

Mathematics, Biology, and Physics: Interactions and Interdependence

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Introduction

Modern science has a solid conceptual framework and considers experimental results as the ultimate litmus test against which to validate any theoretical construct. Its birth can be traced back to the sixteenth and seventeenth centuries. The work of people like Nicolaus Copernicus, Galileo Galilei, Isaac Newton, Johannes Kepler, William Harvey, Vesalius, and others was seminal to this development. Before the so-called scientific revolution, natural philosophers (the forefathers of scientists as we know them today) did not perform experiments, as manual labor was considered a lower-class activity. This attitude, inherited from the Greeks, changed between the sixteenth and the eighteenth centuries, as merchants and craftsmen gained economic and political power. As a result, economics, politics, and science went through significant changes. In that period, democracy, capitalism, and modern science were founded and emerged as the cornerstones of a new era.

During the Enlightenment, in the latter part of the eighteenth and early part of the nineteenth centuries, scientific disciplines started to be hierarchically classified. This classification works well in some instances, and without it, dealing with the rapidly growing body of knowledge of the past two hundred years would have been difficult. However, it fails to fairly represent the interdisciplinary work which has been, and continues to be, highly important. In this paper we give a taste of the rich

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historical relation between physics, mathematics, and the biological sciences. We argue that this will continue to play a very important role in the future, based on historical examples and on a brief review of the current situation.

The 18th and 19th Centuries

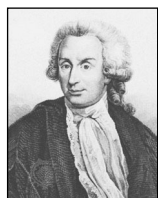
Electrophysiology is the science that studies the interaction between electromagnetic fields and biological tissues. This includes the generation of electric or magnetic fields and electric currents in some specialized organs, the intrinsic electric and magnetic properties of tissue, the response of specialized cells (like neurons and muscle cells) to stimulation, etc. Up to the middle of the nineteenth century, the historical development of electrophysiology paralleled that of electromagnetism. The first electric generating machines and the Leyden jar were constructed to produce static electricity for a specific purpose: to “electrify” and stimulate humans. The Voltaic pile was developed with the idea of galvanic (i.e. direct current, as opposed to faradic or alternating current) stimulation. Bioelectric and biomagnetic measurements were the incentive for the development of sensitive measurement instruments, like the galvanometer and the capillary electrometer. Thus, it is no surprise that some scientists of the time made important contributions to the development of both the biological and the physical sciences. In the following paragraphs we present a brief review of the contributions of some of these interdisciplinary workers. We do not attempt to present a detailed review of the history of electrophysiology, as our purpose is only to exemplify the rich interdisciplinary interactions of the eighteenth and nineteenth centuries.

The essential invention necessary for the application of a stimulating electric current was the Leyden jar (a capacitor formed by a glass bottle covered with metal foil on the inner and outer surfaces), independently invented in Germany (1745) and The Netherlands (1746). With it, Benjamin Franklin's experiments allowed him to deduce the concept of positive and negative electricity in 1747. Franklin also studied atmospheric electricity with his famous kite experiment in 1752. Many American school children have heard the apocryphal stories of Franklin flying kites during thunderstorms with strings soaked in salt water.



Franklin

The most famous experiments in neuromuscular stimulation of the time were performed by Luigi



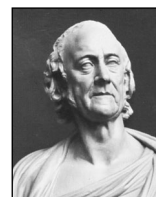
Galvani

Galvani, professor of anatomy at the University of Bologna. His first important finding is dated January 26, 1781. A dissected and prepared frog was lying on the same table as an electric machine. When his assistant touched the femoral nerve of the frog with a scalpel, sparks were simultaneously discharged in the nearby electric machine, and violent muscular contractions occurred. (It has been suggested that the assistant was Galvani's wife, Lucia, who is known to have helped him with his experiments). This is cited as the first documented experiment in neuromuscular electric stimulation.

Galvani continued the stimulation studies with atmospheric electricity on a prepared frog leg. He connected an electric conductor between the side of the house and the nerve innervating the frog leg. Then he grounded the muscle with another conductor in an adjacent well. Contractions were obtained simultaneously with the occurrence of lightning flashes. In September 1786, Galvani was trying to obtain contractions from atmospheric electricity during calm weather. He suspended frog preparations from an iron railing in his garden by brass hooks inserted through the spinal cord. Galvani happened to press the hook against the railing when the leg was also in contact with it. Observing frequent contractions, he repeated the experiment in a closed room. He placed the frog leg on an iron plate and pressed the brass hook against the plate, and muscular contractions occurred. Systematically continuing these experiments, Galvani found that when the nerve and the muscle of a frog were simultaneously touched with a bimetallic strip of copper and zinc, a contraction of the muscle was produced. This experiment is often cited as the classic study to demonstrate the existence of animal electricity. Galvani did not understand the mechanism of the stimulation with the

bimetallic strip. His explanation for this phenomenon was that the bimetallic strip was discharging the animal electricity existing in the body.

Galvani's investigations intrigued his friend and colleague Alessandro Volta (professor of physics in Pavia), who eventually came up with a totally different (and correct) explanation for the phenomena that Galvani was trying to explain. In the process, Galvani and Volta maintained their friendship (in spite of their differences of scientific opinion), and Volta developed the ideas that eventually led to the invention of the Voltaic pile in 1800 (forerunner of the modern battery), a battery that could produce continuous electric current. Incidentally, Volta completed the equivalent of his doctoral dissertation when he was fifty years old!



Volta

All of these contributions to electrophysiology were experimental. The first significant theoretical contributions were made by the German scientist and philosopher Hermann Ludwig Ferdinand von Helmholtz. A physician by education and appointed professor of physiology at Königsberg in 1849, he moved to the chair of physiology at Bonn in 1855. In 1871 he was awarded the chair of physics at the University of Berlin. Helmholtz's fundamental experimental and theoretical scientific contributions in the field of electrophysiology included the demonstration that axons are extensions of the nerve cell body, the establishment of the law of conservation of energy (the First Law of Thermodynamics), the invention of the myograph, and the first measurement of the action potential conduction velocity in a motor nerve axon. Besides these, the contributions of Helmholtz to other fields of science include fundamental work in physiology, acoustics, optics, electrostatics, thermodynamics, and meteorology. He invented the ophthalmoscope and was the author of the theory of hearing from which all modern theories of resonance are derived. Another important contribution to the development of biophysics was Helmholtz's philosophical position in favor of founding physiology completely on the principles of physics and chemistry at a time when physiological explanations were based on vital forces that were not physical in nature.



von Helmholtz

The 20th Century

In the eighteenth and nineteenth centuries interdisciplinary research bridging physics, mathematics, and biology was carried out by scientists educated as physicians. The twentieth century witnessed a reversal of this trend, with major contributions to

biology from people with solid backgrounds in physics and mathematics. There are two of these disciplines in which the contributions by physicists and mathematicians were particularly important: electrophysiology (following the tradition of Galvani, Volta, Helmholtz, etc.) and molecular biology.

Electrophysiology

The growth of biophysics owes much to A. V. Hill, whose work on muscle calorimetry was essential to our understanding of the physiology of muscle contraction. Hill received an undergraduate degree in physics and mathematics and a doctorate in physiology, all from Cambridge. Besides his work on muscle contraction, Hill also addressed problems related to the propagation of the nervous impulse, the binding of oxygen by hemoglobin, and calorimetry of animals. He discovered that heat



Hill

is produced during the nerve impulse. Hill's original papers reveal an elegant mixture of biological concepts and experiments, together with physical and mathematical theory and insight. His discoveries concerning the production of heat in muscle earned him the Nobel Prize in 1922, and his research gave rise to an enthusiastic following in the field of biophysics. He was instrumental in establishing an extremely successful interdisciplinary school in Cambridge, whose investigators received a number of Nobel Prizes.

A few years later, Bernard Katz, working at University College London with his student Paul Fatt, made a major advance in our understanding of the chemical and quantal nature of synaptic transmission. The papers "An analysis of the end-plate potential recorded with an intra-cellular electrode" and "Spontaneous subthreshold activity at motor nerve endings" were marvels of experimental investigation combined with mathematical modelling of stochastic processes.



Katz

Katz was one of the recipients of the 1970 Nobel Prize for "discoveries concerning the humoral transmitters in the nerve terminals and the mechanism for their storage, release and inactivation."

Jumping back a few decades, the German physical chemist Walter Nernst was interested in the transport of electrical charge in electrolyte solutions. His work intrigued another physicist, Max Planck, one of the fathers of modern quantum theory. He extended Nernst's experimental and theoretical work, writing down a transport equation (the Nernst-Planck equation) describing the current flow in an

electrolyte under the combined action of an electric field and a concentration gradient.

This work lay largely forgotten until the 1930s, when it was picked up by the physicist Kenneth S. Cole at Columbia University and his graduate student David Goldman (originally trained in physics). They realized that the work of Nernst and Planck (in the form of the Nernst-Planck equation) could be used to describe ion transport through biological membranes and did so with great effect. Their work resulted in the development of the Goldman equation, which describes the membrane equilibrium potential in terms of intra- and extracellular ionic concentrations and ionic permeabilities. This background theoretical work of Nernst and Planck was also instrumental in helping Cole to experimentally demonstrate that there was a massive increase in membrane conductance during an action potential.



Nernst



Planck

Two of the most distinguished alumni of Hill's Cambridge interdisciplinary school were A. L. Hodgkin and A. F. Huxley. Both studied physics, mathematics, and physiology at Trinity College, Cambridge. At the time, high table included an astonishing array of scientific talent with people like J. J. Thomson, Lord Rutherford, F. W. Aston, A. S. Eddington, F. G. Hopkins, G. H. Hardy, F. J. W. Roughton, W. A. H. Rushton, A. V. Hill, and E. D. Adrian. Hodgkin and Huxley developed a long-lasting collaboration, interrupted only by the outbreak of World War II.



Cole

In 1938 Hodgkin spent the summer with Cole at Woods Hole, and they demonstrated the overshoot of the action potential, which had significant implications in terms of potential ionic mechanisms. It seems reasonable to suppose that Cole and Hodgkin discussed the possible meanings of these discoveries and what types of experiments were needed to determine exactly what was going on. Because of their training they would have seen that some means must be found to bring under experimental control the variable (either membrane current or membrane voltage) that is responsible for the all-or-nothing behavior of the action potential. Hence taming the action potential required controlling either the current or the voltage. They realized that space clamping was necessary for both current and voltage clamping. Since both knew cable theory, they knew that space clamping was best done by drastically reducing internal resistance (space clamping), so the

space constant was much longer than the length of the axon under study.

The Second World War interrupted these investigations, and Cole, like hundreds of other scientists, was caught up in the war effort. Cole moved from Columbia to the Manhattan Project in Chicago and worked on radiation dosimetry and radiation damage in tissues during the war. After the war he was at the University of Chicago for a few years. When the war was over, one of the positive outcomes was the existence of high transconductance vacuum tubes, which had been developed for the amplifiers in radar receivers. Cole, working with Marmont in Chicago, used these new electronic advances to build a feedback circuit that allowed them to space clamp axons. These axons developed an all-or-none action potential when sufficiently depolarized. The implication was that voltage clamping was necessary to tame the axon to measure the dependence of membrane current on membrane voltage.

Shortly after the war (1948), Hodgkin visited the United States and Cole's laboratory in Chicago and realized that the results of the space clamp experiments meant that voltage clamping was the way to go. On his return to England he teamed up with Huxley to really measure what was going on during the generation of an action potential in the squid giant axon. This work was published in a brilliant series of five papers in the *Journal of Physiology* in 1952. The final one is an intellectual tour de force combining both experimental data analysis and mathematical modelling (the Hodgkin-Huxley equations). This work won Hodgkin and Huxley the Nobel Prize in 1963, along with J. C. Eccles, "for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane."

Huxley, the mathematician/physiologist, was not content to stop there, however, and went on to publish in 1957 his celebrated review of muscle contraction data and its synthesis into the mathematically formulated cross bridge theory, a theory that still stands in its essential ingredients today.

The Hodgkin-Huxley model for excitability in the membrane of the squid giant axon is complicated and consists of one nonlinear partial differential equation coupled to three ordinary differential equations. In the early 1960s Richard FitzHugh applied some of the techniques that he had learned from the Russian applied mathematics literature to an analysis of the Hodgkin-Huxley

equations. That reduction of the Hodgkin-Huxley equations later became known as the FitzHugh-Nagumo model and has given us great insight into the mathematical and physiological complexities of the excitability process. Another consequence of the Hodgkin-Huxley model, taken to its interpretational extreme, was the implication that there were microscopic "channels" in the membrane through which ions would flow and which were controlled by membrane potential. There were strong experimental data also leading to the same conclusion, including the binding of tetrodotoxin (TTX) to nerve membranes to block sodium currents, titration studies indicating that there were about 20 TTX binding sites per square micrometer, and membrane noise measurements.

However, it was left to the German physicist Erwin Neher, in conjunction with the physiologist Bert Sakmann, to develop the patch clamping technology and techniques that eventually allowed them to demonstrate the existence of these ion channels. They were awarded the Nobel Prize in 1991 for this work. Modifications of the Hodgkin-Huxley equations were soon proposed for cardiac tissue as well as a myriad of other excitable cells.

Extensions of the work of Hodgkin and Huxley soon followed. For example, J. W. Woodbury (a physicist turned physiologist) and his student W. E. Crill found that current injected into one cell in a sheet of heart muscle changed the membrane voltage in nearby cells in an anisotropic manner. This showed that there must be low resistance connections between abutting cells in heart tissue and paved the way for the discovery and characterization of gap junctions between the cells (in a variety of tissues such as epithelia). Woodbury also showed that Eyring reaction rate theory (learned from his famous foster thesis advisor, Henry Eyring) can be used to explain the linear current-voltage relationship of open sodium channels. This is done by choosing the appropriate electrochemical potential profile encountered by a sodium ion while traversing a Na ion channel. This, together with other lines of experimental evidence mentioned above, established the feasibility of the ion channel concept before single-channel conductances were directly measured by Neher.

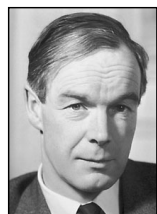
One of the most remarkable individuals interested in the dynamic behavior of simple nervous



FitzHugh



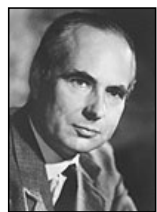
Neher



Hodgkin



Woodbury



Huxley

systems was H. K. Hartline of the Johns Hopkins University. Hartline was trained as a physiologist, and following receipt of his M.D., he spent an additional two years at Hopkins taking mathematics and physics courses. For some unaccountable reason he was still not satisfied with his training and obtained funding to study for a further year in Leipzig with the physicist Werner Heisenberg and



Hartline

a second year in Munich with Arthur Sommerfeld. Armed with this rather formidable training in the biological, mathematical, and physical sciences, he then devoted the majority of his professional life at Hopkins to the experimental study of the physiology of the retina of the horseshoe crab *Limulus*. His papers are a marvel of beautiful experimental work combined with mathematical modelling designed to explain and codify his findings. His life work justly earned him the Nobel Prize in 1967 (with George Wald) “for his discoveries concerning the primary physiological and chemical visual processes in the eye.” As an aside, we should point out that FitzHugh (of the FitzHugh-Nagumo reduction of the Hodgkin-Huxley model) received his Ph.D. in biophysics (where he learned mathematics, physics, and chemistry) under Hartline after completing his biological studies at the University of Colorado.

One can hardly underestimate the impact that this work in excitable cell physiology has had on the biological sciences, since the impact is so broad and pervasive. The *Notices of the American Mathematical Society* (December 1999) has a very nice article by Nancy Kopell with some of the mathematical side of the story, and *Nature Neuroscience* (November 2000) featured some of this from a biological perspective in an interesting and lively series of survey articles.

Molecular Biology

Genetics started in 1866, when Gregor Mendel first deduced the basic laws of inheritance. However, modern genetics, with its capacity to manipulate the very essence of living things, came into being only with the rise of molecular investigations, culminating in the breakthrough discovery of the structure of DNA, for which Francis Crick, James D. Watson, and Maurice Wilkins received the Nobel Prize in 1962. The contribution of physics and physicists to this—what Watson calls Act 1 of molecular biology’s great drama—was seminal. Here we review the work of some of the physicists who helped shape molecular biology into the exciting science it currently is.

Max Delbrück received his doctorate in theoretical physics from the University of Göttingen and then spent three postdoctoral years in England,



Delbrück

Switzerland, and Denmark. His interest in biology was aroused during his stay in Denmark by Niels Bohr’s speculation that the complementarity principle of quantum mechanics might have wide applications to other scientific fields and especially to the relation between physics and biology. Back in Berlin, Delbrück initiated an interdisciplinary collaboration with Nikolai W. Timofeeff and Karl G. Zimmer on biologically inspired problems. Based on x-ray-induced mutagenesis experiments and applying concepts from quantum mechanics, they suggested that chromosomes are nothing more than large molecules and that mutations can be viewed as ionization processes. These results were published in 1935. Schrödinger’s little book *What Is Life?* (1944) was in part inspired by this paper.

In 1937 Delbrück moved from Germany to the United States and decided to remain after the start of World War II. At that time he initiated a fruitful collaboration with Salvador Luria on the genetic structure of bacteriophage (bacteria-infecting viruses) and on the genetic mechanism of DNA replication. After the outbreak of the war, Delbrück and Luria were classified as “enemy aliens” by the American government despite their open opposition to the Nazi and Fascist regimes. This classification fortuitously allowed them to pursue their own investigations without having to join any military project. For “their discoveries concerning the replication mechanism and the genetic structure of viruses,” Delbrück and Luria were awarded the Nobel Prize in 1969, along with Alfred D. Hershey. In the early 1950s Delbrück’s research interests shifted from molecular genetics to sensory physiology, with the goal of clarifying the molecular nature of the primary transduction processes of sense organs. Delbrück was also involved in setting up an institute of molecular genetics at the University of Cologne. It was formally dedicated on June 22, 1962, with Niels Bohr as the principal speaker. His lecture, entitled “Light and life revisited”, commented on his original lecture of 1933, which had been the starting point of Delbrück’s interest in biology. It was to be Bohr’s last formal lecture. He died before completing the manuscript of this lecture for publication.



Bohr



Schrödinger

Erwin Schrödinger is regarded as one of the fathers of quantum mechanics. However, his interests went far beyond physics. He was particularly interested in philosophy and

biology. Early in his career, he made substantial contributions to the theory of color vision. Schrödinger's personal life was tumultuous. He participated as an officer in World War I on the Italian front. For a variety of reasons, Schrödinger moved constantly, holding positions in Austria, Switzerland, Germany, England, and then Austria again. Soon after he took up this last position in Graz, Austria fell into the hands of the Nazis, and Schrödinger escaped to Ireland, since his initial departure from Berlin when the National Socialists took power was considered an unfriendly act.

In Ireland, Schrödinger joined the Institute for Advanced Studies in Dublin. His contract required him to give a yearly series of public lectures. In 1943 he elected to discuss whether the events in space and time which take place within the spatial boundary of a living organism can be accounted for by physics and chemistry in light of the most recent developments in quantum mechanics and its application to genetics. These lectures were published in book form in 1944 under the title *What Is Life?*

After discussing how thermodynamics plays a role in the processes of life and reviewing the not-so-recent results on mutagenesis by Delbrück et al., Schrödinger argued in *What Is Life?* that life could be thought of in terms of storing and transmitting information. Chromosomes were thus simply bearers of information. Because so much information had to be packed into every cell, Schrödinger argued it must be compressed into what he called a "hereditary code-script" embedded in the molecular fabric of chromosomes. To understand life, then, it was necessary to identify these molecules and crack their code. Schrödinger's book had the very positive effect of popularizing the Delbrück paper and of rephrasing some important questions derived from it in a language accessible to the nonexpert. The book's publication could not have been better timed, and it was tremendously influential. Many of those who would play major roles in the development of molecular biology were drawn to this field after reading *What Is Life?* Schrödinger's recruits included Francis Crick, James D. Watson, Maurice Wilkins, Seymour Benzer, and François Jacob.

Francis Crick studied physics at University College London. After graduating, he started research for a doctorate, but this was interrupted by the outbreak of World War II. During the war he worked as a scientist for the British Admiralty, mainly on magnetic and acoustic mines. When the war ended, Crick had planned to stay in military research, but, on reading Schrödinger's book, he joined the Medical Research Council Unit in Cambridge to study biology. In 1951 Crick started a collaboration with James D.

Watson, who came to Cambridge as a postdoctoral fellow. Watson had originally considered being a naturalist, but he was also hooked on gene research by Schrödinger's book. Linus Pauling had discovered the alpha helix protein structure by making scale models of the different parts of the molecule and working out possible 3-dimensional schemes to infer which type of helical fold would be compatible with the underlying chemical features of the polypeptide (amino acid) chain. Following Pauling's approach, Watson and Crick started to look for the structure of DNA, which in 1944 had been discovered to be the substance making up the chromosomes. They finally succeeded in the spring of 1953. Not only did they determine the structure of DNA, they also proposed a scheme for its replication.

Essential for the work of Watson and Crick were the experimental results of Rosalind Franklin and Maurice Wilkins. Franklin had a background in chemistry, while Wilkins was a physicist. During World War II, Wilkins worked in the Manhattan Project. For him, as for many other of the scientists involved, the actual deployment of the bombs in Hiroshima and Nagasaki, the culmination of all their work, was profoundly disillusioning. He considered forsaking science altogether to become a painter in Paris. However, he too had read Schrödinger's book, and biology intervened. Franklin, working in Wilkins's lab, recorded the DNA x-ray diffraction patterns that allowed Watson and Crick to beat Pauling in the race to determine the structure of DNA. Crick, Watson, and Wilkins received the Nobel Prize in 1962 "for their discoveries concerning the molecular structure of nuclear acids and its significance for information transfer in living material." Rosalind Franklin had died at an early age a few years before and was not recognized for her essential contributions.

Knowing the structure of DNA was only the start. Next it was necessary to find the sequence of genes and chromosomes, to understand the molecular machinery used to read the messages in DNA, and to understand the regulatory mechanisms through which the genes are controlled. These questions were answered by a second generation of molecular biologists like Seymour Benzer, Sydney Brenner, François Jacob, Jacques Monod, and Walter Gilbert. Seymour Benzer and Walter Gilbert had



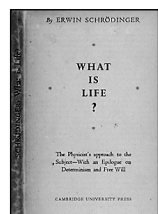
Crick



Wilkins



Benzer



both been educated as physicists but were attracted to the excitement of the new science. Seymour Benzer also heeded the clarion call of the Schrödinger book. He was a pioneer of gene sequencing. Among other things, Benzer was the first to produce a map of a single bacteriophage gene, rII, showing how a series of mutations (all errors in the gene script) were laid out linearly along the viral DNA.



Gilbert

Walter Gilbert received his doctorate in theoretical physics and after becoming a professor at Harvard, worked on particle physics and quantum field theory for a number of years. Then his interests shifted. In 1960 Gilbert joined James Watson and François Gros in a project to identify messenger RNA. After a year of work on this problem, Gilbert returned to physics only to re-return to molecular biology shortly afterwards. Some of the more important contributions of Gilbert and his collaborators to this field are: the discovery that a single messenger molecule can service many ribosomes at once and that the growing proteinic chain always remains attached to a transfer RNA molecule; the isolation of the lactose repressor, the first example of a genetic control element; the invention of the rolling circle model, which describes one of the two ways DNA molecules duplicate themselves; the isolation of the DNA fragment to which the lac repressor binds; and the development of rapid chemical DNA sequencing and of recombinant DNA techniques. Walter Gilbert and Frederick Sanger received the Nobel Prize in 1980 “for their contributions concerning the determination of base sequences in nucleic acids.”

Present and Future Perspectives

What we have described so far have been a few of the significant advances made in the study of systems in which there was a certain clear and obvious physics and mathematics component to the research being carried out. The advances made in the biological understanding were often quite dependent on the application of physical and mathematical principles, or the development of the physics and the mathematics was clearly driven by observations in biology. This strong interdependence is mirrored in the highlighting of biologically oriented problems in the new millennium (January 2000) issues of *Physics Today* and the *Notices of the American Mathematical Society*, as well as the special November 2000 *Nature Neuroscience* issue “Computational Approaches to Brain Function”. The *Notices of the American Mathematical Society* has on several occasions focussed on problems involving biomathematics (September 1995) or molecular biology (April and May 2002).

Many major universities in the world have at least one research group working in these fields. However, listing them all is beyond the scope or the intent of this article. Our purpose has been only to illustrate how widespread and important biophysics and biomathematics have been in the past few centuries and the increase in their importance in the past few decades.

Darwin’s theory states that, given the environmental conditions, the fittest individuals are the ones that survive and reproduce. However, it is impossible to identify the current fittest individuals whose genes are going to pass to the next generation. They can be pinpointed only after they have survived. Thus, according to some, Darwinism is tautological, since it predicts only the survival of the survivors. In trying to foresee the future of science, we face the same problem. It is not possible to identify the current areas of scientific research that will play a relevant role in the development of science and technology. We acknowledge this problem. However, it is our belief that given the fruitful historical relation and the present blooming of biological, physical, and mathematical interdisciplinary sciences, they are going to be so important in the near future that the avant garde biological scientists will be those with a strong background in both the biological and the physical-mathematical sciences.

The mathematical and computational modeling of biological systems is a subject of increasingly intense interest. The accelerating growth of biological knowledge, in concert with a growing appreciation of the spatial and temporal complexity of events within cells, tissues, organs, and populations, threatens to overwhelm our capacity to integrate, understand, and reason about biology and biological function. The construction, analysis, and simulation of formal mathematical models is a useful way to manage such problems. Metabolism, signal transduction, genetic regulation, circadian rhythms, and various aspects of neurobiology are just a subset of the phenomena that have been successfully treated by mathematical modelling. What are the likely areas of advancement for the future? Predicting the future has fascinated and confounded man for centuries, probably for as long as he has been able to articulate the concept of the future. For example, some relatively recent predictions were:

Physics is finished, young man. It’s a dead-end street.

—Unknown teacher of Max Planck,
late nineteenth century

I believe that the motion picture is destined to revolutionize our educational system and that in a few years it will

supplant largely, if not entirely, the use of textbooks.

—Thomas Edison, 1922

It is probable that television drama of high caliber and produced by first-rate artists will materially raise the level of dramatic taste of the nation.

—David Sarnoff, 1939

Being aware of the almost certain folly of trying to predict the future, as illustrated by these quotations, we nevertheless take the leap and mention several areas in which we feel that significant advances are likely to take place over the present century.

- The sequencing of human and other genomes has provided a spectacular amount of data which needs to be organized and analyzed before its significance becomes clear. The mathematical techniques necessary to do so are still to be developed. This has opened a whole new area of research known as bioinformatics, which is rapidly growing and presumably will keep on growing at an accelerated pace in the next few years. However, we are of the opinion that the sequence analysis component of bioinformatics will quickly evolve to become a mere tool widely and easily used by scientific practitioners (in analogy with the transition from scientific computing being done on large mainframe computers a few decades ago and now being almost exclusively carried out on inexpensive workstations).
- The classification aspects of bioinformatics will be rapidly replaced by efforts to understand the regulation of gene networks using established and new techniques from nonlinear dynamics. Mathematical modelling and analysis of the mechanisms of gene regulation will continue at an ever-accelerating pace. This, in conjunction with the already established ability to produce “designer” molecular circuits, will be instrumental in the targeted treatment of disease through gene therapy.
- Attempts to understand the noisy interactions in gene regulation and expression at the single-cell level will lead to the development of new mathematical techniques for dealing with chemical reactions in which the law of large numbers cannot be invoked.
- The Herculean efforts of countless neurobiologists over the past century have given us much insight into the functioning of single neurons as well as the behavior of simple neural circuits and some extremely simple sensory and motor systems. This progress will continue and lead to the efficient treatment of many neuron-related diseases, to a better design of prostheses, and

perhaps to a deeper understanding of the relation between brain and mind. Shall we at some time be able to really understand phenomena like cognition and memory? Maybe, maybe not. Perhaps, as some philosophers maintain, the human mind is unable to understand itself. However, we firmly believe that the neurophysiological sciences will thrive in the near future, with physics and mathematics playing a central role in such progress. Examples are the use of vagal stimulation to abort epileptic seizures and deep brain stimulation to control the tremor of Parkinson’s disease.

- Biophysical advances in determining the structure and dynamic properties of membrane channels and receptors have proceeded at a rapid pace over the past decade. There is every reason to anticipate that this will only accelerate in the future. The accumulated knowledge, in conjunction with modelling and production of designer molecules, will enable the efficient development and production of drugs specifically targeted to the elimination of disease symptoms, if not the disease itself.
- The accelerated rhythm at which technology is progressing makes us believe that in the near future it will be possible to combine knowledge and techniques from biology, chemistry, biochemistry, computer science, engineering, and physics to engineer designer molecules for specific medical and industrial purposes.
- Interdisciplinary work focussed on the development of biomaterials, bioelectronic devices, and biomechanical systems will improve the design of artificial organs, prostheses, and implants through the development of hybrid animate-inanimate devices.
- Epidemiological research aided by mathematical modelling and statistical analysis will help us understand the dynamics of disease transmission and design more efficacious treatment and vaccination strategies.
- The difficulty in collecting high-resolution temporal and spatial data from ecological and meteorological systems has limited the success of mathematical modelling approaches in these fields. The availability of more sophisticated geographic information systems and massive parallel computational power will alleviate these problems.

Summary

There has been a long and rich tradition of fruitful interdisciplinary interplay between the physical and biological sciences extending over several centuries, as we have illustrated with a few examples. Many other examples could have been offered to illustrate the point and would simply serve to highlight the rich interactions between apparently

disparate branches of science. We expect that these interactions and interdependence will continue and become even stronger in the future.

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