

Tissue Growth and Morphogenesis: from Genetics to Mechanics and Back (12w5048)

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1 Overview of the Field

Tissue growth and morphogenesis are fundamental processes in developmental biology. On the cellular level, cell size growth, cell division, and cell shape changes are controlled by signaling molecules that, in turn, are expressed according to a genetic blueprint. On the tissue level, different cell types arrange themselves in spatial patterns that eventually form the tissue or organ. Evidently, morphogenesis involves biochemical and mechanical mechanisms on several length and time scales, and thus has attracted the attention of scientists from several fields, including genetics, cell biology, soft matter physics and mechanics of solids and fluids.

Past work on growth and morphogenesis has followed three distinct lines, corresponding to molecular, cellular and tissue scales. Most of our current understanding of tissue growth and morphogenesis has come from molecular-genetic studies, which elucidate what genes carry the blueprint of how the organism will develop, and how the blueprint is implemented through pathways and networks of causal relationships among signaling proteins. Besides its genetic aspect, it has long been recognized that morphogenesis is also a physical process that involves the adhesion, deformation and movement of cells in a temporal-spatial framework. On the cellular scale, physical scientists have undertaken studies on the intracellular mechanisms that cause prototypical deformation of cells such as apical constriction and convergent-extension, on how like cells migrate and aggregate and dissimilar ones segregate into domains, and on cell adhesion to an extracellular matrix or substrate. On the coarser tissue level, relevant to growth, development, and wound healing, continuum mechanics models have been developed. But they tend to be simplistic and lack a connection to molecular and genetic mechanisms. Feedback of mechanics on chemical processes in development and pattern formation remains largely unexplored, although its importance is widely recognized.

A good example to illustrate the unique complexity of developmental processes is cell sorting [1, 2, 3]. During embryogenesis, cells destined for different organs must organize themselves into domains and structures. First and foremost, these domains are determined by the so-called selector genes, which are expressed in different regions so as to establish an initial boundary between the cells. With cell proliferation and tissue deformation, these boundaries are liable to distortion, and cells of different lineage may intermingle (Fig. 1). Yet in successful development, these boundaries typically retain their integrity; cells that transgress into the other side are promptly brought back. The maintenance of boundaries in development turns out to require intricate cooperation among gene expression, molecular signaling and the physics of force generation and cell and tissue deformation. For the *Drosophila* wing primordium, geneticists have more or less clarified the signaling network via knock-out studies (Fig. 2), and the downstream effect appears to be the enrichment

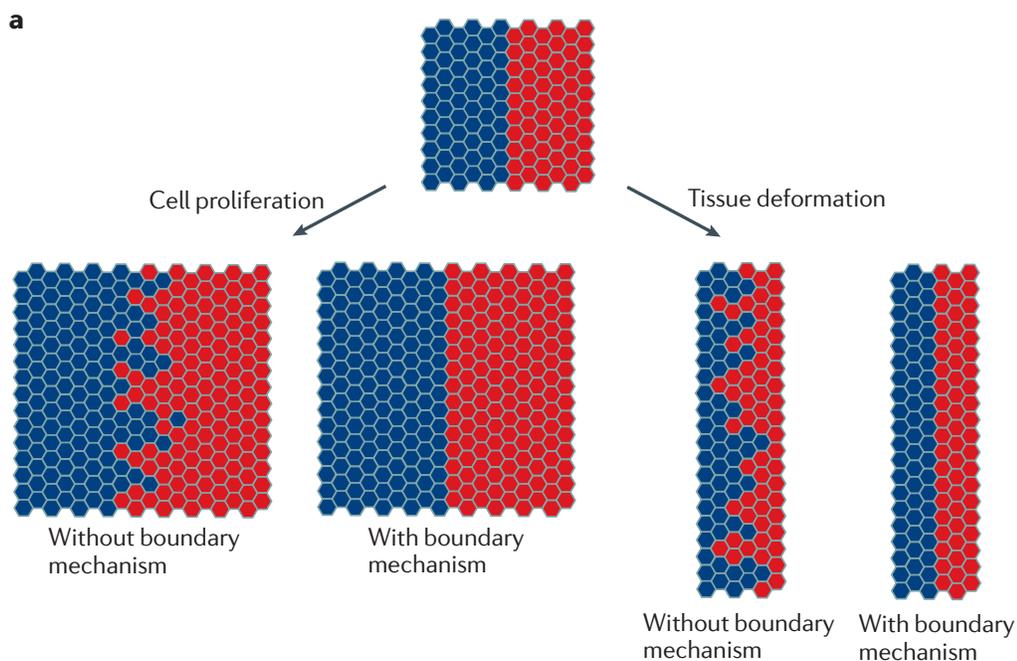


Figure 1: Schematic showing the maintenance of straight boundaries between cells of different lineage against challenges posed by proliferation and tissue deformation. Adapted from Ref. [3], first published by Nature Publishing Group, a division of Macmillan Publishers Limited.

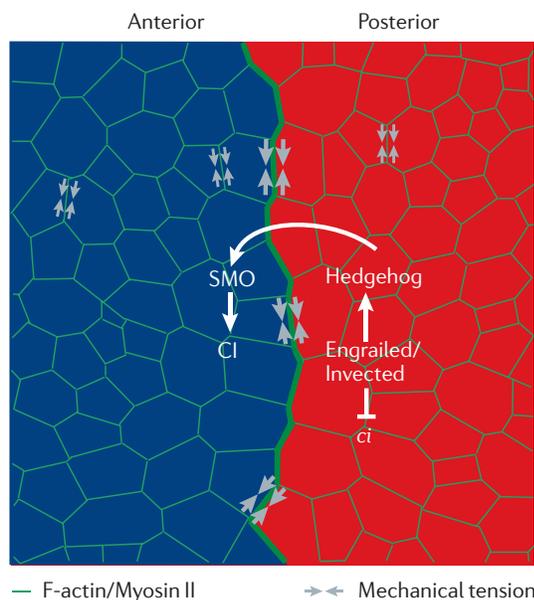


Figure 2: The Hedgehog signaling pathway that moderates the maintenance of the anterior-posterior (A-P) boundary on the wing disc of *Drosophila melanogaster*. Adapted from Ref. [3], first published by Nature Publishing Group, a division of Macmillan Publishers Limited.

of actin and myosin along the boundary between the anterior and the posterior domains. Yet, we have only a rudimentary understanding of how this translates into mechanical forces and how the forces in turn maintain the boundary. Using an energy-minimization procedure, it has been shown that increasing the tension on the

cell bonds does tend to reduce the roughness of the boundary [2, 4]. Quite unrelated to the modern genetic studies, there have been ideas of drawing an analogy between the spontaneous segregation of cell colonies and that of immiscible fluids. This so-called differential adhesion hypothesis has been under continuing debate [1, 5]. Despite the progress on separate fronts, an integrated understanding, encompassing the temporal-spatial distribution of the morphogens and the mechanical deformation of the tissue as a whole, has yet to be established. A consensus is forming that such an integrative approach calls for the close interaction between geneticists, biophysicists and mathematicians.

So far research dealing with the genetic, cellular and tissue aspects of morphogenesis has largely progressed independently, with insufficient conversation among the different communities of scientists. Yet, it is clear from the brief overview above that the problem at hand is multidisciplinary and calls for a coordinated approach that integrates insights and knowledge from the different approaches. One can envision a close coupling of the different length scales via propagation of information in both directions. For example, genetic-molecular pathways may predict or rationalize the abundance of certain signaling molecules such as the Hedgehog. This information can then be utilized on the cellular level to explain apical constriction. In the meantime, intracellular mechanical and geometric cues will affect the reaction-diffusion of active chemical messengers that modifies the genetic-molecular expression in return.

The latest advances on the three scales (genetic, cellular and tissue) and the emerging efforts at integrating them suggest that the time is ripe for a concerted assault. The general objective of this workshop is to bring together the leading researchers in tissue growth and morphogenesis across several disciplines, including biologists, physicists and mathematicians, to foster awareness and cross-disciplinary transfer of ideas on this burgeoning topic.

2 Recent Developments and Open Problems

New challenges are arising in measuring the mechanical properties of living organisms at different scales and in modeling them mathematically. Rapid development of experimental tools, such as high-resolution luminescence and fluorescence microscopy for molecule tracking, laser ablation, probing using automated tuning and matching (ATM) devices, and local traction measurements for mechanical response, provides abundant data of increasing resolution. These results are often not explained by cell- and tissue-level mechanical models. Physicists and mathematicians may not understand these data sufficiently well to choose a suitable modeling framework. The disconnect between the genetic, cellular and tissue scales is manifested by the following outstanding problems:

- Understanding the role of mechanical forces in morphogenesis through balances and feed-backs between genetic and mechanical inputs;
- Interaction between processes on different scales (subcellular, multicellular) and multiscale modeling (from molecular effectors to multicellular shape);
- Building a full morphogenetic pathway from molecules to shape via sequences of emerging properties, e.g. translating the activity of a microtubule regulator into morphogenetic out-put;
- Solving biologically important inverse problems, e.g. finding ways to construct a desired morphogenetic pattern;
- Developing tools to test hypothesis in different organisms and on different scales, and identifying similarities and differences between animals, plants, yeasts, etc;
- Comparing non-matched data sets, e.g. from different animals of the same or different phenotypes or between experimental and modeling data.

Clearly, there is a need for integrating biomolecular and mechanical studies, and for developing multiscale models that bridge the genetic, cellular and tissue levels. Integrating two or all three scales may be achieved by applying novel multiscale techniques being developed in fluid and solid mechanics, such as particle-based models incorporating intracellular transport of signaling molecules into mechanical representation of deformation of multiple cells or tissues.

3 Presentation Highlights

We had some 40 presentations covering the biological and mathematical aspects of cell and tissue dynamics. Despite the great diversity and scope of these talks, several key topics emerged that were notable for the fact that there were multiple groups working on them from different angles, and the interaction at the workshop provided a particularly fruitful forum for taking stock of recent achievements and looking ahead at the next steps. These are highlighted in the following.

(1) Collective motion of cell colonies. The coordinated motion of a group of cells is important for a large number of physiological and biological processes, including embryogenesis and wound healing. The key element is the signaling and coordination among cells, through both biochemical and mechanical pathways. Several speakers presented their latest experimental findings and theoretical models on this.

Pascal Silberzan spoke about the collective motility of epithelial cells that maintain strong adhesions between them during their migration. They 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 is characterized by Particle Image Velocimetry, and features 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. Silberzan focused on the properties of the migration fingers, which have been characterized 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.

Xavier Trepats discussed mechanical waves during tissue growth in his talk. 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. Using the micropatterned epithelial monolayer as a model system, the Trepats group discovered an unexpected 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.

Cristian Dahmann and Daiki Umetsu presented two talks on the fascinating process of cell sorting. Dahmann discussed 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. Dahmann and coworkers studied the mechanisms underlying cell sorting at compartment boundaries in *Drosophila*. Results show that the 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. Umetsu further reported live imaging that elucidates dynamics of cell sorting at lineage restriction boundaries in *Drosophila*. He combined long-term live imaging with quantitative image analysis to demonstrate 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.

These novel experimental findings were matched by several theoretical modeling efforts of collective cell motion. The models of Michael Koepf and Nir Gov are both inspired by the cell motion and pattern formation in the experiments. In collaboration with Len Pismen, Koepf formulated 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. Nir Gov presented a model for the evolution of the outer contour of cellular aggregates. Such circumstances occur during wound-healing, cancer growth and morphogenesis. He demonstrated 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. Finally, Joshua Shaevitz discussed collective pattern formation in groups of moving bacteria. He reviewed his group’s recent work on studying force production, motion control and coordination on the molecular, cellular and 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.

(2) Cytoskeletal dynamics: structure and mechanics. Going down to the intracellular length scale, several talks were devoted to the mechano-biochemical dynamics of the filamental actin and molecular motors that drive the machinery of cell motion and deformation. Again both experimental and theoretical approaches are well represented at the workshop.

In his talk entitled “Actin polymerization and depolymerization is critical for force generation and epithelial invagination”, Adam Martin explored the role of actin networks coupled to adhesive complexes in morphogenetic processes such as 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, Martin and coworkers performed live imaging and quantitative analysis of F-actin during *Drosophila* gastrulation. Unexpectedly, they found that F-actin levels decrease during apical constriction, suggesting net F-actin depolymerization during constriction. Using various drugs to block actin depolymerization and barbed end growth, they saw 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. They proposed that F-actin turnover is critical for apical constriction and is required for cellular contraction and to maintain attachments between cells.

Fred Mackintosh spoke about active stresses and self-organization in intra/extracellular networks. He described recent advances in theoretical modeling of such networks and in experiments on reconstituted in vitro actomyosin networks and living cells. His group was able to elucidate how 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. He also showed 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 pico-Newton compressive loads.

Len Pismen’s presentation focused on strain dependence of cytoskeleton elasticity. He described 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.

Dimitrios Vavylonis’s study is centered on the organization of actin filaments, myosin motors, and actin filament cross-linkers and on the kinetics of this organization in single cells. His group 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 of D. Laporte and J.-Q. Wu 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, they carried out 2D Monte Carlo simulations on 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.

Yuan Lin presented another computational study of actomyosin bundles and stress fibers. Using a combined finite element-Langevin dynamics (FEM-LD) approach, he described the shape fluctuations of extended objects like bio-filament and cell membrane, and developed methods to implement a stochastic partial differential equation 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. As an application, they applied their method to investigate the mechanical response of an actin filament network. The 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.

(3) Cell interaction and migration through extracellular matrix. Cells migrate as part of their normal physiological function or, in the prominent case of cancer cells, to metastasize to other organs. For both the fundamental and medical significance of this process, several groups have concentrated on the process of cell-matrix interactions during cell migration.

Daphne Weihs delivered a talk entitled “Initial stages of metastatic penetration require cell flexibility and force application”. She explained that 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 various mechanisms of invasion have been studied, the mechanics and forces applied by cells especially during the initial stages of metastatic penetration are unknown. Her group evaluated cell-substrate mechanics when an impenetrable substrate is indented by cells in a controlled way. During indentation, cells change shape and apply mechanical forces depending on the substrate stiffness as well as on the metastatic potential of the cells. 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. They proposed a model for the cell-indentation mechanism and highlight a special role for the nucleus.

Josef Käs raised the following questions: Do cancer cells care about physics? Are fundamental changes in a cell’s material properties necessary for tumor progression? In a review of the state of the art, he noted that in tumour biology an overwhelming complexity arises from 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. Therefore, passive and active biomechanical behaviour of tumour cells, cell jamming, cell demixing and surface tension-like cell boundary effects are key factors to stabilize or overcome compartment boundaries. He discussed how insights into changes of these properties during tumour progression may lead to selective treatments.

Ben Fabry spoke about the physical principles of cell migration in three dimensions (3D). He described how 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 3D. Despite these differences, there are also striking similarities. He proposed a treatment of 3D migration as a super-diffusive random process with directional and speed persistence. Moreover, unlike migration in a 2D 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 3D migration.

(4) Dorsal closure: new data and numerical modeling. Dorsal closure (DC) is a morphogenetic process during the development of the embryo of the fruit fly *Drosophila*. It is a complex, multi-faceted process that involves close coordination among molecular signaling, intracellular and intercellular force generation and whole-tissue deformation. As such it has received much attention from developmental biologists, and more recently mathematicians and physicists have started to rationalize the observations into models.

Nicole Gorfinkiel discussed contractile activity of amnioserosa (AS) cells during dorsal closure. She pointed out 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. Thus her lab focuses on 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. Using dorsal closure as a model system and employing quantitative and biophysical tools, she presented data showing that 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. But how do AS cells switch from a predominantly fluctuating behaviour to a predominantly contractile behavior? Quantitative analysis suggested that the decision to contract is taken at the single cell level, and 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 behavior.

Jerome Solon continued on the theme of tissue contraction during DC. With high-resolution selective plane illumination microscopy (SPIM), Solon's group has obtained a 3D view of the cellular remodeling occurring during DC. This 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. 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, they observed the occurrence of cell delamination. The volume shrinkage and cell delamination determine the dynamics of DC at that stage and allow the proceeding of the closure. In the last phase, the cells undergo a squamous-columnar transition by elongating towards the basal surface and will eventually invaginate. A key finding is 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 upon experiencing tension-pressure during the process.

Shane Hutson's work tested the hypothesis that oscillatory changes in AS apical area are driven by stretch-induced contractions—with the contraction phase of one cell driven by the contraction of neighboring cells. Using holographic laser-microsurgery to nearly instantaneously isolate a single amnioserosa cell, he found that 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. The new results instead suggest that oscillatory shape changes are more cell autonomous and that the tensed epithelium is nevertheless under low strain. Hutson then presented a revised model that is able to reconcile prior experiments with the new results.

The talk of Dan Kiehart focused on new observations that show a unique frequency behavior of amnioserosa cells that ingress during the course of closure. Using molecular and classical genetics, pharmacology, laser surgery and biophysical modeling, his group has investigated cell and tissue kinematics (cell shape changes and movements) and dynamics (the forces that drive such kinematics) during dorsal closure. A variety of signaling pathways are required for closure, and he discussed how these pathways regulate the assembly and function of these distinct actomyosin arrays in order to generate the emergent behaviors that drive closure.

Feng and coworkers presented a mathematical model on dorsal closure that strives to incorporate the key experimental observations. They 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.

(5) Mathematical modeling across length and time scales. While the biologists presented latest observations and increasingly quantitative measurements, the mathematicians and physicists contributed outstanding talks on modeling the mounting and sometimes bewildering experimental data. A few notable highlights are given below.

Alain Gorieli gave a systematic review of the state of the art in his talk entitled “Mathematical methods

and challenges in the theory of biological growth”. The review covered ten types of models, from the conceptually simple to the technically formidable. These 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. Befitting the context of the Banff workshop, he identified and compared various attempts to describe growth in biological structures. Are they equivalent? Is one better suited for a certain type of analysis (experimental, mechanical, mathematical)? He pointed out the importance of matching the modeling approach to the special features of the target process and concluded with a list of mathematical/scientific challenges and open problems in the theory of growth.

Hisao Honda spoke about three-dimensional cell model for tissue morphogenesis. His starting point is the development of an equation of motion for cell behavior, which would be a powerful tool for understanding cell morphogenesis. He used a geometrical model (Dirichlet or Voronoi geometry) to describe polygonal cell patterns, and made a cell boundary-shortening model to describe an epithelial tissue. The model was useful to understand epithelial cell properties. A two-dimensional cell vertex dynamics model has been extended to 3D and applied to investigate morphogenesis of mammalian blastocyst from morula, and cell intercalation observed in sea urchin gut elongation, amphibian gastrulation, *Drosophila* germ band extension, among other processes. The 3D cell model has been useful in explaining tissue morphogenesis in terms of cell behavior, liquid secretion of cells, contraction of specific edges of cells and apical extension/contraction of cells.

Wayne Brodland focused on multi-scale modeling in his talk “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.

On a larger spatial scale, Kasia Rejniak presented an integrative IBCell model for normal and malignant remodeling of epithelial tissues. The computational model IBCell (Immersed Boundary model of a eukaryotic Cell) is used 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, she identified core trait alternations in cells expressing a mutant HER2 receptor, such as a loss of negative feedback from autocrine secreted ECM. Finally, she discussed how the IBCell model can be used to investigate other cell process involved in epithelial morphogenesis and carcinogenesis.

4 Outcome of the Meeting

The study of tissue morphogenesis has an increasingly diverse constituency, made up of cell and developmental biologists, biophysicists, mathematicians and engineers. The workshop has included mathematical experts on modeling and computations, leading biophysicists specializing in cell-level measurements and characterization, and geneticists and developmental biologists actively exploring the connection between gene expression and tissue mechanics. Geographically, the workshop gathered scientists from Canada, US,

Israel, Spain, Netherlands, Germany, France, China, Hong Kong and Japan, at different stages of their careers, and provided a rare opportunity for exchange among people who would otherwise not have interacted regularly across the disciplinary boundaries. In particular, we have included a significant number of younger researchers, with the aim of connecting them with more established research groups.

The exchange of ideas have benefited modellers as well as experimenters. The former gathered the latest observations and insights from the top labs in this field, and heard about novel processes and phenomena that may lead to new directions of research. The latter learned about new physical conceptualization of biological processes and powerful computational tools that can help make sense of experimental data. The relatively small size of the workshop facilitated many informal but in-depth discussions among the attendees. Many new connections were made that promise fruitful collaborations in the future. Although it is difficult to quantify the value and outcome of such connections, all agree that this had been a most stimulating and rewarding gathering.

On the scientific side, we have set out a number of objectives that have been successfully fulfilled:

(1) To survey the state of the art on tissue growth and morphogenesis, and highlight it as an important emerging area in applied mathematics. Experimentalists have described new observations and measurements on processes such as morphogen spreading, collective cell migration, gastrulation movements, dorsal closure, cell sorting, and force sensing. Theoreticians and numerical analysts have summarized the predictive capabilities of their models, including continuum and discrete numerical methods. The two sides have compared notes and come up with a common understanding of our current knowledge in this area.

(2) To identify the most pressing scientific problems. Experimentalists have underscored several phenomena that cannot yet be readily rationalized or explained, e.g. collective cell motion and dorsal closure. Key missing pieces in our understanding include actuation of mechanical forces by chemical signaling, and mechanical feedback on gene expression. Theoreticians have identified multi-scale modeling and computation as a critical problem, and recommended explorations of multi-scale approaches to prototypical events such as the apical constriction in epithelial invagination.

(3) To develop promising research strategies for the future. In view of the list of high-priority research problems, the workshop has conducted an inventory of the cutting-edge observational, modeling and computational techniques, and suggested strategies for tackling the problems. For example, it has become clear that modeling cell sorting and dorsal closure needs a more integrative approach that adequately reflects the intricacies of the signaling pathways. On the experimental side, quantitative measurement of intracellular forces is considered a promising route to unraveling the complexities of tissue development.

(4) To facilitate the pursuit of these strategies by initiating interdisciplinary collaborations. The workshop saw broad and lively discussions of all the theoretical developments, computational methodologies and experimental discoveries. Out of the formal and informal interactions, new opportunities have emerged for collaborations between researchers with complementary skills and expertise. In particular, younger scientists have benefited from direct interactions with more established experts, and from the opportunity to integrate or distinguish themselves in this exciting multi-disciplinary community.

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