

Living matter—nexus of physics and biology in the 21st century

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ABSTRACT Cells are made up of complex assemblies of cytoskeletal proteins that facilitate force transmission from the molecular to cellular scale to regulate cell shape and force generation. The “living matter” formed by the cytoskeleton facilitates versatile and robust behaviors of cells, including their migration, adhesion, division, and morphology, that ultimately determine tissue architecture and mechanics. Elucidating the underlying physical principles of such living matter provides great opportunities in both biology and physics. For physicists, the cytoskeleton provides an exceptional toolbox to study materials far from equilibrium. For biologists, these studies will provide new understanding of how molecular-scale processes determine cell morphological changes.

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The distinction between being “alive” or “not alive” has been a long-standing question for those interested in our natural world. In many ancient cultures, the difference between living organisms and inorganic matter was thought to be due to innate differences arising from a “vital force,” such that biology operated with different fundamental properties than the physical world. The ability to disprove such theories came about over the course of the 17th to the 19th centuries, as scientists developed theories of atoms and were able to synthesize organic matter from inorganic constituents. Over the past 100 years, developments in molecular biology and biochemistry have provided a wealth of information on the structure and function of biological molecules, much of which was acquired in collaborations between physical and biological scientists. Application of X-ray-scattering techniques first developed to study metals enabled discovery of the structure of complicated biological molecules ranging from DNA to ion channels. Use of laser trapping techniques first



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developed to trap and cool atoms enabled precise force spectroscopy measurements of single molecular motors. We now know that biological molecules, while more complicated than their inorganic counterparts, must obey the rules of physics and chemistry.

This wealth of molecular-scale information does not directly inform the behaviors of living cells. The organelles within cells are made up of complex and dynamic assemblies of proteins, lipids, and nucleic acids, all immersed within an aqueous environment. These assemblies are somehow able to build materials that can robustly facilitate the plethora of morphological and physical behaviors of cells at the subcellular (intracellular transport), cellular (division, adhesion, migration), and multicellular (tissue morphogenesis, wound healing) length scales. The dynamic cytoskeleton transmits information and forces from the molecular to the cellular length scales. But what is it about the behaviors of biological molecules that endow cells with the ability to respire, move, and replicate themselves robustly—all qualities we consider essential to “life”? For these questions, understanding of the physics and chemistry of systems of biological molecules is needed. Interactions that occur within ensembles of molecules lead to emergent properties and behaviors that cannot be predicted at the single-molecule level. These emergent chemical and physical properties of living matter are likely fundamentally different from inorganic or “dead” materials. Discovering the underlying principles of living matter provides fantastic opportunities to learn new physics and biology.

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The fields of condensed matter physics and materials science study the physical properties that emerge when objects (e.g., atoms, molecules, grains of sand, or soap bubbles) are placed in sufficiently close proximity, such that interactions between them cannot be ignored. Interatomic or intermolecular interactions give rise to emergent properties that are not seen in isolated species. Familiar examples involve electron transport across a material or a material's response to externally applied magnetic fields or mechanical forces. These emergent properties, such as conductivity, elasticity, and viscosity, enable us to predict the behavior of a collection of objects in these condensed phases. In this paper, I will focus on my perspective of how approaches to understanding the mechanical properties of physical materials can inform understanding of the mechanical properties of living matter found within cells.

In a crystal of metal, precisely organized atoms are located nanometers apart, and the energies of their interactions are on the scale of an electron volt (40-fold larger than thermal energy or twice the energy released on the hydrolysis of a single ATP molecule). These give rise to an energy density, or elastic modulus, on the order of gigapascals, which underlies the rigidity of metals. For small deformations, the restoring force between atoms means that this metal behaves like an elastic spring: after a force is applied, the metal returns to its original shape. Understanding force transmission through crystalline metals was facilitated by the development of elasticity theory in the 16th and 17th centuries. Fluids, such as water, lack crystalline order, but predictive understanding of fluid flows and forces was captured through development of theories of fluid dynamics. Now think of another material, Silly Putty, which behaves elastically at short timescales (it bounces like a rubber ball) but then oozes and flows at long timescales, acting like a viscous fluid. Silly Putty is made of long polymers that are trapped by one another at short timescales, but thermal energy is sufficient to allow them to diffuse and translocate at long timescales. Silly Putty is also a "soft material," in that the polymer's interaction energies are at the thermal energy level, and its length scale is at the micrometer level. Materials like Silly Putty were thought to be too complicated for analytical theory. It was only in the middle of the 20th century that the theoretical framework to understand these "messy" and "disorganized" polymer-based materials was developed.

The most powerful theories for understanding these vastly different forms of physical matter were developed in the absence of even the simplest of computers. The theories relied on developing physical properties or parameters to describe the material with a "mean field," a type of coarse-graining that identifies the essential properties of individual constituents and interactions but ignores many other details. These mean fields give us new intuitions concerning the origin of material properties and give rise to definitions of physical parameters, such as elasticity and viscosity. However, these theories also require materials that do not jostle around a lot and remain close to equilibrium. In fact, understanding materials "far from equilibrium" has been identified as a major challenge in physics for the next century (National Research Council, 2007).

Materials formed by dynamic protein assemblies in the cytoskeleton are disorganized, heterogeneous, and driven far from equilibrium. Motor proteins generate local stresses, and their activity is spatially modulated. The polymerization and depolymerization of cytoskeletal polymers is controlled by a myriad of regulatory proteins. All these dynamic molecular processes endow the cytoskeletal assemblies with unique behaviors that enable them to support complex physiological tasks. It is likely these dynamics also provide underlying robustness of the cells in

response to fluctuating and changing environments. These properties make living cells exquisite materials that cannot be captured by existing frameworks of physical matter. I suspect that we have not yet identified the important parameters needed to characterize their properties. The rich dynamics created by active biological matter present a formidable challenge in the area of materials science.

How do we hope to understand the properties of these complex cytoskeletal assemblies and materials? It may seem as though understanding cytoskeletal machinery is an insurmountable feat, the approaches that have been successful for physical materials will not work, and we must rely on complex simulations that require modeling of all individual components. This may be true. However, I think that this is a pessimistic view. Just consider how complicated physical materials would be if we did not have the appropriate parameters to describe the macroscopic responses and had instead become obsessed about knowing the details of all the interactions between underlying atoms and molecules? In the same vein, I believe that predictive insights into biological matter will emerge through development of new physical theories that use mean-field approaches to understanding materials that contain active components and are driven far from equilibrium. The burgeoning field of active-matter physics is currently considering these questions (Ramaswamy, 2010). However, these theoretical approaches require physical measurements of cells and cellular proteins that may not be clearly linked to a physiological process or have a clear biological context. Materials built from cytoskeletal proteins *in vitro* should also provide an excellent source of experimental measurements, but closer collaboration with theorists working in this field and collaboration between biochemists and experimental physical scientists is needed to develop control over such materials. Developing predictive physical theories of the cytoskeleton will elucidate principles of why "the whole is more than the sum of its parts" that will provide greater control and design over living matter, in the same way that engineering has provided great advances in applications of materials from the physical world.

What do biologists gain from theories of living matter? These theories will provide a crucial link between molecular and cellular length scale behaviors and will provide insight into the mechanisms of why specific molecular perturbations alter cell behavior. Moreover, they should provide us with general design principles of living matter. What are the basic aspects of a machine needed to separate chromosomes, establish polarity, or generate contractile forces that is utilized across different cell types? Can knowing these aspects provide insight into the evolution of cellular machines and the robustness of cell behavior? Thus, study of cellular materials both provides new opportunities for physicists and will provide crucial predictive understanding of cell physiology.

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