

Voices

Physics meets biology: The joining of two forces to further our understanding of cellular function

Some biological questions are tough to solve through standard molecular and cell biological methods and naturally lend themselves to investigation by physical approaches. Below, a group of formally trained physicists discuss, among other things, how they apply physics to address biological questions and how physical approaches complement conventional biological approaches.



Michelle D. Wang
Professor of physics, Cornell University
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Physics of fundamental biological processes

I am fascinated by molecular motor proteins that operate on DNA. Because of the helical structure of DNA, motor proteins that translocate along DNA must also rotate around it. My lab investigates how these motors translocate and rotate, how they generate forces and torque, how they collide and navigate, and how their activities are regulated by the mechanics of their DNA substrates. These processes are highly mechanical in nature and thus naturally lend themselves to investigation by physical approaches.

A direct example of this is seen in my lab's development of optical trapping tools that are tailored to control and measure forces and torques at the molecular scale. Employing these techniques on the single molecule scale provides novel insights and complements approaches from other fields.

We developed a versatile suite of DNA unzipping techniques, which are based on mechanical separation of the two DNA strands. The “unzipping mapper” maps protein-DNA interactions to exceptional resolution and is unique in that it quantitatively measures the interaction strengths while mapping their locations to base-pair accuracy and precision. For example, the histone-DNA interaction map of a nucleosome serves as a roadmap of roadblock locations for RNA polymerase transcription through a nucleosome. The “unzipping tracker” allows real-time tag-free tracking of a DNA translocase, such as RNA polymerase or Mfd, while the “unzipping staller” measures how a DNA translocase works against a DNA fork before being stalled.

Our angular optical trap (AOT) is ideally suited for torsional studies of motor proteins and their substrates via direct torque detection of a biological molecule, adding an entirely new dimension to traditional optical trapping methods. In an AOT, a nanofabricated birefringent quartz cylinder is trapped and rotated via rotation of the trapping laser's polarization. The torque exerted on the cylinder is directly measured via the change in the angular momentum of the transmitted light. Using an AOT, we found that the torque that an RNA polymerase can generate is sufficient to melt DNA, which is important for gene expression regulation. This also establishes a physiologically relevant torque scale for processes on DNA. We also recently determined that a single chromatin fiber is torsionally much softer than a braided chromatin fiber, suggesting a completely new role for chromatin dynamics in simplifying DNA topology during replication. These types of studies provide unique insights into fundamental biological problems that are difficult to obtain through more conventional approaches.



Mario Nicodemi

Professor of theoretical physics, University of Naples

Chromatin architecture: Where physics meets biology

Molecular biology is currently making impressive scientific progress, with paradigm shifting discoveries emerging every few years, perhaps as physics did at the beginning of the last century with the development of quantum, relativistic, and statistical mechanics. I find the exploration of those new research territories intellectually exciting, especially because novel technologies are producing a wealth of quantitative and complex biological data, which demand the combination of life and hard science approaches to be understood.

For example, it has been discovered that the mammalian genome has a complex spatial organization within the cell nucleus, which serves vital functional purposes as, for instance, physical contacts must be established between genes and distal DNA regulatory regions to control transcription. Disruptions to such an organization can induce gene mis-expressions and human diseases as a consequence of the rewiring of regulatory interactions. The study of chromosome architecture is a perfect ground where physics meets biology as, after all, chromosomes are polymers and statistical physics naturally steps in here. My research team, for example, has been working to develop novel methods to probe chromosome structure with high accuracy and to understand, via quantitative and computational approaches, the physical mechanisms whereby DNA interactions are spontaneously established and orchestrated in the cell, at a molecular and at a system level.

While we are delving into the very functioning of life, those new discoveries and technologies have important applications well beyond fundamental science. They can be used, for example, to predict the medical implications of mutations, in single patients or even in single cells, and to develop novel treatments for diseases such as congenital disorders or cancer. That is part of the current scientific revolution at the frontier between life and physical sciences, which will fundamentally advance our understanding of nature and biomedicine for the next generations.



Nynke H. Dekker

Professor of biophysics, Delft University of Technology

Single-molecule biophysics is here to stay

Single-molecule biophysics really started with an experimental challenge: could you examine and study a single biological molecule? And how would you do it? Different approaches were developed: fluorescence spectroscopy, ion channel recordings, force spectroscopy.

As a science, single-molecule biophysics was initially regarded as a curiosity: what it could yield in terms of scientific understanding seemed initially marginal. But we owe much of our quantitative understanding and many of the models of how molecular machines function from the single-molecule biophysics experiments that were performed over the years.

Physics primarily comes into single-molecule biophysics in two ways: through the development of instrumentation, and through the analysis of results. Sometimes also in the conceptual design of the experiment, in the sense of what question should be asked, though frankly sometimes physicists don't always pose the most relevant questions here because they don't understand the biological system sufficiently deeply. That's why collaboration with biologists and biochemists remains so crucial.

The one thing I regret about single-molecule biophysics is that while you may discover new mechanisms that can well be important, the chance that you would discover a totally new phenomenon is smaller than in other fields: it's unlikely that you're going to discover a new protein with previously unheard-of functionality, for instance. But I remain delighted every time I see clear real-time traces of molecular motor activity that shed new light on their functionality!

What I am most proud of is that as a field we have changed a large and established field such as biochemistry. The first single-molecule biophysics experiments were *tour-de-force* (no pun intended) curiosities; nowadays, you can't attend a meeting on DNA-protein interactions without core contributions from biophysics. Single-molecule biophysics has been challenging at times, but also fun, and it's here to stay!



Thomas Gregor
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A different perspective on the phenomena of life

The discipline of physics provides a general framework for thinking about natural phenomena of any kind. It starts with the conceptualization and phrasing of the phenomena as a theory using the language of mathematics. Understanding is gained by testing the theory experimentally, possibly with subsequent refinements until a general principle emerges. It should thus come as no surprise that physicists have started to apply such an approach to the rich phenomena of complex biological systems. Physicists thus bring a different perspective to the phenomena of life, searching for unifying general principles. What makes this enterprise particularly exciting is that there is clearly something very fundamental that distinguishes inanimate from living systems, and what drives my research is the belief that the same physical laws must govern both classes of systems. Life magically emerges within this framework, leading us to new areas of physics and of biology, which we hope to discover. The expectation is that these discoveries will reshape our fundamental understanding of the most striking natural phenomena, and eventually one can use this understanding to solve practical human problems.

Faced with the same phenomena, biologists and physicists ask different questions and expect different kinds of answers. Take for example the fundamental observation of reproducibility and precision in developmental processes. When confronted with fluctuating answers in an experiment across biological replica, the tendency in biology is to try to understand how the system copes with such fluctuations and how it achieves robustness. And this approach works very well in many situations. The tendency in physics, however, is to cut down the system to its bare minimum, to achieve greater control over all relevant variables. The result is a restricted space of acceptable specimen in the sample distribution, and thereby reduced fluctuations across replica down to the limits of measurement precision. Pursuing the latter approach brought us to the striking conclusion that biological systems often operate at the limit of what is physically possible, governed by fundamental physics laws, sometimes, e.g., down to biological sensors counting individual molecules. It also demonstrated that biological systems can indeed be measured with similar precision and rigor than what is typical for measurements in inanimate systems, allowing us to assess raw physical variables directly instead of their proxies, thus providing more stringent quantitative tests of the theory. Both approaches are of course highly complementary and what is exciting about the field currently is that the synergies between these different approaches lead to insights that dealt with independently would not have emerged.



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Biology without modeling is like living without computers

Computer science allows managing large datasets in life sciences. Algorithms are designed to extract motifs, to classify automatically features in images or time series, and more is expected from artificial intelligence. However, the role of mathematical modeling, statistical physics, numerical simulations in biology has been less spectacular. Finding mechanisms or laws hidden in large amounts of data at molecular, cellular, and organism levels starts with models.

In the past 20 years, models reached the degree of complexity so that they can guide experiments and do not simply serve as quantifying parameters for statistical comparisons. The models can now be used to predict molecular organization, local physiology, and offer the frame to merge results from different types of experiments. In nanophysiology, at the limit of live space-and-time microscopy resolution, stochastic analysis of large amount of single particle trajectories (SPTs) requires a physical model for particle motion (molecules, receptors, channels, proteins, etc.). This representation allows us to extract biophysical parameters but also to reveal the underlying structural organization of the subcellular level. This led to the recent understanding that the flow in the ER lumen or mitochondria network depends on their topology. Numerical simulations of calcium dynamics in nanodomains such as dendritic spines, dendrites, or astrocytic protrusion revealed the local nanometrics underlying organization or local regulation of the associated interacting receptors or channels required for the initiation of learning and memory. Mathematical

formulas derived from physical models reveal the secret relation between various parameters, which is often difficult to explore numerically or experimentally. Yet these formulas are the expressions of the biophysical or physical laws, equivalent to the formerly Newton's law of motion for classical mechanics. Chromatin organization in the cell nucleus is another example where polymer models are used to interpret single-locus data experiments or chromatin configuration associated with the large HiC matrices.

Physical models, mathematical analysis implemented in model-machine-learning and classification approaches are now fundamental tools to generate new knowledge in molecular and cell biology and to reveal causality or to identify novel function from the molecules to complex organisms such as the brain and more.



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Physical thinking in biology

It has been 20 years, but I will always remember it. Me, the physicist with a shiny new PhD, sitting at the back of an enormous lecture theater surrounded by hundreds of 18-year-olds, listening to the introductory lecture of a first-year molecular biology class. That lecture turned me into a biophysicist and I never looked back. The beauty of biophysics as a field is its diversity. The annual conference of the discipline's main society, The Biophysical Society, is one of the highlights of the year (COVID, go away!): a wonderful journey through research areas that integrate physics and biology in many different ways, leveraging physics as a tool to measure biology and using it as a framework to understand how life works. I have always tried to do both: our lab develops new methodologies based on physical tools to visualize how proteins work and uses physical principles to describe that behavior.

In working with many talented biologists over the years, I've discovered a surprising benefit of physical thinking in biology: using quantitative reasoning to inform the design and interpretation of biological experiments. An intuitive and quantitative understanding of the length, time, and energy scales involved in biomolecular processes and being able to assess how they are impacted by experimental design has an important place in the toolbox of every molecular life scientist. Many experiments (even entire projects!) in our lab were brought back from near death by doing a quick back-of-the-envelope sanity check based on relevant physical parameters.

Sadly, with our undergraduate teaching structures still largely separating the disciplines of biology and physics, most of our biology graduates will not have been trained to automatically and intuitively apply elements of physical reasoning to their experiments. One barrier is how high-school students are used to treat quantitative problems as "plug 'n chug": taking a pre-existing equation, plugging in the variables, and accepting the answer at face value. More and more interdisciplinary undergraduate programs are introducing a different approach by teaching students how to deal with ill-defined problems, to estimate order-of-magnitude values, and to use dimensional analysis to figure out solutions. Such an approach results in rough answers that might not pass muster when building finely-tuned race cars, but that are immensely valuable in designing and interpreting biological assays that are almost by definition quite messy and ill-defined.



Suliana Manley

Associate professor of physics, EPFL

Credit: Suliana Manley; photo by EPFL/Alain Herzog

The mixing of scientific cultures

The first and last formal biology course I took was in high school. Like many physicists with dusty memories of biology, I recall finding the focus on naming and describing things disorienting. Physics offered an analytical framework and grand notions of universality. And yet, when I entered the world of research, I found myself drawn to the frontier of complex systems, where physics, chemistry, and biology meet. Here, I saw evidence that ideas, tools, and systems were coming online that could also find universality among the complexity. And those discoveries could even extend to biological systems: after all, despite evolutionary diversity offering multiple solutions to a given problem, those solutions were still subject to the laws of physics in a fundamental way.

Now, it seems to me sometimes that physicists focus too much on naming things: physics of biology, biophysics, active matter. Is physics meant to develop new tools for biology, or are biological systems to be harnessed to discover laws that govern non-equilibrium statistical mechanics and universal emergent behaviors? The evidence says that both approaches can be wildly successful, with the added joy that comes from mixing very different scientific cultures.

My group has been riding a wave that shifts between, on the one hand, developing super-resolution and computational microscopy tools and, on the other, using those tools to discover patterns in subcellular organization and dynamics. Initially, we focused on technologies for automation and illumination flat-fielding for high-throughput acquisition. Now, we are turning more toward adaptive and intelligent measurements, enabled by integrating neural networks into our instrument control. The most joyful part for me is then using instruments we build to capture wide-ranging systems, from centrioles to the bacterial divisome and the mitochondrial fission machinery.