Where Physics Meets Biology

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Abstract

The frontier between Life and Physical Sciences currently includes the strategic research field where the wealth of data produced by new quantitative technologies in molecular biology naturally meets the advanced analysis and modelling tools of theoretical physics. For its profound scientific implications and huge potential impacts in biomedicine it is attracting substantial interest. Here I briefly review some of the developments in such a field.

1. Introduction

Molecular Biology has made impressive scientific progress in the last decades, with a sequence of paradigm shifting breakthroughs occurring every few years, as perhaps happened in Physics at the beginning of last century with the development within just 30 years of quantum, relativistic and statistical mechanics. The interest of theoretical physicists for molecular biology begun right after those years. It is little known, for instance, that Richard Feynman, who would win the Nobel Prize in Physics in 1965 for his studies on elementary particles (for the theory of quantum electro-dynamics), devoted himself in the late 1950s and early 1960s to working on genetics with Robert S. Edgar in Max Delbruck's lab at Caltech. In the mid '60s Feynman acknowledged the major progresses of biology also in his very popular textbook *Lectures on Physics* where he wrote that

> certainly no subject or field is making more progress on so many fronts at the present moment, than biology, and if we were to name the most powerful assumption [...] to understand life, it is that all things are made of atoms, and that everything that living things do can be understood in terms of [...] atoms (Feynman et al., 1964-2005).

His sentence encapsulates the very ambitious project to explain biological phenomena from the fundamental principles of physics, as done for other many-body systems of nature, from superconductivity to soft-matter physics, because ultimately biological systems are made of atoms and therefore must obey the laws of physics.

The ideal project summarized in Feynman's sentence is being materialized in recent years because of the substantial technological advancements made in molecular biology. Those new technologies are producing highly reproducible, quantitative experimental data on biological systems at the single molecule level. The wealth and complexity of those data naturally requires the use of advanced analysis tools and models from hard sciences to be interpreted

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and understood. For such a reason, the science at the frontier between molecular biology and theoretical physics has become a strategic research field.

2. Where Theoretical Physics Meets Molecular Biology

The completion in 2001 of the Human Genome Project, for example, has provided the details of the sequence of the human genome and, in particular, of our genes. The fundamental question, however, on how the system works remains open. Why is a gene active in certain tissues and not in others? Why an oncogene, remained silent for years, suddenly becomes active in a cell leading to cancer? Quantitative experimental data of the post-genomic era are opening the way to answer those questions by combining biology and the methods of physics because, after all, the human genome is only one of the complex systems of physics, as highlighted by Feynman. The answers to those questions will explain the functioning of life itself and will usher in new approaches to personalized medicine for the treatment of diseases such as cancer or congenital disorders.

In recent years it has been discovered, for example, that the human genome has a complex spatial organization within the cell nucleus that serves vital functional purposes (Dekker, 2016; Dixon, 2016; Finn, 2019; Sigal, 2018; Kempfer, 2019). To regulate their activity, genes must establish physical contacts with remote regulatory regions along the DNA, millions of bases away, that control transcription. The result is a complex architecture in which our 20000 genes are brought into contact with their corresponding regulators (it is estimated that each gene has on average four remote DNA regulatory sequences) in an impressive example of self-organization. The complex three-dimensional structure of our DNA defines the activity and, therefore, the fate of a cell, by establishing the genes to be activated and those to be silenced. Alterations of the genome spatial organization can modify gene expression and lead to disease (Spielmann, 2018).

The study of the spatial architecture of chromosomes is a perfect ground where theoretical physics has fruitfully met biology because chromosomes are polymers and physics naturally intervenes in the description and understanding of polymer behaviors (de Gennes, 1979). My research group, for example, has worked to develop new methods to experimentally measure the structure of chromosomes with high precision (Beagrie, 2017; Fiorillo, 2021) and to understand, via Statistical Mechanics, the physical mechanisms that shape their three-dimensional conformation and bring together genes and their regulators (Barbieri, 2012; Barbieri, 2017; Bianco, 2018; Conte, 2020).

3. The Mechanisms that Regulate our Genome

The mentioned discoveries on the architecture of the genome have radically changed the way we look at our DNA. They have shown that to understand how the system works, we must not only decipher its linear sequence of bases (the ATCG letters of its alphabet), but we must also understand its complex three-dimensional structure, i.e., how DNA folds on itself in the space of the nucleus.

Genes are important because they encode the production of proteins, the building-blocks of cells to function. It is less known, however, that they comprise only 2% in length of the human

genome. The role of the remaining 98% has remained mysterious for years. It was named "junk DNA" according to the idea that it is a useless relic left by millions of years of evolution. It is now established that, far from being junk, it contains for instance the remote sequences that regulate genes and therefore the key to gene functioning (Andersson, 2014). We have also discovered that our DNA is folded in the cell nucleus in a hierarchical structure made of domains-within-domains (Fraser, 2015), like Chinese boxes, where the complicated interactions between genes and their regulators take place. Additionally, those interactions have been shown to typically involve the simultaneous colocalization of different chromosomal regions adding another level of complexity to the system (Beagrie, 2017).

We are also beginning to understand the physical mechanisms that define the three-dimensional structure of the genome, i.e., how and why regulatory contacts are formed. We have discovered that they are based, for example, on thermodynamic phase transitions involving the DNA polymer and a number of molecular factors with which it interacts. *Coil-to-globule* transition mechanisms serve, for example, to establish contacts between remote sequences (Barbieri, 2012; Bianco, 2018), while *phase-separation* mechanisms are used to isolate distinct regions that should not interact (Barbieri, 2017; Conte, 2020). In this way, we begin to understand why and how genetic mutations that do not affect gene integrity can lead to disease: they can alter the three-dimensional structure of DNA by modifying the network of regulatory contacts between genes and regulators hence producing incorrect activations or repressions (Bianco, 2018; Dellino, 2019).

4. Discussion

While the discoveries at the frontier between molecular biology and physics are unveiling the very functioning of life, the scientific and technological progresses made in recent years have the potential to revolutionize medical applications far beyond basic science. Combined with the clinical use of the new powerful methods of DNA sequencing, they can be used, for example, to predict the medical implications of mutations in single patients and even in single cells. We are beginning to understand the complex origin of genetic diseases such as congenital disorders (Bianco 2018; Kragesteen 2018) or cancer (Dellino, 2019), and those new discoveries are paving the way for the development of new diagnostic and treatment methods. Those advances are part of the current broader scientific revolution taking place at the frontier between life and hard sciences, which will provide a fundamental understanding of the mechanisms of life and will revolutionize biomedical and clinical applications for the generations to come.

All major technological developments, ranging from nuclear energy to artificial intelligence, rise high hopes for a better life for humankind as well as important concerns and ethical issues. Human knowledge and scientific progress must not be stopped, for no reason. Yet, practical applications of those discoveries ought to be carefully evaluated and planned as they may challenge fundamental human values and the very essence of human existence. For example, as we delve into the mechanisms of genetics, we can interfere at an unprecedented scale with the course of life of single individuals and of populations, i.e., with human evolution. That can erode one of the very founding concepts of modern nations and civilizations whereby equal rights are granted to all. As novel clinical methods require advanced and expensive technologies, they might become available to only the more affluent of nations or even to only

wealthier individuals, independent of universal rights or individual merits. To avoid turning hope into despair and unrest, I think all measures must be implemented to account for ethical issues and to deliver progress to the entire humankind.

Keywords

Technology management; ethical organizations; physics; biology.

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