Banff International Research Station

for Mathematical Innovation and Discovery

Tissue Growth and Morphogenesis: from Genetics to Mechanics and Back (12w5048) July 22-27, 2012

MEALS

*Breakfast (Buffet): 7:00 – 9:30 am, Sally Borden Building, Monday – Friday
*Lunch (Buffet): 11:30 am – 1:30 pm, Sally Borden Building, Monday – Friday
*Dinner (Buffet): 5:30 – 7:30 pm, Sally Borden Building, Sunday – Thursday
Coffee Breaks: As per daily schedule, in the foyer of the TransCanada Pipeline Pavilion (TCPL)
***Please remember to scan your meal card at the host/hostess station in the dining room for each meal.**

MEETING ROOMS

All lectures will be held in the new lecture theater in the TransCanada Pipelines Pavilion (TCPL). LCD projector and blackboards are available for presentations.

SCHEDULE

Note: The total time allocated to each speaker is 30 min, including 5 min at the end for questions and changeover.

Sunday

16:00 Check-in begins (Front Desk – Professional Development Centre - open 24 hours)
17:30-19:30 Buffet Dinner
20:00 Informal gathering in 2nd floor lounge, Corbett Hall
Beverages and small assortment of snacks are available on a cash honor system.

Monday

7:00-8:45 Breakfast

8:45-9:00 Introduction and Welcome by BIRS Station Manager, TCPL

Chair: C. Dahmann
9:00-9:30 P. Silberzan: Collective migration of epithelial cells
9:30-10:00 D. Weihs: Initial stages of metastatic penetration require cell flexibility and force application
10:00-10:30 D. Weitz: Mechanics of cell-substrate interactions

Coffee Break, TCPL, 10:30-10:50 am

10:50-11:20 B. Fabry: Physical principles of cell migration in 3 dimensions
11:20-11:50 J. Fredberg/D. Tambe: Collective cell guidance by cooperative intercellular forces - Plithotaxis

11:50-13:00 Lunch
13:00-14:00 Guided Tour of The Banff Centre; meet in the 2nd floor lounge, Corbett Hall
14:00 Group Photo; meet in foyer of TCPL (photograph will be taken outdoors so a jacket might be required).

Chair: C. Marchetti
14:30-15:00 L. Montell, Measuring, monitoring and manipulating morphogenesis with light

Coffee Break, TCPL, 3:00-3:30 pm

15:30-16:00 F. Mackintosh: Active stresses and self-organization in intra/extracellular networks
16:00-16:30 L. Pismen: Strain dependence of cytoskeleton elasticity
16:30-17:00 U. Schwarz: Modeling active contractility of cells and tissues

17:30-19:30 Dinner (20:00: Informal gathering in 2nd floor lounge, Corbett Hall)

Tuesday

7:00-9:00 Breakfast

Chair: I. Aranson
9:00-9:30 R. Keller: Forces that close the blastopore in amphibians
9:30-10:00 D. Discher: A nuclear rheostat: microenvironment rigidity coupling to cell lineage
10:00-10:30 A. Martin: Actin polymerization and depolymerization is critical for force generation and epithelial invagination

Coffee Break, TCPL, 10:30-10:50 am

10:50-11:20 J. Käs: Are fundamental changes in a cell's material properties necessary for tumor progression?
11:20-11:50 C. Dahmann: Signals and mechanics guiding cell sorting in animal development
11:50-12:20 O. Hamant: Mechanical signals control microtubule behavior and growth coordination in plant meristems

12:20-13:30 Lunch

Chair: K. Rejniak
14:00-14:30 X. Trepat: Mechanical waves during tissue growth
14:30-15:00 G. Wasteneys: Chaos, collisions, catastrophes and the edge effect: the self-organizing cortical microtubule array

Coffee Break, TCPL, 3:00-3:30 pm

15:30-16:00 N. Gov: Modeling active motion of multi-cellular aggregates
16:00-16:30 S. Lubkin: Embryonic airway morphogenesis: the mechanical framework
16:30-17:00 D. Vavylonis: Modeling the assembly of contractile actomyosin bundles

17:30-19:30 Dinner (20:00: Informal gathering in 2nd floor lounge, Corbett Hall)

Wednesday

7:00-9:00 Breakfast

Chair: J. Solon
9:00-9:30 A. Goriely: Mathematical methods and challenges in the theory of biological growth
9:30-10:00 K. Rejniak: Normal and malignant remodeling of epithelial tissues: an integrative IBCell model
10:00-10:30 H. Honda: Three-dimensional cell model for tissue morphogenesis

Coffee Break, TCPL, 10:30-10:50 am

10:50-11:20 Y. Lin: Analyzing the mechanical behavior of bio-filament networks via a combined finite element-Langevin dynamics (FEM-LD) approach
11:20-11:50 M. Koepf: Chemo-mechanical instabilities in polarizable active layers
11:50-12:20 C. Marchetti: Modeling contractile stresses in adhesive cells and cell colonies

12:20-13:30 Lunch

Free afternoon

17:30-19:30 Dinner (20:00: Informal gathering in 2nd floor lounge, Corbett Hall)

Thursday

7:00-9:00 Breakfast

Chair: X. Trepat
9:00-9:30 J. Solon: Closing the gap: How the contractile amnioserosa tissue controls *Drosophila* dorsal closure dynamics
9:30-10:00 N. Gorfinkiel: Contractile activity of amnioserosa cells during Dorsal Closure in *Drosophila*
10:00-10:30 J. Feng: A cell-level mechanobiological model of *Drosophila* dorsal closure

Coffee Break, TCPL, 10:30-10:50 am

10:50-11:20 S. Hutson: Probing oscillatory cell shape changes using holographic laser microsurgery
11:20-11:50 E. Farge: Mechanotransduction in early embryogenesis and evolution: mechanisms and origins of primary invagination and endo-mesoderm differentiation in early muti-cellular epithelia

11:50-13:30 Lunch

Chair: D. Weihs
14:00-14:30 D. Kiehart: Dorsal closure in Drosophila as a model for investigating the coordination of contractility and morphogenesis
14:30-15:00 J. Zallen: Shaping the embryo: cellular dynamics in development

Coffee Break, TCPL, 3:00-3:30 pm

15:30-16:00 W. Brodland: From genes to morphogenetic movements
16:00-16:30 T. Harris: Development of epithelial structure in the *Drosophila* embryo
16:30-17:00 E. Zelzer: Muscle-induced mechanical loads regulate key aspects of skeletogenesis

17:30-19:30 Dinner (20:00: Informal gathering in 2nd floor lounge, Corbett Hall)

Friday

7:00-9:00 Breakfast

Chair: B. Fabry
9:00-9:30 B. Ji: Mechanics in mechanosensitivity of cell adhesion and its roles in cell migration
9:30-10:00 D. Umetsu: Live imaging reveals dynamics of cell sorting at lineage restriction boundaries in *Drosophila*
10:00-10:30 J. Munoz: Tissue viscoelasticity versus cell activity

Coffee Break, TCPL, 10:30-10:50 am

10:50-11:20 J. Shaevitz: Collective pattern formation in groups of moving cells
11:20-11:50 I. Aranson: Phase-field model of self-polarization and cell movement

11:50-13:30 Lunch

Checkout by 12 noon.

** 5-day workshop participants are welcome to use BIRS facilities (BIRS Coffee Lounge, TCPL and Reading Room) until 3 pm on Friday, although participants are still required to checkout of the guest rooms by 12 noon. **

Abstracts follow in alphabetical order by last name of speaker.

ABSTRACTS

(in alphabetic order by speaker surname)

1. Speaker: Igor Aranson

Phase-Field Model of Self-Polarization and Cell Movement

Igor S Aranson[1], Falko Ziebert[2], and Sumanth Swaminathan[3]
[1]Materials Science Division, Argonne National Laboratory, 9700 S Cass Av, Argonne, IL60439, aronson@anl.gov
[2]Institut Charles Sadron, 23 rue du Loess, 67034 Strasbourg Cedex 2, France
[3]Department of Materials Science and Engineering, Northwestern University, Evanston, IL 60208

Modeling the movement of living motile cells on substrates is a formidable challenge; regulatory pathways are intertwined and forces that influence cell motion on adhesive substrates are not fully quantified. Additional challenges arise from the need to describe a moving deformable cell boundary and contact line dynamics. Here, we present a simple mathematical model coupling cell shape dynamics, treated in the framework of the Ginzburg-Landau-type equation for auxiliary mass density (phase field), to a partial differential equation describing the mean orientation (polarization of actin filaments) of the cell's cytoskeletal network [1]. In order to maintain the total area of the cell, the phase field equation is subject to a global conservation constraint. Correspondingly, the equation for mean polarization incorporates key elements of cell mechanics: directed polymerization of actin network at the cell membrane, decay of polarization in the bulk of the cell, and formation of actin bundles (stress fibers) in the rear. The model successfully reproduces the primary phenomenology of cell motility: discontinuous onset of motion, diversity of cell shapes and shape oscillations, as well as distribution of traction on the surface. The results are in qualitative agreement with recent experiments on the motility of keratocyte cells and cell fragments. The asymmetry of the shapes is captured to a large extent in this simple model, see Figure 1, which may prove useful for the interpretation of recent experiments and predictions of cell dynamics under various conditions.

References:

[1] Falko Ziebert, Sumanth Swaminathan, and Igor S. Aranson, Model for self- polarization and motility of keratocyte fragments, J. R. Soc. Interface, doi:10.1098/rsif.2011.0433

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2. Speaker: Wayne Brodland, University of Waterloo, Department of Civil and Environmental Engineering

From Genes to Morphogenetic Movements

A multi-scale model was developed with the goal of tracing the sequence of causal events from gene expression to neurulation, a crucial tissue reshaping process that occurs during early embryo development. During this process, a sheet of tissue reshapes and rolls up to form a tube, the precursor of the spinal cord and brain; errors in this process are a common source of birth defects. The model assumes that, at the sub-cellular level, genes regulate the construction and operation of specific structural components. They, in turn, affect the cell level forces generated. Cell-level computational models were then developed to explore how planar collections of cells (i.e., tissues) with various

properties would generate and respond to forces, and to derive a system of cell-based constitutive equations. These equations were then calibrated for specific tissue types, locations and developmental stages against tensile tests of real embryonic tissues. A whole-embryo finite element simulation of neurulation was then carried out. In this model, tissues were modeled using "super elements" that represented tens of cells and that were governed by the calibrated constitutive equations. Ultimately, it was possible to trace how genes affect structural components and how these changes subsequently affect cell properties, then tissue properties, tissue mechanical interactions, tissue motions and finally whether the resulting embryonic phenotype is normal or abnormal. The talk will include movies of cell- and whole embryo-level simulations and a discussion of what it means to model something.

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3. Speaker: Christian Dahmann, Institute of Genetics, Dresden University of Technology, Dresden, Germany

Signals and mechanics guiding cell sorting in animal development

The sorting out of cells with different identities and fates during animal development is an important process to organize functional tissues and organs. Previous hypotheses have explained the sorting out of cells by differences in cell adhesion or surface tension. However, the mechanisms that guide cell sorting in animal development remain poorly understood. We study the mechanisms underlying cell sorting at compartment boundaries in Drosophila. Compartment boundaries are lineage restrictions that partition tissues into adjacent, but non-mixing cell populations. They play important roles in tissue growth and patterning by stabilizing the position of organizing centres. Establishment of compartment boundaries in the developing Drosophila wing requires signaling by the Hedgehog, BMP, and Notch pathways. Recent data indicate that these pathways control cell sorting by locally increasing mechanical tension at cell junctions along the compartment boundaries. Cell sorting at compartment boundaries therefore provides an excellent model system to study the interplay between signaling and cell mechanics in animal development.

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4. Speaker: Dennis Discher, University of Pennsylvania, Department of Chemical and Biomolecular Engineering

A nuclear rheostat: microenvironment rigidity coupling to cell lineage

A solid tissue can be soft like fat or brain, stiff like striated muscle and heart, or rigid like bone. Extensive expression profiling of tissue shows that Lamin-A/C increases almost 100-fold and in near proportion to varied micro-elasticity of tissue whereas Lamin-B proves constitutive. Lamin-A/C has been implicated in aging syndromes that affect muscle and fat but not brain, and we find nuclei in brain-derived cells are indeed dominated by Lamin-B and are much softer than nuclei derived from muscle cells with predominantly Lamin-A/C. In vitro, matrix elasticity can affect expression of nuclear envelope components in adult stem cells and major changes in Lamin-A/C direct lineage: lower levels favor soft tissue and higher levels promote rigid tissue lineage. At a molecular level, tagging of cryptic sites while physically stressing isolated nuclei reveals stress-driven, mass spectrometry-mapped changes in various nuclear proteins including Lamin-A/C, consistent with cell and tissue evidence that the nucleus transduces physical stress.

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5. Speaker: Ben Fabry, Director, Center for Medical Physics and Technology Biophysics Group Erlangen University Ben.Fabry@biomed.uni-erlangen.de

Physical principles of cell migration in 3 dimensions

Some cell types such as many cancer cells, stem cells, fibroblasts, and cells of the immune system are able to migrate through dense connective tissue. Cell migration through a connective tissue matrix depends strongly on the mesh size, the mechanical properties, and the functionalization of the matrix with adhesive ligands. Moreover, different cell types employ fundamentally divergent (e.g. mesenchymal or amoeboid) migration strategies in 3-D. Despite these differences, there are also striking similarities. 3-D migration is a superdiffusive random process with directional and speed persistence. Moreover, unlike migration in a 2-D environment, the ability to generate traction forces and to direct these forces non-isotropically is key to understand how cells can overcome the steric hindrance of the matrix for efficient 3-D migration.

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6. Speaker: Emmanuel Farge, Mechanics and Genetics of Embryonic and Tumour Development, UMR168 Physico-Chimie, Institut Curie, 11 rue Pierre et Mare Curie, 75005 Paris. efarge@curie.fr

Mechanotransduction in early embryogenesis and evolution: mechanisms and origins of primary invagination and endo-mesoderm differentiation in early muti-cellular epithelia

The modulation of developmental biochemical pathways by mechanical cues is a recently established feature of animal development (1), with, among other cases, critical involvement required in the triggering of mesoderm invagination (2) or in vital anterior midgut differentiation (3,4) at Drosophila embryo gastrulation. However, the role of mechanotransduction in evolution has been unexplored so far.

First we describe the role of mechanotransduction biochemical pathways controlling Myo-II behaviour in the coordination of the collective apical constriction of mesoderm cells that is necessary for mesoderm invagination (2,3). We suggest Myo-II mechanosensitivity involved during invagination at the origin of Haeckel Gastrae first organism emergence from multicellular colonies of cells (2).

Second, we present experimental data showing that a common mechanosensitive pathway involving the beta-catenin specifies mesodermal identity at gastrulation in both zebrafish and Drosophila. We find that mechanical strains developed by zebrafish epiboly and Drosophila mesoderm invagination trigger the phosphorylation of beta-catenin that impairs its interaction with the E-cadherin in adherens junctions into the future mesoderm. This leads to the release of b-catenin into the cytoplasm and nucleus, where it triggers and maintains, respectively, the expression of the zebrafish brachyury homologue notail and of Drosophila twist, both crucial transcription factors for early mesoderm differentiation and development.

The search of a common biochemical pathway leading to mesoderm formation across Bilateria has so far proved to be difficult (5-8). Here the conserved role of the beta-catenin mechanosensitive pathway in the establishment of mesoderm identity at such large evolutionary distances converges to mesoderm speciation as mechanically induced by gastrulation morphogenetic movements back to the last common Protostome-Deuterostome ancestor.

1- Farge, E. Curr Top Dev Biol, 2011. 95: p. 243-65.
2- Pouille, P.A., et al. Sci Signal, 2009. 2(66): p. ra16, Driquez B. and Bouclet et al, Phys. Biol Dec;8(6) 2011
3- Farge, E. Curr Biol, 2003. 13(16): p. 1365-77.
4- Desprat, N., et al. Dev Cell, 2008. 15(3): p. 470-7.
5- Arendt, D. , C.D. Stern, Editor 2004, University College London: London. p. 679-693.

6- Martindale, M.Q., K. Pang, and J.R. Finnerty. Development, 2004. 131(10): p. 2463-74.
7- Schohl, A. and F. Fagotto, Embo J, 2003. 22(13): p. 3303-13.
8- Harvey, S.A., et al. Development, 2010. 137(7): p. 1127-35.

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7. Speaker: James J. Feng, University of British Columbia, Departments of Mathematics and Chemical and Biological Engineering

A cell-level mechanobiological model of *Drosophila* dorsal closure

Qiming Wang (UBC), James J. Feng (UBC) and Len Pismen (Technion)

We report a model describing the various stages of dorsal closure of Drosophila. Inspired by experimental observations, we represent the amnioserosa by 81 hexagonal cells that are coupled mechanically through the position of the nodes and the elastic forces on the edges. Besides, each cell has radial spokes on which myosin motors can attach and exert contractile forces on the nodes, the myosin dynamics itself being controlled by a signaling molecule. In the early phase, amnioserosa cells oscillate as a result of coupling among the chemical signaling, myosin attachment/detachment and mechanical deformation of neighboring cells. In the slow phase, we test two "ratcheting mechanisms" suggested by experiments: an internal ratchet by the myosin condensates in the apical medial surface, and an external one by the supracellular actin cables encircling the amnioserosa. The model predictions suggest the former as the main contributor to cell and tissue area reduction in this stage. In the fast phase of dorsal closure, cell pulsation is arrested, and the cell and tissue areas contract consistently. This is realized in the model by gradually shrinking the resting length of the spokes.

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8. Speaker: Jeffrey J. Fredberg, Harvard University, Department of Environmental Health [to be given by Tambe, Dhananjay?]

Collective cell guidance by cooperative intercellular forces - Plithotaxis

Cells comprising a tissue migrate as part of a collective. How collective processes are coordinated over large multi-cellular assemblies has remained unclear, however, because mechanical stresses exerted at cell-cell junctions have not been accessible experimentally. We developed a technique to recover stresses within and between the cells comprising a monolayer. Within the cell sheet there arise unanticipated fluctuations of mechanical stress that are severe, emerge spontaneously, and ripple across the monolayer. Within that stress landscape, local cellular migrations follow local orientations of maximal principal stress. Migrations of both endothelial and epithelial monolayers conform to this behaviour, as do breast cancer cell lines before but not after the epithelial-mesenchymal transition. Collective migration in these diverse systems is seen to be governed by a simple but unifying physiological principle: neighbouring cells join forces to transmit appreciable normal stress across the cell-cell junction, but migrate along orientations of minimal intercellular shear stress.

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9. Speaker: Nicole Gorfinkiel, Centro de Biología Molecular, ngorfinkiel@cbm.uam.es, Spain.

Contractile activity of amnioserosa cells during Dorsal Closure in Drosophila

It is increasingly evident that long standing questions in developmental biology such as morphogenesis, tissue homeostasis and organ growth cannot be understood using the reductionist approach of classical genetics but will require more systems biology approaches. In my lab, we are interested in how coordinated movements of cells in the context of embryonic development emerge

from the integration of events occurring at the molecular, cellular and tissue scales. We tackle this general question using dorsal closure (DC) as our experimental system. In the last years, Dorsal Closure has emerged as a reference model system in which to study dynamic morphogenetic processes using quantitative and biophysical tools. DC is a morphogenetic process that takes place during Drosophila embryogenesis, in which interactions between two tissues, the amnioserosa (AS) and the epidermis, close a discontinuity at the dorsal side of the embryo and generate the final form of the larvae. The AS generates one of the main driving forces of DC through the apical contraction of its individual cells. Apical contraction in AS cells is pulsed with oscillations in apical cell area correlating with the activity of dynamic and intermittent actomyosin networks that flow across the apical cortex of these cells. These observations have raised several questions. In particular, I will discuss the question of how AS cells switch from a predominantly fluctuating behaviour to a predominantly contractile behaviour. Quantitative analysis of how AS cell area evolves during DC in single cells suggest that the decision to contract is taken at the single cell level. We have not detected any spatial pattern to the onset of the contractile activity but rather this decision seems to be made locally, at the scale of small groups of cells. Our results suggest that both changes in the architecture of the actin cytoskeleton and in the activity of Myosin II motors underlie the transition from a fluctuating to a contractile behaviour and suggest that proper localization of Myosin at the level of junctions is crucial for active contraction.

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10. Speaker: Alain Goriely, University of Oxford, Mathematical Institute

Mathematical methods and challenges in the theory of biological growth

With an increase in the interest to study biological growth and morphogenesis from a physical or mathematical perspective over the past two decades, many different approaches to model growth have been proposed. The different proposals to describe growth include: fluid flows, plastic flows, a nonlinear solid with evolving reference configuration, a multiplicative decomposition of the deformation gradient, a discrete assembly of interacting springs with evolving reference lengths, a set of interacting and dividing spheres, or a manifold with evolving connection and metric. Within the context of the Banff workshop, it is of interest to identify and compare various attempts to describe growth in biological structures. Are they equivalent? Is one better suited for a certain type of analysis (experimental, mechanical, mathematical?). Also, I will try to conclude with a list of mathematical/scientific challenges and open problems in the theory of growth.

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11. Speaker: Nir Gov, Weizmann Institute of Science, Department of Chemical Physics

Modeling active motion of multi-cellular aggregates

We present a simple model for the evolution of the outer contour of cellular aggregates. Such circumstances occur during wound-healing, cancer growth and morphogenesis. We demonstrate that there is a feedback between the cell shape at the culture contour and the motile activity of the cell. This feedback can give rise to a Turing-type instability, resulting in the spontaneous formation of cellular "fingers". When these fingers undergo tip-splitting the morphology can become branched. This simple mechanism may explain many observed patterns in embryogenesis, where there are multiple chemical cues that regulate this instability and refine the resulting shapes.

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12. Speaker: Olivier Hamant, Ecole Normale Supérieure de Lyon, Laboratoire de Reproduction et Développement des Plantes

Mechanical signals control microtubule behavior and growth coordination in plant meristems

The presence of diffuse morphogen gradients in tissues classically supports a view in which growth is locally homogenous. Here we challenge this view: using a high resolution quantitative approach, we revealed significant growth variability among neighboring cells in the shoot apical meristem, the plant stem cell niche. This variability was strongly decreased in a mutant impaired in the microtubule severing protein katanin. Major shape defects in the mutant could be related to local decrease in growth heterogeneity. Mechanistically, we show that katanin is required for the cell's competence to respond to the mechanical forces generated by growth. This provides the basis for a model where microtubule dynamics allows the cell to respond efficiently to mechanical forces. This in turn can amplify local growth rate gradients and yield more heterogeneous growth.

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13. Spekaer: Tony Harris, Cell and Systems Biology, University of Toronto

Development of epithelial structure in the Drosophila embryo

My group studies how polarity, trafficking, cytoskeletal and cell adhesion complexes interact to control epithelial cell structure and morphogenesis in the Drosophila embryo. We focus on the polarity regulators Bazooka (PAR-3) and aPKC; the Arf G protein regulators Steppke and dASAP; and the cytoskeletal/polarity regulator RhoGAP19D. My talk will examine endocytic restraint of the membrane cytoskeleton. Actin networks push, pull and internalize the plasma membrane to control cell structure and behavior. Endocytosis also controls the structure and dynamics of the plasma membrane, suggesting plasma membrane removal could, in principle, regulate actin networks. We found that Steppke, a cytohesin Arf-GEF, couples endocytosis with membrane cytoskeleton inhibition as plasma membrane furrows cellularize the Drosophila embryo. Steppke loss-of-function caused endocytosis defects at the tips of ingressing furrows. Simultaneously, actomyosin-coated plasma membranes abnormally expanded from these sites and encroached upon individual nuclei, expelling many from the presumptive epithelium. Steppke overexpression had opposite effects. Moreover, Steppke localized to the furrows and acted via Arf G protein activity. Significantly, the overall Steppke loss-of-function phenotype was suppressed by reducing actomyosin activity. We propose Steppke induces local endocytosis to restrain the membrane cytoskeleton of individual cell compartments for coordinated actomyosin activity across the bases of all cell compartments of the developing epithelium.

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14. Speaker: Hisao Honda, Hyogo University, Health Science, Kakogawa, Japan and RIKEN, CDB, Kobe, Japan

Three-dimensional Cell Model for Tissue Morphogenesis

Multi-cellular organisms consist of cells and cell products. Their morphogenesis (the development of the shape of multi-cellular organisms) results from cell behaviors. In contrast to biological systems, analysis of physical materials, such as solid crystals, liquids and gases, consists of atoms. One of the reasons why the physical sciences have made such great advances is that physicists have developed equations of motion for atoms. These equations have led to understanding of the properties of physical materials. Thus, development of an equation of motion for cell behaviors would be a powerful tool for understanding cell morphogenesis.

We used a geometrical model (Dirichlet or Voronoi geometry) to describe polygonal cell patterns (1978), and made a cell boundary-shortening model to describe an epithelial tissue (1980). The model was useful to understand epithelial cell properties. Introducing mathematics of differential equation, the model was sophisticated to be a two-dimensional cell vertex dynamics model (2001) including an equation of

motion for cells. The two-dimensional model has been extended to be three-dimensional in cooperation with Professors Masaharu Tanemura and Tatsuzo Nagai (2004). The three-dimensional vertex dynamics model has been shown to be powerful to investigate morphogenesis of mammalian blastocyst from morula (2008), and cell intercalation (2008) observed in sea urchin gut elongation, amphibian gastrulation, Drosophila germ band extension and so on. Furthermore, the three-dimensional cell model was remodeled and adapted for investigation of epithelial cell invagination in cooperation with Dr. Shigeo Hayashi (RIKEN, Kobe). I will report that properties of apical surface of epithelial cells are essential for epithelial cell invagination. Circumferential boundary length of apical face of each epithelial cell contracts and relaxed, place to place, which causes planar cell intercalation to lead epithelial invagination.

Using the three-dimensional cell model, we are succeeding in explanation of tissue morphogenesis in terms of cell behaviors, liquid secretion of cells, contraction of specific edges of cells, extension/contraction of apical face of cells.

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15. Speaker: M. Shane Hutson, Vanderbilt University

Probing oscillatory cell shape changes using holographic laser microsurgery

During several stages of fruit fly embryogenesis, select epithelial cells undergo oscillatory changes in cell shape. These changes are mostly, but not uniformly, out-of-phase in adjacent cells. Examples include the early stages of ventral furrow formation, germband extension and dorsal closure. The shape changes in dorsal closure are manifest in amnioserosa cells as ~ 4-minute long oscillations of apical area. It has been hypothesized that these oscillatory changes in apical area are driven by stretch-induced contractions – with the expansion phase of one cell driven by the contraction of neighboring cells. We have tested this hypothesis using holographic laser-microsurgery to nearly instantaneously isolate a single amnioserosa cell – i.e. to sever all of its connections to the surrounding epithelium. Interestingly, not all isolated cells immediately collapse their apical area. Cells that were expanding just prior to isolation pause or even continue expansion for 30-60 seconds before collapsing. These results contradict a previous quantitative model for the cell shape oscillations that coupled stretch-induced contractions with a highly strained epithelium. Our results instead suggest that oscillatory shape changes are more cell autonomous and that the tensed epithelium is nevertheless under low strain. We have included low strain and increased autonomy in a revised model that continues to reproduce prior results, but also matches these new results.

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16. Speaker: Baohua Ji, Biomechanics and biomaterials laboratory, Department of Applied Mechanics, Beijing Institute of Technology, Beijing 100081, China
bhji@bit.edu.cn

Mechanics in mechanosensitivity of cell adhesion and its roles in cell migration

Cells sense and respond to their environment and external stimuli through focal adhesions complexs (FACs) to regulate a broad range of physiological and pathological processes, including cell migration. Currently, the basic principles in mechanics/mechanobiology of the mechanosensitivity of cell adhesion and migration have not yet been fully understood. This talk will be focused on the environment and stimuli dependent properties of cell adhesion and migration. A microscopic model of the FAC is proposed for understanding the responses of cell adhesion to the forces of different magnitudes, in which the FAC is modeled by a molecular cluster. We showed that there exist two force threshold values that define different

dynamic states of FACs, which allows the cell adhesion to exhibit a stabilizing to disruptive transition responding to the mechanical force. Furthermore, a multiscale mechano-chemical coupling model is proposed for studying the cell migration behaviors by considering the dynamics of focal adhesion, in which the effect of cell shape on cell traction force distribution, as well as the rigidity of matrix and rigidity gradient are considered. Our simulations showed that cell migration speed biphasically depends on the matrix stiffness and this dependence can be tuned by rigidity gradient. The underlying mechanism is that the matrix stiffness can influence the balance of competition of the stability of cell adhesion between cell front and cell rear, which consequently controls the driving force of cell migration. The rigidity gradient biases this competition which allows cell to exhibit a durotaxis behavior. Furthermore, a motility factor is suggested for characterizing the driving force of cell migration that is largely determined by cell shape and matrix stiffness.

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17. Speaker: Josef Käs, University of Leipzig

Are fundamental changes in a cell's material properties necessary for tumor progression?

Josef Kas, Anatol Fritsch, Tobias Kiessling, David Nnetu, Steve Pawlizak, Roland Stange, Franziska Wetzel and Mareike Zink
Division of Soft Matter Physics, University of Leipzig

With an increasing knowledge in tumour biology an overwhelming complexity becomes obvious with its roots in the diversity of tumours and their heterogeneous molecular composition. Nevertheless in all solid tumours malignant neoplasia, i.e. uncontrolled growth, invasion of adjacent tissues and metastasis, occurs. Recent results indicate that all three pathomechanisms require changes in the active and passive cellular biomechanics. Malignant transformation causes cell softening for small deformations which correlates with an increasing rate of proliferation and faster cell migration. The tumour cell's ability to strain harden permits tumour growth against a rigid tissue environment. A highly mechnosensitive, enhanced cell contractility is a prerequisite that tumour cells can cross its tumour boundaries and that these cells can migrate through the extracellular matrix. Initial tumour growth is limited to the developmental compartments from which the tumour cells originate. The observation that compartmentalized cell growth is not merely found during development but throughout tumour progression does not only radically redefine how tumours have to be resected, it also has critical impact on how a tumour progresses and what the target cells must be when screening for new cytostatics. It is the cells that can cross compartment boundaries and thus are not restricted to local tumour growth that have to be fought by chemotherapy. Therefore, passive and active biomechanical behaviour of tumour cells, cell jamming, cell demixing and surface tension-like cell boundary effects are investigated as key factors to stabilize or overcome compartment boundaries. Insights into changes of these properties during tumour progression may lead to selective treatments. Such drugs would not cure by killing cancer cells, but slow down tumour progression with only mild side effects and thus may be an option for older and frail patients.

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18. Speaker: Ray Keller, University of Virginia, Department of Biology

Forces that close the blastopore in amphibians

Ray Keller[1], Lance Davidson[2], Katherine Pfister[1], Ana Rolo[3], David Shook[1] and Paul Skoglund[1]

[1]Department of Biology, University of Virginia, Charlottesville, VA, [2] Department of what? Engineering, University of Pittsburgh, Pittsburgh, PA, [3]University College, London

Indirect evidence suggests that closure of the blastopore, an important event in gastrulation of anamniotes, is driven by specific convergence movements of the tissues around the blastopore in amphibians. These movements include convergent thickening (CT) and convergent extension (CE) of the marginal zone of anuran amphibian embryos, such as those of *Xenopus laevis*, and epithelial-mesenchymal transition (EMT) in others, such as the urodeles Ambystoma and Taricha, but there is no direct evidence for these forces. We measured the tensile forces and mechanical properties of the marginal zone by "sandwiching", two marginal zones together with their inner, adhesive surfaces facing one another, and allowing them to attach to two tabs of fibronectin-coated plastic inserted between their ends; these tabs were then attached to a measuring apparatus. Such explants of Xenopus can generate tensile, convergence forces over 1.5 μN during gastrulation and over 4 μN during neurulation and tailbud stages. These measurements contributed to the finding that the entire involuting marginal zone (IMZ) exerts convergence forces by CT prior to involution, and on involution the presumptive notochordal, somitic, and posterior neural tissue exert convergence force by CE. Explants from ventralized embryos, which lack the tissues expressing CE and only express CT, produce up to 1.5 μN of tensile force by CT alone. These results directly establish and measure the convergence forces generated by CT and CE that contribute to closure of the blastopore and elongation of the body axis of vertebrates. In conjunction with knockdowns of myosin II function, these measurements also contribute to a new understanding of the relative roles of CT, CE, and a third major movement, vegetal rotation, in gastrulation of anuran amphibians. Using a similar technique, we show that comparable convergence forces are generated by epithelial-mesenchymal transition at the vegetal margin of the IMZ in urodele gastrulation. These findings illustrate the diversity of the cellular force generating mechanisms, the biomechanical strategies, and the evolution of blastopore closure mechanisms in anamniotes. Supported by NIHNICHD R37 HD025594 MERIT AWARD to R. Keller and NIH grant R01 HD044750 to Lance Davidson.

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19. Speaker: Dan Kiehart, Duke University, Department of Biology

Dorsal closure in *Drosophila* as a model for investigating the coordination of contractility and morphogenesis

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Dorsal closure in Drosophila embryogenesis is a model system for the analysis of morphogenesis and wound healing. In closure, we investigate cell and tissue kinematics (cell shape changes and movements) and dynamics (the forces that drive such kinematics). We use molecular and classical genetics, pharmacology, laser surgery and biophysical modeling to probe closure. Movements are driven by three distinct actomyosin arrays. 1) Contractile, supracellular purse strings in the leading edge cells of the lateral epidermis have an almost sarcomere-like arrangement of actin, myosin, α-actinin and zyxin and both maintain tension and actively contract (shorten), particularly as "free" leading edge is incorporated into a seam during zipping. 2) Contractile belts associated with cell-cell junctions in the amnioserosa and with junctions between the amnioserosa and the lateral epidermis. These belts play a role in the contractility of the amnioserosa cells. 3) Apical medial arrays are transient, actomyosin rich networks that span the apical ends of cells and also participate in contraction. Closure is robust: forces generated by each tissue are two to three orders of magnitude greater than the net force that drives closure and removal of any one force does not prevent closure. We find a role for mechanically gated channels and Ca2+ transients in mediating contractility. In

addition, we find a role for tension and specialized cell junctions that include zyxin and α-actinin for maintenance of the supra-cellular purse strings. Finally, we find a unique frequency behavior of amnioserosa cells that ingress during the course of closure. A variety of signaling pathways are required for closure. How these pathways regulate the assembly and function of these distinct actomyosin arrays in order to generate the emergent behavior(s) that drive closure are a key focus of our research.

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20. Speaker: Michael H. Koepf

Chemo-mechanical instabilities in polarizable active layers

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We formulate and explore a generic continuum model of a polarizable active layer with neo-Hookean elasticity and chemo-mechanical interactions. Homogeneous solutions of the model equations exhibit a stationary long-wave instability when the medium is activated by expansion, and an oscillatory short-wave instability in the case of compressive activation. Both regimes are investigated analytically and numerically. The long-wave instability initiates a coarsening process, which provides a possible mechanism for the establishment of permanent polarization in spherical geometry.

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21. Speaker: Yuan Lin, University of Hong Kong, Department of Mechanical Engineering

Analyzing the mechanical behavior of bio-filament networks via a combined finite element-Langevin dynamics (FEM-LD) approach

A Langevin dynamics based formulation is proposed to describe the shape fluctuations of extended objects like bio-filament and cell membrane. We show that, for simple problems, solutions of the resulting stochastic partial differential equation(SPDE) asymptotically reduce to predictions from classical modal analysis. Methodologies are then developed to implement this formulation in finite element (FEM) simulations of the mechanical behavior of bio-polymer networks where, besides entropy, the finite deformation of filament has also been taken into account. The validity of the proposed finite element-Langevin dynamics (FEM-LD) approach is verified by comparing simulation results with those from renowned FEM software as well as various theoretical predictions. Finally, as an application example, our method is used to investigate the mechanical response of an actin filament network. Our results clearly and quantitatively demonstrate that entropy dictates how such actin network responds at small strains while elasticity gradually takes over as the dominant factor as deformation progresses. Furthermore, we find that the crossover strain, around which the transition of network behavior from being entropy dominated to enthalpy governed takes place, increases by order of magnitude when the mesh size of the network grows from less than 100 nanometers to a few microns.

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22. Speaker: Sharon Lubkin, North Carolina State University, Raleigh, NC USA. lubkin@ncsu.edu

Embryonic Airway Morphogenesis: the Mechanical Framework

The developing lung is a fluid filled, at times almost glandular structure that undergoes cyclic rounds of epithelial branching under cues from the surrounding mesenchyme and its derivatives. Some of these cues are mechanical, so full understanding of lung morphogenesis requires study of the

mechanics of the developing lung. Fetal studies have revealed that the liquid filled developing airway is at a positive pressure relative to the amniotic fluid (from which it is distinct) and that this is maintained by net secretion by the lung. However the developing lung is also subject to a range of mechanical interactions including growth pressures, diaphragmatic 'breathing movements,' and airway peristalsis. We have developed and will present a suite of models of the mechanics of embryonic airway morphogenesis, at various length and time scales, all constructed to maximize the ratio of insight to detail.

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23. Speaker: Fred MacKintosh, Department of Physics and Astronomy, VU University Amsterdam, The Netherlands Email: fcm@nat.vu.nl

Active stresses and self-organization in intra/extracellular networks

Much like the bones in our bodies, the cytoskeleton consisting of filamentous proteins largely determines the mechanical response and stability of cells. Unlike passive materials, however, living cells are kept far out of equilibrium by metabolic processes and energy-consuming molecular motors that generate forces to drive the machinery behind various cellular processes. We describe recent advances both in theoretical modeling of such networks, as well as experiments on reconstituted in vitro acto-myosin networks and living cells. We show how such internal force generation by motors can lead to dramatic mechanical effects, including strong mechanical stiffening. Furthermore, stochastic motor activity can give rise to diffusive-like motion in elastic networks. This can account for both probe particle motion and microtubule fluctuations observed in living cells. We also show how the collective activity of myosin motors generically organizes actin filaments into contractile structures, in a multistage non-equilibrium process. This can be understood in terms of the highly asymmetric load response of actin filaments: they can support large tensions, but they buckle easily under piconewton compressive loads.

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24. Speaker: M. Cristina Marchetti, Physics Department & Syracuse Biomaterals Institute, Syracuse University, Syracuse, NY 13244, USA

Modeling contractile stresses in adhesive cells and cell colonies

Measurements of traction forces exerted by adhering cells or cell layers on soft substrates and micropillar arrays have yielded new insight on how the mechanical and geometric properties of the substrate affect many cell functions, such as spreading, growth, differentiation and migration. In this talk I will describe a simple model of cells as continuum active elastic media that captures the spatial distribution of traction and cellular stresses and their dependence on substrate thickness and stiffness and strength of focal adhesions. When used to describe the behavior of cohesive cell layers, the model predicts a linear scaling of traction forces with the colony size, for large colonies, in agreement with recent experiments. This scaling suggests the emergence of an effective surface tension as a scale-free material property of the adherent tissue.

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25. Speaker: Adam Martin, Department of Biology, MIT, acmartin@mit.edu

Actin polymerization and depolymerization is critical for force generation and epithelial invagination

Adam C. Martin, Frank M. Mason, Mike Tworoger

Embryonic development requires that coordinated cell shape changes collectively deform tissues to generate organs with diverse forms and functions. Cell shape changes result from forces generated by actin networks that are coupled to adhesive complexes. During Drosophila gastrulation, pulsed contraction of an apical actin and myosin II network coupled to adherens junctions drives apical constriction of mesoderm cells, which is important for epithelial invagination. While the role of actin assembly and disassembly/turnover is well established for individual cell migration, the importance of actin turnover for the coordinated movement of an epithelial sheet is not known. To examine the importance of actin turnover, we performed live imaging and quantitative analysis of F-actin during Drosophila gastrulation. Unexpectedly, we found that F-actin levels decrease during apical constriction, suggesting net F-actin depolymerization during constriction. Injection of phalloidin, which blocks depolymerization, results in F-actin accumulation in a single spot on the medial apical surface of the cell, indicating a zone of F-actin depolymerization. To test the function of F-actin polymerization, we injected cytochalasin D, which blocks barbed end growth, at a concentration range spanning two orders of magnitude. We observed a transition from a general disruption of contractility in all cells with high doses of cytochalasin D to a mesoderm specific disruption in cell-cell connections at low doses. At low cytochalasin D concentrations, neighboring actomyosin networks continually lost and reformed connections, resulting in an unbalanced "tug-of-war" between cells of the mesoderm. A similar phenotype was observed in mutants for the formin, dia, suggesting that formin mediated actin polymerization is required to maintain cell-cell connections. We propose that F-actin turnover is critical for apical constriction and is required for cellular contraction and to maintain attachments between cells.

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26. Speaker: Denise Montell, Department of Biological Chemistry, Director, Center for Cell Dynamics, Johns Hopkins School of Medicine, Baltimore, MD 21205-2185. dmontell@jhmi.edu

Measuring, Monitoring and Manipulating Morphogenesis with Light

The ultimate goal of tissue engineering and regenerative medicine is to build functional artificial tissues. In order to achieve this, it is necessary to understand not only how each cell type is specified but also how cells self-assemble into functional three-dimensional architectures. One approach is to decipher, and ultimately to harness, the mechanisms governing normal morphogenesis. My laboratory has focused on border cells in the Drosophila ovary which migrate as a group in between other cells as a genetically tractable experimental model for understanding morphogenetic movements. In contrast to cells that undergo an epithelial to mesenchymal transition, cells that migrate collectively maintain cell-cell adhesion as they move. Border cells in fact express higher levels of E-cadherin than cells that remain immobile in the follicular epithelium. I will show the dramatic morphological consequences of cell-type specific knock-down or over-expression of E-cadherin and present data using a new FRET based E-cadherin tension sensor.

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27. Speaker: Jose J Munoz, Universitat Polit√®cnica de Catalunya, Department of Applied Mathematics

Tissue viscoelasticity versus cell activity

During the last decade, the mechanics of the embryonic tissue during morphogenesis have been successfully modelled and many of the observed deformations have been reproduced in silico. Despite these progresses, the models developed in the literature resort to substantially different material assumptions. While some models consider a purely viscous tissue, others are based in purely elastic materials. Therefore, the proper characterisation of the tissue properties remains as yet an open issue. Furthermore, it is recognised that the viscous properties of the cells do not stem from the fluid content in the cytoplasm, but rather from other sources, which have not yet been fully determined.

In this study, we simulate the viscous component of the viscoelastic cell tissue by an intracellular remodelling process that changes the rest length of the cytoskeleton in a stress dependent manner. We analyse the stress-strain response of this cell model, and mimic the response of non-linear visocelastic materials. In doing so, we identify a potential source of the viscous nature of cells, and at the same time simulate the morphogenesis process using the proposed model. In order to ease the actual implementation and the mechanical analysis of the tissue under large deformations, the epithelial cells are replaced by a truss system that is able to undergo topology changes, as experimentally observed in cellular tissues.

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28. Speaker: Leonid Pismen

Strain dependence of cytoskeleton elasticity

L. M. Pismen and K. I. Morozov
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We describe the mechanosensing mechanism in actin-myosin networks based on the tension dependence of the motor detachment rate and a possibility of rupture of actin filaments under strain. Both effects, operating at different orientations to the applied strain, induce orientational anisotropy of the network. The theory is applied to explain quantitatively the drastic reduction of the elastic modulus under oscillatory strain observed in the experiment.

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29. Speaker: Katarzyna A. Rejniak, H. Lee Moffitt Cancer Center & Research Institute, Mathematical Oncology Department, Tampa FL

Normal and malignant remodeling of epithelial tissues: an integrative IBCell model

Epithelial morphogenesis is a complex multicellular process requiring interactions between both individual epithelial cells and cells with their microenvironment. Moreover, disruption of epithelial morphogenesis is thought to be involved in the initiation of cancer. We use a computational model IBCell (Immersed Boundary model of a eukaryotic Cell) to first reconstruct in a quantitative way the development of a normal tissue (such as epithelial acini grown in 3D culture), and then to investigate how perturbations in model parameters lead to formation of abnormal structures (such as tumor-like acinar mutants). Epithelial cell self-organization into a hollow polarized acinus is achieved in the model by a combination of cell proliferation, cell-cell adhesion, and self-secretion of ECM proteins. In contrast, by changing the ratio between cell-cell and cell-ECM adhesion receptors expressed on cell membrane, the model produces aberrant, mutant-like morphologies. Thus, by using this computational framework to test cell intrinsic sensitivity to extrinsic cues we identified core trait alternations in cells expressing a mutant HER2 receptor, such as a loss of negative feedback from autocrine secreted ECM.

We also discuss how the IBCell model can be used to investigate other cell process involved in epithelial morphogenesis and carcinogenesis.

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30. Speaker: Ulrich S. Schwarz, Heidelberg University, BioQuant and Institute for Theoretical Physics, Philosophenweg 19, 69120 Heidelberg, Germany. Ulrich.Schwarz@bioquant.uni-heidelberg.de

Modeling active contractility of cells and tissues

Active contractility by myosin II motor activity in the actin cytoskeleton has emerged as a key determinant of many essential processes both on cellular and tissue levels. This raises the interesting question how contractility can be modeled in a manner which satisfies the needs of biology (including regulation of myosin II motor activity and actin polymerization, and in general coupling to biochemical and genetic pathways) and the standards of materials science (including the sophisticated schemes provided by the finite element method (FEM) to analyze stresses and strains in passive materials with different material laws and complicated geometries). Recently we have found that the shape of contractile model tissue pinned at discrete sites can be described neither by tension-based Laplace laws nor by traditional elasticity theory [1]. Rather a satisfying theoretical explanation of tissue shape as a function of pinning geometry could be achieved only by combining elements of tension and elasticity in the theoretical framework of actively contracting cable networks [1,2]. In contrast to spring networks, which correspond to material laws often used in FEM-work, cable networks do not propagate compression. Under active contraction, they do not have a reference shape and therefore are only stable in combination with adhesion sites. Actively contracting cable networks are well suited for multi-scale modeling in the biological context, because their locally defined structural properties can be easily coupled to additional degrees of freedom. In contrast, FEM-models are especially suited if global systems properties are of high importance. Here contractility can be modeled by including a negative pressure into the elastic equations (like for thermal cooling). We demonstrate the application of this approach by predicting the experimentally observed localization of stresses and strains to the periphery of epithelial monolayers [3].

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31. Speaker: Joshua W. Shaevitz, Princeton University, Department of Physics

Collective pattern formation in groups of moving cells

From wildebeest herds to bacterial biofilms and every scale in between, how individuals self-assemble into large, spatially complex groups is a key problem in understanding collective behavior, multicellularity and development. The coordinated motion of individuals at the cellular level can drive the formation of higher-scale structure is tissues, organisms and even populations. These phenomena arise statistically as cells modulate their direction and speed in response to both local and global cues. A full understanding of how collective behavior in cell populations arises has been difficult to achieve because we currently lack the ability to cross spatial scales and draw connections between sensory input, motor control and group formation. Experiments examining the effect of specific mutations on

single cell movement and group morphology have identified many important molecular players but lack the ability to probe the behavior of individuals within groups or physical aspects of coordination. I will present some of my group's recent work studying force production, motion control and coordination on the molecular to the population scales using the model social bacterium Myxococcus xanthus, a fascinating organism that takes advantage of multi-cellular, coordinated motility to feed on colonies of bacteria in large, pack-like groups and to form giant, spore-filled fruiting bodies during starvation.

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32. Speaker: Pascal Silberzan, Institut Curie - Centre de Recherche 11, rue Pierre et Marie Curie, 75005 Paris - France

Collective migration of epithelial cells

We experimentally study the collective motility of epithelial cells that maintain strong adhesions between them during their migration. We grow epithelial (MDCK) cells within the apertures of micro-stencil previously put on the substrate. The removal of the stencil triggers the migration without damaging the border cells.

This collective motility can be characterized by using Particle Image Velocimetry. It involves long-range coordinated displacements of large groups of cells well within the monolayer that are well described by a simple model of self-propelled interacting particles. In a second stage, the edges of these epithelia roughen drastically and exhibit a strong directional fingering led by a cell of different phenotype (a “leader cell”) initially not discernible from the others. Interestingly, similarly looking leader cells are found in a large number of different situations in morphogenesis or local invasion from tumors. In this talk I’ll question the nature of these cells and the properties of the migration fingers by using a variety of physical techniques (image analysis, force measurements, laser photoablation) together with the mapping of the biochemical activity of migration-involved small GTPases.

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33. Speaker: Jerome Solon, Centre for Genomic Regulation, Barcelona

Closing the gap: How the contractile amnioserosa tissue controls Drosophila dorsal closure dynamics

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How does a tissue contract during development? Tissue constriction is a fundamental process occurring several times during development. Drosophila dorsal closure (DC), a wound healing-related process, is an appropriate model system to study tissue constriction. DC is a late Drosophila embryogenesis process that consists in the closing of a gap on the dorsal side of the embryo. The amnioserosa tissue, covering the gap, constricts itself to allow the final fusion of the two neighboring epidermal layers. During this constriction, the amnioserosa cells undergo a dramatic shape remodeling, from flat and elongated to conical cells. How is this collective cellular remodeling coordinated? Does the amnioserosa cells can influence DC via their remodeling? With high-resolution selective plane illumination microscopy (SPIM), we have obtained a tri-dimensional view of the cellular remodeling

occurring during DC. We have revealed three different phases of contractions. During the first phase, the cells remain flat and elongated and generate pulses of contraction to power the closure (1). The arrest of these pulses correlates with the start of a second phase where the tissue is now remodeling itself by shrinking the volume of individual cells. At the same time, we can observe the occurrence of cell delamination. We show that volume shrinking and cell delamination determine the dynamics of DC at that stage and allow the proceeding of the closure. By specifically interfering with actin density in the tissue or with the cell delamination, we are able to quantitatively define the contribution of both the shrinking of the volume of the cells and the number of delaminations. In a last phase, the cells undergo a squamous-columnal transition by elongating towards the basal surface and will eventually invaginate. We show that the cells exert a tight mechanical control of DC by means of shrinking and cell apoptosis in a complementary fashion and that the amnioserosa tissue adopts different strategies to contract following the experienced tension-pressure during the process.

(1) “Pulsed forces timed by a ratchet-like mechanism drive directed tissue movement during dorsal closure”, Solon J. et al, Cell, 2009.

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34. Speaker: Xavier Trepat, Universitat de Barcelona, Cell and Tissue Dynamics Laboratory

Mechanical waves during tissue growth

Essential features of morphogenesis, wound healing and certain epithelial-derived diseases involve expansion of an epithelial monolayer sheet. Epithelial expansion is driven by mechanical events that remain largely unknown, however. Using the micropatterned epithelial monolayer as a model system, I will report the discovery of an unanticipated mechanical wave that propagates slowly to span the monolayer, traverses intercellular junctions in a cooperative manner, and builds up differentials of mechanical stress. Essential features of wave generation and propagation are captured by a minimal model based on sequential fronts of cytoskeletal reinforcement and fluidization. These findings establish a novel mechanism of long range cell guidance, symmetry breaking, and pattern formation during monolayer expansion.

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35. Speaker: Daiki Umetsu, Institute of Genetics, Dresden University of Technology, Germany

Live imaging reveals dynamics of cell sorting at lineage restriction boundaries in Drosophila

Cell sorting plays important roles in building body plans by separating cells with different identities and functions during tissue morphogenesis both in vertebrates and invertebrates. Although it has long been studied how cells sort out, it remains poorly understood how cells behave at the interface of non-mixing groups of cells in vivo. We used lineage restriction boundaries in the developing Drosophila abdomen as a model to study the dynamics of cell sorting in living tissues. We combined long-term live imaging with quantitative image analysis in order to understand how individual cells behave at the boundaries to prevent cell mixing. We found clear differences in the dynamic behavior of cells at the compartment boundaries compared to cells further away. These differences in dynamic behavior result from distinct mechanical properties of cell bonds along the compartment boundaries. Our study provides new insights into the mechanisms that mediate cell sorting during tissue morphogenesis.

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36. Speaker: Dimitrios Vavylonis, Lehigh University, Department of Physics

Modeling the assembly of contractile actomyosin bundles

D. Vavylonis, N. Ojkic, W. Nie (Department of Physics, Lehigh University)

Actin filaments, myosin motors, and actin filament cross-linkers self-organize into contractile structures within cells. The subcellular distribution of these structures is important for cell polarization and for the mechanical integrity of tissue. I will present modeling work of the kinetics of this organization in single cells. Fission yeast cells assemble a contractile actomyosin ring by the condensation of a broad band of membrane-bound nodes containing myosin motors. Formins nucleate actin filaments from these membrane nodes and establish transient actomyosin connections among them. The movements of the nodes depend on actin filament cross-linkers that bundle the growing actin filaments. We developed numerical simulations modeling actin filaments as semiflexible polymers polymerized by formins, pulled by myosin, and represented cross-linking as an attractive interaction. The simulations show that actin cross linkers regulate actin-filament orientations inside actin bundles and organize the actin network. These simulations reproduce experimental observations by D. Laporte and J.-Q. Wu who observed that mutations and changes of the concentrations of cross-linker alpha-actinin in live cells causes the nodes to condense into different morphologies, forming clumps at low cross-linking and extended meshworks at high concentrations. To study the process of stress fiber formation in animal cells we observed the kinetics of stress fiber formation in Hela cells expressing myosin light chain marker MRLC-GFP, after removal of myosin inhibition by blebbistatin. We observe transient myosin foci formation on the cell cortex that most likely correspond to myosin minifilaments. This is followed by contractile activity and alignment that leads to stabilization of the foci. A 2D Monte Carlo simulation incorporating the above features can explain the kinetics of stress-fiber network formation observed in experiments. This work supports a hierarchical process of self-organization involving components drawn together from distant parts of the cell followed by progressive stabilization and alignment by cross-linker and other proteins.

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37. Speaker: Geoff Wasteneys, University of British Columbia, Department of Botany

Chaos, Collisions, Catastrophes and the Edge Effect: The self-organizing cortical microtubule array

For nearly 50 years, researchers have endeavoured to understand the mechanisms by which microtubules are organized in eukaryotic cells. In animal cells, the centriole-based centrosome acts as a central microtubule organizing centre and confines assembly of microtubule arrays to spindle poles, perinuclear radial arrays and flagella. Most plant cells lack centrosomes and microtubules are far more dispersed, especially during interphase when arrays form at the cell cortex that consist of many disconnected yet highly ordered microtubules. The parallel organization of these cortical arrays is essential for the unidirectional growth of plant cells, tissues and organs, with the axis of elongation running perpendicular to the predominant microtubule orientation. In this seminar I will outline recent research we have conducted to understand the mechanisms that drive spatial organization of the plant cortical array. Using a combination of genetic strategies, live cell imaging and computational simulations, we have identified the dynamic parameters required to establish both parallel order in 2 dimensions and have also discovered how cell geometry and the unique properties of one microtubule associated protein determine how microtubule orientation is controlled in 3-dimensions on all faces of polyhedral plant cells.

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38. Speaker: Daphne Weihs <daphnew@bm.technion.ac.il> Department of Biomedical Engineering, Technion

Initial stages of metastatic penetration require cell flexibility and force application

Revital Muscal, Liron Dvir, and Daphne Weihs

Department of Biomedical Engineering, Technion

The process of invasion is of special importance in cancer metastasis, the main cause of death in cancer patients. Cells typically penetrate a matrix by degrading it or by squeezing through pores. While mechanisms of invasion have been studied, the mechanics and forces applied by cells especially during the initial stages of metastatic penetration are still unknown. Hence, we evaluated cell-substrate mechanics during initial stages of penetration, as an impenetrable substrate is indented by cells. During indentation, cells change shape and apply mechanical forces depending on substrate stiffness and as we show here also depending on metastatic potential of the cells. We show that while increased metastatic potential (MP) results in cells being more pliable internally and externally, allowing rapid changes in morphology, at the same time those cells are also able to apply stronger forces.

Differences relating to cancer aggressiveness arise in applied force, obtained morphologies, and number of indentation attempts applied by the cells. We show that both high and low metastatic potential breast-cancer cells initiate penetration even on a non-degradable polyacrylamide substrate with small, sub-micron pores. Non cancerous cells do not attempt invasion and do not indent a 2D substrate. We compare cell-substrate interactions of the cells distinguishing different forces and two morphologies as cells indent the gels: skirt-like and blebbing. Applied forces depend on substrate stiffness, which affects cell dimensions as well as indentation capability. Cells repeatedly attempt penetration over several hours, where more attempts and stronger forces are applied on the stiffer gel and by the high metastatic potential cells. We propose a model for the cell-indentation mechanism and highlight a special role for the nucleus.

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39. Speaker: David A. Weitz, Harvard University, Division of Engineering and Applied Sciences

Mechanics of cell-substrate interactions

This talk will describe measurements that probe the nature of the interaction between cells and their substrate to determine the dependence of the stiffness of the cell on the stiffness of the substrate. The results suggest that the commonly measured relationship between cell and substrate stiffness may, in fact, be controlled by other parameters.

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40. Speaker: Jennifer Zallen, HHMI and Developmental Biology Program, Sloan-Kettering Institute

Shaping the embryo: Cellular dynamics in development

A major challenge in developmental biology is to understand how large-scale changes in tissue structure are generated on a cellular and molecular level. In my lab we address this question through the study of convergent extension, a conserved morphogenetic process involving hundreds of cells that generates a prominent feature of embryonic form – the body axis. During body axis formation in *Drosophila*, the embryo more than doubles in length along the anterior-posterior (AP) axis and simultaneously narrows in width along the dorsal-ventral (DV) axis to produce the basic layout of the

body plan. Axis elongation in *Drosophila* is driven by cell intercalation, which provides the driving force for elongation in many organisms including frogs, fish, and chicks. We identified a novel cellular mechanism of intercalation in which groups of cells assemble into multicellular rosette structures that form and resolve directionally (Blankenship et al., 2006). Rosette formation has since been shown to occur during epithelial elongation in several tissues in vertebrates, including the chick neural plate and primitive streak (Nishimura and Takeichi, 2008; Wagstaff et al., 2008) and may represent a general mechanism linking cellular asymmetry to tissue elongation.

Contractile actomyosin networks generate the forces that drive axis elongation in *Drosophila*, and an initial asymmetry in myosin localization is amplified by mechanical signals to form higher-order rosette structures (Fernandez-Gonzalez et al., 2009). We found that an applied force is sufficient to recruit myosin to the cortex and conversely, relieving tension leads to a rapid decrease in cortical myosin. Quantitative imaging and FRAP experiments reveal that myosin II cortical localization is selectively stabilized in regions under increased tension. These results indicate that myosin dynamics are regulated by tension in a positive feedback loop that leads to rosette formation and tissue elongation. In addition, cell adhesion must be dynamically regulated to translate these polarized forces into a permanent change in tissue structure. We recently demonstrated that adherens junctions that are targeted for disassembly during actomyosin contraction are sites of increased tyrosine kinase signaling (Tamada et al., 2012). In particular, phosphorylation of β-catenin by the Abl tyrosine kinase promotes β-catenin turnover and rosette formation. These results suggest a role for tyrosine kinase signaling in spatially regulated cell adhesion during development.

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41. Speaker: Elazar Zelzer, Weizmann Institute of Science, Department of Molecular Genetics

Muscle-induced mechanical loads regulate key aspects of skeletogenesis

The involvement of embryonic movement and muscle contraction in skeletogenesis has long been recognized. Nevertheless, several important questions about this effect are yet to be elucidated. In our studies, we seek to determine the scope of this involvement and to identify mechanical and molecular signals that mediate it. The third question regards the integration of these two types of signal into one developmental program.

Synovial joints develop from a pool of progenitor cells that differentiate into various cell types. Using several murine models that lack either limb musculature or its contractility, we show that muscle contraction is required to maintain joint progenitors committed to their fate. In its absence, the differentiation sequence was disrupted, resulting in impaired cavitation and morphogenesis. We then show that contraction-dependent activation of -catenin is the mediating molecular mechanism. Our findings link between cell fate determination and embryonic movement during organogenesis.
In another work, we study the role of intrauterine muscle-induced mechanical loads in bone morphogenesis. Analysis revealed that developing mouse bones are subjected to significant and increasing mechanical challenges. Using daily micro-CT scans of appendicular long bones, we identified a developmental program we name preferential bone growth, which determines the specific circumferential shape of each bone by employing asymmetric mineral deposition and transient cortical thickening. Computer models demonstrate that the resulting bone structure has optimal load-bearing capacity. Finally, we used muscular dysgenesis mice to show that in the absence of muscle contractions, the typical circumference of each bone is lost, leading to development of mechanically inferior bones. This study identifies muscle force regulation of bone preferential growth as a common module that shapes the distinctive outline of long bones and optimizes their load baring capacity.

A third study explores the involvement of muscle contraction in zebrafish skeletal morphogenesis, demonstrating its role in regulation of chondrocyte intercalation. Analysis of chemically and genetically paralyzed embryos revealed shortening of pharyngeal cartilage elements, accompanied by marked changes in cell morphology and organization. Chondrocytes in paralyzed zebrafish were smaller and more rounded and exhibited abnormal stacking patterns, indicating aberrant intercalation. Impaired chondrocyte intercalation in growth plates of “muscle-less” mouse embryos implied evolutionary conservation of this effect. These findings uncover a new role for muscle-induced mechanical loads in skeletal morphogenesis by regulating chondrocyte intercalation in two different vertebrate models.