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PERSPECTIVE

Biological physics in México

Review and new challenges

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Abstract Biological and physical sciences possess a long-standing tradition of cooperativity as separate but related subfields of science. For some time, this cooperativity has been limited by their obvious differences in methods and views. Biological physics has recently experienced a kind of revival (or better a rebirth) due to the growth of molecular research on animate matter. New avenues for research have been opened for both theoretical and experimental physicists. Nevertheless, in order to better travel for such paths, the contemporary biological physicist should be armed with a set of specialized tools and methods but also with a new attitude toward multidisciplinarity. In this review article, we intend to somehow summarize what has been done in the past (in particular, as an example we will take a closer look at the Mexican case), to show some examples of fruitful investigations in the biological physics area and also to set a proposal of new curricula for physics students and professionals interested in applying their science to get a better *understanding* of the physical basis of biological function.

Keywords Biological physics in México · Review and perspectives · New curricula

1 Introduction

Contemporary biological physics is becoming a new *grand frontier* of science. The old but re-emerging field of biological physics (BP) now represents a great deal of

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cross-fertilization between methods and ideas from biology and biochemistry on one side and physics (especially from the theory of complex systems) in the other. The original links between physics and biology could be traced back to the days of Volta and Galvani with the advent of electrophysiology. However, we could state that biological physics, as such, really emerged during the twentieth century motivated by the pioneering work of Erwin Schrödinger in his book *What is life?* [1]. This book was the first concise attempt to describe the *living state* of matter on *purely physical* grounds. In Schrödinger's words, his book asks "... how can the events in space and time which take place within the spatial boundary of a living organism be accounted for by physics and chemistry?..." and his conclusions are that "... the preliminary answer which this little book will endeavor to expound and establish can be summarized as follows: the obvious inability of present-day physics and chemistry to account for such events is no reason at all for doubting that they can be accounted for by those scientists..." [1]. *What is life?* was written in 1944, before molecular biology was born. In fact, many people ascribe the birth of molecular biology, a discipline founded years later by physicist Max Delbrück and his *Phage Group*, to ideas in this book. In present times, however, biology (and molecular biology, genomics and proteomics, as well as modern electrophysiology and imaging) is entering a new era, one of extremely fast advances and paradigm shifts, in particular with regards to its capacity of generating new data in vast amounts and also digging more and more into the molecular basis of biological function. Research in biological settings is now turning from purely descriptive accounts to process-driven, multi-scale analyses now commonly termed *systems biology*. The new frontier is represented then by the study of complex biological systems. In these analyses, the integrative vision of the physicist becomes mandatory. The reason is that data alone are insufficient to create a real understanding of these complex processes. Nevertheless, research in complex biological systems has revealed foundational principles in physics such as self-organization, criticality, and robustness, but the biological implications of these phenomena are still being revealed.

2 Some historical remarks on biological physics México

The history of BP in México is short and in some instances very recent. To the best of our knowledge, there is no published account of the development of biophysics and biological physics in México; however, interesting and well-documented revisions of Mexican physics (and physicists) could be found in references [3] and [4]. For many years, research in biological physics in México consisted mainly in a series of well intentioned but unfortunately isolated efforts, most of them closer in scope to traditional biophysics and physiology. This situation is in sharp contrast with what is happening in more recent times. In the year 2006, a group of Mexican academics in the area of biological physics (leaded by Professor Leopoldo García-Colín Scherer), most of them based at the *Universidad Autónoma Metropolitana* [5–10] launched an ambitious project that crystallized in the form of a research book in biological physics, *La Física Biológica en México: Temas Selectos* [11], that was followed two years later by a second volume *La Física Biológica en México: Temas Selectos 2* [12]. The former book is about to sell out its second edition while the follow-up is also doing fine. The sales of these volumes have reached the rank of a few thousands, so that they have become some of the best-selling publications of *El Colegio Nacional*, ranking alongside general literature books such as *The complete works of Octavio Paz*. These efforts pointed to the need for a textbook in biological physics, a project that has

been attained and that grew to the size of a 3-volume opus [13]. The same core of academics has made efforts to include biological physics within the program for the *Mexican Meeting on Mathematical and Experimental Physics*, a triennial scientific meeting that has been held four times, giving place for the discussion and even publication of the research work presented therein (the first one as a research book published by Kluwer Academic Press [14] and since its second meeting as American Institute of Physics Conference Proceedings issues [15, 16]). We could also stress the important contributions to BP by groups in the *Instituto de Física "Manuel Sandoval Vallarta"* at the Universidad Autónoma de San Luís Potosí (IFUASLP), a small but developing research core that is now facing the creation of a bachelor's degree in biophysics, one of the first of its kind in México; examples of their research can be found in references [17–22]. Some years ago, a Ph.D. program specialized in biophysics was established at the *Universidad Autónoma del Estado de Morelos* [4, 23] but it seems that this is no longer available. The efforts at the Universidad de Sonora that in the year 2000 established a summer school in molecular biophysics is also worth mentioning—the *Escuela de Biofísica Molecular* [24] with more than 40 short courses and a similar number of talks given. Biological physics research at Universidad de Sonora [25–29] has been growing well in recent years. Although institutions like the *Instituto de Fisiología Celular* [30–32] at UNAM and the Center for Research and Advanced Studies (Cinvestav) offer graduate programs in biophysics, their emphasis is more in the biological side of the subject [32, 33]. With regards to BP, Cinvestav's physics department is already developing a research core [34–39], which other departments at Cinvestav are also doing research in biological physics and related issues [40–57]. We also should account for the work at the biophysics group in the *Instituto de Física y Matemáticas* of the Universidad Michoacana San Nicolás Hidalgo [58], as well as the *Instituto de Ciencias Físicas* [59–72], *Instituto de Física* [73–76], and *Facultad de Ciencias* [77, 78], all three at UNAM. Some very recent endeavors in biological physics research are under gestation at the *División de Ciencias e Ingeniería* at Universidad de Guanajuato in León (DCI-UG, formerly UG Physics Institute, IFUG) [79–81], the *Facultad de Física e Inteligencia Artificial* at Universidad Veracruzana [82, 83] and the *Centro de Ciencias de la Complejidad* (C3) UNAM [61, 64, 84–88, 132, 133]. Other research institutions have also been involved to some extent in biological physics, among these we could mention the Potosinian Institute for Science and Technology [89–92], the Institute of Biotechnology at UNAM [93, 94], the University of Colima [95, 96], and the School of Medicine (also at UNAM) [97, 98].

In some sense, México entered the arena of biological physics a little bit later after the revival of the discipline. For example, as early as 1999, Harold Varmus, then Director of the US National Institutes of Health (NIH) declared at that year's of the American Physical Society March Meeting that "... The weight of historical evidence and the prospects for the future place physics and chemistry most prominent among the disciplines that ...[can help us to] ... wage an effective war on disease..." [99]. Varmus was not only referring to the obvious role of instrumentation in medical physics or any other technological devices, when he boldly stated "... I would like to stress a deeper set of contributions that physics makes to biology - through the efforts of physicists who themselves seek to understand the rules of living systems..." and also "... Biology is rapidly becoming a science that demands more intense mathematical and physical analysis than biologists have been accustomed to, and such analysis will be required to understand the workings of cells..." [99]. Some time later, the April/May 2003 issue of *The Industrial Physicist* published an editorial article entitled *Switching from Physics to Biology* [100]. In this article, the author discusses how the new curricula in physics should fit in the paradigm of BP well beyond what has been

done in biophysics because "... Physicists are well positioned by their training to contribute to the development of a theoretical framework in biology, a field that has matured to the point where sufficient quantitative data and sophisticated experimental tools exist to test biological theories...". Some clues to potential converts were given and many leading universities and research institutions took the call seriously into account. In fact, Varmus talked about the suggestion by the NIH to US universities and research centers, of three central areas in which physics (and physicists) could make a big impact on biological research: (1) more subtle and precise technological advances in experimental and clinical tools, (2) the computational experience of physical scientists which is needed to help interpret complex data sets in high-throughput biological experiments, and last but not least, (3) building a *radical physical explanation* of cell, organism, and ecological function.

3 New challenges for biological physicists in the post-genomic era

3.1 High-throughput data and the dimensionality problem

DNA sequencing is one of the most powerful ways to study the incredible amounts of information contained in our genomes. An interesting point is that one key technique of DNA sequencing called *Maxam-Gilbert sequencing* was developed by biologist Allan Maxam, alongside physicist Walter Gilbert. Gilbert was trained as a quantum field theorist under Abdus Salaam, and it was his training which enabled him to devise the so-called circular DNA loop which is the theoretical basis of such technique. For this and other experimental breakthroughs in molecular biology, Walter Gilbert received the 1980 Nobel prize in chemistry (biochemistry), shared with biochemists Paul Berg and Frederick Sanger "... for their contributions concerning the determination of base sequences in nucleic acids..." [101]. DNA sequencing will be our first example of what we will call the *dimensionality problem*. A typical DNA sequencing experiment nowadays produces thousands or millions of sequences at once. The typical algorithms for sequence reconstruction are of a highly combinatorial nature [102, 103]. Hence, there is a need to possess strong computational and mathematical skills, such as those developed in computational physics, statistical mechanics and high energy physics to successfully manage such enormous amounts of data. Gene expression analysis is probably one of the most fertile fields to develop new biological physics theories and techniques. The complex mechanisms behind whole genome transcriptional regulation has attracted many physicists, for the subtleties of the associated physicochemical mechanisms, for the intricacy of the implicit stochastic dynamics and also for the challenges presented in the analysis and inference of regulatory networks, both from the mathematical and computational standpoints. Physicists have gained great insight into different aspects of such phenomena [104–110]. In México, several groups of biological physicists have entered into the genomic regulation arena [18, 61–64, 66, 131–134]. With regards to the dimensionality problem, the question is that whole genome expression experiments for higher species comprise several tens of thousands of variables (namely, the mRNA concentration or gene expression for each gene) and for technical, economic, and logistical reasons, the number of experimental samples runs on the order of a few hundreds at most. As a result, it is not feasible to use classical statistical approaches. Instead, some tools developed and used in statistical physics have been applied to this end, ranging from information theoretical approaches [104, 105, 133] to maximum entropy techniques [106, 134]. Proteomics is yet another area in which the vast amount of data

requires special mathematical training and computational expertise to be handled in an appropriate manner. The challenge of studying proteins in a global (whole-proteome) way is driving the development of new methods and theoretical–computational tools for systematic and comprehensive analysis of protein structure and function [111–114]. Not only did experimental techniques raise the problem of high dimensionality of the datasets but physical phenomena also present complications due to the large sampling space of configurations. To illustrate, a typical structural subunit of a biological macromolecule has approximately 10^4 internal degrees of freedom [2]. The numbers of conformational states grow astronomically: for example, a typical protein domain with 200 residues could present roughly 10^{200} global conformational states. This enormous number of configurations has given rise to the so-called Levinthal paradox in protein folding [115]. However, only a small fraction of these global states are actually occupied under physiological conditions. Due to steric constraints and environmental entropic effects [116], free energies for most conformational states are exceedingly high, thus making these states practically non-existent [117, 118]. This, combined with the fact that DNA in vivo is almost always bound to proteins, thus determining DNA dynamics, has made protein folding a quintessential problem in biological physics. A characteristic feature of biologically active proteins in physiological conditions is their well-defined spatially folded structure [119–122].

3.2 Rate processes, transport and activation

In the eukaryotic cell, various supramolecular structures of intermediate size between organelles and single proteins or RNA macromolecules exist within intracellular buffer media. Specific metabolic processes occur in their respective cell compartments or on membranes that enclose them [130]. In the cell nucleus, nucleic acid synthesis takes place; in lysosomes, a number of biopolymer hydrolysis reactions occur; in the mitochondrial matrix, Krebs cycle and fatty acid degradation reactions take place at different rates; on the internal membranes of mitochondria, oxidative phosphorylation takes place under delicate controlling mechanisms; on the thylakoid membranes of chloroplasts, photophosphorylation takes place under even more subtle switching [130]. Delicate and extremely sensible molecular biology experiments have shown all these processes to be rate processes, that is, kinetic-guided phenomena determined by previous systems' settings [124]. As all of these settings correspond to complex non-equilibrium phenomena, a physical description of these vital functions of the cell remains generally elusive [2]. On the other hand, transport across membranes that divide particular compartments of the eukaryotic cell is essential for its functioning. Lipid bilayer membranes are not always permeable either for water molecules with their high electric dipole moment or for ions endowed with an electric charge. For this purpose, various protein channels are necessary. Only very recently have we begun to understand the role of aquaporin channels in facilitating this transport [125]. Individual water molecule transitions through the channel are very short timed, in the 300 ps regime. The permeation mechanism was proposed on the basis of molecular dynamics simulations [126, 127] and helped to elucidate both the high water-permeation rate and the filtering properties with respect to protons and, with this, the actual biological mechanism of cell hydration [128]. The analysis of aquaporin-mediated transport also pointed to the presence not just of *channels* or passive cellular *gates* but also enabled the better understanding of the role of *transporters* and, with it, of active transport, i.e., the combination of subcellular diffusion and complex transport mechanisms mediated by molecular motors [129]. Thermodynamic analysis of such transport processes

has led to identifying actual mechanisms. All channels considered previously in biophysical research carry ions passively in the direction of lower concentration, i.e., the only driving force was the difference in electrochemical potential on either side of the membrane. However, it was discovered that there is a large group of channels that conduct the ions actively, against the concentration gradient. This so-called active transport in the direction contradicting the second law of thermodynamics is possible only at the expense of coupling to another chemical reaction, usually ATP hydrolysis, which serves as a free energy donor. The role of physics in these important biological discoveries was central. From electro-hydrodynamics, statistical mechanics and molecular dynamics, ultra-fast spectroscopy, and thermodynamics, the whole theory of aquaporin-mediated transport rests on solid physical grounds.

Biological thermodynamics also plays a central role in the physicochemical mechanisms behind life-sustaining functions. Each biological molecular process is usually catalyzed by a specific set of enzymes [130]. Given that the cell requires these processes to occur only at certain places and times, enzymatic catalysis must be a controlled process. Common mechanisms of control of biological molecular processes occurs on two levels: expression of information recorded on genes via synthesis of appropriate enzymes and regulation of the activity of these enzymes. With regards to turning gene transcription on or off (or even more precisely, setting an appropriate level of gene expression), a complex set of processes involving DNA and various forms of RNA as well as proteins and protein complexes takes place. These processes are generically termed transcriptional regulation. Statistical mechanical methods and irreversible thermodynamic analysis of transcriptional regulation are currently leading to the elucidation of complex patterns of control and regulation [131–135]. On the other hand, enzymatic activity regulation [136], takes place by different mechanisms. There are at least six different forms of enzyme activity regulation: proteolytic precursor activation, covalent precursor modification, anchoring in the membrane, competitive inhibition, feedback inhibition, and allosteric control. Each one represents a theoretical challenge, since most of the physical chemistry of such processes, although well characterized, experimentally lacks for a sensible theoretical explanation [137]. A notable exception indeed occurs with regards to direct binding means of allosteric control, in this case a simple but formal statistical mechanical model (a decorated Ising model) was developed more than 40 years ago [138]. In general, after synthesis on the ribosome, most proteins are inactive precursors of enzymes. Activation proceeds only after they are subjected to additional chemical modifications. The common mechanism involves cutting off some fragments of the main chain. A well-known example is the action of chymotrypsin (CT) [139], an enzyme that hydrolyzes specific peptide bonds of proteins. CT is synthesized within the chief cells in gastric glands as an inactive precursor called chymotrypsinogen (CTG), consisting of a single polypeptide chain. CTG does not attack the chief cells. Only in the medium of low pH outside the cell can a proteolytic reaction proceed in which active CT molecules hydrolyze specific peptide bonds in CTG molecules and transform them into active three-chain CT molecules, thereby initiating the whole chain of lysis reactions [137].

3.3 Cellular signaling

In order to survive, a living organism has to react efficiently to even extremely weak external signals. Typical examples are well documented, e.g., the reaction of the human eye to a single photon of light [140, 141] or the reaction of a butterfly male to a single pheromone molecule coming from a female at a distance of several kilometers [142].

Receptors of internal cells of biological organisms react to hormones, cytokines or antigens at very low concentrations. This phenomenon of strong reaction to a weak impulse is attained by an amplification process which is performed by means of special pathways of free energy transduction. Mechanisms such as immune system response, thermal-shock inhibitions and cardiovascular rearrangement in response to environmental changes are all mediated by signaling processes. Signal transduction (information flow) is equally important, if not more important, for the functioning of a living organism than metabolism and energy flow. However, the signal transduction system is much more complex than either of these other systems. Only intensive studies of the mechanisms of human transplant rejection and oncogenesis in the past two decades have given some insight into the way this system is organized on the intracellular level. The vast cellular machinery involved in these communication processes also presents challenges of considerable interest for the physical scientist: chemical signals defy the common understanding of chemical potential landscapes by means of non-equilibrium energy flows.

3.4 Complexity

Physical complex systems cannot be reduced to simple closed thermodynamic systems. When the description level for a phenomenon has reached the level of description that can no longer be simplified, it can be called an *irreducible* or *minimal* complex system [143–145]. As an example, biochemical reactions are catalyzed by protein enzymes or, currently very seldom, by the more archaic RNA-based ribozymes. Besides accelerating chemical reactions, enzymes fulfill two other important functions. Firstly, they control reactions, which means that a given reaction takes place in a cell only at an appropriate moment and at the desired location. Secondly, enzymes couple reactions. To make use of a chemical reaction in a process of biological free energy transduction, it must occur simultaneously with another reaction at the same multi-enzymatic complex. Therefore, enzymes must be characterized by high specificity. Each metabolic reaction is catalyzed by its own enzyme [130, 137]. In order for the enzymatic complex to work, but also to be controlled, *all* the elements, activators and repressors as well as competitive inhibitors, must be present. The enzymatic system is thus *minimally complex*; one just cannot take away some element or part of the system to further *simplify* the model [130]. Another instance in which one cannot simplify the model by obviating some parts of the process is that of *molecular machines* [146]. To illustrate, besides simple phosphorylation reactions, the reaction of ATP hydrolysis is coupled to many other biological processes [147, 148] by means of *molecular pumps* [149]. The corresponding chemomechanical machines are called molecular motors. Transport across membranes can also be coupled to a rotational mechanical motion, which biologists have called molecular turbines [150]. Although the names of these molecules can be in some sense misleading, what it is true is that they are machines, i.e., their functioning is only possible if all of their parts are present and work well together. The action of such biological molecular machines has been depicted in terms of simple chemical kinetics. Protein complexes are highly organized assemblies of *mechanical* elements: levers, hinges, springs (or pistons) and triggers, hence the name *machines* [151]. All these elements are involved in cooperative collective behavior like the elements of macroscopic machines. Molecular machines act very often due to the effect of thermal fluctuations: i.e., energy is exchanged with the surroundings [149]. Irreversible ATP hydrolysis makes this process unidirectional. Hence, molecular machines have to be treated just as common chemical reactions, except that a multitude of specially organized conformational substates have to

be taken into account. One question that remains open is how to combine chemistry and mechanics to describe the mechanism of chemomechanical coupling for molecular motors. This question needs to be addressed by theoreticians (and also experimentalists) in statistical physics, chemical physics and mechanics.

Complexity in biology consists not only in the complex structural features we have already discussed but also in the riches of the dynamical processes related to life-sustaining functions. Physicists have studied for decades the complex dynamics of time series embedded in fractal support spaces [152–156]. In the analysis of time series, self-similar patterns can constitute a hierarchy of temporal and spatial scales. These scales would range between macroscopic-long-term observable behavior and high frequency-fine scale molecular fluctuations, and thus would account for the information flow between such disparate scales. To set an example coming from neurophysiology, the brain has been characterized as a complex system in a regime of criticality [157–161] as it is understood in statistical physics [162].

3.5 The role of noise and fluctuations

In order to perform the vast number of complex processes needed to sustain life, organisms need to control the rates of literally thousands of chemical reactions. The great majority of such reactions occurs due to fluctuations [163, 164]. One important theoretical shortcoming in the description of non-equilibrium systems is how to describe activation kinetics, i.e., how to reconcile Arrhenius's law with Boltzmann's description at least at an asymptotic level. Biological molecules—such as the proteins which act as enzymes, catalyzing specific chemical reactions of importance in the cell—are, in general, extremely large, and due to this fact and to their chemical composition (mostly covalent) are also very flexible. Their reaction rates change not only for purely chemical reasons (electronic exchange) but also the effective barrier for the reaction changes depends on their conformation. The observed activation energies have then two components, one measured along the reaction coordinate, usually reduced by *waiting* for the protein to re-arrange properly, and the other energy related to the distortion of the protein itself. An interesting experimental evidence is already known: By freezing a solution of the protein myoglobin, and then detecting when the oxygen is bound to the iron atom at the active site of the protein, it is possible to break the bond with a flash of light; further, one can monitor the rebinding of the oxygen to the iron by changes in the absorption spectrum of the protein. This was done with oxygen, and also with carbon monoxide taking the place of the oxygen [123]. The reaction rates varied enormously once thermal agitation (hence non-equilibrium fluctuations) was severely diminished. Biochemical reactions are thus the result of fluctuations at the molecular level. This is but one classical example in which non-equilibrium fluctuations determine biological functions. Stochastic phenomena are also related to the dynamics of complex transcriptional events and their regulation [131]. Information encoded in DNA is read out to make proteins, but this is far from being a direct error-free process, and there are a number of steps where errors can occur. All these complex processes are thus dominated by noise and fluctuations and the control mechanisms should be thus stochastically regulated. Stochasticity in biological systems is thus not a measurement artifact or a sign of systemic malfunctioning; instead, it is closely related to the important phenomena of information flow [171]. To fully understand the physics of life, one has to understand not just the flow of energy (as one must do in inanimate systems) but also the flow of information. The issues related with the role of information flow within noisy, stochastic-driven environments need to be addressed in

order to understand the physical functioning of biological systems. There, is a wide variety of views and scopes that need to be considered while working in BP, which in turn points out to the necessity of multidisciplinary approaches to the subject. In the next section we will examine some instances in which this multidisciplinarity appears, and how to deal with it.

3.6 How to cope with multidisciplinarity?

To succeed as a researcher in modern BP, one has to actually learn how to interact with professionals from many different backgrounds, including molecular biologists, geneticists, physicians, biochemists, biomedical engineers, bio-technologists, computer scientists, mathematicians, and systems engineers. The general paradigm in all these fields is much too disparate and a special effort has to be exercised in order for the collaborative efforts to be fruitful. As physicists, we learned that simplicity and generality are beautiful, that models should tend to be universal, and that the specific details of every individual phenomenon (or experimental piece of evidence) should, in some ways, conform to a rather accessory role, to decorate the general and universal explanation. Having physics been so successful by conforming to this standard, no one can blame us for being universalists. Biologists on the other hand, descend from a long tradition of *descriptive* science and they have become fascinated with the variety, diversity and complexity of life in all its forms. They live for detail. For *their* science, there are no universal principles, but rather a symphony of exquisite subtleties and exceptions. How then can we reconcile such disparate points of view? In some sense, the answer already began to be sketched on several fronts: chaos theory, nonlinear dynamics, fractals, non-equilibrium phenomena and complex systems have shown us physicists that not everything in this world is Hamiltonian, integrable and invariant. General systems theory, genomics, systems biology, and complex networks have in turn shown biologists that even within life's infinite diversity there are general underlying principles. Under such circumstances it is no surprise that some difficulties arise. The new generation of biological physicists need to be trained in such a way that, while still being able to think as physicists do (in general, simple and universal terms) they will be also enabled to understand the views of biological scientists. One way to reach that goal is giving our BP students *some* actual training in biology so that they could experience *hands-on* what the biologist lives on his/her everyday research activities. This, and our other previous comments, should lead us to rethink how we are forming our students, what we teach them and how we do it. This issue will be touched on the next section.

4 The need for new curricula

In order to face the challenges that come from the new developments of modern bioscience, the biological physicist should possess a highly unique and, in some sense specialized, set of skills. However, this by no means imply that he or she has to abandon the traditional training within the physics program. On the contrary: what has made the role of physicists (especially theorists) so central to the development of the foundational principles of the *new biology* is precisely their *physicist-ness*. When considering the vast set of tools a modern physicist has to possess in order to grow and develop as a scientist, it comes as no surprise that a remarkable majority of the leading names in systems biology and theoretical biology

come from theoretical physics and even from astrophysics or cosmology backgrounds. In fact, there is a claim that the actual birth of *systems biology* could be dated during the 1980's to the works of theoretical physicist Walter Elsasser [165–167]. The small set of examples we have provided with regards to cellular and subcellular level BP have pointed to several physics subdisciplines that a prospective biological physicist should master in order to face the scientific challenges of his/her field. Among these we can mention: statistical mechanics and thermodynamics for equilibrium and non-equilibrium systems, mechanics, complex systems theory, electrodynamics, hydrodynamics of simple and complex fluids, quantum mechanics, stochastic processes, chemical physics, elasticity, optics, mathematical methods of physics, etc. All of these issues are considered to some extent in the current curricula of most graduate students in the physical sciences. However, apart from this *traditional* training, there are a number of additional items that will provide the lacking ingredients to form a well-trained professional in modern biological physics. Among these latter we could mention: rudiments of molecular biology and cell biology both at the theoretical and experimental levels, a stronger training (or should I say *some* actual training) in probability theory and modern statistics as well as working levels of programming and computer science (Fig. 1).

Some excellent books in biological physics have appeared in recent times, outstanding examples among these being the books by Nelson [168], Phillips et al. [169] and Cotterill [170]. The curricular outline sketched by Nelson and Phillips et al. is closer to our conception of modern biological physics, whereas the program of Cotterill is similar in appeal to traditional biophysics. Nelson covers aspects of thermodynamics, molecular physics, statistical mechanics and hydrodynamics to a good extent, also touches on biological cooperativity, molecular motors, membrane electrostatics and transport and even gives

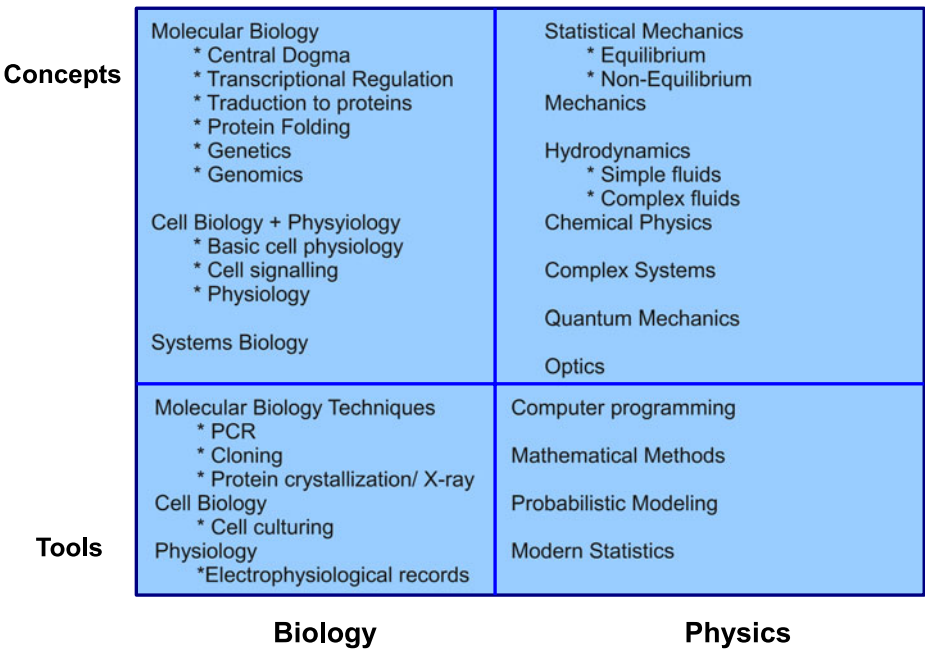

Fig. 1 Proposed curricula for biological physicists

an introduction to neurophysiology and biological neural networks. Phillips et al. give a comprehensive description of the physics of cell biology. Their approach is useful because they present a detailed biological introduction to important concepts in physics, such as mathematical modeling and idealization, the need for a quantitative description and multi-scale phenomena. Mechanics, thermodynamics, electrostatics, membrane physics, transport theory, molecular motors, as well as neurophysiology are given a role in the way to understanding the behavior of living matter. Of particular importance is the introduction to complex regulatory networks. Much of what we propose for a new curricula in biological physics could be found by combining the contents of Nelson (written from the standpoint of theoretical physics) and Phillips et al. (which seems to have a debt to the book by Alberts [130] far beyond just the name). The text of Cotterill, although good in contents is still founded in a somewhat classical (and in our view, a little bit outdated) conception of biophysics. It covers well bioenergetics, classical transport processes, biopolymers, membranes and physiological signals but many of today's more intriguing topics such as those of genomics and proteomics are almost entirely left out [171].

For what we have just stated, it may seem that the curricula for becoming a biological physicist is way too ambitious, but the very fact that a growing number of professional physicists have successfully shifted their careers towards biological physics shows that it is a realistic goal. And those of us who are actually practising the discipline have found a rich and fertile ground for the development of extremely exciting physical insight and worthwhile scientific research.

5 Perspectives

There are some key problems in the understanding of biological physics. Most of them are related to the issues of non-equilibrium phenomena, complexity, noise, and fluctuations and activation kinetics. Physics and physicists will necessarily play a role in the development of twenty-first century biology, but in order to accomplish such a great task we need to be prepared for challenges such as the ones sketched here and many others. There is a vast amount of *Terra incognita* to discover in the realm of biological physics, and it is thus our duty to be prepared, and to educate generations of physicists to come to fulfill our expectations.

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