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The Impact of Physics on Biology and Medicine

by Harold Varmus

For at least several hundred years, physicists—and especially their principles, methods and machines—have been illuminating our views of the human body and of every other living thing.

This notion was brought home to me very early in life when my father — a general practitioner whose office was directly connected to our house — showed me how X-rays and fluorography could reveal the bones and lungs of our pets and his patients, and make diagnoses of disease. The significance of using the discoveries of physics to perceive biological function was further impressed on me at college, when one of my first independent projects required that I try to explain the repeating peaks and valleys of my electrocardiogram as a record of voltage changes in the salty sea of a human body. And yet again at medical school, when I learned that the doyens of our biochemistry department had become famous by being the first to tag red blood cells with easily detected radioisotopes to learn how long such cells survived in the body.

These are just a sampling of the hundreds of physics-based methods that have been applied to view living bodies without the disruption of anatomical dissection or to visualize very small components of living things. Many such methods can be classified as those that permit us to visualize the inner parts of working bodies of humans (and other animals) at successively higher levels of resolution and those that allow us to see smaller and smaller elements of bodily components. The methods of "macro-imaging" include conventional X-radiology, computerized tomography scanning, ultrasound, positron-emission tomography (PET), and magnetic resonance imaging (MRI). The impact of these procedures on medical practice is unquestioned and continues to grow as new methods and new applications appear.

"Micro-imaging" began with the use of optical principles to devise the light microscope, but has progressed to much higher levels of resolution with electron microscopy, X-ray crystallography, and nuclear magnetic resonance. Sometimes a collection of methods proves important, as in the use of molecular hybridization, fluorochrome chemistry, wave optics, and computer science in spectral karyotyping, a procedure that allows rapid identification of each of the 23 pairs of normal human chromosomes and the origins of recombined chromosomes that often appear in cancer cells. Long-awaited success in using a time-honored technique, X-ray crystallography, to solve the structure of proteins embedded in biological membranes has recently transformed the study of cell function and disease.

In a 1967 commentary on the role of physics in biology and medicine, Sergei Feitelberg, a physicist from Mt. Sinai Hospital in New York, noted that while such "spectacular developments created a clear and unequivocal need for physicists and their help, the role of the physicist was that of a glorified technician engaged in methodology and instrumentation, dignified only by the strangeness of his doings and the mysteriousness of his tools." I do not accept that interpretation. We need to show our appreciation of physics-based technology by investing NIH funds more aggressively in its development. We have begun to do just that through a new Bioengineering Consortium and a trans-NIH emphasis on technology development.

Physicists and the rise of molecular biology

There are multiple intellectual lineages connected with physics that helped to create the modern world of molecular biology. Max Delbruck, a leading physicist who had made a conversion to biology some years earlier, had been a student of Niels Bohr; a successful physicist; and then a powerful proselytizer for biology, attracting many other physicists to biology. The effects of his missionary zeal were powerful, not just because some very smart people started to do biology, but because they brought to biological problems a quantitative, analytic approach, creating the atmosphere in which principles of molecular biology were discovered by seeking the physical basis of heredity. Leo Szilard was among the converts, and claimed that what physicists brought to biology was "not any skills acquired in physics, but rather an attitude: the conviction which few biologists had at that time, that mysteries can be solved".

Delbruck and his friends were gripped by some fundamental questions: What is the physical form in which hereditary information is stored? How is it reproduced when a cell divides? Or, even more impressively, when a single virus particle invades a cell and makes hundreds or thousands of copies of itself? How is the information reassorted during sexual reproduction? How does the information change when mutations occur?

Answers to many of these questions came from the so-called "phage school" that he founded, a group of former physicists and some biologists who shared his passion for reducing the problem of heredity to simple rules, physical entities, and conserved energy by studying the replication and genetic behavior of bacterial viruses in their bacterial hosts. The studies culminated in findings that form the pillars of modern molecular biology: the identification of DNA as genetic material, a description of the physical organization of DNA through X-ray crystallography, the deduction of the principles of base pairing and the strategy of replication from the organization of the double helix, and the deciphering of the genetic code as triplets chosen from a set of four nucleotides.

Warren Weaver was a mathematical physicist turned science administrator, who, in 1932, first used the term "molecular biology." British scientists with a strong physical bent, such as Astbury, Bragg, and others, used X-ray diffraction to study the organization of fibers of many kinds, mainly proteins found in textiles, in an intellectual lineage that led to Wilkins and Franklin and, of course, DNA. The American geneticists, T.H. Morgan and H.J. Muller used physical agents, X rays, to induce mutations in fruit flies. Muller's affinity for the principles of physics was especially strong. He was fond of noting the potential similarities of mutation of genes to transmutation of elements, calling the prospect of understanding these events in physical terms "the two keystones of our rainbow bridges to power".

Bringing physics to the problems of biology

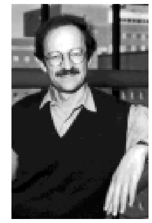
In the birth of modern molecular genetics, physicists contributed their analytic skills but they were not really doing physics, and many were not even using the computational or imaging tools of physics as many biologists do. But contemporary biology, especially the deciphering of genomes by nucleotide sequencing, is about to change that. Biology is rapidly becoming a science that demands more intense mathematical and physical analysis than biologists have been accustomed to, and such analysis will be required to understand the workings of cells.

In the past 50 years, molecular and cell biologists have moved much closer to the "radical physical explanation" of cell behavior that Delbruck sought. Certainly the chemical elements — especially the genes, the RNAs, and the proteins — and some of their basic functions are coming into view. What is lacking is a sense of how these functions are integrated to allow cells to manifest their physiological traits. There are three arenas of biology in particular where I believe the skills of physicists can be most productively used.

First, methods are now available for examining the physical and chemical properties of single macromolecules and single complexes of large molecules. These include laser traps ("optical tweezers") to study the energetics of molecular motors used for transport, for contraction, and for flagellar motion. (The recently decorated Nobel Laureate Steven Chu of Stanford has made significant contributions to this problem in collaboration with his cell biologist colleague, Jim Spudich.) Laser traps can also be used to measure the force of an enzyme complex, such as the one that copies DNA sequences into RNA. Fluorescence spectroscopy and scanning tunnel microscopy can visualize the conformation of single large molecules, and methods now in development may soon be able to determine the order of bases in single long DNA molecules.

Second, the computational experience of physical scientists is needed to help interpret complex data sets. New methods, built on the availability of a piece of DNA from each gene, allow measurement of the extent to which genes are read to form RNA (and subsequently protein) in different tissues and under different environmental conditions. These micromethods, called "expression arrays" are coming into wide use to study bacteria (with several hundred to a few thousand genes), yeast (6200 genes), worms (19,100 genes), and vertebrates (whose still incompletely analyzed genomes are predicted to contain about 80,000 genes). Some progress has been made through computer-based "cluster analysis" to begin to interpret the voluminous data that such experiments generate, but biologists are generally unused to such complex data sets. Recently, I spent an evening at the Carnegie Institution's Chilean observatory at La Serena watching astrophysicists gather amazingly similar data sets to search for supernovae and to measure the chemical composition of distant stars. We are all likely to benefit from an interdisciplinary exchange of computational approaches.

Third, in the past 20 years, biomedical investigators have constructed many so-called "signaling pathways" that link molecular interactions at the cell surface to changes in gene expression in the nucleus. While there is consensus that these linear pathways are over-simplified, the way forward is far from clear. The pathways doubtless have many unrecognized components; the information is certainly flowing between, not just along, the several pathways; and the pathways are probably regulated in complicated ways through feedback mechanisms and others. A few investigators are beginning to grapple with these issues but there is an obvious need to apply experiences with potentially analogous complex machines.



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Moving between disciplines

Self-identification in science is commonly linked to the source of one's graduate degree, and departmental names on diplomas can become limits to exploration in adjacent fields. But many of us in biology expect that, as studies of cells and molecules become more obviously in need of several disciplinary approaches, it will become increasingly difficult to label the sciences and to predict the kinds of degrees people doing it should have. At the NIH, we have become concerned about how people should be trained in college and in graduate studies to pursue biological problems over the next 50 years. I also agree with Leon Lederman, who has been leading the movement to establish a more logical order of sciences — physics, chemistry, and then biology — in high school curricula. But these activities will come to fruition only after many years, and it is important to consider as well the more immediate need to transport intellects across artificial disciplinary boundaries.

I sense increasing interest in attempting to open borders that have been traditionally hard to cross. Workshops on computational biology and approaches to complex systems have recently been organized by the National Institute of General Medical Sciences and the Department of Energy. New funding opportunities for interdisciplinary work are available through our Bioengineering Consortium (BECON) and other programs. (At present, total NIH funding of physics projects is estimated to be about $287 million.) There are many anecdotal accounts of successful interdisciplinary training programs. Within our intramural research program at the NIH, physicists and physics trainees from the US and abroad do graduate thesis work, take courses in biological topics, and engage in post-doctoral training that promotes interactions with biologists and clinicians.

The NIH can wage an effective war on disease only if we — as a nation and a scientific community, not just as a single agency — harness the energies of many disciplines, not just biology and medicine. These allied disciplines range from mathematics, engineering, and computer sciences to sociology, anthropology, and behavioral sciences. But the weight of historical evidence and the prospects for the future place physics and chemistry most prominently among them.

Harold Varmus, M.D., is director of the National Institutes of Health. The above text was condensed and adapted from his plenary lecture at the APS Centennial meeting in Atlanta on March 22, 1999. The full text, complete with references and illustrations, can be found online at http://www.nih.gov/welcome/director/varmus.htm.

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