Phase-field model of collective cell migration

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Collective migration of eukaryotic cells plays a fundamental role in tissue growth, wound healing and immune response. The motion, arising spontaneously or in response to chemical and mechanical stimuli, is also important for understanding life-threatening pathologies, such as cancer and metastasis formation. We present a phase-field model to describe the movement of many self-organized, interacting cells. The model takes into account the main mechanisms of cell motility - actomyosin dynamics, as well as substrate-mediated and cell-cell adhesion. It predicts that collective cell migration emerges spontaneously as a result of inelastic collisions between neighboring cells: collisions lead to a mutual alignment of the cell velocities and to the formation of coherently-moving multi-cellular clusters. Small cell-to-cell adhesion, in turn, reduces the propensity for large-scale collective migration, while higher adhesion leads to the formation of moving bands. Our study provides valuable insight into biological processes associated with collective cell motility.

Strong anomalous diffusion: beyond the central limit theorem

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Spatiotemporal actin patterns in the cortex of motile amoeboid cells

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Anomalous dynamics of murine neutrophils under chemotacting conditions

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Motility of cells and their ability to sense and react to changes of their environment are of fundamental importance for an efficient immune response. Chemoattractants trigger receptor initiated signaling cascades including the activation of plasma membrane Ca^{2+} channels of the canonical transient receptor potential channel family (TRPC). Here we analyze the influence of TRPC6 channels on cell migration paths of murine neutrophils during chemotaxis towards the keratinocyte-derived cytokine KC. Time lapse sequences are processed to obtain cell paths as a function of time for wildtype neutrophils and TRPC6 knock-out cells. In addition, the KC receptor CXCR2 is blocked. Wildtype cells show a clear mean drift towards the increasing chemotactic stimulus superimposed by correlated fluctuations, whereas drift is reduced and fluctuations are modified for knock-out cells and during receptor blockade. This behavior can be modeled with a fractional Langevin equation driven by Mittag-Leffler correlated fluctuations. Fitting the first and second moments to the analytical results of the Langevin equation allows the estimation of the parameters of the fractional Langevin equation. We discuss changes of these parameters describing anomaly, persistence, mean squared velocity and mean drift and their changes under the different experimental conditions. This allows differentiating the influence of the CXCR2 receptor and TRPC6 channels on cell dynamics. Finally, simulations of the fractional Langevin equation with parameters for the observed experimental conditions are performed to predict the search behavior of cells for longer times and distances similar to in-vivo conditions.

Pattern Formation in Cellular Processes

Frey, Erwin

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Mechanochemical pattern formation

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Entropic transport in corrugated channels: kinetics, rectification & particle separation

Hänggi, Peter
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Excitable behavior and directed cell motility

Iglesias, Pablo
(The Johns Hopkins University, Whiting School of Engineering, Department of Electrical & Computer Engineering, Baltimore, USA)

Distributed classifiers based on synthetic genetic circuits

Ivanchenko, Mikhail
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Elastic responses of tissues and networks under compression

Janmey, Paul
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Brownian and non-Brownian properties of passive particles in an active fluid

John, Thomas
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Microswimmers are present in mostly all aqueous suspensions on earth. Due to the enhanced mixing in such fluids, they are called active fluids. The continuous energy input by swimmers and loss by viscosities show interesting phenomena.
In our experimental investigations we use suspensions of the green alga Chlamydomonas reinhardtii to study the diffusion of passive tracers. The alga has a nearly spherical body of 5 to 10 µm diameter and two flagella, which allow it to swims as a puller. We use polystyrene particles with diameters of few µm as passive tracer particles in the fluid. The position of the alga and the tracer particles are tracked by video microscopy. We analyze the trajectories of the passive tracer particles statistically, e.g. we compute the mean squared displacement or the probability density function of the displacements. We find diffusion characteristics which can be

interpreted as enhanced Brownian diffusion. But the same trajectories show also non Brownian statistics, like a non-Gaussian probability density function of the displacements. The experimental details will be presented on the poster of Levke Ortlieb with the same title.

Shaping a fly wing

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Exact embryonic control of the timing of genome activation in zebrafish: Interplay between the numbers of nucleosomes and transcriptional machinery

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In a developing zebrafish embryo, DNA is initially incompetent for RNA synthesis, so that cells only rely on egg-provided resources during the first rounds of division. Then, once a certain number of cells has been produced, RNA transcription can start. However, the orchestration of transcription repression and activation is a topic of strong debate. In accordance to previous experiments, we now show nucleosomes to function as a highly abundant repressor of DNA in zebrafish.

To address its particular role, we propose a theoretical model consisting of an activator (which only binds to few specific sites) and a repressor (which has uniform probability to bind anywhere on the DNA). We consider the exponential increase of DNA during the first dozen division cycles of an early embryo with fixed repressor/activator concentrations. The model shows that initially DNA stays strongly repressed; yet as DNA replicates free repressors become sparse. This then allows for activators to bind to previously repressed sites and trigger genome activation.

Predictions of the model are in line with our experiments: by adding or depleting the level of nucleosome forming proteins in the early embryo we were able to shift the time when transcription starts. Additional theoretical modifications such as a set of gene specific activators, nonlinearities in the repressor binding to DNA, and variability of cell sizes during divisions can explain the variation in timing of activation for different genes as well as stochasticity of activation on the cellular level. Nonetheless, our main conclusion—repressor levels dictate the point of genome activation—remains unaffected.

Dynamics of active cytoskeletal networks

Koenderink, Gijsje
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Chromosome Folding in Cells

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Spiral actin-polymerization waves can generate amoeboidal cell crawling

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Amoeboidal cell crawling on solid substrates is characterized by protrusions that seemingly appear

randomly along the cell periphery and drive the cell forward. For many cell types, it is known that the protrusions result from polymerization of the actin cytoskeleton. However, little is known about how the formation of protrusions is triggered and whether the appearance of subsequent protrusions is coordinated. Recently, the spontaneous formation of actin-polymerization waves was observed. These waves have been proposed to orchestrate the cytoskeletal dynamics during cell crawling. Here, we study the impact of cytoskeletal polymerization waves on cell migration using a phase-field approach. In addition to directionally moving cells, we find states reminiscent of amoeboidal cell crawling. In this framework, new protrusions are seen to emerge from a nucleation process, generating spiral actin waves in the cell interior. Nucleation of new spirals does not require noise, but occurs in a state that is apparently displaying spatio-temporal chaos.

A new strategy to regulate bi-directional cargo transport by molecular motors

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Intra-cellular transport by molecular motors Kinesin and Dynein along microtubules is a critical mechanism of cargo transport in eukaryotes, which is driven by the mechanochemical activity of these motors. Intra-cellular cargos in eukaryotes moving along MTs often move bidirectionally in a back and forth manner, reflecting the opposite motile activity of kinesin and dynein motors. It is clear from recent studies that bidirectional intracellular cargo transport is regulated in cells with the help of several regulatory proteins. Here, I will discuss a new strategy to regulate the bidirectional cargo transport by opposing motors.

Deciphering bacteria-surface interaction and early biofilm development with Reflection Interference Microscopy

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Using a unique experimental setup and extensive image analysis, we study the dynamics of Pseudomonas aeruginosa bacteria adhering to a surface under flow, and forming microcolonies.

Interference contrast microscopy enables the measurement of the precise angle between each bacteria and the substrate, fluorescence microscopy provides a visual detection of specific gene expression within the cells, while post-aquisition image analysis gives the motility of each cell. Together, these techniques give a complete picture of the dynamics of a population of bacteria upon surface attachment and of the modifications at stake. In particular, we highlight the co-existence of several subpopulations of cells with radically different phenotypes, and the role of each of them in early biofilm development.

Dynamics of circulating cancer cells

Lio, Pietro
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An important paradigm in proteomics is ‘structure makes function’. High-throughput Chromosome Conformation Capture (3C) technologies, detecting contact frequencies between genomic segments, have made it possible to test this paradigm for genome architecture. However, despite the large availability of Omics data, such as methylation, Histone modification and gene regulation, and of High-throughput 3C data, such as 5C and Hi-C, there are currently limited methodologies for putting together spatial and functional genomic information. Such integration is especially challenging due to differences in resolution between data sets. We present a unified framework for the analysis of 3C and multi-omic data, that will consider fluorescent images and will focus on a multi-scale (fractal) model of genome packing. We show that our approach could provide insights into the complex structure of chromosomes and present derived metrics for testing for causality between spatial and omics data. This approach could further prove useful for studying how structure and function at the nucleus act and react together with respect to

external signals, and how this in turn translates into phenotype and disease conditions.

The cyanobacterial circadian clock, from test tube to cell

Lubensky, David K.
(University of Michigan, Physics, Ann Arbor, USA)

Bacterial segregation dynamics succeeding genetic variation

Maier, Berenike
(Universität zu Köln, Biozentrum, Köln, Germany)

Facilitated diffusion and rapid search hypothesis

Metzler, Ralf
(Uni Potsdam, Physics & Astronomy, Potsdam, Germany)

Long-range ordered vorticity patterns in living tissue induced by cell division

Oddershede, Lene
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In healthy blood vessels with a laminar blood flow, the endothelial cell division rate is low, only sufficient to replace apoptotic cells. The division rate significantly increases during embryonic development and under halted or turbulent flow. Cells in barrier tissue are connected and their motility is highly correlated. We investigated the long-range dynamics induced by cell division in an endothelial monolayer under non-flow conditions, thus mimicking the conditions during vessel formation or around blood clots. We found that cell divisions induce long-range, well-ordered vortex patterns extending several cell diameters away from the division site, in spite of the system's low Reynolds number [1]. Our experimental results are well reproduced by a hydrodynamic continuum model simulating division as a local pressure increase corresponding to a local tension decrease [1]. Such long-range physical communication may be crucial for embryonic development and for healing tissue, for instance around blood clots.

[1] N.S. Rossen, J.M. Tarp, J. Mathiesen, M.H. Jensen, L.B. Oddershede, Long-range ordered vorticity patterns in living tissue induced by cell division, accepted for publication in Nature Communications (2014).

Non-linear auditory dynamics and critical oscillators in insect ears

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Contractility-mediated scaling of diffusive mechano-morphogen gradients

Safran, Samuel
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Active transport along cytoskeletal filaments in the presence of anisotropy

Shaebani, Reza
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Cytoskeleton consists of a variety of interconnected biopolymer networks, including filamentous actin, microtubules, and several types of intermediate filaments. Motor proteins perform directed motion along cytoskeleton due to the structural asymmetry of the filaments. The long distance intracellular transport becomes feasible through the active transport on microtubule networks which span through the entire cell. On the other hand, the dynamics is relatively slow on actin filaments which can be found e.g. near the cell membrane, and have a more random structure i.e. a more uniform polarity. One usually observes a gradual change in the cytoskeletal anisotropy from the nucleus to the cell membrane, as the relative contribution of the microtubules and actin filaments changes. We study the effect of cytoskeletal anisotropy on the transport properties of motor proteins. Different scenarios for the gradient of anisotropy are investigated in the framework of a previously developed analytical approach, and the results are compared with Monte Carlo simulations.

Dissecting bacterial motility strategies across scales

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3D tracking reveals bacterial motility strategies and their mechanical constraints

Taute, Katja
(FOM Institute AMOLF,)

Many bacteria swim in liquids and demonstrate complex motility patterns. The increasingly recognized diversity of these random-walk strategies for space exploration and resource exploitation raises intriguing questions about the underlying physical mechanisms and their optimization by evolutionary selection. To efficiently characterize these diverse motility strategies, we have developed a novel 3D bacterial tracking method capable of simultaneously following tens of micron-sized bacteria at micron-scale resolution over a range of $sim 350times300times200mu$m. Here, we present two example applications that highlight the role of physical constraints in bacterial motility.
First, we perform a high throughput study on the well-known run-tumble motility of the model bacterium {it E. coli}, consisting of alternating phases of smooth translational movement (“runs”) and brief reorientation events (“tumbles”). Remarkably, our analysis reveals a number of features never previously reported, including a relationship between the run speed and the average turning angle $theta$ incurred during tumbles. We use our data to infer mechanical constraints on run-tumble motility and relate our findings to analytical models for optimality considerations~[1,2].
Second, we observe run-reverse-flick motility of the marine bacterium {it V. alginolyticus} where reorientation events alternate between reversals and “flicks” of a smaller angle. The previously observed broad population distribution of flick angles with a mean near 90^circ suggests a complete randomization of the swimming direction during the flick, corresponding to zero persistence: $langlecosthetarangle=0$~[3]. Instead, we show that $sim 80$% of the population variance results from differences between individuals. For each individual, the flick angles are nearly constant and correlate with its body length, consistent with hydrodynamic models~[4].
Our findings not only permit insight into the mechanisms underlying bacterial reorientation events but also point to mechanical individuality as a source of behavioural diversity in motile bacterial populations.
[1] Locsei, J. Math. Biol. 55:41, 2007.
[2] Taktikos, Stark, Zaburdaev. PloS ONE 8:e81936, 2013.
[3] Xie, Altindal, Chattopadhyay, Wu. PNAS 108:2246, 2011.
[4] Son, Guasto, Stocker. Nature Physics 9:494, 2013.

Spindle assembly via rotational diffusion of microtubules

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Mechanisms enabling plasticity of cancer cell motility under changing extracellular matrix conditions

Tozluoglu, Melda
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Not-so-random walks: How motility appendages, exopolysaccharides, and cdiGMP signals impact early biofilm motility and organization

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