Introduction to Biophysics Week: What is Biophysics?

Biophysics is a thriving discipline, as is evident by the breadth and depth of the science that is being presented at the Biophysical Society Annual Meetings and published in *Biophysical Journal*. Yet, biophysics also has an identity problem—due to the wide range of research topics that properly fall under the general rubric of biophysics—and biophysicists often find themselves challenged when asked to describe what the term actually represents.

Biophysics, as a distinct discipline, can be traced to a "gang of four": Emil du Bois-Reymond, Ernst von Brücke, Hermann von Helmholtz, and Carl Ludwig—all four being physicians and the former three being students of the great German physiologist Johannes Müller, who, in 1847, got together to develop a research program based on the rejection of the, at the time, prevailing notion that living animals depend on special biological laws and vital forces would differ from those that operate in the domain of inorganic nature. In contrast, the group sought to explain biological function using the same laws as are applicable in the case of physical and chemical phenomena. As stated by Ludwig and quoted from Cranefield (1) "We four imagined that we should constitute physiology on a chemico-physical foundation, and give it equal scientific rank with Physics." They coined the term "organic physics," and du Bois-Reymond stated, in the introduction to his seminal work *Untersuchungen über thierische Elektrizität* (http://vlp.mpiwg-berlin.mpg.de/library/data/lit28623/index_html?pn=1&ws=1.5), that (translation by Cranefield (1)) "it cannot fail that … physiology … will entirely dissolve into organic physics and chemistry."

It did not quite work out that way and, despite the scientific accomplishments of these four, in particular Helmholtz and Ludwig, the program faltered. In 1982, when Karl Pearson introduced the term "Bio-Physics" in *The Grammar of Science* (2) to describe the science that links the physical and biological sciences, he also noted "This branch of science does not appear to have advanced very far at present, but it not improbably has an important future."

Indeed, more or less as Pearson wrote these pithy comments, Julius Bernstein (3) published his description of a possible mechanistic basis for the development of transmembrane potential differences based on studies by Nernst and Planck on electrodiffusion. A few years later, Archibald V. Hill published his seminal work on the Hill equation (4). Both studies are reminiscent of the 1847 group's program and serve as prototypical examples of biophysics as the quantitative study of biological phenomena.

The mainstay of biophysical research in the early part of the twentieth century was neuro- and muscle physiology, disciplines that lend themselves to quantitative analysis and in which most of the investigators had trained in biology or medicine. In the latter half of the century, an increasing number of biophysicists were trained in chemistry, physics, or mathematics, which led to the development of the modern generation of optical and electron microscopes, fluorescent probes (whether small molecules or genetically encoded proteins), synthetic oligonucleotides, magnetic resonance and diffraction methods, as well as the computational methods that, by now, have become indispensable tools in biophysical research. Yet, we continue to face the question, "What is biophysics?" Maybe the best way out of this conundrum is to heed the advice of A.V. Hill, who long ago noted that "the employment of physical instruments in a biological laboratory does not make one a biophysicist," rather it is "the study of biological function, organization, and structure by physical and physicochemical ideas and methods" (5). It is the mindset—the focus on the importance of providing a quantitative, theoretically based, analysis of the problem under study—that is important! This emphasis on theory and quantitation is central to the methodological developments that provide the foundation for current biophysical research. It also leads to a possible answer to question in the title—biophysics is the quantitative approach to the study of biological problems.

Indeed, we are beginnning to fulfill the vision of the "gang of four" in 1847, based in large part on the emerging convergence of increasingly sophisticated quantitative experimental approaches together with computational studies, such as molecular dynamics simulations that use classical and statistical mechanics to explore protein function. Some of these developments are summarized in the following series of articles which has been compiled by the Biophysical Society's Publications Committee in conjunction with Biophysics Week to provide an overview of the state of biophysical studies and to heighten the awareness of the importance of biophysics as a central discipline in modern biological research.

One of the driving forces in current biophysical research has been the development of novel microscopes that make it possible to visualize structures at spatial resolutions that transcend the diffraction barrier. The diffraction barrier limits the ability of optical microscopes to distinguish among points that are separated by (lateral) distances less than one-half the wavelength of the light that is used to

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visualize the specimen of interest. Another force in biophysical research has been the development of (usually) fluorescent probes that make it possible to visualize living cells, including cells deeply embedded in tissues and even live animals. Many of the exciting advances in optical microscopy are summarized in the contribution by Rick Horwitz "Cellular Biophysics."

Genetically encoded fluorescent probes have proven to be particularly powerful tools because they can be targeted to specific cells and intracellular organelles, thereby facilitating exploration of problems that were beyond the capability of chemical probes. Targeting probes to specific cell types in a tissue means that investigators can study living cells and tissues at high spatial and temporal resolution and can use focused light impulses to manipulate genetically encoded targets, thereby manipulating cell function at the whole organism level. In this latter approach, the role of the microscope has changed fundamentally from being a tool to observe biological function to becoming a tool to manipulate biological function. The discoveries that led this important and novel field, coined optogenetics, are discussed in the contribution by Adam E. Cohen "Optogenetics: Turning the Microscope on Its Head."

The power of optical microscopy also enables researchers to probe the forces that underlie macromolecular function at the single-molecule level. The ability to visualize the function and motions of individual molecules leads to qualitatively different studies than are possible using measurements on ensembles of molecules, which only report on the average behavior of the ensemble. For example, if you want to elucidate the mechanics of human locomotion, it would not be very helpful to observe the movement of marathon runners across the Verrazano-Narrows Bridge in the New York Marathon; you would need to focus on the motion of individual runners to understand the sequence of events. Proteins and nucleic acids similarly undergo complex motions that best are examined at the single-molecular level, and Taekjip Ha's article "Probing Nature's Nanomachines One Molecule at a Time" describes some of the exciting developments in this rapidly expanding field.

The advances described by Horwitz, Cohen, and Ha build on developments in optical microscopy; equally important advances have taken place in electron microscopy. A new generation of cryo-electron microscopes with direct electron detectors enables atomic resolution studies on macromolecular structures based on images of thousands of individual molecules. This approach differs fundamentally from the analysis of crystal diffraction patterns or distance constraints obtained in nuclear magnetic resonance studies, and the novel developments allow researchers to determine the atomic resolution structures of macromolecules that cannot be crystallized, which has led to a revolution in structural biology. Edward H. Egelman's "The Current Revolution in Cryo-EM" traces the key methodological advances that underlie the current revolution, which depend not only on the advances in the hardware, but also on advances in the software that is required to process the large amount of data needed for the elucidation of atomic resolution structures.

As noted in Taekjip Ha's contribution, proteins are nanoscale machines that underlie much of what we consider to be characteristic of life. Because normal life (health) is so critically dependent on the proper function of these nanoscale machines, it often has been assumed that proteins need to be folded into well-defined structures to accomplish their intended functions; this turns out to be incorrect! Over the last 20 years or so, it has become apparent that many important proteins have amino acid sequences that cannot fold into conventional folded structures. This has led to a fundamental revision of the relation between protein sequence, structure, and function. These developments are summarized by H. Jane Dyson in "Intrinsically Disordered Proteins." Somewhat surprisingly, many intrinsically disordered proteins, or disordered regions within otherwise well-folded proteins, turn out to function as key elements in protein interaction networks. Moreover, because these sequences are disordered, they are susceptible to chemical modification that often is critical for normal (as well as abnormal) function, which makes them useful for designing targeted interventions.

Many human diseases result from mutations that alter the sequence and thus the function of important proteins. In some cases, the changes in function can be understood "simply" from how a given mutation alters the function of the cells that host the protein; in other cases, it becomes necessary to understand how the mutation alters the function of systems of interacting cells. This change in thinking, from focusing on the intrinsic properties of, for example, proteins or cells in isolation, to exploring the complex interactions that occur at the molecular, cellular, and system levels becomes important for understanding not only how normal body function is maintained, but also how human disease develops. In their article "Inherited Arrhythmias: Of Channels, Currents, and Swimming" Maura M. Zylla and Dierk Thomas discuss how inherited arrhythmias are best understood through such multiscale approaches, using the family of diseases that are lumped under the rubric, the long QT syndrome, which may cause sudden cardiac death due to the development of fatal arrhythmias. Most cases of sudden cardiac death are due to degenerative changes in the coronary vessels. A small fraction, however, results from changes in the function of a family of membrane proteins, the ion channels, that are responsible for normal cardiac rhythmicity. These changes in rhythmicity can lead to sudden loss of consciousness and even death—often in young people. As noted by Zylla and Thomas, an abnormal increase in the duration of the electrical impulses (the action potentials) that drive the heart and pump blood throughout the body may paradoxically lead to an, often sudden, increase in heart rate that may

compromise the heart's ability to move blood through the body. Reduced blood flow to the brain may lead to the sudden unconsciousness and death that are characteristic of this class of diseases. This is a situation where it becomes important to be able to sort through the underlying problems at many different levels of complexity, ranging from isolated channels to cells to how the cells are organized and interact in the tissues of the heart. Once these interactions are understood through biophysical analysis, it becomes possible to develop rational therapies.

The importance of multiscale approaches to understand both normal and abnormal body function is developed further by Andrew D. McCulloch in "Systems Biophysics: Multiscale Biophysical Modeling of Organ Systems." Focusing again on the heart, McCulloch emphasizes how it becomes important to understand the system at many different, mutually interacting, levels of complexity. The electrical system triggers the contractions of the cardiac cells that make the heart an efficient pump; however, to fully understand the heart's mechanical performance, it is necessary to delineate the coupling between the atria and the ventricles as well as the dynamics of the heart valves and the blood flow through the coronary circulation. Problems must be approached from the molecular to the tissue level and then coupled with the electrical and mechanical performance to develop an understanding of overall heart function, which can be accomplished through multiscale computational modeling.

The final contribution in this series, "How Viruses Invade Cells," is by Fred Cohen, who describes the mechanism(s) by which important viruses, such as influenza, HIV, and Ebola, are able to infect cells and "highjack" cellular processes. These cellular processes would normally support the regulated turnover of membrane components as well as cell division, but they are diverted to produce proteins encoded by the virus genome, which is necessary for viral replication and exit from the cells, leading to the infection of other cells. A key first step in viral infection is to insert the viral genome into the cell that is being attacked. This often happens through a series of processes that begin with viral uptake into lysosomes that normally are charged with hydrolyzing ingested materials. Once in the lysosome, the viral envelope fuses with the lysosomal membrane, a process that is activated by the very acid environment in the lysosome, and the viral genetic enters into the host cell's cytoplasm. As noted by Cohen, the most reliable way to prevent infection is to eliminate viral entry. To do so, however, requires understanding the underlying mechanisms of this process, which depends on the sophisticated methods that have been described in other contributions in this collection.

The contributions in this collection are not intended to provide a comprehensive overview of the excitement and importance of biophysical research. Rather, they provide examples of how one can use the power of the biophysical approach—the methods and analysis, the emphasis on quantitation, and the conceptual approach to problem solving—to understand important questions related to both normal and abnormal biological function, including human disease.

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REFERENCES

1. Cranefield, P. F. 1957. The organic physics of 1847 and the biophysics of today. *J. Hist. Med. Allied Sci.* 12:407–423.
2. Pearson, K. 1900. The Grammar of Science, 2nd Ed. Adam and Charles Black, London.
3. Bernstein, J. 1902. Untersuchungen zur Thermodynamik der bioelektrischen Ströme. Arch f. *Physiologie.* 92:521–562.
4. Hill, A. V. 1910. The possible effects of the aggregation of the molecules of hæmoglobin on its dissociation curves. *J. Physiol.* 40:iv–vii.
5. Hill, A. V. 1956. Why Biophysics? *Science.* 124:1233–1237.