BP 1: Cell migration

Time: Monday 9:30–13:00 Location: H43

Invited Talk BP 1.1 Mon 9:30 H43

Motor-clutch model for substrate stiffness sensing by living cells — •David Odde[1], Benjamin Bangasser[1], and Steven Rosenfeld[2] — [1]Department of Biomedical Engineering, University of Minnesota, Minneapolis, MN, USA — [2]Brain Tumor and Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH, USA

Cells sense the mechanical stiffness of their environment to control cell shape, differentiation, survival, proliferation, and migration. How cells sense the Young's modulus of an elastic environment to make these vital decisions is not clear. We recently showed that a simple 'motor-clutch' model exhibits stiffness sensitivity (Chan and Odde, Science, 2008). In particular, the F-actin retrograde flow rate and traction force exhibit a biphasic response to substrate Young's modulus, an effect that we confirmed using embryonic chick forebrain neurons. We now further explore the behavior of the motor-clutch model, and assess which model parameters control the stiffness at which sensing is optimal. Our exploration of parameter space reveals that no single parameter in the motor-clutch model can strongly control the set-point for optimal stiffness sensing. Rather, parameters need to be changed coordinately to effectively change the set-point. In particular, coordinate increases of both motor and clutch numbers effectively increases the set-point stiffness. Our recent experimental studies with glioma cells are consistent with predictions of the motor-clutch model. We speculate that the motor-clutch model may be useful for in silico identification of combination drug targets for brain cancers.

BP 1.2 Mon 10:00 H43

Mechanics of Collagen Gels - What Cells Feel — •Julian Steinwachs, Claus Metzner, Stefan Münster, Nadine Lang, and Ben Fabry — University of Erlangen-Nürnberg, Germany

Collagen gels are frequently used to study cell migration in a three-dimensional environment. Their mechanical properties are governed by non-affine deformation of the collagen fibrils, such as buckling and tautening, resulting at the macroscopic scale in pronounced strain stiffening under shear and strong lateral contraction under stretch. It is currently unknown how these properties play out at the microscopic scale of a migrating cell. To explore this question, we develop a nonlinear elastic material model for collagen gels based on observations from confocal microscopy that fibrils evade mechanical stress by deforming in a non-affine manner, resulting in a nonlinear force-length relationship. Our model replicates the macroscopic strain stiffening and lateral contraction of collagen and predicts that tautening of fibrils results in a strong stiffening against expanding forces that can arise, for example, when the diameter of a migrating cell is larger than the network pore diameter. Using the model, we compute cell induced stresses and local material properties during cell migration from collagen fiber displacements measured with confocal reflection microscopy. We find that mesenchymally migrating cells exert highly localized forces onto the matrix with an average magnitude of 65nN. As a result, the collagen matrix stiffens locally by approximately two-fold.

BP 1.3 Mon 10:15 H43

Effects of adhesion dynamics and substrate compliance on shape and motility of crawling cells — •Falko Ziebert[1,2] and Igor Aranson[3,4] — [1]Physikalisches Institut, Albert-Ludwigs-Universität, 79104 Freiburg, Germany — [2]Institut Charles Sadron, 67034 Strasbourg, France — [3]Materials Science Division, Argonne National Laboratory, Argonne, IL 60439, USA — [4]Engineering Sciences and Applied Mathematics, Northwestern University, Evanston, IL 60202, USA

Understanding physical mechanisms of cell motility and its relation to substrate properties is essential e.g. for morphogenesis or wound healing or for the development bio-active surfaces. We present an effective computational model, based on the cell's shape deformation mediated by the actin cytoskeleton, coupled to the dynamics of adhesion site formation and the elastic response of the substrate. We reproduce and analyze key experimental observations, like transitions from steady cell motion to stick-slip motion with concomitant shape oscillations. We present 'phase' diagrams for the different types of motion as a function of the determining parameters like actin protrusion rate, substrate stiffness, and the rates of adhesion site formation. The model also has been investigated for substrates with stripe-patterned adhesiveness: on hard adhesive substrates, cells move along the stripes, while for softer and/or less adhesive substrates motion perpendicular to the stripes occurs, a prediction that might be relevant for the design of selective bio-active substrates for e.g. cell sorting.

BP 1.4 Mon 10:30 H43

Cytoskeletal polarization during amoeboid motion in narrow microfluidic channels — •Oliver Nagel[1], Matthias Theves[1], Meghan Driscoll[2], Can Guven[2], Wolfgang Losert[2], and Carsten Beta[1] — [1]Institute of Physics and Astronomy, University of Potsdam, Germany — [2]Department of Physics, University of Maryland, MD, USA

We study the quasi one-dimensional motion of *Dictyostelium discoideum* amoebae inside narrow microfluidic channels with a cross section of 10 x 20 micrometer. While many cells perform a quasi one-dimensional random walk with frequent switches in the direction of motion, we regularly observe cells that show a markedly different type of motion. They move persistently in one direction along the channel for more than half an hour without reversing their direction of motion. We perform laser scanning confocal imaging with a transfected *Dictyostelium* cell line that expresses myosin II-GFP together with LimE-mRFP, a marker for filamentous actin. Our experiments reveal a polarized structure of the cell cortex that differs from polarized cells in absence of confinement. We characterize this type of polarized cell motion using custom made software tools for cell shape analysis to monitor the dynamics of local protrusions and retractions on the membrane together with the accompanying intracellular distributions of actin and myosin II in the cell cortex.

BP 1.5 Mon 10:45 H43

Spatiotemporal dynamics of self-organized waves in electrofused amoeboid cells. — •Matthias Gerhardt, Michael Walz, and Carsten Beta — Institut für Physik und Astronomie, Karl-Liebknecht-Strasse 24/25, 14476 Potsdam, Germany

We investigated the intracellular dynamics of PIP3 and F-Actin in electro-fused Dictyostelium discoideum cells by confocal laser scanning microscopy, using the markers PHCRAC-GFP and LimE-mRFP, respectively. The obtained fusion products were approximately 10-100 times larger than native Dictyostelium cells. In the substrate-attached cortex, they exhibit self-organized actin waves, similar to non-fused cells. However, due to the increased size of the fused cells, we can now observe the dynamics of the actin waves for the first time in much larger spatial domains. The wave patterns show many characteristic features that are well known from excitable reaction-diffusion systems. The dynamics is characterized by expanding circular and elliptic waves as well as rotating spirals. If such waves collide, they annihilate each other. The distribution of the fluorescent markers indicate that F-actin is concentrated at the leading front of the wave followed by a PIP3 enriched zone containing only little F-actin. Using a custom written software, the recorded wave patterns were fitted either by ellipses or spiral-functions to determine the cell displacement, the wave velocity, and the curvature of individual waves for further analysis. Furthermore, our data suggest an important role of the F-actin waves in cell motility, an observation that can be accounted for in terms of a simple mechanical model.

BP 1.6 Mon 11:00 H43

Mechanics of bleb formation in filamin-negative cancer cells — Julia Peukes and •Timo Betz — Institut Curie, UMR 168, Paris, France

The formation of cellular blebs is a well described dynamical process that can be associated with cell motility, cell division and apoptosis. While recent research has shown a direct relation between cell contractility, cell cortex mechanics and bleb formation, a detailed mechanical model of cell bleb formation containing quantitative values for the mechanical parameters is still under work. Here we show new quantification of the membrane advancement of filamin negative cancer cells during bleb formation as measured by an interferometric technique that gives sub-nm precision at kHz repetition rate. These new experiments allow to determine the fluctuations of the cell bleb membrane during the extension of the bleb, the polymerization of the actin cortex and the myosin driven bleb retraction. Using simple arguments we can

translate the fluctuations into an effective actin-cortex tension that is consistent with previous measurements. More detailed analysis of the fluctuation shows mechanical details of the different bleb phases. Furthermore, we can identify clear separations of the bleb growth rates into distinct extension velocity regimes that we attribute to different levels of the actin polymerization under the cell membrane. These findings give hints towards a more detailed model on the different events involved in cellular blebbing.

15 min break

BP 1.7 Mon 11:30 H43

Sensing the surface: shortcuts for bacteria — •Siddharth Deshpande[1], Isabelle Hug[2], Urs Jenal[2], and Thomas Pfohl[1] — [1]Department of Chemistry, University of Basel, Switzerland — [2]Biozentrum, University of Basel, Switzerland

Caulobacter crescentus is an oligotrophic bacterium which divides asymmetrically to generate a sessile stalked cell and a flagellated swarmer cell. While the stalked cell immediately enters the next cell cycle, the swarmer cell remains in G1 phase for a definite time before differentiating into a stalked cell by losing the flagellum, pilli and producing an adhesive organelle, the holdfast. This cell cycle progression is controlled by cyclic di-GMP signaling and associated phosphorylation networks. We have developed a microfluidic assay to show that swarmer cells can attach immediately after the cell division if they encounter a surface during growth, suggesting that the cell cycle program for motile-sessile transition can be overridden when cells mechanically sense the surface.

By controlling the fluid flow in the microchannel, we find that a drag force of about 20 pN is sufficient to induce $> 50\%$ of the 'newborn' swarmer cells to attach immediately after the division. This surface mediated attachment is strongly dependent on pilli, active flagellum, intact holdfast production and cyclic di-GMP concentration. High speed imaging studies show that swarmer cells, which do not attach immediately, have a tendency to rotate $(20 - 30$ Hz) just before they separate from the stalked cell. Immediately attaching swarmers do not rotate but show a directional creeping suggesting surface attachment.

BP 1.8 Mon 11:45 H43

Search patterns of human T-cells — •Marc Neef[1], Hélène Lyrmann[2], Carsten Kummerow[2], Markus Hoth[2], and Karsten Kruse[1] — [1]Theoretische Physik, Universität des Saarlandes, 66041 Saarbrücken — [2]Biophysik, Universität des Saarlandes, 66421 Homburg

At the start of immune response, the T-cells have no detailed information about the locations of their target cells, so they have to perform a random search. The effectiveness of this search depends on the geometry of the search area as well as on the type of the random search. We track primary human T-lymphocytes using in vitro time-lapse microscopy and compare the experimental tracks to theoretical models like Lévy-Walks, persistent random walks and more complex models. We analyse displacements, gyration and velocity auto correlation of experimental and theoretical tracks and find, that these features are best fitted with a model, that alternates between persistent motion and a resting phase.

Furthermore we test the effectiveness (i.e. average search time) of different search models in simple geometries. We find that the most effective model as well as the optimal parameters for this model strongly depend on the system size.

BP 1.9 Mon 12:00 H43

Modelling malaria parasite motility in heterogeneous environments — •Anna Battista[1], Friedrich Frischknecht[2], and Ulrich Schwarz[1] — [1]ITP, Heidelberg University, Germany — [2]University Clinics Heidelberg, Germany

Plasmodium sporozoites are the parasites responsible for malaria transmission from a mosquito to a vertebrate host. The movement of a sporozoite in the skin of the host appears to be irregular, whereas the same parasite describes a roughly circular trajectory on a flat substrate and a roughly helical trajectory in an unstructured 3D environment [1, 2]. Experiments performed in the Frischknecht group at Heidelberg University focused on the motion of sporozoites within regularly patterned micropillar arrays [3], corroborating the idea that the movement of the parasite is strongly determined by the nature of the surrounding environment. It is expected that the parasite has evolved a strategy to cope with irregularities in its environment, because malaria can develop only if a sporozoite reaches a blood vessel within a relatively short time after injection. We present a first theoretical model which predicts trajectories based on geometrical and energetic considerations. In particular, we discuss different scenarios for the interaction with obstacles and how these change the circular/helical path in 2D/3D environments. [1] S. Muenter et al., Cell Host & Microbe Vol. 6, 2009. [2] R. Amino et al., Nat. Med. Vol. 12, 2006. [3] J.K. Hellmann et al., Plos Pathogens Vol. 7, 2011.

BP 1.10 Mon 12:15 H43

Swimming mechanism of the African trypanosome using mesoscale hydrodynamics simulations — •Davod Alizadehrad and Holger Stark — ITP, TU Berlin

The African trypanosome is a microswimmer with a unique morphology that migrates through the blood-brain barrier and causes the devastative sleeping sickness. The trypanosome has a single flagella, which is firmly attached along its length to the membrane of the elongated cell body and has a free anterior part beyond the cell body [1]. A bending wave propagating along the flagellum pulls the cell body forward [1].

We simulate the swimming behavior of the trypanosome using a mesoscale particle base model with parallel computing on supercomputers. Our simulation reproduces the swimming dynamics of the trypanosome perfectly. The numerical results demonstrate that the free anterior part of the flagella together with its helical attachment to the cell body determines the swimming behavior and dynamics of the trypanosome. Simulation results for the swimming velocity and the ratio of the body rotational frequency to the propogating wave frequency agrees very well with experimental observations [1]. The simulations predict how the mechanical properties of the flagella, the cell body and the surrounding fluid affect the trypanosome locomotion and morphology. Furthermore we study the trypanosome locomotion within a crowded environment containing red blood cell sized particles.

1. Heddergott N, et al. (2012) PLoS Pathog 8(11): e1003023.

BP 1.11 Mon 12:30 H43

Analyzing the mechanics and energetics of motile bacteria with object-adapted optical traps — •Julian Roth, Matthias Koch, and Alexander Rohrbach — Lab for Bio- and Nano-Photonics, University of Freiburg, Georges-Koehler-Allee 102, 79110 Freiburg, Germany

The spread of bacterial diseases and their pathogenicity can often be directly linked to their ability to move under different environmental conditions. In order to understand the basic locomotion principles of single helical bacteria, we use the recently developed object-adapted optical trapping and shape-tracking technique [1] to analyze their complex movements. In particular, we investigate Spiroplasma melliferum and the Spirochetes Borrelia japonica. Spiroplasma belong to the smallest and simplest forms of life, they cause tremendous agricultural damage, but their motility is not completely understood so far. As we show, Spiroplasma can rapidly undergo continuous transitions between different states of mechanical energy during motility. These transitions are related to conformational changes of the molecular subunits of their unique fibril-like cytoskeleton. We track their shape with nm precision at rates up to 1 kHz and estimate the energetics and forces involved in this process. In this project, we develop a model describing the potential landscape of the cytoskeletal ribbon and try to link it to different environmental influences, which we control by the addition of drugs, changes of the viscosity or the pH value of the surrounding medium. First experimental and computational results are presented.

[1] Koch, M. & A. Rohrbach (2012). Nature Photonics 6(10): 680-686

BP 1.12 Mon 12:45 H43

The Physical Bounds of In Vivo Cell Motility — •Josef A. Käs — Division of Soft Matter Physics, Institute for Experimental Physics I, University of Leipzig

Migration of cells through tissues is quintessential for wound healing, neuronal plasticity, and the functioning of the immune system. In disease it is also a key determinant of cancer metastasis and nerve regeneration. Mammalian tissues are a new state of active fluid matter. A broad range of different cell types demix like non miscible fluids building natural boundaries for migrating cells. At least to some extent the cells are hold back by an effective surface tension, which is determined by cell-cell adhesion and cell contractility. Individual cells in tissues behave very much like active soft colloids. Thus, cells have

a high probability to get jammed when moving through tissues and collective cell assemblies are close to be frozen by the glass transition. Cells that effectively move through tissues and are able to transgress tissue boundaries are softer and more contractile than cells that stay local in tissues. Soft and contractile avoids jamming and is optimal to overcome boundaries. Naturally, softness has to have its limits. So neuronal growth cones are too soft to carry large loads and thus excessively weak to move efficiently e.g. through scar tissue, which is required for nerve regeneration. Whereas cancer cells optimize their biomechanical and contractile properties for metastasis during tumor progression. In synopsis, the physical bounds that the functional modules of a moving cell experience in tissues may provide an overarching motif for novel approaches in diagnosis and therapy.