Moving beyond molecular mechanisms

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A major goal in cell biology is to bridge the gap in our understanding of how molecular mechanisms contribute to cell and organismal physiology. Approaches well established in the physical sciences could be instrumental in achieving this goal. A better integration of the physical sciences with cell biology will therefore be an important step in our quest to decipher how cells work together to construct a living organism.

Over the past 60 years, the field of cell biology has been firmly rooted in understanding the molecular basis of complex cellular processes including genome replication, migration, metabolism, and adhesion. This progress has been enabled by advances in molecular biology, biochemistry, physical chemistry, single-molecule physics, and microscopy. Bringing together these disciplines has been successful in identifying the molecular composition of macromolecular machines, characterizing the structure and physical properties of single proteins within cells, reconstituting complex macromolecular machinery in vitro, and imaging the dynamics and function of these machines in vivo.

Despite this amazing progress, a major challenge facing cell biology is understanding how the chemical and physical properties of molecular machinery come together to guide cell processes. How do varied physical and chemical signals in the environment determine whether a cell survives, proliferates, or migrates? What circuitry allows for a complex body plan to be constructed out of a single-celled embryo? The signals in the environment are noisy, with fluctuations in both time and space. Moreover, as anyone who has tried to characterize cells is aware, cell phenotypes are variable both across individual cells and within a single cell over time. In the presence of all this noise, cells execute some processes exceedingly reliably (e.g., DNA segregation in cell division). Others, such as the determination of protrusive activity in a migrating cell, appear to be more variable. How does this complex network of stochastic chemical and mechanical machinery enable robust and complex decision making at the cell scale?

The answers to these questions require knowledge of cell structure at the scale between single molecules and whole cells (Fig. 1). This intermediate, or mesoscopic, length scale has different names depending on who you ask. You can think of it as a "system" or interconnected network of biochemical interactions that provide a logic circuit as to how cells process a signal to decide on an output. It can be a subcellular machine consisting of a collection of macromolecules designed to work together for a desired mechanical output, such as cargo transport, DNA segregation, or cell movement. There is a significant gap in our understanding at this scale. To make an analogy between a cell and a car: most of us have a good understanding of the car's component materials (e.g., rubber, metal), and in some cases we understand the individual machines that make up parts of the whole (e.g., the engine, transmission). However, we do not have a good understanding of the essential control parameters of the machines or how these are wired together to form productive, more complex machinery (e.g., creating the forward, backward, and turning motions). Understanding the control parameters that regulate macromolecular assemblies, and how these are wired together to enable complex cell outputs, represents an exciting frontier in cell biology.

Many areas of the physical sciences have been devoted to studying how collections of objects work together to construct a material or machine. In this construction, new properties emerge that could not be predicted or understood by studies of objects in isolation. For instance, electrical engineers need to know how circuit elements are connected in order to predict the circuit response. Or, in condensed matter physics, interactions between atoms and/or molecules result in properties such as elasticity or viscosity. In these areas of science, it is well appreciated that knowledge of individual components (in isolation) cannot predict the output of the entire system. By analogy, this would imply that understanding the molecular components of a cell, which has been the gold standard of cell biology, is insufficient. As cell biology starts to address questions wherein cells are thought of as "systems," "materials," or "machines," there are numerous challenges that can be informed by approaches that have proven successful in the studies of materials and machines in the physical world.

Developing a common community

Cell biology is an inherently multidisciplinary science, requiring approaches from genetics, chemistry, physics, applied mathematics, and engineering. While biochemical and genetic approaches

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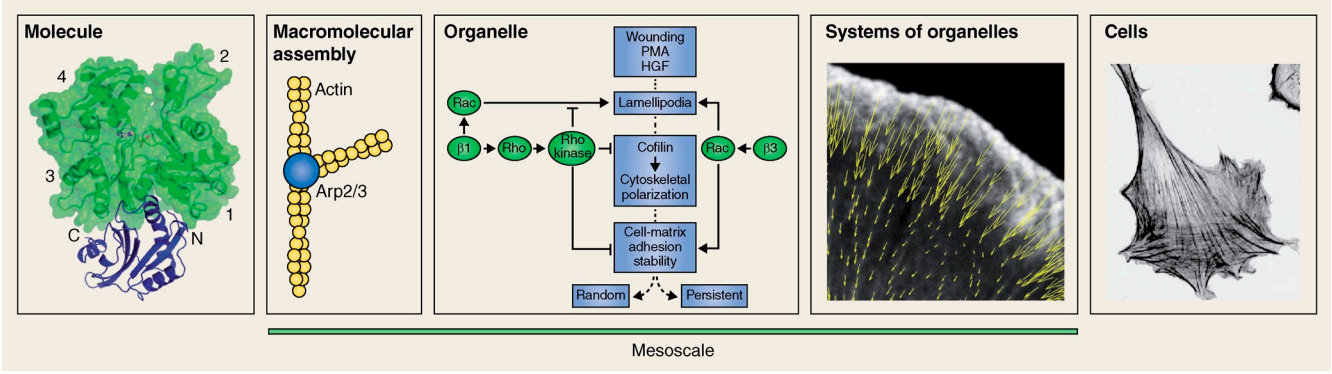

Figure 1. **The scales of cell biology.** Shown are images illustrating the range of scales in cell biology. At the smallest ($\sim 10^{-9}$ m) is that of molecules represented by the structure of G-actin (left; reproduced from Paavilainen et al. 2008. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.200803100) and the largest (10^{-5} to 10^{-4} meters) is that of cell physiology, represented by a migrating fibroblast with a labeled actin cytoskeleton (right; image courtesy of Patrick Oakes). In between these length scales reside: macromolecular assemblies (10^{-8} to 10^{-7} m) of individual proteins, represented by a schematic of an Arp2/3-mediated F-actin branch (second from the left); and organelles (10^{-7} to 10^{-5} m), such as lamellipodia (third from the left), which are formed by the integration of macromolecular assemblies into a mechanochemical machine depicted as a pathway diagram. At the next level are organelle systems (10^{-4} to 10^{-5} m) that integrate organelles together for a specific aspect of cell physiology, represented by a fluorescent image of actin overlaid with vectors of actin flow at the leading edge that result from the coordination of numerous regulatory organelles across the cell (second from the right; reproduced from Thievessen et al. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201303129). Understanding the processes at this intermediate scale will greatly aid in our knowledge of how molecules construct living cells.

have been successfully integrated into the field, other disciplines require more effort. Physical scientists that join the field of cell biology retain the training and language from their physical discipline, which has been specialized for specific purposes. Applied mathematicians, condensed matter physicists, and mechanical engineers all have unique perspectives on how to model complex biological phenomena (Fig. 2). This has led to the development of parallel theoretical and experimental approaches for modeling cell biological phenomena that are difficult to directly compare or rigorously test. A challenge for the future is to develop a community of researchers that will integrate these diverse physical approaches to identify strengths, resolve differences, and determine the best approaches for modeling cell behaviors.

Precision in language

One of the simplest solutions to implement is to develop a consistent and precise language to describe measurements or ideas. In my field, which centers on how mechanical forces are sensed and generated by cells, terms like "mechanosensing" or even "stiffness sensing" are used without precision, resulting in confusion of what is known versus just "thought to be true." Precision of language is essential for standardizing experimental protocols and measurements and in being able to clearly communicate conclusions and ideas.

Construction and validation of physical methods

One historical role of physical scientists in biology has been the introduction of new experimental and analytical tools. Some of these tools, such as microscopy and scattering techniques, have been developed extensively. However, in other cases, the nature of measurements require small apparatuses that can be difficult to replicate or operate (magnetic tweezers are a notorious example), making it difficult for other laboratories to build upon this knowledge. Similar issues arise in analysis and methods. It is extremely important for these methods to be used and validated by different laboratories to confirm results independently and by many individuals so that the language used to describe physical concepts and results can be made more precise. Being able to directly compare two different measurement techniques so that the same parameters can be used is essential for resolving discrepancies.

Even though the goal is to understand cell physiology, model testing will require physical characterization that may not immediately inform a biological process. To use an analogous example: the work in basic materials science of magnetism that needed to be performed before we could construct and build computer hard drives. It is my hope that the cell biology community will remain interested in these advances in characterization of biological materials and systems, as they are crucial to uncovering synergies that are not currently apparent.

Feedback between modeling and experiments

In the physical sciences, research has evolved so that individuals typically focus on either theory or experimentation. Of course, each of these can be further subdivided into analytical theory versus computer modeling, as well as sample preparation versus characterization. This specialization has emerged as both the questions and fields themselves become more mature. It also has led to a vigorous feedback between theoretical prediction, experimental measurement, and new materials development. To be useful, models need to be falsifiable. There is increasing evidence that many of the models used in biology are over-parameterized and, consequently, difficult (or impossible) to falsify. That is, when parameters are assigned with molecular-level details, the number of parameters quickly becomes large. In these scenarios, changes in the parameter value have little effect on the model predictions and make it difficult to verify the accuracy of the model (for more details, see

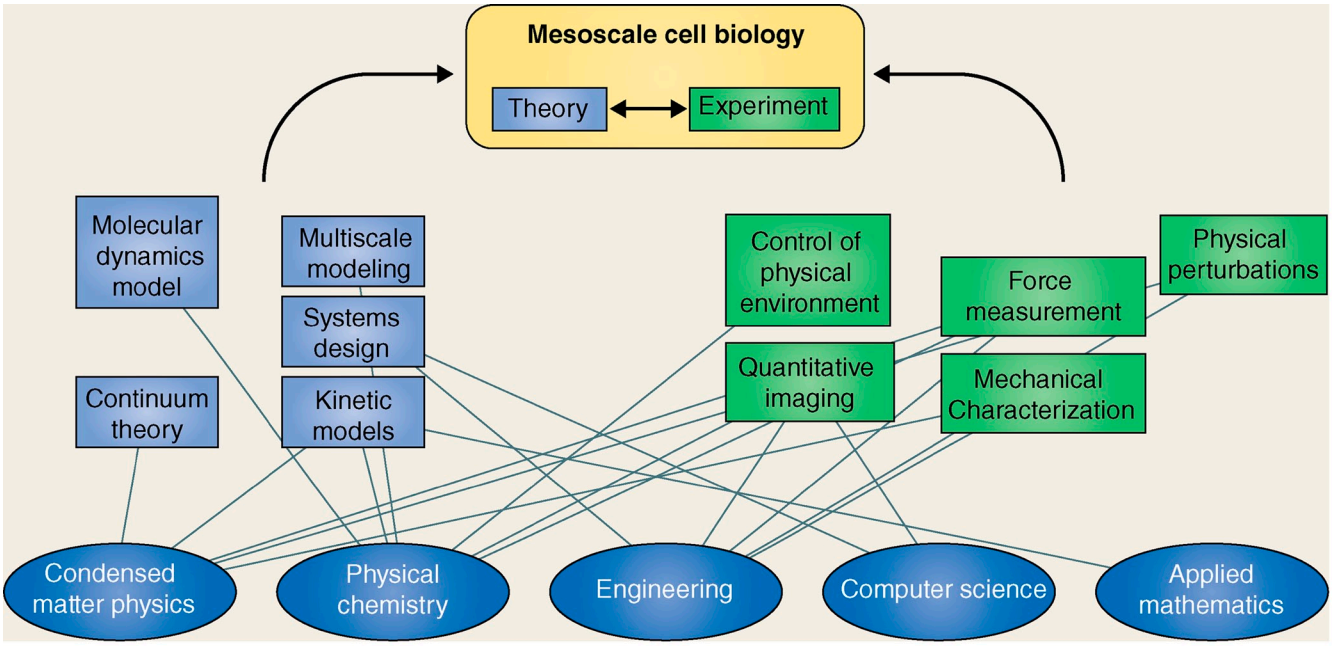

Figure 2. **The integration of physical sciences with cell biology.** A flow chart showing examples of how various disciplines from the physical sciences (bottom) have optimized a variety of theoretical/modeling tools (left) as well as experimental techniques (right) that have been applied to cell biological problems. However, these experimental and theoretical tools have been optimized for their home disciplines. A current challenge is to systematically have them benchmarked against each other and identify their weaknesses and strengths before using them to provide a new framework optimized for mesoscale cell biology.

http://www.lassp.cornell.edu/sethna/Sloppy/). Identifying order parameters that encompass the physical quantities or metrics (e.g., elastic modulus, organelle transport) that make up many of the molecular details is essential for developing models with fewer control parameters. Such order parameters will provide crucial insight into understanding regulation of the individual macromolecular machinery.

The word mechanism in cell biology typically refers to a molecular mechanism that is explored rigorously by genetic and biochemical testing. Understanding the physical mechanism requires both identification of the parameters controlling a system and then elucidation of the regulation of parameter values. Thus, seldom does a single molecular mechanism tie directly into a physical parameter. Moreover, understanding how molecular interactions give rise to a single physical parameter is not straightforward, and may require years of work. It is quite natural to apply models and approaches that we have used to engineer machines, such as the flow of decision making in electrical circuits or mechanic designs. However, cells are working under different sets of constraints, and a future challenge of understanding cellular machines is that completely different design principles may be used.

Establishing a culture that encourages dynamic feedback between theory, experimentation, and physiology is crucial to advancing the integration of physical sciences with cell biology. A potentially very exciting possibility is that understanding the physical mechanisms controlling biological machines will enable a completely new set of design principles that provide insight into how living cells are able to respond and adapt to highly variable environments. This will enable understanding of how these states change during disease progression and the capability of engineering biological cells to maintain a healthy phenotype.

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