The Biological Frontier of Physics

Problems at the interface between biology and physics offer unique opportunities for physicists to make quantitative contributions to biology. Equally important, they enrich the discipline of physics by challenging its practitioners to think in new ways.

Rob Phillips and Stephen R. Quake

In the introduction to his classic magnetic-monopole paper of 1931, Paul Dirac remarked,

> There are at present fundamental problems in theoretical physics awaiting solution, e.g. the relativistic formulation of quantum mechanics and the nature of atomic nuclei (to be followed by more difficult ones such as the problem of life), the solution of which problems will presumably require a more drastic revision of our fundamental concepts than any that have gone before.[1]

Dirac was famously and fanatically economical with words; his observation is therefore probably more than just a flight of fancy or a throwaway comment. Dirac posits that the nature of life is a fundamental and central question not only for biologists, but for physicists as well. In the excitement of the quantum revolution, however, that view was never widely adopted, and only a small fraction of the physics community took up Dirac's challenge.

Today, humanity is reaping the fruits of nearly 100 years of basic research into the quantum world. Many great fundamental problems have been solved, and much effort is now spent on developing engineering applications of quantum mechanics in such diverse areas as communication, metrology, and computation. One can therefore ask, If many of the central ideas that have dominated physics for a century are now maturing into engineering tools, what are the next great fundamental problems for physicists to work on?

We think that any top-10 list of challenges for physicists would have to include some items that address the startling complexity of the living world. Many beautiful and mysterious problems are revealed in the puzzling variety of living organisms that range from viruses—molecules that copy themselves—to rock-eating bacteria to beings with complex and conscious thought and action. Furthermore, the stunning successes of molecular and structural biology, biochemistry, and genetics have yielded an explosion of biological data that are increasingly quantitative in character. For example, gene expression is routinely characterized in terms of how much, when, and where. Similarly, data on some machinery of the cell are reported graphically in terms of force–velocity curves. As a result, despite the field's reputation as a soft science, nearly all of biology is now ripe for quantitative analysis of the sort that physicists are used to. The opportunities are analogous to those that came to astrophysics once astronomical observations were coupled to spectrometry.

Life presents many interesting questions for physicists. As illustrations, we discuss three problems at the interface between physics and biology—steppingstones to more general thinking that will enrich physics. First, we describe the molecular machines that form the basis of life. The energies and length scales at which those machines operate are intriguing because they are in the regime where the energy-versus-length curves for a host of different phenomena converge. Our second thrust concerns biological "many-body" problems, in particular the orchestrated activities of the macromolecular assemblies within the cell. Our third illustration concerns the need for a theory of biological dynamics that respects not only the many-body character of biological systems, but also their far-from-equilibrium operation.

The scope of this article is limited—other authors would emphasize different problems and examples—but its main argument is indifferent to the particular case studies. In many ways, we who work at the biological frontier of physics are only getting our first inklings of the rich interplay between biological phenomena and the physical principles that animate them (see the article by Ray Goldstein, Phil Nelson, and Tom Powers, PHYSICS TODAY, March 2005, page 46). As a result, the study of living matter should be seen as an exciting and substantive part of the modern definition of physics.

The machinery of life

Molecular machines are the basis of life. DNA, a long molecule that encodes the blueprints to create an organism, may be life's information storage medium, but it needs a bevy of machines to read and translate that information into action. The cell's nanometer-scale machines are mostly protein molecules, although a few are made from RNA, and they are capable of surprisingly complex manipulations. They perform almost all the important active tasks in the cell: metabolism, reproduction, response to changes in the environment, and so forth. They are incredibly sophisticated, and they, not their manmade counterparts, represent the pinnacle of nanotechnology. Yet sci-

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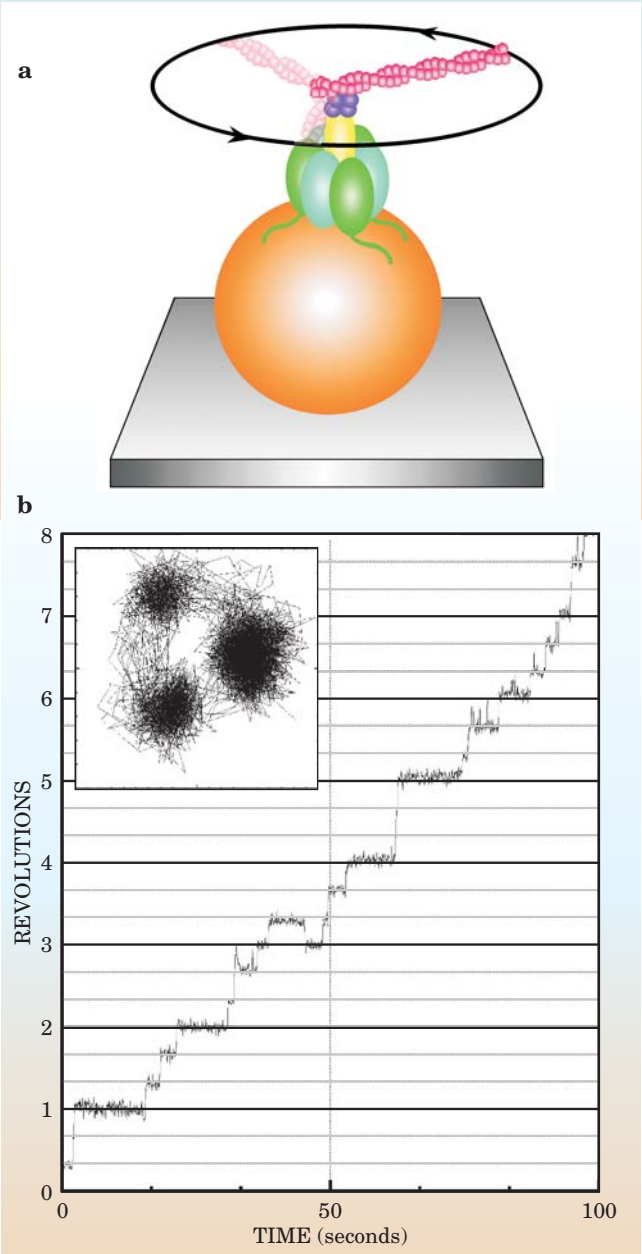


Figure 1. The incredibly small motor ATP synthase adds a phosphate group to adenosine diphosphate to make adenosine triphosphate. When run in reverse, it converts chemical energy stored in ATP to mechanical energy of rotation. **(a)** An actin filament (pink) added to the shaft of the ATP synthase enables the shaft's rotation to be imaged with an optical microscope. Each ATP-to-ADP reaction causes the actin propeller to rotate counterclockwise by 120°. In the experiment depicted here,[3] a subcomplex of the ATP synthase was attached to a bead (orange) and cover slip. **(b)** The plot shows the discrete shifts in propeller position that accompany the chemical reactions. The inset tracks locations of the propeller. Note the single clockwise rotation just before the 50-second mark; a thermal fluctuation has caused the propeller to rotate in the "wrong" direction. (Images courtesy of Kazuhiko Kinosita Jr, Waseda University, Japan.)

entists have no general theory for their assembly or operation. The basic physical principles are individually well understood; what is lacking is a framework that combines the elegance of abstraction with the power of prediction.

Proteins are quite different from the simple diatomic molecules that represent the traditional border between physics and chemistry; they are enormously large, and for many purposes quantum mechanics plays a negligible role in their function. Of course, if the question of interest happens to be the chemistry that takes place in the active site of an enzyme, one must ultimately look to quantum mechanics as the basis for understanding. Quantum mechanics can be neglected in the same sense that it is ignored in dynamical descriptions of everyday objects: On the smallest length scales, all atoms are fundamentally quantum, but Planck's constant is not needed to formulate and apply the principle of least action. Indeed, one would be hard put to describe many physical phenomena, ranging from protein behavior to critical phenomena to galaxies, if a fully quantum mechanical description were required. Proteins as molecules are polymers, and can often be treated with a combination of continuum mechanics and statistical mechanics. They act, in other words, as essentially classical objects.

How much can one molecule do? Consider, for example, ATP (adenosine triphosphate) synthase. This macromolecular assembly, only about 10 nanometers on a side, is an essential part of the cellular factory that produces ATP, the universal energy currency of life. We will not get into the details of the biological role of ATP synthase in the cell, but consider merely what it is capable of doing in isolation: It is a rotary motor. In the presence of a proton gradient, this remarkable machine turns a spindle as it adds phosphate groups to molecules of adenosine diphosphate to produce ATP.[2] And every day, as discussed in box 1, the cells in your body perform this phosphate-addition reaction to produce roughly your body weight in ATP molecules.

But that is not all: ATP synthase can run in reverse. It can consume ATP, and with each ATP molecule that is hydrolyzed, the central shaft of ATP synthase turns by 120 degrees, directly converting chemical to mechanical energy. That reverse operation was explicitly demonstrated through a series of elegant experiments in which a molecular propeller was attached to the shaft and then imaged with optical microscopy (see figure 1).[3] The propeller rotated in the presence of ATP, with absolute thermodynamic efficiencies of up to 90%. Despite the tremendous strides made in nanotechnology, no device of similar functionality can yet be fabricated with inorganic materials. Furthermore, many questions remain about the basic principles by which molecular machines such as ATP synthase convert chemical energy to mechanical forces.

Working in a noisy environment

As noted in our introductory remarks, molecular machines operate at energies and lengths common to a host of different processes. In addition to being intriguing, that regime adds to the challenge of analyzing the cell's machines. Figure 2 shows how thermal, chemical, mechanical, and electrostatic energies scale with the size of an associated object, and illustrates the confluence of energies. As the characteristic size approaches that of biological macromolecules, all the energies converge. The convergence is remarkable, since the energies range over 20 orders of magnitude as object size scales from subatomic to macroscopic; its existence is an opportunity for complex physical phenomena and processes that are evidently utilized by life. Broadly speaking, the interplay between thermal and deterministic forces is what gives rise to the rich behavior of molecular machines. For example, thermal effects permit such processes as diffusion, conformational

Box 1. Biological Budget Keeping

The biologist François Jacob is said to have remarked that the dream of every cell is to become two cells. Fulfilling that dream requires a vast inventory of molecular building blocks and the energy to fuel their assembly.

To illustrate how vast an inventory and how great the energy involved, we consider the division of *Escherichia coli*, a bacterium that has the same legendary status in biology that the Ising model or hydrogen atom has in physics. A typical *E. coli* has a characteristic size of roughly one micron, implying a volume of one μm^3, or one femtoliter. The corresponding cell mass is a picogram, and the surface area is approximately 6 μm^2. Given that roughly 70% of the mass of the cell is water, the proteins, nucleic acids, lipids, and other materials that make up the cell's macromolecular contents have a mass of 0.3 pg. Furthermore, about half of the dry mass of a cell is protein. Thus, if we assume that a typical protein has a mass of 30 000 Da (a dalton is the mass of a hydrogen atom), then each *E. coli* bacterium contains roughly 3×10^6 protein molecules.[9]

The carbon mass in the cell, like the protein mass, is about half the cell's dry mass. Thus each cell contains about 10^{10} carbon atoms. That figure implies that when *E. coli* is grown on minimal media with glucose as the sole sugar source, glucose molecules are taken on board at a rate in excess of 10^6 molecules every second during the course of the roughly 2000 seconds of the cell cycle. That glucose uptake is carried out by amazing molecular machines such as those considered in the main text.

In most cases, the energy budget of cells is ultimately mediated by adenosine triphosphate (ATP). To get a sense of the cellular ATP budget, consider the ATP produced daily, given a human dietary intake of 2000 kcal.[10] We assume that half of the energy input in the form of our diet is turned into ATP. Then, since the energy liberated by the hydrolysis of ATP is 12 kcal/mole, the number of moles of ATP synthesized each day is [(1000 kcal/day)/(12 kcal/mol)] = 80 moles/day. Given that the molecular weight of ATP is roughly 0.5 kg/mole, that implies a daily turnover of some 40 kg of ATP!

changes, the dissolution of hydrogen bonds, and the wandering of charges from their molecular hosts. Those processes, in turn, often serve as the basis of macromolecular functions ranging from copying and reading DNA to the motor action of molecules, such as myosin, that power our muscles.

One of the most important distinctions between molecular machines and their macroscopic counterparts is that molecular machines live in an environment of large thermal forces. As a result of the interplay between thermal and deterministic forces, statistical mechanics is an essential tool in understanding molecular machines. To get a feel for the importance of thermal effects, note that the natural energy unit of physical biology is the piconewton-nanometer: The piconewton is the characteristic force generated by molecular machines, as determined through single-molecule experiments for example, and the nanometer is the typical length scale. A molecular machine that operates with 100% efficiency and uses up one ATP per cycle produces about 100 pN-nm of work. By comparison, the thermal energy kT is roughly 4 pN-nm.

It is surely one of the triumphs of evolution that Nature discovered how to make highly accurate machines in such a noisy environment. One marvelous example is DNA polymerase, a molecular copying machine only 13 nanometers in size, capable of copying DNA molecules with an intrinsic error rate approaching one part per million. Much remains to be understood about the general principles behind such impressive fidelity, especially as it is achieved in the violent thermal environment of a test tube or a cell.

Molecular machines need to be accurate in the face of noise, but they can also use fluctuations as an essential part of their function. As an example, consider restriction enzymes—proteins that recognize and cut specific DNA sequences. Those enzymes are extremely efficient at searching through a genome consisting of millions, sometimes even billions, of base pairs to find and bind to their recognition sequences. The rates at which they accomplish their tasks are inconsistent with simple one-dimensional diffusion along the DNA molecule or strictly three-dimensional diffusion and binding to the DNA target site. Instead, restriction enzymes take advantage of the entropic forces that cause long DNA molecules to fold into a compact coil. They hop from one strand to another, which speeds up the search process relative to 1D diffusion.

A complete theory of molecular machines needs to take into account all the effects illustrated in figure 2 and so must include ideas from continuum mechanics, statistical mechanics, chemical kinetics, and fluid mechanics. It should provide a predictive, unifying framework that, without resorting to a full atomic description, allows an accurate description of the dynamic behavior of any molecular machine. Paradoxically, the challenge is to take the hard-won atomic-level coordinates that fill structural databases such as the Worldwide Protein Data Bank and to build models that no longer make explicit reference to those coordinates. Indeed, one of the most intriguing challenges for physicists to tackle in their analysis of cellular machines is to find out to what extent it will be possible to construct coarse-grained models of those machines. Box 2 offers a fable that speaks to the dangers of ignoring that challenge.

Machines do not a cell make

Scientists have made dramatic progress in understanding the molecular machines that operate in cells. They have determined many of their structures, characterized individual motors for their ATP activity and force–velocity properties, explored the connections between mutations and function, and more. Nonetheless, dissecting individual machines is only a step toward understanding how collections of such machines give rise to the activities of living organisms. Though many quantitative models treat cells as a "bag of enzymes," in reality cells have a great deal of internal structure.

One of the key hallmarks of biological function is ordering in space and time, and at least two great classes of biological orchestration should serve as a call to action for physicists: the coordination of physical structures and processes and the orchestration of information. In a sense, we offer in this section a counterpoint to our presentation of the machinery of life. That discussion celebrated magnificent molecular machines and some of the challenges scientists must face to understand them individually. By way of contrast, this section argues that even a perfect understanding of each and every individual molecular machine would be inadequate for explaining what goes on in a cell, just as an understanding of the hydrogen atom is merely a prelude to explaining the electronic behavior of crystalline solids and, more dramatically, collective effects like the quantum Hall effect.

In many instances, the machines of the cell are integrated into collections of many parts, often with proteins, nucleic acids, lipids, and other molecules working in concert. One of the most important ways that physicists come to terms with systems comprising many interacting de-

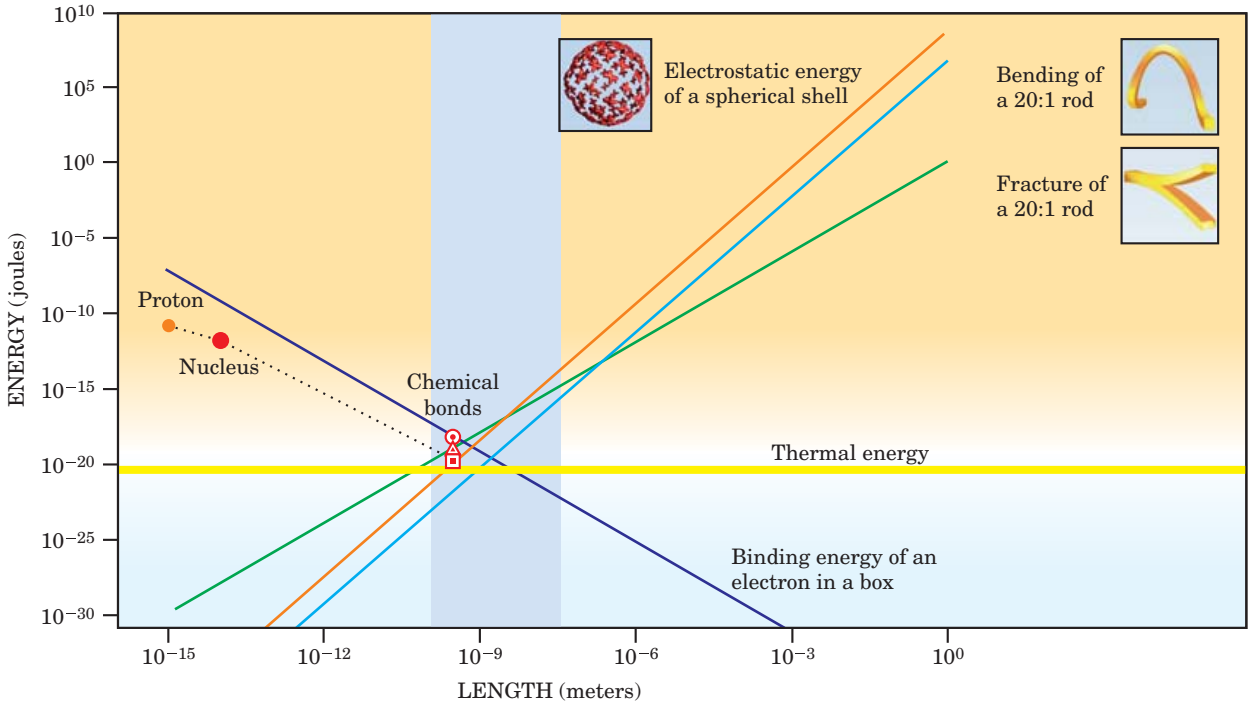


Figure 2. The confluence of energy scales is illustrated in this graph, which shows how thermal, chemical, mechanical, and electrostatic energies associated with an object scale with size. As the characteristic object size approaches that at which molecular machines operate (shaded), all the energies converge. The horizontal line shows the thermal energy scale kT which, of course, does not depend on an object's size. We estimate binding energy (purple) by considering an electron in a box; for comparison, the graph shows measured binding energies for hydrogen bonds (square), phosphate groups in ATP (triangle), and covalent bonds (circle), along with characteristic energies for nuclear and subatomic particles. In estimating the bending energy (blue), we took an elastic rod with an aspect ratio of 20:1 bent into a semicircular arc, and to compute the fracture energy (green) we estimated the energy in chemical bonds in a longitudinal cross section of the rod. The electrostatic energy (orange) was obtained for a spherical protein with singly charged amino acids of specified size distributed on the surface.

grees of freedom is to consider collective excitations. For example, phonons characterize the vibrations of a crystalline solid and magnons describe collective excitations of magnetic spins.

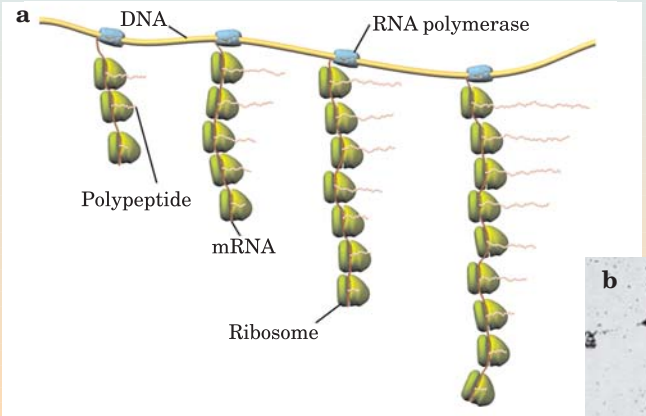
Indeed, physicists talk of "-ons" of all kinds. The biological setting provides a loose analogy because some biological structures are characterized with the label "-somes," which derives from the Greek word for "body." The term refers to macromolecular assemblies that are made from multiple molecular components that act in a collective fashion to perform multiple functions. Some of the most notable examples include the ribosome, used in protein synthesis; the nucleosome, which is the individual packing unit for eukaryotic DNA; the proteasome, an assembly that mediates protein degradation; and the transcriptisome, which mediates gene transcription. By mechanisms and principles that are still largely unknown, proteins assemble into -somes, perform a task, and then disassemble again.

One of the most pleasing examples of biological collective action is revealed by the machines of the so-called central dogma. The term refers to the set of processes whereby DNA is copied (replication), genes are read and turned into messenger RNA (transcription), and finally, messenger RNA is turned into the corresponding protein by ribosomes (translation). Such processes involve multiple layers of orchestration that range from the assembly of macromolecular complexes to the simultaneous action of multiple machines to the collective manner in which cells may undertake the processes. Figure 3 shows the machines of the central dogma in bacteria engaged in the processes of transcription and translation simultaneously.

The theme of collective action is also revealed in the flow of information in biological systems. For example, the precise spatial and temporal orchestration of events that occurs as an egg differentiates into an embryo requires that information be managed in processes called signal transduction. Biological signal transduction is often broadly presented as a series of cartoons: Various proteins signal by interacting with each other via often poorly understood means. That leads to a very simple representation: a network of blobs sticking or pointing to other blobs. Despite limited knowledge, it should be possible to develop formal theories for understanding such processes. Indeed, the general analysis of biological networks—systems biology—is now generating great excitement in the biology community.

Information flow in the central dogma is likewise often presented as a cartoon: a series of directed arrows showing that information moves from DNA to RNA to proteins, and from DNA to DNA. But information also flows from proteins to DNA because proteins regulate the expression of genes by binding to DNA in various ways. Though all biologists know that interesting feature of information flow, central-dogma cartoons continue to omit the arrow that closes the loop. That omission is central to the difference between a formal theory and a cartoon. A closed loop in a formal theory would admit the possibility of feedback and complicated dynamics, both of which are an essential part of the biological information management implemented by the collective action of genes, RNA, and proteins.

Understanding collective effects in the cell will require merging two philosophical viewpoints. The first is that life is like a computer program: An infrastructure of machines carries out arbitrary instructions that are encoded into DNA



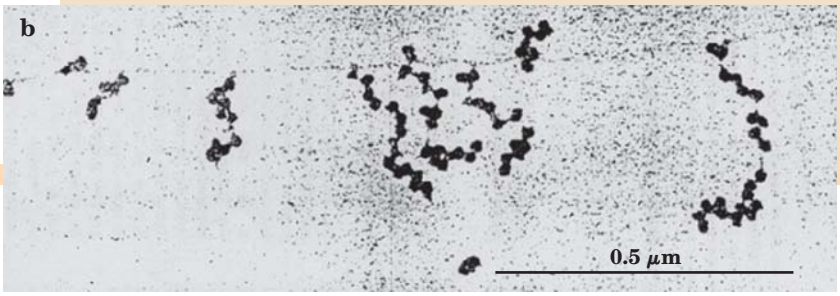


Figure 3. Machines in *Escherichia coli* act in concert. **(a)** In this sketch, RNA polymerase (blue) moves to the right along strands of DNA (yellow) and spools out messenger RNA (red) in a process called transcription. At the same time, cellular machines engage in translation: Ribosomes (green) move along the RNA and make polypeptides, strings of amino acids. Ultimately, those polypeptides will form proteins. **(b)** An electron micrograph of simultaneous transcription and translation. (Adapted from ref. 6.)

software. The second viewpoint is purely physical: Life arises from a mixing together of chemicals that follow basic physical principles to self-assemble into an organism. Presumably, the repertoire of available behaviors is more limited in the latter. The two viewpoints are complementary, not incompatible: Either one could best describe cell behavior, depending on the particular situation.

Time in its place

One popular way to capture biological thinking about the machines of the cell is through the linked qualities of structure and function. With increasing regularity, structure is being brought under control, as evidenced by huge databases, including the Worldwide Protein Data Bank, that are the repository for the hard-won successes of structural biologists. On the other hand, function is inherently a question about dynamics. And for the moment, it is a question that remains unanswered in any general way. As a result, one of the most compelling challenges for those trying to shed light on the function of the cell's machines is to put time in its rightful place.

In a deep sense, the problem of the dynamics of macromolecules and their assemblies, of organelles, and of cells themselves strikes right to the heart of just how much physicists will be able to do with systems that are far from equilibrium. Indeed, we believe that biological dynamics is *the* example of nonequilibrium physics. Until now, much of the emphasis in the study of nonequilibrium systems has been on small departures from equilibrium. Furthermore, in many instances the debate that has swirled around questions of nonequilibrium has been philosophical rather than centered on making predictions about specific experimental case studies. Biology, though, may provide the jumping-off point for systematic and predictive ideas on nonequilibrium physics because of the existence of so many manifestly important and well-characterized systems.

Erwin Schrödinger appreciated that understanding biology requires understanding nonequilibrium systems and enunciated that view in his classic 1944 essay *What Is Life?* (Cambridge U. Press, 1992). He called for a new theory of physics that is concerned with understanding the behavior of single molecules far from equilibrium. When Schrödinger wrote, scientists did not know the identities of the molecules that form the basis of life. Still, it was possible to infer that the gene was a molecule and that understanding the mechanisms of life depended on understanding the properties of molecules as machines.

Several categories of thinking may be applied to the subject of nonequilibrium systems. The pessimistic view argues that the search for general principles is doomed and that one will likely do no better than to solve problems on a case-by-case basis. Some observers have expressed impatience with that point of view. Physicist Percy Bridgman, for example, has eloquently noted that "the admission of general impotence in the presence of irreversible processes appears on reflection to be a surprising thing. Physics does not usually adopt such an attitude of defeatism. Of course this may be made a matter of words if one chooses, and one can say that thermodynamics by definition deals only with equilibrium states. But this verbalism gets nowhere; physics is not thereby absolved from dealing with irreversible processes."[4] The study of biological systems demands that physicists redouble their efforts to make progress on nonequilibrium processes since biological systems are intrinsically out of equilibrium. Moreover, there is a growing list of biological examples whose nonequilibrium behavior has been characterized quantitatively.

A key feature of the cellular interior that makes studying cells especially challenging is its intense crowding, beautifully illustrated in the paintings of David Goodsell (see the cover of this month's issue).[5] As an example, the standard apparatus of equilibrium statistical mechanics needs to be called into question for the dynamic assemblies seen at the leading edge of motile cells. Not only are they far from equilibrium, but standard approaches to such systems are often dominated by chemical potentials based on dilute solutions and on diffusion equations suitable for dilute and homogeneous bulk systems. As a result, the study of the crowded and bustling interior of living cells raises

Box 2. Abstraction Is the Essence of Physics

In that Empire, the Art of Cartography attained such Perfection that the map of a single Province occupied the entirety of a City, and the map of the Empire, the entirety of a Province. In time, those Unconscionable Maps no longer satisfied, and the Cartographers Guilds struck a Map of the Empire whose size was that of the Empire, and which coincided point for point with it. The following Generations, who were not so fond of the Study of Cartography as their Forebears had been, saw that that vast Map was Useless, and not without some Pitilessness was it, that they delivered it up to the Inclemencies of Sun and Winters. In the Deserts of the West, still today, there are Tattered Ruins of that Map, inhabited by Animals and Beggars; in all the Land there is no other Relic of the Disciplines of Geography.[11]

—Jorge Luis Borges and Adolfo Bioy Cesares,
"On Exactitude in Science."

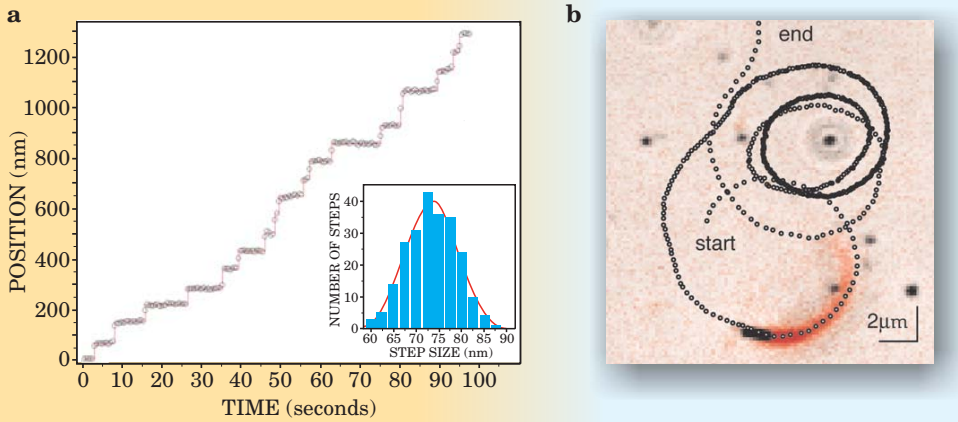


Figure 4. Trajectories of biological systems can be precisely measured. **(a)** The graph shows the position of the individual molecular motor myosin V as a function of time.[7] The position can be determined by examining the intensity of fluorescent light emitted from molecules attached to the motor. The inset histogram summarizes 231 steps. A typical step size is about 75 nm and a typical measurement error is about ±2.5 nm. (Courtesy of Paul Selvin, University of Illinois at Urbana-Champaign.) **(b)** Equal-time steps are shown in the trajectory of the bacterium *Listeria monocytogenes*.[8] The bacterium tricks the host cell into constructing a network of actin filaments that propel the *Listeria* forward. The unequal spacing between steps shows that *Listeria* does not move at a constant speed. Rather, it moves faster when the temperature is higher. Superimposed on the trajectory is an image, taken at a specific time, of the bacterium (black smudge near bottom) and its trailing actin filaments, rendered in pink. (Courtesy of Julie Theriot, Stanford University, and Fred Soo, University of Washington.)

numerous questions about physical materials that are neither dilute, static, nor homogeneous.

With increasing regularity, experimental observations on single molecules, macromolecular assemblies, and even cells themselves are couched in terms of trajectories (see the article by Carlos Bustamante, Jan Liphardt, and Felix Ritort, PHYSICS TODAY, July 2005, page 43). That is, scientists have recognized that the temporal evolution of biological systems and their building blocks is measurable, interesting, and reproducible. For example, a beautiful set of recent experiments whose results are illustrated in figure 4a showed that it is possible to monitor the trajectories of individual molecular motors for extended periods of time and with extremely high spatial resolution. Not only do such experiments get at the mechanism by which motors move, but they also reveal something about both the collective action of motors and the fluctuations suffered by individual motors. As shown in figure 4b, trajectory analysis also proves useful at larger scales. Indeed, the trajectories of motile cells exposed to a time-varying temperature provide clues about the dynamics and control of cytoskeletal proteins' rich behavior.

Beyond the cartoons

In the 75 years since Dirac posed his challenge, scientists have made tremendous progress in discovering and cataloging the molecules that form the basis of life. In what respect is their pursuit intellectually distinct from the "stamp-collecting" mindset of the pre-molecular era? One of the biggest opportunities provided by the explosion of biological data is the chance to revisit biological phenomena and use the quantitative interplay between theory and experiment as a measure of understanding. In this article we have outlined major areas that are amenable to the kinds of experiments and theories that physicists are used to: understanding the operational principles of molecular machines and assemblies, understanding the collective effects that give rise to the exquisite orchestration in space and time revealed by cellular life, and developing new ideas on nonequilibrium statistical mechanics that provide a suitable framework for understanding in vivo cellular processes. Clearly, biologists have already thought deeply about those issues, but we believe a physics perspective brings its own unique contributions.

The advent of a host of powerful experimental techniques is opening new windows into the study of living matter. Full genome sequencing and gene-expression analysis serve as a reminder that organisms are finite, closed systems, and that data limit the number of possible models. In addition, one can make exhaustive measurements of the effects of perturbations on both cells and their environments. Such investigations admit a new conceptual point of view in which one makes a systemwide analysis of the effects of perturbations rather than an incomplete, piecemeal assessment. Single-molecule biophysics techniques, which create new ways to observe, study, and characterize macromolecular machines (see the article by Terence Strick, Jean-François Allemand, Vincent Croquette, and David Bensimon, PHYSICS TODAY, October 2001, page 46), are providing exactly the sort of data needed to address some of the problems we have described in this article. We are convinced that such problems will pose fruitful challenges for experimental and theoretical physicists for a long time to come.

We are grateful to Robert Bao, Seth Blumberg, Curt Callan, Ken Dill, Dave Drabold, Hernan Garcia, Bill Gelbart, Paul Grayson, Mandar Inamdar, Marc Kamionkowski, Jané Kondev, Albion Lawrence, Phil Nelson, Eric Peterson, David Politzer, Paul Selvin, Julie Theriot, David Van Valen, and Jon Widom for commenting on the manuscript.

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