Scientific Life

Interface between Physics and Biology: Training a New Generation of Creative Bilingual Scientists

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Whereas physics seeks for universal laws underlying natural phenomena, biology accounts for complexity and specificity of molecular details. Contemporary biological physics requires people capable of working at this interface. New programs prepare scientists who transform respective disciplinary views into innovative approaches for solving outstanding problems in the life sciences.

> C'est ce que nous pensons déjà connaître qui nous empêche souvent d'apprendre.
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> It is what we think we know already that often prevents us from learning.
>
> Claude Bernard

Nurturing Ideas in Biology and in Physics.

Biology and physics have been intricately related and have profited from each other. For example, von Helmholtz, a physiologist by training and driven by the urge to show the absence of a vital force, arrived at the concept of energy conservation by analyzing skeletal muscle in action and turned it into a general principle [1]. He also applied his knowledge of physics to develop the first theories of light and sound perception. Delbrück, a theoretical physicist, sought a physical explanation of genes, which ultimately led to the foundation of molecular biology and to establishing DNA as the material basis of genes. Through a careful, stochastic analysis, he showed that mutations were random events [2]. Translating a fundamental biological question into the language of physics allowed them to obtain deep biological and physical insight and led to the development of conceptually new ways of thinking about biology. This required profound familiarity with both disciplines.

The physicists' way of perceiving cells and tissues (Box 1) has provided a fresh look on biological phenomena. In addition, the specific features of living matter require physicists to think beyond the existing concepts of statistical mechanics and to further enlarge the toolbox for their analysis. However, this approach often poses problems to biologists who have been trained differently. For example, where physicists see a need for exploring phase space by changing some system parameters, biologists often see 'unphysiological' and hence irrelevant experiments. Where a physicist thinks that a reconstituted system can be of enormous help to identify the essential mechanisms underlying a phenomenon, biologists often see just a caricature that misses important constituents. Vice versa, physicists have a tendency to neglect the biological context of a phenomenon: where physicists emphasize self-organization, biologists know about essential input through signaling pathways. This holds even more, if one does not want to simply view biological systems as just another class of physical systems, but to do justice to their functions in nature. Developing concepts and proposing experimental strategies for studying specific biological systems and their intrinsic regulations requires a deep knowledge of the biological complexity to appreciate the choice of a model organism: which genetic and biochemical techniques are available for studying this organism, which aspects are conserved and which features differ between model systems, what is their inner logic with respect to evolution and phylogenetic relations? This necessity for a thorough understanding of physics concepts and a broad knowledge of genuine biology to make contributions in the spirit of Helmholtz and Delbrück calls for a new way of training the coming generation in this interdisciplinary field.

This need comes at a time when the approaches of molecular biology and

Box 1. A New Era of Physics in Biology

Research at the interfaces between biology and other sciences has been experiencing a shift since the 1990s. Spectacular advances in imaging techniques have put into focus aspects of cellular processes that remained largely unappreciated when using the powerful tools of molecular and structural biology or biochemistry. Time-resolved microscopy explicitly showed fluctuations in single molecule experiments *in vitro*, for example, molecular motors [7]. The stochasticity of gene expression [8] challenged the established paradigm 'one gene–one phenotype'.

In parallel, it became inevitable to understand collective effects, which emerge from the interaction of many biomolecules. The characterization of molecular interactions typically fails to predict the behavior of large collections even of identical proteins. The enhancement of sensitivity by the formation of large receptor clusters in *Escherichia coli* [9,10], the spatiotemporal patterns formed by the division-site-selecting Min proteins in the same organism [11,12], axonemal beating [13], and the mechanical reinforcement of adhesive contacts [14,15] are but few examples, where a detailed understanding of molecular properties does not suffice to grasp the supramolecular properties. Similarly, a detailed understanding of single cell dynamics does not readily extend to a comprehension of tissue dynamics or embryonic development.

Stochastic processes and collective effects have traditionally been a central topic of physics. The framework of statistical mechanics encompasses fundamental concepts of free energy, macroscopic order parameters, phase transitions, and universality as well as powerful techniques for their analysis. The idea of models that capture the essence of a certain class of phenomena has provided many insights into collective effects and stochastic processes. In the past 25 years, physicists have regained interest in applying statistical mechanics to the world of living matter.

the universality of theory tend to blur the broad picture. As Claude Bernard wrote, 'It is what we think we know already that often prevents us from learning.' The classical vision of molecular biology can be a stumbling block in the research process: at one end, a full list of the molecular inventory and the intermolecular interactions in terms of connections representing activation or inhibition is meant to comprehensively explain the phenotypes of cells, tissues, and organisms. At the other end is the claim of universality of theoretical physics that often neglects the specificity of biological systems and their capacity for adaptation.

The Need for Forming Translators

We need translators who are able to rephrase a specific biological phenomenon in the language of physics and vice versa. The vocabulary differs dramatically between physics and biology. As an example [3] a model in physics isolates the essential features of a phenomenon (symmetry, conservation laws . . .) and poses the rules of interaction of the constituting units in their simplest possible way. This allows one to study the phenomenon independently of the specific realization (Box 1). For example, the Ising model of magnetism led to a detailed understanding of phase transitions. At the same time, the insights gained in this way are relevant to a large class of systems that at first sight have nothing in common with magnets, for example, chemotactic receptors [4]. Physical models also help to identify relevant experimental measures. By contrast, a model in molecular biology is often a potential wiring between molecular interactors, but rarely with true predictive power in terms of quantitative readouts. In developmental biology, models can be species such as *Drosophila*, zebrafish, or *Arabidopsis* that allow the study of processes thought to be relevant for human development. Furthermore, the notions of proof, explanation, and understanding differ largely in the two fields. The translators need to be able to explain the specificities associated with the corresponding approaches to researchers in the other field.

The Need for New Training Programs

In our experience, individualized training programs rarely allow for a sufficiently thorough preparation to assume the role of a translator. We propose that students receive their first degree in their major fields of interest. Learning the scope, vocabulary, and methods of one field seems essential to acquire a scientific 'identity', and this takes time, typically 4 years at least. The focus on one field would assure the maturation of consistent knowledge embedded in a specific vocabulary.

After this initial training, a full year dedicated to the interface between biology and physics – typically at the beginning of graduate school – would make the students proficient in the respective other field. They would learn to translate physical parameters into biological measures and vice versa. This requires intense training in fundamental principles at the beginning of the year, followed by lectures in which both languages are used side by side and sessions at the board where translation is practiced. The aim is not to reach the same level of expertise as the 'native speakers'. Instead, for example, biologists would be exposed to simple cases, where they understand key equations in detail, but without the need to solve them in complicated cases. In this way they would understand the strengths and limitations of a model in a physical sense. As a result, students should get a thorough understanding of how data and methods from each field should be selected and interpreted. Importantly, this would allow them to spot possible problems in these approaches.

This classroom training would be associated with intense weekly hands-on laboratory activities in biology and in physics. They should mainly intersect between physical mechanisms and biological functions with some excursions into each field. Examples include observations of developing embryos of different model organisms, gene editing using CRISPR-Cas9, numerical solutions of a differential equation, and statistical analysis of gene expression data, imaging, and image analysis. In this way students should understand how to choose appropriate parameters, to obtain reproducible results, and to interrogate the systems in all possible ways. They should be able to set proper expectations.

This classroom and practical training would be enhanced by careful reading of seminal texts in the field about fundamental ideas in biology. Texts of D'Arcy Thompson, Waddington, Turing, Feynman, Wolpert, Anderson [5], and Purcell [6] among others would communicate to students the need to think beyond the most recent breakthroughs and to develop a broader picture of biological processes. In effect, these researchers approached science with integrated questions that helped many in the field to bridge the gap between physics and biology. Finally, weekly meetings will be instrumental. Here, the topics of the lectures would be re-articulated by the students. They would be assisted to bridge gaps or discrepancies between lectures, which is an authentic exercise in translation.

New Examples of Training

Several scientific sites have designed new programs towards this direction. The Woods Hole Physiology course includes 1 month of training where students are first trained in basic principles of biology and physics as well as in mathematics. This is followed by intense experiments on open topics where the students acquire data – typically movies of living matter, measure readouts to be compared to models, fit data and propose potential mechanisms.

At Strasbourg University in France, a cell physics master program was recently launched (http://www.cellphysics-master.com/). During a 1-year program, students learn this interdisciplinary approach of using physics, biology, mathematics, and chemistry to solve problems of biological relevance with inputs from systems biology, active matter, and chemical and mathematical biology. The year starts with a month-long intensive training on the basic principles of the four fields, and continues with weekly experimental training throughout the year in optics, molecular and cellular biology, and numerical simulations. In addition, students spend time in the machine shop to generate new pieces and to design new microfluidic devices for studying cells and tissues. Students conclude the year with an internship in a laboratory.

Towards an International Initiative

How could such programs be generalized and spread globally? Several initiatives could be launched: the current ease in sharing lectures over the internet could ensure common lectures are taught in international institutions with reduced costs. Experiments could be performed in specific places with the appropriate equipment and organized in networks of open platforms in the United States and in Europe. Students could be evaluated through online tests with dedicated lecturers identified throughout the world. This training would generate new standards and would give proper credit to advancements resulting from this new interdisciplinary field. Local science should be encouraged as well, and the original training of students in their original universities could keep these local strengths in place. Diplomas could be given through reciprocal agreements between universities, or through international graduations inspired by the massive open online course (MOOC) systems with international labels of recognized scientific organizations. Several implementations can be envisioned, for example, in the form of cross-institutional programs, where one would be trained in multiple institutions and obtains one common diploma signed by all participating institutions, or in the form of cross-departmental programs, where the student graduates from one institution but holds a degree from multiple departments.

Scientific, educational, and administrative challenges abound in this endeavor to form upcoming generations of scientists at the interface between physics and biology, but we anticipate that the gain in quality for this interdisciplinary field will benefit science in general and throughout the world. The need for such scientists appears to be essential to answer the new challenges in biology.

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[1]The modern references above are just illustrations of ideas presented in this paper, and not an exhaustive list of original articles in this interdisciplinary field.

Spotlight

TREX1 Cuts Down on Cancer Immunogenicity

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Demaria and colleagues have recently identified three prime repair exonuclease 1 (TREX1) as a key determinant for the limited immunogenicity of cancer cells responding to single high-dose radiation. TREX1 stands out as a promising target for the development of novel strategies to boost anticancer immune responses driven by radiation therapy (RT).

Robust preclinical and clinical data demonstrate that cancer cells succumbing to specific treatments can elicit a therapeutically relevant immune response in the absence of exogenously provided immunological adjuvants [1]. Considerable insights into the molecular and cellular mechanisms that underlie such an immunogenic variant of cell death have been acquired over the past decade. In particular, immunogenic cell death (ICD) has been shown to impinge on: (i) the timely release of danger signals cumulatively known as damage-associated molecular patterns (DAMPs) from