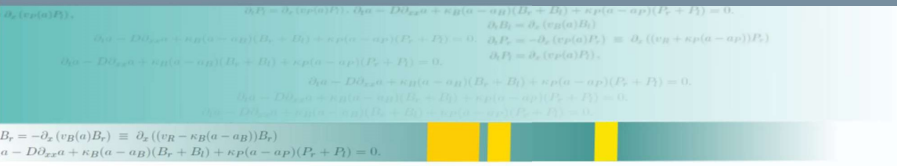
Universität Münster



Workshop on Cell Dynamics and Mathematical Modeling

November 27 – December 1, 2023
Münster

Book of Abstracts

Organizer

Angela Stevens (University of Münster)

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MM Mathematics Münster
Cluster of Excellence

Workshop on Cell Dynamics and Mathematical Modeling

27 Nov - 1 Dec 2023, in Münster, Germany

	Monday 27 Nov	Tuesday 28 Nov	Wednesday 29 Nov	Thursday 30 Nov	Friday 1 Dec
9:00-9:30	*Registration*				
9:30-10:15	Sara Wickström	Erez Raz	Wolfram Pönisch	Georgios Grekas	Round Table Discussion
10:30-11:00	*coffee break*				
11:00-11:45	Davide Ambrosi	Pierre Sens	Christian Schmeiser	John King	
12:00-14:00	*lunch break*				
14:00-14:45	Carl-Philipp Heisenberg	Shubhadeep Sadhukhan	Alba Diz-Munoz	Juan José López Velázquez	
15:00-15:30	*coffee break*				
15:30-16:15	Dimitri Fabrèges	Zoltan Pethö/André Schlichting	Oliver Jensen		
	Reception: Wine + Cheese SRZ Foyer 2nd floor *- for all participants -*		Conference Dinner Schloss Wilkinghege, Steinfurter Str. 374, 48159 Münster *- by invitation / by request -*		

General information

Venue. The main workshop venue is the MM-conference center located on the second floor of the Seminarraumzentrum (SRZ) at Orléans-Ring 12, 48149 Münster (see map on p. 3). You will find the registration there. Moreover, the coffee breaks and the reception take place in the lounge of the seminar building SRZ (second floor) right in front of the seminar room.

Wi-Fi access. If you are part of the eduroam community, you may connect to the network "eduroam" as usual. Otherwise you can connect to the SSID "GuestOnCampus" and start any web browser. You will automatically be redirected to the login page. Confirm the terms of use and click on "log in for free". 1 GB data volume is available per device and day. Please note that the connection is not encrypted.

Reception. There is a Wine + Cheese reception for all participants of the workshop on Monday evening after the talks in the lounge of the MM-conference center (Seminarraumzentrum (SRZ), second floor, Orléans-Ring 12).

Conference dinner. The conference dinner takes place on Wednesday 29 November at 18:00 at Schloss Wilkinghege (Steinfurter Strasse 374, 48159 Münster). There will be a bus shuttle. Attendance is for speakers, and by invitation. In case you want to take part, please contact dr.lueckert-ag-stevens@uni-muenster.de and we will check if there are still seats available.

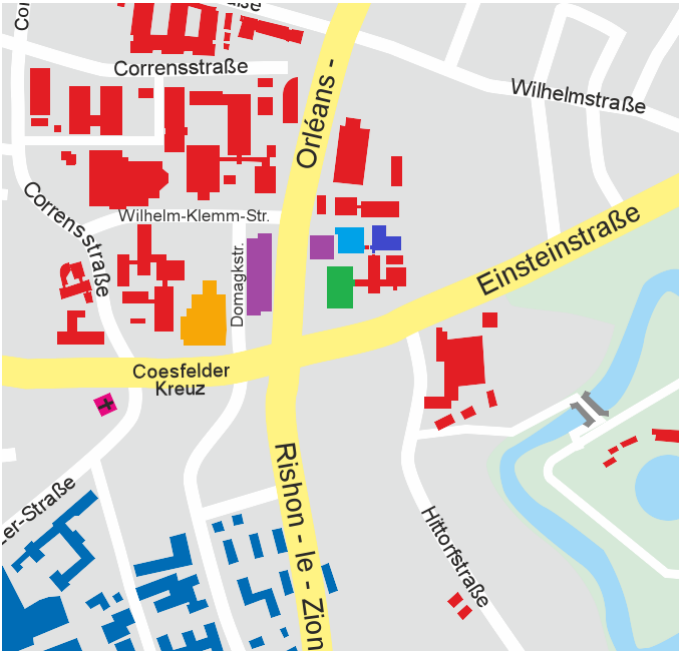
Coffee break/Lunch. We provide coffee and snacks during the coffee breaks.

There are a couple of restaurants for lunch in the vicinity:

- Canteen – Mensa am Ring, Domagkstraße 61 (all non-local participants receive vouchers (1 meal + 1 drink per day) for the canteen during registration)
- Ristorante Milano (Italian), Wilhelmstraße 26
- King Kebab (Fast Food), Corrensstraße 80
- Il Gondoliere (Italian), Von-Esmarch-Straße 28 (closed Mondays)
- Buddha Palace (Indian), Von-Esmarch-Straße 18 (closed Tuesdays)
- La Gondola D'oro (Italian), Hüfferstraße 34
- Gustav Grün (Green Fast Food), Wilhelmstraße 1
- Aro (Green Fast Food), Neutor 3

Public transportation. You can check the bus schedule on the website of Stadtwerke-Münster (in German and English), or use Google maps.

Questions. In case of further questions, please send an Email to: dr.lueckert-ag-stevens@uni-muenster.de



SRZ (workshop venue, 2nd floor)
Math Department
canteen
multi-storey car park.

Book of abstracts

Active cell mechanics

Davide Ambrosi Mon 11:00

(Politecnico di Torino, Italy)

Cell motility is a fertile environment for applied mathematics: first principles of mechanics, balance of forces and thermodynamic inequalities, offer a powerful tool to investigate the inner mechanisms of cell migration. In my talk I will discuss three issues of active cell mechanics: the kinematics of actin in cell motility, the competition between energy storage and energy dissipation in cell polarity and a possible role for memory in collective cell mechanics. The common denominator of these different sides of the same problem is the active stress produced by the cell by their actomiosin machinery. From a mathematical point of view, cells are the paradigmatic example of active mechanical system, where the interplay between external stimuli, passive mechanical properties, molecular diffusion and active control orchestrates the complex behavior of cell motion. The formalization of physical principles in terms of differential equations and their numerical integration may provide a contribution to unveil the rich observed phenomenology.

The missing link of surface mechanics: How membrane fluidity and its attachment to the cortex synergistically regulate cortical dynamics

Alba Diz-Muñoz Wed 14:00

(EMBL Heidelberg, Germany)

Animal cell shape changes are primarily driven by its surface, a composite interface comprising a thin cortical actin network physically tethered to the plasma membrane by specialized membrane-to-cortex attachment (MCA) proteins. Previous studies have focused on how gradients in myosin motors or actin network architecture drive cell deformations, overlooking any mechanical contribution of the membrane per se. Here, we identify membrane fluidity and the length of MCA proteins as additional forces that synergistically regulate cortical dynamics. By combining in silico, in vitro and in cellula approaches we show that contractility in actin networks scales linearly with membrane fluidity when MCA proteins are short (< 8nm). However, this effect becomes significantly amplified by several orders of magnitude with intermediate (10-15nm) or long (>24nm) linker proteins due to their caging, ultimately blocking actin network remodelling by myosin motors. On the basis of our findings, we propose that local changes in lipid composition or the choice of MCA protein allow cells to confine cortical tension changes leading to cellular morphogenesis.

Joint work with Srishti Dar, Anusha B. Gopalan, Zachary Sun, Richard R. Sprenger, Ivan Palaia, Michael Murrell, Anđela Šarić, Julio Belmonte, Christer S. Ejsing, Maria Leptin

Temporal variability and cell mechanics control robustness in mammalian embryogenesis

Dimitri Fabrèges Mon 15:30

(Hubrecht Institute Utrecht, Netherlands)

How living systems achieve precision in form and function despite their intrinsic stochasticity is a fundamental yet open question in biology. Here, we establish a morphomap of pre-implantation embryogenesis in mouse, rabbit and monkey embryos, which reveals that although blastomere divisions desynchronise passively, 8-cell embryos display robust 3D morphogenesis. Using topological analysis and genetic perturbations, we show that embryos progressively change their cellular connectivity to a preferred topology, which can be predicted by a physical model where actomyosin-contractility and noise facilitate topological transitions lowering surface energy. This favours embryo packing, promoting higher number of inner cells in the 16-cell embryo. Synchronised division reduces embryo packing and generates significantly more mis-allocated cells and less inner-cell-mass cells, suggesting that stochasticity in division timing contributes to robust patterning.

Cells Exploit a Phase Transition to Mechanically Remodel the Fibrous Extracellular Matrix

Georgios Grekas Thu 9:30

(FORTH Heraklion, Greece)

Through mechanical forces, biological cells remodel the surrounding collagen network, generating striking localised deformation patterns. Tether-like paths of high densification and fiber alignment form between cells, and radial hair-like bands emanate from cell clusters. While tethers may facilitate cell communication, the mechanism for their formation is unclear. We combine modelling, simulation and experiment to show that tether formation is a densification phase transition of the fibrous extracellular matrix, caused by microbuckling instability of network fibers under compression. The mechanical behaviour of the extracellular matrix (ECM) caused by cell contraction is modelled and analysed from a discrete and a macroscopic perspective employing the theory of nonlinear elasticity for phase transitions. From the one dimensional response of a single fiber a two dimensional, macroscopic strain energy landscape is constructed that fails to be rank one convex and exhibits bistable, multi-well structure. This implies a loss of ellipticity of the Euler-Lagrange PDEs of the corresponding energy functional. Simulations predict strain discontinuities between the undensified and densified phase, which localizes within tethers between contracting cells and radial hair-like microstructures around them, as experimentally observed.

To explore further the effects of the discrete character of the fiber network, we also develop a discrete model, in the form of a nonlinear truss whose elements represent individual fibres and can undergo large stretches and rotations, and can buckle under compression. Various instabilities arise in this model, leading to localised densified

microstructures. The behaviour of the discrete model has interesting similarities and differences to the continuum model.

Friction forces determine cytoplasmic reorganization and shape changes of ascidian oocytes upon fertilization

Carl-Philipp Heisenberg Mon 14:00

(IST Klosterneuburg, Austria)

Contraction and flow of the actin cell cortex have emerged as a common principle by which cells reorganize their cytoplasm and take shape. Yet, how these cortical flows interact with adjacent cytoplasmic components, changing their form and localization, and how this affects cytoplasmic organization and cell shape remains unclear. Here, we show that in ascidian oocytes, a well-established model of oogenesis, the cooperative activities of cortical actomyosin flows and deformation of the adjacent mitochondria-rich myoplasm drive oocyte cytoplasmic reorganization and shape changes following fertilization. By combining biophysical experimentation and theory, we show that vegetal-directed cortical actomyosin flows, established upon oocyte fertilization and resisted by friction with the subcortical myoplasm, lead to the accumulation of cortical actin at the vegetal pole of the zygote and compression and local buckling of the adjacent elastic solid-like myoplasm layer. Once cortical flows have ceased, the multiple myoplasm buckles resolve into one larger buckle, which again drives the formation of the contraction pole, a protuberance of the zygote s vegetal pole where maternal mRNAs accumulate. Thus, our findings reveal a novel mechanism of cortical actomyosin network flows that determine cytoplasmic reorganization

and cell shape by deforming adjacent cytoplasmic components through friction forces.

Discrete mechanics of multicellular tissues

Oliver Jensen Wed 15:30

(University of Manchester, UK)

The vertex model is a popular tool in developmental biology, allowing researchers to explore via simulation the impact of the mechanical environment on the behaviour of individual cells. According to this model, an epithelial layer (for example) can be represented as a tiling of the plane by irregular polygons; the vertices of the polygons move towards an equilibrium state down a gradient of mechanical energy. This approach allows the prediction of stress distributions across growing tissues, capturing features that risk being "washed away" using traditional homogenisation approaches, while exploiting geometric features that are readily measured experimentally. Complementing numerical simulations, I will explain how discrete calculus methods provide a powerful set of tools with which to analyse the vertex model, showing how this approach has revealed features such as couple stresses at tricellular junctions in spatially disordered cellular monolayers.

Wavefront behaviour for singular nonlinear diffusivities

John King Thu 11:00

(University of Nottingham, UK)

Limiting cases of simple multiphase models for tissue growth involve reaction-diffusion equations that may feature singular behaviour at both small and larger cell volume fractions. The effects on the resulting dynamics will be described in a number of such circumstances.

Stiffness-directed movement of pancreatic stellate cells depends on mechanosensitive ion channels

Zoltan Pethö / André Schlichting Tue 15:30

(University of Münster, Germany)

Increased tissue stiffness is a distinctive feature of solid tumors such as pancreatic ductal adenocarcinoma (PDAC). Pancreatic stellate cells (PSCs) are primarily responsible for producing the stiffening tumor tissue. Thereby, PSCs generate a stiffness gradient between the soft healthy pancreas and the stiff tumor. This gradient induces a specific form of directional cell migration called durotaxis, which is driven by differential stiffness. The molecular sensors behind durotaxis are still unclear.

Here, we examine the impact of mechanosensitive ion channels in the durotaxis of PSCs. For this purpose, we established a two-dimensional linear stiffness gradient mimicking PDAC. Using pharmacological and genetic methods, we investigated the role of the ion channels Piezo1, TRPC1, and TRPV4 in durotaxis of primary murine PSCs. We found that PSCs migrate towards a stiffer substrate, which is abolished by inhibiting or activating Piezo1. Moreover, we investigated TRPV4 and TRPC1, which are vital in translating mechanical forces in PSCs. Disrupting TRPC1 along with TRPV4 abolishes PSC durotaxis even when Piezo1 is functional. These findings suggest that mechanosensitive ion channels, particularly Piezo1, detect the mechanical microenvironment to guide PSC migration.

In an mathematical model of partial differential equations we analyze and numerically simulate durotaxis behavior and its relation to the dynamics of mechanosensitive ion channels.

Joint work with Ilka Budde, David Ing, Sandra Schimmelpfennig, Joelle M-J Romac, Sandip M Swain, Rodger A Liddle, Angela Stevens, Albrecht Schwab

Stochastic dynamics of cell shape changes during cellular state transitions

Wolfram Pönisch Wed 9:30

(University of Cambridge, UK)

The development of an organism involves a series of state transitions in which cells progressively specialize. Understanding the dynamics of these transitions is crucial for understanding the mechanisms governing cell fate determination and for developing new strategies for

regenerative medicine and disease modelling. Nevertheless, deciphering the dynamics of individual cells during these transitions remains a challenge in developmental biology. Many state transitions coincide with changes in cell shape, and emerging evidence suggests that cell shape is intricately linked to cellular states. While there have been extensive efforts to study gene expression changes during these transitions, there is only limited understanding of how cell morphology changes during state transitions and the accompanying dynamics of cellular shape remains poorly understood. To address this challenge, we have developed a morphometric pipeline that leverages cellular morphology to gain insights into individual cell characteristics during state transitions. Our approach utilizes shape descriptors, such as spherical harmonic descriptors, to objectively quantify cell shapes and map cell shape trajectories in a low-dimensional morphospace. We initially apply this pipeline to investigate the formation of the notochord during amphioxus development, a basally branching chordate. By quantitatively analysing and comparing the shapes of thousands of cells from fixed embryos at different developmental stages, we deduce morphological trajectories of the cell population based on their spatial location within the notochord. This spatial mapping reveals significant regional variations in developmental timing and trajectory topology. While the analysis of fixed samples yields valuable insights into tissue developmental dynamics, it provides limited access to the underlying dynamics of individual cells, including the role of shape fluctuations during state transitions. To address this limitation, we examine the epithelial-to-mesenchymal transition (EMT) in MDCK cells. EMT involves cells transitioning from a tightly connected epithelial state to a migratory and invasive mesenchymal state, accompanied by substantial changes in cell shape. By modelling shape trajectories as a Langevin process, we infer the potential landscape driving the shape transition and capture temporal dynamics of cell shape fluctuations during the transition. Our findings reveal a notable peak in cell shape fluctuations coinciding with the time of spreading during EMT. Based on the findings from our quantitative framework, we interrogate potential feedbacks between cell shape, the underlying cellular mechanics, and

cell state. To accomplish this, we employ mathematical modelling to integrate our findings and gain a deeper understanding of the underlying biophysical mechanisms.

Joint work with Iskra Yanakieva, Belle Sow, Aki Stubb, Alex Winkel, Guillaume Salbreux, Ewa Paluch

The mechanisms controlling polarisation and loss of polarity of PGCs and their role in migration towards the attractant Cxcl12

Erez Raz Tue 09:30

(University of Münster, Germany)

Zebrafish primordial germ cells (PGCs) are guided towards their target, the region where the gonad develops by the chemokine Cxcl12. This process requires polarisation of the cells, such that bleb-type protrusions are formed at the cell front, while actomyosin-driven transport of ERM proteins away from this aspect of the cell defines the cell back, where blebbing is inhibited. This robust polarisation process can be biased by the distribution of the chemokine in the tissue, such that polarised cells migrate towards regions in the embryo where the attractant is expressed at higher levels. Importantly, we found that during their migration the PGCs periodically loose their polarity, which allows them to introduce changes in their migration direction and adjust their path to reliably reach the source of Cxcl12. To define the molecular basis responsible for the recurring loss and gain of polarity, we analysed the polarisation loss events with respect to the distribution of different molecules within the cell. This analysis suggests that actin polymerisation is key for dictating the polarisation state of the cell.

Accordingly, we identified positive and negative regulators of rac1 that control the process in a way that facilitates the cycling between polar and apolar cellular states.

Modelling how curved active proteins and shear flow pattern cellular shape and motility

Shubhadeep Sadhukhan Tue 14:00

(Weizmann Institute of Science, Israel)

Cell spreading and motility on an adhesive substrate are driven by the active physical forces generated by the actin cytoskeleton. We have recently shown that coupling curved membrane complexes to protrusive forces, exerted by the actin polymerization that they recruit, provides a mechanism that can give rise to spontaneous membrane shapes and patterns. In the presence of an adhesive substrate, this model was shown to give rise to an emergent motile phenotype, resembling a motile cell. Here, we utilize this "minimal-cell" model to explore the impact of external shear flow on the cell shape and migration on a uniform adhesive flat substrate. We find that in the presence of shear the motile cell reorients such that its leading edge, where the curved active proteins aggregate, faces the shear flow. The flow-facing configuration is found to minimize the adhesion energy by allowing the cell to spread more efficiently over the substrate. For the non-motile vesicle shapes, we find that they mostly slide and roll with the shear flow. We compare these theoretical results with experimental observations, and suggest that the tendency of many cell types to move against the flow may arise from the very general, and non-cell-type-specific mechanism predicted by our model.

Adhesion independent cell migration in confined environments

Christian Schmeiser Wed 11:00

(University of Vienna, Austria)

Experiments have shown that leukocytes are able to move without adhesion in structured confined environments. Recent modelling efforts will be presented, which provide a possible explanation based on cortical flow. Also the influence of nucleus mechanics is investigated based on a rough model of nucleus deformation and positioning by microtubules, with nucleus stiffness sometimes preventing the passage through narrow channels.

Physical principles of cell volume and density regulation

Pierre Sens Tue 11:00

(Institut Curie Paris, France)

The size and density of living cells are the result of passive physical constraints and active biological processes. Their interplay leads to the appearance of robust and ubiquitous scaling laws relating linearly cell size, dry mass, and nuclear size. One remarkable feature is that the protein density within a cell remains constant during cell growth. I will discuss how the different scaling laws can be explained quantitatively by a single model of size regulation based on three simple, yet generic,

physical constraints - osmotic balance, hydrostatic balance, and electroneutrality - defining the "the Pump-Leak model" (PLM). I will show how cell density homeostasis can be understood by coupling the PLM with a simple model of gene expression. I will then discuss how cell mechanics may modify the different scaling law. I will end with the interesting case of fresh-water single celled organism, which have evolve specific ways of dealing with particularly acute osmotic challenges.

A free boundary problem of cell polarization

Juan José López Velázquez Thu 14:15

(University of Bonn, Germany)

In this talk I will discuss the properties of a model of cell polarization that describes the distribution of active receptors on the surface of a cell. The model is a reaction diffusion system whose solutions approach in a suitable scaling limit the solutions of a free boundary problem. This limiting problem has many similarities with the classical obstacle problem, but it has, as a distinctive feature, a mass conservation property. As a result of this, the solutions of the problem exhibit interesting pattern formation properties which do not appear in the classical obstacle problem, and that will be discussed in detail. Further, the behavior of the interfaces separating the polarized region from the unpolarized region will be described.

Coordination of cell states and tissue architecture by mechanical forces

Sara A. Wickström Mon 9:30

(MPI for Molecular Biomedicine, Münster, Germany)

The structure of tissues is tightly linked to their function. During formation of functional organs, large-scale changes in tissue elongation, stretching, compression, folding/buckling, and budding impact the shape, position, packing, and contractility state of cells. Conversely, changes in single cell contractility, shape and position locally alter tissue organization and mechanics. Thus, forces function as important ques that are transmitted to the nucleus to coordinate gene expression programs to control cell states. On the other hand, excessive mechanical stresses have the potential to damage cells and tissues. In my presentation I will discuss our recent research on how cells use the nucleus and the nuclear envelope/chromatin interface to sense mechanical forces and how these mechanosignals are integrated with biochemical inputs to alter cell states and to generate and maintain tissue architecture.

Acknowledgements

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www.uni-muenster.de/MathematicsMuenster