A call for interdisciplinary science: physics and mathematics in life sciences and medicine

D. Holcman and Z. Schuss

IBENS, EcoleNormale Sup\'erieure, 46 rue d'Ulm 75005 Paris, France and
Department of Mathematics, Tel-Aviv University, Tel-Aviv 69978, Israel.

Preamble

Molecular and cellular biology are becoming more and more exact as sciences, as the result of the development and progress of higher resolution measurements. This progress has led to the emergence of physical processes as determinants of molecular and cellular function. The different physical properties of these functions can now be studied under controlled conditions, much as in chemistry and physics. We now know, for example, that both geometrical structure and chemical properties can be important determinants of molecular dynamics and cellular function. We also have new information about how subcellular structures work as physical devices. The physical sciences are now called upon to provide quantitative descriptions of biological function and to predict function from structure in order to understand changes brought about by pharmacology and genetics. Great progress should be expected from this integration of mathematical and physical sciences with biology. New means of communication have to be developed among these disciplines. Mathematicians and physicists interested in the biological sciences will have to become familiar enough with biological disciplines that they can form their own judgment about experimental data. They need also to become acquainted with the realities of the biological laboratory. On the other hand, biologists should enlist the physical scientists in their studies. Once the physical scientists begin to collaborate with the biologists, not only for the development of instrumentation but also for the interpretation of experimental data, great progress can be expected, much like the contribution of the physical sciences to engineering.

Introduction

Mathematical physics, traditionally referred to as applied mathematics, has shifted its focus in the 21st century from the classical physics of continuum and quantum mechanics and from numerical methods for solving its partial differential equations to the mathematics of life sciences and medicine, which are emerging into the mainstream of modern physical sciences. The role of applied mathematics in these fields has expanded from assisting scientists in analyzing mathematical models derived from classical and modern physics to taking part in creating appropriate mathematical frameworks, as well as constructing mathematical models, coarse-graining and deriving equations, guiding and interpreting measurements and experimentation, reducing the huge number of degrees of freedom of molecular biophysics, developing new computational and computer simulation methods, and participating in many other related points of contact with experimental life sciences. The equations of applied mathematics in the life sciences pose new questions and call for the development of new analytical asymptotic-approximation methods for their solution. They also require the design of new numerical simulations of the inherently stochastic particle systems that represent the micro devices of molecular and cellular physiology, and in particular of neurophysiological phenomena. Mathematical problems arising at different levels of resolution—including atomic, molecular, and systemic—require mostly classical physics. The new aspect here is the huge number of degrees of freedom. The aim of the new mathematics is to reduce the statistical physics of complex biological systems to the exploration of low-dimensional spaces of measurable physical parameters.

What has changed from the last century?

Science in the previous century was for the most part separated into distinct tasks. The task of modeling was reserved for physicists, who derived coarse-grained models and analyzed large systems with the methods of statistical physics. Large computer simulations were relegated to chemistry and biochemistry. Electrical engineers and computer scientists were left in charge of signal and image processing and of handling large data sets. Mathematical analysis, by and large, adopted the mission of proving the existence and uniqueness of solutions of the equations of mathematical physics, while many mathematicians concentrated on studying the convergence of schemes for the numerical solution of these equations. The separation of roles brought some progress in some fields but also created fragmentation and division, leaving large gaps in our understanding of these areas of science and technology.

What changed in the past 15 years?

Traditional applied mathematics in the 20th century served the needs of various fields of science and technology, such as fluid dynamics (especially in the aerospace industry), the design and manufacturing of micro-electronic devices, atomic and nuclear physics, control and communication theory, guidance, robotics, wave theory (e.g., for radar and underwater acoustics), inverse problems for medical image reconstruction (e.g., in X-ray computed tomography and MRI), to name but a few.

In the past 15 years new technologies have emerged that allow biologists to see biological function in vivo at an unprecedented high spatiotemporal resolution. Live-cell imaging has brought into view live dynamics of molecules, leading to major progress in molecular and cell biology that has enhanced our understanding of cellular function at the molecular level. Major progress came also from combining techniques from genetics and physiology (e.g., silencing a gene to shut down the expression of proteins), or from making perturbations that lead to the resolution of the role of specific pathways. New physical insight into the workings of biological devices has attracted the attention of the physics and chemistry communities to biophysics and to cell biology.

To address these insights, it has become necessary to integrate methods developed in mathematical and physical sciences and to derive new physical and mathematical models of biological micro devices and processes, as well as to solve new mathematical problems for the old equations of mathematical physics and to devise accessible molecular-level simulations. The division of tasks among the different disciplines in molecular and cellular biology came to an end with the advent of these new approaches, which have generated an emerging trans-disciplinary methodology.

What are the new directions?

Mathematical models of biophysical devices based only on the physical properties of these devices are among the most challenging models to generate. They should mostly be derived from the classical physical properties of ions and other microscopic particles in solution. The aim of these models is to predict the behavior of cells and subcellular phenomena. There is a concentrated effort afoot to base physiology and cellular biology on physics. Examples (among many) are the description of the diffusional motion of ions in cells such as cardiac myocytes, neuronal cells, or pancreatic beta-cells; the description of how cells move and grow, based on molecular trafficking; and the explanation of how viruses find their targets inside a cell.

Understanding the organization of the nucleus from polymer physics is also a new challenge, which requires extracting information from the large data sets of distances between points on chromatin. Understanding the function of the brain during external activity or after the application of drugs is a new challenge that may hopefully lead to the development of methods to prolong the period of independence of older patients during aging. The design of neural networks based on rational models of synaptic dynamics remains a difficult challenge, because 10^{11} neurons are involved. A mathematical framework for analyzing neuronal activity is still needed. The effect of changing geometry of neurons, axons, and dendrites during learning or pregnancy is a current subject of mathematical modeling. The basis of the necessary multi-scale geometry of cells and their assemblies is contained neither in classical physics nor in classical geometry and remains to be developed.

Mathematical models used in medicine have been mostly empirical, because there are too many stages of coarse-graining from the molecular to the physiological level. Mathematical models for bridging between scales are still needed, but even empirical models may lead to interesting predictions and to direct medical applications (e.g., the cycle of aspirin). It is still unclear whether models of cancer can lead to direct and immediate progress.

The challenge posed by recent progress in biology requires interdisciplinary research by members of the applied mathematics and physics community. It is up to applied mathematicians to demonstrate that they can rise to the new challenge of these new results with new methods, new analysis, new predictions, new algorithms, and new simulations for biological phenomena. Interdisciplinary research requires the publication of applied mathematical research in various fields of application to be accessible to a wide readership. Thus applied mathematical research concerned with physical and biological modeling and analysis should be published not only in applied mathematics journals, but also in journals typically used to publish research in the studied area. For example, such work should be published not only in Phys. Rev. Lett., Phys. Rev. E, Phys. Lett. A, J. Phys. A, J. Chem. Phys.; but also in the Nature journals, Proc. Nat. Amer. Sc., Science, Biophys. J., Cell, PLos journals, Frontiers, J. Comp. Neuroscience, the Journal of Neuroscience, Neuron, and so on. These different areas are now listed in Isiknowledge.

The educational challenge

The reconfiguration of the mathematical sciences calls for a new generation of researchers who should be trained to be able to find new problems rather than to wait for these problems to be put forward by researchers in other disciplines. This new generation of scientists should be able to exercise its own judgment about writing new models and equations. This ability must be acquired by hands-on training in the studied disciplines in experimental laboratories. Then the mission of applied mathematics should be to analyze and solve the requisite equations, giving precise quantification, making predictions, and reporting new features hitherto unobserved.

The training of applied mathematicians and physicists for interdisciplinary research requires a major deviation from traditional disciplinary educational programs. In effect, it requires the extension of the scientific background of students from a single discipline to several disciplines. The basis of training should still be classical applied mathematics, including all branches of classical analysis, probability, modern statistics and stochastic processes, differential geometry, approximation methods and asymptotic analysis, complex variables, dynamical systems, fluid dynamics, numerical simulations, computer science, and modern harmonic analysis and its applications. The interdisciplinary program requires in addition a formation in complementary fields such as a full curriculum of undergraduate classical physics, including statistical physics, chemistry and physical chemistry. To establish communication with life scientists, it is necessary for the student to acquire at least an undergraduate training in the biochemistry of the cell, and in cellular and molecular biology, biophysics, neurobiology, genetics, and any field of life science of interest. This training should include lab work and familiarity with laboratory instrumentation and experimentation. Additional preparation in computer science should include scientific computer programming for writing heavy computational codes for the numerical solution of partial differential equations and for simulation of stochastic processes, signal processing and analysis of large sets of data. A complete interdisciplinary training requires perforce a much more intense period of learning than the traditional disciplinary program but should still be manageable within the time normally taken to acquire a PhD.

Afterword

The complexity of biological structure and function exceeds that of all other disciplines combined together, because living organisms are creations of a billion years of evolution of many configurations of very few elements on many different scales. Unraveling some of this complexity poses a new challenge to mathematical thinking. We must endeavor to train a new generation of scientists who can meet this challenge.

Acknowledgement: We thank Gordon Fain for comments on this program.