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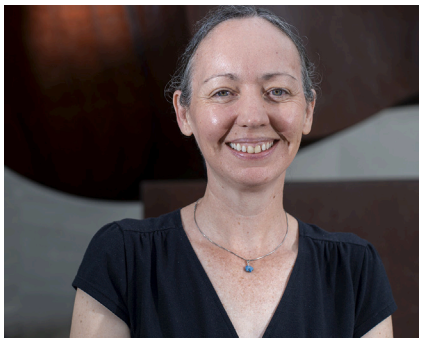
Cell
Leading Edge

Voices

Mechanobiology: Shaping the future of cellular form and function

Mechanobiology—the field studying how cells produce, sense, and respond to mechanical forces—is pivotal in the analysis of how cells and tissues take shape in development and disease. As we venture into the future of this field, pioneers share their insights, shaping the trajectory of future research and applications.

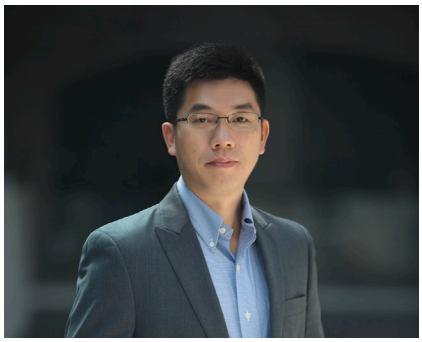


Celeste M. Nelson
Princeton University

The new mechanical era of biology

Over 100 years ago, before the discoveries that led to the modern genomics era, mechanics was central to cell and developmental biology. Wilhelm His, D'Arcy Thompson, and their contemporaries viewed living forms as exactly that: forms, which were subject to the same physical principles as nonliving matter. These viewpoints were sidelined by the gene theory of biology, which has both transformed our understanding of living systems and generated remarkable technological advances that allow us to peer deep inside individual cells, including the latest breakthroughs in single-cell and spatial-omics approaches. Cells and tissues are now defined by the panoply of genes that they express.

Yet, in many ways, we have come full circle. Appreciation for mechanobiology has increased with the discoveries of some of the genes and proteins that give cells and tissues their physical forms and that permit these living systems to generate and respond to mechanical forces. However, a true understanding of mechanobiology will require integration with gene theory and a parallel suite of technological breakthroughs in our ability to measure the mechanical properties and physical forces imposed upon and generated by living systems, ideally with high spatial and temporal resolution. Imagine being able to quantitatively monitor the elastic, storage, and loss moduli of a tissue, in real time, without fixing, freezing, or poking it. Or being able to measure the compressive or shear stresses that each cell in that tissue feels. Such measurements would help us to translate between the language of physics and that of the genome and open a new mechanical era in cell biology.



Bailong Xiao
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Feeling the force

Life is physical in nature and must follow the laws of physics. Mechanical force is an essential physical element that drives the formation and function of life. Cells utilize specialized force-sensing proteins such as mechanically activated ion channels to effectively convert mechanical forces into biological activities ranging from cell proliferation and differentiation to tissue development and homeostasis to the physiological senses of touch, pain, and hearing, which is generally termed mechanotransduction. The discovery and characterization of *bona fide* mechanosensors such as the evolutionally conserved and mechanically activated PIEZO channels, including PIEZO1 and PIEZO2 in mammals, has transformed our understanding of the mechanotransduction process at the atomic, molecular, cellular, physiological, and pathophysiological levels, which was recognized with the 2021 Nobel Prize in Physiology or Medicine. PIEZO channels utilize their elegant all-in-one structural designs and adopt physical principles such as force-induced deformation and lever-like mechanism to effectively and specifically convert piconewton levels of mechanical stimuli into a vast variety of cellular and physiological processes. I hope that we might harness the in-depth understanding of PIEZO channels to develop novel therapeutics for treating human diseases such as tactile pain and continue to identify and characterize novel force-sensing proteins that might mediate PIEZO-independent mechanotransduction processes, such as acute mechanical pain and hearing, which will provide a more complete understanding of how life might make the best use of forces.

Sara A. Wickström
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Mechanochemical feedback across scales

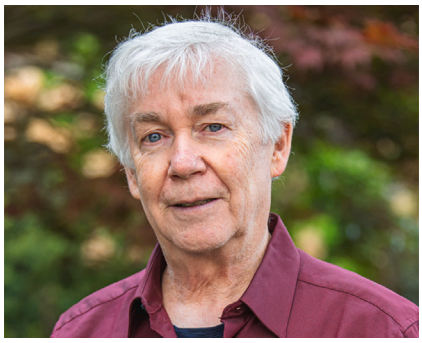
Research in the last decade has revealed the importance of mechanical forces in influencing most, if not all, aspects of cell behavior. However, mechanosignaling has often been understood as an independent input that operates on cellular and molecular scales to regulate signaling, metabolism, and gene expression. Emerging research, however, points to extensive feedback loops between mechanical force and biochemical signaling that operate across scales: tissue-scale mechanical changes can determine the length and timescales of biochemical signals, whereas biochemical signals alter the way cells and tissues perceive and transmit mechanical signals. The next decade of mechanobiology will focus on deciphering the exact nature of these feedback loops, explaining previously observed phenomena and predicting new interactions and emergent behaviors that arise from these interactions.

What is needed to achieve this? Developing ways to more directly image and quantify dynamic forces in living, moving tissues will be of central importance. Coupling these methods with more precise and subtle manipulations of the key molecular machineries involved in force generation, sensing, and transmission will be equally pivotal. Also, new theoretical and simulation approaches and new ways to integrate mesoscale phenomena and coarse-grained models such as vertex models with molecular-scale events and models are required. This integrative, multiscale approach will allow us to understand the rules of organ development, steady-state tissue maintenance, and pathological changes that drive initiation of disease.

Yves F. Dufrêne
Louvain Institute of Biomolecular Science and Technology, UCLouvain

Stress-activated catch-bond adhesions

While the mechanobiology of mammalian cells has been thoroughly investigated, the mechanics of bacteria have received less attention. However, the emergence of advanced biophysical techniques has enabled us to demonstrate that bacterial pathogens sense various mechanical cues generated by fluid flow and cell surface contact. Under external shear, bacteria and their surface molecules feature a variety of mechanical responses to enhance functions like motility and adhesion. One of the most exciting and important questions lies in understanding the mechanisms behind the formation of catch bonds, i.e., receptor-ligand bonds that, unlike most biological bonds, reinforce under mechanical stress. For many years, the widely studied, prototypical example had been the binding of the *Escherichia coli* FimH adhesin to mannose residues on epithelial cells. The FimH-mannose catch bond promotes strong adhesion under a high fluid flow rate during urinary tract infections. Recent reports showed that staphylococcal pathogen adhesins can also engage in catch-bond interactions with human host ligands, with a strength that is orders of magnitude higher than that of previously investigated biomolecular complexes. These ultrastrong catch-bond mechanisms of force-enhanced adhesion are believed to play a critical role in host and biomaterial colonization during infection. The grand challenges ahead include (1) to discover novel catch-bond mechanisms in pathogen adhesion, (2) to dissect the precise role of these stress-dependent interactions during host infection, (3) to understand the mechanistic molecular origins of catch-bond adhesion, and (4) to identify peptides or antibodies that interfere with adhesion mechanisms and develop anti-adhesive therapies to complement antibiotic treatments.



Daniel J. Cosgrove
Pennsylvania State University

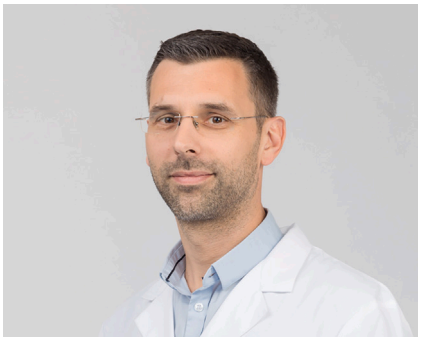
Mechanobiology of plant cell walls

The cell wall has emerged as a versatile leading actor in plant mechanobiology. With its ramifying 2D network of long crystalline cellulose microfibrils, the wall is the strongest cell organelle. At the same time, it is flexible and "alive" with numerous sensors (receptor-like kinases) that bind soft components (like pectin and signaling proteins) and initiate internal signals that quickly modulate wall growth and other cell processes. In a sense, the wall combines properties and roles of skin and bone in our bodies (protective, sensory, and structural). By transmitting tensile forces across organs, cell walls help coordinate organ-wide growth and morphogenesis. Remarkably, microtubules within growing cells often orient along the direction of maximal wall stress. Microtubules guide the deposition of cellulose microfibrils, thereby reinforcing the wall in the direction of maximal stress and reducing wall stress—a striking biomechanical feedback loop that is still mysterious. Genes and membrane processes respond dynamically to mechanical stimuli like wind, touch, and even the soft footsteps of a caterpillar on a leaf. Walls presumably transmit these forces. How do cytoplasmic and nuclear processes connect to and integrate such stimuli, which span vastly different forces and timescales? At the molecular scale, how are tensile forces transmitted within the structurally complex wall? Wall models that connect structure with mechanics have recently emerged: tensile and shear stresses within the cellulose network dominate force transfer. Are cellulose stresses sensed by the cell, or is another correlate of wall stress involved? Much remains to be discovered!

Carl-Philipp Heisenberg
Institute of Science and Technology Austria

Diversity counts

Studying cell and tissue mechanics is not a transient fashion but an indispensable effort in understanding morphogenetic processes in biology. Previous work has provided crucial insight into how the crosstalk between biochemical and mechanical signals orchestrates morphogenesis. This has led to the identification of core functional morphogenetic modules based on the overall principles and patterns dictating their organization. While this represents a major step ahead in understanding the mechanochemical basis of morphogenesis, the evolutionary adaptation and physiological modulation of these morphogenetic modules still remain to be uncovered. For instance, different aquatic animals are exposed to water of very different osmolarities, resulting in osmotic forces that can vary by orders of magnitude. Also, the specific internal metabolic state of an organism can have profound effects on morphogenetic processes not only by providing energy but also by metabolic enzymes and metabolites directly interfering with the cell cytoskeleton. Studying the evolutionary adaptation and physiological modulation of these morphogenetic modules requires moving beyond established model organisms and analyzing non-model organisms at key points of the phylogenetic tree and in varying environmental conditions reflecting their natural habitat. Such a comparative approach focusing on diversity will help not only by unveiling how morphogenetic modules are adapted and modulated in different species but also by extracting their core design principles. With gene editing tools and imaging techniques becoming more broadly applicable and theoretical modeling approaches becoming more powerful in conceptualizing experimental observations, this next step in mechanobiology is within reach.



Sirio Dupont
University of Padova Medical School

Force dictates function

I was brought to mechanobiology by the stunning observation that forces not only constrain the shape of cells and propel the morphogenesis of tissues but also act as true signals to steer cell behavior. In its simplest display, this entails the remodeling of cytoskeletal and adhesion structures to resist forces. However, this can have more profound effects, including the coordinated rewiring of organelles' functions, metabolic pathways, gene transcription, and epigenetics and thus, ultimately, cell fate. This subversion of the "function dictates form" principle provided a powerful concept to explain how tissues adapt to forces and indicated the possibility that altered forces can promote disease. Yet, while some important tiles of this puzzle have been identified, we are far from approaching a complete picture, and many exciting questions and challenges remain for the future. How is the force-dependent remodeling of cell structures encoded and transmitted to the rest of the cell? How many mechanotransduction pathways exist, how general are they across cell types, and how are they conserved in evolution? What are these pathways' players, and what is their requirement in tissue physiology and disease? Can we build on this knowledge to identify markers and visualize the mechanoresponsive status of a cell in a tissue? Can we understand the underlying molecular mechanisms to the extent that we can design drugs that control the ability of cells to respond to forces? If we can drug molecular mechanisms of mechanobiology, is this going to hold the promise of the development of mechanomedicine therapy approaches?

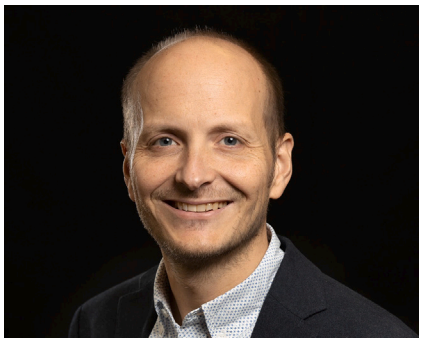
Amy E. Shyer & Alan R. Rodrigues
The Rockefeller University

Mechanobiology of the supracellular

How biological systems obtain their shape and structure is a fundamental question with many practical implications. Like much of biology, over the last several decades, tissue and organ morphogenesis has focused on uncovering regulatory mechanisms at the cellular and subcellular scales. Such studies have either implicitly or explicitly reified the view that the creation of form is instructed or controlled by a combination of genetic, biochemical, and cell biological processes.

However, pioneering early 20th-century investigators such as Conrad Waddington and Paul Weiss cautioned against the total subsummation of developmental biology by, for instance, molecular biology. By coining terms such as "epigenotype," they argued for the significance of processes beyond the cellular scale that were inextricably based on mechanical processes ("Entwicklungsmechanik" or developmental mechanics). In our view, one of the most important roles of mechanobiology is to help uncover epigenetic regulation beyond the cell at the "supracellular" scale.

Uncovering conserved processes at the supracellular scale is critical in large systems composed of many cells (e.g., vertebrate organs and tumors) where levels of organization beyond individual or small clusters of cells arise. Supracellular levels of organization can have mechanical properties that are emergent and therefore not discernable through cell scale analysis alone. Moreover, such supracellular mechanics can exhibit top-down influence (via mechanotransduction) and therefore have causal influence over lower levels of organization (e.g., gene expression and cell behavior and fate). We envision that rigorous and imaginative use of physical concepts will lead to breakthroughs in the organizing role of the supracellular scale in morphogenesis.



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Institute for Bioengineering of Catalonia, BIST, ICREA, and CIBER-BBN

Toward synthetic mechanobiology

As scientific fields mature, they evolve from primarily generating fundamental knowledge to being able to engineer controlled systems. In the field of cell biology, this evolution has led to the advent of synthetic biology, a discipline that designs gene circuits to engineer specific cellular responses to specific stimuli. In current synthetic biology, the main components of the engineered system—comprising the stimulus, the internal processing, and the resultant cellular behavior—are predominantly biochemical. Yet, mechanobiology has taught us that cells can interpret mechanical cues, that regulatory mechanisms can be tuned by physical forces, and that cellular responses can be physical in nature, such as motility or deformation.

Mechanobiology is rapidly reaching a level of understanding that will lead to the emergence of "synthetic mechanobiology." This progress will allow us to engineer cells that respond to mechanical stimuli, with applications such as softening abnormally stiff tissues in diseases like cancer or fibrosis. Another potential application might be engineering immune cells equipped with mechanochemical feedback loops to adapt their motility to their mechanical environment, improving immune infiltration in immunotherapies. At the supracellular scale, the generation of programable cellular layers capable of undergoing folding patterns will enhance regenerative responses and enable the design of multifunctional biohybrid devices.

As we begin to tackle these challenges, we still need to strengthen our fundamental knowledge of mechanobiology, including better understanding mechanotransduction mechanisms, their processing, and their integration with material properties of cells and their extracellular matrix.

Alba Diz-Muñoz
European Molecular Biology Laboratory (EMBL)

Greater than the sum of their parts

Generating the multeity of cell shapes present across the tree of life requires mechanical balance, whereby structure and integrity are maintained while simultaneous dynamic processes such as nutrient exchange and cell division take place. This adaptability of living materials stems from their active, dynamic nature and continuous turnover, setting them apart from their nonliving counterparts. Thus, to understand cellular materials, we must study them in both space and time. But how do we precisely—and quantitatively—describe mechanical parameters and their dynamics across the scale of an entire cell, all while maintaining sufficient spatial resolution? Tackling this challenge will require scale-bridging approaches and demand the integration of expertise from biology, physics, and engineering. I envision that this will lead to conceptual breakthroughs emerging from a deeper understanding of cells' out-of-equilibrium nature and of emergent phenomena arising from the coupling of diverse components in the cellular composite.

This is an exciting time to study mechanobiology, a field that fosters collaborations across some diverse communities but also ignites others. The identification of unifying biophysical principles that apply across scales and life kingdoms, along with the discovery of novel mechanochemical principles, will open up new therapeutic frontiers. Mechanomedicines represent an exciting and innovative approach to treating disease and combating the effects of age-related degeneration, showcasing the interdisciplinary power of cell biology viewed through the prism of materials science, a vision that I can easily foresee!

DECLARATION OF INTERESTS

S.A.W. is affiliated with the Stem Cells and Metabolism Research Program and the Helsinki Institute of Life Science at the University of Helsinki.