Commentary: New mathematical physics needed for life sciences
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Citation: Physics Today 69(1), 10 (2016); doi: 10.1063/PT.3.3036
View online: http://dx.doi.org/10.1063/PT.3.3036
View Table of Contents: http://scitation.aip.org/content/aip/magazine/physicstoday/69/1?ver=pdfcov
Published by the AIP Publishing
Commentary

New mathematical physics needed for life sciences

The complexities of biological structure and function far exceed those in any other discipline. The evolution of living organisms began four billion years ago and has involved untold numbers of configurations of a few chemical elements on many different scales of length and time. Unraveling some of those complexities challenges the mathematics and physics communities to train a new generation of scientists. (See, for example, the article by Rob Phillips and Steve Quake, PHYSICS TODAY, May 2006, page 38.)

In the past 15 years, new technologies have allowed biologists to see biological functions in vivo at an unprecedentedly high spatiotemporal resolution. Live-cell imaging has led to significant advances in understanding cellular function at the molecular level. Major progress in understanding how biology gets the job done has also come from combining techniques from genetics and physiology, such as silencing a gene to shut down the expression of proteins, or from making perturbations that elucidate specific molecular pathways. The physics and chemistry communities have brought physical insights to biophysics and cell biology. The division of tasks among the different disciplines in molecular and cellular biology essentially ended with the advent of those and other new transdisciplinary approaches.

Mathematical physics, or applied mathematics, is slowly shifting its focus from quantum mechanics and the classical mathematics of continuous media to the mathematics of life sciences and medicine, which are rapidly becoming a part of the mainstream physical sciences. The new aspect here is the huge number of degrees of freedom. The aim of the new mathematics and theoretical physics is to simplify the statistical physics of complex biological systems by recasting it as the exploration of measurable physical parameters in low-dimensional spaces.

The role of applied mathematics in emerging fields needs to shift from analyzing mathematical models derived from classical and modern physics to creating appropriate new mathematical frameworks. Such frameworks are needed for developing new mathematical models, coarse-graining and deriving equations, and guiding and interpreting measurements and experiments. They are also necessary for reducing the huge number of degrees of freedom of molecular biophysics and devising new computational and computer simulation methods. The equations of applied mathematics in the life sciences will raise new questions. Their solutions will require designing new asymptotic approximation methods and numerical simulations of the inherently stochastic particle systems that represent the microstructures of molecular and cellular physiology, including neurophysiological phenomena.

New directions

For biological components and their physical properties, mathematical models based only on the physical properties of the structures are among the most challenging to generate. They should mostly arise from the classical physical properties of ions and other microscopic particles in solution. The aim of such models is to predict the behavior of cells and subcellular phenomena. For example, they could be used to describe the diffusional motion of ions, molecules, proteins, and fluxes in cardiac myocytes, neuronal or glial cells, or pancreatic beta cells.

Publications in reference 2 illustrate the role of stochastic modeling in the analysis of large data sets of single-particle trajectories. That modeling led to the discovery of local wells; their origin is still unknown, but they appear to regulate molecular trafficking in several microdomains. Other theoretical problems raised by large data sets are the reconstruction of a cell’s surface and its local structure from the planar projections of trajectories of diffusing molecules, solved by deriving new nonlinear partial differential equations. Models are needed to describe how cells move and grow based on molecular trafficking, how a cell can repair itself, or how viruses and their DNA or RNA find targets inside a cell.

Using polymer physics to understand the organization of the nucleus is a challenge that requires extracting information from the large data sets of distances between monomers on chromatin, the macromolecular complex in a nucleus that helps compactify DNA. In a different direction, understanding and predicting the function of the brain during external activity or after the application of drugs...
may help in developing methods to prolong the independence of aging patients. The design of neural networks based on rational models of synaptic dynamics is difficult given that the human brain contains around 100 billion neurons. The effect of the changing geometry of neurons, axons, and dendrites during learning or fetal development is a compelling subject for mathematical modeling. Its solution is likely to entail the development of a new multiscale geometry of cells and their assemblies.

A plethora of unsolved questions calls for novel ideas in modeling, analysis, numerical simulations, and statistics. For example, it is unclear how to model the motion of charged particles in cellular microdomains or at what scale electroneutrality is satisfied. New charge-conservation equations and their analyses are needed for understanding how electrical current is regulated in cells. The diffusion of shaped molecules in nano- and microdomains remains a challenge, especially at synapses where the molecule’s position is a key determinant of the signal transmission between neurons. Additionally, computing the diffusion flux through shaped windows, such as two-dimensional rectangles, is still an open mathematical question.

A few novel mathematical and physical methods have already been developed in attempts to answer biophysics and cell biology questions. A recent one is the narrow escape theory—a known as the small hole theory—for computing both the mean time for a diffusing particle to find a small target and the flux through narrow openings under various geometrical constraints.

**The educational challenge**

The reconfiguration of the mathematical sciences calls for a new generation of researchers who are trained to find problems rather than wait for them to emerge from other disciplines. These scientists need to exercise their own judgment about writing models and equations, abilities that must be acquired by hands-on training and experiment. The new applied mathematicians should be able to develop, analyze, and solve the requisite equations; give precise quantification; make predictions; and report novel features.

The training of applied mathematicians and physicists for biological research requires a major deviation from traditional disciplinary educational programs. It needs to broaden students’ scientific background beyond a single discipline. We are heartened to note that the undergraduate physics curriculum is beginning to address such relevant issues as conceptual and vocabulary mismatches between physics and the life sciences (see the article by Dawn Meredith and Joe Redish, PHYSICS TODAY, July 2013, page 38).

The basis of graduate-level training should still be classical applied mathematics, including all branches of analysis, probability, modern statistics, differential geometry, approximation methods, dynamical systems, fluid dynamics, and numerical simulations. In addition, the interdisciplinary program requires work in complementary fields: a full curriculum of undergraduate classical physics, chemistry, and physical chemistry. To work effectively with life scientists, students also need at least undergraduate training in cell biochemistry, cellular and molecular biology, biophysics, neurobiology, and genetics. That training,
which should include laboratory instrumentation and experimentation, is essential to develop students’ judgment about experimental data. Complete interdisciplinary training is perforce much more intense than the traditional single-discipline program, but it should still be manageable within the time normally needed to earn a PhD.

To benefit from this new generation of theoreticians, experimental biologists should also enlist physical scientists in their studies. That collaboration would cover two areas—the development of instrumentation and the interpretation of experimental data. With such interdisciplinary cooperation, great progress can be expected, much like the contribution of theoreticians, experimental biologists and physicists to nuclear power plants.

We thank Gordon Fain for comments on this manuscript.

References