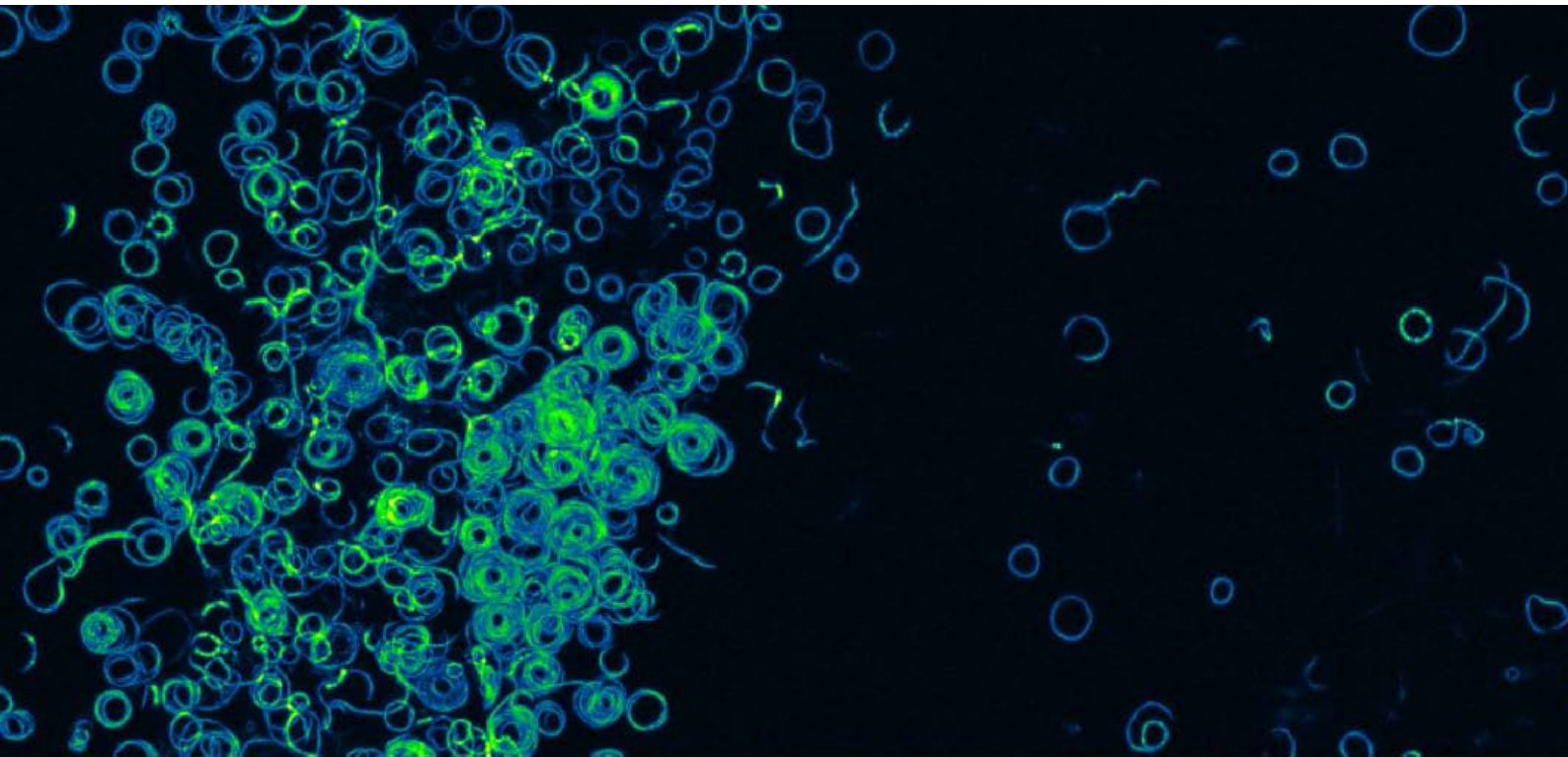


IWH-SYMPOSIUM

COLLECTIVE CELL MIGRATION

Heidelberg, July 14-15, 2015



Organizers:

Heike Böhm, Friedrich Frischknecht, Ulrich Schwarz

www.cellmigrationsymposium.de

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Internationales Wissenschaftsforum der Universität Heidelberg
Hauptstrasse 242
69117 Heidelberg
Germany

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The cover illustration shows an overlay of the trajectories of many malaria sporozoites (courtesy of Friedrich Frischknecht).

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SEIT 1386



THEORETISCHE PHYSIK



PROGRAMME

day before, July 13 (Monday)

19:00 - 21:00 Registration and reception at the IWH

1st day, July 14 (Tuesday)

Session 1: Dynamics of cell monolayers I

09:00 - 09:40: Pascal Silberzan, Confined and shaped monolayers

09:40 - 10:20: Franziska Matthäus, Signaling effects in the collective migration of non-small cell lung cancer

10:20 - 10:40: Ana Smith, Organization and collective motion of cells in MDCK cell sheets: Experiment and theory

10:40 - 11:20: coffee break

Session 2: Cell cycle control in wound healing

11:20 - 12:00: Lars Hufnagel

12:00 - 12:40: Niels Grabe

12:40 - 13:00: Stuart Johnston, Interpreting scratch assays using pair density dynamics and approximate Bayesian computation

13:00 - 14:30: lunch / posters / discussion

Session 3: Tissues and development

14:30 - 15:10: Darren Gilmour

15:10 - 15:50: Roberto Major, Collective cell migration of mesenchymal cells

15:50 - 16:10: Lukas Schütz, The dorsal folds in *Drosophila* as approach to study robustness in development

16:10 - 16:40: coffee break

Session 4: Molecular mechanisms

16:40 - 17:20: Sandrine Etienne-Manneville, Keeping in contact during collective cell migration

17:20 - 18:00: Michael Sixt

18:00 - 18:40: Tamal Das, Mechanoregulation of collective migration of epithelial cells

19:00 Buffet dinner

2nd day, July 15 (Wednesday)

Session 5: Dynamics of cell monolayers II

09:00 - 09:40: Xavier Trepap

09:40 - 10:20: Thomas Angelini, Cell volume fluctuations and intercellular fluid flow

10:20 - 10:40: Ruth Baker, Cell-based models

10:40 - 11:20: coffee break

Session 6: Cell interactions

11:20 - 11:40: Christine Selhuber, Microporous 3D hydrogels for controlling cell migration

11:40 - 12:00: Jae Hun Kim, Unjamming and intercellular adhesive forces in airway epithelial cells

12:00 - 12:20: Wolfgang Losert, Physical guidance of cell migration

12:20 - 12:40: Benedikt Sabass, Cooperative migration of *Myxococcus Xanthus*

12:40 - 13:00: Till Kranz, Effective dynamics of microorganisms that interact with their own trail

13:00 - 14:30: lunch / posters / discussion

Session 7: Role of geometry

14:30 - 15:10: Celeste Nelson, Dynamics of cell-generated forces during 3D collective migration

15:10 - 15:50: Alexander Kabla, Collective dynamics of cell migration and cell rearrangements

15:50 - 16:10: Irina Surovtsova, Elastic force balance for tissue shape on patterned substrates

16:10 - 16:40: coffee break

Session 8: Physics of cell migration

16:40 - 17:20: Joachim Rädler, Cell migration in confined geometries

17:20 - 17:40: Dapeng Bi, Rigidity and glassy dynamics in confluent biological tissues

17:40 - 18:00: Christian Franck, High resolution, large deformation 3D traction force microscopy

18:00 - 18:20: Ulrich Schwarz, Malaria parasite swirls

19:00 Buffet dinner

ABSTRACTS

TALKS

Confined and shaped monolayers

P. Silberzan, Institut Curie, Paris

Cell monolayers routinely exhibit collective behaviors largely controlled by cell-cell interactions. In this context, confinement and boundary conditions play an important role in the organization and dynamics of these cell assemblies. Interestingly, many *in vivo* processes, including morphogenesis or tumor maturation, involve small populations of cells within a spatially restricted region.

We report experiments in which epithelial monolayers confined in circular disks exhibit low-frequency periodic radial displacement modes. When the boundary is removed, cells collectively migrate on the free surface. The essential characteristics of the collective dynamics in these two situations are well-accounted for by the same theoretical model in which cells are described as persistent random walkers which adapt their motion to that of their neighbors. In contrast, elongated fibroblasts that do not develop cell-cell adhesions self-organize until reaching a perfect nematic order upon confinement.

After days in culture, the confined epithelia develop a tridimensional structure in the form of a peripheral cell cord at the domain edge. Confinement by itself is therefore sufficient to induce morphogenetic-like processes including spontaneous collective pulsations, global orientation and transition from 2D to 3D.

Finally, culturing cell monolayers on cylindrical wires reveals some specific traits of the out-of-plane curvature on the dynamics and architecture of epithelia, independent on the lateral confinement.

Signaling effects in the collective migration of non-small cell lung cancer

A.M. Middleton¹, D. Stichel¹, K. Breuhahn² and F. Matthäus¹

¹ Complex Biological Systems Research Group, Center for Modeling and Simulation in the Biosciences, University of Heidelberg, Germany

² Department of Pathology, University Hospital Heidelberg, Heidelberg, Germany

Many lung cancer cell lines show collective migration, a common phenomenon in epithelial cancers. The enhanced migratory phenotype of these cell lines is partly a result of a set of mutations, often involving the activation of growth factor signaling pathways. Therefore specific signaling pathway inhibitors are used as therapeutic agents in lung cancer therapy. However, treatment with growth factors, inhibition of their respective receptors, or downstream pathway components, significantly affect cell proliferation but also cell migration. We here use mathematical modeling and data analysis to quantify the effect of these treatments on the migratory phenotype of non-small cell lung cancer cell lines. The experimental setup involves a classical lateral migration assay after treatment with growth factors or selective receptor tyrosine kinase inhibitors. Depending on the treatment, we observe different qualitative behaviors, involving traveling fronts and individual streams. Analysis using particle image velocimetry (PIV) provides quantitative data on the spatio-temporal velocity distribution. To better understand the underlying mechanical properties leading to the differences in the observed collective behavior we developed a mathematical model based on a Langevin approach. The model describes intercellular forces, random motility, and stimulation of active migration by mechanical interaction between cells. Simulations based on the model are able to reproduce the observed behaviors. Re-formulation of the model allows the inference of model parameters from quantities measurable by tracking and segmentation. Tests of the parameter inference method based on simulated data yields very good results. Thus, our approach provides a means to identify which mechanical aspects (on the individual cell level) are affected by the treatment, which eventually lead to the observed changes in the migratory phenotype of the monolayer.

Interpreting scratch assays using pair density dynamics and approximate Bayesian computation

Stuart Johnston, Matthew J. Simpson, D. L. Sean McElwain, Benjamin J. Binder
and Joshua V. Ross

Quantifying the impact of biochemical compounds on collective cell spreading is an essential element of drug design, with various applications including developing treatments for chronic wounds and cancer. We compare various types of information that can be extracted from images of a scratch assay and quantify the unbiased cell motility, D , and the cell proliferation rate, λ , using discrete computational simulations and approximate Bayesian computation. Estimating D and λ is important for investigating the efficacy of a potential treatment and provides insight into the mechanism through which the potential treatment acts. We show that it is possible to robustly recover estimates of D and λ from synthetic data as well as a new set of experimental data. For the first time our approach also provides a method to estimate the uncertainty in our estimates of D and λ .

The dorsal folds in *Drosophila* as approach to study robustness in development

Lukas Schütz, Silvia Urbansky, Maike Wosch, Steffen Lemke

Gastrulation is a key feature of all higher animals and results in the formation of three distinct germ layers that set up the developing animal body. Far, but also closely related species exhibit various climatic conditions during development; however, gastrulation seems to be robust enough to work under these various conditions. Which structures exist to create or promote this robustness remains to be solved. In *Drosophila melanogaster*, a well described model system, almost every single of the more than 6000 cells moves during gastrulation. Muvi-SPIM microscopy shows, that these cells move coordinated in several groups with one direction per group. We suppose that certain mechanisms and structures, which coordinate and regulate this motion, are present in the embryo. The dorsal folds and the cephalic furrow are two of these structures to be considered for such a function. The cephalic furrow is an evolutionary novelty which is new within the Diptera, it surrounds the embryo and separates the head from the trunk region and can undergo a rotation during germband extension. The dorsal folds reach from the dorsal side of the embryo down to the lateral sides; their shape changes during germband extension. Both the dorsal folds and the cephalic furrow are barriers within the streams of moving cells during germband extension. We hypothesize that structures like the dorsal folds and / or the cephalic furrow are necessary to make germband extension, a crucial part of development, in *Drosophila* and other flies under certain climatic conditions robust. To test this we will analyze the dorsal fold size in *Drosophila* species from multiple climatic regions in fixed tissue and complement this with Muvi-SPIM data to show the interaction of cells with furrows and folds of different sizes.

Keeping in contact during collective cell migration

Sandrine Etienne-Manneville
Institut Pasteur Paris

Collective cell migration is essential during development as well as in adult organisms where it participates, for instance, in tissue renewal, wound healing or cancer invasion and metastasis. As cells migrate collectively, intercellular junctions maintain the integrity of the cell monolayer while allowing differential movement and rearrangements of adjacent cells. In astrocytes, intercellular contacts are mainly formed by N-cadherin-mediated adherens junctions. Downregulation of N-cadherin is frequently observed in astrocyte derived tumors, gliomas and promotes single cell migration while perturbing cell polarity and increasing cell velocity.

To understand how cells can maintain stable intercellular junctions and simultaneously rearrange them to accommodate cellular displacement, we have investigated cadherin dynamics during astrocyte collective migration. We show adherens junctions undergo a continuous retrograde movement compensated by a polarized recycling of cadherin from the rear to the leading edge. Such dynamics allows the cells to maintain stable contacts while permitting changes of cellular interactions. In glioma cells, N-cadherin dynamics and consequently the maintenance of cell-cell contacts are perturbed leading to loss of cell polarity and to increased migration.

Mechanoregulation of Collective Migration of Epithelial Cells

Tamal Das

*Department of New Materials and Biosystems, Max Planck Institute for
Intelligent Systems, Stuttgart - 70569, Germany.*

*Department of Biophysical Chemistry, University of Heidelberg, Heidelberg -
69120, Germany.*

Collective migration of epithelial cells is critical for embryonic morphogenesis, cancer, and wound healing. Yet the principal molecular mechanism that enables the cells to coordinate their motions over large-distances remained elusive for long time. To this end, we have recently provided a comprehensive answer to this question, for the first time, by revealing a complete molecular mechanism [1]. Our study has illustrated how a tumor-suppressor protein, merlin, converts cellular forces to collective motions of epithelial cells, by acting as a mechanochemical transducer. In static epithelia, merlin localizes to cell cortex and inhibits Rac1, an important inducer of cell migration. During migration, cell-cell pulling forces relocalize merlin to cytoplasm. This event then triggers spatially polarized Rac1 activation and lamellipodium formation, prompting the standing cell to follow its moving neighbor. These findings link intercellular mechanical forces to collective cell movements and have important implications in wound healing and cancer biology [2].

When epithelial cells move together to close a wound, some of the cells in the front row - one in every five approximately - may get structurally polarized to form actin-rich expanded protrusions called lamellipodia. These 'leader cells' drive the collective migration during wound closing. In spite of the significance, exact roles of these leader cells and the mechanism by which they influence the collective migration remained unknown for long time. We have looked into these issues from both biophysical and biochemical perspectives. Using micropatterning techniques, we have shown that geometric cues like local variation of curvature in the wound perimeter can trigger leader cell formation [3]. Leader cells preferentially originate from high curvature regions. This tendency is governed by the cytoskeleton tension due to actomyosin contractility, as revealed by actin imaging in live cells and traction force microscopy. Complementing these findings, in another study, we have recently found that once formed, leader cells also inhibit formation of other leaders within 4-5 cell-diameter distance through a mechanotransduction process. This

process again depends on the actomyosin contractility and leads to preferential recruitment of WAVE2-Arp2/3 actin-nucleation and branching complex to cell-cell junctions. Instead of generating its own lamellipodium towards the free space, the non-leader marginal cells then reorient their cell-substrate focal adhesion towards the nearest leader cell and follow its migration direction. Together these studies have revealed how physical forces are linked to biochemistry in regulating the leader cell formation relevant to wound healing, embryonic development, and oncogenesis.

References:

1. T. Das, K. Safferling, S. Rausch, N. Grabe, H. Boehm, and J.P. Spatz, *A molecular mechanotransduction pathway regulates collective migration of epithelial cells*. Nature cell biology, 2015. **17**(3): p. 276-87.
2. A. Zoch and H. Morrison, *Merlin's wizardry guides cohesive migration*. Nature cell biology, 2015. **17**(3): p. 212-3.
3. S. Rausch, T. Das, J.R. Soine, T.W. Hofmann, C.H. Boehm, U.S. Schwarz, H. Boehm, and J.P. Spatz, *Polarizing cytoskeletal tension to induce leader cell formation during collective cell migration*. Biointerphases, 2013. **8**(1): p. 32.

Cell volume fluctuations and intercellular fluid flow

Thomas Angelini
University of Florida, USA

Tissue cell mechanics and motion are intimately tied to cytoskeletal contraction, which is driven by molecular motors. Contraction generated tension within a cell is balanced by deformation of the cell's microenvironment, by internal cytoskeletal structures, and by the incompressible cytosolic fluid contained within the cell membrane. However, contraction generated pressures cannot be supported by the cytosol if fluid transport occurs across the cell membrane. The cell membrane is highly permeable to water, though water transport is tightly regulated by the control of osmotic pressure with ion pumps. Within cell monolayers, permeable protein plaques called gap junctions connect neighboring cells, allowing small molecules to pass between cells even at uniform osmotic pressure. Thus, if gap junction permeability is high enough, cell contractions may drive fluid between cells. In this talk I will discuss measurements of contraction driven fluid movement across gap junctions connecting neighboring cells. We observe contracting cells pushing fluid into their neighbors. To study the mechanics of intercellular fluid flow, we apply biologically relevant pressures to large regions of cells in a monolayer with a micro-indentation system. We directly measure indentation force and volume as a function of time to determine fluid flow rates and associated stresses between cells. We find that gap-junction permeability does not limit fluid transport between cells, and that fluid flow is controlled by a balance of cytoskeletal tension throughout the cell monolayer. These results suggest that cells act like micro-scale pumps – cell monolayers can be thought of as networks of pressure sources and sinks connected by semi-permeable conduits.

Cell-based models

Ruth Baker
University of Oxford

The visceral endoderm (VE) is a simple epithelium that forms the outer layer of the egg-cylinder stage mouse embryo. The anterior visceral endoderm (AVE), a specialised subset of VE cells, is responsible for specifying anterior pattern. AVE cells show a stereotypic migratory behaviour within the VE, which is responsible for correctly orientating the anterior-posterior axis. The epithelial integrity of the VE is maintained during the course of AVE migration, which takes place by intercalation of AVE and other VE cells. Though a continuous epithelial sheet, the VE is characterised by two regions of dramatically different behaviour, one showing robust cell movement and intercalation (in which the AVE migrates) and one that is static, with relatively little cell movement and mixing. Little is known about the cellular rearrangements that accommodate and influence the sustained directional movement of subsets of cells (such as the AVE) within epithelia like the VE.

This study uses an interdisciplinary approach to further our understanding of cell movement in epithelia. Using both wild-type embryos as well as mutants in which AVE migration is abnormal or arrested, we show that AVE migration is specifically linked to changes in cell packing in the VE and an increase in multi-cellular rosette arrangements (five or more cells meeting at a point). To probe the role of rosettes during AVE migration, we develop a mathematical model of cell movement in the VE. To do this, we use a vertex-based model, implemented on an ellipsoidal surface to represent a realistic geometry for the mouse egg-cylinder. The potential for rosette formation is included, along with various junctional rearrangements. Simulations suggest that while rosettes are not essential for AVE migration, they are crucial for the orderliness of this migration observed in embryos. Our simulations are similar to results from transgenic embryos in which Planar Cell Polarity (PCP) signalling is disrupted. Such embryos have significantly reduced rosette numbers, altered epithelial packing, and show abnormalities in AVE migration. Our results show that the formation of multi-cellular rosettes in the mouse VE is dependent on normal PCP signalling.

Taken together, our model and experimental observations suggest that

rosettes in the VE epithelium do not form passively in response to AVE migration. Instead, they are a PCP-dependent arrangement of cells that acts to buffer the disequilibrium in cell packing generated in the VE by AVE migration, enabling AVE cells to migrate in an orderly manner.

Microporous 3D hydrogels for controlling cell migration

S. Gutekunst, S. Paveenkittiporn, K. Göpfert, I. Hölken, R. Adelung, C. Selhuber-Unkel

University of Kiel, Institute for Material Science

3D biomaterial scaffolds are promising materials for mimicking the natural environment of many cell types, which are in vivo normally integrated into well-structured and dense material structures. In particular, materials with high structural flexibility offer interesting possibilities, e.g. for mimicking extracellular matrix and bone structures. Based on 3D networks of ZnO tetrapods, we have developed a method to generate 3D biomaterials that contain interconnected mazy channels in the micrometer and nanometer range. These materials mimic in vivo conditions in the extracellular matrix, where cells are embedded into a dense network of fibers and only occupy a tiny fraction of space. Importantly, we can define the overall shape and size of the scaffold, channel size, porosity, scaffold stiffness and surface functionalization independently from each other. The interconnectivity of our hollow multi-channel structure is always guaranteed by the fabrication procedure and that interconnectivity is independent of channel and pore density. Our novel method is based on hydrogels so that enough nutrients reach the cells in spite of the small channel diameters. Besides, the cells can be guided through these channels with the aid of chemotactic reagents. Intriguingly, cells can grow deeply into such scaffold materials and control cell migration by channel diameter. If it is not possible to give a contributed talk, I would like to present our work on a poster.

Unjamming and intercellular adhesive forces in airway epithelial cells

Jae Hun Kim, Dapeng Bi, Jennifer A. Mitchel, Jin-Ah Park, Maureen McGill, Nader Taheri Qazvini, Robert L. Steward, Stephanie Burger, Jacob Notbohm, Elizabeth Henske, Scott H. Randell, James P. Butler, M. Lisa Manning, Jeffrey M. Draze, Jeffrey J. Fredberg

Harvard T.H. Chan School of Public Health

Introduction

From coffee beans flowing in a chute to cells remodeling in a living tissue, a wide variety of particulate, close-packed, collective systems –both inert and living– have the potential to jam. However, the transition between unjammed versus jammed phases remains poorly understood. In as yet unpublished studies (Park, Kim et al. Nature Materials, 2015, in revision) we report that human bronchial epithelial cells (HBECs) from non-asthmatic donors spontaneously transition from an immature, hypermobile, fluid-like phase over the course of 6-8 days of air-liquid-interface culture into a mature, jammed, solid-like phase. By contrast, in HBECs from asthmatic donors this unjammed-to-jammed transition is substantially delayed. In inert particulate matter, reduced particle-particle adhesion leads to unjamming, and therefore reduced cell-cell adhesion might be reasoned to be a plausible mechanism for increased fluidity in asthmatic cells. We tested the hypothesis that unjamming is accompanied by attenuated cell-cell adhesion as reflected by attenuated adhesive forces.

Methods

We used intercellular forces transmitted across cell-cell junctions as a direct measure of cell-cell adhesive forces. To measure local tractions that cells exert upon their substrate (Monolayer Traction Microscopy), and intercellular forces that cells exert upon their immediate neighbors (Monolayer Stress Microscopy), we seeded HBECs from non-asthmatic and asthmatic donors on polyacrylamide gels. Cooperativity of intercellular tension was quantified by measuring fluctuations of tension and the correlation length of those fluctuations. We also measured cellular shape and compared those measured changes to predictions from the vertex model of epithelial dynamics (<http://arxiv.org/abs/1409.0593v4>).

Results

In the HBEC layers derived from asthmatic versus non-asthmatic donors, RMS tractions exerted upon the substrate were not statistically different but tended to be larger. However, intercellular tensions exerted by each cell upon its neighbors were larger by 1.5- to 5-fold. Moreover, tension correlation decayed over several hundred micrometers but with faster spatial decay in cells derived from asthmatic versus non-asthmatic subjects, thus confirming that HBECs derived from asthmatic versus non-asthmatic donors bear higher but more localized intercellular tension. These results show that unjamming of HBECs accompanies intensified intercellular adhesive forces but not their attenuation. Moreover, we discovered that as cells approach the jamming transition the measured cellular perimeter-to-area ratio systematically approaches the critical value predicted by the vertex model. Paradoxically, this model predicts that increased adhesion can work to unjam the cellular collective.

Conclusions

Unexpectedly, unjamming of HBECs is associated with intensification rather than attenuation of intercellular adhesive forces. These findings suggest a new physical picture of airway epithelium in which cells migrate collectively under the influence of cooperative physical forces. Intensified intercellular forces appear to agitate the cellular collective, overcoming energy barriers needed for cellular rearrangements, which leads to unjamming of the airway epithelial layer.

Physical guidance of cell migration

Wolfgang Losert

University of Maryland, USA

The migration of cells in streams, and the crossover from collective cell behavior to individual cell migration is one of the key physical steps in cancer metastasis. This migration occurs in the context of a microenvironment with specific mechanics and texture that may guide the metastatic process. Studies on cell lines indicate that an increasing metastatic potential of cells is associated not with changes in migration speed, but with a decrease in collective motion and increasing chaotic movement fields of groups of cells. I will describe how an underlying wave-like process of the cellular scaffolding that drives persistent migration contributes to the ability of cells to move collectively. I will further show that the same internal waves also allow cells to recognize and follow surface nanotopography on scales comparable to these internal waves. This facilitates contact guidance by the texture of their environment.

Cooperative migration of Myxococcus Xanthus

Benedikt Sabass, J. Shaevitz, H.A. Stone
Princeton, USA

Myxobacteria are rod-shaped, social organisms that inhabit soil and dung. While unable to swim, these bacteria possess two distinct machineries for migration in a solid or semi-solid environment: Firstly, they extend protein threads called pili to pull themselves forward in a hand over hand fashion. Secondly, they glide on surfaces by continuously translating localized adhesion patches along their body. Myxobacteria can migrate individually to explore their environment for food. However, they also join up to form a quasi two-dimensional sheet and then move as groups to eventually form large aggregates. Here, we study the forces during these migration stages by using Traction Force Microscopy. Forces during pilus-based motion are very distinct from those during gliding motility. The dynamic nature of pilus retraction and adhesion site formation leads to force fluctuations on a timescale of seconds. Collectivity strongly affects frequency, directionality, and magnitude of these changes. For group migration, we find evidence that pili are used to distribute stress and conserve integrity of the system. However, in contrast to common tissue model systems, traction only occurs in local hotspots and constant tension or pressure is not present. This difference might be attributed to the biological function of bacterial migration where fast, directed migration is more important than organization and structure of the group.

Effective dynamics of microorganisms that interact with their own trail

Till Kranz, Anatolij Gelimson, Ramin Golestanian
University of Oxford

Every collective phenomenon needs some form of interaction between the particles or cells. In loose assemblies (e.g., in the early stages of clustering) this interaction must be long ranged to be effective. Diffusion of signalling molecules bridges the distance in the more well studied examples of chemotaxis (e.g., in slime molds). On the other hand, persistent trails consisting of slowly diffusing (sticky) macromolecules left behind by moving cells is a largely unexplored means of chemotaxis. We will discuss a simple model for the trail-mediated self-interaction of cells that shows a surprisingly rich phenomenology. Depending on the strength of the coupling, the dynamics exhibits effective diffusion in both orientation and position, orientational oscillations, and a localization transition with a divergent orientational correlation time.

Dynamics of cell-generated forces during 3D collective migration

Celeste M. Nelson
Princeton, USA

Collective cell migration drives tissue remodeling during development, wound repair, and metastatic invasion. The physical mechanisms by which cells move cohesively through dense three-dimensional (3D) extracellular matrix (ECM) remain incompletely understood. Here, we show directly and quantitatively that migration of multicellular cohorts through collagenous matrices occurs via a dynamic pulling mechanism, the nature of which had only been inferred qualitatively in 3D. Tensile forces accumulate at the invasive front of cohorts, serving a physical, propelling role as well as a regulatory one by conditioning the cells and matrix for further extension. These forces elicit mechanosensitive signaling within the leading edge and align the ECM, creating microtracks conducive to further migration. Moreover, cell movements are highly correlated and in phase with ECM deformations. Migrating cohorts use spatially localized, long-range forces and consequent matrix alignment to navigate through the ECM. These results suggest biophysical forces are critical for 3D collective migration.

Collective dynamics of cell migration and cell rearrangements

Alexandre J. Kabla

Cambridge University

Understanding multicellular processes such as embryo development or cancer metastasis requires to decipher the contributions of local cell autonomous behaviours and long range interactions with the tissue environment. A key question in this context concerns the emergence of large scale coordination in cell behaviours, a requirement for collective cell migration or convergent extension. I will present a few examples where physical and mechanical aspects play a significant role in driving tissue scale dynamics.

(i) Geometrical confinement is one of the key external factors influencing large scale coordination during collective migration. Using a combination of in vitro experiments and numerical simulations, we show that the velocity correlation length, measured in unconfined conditions, provides a convenient length scale to predict the dynamic response under confinement. The same length scale can also be used to quantify the influence range of directional cues within the cell population.

(ii) Heterogeneity within motile cell populations is frequently associated with an increase in their invasive capability and appears to play an important role during cancer metastasis. Using in silico experiments, we studied the way cell invasion is influenced by both the degree of cell coordination and the amount of variability in the motile force of the invading cells. Results suggest that mechanical heterogeneity dramatically enhances the invasion rate through an emerging cooperative process between the stronger and weaker cells, accounting for a number of observed invasion phenotypes.

(iii) Effective convergent extension requires on a consistent orientation of cell intercalation at the tissue scale, most often in relation with planar cell polarity mechanisms to define the primary axes of deformation. Using a novel

modelling approach for cells mechanical interactions, we studied the dynamics of substrate free motile cell populations. Ongoing work shows in particular that nematic order emerges from interacting cells without the need for biochemical cues setting tissue polarity.

Elastic force balance for tissue shape on patterned substrates

I.Surovtsova , M.Deforet, P.Silberzan, U.Schwarz
Heidelberg University BioQuant - Center for Quantitative Biology

In many important biological situations, most prominently in wound healing, cell monolayers are advancing into new territory. Patterned substrates can be used to study quantitatively how cell monolayers cope with heterogeneities in their environment. For MDCK-cells on pacman-shaped adhesive patterns, we find

experimentally that the cell monolayer can bridge the non-adhesive wedge only up to a distance that decreases in a characteristic fashion with the opening angle of the wedge. This finding can be quantitatively explained by a theory that assume that at equilibrium, the propulsive force at the leading edge is balanced by the elastic forces arising in the contracting cell sheet. Our theory also predicts the non-circular shapes of the invaginations, the stress distribution in the cell monolayer and the pulling forces on the adhesive sites.

Rigidity and glassy dynamics in confluent biological tissues

Dapeng Bi, Lisa Manning
Syracuse University / Rockefeller University

Cells must move through tissues in many important biological processes, including embryonic development, cancer metastasis, and wound healing. Often these tissues are dense and a cell's motion is strongly constrained by its neighbors, leading to glassy dynamics. Although there is a density-driven glass transition in self-propelled particle (SPP) models for active matter, these cannot explain liquid-to-solid transitions in confluent tissues, where there are no gaps between cells and the packing fraction remains fixed and equal to unity. We have recently described a different type of rigidity transition that occurs in confluent tissue monolayers in the limit of vanishing cell motility, where the onset of rigidity is governed by changes to single-cell properties such as cell-cell adhesion and cortical tension. Here we alter the model to include cell motility using an equation for polarization similar to those in SPP models. We identify a glass transition line that originates at the critical point of the rigidity transition, and compare the results to an analytic trap model. The model provides a novel signature for mechanical behavior in confluent tissues, which has been successfully tested in experimental systems. I will also demonstrate that this model provides a framework for studying the Epithelial-to-Mesenchymal transition in cancer invasion and cell sorting during embryonic development.

High resolution, large deformation 3D traction force microscopy

Christian Franck, Jennet Toyjanova, Eyal Bar-Kochba, Cristina Lopez-Fagundo,
Diane Hoffman-Kim, Jonathan Reichner
Brown University, Richmond USA

Traction Force Microscopy (TFM) is a powerful approach for quantifying cell-material interactions that over the last two decades has contributed significantly to our understanding of cellular mechanosensing and mechanotransduction. In addition, recent advances in three-dimensional (3D) imaging and traction force analysis (3D TFM) have highlighted the significance of the third dimension in influencing various cellular processes. Yet irrespective of dimensionality, almost all TFM approaches have relied on a linear elastic theory framework to calculate cell surface tractions. Here we present a new high resolution 3D TFM algorithm which utilizes a large deformation formulation to quantify cellular displacement fields with unprecedented resolution. The results feature some of the first experimental evidence that cells are indeed capable of exerting large material deformations, which require the formulation of a new theoretical TFM framework to accurately calculate the traction forces. Based on our previous 3D TFM technique, we reformulate our approach to accurately account for large material deformation and quantitatively contrast and compare both linear and large deformation frameworks as a function of the applied cell deformation. Particular attention is paid in estimating the accuracy penalty associated with utilizing a traditional linear elastic approach in the presence of large deformation gradients.

Malaria parasite swirls

K. Beyer¹, S. Rossberger², A. Battista³, F. Mehta²,
H. Böhm², F. Frischknecht², U. Schwarz³

Heidelberg University

¹Parasitology, ²Physical Chemistry, ³Theoretical Physics

Sporozoites are the form of the malaria parasite that is injected by the mosquito into the skin of the mammalian host. Single sporozoites move at high speed through the skin in search for blood vessels to penetrate. From there, they proceed to the liver and then to the blood stages of the disease. Recently, we found that sporozoites dissected from the salivary gland of the mosquito form swarming patterns, in which many parasites rotate around a common center. Each of these swirls consists of 5-100 gliding sporozoites and occasionally exchanges sporozoites with neighboring swirls. We have investigated the pattern formation by quantitative image processing and have simulated it with an agent-based computer model. We find that sporozoite rigidity is one of the main determinants of swirl stability.

POSTERS

- Francesco Alaimo: A phase field crystal model for active particles
- Christiane Antoni: Controlling cell adhesion in collective migration
- Konrad Beyer: Swarm-like behaviour of Plasmodium sporozoites
- Dimitris Missirlis: Directional persistence in single fibroblast migration as a function of specific integrin engagement
- Mendi Muthinja: Dissecting the role of curvature in Plasmodium parasite
- Medhavi Nagpal: Mechanotransductional regulation of leader cell formation during collective migration of epithelial cells
- Sabrina Rossberger: Automated analysis of collective migrating malaria Plasmodium sporozoites
- Axel Voigt: Collective cell migration - a modeling approach using phase fields

List of Participants

Alaimo Francesco, Institute of Scientific Computing, TU Dresden,
francesco.alaimo@tu-dresden.de

Albert Philipp, Heidelberg University,
philipp.albert@bioquant.uni-heidelberg.de

Angelini Thomas E., University of Florida, USA,
t.e.angelini@ufl.edu

Antoni Christiane, MPI f. Intelligent Systems & Inst. f. Physical Chemistry, Heidelberg Univ.,
antoni@is.mpg.de

Baker Ruth, University of Oxford, UK,
ruth.baker@maths.ox.ac.uk

Beyer Konrad, Heidelberg University, Parasitology,
Beyer.konrad@gmail.com

Bi Dapeng (Max), Syracuse University / Rockefeller University, USA,
bdpmax@gmail.com

Boehm Heike, MPI for Intelligent Systems, Stuttgart & Heidelberg Univ.,
boehm@is.mpg.de

Cavalcanti Ada, Heidelberg University,
ada.cavalcanti-adam@urz.uni-heidelberg.de

Cyrklaff Marek, Heidelberg University, Parasitology,
cyrklaff@me.com

Das Tamal, MPI for Intelligent Systems, Stuttgart,
Das@is.mpg.de

Dickmann Johanna, Inst. f. Physical Chemistry, Heidelberg Univ.,
dickmann@is.mpg.de

Erdmann Thorsten, Heidelberg University,
thorsten.erdmann@bioquant.uni-heidelberg.de

Etienne-Manneville Sandrine, Institut Pasteur Paris,
setienne@pasteur.fr

Franck Christian, Brown University, Richmond, USA,
franck@brown.edu

Frechin Mathieu, University of Zurich, Switzerland,
mathieu.frechin@uzh.ch

Frey Felix, Heidelberg University,
f.frey@thphys.uni-heidelberg.de

Frischknecht Friedrich, Heidelberg University,
freddy.frischknecht@med.uni-heidelberg.de

Gilmour Darren, EMBL Heidelberg,
gilmour@embl.de

Grab Anna Luise, Heidelberg University,
agrab@ix.urz.uni-heidelberg.de

Grabe Niels, Heidelberg University,
niels.grabe@bioquant.uni-heidelberg.de

Grünbein Marie, Heidelberg University,
marie.gruenbein@gmx.de

Haubold Carsten, Heidelberg University, HCI,
carsten.haubold@iwr.uni-heidelberg.de

Hufnagel Lars, EMBL Heidelberg,
hufnagel@embl.de

Johnston Stuart, Queensland University of Technology, Australia,
stuart.johnston@student.qut.edu.au, sef.mathsfinance@qut.edu.au

Kabla Alexandre J., Cambridge University, UK,
ajk61@eng.cam.ac.uk

Kim Jae Hun, Harvard T.H. Chan School of Public Health, USA,
kim@hsph.harvard.edu

Kranz Till, University of Oxford, UK,
kranz@physics.ox.ac.uk

Losert Wolfgang, University of Maryland, USA,
wlosert@umd.edu

Matthäus Franziska, BIOMS Heidelberg,
franziska.matthaeus@iwr.uni-heidelberg.de

Mayor Roberto, University College London, UK,
r.mayor@ucl.ac.uk

Mehta Freya, Heidelberg University,
freya.mehta@gmail.com

Missirlis Dimitris, MPI for Intelligent Systems, Stuttgart & Heidelberg Univ.,
missirlis@uni-heidelberg.de

Muthinja Mendi, Heidelberg University, Parasitology,
julimendi@gmail.com

Nagpal Medhavi, MPI for Intelligent Systems, Stuttgart,
nagpal@is.mpg.de

Nelson Celeste, Princeton, USA,
celesten@princeton.edu

Parker Andrew, University of Oxford, UK,
parker@maths.ox.ac.uk

Probst Dimitri, Heidelberg University,
d.probst@thphys.uni-heidelberg.de

Rädler Joachim, LMU Munich,
raedler@lmu.de

Ross Robert, University of Oxford, UK,
ross@maths.ox.ac.uk

Rossberger Sabrina, Inst. f. Physical Chemistry, Heidelberg Univ.,
rossberger@is.mpg.de

Sabass Benedikt, Princeton Univ., USA,
bsabass@princeton.edu

Schnellbacher Nikolas, Heidelberg University,
nikolas.schnellbaecher@bioquant.uni-heidelberg.de

Schwarz Ulrich, Heidelberg University,
Ulrich.Schwarz@bioquant.uni-heidelberg.de

Schütz Lucas, Heidelberg University, COS,
lucas.schuetz@cos.uni-heidelberg.de

Selhuber-Unkel Christine, University of Kiel, Institute for Material Science,
cse@tf.uni-kiel.de

Silberzan Pascal, Institut Curie Paris,
pascal.silberzan@curie.fr

Sixt Michael, IST Vienna,
sixt@ist.ac.at

Smith Ana-Suncana, FAU Erlangen, PULS group,
smith@physik.uni-erlangen.de

Spatz Joachim, MPI for Intelligent Systems, Stuttgart & Heidelberg University,
spatz@is.mpg.de

Surovtsova Irina, Heidelberg University,
irina.surovtsova@bioquant.uni-heidelberg.de

Sütterlin Thomas, Hamamatsu TIGA Center (BioQuant),
thomas.suetterlin@bioquant.uni-heidelberg.de

Szczygiel Magdalena, DKFZ, Heidelberg,
m.szczygiel@dkfz-heidelberg.de

Trepat Xavier, Barcelona, Spain,
xtrepat@ibecbarcelona.eu

Voigt Axel, TU Dresden,
axel.voigt@tu-dresden.de

Zambarda Chiara, Inst. f. Physical Chemistry, Heidelberg Univ.,
chiara.zambarda@pci.uni-heidelberg.de