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 biophysical 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.[1] 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,[3] but they appear to regulate molecular trafficking in several microdomains. Other theoretical problems raised by large data sets[4] 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

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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[1]—also 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,

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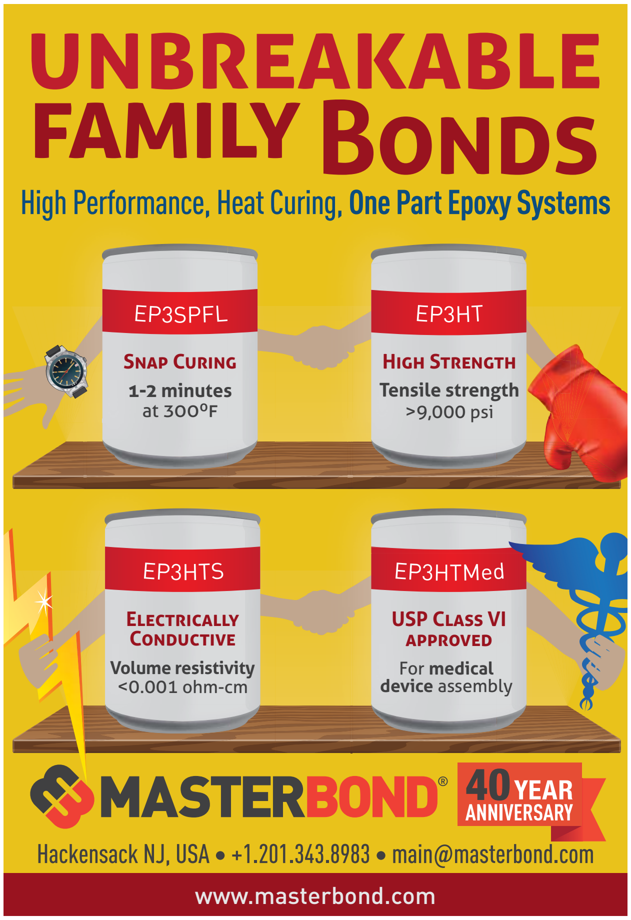

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which should include laboratory instrumentation and experimentation, is essential to develop students' judgment about experimental data. Complete interdisciplinary training is perforce much more intense than the traditional single-discipline program, 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[5] and the interpretation of experimental data. With such interdisciplinary cooperation, great progress can be expected, much like the contribution of the physical sciences to engineering. Naturally, interdisciplinary research requires that results be accessible to a wide audience, so the relevant mathematical research must be published not only in applied math journals but also in journals in other studied fields.

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LETTERS

Low-dose radiation exposure should not be feared

Scientific achievement has a muddled, disordered topography, with landscapes that include both great pinnacles of success and deep crevices of failure. We focus on one failure that remains uncorrected: the linear no-threshold (LNT) model of radiation-induced cancer, on which governments and advisory bodies have based regulatory policy for 70 years. High-dose radiation can cause cancer, but no such correlation has ever unequivocally been shown at low doses in the range of x-ray and computed tomography (CT) examinations or in the vicinity of nuclear power plants.

The proven consequence of high doses of radiation has simply been assumed to apply even at doses near zero, and no threshold has been given below which it is harmless. Consequently, all doses have been predicted to cause cancer. But as many studies prove,[1,2] the body responds differently to radiation at high and low doses: At low doses, the body eliminates the damage through various protective mechanisms that have evolved in humans from eons of living in a world bathed in low dose-rate but sometimes high-dose natural radiation.

Based on the Japanese government's unwarranted fear that any radiation exposure would increase cancer cases, residents were forcibly evacuated from around the Fukushima nuclear plant, a decision that according to the government's own figures resulted in more than 1600 deaths. The Japanese Cabinet recently decided to lift evacuation orders; whether residents will actually return is uncertain due to the radiophobia instilled in them over the past four years. Reliance on the LNT model has resulted in even larger health and economic impacts at Chernobyl. All such devastating consequences of using the LNT model to form policy and standards have prompted three recent petitions to the US Nuclear Regulatory Commission to reject the flawed model, whose origin can be traced to the work of Hermann Muller and colleagues.

Nobelist Muller, a founding proponent of the LNT model, investigated x-ray effects on fruit-fly gene mutations. He claimed in his 1946 Nobel lecture that the mutation rate was a linear function of dose down to zero, independent of dose rate, with no threshold below which there is no effect. Muller based his claim on his testing at doses that are actually high—at least 4000 mGy. For comparison, US natural radiation exposure averages 3 mGy annually, and a typical CT scan is 10 mGy. Thus Muller's extrapolation of harm down to zero dose was untrue.

In 1948–49, research by Muller's colleague Curt Stern[3] found that at doses below 500 mGy, flies often had mutation rates similar to or even lower than unirradiated flies, and these mutation rate differences decreased if the dose rate was reduced. Those findings clearly suggest protective responses and a no-harm threshold somewhere below 500 mGy. Some of the results were inconsistent, but rather than continue testing, the researchers arbitrarily decided that there was no threshold and that dose rate was irrelevant; they thus reinforced Muller's false claim.

Fortunately, those researchers left a trail of published data that does confirm a threshold, contrary to their claim. Apparently, neither they nor any others noticed that result until we recently discovered it.[4]

Muller's and Stern's approaches survive in the LNT model of today, which says that low-dose radiation increases cancer risk. However, while linearity—the "L" in LNT—was demonstrated only at high doses, the absence of a threshold has never been demonstrated. The only scientific conclusion from the data from 1949 through today is that the linear threshold (LT) model, not the LNT, is correct, and it has a low-dose threshold below which radiation is harmless. Even data from atomic-bomb survivors, the gold standard of dose-response data, do not support the LNT model; adaptive protections mitigate radiation-induced damage at low doses and low dose rates. No epidemiological studies have ever demonstrated a causal relationship between low-dose radiation exposure and carcinogenesis.

Many people, though they admit the absence of evidence, nevertheless believe that "precautions" derived from the LNT