the parameters of 2D shape and 2D motility. In addition, effects of substrate stiffness on the guided cell mobility are investigated by tuning the elastic modulus of the micropatterned surface. We finally discuss phenomenologically how immune cell shape and motility are dynamically correlated under the interaction with interfacial anisotropy and elastic energy [1,2].

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C.51 Sprouting angiogenesis relies on tip cell pulling forces

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Acto-myosin generated cellular forces are indispensable for angiogenesis, the formation of new blood vessels from preexisting ones. Up till now, one has speculated whether angiogenic sprout progression relies more on pulling forces exerted by tip cells, pushing forces originating from stalk cells, or both. Here, we provide evidence for the dominating role of pulling forces during early events of sprout progression. We adapted an in vitro model of endothelial cell invasion to make it compatible with 4D traction force microscopy. Detailed, spatially and temporally resolved matrix displacement fields were acquired around angiogenic sprouts that were invading in collagen hydrogels [1]. Matrix displacement patterns were consistent among a variety of sprout morphologies and suggested sprout mechanical activity that resembled that of a force dipole, with pulling forces concentrated at the sprout tip and base. Forces were estimated using a computational model of collagen mechanics and tip cell pulling forces were found to be of the order of only a few nN. We then zoomed in on single sprout protrusions to further unravel the nature of cell-matrix forces and found that extending protrusions were mainly building up pulling forces, while retracting protrusions were releasing pulling forces. Together, these data underline the importance of tip cell pulling for angiogenic sprout progression.

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C.52 Effect of substrate stiffness on balance of active cell-cell and cell-ECM forces studied through a computational model of a deformable cell pair

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Cells communicate with their environment and neighboring cells, transmitting forces. The interplay between cell-cell and cell-ECM adhesions is complex, with junction types being connected to one another via the cytoskeleton. Cell-pair studies on patterned substrates provide one of the simplest collective cell in vitro models. We developed a computational model of this setup in which subcellular force exertion mechanisms are taken into account. We compare simulated traction maps with those recovered in vitro through traction force microscopy. The discrete element method (DEM) is used to model the actin cortex mechanics [1]. We model two cells on a rectangular pattern; the cells forms an interface with the substrate and with each other. The discrete nature of the method is used to model focal adhesions and adherens junctions simultaneously. Stress fibers connect adhesions to one another and exerting a contractile force. Mechanosensing is incorporated in the form of force-dependent lifetime of adhesions and reinforcement of actomyosin contraction with fiber stalling. In agreement with experiments, the model shows decoupling of cells, increase in number of focal adhesions, and increase in contractile strength with increased substrate stiffness. Results suggest the stiffness of the cell-cell interface becomes a tipping point for substrate stiffness to define mechanosensing dynamics.

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C.53 Filamentous active matter: band formation, bending, buckling, and defects

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Motor proteins drive the persistent motion of cytoskeletal filaments in vivo as well as in vitro.

We perform component-based Brownian dynamics simulations of polar semiflexible filaments and molecular motors. This allows for linking the microscopic interactions and the filament activity to self-organisation and dynamics from the fundamental two-filament level all the way up to the of mesoscopic domain level. Dynamic filament crosslinking and sliding, and excluded-volume interactions promote formation of motor-bound bundles at small filament densities, and of active polar nematics at high densities. An Euler buckling-type instability sets the size of the polar domains and the density of topological defects. We predict a universal scaling of the active diffusion coefficient and the domain size with the active force, and its dependence on parameters like motor concentration, filament concentration and persistence length.

C.54 Does estrogen receptor drug binding influence breast cancer cell viscoelasticity?

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Mechanical properties of cells have recently been linked to properties of cancerous cells and tissue, such as invasivity, tumor progression and aggression [1]. Thus studying cancer cell mechanics has gained increasing interest over the last years [2]. The majority of cases of breast cancer are estrogen receptor positive, and remodeling of estrogen receptor signaling is known to occur during tumorigenesis. This affects other signaling pathways such as the wnt/ß-catenin pathway, promoting transitions associated with higher malignancy, e.g. the epithelial to mesenchymal transition (EMT) [3].

We employed Atomic Force Microscopy (AFM) to study the viscoelastic properties of MCF7 breast cancer cells at a single cell level. The influence of time exposure and concentration of 3 different drugs which interact with the estrogen receptor has been studied. We used combined stress relaxation and creep measurements to determine properties such as the relaxation times, viscosities and different elastic moduli [4]. This work deepens the understanding of changes present in cancer formation and progression.

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[4] S. Moreno-Flores et al. Nanotechnology 21 (44), (2010). 10.1088/0957-4484/21/44/445101.

C.55 Kinetic uncertainty relations in stochastic control

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Non-equilibrium stochastic reaction networks are commonly found in both biological and non-biological systems, but have remained hard to analyze because small differences in rate functions or topology can change the dynamics drastically. Here we conjecture exact quantitative inequalities that relate the extent of fluctuations in connected components, for various network topologies. Specifically, we find that regardless of how two components affect each other's production rates, it is impossible to suppress fluctuations below the uncontrolled equivalents for both components: one must increase its fluctuations for the other to be suppressed. For systems in which components control each other in ring-like structures, it appears that fluctuations can only be suppressed in one component if all other components instead increase fluctuations, compared to the case without control. Even the general *N*-component system—with arbitrary connections and parameters—must have at least one component with increased fluctuations to reduce fluctuations in others. In connected reaction networks it thus appears impossible to reduce the statistical uncertainty in all components, regardless of the control mechanisms or energy dissipation.

C.56 Collective behaviour of epithelial cells under different coordinated dynamics of cell polarisation

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The coordinated motion of epithelial cells is determined by dynamics of cell polarisation through cell-cell interactions. According to experimental results, cell polarisation may couple to different variables such as local velocity [1], orientation of cells [2] etc. which leads to different collective motions. For example, aligning cell polarisation to its local velocity can result in flocking motion [3]. While the coupling between polarisation and anisotropy in cell shape is still not fully understood.

We apply phase field method to model cells, which incorporates features of cell elasticity, cell-cell adhesion, steric interaction and polarisation of cells. In addition, deformation of cells caused by actin-myosin cortex is modelled by nematic dipolar stress. To unveil the effect of coordinated dynamics, we impose different polarisation coordinated dynamics to the system.

We compare the difference between different dynamics. In our simulation, the coupling between cell polarisation and elongation can give rise to gap formation where there is free space with no cell but only ECM. Also, cell-cell adhesion inducing deformation plays an important role in this polarisation-elongation coupling dynamics.

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Poster Abstracts

P.1 The KDEL receptor – New interaction partners and functions on the cell surface

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The retention of important ER resident proteins is a crucial factor for maintaining the ER proteome and fundamental cellular functions. KDELRs (KDEL receptor 1-3) are able to bind proteins with a C-terminal KDEL-like amino acid sequence in the Golgi and retrotransport them back into the ER [1]. This transport function is accompanied by the ability to modulate a broad range of cellular functions via activation of G-proteins and kinase associated signal cascades [2]. Previous studies also suggest new roles of KDELRs at the plasma membrane and demonstrate that KDEL cargo binding promotes KDELR clustering at the cell surface of HeLa cells [3]. By performing live cell imaging experiments on various species and different cell types, a similar KDELR cluster dynamic could be observed in most of the human and mouse cell lines. Interestingly, human and murine macrophage cell lines did not show any cluster formation. However, KDELR expression based on RT-qPCR studies did not show a correlation with the clustering behavior in the diverse cell types or with the absence of clusters in macrophages, suggesting differences in KDELR localization or internalization. Subsequently, the PM localizations on various cell types will be investigated by cell surface biotinylation in the future, which should bring new insights into the role of KDELRs in mammalian cells.

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P.2 An approach to identify potential KDEL receptor interaction partners

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Eukaryotic KDEL receptors represent seven trans-membrane proteins which are not only localized in the ER and Golgi apparatus, but also be found to a minor amount at the cell surface of mammalian cells. Until now, it was postulated that KDELRs are mainly responsible for the retention of KDEL bearing proteins from the Golgi back to the ER. In the last years, a wide range of new KDELR functions are discovered including their role in (i) A/B toxin endocytosis, (ii) extracellular matrix degradation, (iii) cell adhesion as well as (iv) maintenance of Golgi homeostasis. Despite the manifold functions and localizations, only a handful of KDELR interactors are experimentally identified at the moment. Here, we try to overcome this limitation by using an engineered ascorbate peroxidase (APEX2) to label potential KDELR interaction partners with biotin in the near proximity (20 nm). In our pilot study, we were able to express biologically active KDELR-APEX2 fusion proteins in HeLa cells. After successful biotin-labeling and enrichment of the biotinylated proteins, potential interaction partner datasets of KDELR1, KDELR2 and KDELR3 could be generated and bioinformatically analysed in more detail.

P.3 Investigation of collective motions of RNA helicases involved in RNA transport via MD simulations

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Helicases are motor proteins, which play a crucial role in translation and transcription of RNA/DNA and in the splicing pathway of pre-mRNA to mRNA. Special attention should be given to the detailed mechanistic work of those enzymes, because it is widely unknown. Key parts for understanding the mechanism are the translocation of RNA, the binding and release of ATP/ADP and the resulting conformational changes. Therefor, we will observe the influence of all ligands and co-factors on the different states of the proteins in this work. We will use molecular dynamics simulations on an atomistic level to be able to investigate the collective motions of the helicases Prp2, Prp22, and Prp43. The simulations are carried out with GROMACS and a AMBER force field. The crystal structures were obtained by our collaboration group Ficner et. al. from the University of Göttingen. Still in the early stages of this project, we already collected information about the ATP binding pocket. Important task for the future is to identify the connection between the conformational changes of the main domains, such as ATP pocket, RNA cleft, cofactor binding side etc.

P.4 Modulating the conformation of the Sec61 protein translocation pore

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The Sec complex is a central component of the cellular machinery that translocates nascent peptides synthesized by the ribosome into the endoplasmic reticulum (ER). The Sec complex also assists membrane protein insertion into eukaryotic ER membranes and protein secretion. Its α-subunit forms the channel pore. The N-termini of Sec61 subunits α, ß and y are typically not fully resolved in atomistic structures. However, there is experimental evidence that the N-terminus of Sec61α is required for post-translational protein import and complex stability [1]. Hence to understand its conformational dynamics and its interaction with other subunits, we modeled the missing N-terminal part of Sec61α by molecular modeling and explored its conformational space using enhanced sampling molecular dynamics simulations. Our results suggest that the N-terminal amphipathic helix (F10-S15) of Sec61α is stable and the N-terminus of its ß subunit (sbh1) is disordered. Furthermore, Sec63 of yeast contributes to post-translational protein translocation. Recent crystallographic data demonstrated that binding of Sec62-Sec63 to Sec61 caused a wide opening of the lateral gate and assists in post-translational import [2]. MD simulations indeed revealed that binding of Sec63 affects the conformations of lateral gate and plug region of Sec61α. Finally, by molecular docking we delineate putative binding locations of the Sec61 inhibitor *Mycolactone*.

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P.5 Protein engineering strategy to design and develop a photo-responsive ICAM-1 domain

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The immunological synapse forms by tight apposition of Antigen Presenting Cells and T-cells. This structure is a complex assembly of spatially organized concentric rings of multiple proteins.[1] The functional role of molecular clustering in the center of immunological synapse is debatable. Numerous reports have shown that the spatiotemporal organization of the ligands, along with the APC's mechanical properties, are vital for the IS to form and function effectively.[2] The aim of our current research work is to establish artificial models of APCs based on hydrogel surfaces that allow light-regulated patterning of IS receptors. In particular, we have synthesized a photoswitchable Intracellular Cell Adhesion Molecule (ICAM). ICAM is an APC transmembrane protein which binds to LFA-1 on T-cells during early adhesion events of IS formation. For making it light switchable, we fused the Light-Oxygen-Voltage (LOV) domain from Avena Sativa to the N-terminus of extracellular domain 1 (D1) of ICAM.[3] This light switchable fusion protein is inactive in the dark, and can be reversibly activated using blue light, thereby allowing the possibility to dynamically modify the spatial distribution of active ICAM when immobilized on hydrogel surfaces. To analyze the dark and light state binding affinities of the photo-switchable D1 fusion proteins (PS-D1) towards LFA-1 αI, a new technique combining quartz crystal microbalance with dissipation monitoring (QCM-D) and nanoplasmonic resonance (NPS) is used.

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P.6 The heat shock protein ClpC affects the intracellular survival capacity of staphylococcus aureus in endothelial cells

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The ability of Staphylococcus aureus to invade non-professional phagocytic cells and to persist intracellularly for longer periods of time is thought to be one of the major reasons for the pathogens capacity to cause chronic and relapsing infections. Here we present data indicating that the Clp ATPase ClpC, a member of the heat shock protein 100 family, attenuates the intracellular survival capacity of *S. aureus.* Inactivation of *clpC* in the biofilm forming S. aureus isolate DSM20231 significantly enhanced the intracellular long-term survival capacity of mutant cells within human endothelial cells, without affecting the adhesion, invasion, and small colony variant formation rates. Transcriptional analyses of total RNAs isolated from intracellular DSM20231 and isogenic *clpC* mutant cells identified alterations in transcription of α-toxin (*hla*), protein A (*spa*), and *RNAIII* (the effector molecule of the *agr* locus), suggesting that ClpC negatively affects the intracellular survival capacity of S. aureus in endothelial cells via the transcriptional modulation of the virulon.

P.7 Reducing electron beam induced radiation damage on SKBR3 cells by graphene coating

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Epidermal Growth factor receptor 2 (HER2) is overexpressed in 20% of all breast cancer cases [1]. It is target by anti-cancer drugs like Trastuzumab but drug resistance remains a major clinical problem [2]. Finding insights into the mechanism of Trastuzumab is assumed to be essential for improvements in cancer treatment. Single cell- and single molecule analysis of HER2 can be performed using correlative fluorescence microscopy and scanning transmission electron microscopy (STEM). For electron microscopy, a high vacuum is required. The drawbacks of imaging biological samples under high vacuum conditions are first the evaporation of water from the sample, and second the collapse of cell material like the cell membrane. We therefore enclose cells in hydrated state in a graphene liquid cell [3]. For stability, the cells are chemically fixed after labeling HER2 with a biotinylated affibody molecule and streptavidin Quantum Dots 655. An important question is how stable these samples are to radiation damage occurring during electron microscopy. Image series were acquired in STEM to evaluate the sample stability to electron beam irradiation at an accumulated dose.

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P.8 Nanoscale architecture of biomembranes

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Biological membranes generate specific functions through compartmentalized regions, such as cholesterol- enriched nanodomains that host selected proteins [1].

Despite the biological significance of membrane nanodomains, details on their molecular structure remain uncertain [1]. They are elusive for most of the microscopic experimental techniques due to their small size, yet there is also a lack of atomistic simulation models able to describe spontaneous nanodomain formation in sufficiently simple but relevant complex membranes.

Here, we present a combined coarse-grained/atomistic (CG/AA) simulation approach in the study of ternary and quaternary lipid mixtures comprising cholesterol and/or sphingomyelin. Our approach allows to overcome the limitations on accessible time-scales and system-sizes of the AA models, and the insufficient accuracy of the CG force-fields [2].

The chosen lipid compositions form stable coexisting liquid-ordered/liquid-disordered (L_o/L_d) phases on a 10-μs time–scale at AA resolution, allowing to study the lateral organization of the lipids, and cholesterol. The Lo domains are characterized by substructures of hexagonally packed saturated hydrocarbon chains nanoclusters, separated by interstitial regions enriched in cholesterol. In the L_d domains, cholesterol shows spontaneous trans-bilayer motion, depending on the lateral heterogeneity of the membranes.

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P.9 The interplay of synaptobrevin-2 transmembrane domain and lipids in membrane fusion

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Ca^{2+}-triggered fusion of vesicles with the plasma membrane is mediated by assembly of SNARE proteins between opposing membranes. While membrane fusion requires not only protein-protein, it also depends on protein-lipid interactions, making membrane bending/curvature a critical determinant in the kinetics of the fusion process. Here, we investigate the role of vesicular SNARE synaptobrevin-2 (syb-2) and phospholipid interactions in Ca^{2+}-triggered neurotransmitter release. Using photolytic uncaging of intracellular Ca^{2+} with membrane capacitance measurements and carbon fiber amperometry in chromaffin cells, we found that structural flexibility of the syb-2 transmembrane domain (TMD) promotes vesicle fusiogenicity and rate of cargo release from single granules. Furthermore, membrane curvature-modifying lipids (inducing either positive or negative curvature) have opposing effects on fusion pore expansion. We also show that the slow fusion pore expansion phenotype seen with syb-2-TMD mutants can be rescued with membrane curvature active agents, demonstrating that protein and lipid functions converge on the same intermediate steps to promote exocytosis. Thus, our results demonstrate that SNARE TMDs play an active role in the fusion process that goes beyond simple anchoring of the protein, and their functional *pas de deux* with lipids determines Ca^{2+} triggered neurotransmitter release.

P.10 Quantitative analysis of bilayer-to-monolayer partitioning of monotopic membrane proteins using *in vitro* microfluidics

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Lipid droplets are subcellular lipid storage organelles. They create a unique physicochemical environment in the cell as their hydrophobic lipid core is separated from the aqueous cytosol by a phospholipid monolayer. The dynamic metabolic function of lipid droplets relies on specific proteins that integrate into the limiting monolayer membrane in a unique monotopic hairpin-type topology. Many hairpin proteins dynamically partition between the endoplasmic reticulum membrane, a phospholipid bilayer, and the lipid droplet monolayer membrane. The hairpin topology in both membranes presumably facilitates this partitioning; yet, the collective processes enabling hairpin proteins to reside in these distinct physicochemical environments as well as the partitioning between them remain unknown. Here, we use UBXD8 as a model hairpin protein to study protein integration into these two types. We aim to purify the protein, label it with a fluorescent dye and reconstitute it into artificial membranes that simultaneously mimic the phospholipid bilayer and the LD environment in a microfluidic chamber. We fused UBXD8 to MBP to increase the solubility and expressed it in E. coli followed by affinity purification and attachment of a fluorophore. Different mutations within the construct will inform us which sequence features influence the membranepartitioning.

P.11 Patterns and molecular determinants of NK cell mediated killing of melanoma cells

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Malignant melanoma is the most deadly form of skin cancer. Due to its genetic heterogeneity and high potential to metastasize, the treatment of melanoma is challenging. Despite the promising result of T-cell based therapeutic strategies in combination with targeted therapies, therapeutic resistance or relapse occur. Natural killer (NK) cells, which show an innate ability to recognize and kill cancer cells without prior sensitization, could be a useful additional therapeutic tool in melanoma immunotherapy. To investigate the therapeutic potential of NK cells, we assessed the cytotoxicity of primary NK cells as well as the NK-92 cell line to genetically diverse human melanoma cell lines. We observed a broad range of susceptibility of different melanomas to activated NK cells, while non-stimulated NK cells showed reduced cytotoxicity against the same cells. Subsequent proteome analyses (RPPA) of melanoma cells identified single proteins as well as signalling pathways influencing NK killing. Furthermore, by using the melanoma proteomic signature, we successfully predicted the NK cell susceptibility of additional and untested melanoma cell lines. In summary, our study reveals new insights in the potential use of NK cells in melanoma treatment by identifying novel prognostic immunotherapy-response biomarkers for melanoma.

P.12 Simulations of shock waves induced by X-ray free-electron lasers and potential effects on biological samples

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X-ray free-electron lasers produce x-ray pulses with very high brilliance and short pulse duration down to a few femtoseconds. These properties allow to investigate the structure of biomolecules using nanocrystals or single particles and to observe conformational changes on the femtosecond timescale. Samples are injected into the laser beam using a liquid jet and high laser pulse repetition rates of a few Mhz are used. Due to the high brilliance of the X-ray beam atoms of the sample and the liquid jet are ionized and a hot electron gas with temperatures of about 50.000 K to 100.000 K is formed [1]. As experiments have shown, shock waves are created, which propagate through the jet and slow down to the speed of sound in water [2]. There are few investigations on effects of the shock waves on biological samples [3, 4], thus further modelling and experimental work has to be done. We use molecular dynamics simulations to model shock waves induced by heated water. The simulations are carried out with GROMACS. Thereby we will get a deeper insight in the dynamics of the experiments and we will be able to see potential effects on biological samples. In particular the effect on protein complexes, such as membrane proteins, will be studied.

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P.13 Establishing a fine-resolution topology map of the monolayer-integrated hairpin protein UBXD8

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Lipid droplets (LDs) are hubs of cellular metabolic energy stored in the form of neutral lipids, particularly triacylglycerols (TGs). These ubiquitous cytoplasmic organelles are dderived from the endoplasmic reticulum (ER) and consist of a hydrophobic core encircled by a phospholipid monolayer. Hence, LDs are unique as they do not separate the two aqueous compartments like other organelles. The lipid monolayer is decorated with either peripheral proteins or with integral membrane proteins that adopt an unorthodox monotopic hairpin topology [1]. The functions of the LDs are mainly executed andregulated by these surface proteins. Current bioinformatics tools are suitable for the topology prediction of transmembrane-spanning proteins; however, are limited in determining the topology of monotopic hairpin proteins [2]. Recent work from our group hasunraveledthetargetingpathwayofUBXD8-aputativehairpinprotein,whichlocalizes to both ER and LDs [3]. It is initially inserted into the cytoplasmic face of the ER bilayer before translocation to the LD monolayer. So far, the intricate details of the UBXD8 topology have not been determined. The goal of this project is to determine the key elements regulating the topology of hairpin proteins using state-of-the-art biophysics, computational, and classical biochemica lapproaches.

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P.15 2.5D Artificial microenvironments to study mechanochemical sensing at intercellular junctions

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The epidermis is a multilayered epithelium consisting of highly specialized cells, the keratinocytes, which organize themselves into an adhesive network with several layers, or 'strata'[1]. During its formation, as well as during homeostasis, keratinocytes in the most-basal layer contacting the extracellular matrix act as stem cells. To form suprabasal layers, basal keratinocytes have to differentiate and migrate upwards, losing their integrin-based contact with the ECM while simultaneously increasing their cadherin-based cell-cell contacts [2]. Recent studies have established that both types of adhesive junctions are able to sense and respond to their mechanical microenvironment [3], [4]. However, how the mechanical and/or molecular components of the intercellular junctions might regulate the differentiation and/or stratification of keratinocytes is not clearly understood. Our lab has recently developed a unique 2.5D artificial microenvironment that would allow us to reconstruct the lateral cell-cell and basal cell-matrix interfaces. Using this platform we will able to study how the external mechanochemical signals integrated by the intracellular junctions affect the differentiation of the keratinocytes and the formation of a functional stratified epidermis.

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P.14 Polarity signaling ensures epidermal homeostasis by coupling cellular mechanics and genomic integrity

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Epithelial homeostasis requires balanced progenitor cell proliferation and differentiation, whereas disrupting this equilibrium fosters degeneration or cancer. Here we studied how cell polarity signaling orchestrates epidermal self-renewal and differentiation. Using genetic ablation, quantitative imaging, mechanochemical reconstitution and atomic force microscopy, we find that mammalian Par3 couples genome integrity and epidermal fate through shaping keratinocyte mechanics, rather than mitotic spindle orientation. Par3 inactivation impairs RhoA activity, actomyosin contractility and viscoelasticity, eliciting mitotic failures that trigger aneuploidy, mitosis-dependent DNA damage responses, p53 stabilization and premature differentiation. Importantly, reconstituting myosin activity is sufficient to restore mitotic fidelity, genome integrity, and balanced differentiation and stratification. Collectively, this study deciphers a mechanical signaling network in which Par3 acts upstream of Rho/actomyosin contractility to promote intrinsic force generation, thereby maintaining mitotic accuracy and cellular fitness at the genomic level. Disturbing this network may compromise not only epidermal homeostasis but potentially also that of other self-renewing epithelia (1).

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P.16 Influence of extracellular vimentin on cell proliferation, migration and adhesion

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Vimentin is a cytoskeletal protein of the family of intermediate filaments which plays a role in cell migration, adhesion and signaling due to its ability to interact with various proteins. Apart from its presence in the cytoplasm, it is also found in the extracellular spaces around various cells, especially in the case of inflammation. Extracellular vimentin has been shown to be involved in processes such as viral infections, cancer progression, inflammation and axonal growth in astrocytes by activating the IGF1 receptor in the same signaling pathway as IGF1. The IGF1/IGF1-R pathway plays significant role in general cellular functions such as cell migration, proliferation, adhesion and invasion.

In this study, we demonstrate the functional similarities of extracellular vimentin and IGF1 in context of cell proliferation, migration and adhesion. Using a MTT proliferation assay, we show that extracellular vimentin increases the proliferation rate in MCF-7 cells. Furthermore, we carried out wound healing assays which suggest that extracellular vimentin promotes MCF-7 cell migration similar to IGF1. We quantified the number of focal adhesions after vimentin treatment in MCF-7 cells and measured the maximum adhesion strength of cells using FluidFM technique. Our results suggest that recombinant vimentin enhances these functions in MCF-7 cells. Consequently, it might be useful for altering and stimulating these cellular functions which would open up the possibility for treating various disease conditions.

P.17 Synthetic hydroxyapatite surface – a perfect dental enamel imitator?

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In contact with saliva, intraorally exposed surfaces are covered within seconds by a layer of adsorbed salivary biomolecules. This initial acellular biofilm is composed of proteins, carbohydrates and lipids and it modulates tooth protection against erosive and abrasive challenges. In the course of time, planktonic microorganisms attach directly to the initial biofilm leading to the formation of a dental bacterial biofilm. Mature bacterial biofilms are highly complex ecosystems comprising up to several hundred different microbial species. They may cause caries, which is characterized by local demineralization of dental hard tissues, initially the enamel. Dental enamel consists of around 96 % hydroxyapatite (HAP). The exact chemical composition of dental HAP differs between individuals depending on their personal history, e.g. living in a region with fluoridated drinking water. Therefore, chemically well-defined, highly compressed and sintered HAP pellets might be a good choice to model tooth surfaces for biofilm formation and biofilm management studies. Preliminary data show potential differences in the in situ formation of initial biofilms (5 s to 120 min) and mature bacterial biofilms (up to 48 h) on HAP pellets compared to dental enamel. The examination includes the assessment of coverage, microstructure, thickness and bacterial viability of the biofilms.

P.18 A phase-field approach for studying actin-wave driven cell migration

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Cells migration is an important part of their search for nutrients, of immunological responses, and of developmental processes among others. It is driven by the actin cytoskeleton a network of actin filaments, molecular motors, and other actin-binding proteins. Although many important factors involved in actin-driven cell motility have been identified and characterized in amazing detail, it is still poorly understood how the network is organized in this process. Spontaneous actin waves have been observed in a large number of different cell types and present an attractive concept to understand orchestration of the cytoskeleton during migration. We introduce a mean-field description of spontaneous actin waves. The actin network is confined to an evolving cellular domain by means of a phase field. We numerically solve the dynamic equations and obtain the corresponding phase diagram. In particular, we find erratic motion due to the formation of spiral waves. We compare these findings to experiments and discuss possible physiological consequences.

P.19 The multifunctional staphylococcus aureus virulence factor extracellular adherence protein (Eap) acts as an invasin addressing different cellular uptake mechanisms

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In the course of the evolutionary arms race, bacteria have developed the ability to invade host cells, which is considered a major immune evasion strategy. Specific proteins facilitate the invasion into non-phagocytic cells, offering protection from the host immune system and from antibiotic treatment. The bacteria can survive intracellularly with a downregulated metabolism and cause relapsing infection outbreaks. *S. aureus*, formerly described as extracellular pathogen is nowadays known as potentially intracellular present pathogen. One of its well described invasins is the extracellular adherence protein (Eap) which is able to alter the cytoskeleton structure of host cells [1] and increase the uptake of substances from the extracellular space. Our recent work demonstrates that Eap promotes the engulfment of particle of bacterial size [2] as well as smaller, virus sized particles [3] and liquids into eukaryotic cells. Eap seems to stimulate different energy dependent and independent uptake processes, depending on the host cell type [3]. Currently we focus on the effect of Eap on mechanisms like clathrin coated pits, calveolae and micropinocytosis using specific inhibitors. First trials for a clinical usage of this function show a significantly increased killing of intracellular *Salmonella enterica* by treating the cells with Colistin filled liposomes functionalized with Eap [3].

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P.20 Fluoride treatment of hydroxyapatite – mechanisms and effects

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Tooth enamel consists by more than 95 % of hydroxyapatite (HAP). Since decades, fluoride treatment of teeth is used due to its caries-prophylactic effect, e.g., in fluoride containing toothpastes or mouthwashes. However, the exact mechanisms of the fluoride uptake are yet to be explored.

We used sintered hydroxyapatite pellets as a model system for a tooth surface and treated it with a NaF-solution. XPS-measurements in combination with Ar-ion-etching revealed that the thickness of the fluoridated layer which forms on the HAP surface is in the range of only a few nanometers [1]. By using different application times of the NaF-solution, we found that both the thickness of the fluoridated layer and the overall amount of fluoride taken up reach a state of saturation on a timescale of about 3 min [1].

Etching experiments with pure and fluoridated HAP surfaces showed a very strong effect of the fluoridation. Although the fluoridated layer is extremely thin and contains only minute amounts of fluoride, AFM-measurements showed a complete inhibition of etching on the fluoridated surface for at least 5 min. The major part of the surface withstood etching even for more than 23 min [2].

These findings give new insight into the mechanisms and especially the timescale of fluoride uptake by HAP and show how the incorporated fluoride in HAP correlates with its protective impact.

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P.21 Noncanonical amino acids in a cell free TX-TL system

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The canonical set of amino acids leads to an exceptionally wide range of protein functionality. Nevertheless, the set of residues still imposes limitations on potential protein applications. The incorporation of non-canonical amino acids can enlarge this scope. For this purpose we use a cell-free expression system to reassign the genetic code within the endogenous translational system. Kinetic proofreading is a process that will counteract the charging of tRNA with other amino acids than the canonical one [1,2], however, the translation machinery still accepts non-canonical amino acids as a surrogate and incorporates it at canonically prescribed locations, i.e., all occurrences of a canonical amino acid in the protein are replaced by the noncanonical one. We managed to replace L-arginine by the noncanonical amino acid L-canavanine within proteins completely [3] while the replacement of L-lysine by L-hydroxy-lysine remains a challenge because of residual L-lysine in the cell-free expression system [4,5]. We plan to study the error rate of amino-acid incorporation in competition to find out about possible non-linearities in the error correction process as opposed to the suggestions by Hopfield.

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P.22 Modelling an artificial synaptic communications with microfluidics

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Neurotransmission is the process by which signaling molecules, so called neurotransmitters are released by the membrane of a neuron (the presynaptic membrane) and react with the protein receptors embedded in the membrane of another neuron (the postsynaptic membrane). Using microfluidics, we are presenting a simplistic realization of this type of cell communication. For that instance, two free-standing bilayer are produced at desired positions in a microfluidic chip applying the DiB (droplet interface bilayer) method. This means in our case that we contact three aqueous buffer droplets into an oily phase where we have dispersed lipidic molecules. Upon contacting the surfaces of the lipid decorated droplets, bilayer are formed within a short time. Two of these bilayers are positioned face-to-face, separated by a distance of a few hundreds of microns, representing the presynaptic and the postsynaptic model membranes. Small unilamellar vesicles are injected near the presynaptic membrane and fuse with it, releasing the vesicle content (i.e model neurotransmitter). This model neurotransmitter is then analyzed by the proteins receptors that are embedded in our postsynaptic model membrane. This model cell communication is recorded in situ by electrophysiological measurements (patch-clamp amplifier) and by direct optical inspection.

P.23 Highly reproducible physiological asymmetric membrane with freely diffusing embedded proteins in a 3D-printed microfluidic setup

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Experimental setups to produce and to monitor model membranes have been successfully used for decades and brought invaluable insights into many areas of biology. However, they all have limitations that prevent the full in vitro mimicking and monitoring of most biological processes. Here, a suspended physiological bilayer-forming chip is designed from 3D-printing techniques. This chip can be simultaneously integrated to a confocal microscope and a path-clamp amplifier. It is composed of poly(dimethylsiloxane) and consists of a ≈100 µm hole, where the horizontal planar bilayer is formed, connecting two open crossed-channels, which allows for altering of each lipid monolayer separately. The bilayer, formed by the zipping of two lipid leaflets, is free-standing, horizontal, stable, fluid, solvent-free, and flat with the 14 types of physiologically relevant lipids, and the bilayer formation process is highly reproducible. Because of the two channels, asymmetric bilayers can be formed by making the two lipid leaflets of different composition. Furthermore, proteins, such as transmembrane, peripheral, and pore-forming proteins, can be added to the bilayer in controlled orientation and keep their native mobility and activity. These features allow in vitro recapitulation of membrane process close to physiological conditions. [1]

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P.25 Detecting the structural and conformational changes of silk fusion proteins

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Silk protein based materials are attracting an increasing interest in many applications, from the textile to the material science and biosensors[1], due to its biocompatibility, biodegradability and the good mechanical properties[2]. For its potential applicability, a deep knowledge of the structural features in response to stimuli, as applied stress or chemical environment, is demanded.

In the present work, silk fusion proteins are investigated at a single molecular level and the conformational changes associated with different salt solutions are studied. In detail, the technique employed is the Atomic Force Spectroscopy, which permitted to pull and stretch single silk proteins and to identify the extensional length in function of different salts and concentrations. Briefly, the proteins of interest are bound to both gold coated tip surface using a Cys terminated SpyTag that reacts with an engineered SpyCatcher terminated silk molecule. By the analysis of the FD peaks recorded at the different environments, changes are observed in contour length, number and force of the unfolding peaks attributed to α-helices or ß- sheets. Eventually, the morphology of the AFM images and the analysis of the force distance curves suggested a more compact structure in presence of phosphate, and an extended coiled one when the salt is exchanged with sodium chloride. The main scope of the work, in a long term prospective, is to develop new functional materials, which the components are bio-based, in order to increase the sustainability and lower the plastic consume.

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P.26 Using TIRM to study cell membranes

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In this project I plan to use the technique of total internal reflection microscopy (TIRM) which is established to measure interactions between colloidal particles and a plane glass substrate to study a) the interactions of (functionalized) colloidal particles with the cell membrane and b) fluctuations of the cell membrane by tracking the motion of particles attached to the cell.

The proposed technique should allow a) to get insight into the dynamics of particles binding to a cell membrane and b) enable to analyze the fluctuation spectra of the cell membrane itself. The latter allow conclusions on the (visco-) elastic properties of the cells by an analysis of the power spectrum.

Due to their flat geometry endothelial cells seem to be a promising starting point for experiments.

P.27 Methods for (bio)materials' surface characterization - an overview

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The selection of substrates and their interaction with deposited layers or (bio)adsorbates is of particular importance in biophysics. Through intermolecular interactions, the substrate can significantly influence the properties of the system, e.g., wettability or adhesion. A precise control of surface properties is therefore essential for understanding the effects that occur. Prominent examples are graphene, a monolayer of graphite or the nm-sized fluorapatite layer on our teeth if using fluoride containing toothpaste. In both systems, the physical properties change dramatically due to only nm-sized layers. Another example is a nanostructured Cu surface, which exhibits an improved antibacterial effect compared to an unstructured Cu surface. Our poster gives an overview of experiments which can characterize the physical and chemical properties of substrate surfaces and how these technicus are applied in our research. We will introduce X-ray photoemission spectroscopy, low energy electron defraction, scanning tunneling microscopy and atomic force microscopy. These techniques allow us to obtain the elementary composition, the orientation of the crystal lattice, atomically resolved images of the surface, electrical and mechanical properties of the surfaces. These methods don't destroy the surfaces during the measurement and allow to investigate livingmicroorganisms.

P.28 Modeling of T-Cell polarization

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Cytotoxic T lymphocytes (T) eliminate pathogen-infected or tumorigenic cells (target cells). Once T-cell identifies a target cell, a tight contact, the immunological synapse (IS), is formed. Subsequently, one observes repolarization of the cell involving the rotation of the microtubule (MT) spindle and the movement of the microtubule organizing center (MTOC) to a position that is just underneath the plasma membrane at the center of the IS. Concomitantly, a massive relocation of organelles attached to MTs is observed, including the Golgi apparatus, lytic granules and mitochondria. Subsequently, T-cell releases lytic granules containing perforin/granzyme and cytokine containing vesicles. Although the polarization was observed experimentally, its inner mechanism remains poorly understood. We devised a theoretical model for the molecular motor driven motion of the MT half-spindle confined between the plasma membrane and nucleus. Multiple scenarios currently discussed in the literature, including capture-shrinkage and cortical sliding mechanisms, are analyzed. We compared quantitative predictions about the spatio-temporal evolution of MTOC position and spindle morphology with experimental observations. The case of two IS including the oscillations of MTOC is examined. We propose that our model opens a way to infer details of the molecular motor distribution from the experimentally observed features of the MT half-spindle dynamics.

P.29 Intracellular activity and mechanics in dividing epithelial cells

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While there is a good understanding of chromosome segregation during cell division, surprisingly little is known about how the different organelles are distributed during this fundamental process. It is generally assumed that organelles are not systematically transported to the daughter cells but that their distribution relies on passive diffusion and hence stochastic transport throughout the cell. Although diffusion will provide fast mixing of small molecules, it is not clear if this can explain the even distribution of larger organelles with low copy number, especially in highly polarized cells.

An attractive mechanism for equal distribution of organelles during cell division is the increase of random mobility. This could be achieved by active, undirected fluctuations, e.g. generated through motor protein activity. To test this hypothesis that active fluctuations help distributing organelles we perform passive and active microrheology measurements using optical tweezers, with exogenous particles inside dividing MDCK cells. The results are used to calculate the intracellular viscoelasticity and mechanical activity to pinpoint the influence of active cytosolic mixing during cell division. We identify that during metaphase the activity decreases while it is enhanced during anaphase.

P.30 Resveratrol-induced temporal variation in the mechanical properties of MCF-7 breast cancer cells investigated by atomic force microscopy

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Atomic force microscopy (AFM) combined with fluorescence microscopy has been used to quantify cytomechanical modifications induced by resveratrol (at a fixed concentration of 50 μM) in a breast cancer cell line (MCF-7) upon temporal variation. The ability of resveratrol to induce cancer cell death, alone and/or in combination with other therapeutic drugs, as well as to prevent growth-factor-induced cancer progression has been already tested [1–3]. Such inhibitory effects on epidermal growth factor receptor (EGFR) expression levels induced changes in morphology and stiffness of single cells [4, 5].

Here, cell indentation has been utilized to determine simultaneous variations of Young's modulus, the maximum adhesion force, and tether formation, thereby determining cell motility and adhesiveness. Effects of Resveratrol treatment have been measured at several time-points (0–6 h, 24 h, and 48 h). An overnight incubation showed to induce the maximum variation in mechanical properties before cell proliferation was compromised, while drug incubation for longer periods (48 h) caused a gradual loss of properties that concluded in cell death. These results confirm the validity of the AFM technique as an optimal tool to detect irreversible transformations at the nanoscale level that might affect normal cell functioning, or even their malignancy, as in the case of cancerous cells.

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P.31 Disentangling the effects of symmetry, shape fluctuations and atomic details on the SAXS curve prediction

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Small-angle X-ray scattering (SAXS) is increasingly-popular technique to study biomolecules under near-native conditions. However, experimental curve contains onlyfew independent data points. To obtain more information from the experiment, methods that allow for the prediction of the scattering curve from a given structural model are constantly developing. Often, curve predicted using the given method do not agree with the experimental curve and the reason for discrepancy is far from obvious. Here, we studied the effects of the model symmetry, shape fuctuations and the atomic details on SAXS curve prediction, by combining all-atom multi-replica MD simulations (following the principle of maximum entropy) and simplifed ellipsoid models.

P.32 Subtomogram averaging of Arp2/3 complex-mediated branches in human macrophage podosomes

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Human macrophages form protrusive adhesion structures called podosomes which are involved in mechanosensing [1]. They consist of an adhesion ring surrounding an F-actin rich core in which actin polymerization occurs through branching mediated by the Arp2/3 complex. How branches are spatially organized and contribute to force production in podosomes remains unknown. Following up on a recent study on actin waves [2], we employed cryo-electron tomography and subtomogram averaging to identify branches in human macrophage podosomes and analyze their spatial organization. The initial approach on in situ tomograms of native podosomes did not allow confident identification of true-positive branches. Simulations ruled out the missing wedge as a limiting factor. Instead, the high density in the podosome core combined with a low signal-to-noise ratio in the data prevented the detection of branches. Improvement of the processing workflow and higher data quality enabled the identification of branches within three tomograms. A low-resolution branch structure was obtained and preliminary analysis showed that ~50% of the branches in the core point toward the cell membrane. Mother and daughter filaments have similar orientations, suggesting that mother filaments may originate from earlier branching events.

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P.33 Self-organized lane formation in bidirectional transport of molecular motors

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Within cells, vesicles and proteins are actively transported several micrometers along the cytoskeletal filaments. The transport along microtubules is propelled by dynein and kinesin motors, which carry the cargo in opposite directions. Bidirectional intracellular transport is performed with great efficiency, even under strong confinement, as for example in the axon, where bidirectional motor-driven transport is carried out on a bundle of parallel microtubules which are embedded in a long, narrow, and crowded channel. For this kind of transport system one would expect generically cluster formation.

In this work we discuss the effect of the recently observed self-enhanced binding affinity along the kinesin trajectories on the MT [1]. We introduce a stochastic lattice gas model, where the enhanced binding affinity is realized via a floor-field. Our model results show that this mechanism can lead to symmetry breaking and lane formation which indeed leads to efficient bidirectional transport in narrow environments.

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P.34 Trapping in and escape from branched structures of neuronaldendrites

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We present a coarse-grained model for stochastic transport of non-interacting chemical signals inside neuronal dendrites and show how first-passage properties depend on the key structural factors affected by neurodegenerative diseases or aging: the extent of the tree, the topological bias induced by segmental decrease of dendrite diameter, and the trapping probabilities in biochemical cages and growth cones. We derive an exact expression for the distribution of first-passage times, which follows a universal exponential decay in the long-time limit. The asymptotic mean first-passage time exhibits a crossover from power-law to exponential scaling upon reducing the topological bias. The analytical predictions are in remarkable agreement with simulations. Our results evidence that structural irregularities can create local traps and heterogeneous patterns of signaltransmission.

P.35 Two studies with a biophysical multitool: *Candida albicans* adhesion to central venous catheters; and the stiffening of human primary CD4⁺ T cells during immunological synapse formation

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Atomic Force Microscopy is a versatile tool for a multitude of life science applications. Here, two approaches are presented in which AFM was used to study cellular interaction with the surfaces of medical devices and immunological model surfaces, respectively.

In a first approach, we addressed the C. albicans adhesion to central venous catheters (CVC), which is a basic condition for catheter-related infections. C. albicans is capable to form two morphotypes (yeast and hyphae). Although the contribution of these types to adhesion is still discussed, the yeast type is considered mostly responsible for initial host adherence [1]. Our force spectroscopy results indicate that C. albicans early state hyphae adhere with a significantly higher force to naïve and plasma-coated CVC than yeast cells, suggesting a bigger contribution of hyphae to initial adherence than previously expected.

In a second approach, the stiffness of T cells during the immunological synapse (IS) formation was studied by elasticity mapping. It is known that T cells are mechanosensitive [2]. However, the impact of cell stiffness on its functions is still discussed. Our experiments showed a reduced cell stiffness on LFA1 antibody-coated surfaces, compared to IS inducing surfaces (coated with LFA1, CD3 and CD28 antibodies), indicating an actively-driven cell stiffening and thus a role of stiffness in the formation of IS.

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P.36 The role and interplay of cytoskeletal filaments in microtentacles

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Circulating Tumor Cells (CTCs) pose a significant threat due to their role in metastasis: It has been proposed that CTCs are able to escape the blood stream and reattach to the tissue by the formation of so-called microtentacles (McTNs) [1].

McTNs are microtubule based membrane protrusions with a diameter of less than 1 µm and a length of tens of µm [2].

In CTCs the balance of the outward growing microtubule and the contractive forces of the actin cortex is disrupted enabling microtubules to form these kind of protrusions. Using cytoskeletal drugs such as Latrunculin A and Y27632, which are targeting the actin cortex integrity and its contractility, we induce McTNs even in non-cancerous RPE1 cells. We investigate the presence of microtubules and actin as well as vimentin, which has been hypothesized to stabilize McTNs [3], under those conditions.

We establish a statistic over the number and lengths of McTNs depending on different drug concentrations applied. Further experiments on the dynamics of McTNs, especially during retraction after drug wash-out, give a better insight in the role of individual cytoskeletal elements.

Understanding the mechanisms of the formation of McTNs may help the development of new cancer therapies targeting CTCs in the microvasculature.

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P.37 Free energy of lipid membrane pores in electric field

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Lipid membranes define biological cells by establishing a semi-permeable barrier. Pore formation plays a role in processes such as membrane fusion and fission, the killing of bacterial cells with antimicrobial peptides, and others. Experiments have provided hints to the free energy of pore formation almost 40 years ago. Although pores are heavily studied with a variety of methods, the free energy profile of the initial stages of the pore formation is still not fully understood. We use molecular dynamics simulations to study the mechanisms and energetics of pore formation. The challenge of exploring the free energy landscape is overcome with Umbrella Sampling along a new reaction coordinate [1]. Electric fields have been used in electroporation to facilitate formation of pores for uptake of genes and drugs. The current work builds on results for tension-free membranes [2] by studying the effects of different electric fields. Our preliminary results show a significant drop in the free energy of the open pore upon introduction of electric fields.

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P.38 Lizard's cornified appendages: what drives the keratin cytoskeleton to organize into high performance materials?

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This study describes the formation mechanism of adhesive setae on gecko's toe pad at the interface between the clear cell layer and the oberhäutchen cell layer. Histological analysis reveals the localization of key cytoskeletal proteins and their organization during formation of the new skin layer in the digits of a virgin gecko (*Lepidodactylus lugubris*). We compare different developmental stages, from premature developing setae to mature, cornified setae.

P.39 Complex geometries of suspended cell cortices

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Most cell types have a defined state of spreading which depends on their function: epithelial cells form cohesive layers, mesenchymal cells adhere to their environment but not much to their neighbors to migrate efficiently, and leukocytes are mostly suspended.

During events like embryogenesis and metastasis however, cells may change their original phenotype. We sought to understand the consequences of such transitions with an emphasis on the cell cortex. This thin meshwork under the plasma membrane, which is mainly composed of F-actin, motors proteins and cross-linkers, is indeed one of the main contributors to cell shape. As such, we hypothesize is that the change in adhesive state must be accompanied by changes in the actin cortex structure and dynamics.

To investigate cortical actin dynamics, we used FRAP (Fluorescence Recovery After Photobleaching) where we detected differences in the dynamics of long, formin elongated, and short, Arp 2/3 nucleated, filaments depending on the adhesion state of the cell. However, the interpretation of the actin turnover in the suspended state of cells revealed to be much more complex than in the case of adhered states.

We observed that cells display small folds of membrane after being brought into suspension. These folds are, contrary to blebs, less dynamic and exhibit an underlying filamentous actin layer. We will discuss here the consequences of such geometries regarding our interpretation of the FRAP data.

P.40 Influence of drainage on the lifetime and reproducibility of free-standing lipid bilayer

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Free-standing lipid bilayers are one of the most used model systems to mimic biological cell membranes. Many experimental setups, like microfluidic chips, have been dedicated to produce such type of suspended lipid bilayers [1]. To achieve high yield and reproducible bilayer formation, most setups require the presence of an oil to stabilize the bilayer. We consider the case of a bilayer obtained by bringing in to contact two lipid monolayers separated by a nanometric oil film, followed by zipping of these two monolayers to form the bilayer upon absorption of the oilfilm [2]. In this article, we discuss the importance of the drainage step on the stability and the lifetime of the formed lipid bilayer. We also investigated that by controlling the pressure of the chambers in the microfluidic chip, we can bend the bilayer and make a curvature. Furthermore, with the curvature of the bilayer, the surface tension of the lipid monolayer can be calculated using Young Laplace pressureequation.

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P.41 Simultaneous measurement of surface and bilayer tension of symmetric and asymmetric bilayer

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Free-standing lipid bilayers are one of the most used model systems to mimic biological cell membranes. Many experimental setups, like microfluidic chips, have been dedicated to produce such type of suspended lipid bilayers. To form a bilayer, we employ two aqueous fingers in a microfluidic chip surrounded by an oil phase that contains lipids. Upon pushing the aqueous fingers into the microfluidic device their interfacegets decorated with a monolayer and eventually zip to form a bilayer when the monolayers get in nanoscopic contact to each other [1]. The bilayer life time is limited to about one hour by a slow drainage of the oily phase into the microfluidic device material consisting of PDMS (Sylgard 184). Using a pressure controlled system the drainage can be minimized resulting in superior bilayer stability and life times of several hours. Applying different pressures to the aqueous fingers in the microfluidic chip, the bilayer can be bent at a desired curvature. Extracting the contact angle and the resulting curvature of the bilayer region as well as of the monolayer regions for a given applied pressure difference, both the bilayer tension and the surface tension of the lipid monolayer can be derived using Young Laplace pressure equation. This approach works also for asymmetric bilayer and enables to directly obtain the tension of asymmetric bilayer.

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P.42 Disrupted mechanotransduction, elastic modulus and cell tension in actinin 1&4 knockout cells

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Actin is the most abundant intracellular proteinin eukaryotic cells and is involved in multiple cell functions such as cell spreading, migration, transduction of mechanical forces and cell tension. A mesh of fine actin fibers provides the cell shape and stability, whereas thick fibers transduce intracellular forces and form togetherwithmyosin2contractilefibersforcellmigration.Therefore,actin filaments are bundled to fibers with actin-crosslinker proteins. Most of the actin fibers are linked to focal adhesion proteins, that are crucial mediators for cell adhesion to the substratum. The non-muscle alpha actinins 1 and 4 (A1/A4) are high abundant F-actin binding proteins and play a crucial role in actin cytoskeleton organization [1]. To investigate the cellular function of A1/A4 in terms of mechanotransduction and intracellular tension we analyzedmurineNIH3T3fibroblastswhereA1/A4wereknockedoutusingCRISPR/Cas9-mediatedgenome engineering [2]. Using atomic force microscope (AFM), we could show that the actin stress fibers are much thinner and deposited around the cell nucleus in A1/A4 KO cells, resulting in another distribution of the elastic modulus. In addition, A1/A4 KO cells largely lost their cell tension resulting in abnormal focal adhesion organization and migrationbehavior.

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P.43 Coupling of membrane nanodomain formation and enhanced electroporation near phase transition

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Biomembranes pass through phase transitions with a change in the environmental temperature. It was experimentally demonstrated that a transition not only involves membrane structural changes, but also a change in ion permeability [1,2]. At the main phase transition temperature T_m, the permeability displays a peak and current fluctuations of quantized amplitude can be measured.

Here, the temperature-dependent structural features of a one-component dipalmitoylphosphatidylcholine bilayer and its stability against an applied electric field was investigated at and close to T_m by means of atomistic molecular dynamics simulations [3]. The simulations demonstrate the dynamic appearance and disappearance of thin, interdigitating and thick, ordered lipid domains in fluid-like bilayers close to T_m, which vanished at higher temperatures. The structures were spatially related and likely represent precursors of the ripple phase forming below T_m. Similarly, a metastable two-phase bilayer consisting of a gel and a fluid domain adopted a thickness minimum at the phase interface formed by interdigitating and splaying lipids. Close to T_m, electroporation was enhanced with pores preferentially forming in the thin nanodomains. Together, these findings provide a link between the increased permeability and structural heterogeneity close to phase transition.

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P.44 First-passage properties of active particles with position-dependent persistency

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We consider an active motion with a single-state of motility in confined geometries. We first investigate the mean first-passage time (MFPT) of a random walk with constant activity on a two-dimensional lattice and verify that the MFPT admits a minimum as a function of the activity. The optimal activity varies with the system size and the boundary conditions. We also study the MFPTs of random walks with position-dependent activity. We consider linearly increasing or decreasing activities versus the distance to the target, as well as nonmonotonic functions. It turns out that these search strategies can be even more efficient than the optimal constant activity choice, for some parameter values. Our results help to better understand the chemokinesis of biological organisms and enables us to propose more efficient search strategies by adapting the particle activity to the local available information about the target.

P.45 Usage of electrochemistry to study physiological parameters on a single cell level

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Understanding physiological events on a single cell level is required for deeper insights into the fundamentals of intra- and intercellular metabolism. Measuring metabolites on a single cell level with electrochemical techniques can be advantageous due to their high specificity, spatial and temporal resolution, as well as the circumstance that cells do not have to be invasively manipulated.

We report about electrochemical measurements using a bare Pt-UME to determine and quantify H2O2, extracellularly produced by primary human and mouse monocytes [1]. Since H2O2 has signaling functions at low (nM to low µM) and pathogenic functions at higher (high µM to mM) concentrations, sensitive and dynamic long-term measurements are crucial to understand redox-regulated cellular processes.

Furthermore, we show the electrochemical measurement of single-cell respiration. Changes in cellular respiration report about the metabolic state of a cell, its responses to specific treatments, to cellular stressors, and can indicate early apoptotic (cell death) processes. Here, we compare the O2 consumption by single human cells (cultured and primary) in the presence and absence of several quinones, which may interfere with the electron transport in the mitochondria of the cell [2].

Finally, we present simultaneous electrochemical and fluorescence measurements from single cells to monitor metabolites, such as H2O2, extra- and intracellularly.

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P.46 Engineered cellular microenvironments decoupling cell-cell and cell-matrix interactions

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In their native microenvironment, cells receive multitude of physical, mechanical and chemical cues from their extracellular matrix (ECM) (cell-matrix adhesions, integrin adhesions) and neighboring cells (cell-cell adhesions, cadherin adhesions), which are critical to regulate their behavior during tissue development and healing. These cues are tightly regulated with high spatial precision at different contact interfaces, to direct cellular functions and cell fate decisions. Recapitulating native spatial characteristics in vitro has become an important strategy in regenerative medicine to generate biomaterials that are close mimics of the native tissue and particularly interesting to target anisotropic tissues (e.g., skeletal muscle and cardiac muscle). In this work, we aim to develop 3D biomaterials strategy for e.g., cardiac-like tissue engineering by incorporating mechanical anisotropy and a regulated formation of cell-cell and cell-matrix adhesions in spatially and mechanically defined matrices. For this purpose, we will use poly (acryl amide) based hydrogel systems enabling orthogonal coupling chemistries, to immobilize ligands specifically targeting integrin and cadherin adhesions with spatial segregation. This platform also presents the ability to separately control mechanical properties of both contact interfaces. Progenitor cell response to defined physical and biochemical cues will be investigated to reveal parameters for functional tissue formation. Finally, this highly tailorable biomimetic material system will not only enable us to develop new biomaterials for regenerative medicine, but can serve as a tool to study fundamental aspects of cellular behavior in both development and disease.

P.47 Lysozym and natural extracts as mouthrinsing solutions against oral bacterial biofilm

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Aim: Subject of the study was to test lysozyme, oleic acid and hops in form of mouth rinsing solutions for their antibiofilm efficacy in vivo.

Material and methods: Lysozyme (1.4 mg/ml), oleic acid and hops were tested. Biofilm was generated in situ on bovine enamel and dentin specimens fixed on upper jaw acrylic splints and worn for 48 hours by three subjects. The mouth was rinsed using the particular test substance three minutes after splint insertion and again every six hours. A water control served as reference with an identical test set-up. Bacterial colonization and viability of the biofilms were analyzed using transmission electron microscopy, scanning electron microscopy and fluorescence microscopy.

Results: In case of lysozyme, none of the used methods showed any significant changes when compared to the control. Neither the thickness, viability, nor the extent of bacterial biofilm showed an effective antibacterial potency. A strong antibacterial effect of hops extract was demonstrated with all analytical methods used. For oleic acid, a clear shift towards dead bacteria was determined, whereas the biofilm thickness and the bacterial morphology were similar to those of the control.

Conclusion: Lysozyme mouth rinsing solution (1,4 mg/ml) showed no antibiofilm effect, whereas hops was demonstrated to possess promising antibacterial properties.

P.48 Optimizing run-and-tumble searches

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Search problems are widespread in nature and technology. They occur on vastly different scales reaching from the search for castaways in the open sea, animals searching for food, Bacteria looking for a favourable environment to intracellular transport of cargo along the cytoskeleton. Because searchers in biological context are often provided with only limited or no mental capacities (foarging animals or bacteria) or being driven by the environment (cellular transport) these searches often happen to be random searches. Succeeding in the search is crucial for the survival of the species or proper function of the organism, thus rendering the efficiency of the applied search strategy an vital issue. To describe and analyse the observed searching behaviour several models have been proposed. Most of them falling either into the category of Lévy walks or two-state search patterns where the searcher switches between states of fast and slow motion. In this contribution we will focus on a Run-and-Tumble Searcher belonging to the latter category: A random walker with two states of different persistency with no temporal and short term directional memory. We will analyse the dependency of the mean search time obtained by Monte Carlo simulations on the persistency, mean duration of the phases.

P.49 How phosphorylation affects protein-peptide interactions

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Large-scale proteomics and transcriptomics studies have unraveled that about half of all proteins in biological cells are targets of post-translational modifications. Since this may have crucial consequences on the protein interactions involving the respective proteins, this severely complicates our understanding of the cellular protein interactome. However, only few model systems have so far been characterized in structural and thermodynamic terms. This project aims at exploring the potential and limitations of molecular dynamics simulations to contribute to the systematic proteomic mapping of the consequences of post-translational modifications on the cellular protein interactome. Here, we are focusing on the interaction of PDZ domains that bind to hundreds of other proteins in human cells. Based on X-ray crystallographic data for PDZ:peptide complexes, we study how well molecular dynamics computer simulations can capture the influence of peptide phosphorylation on their binding to PDZ domains in structural and energetic terms.

P.50 Epigenetic regulation of *E. coli* pilus phase-variation-mechanism

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The gram-negative bacterium *E. coli* is a non-pathogenic microorganism, predominating in the colonic flora of humans. Usually it remains harmlessly, but some strains can lead to diseases in the central nervous, or the urinary system [1]. In the latter case, uropathogenic strains of *E. Coli* (UPEC) are responsible for cystitis or pyelonephritis in 75 to 95% of cases [2]. For the migration of the bacteria through the urinary tract, so-called pyelonephritis-associated pili (pap) can be formed which allow them to bind to the urothelium [3,4]. These pili belong to the class of the chaperone-usher pili which is well characterized in its composition and function. By means of a phase-variable mechanism, regulated at the transcriptional level, UPECs can switch between a stable ‚on phase' where the pap genes are expressed and a stable ‚off phase' where their transcription is repressed. Using an in vitro expression system, our group has observed that, unlike previously thought, this phase-variation mechanism does not rely heavily on cooperative binding of the co-regulators Lrp and PapI. Moreover, there is strong evidence that the topology of DNA itself contributes to the phase variation mechanism [5].

The subject of this work is to clarify the phase variation mechanism of UPEC with respect to the effect of the DNA structure in the pap regulatory region on pili formation. Besides revealing a so far unknown, DNA based mechanism for hysteretic switching of transcription, we expect our work to contribute to the development of new therapies for urinary tract diseases.

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P.51 Revealing the DNA loading mechanism during the initiation of the transcription of RMA polymerase II

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The RNA polymerase II is a cornerstone of the central molecular biology dogma, as it is the enzyme allowing the transcription of DNA to RNA, from which protein translation (by mRNAs) and molecular regulation (by non coding RNAs) are possible.

Therefore, understanding the underlying mechanism of this macromolecular complex is of paramount importance for sharpening our comprehension of life.

This study aims to reveal the transition between the open and close conformation of the DNA within the RNA polymerase II, during the initiation of the transcription.

To do so, we will use molecular dynamics (GROMACS engine) and enhanced sampling methods to be able to capture such an important conformational change. Furthermore, with respect to the use of sampling algorithms, a new reaction coordinate will also be studied. This new reaction coordinate will be implemented thanks to the PLUMED software. Therefore, we intent to be able to derive the pathway of this conformational transition and its free energy landscape.

Finally, particular attention will be given to the TFIIE transcription factor, to understand how it drives DNA opening and its influence on Pol II cleft obstruction in the closed complex.

P.52 Spheroids morphology, cell number, indentation forces and nuclei positioning as responsible for *in vitro* cancer intravasation.

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In cancer pathologies, cell intravasation is known as one of the first steps of metastasis. This is described as the release of entrapped cells from the tumors into the blood/lymph fluids, prior to colonize foreign organs.

Due to the dynamic character of malignant pathologies, there is a series of challenges to analyze this step of cancer progression in vitro and in vivo. (1)To this purpose, we developed a new type of hydrogel-based three- dimensional scaffold named "3D tumor-like microcapsules". 3D tumor-like microcapsules were defined by their semi-degradable capabilities and their tunable elasticity (mimicking values of stiffness reported in vivo). As a secondary relevant characteristic, these matrices have a core-shell morphology. The external shell is mostly constituted by non-degradable and highly crosslinked polymer chains, while the internal bulk is made of a soft tailored-biodegradable hydrogel.

These scaffolds were utilized to entrap the healthy-like cell lines MCF10A and EA.hy926, and the metastatic breast cancer cells MDA-MB-231 and MCF7. Our results show that just cancer cells were able to migrate, proliferate and be released from confinement, while in healthy-like cell lines this behavior was not observed.

Using this system, the generation of cellular aggregates from single cells was studied in vitro. Interestingly, spheroids were mostly localized at the scaffold boundary, after a preliminary stage of migration within these matrices. After proliferation, spheroids started exerting forces in radial directions, aimed to disrupt the matrix boundary. After 5 days post-entrapment, indentation forces generated a fracture on the matrix surface, allowing cell release from entrapment (i.e. intravasation-like). Remarkably, delivered populations exhibited morphological heterogeneity, with differences in mechanical forces and size.

With the purpose to determine the main biophysical factor responsible for the phenomenon of cell release, we performed experiments in presence of Tissue Inhibitors of Metalloproteinases (TIMPs) and Blebbistatin. Studies done in presence of TIMPs show that cells can still be released, after a short delay in comparison with control experiments. On the other hand, Blebbistatin restricted the generation of indentation forces, and cell intravasation was not observed.

With the purpose to determine the relevance of the nuclei in such events, analysis of cell morphology, nuclei positioning and cell release are currently ongoing.

Preliminary results are showing that aggregates require a minimum number of cells to generate total forces enabling their release. The nuclei positioning, as well as the size of whole spheroids are also two other factors playing a strong role on intravasation-like process, indicating that cell release is indeed a highly coordinated, cooperative and collective process in cancer progression.

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P.53 Non-specific centering of large objects in prophase I and meiosis I oocytes

Alexandra Colin[1], **Gaëlle Letort**[2], Nitzan Razin[3], Maria Almonacid[2], Wylie Ahmed[4], Timo Betz[5], Marie-Emilie Terret[2], Nir S Gov[3], Raphaël Voituriez[6], Zoher Gueroui[1], Marie-Hélène Verlhac[2]

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Previous theoretical considerations suggest that a gradient of motile activity of small particles can generate a pressure gradient that will center large objects [1]. Such phenomenon could explain the robust centering observed for the mouse oocyte nucleus [2], possibly due to a gradient of activity of actin-positive vesicles. We tested the plausibility of this model by implementing 3D center-based numerical simulations tuned to the properties of Prophase I oocytes. Simulations demonstrated how a gradient of persistence of the actin-positive vesicles would indeed center the nucleus, but also other passive objects above a threshold size. By microinjecting oil droplets and fluorescent beads into Prophase I oocytes, we verified experimentally the non-specificity and size-dependency of the centering. Strikingly, we also observed this non-specific centering during Meiosis I, concomitant with meiotic spindle off-centering towards the cortex, a process partially depending on the same myosin activity. Our experimental and numerical observations suggested that this centering gradient was still present but less efficient due to a decrease in the recruitement of actin-positive vesicles.

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P.54 Modelling pattern formation in competitive bacterial biofilm growth

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Mechanical and genetic heterogeneity of bacteria are known to be important factors in biofilm growth. These inhomogeneities can lead to cell sorting, sector formation and gene surfing which increase the evolutionary fitness of otherwise disadvantaged sub populations. Range expansion experiments and modelling have been used to study the influence of genetic drift with or without selective advantage [1].

Zöllner et al. introduced bacterial strains with different tunable mechanical interactions and division times to study their influence on colony growth and range expansion [2,3]. They used a strong interacting fast growing strain and a slow growing weak interacting strain where the weak interacting strain got sorted to the perimeter of the colony and therefore could surf and outgrow the faster growing strain.

We study this setup with different interacting strains as a lattice gas model with dividing, swapping and pushing particles. We reproduce the pattern formation observed and find in accordance with these experiments that strains with even 1.9 faster division time cannot outgrow the weak interacting population which surf at the frontier of the expanding colony.

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P.55 Label-free tumor cell detection in microfluidic flow

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Circulating tumor cells (CTCs) are released in the blood by primary tumors during dissemination. Depending on the type of cancer, this step can happen early in cancer development, which makes the CTCs a good marker for early cancer diagnostic [1,2]. Most of the current CTCs detection methods require expensive and time-consuming procedures, including enrichment steps and immunoassays or genomic analysis [1-3] and are not applicable in a routine screening.

We propose a microfluidic approach to classify blood cells taking advantage of their distinctive shape in flow. To extract the characteristic signature for each cell type, we use high-speed microscopy (40,000Hz) on blood cells that are pumped through microfluidic channels. Besides, the future device will be designed with a tilted microfluidic channel to capture the 3D shape of cells while they are passing the focal plane.

Preliminary results are based on red blood cells (RBCs) passing through rectangular microfluidic channels. The processing applies a numerical slit mask. This approach enables us to differentiate the two most abundant shapes of RBCs in flow, parachute and slipper, comparing the signatures to empirically established references. The next step is to distinguish white blood cells from cancer cells by their deformation in a microfluidic constriction.

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P.56 Narrow escape: How long does it take for a camel to go through the eye of a needle?

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The narrow escape problem (NEP) is a common problem in biology and biophysics. It deals with Brownian particles confined to a given domain with reflecting borders and only a small escape window where particles are absorbed. The mean first passage time, the time it takes a set of particles to escape, can be analytically calculated in 2D and 3D for several geometries.It depends on three parameters which are the area of the domain, the size of the escape window as well as the diffusion coefficient of the particle.We aim to systematically test the analytical solution of the NEP in 2D by variation of the relevant parameters. Experiments are being complemented by matching Monte Carlo simulations. For the experimental test, we prepared micro-patterned phospholipid bilayers from a combination of colloid lithography and vesicle fusion. We imaged fluorescently labeled lipids diffusing in circular membrane patches with diameters of 5-10 µm using single-molecule fluorescent microscopy at 100 Hz and a localization precision of 15 nm. While the area of the membrane was tuned during colloid lithography, the size of the escape window was adjusted in the course of theanalysis.

We will present our first results on membrane patterning as well as a comparison of our experimental and simulation results with the theoretical prediction for the mean first passage time.

P.57 Staphylococcus aureus adhesion to titanium, hydroxyapatite and bovine enamel

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Bacteria adhere to virtually every surface and promote the formation of sometimes desirable but often unwanted biofilms. In the oral cavity, dental implants or restorative materials can act as a gateway for infections with *Staphylococcus aureus*, leading to occurrences of inflammation of the gum and/or the teeth. As the adhesion of single bacterial cells is the critical initial step in biofilm formation, we evaluated the adhesion of S. aureus using single cell force spectroscopy on titanium, hydroxyapatite and bovine enamel samples. To specify the surfaces, we measured the equilibrium advancing contact angle as well as (by atomic force microscopy) the surface roughness and via X-ray photoelectron spectroscopy (XPS) the elemental composition of the surface. As part of the oral cavity, the influence of salivary pellicle on the cell-surface interaction was investigated.

P.58 Stochastic modeling of intracellular transport performed by kinesin-1 and mammalian dynein

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Intracellular transport is a bidirectional, biased stochastic motion carried out by teams of kinesin and dynein motor proteins. Dynein and kinesin walk actively in opposite directions along polar intracellular filaments, called microtubules. In general, a cargo is transported bidirectionally, meaning both kind of motors (kinesin and dynein) are involved. Kinesin and dynein motors are large proteins with complex dynamic behaviors which are not yet fully understood. In close collaboration with the biologists, we use all known biological properties to develop stochastic models for kinesin and dynein motors [1,2]. In our study we focus on conventional kinesin (kinesin-1) and cytoplasmic mammalian dynein. Mammalian dynein is known for needing an activation process to be able to walk pointedly along the microtubule. Our model [1] predicts a mechanical activation, where dynein motors activate by being stretched. In [1] we show that our kinesin and dynein models reproduce the experimental observations in the case of unidirectional transport, where either only kinesin or only dynein motors are involved. In our present work we demonstrate the agreement of simulation and experiment for the bidirectional transport, where both, kinesin and dynein motors are in involved and moreover investigate the influence of external control parameters like *i.e.* ATP concentration and hindering obstacles.

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P.59 Pearling effect induced by presence of nano-particles and focused laser beam using digital holographic microscopy

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Dynamics of liquid-crystalline Myelin Figures (MFs) is a multifaceted issue depending on various elements, which have not been fully resolved yet which could be find in disease living cells and their formation and dynamics in various conditions have been of high interest. Myelin Figure is formed at membranes as a consequence of cellular swelling in cell injury. The major part of a cell membrane consists of phospholipids that is crucial in the study of the morphology of MFs deformation.

In this paper, we present a systematic experimental study on MFs deformation induced by presence of nanoparticles and focused laser beam using Optical Tweezers (OT). Quantitative analysis of MF dynamical behavior was performed using Digital Holographic Microscopy (DHM). Our study reveals that by applying the focused laser beam, MF tubes are stimulated and fluctuations on their surface could be seen. Our experimental results show that if the duration of applying the laser beam is short, they can be slowly returned to the previous state. But as the time increases, the tubes are deformed to form a chain of pearls.

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P.60 The influence of vimentin on actin dynamics

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The cytoskeleton is a network of polymers which extends inside the cytoplasm to form and maintain the cell shape. It is composed of three main types of filaments: microtubules (MTs), actin filaments, and intermediate filaments (IFs). Vimentin belongs to the family of IFs and is involved in fixing organelles in the cytoplasm and regulating cell migration. It forms non- polar filaments and has, therefore, no known molecular motor directly interacting on it. Vimentin is linked via plectin protein cross-linker to MTs and actin filaments as well as to itself. Vimentin has been further shown to colocalize to actin stress fibers (SFs). These are bundles of actin filaments assembled by the myosin II molecular motors and crosslinker proteins. Actin SFs play a key role in cell contractility and cell migration. In earlier works, we investigated the effect of vimentin in processes like cell migration, which are known to be initiated by forces generated by actin filaments and the molecular motor myosin. To understand how vimentin IFs are involved in these processes, we study the dynamics of the actin SFs in Retinal Pigment Epithelial (RPE1) cells with different amounts of vimentin. We also consider the role of plectin on SF dynamics. We demonstrate that actin SFs are less dynamic in vimentin depleted cells compared to SF in vimentin wild-type cells. We could further show that the dynamics of actin SFs is not influenced by plectin, suggesting a role of vimentin itself on actin SF dynamics. Since myosin motor molecules are, together with actin involved in cell migration and force generation, we were motivated to additionally investigate the amount of myosin in RPE1 cells with and without vimentin by immunofluorescence and western blottechniques.

P.61 Hydrophobin bilayers (HFBI) and their water permeability

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Hydrophobins are small, compact and amphiphilic and even stable in aqueous surrounding [1]. One class of these proteins is characterized by a very compact conformation allowing for a 2-D crystal-like packing of these proteins in interfacial layers [2]. As a result, the cohesion of these protein layers is extremely large, giving rise to very stable interfacial layers, in which the proteins adopt a defined orientation.

In a recent study, we used the unusual properties of layers from HFBI a hydrophobin produced by the filamentous fungus *Trichoderma reesei*, to create protein double layers by bringing two protein populated interfaces together [3]. Thus, we could create stable, pure protein bilayers between aqueous (or gaseous) and oily compartments. Our current aim is to determine the physical properties of these bilayers in order to evaluate their suitability as replacement of lipid membranes in, e.g., artificial cell-like entities. In a first step, we investigate the water permeability of these bilayers since this is a main feature of biological membranes and for the proper functioning of important biological processes.

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P.62 Change in physicochemical properties in the lungs in response to chemically modified two-dimensional substrates with controlled elasticity

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The main goal of the presented results is a performance of comparative analysis of physico-chemical properties of originating from two distinct Interstitial Lung Diseases (ILD) - idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonia (NSIP) cultured on two- and three-dimensional elastomer (PDMS) substrates with tuned mechanical and chemical properties and defining a set of parameters enabling label-free distinction between them.

Chemical properties of cells will be characterized using time-of-flight secondary mass spectroscopy (ToF-SIMS) while their mechanical properties will be determined using atomic force microscopy (AFM) working in force spectroscopy mode.

This brings a capability to study cell-substrate interactions at both single- and multi-cell levels as well as the combined influence of different external factors on cell adhesion and proliferation process. Such complex analysis, especially performed on 3D substrates imitating porous lung tissue will enable deeper understanding of environmental factors and mechanisms favoring fibrotic process and will contribute to recognition of its etiology. Subsequently a set of parameters enabling unambiguous distinction of fibroblasts originating from IPF and NSIP will be defined, which can be used as a basis for effective label-free identification of cells, delivering powerful tool for early stage diagnosis and personalized therapy.

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P.63 Single protein visualization of ORAI1 calcium channels with liquid-phase electron microscopy

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ORAI proteins can assemble to form Ca^{2+} channels in the plasma membrane, thus playing a crucial role in intracellular Ca^{2+} homeostasis. A still controversial question is the stoichiometry of ORAI protein subunits under resting conditions. Earlier studies supported tetra- and dimeric configurations, whereas recently, drosophila ORAI was found to be hexameric. Using liquid-phase electron microscopy (LPEM) we set out to visualize single human ORAI1 subunits, and three different concatenated, dimeric ORAI1 constructs, all supplied with hemagglutinin tags. These ORAI1 constructs were expressed in HEK cells lacking endogenous ORAI proteins (created using CRISPR/Cas9), and labeled with an anti-HA Fab and a fluorescent quantum dot nanoparticle, assuring a QD:ORAI1 labeling ratio not exceeding 1. The labeled, intact cells were kept hydrated under a graphene layer, and imaged with scanning transmission electron microscopy (STEM) detection. STEM images were automatically processed to obtain the label position coordinates. Subsequent analysis used the pair correlation function g(r), which measures any deviation from a random distribution. 298.452 labeled ORAI positions on 49 cells were analyzed revealing that ORAI1 channels at rest are present in higher order oligomers. We also show how the ORAI1 distribution but not necessarily the stoichiometry changes upon activation.

P.64 Curvature dependence of SNARE TMD mediated membrane fusion

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Membrane fusion is a key event in a wide range of biological processes like exocytosis, fertilization and intracellular trafficking. Soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins are thought to be involved in all steps of the fusion process, e.g. docking the membranes, initializing hydrophobic contacts, and reducing bending energies [1]. However, microscopic details and the role of the specific domains of the SNARE proteins remain elusive.

Mutating the primary structure of the SNARE transmembrane domain (TMD) was shown to alter vesicle fusion by altering the initiation and pore opening [2]. Molecular dynamics (MD) simulations of flat membranes were used to obtain a molecular description of these effects. The TMD regulates lipid mobility, and hence lipid protrusion events leading to first hydrophobic contacts between the merging membranes [3]. Furthermore the specific TMD primary structure regulates the oligomerization propensity [4], which is key for efficient membrane fusion.

However, previous studies neglect effects of membrane curvatures involved in fusion. Hence, we extend previous work on the properties of SNARE TMDs and SNARE TMD mutants using coarse-grained MD simulations allowing for strongly curved membrane geometries. In a first step we investigate the curvature dependence of the localization of SNARE TMDs and their oligomers.

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P.65 Lipid specificity of the glycoprotein B of pseudorabies virus

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Viral fusion proteins drive fusion of viral and host cell membranes in a series of complex structural transition events. Although the structure of several fusion proteins has been solved, the characterization of membrane fusion mechanism at atomistic resolution is still missing. Recently, glycoprotein B (gB) ectodomain of pseudorabies virus (PrV) was resolved and the structure adopts a typical class III postfusion trimer conformation [1], however, the interactions with the membrane was not well established. Membrane interactions of fusion proteins are conserved and occur via fusion peptides (FPs) in class I and fusion loops (FLs) in class II/III proteins. Previously, we had characterized the glycerophospholipid binding in class II fusion protein glycoprotein C (gC) of Rift Valley fever virus (RVFV) [2] and in this study we aim to understand if class III protein are anchored to the membrane by specific lipid binding pockets as found for RVFV. Molecular dynamics (MD) simulations is an excellent technique to understand how gB associates with lipid membrane at atomistic resolution, thus providing structural insights into lipid contact sites and membrane insertion depth of FL residues.

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P.66 3D-printed microfluidic chip to study protein organization in lipid bilayer

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To explore the dynamic protein organization embedded in a lipid bilayer, it is needed to form a horizontal free-standing bilayer to perform direct optical measurements. To that aim, the created microfluidic device addresses to form horizontal free-standing bilayers by using an easy approach. As a first step of this study, we developed a layout for a 3D microfluidic chip whose master can be fabricated by 3D-Printing technique. Inside the microfluidic device a lipid bilayer is formed in a quasi-automatic manner by contacting two water droplets that are immersed in an oil phase, where lipid molecules have been dissolved. This microfluidic platform is passive and does not require active microfluidic manipulation. Besides, for the ease of its use it is perfectly suited to screen an extended parameter space for different phospholipid compositions. The bilayer formation is demonstrated by electrophysiological measurements (Patch-Clamp) and optical investigations with a normal view direction onto the bilayer. This system allows us to reconstitute membrane proteins in this bilayer and follow their dynamical self-organization properties by fluorescence microscopy methods.

P.67 A neuron specific alternative STIM1 splice variant differentially influences SOCE and synaptic plasticity

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Store-operated Ca^{2+} entry is a ubiquitous mechanism that contributes to the regulation of basal and receptor-triggered Ca^{2+} concentrations thereby governing signaling and cell homeostasis. The two known isoforms STIM1 and STIM2 sense the ER Ca^{2+} content and oligomerize to trigger Ca^{2+} entry by gating Orai channels. Here, we characterize a novel STIM1 splice variant, STIM1B, where neuronal-specific insertion of an additional short exon (11B) results in a C-terminally truncated STIM1 lacking 145 amino acids including part of the C-terminal inhibitory domain (CTID), microtubule associated EB binding sites, the S/P rich region and the polybasic domain. STIM1B shows slower kinetics of cluster formation and I_{CRAC} activated by STIM1B shows reduced slow calcium-dependent inactivation (SCID). STIM1B is the predominant STIM1 isoform in cerebellar Purkinje neurons but also displays prominent expression in hippocampal as well as other neurons where it preferentially localizes to neurites in contrast to a more somatic STIM1wt localization. Specifically in autaptic hippocampal neurons, STIM1B, but not STIM1 causes synaptic facilitation upon high frequency stimulation, demonstrating that cell-type specific splicing may adapt neuronal SOCE to support synaptic function.

P.68 Octenidine rinsing inhibits biofilm formation and causes biofilm disruption on dental enamel *in situ*

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Aim: To evaluate the effects of octenidine (OCT) mouth rinsing on biofilm formation and moreover on the disruption of existing dental biofilms.

Methods: Biofilms were formed *in situ* by five volunteers on enamel specimens fixed to acrylic splints. For biofilm formation analysis, the volunteers intraorally exposed the splint for 48 h. Every 12 h, the OCT rinsing (0.1%) was applied for 30 s. For analysis of biofilm disruption, 48-h mature biofilms were taken as a control. Subsequently, the first OCT rinsing was performed and two pairs of specimens were evaluated. A second rinse was done 12 h after the first one. The last pairs of samples were evaluated after 72 h. The samples were analyzed by transmission electron microscopy (TEM) and fluorescence microscopy. 0.1% Chlorhexidine (CHX) was used as a positive control and water as a negative control.

Results: The fluorescence and TEM analyses showed that OCT significantly reduced bacterial adhesion and biofilm viability. Moreover, the biofilm thickness on enamel specimens was clearly reduced by OCT rinsing. Remarkably, a single application of OCT to a 48-h mature biofilm caused biofilm ultrastructure alterations and induced a substantial biofilm disruption.

Conclusions: OCT rinses induced a significant inhibition of biofilm formation comparable to the gold standard CHX. In addition, OCT had a strong biofilm disruption activity *in situ*.

P.69 Theoretical modeling of dynamic self-assembly of class II hydrophobins from T. reesei at the air-water interface

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Hydrophobins are amphiphilic proteins which for instance assemble at the interface between aquas phase and hydrophobic phase, e.g. at the air-water interface. We investigate the dynamics of interfacial self-assembly of wild-type hydrophobins HFBI and HFBII both experimentally and theoretically. Experimentally, the kinetics were measured by monitoring the accumulated mass at the interface via non-destructive ellipsometry measurements. The measured kinetics for wild-type HFBI and HFBII showed not the expected typical Langmuir-type behavior but linear kinetics for a monolayer formation. In order to clarify the underlying microscopic mechanism, we introduce a stochastic model. The model includes electrostatics and van der waals interactions. Also the model includes microscopic movements in the air-water interface and in the solution. In our model, proteins are accumulated in the interface via two-step adsorption, i) pre-adsorption, in which proteins adsorb from the solution to the subsurface and ii) final adsorption from subsurface to the interface. We showed that the experimental kinetics can be reproduced if the pre-adsorption is sufficiently low enough compare to the diffusion.

P.70 A minimal model for fluid-like collective cell migration

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The collective dynamics of cell plays the key role in many fundamental biological processes like morphogenesis, tissue repair and tumor metastasis etc. Madin-Darby canine kidney (MDCK) cells have been established as one model system to study collective cell migration. On adhesive substrates, cells grow in roughly circular colonies, expanding with time and displaying fascinating motile behavior. Two aspects of their motion lie at the heart of this study: (a) Cells move throughout the colony, forming large scale patterns like swirls or fingers at the edge; reflecting a fluid like behaviour of the cell colony. At the same time, (b) the colonies are extremely cohesive. The colony is not maintained by a constant flux of cells leaving and entering from the surrounding. Instead, the surrounding is devoid of cells, one might say these colonies display liquid-vacuum coexistence.

The active Brownian particle (ABP) model has been used intensively to model such motile cell colonies.

However, "normal" ABP's show either liquid-gas coexistence - with a finite density of cells away from the colony, or crystallize, if the adhesion is strong enough to prevent particles from escaping.

We propose a novel particle-particle interaction potential that allows for cells to move, despite strong adhesion. We show that this model results in colonies with fluid like properties while remaining cohesive in nature at the same time. Furthermore, these colonies can be under tensile stress, as reported for growing MDCK colonies [1]. In combination with velocity alignment, cells can escape the mother colony collectively. A group of cells can form a finger that eventually pinches of.

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P.71 Single filament interaction of microtubules and vimentin intermediate filaments

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Many cellular functions such as cell shape, mechanics and intracellular transport rely on the organization and interaction of actin filaments, microtubules and intermediate filaments, which are the main constituents of the cytoskeleton. Intermediate filaments are the least well characterized cytoskeletal polymers, and the nature of their interplay with other components of the cytoskeleton is far from being well understood. Here, we study the interaction between vimentin, one of the most ubiquitous members of the intermediate filament family, and microtubules on a single filament level. Using quadruple optical tweezers, we measure the force necessary to break the interaction between microtubules and vimentin filaments.

P.72 Effectiveness of Ca^{2+} clearance by PMCA-pumps

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Ca^{2+}influx through voltage-gated (Cav) channels leads to an increase in the intracellular Ca^{2+}-concentration ($[Ca^{2+}]_i$) that can be monitored by BK-type Ca^{2+}-activated K^+ channels. Due to their large-conductance and their particular gating kinetics BK- channels may be used as fast and reliable sensors for $[Ca^{2+}]_i$ underneath the plasma membrane, thus contrasting the commonly used FURA sensors (sensing $[Ca^{2+}]_I$ in the entirecell).In this project,K^+currents through BKchannels were used to determine the Ca^{2+} transport activity of Ca^{2+}-ATPases of the plasma membrane (PMCA), the classical Ca^{2+}pumps that were recentlyshown to be complexes from two-PMCA-subunits and two Neuroplastin or Basigin proteins.

Experimentally we monitored PMCA-mediated Ca^{2+} clearance (or transport) by the decay of BK-currents following their activation by a short (0.8 ms) period of Ca^{2+}-influx through Cav2.2 channels. Our theoretical model describes the Ca^{2+} diffusion within a spherical cell. Time- and Ca^{2+} concentration- dependent boundary conditions model the initial Ca^{2+} influx by the Cav channels and the following outflow via the PMCA pumps. The time scale of this diffusion process is used to predict the strength of the PMCA pumps. Based on the experimentally determined density of Cav channels and PMCA pumps within the membrane we predict a PMCA pump strength that is at least 1.5 orders of magnitude larger than what has been assumed sofar.

P.73 Subtomogram averaging of Arp2/3 complex-mediated branches in human macrophage podosomes

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Human macrophages form protrusive adhesion structures called podosomes which are involved in mechanosensing [1]. They consist of an adhesion ring surrounding an F-actin rich core in which actin polymerization occurs through branching mediated by the Arp2/3 complex. How branches are spatially organized and contribute to force production in podosomes remains unknown. Following up on a recent study on actin waves [2], we employed cryo-electron tomography and subtomogram averaging to identify branches in human macrophage podosomes and analyze their spatial organization. The initial approach on *in situ* tomograms of native podosomes did not allow confident identification of true-positive branches. Simulations ruled out the missing wedge as a limiting factor. Instead, the high density in the podosome core combined with a low signal-to-noise ratio in the data prevented the detection of branches. Improvement of the processing workflow and higher data quality enabled the identification of branches within three tomograms. A low-resolution branch structure was obtained and preliminary analysis showed that ~50% of the branches in the core point toward the cell membrane. Mother and daughter filaments have similar orientations, suggesting that mother filaments may originate from earlier branching events.

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[2] Jasnin, M. et al. The architecture of traveling actin waves revealed by cryo-electron tomography. Structure 27,1211 (2019).

P.74 Hydrophobins at the water/air interface: A model system for protein self-assembly

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Hydrophobins are a family of proteins that are characterized by a large exposed hydrophobic region, which makes them strongly amphiphillic. Hydrophobins of class II self-assemble into membranes at a water/air or water/oil interface where they form long ranged ordered hexagonal structures [1,2]. However the atomic details of the lateral assembly process at the interface remain widely unknown. Furthermore due to the reduced dimensionality and the high stability of the individual monomers, hydrophobins provide a simplified model system for studying assembly processes of proteins in general. In this project, we aim to understand the free-energy landscape and the kinetics of the formation of monolayers of HBFI at the water/air interface using atomistic and coarse-grained molecular dynamics simulations. In this early stage of the project, we focus on the formation of HFBI dimers and trimers by combining free MD simulations with Markov state models. The long-term goal is to simulate the entire assembly process in atomic detail.

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[2] Hähl, Hendrik, et al. "Pure protein bilayers and vesicles from native fungal hydro- phobins". Advanced Materials 29.1 (2017): 1602888.

P.75 Vimentin intermediate filament rings deform the cell nucleus during the first hours of adhesion

Emmanuel Terriac[1], Doriane Vesperini[1], Susanne Schütz[2] and Franziska Lautenschläger[1,2]

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Cells are forced to change their adhesion state during events such as epithelial to mesenchymal (or the reverse mesenchymal to epithelial) transitions or during in vitro experiments. Many changes, such as mechanical properties [1] or pathways regulations [2], may occur during such transitions.

We investigated the effect of adhesion on the vimentin intermediate filament, a component of the cytoskeleton, together with microtubules and actin microfilaments. We observed that during the first 6 to 12 hours of adhesion, vimentin formed juxtanuclear knot-like structures which were on many occasions accompanied by rings that deformed the nucleus [3].

Those vimentin structures may also appear after mitosis, when cell spread back on the surface. We further measured dynamic properties of vimentin using Fluorescent Recovery After Photobleaching, and observed differences depending on the vimentin location (lamelipodium, knots or rings).

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P.76 Individual proteomic analysis of the initial pellicle formed in situ on dental enamel

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The dental pellicle formation is a continuous process starting immediately after oral hygiene due to the adsorption of mostly salivary proteins to the tooth surface. It protects the dental surface from mechanical damages and demineralization processes caused by acids. Till this day no proteomic data of individual pellicle profiles formed on dental enamel are available.

The aim of the current study was to characterize individual proteomic profiles of the 3-min pellicle formed on dental enamel and to compare them to the corresponding salivary profiles to obtain information on potentially occurring selective adsorption patterns. Therefore the initial pellicle of five subjects was generated *in situ* on bovine enamel, eluted chemically and analyzed by tandem nano-mass spectrometry. The corresponding saliva was analyzed in parallel, resulting in the identification of up to 498 pellicle proteins and 1032 salivary proteins in the individual samples. Despite major individual differences in the proteomic profiles, 19 proteins were found to be significantly enriched and 22 proteins were found to be significantly depleted in the 3-min pellicle off all subjects. The results state the initial pellicle formation to rely on selective adsorption processes most likely induced by the physico-chemical properties and molecular functions of the salivary proteins.

P.77 Migration of immune cells in an obstacle park

Doriane Vesperini[2], **Zeinab Sadjadi**[1], Franziska Lautenschläger[2, 3], Heiko Rieger[1]

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Several crucial processes in biological systems can be described as a search problem such as: finding food resources or pathogens. The presence of obstacles like non-targeted cells or extracellular matrix in biological environments induces a perturbation of the initial cell trajectory. For example, the presence of bystander cells has been shown to increase the velocity and the persistency of natural killer cells [1]. Besides obstacles density, their spatial disposition may also influence the search efficiency. It has been demonstrated that the density and geometry of pillar lattices affect the guidance and migration strategies of Dictyostelium discoideum cells [2].

Here, we investigate how search efficiency is influenced by spatial arrangement of obstacles. Migration patterns of cells are studied experimentally and in computer simulations. In experiments, a microfluidic device is designed to track HL-60 cells differentiated into neutrophils in confined 2D environments whose thickness vary from 3 µm to 10 µm. Our device consists of pillar forests of different diameters distributed in triangular, square or random arrangements. The device, fabricated in PDMS and sealed in a glass bottom dish, is mounted on an inverted microscope. Cell nuclei are stained with Hoechst in order to track cell location overtime. We study similar geometries by means of numerical simulations. We calculate the mean first passage time and diffusion properties of the searcher in different densities and geometries of pillars and investigate the influence of key parameters on the searchefficiency.

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[2] M. Gorelashvili, M. Emmert, K.F. Hodeck and D. Heinrich, New Journal of Physics. 16, 075012(2014).

P.78 Auxiliary subunits regulate dendritic turnover rates of AMPA receptors in hippocampal neurons

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AMPA-type glutamate receptors (AMPARs) mediate synaptic transmission at the vast majority of glutamatergic synapses in the central nervous system, and their dynamic recruitment to postsynaptic sites putatively underlies synaptic plasticity as well as homeostatic synaptic scaling. AMPARs associate with different auxiliary subunits that facilitate their forward trafficking from ER to plasma membrane and also modulate channel function. While two prominent auxiliary subunits, TARPγ8 and CKAMP44a, were shown to govern AMPAR function in hippocampal neurons, the role of these auxiliary subunits in local dendritic receptor turnover has remained unclear. Here, we show that the basal turnover of AMPAR via recycling endosomes is strongly regulated by the abundance of TARPγ8 or CKAMP44a: Overexpression of either auxiliary subunit prolongs the lifetime of extrasynaptic AMPA receptors on the surface by reducing constitutive internalization rate. Under basal conditions, AMPAR surface expression remains largely unchanged, when TARPγ8 or CKAMP44a are overexpressed, and accordingly we not only found a reduced pool of AMPAR in recycling endosomes but also a diminished fusion rate of AMPAR-containing transport organelles with the plasma membrane. These novel data indicate that association with auxiliary subunits protects AMPAR from rapid turnover, thus stabilizing the extrasynaptic receptor pool.

P.79 Measuring intracellular stiffness in epithelial cells

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Epithelial cells form the boundary between an organ (or an entire organism) and its environment. Hence, epithelial cells experience a strong asymmetry in their environment – "out" versus "in". It is therefore not surprising that epithelial cells are strongly polarized; for example, the actin meshwork is denser at the apical, or "outward facing"-side of the cell, while the nucleus is always located at the basal, or "inward facing"-side of the cell. However, to date it remains unclear if and how mechanical processes play a role in establishing and maintainingpolarity.

Here I will present a project that focuses on measurement of intracellular activity and stiffness in MDCK-cells. Using both active and passive microrheology, we obtain cellular stiffness and activity as a function of position within the MDCK-cell. Once this is established, we can use drugs to up- or downregulate specific components of the cytoskeleton. Furthermore, since the mechanical environment is of crucial importance to cells, we hypothesize that variations in the extracellular matrix also have an influence on intracellular mechanics.

P.80 Spatial analysis of HER2 expression at focal adhesions

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The human epidermal growth factor receptor 2 (HER2), or ErbB2, is overexpressed in a variety of cancer types driving proliferation and survival. Integrins, among other adhesion proteins, enable epithelial cells to adhere to their surrounding tissue and thereby also promote survival signals. We investigated whether HER2 expression is enriched or spatially linked to focal adhesions by transduction of a focal adhesion marker followed by extra- or intracellular labeling of HER2 with nanoparticles on breast cancer cells. Cells were analyzed by brightfield and total internal reflection fluorescence microscopy. We were able to analyze the HER2 expression at the cell/substrate interface only by intracellular labeling but observed no altered HER2 receptor distributions for focal adhesion areas on breast cancer cells. Thus, our established intracellular labeling protocol allows fluorescent analysis of extracellular non-accessible membrane proteins.

P.81 Differential analysis of combinatorial protein complexes with compleXchange

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Many proteins operate in multiprotein complexes and not on their own. Unlocking this complexome in a condition-specific manner thus promises a deeper understanding into the cellular wriring and what happens upon cell fate transitions. Although there exist large amounts of transcriptomic data and an increasing amount of data on proteome abundance, quantitative knowledge on the dynamics of complexomes is lacking.

We present CompleXChange, a tool for differential analysis of protein complexes based on predicted complexes and inferred complex abundances. For simulated data the results obtained by our complex abundance estimation algorithm are in better agreement with the ground truth and biologically more plausible than previous efforts that used linear programming. Also, execution time is much shorter. The practical usability of the method was assessed in the context of transcription factor complexes predicted for human monocyte and lymphoblastoid samples. We demonstrate that our new method is robust against false-positive detection and reports deregulated complexomes that can only be partially explained by differential analysis of individual protein-coding genes. Furthermore we show that deregulated complexes identified by the tool potentially harbor significant yet unused information content compared to gene- and protein-centric analyses.

P.82 High glucose enhances cytotoxicity-mediated by cytotoxic T lymphocytes

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[2]*Biophysics, Center for Integrative Physiology and Molecular Medicine (CIPMM), School of Medicine, Saarland University, Homburg, Germany*

High glucose, also termed hyperglycemia, is a typical symptom of diabetes. Uncontrolled high glucose is implicated in the pathogenesis of diabetes-associated complications such as heart attack, diabetic nephropathy, nerve damage and higher risk for infection. Cytotoxic T lymphocytes (CTLs) play a central role in destruction of pathogen-infected or tumor cells via killing mechanisms such as perforin/granzymes, Fas/FasL pathway and pro-inflammatory cytokines. Growing evidence indicates that CTLs are the key factor in initiation and progression of diabetes. However, the impact of high glucose on effector functions of T cells still remains elusive. In this study, we used normal glucose (5.6 mM) and high glucose (25 mM) to mimic healthy and diabetic conditions, respectively. We found that high glucose induces enhanced cytotoxicity of cytotoxic T lymphocytes. To investigate the underlying mechanisms, we analyzed the expression of cytotoxic proteins, including perforin, granzymes, FasL and TNF-related apoptosis inducing ligand (TRAIL). Interestingly, we identify that among those cytotoxic proteins, only TRAIL is significantly up-regulated in CTLs by high glucose compared to normal glucose. Our results also show that CTLs cultivated in high glucose can substantially enhance the destruction of human beta-cells in an antigen-independent manner in comparison with their counterpart in low glucose. Our findings, therefore, suggest a novel mechansim of CTL-mediated destruction of beta cells, which might play an important role in progression of diabetes.

P.83 A time resolved study of blood platelet spreading

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Human blood platelets are non-nucleated fragments of larger cells (megacaryocytes) and of high importance for blood clotting. The hemostatic function of platelets is directly linked to their mechanics and cytoskeletal morphology. However, the exact mechanism of spreading and contraction remains elusive. In our study we focus on the investigation of single blood platelets in vitro employing Traction Force Microscopy (TFM) and Metal-Induced Energy Transfer (MIET) imaging. By combined TFM and microscopy, we are able to correlate the force generation with the emerging actin structures in a time resolved manner. Our force maps show a hot spot distribution, typically in spindle like, triangular or circular shape. Additionally, from fast scanning and static MIET experiments, we reconstruct the temporal evolution of the membrane-to-surface distance during adhesion and spreading with nanometer resolution. We observe, analogous to the TFM, hot spot distribution shapes of areas with lower membrane-to-surface distances.

P.84 Engineered T cell ligands arrays on hydrogel as artificial antigen presenting cells to study TCR-mediated mechanotransduction

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Recognition of peptide presented by the major histocompatibility complex (pMHC) molecule on antigen presenting cell (APC) by T-cell receptor (TCR) triggers T cell activation with a formation of segregated microscale structure known as the immunological synapse (IS).[1] It has become increasingly clear that many cell surface receptors are mechanically sensitive and T cells could use mechanical force to transmit biological information across IS.[2] TCR/CD3 complex has been proven to play a leading role in T cell mechanotransduction, and many T cell functions can response to mechanical cues by using material-based artificial antigen presenting surface.[3] However, most studies focused on the late outcome of T cell signaling, thus how the early T cell signaling events are influenced by substrate stiffness needs to be further examined. In addition, almost all the stimulating ligands were uniformly coated on substrate surfaces in the studies of T cell mechanotransduction, which means the biophysical information of a native microscale structure of IS is missing. Therefore, we here recapitulate key features of a physiological IS using planar arrays containing antibody against CD3 surrounded by intercellular cell adhesion molecule-1, generated by microcontact printing on hydrogel with different stiffness, to study how the early T cell signaling is affected by substrate stiffness.

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P.85 High stiffness three-dimensional environment impairs cytotoxic T lymphocyte cytotoxicity

Renping Zhao[1], Essak Khan[2], Shifang Zhao[2], Rouven Schoppmeyer[1], Carsten Kummerow[1], Aránzazu del Campo, Eva C. Schwarz[1], Markus Hoth[1], Bin Qu[1]

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[2]*INM - Leibniz Institute for New Materials, Campus D2 2, 66123 Saarbrücken, Germany*

High stiffness, a prominent physical feature of solid tumor environment, is one of the potential reasons to impair the immune surveillance against tumor cells. Cytotoxic T lymphocytes (CTLs) are the key players to eliminate tumor cells. However, how CTLs behave in solid tumor remains unknown. To answer this question, we mimicked the stiffness of healthy and solid tumor tissue with different concentrations of bovine collagen I. Live-imaging data showed in high stiffness, CTL killing efficiency and migration velocity was reduced, while the target searching duration was increased. Moreover, high stiffness induced CTL nucleus deformation and further nuclear DNA damage resulting in cell death. Both above mentioned factors hinder CTL to eliminate cancer cells. To investigate the underlying mechanisms how high stiffness impairs CTL cytotoxicity, we focused on the role of cytoskeleton in different stiffness environment. Using flow cytometry, we found that assembled actin and tubulin were up-regulated in high stiffness. Furthermore, nocodazole, a tubulin disruptor, enhanced CTL killing efficiency in high stiffness environment despite of a reduction in CTL survival. Our data strongly suggest that high stiffness environment impairs CTL cytotoxicity, and tubulin disruption improve CTL cytotoxicity under high stiffness environment.

P.86 T cells polarize natural killer cells to a mobile killing-potent subpopulation

Xiangda Zhou[1], Wenjuan Yang[1], Renping Zhao[1], Carsten Kummerow[1], Eva C. Schwarz[1] and Bin Qu[1]

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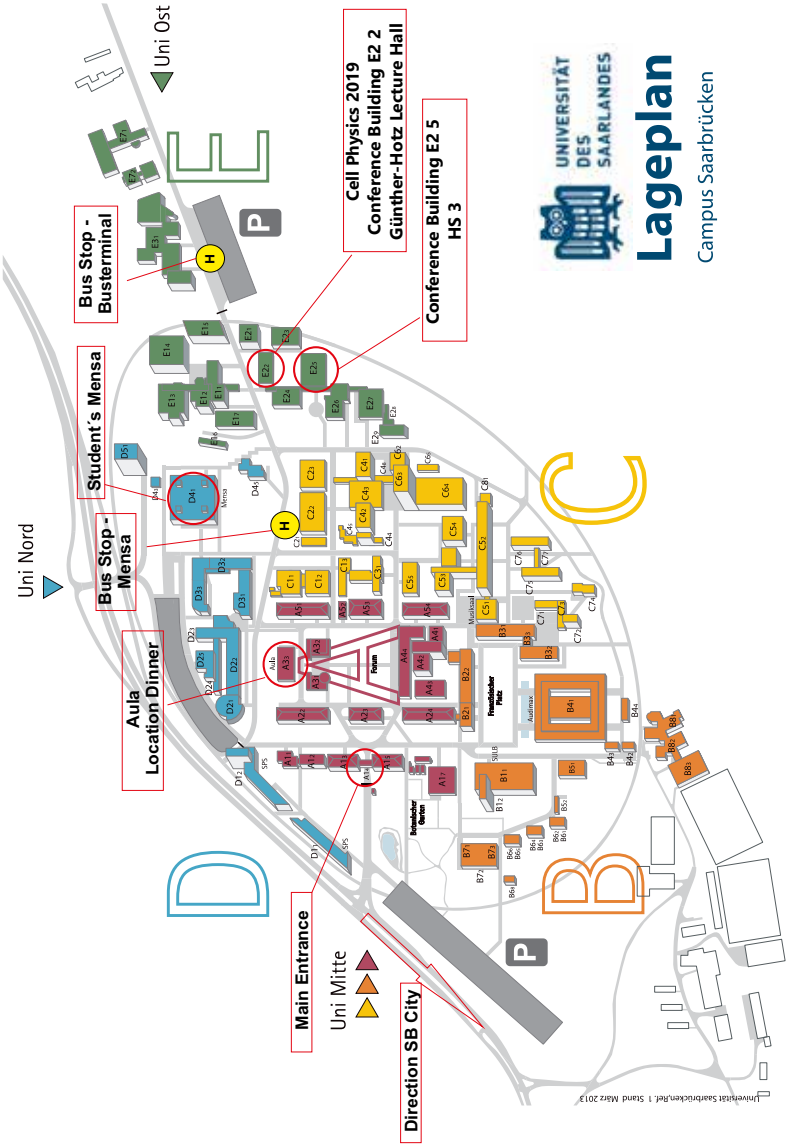
Natural killer (NK) cells are an important part of the innate immune system, which are capable of recognizing and destroying a wide variety of target cells. T cells, on the other hand, play a central role in the adaptive immunity. T cells are classified in two categories: T helper (Th) cells, also known as CD4+ T cells, and cytotoxic T lymphocytes (CTLs), also known as CD8+ T cells. Th cells coordinate immune responses mainly by secretion of cytokines, and CTLs eliminate pathogen-infected or tumor cells upon recognition of matching antigens presented by MHC class I molecules. In this work, we investigated the impact of T cells on NK killing efficiency and the underlying mechanisms. Our results show that after co-culture with activated T cells, NK cells exhibit a substantial enhancement in killing efficiency compared with alone-cultured NK cells. We further found that the cytokines released by T cells per se were not able to elevate NK killing, indicating that physical contact between T cells and NK cells is required to maximize NK killing activity. In addition, we found that IL-2 receptors and the adhesion molecule ICAM-1 play an essential role in T cell-boosted NK killing. We further identify that the motility of NK cells is substantially enhanced by T cells. Our findings reveal a previously unknown interplay between T cells and NK cells and the corresponding molecular basis.

Autoren Index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Registration takes place on Wednesday (9.10.) 7:30-8:20

Wednesday (9.10.)	Thursday (10.10.)	Friday (11.10.)	
	8:20-8:30 Opening		
8:30-10:30 **Actin I** Koenderink Lenz Janshoff Bernheim	8:30-10:30 **Tissues / Cancer** Friedl Charras Betz Thirumalai	8:30-10:30 **Actin II** Bassereau Steinem Blanchoin Janke	
	10:30-11:00 Coffee Break		
11:00-13:00 **Immune Cells** Sengupta Theodoly Paszek Lenon-Duménil	11:00-12:30 **Cell State** Huang **Membrane proteins** Hub Hummer	11:00-13:00 **Tissues & Morphogenesis** Höhn Lubatti Chan Guillamat-Blanch-Mercader Zhang Kurniawan	**Membranes** Barberi Hafner Farago Bächer Kruss Sitarska Forster Hähl
13:00-14:00 Lunch Buffet & Poster	12:30-13:30 Lunch Buffet & Poster	13:00-14:00 Lunch Buffet & Poster	

14:00-15:00		13:30-15:00		14:00-14:45	
Cell Mechanics I Lesman Oosterwyck Sung Kidoaki	**Nano Probes** Monzel Falconieri Han Komaragiri	**Cancer** Büscher Fredrich Rosenbauer Leal-Egana Prunet Weber	**Actomyosin Networks** Campillo Abu Hamed Flormann Dahmke Vliegenthart Makuch	**Bacteria** Pearce Najafi Sankaran	**Membrane Channels** Alansary Ivanović Romanova
15:00-15:20 Coffee Break				14:45 - 15:00 Coffee Break	
15:20-16:20		15:20-16:20		15:00-17:00	
Cell Mechanics II Armistead Fregin Dietz Yan	**Intra-cellular Transport** Rueang-kham Shaebani Mangeat Chatterjee	**Adhesion** Vargas Spengler Ghorbani	**Intermediate Filaments** Schepers Lautenschläger Kraxner Lorenz	**Microtubules** Svitkina Bershadsky Merkel Tolić	
16:30-17:30		16:30-17:30		17:00	
Cell nucleus Hawkins Discher		**Adhesion** Smith Gaub		Fin	
17:30-19:00 Posters & Snacks					
19:00 Social Dinner (Aula)		19:00 Social Dinner (Marquee)			