BP 1: Cell Migration and Tissue Dynamics

Time: Monday 9:30–13:00 Location: C 243

Invited Talk BP 1.1 Mon 9:30 C 243

Chemotaxis and Cell Migration: Sensing and Intracellular Dynamics — •Eberhard Bodenschatz, Carsten Beta, Albert Bae, and Gabriel Amselem — MPI for Dynamcis and Self-Organization, Goettingen, Germany

We report on chemotaxis and cell migration of the eukaryote Dictyostelium d.(Dicty) under well-controlled spatial and temporal stimuli in microfluidic devices. First the chemotactic response to stationary, linear gradients of cAMP will be reported. In shallow gradients of less than 10ˆ-3 nM/μm, the cells showed no directional response and exhibited a constant basal motility. In steeper gradients, cells moved up the gradient on average. In very steep gradients, above 10 nM/μm, the cells lost directionality and the motility returned to the sub-threshold level. We found cells to be able to chemotact well even when the average difference in receptor occupancy at the front and back of the cell is estimated to be only about 10 receptor molecules. Then we report experiments on the intracellular response of of PH-domain proteins to well controlled chematractant gradients. We use the photo-chemical release of caged cAMP in microfluidic devices to expose single chemotactic cells to spatio-temporally well controlled chemoattractant stimuli (switching time approx. 0.5 sec and arbitrarily shaped gradients). We found that the translocation signal sets in with a finite response only for steep gradients. At shallow gradients no translocation signal could be measured. A theory describing polarization of the intracellular signaling system will be presented. This work is in collaboration with W. Loomis, H. Levine and W. Rappel at UCSD.

Invited Talk BP 1.2 Mon 10:00 C 243

Regulation of Growth during Development: Role of Mechanics — •Lars Hufnagel — EMBL Heidelberg, Heidelberg, Germany

A fundamental and unresolved problem in animal development is the question of how a growing tissue knows when it has achieved its correct final size. A widely held view suggests that this process is controlled by morphogen gradients, which adapt to tissue size and become flatter as tissue grows, leading eventually to growth arrest. I will discuss the spatio-temporal dynamics of that the decapentaplegic (Dpp) morphogen distribution in the developing Drosophila wing imaginal disk and present an alternative model for wing size determination and proliferation control in tissues.

15 min. break

BP 1.3 Mon 10:45 C 243

A generalized Laplace law describes cell and tissue shape — •Ilka Bischofs[1], Franziska Klein[2], Dirk Lehnert[2], Martin Bastmeyer[2], and Ulrich Schwarz[3] — [1]Department of Bioengineering, UC Berkeley, USA — [2]Institute of Zoology I, University of Karlsruhe, Germany — [3]BIOQUANT, University of Heidelberg, Germany

Cues from adhesion geometry, tension and elasticity are important decision factors controlling cell and tissue differentiation. Here we study biological shape determinants across cell and tissue scales. Quantitative microscopy reveals that in both cases edges spanning adhesion sites form circular arcs with a distance dependent curvature. Computer simulations suggest that this is a universal result from isometric tension generated in a filamentous network whose mechanics is controlled by a cable-like, asymmetric response to tension and compression. The model yields a generalized Laplace law that maps onto an elastic contour model of competing line and surface tension. Actomyosin inhibition experiments in conjunction with model fitting are then used to address how cells control shape by actively modulating motor tension and contour elasticity.

BP 1.4 Mon 11:00 C 243

Pattern formation by biological cells: the influence of mechanical boundary conditions — •Pablo Fernández and Andreas R. Bausch — E22 Biophysik, Technische Universität München, D-85748 Garching, Germany

Mechanotransduction, the ability of living cells to sense mechanical tension and accordingly modify their phenotype, is drawing increased attention both from biologists and physicists as a general phenomenon in eukaryotic cells, comparable to chemotaxis in its physiological importance. As most cells spontaneously exert contractile forces under adhesive conditions, the possibility arises of their mechanical cross-talk through the extracellular matrix, with fascinating implications for the formation of tissues. Here, we study pattern formation in cell collections as a function of the mechanical boundary conditions. We place osteoblasts inside collagen gels of sizes 0.3–3 mm with various shapes. Within 1–2 days cells elongate into patterns following the asymmetries dictated by the gel shape. The edges of the gel are free and thus provide "zero tension" boundary conditions. Inclusion of pillars to anchor the gel renders them "zero displacement" and changes the cell pattern. As expected for a cooperative effect based on mechanical interactions, a strong effect of cell density is observed. The experiment thus offers a possible approach for a quantitative characterisation of mechanical interaction between cells.

BP 1.5 Mon 11:15 C 243

Strain Energy during Cell Invasion in Three-Dimensional Collagen Gels — •Thorsten M. Koch[1], Stefan Münster[1], Claudia T. Mierke[1], Philip Kollmannsberger[1], James P. Butler[2], and Ben Fabry[1] — [1]Department of Physics, University of Erlangen-Nuremberg, Germany — [2]Physiology Program, Harvard School of Public Health, Boston, USA

Cell invasion through a dense 3-dimensional matrix is believed to sensitively depend on the ability of cells to generate traction forces. To quantify cell tractions, we measured the strain energy of MDA-MB-231 breast carcinoma cells that invaded into a reconstituted collagen gel ($G' = 80$Pa, 500μm thickness, average mesh size 1μm). Alternatively, we also suspended cells in the collagen solution prior to polymerization. In both cases, cells assumed an elongated spindle-like morphology and locally contracted the gel. The undeformed state of the gel was measured after addition of the actin-disrupting drug cytochalasin-D. Gel deformations were quantified by tracking the spatial positions of fluorescent beads (⌀1μm) embedded in the gels. The bead positions served as nodes for a finite element tessellation. From the local strain of each element and the elasticity of the collagen, we computed the local strain energy stored in the collagen gel surrounding the cell. This technique was verified by indenting the surface of the gel with a steel sphere (⌀100μm, gravitational force 35.4nN). The strain energy of invaded cells was 14pJ, compared to only 1.01pJ of cells on a 2-D planar surface. These results demonstrate that tumor cells exert substantial traction forces during invasion.

BP 1.6 Mon 11:30 C 243

Cell migration through connective tissue in 3-D — •Claudia Tanja Mierke, Philip Kollmannsberger, Thorsten Koch, Daniel Paranhos-Zitterbart, and Ben Fabry — Universität Erlangen, Biophysik, Erlangen, Deutschland

A prerequisite for metastasis formation is the ability of tumor cells to invade and migrate through connective tissue. We analyzed the role of matrix-degrading enzymes, adhesion receptor expression, contractile force generation, and remodeling of cytoskeletal structures for cell invasiveness. We studied 51 well-established tumor cell lines regarding their ability to migrate through a collagen matrix. 27 cell lines were found to be non-invasive, and 24 cell lines were invasive to different degrees that we quantified by the number density of cells that invaded into the gels, multiplied with the average invasion depth. 2-D and 3-D traction microscopy was used to measure contractile forces. Adhesion strengths, cytoskeletal stiffness and molecular turn-over rates were measured using magnetic tweezer microrheology. The speed of cytoskeletal remodelling processes was characterized using nanoscale particle tracking. MMP-14 matrix metalloproteinase and 14 integrin adhesion receptor expression was measured using FACS analysis. We found that cell invasiveness correlated with increased expression of MMP-14 matrix metalloproteinase and integrin receptors (alpha3 and 5), increased contractile force generation, and increased speed of cytoskeletal reorganization. In summary, our results may help identify molecules and signal transduction pathways that control tumor invasion and metastasis formation.

BP 1.7 Mon 11:45 C 243

Stochastic Lamellipodium Dynamics and Forces in Cell Motility — •Daniel Koch[1], Melanie Knorr[1], Thomas Fuhs[1],

Timo Betz[2], Ulrich Behn[1], and Josef Käs[1] — [1]University of Leipzig, Leipzig, Germany — [2]Institute Curie, Paris, France

Cell motility is fundamental for cell migration and cell growth and therefore it is a basis for the understanding of many processes in natural phenomena such as development, neuronal plasticity, and cancer metastasis. The dynamics and forces in the lamellipodium of cells, a thin veil-like structure at the leading edge, are governed by the polymerization of actin filaments and the forces generated by the molecular motor myosin.

Investigation of the leading edge dynamics in combination with flow and force measurements in neuronal growth cones, fish keratocytes, and fibroblasts, gives new insight into the interplay of actin polymerization and retrograde flow and allows comparing the differences and similarities in motility in these different cell systems. We have developed a stochastic model that consistently describes actin polymerization, retrograde flow and edge dynamics in these cell systems. Furthermore, the measurement of the internal flow as well as the viscoelastic material properties of the cell allows calculating the internal force field acting within the lamellipodium. Finally, the measurement of the external traction forces completes the picture of the forces acting on a cell. All this information is combined into a complete picture of cell motility to address the question of universal mechanisms in the motility machinery of cells.

BP 1.8 Mon 12:00 C 243

Phase transitions in tissue growth — •Reza Farhadifar[1], Jens-Christian Röper[2], Benoit Aigouy[2], Suzanne Eaton[2], and Frank Jülicher[1] — [1]Max Planck Institute for the Physics of Complex Systems, Nöthnitzer Straße 38, 01187 Dresden — [2]Max Planck Institute of Molecular Cell Biology and Genetics, Pfotenhauer Straße 108, 01307 Dresden

We present a theoretical study of growing epithelia using a vertex model. The network of adherence junctions is represented by a network of polygons. The mechanics of cells and their adhesive interactions are described by area elasticity, perimeter contractility and line tension. The ground state diagram of the model reveals a solid-liquid transition. Simulating tissue growth by repeated division of randomly selected cells we generate epithelial tissue morphologies. These tissue morphologies exhibit phase transitions between solid and soft network as a function of parameter values. We study the behavior of the order parameter of the transition which is the shear modulus of the network. The solid network first becomes semi-soft and subsequently it becomes fluid. In the fluid phase, T1 transitions can occur without work which permits the network to shear at vanishing shear modulus.

BP 1.9 Mon 12:15 C 243

Kinetics and scaling laws of growing cell populations — •Markus Radszuweit[1], Michael Block[1], Eckehard Schöll[1], and Dirk Drasdo[2] — [1]Institut f. Theo. Physik, Sekr. EW 7-1, Technische Universität Berlin, Hardenbergstr. 36, 10623 Berlin, Germany — [2]INRIA, Rocquencourt, France

We study the growth kinetics and the critical surface dynamics of cell monolayers by a class of computationally efficient cellular automaton models avoiding lattice artifacts [1]. Our numerically derived front velocity relationship indicates the limitations of the Fisher-Kolmogorov-Petrovskii-Piskounov (FKPP) equation for tumor growth simulations. The critical surface dynamics corresponds to the Kardar-Parisi-Zhang (KPZ) universality class, which disagrees with the interpretation by Bru et al. [2] of their experimental observations as generic molecular-beam-epitaxy (MBE)-like growth. By comparison with a new cellular automaton for three-dimensional growth we demonstrate the agreement of the cell population kinetics in two and three dimensions.

References:
[1] M. Block, E. Schöll, and D. Drasdo, Phys. Rev. Lett. (accepted) 2007.
[2] A. Brú, S. Albertos, J. L. Subiza, J. L. García-Asenjo, and I. Brú, Biophys. J. 85, 2948 (2003).

BP 1.10 Mon 12:30 C 243

Dynamics of Anisotropic Tissue Growth — •Thomas Bittig[1], Ortrud Wartlick[2], Anna Kicheva[2], Marcos González-Gaitán[2], and Frank Jülicher[1] — [1]Max Planck Institute for the Physics of Complex Systems, Nöthnitzer Straße 38, 01187 Dresden, Germany — [2]Department of Biochemistry and Department of Molecular Biology, Geneva University, Sciences II, Quai Ernest-Ansermet 30, 1211 Geneva 4, Switzerland

During the development of multicellular organisms, organs grow to well-defined shapes and sizes. The proper size and patterning of tissues are ensured by signaling molecules as e.g. morphogens. Secreted from localized sources, they form graded concentration profiles in the target tissue which provide positional information to the cells.

We describe the growing tissue as a viscous fluid medium in which cell division induces active stresses that drive cell rearrangements. We focus on the case where cell division is anisotropic and a preferred orientation of cell division exists. We determine cellular flow fields using both analytical and numerical methods. If cell division and cell death balance, there is no net growth, but for anisotropic cell division the tissue undergoes spontaneous shear deformations. This is an example of convergence-extension movements which are often observed in developing tissues. Our theory of tissue growth provides a basis for the study of the transport of signaling molecules in growing tissues. Using our theory, we discuss the diffusion and degradation of morphogens in the growing Drosophila wing disk, a precusor of the fly wing.

BP 1.11 Mon 12:45 C 243

Simulations and model validation by measurements in an isolated rabbit heart — •Steffen Bauer[1], Inaki Romero[1], Rodrigo Weber dos Santos[2], Hans Koch[1], and Markus Bär[1] — [1]PTB Berlin — [2]Univ. Juiz de Fora, Brazil

Time-resolved surface activation time maps recorded from isolated rabbit hearts were analyzed in order to compare them with analogue maps generated by a computer model. Recordings were obtained under normal conditions as well as after the administration of ajmaline and palmitoleic acid (PA). In parallel, the measured quantities were simulated in a realistic computer model of the rabbit heart. The effect of ajmaline was reproduced by reducing the conductivity of sodium channels G_Na in the model. It was observed that addition of a given amount of ajmaline leads to an increase of the QRS time of up to 33 % and a decrease of typical velocities by 20-40 % with respect to normal conditions. A velocity decrease of about 20 % was reproduced in the computer model by a reduction of the G_Na by 60 %. Such a change in the model induces a corresponding increase of the QRS time by 20%. In contrast, administration of PA leaves the QRS time unchanged, while it reduces the speed by a similar margin as the ajmaline.