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News and Views: Biology—Where the Action Is

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Abstract The latest golden age of physics was the first half of the twentieth century, when quantum mechanics was developed. A comparable revolution is under way in biology.

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Several years ago, a popular T-shirt among aspiring or professional physicists displayed the inscription: "PHYSICS, WHERE THE ACTION IS!" along with the symbolic representation of an action integral. I am going to argue that biology is nowadays a better candidate for this slogan, with "action" taken in its literal, not Lagrangian, sense.

What I mean is that exciting new and even revolutionary developments are now taking place in biology, much faster than in physics. The latest golden age of physics was the first half of the twentieth century, when quantum mechanics was developed. A comparable revolution is under way in biology, challenging its central dogma. Formulated by Francis Crick, who thought that "dogma" meant only a hypothesis with little direct experimental support, it states that the path of information in biological systems must be from DNA to RNA to protein.

With his typical physicist's arrogance, Crick walked into a Cambridge pub in 1953 to state that he and Watson had just discovered "the secret of life." Though, until recently, DNA indeed seemed to be the central player, it has now been dethroned by RNA, which, besides transmitting genetic information, contributes to the crucial task of regulating gene expression and is the most plausible candidate for explaining the origin of life.

It was Darwin who came upon a truly central biological idea. As remarked by the geneticist Theodosius Dobzhansky, "nothing can be understood in biology except in the light of evolution." As stated by François Jacob, however, evolution is a tinkerer, not an engineer: Rather than striving for perfection, once it finds good enough solutions, it tends to combine and make use of them in different ways. Physicists should also keep in mind that biological systems, in contrast with the usual objects of study in physics, have a program: survival and replication.

There does not seem to be a "hydrogen atom of biology." The simplest living cell already has the same universal genetic code, over a hundred genes, transcription, translation, and metabolism, involving thousands of chemical reactions. How can one study such a fantastically complex system? Besides the reductionist "bottom-up" approach of molecular cell biology, a promising "top-down" or "systemic" approach investigates common functional modules and networks within cells. However, progress in biology still arises almost entirely from experiments.

Physics has contributed many of the basic tools employed. Among them, one of the latest acquisitions, optical tweezers (OT), is a central link between biology and physics. Arthur Ashkin, who invented OT at Bell Labs, created the whole field of optical trapping and cooling, as well as the application to biology.

OT are optical traps for neutral particles, capturing them with the gradient forces of a strongly focused laser beam, a miniaturized version of the tractor beams in Star Trek. For quantitative applications, transparent silica or polystyrene microspheres are employed as handles and force transducers,

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since the light forces on them can be precisely calibrated. OT forces range from fractions of piconewtons to a few hundred piconewtons, just right for applications to cell biology.

Near-infrared light in the 1-μm range is usually employed because it falls in a transparency window for the water inside cells, preventing damage and allowing the manipulation of living cells. Focusing is done by a microscope objective, employing also visible illumination to follow the course of the experiments by video microscopy.

One of the most successful applications of OT has been the study of interactions among cells and motor proteins, at the level of single molecules. Motor proteins are marvelous molecular machines, which perform direct conversion of chemical energy to work. They play crucial roles in fundamental cell processes, such as catalysis, motility, cell division, energy generation, cargo transportation, DNA transcription, and many more. How can they be so versatile?

Jacques Monod suggested a key aspect of the explanation: Proteins are Maxwell demons. In Maxwell's 1867 argument, a demon's acquisition of information about molecular velocities allows her/him to segregate fast from slow molecules by operating a trap door with negligible work, apparently violating the second law of thermodynamics. Landauer's deep resolution of this conundrum, almost one century later, was that the compensating entropy increase is produced by the need to erase the demon's memory.

A vivid illustration of an automatic Maxwell demon, proposed by Smoluchowski and popularized by Feynman in his lectures, is the ratchet and pawl mechanism. A connected axle with vanes bombarded by gas molecules drives unidirectional ratchet rotation and would allow a weight to be lifted. Feynman shows clearly that the second law is not violated, but that unidirectional motion can be generated because the system acts as a rectifier of Brownian fluctuations. A system of this type is now referred to as a thermal or Brownian ratchet.

Motor proteins can generate unidirectional behavior by rectifying Brownian fluctuations, acting as thermal ratchets. They have been called "Darwin's motors" because they operate by natural selection of favorable Brownian fluctuations. One of them, adenosine triphosphate (ATP) synthase, a reversible rotary motor, is responsible for the synthesis of ATP, the universal fuel that supplies the energy to drive virtually all biological processes. Feynman's 1959 challenge (met within months after his proposal) to build a working electric motor of millimeter dimensions pales to insignificance in comparison with ATP synthase, which is about 10 nm in size, running with an efficiency close to 100%.

Motor proteins employed to transport cargos within cells "walk" along cytoskeleton filaments with steps of a few nanometers, and they exert typical forces of a few piconewtons. Step sizes and forces have been measured employing OT in assays on single molecules. The pull exerted by a single molecule of the motor protein myosin on an actin filament, the basis for muscle contraction, has also been measured with OT. Such single-molecule quantitative OT data have stimulated considerable progress in understanding these and many other biological processes. Thermal ratchet effects indeed play a significant role.

Relevant branches of physics involve the statistical mechanics of small, open, highly heterogeneous systems far from equilibrium. Material properties are reminiscent of soft matter. Typical forces are very small: hydrogen bonds, van der Waals, and electrostatic interactions. This is consistent with the flexibility required of biopolymers for the rapid continuous dynamic rearrangements that they undergo within cells.

Besides explaining the basic structure of molecules that are the building blocks of biopolymers, quantum mechanics does not appear to be relevant in cell biology. In a wet environment at temperatures of the order of 300 K, decoherence times are many orders of magnitude smaller than typical biological reaction times, rendering proposals such as those of Penrose for coherent quantum effects on consciousness in the brain completely incongruous. Very recently, preliminary evidence has been found for possible quantum coherent enhancement of electronic excitation transfers in photosynthesis, but this seems to be one of the very few exceptions.

My own involvement with cell biology was sparked by my work on Mie scattering. Ashkin wrote me in connection with his observations of very sharp Mie resonances in droplet levitation by laser light, and I got acquainted with his beautiful work on optical tweezers, including the applications to cell biology.

Years later, faced with the choice of a multidisciplinary cutting edge research area for the Coordination of Advanced Study Programs at the Federal University of Rio de Janeiro, it occurred to me that an optical tweezers laboratory would be just right. Setting it up, as happens with all experimental work in Brazil, required a prolonged battle with bureaucracy.

During this installation period, in collaboration with Paulo Américo Maia Neto, we started a research program aimed at an absolute calibration of optical tweezers. Since Mie theory describes light scattering by microspheres with an accuracy comparable to that of QED, a first-principles theory of OT forces only requires in addition an accurate description of a strongly focused laser beam. It turned out that existing theories of OT were based on incorrect descriptions.

Our group worked out an amended theory and proceeded to perform an experimental test at our lab, in collaboration with the Oscar Nassif de Mesquita lab at the Federal University of Minas Gerais. The results convinced us that we now had a first-principles understanding and control

over the instrument. This turned out to be invaluable for later applications.

It was also important that our lab was set up within the Biomedical Sciences Institute, so that we could employ its facilities for the preparation of living cell samples. Beginner's luck or serendipity, one of our first samples of brain tumor cells, left overnight, sprouted a number of long thin connections between cells. Similar linkages had recently been described in a Science paper, which named them "tunneling nanotubes" because molecules could be transferred through them from one cell to another one.

They were described as extremely fragile, so that we decided to measure what force would be required to break one up, by attaching a microsphere to a nanotube and pulling it with the OT. The result was a surprise: The initial V-shaped deformation, instead of breaking, developed a new branch. We called this a V–Y bifurcation. By analysis of the force×deformation curve, we determined for the first time the elastic constants (surface tension and bending modulus) of the tunneling nanotube.

We had inadvertently stumbled upon a fascinating new area of cell biology, now known as the study of intercellular nanotubes. They have been found to occur among many different types of cells, and their roles in cell–cell communication are just starting to be investigated. Many similarities with the nervous system seem to be present, although those are not neural cells. Their discovery is recent, but they must be very ancient evolutionary features: Pathogens that include virus, bacteria, and prions have learned to employ them as conduits for invading cells.

We engaged in a detailed study of the force×deformation curve while pulling a nanotube (known as a tether) directly from a cell surface. We found several features that directly contradicted a previous study with the same cell type, published in a prestigious journal. After an 8-month battle involving a succession of four referees, our paper was finally accepted. An important argument in our favor was our previous experimental proof that we can manage absolute calibration of our instrument.

The aim of the above description of my own conversion from theoretical and mathematical physicist to experimental cell biologist was to exemplify that such a transition is quite feasible. I have had no occasion to regret it.

I append a short list of references that may be helpful to those who want to find out where the action is:

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