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# Forum

# The Material Basis of Life

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**The manner by which the organization and behaviors of cells arise from the activities of their constituent molecules remains poorly understood. Approaches from the physical sciences for studying collective properties may help with this difficult problem, but they must be adapted to account for the specific attributes of biological molecules.**

## Subcellular Organization Arises from Collective Behaviors of Biomolecules

Despite tremendous achievements in biology, we lack predictive theories of even the most well-studied subcellular processes. A fundamental challenge is that it remains unclear how to understand the collective behaviors of biological molecules that ultimately give rise to cell biology, in part because much of biology has focused at the molecular level, while the collective properties of matter have primarily been studied by researchers in the physical sciences. Advances in both these areas have now led to exciting opportunities at their interface: to establish principles underlying the collective behavior of biological molecules and to explore their implication for cell biology. The resulting interdisciplinary efforts will enrich both the biological and physical sciences, and will provide a basis to formulate theories of subcellular organization.

What are collective behaviors and how can they be studied? The basic idea is simple: individual molecules of water are not wet and the individual molecules that compose glass are not brittle, the wetness of water and the brittleness of glass are collective phenomena that arise from the interactions of billions of molecules. The simplest molecules organize into gases, liquids, or solids, depending on conditions, with drastically different collective priorities. Thus, while a water molecule is chemically the same in ice and vapor, ice cubes and water vapor behave differently from one another. The detailed theoretical understanding of the behaviors of the simplest fluids and solids provide a quantitatively accurate description of a vast number of situations of interests, with predictions that are so successful that they are widely used in engineering. However, such theories are only valid in a limited range of circumstances. For example, while use of the simplest fluid theory is an intrinsic aspect of modern aircraft design, this theory breaks down near the speed of sound, necessitating a more elaborate theory. So how can we know which theory applies to a system of interest? The general procedure, which is the cornerstone of physics, was succinctly stated by Richard Feynman: 'First, we guess...Then we compute the consequences of the guess, then we compare the computation results to nature, or we say compare to experiment or experience. If it disagrees with experiment, it's wrong.' This process only works if the consequences of the theory can be unambiguously determined and unambiguously compared with experiments, hence the importance of mathematical theories and quantitative experiments.

## Soft Condensed Matter Physics and Collective Behaviors of Biomolecules

The large molecules that are ubiquitous in biology rarely form simple fluids or solids: their behaviors, individually and collectively, are usually different from smaller molecules. Polymer networks exhibit unusual mechanical properties, resisting like a solid when quickly deformed but flowing like a liquid at longer times. Elongated molecules, such as cholesteryl esters, can form partially ordered, liquid crystalline states in which they spontaneously orient with each other while remaining positionally disordered. Lipids self-assemble into mesoscopic structures: micelles, vesicles, and networks. The quantitative study of such complex materials is the domain of soft condensed matter physics [1]. In soft condensed matter physics, an intimate interplay between quantitative experiments and theory has been used to understand a wide variety of specific phenomena, and a general framework has been constructed for describing the behaviors and collective properties of these systems. The great success of soft condensed matter physics in studying biological materials has inspired many researchers to propose that principles from that field might help explain the collective organization of molecules in cells [2–4]. This work is providing novel perspectives on difficult biological problems and is inspiring a range of new experiments. While highly promising, there are many challenges in combining conventional soft condensed matter physics with cell biology. One difficulty is that much of soft condensed matter physics is grounded in the assumption that the system under consideration is at or near equilibrium, meaning that its structure and behavior are determined by its free energy. A systems free energy results from the energetics of molecular distortions and interactions, so ultimately the properties of these systems arise from molecular energetics. Life, however, is far from equilibrium.

## Subcellular Structures are Out of Equilibrium

There is one way to be in equilibrium and many ways to be out of equilibrium: the mathematician John von Neumann said that attempting to develop a theory of non-equilibrium systems is like attempting to develop 'a theory of non-elephants'. Luckily, when studying cell biology we only need to understand systems that are non-equilibrium in the manner that cells are non-equilibrium. But what manner is that? It is helpful to consider three different ways to be out of equilibrium: (i) a system can be prepared in a non-equilibrium state, and

allowed to relax without any energy input; (ii) energy entering through the systems boundaries can drive it out of equilibrium; or (iii) energy can enter at the molecular level.

### No Energy Input

The simplest scenario is a system that is prepared in a non-equilibrium state and relaxes without any energy input, for example, a supersaturated protein solution that eventually forms crystals (Figure 1A). While the resulting crystals can be well described by equilibrium physics, the nucleation and growth of the crystal is a non-equilibrium process. Molecular energetics may still fundamentally determine the properties of these systems, but equilibrium processes are not sufficient to characterize their evolution. Other systems may never truly equilibrate, because the time to reach equilibrium may be extremely long, so the structures seen to form depend on the systems dynamics. For example, even when fully assembled capsids are the equilibrium configuration of viral capsid proteins, the fraction of capsids that actually perfectly form depends on the assembly pathway [5].

### Energy Entering at the Boundaries

Systems can also be forced out of equilibrium by inputting energy, forming non-equilibrium steady states that are radically different from equilibrium systems. There is a long history of studying non-equilibrium pattern formation in driven systems [6]. A paradigmatic case is a liquid heated from the bottom and cooled from the top: if the temperature difference is large enough, then the liquid will spontaneously flow and organize into convection cells (Figure 1B). This instability, known as Rayleigh–Bénard convection, is an example of a non-equilibrium steady state generated by energy flowing in through the boundaries. Just as in equilibrium, the material properties in such systems ultimately arise from molecular energetics, but the energy entering through the boundaries can drive complex, out of equilibrium behaviors.

### Energy Entering at the Molecular Level

Many cell biological systems, including the spindle, nuclear structures, and the Golgi apparatus, are non-equilibrium, steady-state structures, maintained by constant energy influx [7,8]. In these systems, which are said to be 'self-organizing', energy does not flow in through the boundaries, but enters at the molecular level. This constitutes a fundamentally distinct type of non-equilibrium system known as 'active matter' (Figure 1C) [9,10]. The molecular input of energy causes active matter to differ from equilibrium materials, and the other types of non-equilibrium systems discussed above, at the most basic level.

## Subcellular Structures are Active Matter

In equilibrium, the rate of all molecular processes is exactly balanced by the rate of the reverse process. This phenomena, called detailed balance, means that there are no net cyclic processes in equilibrium: the rate forward through any series of states exactly equals the reverse rate through those states (Figure 2A). For example, the acetylcholine receptor can exist in three states: closed, closed-bound to ligand, or open-bound to ligand. In an equilibrium *in vitro* experiment, the rate of transition through the cycle closed to closed-bound to opened-bound back to closed, is perfectly balanced by the rate of transition through the cycle closed to open-bound to closed-bound back to closed (Figure 2B); that is, no net cycles. Inside cells, the ratio between ATP and ADP and the ratio between GTP and GDP are kept far from their equilibrium values by cellular metabolism. This source of free energy acts like a battery that can be tapped by coupling protein conformational changes to nucleotide hydrolysis, which biases the rates of reactions and allows detailed balance to be broken [11]. For example, tubulin-GTP is primarily incorporated into assembling microtubules. Hydrolysis occurs and tubulin-GDP is released during microtubule disassembly, whereupon tubulin-GDP can be converted to tubulin-GTP, which is a net cycle that violates detailed balance (Figure 2C). ATP hydrolysis by molecular motors can drive a cyclic steady state, which is not possible in systems with detailed balance, whereby motors bind and release cytoskeletal filaments and

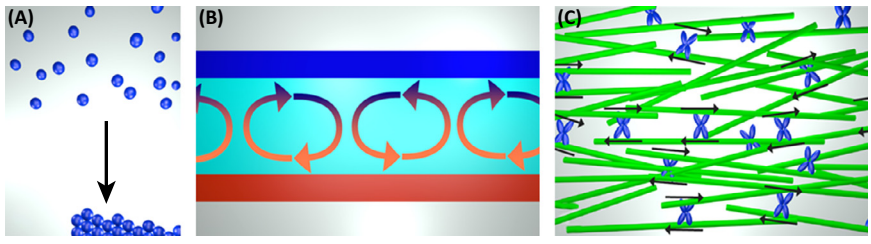


Figure 1. Different Ways to be Out of Equilibrium. (A) A system can be prepared in a non-equilibrium state and allowed to relax without energy input. A supersaturated protein solution, which will eventually crystalize over time, is an example of such a system. (B) Energy may flow in at the boundaries, eventually producing a non-equilibrium steady state. A fluid heated from the bottom (red) and cooled from the top (blue) may give rise to Rayleigh–Bénard convection in which the fluid continually circulates in rolls. (C) In active matter, energy flows in at the molecular level. Collections of microtubules (green) and motors (blue), which transduce energy and exert forces on microtubules (black arrows), are an example of active matter.

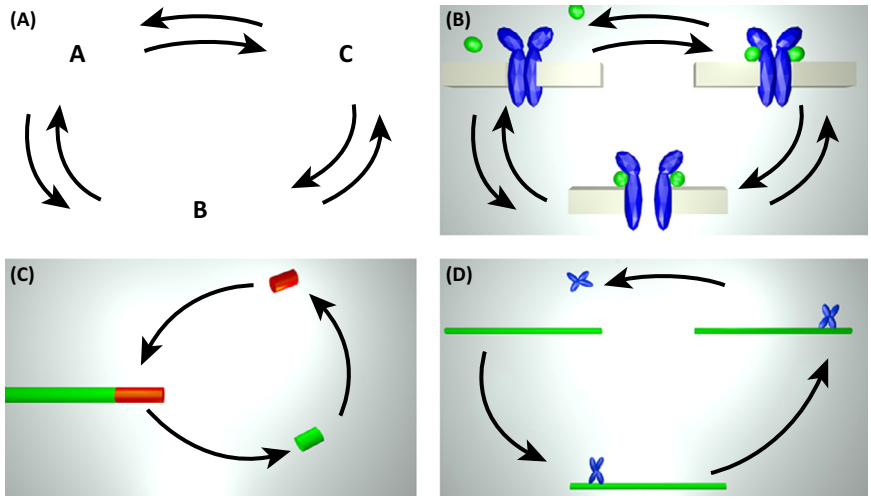


Figure 2. Detailed Balance and its Violation. (A) In equilibrium, all molecular transitions obey detailed balance: the rate of any process equals the rate of its reverse, so net cycles through series of states (A, B, and C) do not occur. (B) The acetylcholine receptor exhibits three states: closed, closed-bound to ligand, or open-bound to ligand. At equilibrium there is no net cycle through these series of states. (C) Coupling to GTP hydrolysis allows detailed balance to be violated during microtubule polymerization. A net cycle occurs from tubulin-GTP (red), to tubulin incorporated in a microtubule, to tubulin-GDP (green). (D) Coupling to ATP hydrolysis allows detailed balance to be violated by molecular motors. For a plus-end directed motor (blue) and a microtubule (green), a net cycle occurs between the soluble motor, motor bound near the minus-end of the microtubule, and motor bound near the plus-end of the microtubule.

continuously walk towards one of the filament ends (Figure 2D). The behaviors of equilibrium and near equilibrium materials result from the collective properties of molecules whose motions obey detailed balance and are determined by the energetics of their interactions and conformational changes. The behaviors of active matter results from the collective properties of molecules that violate detailed balance.

Recent work has greatly clarified the properties of active matter and the study of such systems is growing into an exciting branch of soft condensed matter physics. Theoretical developments have established a framework for investigating active materials, while new experiments of model systems continue to reveal their remarkable behaviors [9,10,12]. This work provides a basis to quantitatively understand the physics, which underlies self-organizing subcellular structures. Despite these advances, it remains unclear to what extent particular biological processes can be understood using simple active matter theories. As in physics, the only way to test the relevance of these approaches is by comparing theory and experiment. It has already been shown that concepts from active matter can be used to quantitatively explain collective behaviors of some subcellular cytoskeletal structures [9,10,13,14]. A key challenge for the future will be to develop, and experimentally test, predictive theories of subcellular organization by combining principles of collective behaviors of active matter with detailed molecular information.

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