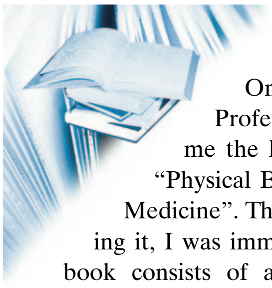


Physical Biology

On my last visit to Caltech, Professor Ahmed Zewail gave me the last book he had edited, “Physical Biology—From Atoms to Medicine”. The moment I started reading it, I was immediately captivated. The book consists of a collection of chapters written by 20 eminent scientists (four of whom are Nobel Laureates), leaders in their respective areas of research. Whoever knows the editor will immediately recognize his imprint on this book. Indeed, it is not merely a collection of advanced research articles; it is about daring visions, innovative thinking, and creative questions in physics and biology at a crucial turning point. Given the wealth of ideas in this book, this review is by no means complete and focuses on a few selected chapters.

Taken in the broad sense of the book (from atoms to medicine), the field of physical biology is not new. In the sense that it aims to “reduce” biological processes to physical phenomena, it started with the birth of the experimental method, initiated by Ibn Al Haytham (Ahhazen in Latin, 10th century) with his studies of optics[1] who in so doing also proposed a physiological theory of vision.[2] This strong link between physics and physiology would last several centuries, until the end of the 19th century, and would be marked by individuals such as the physiologist Joseph Black, known for his work on specific heat, Julius Mayer, who worked on the mechanical theory of heat, and the famous Hermann von Helmholtz, who established the first principle of thermodynamics from his studies of the heat produced by muscular efforts.

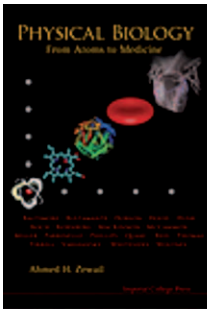
What happened since then is that with increasing specialization, science has become separated into several disciplines. Physics has become largely the study of inanimate objects, while the life sciences are often descriptive, “isolating much of the biological mainstream from quantitative description as the rule rather than the exception” to quote R. Phillips (Chapter 10), although the link was maintained by famous figures such as Linus Pauling, Max Delbrück, Max Perutz, and Francis Crick. This book is about recent developments in the life sciences, showing that this unnatural barrier continues to disappear; the resulting interdisciplinary science will benefit both physics and biology. The excellent collection of contributions spans all aspects of this “revival”: historical, philosophical, methodological, and technical. Reading this book is a must for anyone interested in the life sciences. The common thread that connects all of these contributions is the reductionist’s view of physics in tackling problems in the life sciences.

The book opens with a visionary exposé by David Baltimore on the concerns of 21st century biology. His optimism is refreshing and contagious, though, in my opinion, it should be moderated by the fact that scientists cannot control the use of their discoveries.

The reductionist’s vision is bluntly expressed by the title of A. Varshavsky’s contribution, “The World as Physics, Mathematics and Nothing Else”. He argues that the names of different sciences (chemistry, astronomy, immunology, linguistics, psychology) only define the location of a specific domain relative to the others. It has affected the unified view of science and its hierarchic structure. For example, chemistry, which in the 19th century, was considered to be very different from physics, has been “reduced” to physics by the intrusion of quantum mechanics in the 1930s. In his view, this hierarchic, “embedded” relationship between physics “proper” and chemistry can be extended to biology, including molecular biology, neurosciences, and even branches such as psychology, sociology, and linguistics. Even though there is no definitive proof that plants, animals, bacteria, and other living organics are merely physicochemical machines of vast but finite complexities, biological systems do not require fundamentally new physical “laws”, and biology will be “reduced” at some stage. Since societal matters cannot, in my opinion, be reduced to physics, we will still need philosophy to discuss them. His harsh criticisms of the philosophers’ lucubrations about scientific questions they don’t always understand and are well taken, though one should not forget that some of these deviations were initiated by physicists.[3]

Varshavsky’s view is echoed in the contributions of R. Phillips (“Biology by the Numbers”) and S. R. Quake (“Precision Measurements in Biology”). Both argue that the results of technological advances have come on the heels of fundamental biology, such that the study of living matter is becoming more and more quantitative. Furthermore, quantitative data demands quantitative models. Both illustrate this point with striking examples on the physical properties of DNA. Phillips also stresses the importance (originating from physics) of “orders of magnitude” estimates in biology, which can indicate whether we are on the right track, and he gives several lively examples. The next stage is a systematic examination of the problem from the points of view of both theory and experiment. By necessity, when biological questions are formulated in precise quantitative terms (as in physical biology) they are sharper and the notion of what it means to understand a phenomenon is tightened.

Phillips also reflects on the “virtues of being wrong”. After all, the flaws of the Dulong and Petit laws on the specific heat of solids, or of Rayleigh’s



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law on blackbody radiation, represented steps where we were poised to learn something new. This is reminiscent of Karl Popper's view of scientific theories. He finishes his brilliant contribution by asking if the quantitative interplay between theory and experiment can reveal anything new, deep, and interesting about the living world. His examples and the other contributions in the book answer this question in the affirmative. One point raised by Philips, which returns as a core issue in Bustamante's and Wolynes's contributions, is the problem of non-equilibrium dynamics. All argue that physics must provide clues on how to think about the non-equilibrium state, because this is the setting of living matter. Bustamante calls for the search for a new thermodynamics. This is further strengthened by the need to arrive at a description of the thermodynamics of small systems, and the limitation of traditional thermodynamics is nicely illustrated with examples on molecular motors and on self-assembly. In the 19th century, the enunciated *principles* of thermodynamics had the great advantage of being "free of any special assumption about the constitution of matter", to quote Pauli on the theory of relativity. Indeed, the same approach was adopted by Einstein for the principles of relativity.[4] Maybe this is the moment where new *principles* should emerge that would describe non-equilibrium phenomena in life and other sciences?

Finally, Bustamante brilliantly argues (as does Leroy Hood, one of its founders) for systems biology. Indeed as he puts it, the great analytical efforts at describing the various parts of the cell separately will not produce a qualitative jump in our understanding of how cells work, because the complexity of biological systems is determined not so much by the number of parts they use but by the number of interactions involved in the regulation of their functions. Physical scientists have an important role there because their quantitative and modeling skills are essential for describing the complexity of these interactions. Drawing once more on a historical example in chemistry (Wöhler's synthesis of urea in 1828), he argues (and so does Baltimore) that a complete understanding of the mechanisms of the cell results from putting all of its individual parts together into a functioning unit (this is synthetic biology!). This aspect is discussed and illustrated in the brilliant contributions of Tirrell ("Reinterpreting the Genetic Code") and of Whitesides et al. ("Designing Ligands to Bind Tightly to Proteins").

Because they have led to the birth of modern biology and play an increasingly important role in physical biology, methods of structural analysis such as X-ray and electron diffraction and microscopy, as well as NMR spectroscopy, are covered by several enlightening and highly stimulating contributions. The first observation of X-ray diffraction by a crystalline protein in 1934[5] ushered in the era of structure determination of macromolecules. D. C. Rees argues that the future of X-ray analysis in biology can be anticipated in three areas: the structural analysis of complex systems, structure determination at even higher resolution, and characterization of the structural dynamics of macromolecules at increasingly faster time scales. The latter statement is evident in biology, since biological functions entail a change of structure on time scales over several orders of magnitude. Yet he likes to reminisce on Pauling's and Bernal's warnings that X-ray analysis alone will not yield the complete structure of proteins. Other methods, such as electron diffraction and microscopy, NMR spectroscopy, single-molecule methods (see also Bustamente's and Quake's contributions), and computation (see Parrinello's and Wolynes's contributions) have to be implemented. This brings me to the central role of electron-based methods in physical biology and their rapid and spectacular development over the past few years. No wonder, as J. M. Thomas argues, that of the three kinds of primary beams (X-rays, neutrons, electrons) suitable for structural determination, electrons are the most powerful in terms of brightness, scattering cross-sections, and even radiation damage. After reviewing different types of microscopy techniques (field-ion, STM, AFM, SNOM, etc…), he discusses electron microscopy for delivering high-quality structures of nanoparticles, ceramics, and complex oxides and in imaging biological molecules. Higher resolution, down to 0.6–0.9 nm, is achieved by cryoelectron microscopy,[6] and a detailed list of structures is provided for a number of macromolecules and molecular assemblies. Like Rees, Thomas points to improvements in time resolution as the next great leap forward. In 1991 he prophesied[7] that if the structural determination of transient chemical species, then achieved by picosecond electron diffraction on molecular beams, could be carried over to the condensed phases, it would mark the dawn of a new era. This prophecy has been fulfilled,[8,9] and the new era is admirably described by its initiator, A. H. Zewail, in his contribution. He focuses mainly on the development of the revolutionary four-dimensional electron microscopy, which is based on the premise that trajectories of coherent and timed single-electron packets can provide the equivalent image of N electrons in conventional microscopes. Thus *real-space and real-time* images as well as diffraction patterns are achieved with the same instrument! The examples he presents are striking and enlightening. They include phase transitions in highly correlated solids, observation of transient species of chemical reactions, phase transitions at interfaces (of water!), nanoscale mechanical and melting phenomena, and order–disorder changes in biological membranes. Studies of rat cells by the instrumentation of ultrafast electron microscopy already points to the next developments from Zewail's lab, as we will soon see the film of a biological function in real space and on time scales over orders of magnitude, as he very remarkably demonstrated for nanostructures in a recent paper.[10] In the race towards real-time structural dynamics of complex systems, there is no doubt that electron techniques have taken a clear lead over X-ray techniques, but the latter are also making major advances, as discussed by Rees and Thomas.[11]

Physical biology also relies strongly on computation for the description of biological phenomena. For short time scales, this is not a major issue, but slow processes such as protein folding require challenging computational times. Using as a title, the famous sentence by Galileo (*Eppur si muove*) to stress that he is dealing with slow events, Parrinello presents a novel strategy to treat this problem, which is based on characterizing the structure of proteins by a number of collective variables and calculating the associated free energy surface. But computation goes beyond understanding the fundamentals; it is now used to help design new drugs, as described by McCammon in his contribution.

Protein folding has so far mainly been described by the "energy landscape" theory. Folding is dominated by a funnel-like energy landscape with minimal ruggedness. The energy landscape theory has led to algorithms for designing proteinlike molecules de novo and for predicting the tertiary structure of smaller proteins. Wolynes argues that although most of the random thermal motion of a protein must be disciplined to achieve the specificity of biomolecular interaction, some thermally allowed motion must remain in a functioning biomolecule. It represents local "unfolding" problems, which is just as important to understand as the folding. Binding sites are often "frustrated" and can be located by energy landscape theory. However, as mentioned before, he and others advocate going beyond these current theories to tackle the far-from-equilibrium dynamics of cell assembly.

This book is like an elaborate piece of music: the more you listen to it, the more facets you discover. I read it twice and flipped through it several times, and on every occasion I discovered new aspects I had missed previously. That is why this review is by no means exhaustive and why I urge scientists to read this book and enjoy it as much as I did.

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