Mathematics of the Cell: Biochemical and Mechanical Signaling Across Scales

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August 12-17, 2018

1 Overview of the Field

A hallmark of biological systems is their ability to integrate external and internal signals and communicate information at different spatial scales (from molecules, cells and tissues to organs and whole organisms) and temporal scales (microsecond scales of molecular rearrangements to developmental and physiological processes that occur over time scales measured in hours to months). From a mathematical point of view, biological signaling is exceedingly complex, involving a multitude of non-linear interactions.

A seminal application of mathematical ideas to understanding the underlying mechanisms in biological signaling was started by the landmark work by Alan Turing in 1952 [9] on how diffusible chemicals can induce macroscopic biochemical patterns and influence organism development. In the 1960s Lewis Wolpert [10] proposed that biochemical gradients can induce downstream cellular signals and generate different cell types in distinct spatial order.

Following these early studies, a number of mathematically deep ideas have emerged that have had profound impact on biology, physiology and medicine. We now have a better molecular understanding of biochemical signals, and recent work has shown that the mechanical environment plays a critical role in regulating many aspects of cell function such as migration and cell fate determination. Mechanical regulation of cell function appears to be widespread, resulting from a conserved set of physical mechanisms. How cells, tissues, organs and organisms integrate and respond to the interplay of mechanical and chemical signals are frontier problems in biology.

The past few years have witnessed a virtual revolution in the application of quantitative approaches to study biological systems, stimulated largely by rapidly developing measurement techniques that allow the monitoring of cellular signals with high precision in space and time, as well as the ability to manipulate gene expression and to genetically engineer a variety of cells and model organisms. These new methods now give biologists unprecedented power to test mathematical models, while allowing mathematicians to formulate abstract yet biologically grounded models.

Mathematical cell biology offers an integrative framework allows modern quantitative data to be ordered within predictive models of sufficient abstraction that is amenable to analysis. However, to do so requires bringing together biologists and mathematicians of different areas of expertise. It is essential that mathematicians be aware of the latest biological discoveries, and that biologists be able to actively participate in model development. It is therefore timely to bring together researchers, including young scientists, to reveal the next round of mathematically deep ideas.

2 Recent Developments and Open Problems

The field of Mathematical Cell Biology has benefited from — and, arguably, emerged into mainstream cell biology with — a series of workshops at BIRS that started in 2005, the first of which was titled "Mathematical Biology of the Cell: Cytoskeleton and Motility" (BIRS 05w5004). This was followed by BIRS workshops in 2011 and 2014. These workshops attracted world-leading biologists and mathematicians, often meeting for the first time, to tackle emerging open questions. The first two meetings focused on the cytoskeleton and cell motility. As the frontiers of knowledge advanced, new questions emerged and the focus of the meeting shifted. The 2014 workshop focused on integrating genes, biochemistry and mechanics. The success of that meeting is evident in the number of collaborations that were initiated at that meeting.

The frontiers of biology have again advanced. Most strikingly, first, new quantitative experimental tools (especially in imaging) are allowing models to be tested and demanding new, integrative models to make sense of a deluge of data. Second, the question of how cells process information — cell signaling — is turning out to be more complex than previously thought, involving not only genes, biochemistry and mechanics, but also collections of cells acting in concert as they interact with their environment, i.e., the tissue, organ or organism in which they reside. In other words, signaling involves biochemistry and mechanics across length scales. This workshop therefore aimed to use the powerful history of the BIRS Mathematical Biology of the Cell workshop series to tackle these emerging questions by enlisting a new generation of researchers.

One of the goals of this diverse group of scientists is to understand the fundamental principles governing cell signaling. This is an ambitious problem because, as noted above (and among many other reasons), it ranges across scales: from single molecules involved in processes such as immune cell recognition and cell division, to integration of environmental signals during cell migration, to cell-to-cell communication involved in wound healing and development. Many of these processes involve the spatiotemporal dynamics of the cytoskeleton which modulates cell mechanics, is critical for cellular force generation, and instrumental in cellular sensing of the chemical and physical environment. This problem is not only of fundamental scientific importance, but also of medical importance, since many new therapies, including cancer immunotherapy, operate by modulating our cell signaling systems.

3 Participants and meeting highlights

The "inputs" of the participants were diverse along many dimensions. There was representation from United Kingdom, Canada, Australia, and the United States, from research universities, public research institutes (e.g., John Innes Center and Francis Crick Institute) and non-profit institutes (Allen Institute for Cell Science). They came from many types of departments besides Mathematics and Applied Mathematics, with the role of Physics being particularly notable compared to previous years (1.5 of the organizers are appointed in Physics departments), but also including Biology, Medicine, Engineering. Many participants have made fundamental contributions to the understanding of the F-actin cytoskeleton, the microtubule cytoskeleton, and their role in cell polarization, self-organizing of subcellular structures such as the mitotic spindle and cytokinetic ring, and cell size control. In addition to intellectual diversity, the diversity also manifested itself in career stage: 4 graduate students and 7 postdoctoral researchers (the majority of whom presented either talks or posters), 5 pre-tenure principle investigators (the number was due to be higher, but participants were promoted between invitation and participation), and 15 female participants.

Many notable outputs arose from these inputs. As senior researchers in their respective fields, Ken Jacobson and Leah Edelstein-Keshet [4] gave presentations overlooking their decades of contributions (in cell membrane organization and cell motility, respectively) and, especially in the discussions that followed formal presentation, anticipated the next few years: What hypotheses might be confirmed or rejected and what technologies might be enabling or over-hyped. Even more memorable were the presentations by 6 postdoctoral researchers. These were mixed approximately equally between mathematical / computational / theoreticians and experimental biologists — however, in many cases, it was impossible to distinguish this separation from their presentations and discussions because they exuded expertise on both sides of the mathematical-experimental interface. This augurs well for the future of the field of Mathematical Cell Biology. In an anonymous post-meeting survey, one reported that "as a postdoc this was a great opportunity for me to meet researchers who could become collaborators in my future career."

3.1 Topics emerging from participants and discussions

The schedule of formal presentations was deliberately not sorted into topics, so that new topics would not be constrained by historically-defined separations, but rather could emerge from the speakers' most current research. As the workshop progressed, we identified five clusters, which we describe in turn below.

The cytoskeleton continues to be a major organizer of researchers (this is fitting, since the cytoskeleton was the theme in the subtitle of previous iterations of this workshop). The cytoskeleton is an integral and ubiquitous part of all eukaryotic cells. Two of the main cytoskeletal components are actin and microtubules filaments, which form networks and higher order structures to determine cell shape and enable the cell to interact with the external environment and mechanical stimuli. Further, these biopolymer filaments undergo dynamic assembly and disassembly in cells. A host of associated proteins regulate these dynamics and crosslink filaments to allow the formation of diverse structures. Additionally, motor proteins are important for transport on these filaments and exertion of forces. These collective dynamics of cytoskeletal filaments, regulatory proteins and molecular motors are important in diverse cellular processes such as cell migration, cell polarization and cell division. Both experimental and mathematical approaches are critical to solving some of the open questions in the field. This workshop brought together scientists from different disciplines and facilitated vibrant discussions on this topic.

3.1.1 Actomyosin Organization

Actin and myosin organization and dynamics is the primary mechanism for force generation in the cell and is hence critical to diverse cellular processes including migration and developmental processes. There were several talks that focused on various aspects related to the organization of actin networks, both in cells and in reconstituted systems from both the experimental and theoretical perspective. The semi-flexible nature of actin filaments and the binding/unbinding kinetics of crosslinkers result in remarkable viscoelastic properties of actin networks, with behaviors such as strain stiffening, nonlinear elasticity and stress-induced reordering. **Moumita Das** spoke about her work on these dynamical mechanical response properties of actin networks. She showed that actin networks can reversibly transition between rigid and non-rigid states (studied experimentally using microfluidic approaches) and that this transition emerges from the assembly and disassembly kinetics of actin filaments as shown from theoretical considerations. Her results highlight how understanding the structural and functional properties of these systems will provide insight into the dynamic response and stability of biopolymer networks. These will be important for predicting behavior across multiple scales — from cells to tissues and may be applicable to tissue repair therapies and soft robotics. **Garegin Papoian** spoke about their work on understanding the emergence of contractility in disordered actomyosin networks as a result of crosslinker binding dynamics. They showed that contractile force dipoles result from the interaction of non-equilibrium dynamics of active motors and passive cross-linkers. Papoian also highlighted an open source software program (Mechanochemical Dynamics of Active Networks – MEDYAN) that his group has developed for simulations of actin and microtubules networks with crosslinking proteins, regulatory proteins and molecular motors. Following this presentation a number of discussions were initiated at this BIRS workshop for further collaborative work. Moving on to cells, **Amy Maddox** [2] gave a cell biologist's perspective on how the actomyosin cytoskeletal network behaves like active living matter, due to the far-from-equilibrium nature of motor contraction and polymerization dynamics. She discussed the contractile behaviors of this network in cells undergoing cell division (cytoskinesis). Her work showed the existence of both positive and time-delayed negative feedback loops that lead to traveling waves of contractility with multiple periodicities of oscillations. Again, they showed that cross-linkers are key elements regulating the frequency of oscillations and that structural reorganizations can give rise to negative feedbacks. These contractility fluctuations may be an emergent property of contractile actomyosin networks. Discussion regarding simulations using MEDYAN as well as mean-field models such as those developed by Das to explain such global behaviors in these networks then ensued. **Orion Weiner** presented his work on higher-level regulation of actin networks, in particular, how the WAVE2 regulatory complex (WRC) self-organizes into ring-like foci. Using super-resolution microscopy they revealed that these act as the fundamental units of organization (templates) of actin sheets which power cell lamellipodia formation during migration, with significant implications for the basic mechanisms underlying motility. He further talked about the use of nanotopographic surfaces to probe curvature sensing by WAVE complex proteins. Adriana Dawes talked about the mechanisms underlying the formation of contractile structures called ring channels in the nematode worm,

C. elegans. Their work used both mathematical modeling (including MEDYAN from the Papoian group) and experimental manipulations to show that two types of myosins motors act in an antagonistic manner to exert orthogonal forces to stabilize these ring channels. **Arpita Upadhyaya** discussed her work on how the actomyosin cytoskeleton self-organizes into characteristic rings during signaling activation in the T cell immune synapse and is responsible for force generation. Finally, **Bill Bement** discussed how the cell cortex behaves as an excitable medium during cytokinesis and the role of both the actin cytoskeleton (which acts as a negative regulator) and membrane organization in this process. He talked about their work on the interplay between chemical and mechanical waves.

3.1.2 Cell Movements: from single-cell to collective cell behavior

A number of talks were devoted to cell motility and the mechanisms underlying directed cell motion from the subcellular single cell level to that of collective motion in multicellular tissues. **Angelika Manhart** addressed the question of how the properties of branched actin networks could be tuned by changing the composition of cofilin (an actin depolymerizing factor). She used mathematical modeling to show that cofilin binding changes the elasticity of actin filaments, which modulated the directionality of actin network growth, thereby directing cell migration. Going to a longer length scale, **Andreas Buttenschoen** showed using a cell based computational model that migrating cells interact with their extra-cellular matrix and can break it down by mechanically adapting to it, with implications for directed cell movements in several biological contexts. Considering even longer length scales, **Rachel Lee** showed that collective motion in epithelial cell clusters can be attributed to a jamming transition and involve an interplay between active cell motility, cell adhesion and cell-cell guidance. **Leah Keshet** gave an overview of her group's work over many years in which they have pioneered the use of mathematical models to couple mechanical interactions between cells to biochemical signaling pathways and thereby predict behavior both at the cellular level (cell migration) to the multicellular level (contractile waves in cell sheets). She highlight some "hot topics" in the field including how the interplay between chemical signaling and mechanical tension which can lead to directed single cell motion as well as collective behavior — in particular how tissue stiffness affects morphogenesis (which was recapitulated by the work from **Otger Campas**).

Several talks focused specifically on **cell movements at the multicellular level** and how cellular interactions led to emergent behaviors at larger length scales. These collective cell behaviors are important during many stages of embryonic development, wound healing and metastases of cancer cells. **Zoltan Neufeld** [8] discussed models for collective migration of cells in different types of geometries — from linear channels to cells in two-dimensional monolayers. Cell motility is regulated by mechanical interactions between cells and their stiffness, resulting in propagating waves. These models are similar to the ones presented by Keshet but extend them by the addition of the external environment as boundary conditions. **Calina Copos** talked about the mechanical coupling between stress fibers and the actin meshworks in cells and how this may facilitate mechanosensing. She continued on the theme of the mechanisms underlying coordinated movements of cells, focusing on the migration of a two-cell system in the ascidian, *Ciona*. She presented her work using computational modeling to study the coupling between actin assembly, actomyosin contractility, cell and extracellular matrix interactions and adhesions to uncover how mechanochemical coordination is achieved in this simple system for collective motion. Insights from this study will be applicable to more complex systems — as were discussed in other talks at the workshop. The theme of cell-cell versus cell-matrix interactions and the interplay between these was discussed again by **James Feng**, who talked about collective migration in neural crest cells, which form clusters that undergo spontaneous persistent migration. He explained this behavior based on models that include biochemical signaling pathways (e.g. modulation of Rho-GTPase) coupled with physical interactions (contact inhibition of locomotion and co-attraction). **Otger Campas** offered an experimental perspective on the mechanical regulation of tissue morphogenesis and how the coordinated motion and deformations of cells direct the elongation of the body axis in developing vertebrates [7]. He presented his work using deformable magnetic microdroplets embedded in tissue to obtain spatiotemporal maps of forces and mechanical properties of the tissue during growth in zebrafish embryos. His work revealed transitions between fluid-like and solid-like tissue states during morphogenesis and suggests that control of tissue mechanical properties could be a fundamental mechanism of morphogenesis. This session highlighted the common themes between mathematical models of collective cellular motion and sparked discussion regarding appropriate coarse-graining approaches that go beyond phenomenological models and can more naturally

yield the observed behaviors in cell aggregates. The session could have benefited from additional experimental speakers who could provide a more empirical perspective. Future workshops may wish to emphasize this aspect as advances in imaging and force measurement techniques are beginning to reveal collective behaviors that challenge existing models.

3.1.3 Microtubule organization

Microtubule organization and dynamics is important for many cellular processes including cell division, cell polarization and migration. **Holly Goodson** discussed her work on understanding the fundamental mechanisms underlying dynamic instability of microtubule filaments using computational models to study microtubule behavior at multiple scales from subunits to populations of filaments. Their work helps to establish how system level properties emerge from molecular characteristics in non-equilibrium systems and may be applicable to many biological systems. Returning to the cellular level, a number of talks in the workshop were devoted to studying the role of microtubules and associated proteins in cellular processes — in particular mitosis — in which proper segregation of chromosomes is achieved by the mitotic spindle. **Dan Needleman** spoke about how forces are coordinated to move the mitotic spindle in *C. elegans*. Using laser ablation to perturb the spindle and theoretical models, they have found that pulling forces drive various spindle movements. Their work establishes general principles for a quantitative understanding of spindle positioning and may be applicable to diverse systems. This work also emphasized the deep connections between different active matter systems (e.g. actin and microtubule networks). **Jay Gatlin** talked about experiments using in vitro reconstituted systems in microfluidic devices (to create tunable cell geometries) in order to examine the mechanisms underlying the positioning of the microtubule aster during cell division and dissected the relative roles of cortical pushing, cortical pulling and cytoplasmic pulling. In contrast to spindle positioning, they found that microtubule pushing forces at the cell cortex can generated forces at long length scales and contribute to aster positioning. Turning to theory and three-dimensional modeling, **Meredith Betterton** showed that the mechanical properties of kinetochores and their interactions with microtubules determine the attachment dynamics of mitotic spindles. **Alex Mogilner** talked about how mechanical positioning of nuclei in large multinucleated cells emerge from coordinated actions of microtubules and associated motors [6]. To explain this, he used mathematical ideas from a large body of work on spindle positioning to describe the possible force balance schemes. How the microtubule cytoskeleton interacts with actomyosin networks to create optimal force balance in cells is a topic that has been relatively less explored but would benefit from both experimental and computational approaches.

3.1.4 Intracellular transport and motor proteins

The interiors of cells are not random mixtures of chemicals but are spatially organized, across micrometer length scales and, e.g., in the case of neuronal cells, organized across millimeter scales and above. One of the major drivers of this organization is the action of molecular motors kinesin and dynein, which use microtubules as tracks. While the broad mechanism of these motors is understood, how they combine with microtubule organization and dozens of regulatory molecules to effect control of cell organization is an open mystery. The objects being transported are generically referred to as "cargo". As a first step between understanding how cargo is transported on a single microtubule, **Matt Bovyn** presented an experimental-theoretical collaboration on how motors confront an intersection between two microtubules [1]. The results demonstrate how the angle and separation of the microtubules can tune the "decision" made by the cargo on which route to take. **Alexandria Volkening** presented her work to understand the case where the cargo is a varicosity, pathological subcellular objects present in neurons following brain injuries. In his presentation, **Bill Holmes** discussed the case where the cargo is an insulin granule in pancreatic cells. The motion of these granules relative to the cell periphery not only explain pancreatic function but provide an example of non-Brownian motion, and, specifically, the mathematically curious case of non-Brownian motion near a boundary (in this case the cell boundary). The action of motors is regulated by molecules including microtubule-associated proteins or MAPs. A particularly visually-striking result was presented when **Jonathan Howard** presented striking images of a single MAP interacting with a microtubule using the technique of interference reflection microscopy.

3.1.5 Membrane organization

Another topic that emerged involves the organization of biological membranes, the lipid-bilayer-based elements that form barriers between cells and the outside world, and around many organelles. While the classical view of cell biology holds that these are fluid sheets that contain a few freely-diffusing embedded molecules, recent research is demonstrating much more complexity, and indeed the role of lipids is taking a backstage to the often dense embedded protein. Several talks discussed the spatial organization of these molecules in the quasi-two-dimensional membrane. For **Alan Lindsay**, the embedded molecules were receptors on a spherical cell ready to receive information from freely diffusing ligands. His work demonstrates that different spatial positioning of the receptors on the surface of the sphere leads to different reaction properties between the ligand and receptors. Interestingly, by assuming the diffusing ligand is emitted from a single source and studying (via simulation and analytic methods) how receptor binding varied as the location of the source changes, his work demonstrated the ability of a cell to sense its environment. This work helped emphasize the importance of surface molecule organization, a theme that was highlighted in several other talks. The driver of this spatial organization varied. In the case of **Daniel Fletcher** [3], it was due to the molecule size (normal to the plane of the membrane). In immune cells like macrophages performing phagocytosis ("eating" target pathogens), these molecules are pushed up against the target, and are thus pushed into specific regions depending on their size and how they interact with other molecules. In the case presented by **Ken Jacobson** [5], spatial organization arises non-diffusion-driven modes of motion. Finally, **Nathan Goehring** presented the example of PAR proteins on the membranes of *C. elegans*, where a dramatic advective motion is driven by the motion of the protein network below the membrane, made of F-actin and termed the cortex.

4 Outcomes

The activities at the workshop already have notable outcomes. Many of these outcomes emerged from the extended discussions following each presentation. For example, after a presentation in which Nathan Geohring hypothesized about the connection between a (yet-to-be-identified) molecule that flows along the cell membrane by interacting with the cell cortex, Ken Jacobson pointed out a strong, but as-yet-unnoticed, analogy with the behavior of the B Cell Receptor, which moves along the membrane and associated with the cortex with some similarities.

Many new collaborations emerged from the workshop. We queried the participants two weeks after the conclusion and have identified **9 new collaborations, some of which are already "underway"** (as stated by the participant in the survey). These include the exploration of using the MEDYAN software by Garegin Papoian's research group to accomplish objectives at the Allen Institute for Cell Science. Another example is between Alan Lindsay (Notre Dame) and Jay Gatlin (U Wyoming) on mathematical modeling of nuclear dynamics. Using experimental data from Gatlin lab and mathematical modeling by Lindsay, this collaboration aims to explain how the structure of the nuclear envelope changes in response to protein import. Yet another example is between Alan Lindsay and Angelika Manhart (CIMS, NYU) to build and analyze mathematical models to the explain the size, shape and spatial organization of nuclei in multiple-nucleated fly muscle cells. A description of one collaboration is particularly striking: "One person made a suggestion while at my poster and took it upon themselves to create some code for me. Then they spent 2.5 hours with me one afternoon teaching me how to use it, extending it, and brainstorming about the project."

4.1 The future of Mathematical Cell Biology

A discussion on the final evening of the workshop was dedicated to the future of the field of Mathematical Cell Biology. There was unanimous agreement that the idea of **"multiple scales"** (alluded to in the workshop's subtitle "across scales") was becoming more important. It is necessary to connect the tremendous progress in understanding single molecules (e.g., Jonathan Howard's work observing a single microtuble-associated protein with a single microtubule using Interference Reflection Microscopy) to understand how combinations of cells form robust structures in tissues (e.g., the migration of cells during development studied by Otger Campas). This will require new mathematical methods, and applied mathematics is particularly suited to the upcoming challenge of "multi-scale" biology.

Another discussion that emerged was the need to integrate new scientific communities, so that the progress of the Mathematical Cell Biology community continues to have maximal impact, and so that the frontiers of life sciences and other disciplines is integrated into our community:

- There is a particular need for the involvement of **control systems engineering**, where we are seeing hints that the lessons of control theory (in human engineered systems) are emergent in living systems as well.
- There was also a discussion about the appropriate involvement of medicine, here meaning specifically the development of **diagnostics and therapeutics**. This is one of the ultimate goals of biological sciences, and mathematical cell biology being no different. As we approach the integration of our communities, it will become increasingly important to involve diagnostics and therapeutics into meetings like this one.
- Finally, there was discussion about the role of bioinformatics, specifically the tremendous progress being made in **transcriptomics**. Here, the links between things like cell mechanics and transcriptomics is most cloudy: The evidence is unequivocal that the proteins being transcribed (and transcriptionally controlled) have a major impact on cell behavior, including the cell dynamics discussed at this workshop. Yet the nature of the link is unknown.

4.2 Participant surveys

Two weeks after the conclusion of the workshop, the organizers sent an anonymous electronic survey to the participants. There were 9 respondents (21%). All ranked it either 9 out of 10 (55.6%) or 10 out of 10 (44.4%) for overall quality. The formal talks were "of excellent quality and variety" and the informal parts of the meeting were "invaluable for sparking new research ideas".

Several comments indicated success in the quest to foster interactions between groups that do not normally interact. We received one comment that "it was super intense for me as a biologist to understand the math talks", a sign that our inclusion of traditionally non-mathematical fields is working (the same respondent scored the overall workshop 10 out of 10). Another said they "met a slice of the field that I don't normally cross paths with at normal meetings."

Suggestions for improvement on the scientific content included "synthesis sessions could be set aside for re-visiting related talks, coming to common ground...", and for posters, that there were "fewer than expected". A valuable suggestion we received in discussion with participants is the scheduling of a session dedicated to funding opportunities for mathematical cell biology.

5 Future impact

Of the many long-term goals of the field of Mathematical Cell Biology, the one identified by this workshop is to understand cells as signal processing machines, where the machinery is based on the spatial organization of the cytoskeleton, membranes, and the molecules with which they interact. We see evidence for future impact towards achieving this goal. This evidence includes:

- The (≥ 9) new collaborations mentioned above are expected to have an impact beyond the participants themselves, by promoting the idea of successful interdisciplinary collaboration. Many of these are examples of convergence across traditional disciplines, e.g., from Mathematics departments and Biology departments.
- The incorporation of new communities were roughly prioritizes as: Control systems, medical diagnostics and therapeutics, and bioinformatics/transcriptomics.
- The growing emphasis on multi-scale methods that connect single molecules to the behavior of groups of cells in tissues, organs and organisms necessitated the development of mathematics that works "across scales".

Beyond within this field, there are examples on both the mathematical side (e.g., asymptotic approximation methods) and experimental side (internal reflection microscopy) of progress in this field that we expect to have an impact in other areas of mathematical and biology. This workshop continues to provide a potent instance of convergence across scientific and mathematical disciplines.

References

[1] Jared P Bergman, Matthew J Bovyn, Florence F Doval, Abhimanyu Sharma, Manasa V Gudheti, Steven P Gross, Jun F Allard, and Michael D Vershinin. Cargo navigation across 3D microtubule intersections. *Proceedings of the National Academy of Sciences of the United States of America*, 115(3):537–542, 1 2018.

[2] Carlos Patino Descovich, Daniel B. Cortes, Sean Ryan, Jazmine Nash, Li Zhang, Paul S. Maddox, Francois Nedelec, and Amy Shaub Maddox. Cross-linkers both drive and brake cytoskeletal remodeling and furrowing in cytokinesis. *Molecular Biology of the Cell*, 29(5):622–631, 3 2018.

[3] Alba Diz-Muñoz, Orion D. Weiner, and Daniel A. Fletcher. In pursuit of the mechanics that shape cell surfaces. *Nature Physics*, 14(7):648–652, 7 2018.

[4] Leah Edelstein-Keshet. Models for Cancer Cell Motility: Regulation and Signaling. *Biophysical Journal*, 112(3):38a, 2 2017.

[5] Ping Liu, Violetta Weinreb, Marc Ridilla, Laurie Betts, Pratik Patel, Aravinda M. de Silva, Nancy L. Thompson, and Ken Jacobson. Rapid, directed transport of DC-SIGN clusters in the plasma membrane. *Science Advances*, 3(11):eaao1616, 11 2017.

[6] Angelika Manhart, Stefanie Windner, Mary Baylies, and Alex Mogilner. Mechanical positioning of multiple nuclei in muscle cells. *PLOS Computational Biology*, 14(6):e1006208, 6 2018.

[7] Alessandro Mongera, Payam Rowghanian, Hannah J. Gustafson, Elijah Shelton, David A. Kealhofer, Emmet K. Carn, Friedhelm Serwane, Adam A. Lucio, James Giammona, and Otger Campàs. A fluid-to-solid jamming transition underlies vertebrate body axis elongation. *Nature*, 561(7723):401–405, 9 2018.

[8] Rashmi Priya, Guillermo A. Gomez, Srikanth Budnar, Bipul R. Acharya, Andras Czirok, Alpha S. Yap, and Zoltan Neufeld. Bistable front dynamics in a contractile medium: Travelling wave fronts and cortical advection define stable zones of RhoA signaling at epithelial adherens junctions. *PLOS Computational Biology*, 13(3):e1005411, 3 2017.

[9] A. M. Turing. The Chemical Basis of Morphogenesis. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 237(641):37–72, 8 1952.

[10] L. Wolpert The mechanics and mechanism of cleavage. *Int. Rev. Cytol.*, 10:163–216, 1960.