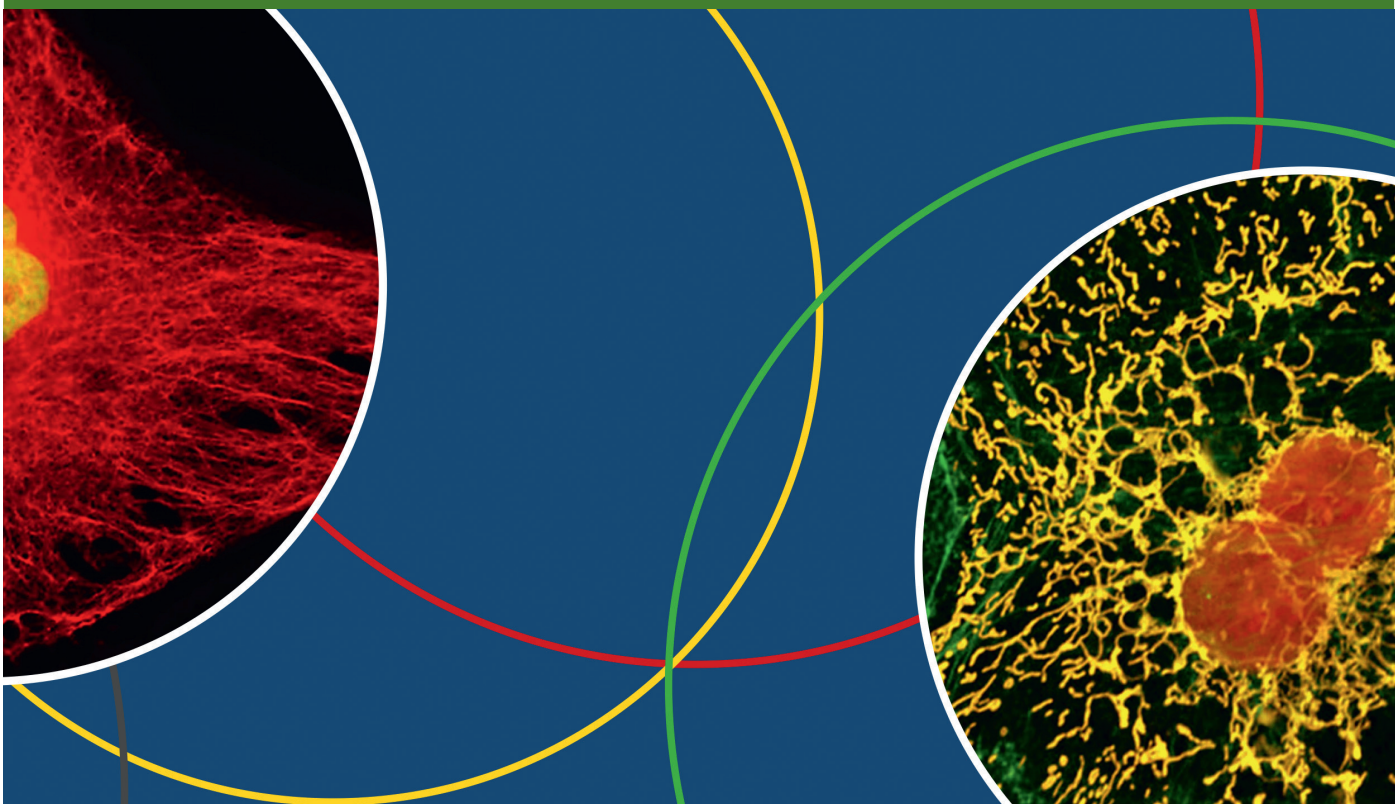
BOOK OF ABSTRACTS



Cell Physics 2016

22.-24. Juni 2016
Saarbrücken

SFB 1027 DFG UNIVERSITÄT DES SAARLANDES

Welcome...

...to the conference "Cell Physics 2016" at the Saarland University in Saarbrücken, Germany, 22.-24.6.2016. The conference is organized and Ginanced 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

- Active Matter
- Cell Signaling
- Membrane Dynamics
- Morphogenesis
- Gene Expression
- Evolutionary Dynamics

The conference will start Wednesday 22.6.2016 at 9:00 am, and finish Friday, 24.6.2016 at 3:00 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

Cell Physics 2016

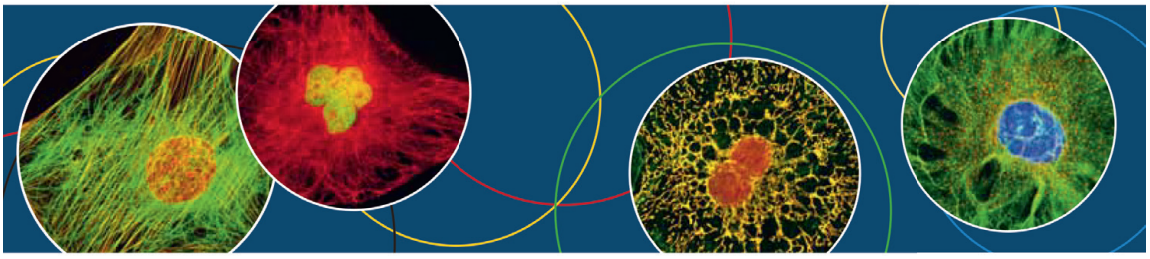
22. - 24. Juni | Saarbrücken

TOPICS

Active Matter
Cell Signaling
Membrane Dynamics
Morphogenesis
Gene Expression
Evolutionary Dynamics

INVITED SPEAKERS

Erez Braun (Technion Haifa, Israel)
Maria Bykhovskaia (Universidad Central del Caribe, Puerto Rico)
Ramin Golestanian (University of Oxford, UK)
Kevin Foskett (University of Pennsylvania, USA)
Simon Foster (University of Sheffield, UK)
Kristian Franze (Cambridge University, UK)
Gerhard Gompper (FZ Jülich, Germany)
Stephan Grill (University of Dresden, Germany)
Frauke Gräter (HITS, Heidelberg, Germany)
Michael Hagan (Brandeis University, USA)
Pavel Jungwirth (Czech. Acad. of Sciences, Prag, Czech Rep.)
Jürgen Klingauf (University of Münster, Germany)
Frédéric Pincet (LPS, ENS, Paris, France)
Aurelien Roux (University of Geneva, Switzerland)
Ralf Schneggenburger (EPFL Lausanne, Switzerland)
Jennifer Stow (University of Queensland, Australia)
Lukas Tamm (University of Virginia, USA)
Lin Zou (Chongqing Medical University, China)



ORGANIZERS (UdS)

Ludger Santen
Heiko Rieger

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

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Conference Program

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16.15 - 16.45	Ramin Golestanian	New results on collective chemotaxis in colonies	I.6
16.45 - 17.00	Moritz Kreysing	Intra-cellular microfluidics to probe the role of physical transport in morphogenesis	C.10
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10.30 - 11.00	**Coffee-Break**		
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15.00 - 15.15	Kinjal Dasbiswas	Mechanobiological induction of long-range contractility by diffusing biomolecules and size scaling in cell assemblies	C.3
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16.00 - 16.30	Lukas Tamm	Multi-level effects of cholesterol on the formation of exocytotic fusion pores	I.17
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P27	Fries, Peter	Repolarization of cells
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P49	Kravchenko-Balasha, Nataly	Brain tumor cellular architectures are predicted through phosphoprotein signaling measurements in two-cell system

P50	Kreten, Fabian Hubertus	A mechanism for contraction of cytokinetic actin rings
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P85	Wasnik, Vaibhav	Physical limits to spatiotemporal cellular signaling
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P97	Will, Thorsten	Towards the rewiring of the proteome during blood development
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Abstracts of Invited Talks

I.1 The living cell as a sloppy dynamical system

Erez Braun

Department of Physics & Network Biology Research Laboratories Technion, Haifa 32000, Israel

The emergence of stable cell states (morphology, metabolism and function) reflects the organization of regulatory modes determining the temporal spectrum of intracellular proteins. In the last decade, our study of cell populations exposed some intriguing characteristics of their behavior, showing that cell-state organization reflects exploratory dynamics in a degenerate, high-dimensional phase-space. I'll discuss these dynamics, arguing that the living cell belongs to a broad class of systems exhibiting sloppy dynamics, characterized by their insensitivity to the underlying parameters yet efficient convergence to a viable state. Understanding of the physics of such dynamical systems remains elusive..

[1] E. Braun, Rep. Prog. Phys. 78 (2015) 036602.

I.2 Molecular Dynamics Simulations of Protein Interactions Leading to Synaptic Vesicle Fusion

Maria Bykhovskaia

Department of Neurology, Wayne State University , Detroit, Michigan, USA

Neurotransmitters are released via the fusion of synaptic vesicles with the neuronal membrane. Vesicles dock to the membrane via a specialized protein complex termed SNARE. The fusion occurs in response to Ca^{2+} inflow, and the vesicle protein Synaptotagmin (Syt) serves as a Ca^{2+} sensor. Syt includes C2A and C2B domains connected by a flexible linker. A cytosolic protein Complexin (Cpx) interacts with the SNARE complex, regulating the fusion time-course. Although molecular interactions of these proteins have been extensively studied, it is still debated how the fusion proteins interact with each other and with lipid bilayers to trigger lipid merging and pore opening. To elucidate this mechanism, we performed molecular dynamics simulations of Syt interacting with the SNARE complex, Cpx and lipid bilayers. Our simulations demonstrated that C2A domain has a strong affinity to lipids, while C2B domain interacts weakly with neutral lipids but deeply immerges into PIP2 containing anionic lipids upon Ca^{2+} binding. Our simulations also suggest that C2B domain tightly interacts with the SNARE-Cpx complex. Altogether, our computations support a model whereby Ca^{2+} binding pocket of Syt C2A domain is attached to the vesicle membrane, while C2B domain interacts with the SNARE complex and Cpx, bridges bilayers, and upon Ca^{2+} binding immerges into the plasma membrane, thus triggering fusion.

I.3 Features of Ca^{2+} release and uptake channels mediating ER-tomitochondrial communication

J. Kevin Foskett

Departments of Physiology and Cell and Developmental Biology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Low-level constitutive inositol trisphosphate receptor ($InsP_3R$)-mediated Ca^{2+} release from the endoplasmic reticulum (ER) and its uptake by mitochondria through the uniporter Ca^{2+} channel complex (MCU) is essential for maintaining cellular bioenergetics. The kinetic features of the channels and their spatial relationships are crucial to mediate this communication. Kinetic responses of single $InsP_3R$ channels in native ER membrane to rapid ligand concentration changes with msec resolution revealed channel activation and deactivation with novel Ca^{2+} regulation and unexpected ligand cooperativity. We measured iCa through an $InsP_3R$ channel in its native membrane environment under physiological ionic conditions to be 0.15 ± 0.01 pA for a ER store with 500 μM $[Ca^{2+}]$ER. The **i**Ca–$[Ca^{2+}]$ER relation suggests that Ca^{2+} released by an $InsP_3R$ channel raises $[Ca^{2+}]$i near the open channel to ~13–70 μM, depending on $[Ca^{2+}]$ER. These kinetic and conductance measurements have implications for Ca^{2+} uptake by MCU. Recent patch clamp recordings of MCU in the mitochondrial inner membrane have provided insights into novel regulation, but high resolution kinetic features of MCU channel gating in response to Ca^{2+} released through an $InsP_3R$ remain to be determined. Modeling will be helpful to determine the required spatial proximity of release and uptake sites and the number of channels involved.

I.4 Bacterial cell wall peptidoglycan architecture and dynamics

Simon J. Foster

The Krebs Institute, University of Sheffield, Firth Court, Western Bank, Sheffield, S10 2TN, UK

Bacterial cell wall peptidoglycan is essential for the life of most bacteria. It determines cell shape, and its biosynthesis is the target for many important antibiotics. The fundamental chemical building blocks of peptidoglycan are conserved: repeating disaccharides cross-linked by peptides. However, despite this relatively simple chemistry, how this is manifested into the myriad bacterial shapes and how this single macromolecule remains dynamic permitting cell growth and division has largely remained elusive. The advent of new microscopy approaches is beginning to revolutionize our understanding of the architecture of this polymer and to reveal novel insights into its biosynthesis and hydrolysis. Atomic force microscopy has demonstrated a complex, nanoscale peptidoglycan architecture in diverse species, which meets the challenges of maintaining viability and growth within their environmental niches by exploiting the bioengineering versatility of the polymer. The application of super-resolution fluorescence microscopy, coupled with new chemical probes has begun to reveal how this essential polymer is synthesized during growth and division.

[1] Wheeler, R. *et al.,* (2015) mBio **6**:e00660
[2] Bailey, R.G. *et al.,* (2014) Biophysical Journal **107**, 2538
[3] Turner,R.D. *et al.,* (2014) Molecular Microbiology **91**, 862
[4] Turner, R.D. *et al.,* (2013) Nature Communications **4**, 1496
[5] Wheeler, R. *et al.,* (2011) Molecular Microbiology, **82**, 1096
[6] Turner, R.D. *et al.,* (2010) Nature Communications **1**, 26

I.5 The physical control of CNS development and pathology

Kristian Franze

Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK

During the development of the nervous system, neurons migrate and grow over great distances. Currently, our understanding of neuronal development and function is, in large part, based on studies of biochemical signaling. Despite the fact that forces must be involved in cell motion, mechanical aspects have so far rarely been considered. Here we investigate how *Xenopus* neurons respond to their mechanical environment. Axonal growth velocities, directionality, fasciculation, i.e., their tendency to grow in bundles, and maturation all significantly depended on substrate stiffness. Moreover, when grown on substrates incorporating linear stiffness gradients, axon bundles were repelled by stiff substrates. *In vivo* atomic force microscopy measurements revealed stiffness gradients in developing brain tissue, which axons followed as well towards soft. Interfering with brain stiffness and mechanosensitive ion channels in vivo both led to similar aberrant neuronal growth patterns with reduced fasciculation and pathfinding errors, strongly suggesting that neuronal growth is not only controlled by chemical signals – as it is currently assumed – but also by the tissue's local mechanical properties.

I.6 New results on collective chemotaxis in colonies

Ramin Golestanian

Rudolf Peierls Centre for Theoretical Physics, University of Oxford, Oxford OX1 3NP, United Kingdom

I discuss two different problems in which a crude phenomenological description of chemotaxis leads to interesting new perspectives. The first question concerns the competition between chemotaxis and cell division, which might at first sight seem completely unrelated. We have developed a simple model to explore any possible interplay between the two processes, and studied it via dynamical Renormalization Groups methods [1]. We find that whereas details of the microscopic behavior of cells do not impact the collective behavior on a large scale, the interplay between the two general processes of growth and chemotaxis leads to a variety of collective phenomena, which includes a sharp transition from a phase that has moderate controlled growth and death, and regulated chemical interactions, to a phase with strong uncontrolled growth/death and no chemical interactions. Remarkably, for a range of parameters, the transition point shows nontrivial collective motion, which can even be described analytically. The second problem concerns the role of slowly diffusing chemical residues on the behavior of bacteria with twitching motility. We find evidence that a non-trivial perpendicular alignment mechanism tends to modulate the orientation of bacteria [2], and that this new coupling allows us to build a complete quantitative description of the observed collective behavior of such bacteria [3].

[1] A. Gelimson and R. Golestanian, Phys. Rev. Lett. 114, 028101 (2015)
[2] W.T. Kranz, A. Gelimson, and R. Golestanian, arXiv:1504.06814
[3] A. Gelimson *et al.*, unpublished (2016)

I.7 Active Brownian particles — spheres, filaments, and mixtures

G. Gompper, A. Wysocki, R.G. Winkler, R.E. Isele-Holder, and J. Elgeti

Institute of Complex Systems, and Institute of Advanced Simulation, Forschungszentrum Jülich, Jülich, Germany

Ensembles of active Brownian particles are highly simplified model systems for a large variety of self-propelled synthetic microswimmers, microorganisms, cells, and biological filaments. The simplicity of the model allows for (i) a description which emphasizes generic behaviors, and (ii) the investigation the collective motion of a large number of particles. The modeling of an active system by Brownian particles emphasizes the roles of volume exclusion, particle shape, and thermal or active noise [1].

Two types of active Brownian particles will be considered. The first is a system of active spheres [2]. This system shows activity-induced phase separation, very similar to a system of passive attractive spheres. However, the collective dynamics is very different, with a spontaneous formation of swirls and jets – despite of the absence of any alignment mechanism. The dynamics becomes even more interesting for mixtures of passive and active particles. Now the interfaces between the dense and the dilute phases become mobile, with a spontaneous symmetry breaking between advancing and receding interfaces [3]. The second is a system of self-propelled filaments, both without [4] and with a load [5]. This is a model, for example, for actin filaments in motility assays. Depending on the size and shape of the load, the bending rigidity of the filament, and the propulsion strength, a large variety of conformations and dynamics is observed, ranging from spiraling and circle-swimming to beating [5].

[1] J. Elgeti, R.G. Winkler, and G. Gompper, Rep. Prog. Phys. **78**, 056601 (2015).
[2] A. Wysocki, R.G. Winkler, and G. Gompper, EPL **105**, 48004 (2014).
[3] A. Wysocki, R.G. Winkler, and G. Gompper, arXiv 1601.00850 (2016).
[4] R.E. Isele-Holder, J. Elgeti, and G. Gompper, Soft Matter **11**, 7181 (2015).
[5] R.E. Isele-Holder *et al.*, submitted (2016).

I.8 Molecular mechano-sensors: translating force into biochemical signals

Frauke Gräter and Camilo Aponte-Santamaria

Interdisciplinary Center for Scientific Computing, Heidelberg University, and Heidelberg Institute for Theoretical Studies, Heidelberg

How can a cell sense force and translate it into downstream signaling cascades leading to changes in cellular behavior such as differentiation, proliferation, or motility? It is increasingly recognized that mechanical force can reversibly change protein conformation, thereby allosterically switching proteins on and off, reminiscent of protein regulation by biochemical signals such as co-factor binding.
I will present recent results of two proteins, the von Willebrand factor (VWF) and focal adhesion kinase (FAK), for which we have successfully revealed how they work as mechano-sensors [1-5]. To this end, we used molecular modeling, Molecular Dynamics (MD) simulations and a novel Force Distribution Analysis to reveal the inner working and change of function of these proteins under the influence of mechanical load.
Our results can be used to extrapolate to the more complex cellular environment of these molecules, and have implications for the underlying processes, namely blood coagulation (VWF) and stem cell differentiation pathways (FAK).

[1] Posch S *et al.,* Struct Biol. 2016 Apr 23. pii: S1047-8477(16)30081-8.
[2] Zhou J *et al.,* PLoS Comput Biol. 2015 Nov 6;11(11):e1004593.
[3] Aponte-Santamaría C *et al.*, Biophys J. 2015 May 5;108(9):2312-21
[4] Zhou J *et al.,* Biophys J. 2015 Feb 3;108(3): 698-705
[5] Goñi GM *et al.,* Proc Natl Acad Sci U S A. 2014 Aug 5;111(31):E3177-86.

I.9 Controlling contractile instabilities in the actomyosin cortex

Stephan W. Grill

BIOTEC, Technische Universität Dresden, Germany

Cells and tissues represent active materials that generate stresses for driving morphogenesis. A fundamental challenge is to understand how spatiotemporal patterns arise in such active biological materials, driven by the interplay of active mechanical processes and regulation by signaling pathways. I will discuss the mechanism of spatiotemporal pattern formation in the highly contractile actomyosin cortical layer, where transient accumulations of myosin motor proteins tend to form pulsatile networks to drive morphogenetic events. Using a novel image analysis technique (COmoving Mass Balance Imaging, COMBI) we have determined the kinetic diagram of myosin activation by RhoA in the cell cortex of the polarizing one-cell stage *Caenorhabditis elegans* embryo. We found that the complete system of myosin activation by RhoA, active stress generation by myosin, and RhoA advection by actomyosin gel flow is unstable. Notably, the dynamic pattern in the unstable regime appears to be under separate regulatory control, and I will discuss general means of how introducing regulatory processes to active materials gives rise to novel pattern forming states.

I.10 Unexpected ordered phases in active matter systems

Michael F. Hagan, Gabriel S. Redner, Caleb G. Wagner, and Aparna Baskaran

Martin Fisher School of Physics, Brandeis University, Waltham, MA, USA

Active matter describes systems whose constituent elements consume energy to generate motion. I will describe computer simulations of two recently developed active matter systems, and unexpected ordered phases that arise as a consequence of activity in these systems. (1) Self-propelled colloids with repulsive interactions and no aligning interactions are a minimal model active matter system. We and others have shown that this system undergoes athermal phase separation. Despite the intrinsically nonequilibrium nature of the phase transition, I will show that the kinetics can be described using a framework analogous to equilibrium classical nucleation theory, governed by an effective free energy of cluster formation, with identifiable bulk and surface terms. I will also show that when these particles are confined they undergo another transition, in which the particles become confined to the boundary, with a density that depends on the local curvature radius of the boundary. (2) Active nematics are liquid crystals which are driven out of equilibrium by energy-dissipating active stresses. The ordered nematic state is unstable to the proliferation of topological defects, which undergo birth, streaming dynamics, and annihilation to yield a seemingly chaotic dynamical steady-state. In this talk, I will show that order emerges from this chaos, in the form of heretofore unknown broken-symmetry phases in which the topological defects themselves undergo orientational ordering.

I.11 Cell Penetration and Membrane Fusion: Molecular Dynamics and Fluorescence Spectroscopy

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First, molecular dynamics simulations, together with fluorescence spectroscopy and biomimetic colorimetric assays, have been performed in search of explanations why arginine rich peptides with intermediate lengths of about ten amino acids translocate well through cellular membranes, while analogous lysine rich peptides do not. We observe a strong tendency of adsorbed arginine (but not lysine) containing peptides to aggregate at the bilayer surface. We suggest that this aggregation of oligoarginines leads to partial disruption of the bilayer integrity due to the accumulated large positive charge at its surface which increases membrane-surface interactions due to the increased effective charge of the aggregates. As a result, membrane penetration and translocation of medium length oligoarginines becomes facilitated in comparison to single arginine and very long polyarginines, as well as to lysine containing peptides.

Second, we aim at understanding of interactions of calcium with lipid membranes at the molecular level, which is of great importance in light of the involvement in calcium signaling, association of proteins with cellular membranes, and membrane fusion. Time-resolved fluorescent spectroscopy of lipid vesicles and second harmonic generation spectroscopy of lipid monolayers are used to characterize local binding sites of Ca^{2+} in zwitterionic and anionic model lipid assemblies while dynamic light scattering and zeta potential measurements are employed for macroscopic characterization of lipid vesicles in calcium-containing environment. To gain an atomistic-level information about calcium binding, the experiments are complemented by molecular simulations that utilize an accurate force field for calcium ions with scaled charges effectively including electronic polarization effects. We demonstrate that the membranes have very high calcium-binding capacity, with several types of binding sites present, with important implications for calcium buffering, synaptic plasticity, and protein-membrane association.

I.12 Single vesicle recordings in hippocampal 'xenapses' reveal diffusional dispersion of synaptic vesicle proteins after fusion

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In order to maintain neuronal transmission after exocytosis of synaptic vesicles (SVs), the vesicular proteins have to be cleared away from the active zone. Until now it remained controversial whether SV components remain clustered during translocation from sites of exocytosis or disperse by free diffusion. To address this question, we developed a novel purely presynaptic neuronal preparation which enables single vesicle recording by TIRFM.

Using click-chemistry we functionalized micropatterned coverglasses with protein domains of synaptic cell adhesion molecules, serving as artificial postsynapses. On these host substrates purely presynaptic boutons form 'en face' directly onto the coverslip, termed 'xenapses'. Serial section TEM as well as focused-ion-beam SEM showed that xenapses contain a few hundred SVs, many of them docked in several clusters at the bottom membrane. 4Pi and TIRF-STORM confirmed the existence of several active zones. Thus, xenapses offer the unique opportunity to record exocytosis of single vesicles by TIRFM. Using fusion constructs of the pH-sensitive pHluorin, single fusion events were visible as diffraction-limited spots on stimulation with single action potentials. We could localize fusion events synchronous to action potentials with ~20 nm precision and follow the fate of released SV proteins. We observed diffusional dispersion of vesicular proteins post fusion with diffusion constants in the range of 0.1 $\mu m^2/s$. Thus, our results point to free diffusion as mechanism for fast clearance.

I.13 Snapshot of sequential SNARE assembling states between membranes shows that N-terminal transient assembly initializes fusion

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Many prominent biological processes are driven by protein assembling between membranes. Understanding the mechanisms then entails determining the assembling pathway of the involved proteins. Because the intermediates are by nature transient and located in the intermembrane space, this determination is generally a very difficult, not to say intractable, problem. In this presentation, I will present a new setup with sphere/plane geometry. Using this setup, we have been able to freeze one transient state in which the N-terminal domains of SNARE proteins are assembled [1]. A single camera frame is sufficient to obtain the complete probability of this state with the transmembrane distance. I will show that it forms when membranes are 20 nm apart and stabilizes by further assembling of the SNAREs at 8 nm. This setup that fixes the intermembrane distance, and thereby the transient states, while optically probing the level of molecular assembly by Förster resonance energy transfer (FRET) can be used to characterize any other transient transmembrane complexes.

[1] Y J Wang *et al.*, PNAS 113, 3533-3538 (2016).

I.14 Buckling the cell membrane

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Cells and organelles are delimited by lipid bilayers. Since these membranes are impermeable to most solutes, in order to exchange material with their environment, organelles and cells have developed a large protein family involved in budding membranes to form membrane carriers,. These carriers transport material between organelles. Proteins involved in intracellular membrane traffic can remodel the membrane by several ways. Clathrin, for example, polymerizes into a spherical cage onto the membrane, forcing it to curve. Here we describe a recently discovered protein complex called ESCRT-III, which has the property of forming spirals at the surface of the lipid bilayer. This unique structural feature did not suggest any known mechanism by which it could deform the membrane. It was theoretically proposed that, while growing into a spiral, it accumulates stress energy which can be released by buckling of the central part of the spiral [1]. By using high-speed AFM and biophysical tools to measure membrane elasticity we show how the elastic and polymerization properties of the ESCRT-III filament are compatible with such model [2]. We further investigate the dynamics of the complex.

[1] M. Lenz, D. Crow, and J.-F. Joanny, Physical Review Letters **103** (2009).
[2] N. Chiaruttini *et al.* , Cell **163**, 866 (2015).

I.15 Overlapping roles of Synaptotagmins 1 and 2 in triggering transmitter release at fast CNS synapses

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At a synapse, an action potential (AP) invading a presynaptic nerve terminal causes the Ca^{2+} - dependent release of neurotransmitter, by opening voltage-gated Ca^{2+} channels in the presynaptic nerve terminal. In this process, the rate of transmitter release evoked by a presynaptic AP („evoked release“) is increased by several orders of magnitude (up to ~ 1-millionfold) as compared to the background rate of release. To enable this high dynamic range, Ca^{2+} must act on a highly non-linear Ca^{2+} sensor, which are represented by the double C2 domain containing proteins Synaptotagmin (Syt)-1, or Syt2.

Combined patch-clamp and Ca^{2+} uncaging studies at the large calyx of Held synapse, have shown that Syt2 KO mice have a shallow Ca^{2+} dose-response curve of transmitter release (slope ~ 1 in double logarithmic coordinates) as compared to wild-type synapses (slope ~ 4; ref. [1]). Thus, the Syt2 protein confers highly-non-linear Ca^{2+} sensing during the triggering of evoked release at the calyx synapse. Interestingly, Syt1 and Syt2 are closely related genes with a high sequence homology. Syt1 is expressed in forebrain, whereas Syt2, an isoform found only in vertebrates, is highly expressed in hindbrain. We now find that in various excitatory and inhibitory hindbrain synapses, Syt1 and Syt2 have overlapping roles. This could either indicate a developmental expression switch from Syt1 towards Syt2 as we showed for the nascent calyx synapse recently [2], or else, some synapses, especially inhibitory synapses, might use both Syt1 and Syt2 to achieve high rates of evoked release.

[1] Kochubey and Schneggenburger (2011). Neuron 69, 736-748.
[2] Kochubey *et al.,* (2016) Neuron, in press.

I.16 Macrophage dorsal ruffles as dynamic platforms for signaling and endocytosis.

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Macrophages engage in surveillance, detection and phagocytosis of pathogens using receptors displayed transiently on the cell surface. We have shown that Toll-like receptors (TLRs), along with regulatory molecules and adaptors and kinases, are localized in surface dorsal ruffles which give rise to macropinosomes and phagosomes, creating sequential signaling environments for differential macrophage outputs. Newly identified signaling adaptors for TLRs further bias signaling outputs. Lattice light sheet imaging reveals the extremely dynamic nature and unique structural features of F-actin-rich dorsal ruffles on activated cells. I will present a sequence of ruffle-associated Rab GTPases and their effectors that control aspects of ruffle behavior and TLR-induced PI3K-Akt-mTOR signaling. 4D live cell imaging and 3D electron microscopy are helping to characterize these signaling membrane domains and the endosomal network responsible for receptor trafficking. The highly dynamic properties of these membrane niches and compartments sheds new light on the spatiotemporal regulation of innate immune responses.

I.17 Multi-level effects of cholesterol on the formation of exocytotic fusion pores

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Cholesterol modulates the structure and dynamics of biological membranes in multiple ways. It changes the fluidity, thickness, mechanical properties and intrinsic curvature of lipid bilayers. Cholesterol also induces phase separations in multicomponent lipid mixtures, partitions selectively between different coexisting lipid phases, and causes integral membrane proteins to respond by changing conformation or redistribution in the membrane. In this contribution, we discuss which of these often overlapping properties are important for the formation exocytotic fusion pores and how they affect the distribution of the relevant SNARE and accessory proteins in the plasma and vesicle membrane. We also discuss how cholesterol affects the balance between hemi- and full fusion as measured by single vesicle fusion with millisecond time resolution [1-4].

[1] Domanska *et al.*, L.K. (2009) J. Biol. Chem. 284:32158-32166.
[2] Murray, D. and Tamm, L.K. (2011) Biochemistry 50:9014-9022.
[3] Kiessling V. *et al.*, L.K. (2013) Biophys. J. 104:1950-1958.
[4] Kreutzberger AJB, Kiessling V, and Tamm LK (2015) Biophys J 109:1-11.

I.18 β-arrestin1 as a pivotal regulator in pediatric leukemia

Lin Zou, Yi Shu, Shan Liu, Haiyan Li, Juan Long, Kang Li, Xiaoyan Zhou, Xinkun Qi, Hongxu Wang

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Leukemia is the most common childhood malignancy. Pediatric acute leukemia (AL) mainly includes acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) subtypes, which occupy approximately 76% and 20% of childhood leukemia respectively. Although the long-term disease-free survival (DFS) and overall survival (OS) rate of pediatric leukemia has been improved recently, there is still about 25% relapse rate. Novel molecular mechnism for therapetic target are still more concerned. β-arrestin1, the multifunctional scaffold protein, is found to mediate many intracellular signaling network, and to be involved in many tumors. However, little is known in leukemia. Here we present the aberrant β-arrestin1 expression and regulation in different kinds of pediatric leukemia subtypes, by binding with several proteins and mediating their corresponding signalings, to be potential therapeutic targets for childhood leukemia.

Abstracts of Contributed Talks

C.1 Curvature-guided motility of microalgae in geometrically confined environments

Tanya Ostapenko, Thomas Böddeker, Fabian Schwarzendahl, Christian Kreis, Marco G. Mazza, Oliver Bäumchen

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The natural habitats of many living microorganisms are complex geometric environments, rather than bulk situations. The confinement and, in particular, the exposure to solid/liquid interfaces is playing an important role with regard to the adhesion of cell populations and, subsequently, the formation of biofilms. The influence of interfaces on the dynamics was recognized as an important factor, and there are differences in the way that pusher- and puller-type swimmers behave close to interfaces. Using microfluidic experiments and molecular dynamics simulations, we report on the motility of single Chlamydomonas microalgae in 2D circular compartments. We find that the radial probability distributions of trajectories display a characteristic wall hugging effect, where swimmers remain trapped at the concave interface. This effect becomes strongly amplified upon decreasing the size of the circular compartment; in fact, its significance is found to scale as the curvature of the compartment walls. For trajectories in the vicinity of the concave wall, an alignment of the local swimming direction with the local wall tangent is observed. Based on geometric arguments involving the swimmer‘s persistence length and the size of the compartment, we explain this entrapment effect at concave interfaces.

C.2 Membrane Curvature Induced by Transmembrane Proteins

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The (local) curvature of cellular membranes can function as a sorting mechanism for membrane proteins, e.g. by accumulation of membrane proteins in regions of specific curvature, as shown recently for potassium channel KvAP and water-pore AQP0 [1]. Until now, the direction of the induced curvature for these proteins, as well as the molecular driving forces for the curvature induced by transmembrane proteins could not be resolved.
Here, using both coarse-grained and atomistic molecular dynamics (MD) simulations, we addressed the curvature induced by KvAP, AQP0, and different transmembrane peptides. KvAP induces a strong negative curvature of -0.036nm-1 while AQP0 hardly affected the spontaneous membrane curvature when embedded in a POPC lipid bilayer, in excellent agreement with experiment [1]. The dominant contribution to membrane curvature is attributed to electrostatic interactions between lipid headgroups and protein charges at the membrane interface.

[1] S. Aimon et al. Developmental Cell 28, 212 (2014).

C.3 Mechanobiological induction of long-range contractility by diffusing biomolecules and size scaling in cell assemblies

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Mechanobiological studies of cell assemblies have generally focused on cells that are, in principle, identical. Here we predict theoretically the effect on cells in culture of locally introduced biochemical signals that diffuse and locally induce cytoskeletal contractility which is initially small. In steady-state, both the concentration profile of the signaling molecule as well as the contractility profile of the cell assembly are inhomogeneous, with a characteristic length that can be of the order of the system size. The long-range nature of this state originates in the elastic interactions of contractile cells (similar to long-range ``macroscopic modes'' in non-living elastic inclusions) and the non-linear diffusion of the signaling molecules, here termed mechanogens. We suggest model experiments on cell assemblies on substrates that can test the theory as a prelude to its applicability in embryo development where spatial gradients of morphogens initiate cellular development.

C.4 Studying growth factor receptor proteins in whole cells in liquid using scanning transmission electron microscopy

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Correlative Liquid scanning transmission electron microscopy (STEM) and fluorescence microscopy were used to study the epidermal growth factor receptor HER2 [1] within the intact plasma membrane of whole SKBR3 breast cancer cells in their native liquid environment. The obtained spatial resolution of 3 nm was sufficient to resolve the constituents of individual protein complexes. Contrast was obtained on specific protein labels consisting of fluorescent nanoparticles, so-called quantum dots (QDs) [2]. On account of the atomic number (Z) contrast of the annular dark field detector of STEM, these nanoparticles of high-Z material were detected within the background signal produced by the low-Z material of the cell and surrounding liquid. The particular distribution of monomers, and homodimers (a protein complex consisting of a pair of HER2 proteins) of these receptors is of relevance for understanding cell growth triggering in cancer cells. Data was obtained from several tens of intact cells thus achieving statistics of thousands of protein positions with nanometer resolution. The signaling-active dimerized form of HER2 dimerization was localized in certain functional membrane regions exhibiting membrane ruffles. Larger-order clusters were also present. Membrane areas with homogeneous membrane topography, on the contrary, displayed HER2 in random distribution.

[1] D.B. Peckys, U. Korf, N. de Jonge, Science Advances 1:e1500165 (2015).
[2] D.B. Peckys, N. de Jonge, N., JoVE, e53186 (2015).

C.5 Stochastic Dynamics of Dorsal Actin Waves on Fibroblasts

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Albeit waves of polymerizing actin are a fundamental element of the motility apparatus of cells, the machinery of Dorsal Actin Waves (DAWs) [1] is poorly understood. In search of the mechanisms organizing DAWs we analyze experimental data of the dynamics of DAWs under well-defined experimental conditions. We find that DAWs show all characteristic features of waves in active media, e.g. oscillatory states, collision annihilation, and spirals. DAWs can be constrained to propagate along a quasi one-dimensional path with periodic boundary conditions via micro-contact printing. Under these conditions DAWs form pronounced and extremely regular, but stochastic spatio-temporal patterns. We use microfluidics to control the biochemical state of cells, which permits us to reversibly switch between different states of actin depolymerization using Latrunculin A. The periods between successive wave events and the propagation velocities of DAWs serve as readouts DAW dynamics in the parameter space of actin depolymerization rate and free actin monomers. We find that the propagation velocity of DAWs can be reduced by a factor of two by increasing depolymerization rates of actin, whereas the periods between successive wave events double. This clearly shows that the wave machinery of DAWs is regulated close to actin itself and not controlled by RhoGTPases.

[1] E. Bernitt *et al.*, PLoS ONE 10, e0115857 (2015).

C.6 Passive Translocation of Hydrophobic Nanoparticles through a Phospholipid Bilayer

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Hydrophobic nanoparticles introduced into living systems may lead to increased toxicity, can activate immune cells or can be used as nano-carriers for drug and gene delivery. The interaction of nanoparticles with bilayers is essential of an in depth understanding of these processes. It is known that small hydrophobic nanoparticles can insert into a lipid bilayer and accumulate in the bilayer core, representing a potential well. Therefore it is generally accepted that escaping the bilayer is unlikely for these nanoparticles. In contrast to this assumption, we demonstrate theoretically how large hydrophobic nanoparticles can cross lipid bilayers with almost no energy barrier, while small hydrophobic nanoparticles stay trapped in the core of the bilayer. This size-dependent translocation was confirmed experimentally using a microfluidic device. Moreover, the kinetic pathway of a single passive translocation event was directly measured and analyzed.

C.7 A mechanism of biological pattern formation through mechanochemical feedback

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The interplay between biochemistry and cell mechanics is critical for a broad range of morphogenetic changes. A key example is the early embryonic development of the *Caenorhabditis elegans* zygote, where flows of the actomyosin cortex occur simultaneously with the establishment of a polarity pattern in partitioning defective (PAR) proteins. However, how the PAR system interacts with and regulates cortical flow has remained elusive. Here, we identify a novel mechanochemical pattern-generating mechanism, which drives the patterning of the PAR polarity proteins.

Using calibrated, quantitative fluorescence microscopy, we first measured the spatiotemporal evolution of the membrane-associated protein concentration of the posterior PAR-2, the anterior PAR-6 and myosin II as the mechanical force generator, as well as the cortical flow field. Next we show that these dynamics can be quantitatively recapitulated, using a reaction-diffusion-advection theory for the concentration fields (myosin II, PAR-2 PAR-6) in combination with an active-fluids theory for the cortical flow field. Remarkably, our physical theory can, for the first time, fully recapitulate the spatiotemporal evolution of all the measured concentration fields as well as the actomyosin flow field, duting the polarization process. We demonstrate that the function of this mechanochemical feedback is to amplify and stabilize cortical flows and thus to promote a rapid transition to the patterned state of the PAR system.

C.8 Red Blood Cell Ghosts for biomedical applications: Blood on a Chip

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The preparation of Red Blood Cell (RBC) Ghosts is a well-known protocol in biological and medical research [1]. It describes the extraction of the membrane from RBCs. Another well-known protocol is the preparation of highly ordered stacks of artificial lipid bilayers on silicon wafers [2]. Such experiments in particular allow the study of the interaction between cell membranes and drugs, small molecules, and bacteria. There are various attempts to adapt this protocol to a native cell membrane [3,4]. For the first time we were able to combine both described protocols and to prepare highly ordered stacks of RBC membranes on silicon wafers. These systems can now be used as inexpensive and safe platforms for testing the effect of drugs and bacteria on RBC membranes in-vitro using biophysical techniques, such as X-ray and neutron diffraction, optical spectroscopy and AFM.
We present the preparation and characterization of "Blood on a Chip" from molecular structure to the morphology of the membrane assemblies. Figure 1 shows the electron desity and a reflectivity curve of a RBC membrane. Aspirin, which is commonly used in the "low-dose-aspirin therapy" was found to have a drastic effect on human blood membranes and to lead to a significant softening and fluidification of the membranes.

[1] James T. Dodge, Carolyn Mitchell, Donald J. Hanahan, *Arch. Biochem. Biophys.* 100, 119 (1963)
[2] T.H. Watts *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **81**, 7564 (1984)
[3] Danny Poinapen, Laura Toppozini, Hannah Dies *et al.*, *Soft Matter*, **9**, 6804 (2013).
[4] Fei-Chi Yang, Robert Peters, Hannah Dies *et al.*, *Soft Matter*, **10**, 5541 (2014).

C.9 Brain tumor cellular architectures are predicted through phosphoprotein signaling measurements in two-cell system.

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Understanding of tumor architectures and the forces that drive their formation is of high importance in cancer research. To understand cell-to-cell spatial organization, we developed a methodology that combines single cell functional proteomics and theoretical analysis. We have found that signal transduction in two interacting glioblastoma (GBM) cancer cells depends on the cell-cell separation distance. Using thermodynamic-based analysis of protein concentrations as a function of cell-cell distance in two interacting cells we were able to identify the cell-cell separation distance that corresponded to the steady state of the cell-cell protein signaling. That length scale was found to be the dominant cell separation distance in bulk tissue culture [1]. Thereby we predicted that aggressive GBM cells would exhibit a scattered distribution, whereas less aggressive GBM cells would closely pack, consistent with the experimental observations of others in vivo. Furthermore we recently demonstrated that proteins secreted by 2 communicating GBM cells generate a free energy gradient that induces a directed cell-cell motion towards the most stable cell-cell separation distance. Neutralizing the secreted proteins most involved in establishing the free energy gradient canceles the directed motion, such that cell pairs show a random Brownian motion, similar to the case of isolated single cells.

[1] Kravchenko-Balasha N. *et al.*, Proc Natl Acad Sci U S A, 2014. **111**(17): p. 6521-6.

C.10 Intra-cellular microfluidics to probe the role of physical transport in morphogenesis

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Whereas modern genetics have provided great insights into the regulatory basis of embryogenesis, the role of physical transport in developing systems remains largely enigmatic due to the lack of suitable perturbation methods.
A particularly important morphogenetic event is cell polarization prior to asymmetric cell division. For the nematode worm C. elegans cell polarization was suggested to result from the interplay of PAR proteins and cortically induced flows.
However, it remains a challenge to show the causal role of flows at the onset of embryogenesis by direct flow perturbation experiments.
Towards this end, we exploit thermo-viscous pumping (Weinert & Braun, J. Appl. Phys. 2008) to control directed flows in living embryos without affecting their biological integrity. By perturbation of wild type-flow patterns, we are able to alter cell polarization dynamically and highly localized. To our knowledge our experiments represent the first non-invasive transport-only perturbation of developing organisms.

C.11 Dynamics of neutrophil extracellular trap (NET) formation

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Neutrophils are the most abundant type of immune cells in the human blood system and central for innate immunity. Recently, it was found that neutrophils and other cells are able to catch and kill pathogens by expelling a fibril network made from their own DNA (neutrophil extracellular traps, NETs). This process, termed NETosis, is distinct from other forms of cell death such as necrosis and apoptosis and is therefore of central importance for cell biology. During NETosis, a massive rearrangement of the materials inside the cell takes place. So far, the mechanisms that govern this complex process are poorly understood. Here, we show how cytoskeleton and membrane structure change the mechanical properties oft the cells, which finally leads to the release of NETs. We show that NETosis can be divided into three distinct phases. DNA passively diffuses out of the disassembled nucleus until it fills the complete cell lumen. Then cells rounds up while they still adhere to the substrate and finally the membrane is ruptured. In summary, these results demonstrate how NETs-release is temporarily regulated by mechanical properties of cell membranes and cytoskeleton.

C.12 Molecules and mechanics of cell adhesion studied by AFM force spectroscopy

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Cell adhesion is a complex process regulated by a number of surface proteins as well as cytoskeleton structure. The former has been recognized to mainly contribute molecular force, while latter governs the mechanical properties (e.g. elasticity) involved in cell adhesion. The importance of characterizing cell surface molecular binding events altered by protein ligation as well as cell elasticity changed due to cytoskeletal re-organization in response to TGF-β1 treatment has recently been highlighted by the authors [1]. Atomic force microscopy force spectroscopy (AFM-FS) has been demonstrated to be a powerful tool for the quantitative study of both-single cell elasticity and surface molecular binding [2]. In this study, we have applied AFM-FS to measure detachment energy, unbinding force between two adherent HK2 cells as well as the elasticity and viscoelasticity of the cells. In combination with single cell indentation test, the measured force-displacement curve of the separation process of the two cells reveal the change of adhesion characteristic contributed from both the surface molecular binding and cell elasticity/viscoelasticity. Moreover, a new model has been proposed to correlate the surface molecular adhesion with single cell mechanics, which may be useful for the fundamental understanding of disease progression and the development of new therapies [3].

[1] E. Siamantouras *et al.*, Nanomedicine: Nanotechnology, Biology, and Medicine, inpress (2016)
[2] E. Siamantouras *et al.*, Cellular and Molecular Bioengineering 8 , 22 (2015)
[3] R. G. Wells, Biochim Biophs Acta 1832, 884 (2013)

C.13 Concentration gradient mediated interactions between active droplets

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Autophoretic swimmers are subject to an interaction with each other that is due to overlap of the chemical gradients that surround them and drive their motion. It is believed to be similar to the interaction between micro-organisms, which also form and respond to solute gradients [1]. This type of interaction is also interesting because it involves the solvent, so it can be non-reciprocal [2]. Even though many particles and micro-organisms interact in this way, very few quantitative studies are available. The main obstacle is that this interaction is often coupled to self-propulsion making it impossible to study the two effects separately. We show that isotropic swimmers, geometrically symmetric active particles, only swim beyond a cutoff particle size and fuel concentration, providing a window of opportunity to study the solute mediated interaction without the complication of swimming. Using optical tweezers we quantified the force between isotropic swimmers due to this solute mediated interaction and show that the force scales with inter-particle distance as $1/r^2$, as is expected for a diffusion dominated process. We propose a functional form for the interaction, based on analogy with electrostatics, that accurately describes our data. This model is in principle applicable to all solute gradient induced interactions and can aid in understanding the behavior of micro-swimmers as well as more complicated biological systems.

[1] Cira, N. J., Benusiglio, A. & Prakash, M. *Nature* **519**, 446–450 (2015).
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C.14 The SNAP-25 linker is an integral regulator of exocytosis

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The formation of membrane-bridging trans-SNARE complexes is a key step in Ca^{2+}-triggered exocytosis. While the transmembrane domain-anchored SNARE proteins Syntaxin-1A and Synaptobrevin-2 each insert a single SNARE motif into the SNARE complex, SNAP-25 is anchored by palmitoylation and contributes two SNARE motifs (Q_b and Q_c) to the assembly. Here, we have investigated whether the integrity and length of the linker between Q_b and Q_c as well as the position of the palmitoylation site are of mechanistic relevance for exocytosis. Thus, we expressed linker mutants in SNAP-25-/- chromaffin cells and characterized secretion by membrane capacitance measurements and amperometry. Co-expression of separated Q_b and Q_c motifs or expression of a mutant whose linker was substituted by a flexible G/S-containing peptide failed to rescue secretion, stressing the functional importance of the linker. While insertion of up to 28 residues near the linker middle did not affect secretion, insertion of G/S-peptides between Q_b and palmitoylation site slowed down triggering and altered fusion pore behavior. This linker extension also further decelerated secretion of palmitoylation mutants, suggesting a stabilizing effect of the normal linker on C-terminal SNARE assembly and membrane interaction. In summary, we show here that the SNAP-25 linker is a positive regulator of SNARE complex formation and membrane fusion.

C.15 Spindle positioning in budding yeast

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Chromosome segregation during cell division depends on a series of highly orchestrated interdependent interactions. Using an agent based approach we built a robust minimal computational model to capture mitotic events in budding yeasts of two major phyla: Ascomycota and Basidiomycota. This model convincingly reproduces experimental observations related to spindle alignment and nuclear migration during cell division in these yeasts. The model converges to the conclu sion that biased nucleation of cytoplasmic microtubules is essential for directional nuclear migration. Two distinct pathways, based on the population of cytoplasmic microtubules and cortical dyneins, differentiate nuclear migration and spindle orientation in these two phyla. In addition, the model accurately predicts the contribution of specific classes of microtubules in chromosome segregation. Thus we present a model that offers a wider applicability to simulate the effects of perturbation of an event on the concerted process of the mitotic cell division [1].

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C.16 Active resistance of living cells against extra-cellular matrix deformation

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In vivo, living cells are continually deformed by their surroundings. We have developed a method to measure the mechanical response of isolated cells to extra-cellular matrix deformation. We measure the change of traction forces within seconds of deformation. This approach enables us to simultaneously probe cells' passive elastic and active contractile responses. Interestingly, we find that the cells' resistance to deformation is dominated by their contractility, not their elasticity.

C.17 Direct observations of transition dynamics from macro- to micro-phase separation in asymmetric lipid bilayers induced by externally added glycolipids

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We present the first direct observations of morphological transitions from macro- to micro-phase separation using micrometer-sized asymmetric lipid vesicles exposed to externally added glycolipids (GM1:monosialotetrahexosylganglioside). The transition occurs via an intermediate stripe morphology state. During the transition, monodisperse micro domains emerge through repeated scission events of the stripe domains. Moreover, we numerically confirmed such transitions using a time-dependent Ginzburg-Landau model, which describes both the intramembrane phase separation and the bending elastic membrane. Our findings could provide important mechanistic clues for understanding the dynamics of the heterogeneities exiting in cell membranes.

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Poster Abstracts

P.1 Molecular mechanisms of redox regulation of Orai1 channels

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Oxidants interacting with reactive cysteine residues can result in altered protein function. Store-operated calcium entry (SOCE) mediated by STIM1 gated Orai1 channels is the major Ca^{2+} entry pathway to activate immune cells and both loss-of-function and gain-of-function mutations lead to immune dysfunction and other pathologies. We have previously shown that pretreatment of the Ca^{2+} selective Orai1 but not its paralogue Orai3 with the oxidant H_2O_2 leads to reduced I_{CRAC} and that C195 is its major ROS sensor [1]. However, the underlying mechanism of inhibition remained elusive. The current work combines patch-clamp analysis, fluorescence microscopy and mutational approaches based on structural information and molecular dynamics simulations with a theoretical reaction diffusion model to explore the molecular mechanisms underlying inhibition of I_{CRAC} by ROS. We show that oxidized Orai1 C195 at the exit of transmembrane domain 3 leads to reduced subunit interaction, slowed diffusion and that either oxidized C195 or its oxidomimetic mutation C195D hinders channel activation by intramolecular interaction with S239 of TM4. Our results reveal the mechanism underlying ROS inhibition of Orai1 and identify a candidate residue for pharmaceutical intervention.

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P.2 Aspirin Inhibits the Formation of Rafts in Fluid Lipid Membranes

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Low doses of Aspirin have become a common treatment for patients with high levels of cholesterol. Cholesterol is a stiff molecule which incorporates into the lipid membrane and orders lipid tails, and plays a leading role in the formation of laterally ordered structures (so called lipid rafts), and also produces crystalline cholesterol plaques at high concentrations [1,2]. From X-ray and neutron diffraction imaging, I present first direct experiment evidence for a non-specific interaction between aspirin and cholesterol in lipid membranes. Using in in-vitro experiments in synthetic lipid membranes, we find that aspirin incorporates into the lipid membrane, increases fluidity, and eliminates membrane domains caused by cholesterol [3-5]. The results present a molecular model and a mode of action for aspirin therapies in patients with high levels of cholesterol. We also find evidence for this effect in oriented red blood cell ghost membranes.

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P.3 Dynamics of mictortubule and microtububle organizing center

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We examined models of microtubule dynamics, which were introduced to explain length regulation of microtubules via kinesin motors [1,2]. In statistical physics, these are variants of the one dimensional exclusion process, where the system length varies [3]. We first investigated a very simplified situation [2], taking into account the following events; polymerization and depolymerization at the plus end of a single microtubule, input of motor proteins at the minus end, and „walks“ of motor proteins with mutual exclusion. We performed a mathematically rigorous analysis, as well as hydrodynamic approach [4]. We showed an exact phase diagram: the parameter space is divided into two phases corresponding to converging and diverging microtubules. Furthermore, we determined sub-phases in the divergent phase, according to the shapes of the density profile of motor proteins, by means of hydrodynamic approach and Monte Carlo simulations. Finally we would like to present a generalized process, by imposing detachment and attachment of molecular motors in the bulk of the microtubule, and the limitation of the system length. We shall discuss on the dynamics of the position of the microtububle organizing center.

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P.4 A technique to distinguish two modes of immune cell killing on single cell level

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Death of cells in the body is involved in many diseases or injuries, but also occurs during development under physiological conditions. The killer cells of the immune system like cytotoxic T lymphocytes (CTL) or natural killer (NK) cells can eliminate malignant cancer cells or virus-infected cells by inducing cell death in their targets. Cell death can occur as a highly organized process during apoptosis or by plasma membrane disruption during necrosis. We have generated cell lines expressing a genetically-encoded FRET-sensor to quantify both necrosis and apoptosis in single living target cells by time-lapse fluorescent microscopy. We have observed that NK cells induce both types of cell death in a clonal population of target cells. Interestingly, individual NK cells can switch from necrosis to apoptosis during serial target cell killing. We postulate that the relative contribution of apoptosis and necrosis is important in regulating the immune response towards cancer and infection. We have also established a high-content protocol for this assay on an automated microscope and an analysis in a three-dimensional collagen matrix using light sheet fluorescence microscopy. This will enable us to use the assay for screening purposes and under conditions as physiological as possible.

P.5 A model for myosin anchored actin protrusions

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Filopodia are usually described as being driven by the lamellipodium, arising through ‚convergent elongation', which states that several filaments converge near the membrane to form a Λ-precursor elongating into a fully-sized protrusion [1]. Still there is also evidence that linear actin filaments, that build the core of filopodia can also be nucleated de novo by Formin and that the formation of lamellipodia and

filopodia are functionally separable as cells can show protrusions with no apparent sign of a lamellipodium [2].
In order to form a protrusion, filaments need to overcome the force of the membrane pushing them back. To do so there must be a physical connection to the cell's cytoskeleton. Based on studies that show that actin protrusions can be affected by Blebbistatin, a myosin II inhibitor, we introduce a model that proposes this connection to be mediated by non-muscle myosin II. We investigate, whether the processive nature of this molecular motor can account for the statistical properties of protrusions we found in HMEC-1 cells.

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P.6 Mechanical properties and adhesion of flagellated eukaryotic cells

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We study the mechanical behavior of Volvox globator, a green algae colony composed of several hundreds of single flagellated cells, forming a cellular monolayer at the surface of the spherical object. The mechanical properties are characterized in vivo by means of micropipette force sensors, a novel technique that is capable of quantifying forces down to the pN level for microscopic objects and that allows for quantitative force-shape correlations, e.g. in adhesion, friction and deformation scenarios. We show that a Kelvin-Voigt model, comprising an elastic and a viscous component, is in excellent agreement with the mechanical response of the cell colony. The viscous component is found to be rate-dependent, giving rise to a shear-thinning, non-New tonian behavior. In the second part, we report on in vivo adhesion experiments on the single cell level in order to characterize the interactions of *Chlamydomonas reinhardtii* and its flagella with interfaces. For this organism, flagella

play a crucial role since they are the source of locomotion and may come into direct contact with interfaces. In micropipette deflection experiments, we observe that only the flagella and not the cell body may adhere to surfaces and provide precise adhesion force measurements of eukaryotic flagella to different model substrates.

P.7 Cargo binding promotes KDEL receptor clustering at the mammalian cell surface

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Transmembrane receptor clustering is a ubiquitous phenomenon in pro- and eukaryotic cells to physically sense receptor/ligand interactions and subsequently translate an exogenous signal into a cellular response. Despite that receptor cluster formation has been described for a wide variety of receptors, ranging from chemotactic receptors in bacteria to growth factor and neurotransmitter receptors in mammalian cells, a mechanistic understanding of the underlying molecular process is still puzzling. In an attempt to fill this gap we follow a combined experimental and theoretical approach by dissecting and modulating cargo binding, internalization and cellular response mediated by KDEL receptors (KDELRs) at the mammalian cell surface after interaction with a model cargo/ligand. Using a fluorescent variant of ricin toxin A chain as KDELR-ligand (eGFP-RTAH/KDEL), we demonstrate that cargo binding induces dose-dependent receptor cluster formation at and subsequent internalization from the membrane which is associated and counteracted by anterograde and microtubule-assisted receptor transport to preferred docking sites at the plasma membrane. By means of analytical arguments and extensive numerical simulations we show that cargo-synchronized receptor transport from and to the membrane is causative for KDELR/cargo cluster formation at the mammalian cell surface [1].

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P.8 The extracellular adherence protein (Eap) of *Staphylococcus aureus* exhibits DNase activity

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Staphyloccocus aureus is equipped with a number of virulence factors allowing it to modulate or circumvent the immune responses of the host. One of these factors is the extracellular adherence protein Eap. We and others have previously shown that Eap interferes with the host innate immune system by reducing NFκB activation in leukocytes, decreasing neutrophil extravasation, and blocking neutrophil serine protease activity. Here we report that Eap also provides exonuclease activity: Incubation of double-stranded DNA with Eap led to a rapid degradation of linearized DNA fragments. Atomic force microscopy confirmed that Eap binds to and degrades linearized DNA in a time-dependent manner, while circular DNA did not interact with Eap and remained undegraded. Eap binding preferentially occurred to the termini of the double-stranded polynucleotide chains of DNA and was not affected by the type of overhang. In a dose-dependent manner, Eap also inhibited/prevented formation of bacteria-killing "neutrophil extracellular traps" (NETs), which represent the entire chromatin content of neutrophils that becomes ejected by incubation of cells with various agonists. These data indicate that Eap, via its DNase-associated activity, appears to express another immune-evading function by degrading NETs and thereby destroying an effective anti-microbial mechanism of the host.

P.9 Functional analysis of KDEL receptors at the mammalian cell surface

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Besides having a central function in the retrieval of soluble ER-resident proteins, KDEL receptors (KDELRs) also play important roles in cell signalling and in maintaining Golgi homeostasis [1]. We and others have recently shown that a fraction of KDELRs is also present in the plasma membrane (PM) and capable to bind KDEL cargo such as neuroprotective MANF (mesencephalic astrocyte-derived neurotrophic factor) and KDEL-bearing A/B toxins [2-4]. Under conditions of thapsigargin-induced ER stress, MANF is secreted and KDELR copy number in the PM is increased, pointing towards a cargo-dependent response in subcellular KDELR distribution. In support of a KDELR function at the cell surface, KDELRs were shown to contain endocytotic motifs which are likely involved in the endocytic removal and receptor down-regulation from the plasma membrane. To analyze cell surface function of KDELRs in more detail, we here focus on KDELR signalling, especially in response to cell surface binding of MANF. In an combined approach of RNAseq and proteomic analyses it should be possible to identify MANF-dependent changes in nuclear gene expression. To proof KDELR-dependency of these changes, a CRISPR/Cas9-mediated KDELR1 knock-out in neuroblastoma cells will be performed. Results from these experiments should enable us to propose a model for KDELR signalling from the mammalian cell surface.

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P.10 Self margination in sickle cell anemia blood flow

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The origin of sickle cell disease (SCD) lies in a recessive point mutation in the gene that encodes for the hemoglobin molecule of its carrier called HbS. Although HbS affinity for oxygen is not much different from its healthy homologe HbA, when it releases its oxygen, the HbS polymerizes into long rope like fibers that give to the cells it chacarteristic sickled shape. This shape was believed in the sixties to be responsible of the characteristic vaso-occlusion phenomena known for sickle cell disease since the more rigid cells will have difficulty to pass in the microcirculation like normal red blood cells do.

However, in the last three decades, SCD pathobiology has been proven to be more complex to explain general vaso-occlusion than the logical and recently, simulations are shown that the rigid, crescent-shaped red blood cells that are the hallmark of sickle cell disease don't cause the red cell blockages on their own [1].

Then, SCD is still a perplexing disease and almost no consequent cellular scale approaches of the study of capillary obstruction dynamics have been proposed in microflow, although the problem of obstruction is in essence a circulatory one.

Knowing that stiffer cells like white blood cells [2] or plaquelets migrate toward the vessel walls in blood flow through a process called margination, that depends mainly on local hematocrit, flow rate, red blood cell aggregation, deformability of different cell components [3], in this research we investigate experimentally the collective behavior of oxygenated arteriol-like sickle red blood cells and their margination process on flow through cylindrical channels with inner diameters comparable in size to a human arteriol. The cells are labelling accordingly to their density, that is associated to their rigidity and flash under different flow conditions on pressure and solutions, including solutions inducing and non-inducing red blood cell aggregation.

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P.11 Mechanobiological induction of long-range contractility by diffusing biomolecules and size scaling in cell assemblies

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Mechanobiological studies of cell assemblies have generally focused on cells that are, in principle, identical. Here we predict theoretically the effect on cells in culture of locally introduced biochemical signals that diffuse and locally induce cytoskeletal contractility which is initially small. In steady-state, both the concentration profile of the signaling molecule as well as the contractility profile of the cell assembly are inhomogeneous, with a characteristic length that can be of the order of the system size. The long-range nature of this state originates in the elastic interactions of contractile cells (similar to long-range ``macroscopic modes'' in non-living elastic inclusions) and the non-linear diffusion of the signaling molecules, here termed mechanogens. We suggest model experiments on cell assemblies on substrates that can test the theory as a prelude to its applicability in embryo development where spatial gradients of morphogens initiate cellular development.

P.12 Studying extremely large lipid membrane curvatures

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We present molecular simulation setup to study membrane curvature induced by artificial ridges. We use the coarse grain Martini force field to simulate pure DOPC and ternary mixtures lipid bilayers deposited on a solid support. For a flat scaffold, we investigate the effect of the support on basic membrane properties such as lateral diffusion and tail order parameters as a function of support properties. For the ternary mixture we additionally the effect on the degree of lateral phase separation. We find that already when the scaffold and bilayer are separated by a small water layer (>0.2 nm), the bilayer properties are unaffected. Next, we introduce a solid

support with blockshaped ridges, which induce strong curvature in the lipid membrane. The effect of curvature on the bilayer properties is investigated. A dependence of the lipid order parameters on local curvature is found, as well as an overal amplifying effect on lateral phase separation.

P.13 Studying growth factor receptor proteins in whole cells in liquid using scanning transmission electron microscopy

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Correlative Liquid scanning transmission electron microscopy (STEM) and fluorescence microscopy were used to study the epidermal growth factor receptor HER2 [1] within the intact plasma membrane of whole SKBR3 breast cancer cells in their native liquid environment. The obtained spatial resolution of 3 nm was sufficient to resolve the constituents of individual protein complexes. Contrast was obtained on specific protein labels consisting of fluorescent nanoparticles, so-called quantum dots (QDs) [2]. On account of the atomic number (Z) contrast of the annular dark field detector of STEM, these nanoparticles of high-Z material were detected within the background signal produced by the low-Z material of the cell and surrounding liquid. The particular distribution of monomers, and homodimers (a protein complex consisting of a pair of HER2 proteins) of these receptors is of relevance for understanding cell growth triggering in cancer cells. Data was obtained from several tens of intact cells thus achieving statistics of thousands of protein positions with nanometer resolution. The signaling-active dimerized form of HER2 dimerization was localized in certain functional membrane regions exhibiting membrane ruffles. Larger-order clusters were also present. Membrane areas with homogeneous membrane topography, on the contrary, displayed HER2 in random distribution.

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P.14 v-SNARE-based protein-lipid interactions catalyze membrane fusion

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Cellular communication requires Ca^{2+}-triggered fusion of vesicles with the plasma membrane, enabling release of neurotransmitters. The fusion process involves a number of energetically complex steps that require both, protein-protein as well as protein-lipid interactions. Here we investigated the interplay between synaptobrevin2 (syb2) and phospholipids that seems crucial for Ca^{2+}-triggered neurotransmitter release. Using a combination of photolytic 'uncaging' of intracellular Ca^{2+} with membrane capacitance measurement in chromaffin cells, we found that reduced flexibility of the syb2 transmembrane domain (TMD) severely impairs exocytosis, whereas mutants which show enhanced TMD flexibility can fully rescue secretion. Analysis of single amperometric spikes revealed that reduced flexibility of the syb2-TMD slows the kinetics of neurotransmitter discharge from single vesicle and reduces the fusion pore dynamics. In contrast, mutants with higher TMD flexibility accelerate fusion pore expansion beyond the rate found for the wildtype protein. Thus, our results demonstrate that SNARE TMDs play an active role in the fusion process that goes beyond simple anchoring of the protein. Specifically, we show that flexibility of TMD determines the magnitude of Ca^{2+} triggered exocytosis and kinetics of cargo discharge from single vesicles.

P.15 Stochastic Dynamics of Dorsal Actin Waves on Fibroblasts

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Albeit waves of polymerizing actin are a fundamental element of the motility

apparatus of cells, the machinery of Dorsal Actin Waves (DAWs) [1] is poorly understood. In search of the mechanisms organizing DAWs we analyze experimental data of the dynamics of DAWs under well-defined experimental conditions. We find that DAWs show all characteristic features of waves in active media, e.g. oscillatory states, collision annihilation, and spirals. DAWs can be constrained to propagate along a quasi one-dimensional path with periodic boundary conditions via micro-contact printing. Under these conditions DAWs form pronounced and extremely regular, but stochastic spatio-temporal patterns. We use microfluidics to control the biochemical state of cells, which permits us to reversibly switch between different states of actin depolymerization using Latrunculin A. The periods between successive wave events and the propagation velocities of DAWs serve as readouts DAW dynamics in the parameter space of actin depolymerization rate and free actin monomers. We find that the propagation velocity of DAWs can be reduced by a factor of two by increasing depolymerization rates of actin, whereas the periods between successive wave events double. This clearly shows that the wave machinery of DAWs is regulated close to actin itself and not controlled by RhoGTPases.

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P.16 Hydra axis formation: The first steps towards spontaneous, collective symmetry breaking - nearest-neighbour communication and the importance of fluctuations

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Symmetry breaking in early embryonic development and in the early evolution of multicellular organisms is based on the polarization of cells and tissue. The underlying biological mechanisms are not yet understood. Prior work from our group presented a nearest-neighbour interaction based model that explains, based on a simple idea, experimentally observed temperature dependent axis orientation as

well as ks1 mRNA expression fluctuations [1]. Here we show the importance of shape fluctuations and mechanotransduction in the early stages of symmetry breaking. We observe self organized polarization in regenerating hydra spheroids. This process is driven by biomechanical oscillations and mediated by the microtubule cytoskeleton.

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P.17 Cell motility generated by actin polymerization waves

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A cell‘s ability to move is one of its greatest merits. It enables the cell to efficiently search for nutrients and drives complex processes in tissues. Cell motility is often driven by the actin cytoskeleton. Although many important factors involved in actin-driven cell crawling have been identified and characterized in amazing detail, it is still poorly understood how the actin filament network is organized in this process. Spontaneous actin waves have been observed in a large number of different cell types. They present an attractive concept to understand actin-network organization during crawling. We introduce a mean-field description for actin assembly by nuclea ting promoting factors, negative feedback of actin filaments on the nucleators‘ activity, and active stress generation by molecular motors. The system can spontaneously generate traveling waves. We study confinement of this system to a cellular domain by means of a phase field and calculate the corresponding phase diagram. In particular, we find erratic motion due to the formation of spiral waves.

P.18 Autonomous and evoked Ca^{2+} activity of inner hair cells during the critical period of cochlear development

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Mammalian Inner hair cells (IHCs) transduce sound into receptor potentials and transmitter release. Together with supporting cells they form the organ of Corti. In the critical period of cochlear development, IHCs generate Ca^{2+} action potentials (AP) whereas ISCs produce Ca^{2+} waves. These Ca^{2+} signals are thought to drive intricate morphological and physiological changes. We performed Ca^{2+} imaging using acute mouse organs of Corti and the indicator Fluo-8 AM. IHCs showed two types of responses: They either autonomously generated fast Ca^{2+} transients, which depended on external Ca^{2+} and the expression of Cav1.3 channels and most likely reflect Ca^{2+} APs of IHCs. The more frequent type of IHC Ca^{2+} signals, however, consisted of slower and longer lasting burst-like Ca^{2+} elevations in neighbouring IHCs, which were triggered by Ca^{2+} waves in adjacent ICSs. The purinergic receptor antagonist PPADs blocked both ISC Ca^{2+} waves and the burst-like behavior of IHCs plus their synchronized activity, but not the fast IHC Ca^{2+} transients. Taken together, we show that IHCs Ca^{2+} signals are either triggered by Ca^{2+} waves of adjacent ICSs or are generated autonomously. Activation of immature adjacent IHCs by ISC Ca^{2+} waves may help to build up tonotopic organization in auditory circuits before the advent of sensory information.

P.19 Probabilistic analysis of apoptosis and necrosis in cancer cells induced by natural killer cells

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Cytotoxic T lymphocytes and natural killer (NK) cells are the main cytotoxic killer cells of the human body to eliminate pathogen-infected or tumorigenic cells. They can kill target cells via the release of cytolytic molecules, which leads to necrosis or apoptosis or induce apoptosis via binding to Fas receptors. Experimentally Backes et al. (unpublished) have observed, that the killing mechanism employed by a single NK cell varies in time and the sequence of the killing mechanisms varies among different cells of a population. Whether these variations indicate the existence of different NK cell phenotypes, or whether it is a purely probabilistic phenomenon is unknown. We rely on experimental data for these time sequences to model the observed sample of killing sequences as realizations of one or more independent stochastic processes. Each process represents different NK cell phenotype with different killing characteristics. In addition, we analyze how parameter variation of the model can optimize the killing efficiency of the killer cell population and discuss potential applications to enhance immune reactions.

P.20 The cell as a liquid motor: intrinsic mechanosensitivity emerges from collective dynamics of actomyosin cortex

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Living cells respond actively to the mechanical properties of their environment. In addition to biochemical mechanotransduction, evidence exists for a purely

mechanical sensitivity to the stiffness of the surroundings at the cell-scale. Using a minimal model that describes the collective behaviour of actin, actin crosslinkers and myosin, we show that the mechanosensitive response of cells spreading between distant elastic microplates is entirely and quantitatively predicted by the behaviour of the actomyosin cortex as a contractile viscoelastic fluid [1]. Indeed, our modelling of actomyosin shows that it is a liquid that exhibits emergent elastic-like properties when in series with a spring. The maintenance of a given shape for such an emergent material results from a balance between actin polymerisation and a cell-scale contractility-driven retrograde flow. The energetic cost of these antagonistic phenomena yields a power curve of cell action against a load similar to Hill's law for muscles: in particular, an internal friction sets the maximum speed of contraction of both cells and muscles, when myosins do not have time to detach after pulling, just as rowers lifting their oar too slowly after their stroke. Conversely the maximum force corresponds to the force at which myosin motor energy is entirely dissipated by their relaxation when crosslinkers eventually unbind from actin.

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P.21 Proteins sense different grain orientations in hydroxyapatite during adsorption

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Protein adsorption is the first step of biofilm formation and can therefore be highly desirable or unwanted. Characterizing protein adsorption on different types of very controlled substrates enables us to gain insight into the governing forces. In this new study, we used hydroxyapatite (HAP) pellets as a model system for tooth enamel. The pellets reach a density of > 97 % of the theoretical crystallographic density of HAP and have been produced by compacting and sintering commercially available HAP powder. They consist of micron-sized crystalline grains of different orientation. Atomic force microscopy (AFM) combined with electron backscatter diffraction

(EBSD) measurements reveal the smoothness and the crystal orientation of the HAP grains on the surface of the pellets. On these surfaces, single molecule BSA adsorption experiments are performed in a microfluidic setup revealing that different grain orientations provoke different adsorption rates. These findings open a pathway to control protein adsorption.

P.22 Interaction between Apatite Nanoparticles and a Phospholipid Bilayer

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Apatite nanoparticles are showing good results for the cryopreservation of red blood cells. In this work, we use a microfluidic technique to explore the interaction between these nanoparticles and a model cell membrane. These results may give a better understanding of the adsorption properties, and possible internalization mechanisms, of these nanoparticles with red blood cells
(in preparation)

P.23 Self-propelled janus droplets for gene extraction and controlled cargo delivery

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We report the existence of a new type of self-propelled Janus droplets, that are obtained from the spontaneous phase separation between two fully miscible fluids (water/solvent) in the presence of surfactants which are preferentially soluble in the solvent phase. At start, the related self-propulsion mechanism is generated by a

Marangoni flow mediated by the solvent dissolution into the oily phase. During this motion, the droplets are absorbing a large amount of surfactant. This dynamic surfactant adsorption leads to spontaneous water/solvent demixing and the formation of Janus droplet. We characterize the hydrodynamics properties of these microwimmers during their different stages of evolution. Interestingly, the squirmer properties evolve in time from a weak pusher to a neutral squirmer and potentially to a dimer of neutral squirmers. Finally, we used this active system as a smart carrier to extract genes in situ and delivering them at a target location. (Submitted)

P.24 New Strategy to Study a Single SNARE Mediated Membrane Fusion Event

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We present an approach to explore the properties of a single SNARE mediated membrane fusion event in a microfluidic chip. In a first step, a single free standing lipid membrane is generated at a defined position with the Droplet Interface Bilayer technique (DiB). In a second step, we inject a solution of divalent cations (Calcium, Ca2+) and small unilamellar vesicles functionalized with T-SNARE proteins (T-SUVs) around the planar membrane using a volume controlled flow. The presence of calcium mediates the direct fusion of the vesicles with the planar membrane, which is incorporating the proteins into the membrane. In a third step, we remove the calcium and the T-SUVs with a buffer solution. After this washing step, a solution of small unilamellar vesicles functionalized with V-SNARE proteins (V-SUVs) is injected around the planar membrane. And finally, we study single fusion event with good optical and electrical access.
(in preparation)

P.25 Passive Translocation of Hydrophobic Nanoparticles through a Phospholipid Bilayer

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Hydrophobic nanoparticles introduced into living systems may lead to increased toxicity, can activate immune cells or can be used as nano-carriers for drug and gene delivery. The interaction of nanoparticles with bilayers is essential of an in depth understanding of these processes. It is known that small hydrophobic nanoparticles can insert into a lipid bilayer and accumulate in the bilayer core, representing a potential well. Therefore it is generally accepted that escaping the bilayer is unlikely for these nanoparticles. In contrast to this assumption, we demonstrate theoretically how large hydrophobic nanoparticles can cross lipid bilayers with almost no energy barrier, while small hydrophobic nanoparticles stay trapped in the core of the bilayer. This size-dependent translocation was confirmed experimentally using a microfluidic device. Moreover, the kinetic pathway of a single passive translocation event was directly measured and analyzed.

P.26 How tumor vessel network morphology determines oxygen concentration

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Oxygenation of tissue depends strongly on the spatial arrangement of blood vessels. During tumor growth the hierarchically organized arterio-venous blood vessel network of the host tissue is transformed into a chaotic heterogeneously distributed tumor vasculature. To investigate this direction we consider algorithmically constructed blood vessel networks and analyze the resulting intravascular oxygen concentration distribution. The fact that oxygen has a very small diffusion range, results in a strong dependence of the oxygen distribution on the location of the vessels. Combined with a low vascular density in tumors, this leads to severe hypoxia which plays an important role in cancer invasion and impedes treatment. Our method computes intra-vascular transport, and extravascular diffusion of oxygen self consistently, where vessels are sources and drains of oxygen. Tumor cells are represented by a continuum approach. We were able to handle system sizes of 8 mm diameter where typical features of tumor vascular morphology manifest themselves. We correlate physiological and topological variations with local oxygen availability and quantitatively reproduce IR mammography data showing the oxygen content of breast carcinomas in vivo. [1]

[1] PLOS Comp. Biol (submitted)

P.27 Repolarization of cells

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The presented project will be my master project carried out in the AG Lautenschläger (A8) and AG Kruse (A1). Cell polarization is important in many physiological fields, e.g. migration. I want to investigate how the cell changes its polarization, if it can only migrate on one axis (forwards or backwards). I aim to understand the question how the front of a migrating cell becomes the rear of this cell in a short time and lack of space.
For this purpose short one dimensional microfluidic channels or PDMS patterns (see attached figure) will be fabricated in order to confine cell migration. The direction of the migration can be controlled by chemoattractants (e.g. chemokines) which are applied at the two ends of the channels and can be changed arbitrarily. I will quantify the frequency of directional change and will further investigate cytoskeletal dynamics during this repolarization. The results will be compared to the two-dimensional migration case where the cell has enough space to turn. Mathematical modelling will be done in order to quantify and understand this repolarization behavior.

P.28 Binding of Transcription Factors to Non-Regulatory DNA:The Gaussian Genome

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Recent studies in biophysics suggest transcription factor interactions with non-regulatory DNA are sequence-dependent and vary along the DNA strand [1]. This makes numerical calculation of the grand canonical partition function [2] cumbersome and renders predictions of genetic activity a seemingly insurmountable task. Using the cumulant-generating function of the normal distribution, we derive the partition function and define an effective energy, a single quantity which accounts for the contributions from the whole spectrum of binding energies. Applying our approach to the *lac* repressor and RNAP, two prominent *lac* operon transcription proteins, we obtain theoretical results which are in good accord with the actual biophysical picture.

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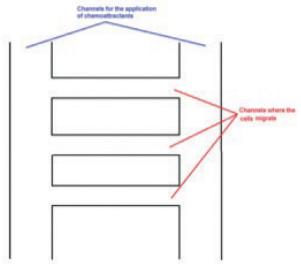

P.29 Dynamics of autocatalytic reaction networks and the origin of life

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An important and open question in understanding the origin of life relates to the origin of self-assembling and self-sustaining organized structures. One of the puzzles is the origin of long molecules such as proteins and RNA molecules starting from much smaller precursors that were abundant on the prebiotic earth, and their buildup in sufficient concentrations to seed life. We use a mathematical model based on an artificial but prebiotically plausible chemistry to investigate how certain specific chemical species can be selected out of a large set of possible combinations. We start by considering a set of small molecules that represent simple molecular species that might have been abundantly present around a hydrothermal vent. We then construct a network of chemical reactions amongst these molecules and their reaction products. The chemical dynamics of the molecular populations is simulated as a set of coupled ordinary differential equations. We find that under certain circumstances, autocatalytic sets (ACSs) come to dominate the chemistry in that the concentrations of the molecules belonging to an ACS are much higher than the background. We describe a cascading mechanism by which large and improbable molecules are formed relatively easily in our system, thereby making more plausible the appearance of macromolecules like proteins, RNAs, etc., in pre-biotic settings.

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P.30 A mechanism of biological pattern formation through mechanochemical feedback

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The interplay between biochemistry and cell mechanics is critical for a broad range of morphogenetic changes. A key example is the early embryonic development of the *Caenorhabditis elegans* zygote, where flows of the actomyosin cortex occur simultaneously with the establishment of a polarity pattern in partitioning defective (PAR) proteins. However, how the PAR system interacts with and regulates cortical flow has remained elusive. Here, we identify a novel mechanochemical pattern-generating mechanism, which drives the patterning of the PAR polarity proteins.
Using calibrated, quantitative fluorescence microscopy, we first measured the spatiotemporal evolution of the membrane-associated protein concentration of the posterior PAR-2, the anterior PAR-6 and myosin II as the mechanical force generator, as well as the cortical flow field. Next we show that these dynamics can be quantitatively recapitulated, using a reaction-diffusion-advection theory for the concentration fields (myosin II, PAR-2 PAR-6) in combination with an active-fluids theory for the cortical flow field. Remarkably, our physical theory can, for the first time, fully recapitulate the spatiotemporal evolution of all the measured concentration fields as well as the actomyosin flow field, duting the polarization process. We demonstrate that the function of this mechanochemical feedback is to amplify and stabilize cortical flows and thus to promote a rapid transition to the patterned state of the PAR system.

P.31 Controlling active gels with addressable soft interfaces

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Living cells feel and respond to the mechanical properties of their environment via the interaction with the constituents of the cellular cortex [1]. As a model system, here, we prepare an active gel from cytoskeletal extracts that we condense onto a soft interface. The addressable anisotropic shear viscosity of this interface allows us to reversibly control the structure and dynamics of the active layer underneath.

The studied active material consists on a network of bundled microtubules (MTs), which are crosslinked and driven by ATP-fueled kinesin motors [2]. In the presence of a soft interface, MTs assemble leading to the formation of a quasi-2d active nematic liquid crystal that features long-range orientational order, although it is constantly permeated by turbulent flows [2]. In our experiments [3], the active nematic is easily commanded by preparing it in contact with a thermotropic liquid crystal, which features Smectic-A (lamellar) phase. Under a uniform magnetic field, the Smectic exhibits an aligned texture at the interface with marked anisotropic viscosity. Under such rheological constraint, the active nematic is rapidly organized in parallel stripes of aligned MT bundles, revealing its intrinsic length- and time-scales, which have been predicted in recent theoretical works [4].
The demonstrated control strategy should be compatible with other viable active biomaterials at interfaces, and we envision its use to condition cell crawling or tissue growth.
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P.32 Spatially Inhomogeneous Search Strategies for Intracellular Transport: A Random Velocity Model

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Intracellular transport is vital for the proper functioning and survival of a cell. Cargo (proteins, vesicles, organelles, etc.) is transferred from its place of creation to its target locations via molecular motor assisted transport along cytoskeletal filaments. The transport efficiency is strongly affected by the spatial organization of the cytoskeleton, which constitutes an inhomogeneous, complex network. In cells with a centrosome microtubules grow radially from the central microtubule organizing center towards the cell periphery whereas actin filaments form a dense meshwork, the actin cortex, underneath the cell membrane with a broad range of orientations. The emerging ballistic motion along filaments is frequently

interrupted due to constricting intersection nodes or cycles of detachment and reattachment processes in the crowded cytoplasm. In order to investigate the efficiency of search strategies established by the cell's specific spatial organization of the cytoskeleton we formulate a random velocity model with intermittent arrest states. With extensive computer simulations we analyze the dependence of the mean first passage times for different search problems on the structural characteristics of the cytoskeleton, the motor properties and the fraction of time spent in each state of motility. We find that a cell can optimize the search of narrow membranous targets by convenient alterations of the spatial organization of the cytoskeleton. An inhomogeneous network with a thin actin cortex constitutes an efficient intracellular search strategy.

P.33 Free-standing protein membranes for lipid-free vesicle production: Formation and energetics, and application of hydrophobin bilayers

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P.34 2D Monte-Carlo Model of Lipid Bilayers

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The phenomenon of lipid rafts where different liquid phases are formed remains one of the major topics in biophysics of the last two decades. In model membranes the raft formation was explicitly shown *in-silico* with coarse-grained Molecular Dynamics (MD) simulation [1]. Nevertheless, for large systems the coarse-grained technique require significant computational power.

Here a 2D Monte-Carlo (MC) lattice model of a lipid bilayer is presented. The order parameter is defined as the main characteristic property of a lipid [2,3]. As an example, the functional form of conformational entropy is explicitly calculated for saturated DPPC and polyunsaturated DLiPC lipids based on the enthalpy term and order parameter distributions obtained from all-atom MD simulations. The proposed 2D MC model is based on a very small input data set which is taken, exclusively, from MD simulations, Although, the conformational entropy is determined only from data of pure MD systems, nevertheless, the model demonstrates extreme predictive power not only for similar pure MC systems at different temperatures and sizes but also for heterogeneous systems. The excellent agreement of phase and aggregation properties of binary MC systems with respective all-atom MD systems makes the proposed approach very promising in studying raft formation of large heterogeneous systems composed of different types of lipids and sterols.

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P.35 Methods for electron microscopy of cells in liquid

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Several different approaches exist to image cells in their native liquid environment using electron microscopy [1]. These methods have opened up a new experimental window for the study of cells avoiding extensive sample preparation of conventional electron microscopy techniques requiring plastic or frozen sections. Method 1: A microfluidic chamber is formed by two microchips with electron transparent windows protecting the sample from the vacuum in the electron microscope. The liquid compartment can be used in a conventional transmission electron microscope (TEM). Method 2: Environmental scanning electron microscopy (ESEM) can be used to study cells covered in a thin layer of liquid in a water vapor environment. Method 3: The wet sample is immobilized on an electron transparent support and covered by a thin membrane, e.g. grapheme, to maintain a thin layer of liquid around the sample. All methods can be used for correlative light- and electron microscopy. Of particular importance is the unique capability of these methods to study membrane proteins within the intact plasma membrane [2]. For this purpose, proteins are specifically labeled with nanoparticles providing contrast in the scanning TEM (STEM) detector.

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P.36 Red Blood Cell Ghosts for biomedical applications: Blood on a Chip

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The preparation of Red Blood Cell (RBC) Ghosts is a well-known protocol in biological and medical research [1]. It describes the extraction of the membrane from RBCs.

Another well-known protocol is the preparation of highly ordered stacks of artificial lipid bilayers on silicon wafers [2]. Such experiments in particular allow the study of the interaction between cell membranes and drugs, small molecules, and bacteria. There are various attempts to adapt this protocol to a native cell membrane [3,4]. For the first time we were able to combine both described protocols and to prepare highly ordered stacks of RBC membranes on silicon wafers. These systems can now be used as inexpensive and safe platforms for testing the effect of drugs and bacteria on RBC membranes in-vitro using biophysical techniques, such as X-ray and neutron diffraction, optical spectroscopy and AFM.
We present the preparation and characterization of "Blood on a Chip" from molecular structure to the morphology of the membrane assemblies. Figure 1 shows the electron desity and a reflectivity curve of a RBC membrane. Aspirin, which is commonly used in the "low-dose-aspirin therapy" was found to have a drastic effect on human blood membranes and to lead to a significant softening and fluidification of the membranes.

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P.37 Organization of Nucleotides in Different Environments: Implications for the Formation of First RNA under Prebiotic Conditions

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How nucleic acids first assembled and then incorporated into the earliest forms of cellular life 4 billion years ago remains a fundamental question of biology. There has been no obvious way for RNA-like molecules to be produced and then encapsulated in cellular compartments in the absence of enzymes and metabolism.
To support the hypothesis that environmental conditions in the neighbourhood of volcanic hydrothermal springs could act to organize monomeric nucleotides through various noncovalent interactions and chemical reactions in the prebiotic era, we investigated 5'-adenosine monophosphate (AMP) and 5'-uridine monophosphate (UMP) molecules captured in different matrices that have been proposed to promote polymerization, namely multi-lamellar phospholipid bilayers, nanoscopic films, ammonium chloride salt crystals and Montmorillonite clay [1]. Two nucleotides signals were observed in our X-ray diffraction experiments, one corresponding to a nearest neighbour distance of around 4.6 Å and a second, smaller distance of 3.45 Å. While the 3.45 Å distance agrees well with the distance between stacked base pairs in the RNA backbone, the 4.6 Å distance can be attributed to un-polymerized nucleotides that form a disordered, liquid-like structure. From the relative strength of the two contributions, the effectiveness of the different environment for producing pre-polymers was determined.

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P.38 Theory on active stress generation in a cytoskeletal network

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We are focusing on active mechanics of a cortical cytoskeleton. Mechanical properties of a cortical cytoskeleton govern not only cell's resistances to deformation but also the motor-induced contractility, which plays crucial roles in dynamic cellular behaviors, such as cytokinesis and cell migration.
In the presentation, I will explain our theoretical work on active stress generation in a cortical cytoskeletal network. I will propose a mechanical model of motor-induced

stress in an isotropic stiff F-actin network with crosslinkers and share our results on motor-induced contractility. In particular, since a cortical cytoskeleton in a living cell should be flowable, we consider the network in which there are few amount of crosslinkers and/or crosslinkers and F-actins can turn over. We found that a finite amount of crosslinkers is significant for motor-induced contractility [1]. We also investigated how turnovers of crosslinkers and F-actins influence the motor-induced stress [1]. The details will be presented on the day.

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P.39 Modeling of T-Cell polarization

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The repositioning of the microtubule organizing center is a part of many fundamental biological processes. It occurs in T-cell lymphocyte immediately after antigen presenting cell is recognized by T-cell. The Dynein's effort to walk to the minus end of the microtubule while being anchored at one place results in microtubule's sliding, and, hence in the repositioning of the microtubule organizing center. Our focus is on development of the model of microtubules and the microtubule organizing center and the calculation of experimental observables. Microtubule dynamics and bending shorter than persistence length plays important role in the process. Multiple mathematical models are used to mimic hydrodynamics of microtubules. Multiple algorithms for Brownian dynamics simulation of microtubules are presented. It is confirmed that algorithms yields predicted values for equilibrium properties. A model of the microtubule organizing center is presented. The entire structure of microtubule organizing center and microtubules is submitted to forces simulating actions of dynein.

P.40 Metabolism of diacylglycerol on the cell membrane enhances cell signaling

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The ubiquitous second messenger Diacylglycerol (DAG) plays critical roles in multiple physiological and pathophysiological processes, such as lipid signaling, cell death, cytoskeletal dynamics, intracellular membrane trafficking, and neurotransmitter release. Currently, research work often focusses on the production and function of DAG on the plasma membrane; however, the detailed mechanism of DAG production and signaling at subcellular membranes is rarely investigated thoroughly. Our previous work reported that novel Protein Kinase C (nPKC) could target the ER membrane and consequently modulate $Ca2^{+}$ mobilization [1]. Production of DAG on the ER membrane is probably responsible for such a targeting. To investigate this hypothesis, we applied confocal microscopy and genetically encoded sensors to monitor the metabolism of DAG in living cells. Interestingly we found that a PKC-C1-domain based DAG sensor accumulated on the ER membrane in naive HEK cells following activation of the cAMP-EPAC signal pathway. In contrast, following ATP stimulation we didn't observe any of DAG production at the plasma membrane. Although, P2Y-receptors activated by ATP triggered the Gαq-PLCβ signaling pathway as indicated by intracellular $Ca2^{+}$ release from the SR. Interestingly, following expression of a Gαq specific design receptor (DREADD) in HEK cells, the DAG sensor highlighted DAG production at the plasma membrane after activation of those receptors with their specific design drug (CNO). When expressing nPKCs we identified a similar translocation pattern for those PKC isoforms when compared to the DAG sensor. Furthermore, our experiment revealed that the lifetime of DAG on the plasma membrane appears to be much shorter than DAG on the ER membrane resulting in non-detectable DAG levels at the former membrane structure. These data strongly indicated that the dynamic metabolism of DAG on cellular membranes may contribute to differential targeting of C1 domain containing proteins and as such represents a novel mechanism of subcellular targeting of PKCs. These mechanisms thus substantially contribute to the cell´s signaling toolbox.

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P.41 Bidirectional motor-driven intracellular transport: Collective effects

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Transport of e.g. vesicles and cell organelles is cell is carried out by molecular motors. The cargo is transported bidirectionally along the cytoskeleton. Recently, the dynamics of individual cargo which is driven by teams of molecular motors has been analyzed in detail [1,2]. In this work our focus is on the collective dynamics in systems of many cargo-motor complexes.
The cargo-motor complexes are transported on a network of microtubules (MT) which is embedded in a cylinder. This choice of the system‘s geometry is based on the MT-network structure of axons. For this system we estimate the waiting time for bypassing processes of such cargoes for different cargo densities by using stochastic simulations. Based on the results of the three-dimensional stochastic transport model, we define and analyse a simplified lattice gas model for the different waiting time characteristics. Here, we find a phase transition between different regimes of the system‘s current and clustering behavior.

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P.42 Contraction dynamics of active actin networks

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Contractile actin structures play a vital role in a large variety of cell types, e.g. in determining their morphology or enabling cell propulsion. Here, we study the

dynamics in a well controlled *in vitro* system consisting of thin sheets of actin, contracting through the activity of embedded myosin motors. These experiments reveal characteristic contraction patterns for such networks. The contraction speed increases linearly at first, before it decays exponentially. For asymmetric initial x-y-aspect-ratios, the contraction dynamics follows this asymmetry. Using a continuous elastic model for the filaments combined with a dynamic equation to take motor activity into account, we are able to qualitatively reproduce the asymmetric contraction and the contraction speed curves, as well as density profiles of the actin gels.

P.43 Impact of the Fibronectin-binding protein cell surface density on adhesion of Livestock associated MRSA

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Livestock-associated methicillin-resistant Staphylococcus aureus (LA-MRSA) is able to overcome the species barrier between Livestock and humans. Especially in regions with a high density of pig farming LA-MRSA is increasingly found in clinical settings, causing severe infections in humans. In 2014, we had described the enhanced adhesive potential of the common LA-MRSA sublineage “spa Type t108”-to human epithelial and endothelial cells and plasma fibronectin, compared to other common LA-MRSA sublineages (spa Type t011 and t034)[1]. Here, this enhanced adhesive potential is confirmed by atomic force spectroscopy with fibronectin functionalized cantilevers on living bacterial cells of eight different LA-MRSA isolates. As the gene expression levels of the fibronectin-binding proteins FnbA and FnbB of spa type t108 isolates clearly exceeded those of spa Type t011 and t034 (factor 5-50), the different adhesive capacities are most probably attributed to a higher density of FnbA and B on the bacterial cell surface of LA-MRSA spa type t108 isolates.

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P.44 Instabilities in growing cultures of Dictyostelium discoideum

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Although, we now have good knowledge about the molecular inventory, the mechanisms involved in patterning biological systems are still not fully understood. In particular, the role of mechanics for pattern formation remains to be explored. Here, we consider the growth of *Dictyostelium discoideum* cultures. When placed on a solid medium, a drop of culture develops wavy structures at the boundaries when growing in size. We present here a setup to quantify the formation of this pattern. In our setup growth conditions for D. *discoideum* are optimised by controlling temperature and by preparing a homogenous carpet of bacteria the culture grows on. In this context, we present possible ways of reducing irregularities in bacterial growth. We observe the growing culture in bright field as well as in dark field. We present different examples of growing cultures to identify the optimal conditions for our setup to obtain reproducible results.

P.45 Local Pheromone Release from Dynamic Polarity Sites Underlies Cell-Cell Pairing during Yeast Mating

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Cell pairing is central for many processes, including immune defense, neuronal connection or sexual reproduction. How does a cell precisely orient towards a partner, especially when faced with multiple choices? During conditions of nitrogen starvation, the model eukaryote *S. pombe* (fission yeast) undergoes sexual sporulation. Because fission yeast are non-motile, contact between opposite mating types is accomplished by polarizing growth, via the Rho GTPase Cdc42, in each mating type towards the selected mate, a process known as shmooing. We used a combination of computational modeling and experiments to show that Cdc42- GTP polarization sites are also zones of pheromone secretion and signaling. Simulations of pair formation through a fluctuating Cdc42-GTP zone show that the combination of local pheromone release, short pheromone decay length, and local sensing leads to efficient pair formation. Experimentally we found that Cdc42-GTP polarization sites contain the M-factor transporter Mam1, the general secretion machinery, which underlies P-factor secretion, and Gpa1, suggesting that these are sub-cellular zones of pheromone secretion and signaling. Pairing efficiency is reduced in absence of the P-factor protease, as predicted by the simulations with longer pheromone decay lengths. Increasing zone pheromone sensitivity in simulations leads to reduction in pairing efficiency. This result matches experimental observations of cells lacking the predicted GTPase-activating protein for Ras, which exhibit stabilized zones at reduced pheromone levels.

P.46 *In situ* generated adhesive spaces trigger endothelial transition to a more mesenchymal phenotype

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Endothelial-to-mesenchymal transition (EndMT) defines the process of endothelial cells that transform into a mesenchymal phenotype. In humans this transition is involved in various physiological and pathological processes like fibrosis and cancer. Many factors can promote this transition. TGF-ß was found to stimulate EndMT during vein graft remodeling [1], cardiac cushin formation [2] or contribute to cardiac fibrosis [3]. Recent results evidence that adhesive cues from the ECM might also trigger the EndMT [4]. Here we describe a new material platform able to in situ trigger and follow EndMT from endothelial monolayers. Using surface layers containing a photo-activatable adhesive peptide, cell adhesive lines, as models for ECM fibers, are opened from confined epithelial monolayers. The appearance of the adhesive lines induces single cell migration events from the cohesive cell layer. With this tool we address the question of migration alone ECM fibers with variable dimensions induces phenotypical changes in the migrating endothelial cells.

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P.47 Redox Microscopy: A sensitive Method to quantify Production and Degradation of H_2O_2 from single human Monocytes

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Hydrogen peroxide (H_2O_2) oxidizes intracellular target molecules, thereby controlling cellular signaling. However, quantification and sensitivity to determine production

and degradation of H_2O_2 from single cells are limited. Using an electrochemical setup (redox microscope) and applying different voltammetric techniques, with a bare disk platinum ultramicroelectrode (10 µm; vs Ag/AgCl), very low [H_2O_2] could be resolved at plasma membrane production sites of single cells: 2 nmol/l (square wave voltammetry), 50 nmol/l (cyclic and linear scan voltammetry) and 500 nmol/l (chronoamperometry, CA). Although offering the lowest sensitivity for H_2O_2 CA measurements are unbeatable for long-term determinations with high temporal resolution (≥ 1 Hz). From single human monocytes, average H_2O_2 production was 1.5 nmol/l/s over 60 minutes following stimulation with the phorbolester TPA. During the initial phase (25 min) rate was 3.4 nmol/l/s (n=23). Considering quantitatively the concomitant H_2O_2 degradation by the same cell, net production rates reached 9.0 nmol/l/s. Single cell measurements were validated in human monocyte populations by electron spin resonance spectroscopy and an adapted fluorescence-based Amplex® UltraRed assay. In summary, physiologically relevant low nanomolar [H_2O_2] can be spatially and temporally resolved direct at the H_2O_2 production sites of single cells.

P.48 Biology of the thioredoxin TXNDC15

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Immune cell function critically depends on store-operated Ca2+-entry (SOCE). TheORAI and STIM dependent activation of immune cells can also lead to local production of intracellular reactive oxygen species (ROS), the physiological function of which is not well understood. A previous screen identified four potential SOCE regulators, all belonging to the family of thioredoxins.

Thioredoxins are oxidoreductases involved in a variety of cellular processes such as catalyzing the formation of disulfide bonds with the endoplasmic reticulum, protecting proteins from oxidative aggregation, helping cells cope with oxidative stress, regulating cell death, acting as growth factors,among others. For each of these functions, subsets of specialized thioredoxins are likely responsible. Common to all thioredoxins is a TRX-Fold with at least one redox active CXX[C/S]-motif. We focused

our work on one of the least studied members of human thioredoxin family, TXNDC15 (Thioredoxin-Domain-Containing-Protein 15). TXNDC15 is a predicted type 1 transmembrane protein with unknown subcellular localization and function. Many other members of the thioredoxin family are found in the ER, mitochondria, nucleus and cytosol. We set out to identify the subcellular localization and function of TXNDC15 on SOCE and to characterize its functional domains. The localization and the (mis) function of TXNDC15 is strongly affected by the type and location of the tag within the protein. A C-terminally tagged protein is retained within the ER and leads to a strong decrease in SOCE. However, placing the tag at a different location, this effect on SOCE is annihilated and localization is now mostly not within the ER but rather TXNDC15 now localizes to the Golgi apparatus, cell surface and lysosomes. Future experiments are aimed at understanding its physiological function and on identifying its interaction partners.

P.49 Brain tumor cellular architectures are predicted through phosphoprotein signaling measurements in two-cell system.

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Understanding of tumor architectures and the forces that drive their formation is of high importance in cancer research. To understand cell-to-cell spatial organization, we developed a methodology that combines single cell functional proteomics and theoretical analysis. We have found that signal transduction in two interacting glioblastoma (GBM) cancer cells depends on the cell-cell separation distance. Using thermodynamic-based analysis of protein concentrations as a function of cell-cell distance in two interacting cells we were able to identify the

cell-cell separation distance that corresponded to the steady state of the cell-cell protein signaling. That length scale was found to be the dominant cell separation distance in bulk tissue culture [1]. Thereby we predicted that aggressive GBM cells would exhibit a scattered distribution, whereas less aggressive GBM cells would closely pack, consistent with the experimental observations of others in vivo. Furthermore we recently demonstrated that proteins secreted by 2 communicating GBM cells generate a free energy gradient that induces a directed cell-cell motion towards the most stable cell-cell separation distance. Neutralizing the secreted proteins most involved in establishing the free energy gradient canceles the directed motion, such that cell pairs show a random Brownian motion, similar to the case of isolated single cells.

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P.50 A mechanism for contraction of cytokinetic actin rings

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In the late stages of cell division, animal cells are cleaved by contraction of the cytokinetic ring. The ring consists of actin filaments, molecular motors, and other proteins. How this ring generates an average net contractile stress is still poorly understood.

Here, we study a mechanism involving the formation of bipolar filaments by joining polar actin filaments of opposite orientation at their barbed ends. We develop a continuum mean-field model for the dynamics of actin filaments and motors. A linear stability analysis shows that the homogenous distribution becomes unstable beyond a critical motor strength. Numerical solutions of the full dynamic equations exhibit a backward-bifurcating non-homogenous state with clustered filaments at distinct positions along the ring.

For sufficiently stable bipolar filaments, the distribution is stationary and reminiscent of muscle sarcomeres. In this state, the total stress is higher than in the

homogenous state for the same parameters. If the bipolar filaments split fast enough into their polar constituting filaments, oscillatory states can be observed.
We discuss these findings in terms of recent experiments.

P.51 Intra-cellular microfluidics to probe the role of physical transport in morphogenesis

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Whereas modern genetics have provided great insights into the regulatory basis of embryogenesis, the role of physical transport in developing systems remains largely enigmatic due to the lack of suitable perturbation methods.
A particularly important morphogenetic event is cell polarization prior to asymmetric cell division. For the nematode worm C. elegans cell polarization was suggested to result from the interplay of PAR proteins and cortically induced flows.
However, it remains a challenge to show the causal role of flows at the onset of embryogenesis by direct flow perturbation experiments.
Towards this end, we exploit thermo-viscous pumping (Weinert & Braun, J. Appl. Phys. 2008) to control directed flows in living embryos without affecting their biological integrity. By perturbation of wild type-flow patterns, we are able to alter cell polarization dynamically and highly localized. To our knowledge our experiments represent the first non-invasive transport-only perturbation of developing organisms.

P.52 Dynamics of neutrophil extracellular trap (NET) formation

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Neutrophils are the most abundant type of immune cells in the human blood system and central for innate immunity. Recently, it was found that neutrophils and other cells are able to catch and kill pathogens by expelling a fibril network made from their own DNA (neutrophil extracellular traps, NETs). This process, termed NETosis, is distinct from other forms of cell death such as necrosis and apoptosis and is therefore of central importance for cell biology. During NETosis, a massive rearrangement of the materials inside the cell takes place. So far, the mechanisms that govern this complex process are poorly understood. Here, we show how cytoskeleton and membrane structure change the mechanical properties oft the cells, which finally leads to the release of NETs. We show that NETosis can be divided into three distinct phases. DNA passively diffuses out of the disassembled nucleus until it fills the complete cell lumen. Then cells rounds up while they still adhere to the substrate and finally the membrane is ruptured. In summary, these results demonstrate how NETs-release is temporarily regulated by mechanical properties of cell membranes and cytoskeleton.

P.53 Stochastic Model for Centrosome Relocation in T-Cells during Polarization

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During activation and killing T-cells establish a contact area, the immunological synapse (IS), with a target cell, towards which then their centrosome, the microtubule organizing center (MTOC), is relocated [1]. The main forces in that process appear to be both a growth based pushing force of the microtubules and a pulling force generated by motor proteins, such as Dynein, at the cell cortex. Those forces are calculated via a determinis-tic model for the distributions of the microtubules [2]. The centrosome‘s motion results from solving the time-evolution for the distributions of the microtubules taking into ac-count the off-centering behaviour of Dynein largely located at the synapse in T-cells. The investigation of the centrosome‘s positioning is extended to a stochastic model based on the microtubules‘ growth [3] and the capturing by Dynein. The study illustrates that, in comparison to ordinary cells, the centrosome‘s adjustment towards the center of the cell, is mainly altered by the asymmetric distribution of motors and nucleation sites.

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P.54 Self-consistent theory of transcriptional control in complex regulatory architectures

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In living cells, the proteins associated with gene regulation, the so-called transcription factors, are often shared between multiple pathways simultaneously. Genes therefore have to compete for transcription factors whose availability may fluctuate. Moreover, multiple copies of identical genes may exist in cells. We have developed a self-consistent model for gene regulation suitable for complex regulatory architectures and shared transcription-factors [1]. It will be shown that the competitive effects of the regulatory environment can be isolated into a single effective concentration, allowing the accurate description of a collection of gene expression data from diverse regulatory situations.

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P.55 Molecules and mechanics of cell adhesion studied by AFM force spectroscopy

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Cell adhesion is a complex process regulated by a number of surface proteins as well

as cytoskeleton structure. The former has been recognized to mainly contribute molecular force, while latter governs the mechanical properties (e.g. elasticity) involved in cell adhesion. The importance of characterizing cell surface molecular binding events altered by protein ligation as well as cell elasticity changed due to cytoskeletal re-organization in response to TGF-β1 treatment has recently been highlighted by the authors [1]. Atomic force microscopy force spectroscopy (AFM-FS) has been demonstrated to be a powerful tool for the quantitative study of both single cell elasticity and surface molecular binding [2]. In this study, we have applied AFM-FS to measure detachment energy, unbinding force between two adherent HK2 cells as well as the elasticity and viscoelasticity of the cells. In combination with single cell indentation test, the measured force-displacement curve of the separation process of the two cells reveal the change of adhesion characteristic contributed from both the surface molecular binding and cell elasticity/viscoelasticity. Moreover, a new model has been proposed to correlate the surface molecular adhesion with single cell mechanics, which may be useful for the fundamental understanding of disease progression and the development of new therapies [3].

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P.56 Modeling migration and search strategy of immune cells.

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Cytotoxic T-lymphocytes (CTLs) and natural killer (NK) cells are the killer cells of the immune system and migrate actively within the tissues to find and eliminate potential dangers such as virus-infected and tumor cells. Upon target cell encounter, the killer cells form a tight connection with them called the immunological synapse that enables killing. However, how migration is regulated in these cells for a rapid finding

of their target remains a central question in immunology. In this work we analyzed the migration of primary human CTLs and NK cells in 2 dimensions in the absence of external cues to mirror the early immune response where no signals guide the killer cells to their target. Our analysis of the mean square displacement and the velocity autocorrelation showed that CTLs and NK cells perform a persistent random walk. Additionally, cell shape analysis enabled us to establish a model for killer cell migration where the movement of the cell is determined by several independent internal "force generators". Each of them can switch between an active and an inactive state independently. We found a correlation between the number of the "force generators" and the duration of their activity to the number and life time of lamellipodia.
Furthermore numerical simulations revealed that the search time in a given space depends on the behavior of cells upon contact with boundaries. Thereby we found that a minimal search time can be reached depending on the persistence of the cells. We believe that simulation of migration and search strategy of killer cells will ultimately lead to an improved understanding of the immune response.

P.57 Concentration gradient mediated interactions between active droplets

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Autophoretic swimmers are subject to an interaction with each other that is due to overlap of the chemical gradients that surround them and drive their motion. It is believed to be similar to the interaction between micro-organisms, which also form and respond to solute gradients [1]. This type of interaction is also interesting because it involves the solvent, so it can be non-reciprocal [2]. Even though many particles and micro-organisms interact in this way, very few quantitative studies are available. The main obstacle is that this interaction is often coupled to self-

propulsion making it impossible to study the two effects separately. We show that isotropic swimmers, geometrically symmetric active particles, only swim beyond a cutoff particle size and fuel concentration, providing a window of opportunity to study the solute mediated interaction without the complication of swimming. Using optical tweezers we quantified the force between isotropic swimmers due to this solute mediated interaction and show that the force scales with inter-particle distance as $1/r^2$, as is expected for a diffusion dominated process. We propose a functional form for the interaction, based on analogy with electrostatics, that accurately describes our data. This model is in principle applicable to all solute gradient induced interactions and can aid in understanding the behavior of micro-swimmers as well as more complicated biological systems.

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P.58 The maximum number of independently hybridizing DNA strands

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In the cell molecular information processing is based on molecular recognition and binding. Although DNA hybridization is sometimes understood as a lock and key interaction, it is not completely clear how the two molecules identify each other. Even with a few mismatched bases, hybridization still occurs and this makes hybridization in crowded and competitive environments difficult to predict. Here we study what amount of difference between two strands is required to avoid competition for the one and the same binding partner. In this work we numerically derive the maximum number of possible sequences that can coexist without competing for binding to the perfectly matching complements of the competitors. Experimentally we determine the appropriate minimum number of mismatched bases and investigate the behavior of DNA in a scenario where many sequences bind to their surface bound

complements so that competition is minimized.

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P.59 Can teeth be armed to the teeth? - Time dependence of fluorine uptake by hydroxyapatite

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In terms of caries prophylaxis, fluoridation of enamel aims at the transformation of hydroxyapatite, $Ca_5(PO_4)_3(OH)$ = HAP, as representing the enamel´s main mineral component, into the isostructural fluorapatite, i.e. Ca5(PO4)3F = FAP. The built-up of a FAP layer is expected to provide an effective firewall to resist bacteria mediated acid attacks. In this *in vitro* study, the uptake of fluorine by synthetic HAP samples is investigated in dependence on the application time of the fluoridation agent (here: 500 ppm NaF buffer at pH ~ 5.5 and at 37 °C) via elemental depth profiling using X-ray photoelectron spectroscopy (XPS) combined with Ar ion etching. It is found that with increasing the application time the sub-surface range of the HAP samples saturates at a 41% HAP - 59% FAP mixture which is very close to the 50% : 50%

distribution as predicted by molecular dynamic simulations [1]. In addition, the mean thickness of the mixed layer does not exceed the range of 13 nm, which is also close to the value reported in previous experiments [2]. The time constants for obtaining the maximum fluorine content as well as the maximum penetration depth are in the range of approx. 1 min. The present results show that the usual daily practice in dental care is yet close to provide the maximum amount of fluorine possible.

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P.60 Identification of Key Player Genes in Gene Regulatory Networks

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Identifying the gene regulatory networks governing the workings and identity of cells is one of the main challenges in understanding processes such as cellular differentiation, reprogramming or cancerogenesis. One particular challenge is to identify the main drivers and master regulatory genes that control such cell fate transitions. In this work, we reformulate this problem as the optimization problems of computing a Minimum Dominating Set (MDS) and a Minimum Connected Dominating Set (MCDS) for directed graphs. Both MDS and MCDS are applied to the well-studied gene regulatory networks of the model organisms *E. coli* and *S. cerevisiae* and to a pluripotency network for mouse embryonic stem cells. The results show that MCDS can capture most of the known key player genes identified so far in the model organisms. Moreover, this method suggests an additional small set of transcription factors as novel key players for governing the cell-specific gene regulatory network which can also be investigated with regard to diseases.
The work proposes a new method to identify key player genes in gene regulatory networks. The tools explained in the paper are available as a Cytoscape plugin and as

supplementary material in [1].

[1] Maryam Nazarieh, Andreas Wiese, Thorsten Will, Mohamed Hamed, Volkhard Helms (submitted).

P.61 Constructing, analyzing and predicting disease-specific or developmental stage-specific transcription factor and miRNA co-regulatory networks

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TFmiR is a freely available web server developed in our group for deep and integrative analysis of combinatorial regulatory interactions between transcription factors, miRNAs and target genes that are involved in disease processes in human [1]. We are currently extending this work by integrating a number of new features such as the MCDS algorithm to identify key player genes in the selected network, construction of tissue-specific networks, and support of mouse networks (beside human). Besides disease processes, the successor of TFmiR can now also be applied to identify regulatory motifs associated with the transitions between different developmental stages from the set of dysregulated genes and miRNAs provided by the user.

[1] Mohamed Hamed, Christian Spaniol, Maryam Nazarieh and Volkhard Helms, Nucleic Acids Res. 43: W283-W288 (2015).

P.62 Atomic Force Microscopy based techniques developed for high spatio-temporal resolution imaging and nanomechanical characterization of cells

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Topography, roughness, adhesion and mechanical properties are relevant characteristics reflecting the cellular state in terms of morphogenesis, differentiation or cell division as well as cellular function. Atomic Force Microscopy (AFM) is a versatile tool suitable for measuring all of these characteristics with nanometer scale resolution under controlled environmental conditions. We have developed a multipurpose AFM device allowing comprehensive characterization of biological samples such as live cells or tissues. True optical integration allows the simultaneous use of advanced optical techniques such as DIC or confocal laser scanning microscopy. With our unique "Quantitative Imaging" (QI™) mode several cell and tissue properties, such as the topography, stiffness and adhesiveness, can be obtained with one measurement. Even more complex data like Young´s modulus images, topography at different indentation forces in terms of tomography, or recognition events can also be obtained. A variety of biological samples have been investigated to demonstrate the capability and flexibility of QI™.

The JPK ULTRA Speed technique allows fast AFM imaging to follow dynamic processes on the cell surface. Morphological changes, like membrane budding events or cytoskeletal reorganization can be viewed with high spatiotemporal resolution.

A variety of accessories are available, e.g. for environmental control or providing additional measurement modes, such as micromanipulation or adhesion measurements up to the single cell level. With the CellHesion® technique, the adhesion of a single cell to any substrate can be measured and validated using comprehensive analysis tools. The Side-view cantilever holder enables a side view of the cell-sample interface while performing adhesion experiments, providing complementary information without expensive z-stacking.

The inherent drawbacks of traditional AFM imaging modes for fast imaging or for challenging samples like living cells can be impressively overcome by the NanoWizard® ULTRA Speed and QI™ mode. We present an enhancement of the AFM technique providing a versatile tool for extensive and convenient characterization of living cells.

P.63 Influence of surface and subsurface modifications of a substrate on bacterial adhesion

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Numerous studies concentrate on finding conditions for preventing biofilms. However, its main constituents, proteins and bacteria, exhibit clever strategies to adhere to various surfaces. Our experiments aim at determining nature and strength of the involved forces by a judicious choice of substrates: Keeping the surface roughness and chemistry constant, differences in the subsurface composition cause distinct changes in the adhesion forces due to a variation of the long-range van der Waals force. Keeping the surface chemistry constant and changing the roughness only also influences bacterial adhesion due to geometry constraints. Comparing hydrophobic and hydrophilic substrates of identical roughness and nearly identical van der Waals forces reveal the influence of short-range, e.g. hydrophobic forces. We review our recent experiments of bacterial adhesion (e.g. *S. aureus, S. carnosus, Strep. oralis, Strep. mutans*) as determined by single cell AFM force spectroscopy.

P.64 Competing oligonucleotides: binding preferences for the best available partner in lieu of a ménage a trois

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The description of macromolecular recognition is usually reduced to the consideration of molecular pairs. In the simplest descriptions the receptor pairs exhibit a lock and key interaction, which mainly depends on the shape of the molecular recognizers, and this is supposed to lead to a highly specific recognition process. Much more refined and quantitative physical descriptions have been proposed, however, they are again based on pairwise interaction, and we remain far from understanding molecular binding in competition as it occurs in a biological organism. Here we present experiments on DNA macromolecular binding in

competition. We identify situations where the binding constant of one DNA strand is strongly dependent on the presence of another, very similar competitor. We interpret our findings as the result of an interaction term that leads to a formal equivalent of a Landau phase transition. We present experimental results from in vitro transcription assays that highlight the existence of other non-trivial competitive situations that may act along similar lines.

P.65 Proteome analysis of the initial in-*situ* biofilm on dentin under erosive challenges

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The acquired dental pellicle is formed by adsorption of salivary proteins and other macromolecules onto the tooth surface and confers protective properties against mechanical and chemical damages. The proteome of the pellicle has been characterized on enamel but not on dentin. Objective of this study is the proteome analysis of the in-situ pellicle formed on dentin and the identification of protective pellicle proteins.
Bovine dentin specimens (surface of 8cm2) were worn in-situ buccally over 3min to enable pellicle formation and were afterwards ex vivo etched with 0,1% and 1% citric acid. The 3min biofilm and the residual pellicle after etching were harvested through chemical elution, the proteins were separated by electrophoresis and after in-gel trypsination the peptides were applied to nano-LC-ESI-MS/MS. Resulting spectra were aligned via SWISS-PROT database for human proteins with Proteome Discoverer Software. Additionally, TEM analysis before and after citric exposition was performed.
Over 450 different proteins were identified, some of them were linked for the first time to the pellicle. Based on the NCBI annotations the majority of the molecular functions are distributed on binding, catalytic activity and enzyme regulator

activity and this distribution didn't change after the acid induced demineralization. The qualitative and quantitative (Top3) analysis indicated, that after etching only a few proteins dissolved completely. The TEM analysis underline this result. The electron dense pellicle layer could be detected even after acidic challenges.
These data show that the initial dentin biofilm is more complex than literature revealed until now and that citric acid has little impact on the qualitative and quantitative composition of the pellicle. Moreover, a multiplicity of proteins seems relevant for the protective properties.

P.66 Spindle positioning in budding yeast

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Chromosome segregation during cell division depends on a series of highly orchestrated interdependent interactions. Using an agent based approach we built a robust minimal computational model to capture mitotic events in budding yeasts of two major phyla: Ascomycota and Basidiomycota. This model convincingly reproduces experimental observations related to spindle alignment and nuclear migration during cell division in these yeasts. The model converges to the conclusion that biased nucleation of cytoplasmic microtubules is essential for directional nuclear migration. Two distinct pathways, based on the population of cytoplasmic microtubules and cortical dyneins, differentiate nuclear migration and spindle orientation in these two phyla. In addition, the model accurately predicts the contribution of specific classes of microtubules in chromosome segregation. Thus we present a model that offers a wider applicability to simulate the effects of perturbation of an event on the concerted process of the mitotic cell division [1].

[1] S. Sutradhar et al., Mol Biol Cell, mbc.E15-04-0236 (2015).

P.67 Determination of ion channel subunit stoichiometry by visualizing single molecules using STEM

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A range of cell functions depend on the dynamics of intracellular $Ca2^{+}$ signals regulated by calcium channels in the plasma membranes of cells. Of key importance for studying their function is knowledge about their stoichiometry, i.e. how these ion channel-forming protein complexes are assembled from their subunits. However, such knowledge is only available from pooled material extracted from many cells. We present a new microscopy approach capable of visualizing the locations of individual subunits within intact cells in liquid. Cells expressing the proteins of interest are first labeled with fluorescent nanoparticles of high atomic number, and then studied with correlative fluorescence microscopy and scanning transmission electron microcopy (STEM) in a liquid environment, thus remaining in their liquid environment [1]. Two different ion channel proteins were explored. 1) Anoctamin-1, also known as Transmembrane Member 16A (TMEM16A), a voltage-sensitive calcium activated chloride channel, expected to form a channel from a pair of proteins. A streptavidin binding tag was included in an extracellular loop of the protein for binding of a nanoparticle, i.e. a streptavidin-conjugated quantum dot. 2) The Orai1 channel, a store operated $Ca2^{+}$ channel of which many open questions exist about its stoichiometry and the possible existence of complexes involving also other members of the Orai family. To render Orai proteins accessible to QD labeling HA-tagged protein analogs were expressed. Statistical analysis of distances between the labeled proteins was used to examine the most probable configuration of these channels.

[1] D.B. Peckys, N. de Jonge, Microsc. Microanal. 20, 346-365, 2014.6 (2014).

P.68 Active Contraction of Biological Fiber Networks

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Large-scale force generation is essential for biological functions such as cell motility, embryonic development, and muscle contraction. In these processes, forces generated at the molecular level by motor proteins are transmitted by disordered fiber networks, resulting in large-scale active stresses. While fiber networks are well characterized macroscopically, this stress generation by microscopic active units is not well understood. I will present a comprehensive theoretical study of force transmission in these networks [1]. I will show that the linear, small-force response of the networks is remarkably simple, as the macroscopic active stress depends only on the geometry of the force-exerting unit. In contrast, as non-linear buckling occurs around these units, local active forces are rectified towards isotropic contraction and strongly amplified. This stress amplification is reinforced by the networks' disordered nature, but saturates for high densities of active units. I will show that our predictions are quantitatively consistent with experiments on reconstituted tissues and actomyosin networks, and that they shed light on the role of the network microstructure in shaping active stresses in cells and tissue.

[1] Pierre Ronceray, Chase P. Broedersz and Martin Lenz, *Fiber networks amplify active stress*, arXiv:1507.05873 (2015).

P.69 H/KDEL receptors mediate host cell intoxication by a viral A/B toxin in yeast

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Microbial A/B toxins such as cholera toxin, Pseudomonas exotoxin A and the yeast killer toxin K28 all contain a KDEL-like amino acid motif at one of their polypeptide chains which ensures retrograde toxin transport through the secretory pathway of a target cell [1]. As key step in host cell invasion, each toxin binds to distinct plasma membrane receptors that are parasitized and utilized for toxin cell entry. Despite intensive efforts, some of these receptors are still unknown. Here we identify the yeast H/KDEL receptor Erd2p as membrane receptor of K28, a yeast viral A/B toxin carrying a C-terminal HDEL motif at its cell binding B/b-subunit. While initial toxin binding to the outer yeast cell wall is unaffected in cells lacking Erd2p, toxin binding to spheroplasts and in vivo toxicity strongly depend on the presence of H/KDEL receptors. Consistent with a role in toxin binding to spheroplasts, intracellular localization of Erd2p is not restricted to membranes of the early secretory pathway but rather extends to the plasma membrane where Erd2p can bind and internalize HDEL-bearing cargo such as K28 toxin, GFPHDEL and Kar2p [2]. Since human KDEL receptors are fully functional in yeast and capable to restore toxin sensitivity in the absence of endogenous Erd2p, toxin uptake by H/KDEL receptors at the eukaryotic cell surface might also contribute to the intoxication efficiency of A/B toxins carrying a KDEL-like motif at their non-cell binding A-subunit(s).

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P.70 Electron microscopic investigation on the morphological changes of the acquired enamel pellicle, treated with astringent solutions

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Objectives: The aim of the present study was to investigate the effect of different astringent solutions on the acquired enamel pellicle in vitro and in situ.

Methods: Bovine enamel slabs, fixed to individual upper jaw splints, served for pellicle formation in situ. The samples were immersed in one of eight astringent solutions (in vitro) and rinsed before they were prepared for scanning electron microscopy (SEM) and transmission electron microscopy (TEM).
Four of the eight astringent solutions were further tested in situ. After pellicle formation, two enamel slabs were removed to serve as a control pellicle. Two more samples were removed directly after rinsing with one of the solutions whereas the last two samples were left intraorally for another 30 minutes. The ultrastructure of the pellicles was investigated by SEM and TEM.
Results: The effects observed on the pellicle's morphology were very different, depending on which astringent solutions were used: Some samples showed electron-denser pellicles in comparison to the control pellicle. For other specimens a demineralization of the tooth, infiltrated with pellicle components, was detected. An increased thickness was observed for other specimens.
Conclusion: Astringent solutions have a great impact on the pellicle's morphology. Comparable effects are observed in situ and in vitro.

P.71 Pressure and state functions of self-propelled particles including hydrodynamic interactions

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Self-propelled particles, such as E. Coli bacteria or self-diffusiophoretic swimmers are one of the easiest examples of active systems. These particles are able to convert intrinsic or environmental free-energy into systematic self-propulsion and are therefore permanently driven out of thermodynamic equilibrium. Nevertheless, pressure, the mean mechanical force acting on a confining wall, is still well-defined. Assuming Brownian Dynamics, the pressure of self-propelled spherical particles does even fulfill an ideal gas-like state function, independent of the explicit wall-particle interaction [1]. More generally, the existence of a state function is conditioned by the absence of wall-induced torques and the type of interaction between the active particles [1]. We are interested in how these results change when using a different model for describing the interaction with the solvent, such as the Multi-particle-collision dynamics technique [2], which includes hydrodynamic interactions between

the self-propelled particles. Even for spherical particles, hydrodynamic torques can arise and make an equation of state less likely to exist.

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[2] G.Gompper et al., Advances in Polymer science 221 p. 1 (2009)

P.72 Active resistance of living cells against extra-cellular matrix deformation

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In vivo, living cells are continually deformed by their surroundings. We have developed a method to measure the mechanical response of isolated cells to extra-cellular matrix deformation. We measure the change of traction forces within seconds of deformation. This approach enables us to simultaneously probe cells' passive elastic and active contractile responses. Interestingly, we find that the cells' resistance to deformation is dominated by their contractility, not their elasticity.

P.73 Nonlinear Fibroblast Mechanics: A story of history

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Cell mechanics is a key player in development, disease and many other biological processes. Living cells exhibit a complex nonlinear response to mechanical cues, which is not understood yet. A stiffening as well as softening is observed, depending on the stimulus and the experimental technique. Here, we apply large amplitude oscillatory shear (LAOS) to a monolayer of fibroblast cells using the cell monolayer rheology technique [1][2]. We find that the nonlinear cell response not only depends on the amplitude and the frequency of oscillations. Moreover, it is highly susceptible to a mechanical preconditioning. Cell response can exhibit hallmarks of nonlinear viscoelasticity, elastoplastic kinematic hardening or inelastic fluidization

for the same steady state oscillations. Experimental results indicate that a preconditioning changes cytoskeletal network structure in a rate dependent way. Network alterations can be driven by passive filament reorganizations, filament rupture and the binding/unbinding of crosslinking proteins. We speculate that the pronounced strain path dependence of nonlinear cell response might obscure the underlying universality of nonlinear cell mechanics on a microscopic scale. Our results highlight the interplay between viscoelastic and inelastic contributions to the cell mechanical response.

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P.74 Spontaneous Calcium Transients in Interdental Cells during the Critical Period of Cochlear Development

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The tectorial membrane (TM) is essential for normal hearing. It stretches across the sensory epithelium of the inner ear, contacts the stereocilia of the outer hair cells and is spiralling along the longitudinal axis of the cochlea. It consists of collagens and glycoproteins. Mutations of these proteins lead to aberrant TM formation and deafness. During the critical period of cochlear development, interdental cells (IDCs) secrete TM proteins into the endolymph. Little is known about the physiology of IDCs and TM formation. We stained cochlear cryosections and performed Ca^{2+} imaging of acutely dissected organs of Corti at postnatal day 4-5 using the indicator Fluo-8 AM. IDCs generated spontaneous Ca^{2+} transients in part of the IDCs at a rate of ~1 event/10 min. Spontaneous Ca^{2+} signals in IDCs were variable in shape and duration. Applying 10 µM ATP evoked Ca^{2+} oscillations in all IDCs at ~0.1 Hz whereas 1 µM led to oscillations in only part of the IDCs at ~0.05 Hz. Ca^{2+} transients never spread to neighbouring cells. Our results emphasize the role of IDCs during the critical phase of cochlear differentiation. Further studies are needed to elucidate the underlying

mechanisms.
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P.75 Spontaneous autocatalysis in a primordial broth

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Driven non-linearities lead to pattern formation. Here we study the dynamics of a complex chemical system, driven by electric discharge that forms from a gas mixture of methane and ammonia in the presence of water. Using real-time mass spectrometry, we observe the generation of a primordial broth composed of thousands of different molecules in a mass range from 50 to 1000 Dalton. The temporal development of the primordial broth reveals the spontaneous emergence and disappearance of oligomeric surfactants [1]. Strong non-linearities are required for these aperiodic chemical oscillations. The phenomenon is robust against different gas compositions and concentrations, temperatures and many details of the experimental set-up. We analyze the chemical composition of the solution by different methods like (high-resolution) mass spectrometry, NMR and gas-chromatography to find high-reactive molecules and possible catalysts. We find that oxidation and doping with small amounts of an active broth can trigger the production of the oligomers. We suggest that surface active molecules lead to phase transfer catalysis in the oil/water mixture and self-organize to a spontaneously emerging autocatalytic network.

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P.76 Profilin-1 downregulation in CTL of pancreatic cancer patients results in increased migration and killing efficiency

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CTL roam the body to find and fight cancerous or pathogen infected cells. Until today little is known how CTL in humans adapt their migration or killing behavior in the cancer context. In this work we found that actin-binding protein profilin-1 (PFN1) levels are significantly downregulated in pancreatic cancer patients compared to healthy individuals. PFN1 overexpression correlated with decreased CTL cytotoxicity, whereas PFN1 down-regulation resulted in increased CTL cytotoxicity, which was paralleled by enhanced CTL migration and invasion. Using the Y59A mutant of PFN1, which cannot bind actin, we show that PFN1 tunes the preference of CTL to form similar-sized (balanced), differently-sized (unbalanced) or single dominant protrusions. Higher probability of dominant protrusion formation correlated with enhanced migration velocity and persistence in a collagen matrix. We conclude that in pancreatic cancer patients PFN1 down-regulation is correlated with increased CTL functionality. Thus, PFN1 down-regulation might well be a compensatory mechanism employed by CTL to fight cancer.

P.77 Numerical study of the efficiency of spatially homogeneous and inhomogeneous intermittent search strategies

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The successful usage of efficient search strategies is one of the most important needs in biology and human behaviour. It is observed on all length scales of life and in all kinds of complexity. Very often, so-called Intermittent Search strategies are observed, which are based on the alternation of a detection phase and a relocation phase. In the detection phase, the searcher is able to recognize the target, but there is less or even no spatial displacement. In the relocation phase, the searcher moves in a fast directed motion within the searching area, but there is no possibility of target detection. This strategy has been proven to be often more efficient than staying in the detection phase for the whole searching time. The model assumption of a searcher which does not remember its past leads to exponentially distributed switches in time between the two phases. Assuming no knowledge about its position within the searching domain would lead to homogeneously distributed relocation directions in space. In real life however, the searcher often "feels" at least some aspects of its position, e.g. chemotaxis sensitive searching killer cells or intracellular search with ballistic relocation along the anisotropic cytoskeleton.

Hence, we numerically compare the efficiency of purely diffusive search to spatially homogeneous and optimized inhomogeneous intermittent search strategies for the following problems: 1) narrow escape problem; 2) detection of an immobile target in the interior of the searching domain; 3) reaction-escape problem, i.e the searcher at first needs to find a diffusive target and has to solve a narrow escape problem afterwards.

Among others, the results indicate that for various intracellular transport problems the cytoskeleton network of cells realizes inhomogeneous search strategies which are more efficient than a homogeneous strategy.

P.78 A coarse-grained elastic model for cell deformation

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A broad range of *in silico* models (e.g., liquid or viscoelastic drop models) has been introduced to reproduce the complex mechanical properties of various cell types [1]. These models are used to understand and quantify experimental measurements. In this work, we employ a coarse-grained cell model which incorporates the membrane properties similar to the RBC-model [2] and an elastic inner mesh to include the cytoskeletal properties. The model is formulated in the framework of the dissipative
particle dynamics simulation method and can include multiple cell compartments with different mechanical properties. We perform various mechanical tests that are similar to experiments [1] to determine the mechanical properties of a single cell. We also investigate the deformation of this cell in fluid flow. We expect that this model will help us better understand the contributions of different cell compartments to overall cell deformation.

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P.79 Measuring the bacterial interaction area to abiotic surfaces by single-cell force spectroscopy on tailored samples

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Bacteria adhere to virtually every surface and promote the formation of – desirable or unwanted - biofilms. Therefore, in many fields, like engineering, medicine, and biology, understanding bacterial adhesion is of great interest in order to support or inhibit the formation of biofilms. Consequently, there exist different models that describe the process of bacterial adhesion. In these models, besides apparent direct values, like the adhesion force and distance, also more indirect quantities, like the

size of the interaction area between bacterial cell and surface, play an crucial role to understand the underlying mechanisms. We present a method to measure the radius of this circular interaction area for *Staphylococci* by taking advantage of the fact that the adhesion force of these cells differs strongly between surfaces with different surface energies [1]. The measurement is done by collecting multiple force/distance curves with single-cell AFM probes at a very sharp interface between hydrophilic silicon and a hydrophobic self assembling monolayer of silanes. The measured radii of the interaction area range from some tens of nanometers up to almost 300 nm depending on the exerted force trigger. These values also give new insights into the properties and distribution of surface molecules in the bacterial cell wall.

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P.80 Actin waves as determinants of circular cell trajectories in cell amoeboid migration

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Amoeboid migration is a specific mode of cell movement adopted by leukocytes, such as dendritic cells (DCs) when migrating in restrained spaces. Actin assembles into polar filaments and is directly implied in cell movement by both driving contractile forces and forming membrane protrusions. Theoretical simulations show that in a confined system, independent of adhesion, such as it is the case of amoeboid cell migration, actin filaments can assemble in circular waves [1]. We hypothesize that actin waves determine cell trajectories during amoeboid migration. Experiments were carried out with DCs confined in two-dimensions by adding a well-defined roof on top of the cells [2]. The migration profile was recorded by time-lapse microscopy. Circular actin waves were observed within the cell via TIRF microscopy and were not restricted to the cell front. The speed of these waves were measured. Single 2D trajectories were evaluated according to mean speed, persistence, path length and mean square displacement. Surprisingly, DCs trajectory analysis revealed curved migration

trajectories with a preferred radius. These experimental trajectories were compared with trajectories generated from a theoretical model on actin waves. Interestingly, we found a preferred radius of migration within these theoretical trajectories as well as in our experimental data sets. We further investigated the relation between the cell speed and the preferred radius of cells and found a strong correlation, both in the experimental dataset and the theoretical dataset. In the theoretical model, actin waves spontaneously occur only in the presence of a nucleation factor, independent of a motor such as myosin II. To address this question we treated cells with the ROCK inhibitor Y27632. Experimental data shows that molecular motors, like myosin II are dispensable for the generation of cytoskeletal waves and the circular trajectories. We assume that the actin waves inside of living cells might be the reason for the circles in the trajectories we see in amoeboid cells. These results suggest that we can use the actin-wave theoretical model to describe dendritic cell amoeboid migration.

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P.81 Revealing contact formation characteristics of bacteria

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Bacteria exhibit an outstanding ability to adhere to various kinds of surfaces. Details of contact formation, however, are hard to gain and single cell AFM force spectroscopy has proven to be a powerful tool to quantify the acting forces if combined with a clever choice of substrates. On hydrophobic surfaces, the hydrophobic interaction plays the main role for the adhesion of bacteria [1] and the contact formation process is dominated by cell wall macromolecules. In our AFM study, we were able to observe the process of making contact by observing the snap-in process in detail [2]. To interpret the data, Monte Carlo simulations were set up, involving a simple model for a bacterium. The simulations yield strikingly matching results, corroborating the interpretation that the contact formation of *S. aureus* relies on thermally fluctuation

cell wall proteins that tether to a surface and subsequently pull the bacterium to the surface. That way, e.g. *S. aureus* is able to attach to surfaces over distances far beyond the range of classic surface forces! Our results therefore suggest that the bacterial adhesion process in general, can be described by solely taking into account the tethered macromolecules between a bacterium and a surface.

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P.82 The role of non-filamentous vimentin in amoeboid cell migration

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The presented project will be a master project carried out in the AG Lautenschläger (A8).
Cell migration is a fundamental function of cells. Without cell migration the formation of multicellular structures of tissues and complex processes in higher life forms would be impossible.
To understand migration, there exist already many studies about the internal cell mechanisms of single cells. However, it is still unknown how all mechanisms work together and which effect external influences have. Based on the work of Luiza Stankevicins, I will analyse the role of vimentin in its *non-filamentous* form compared to its *filamentous* form in amoeboid cell migration. These experiments will be carried out under one (see Fig 1 as example) and two dimensional confinement. In order to compare the migration in our confining setups with the migration in an *in-vivo* environment I will inject the cells in a flatworm called Planarian and analyse its migration in this environment.

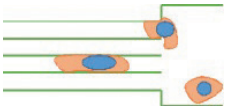

Figure 1: *1D confinement: Schematic model of cells migrating in micro-channels and confocal image of HL-60 cell stable transfected with vimentin GFP (filamentous form) migrating in micro-channels measuring h-5-µm, w-5µm. Figure courtesy of Luisa Stankevicins.*

P.83 Tug-of-war between elastically coupled molecular motors

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Intracellular transport is based on molecular motors that pull cargos along cytoskeletal filaments. Many cellular cargos are observed to move bidirectionally, with fast transport in both directions. This behavior can be understood as a stochastic tug-of-war (ToW) between two teams of antagonistic motors. The original ToW model introduced in [1] was based on two simplifying assumptions: (i) both motors move with the same velocity in the direction of the stronger motor, and (ii) this velocity matching and the associated force balance arise immediately after the rebinding of an unbound motor to the filament. In this study, [2] we extend the ToW model by including an elastic coupling between the antagonistic motors, and by allowing the motors to perform discrete motor steps. Each motor step changes the elastic coupling and generates a force that acts on all motors. Depending on the strength and stability of the motors (characterised by their stall and detachment forces), as well as on the stiffness of the elastic coupling, the motors can perform multiple steps before they reach a state of force balance.

In general, the ToW model with elastic coupling is found to generate a lower average force between the motors compared to the original model. The behavior of the latter model is recovered in the limit of small unbinding rates of the motors. In all cases, we determine the time needed to reach a state of force balance. This time scale becomes larger when the elastic coupling becomes weaker.

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P.84 Accumulation of apatite on initial biofilm *in-situ*

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Natural remineralization of enamel is promoted by calcium phosphate from saliva. Neomineralization of enamel due to biomimetic nanoparticles of calcium hydroxyapatite (HA) are evolved as a new protection opportunity additional to elemental mechanism. Accumulation HA nanoparticles during *in situ* formation of initial biofilm (pellicle) was investigated in this study.

Initially biofilm was formed for 3 min on the buccally placed enamel specimens. The oral cavity was rinsed with 5% HA suspension or 10% HA tooth gel was applicated once in 30-min experiment. The same procedure was repeated ten times every 30 min in 5-h experiment. The in situ formation of pellicle followed for 30 min after each application.

Accumulation of HA nanoparticles was qualitative and quantitative analyzed by means of scanning electron microscopy and energy dispersive X-ray spectroscopy. Using the apatite containing suspensions or tooth gels induce a sustainable modification of pellicle development and accumulation of apatite in and on the pellicle. The most effect exhibit suspension with 5% HA.

P.85 Physical limits to spatiotemporal cellular signaling

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Cells need to respond to spatiotemporal signals. Physical limits on the detection of such signals are poorly understood. Here we study the detection of spatiotemporal Ca^{2+}-signals by the conventional Protein Kinase C-α (PKC-α). Protein kinases C are ubiquitously expressed and, together with Calmodulin, form the basic read-out module for Ca^{2+} -signals. In order to activate PKC-α, it needs to simultaneously bind to Ca^{2+} and to Diacylglycerol (DAG) on the plasma membrane. On the membrane, PKC-α forms clusters. We explore the consequences of cluster formation for signal transduction. In particular we show that PKC-α acts as a low pass filter and determines the accuracy of the readout. Our study highlights the possible role of collective effects for cellular signal transduction.

P.86 Stuttering of Min oscillations is induced by stochastic effects

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The site of cell division in wild type E. coli bacteria is determined through pole-to-pole oscillations of the Min proteins. Although the oscillations are fairly stable across a wide variety of cell shapes and protein concentrations the emerging patterns are subject to molecular noise, due to the small copy number of proteins in a single cell. This causes the oscillations to sometimes „stutter“ and remain in the same polar con-guration. We use a simple, generic model of protein interactions which shows similar behaviour as the Min-system and analyze the stochastic dynamics in the limit of weak noise to understand the underlying effects.

P.87 Towards the rewiring of the proteome during blood development

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Protein–protein interaction networks (PPINs) are an important component of modern systems biology. Yet, comparatively few efforts have been made to tailor their topology to the actual cellular condition being studied. We developed PPIXpress, a network construction method that exploits expression data at the transcript-level and thus reveals alterations in protein connectivity not only caused by differential gene expression but also by alternative splicing [1]. We achieved this by establishing a direct correspondence between individual protein interactions and underlying domain interactions in the full but condition-unspecific PPIN. When we compared contextualized interaction networks of matched normal and tumor samples in breast cancer, our transcript-based construction identified more significant alterations that affected proteins associated with cancerogenesis than a method that only uses gene expression data [1]. As an extension of this work, we developed the differential PPIN tool PPICompare to compare the inferred interaction networks between samples of two groups. The tool determines statistically significant between-group rewiring events and their causes. A first application of the novel software is shown in the context of hematopoiesis. To our best knowledge this work represents the first study of rewiring processes of the protein interactome during development.

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P.88 Identifying transcription factor complexes and their roles

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Eukaryotic gene expression is controlled through molecular logic circuits that combine regulatory signals of many different factors. In particular, complexation of transcription factors and other regulatory proteins is a prevailing and highly conserved mechanism of signal integration within critical regulatory pathways and enables us to infer controlled genes as well as the exerted regulatory mechanism. Common approaches for protein complex prediction that only use protein interaction networks, however, are designed to detect self-contained functional complexes and have difficulties to reveal dynamic combinatorial assemblies of physically interacting proteins. We developed the novel algorithm DACO that combines protein-protein interaction networks and domain-domain interaction networks with the cluster-quality metric cohesiveness. The metric is locally maximized on the holistic level of protein interactions and connectivity constraints on the domain level are used to account for the exclusive and thus inherently combinatorial nature of the interactions within such assemblies. When applied to predicting transcription factor complexes in yeast, the proposed approach outperformed popular complex prediction methods by far. Furthermore, we were able to assign many of the predictions to target genes, as well as to a potential regulatory effect in agreement with literature evidence.

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P.89 Molecular Darwinism

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From the origin of life Darwinian evolution has continuously led to new and different species that make up a highly complex biosphere. Reproduction in conjunction with variation leads to the permanent selection and emergence of new species. How Nature avoids an evolutionary stall and keeps on to innovate remains poorly understood. Many aspects of Darwinian evolution have been described by experimental as well as theoretical approaches. However, a realization of Darwinian evolution on long time scales that does not end up in the selection of a single fittest evolutionary winner is still required. We introduce an experimental system that consists of linear DNA molecules of the same length that are able to reproduce in a template-directed way. Longer molecules appear by spontaneous ligation. A DNA species is formed by DNA strands of a certain length that feed on shorter strands and that eventually outcompete other existing DNA molecules. An evolutionary stall is avoided if these new species in turn serve as a niche that can be exhausted by succeeding mutants. Like this, our molecular evolutionary system is principally able to progress indefinitely.

P.90 Model platforms for studying mechanical factors involved in T cell activation

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T cells can be activated via binding of T cell receptors (TCRs) to peptide-major histocompatibility complex (pMHC) molecules displayed on the surface of antigen presenting cells (APCs). The process is accompanied by clustering of TCRs and other co-receptors for the formation of the immunological synapse (IS) [1]. Experimental evidence shows that mechanical forces are involved in this process. However, the possible roles of mechanical force in ligand discrimination, clustering of TCRs or in the final activation or deactivation of T cells remain elusive. We present cushioned-lipid bilayers as models of APCs for studying T cell activation. We use hydrogels with controllable mechanical properties and tunable immobilized ligands for TCR, costimulatory and adhesion molecules, acting as supports for the lipid bilayers. This synthetic surface is used as 'artificial APCs' to study mechanism of T cell activation.

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P.91 The role of TMX1 and TMX3 in melanoma

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Melanoma in later stages is highly lethal due to the strong resistance towards conventional therapies. It has been reported that transcriptional factor NFAT contributes to apoptotic resistance, enhanced proliferation and motility in cancer cell lines [1]. Additionally it also plays an important role in melanoma genesis and metastasis [2].

Our results show that two members of the disulfide-isomerase family, TMX1 and TMX3 are highly expressed in both of melanoma cell lines and patient samples. And siRNA-mediated knockdown of TMX1 and TMX3 leads to a decrease of nuclear import of NFAT and an increase of cytosolic hydrogen peroxide in melanoma cell lines, accompanied by suppression of melanoma proliferation and migration. Further experiments showed the oxidative modification of calcineurin, the phosphatase catalyzes dephosphorylation of NFAT, might be responsible for the compromised NFAT translocation. Since TMX1 and TMX3 are reported as endoplasmic reticulum residing proteins, our work provided implications about possible link between ER dysfunction induced ROS generation and melanoma suppression.

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P.92 *In vitro* recapitulation of neuronal somal translocation and mechanism of external triggers

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Neuronal somal migration during cortex development determines the final position of neuron and cortical layer formation. It is difficult to figure out mechanism of external environment for somal translocation in vivo, because the cell-cell interaction and multi-component Extracellular matrix (ECM). Recent studies have shown that there is spontaneous neuron migration observed by chance in vitro, however, the somal migration is rarely observed and the external triggers from the environment remain unknown. By coupling of different ECM components or peptides (Polylysine, IKVAV, Reelin, fibronectin, collagen and RGD) in restricted region of substrate separately, we triggered directional somal migration to preselected positions on the substrate and examined the mechanism underlying the external cues for somal translocation. Through controlling the protein type, we were able to systematically study the influence of different protein on somal translocation. Further, somal translocation can be triggered by changing the “adhesiveness” of the substrate through polylysine gradient. All features of somal translocation in vivo were observed, including the spreading of the growth cone at the leading process tip being a crucial step for triggering somal translocation. This platform allows in vitro studies of directional neuron somal translocation, a very important step towards understanding the molecular mechanisms underlying cortical layer formation during embryogenesis and their disturbance in human migration disorders.

Key words: Somal Translocation, Neuron, ECM, Adhesiveness Contrast, Microcontact Printing

P.93 Mitochondria are passively transported to the immunological synapse along with microtubule network reorientation

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At the process of cytotoxic T lymphocytes (CTL) killing, it is required to form a tight junction between the CTL and the target cell, which is termed the immunological synapse (IS). Upon the IS formation, a fundamental reorientation of organelles, including microtubule-organizing center (MTOC), mitochondria, and lytic granules, takes place in the cytotoxic T lymphocytes [1]. To understand how the movements of organelles are orchestrated, we focus on the correlation of transportations between MTOC and mitochondria. We performed live cell imaging to visualize movements of MTOC and mitochondria during IS formation. We found that MTOC velocity increased significantly (form 1.4 to 2.7 μm/min) during IS formation compared to control.
In addition, we also found that the speed of MTOC was dependent on the distance between MTOC and IS, which is in good agreement with previous study [2]. Meanwhile, our data showed that mitochondria accumulation displayed similar moving pattern as MTOC during IS formation. Furthermore, by labeling tubulin and mitochondria, we observed that mitochondria were translocated towards the IS along with microtubule-network. In summary, MTOC guides mitochondria to immune synapse via microtubule in cytotoxic T lymphocytes.

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P.94 Pairing, an economic way for cytokine carrier transportation and fusion

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$CD4^+$ T helper cells establish immunological synapses and secrete cytokines following antigen recognition at the late stage of TCR signaling [1]. It is already known that T cells use two directionally distinct pathways for cytokine secretion. Some cytokines, like interleukin 2(IL-2), can be delivered exclusively to the immunological synapse (IS), whereas others, like tumor necrosis factor α (TNFα), are delivered multi-directionally in $CD4^+$ T cells[2]. However, mechanisms coordinating these two secretion patterns are not yet uncovered. Here, we show that temporally the expression of TNFα and IL-2 in primary human $CD4^+$ T is induced differently upon stimulation. Spatially, both of TNFα+ and IL-2^+ carriers are transported to their secretion sites tethering with lysosome-related organelles (LROs) and are released prior to LROs fusion with the plasma membrane. Like pairing between CD3 and lytic granule (LG) mediated by SNARE protein Vti1b in $CD8^+$ T cells [3], the tethering between cytokine carriers and LROs is highly dependent on Vti1b via interaction with EpsinR. Using super-resolution structured illumination microscopy (SIM), we found that in most cases endogenous kinesins reside exclusively on LROs but not TNFα+ carrier for TNFα/LRO pairs; in comparison the single TNFα+ carriers also did not colocalize with endogenous kinesin. As predicted by our mathematical model, the following experiments proved that the two directionally distinct secretion patterns are mainly determined by the count of cytokine carriers via tethering with LROs. Thus our findings unveil that tethering of cytokine carriers with LROs is essential for cytokine delivery in $CD4^+$ T cells and the delivery pattern of cytokines is mainly determined by the count of newly derived cytokine carriers.

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P.95 Explosive percolation in molecular evolution

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We analyze an autocatalytic model for evolution of linear polymers. The system concatenates linear polymers either spontaneously or autocatalytically, eventually leading to a giant polymer, exhibiting a percolation phase transition. Ordinary percolation phase transitions show self-averaging. Here, we analyze the transition to an autocatalytical growth with respect to (non) self-averaging behaviors. We find a rich dynamical behavior, i.e., for autocatalytical growth a staircase of the order parameter.

P.96 Motility states in bidirectional cargo transport

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Inside cells many cargos are transported along cytoskeleton filaments by teams of molecular motors. Intriguingly, the motors involved in long-range transport generally have opposite pulling directions. This results in stochastic bidirectional cargo dynamics. It remains an open question whether the characteristics of their motion can result from pure stochastic fluctuations or whether some coordination of the motors is needed.

The results of a mean-field model of cargo-motors dynamics, which was proposed by Müller et al., suggest the existence of states which are characterized by a symmetric bimodal distribution of cargo velocities and number of attached motors. In their model these states would result from a stochastic tug-of-war. The influence of the mean field assumption on the cargo motion is analyzed by considering a model which takes explicitly the position of each motor into account. We show that the existence of those bimodal states occur only due to that mean field assumption. The implicit motor synchronization can be reproduced in the limit of many motors and a strong motor-motor activation. Therefore, we conclude that these states are not relevant for intracellular transport.
Furthermore, we show that our explicit model reproduces the superdiffusive as it was found experimentally.

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