Program

Invited Speakers

Karen Alim (Germany) • Ingo Bechmann (Germany) •Stefan Diez (Germany)
Ben Fabry (Germany) • Clemens Franz (Germany) • Erwin Frey (Germany)
Ramin Golestanian (UK) • Kay Gottschalk (Germany) • Stephan Grill (Germany)
Jochen Guck (Germany) • Mohit Kumar Jolly (USA) • Ulrike Köhl (Germany)
Nastaran Zahir (USA) • Jan Lammerding (USA) • Rudolf Merkel (Germany)
Jae Hun Kim (USA) • Marija Plodinec (Switzerland) • Karsten Rippe (Germany)
Jennifer Schwarz (USA) • Pascal Silberzan (France)
Ana-Suncana Smith (Germany) • Joachim Spatz (Germany)
Daniel Sussman (USA) • Aftab Taiyab (Canada) • Xavier Trepat (Spain)
Katarina Wolf (The Netherlands) • Tobias Zech (UK)

Organizing Committee

Carsten Beta (Germany) • Josef A. Käs (Germany)
Harald Herrmann (Germany) • David M. Smith (Germany)

General Information

Dear participants,

welcome to the 8th *Annual "Physics of Cancer" Symposium* held at the *Max Planck Institute for Evolutionary Anthropology* and *Centre for Biotechnology and Biomedicine.* This fall, we look forward to a meeting again assembling scientists worldwide pioneering in the investigation of the physical mechanisms underlying cancer progression.

For more information, please visit our conference website:

http://conference.uni-leipzig.de/poc/2017/

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Imprint

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City of Leipzig

Leipzig is a vibrant metropolis in the heart of former East Germany. It is well known for its cultural, especially musical, history and famous for its trade fairs and exhibitions. Leipzig played a significant role in the peaceful revolution of 1989, which led to the fall of the Berlin Wall and finally of communism in Eastern Europe.

Photo: Michael Bader, CC-BY

The *University of Leipzig*, being one of Europe's oldest universities, looks back to a long tradition. Many famous names, including Bach, Mendelssohn, Goethe, Lessing, Leibniz, Debye, Ostwald, Bloch, Hertz, and Heisenberg, are associated with Leipzig and its university.

Leipzig's Public Transport System

The city of Leipzig and its surrounding areas are part of *MDV local public transport association*. It consists of **tram and bus lines** as well as a metro-like railway called **S-Bahn** (and some regional trains). Trams and buses are operated by the *LVB*, while the S-Bahn is operated by *DB (Deutsche Bahn)*. However, they all share the same ticket system. Ticket fees are distance-based (zones). Here are some examples:

- *"Kurzstrecken-Fahrkarte"* (short distance ticket) is valid for a maximum of four stops with tram or bus within the city of Leipzig (zone 110) without interchange option or for a maximum of one stop with the S-Bahn (fee 1.90 EUR).
- *"Einzelfahrkarte - 1 Zone Stadt Leipzig"* (full single ticket for 1 zone city of Leipzig) is valid for 1 hour for travel within the city of Leipzig (zone 110) with the option to interchange to any other tram, bus, and S-Bahn lines (fee 2.60 EUR).
- *"Einzelfahrkarte - 2 Zonen"* (full single ticket for 2 zones) is valid for 1,5 hours for travel within two zones with the option to interchange to any other tram, bus, and S-Bahn lines (fee 3.30 EUR).
- There also options for day or week tickets which are also distance-based.

Tickets are bought at ticket machines located on most platforms and in some trams (not S-Bahn!) as well as directly from bus drivers. The machines accept cash. Tickets have to be validated prior travelling using the stamping machines located on the platforms (S-Bahn) or inside the vehicle (trams and buses).

General information on Leipzig's public transportation system, timetables, and a connection planner can be found at **www.lvb.de**. There, you also find network maps for day and night.

(Note: The *DB (Deutsche Bahn)* additionally operates inter-city trains (called "IC" and "ICE") and some regional trains (called "RB" and "RE") which are included in the *MDV local public transport association*. These trains have a separate DB ticket system. DB ticket machines offer both, MDV tickets and DB tickets. LVB and MDV ticket machines, on the other hand, offer MDV tickets only.)

Conference Venues

The "Physics of Cancer" symposium will take place at:

Max Planck Institute (MPI)
for Evolutionary Anthropology
Deutscher Platz 6
04103 Leipzig, Germany
second floor

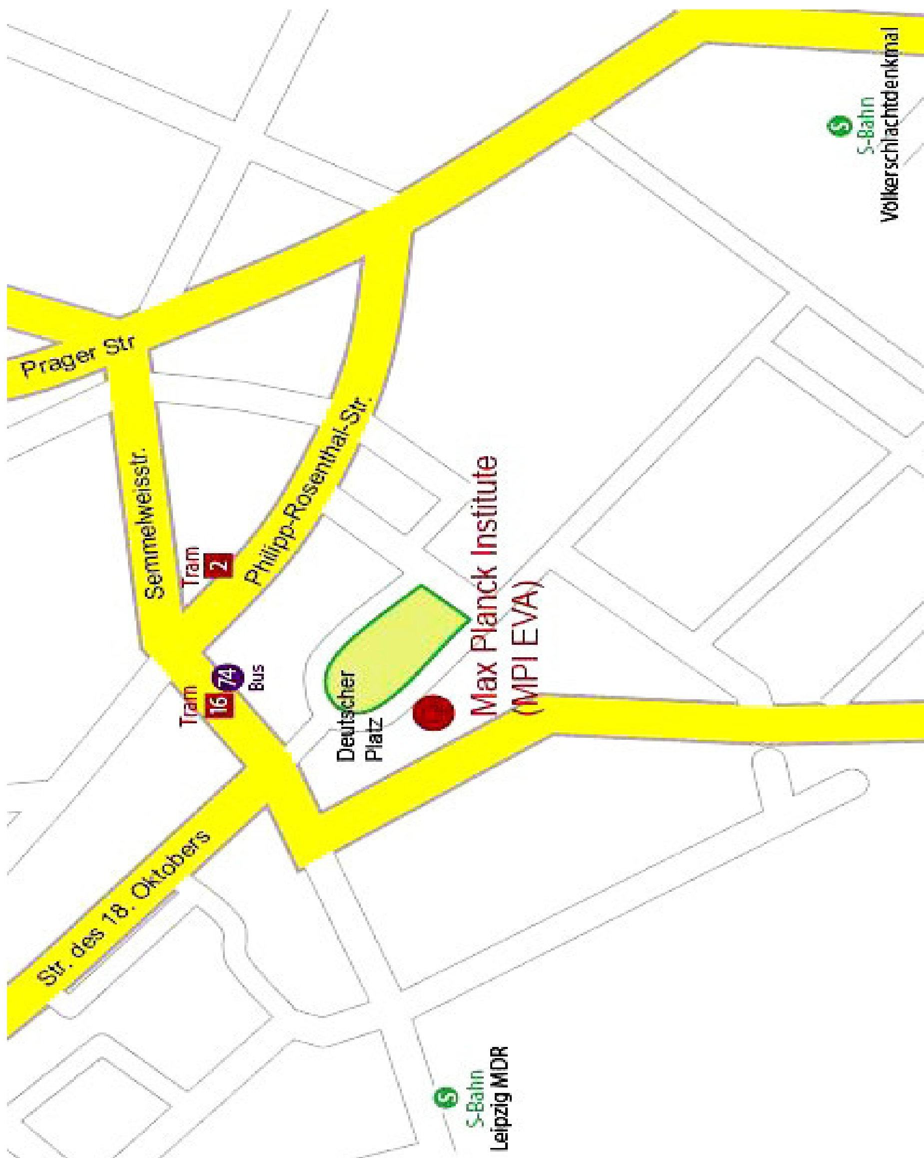
and

Biocity Leipzig - University of Leipzig
Center for Biotechnology and Biomedicine (BBZ)
Deutscher Platz 5
04103 Leipzig, Germany
foyer/ ground floor

You quickly reach the venues from Leipzig main station by tram. Buy a ticket "Einzelfahrkarte Leipzig" at one nearby automat and stamp it on the tram after entering it. Take tram number 16 (direction "Lößnig"), leave tram at stop called "Deutsche Nationalbibliothek". Turn to the left, go across "Semmelweissstraße" towards a park-like area. The buildings are situated on the right hand side.

A taxi ride from the airport to the MPI for Evolutionary Anthropology costs about 40 EUR.

For more information on how to get to Leipzig, have a look at the travel information on our conference website.



Source: http://www.eva.mpg.de/directions.html?Fsize=0durchFehn

Presentations

Scientific presentations will be held either orally (talk) or by poster.

Talk sessions will take place in the large auditory hall of the *Max Planck Institute for Evolutionary Anthropology*. The room is equipped with a video projector with VGA input. Contributed talks are allocated 15 min (including discussion), whereas invited talks are allocated 20 min plus 10 min discussion.

The poster session will be on Thursday, October 5th, 2017 at 12:30 at the foyer of the *Center for Biotechnology and Biomedicine (BBZ)*. During this session, a lunch buffet will be provided for all participants. Authors can already mount their posters on Wednesday, October 4, starting from 11:00. Poster boards will be marked with numbers according to the scientific program. Push pins for mounting will be provided. Please remove your poster after the Postersession.

Weekend and National Holiday

In case you arrive some days earlier, please note that in Germany most shops including grocery stores and supermarkets are closed on Sundays and Holidays. However, most restaurants will be open.

On Tuesday, October 3, 2017 there is the national holiday of Germany ("Day of German Unity"). Hence, most shops will not be open.

In Case of Questions...

… or any problems, do not hesitate to ask the conference organizers and assistants for help. You will recognize them by their name badges with names printed in red (in contrast to the black printing of normal name badges).

11:00 – 13:00 *Conference check-in and on-site registration*

13:00 – 13:15 ***Opening and welcome***
JOSEF A. KÄS (University of Leipzig)
ULRICH HÖRNING (City of Leipzig)

Session I: Cell Migration & Invasion

13:15 – 13:45 **Slice Cultures as Tool to Study Cancers in Vitro**
INGO BECHMANN (University of Leipzig, Germany)

13:45 – 14:15 **Hybrid Epithelial/ Mesenchymal Phenotype (E/M) – a "Metastatic Sweet Spot"**
MOHIT KUMAR JOLLY (Rice University, USA)

14:15 – 14:45 **Control of Cancer Cell Invasion by Nuclear Deformability**
KATARINA WOLF (Radboud Institute for Molecular Life Sciences, The Netherlands)

14:45 – 15:00 **High Shear Stresses under Exercise Condition Destroy Circulating Tumor Cells in a Microfluidic System**
SAGAR REGMI (Nanyang Technological University, Singapore)

15:00 – 15:30 **Matrix Adhesion Site Function in Polarised Invasive Migration**
TOBIAS ZECH (University of Liverpool, UK)

15:30 – 16:00 Coffee break

Special Focus Session: Collective Cell Behavior

16:00 – 16:30 **Control of Mechanochemical Self-Organization during Cell Polarization**
STEPHAN GRILL (Technical University Dresden, Germany)

16:30 – 17:00 **Physical Forces Driving Migration, Division and Folding of Epithelial Sheets**
XAVIER TREPAT (IBEC Barcelona, Spain)

17:00 – 17:15 **Mechanisms of Collective Cell Migration and the Influence of the Microenvironment**
ANDREW CLARK (Institute Curie, France)

17:15 – 17:45 **Unjamming and Cell Shape Changes in Breast Cancer**
JAE HUN KIM (Harvard T.H. Chan School of Public Health, USA)

17:45 – 18:15 **Tissue Surface Tension in Simple Models of Dense Biological Tissues**
DANIEL SUSSMAN (Syracuse University, USA)

18:30 ***Welcome Dinner***
Faculty of Physics and Earth Sciences
Linnéstr. 5, 04103 Leipzig, first floor, assembly room.

Session II: Biomechanics

08:15 – 08:30 **Guiding 3D Cell Migration Inside Strained Synthetic Hydrogel Micro-Structures**
MIRIAM DIETRICH (Ludwig-Maximilians-University, Germany)

08:30 – 09:00 **The Weakness of Senescent Fibroblasts**
KAY GOTTSCHALK (University of Ulm, Germany)

09:00 – 09:30 **Cytoskeletal Intermediate Filaments – from Self-Assembly to Cell Mechanics**
JAN LAMMERDING (Cornell University, USA)

09:30 – 10:00 **Interactions of Natural Killer Cells with Cancer Cells in a 3-D Environment**
BEN FABRY (Friedrich-Alexander-University of Erlangen-Nuremberg, Germany)

10:00 – 10:30 ***Coffee break***

10:30 – 11:00 **Integrating Scales in Cancer Mechanobiology: The NCI Physical Sciences – Oncology Network**
NASTARAN ZAHIR (National Cancer Institute, USA)

11:00 – 11:15 **Light Sheet Fluorescence Microscopy: Advantages for Living Specimens**
ULF-DIETRICH BRAUMANN
(Fraunhofer Institute for Cell Therapy and Immunology, Germany)

11:15 – 11:45 **From "CAR T Cells" to CAR Expressing NK Cells for Cancer Retargeting**
ULRIKE KÖHL (Hannover Medical School, Germany)

11:45 – 12:15 **Collectively Emerging Nematic Order in Populations of Fibroblasts**
PASCAL SILBERZAN (Institute Curie, France)

12:15 – 12:30 **Disrupting Chemotaxis Using Contact Guidance of Nanotopography**
SEBASTIAN SCHMIDT (University of Maryland, USA)

POSTER SESSION
12:30 – 15:00
- Presentation of contributed posters with discussions and lunch buffet -

Afternoon **Social Event for Invited Speakers**
(tours "St. Thomas Church" and "Bach Museum", dinner at "Ratskeller Leipzig")

Poster Session

12:30 – 15:00 *Presentation of the contributed posters with discussions and lunch buffet.*

1 **An intriguing similarity between cancer metastasis and financial markets**
CHRISTOPH MARK (Friedrich-Alexander University Erlangen-Nuremberg, Germany)

2 **Direct measurement of surface charge distribution in phase separating supported lipid bilayers**
THOMAS FUHS (University of Leipzig, Germany)

3 **High shear stresses under exercise condition destroy circulating tumor cells in a microfluidic system**
SAGAR REGMI (Nanyang Technological University, Singapore)

4 **Polarization dynamics of single cells and small groups of cells on micropatterns**
SOPHIA SCHAFFER (Ludwigs-Maximilians-University Munich, Germany)

5 **Disrupting Chemotaxis using Contact Guidance of Nanotopography**
SEBASTIAN SCHMIDT (University of Maryland, USA)

6 **Cell morphology of healthy and cancerous oral mucosa**
MAJA STRUGACEVAC (Heinrich-Heine-University Düsseldorf, Germany)

7 **Mechanisms of collective cell migration and the influence of the microenvironment**
ANDREW CLARK (Institute Curie, France)

8 **Blue fluorescent protein as marker for carcinoma cells**
LORENA HENTSCHEL (Heinrich-Heine-University Düsseldorf, Germany)

9 **Bursts of activity in collective ell migration**
OLEKSANDR CHEPIZHKO (Innsbruck University, Austria)

10 **Applications of mass spectrometry and NMR spectroscopy to study cancer-related alterations of the lipid composition**
JENNY SCHRÖTER (University of Leipzig, Germany)

11 **Optical tweezers combined with AFM – Investigating cell mechanics and single molecules on multiple scales**
CARMEN PETTERSSON (JPK Instruments AG)

12 **Insights into cancer progression from in silico simulations of solid tumors with the Virtual Biophysics Laboratory (VBL) program**
SABRINA STELLA (University of Trieste, Italy)

13 **Cell migration through a confined micro-environment: an attempt to understand cancer invasion**
CARLOTTA FICORELLA (University of Leipzig, Germany)

14 **Electron irradiated hydrogels: Reagent-free modification towards biomedical applications**
STEFANIE RIEDEL (Leibniz Institute for Surface Modification, Germany)

15 **Investigation of the effect of snake venoms on different cancer cell lines regarding cell-cell and cell-matrix-interactions**
GERDA SCHICHT (Leipzig University Hospital, Germany)

16 **Cell force-mediated breast cancer invasion is attenuated by basement membrane integrity**
ERIK NOETZEL-REISS (Forschungszentrum Jülich GmbH, Germany)

17 **Guiding 3D cell migration inside strained synthetic hydrogel microstructures**
MIRIAM DIETRICH (Ludwig-Maximilians-University Munich, Germany)

18 **Dynamics of MCF10A cells in microchannels of varying height: experiments and modelling as active nematic**
FELIX KEMPF (Ludwig-Maximilians-University Munich, Germany)

19 **Non-linear compliance of elastic layers to indentation**
ADRIAN FESSEL (University of Bremen, Germany)

20 **Glassy dynamics in composite biopolymer networks**
TOM GOLDE (University of Leipzig, Germany)

21 **E-Cadherin as an upstream regulator of mechanical responses in the early EMT and cancer development**
ERIK W. MORAWETZ (University of Leipzig, Germany)

22 **Altering synthetic semiflexible DNA nanotube networks by tunable crosslinking**
MARTIN GLASER (University of Leipzig, Germany)

23 **Dynamics of cell jamming**
JÜRGEN LIPPOLDT (University of Leipzig, Germany)

24 **Contractility might determine differential adhesion hypothesis during EMT**
Enrico Warmt (University of Leipzig, Germany)

25 **Intricate features of cancer cell migration revealed by collagen live invasion assays**
Steffen Grosser (University of Leipzig, Germany)

26 **MR Elastography on polymer networks: a proof of concept for collagen gels**
Frank Sauer (University of Leipzig, Germany)

27 **Light Sheet Fluorescence Microscopy: Advantages for living specimens**
Ulf-Dietrich Braumann
(Fraunhofer Institute for Cell Therapy and Immunology Leipzig)

28 **Acoustic Force Spectroscopy (AFS): A novel, highly parallel method for cell manipulation and single-molecule force spectroscopy**
Philipp Rauch (LUMICKS, Germany)

29 **Advanced thermorheology of living cells**
Andriy Goychuk (Ludwig-Maximilians-University, Germany)

30 **Mechanical properties of anisotropic polymer structures**
Paul Mollenkopf (University of Leipzig, Germany)

Session III: Cellular Organization

08:15 – 08:30 **Non-Linear Compliance of Elastic Layers to Indentation**
ADRIAN FESSEL (University of Bremen, Germany)

08:30 – 09:00 **Mechanotransduction in Collective Cell Migration**
JOACHIM SPATZ (Max Planck Institute for Medical Research and University of Heidelberg, Germany)

09:00 – 09:30 **Of Active Motors and Passive Crosslinker: Reconstituting Adaptive Microtubule Networks**
STEFAN DIEZ (Technical University Dresden, Germany)

09:30 – 10:00 ***Multiscale Cell Motility: From Substrate Deformation to Collective Migration***
ERWIN FREY (Ludwig-Maximilians-University Munich, Germany)

10:00 – 10:30 ***Coffee break***

10:30 – 11:00 **Emergent Cancer-like Phenomenology in a Simple Model of Cells with Growth and Chemical Signalling**
RAMIN GOLESTANIAN (University of Oxford, UK)

11:00 – 11:15 **Electron Irradiated Hydrogels: Reagent-Free Modification towards Biomedical Applications**
STEFANIE RIEDEL (Leibniz Institute of Surface Modification, Germany)

11:15 – 11:45 **Establishing Nuclear Subcompartments and Chromatin Patterns to Regulate Gene Expression**
KARSTEN RIPPE (German Cancer Research Center Heidelberg, Germany)

11:45 – 12:15 **Strain-Controlled Rigidity Transitions in Cells and the Role of the Cell Nucleus**
JENNIFER SCHWARZ (Syracuse University, USA)

12:15 – 12:45 **Physicochemical Properties of Basement Membranes Formed by a Cell Culture Model of Human Breast Glands**
RUDOLF MERKEL (Forschungszentrum Jülich, Germany)

13:00 – 14:00 ***Lunch break***

Session IV: Tissue Organization

14:00 – 14:30 **Morphology Control by Active Fluid Flows**
KAREN ALIM (Max Planck Institute for Dynamics and Self-Organization, Germany)

14:30 – 14:45 **An Intriguing Similarity between Cancer Metastasis and Financial Markets**
CHRISTOPH MARK (Friedrich-Alexander University of Erlangen-Nuremberg, Germany)

14:45 – 15:15 **t.b.a.**
ANA-SUNCANA SMITH
(Friedrich-Alexander University of Erlangen-Nuremberg, Germany)

15:15 – 15:45 **Physical Aspects of Successful Cell Circulation and Migration**
JOCHEN GUCK (Technical University Dresden, Germany)

15:45 – 16:15 Coffee break

16:15 – 16:45 **Mapping Cadherin-Dependent Cell Adhesion and Elasticity Changes in Tissue Explants during Transition from Collective to Single-Cell Migration**
CLEMENS FRANZ (Karlsruhe Institute of Technology, Germany)

16:45 – 17:15 **Regulation of Actin Cytoskeleton during Epithelial to Mesenchymal Transition – The Ocular Lens Perspective**
AFTAB TAIYAB (McMaster University, Canada)

17:15 – 17:45 **t.b.a.**
MARIJA PLODINEC (University of Basel, Switzerland)

18:00 ***Prospective end***

Session I: Cell Migration & Invasion

Invited Talk Wed 13:15

Slice Cultures as Tool to Study Cancers in Vitro

Ingo Bechmann - University of Leipzig, Medical Faculty, Anatomy, Oststr. 25, 04317 Leipzig, Germany

We have previously established slice cultures from human tumors derived from surgery and biopsies and established methods to study their individual susceptibility to treatments with X-ray, heavy ions, chemotherapy, and novel biologicals. The open access of the system allows for such treatments, but also for life imaging. Deep sequencing has been used to better understand mechanism of tumor resistance to individual therapies. The ultimate goal is to predict the most effective in a personalized way. Funded by the BMBF.

Invited Talk Wed 13:45

Hybrid Epithelial/Mesenchymal Phenotype (E/M) – a 'Metastatic Sweet Spot'

Mohit Kumar Jolly - Rice University, 1080 B, Bioscience Research Collaborative (BRC), 6500 Main St. Houston, TX 77030, USA

Metastases claim more than 90% of cancer-related patient deaths and are usually seeded by a subset of circulating tumor cells (CTCs) shed off from the primary tumor. In circulation, CTCs are found both as single cells and as clusters of cells. The clusters of CTCs, although many fewer in number, possess much higher metastatic potential as compared to that of individual CTCs. This talk will highlight insights gained via an integrated theoretical-experimental framework into molecular mechanisms that can enable the formation of these clusters - (a) hybrid E/M (epithelial/ mesenchymal) phenotype of cells that couples their ability to migrate and adhere, and (b) intercellular communication that can spatially coordinate the cluster formation and provide survival signals to cancer cells. Building upon these molecular mechanisms, we also offer a possible mechanistic understanding of why clusters are endowed with a higher metastatic potential. Finally, we discuss the highly aggressive Inflammatory Breast Cancer (IBC) as an example of a carcinoma that metastasizes via clusters and corroborates the proposed molecular mechanisms.

Invited Talk Wed 14:15

Control of cancer cell invasion by nuclear deformability

Katarina Wolf - Department of Cell Biology, RIMLS, Radboud University Medical Centre, 6500 HB Nijmegen, The Netherlands

Tumor cell migration through 3D tissue depends on a physicochemical balance between tissue constraints, contact-dependent ECM degradation, and deformability of cell and nucleus, respectively. With a focus on lamin- and chromatin-mediated mechanics of the cell nucleus, I will dissect the relative contributions of these parameters under conditions of space confinement in substrate geometries that mimick connective tissue structures in vivo.

Contributed Talk Wed 14:45

High Shear Stresses under Exercise Condition Destroy Circulating Tumor Cells in a Microfluidic System

Sagar Regmi[1], Afu Fu[1], Sierin Lim[1], Kathy Qian Luo[2] —

1 School of Chemical and Biomedical Engineering, Nanyang Technological University, Singapore

2 Faculty of Health Sciences, University of Macau, Taipa, Macau, China

Circulating tumor cells (CTCs) are the primary targets of cancer treatment as they cause distal metastasis. However, how CTCs response to exercise-induced high shear stress is largely unknown. To study the effects of hemodynamic microenvironment on CTCs, we designed a microfluidic circulatory system that produces exercise relevant shear stresses. We explore the effects of shear stresses on breast cancer cells with different metastatic abilities, cancer cells of ovarian, lung and leukemic origin. Three major findings were obtained. 1) High

shear stress of 60 dynes/cm2 achievable during intensive exercise killed more CTCs than low shear stress of 15 dynes/cm2 present in human arteries at the resting state. 2) High shear stress caused necrosis in over 90% of CTCs within the first 4 h of circulation. More importantly, the CTCs that survived the first 4 h-circulation, underwent apoptosis during 16–24 h of post-circulation incubation. 3) Prolonged high shear stress treatment effectively reduced the viability of highly metastatic and drug resistant breast cancer cells. As high shear stress had much less damaging effects on leukemic cells mimicking the white blood cells, we propose that intensive exercise may be a good strategy for generating high shear stress that can destroy CTCs and prevent cancer metastasis.

Reference:

Regmi, Sagar. et al. High Shear Stresses under Exercise Condition Destroy Circulating Tumor Cells in a Microfluidic System. Sci. Rep. 7, 39975; doi: 10.1038/srep39975 (2017).

[1] Regmi, Sagar. et al.: High Shear Stresses under Exercise Condition Destroy Circulating Tumor Cells in a Microfluidic System, Sci. Rep. 7, 39975; doi: 10.1038/srep39975. (2017)

Invited Talk Wed 15:00

Matrix Adhesion Site Function in Polarised Invasive Migration

Tobias Zech[1,4], Daniel Newman[4], Thomas Waring[4], Louise Brown[4], Ewan MacDonald[4], Iben Ronn-Vehland[1], Ourania Chatzidoukaki[4], Arthur Charles-Orszag[1], Vineetha Vijayakumar[2], Gareth E. Jones[2], Patrick T. Caswell[3], Mark R. Morgan[4], Laura M. Machesky[1]

1 The Beatson Institute for Cancer Research, Switchback, Rd., Bearsden, Glasgow, G61 1BD, UK

2 Randall Division of Cell & Molecular Biophysics, King's College London, London, SE1 1UL, UK

3 Wellcome Trust Centre for Cell Matrix Research, Faculty of Life Sciences, University of Manchester, Manchester M13 9PT, UK

4 Cellular and Molecular Physiology, Institute of Translational Medicine, University of Liverpool, Liverpool, L69 3BX

The nucleus is a major constraint on the ability of cells to migrate through dense 3D matrix. In order to progress cells must actively translocate their nuclei through restrictive pores present in the dense extracellular matrix. Using a Nesprin2 based FRET/FLIM biosensor we demonstrate that the nuclei of cells migrating through dense 3D matrices experience greater actomyosin mediated tension in comparison to cells in a less dense or 2D matrix. Further we provide the first indication that the nucleus is being actively pulled forward when cells migrate through 3D matrices in a Nesprin-2 dependant manner. This study set out to examine the mechanisms responsible for the generation of polarised nuclear tension that is required for 3D invasive cell migration. Cancer cells migrating through dense 3D matrices form actin rich degradative adhesion sites, which share properties of both focal adhesions and invadopodia. Using novel proximity labelling (BioID) based interaction screens we have identified a novel interaction module consisting of N-WASP/WIP -> ARHGEF7 -> Myosin18 that is present in invasive 3D adhesion sites. While the loss of this interaction module does not impede protrusion dynamics or matrix degradation, it is essential for differential localisation of non-muscle MyosinIIa (NMIIa) and non-muscle MyosinIIb (NMII2b) at adhesion sites at the protrusive front of the cell and the perinuclear region of cells cancer cells, respectively. The workload difference of NMIIa and NMIIb has the potential to generate contraction force gradients along actomyosin fibers in migrating cells. ARHGEF7 and Myosin18a are therefore essential for the generation of a force gradient from adhesions sites at the leading edge to the nucleus that is required for front–rear polarity of migrating cells. This leads us to hypothesise that actin based nuclear force coupling from adhesion sites in the foundation of polarity in migration and adhesion based cellular motility in 3D matrix.

Invited Talk Wed 16:00

Cytoskeleton Mechanics and Forces in Cancer

Stephan W. Grill — Biotechnology Center TU Dresden, Tatzberg 47/49, 01307 Dresden, Germany

Biological pattern formation often relies on self-organization, integrating chemical with mechanical patterning processes. Guiding cues ensure that the

correct pattern forms at the right time and place, but how they control processes of self-organization to steer pattern formation remains unknown. Here we investigate PAR polarity establishment in C. elegans zygotes, by combining measurements of the spatial distribution of protein numbers and fluxes with a physical theory. We characterize the handover from a pre-pattern to mechanochemical self-organization, and find that guiding cues from the centrosome steer a patterning system comprised of PAR proteins and the actomyosin cortex to a transition point beyond which the patterned state becomes self-organized. This mechanism of controlled pattern formation integrates mechanical and molecular aspects of biological pattern formation with guiding cues.

Invited Talk Wed 16:30

Physical Forces Driving Migration, Division and Folding of Epithelial Sheets

XAVIER TREPAT — Institute for Bioengineering of Catalonia (IBEC), Edifici Clúster c/ Baldiri Reixac 10-12 08028 Barcelona, Spain

Biological processes such as morphogenesis, tissue regeneration, and cancer invasion are driven by collective migration, division, and folding of epithelial tissues. Each of these functions is tightly regulated by mechanochemical networks and ultimately driven by physical forces. I will present maps of cell-cell and cell-extracellular matrix (ECM) forces during cell migration and division in a variety of epithelial models, from the expanding MDCK cluster to the regenerating zebrafish epicardium. These maps revealed that migration and division in growing tissues are regulated cooperatively. I will also present direct measurements of epithelial traction, tension, and luminal pressure in three-dimensional epithelia of controlled size and shape. By examining epithelial tension over time-scales of hours and for nominal strains reaching 300%, we establish a remarkable degree of tensional homeostasis mediated by cellular adaptations.

Contributed Talk Wed 17:00

Mechanisms of Collective Cell Migration and the Influence of the Microenvironment

ANDREW CLARK, DANIJELA VIGNJEVIC — Institut Curie, 12 rue Lhomond, 75005 Paris, France

Tumor invasion, the process by which carcinoma cells exit the primary tumor and enter the stroma, is one of the first steps in metastasis. This process involves a dramatic change in the microenvironment, from an epithelium encapsulated by a basement membrane to a stromal network of primarily collagen-I fibers and other ECM components, including fibronectin. Although previous studies have largely focused on dissemination of single cells in this process, it is becoming increasingly clear that in vivo, tumor cells often invade by collective migration of groups of cells. However, it is poorly understood what controls single-cell vs. collective migration in different environments and how the microvenvironment itself affects collective migration.

To address these questions, we are investigating the mechanisms of collective migration of clusters of A431 cells, a squamous cell carcinoma line, in various 2D and 3D environments in vitro. While cancer cell clusters exhibited little to no migration in isotropic 3D networks, these clusters partially spread and migrated collectively and persistently on the surface of collagen networks and at confined interfaces with collagen networks. Strikingly, clusters migrated with significantly higher persistence (along straighter paths) compared with single cells, and depending on the stiffness of the collagen network, clusters were able to migrate efficiently with or without focal adhesions. In contrast, on the surface of Matrigel, which mimics the basement membrane, clusters formed spheres with tightly apposed epithelial-like cell-cell junctions. On the surface of fibronectin or monomeric collagen, clusters spread, but cells did not migrate collectively or persistently. Localization studies by immunostaining have revealed a substrate-dependent relocalization of integrins as well as integrin- and EMT-related signaling components. Currently, we are investigating the functional roles of these components in collective cell migration. We are also investigating polarity mechanisms in migrating clusters to determine whether clusters migrate using a front "leader" cell or employ cooperative migration of many cells within the

cluster. This work will advance our understanding of collective cell migration and microenvironment adaptation as well as the process of tumor invasion.

Invited Talk Wed 17:15

Unjamming and Cell Shape Changes in Breast Cancer

JAE HUN KIM — Harvard T.H. Chan School of Public Health, 665 Huntington Avenue, Boston, Massachusetts, USA

Cancer cells most often invade neighboring tissues as collective groups, e.g. protruding sheets, clusters or strands [Friedl et al. Nat cell bio 14, 777, 2012]. Dogma holds that in order to migrate such cells would have to undergo an epithelial-to-mesenchymal transition (EMT) or partial EMT [Lambert et al. Cell 168, 670, 2017]. But to the contrary, these migrating clusters retain epithelial markers [Cheung et al., Cell 155, 1639, 2013; Fischer et al., Nature 527, 472, 2015; Zheng, X. F. et al., Nature 527, 525, 2015]. This finding suggests that instead of EMT, some alternative migratory program might be activated. Here we propose that such a program might be provided by the unjamming transition, a process in which a cellular collective undergoes a transition from a solid-like phase to a liquid-like phase [Park & Kim et al. Nat Mater 14, 1040, 2015]. This transition is marked not by EMT markers but by characteristic changes of cell shape [Bi et al. Nat Phys 11, 1074 2015]. Across vastly diverse epithelial systems, cell shape variation collapses to a family of distributions that is common to all and potentially universal; as a cell layer becomes more and more unjammed, cell shape becomes progressively elongated and more variable [Atia et al., arXiv]. Using genetically engineered breast-cancer models, MCF10A cells expressing vector, ErbB2 and 14-3-3ζ [Lu et al. Cancer cell 16, 195, 2009], we tested how diverse levels of transforming potential affect the jamming index, cell shape. Surprisingly, regardless of transforming potential, expression of cell–cell adhesion, or cell proliferation, cell shape variation of all three MCF10A cell lines fall on the same distribution. Moreover, compared to control vector cells, ErbB2 cells that are highly proliferative or 14-3-3ζ cells that lack E-cadherin tended to be elongated and more variable in their shapes showing that tumorigenic cells tend to be more unjammed. We then tested the theoretical prediction in which as adhesion outcompete cortical contraction cells tend to be elongated and to be more unjammed [Bi et al. Nat Phys 11, 1074 2015; Atia et al., arXiv]. Indeed, when we measured adhesion forces exerted across cell-cell adhesion in three cell lines, adhesion forces were larger in ErbB2 and 14-3-3ζ cells that are more unjammed versus control cells. When we tested this prediction in a highly malignant breast cancer cell line, MDA-MB-231, versus non-malignant cell line, MCF10A, adhesion forces were not statistically different, but tended to be larger in MDA-MB-231 cells. Note that in both of MCF10A.14-3-3ζ and MDA-MB-231cells loss of E-cadherin did not abolish adhesion forces; this observation contradicts the prevailing dogma in which loss of cell-cell adhesion is required for tumor cell migration, but instead suggests that increased adhesion forces promote unjamming. Together, these results suggest that unjamming provides tumor cells a gateway to collective cellular motility.

Invited Talk Wed 17:45

Tissue Surface Tension in Simple Models of Dense Biological Tissues

DANIEL SUSSMAN - Syracuse University, College of Arts and Sciences, Department of Physics, Syracuse, NY 13244, USA

Recent experimental work has found that tissues – in contexts ranging from wound healing to embryonic development to cancer metastasis – often lie close to a transition between a fluid and solid state. Recent theoretical efforts have interpreted these systems in terms of vertex-like models that describe dense cells as interacting polygons or polyhedra. We now have direct evidence that the origin of the fluid-solid transition in these models is of an unusual character, and we briefly comment on the relevance of this unusual transition to experimental data. In addition, while these models are able to capture many essential features of interacting cells, relatively little work has been done to understand the effects of interfacial surface tension, which may be important for understanding the integrity of cancer tumor boundaries. Here we extend existing models by allowing cells to independently regulate their (a) homotypic interfacial tensions (governed by adhesion between cells of the same type) and (b) heterotypic interfacial tensions

(between cells of different types). This generates a direct mechanism for cell segregation – the effective surface tension between two tissue types. We measure this quantity in simulations using parallel plate compression and find that it is directly proportional to the single-cell heterotypic interfacial tension. Quite surprisingly, however, it does not match the value for surface tension extracted by monitoring fluctuations at the interface: the interface between unlike cell populations is an order of magnitude sharper than expected. We develop a novel stability argument to explain this result.

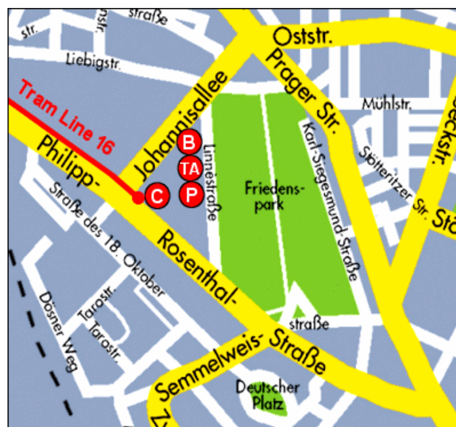
Welcome Dinner Wed 18:30
Faculty of Physics and Earth Sciences, Linnéstr. 5,
04103 Leipzig, first floor, assembly room.

Directions from MPI to Faculty

The Faculty of Physics and Earth Sciences is within walking distance (about 10 min.) from Max Planck Institute for Evolutionary Anthropology.

Walk in direction "Semmelweisstraße", straight up to Russian Memorial Church. Now turning to the left, please follow "Philipp Rosenthal-Straße" to reach "Linnéstraße". Turn to the right and go straight ahead to arrive at the Faculty of Physics and Earth Sciences in Linnéstr. 5.

Enter the building, go to first floor – you have reached your destination!



C Faculty of Chemistry and Mineralogy (Johannisallee 29)

P Faculty of Physics and Earth Science (Linnéstraße 5)

TA "Technikum-Analytikum" (Linnéstraße 3)

B Botanical Garden (Linnéstraße 1)

Session II: Biomechanics

Contributed Talk Thu 08:15

Guiding 3D Cell Migration inside Strained Synthetic Hydrogel Micro-Structures

Miriam Dietrich[1,2], Hugo Le Roy[3], David Brückner[4], Hanna Engelke[5], Roman Zantl[2], Joachim O. Rädler[1], Chase P. Broedersz[4]

[1] Faculty of Physics and Center for NanoScience, Ludwig-Maximilians-University, Munich, Germany

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The mechanical properties of the extracellular matrix are fundamental guidance cues for cell migration in 3D. To prevent cross-signaling of different stimuli present in naturally derived hydrogels, synthetic hydrogels with a defined composition and therefore reduced complexity are often used to analyze the underlying mechanisms of directed cell migration. We are interested in how static strains in these matrices influence migration of embedded HT-1080 cells.

We use a novel method to introduce uniaxial static strain in matrices. In a photo-induced polymerization reaction, a polyethylene glycol (PEG) based hydrogel, functionalized with small peptide sequences, is microstructured in thin strips via simple photolithography inside a channel slide. Due to the confinement of the channel, hydrogel strips swell anisotropically, thereby inducing uniaxial strain in the network. Embedded HT-1080 cells show a highly anisotropic migration response parallel to the strain direction, with maximal anisotropy at intermediate strain levels. We can account for this non-monotonic response with a theoretical model of a durotactic cell on a 2.5 D lattice performing proteolytic migration. Straining of this lattice results in anisotropic movement of the cell similar to the experimental result.

Our model shows that a geometric anisotropic stiffening of the meshwork on the microscale due to the macroscopically applied strain, can act as a guidance cue for directed cell migration. This work highlights that it is crucial to consider the network properties on the cellular scale when trying to find the guidance cues that are most important for cell behavior.

Invited Talk Thu 08:30

The Weakness of Senescent Fibroblasts

Kay E. Gottschalk — University of Ulm, Institute for Experimental Physics, 89069 Ulm

Cellular senescence and cancer are to sides of one coin. Senescence can be thought of as a mechanism to prevent aged cells going bad. However, while lots of efforts have been committed to characterize the properties of cancer cells, the characterization of the biophysical manifestation of cellular senescence is still in its infancy. Here, we thoroughly characterize the biophysical state of senescent dermal fibroblasts using a combination of single-cell techniques. Our results demonstrate that changes in composition of the cytoskeleton together with loss of myosin-II activity lead to a decrease in the elasticity and tension of senescent fibroblasts cytoskeleton. This is accompanied by nuclear deformations, a significant loss of traction forces, and a decrease in the wound healing capacity. Taken together, we show that the ability of senescent dermal fibroblasts to generate intra- or extracellular tension is severely attenuated. A lack of tension has deleterious effects for building the extracellular matrix, for wound healing, and may lead to epigenetic changes involved in senescence.

Invited Talk Thu 09:00

Cytoskeletal Intermediate Filaments - from Self-Assembly to Cell Mechanics

Bell Emily, Shah Pragya, McGregor Alexandra, Isermann Philipp, Dongsung Kim, Smolka Marcus, Lammerding, Jan — Weill Institute for Cell & Molecular Biology, Department of Biomedical Engineering, Cornell University, 235 Weill Hall Ithaca, NY 14853-7202, USA

During cancer cell invasion and metastasis, cancer cells migrate through interstitial spaces and transendothelial openings as small as 2 μm in diameter. The deformability of the large and relatively rigid cell nucleus constitutes a rate-limiting factor in the passage of cells through such confined environments. Since the nuclear envelope proteins lamins A and C are a major determinant of nuclear deformability and their expression is misregulated in many cancers, we examined whether reduced levels of lamin A/C correlated with increased nuclear deformability, increased invasion potential in confined environments, and an increased risk of disease progression in breast cancer. Patient-derived breast tumor tissues and cell lines had significantly lower lamin A levels than normal tissues, and particularly metastatic cell lines had significantly lower levels of lamin A/C than less aggressive cancer cell lines. Levels of lamin A/C inversely correlated with nuclear deformability, with claudin-low subtype cells exhibiting the lowest levels of lamin A/C and the highest nuclear deformability. Breast cancer cells with low levels of lamin A/C migrated faster through micron-scale microfluidic constrictions and dense collagen matrices than cells with high levels of lamin A/C. Increasing expression of lamin A in breast cancer cells with normally low levels of lamin A/C significantly impaired their invasive properties, while depletion of lamin A/C in cells with normally high levels of lamin A/C increased their invasive potential. Increasing lamin A expression in metastatic cells also decreased cell proliferation and altered expression of several cell adhesion proteins, extracellular matrix proteins, and regulators of cell metabolism, as revealed by stable isotope labeling with amino acids in cell culture (SILAC) mass spectroscopy analysis, suggesting additional pathways by which lamins impact cancer cell invasion and disease progression. These studies indicate that downregulation of A-type lamin levels in breast cancer cells could coordinate both tumor cell invasion and outgrowth, thus providing an important point of control over the development of metastases. Insights gained from these studies could improve current diagnostic and prognostic approaches. Ultimately, targeting newly identified regulator pathways affected by altered lamin expression could offer novel therapeutic avenues to control metastatic disease in breast cancer.

Invited Talk Thu 09:30

Interactions of Natural Killer Cells with Cancer Cells in a 3-D Environment

C. Mark[1], S. Roessner[2], A. Mainka[1], N. Bauer[1], T. Götz[1], G. Schuler[2], B. Fabry[1], C. Voskens[2]

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[2] Friedrich-Alexander Universität Erlangen-Nürnberg, Dermatology, Erlangen, Germany

Natural killer (NK) cells are important effector cells in the immune response to cancer. Small clinical trials on adoptively transferred NK cells, however, have thus far failed to demonstrate antitumor responses. As NK cells need to pass a stringent evaluation before being transferred into a patient, the cells are cryopreserved and thawed again to bridge this evaluation time. Classic degranulation and chromium release assays where the NK cells are in direct contact with K562 tumor target cells show no significant decrease in the cytotoxic function of cryopreserved NK cells. However, when NK cells and target tumor cells are embedded in collagen gels, we find that 34% of freshly isolated NK cells are motile, compared to only 5% of cryopreserved cells. Of those motile cells, the killing efficiency is further reduced to 15% after cryopreservation. These findings explain the persistent failure of antitumor therapy with NK cells and highlight the crucial role of a 3D environment for testing NK cell function.

Invited Talk Thu 10:30

Integrating Scales in Cancer Mechanobiology: The NCI Physical Sciences – Oncology Network

NASTARAN ZAHIR — Division of Cancer Biology, National Cancer Institute, National Institutes of Health, Rockville, MD 20850, USA

The U.S. National Cancer Institute (NCI) leads, conducts, and supports cancer research across the nation to advance scientific knowledge and help all people live longer, healthier lives. Since 2009, the NCI has supported the NCI Physical Sciences – Oncology Network (PS-ON) program that aims to better understand the emergence and behavior of cancer through the perspective of the physical laws and principles that shape and govern this disease. The transdisciplinary PS-ON teams integrate physical sciences perspectives with cancer research to complement and expand on our current understanding of cancer across many biological length- and time-scales. Thematic areas under investigation in the PS-ON include transcriptional dynamics and genomic architecture, modeling evolutionary dynamics of treatment response, cancer mechanobiology and the physical microenvironment, and multi-scale computational modeling approaches to integrate data across length scales. In this presentation, projects examining aspects of cancer mechanobiology will be described to highlight the transdisciplinary physical oncology approaches and perspectives towards understanding the interplay between the physical microenvironment and tumor and stromal cells in primary and metastatic disease.

Contributed Talk Thu 11:00

Light Sheet Fluorescence Microscopy: Advantages for Living Specimens

ULF-DIETRICH BRAUMANN - Cell-functional Image Analysis Group, Fraunhofer Institute for Cell Therapy and Immunology Leipzig, Perlickstr. 1, 04103 Leipzig

We will briefly introduce the principles of light sheet fluorescence microscopy (LSFM, or single plane illumination microscopy - SPIM), will continue with its major advantages (short/selective laser exposure; low phototoxicity) which in particular allow for long-term monitoring of living specimens. Further, we will present our own experimental SPIM platform at Fraunhofer IZI, ending up with some recent applications.

Invited Talk Thu 11:15

From "CAR T cells" to CAR expressing NK cells for cancer retargeting

ULRIKE KÖHL[1], OLAF OBERSCHMIDT[1], MICHAEL MORGAN[2], MICHAEL HEUSER[3], JULIA SUERTH[2], JULIA DAHLKE[2], RUTH ESSER[1], WOLFGANG GLIENKE[1], KRASIMIRA ALEKSANDROVA[1], CHRISTOPH PRIESNER[1], JANA LEISE[1], LUBOMIR ARSENIEV[1], AXEL SCHAMBACH[2], STEPHAN KLOESS[1] -

[1] INSTITUTE OF CELLULAR THERAPEUTICS, HANNOVER MEDICAL SCHOOL (MHH), HANNOVER, GERMANY

[2] INSTITUTE OF EXPERIMENTAL HEMATOLOGY, MHH, HANNOVER, GERMANY

[3] HEMATOLOGY, HEMOSTASIS, ONCOLOGY AND STEM CELL TRANSPLANTATION, MHH, HANNOVER, GERMANY

A short summary of clinical studies using chimeric antigen receptor (CAR)-modified T cells for the treatment of malignancies will be presented, which is an increasing field leading to promising results with improved survival in patients with leukemia. Recently, we optimized a fully closed and automated system for the manufacturing of autologous CAR T cells in order to treat patients with Melanoma in a phase I trial.

In contrast to T cells, natural killer (NK) cells are known to mediate anti-cancer effects without the risk of inducing graft-versus-host disease, which makes them a promising source for third-party-donor immunotherapy. However, tumor cells can escape NK cell cytotoxicity by tumor immune escape mechanisms (TIEMs). In order to overcome TIEMs and to make NK cell-based therapies more specific, we engineered primary human NK cells to express a CAR designed to recognize CD19 or CD123, which is highly expressed on the surface of primary acute lymphoblastic or myeloid leukemia, respectively. NK cells were transduced with state-of-the-art alpharetroviral self-inactivating (SIN) vectors encoding EGFP alone as control or a third generation CAR engineered with an anti-CD19 or anti-CD123 single chain variable fragment (scFv) and containing the CD28

transmembrane domain, the 4-1BB costimulatory domain, the CD3ζ signaling domain and an internal ribosomal entry site (IRES) element for EGFP expression. CAR-modified NK cells showed a strongly improved cytotoxicity against leukemic cells compared to activated NK cells with a nearly complete elimination of leukemic cells after 48 h. Finally, this will be reviewed in the context of mainly pre-clinical data published on retargeting NK cells, with an outline of possible advantages using these short-lived donor effector cells as an "off the shelf product".

Invited Talk Thu 11:45

Collectively Emerging Nematic Order in Populations of Fibroblasts

PASCAL SILBERZAN — Institut Curie, Centre de Recherche, 26 rue d'Ulm, 75248 Paris Cedex 05, France

Cancer-associated fibroblasts (CAFs) self-organize in thin "shells" around tumors. In these circumstances, these CAFs spontaneously orient along a common local direction and form a nematic phase. Such a situation can be reproduced in vitro with cultures of spindle-shaped cells such as NIH-3t3 fibroblasts. In undefined monolayers, these cells form domains of common orientation that don't fuse because of the presence of intrinsic topological defects characteristic of these nematic phases. The characteristic size of these domains is very large compared to a cell size (~ 500 μm).

To control the density and position of these defects, we confine the nematic monolayers in well-defined micropatterned geometries such as linear stripes or circular domains. In stripes, cells can reach a perfect macroscopic alignment. In contrast, the disk geometry imposes a pair of defects whose position indicates that cell activity is eventually overcome by friction with the underlying substrate.

Finally, we will describe other situations where the nematic arrangement is more complex and is coupled to spontaneous flows. This particular situation is very similar to in vivo observations where strands of cancer cells escaping collectively from a tumor can locally migrate in antiparallel directions within the same strand.

[1] Duclos G., Erlenkämper C. Joanny J.-F. Silberzan P.: Topological defects in confined populations of spindle-shaped cells, Nat. Phys. 13, 58 (2017)

[2] Duclos G., Garcia S., Yevick H. G., Silberzan P.: Perfect nematic order in confined monolayers of spindle-shaped cells, Soft Matter 10, 2346 (2014)

Contributed Talk Thu 12:15

Disrupting Chemotaxis using Contact Guidance of Nanotopography

SEBASTIAN SCHMIDT[1], MOLLY MOSHER[2], JOHN FOURKAS[3], WOLFGANG LOSERT[1] -

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[3] UNIVERSITY OF MARYLAND, DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND, COLLEGE PARK, MD, USA

Cell migration is important in many processes such as wound healing and cancer metastasis. The physical features of the surface over which cells move affect migration outcomes. In this context, we aim to examine the effect of ridged surface textures on collective cellular migration. The well-studied social amoeba Dictyostelium discoideum (Dicty) is a model system with a well-defined developmental cycle. When starved, Dicty cells follow each other and migrate together in streams to form clumps of cells called mounds. Cyclic AMP signaling facilitates this migration, resulting in directional polymerization of the cytoskeletal protein actin. The textured surface causes a distinct phenotype change when compared to the control: Initially the cells are more active, however, the cells are not able to enter the streaming part of their developmental cycle. We demonstrate that the competition between the directional cues from the surface and the chemical cues from the autocrine cAMP signaling is sufficient to disrupt the development cycle of the amoeba.

Poster Session

Poster 1

An Intriguing Similarity between Cancer Metastasis and Financial Markets

CHRISTOPH MARK, CLAUS METZNER, LENA LAUTSCHAM, BEN FABRY — Friedrich-Alexander University Erlangen-Nürnberg, Department of Physics, Biophysics group, Henkestraße 91, Erlangen, Germany

Invasive cancer cells and exchange-traded stocks (or funds) share a common feature: they are complex systems. In cancer metastasis, the apparently random motions of migratory cancer cells are the result of a vast network of underlying intra-cellular processes that act on different time-scales and drive cell migration. Furthermore, the cell may interact with a highly heterogeneous extra-cellular matrix. In the same way, the price fluctuations of a financial asset are the result of a multitude of transactions, carried out on time-scales that differ in several orders of magnitudes. While traditional investors may hold positions for several years, day traders carry out multiple transactions per day, and high-frequency hedge funds even trade in the milli- and microsecond regime. As a result of these broad ranges of underlying driving processes, the observable data (cancer cell movements and price fluctuations) do not follow conventional statistics. Both the step width distribution of migratory cells and the distribution of stock log-returns resemble a two-sided exponential distribution (also called Laplace distribution), instead of the ubiquitous Bell-shaped normal distribution. In other terms, extreme fluctuations, whether in cancer cell movements or stock price variations, are significantly underrepresented by conventional models that rely on the normal distribution. In fact, the use of the normal distribution in financial risk assessment is suspected to have played a significant role in recent financial crises.

Here, we present a novel method to rescue the use of simple, well-known statistical models like the normal distribution to describe the dynamics of complex systems, by proposing a hierarchy of two models. On short time scales, we have found that the movements of cancer cells as well as the stock price fluctuations still adhere to the normal distribution. On longer time scales however, the parameters of this normal distribution (i.e. the mean value and the variance) themselves show significant stochastic variations. By combining a low-level Gaussian model with a high-level model that describes how the low-level parameters change over time, we can provide a better fit to the observed data, compared to a model with static parameters. The "anomalous" two-sided exponential distribution then arises naturally from the superposition of normal distributions with varying variances. Furthermore, this two-level approach is able to uncover essential details about the dynamics of complex systems that would have been averaged out by the use of static parameters.

Comparing the migration dynamics of four different cell types on a 2-dimensional substrate, we find that cells that exhibit phases of simultaneously high directional persistence and migration speed are also more invasive in 3-dimensional collagen gels. These efficient phases of both high persistence and speed also exist in the price dynamics of stock markets. Comparing the daily close prices from 2010 to 2016 of all stocks in the NASDAQ-100 index, we find that stocks that exhibit phases of simultaneously high volatility (analogous to cell speed) and momentum (analogous to directional persistence) perform better, compared to stocks for which volatility and momentum are non-correlated or negatively correlated.

The work not only provides new insights into both cancer cell migration and trading dynamics, but further illustrates the importance of reaching out to different fields of research (even all the way down to finance) in the effort to unravel the underlying principles that govern complex systems.

Poster 2

Direct Measurement of Surface Charge Distribution in Phase Separating Supported Lipid Bilayers

THOMAS FUHS[1,2,3], LASSE HYLDGAARD KLAUSEN[2,4], STEFFAN MØLLER SØNDERSKOV[2], MINDONG DONG[2,4], XIAOJUN HAN[1]

[1] State Key Laboratory of Urban Water Resource and Environment, School of Chemistry and Chemical Engineering, Harbin Institute of Technology, 92 West Da-Zhi Street, Harbin, 150001, China

[2] Interdisciplinary Nanoscience Center (iNANO), Aarhus University, Gustav Wieds Vej 14, Aarhus C, DK-8000, Denmark

[3] Peter Debye Institute for Soft Matter Physics, Faculty of Physics and Earth Sciences, Leipzig University, Linnéstr. 5, 04103 Leipzig, Germany

[4] Department of Chemistry, Stanford University, Stanford, CA 94305, USA

The local surface charge density of the cell membrane influences regulation and localization of membrane proteins. The local surface charge density could, until recently, not be measured directly under physiological conditions, and it was largely a hypothetical yet very important parameter. Here we use unsaturated lipids of distinct charge (DOTAP, DOPC, DOPG) and a neutral fully saturated lipid (DPPC) to create model membranes with phase separating domains of defined charge. We then apply quantitative surface charge microscopy (QSCM) to investigate the local surface charge density; this is a technique based on the scanning ion conductance microscope (SICM) capable of measuring surface charge density with nanoscale lateral resolution. We are able to clearly distinguish lipid domains from charge and topography in all three model membranes. The measured surface charge densities furthermore reveal that disordered domains formed by charged lipids are in fact not pure, but also incorporate uncharged saturated lipids. We estimate that at least 30% of disordered domains in DOPG:DPPC and DOTAP:DPPC will be DPPC. These ratios could present a limit for the formation of charged domains in lipid membranes.

Poster 3

High Shear Stresses under Exercise Condition Destroy Circulating Tumor Cells in a Microfluidic System

SAGAR REGMI[1], AFU FU[1], SIERIN LIM[1], KATHY QIAN LUO[2]

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[2] FACULTY OF HEALTH SCIENCES, UNIVERSITY OF MACAU, TAIPA, MACAU, CHINA

Circulating tumor cells (CTCs) are the primary targets of cancer treatment as they cause distal metastasis. However, how CTCs response to exercise-induced high shear stress is largely unknown. To study the effects of hemodynamic microenvironment on CTCs, we designed a microfluidic circulatory system that produces exercise relevant shear stresses. We explore the effects of shear stresses on breast cancer cells with different metastatic abilities, cancer cells of ovarian, lung and leukemic origin. Three major findings were obtained. 1) High shear stress of 60 dynes/cm2 achievable during intensive exercise killed more CTCs than low shear stress of 15 dynes/cm2 present in human arteries at the resting state. 2) High shear stress caused necrosis in over 90% of CTCs within the first 4 h of circulation. More importantly, the CTCs that survived the first 4 h-circulation, underwent apoptosis during 16–24 h of post-circulation incubation. 3) Prolonged high shear stress treatment effectively reduced the viability of highly metastatic and drug resistant breast cancer cells. As high shear stress had much less damaging effects on leukemic cells mimicking the white blood cells, we propose that intensive exercise may be a good strategy for generating high shear stress that can destroy CTCs and prevent cancer metastasis.

Reference:

Regmi, Sagar. et al. High Shear Stresses under Exercise Condition Destroy Circulating Tumor Cells in a Microfluidic System. Sci. Rep. 7, 39975; doi: 10.1038/srep39975 (2017).

[1] Regmi, Sagar. *et al.*: High Shear Stresses under Exercise Condition Destroy Circulating Tumor Cells in a Microfluidic System, Sci. Rep. 7, 39975; doi: 10.1038/srep39975. (2017)

Poster 4

Polarization Dynamics of Single Cells and Small Groups of Cells on Micropatterns

SOPHIA SCHAFFER[1], ANDRIY GOYCHUK[2], FANG ZHOU[1], CHRISTOPH SCHREIBER[1], ERWIN FREY[2], JOACHIM RÄDLER[1]

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The GTPases Rac1 and RhoA are key regulators of actin dynamics in cell migration. At the front of the polarized cell, Rac1 drives actin branching, whereas RhoA controls actomyosin contractility at the back . Understanding how key regulators accomplish cell polarity and how polarity is communicated to neighboring cells is of fundamental importance to connect single cell- to collective cell-migration.

Micropatterns allow for controlled confinement of cell motion and hence systematic investigation of external cues and internal fields. We study migration of breast cancer cells on short lanes, ring-shaped lanes and Y-shaped lanes using Life-act labeling and a marker for Rac1. To investigate the role of focal adhesions and the effect of cell to cell coupling, we designed specific cell collision or contact patterns.

The dynamic actin patterns will be compared to simulations with a Cellular Potts Model (CPM) that includes internal dynamics of cytoskeleton components. In the long run, we want to calibrate the CPM for different cell lines, which will then allow us to specifically modify certain parameters without the experimentally omnipresent cross-talk of regulatory molecules.

Poster 5

Disrupting Chemotaxis using Contact Guidance of Nanotopography

SEBASTIAN SCHMIDT[1], MOLLY MOSHER[2], JOHN FOURKAS[3], WOLFGANG LOSERT[1]

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[3] University of Maryland, Department of Chemistry, University of Maryland, College Park, MD, USA

Cell migration is important in many processes such as wound healing and cancer metastasis. The physical features of the surface over which cells move affect migration outcomes. In this context, we aim to examine the effect of ridged surface textures on collective cellular migration. The well-studied social amoeba Dictyostelium discoideum (Dicty) is a model system with a well-defined developmental cycle. When starved, Dicty cells follow each other and migrate together in streams to form clumps of cells called mounds. Cyclic AMP signaling facilitates this migration, resulting in directional polymerization of the cytoskeletal protein actin.

The textured surface causes a distinct phenotype change when compared to the control: Initially the cells are more active, however, the cells are not able to enter the streaming part of their developmental cycle. We demonstrate that the competition between the directional cues from the surface and the chemical cues from the autocrine cAMP signaling is sufficient to disrupt the development cycle of the amoeba.

Poster 6

Cell Morphology of Healthy and Cancerous Oral Mucosa

MAJA STRUGACEVAC[1], NINA BARTELS[1], MONA PLETTENBERG[1], LISA ROHDE[1], CONSTANZE WIEK[2], JULIA KRISTIN[2], MARCEL GLAAS[2], JÖRG SCHIPPER[2], MATHIAS GETZLAFF[1]

[1] Heinrich-Heine-Universität Düsseldorf, Institute of Applied Physics, Universitätsstr. 1, 40225 Düsseldorf, Germany

[2] Düsseldorf University Hospital, Department of Othorinolaringology, Moorenstrasse 5, 40225 Düsseldorf, Germany,

Our group is investigating mechanical properties of squamous cell carcinoma cells and non-tumor cells of the head-neck area. Fluorescence microscopy is used to

obtain more information about cell morphology and physical properties of cells and highlight the differences between carcinoma and non-tumor cells.

Using cytoskeleton staining kits SiR-actin and SiR-tubulin actin filaments and microtubules were observed. In tumor cells actin filaments are accumulated in the cortical layer what is not observed in non-tumor cells. Additional differences in cytoskeleton filaments of different cell lines due to tumor localization will be shown in this contribution.

Cell nuclei was stained using Hoechst 33342 staining kit in order to obtain properties of cell morphology. Confocal laser-scanning microscope enables us to create a three-dimensional images of cell nuclei. Using these images we were able to determine the size of cell nuclei. The differences in nucleus size between our investigated cell lines were observed and the correlation between cell nucleus size and tumor localization will be discussed as well.

Poster 7

Mechanisms of Collective Cell Migration and the Influence of the Microenvironment

ANDREW CLARK, DANIJELA VIGNJEVIC

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Tumor invasion, the process by which carcinoma cells exit the primary tumor and enter the stroma, is one of the first steps in metastasis. This process involves a dramatic change in the microenvironment, from an epithelium encapsulated by a basement membrane to a stromal network of primarily collagen-I fibers and other ECM components, including fibronectin. Although previous studies have largely focused on dissemination of single cells in this process, it is becoming increasingly clear that in vivo, tumor cells often invade by collective migration of groups of cells. However, it is poorly understood what controls single-cell vs. collective migration in different environments and how the microvenvironment itself affects collective migration.

To address these questions, we are investigating the mechanisms of collective migration of clusters of A431 cells, a squamous cell carcinoma line, in various 2D and 3D environments in vitro. While cancer cell clusters exhibited little to no migration in isotropic 3D networks, these clusters partially spread and migrated collectively and persistently on the surface of collagen networks and at confined interfaces with collagen networks. Strikingly, clusters migrated with significantly higher persistence (along straighter paths) compared with single cells, and depending on the stiffness of the collagen network, clusters were able to migrate efficiently with or without focal adhesions. In contrast, on the surface of Matrigel, which mimics the basement membrane, clusters formed spheres with tightly apposed epithelial-like cell-cell junctions. On the surface of fibronectin or monomeric collagen, clusters spread, but cells did not migrate collectively or persistently. Localization studies by immunostaining have revealed a substrate-dependent relocalization of integrins as well as integrin- and EMT-related signaling components. Currently, we are investigating the functional roles of these components in collective cell migration. We are also investigating polarity mechanisms in migrating clusters to determine whether clusters migrate using a front "leader" cell or employ cooperative migration of many cells within the cluster. This work will advance our understanding of collective cell migration and microenvironment adaptation as well as the process of tumor invasion.

Poster 8

Blue Fluorescent Protein as Marker for Carcinoma Cells

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Our group's research deals with the morphological and structural differences between squamous cell carcinoma cells and non-tumor dysplastic oral keratinocytes of the head-neck area. Using fluorescence microscopy, e.g. cell membrane and mitochondria can be investigated in detail.

For simultaneous investigation of both cell types a specific labelling is necessary in order to distinguish the cancer cells from the non-tumor cells unambiguously. A lentiviral vector is applied to the carcinoma cells which results in translating a blue fluorescent protein. This method allows the research of two co-cultivated different cell types under the same experimental conditions.

Cell membrane and active mitochondria are stained with CellMask Green and MitoTracker Orange. Using a laser-scanning microscope the organelles of interest are observed precisely. As mitochondria play a huge role in the development of cancer cells, we focus on the investigation of their differences in the two observed cell types. Our latest results will be discussed in this contribution.

Poster 9

Bursts of Activity in Collective Cell Migration

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Dense monolayers of living cells migrate collectively, for example during wound healing [1,2] and in cancer invasion. They are driven by active forces [3,4] and invade when free space is available. Here we show that this motion occurs in bursts [5] similar to the ones observed in other driven systems, such as the propagation of cracks, fluid fronts in porous media, and ferromagnetic domain walls. In analogy with these systems, the distribution of activity bursts displays scaling laws that are universal in different cell types (human cancer cells and epithelial cells, mouse endothelial cells) and for cells moving on different substrates (plastic, soluble and fibrillar collagen) and in different conditions (vascular endothelial (VE)-cadherin knockdown). This main feature of the dynamics is captured by a model of interacting active particles moving through disordered landscape. Our results demonstrate that living systems display universal nonequilibrium critical fluctuations, that are usually associated with externally driven inanimate media.

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Poster 10

Applications of Mass Spectrometry and NMR Spectroscopy to Study Cancer-Related Alterations of the Lipid Composition

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There is a general approved assumption that the metastatic potential of cells is dependent on their membrane rigidity and cellular deformability. Recent studies have pointed out differences in the lipid composition between malignant and healthy cells. It is also known that the moieties of different phospholipids with different double contents partially regulate the membrane fluidity which is dependent on rigidity.

Thus, there is increasing evidence that cancer diseases are accompanied by changes of the (phospho)lipid (PL) compositions of the corresponding tissues and cells which are also reflected by changes in the mechanical properties of the related cancer cells. The changes of the lipid composition comprise in particular (i) differences in the relative moiety of the individual lipid classes (ii) differences in the number of carbon atoms in the fatty acyl residues and (iii) alterations in the number of double bonds, i.e. the extent of unsaturation.

We will show here that methods like mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopic techniques are powerful tools for lipid analysis which may excellently supplement the data on the mechanical properties obtained by physical methods. It will also be shown that MS and NMR methods enable the selective determination of lipid oxidation products such as chain-shortened lipids and lysolipids. This is of significant relevance because cancer diseases are characterized by inflammatory processes and, thus, the generation of reactive oxygen (ROS) and nitrogen species (RNS).

Although matrix-assisted laser desorption/ionization (MALDI) MS often but not exclusively coupled with a time-of-flight (TOF) mass analyzer is particularly established in the protein field, there is increasing evidence that MALDI MS is also very useful in lipid research: MALDI MS is fast, sensitive, tolerates sample impurities to a considerable extent and provides very simple mass spectra with (often) negligible fragmentation of the analyte. Additionally, MALDI mass spectrometers originally purchased for "proteomics" can be used also for lipids without the need of major system alterations. The particular advantage of this technique is that there is no absolute need of lipid extraction prior to MS characterization but the "intact" cells can be directly analyzed. This prevents, on the one hand, the lipid losses by the extraction process and enables, on the other hand, the characterization of lipids obtained from a single cell: a typical cell with a radius of 5 µm has a surface of about 3×10-10 m2. Assuming the typical space required by a phospholipid (PL) molecule with (5×10-10)2 m2, one calculates that a single cell contains about 1.2×109 PL molecules, corresponding to about 2 femtomole. Using a typical molecular weight of 800 g/mol for a single PL, this indicates that one cell contains about 1.6 pg of lipid. As the so far established detection limits are in the order of magnitude of 20 pg, this emphasizes that already this tiny amount of lipid is sufficient for successful analysis. Of course, this will enable the detection of major phospholipids (such as phosphatidylcholines) only which are most sensitively detectable. Although the detailed role of the matrix in the ionization process is not yet completely understood, it is clear that the careful choice of the matrix is crucial in order to be able to detect all compounds of interest in a mixture. This is particularly important regarding the detection of less abundant compounds such as phosphoinositides. We do not exclusively rely on MALDI MS but will also use electrospray ionization (ESI) MS. Since not all oxidized phospholipid species are detectable by MALDI MS, the softer ionization process of ESI MS helps to overcome the problems generated under MALDI conditions. We will demonstrate this aspect by analyzing selected oxidized phosphatidylcholines: it will be shown that hydroperoxides, which are primary products under conditions of the Fenton reaction (i.e. ferrous ions and hydrogen peroxide), are exclusively detectable by ESI MS.

MS is unequivocally the method of choice to identify and to determine quantitatively the concentration of known metabolites, lipids or lipid oxidation products. Nevertheless, unknown "new" metabolic products are normally not identified by MS alone but require the additional application of NMR although this technique is orders of magnitude less sensitive than MS. Therefore, NMR is an indispensable tool in lipid research and helps to analyze complex lipid samples. We will show that 31P NMR is a powerful method to quantify phospholipids according to chemical shift differences in their headgroups. In comparison to quantitative MS analysis

this has the advantage that only a single internal standard is necessary. This is a major advantage in comparison to MS where each lipid class requires an individual standard. Finally, 1H NMR is the method of choice to determine the contents of saturated, monounsaturated and polyunsaturated fatty acids. Finally, 13C NMR enables the assignment of the individual fatty acyl residues to the sn-2 or sn-1/3 position at the glycerol backbone although this method can be only applied if there are unsaturated residues.

Poster 11

Optical Tweezers Combined with AFM – Investigating Cell Mechanics and Single Molecules on Multiple Scales

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While optical tweezers (OT) and AFM have a successful history in biophysical research, setups that successfully combine the advantages of both methods are rarely found. In some studies, the two methods have been used subsequently on the same type of sample to perform force spectroscopy at different scales. Truly simultaneous optical trapping and AFM measurements, however, have not been available.

Here we present a novel OT-AFM setup that combines high precision optical manipulation, camera-based force detection and the full spectrum of AFM methods on the same sample at the same time. This opens up new approaches to complex experimental designs that are not accessible by AFM or OT alone. It was used in immune-biology experiments to characterize the influence of dendritic cell + T-cell interaction on cellular adhesion. In addition to results from these measurements, we will introduce further application examples from the field of single-molecule interactions, cell mechanics and medicine.

Poster 12

Insights into Cancer Progression from in Silico Simulations of Solid Tumors with the Virtual Biophysics Laboratory (VBL) Program

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Virtual Biophysics Lab (VBL) is a cell-based and multiscale numerical model aimed at simulating tumor growth. Its basic blocks are the individual cell that can grow and duplicate according to the combined interaction of a discrete mathematical model for the diffusion and transport of nutrients, and the occurring of discrete and stochastic events that simulate the cell-cycle, cell division and death . A population of cells grows and duplicates in a 3D and off-lattice environment, and the overall shape of the aggregate is determined by the biomechanical interactions among cells.

VBL software is implemented in C++, it also exploits parallel programming technology, such as OpenMP interface and GPU graphic cards, to manage the computational workload originated by the complexity of the numerical model.

The mathematical model can reproduce many quantitative features of the tumor biology [1] and, although VBL does not include the whole complexity of the tumor microenvironment, it can be exploited to perform in-silico experiments to investigate many aspects of cancer initiation and progression.

Here we focus our analysis on cell mutations that target cell metabolism and show how they can modify the tumor microenvironment and drive the tumor growth process.

We perform different sets of in-silico simulations in which a given population of cells – having a reference phenotype, grows in competition with a mutated type population forming a single tumor spheroid. We compare the growth curves as well as the geometrical configurations of the two populations for different simulations. Preliminary results show that a better fitness is observed for those mutated phenotypes that produce cells with a bigger size which – for biomechanical reasons – are pushed towards the spheroid surface where the concentration of nutrient is higher.

Our approach allows to investigate cell evolution in real time and to analyze biological processes that would not be easily observable by any other means.

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Poster 13

Cell Migration through a Confined Micro-Environment: an Attempt to Understand Cancer Invasion

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Metastasis formation involves migration of tumor cells through narrow interstitial spaces. When cancer cells succeed in surmounting the boundaries of a tissue, they undergo environmental stresses (low PH, lack of nutrients, effect of reactive oxygen species that are able to detect an invading pathogen and mobilize a response to it, etc.) [1]. The environmental pressure selects those cells that maintain the ability of growing despite these obstacles and causes them to acquire an aggressive phenotype.

Micro-fabrication techniques have started to be employed in the last years to simulate the migration path of cancer cells in vitro. This study is an initial attempt to investigate the dynamics of cancer cells of both benign and invasive nature by confining cell groups in chips equipped with funnel-shaped micro-constrictions. Different coating solutions have been applied to the glass surface of the chips to enhance cell motility, whereas directional migration was obtained by using the epithelial growth factor and chemoattractant. Our findings show that the motion through the micro-constrictions is the same for different cells types moving on different substrates and with different migration patterns.

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Poster 14

Electron Irradiated Hydrogels: Reagent-Free Modification towards Biomedical Applications

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The hydrogels collagen and gelatin have attracted considerable interest in biology and medicine during the past years. Due to their strong biocompatibility and biodegradability, they are highly attractive materials for biomedical applications such as extracellular matrix components. Thereby, adaptation of structure and mechanics as well as stimuli-response is an interesting aspect of the modification of these materials. Reagent-free modification of hydrogels can be achieved by utilizing high energy irradiation e.g. electron irradiation to crosslink.

We will demonstrate how crosslinking with high-energetic electrons allows fine-tuning of materials properties such as structure and mechanics. Furthermore, we will present the development of stimuli-responsive systems as well as topographically and mechanically patterned hydrogel substrates for biomedical applications.

Poster 15

Investigation of the Effect of Snake Venoms on Different Cancer Cell Lines Regarding Cell-Cell and Cell-Matrix-Interactions

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Liver cancer is a malignant tumor disease with increasing incidence and prevalence. Primary hepatocellular carcinoma (HCC) represents the most frequent type of liver cancer diagnosed. Main cause of the development are chronic liver diseases, as alcoholic fatty liver disease (AFLD), non-alcoholic fatty liver disease (NAFLD) and hepatitides. Existing therapeutic approaches are restricted in most cases to surgical liver resection. Sorafenib is the only available systemic therapy for HCC but it fails in many HCC patients. Hence there is an urgent need to identify new therapeutic targets and drugs for the therapy of HCC. HCC often occurs in cirrhotic or fibrotic liver, which is linked to a change in the extracellular matrix (ECM) pattern. Additionally, the expression of the integrin pattern which forms the cell-matrix interactions, varied in hepatoma cells. Snake venoms have gained increased attention due to disintegrins contained in their composition. Disintegrins can disturb the attachement of tumor cells and stroma cells on the ECM and consequently influence intracellular signalling.

Aim of the present study was to investigate the effects of snake venom components on hepatoma cell lines and to examine their potential as new anti-cancer drugs by specifically targeting the ECM-integrin axis.

We investigated the effect of the snake venoms Vipera palaestinae (VP), Calloselasma rhodostoma (CR) and Echis sochureki (ES) on a cellular level (MTT, LDH release), on cell-cell-connections (Caco2 permeability assay) and on cell-matrix-interactions (adherence test). Cell-matrix interactions were tested with collagen I (c-I), collagen IV (c-IV), fibronectin (Fn) and laminin (Lm).

In our in vitro models, we used HepG2 as a HCC tumor cell line, the fibroblast cell line Fi301 as stroma simulation and Caco2, a colon carcinoma cell line.

Considering MTT measurements and LDH release we determined NOAELs from dose response curves for all cell lines (VP: 0.5 µg/ml, CR: 1 µg/ml, ES: 5 µg/ml). The adherence assay showed that treatment of cell lines with ES caused a reduction of adherence on Fn and Lm coated plates in comparison to untreated controls. Additionally, the incubation of cells with VP inhibited the adherence on Lm coated surfaces. The tested concentration of the venom from CR seems not to have any effect on the binding of cells on the various ECM components. The permeability assay revealed no impact of different snake venoms on the multi-cellular arrangement. Cells treated with the chemotherapeutic agent 5-fluorouracil (5-FU) in combination with snake venoms results in reduced IC50 values of ES and VP.

The results implicate that snake venom components of ES and VP acting as disintegrins and inhibit cell-matrix interaction especially with Fn and Lm. Moreover, a synergistic effect was observed in co-incubation experiments of snake venoms and 5-FU. IC50 values of 5-FU have been reduced by snake venoms, which characterises snake venom disintegrins as a potential option in treatment of HCC.

Further experiments are needed to identify the active compounds in snake venoms and to investigate their action on intracellular signalling pathways.

Poster 16

Cell Force-Mediated Breast Cancer Invasion is Attenuated by Basement Membrane Integrity

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Rational: Form and Function of human breast gland tissue are tightly regulated by a complex balance between compressive and expansive stresses, as well as the mechanical properties of the extracellular matrix (ECM). Disruption of this mechanobiological homeostasis fundamentally contributes to tumor progression and invasion – processes that finally raise patients mortality rates dramatically. In vivo, human breast gland tissue consists of polarized luminal cells which are surrounded by a basement membrane (BM). The BM forms a physical barrier separating the breast gland from the extracellular matrix (ECM). The main structure lending component of the BM is collagen IV, which is endogenously expressed and secreted by epithelial cells. During tissue differentiation BM scaffolds develop in terms of thick-

ness. Recently we characterized the BM scaffold as crucial mechanical stabilizer unit for breast gland acini [1].

In the present study, we hypothesize that the BM functions as meaningful but less understood mechanical anti-invasion barrier. The invasion fostering effects of tumor associated ECM-stiffening and BM integrity loss were addressed. Moreover, we aimed to characterize cell force generation as non-proteolytic mechanism of BM disruption and breast cancer invasion.

Methods: We established 3D cell cultures of MCF10A breast acini featuring ether low-developed BM (weak BM acini) or highly-developed BM (intact BM acini) to mimic tumorous or healthy breast glands, respectively [1]. Acini were seeded onto silicone rubber substrates (PDMS) resembling a normal (0.12 kPa) and a tumor-like (12 kPa) ECM stiffness. Resting acini were primed for invasion by applying a tumor-resembling growth factor stimulus (EGF). Life cell imaging (LCI) was used to characterize the chronological sequence of BM-transmigration, incidence and exact cell spreading time points under normal and pathological scenarios. Immune fluorescence (IF) stainings and 3D reconstruction of confocal image stacks illustrated morphological changes of acini at early and late stages of invasion. A 2D traction force microscopy approach was applied to quantify the emerging cell forces (strain energy [femtojoule] was used as robust measure for cell force) before, during and after BM disruption and cell outgrowth. In order to exclusively analyze cell force as non-proteolytic BM-disruption mechanism, matrix metalloprotease (MMP) activity was pharmacologically blocked (pan-MMP inhibitor treatment).

Results: LCI and IF analyses revealed a reproducible invasion process (up to 70 hours) that can be divided into three general phases: 1. rotational acini movement (rolling), 2. BM-disruption and breakdown with emerging cell-matrix adhesion, 3. collective and single cell outgrowth with subsequent BM shell collapse. A stepwise gain of strain energies during the entire invasion process was found for all sample groups. Importantly, healthy tissue conditions (full BM integrity and normal-like ECM stiffness) to showed the largest impact on BM-breakdown and cell outgrowth: Compared with to tumor tissue resembling scenario (weak BM, tumor-like ECM), the mean spreading time point was clearly prologated by 13 hours under normal conditions. This deceleration correlated with a reduced invasion incidence (33%) and 200 times reduced strain energy amplitudes ($p<0.0001$). Mean strain energy amplitudes ranged from 0.02 to 4 femtojoule (early rolling phase), 0.15 to 30 femtojoule (late rolling phase) and 1.5 to 30 femtojoule (BM-disruption and cell outgrowth) when comparing normal and tumor conditions, respectively. Blockade of enzymatic BM damage by MMP-inhibition led to a partial reduction of invasion incidence and to an slight delay of spreading time point in all experimental conditions whereas cell force generation remained completely unaffected. However, BM transmigration was still frequently observed without proteolytic BM degradation.

Conclusion: Our data indicate that the BM acts as crucial breast cancer cell invasion barrier. Tumor-associated ECM-stiffening and BM integrity loss are accompanied by accelerated BM transmigration and strongly enhanced cell forces. We postulate a MMP-independent but cell force-mediated mechanism that is capable to foster BM breakdown efficiency and invasive tumor progression. In a next step, the underlying cellular sensing mechanism will be addressed to decipher the mechanobiological regulation circuits of human breast cancer.

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Poster 17

Guiding 3D Cell Migration inside Strained Synthetic Hydrogel Micro-Structures

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The mechanical properties of the extracellular matrix are fundamental guidance cues for cell migration in 3D. To prevent cross-signaling of different stimuli present in naturally derived hydrogels, synthetic hydrogels with a defined composition and therefore reduced complexity are often used to analyze the underlying mechanisms of directed cell migration. We are interested in how static strains in these matrices influence migration of embedded HT-1080 cells.

We use a novel method to introduce uniaxial static strain in matrices. In a photo-induced polymerization reaction, a polyethylene glycol (PEG) based hydrogel, functionalized with small peptide sequences, is microstructured in thin strips via simple photolithography inside a channel slide. Due to the confinement of the channel, hydrogel strips swell anisotropically, thereby inducing uniaxial strain in the network. Embedded HT-1080 cells show a highly anisotropic migration response parallel to the strain direction, with maximal anisotropy at intermediate strain levels. We can account for this non-monotonic response with a theoretical model of a durotactic cell on a 2.5 D lattice performing proteolytic migration. Straining of this lattice results in anisotropic movement of the cell similar to the experimental result.

Our model shows that a geometric anisotropic stiffening of the meshwork on the microscale due to the macroscopically applied strain, can act as a guidance cue for directed cell migration. This work highlights that it is crucial to consider the network properties on the cellular scale when trying to find the guidance cues that are most important for cell behavior.

Poster 18

Dynamics of MCF10A Cells in Microchannels of Varying Height: Experiments and Modelling as Active Nematic

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We study the short- and long-term flows of MCF10A human mammary epithelial cells, which are widely used for in vitro studies of breast tissue, as they move through microchannels with variable width. When a bottleneck is present, we observe experimentally that flow velocities are higher in the narrow region of the channel and backflow at the bottleneck entrance. As a simple model for tissue invasion we also investigate the the system in the region where the channel widens at the end of the bottleneck. We find diverse behaviour as the epithelial sheet tends to protrude deep into the unoccupied region before filling up the whole width of the broader section.

For theoretical description we use the model of a biphasic system that combines an active nematic and an isotropic phase [1, 2]. First computer simulations give results similar to experiments: flow of the advancing nematic phase is increased inside the tight part of the channel and we observe protrusions as the channel widens.

This work builds on previous studies of cell growth in straight channels [3] and will contribute to our understanding of the dynamics of epithelial sheets in complex environments and of tissue invasion, also in the context of cancer research.

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Poster 19

Non-Linear Compliance of Elastic Layers to Indentation

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In cells and tissues, diseased states are often accompanied by changes in elastic behavior, motivating diagnostic application. Methods targeting the elasticity of soft matter are as diverse as the requirements they need to meet. While other methods focus on e.g., throughput, we address here indentation testing, a method that stands out in the sense that it enables spatial mapping of material properties, and may impose well-defined deformations prompting even a non-linear elastic response if desired. Indentation testing is applicable on various length scales, starting at the sub-cellular level when implemented via an atomic force microscope. However, researches performing indentation tests are faced with the challenge of having to adapt their analyses to sample geometry, as biological samples quite often cannot be shaped to fit the needs of the experiment without altering their properties.

In detail, thin samples, such as cells adherent to a rigid substrate, are considerably less compliant to indentation when compared to specimens that are not geometrically confined. Analytical corrections to this so-called substrate effect exist for various types of indenters but are not applicable when large deformations are possible, as is the case in biological materials. To overcome this limitation we construct a non-linear scaling model characterized by one single exponent, which we explore employing a parametric finite element analysis. The model is based on asymptotes of two length scales in relation to the sample thickness, i.e., indentation depth and radius of the contact area.

For small indentation depth we require agreement with analytical, linear models whereas for large indentation depth and extensive contact area, we recognize similarity to uniaxial deformation, indicating a divergent force required to indent non-linear materials. In contrast, we find linear materials not to be influenced by the substrate effect beyond first order, implying that separation between non-linear effects originating either from the material or geometric confinement is only possible in thin samples. In a large indentation setting where the contact is small in comparison to sample thickness, we observe non-linear effects independent of material type that we attribute to a higher order influence of geometrical confinement.

We apply a viscoelastic extension of the scaling model to data obtained from indentation experiments performed on microplasmodia of the unicellular slime mold Physarum polycephalum that serve as a model system. We identify the multi modal distribution of parameters such as Young's moduls, Poisson's ratio and relaxation times associated with viscous processes that cover five orders of magnitude. Results suggest a characterization of microplasmodia as porous, compressible structures that act like elastic solids with high Young's modulus on short time scales, whereas on long time-scales and upon repeated indentation viscous behavior dominates and the effective modulus is significantly decreased.

Poster 20

Glassy Dynamics in Composite Biopolymer Networks

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The upregulation of the intermediate filament vimentin is a marker for the epithelial-mesenchymal transition (EMT). EMT leads to an increase of cell motility, which is in term mainly associated with actin. To explore the interplay of these cytoskeletal components and their role for EMT, we studied reconstituted composite networks of actin and vimentin in vitro.

Embedded fluorescent tracer filaments were employed to verify the scaling behavior of the tube width as predicted by the tube model for semi-dilute solutions of entangled semiflexible polymer networks [1]. Therefore, we were able to determine the mesh size from single filament fluctuations. Keeping this important parameter for network stiffness constant ensures the comparability of different composite mixtures. Utilizing bulk shear rheology, we find that the elastic properties of composite networks in the linear regime can be derived from a superposition of the two underlying networks. In the non-linear regime, we see qualitative different behavior for actin and vimentin, whereas composite networks reveal again intermediate properties. We can explain our data with the glassy wormlike chain model [2] in both the linear and non-linear regime, by identifying a higher stickiness of vimentin filaments compared to actin filaments.

In conclusion, our results reveal no direct interaction between actin and vimentin in contrast to previous studies indicating emergent behavior [3]. By linking single filament behavior directly with macroscopic network properties, we might be able to solve the recently demonstrated discrepancies between the established models and experimental results of entangled semiflexible polymer networks [4].

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Poster 21

E-Cadherin as an Upstream Regulator of Mechanical Responses in the Early EMT and Cancer Development

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The large majority of tumor diseases become a fatal threat, once cells start to invade surrounding tissue. Whether cells developed the trait of intravasation and start to form metastases, or the tumor expands as a bulk with diffuse border into the enveloping stroma, it always marks the step from a benign neoplasm to cancer. Treatment by surgery, chemotherapy, and/or radiation therapy is urgent necessity from this point. Biochemical triggers that enable a cancerous cell to leave the primary tumor are well known. Yet the exact physical requirements are still to be pinpointed. One of the most fundamental and first steps of a malignant transformation in carcinomas is the epithelial to mesenchymal transition (EMT). This process starts off with the loss of epithelial cadherin (E-Cad). While the loss of adhesiveness might be an obvious step leading to increased migration, associated pathways seem to play an even bigger role. We access the early EMT in a model system consisting of healthy MCF-10A epithelial cells of the mammary gland that are treated with epidermal growth factor (EGF). EGF directly decouples E-Cad from the underlying cytoskeletal cortex, resulting in a release of linker proteins, most importantly beta-catenin. Beta-catenin initiates the wnt-pathway, well known to promote cancerous behavior. We investigate the biomechanical changes, cells undergo in the early EMT by

measurements in the Optical Stretcher. Additional fluorescent staining of E-Cad in the measured cells gives an individualized correlation between progress of the EMT and single cell mechanical behavior. By evaluating not only fluorescence intensity, but also the clustering of E-Cad on the cell surface, we are able to show, that a deactivation and mobilization of E-Cad in the cell membrane is coupled to a softening of the cell body. Cell softness has already been established as a marker in the physics of cancer and is strongly related to increased invasive behavior. Our experiment shows how the detachment of E-Cad in the early EMT already gives rise to a significant change in the mechanical response of epithelial cells. These results suggest that E-Cad might be an upstream regulator of cancerous behavior, and its downregulation the very first step towards the physical enabling of cancerous cells to invade the surrounding stroma.

Poster 22

Altering Synthetic Semiflexible DNA Nanotube Networks by Tunable Cross-linking

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The mechanical properties of complex soft matter have been subject to various experimental and theoretical studies in the past years. The underlying constituents often cannot be modeled in the classical physical frame of flexible polymers or rigid rods. Polymers in the semiflexible regime, where the finite bending stiffness leads to a non-trivial mechanical contribution, are a highly interesting subclass and can be found in the cytoskeleton of every living cell. A natural occurring model system for such polymers is the protein actin [1].
However, experimental studies of actin networks to validate existing theories [2], are limited since the persistence length cannot be altered. Here, we establish a tunable system of cross-linked, synthetically DNA nanotubes to overcome this limitation. We present first results of the impact tunable cross-linking has on the well characterized entangled DNA nanotube networks [3]. These studies enable investigations of the impact of a crucial parameter of semiflexible polymers, namely the persistence length, on resulting network properties.
Also, the study will allow a deeper insight into the underlying mechanics of biomaterials, such as hydrogels, which are extensively used for in vitro as well as in vivo applications [4].

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Poster 23

Dynamics of Cell Jamming

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The ability of cells to migrate in their environment is critical in many aspects of biology. Especially interesting is the apparent difference between solid-like tissues were cells stay at their place and a fluid-like structure of a developing embryo or a metastatic cancer. A promising hypothesis explaining the root cause for is difference in behaviour is a jamming or glass transition. Theoreticians usually quantify a jamming transition by energy barriers for T1 transitions, the minimal requirement for a neighbourhood change. Those are inaccessible in experiments. Current experimental approaches rely on statistical analysis of a large number of cells and time steps, making it hard to analysis heterogeneities and changing individual properties cells. We introduce a

new measure of jamming, which allows for a heterogeneous analysis of experiments and simulations alike.
We use cells with stained nuclei to obtain cell tracks from time series. We then performed a Voronoi tessellation for each image around the middle of the cell nuclei, to investigate the neighbour relations. Even for a dense layer of epithelial cell, T1 transitions do still occur. This is might be in part, because the tessellation does not depict the actual cell shape, which is hard to obtain for a movie, especially for mesenchymal cells. The other reason is that cells can wiggle in their cavities. Therefore, the occurrence of T1 transitions is not a good measure to quantify jamming. We used two different approaches. Firstly, we counted the number of new neighbours a cell obtained in a certain time limit, which did not share a neighbour with the cell at start. This quantifies the number of neighbourhood exchanges near the cell and gives a good measure of how fluid the region is in that timeframe. A jammed system has nearly no neighbourhood exchanges. The second approach was to look for cell that squeeze through two of their neighbours. Those events should have a high energy barrier in a jammed system and are extremely rare for them. One sees a critical slowing down of the time required for a squeezing event during the jamming transition. The data shown here is in very good agreement with the SPV (self-propelled Voronoi) model, which predicts a jamming transition governed by the cell shape. While density is correlated to the jammed state, as classical jamming theories assume, even the shape parameter of the Voronoi tessellation (and not the real shape, or an evolved surface) has a stronger correlation.

Poster 24

Contractility Might Determine Differential Adhesion Hypothesis during EMT

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How single metastatic cells are able to escape from a compound tumor, is still an unanswered question in the biophysical community. Firstly, one need to understand, how cells are collectively bound to keep its compound organization. Secondly, what changes in cellular assembly and thus functionality to enable single cells to escape the tight tumor complex. One promising approach gives the differential adhesion hypothesis (DAH) which can explain a high tissue surface tension due to high adhesion forces between neighboring cells. However, segregation experiments of epithelial and mesenchymal cells cannot fully described by DAH (Pawlizak et al. 2015[1]).

Here we suggest to add cellular contractility as a further fundamental feature within the DAH. The strong related interplay of intercellular adhesion and collective contractility might define different tissue surface tensions in epithelial and mesenchymal cells.

We investigated epithelial (MCF10A) and mesenchymal (MDA-MB-231) cells concerning its contractility in an Optical Stretcher device. We observe active contractile forces within suspended cells, counteracting external optical pulling forces, leading to cell shrinkage. These internal forces might be closely related to cells cortical tension. Since, mesenchymal cells behave less contractile, they have lower cortical tension which might enhance its motility (further verified in migration assays) and eventually its ability to escape a tumor compound.

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Poster 25

Jamming Transition in 3D tumour Spheroids

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Traditionally, tissues are considered to be fluid on long timescales. On substrates, a jamming transition has been observed that is connected to cell number density as well as cell shape.

We observe similiar behaviour in 3D breast cancer spheroids of varying metastatic potential using tissue

droplet fusion assays. Full 3D segmentations of the tissue architecture reveal that cell density and cell shape seem to be connected to this transition, too. Our findings support the conjecture that malignant progression is linked to an unjamming transition.

Poster 26

MR Elastography on Polymer Networks: a Proof of Concept for Collagen Gels

FRANK SAUER[1], LINDA OSWALD[2], ANGELA ARIZA DE SCHELLENBERGER[3], HEIKO TZSCHÄTSCH[3], TOM KUNSCHMANN[1], JÜRGEN BRAUN[4], JOSEF A. KÄS[2], CLAUDIA T. MIERKE[1], INGOLF SACK[3]

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Magnetic resonance elastography (MRE) allows for the measurement of intrinsic material parameters by inducing shear waves within a bulky sample with a piezo actuator and measuring their propagation with the help of medical imaging (MRI). MRE of small tissue samples covers a frequency range which usually exceeds that of standard rheology [1]. Collagen polymer networks are of great interest in biophysical research since they provide 3D matrices for cell experiments and can simulate the cellular environment in biological tissues. We test the applicability of multifrequency MRE to characterize untreated [2] and crosslinked [3] collagen polymer gels by their shear modulus dispersion functions and powerlaw behavior using a tabletop MRE device. The crosslinking of collagen due to treatment with glutaraldehyde was well detectable by an increased shear modulus and reduced powerlaw constant.

Our results indicate that tabletop MRE is a suitable method to reproducibly characterize viscoelastic constants of collagen gels over a wide frequency range which cannot be examined by standard oscillatory rheology.

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Poster 27

Light Sheet Fluorescence Microscopy: Advantages for Living Specimens

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We will briefly introduce the principles of light sheet fluorescence microscopy (LSFM, or single plane illumination microscopy - SPIM), will continue with its major advantages (short/selective laser exposure; low phototoxicity) which in particular allow for long-term monitoring of living specimens. Further, we will present our own experimental SPIM platform at Fraunhofer IZI, ending up with some recent applications.

Poster 28

Acoustic Force Spectroscopy (AFS): A Novel, Highly Parallel Method for Cell Manipulation and Single-Molecule Force Spectroscopy

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Force spectroscopy has become an indispensable tool to unravel the mechano-biological properties of cells, during cell-cell and cell-material interactions. Acoustic Force Spectroscopy (AFS) is a new acoustic manipulation method that consists of an acoustic resonator integrated into a micro-fabricated fluidic chip. This technology, allows creating a homogeneous acoustic pressure gradient throughout the sample, which can be used for exerting forces on (living) cells. By changing the amplitude of the driving voltage,the pressure gradient can be tuned, enabling an accurate control of the force applied. This approach allows exerting acoustic forces from sub-pN to hundreds of pN to thousands of cells in parallel, with sub-millisecond response time and inherent stability.Therefore, AFS can be used to apply forces and study mechano-biological parameters at a range of microscopic objects including not only cells but also other surface tethers (proteins, DNA, RNA). Here we present multiple applications of this technology and introduce a commercial instrument that provides ease of operation to users of all disciplines.

Poster 29

Cell Migration on Soft and Rigid Substrates

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Cells are greatly influenced by the mechanical properties of their environment. To study the cellular response to traction-induced substrate deformations, we extend a cellular Potts model of actively polarizing cells with a coarse description of the viscoelastic substrate. Apart from the influence of substrate stiffness, we demonstrate the importance of dissipative effects in the form of viscous friction, and provide a coherent description of previously conflicting experimental observations.

Poster 30

Mechanical Properties of Anisotropic Polymer Structures

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The cytoskeleton, which dominates the main mechanical functions of the cell, is a meshwork of different biopolymers. To fulfill the many-faceted tasks of a cell, most of them are mechanically in the semiflexible regime arranged in different structures such as networks or bundles. On two examples we show the versatile application of optical tweezers technology to determine mechanical properties of anisotropic polymer structures:

1. The extensibility of individual filaments is a potential energetic contribution to its energy operator. Extensibility measurements using optical tweezers setups shall reveal the force-extension relation of single filament in a force range of 15 pN.
2. The bending stiffness is the crucial mechanical quantification of polymers. We present a new method to determine the bending stiffness of individual, anisotropic polymer structures by measuring the decay of an oscillation, actively induced using optical tweezers. In especially this approach allows to systematically test bundled polymer structures.

Session III: Cellular Organization

Contributed Talk Fri 08:15

Non-Linear Compliance of Elastic Layers to Indentation

Adrian Fessel, Christina Oettmeier, Hans-Günther Döbereiner — Institut für Biophysik, Universität Bremen, Bremen, Germany

In cells and tissues, diseased states are often accompanied by changes in elastic behavior, motivating diagnostic application. Methods targeting the elasticity of soft matter are as diverse as the requirements they need to meet. While other methods focus on e.g., throughput, we address here indentation testing, a method that stands out in the sense that it enables spatial mapping of material properties, and may impose well-defined deformations prompting even a non-linear elastic response if desired. Indentation testing is applicable on various length scales, starting at the sub-cellular level when implemented via an atomic force microscope. However, researches performing indentation tests are faced with the challenge of having to adapt their analyses to sample geometry, as biological samples quite often cannot be shaped to fit the needs of the experiment without altering their properties.

In detail, thin samples, such as cells adherent to a rigid substrate, are considerably less compliant to indentation when compared to specimens that are not geometrically confined. Analytical corrections to this so-called substrate effect exist for various types of indenters but are not applicable when large deformations are possible, as is the case in biological materials. To overcome this limitation we construct a non-linear scaling model characterized by one single exponent, which we explore employing a parametric finite element analysis. The model is based on asymptotes of two length scales in relation to the sample thickness, i.e., indentation depth and radius of the contact area.

For small indentation depth we require agreement with analytical, linear models whereas for large indentation depth and extensive contact area, we recognize similarity to uniaxial deformation, indicating a divergent force required to indent non-linear materials. In contrast, we find linear materials not to be influenced by the substrate effect beyond first order, implying that separation between non-linear effects originating either from the material or geometric confinement is only possible in thin samples. In a large indentation setting where the contact is small in comparison to sample thickness, we observe non-linear effects independent of material type that we attribute to a higher order influence of geometrical confinement.

We apply a viscoelastic extension of the scaling model to data obtained from indentation experiments performed on microplasmodia of the unicellular slime mold Physarum polycephalum that serve as a model system. We identify the multi modal distribution of parameters such as Young's moduls, Poisson's ratio and relaxation times associated with viscous processes that cover five orders of magnitude. Results suggest a characterization of microplasmodia as porous, compressible structures that act like elastic solids with high Young's modulus on short time scales, whereas on long time-scales and upon repeated indentation viscous behavior dominates and the effective modulus is significantly decreased.

Invited Talk Fri 08:30

Mechanotransduction in Collective Cell Migration

Joachim P. Spatz — Max Planck Institute for Medical Research, Dept. of Cellular Biophysics/ University of Heidelberg, Dept. of Biophysical Chemistry, Heidelberg, Germany

The collective movement of epithelial cells drives essential multicellular organization during various fundamental physiological processes like embryonic morphogenesis, cancer, and wound healing. Hallmarks of collective behavior in migrating cohesive epithelial cell sheets are the emergence of so called leader cells and the communication between adjacent cells to move correlated to each other. Here we discuss three phenomena of this natural phenomena and, fourth, how one can synthesis such behavior synthetically:

(i) Autonomy of leader cell appearance: emergence of leading individuals, who provide directional guidance for the group movement, is a ubiquitous and critical feature among collectively migrating biological entities. Here we discuss if the leader cells at the epithelial wound-margin appear through a non-cell autonomous or autonomous process.

(ii) Cellular hierarchy within collectively migrating cell layers: the margin of an epithelial wound contains the seed for the ensuing collective cell migration towards the wound closure. Of special significance, in this context, are the leader and non-leader hierarchy. Here we reveal distinct temporal phases of cellular dynamics at wound margin.

(iii) Molecular communication mechanism: within this cohesive group each individual cell correlates its movement with that of its neighbours. We investigate the distinct molecular mechanism that links intercellular forces to collective cell movements in migrating epithelia.

Invited Talk Fri 09:00

Of Active Motors and Passive Crosslinker: Reconstituting Adaptive Microtubule Networks

STEFAN DIEZ — Technical University Dresden, B CUBE - Center for Molecular Bioengineering, Arnoldstrasse 18 01307 Dresden, Germany

For a long time, the mechanical forces driving the sliding of overlapping microtubules relative to each other have been attributed to the action of molecular motors and the dynamics of cytoskeletal filaments, which both consume chemical energy. By contrast, non-enzymatic filament cross-linkers have been regarded as mere friction-generating entities. Recently, we experimentally demonstrated that diffusible microtubule cross-linkers of the Ase1/PRC1/Map65 family can also generate directed microtubule sliding when confined between partially overlapping microtubules. Strikingly, the Ase1-generated forces were sufficient to antagonize kinesin-14, Ncd, driven microtubule sliding. We quantitatively explained the underlying force generation by the entropic expansion of confined Ase1 molecules diffusing within the microtubule overlaps. The thermal motion of passive cross-linkers is thus harnessed to generate mechanical work analogous to compressed gas propelling a piston in a cylinder. Currently, we are extending our studies towards motor proteins, which are capable of combining active force generation and entropic expansion in one kind of molecule. For example, we found that the sliding velocity of microtubules driven by human kinesin-14, HSET, decreases when microtubules start to slide apart, resulting in the maintenance of finite-length microtubule overlaps. We quantitatively explain this feedback by the local interaction kinetics of HSET with overlapping microtubules causing retention of HSET in the shortening overlaps. Consequently, the increased HSET density in the overlaps leads to a density-dependent slowdown of the sliding velocity and the generation of an entropic force antagonizing the force exerted by the motors. Our results demonstrate that a spatial arrangement of microtubules can regulate the collective action of molecular motors through local alteration of their individual interaction kinetics.

Invited Talk Fri 09:30

Multiscale Cell Motility: From Substrate Deformation to Collective Migration

ERWIN FREY — Ludwig-Maximilians-Universität München, Theresienstrasse 37, München, Germany

A large number of physiological functions involved in both the development and maintenance of multi-cellular organisms, crucially depend on the ability of cells to migrate through and adapt to their respective environments. The capability of cells to do so is impacted by several different factors, including mechanical confinement and the viscoelastic properties of the underlying surface. We have developed a highly versatile computational model which is specifically designed to study the dynamics of cell migration at various scales, ranging from solitary crawling cells to small cell cohorts up to the scale of tissues. Using the model to investigate the motions of single cells and small cell groups confined in circular territories demonstrates that persistency of cellular movements is significantly impacted by cell contractility and cell polarizability. At the monolayer level, we predict how stress distributions and front morphologies depend on single cell features. Moreover, we show how a coarse description of substrate viscoelasticity yields rather unexpected results. The viscous

properties of the environment determine whether a single cell speeds up or slows down on surfaces with increasing stiffness, leading to the emergence of durotaxis. On macroscopic scales, cell-induced substrate deformations are detected by nearby cells and hence serve as a mechanism for long-range mechanical communication.

Invited Talk Fri 10:30

Emergent Cancer-Like Phenomenology in a Simple Model of Cells with Growth and Chemical Signalling

RAMIN GOLESTANIAN — Rudolf Peierls Centre for Theoretical Physics, University of Oxford, 1 Keble Road, Oxford OX1 3NP, UK

Using a simple model, I will address the question of stability when we study a collection of living cells, when they all send and receive chemical signals and undergo growth and death. How can we guarantee that a community of such cells can maintain a stable – homeostatic – state? The answer is not trivial, because each process on its own leads to unstable states. Such a crude phenomenological description of chemotaxis leads to interesting new perspectives. 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. We find that whereas details of the microscopic behaviour of cells do not impact the collective behaviour 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.

Contributed Talk Fri 11:00

Electron Irradiated Hydrogels: Reagent-Free Modification towards Biomedical Applications

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The hydrogels collagen and gelatin have attracted considerable interest in biology and medicine during the past years. Due to their strong biocompatibility and biodegradability, they are highly attractive materials for biomedical applications such as extracellular matrix components. Thereby, adaptation of structure and mechanics as well as stimuli-response is an interesting aspect of the modification of these materials. Reagent-free modification of hydrogels can be achieved by utilizing high energy irradiation e.g. electron irradiation to crosslink.

We will demonstrate how crosslinking with high-energetic electrons allows fine-tuning of materials properties such as structure and mechanics. Furthermore, we will present the development of stimuli-responsive systems as well as topographically and mechanically patterned hydrogel substrates for biomedical applications.

Invited Talk Fri 11:15

Establishing Nuclear Subcompartments and Chromatin Patterns to Regulate Gene Expression

KARSTEN RIPPE — German Cancer Research Center (DKFZ) and Bioquant, Division of Chromatin Networks, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany

The cell nucleus lacks internal membrane boundaries and soluble protein factors are rapidly distributed on the 10 μm length scale by free diffusive transport within seconds. Nevertheless, the cell establishes specific patterns of active and silenced genes. The underlying chromatin states are characterized by a distinct composition of chromosomal proteins and RNA, patterns of histone modifications and DNA methylation marks as well as structural features like the position and density of nucleosomes and the 3D folding of the nucleosome chain. To understand the interplay between these features, we investigate the mobility and chromatin interactions of protein factors to dissect the formation of transcriptional active or repressive nuclear subcompart-

ments by a combination of fluorescent microscopy methods in living cells. Based on these measurements biophysical models are derived that address the following questions: (i) How do chromatin modifying enzymes and transcription factors translocate in the nucleus to find their target loci? (ii) What mechanisms drive the assembly of chromatin subcompartments like pericentric heterochromatin? (iii) How is the induction of gene expression coupled to the chromatin state?

Invited Talk Fri 11:45

Strain-Controlled Rigidity Transitions in Cells and the Role of the Cell Nucleus

JENNIFER SCHWARZ — Syracuse University, College of Arts and Sciences, Department of Physics, Syracuse, NY 13244, USA

What happens to a stationary cell when it is squeezed at large strains? Does the cell become more rigid mechanically, i.e. compression stiffen? Or does it yield and become floppy? Since the cellular cytoskeleton gives the cell structural support and the cytoskeleton is composed of semiflexible polymers that can buckle, i.e. yield, then one might conclude that the cell softens as it is squeezed. I, however, will present modeling demonstrating compression stiffening in cells using rigidity transitions as a framework and show how mechanical coupling between the cellular cytoskeleton and the nuclear cytoskeleton affects the stiffening.

Invited Talk Fri 12:15

Physicochemical Properties of Basement Membranes Formed by a Cell Culture Model of Human Breast Glands

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Basement membranes (BMs) are present in almost all tissues. Throughout the entire life cycle they are decisive for tissue development, maintenance, and repair. Moreover, they are important mechanical barriers against tumor cell invasion and metastasis. At the same time the porous BM protein scaffolds function as growth factor reservoirs and affect the diffusion of biomacromolecules which influences cell differentiation and final tissue function. Despite the paramount importance of BMs, their material properties are still insufficiently understood.

Here, we used a non-tumorigenic epithelial cell line (MCF10A) originally isolated from human breast gland tissue. Upon cultivation in Engelbreth Holm Swarm (EHS) hydrogel (3D culture), these cells form hollow, multi-cellular spheroids enclosed by an endogeneously formed BM structure. We separated such BM covered MCF10A acini from the EHS matrix and imaged their structures with scanning force microscopy (AFM), scanning electron microscopy and high-resolution confocal fluorescence microscopy (Airyscan super-resolution technology). Moreover, the resistance against indentation of intact BM shells was tested at different developmental stages. Beyond these structural investigations we exposed BM shells to fluorescent dextran solutions and observed delayed permeation for larger molecular weights and fully matured spheres.

Taken together, we used MCF10A derived acini as model systems for physiological basement membranes and characterized their structure, mechanics and permeability for macromolecules. This model system enables clear-cut experiments towards a better understanding of healthy breast gland tissue function and mechanobiological processes in breast cancer invasion.

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Session IV: Tissue Organization

Invited Talk Fri 14:00

Morphology Control by Active Fluid Flows

KAREN ALIM — MPI for Dynamics and Self-Organization, Am Faßberg 17, 37077 Göttingen, Germany

Fluid flows can induce long-ranged interactions and propagate information on large scales. Especially during the development of an organism, coordination on large scales in short time is essential. We aim to discover the principal mechanisms of how fluid flows induce, transmit and respond to biological signals and thus orchestrate the morphing of an organism. The role of fluid flows in patterning and morphing is particularly prominent during the growth and adaptation of transport networks like vascular networks. Here, the network-forming slime mold Physarum polycephalum emerged as a new model to study the complex dynamics of transport networks. Investigating the pivotal role of fluid flows in this live transport network we find that flows are patterned in a peristaltic wave across the network thereby optimizing transport. In fact, flows are hijacked by signals to propagate throughout the network promoting their own transport by invoking a propagating front of increased flow. These simple nonlinear dynamics are sufficient to explain surprisingly complex dynamics of the organism like finding the shortest path through a maze.

Turning to vascular networks of plants and animals we investigate the requirements on the network to provide uniform supply of metabolites to surrounding tissues. Solving for metabolite absorption dynamics we identify the fluid inflow rate as the most important factor. Theoretically uncovered rescue responses to counteract sub-optimal inflow match observations of network adaptation in plant and animal vasculature.

Contributed Talk Fri 14:30

An Intriguing Similarity between Cancer Metastasis and Financial Markets

CHRISTOPH MARK, CLAUS METZNER, LENA LAUTSCHAM, BEN FABRY – Friedrich-Alexander University Erlangen-Nürnberg, Department of Physics, Biophysics group, Henkestraße 91, Erlangen, Germany

Invasive cancer cells and exchange-traded stocks (or funds) share a common feature: they are complex systems. In cancer metastasis, the apparently random motions of migratory cancer cells are the result of a vast network of underlying intra-cellular processes that act on different time-scales and drive cell migration. Furthermore, the cell may interact with a highly heterogeneous extra-cellular matrix. In the same way, the price fluctuations of a financial asset are the result of a multitude of transactions, carried out on time-scales that differ in several orders of magnitudes. While traditional investors may hold positions for several years, day traders carry out multiple transactions per day, and high-frequency hedge funds even trade in the milli- and microsecond regime. As a result of these broad ranges of underlying driving processes, the observable data (cancer cell movements and price fluctuations) do not follow conventional statistics. Both the step width distribution of migratory cells and the distribution of stock log-returns resemble a two-sided exponential distribution (also called Laplace distribution), instead of the ubiquitous Bell-shaped normal distribution. In other terms, extreme fluctuations, whether in cancer cell movements or stock price variations, are significantly underrepresented by conventional models that rely on the normal distribution. In fact, the use of the normal distribution in financial risk assessment is suspected to have played a significant role in recent financial crises.

Here, we present a novel method to rescue the use of simple, well-known statistical models like the normal distribution to describe the dynamics of complex systems, by proposing a hierarchy of two models. On short time scales, we have found that the movements of cancer cells as well as the stock price fluctuations still adhere to the normal distribution. On longer time scales however, the parameters of this normal distribution (i.e. the mean value and the variance) themselves show significant stochastic variations. By combining a low-level Gaussian model with a high-level model that describes how the low-level parameters change over time, we can provide a better fit to the observed data,

compared to a model with static parameters. The "anomalous" two-sided exponential distribution then arises naturally from the superposition of normal distributions with varying variances. Furthermore, this two-level approach is able to uncover essential details about the dynamics of complex systems that would have been averaged out by the use of static parameters.

Comparing the migration dynamics of four different cell types on a 2-dimensional substrate, we find that cells that exhibit phases of simultaneously high directional persistence and migration speed are also more invasive in 3-dimensional collagen gels. These efficient phases of both high persistence and speed also exist in the price dynamics of stock markets. Comparing the daily close prices from 2010 to 2016 of all stocks in the NASDAQ-100 index, we find that stocks that exhibit phases of simultaneously high volatility (analogous to cell speed) and momentum (analogous to directional persistence) perform better, compared to stocks for which volatility and momentum are non-correlated or negatively correlated.

The work not only provides new insights into both cancer cell migration and trading dynamics, but further illustrates the importance of reaching out to different fields of research (even all the way down to finance) in the effort to unravel the underlying principles that govern complex systems.

Invited Talk Fri 14:45

t.b.a.

Ana-Suncana Smith — Friedrich-Alexander University Erlangen-Nuremberg, Henkestraße 91, Erlangen, Germany

Invited Talk Fri 15:15

Physical Aspects of Successful Cell Circulation and Migration

Jochen Guck — Technical University Dresden/ Biotec, Tatzberg 47/49, 01307 Dresden, Germany

It is often repeated as a matter of fact that cancer cells, and in particular metastatic cancer cells, are more compliant than their healthy counterparts so that they can better spread through the body to form metastases. Our research over the last years has shown on the one hand that there is at least one exception to the general finding that cancer cells are more compliant. In the hematopoietic system, the leukemic blast cells are actually stiffer than the healthy mature blood cells. On the other hand, we have also shown that the seemingly obvious connection between cell compliance and improved spreading has to be modified, especially considering the timescales involved in the mechanical probing as they relate differently to cell circulation through the vasculature and to migration through tissue. Considering these aspects, cell properties can be tuned to improve circulation characteristics, for example in the use of mesenchymal stromal cells for immunomodulation during transplantation to suppress graft-vs-host-disease. Overall, there is an emergent consistent view of the importance of these physical properties for a better understanding of how cells spread and as possible targets to prevent disease.

Invited Talk Fri 16:15

Mapping Cadherin-Dependent Cell Adhesion and Elasticity Changes in Tissue Explants during the Transition from Collective to Single-Cell Migration

Carina Blaue, Jubin Kashef, Clemens M. Franz — Karlsruhe Institute of Technology, Wolfgang-Gaede-Str. 1a, 76137 Karlsruhe, Germany

During development neural crest cells (NCs) undergo epithelial-to-mesenchymal transition and switch from cooperative to single-cell migration, a process which has been compared to cancer cell detachment during metastasis. Here we have used atomic force microscopy (AFM) to investigate adhesive and mechanical changes associated with cell dissociation from cohesive NC explants. AFM-based single-cell force spectroscopy revealed a uniform distribution of cell-cell adhesion forces within tissue explants, including semi-detached leader cells in the process of delaminating from the explant edge, suggesting that cell dissociation does not require prior weakening of cell-cell contacts. However, mapping NC sheet elasticity demonstrated strongly reduced cell stiffness in semi-detached leader cells compared to neighbouring cells in the NC sheet periphery. Reduced leader cell stiffness coincided with enhanced cell spreading and high substrate traction,

indicating a possible mechano-regulation of leader cell delamination. In support, reducing cell tension by inhibiting actomyosin contractility induces rapid spreading, possibly maximizing cell-substrate interactions as a result. Depletion of cadherin-11, a classical cadherin with an essential role in NC migration and substrate adhesion, prevented the tension reduction necessary for NC spreading, both in individual cells and at the edge of explanted sheets. In contrast, overexpression of cadherin-11 accelerated spreading of both individual cells and delaminating leader cells. As cadherin-11 expression increases strongly during NC migration, this suggests an important role of cadherin-11 in regulating cell elasticity and spreading at later stages of NC migration. We therefore propose a model in which high tension at the cell sheet periphery prevents premature spreading and delamination during early stages of NC migration, while a cadherin-11-dependent local decrease in cell tension promotes leader cell spreading and delamination at later stages of migration. Cadherin-11 is also frequently upregulated in invasive breast cancer, raising the intriguing possibility that cadherin-11 plays similar roles in human tumour progression.

[1] C Blaue, J Kashef and CM Franz: Cadherin-11 promotes neural crest cell spreading by reducing intracellular tension—mapping adhesion and mechanics in neural crest explants by atomic force microscopy, Seminars in Cell & Developmental Biology (2017)

[2] RP Langhe et al.: Cadherin-11 localizes to focal adhesions and promotes cell–substrate adhesion, Nature communications (2016).

Invited Talk Fri 16:45

Regulation of Actin Cytoskeleton during Epithelial to Mesenchymal Transition - The Ocular Lens Perspective

Aftab Taiyab, Judith West-Mays — McMaster University, Department of Pathology and Molecular Medicine, 1280 Main Street West, L8S4L8, Hamilton, Ontario, Canada

Posterior Capsular opacification (PCO) or secondary cataract is the pathology of the ocular lens that results from transformation of remnant lens epithelial cells to mesenchymal cells following primary cataract surgery. Previous studies have implicated transforming growth factor (TGF)-β-induced epithelial-mesenchymal transition (EMT) of lens epithelial cells to be the major cause of PCO. Features of transformed lens epithelial cells include extensive cytoskeletal remodeling, including downregulation of epithelial cadherin (E-cadherin), F-actin polymerization and upregulation of α-smooth muscle actin (α-SMA). We have previously demonstrated the role of matrix metalloproteinase 9 (MMP-9) in the induction of TGF-β-induced lens fibrosis. Further, we have also shown that TGF-β-induced remodeling of the actin cytoskeleton is mediated through Rho- and β-catenin-signaling cascade. In addition, our work also suggests that myocardin related transcription factor A (MRTF-A), an actin-binding protein, is an important mediator of TGF-β-induced EMT in the lens. We are now extending our studies to understand the interplay between these key signaling molecules (MMP-9, Rho kinase, β-catenin and MRTF-A) during TGF-β-induced EMT in the lens. Together, our results demonstrate that these key signaling molecules act in conjunction with each other and reveal unexpected interaction during the progression of secondary cataract.

Invited Talk Fri 17:15

t.b.a.

Marija Plodinec — University Center Basel, Klingelbergstrasse 50 / 70, 4056 Basel, Switzerland

Prospective End Fri 18:00

8th Symposium

PHYSICS OF CANCER

October 4- 6, 2017 | Leipzig, Germany

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Time	Wednesday, Oct. 4, 2017
11:00	Conference check-in
13:00	Welcome
	Session I: Cell Migration & Invasion
13:15	Ingo Bechmann
13:45	Mohit Kumar Jolly
14:15	Katarina Wolf
14:45	Sagar Regmi (CT)
15:00	Tobias Zech
15:30	Coffee break
	Special Focus Session: Collective Cell Behavior
16:00	Stephan Grill
16:30	Xavier Trepat
17:00	Andrew Clark (CT)
17:15	Jae Hun Kim
17:45	Daniel Sussman
18:30	Welcome Dinner Faculty of Physics and Earth Sciences Linnéstr.5 - 04103 Leipzig (first floor, assembly room)

Time	Thursday, Oct. 5, 2017
	Session II: Biomechanics
08:15	Miriam Dietrich (CT)
08:30	Kay Gottschalk
09:00	Jan Lammerding
09:30	Ben Fabry
10:00	Coffee break
10:30	Nastaran Zahir
11:00	Ulf-Dietrich Braumann (CT)
11:15	Ulrike Köhl
11:45	Pascal Silberzan
12:15	Sebastian Schmidt (CT)
12:30	**POSTER SESSION** Presentation of contributed posters with discussions and lunch/ BBZ foyer
16:00	Social Event for Invited Speakers: Tours "St. Thomas Church", "Bach Museum", dinner at "Ratskeller Leipzig"

Time	Friday, Oct. 6, 2017
	Convergent Science Physical Oncology
	Session III: Cellular Organization
08:15	Adrian Fessel (CT)
08:30	Joachim Spatz
09:00	Stefan Diez
09:30	Erwin Frey
10:00	Coffee break
10:30	Ramin Golestanian
11:00	Stefanie Riedel (CT)
11:15	Karsten Rippe
11:45	Jennifer Schwarz
12:15	Rudolf Merkel
13:00	Lunch
	Session IV: Tissue Organization
14:00	Karen Alim
14:30	Christoph Mark (CT)
14:45	Ana-Suncana Smith
15:15	Jochen Guck
15:45	Coffee break
16:15	Clemens Franz
16:45	Aftab Taiyab
17:15	Marija Plodinec
18:00	Prospective end

Notes

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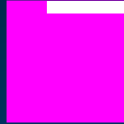

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