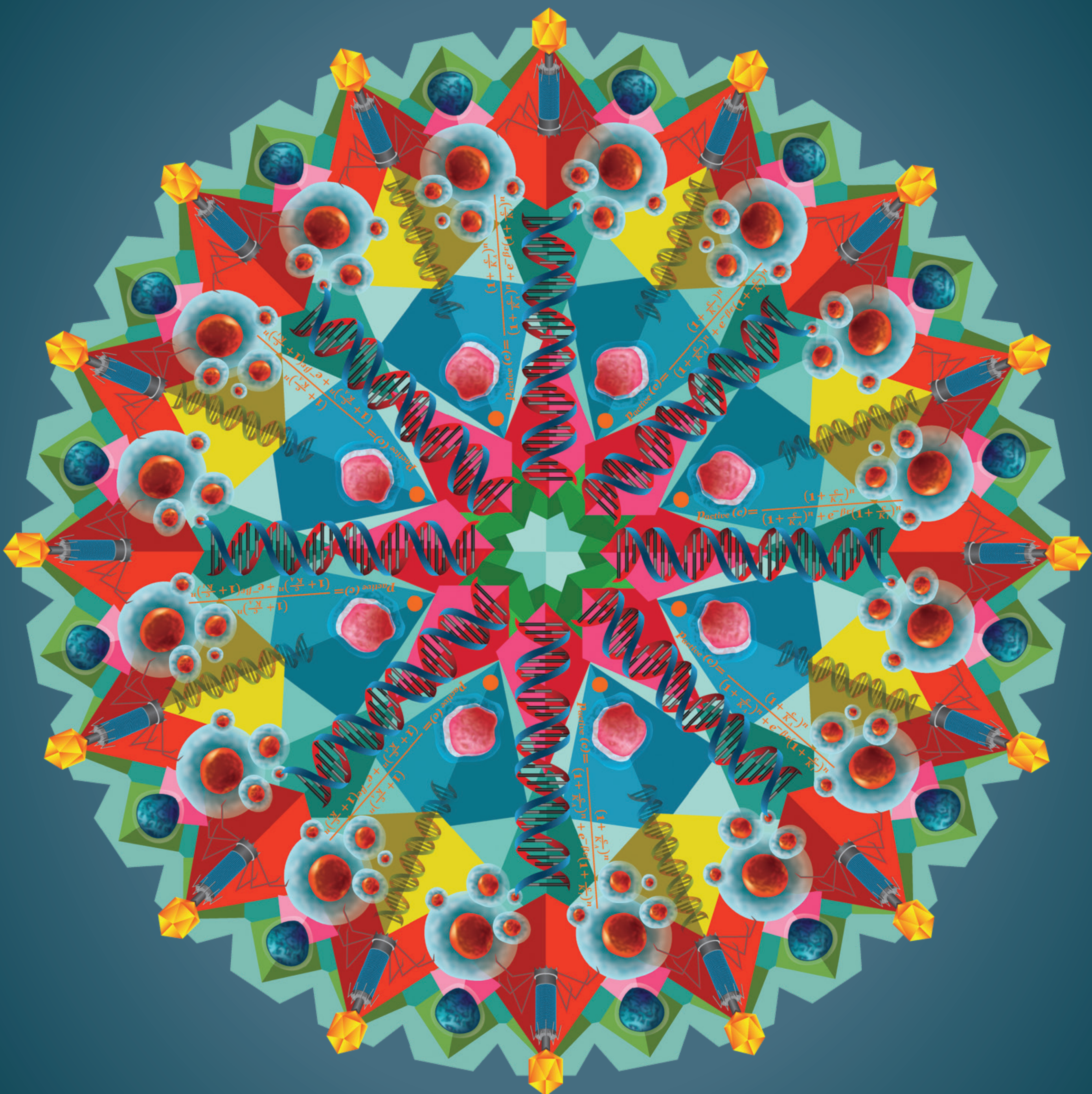

Biology through the Eyes of a Physicist

A look at the multifaceted, interdisciplinary world of biophysics

by Whitney Clavin

DNA, the quintessential molecule of all living beings, is composed of two twisted strands that wind around each other in the shape of a helix. The structure was famously discovered in 1953 by Francis Crick and James Watson; prior to that, scientists knew of the existence of DNA but could not crack the mystery of its 3-D structure, nor were they even sure that it was the storehouse of genetic information. One integral piece of the puzzle came in the form of X-ray diffraction images of DNA strands, meticulously captured by Rosalind Franklin and Maurice Wilkins. The images revealed a cross-shaped pattern suggestive of a helix and ultimately helped Watson and Crick solve the mystery as well as propose how DNA's ability to unwind allows for it to be copied and passed on.

The discovery of the double helix exemplifies the multifaceted field of biophysics, in which biology is viewed and better understood through the lens of physics. In this case, the X-ray-based tools of physicists were applied to living matter; in fact, Franklin began her career as a physical chemist, and Wilkins and Crick as physicists.

Recently, Caltech's Division of Physics, Mathematics and Astronomy (PMA), which traditionally includes professors and students who study everything from subatomic particles to exploding stars, hired physics professor Ibrahim Cissé, who is an expert in the imaging of single molecules in living cells. "The questions the physicist will ask, even if they are studying the exact same material as a biologist, are going to be different," says Cissé. "I am a physicist whose subject is living matter."

Cissé and his team use cutting-edge microscopy tools to study the real-time behaviors of individual molecules in cells as a way to understand the fundamental nature of life itself. Having Cissé in the division, says Fiona Harrison, the Kent and Joyce Kresa Leadership Chair of PMA, will help further catalyze the growing interdisciplinary field of biophysics across Caltech.

"Physicists approach problems using fundamental, quantitative principles," says Harrison. "PMA sees the expansion of our efforts in biophysics as an opportunity to apply this approach to issues in biology. This kind of fundamental look at scientific problems is well suited to Caltech, which focuses on basic research."

In the same spirit, chemists and biologists across the Caltech campus use the tools and approaches of biophysics to probe the mysteries of life, including everything from the mechanics of the living cell to the structure of biomolecules. As Cissé explains, there is a lot of overlap among the various fields of science.

"The cell doesn't care if your training is in chemistry, biology, or physics," he says. "It uses all of them. And to understand the cell, we really have to integrate all these different disciplines and bodies of knowledge together."

Condensation in Cells

Cissé specializes in visualizing single molecules inside living cells using a technique called super-resolution imaging, in which the limits of optical light itself, specifically the diffraction limit, are surpassed and cellular structures on the scale of a few nanometers can be resolved.

Cissé and his team have adapted and further developed the tool of super-resolution microscopy to study clusters of molecules that are not static but rapidly assemble and disassemble in living mammalian cells. "We want to push super-resolution microscopy to detect clusters that form in very crowded environments and that are highly dynamic," he says.

One bustling environment of interest is the nucleus of a cell. There, DNA is transcribed into messenger RNA, which ultimately provides the building instructions for the proteins that run the daily business of a cell. In order for the DNA to be transcribed, proteins called RNA polymerases, along with a host of associated proteins, must sit down on, or attach themselves to, the DNA strands and go to work. But how do the proteins gather together?

Using their super-resolution microscopy tools, Cissé and his team were able to see what was actually happening. They learned that the proteins come together in clusters like workers quickly gathering at a construction site. "There is a level of cooperation between the proteins,"

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Physics professor **Ibrahim Cissé,** who uses super-resolution microscopy to study protein dynamics, recently joined Caltech's Division of Physics, Mathematics and Astronomy (PMA). His arrival, says Fiona Harrison, Kent and Joyce Kresa Leadership Chair of PMA, will help advance the growing interdisciplinary field of biophysics across the Institute.

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he says. What triggers this sudden condensation? From a physicist’s point of view, you can quickly condense things with a phase transition, for example when vapor spontaneously condenses into a liquid droplet. “Phase transitions have been thoroughly studied in the realm of physics, and now we are able to study their role in regulating biological processes in the living cell.”

Ultimately, Cissé says, understanding a process as complex as DNA transcription requires an integration of physics with biology and chemistry. “We are studying how the cell works and discovering that living matter exhibits some of the same emergent phenomena, like phase transitions, that we also see in nonliving matter. There may even be a new physical understanding of how nature works that comes out of this line of investigation. Through biology, we are gaining new insights about physics.”

By the Numbers

One distinguishing trait of physicists is the drive to quantify and measure processes in nature. Rob Phillips, Fred and Nancy Morris Professor of Biophysics, Biology, and Physics, exemplifies this with his by-the-numbers approach to the study of biology. For instance, in 2018, he and his longtime collaborators Ron Milo and Yinon Bar-On of the Weizmann Institute of Science made quantitative estimates of the amount of biological matter, or biomass, covering our planet, including everything from bacteria to humans. Their research revealed, among other factoids, that humans and their livestock outweigh all wild animals by a factor of 20.

More recently, the trio, along with Avi Flamholz, a postdoctoral scholar at Caltech, published a similar by-the-numbers report, this time detailing those numbers that describe the COVID-19 virus, such as average concentrations throughout the body, number of genes, infection rate, and more.

“My approach to biophysics involves coming up with principles and theories first. It’s a certain style of inquiry, and it’s about quantifying and measuring things at all scales,” says Phillips, who is also co-author, along with Ron Milo, of the popular book *Cell Biology by the Numbers.* “It is physics unleashed on the nature of living organisms. That runs the gamut from very specific questions about the nature of proteins that interact with DNA all the way up to giant ecosystems.

“Astrophysicists study the cosmos, condensed matter physicists study nonliving matter, and biological physicists study living matter,” he says. “Personally, you will have a hard time convincing me that you and I and other living creatures are not the most interesting matter in the universe.”

Of course, an integral tool for quantifying nature is math. Phillips says that math is front and center in more or less every discussion in his group. “The language we speak in my lab,” he jokes, “is not English but math.” He recalls his graduate school teacher who had a blackboard on his door: “When I would come into his office, he would shut the door and tell me that if I had something to say, I needed to write it down in equations. I’m a devotee of mathematics now. We want to observe and measure.”

Shu-ou Shan, Altair Professor of Chemistry at Caltech, also sees math and quantitative modeling as part of the mindset of a biophysicist. One of Shan’s areas of research focuses on how proteins in cells are sorted to the proper locations as well as folded into the correct 3-D structures. Though her work lies in the field of biochemistry, she says her methods are rooted in both physics and chemistry.

“The biophysical side of our work involves making quantitative measurements, modeling molecular events

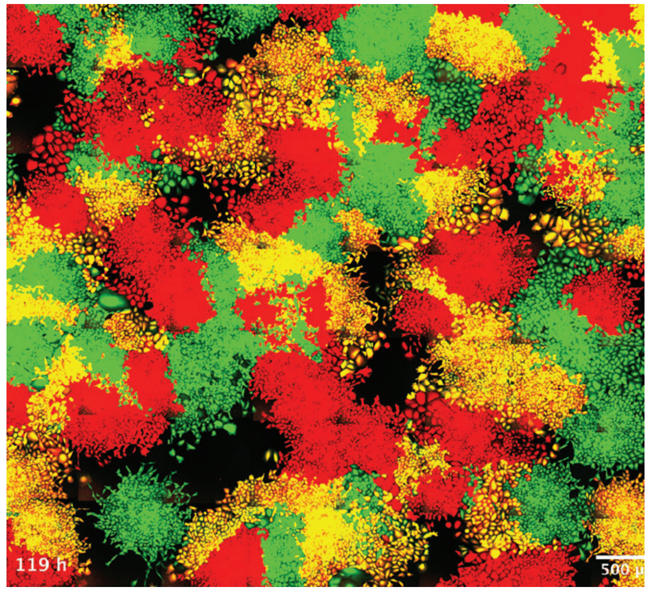
Rob Phillips, Fred and Nancy Morris Professor of Biophysics, Biology, and Physics (seen here pre-pandemic), takes a by-the-numbers approach to biology, exemplified by quantitative reports that describe the COVID-19 virus and Earth’s biomass.

based on first principles, and making predictions," she says. "We also use microscopy and spectroscopy tools that have been developed by physicists." In fact, Shan is leaving this month for a sabbatical at UC San Francisco, where she plans to learn the powerful tool of cryogenic electron microscopy (cryo-EM) for visualizing the structures of biomolecules. "Tools like cryo-EM and NMR [nuclear magnetic resonance] spectroscopy involve math, principles of light scattering, Fourier transforms, and so on. Physics helps us improve these techniques."

Simplicity First

Biophysics is also not the primary field in which Michael Elowitz, professor of biology and bioengineering at Caltech, works. But, he says, his experiences with the principles of physics have given him a taste for a different type of questioning.

"Physicists seek the minimal set of components and assumptions that can explain a phenomenon and then develop models that one can understand as deeply as possible," he says. "Even though, or perhaps because, biological systems are incredibly complex, it is critical to try to identify simplifying underlying principles."



Michael Elowitz, professor of biology and bioengineering at Caltech, seeks to identify the underlying principles behind biological systems. The image above shows a synthetic cellular system created in his lab that maintains cell colonies in distinct cell "fates," indicated by different colors.

Shu-ou Shan, Altair Professor of Chemistry at Caltech, sees quantitative modeling as part of the mindset of a biophysicist. One of her areas of research focuses on how proteins in cells are sorted to the proper locations as well as folded into the correct 3-D structures.

Elowitz and his lab use this approach to create and study synthetic cellular systems. For example, he and his graduate student Ronghui Zhu, along with other collaborators, recently asked what minimal biological-circuit designs could account for the ability of our own cells to take on many different "fates": becoming liver cells, neurons, or other cell types. To find out, they designed a synthetic gene circuit in living cells based on mathematical models and inspired by aspects of natural cell-fate control circuits. The synthetic system establishes multiple stable cell fates and allows researchers to switch a cell from one fate to another. Built "from scratch," as Elowitz says, the system provides insight into critical biological processes and could eventually play a role in the emerging paradigm of engineered-cell therapy, in which researchers design cells, rather than drugs, to target cancer and other disease states.

Elowitz says the approach of building biological systems as a means to understand them takes inspiration from a quote, often cited in the field of synthetic biology, by the late Caltech physicist and Nobel laureate Richard Feynman. The quote, discovered in the upper corner of Feynman's blackboard after his death in 1988, read: "What I cannot create, I do not understand."

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A Tradition of Crossing Disciplines

Feynman himself dabbled in biology; in addition to other pursuits, he spent a year in the laboratory of the late Max Delbrück, a Nobel laureate and longtime Caltech professor who helped launch the modern field of molecular biology. While Feynman's interests largely lay in pure physics, Delbrück is a prime example of a physicist turning an eye toward biology.

Delbrück, who was born in Germany in 1906, studied quantum mechanics with some of the great physicists of his time, including Niels Bohr, who reportedly piqued Delbrück's interest in biology. Ultimately, Delbrück and his colleagues Alfred Hershey and Salvador Luria, in the 1940s, would learn the secrets of viral genetics through their studies of bacteriophages, viruses that infect bacteria. According to the press release for their 1969 Nobel Prize in Physiology or Medicine, the scientists "worked out rigorous quantitative methods and this turned bacteriophage research into an exact science."

Today, a strong current of biophysics runs through the Institute, crossing numerous divisions and sparking collaborations among a wide range of scientists. "That's one of the beautiful things about Caltech: we can be in more than one department and have our collaborations be meaningful and real," says Phillips.

"There are no barriers to integrating all of this science," says Cissé. "Once you get a critical mass of people, you can really work together and nucleate new and exciting ideas."

Left to right: Jean Jacques Weigle, Ole Maaloe, Elie Wollman, Gunther S. Stent, **Max Delbrück,** and G. Soli. Delbrück, a Nobel laureate and longtime Caltech professor, helped launch the modern field of molecular biology.