FEATURE

Switching from Physics to Biology

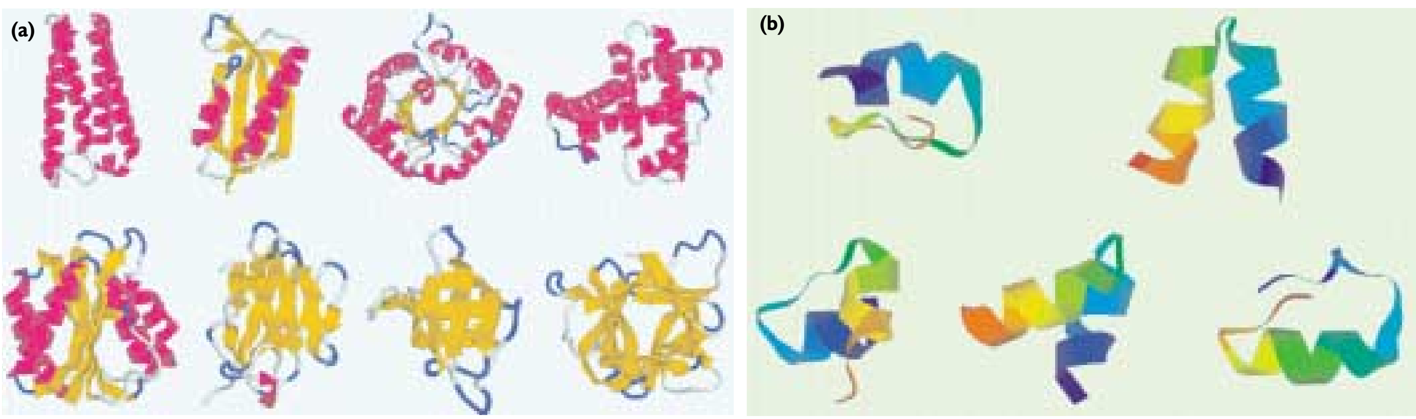
by Jennifer Ouellette

Physicists in transition help shape biological theory

Many in physics chafe at the oft-quoted maxim that the 21st century is the "age of biology." Others see the biological boom as offering unique opportunities for physicists—and not just in the traditional area of building instrumentation for experimental research. 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.

"An experimental field without theory eventually becomes awash in data," says Ned Wingreen of NEC Laboratories America, Inc. (Princeton, NJ). "There is just so much data being generated in biology today that the only way scientists will be able to organize it is by developing theoretical frameworks."

As industry moves toward greater interdisciplinary efforts involving researchers from both the physical and biological sciences, some traditionally trained physicists have transformed themselves into biophysicists and found rewarding new challenges. Wingreen and Stephen Laderman of Agilent Technologies have made that career trek, and their experiences illustrate the fascination of biophysics and its importance to shaping the theoretical basis of modern biology.



NEC Laboratories America, Inc.

Figure 1. Only about 1,000 distinct folds (as shown by these ribbon diagrams with characteristic secondary structures shown as red helices and yellow arrows) occur in natural proteins (a). Other highly designable protein backbones may be possible, such as the one at lower right in (b), which has not been found in nature.

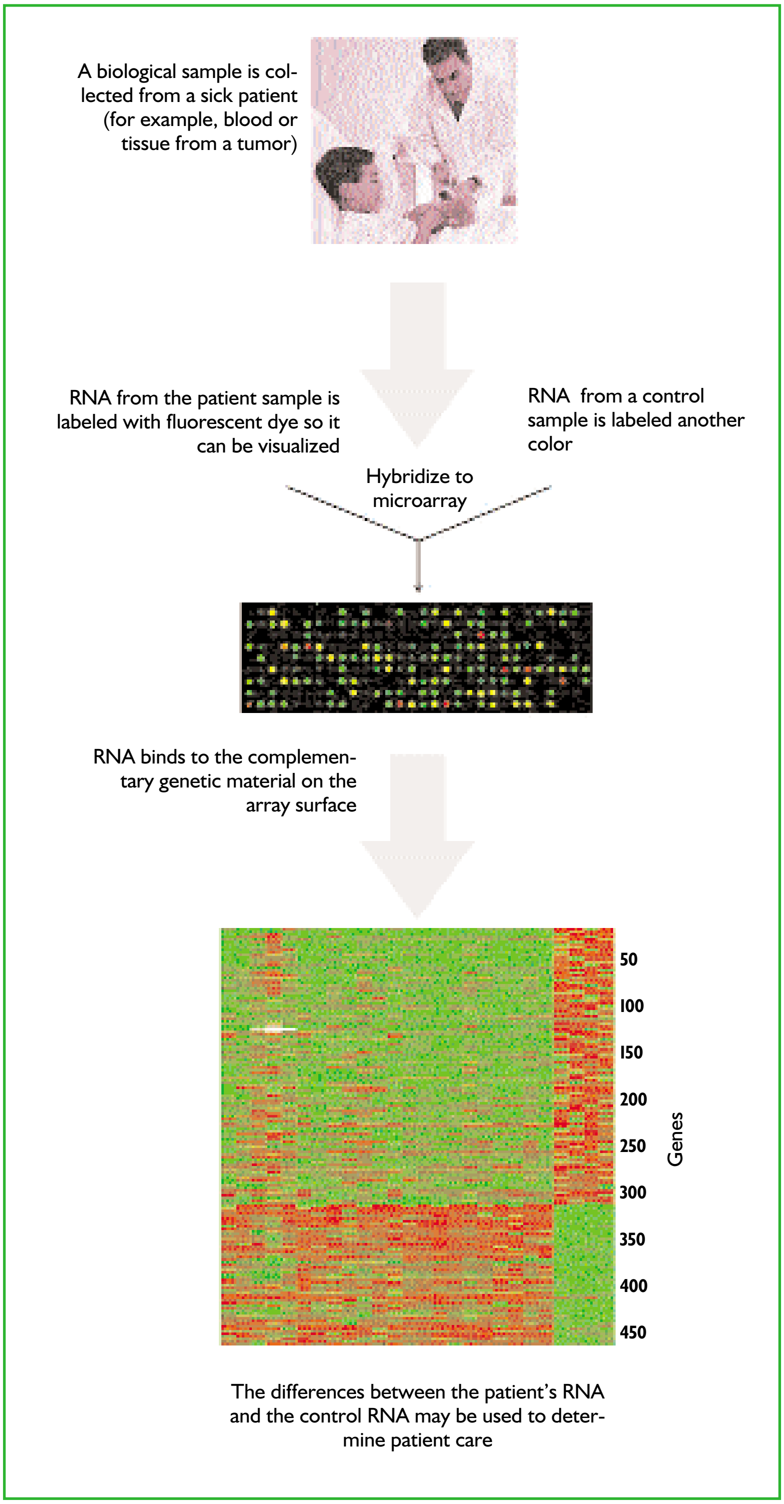
Bioinformatics

Originally trained as a condensed-matter physicist, today **Ned Wingreen** runs a bioinformatics research group along with fellow physicist Chao Tang. Bioinformatics—which uses the tools and techniques of computer science, mathematics, and statistics to analyze and manage biological data—is a new area for NEC, a company primarily associated with computers and communications equipment. But its investment in bioinfomatics research reflects its view of the future of information technology. "NEC isn't trying to become a pharmaceutical company, but they believe their customers are increasingly going to be in the biomedical sector," says Wingreen. "So they are interested in developing their own in-house expertise to generate both products and intellectual property."

His interest in math and science dates to his childhood in Los Angeles, and he chose to major in physics after taking a Saturday course at Caltech taught by an undergraduate. "Every week he would write down a problem in physics on the board and for the next two hours essentially fail to solve it," says Wingreen. "But it was such an exciting process, and made me realize that physics is very much about the excitement of the chase." When it came time to choose a graduate school, he opted to study condensed-matter physics at Cornell University under John Wilkins, earning a Ph.D. in 1989. After completing a postdoctoral fellowship at the Massachusetts Institute of Technology, he joined NEC in 1991.

Wingreen's initial work for NEC focused on theoretical studies of quantum transport, a far cry from his current work. His transition to biophysicist was largely due to serendipitously overhearing Tang, housed in the next office, engage almost daily in lengthy arguments with a postdoc about proteins. "At some point, I decided I couldn't get any work done, so I put down my pencil, went next door, and started talking to them," he says. "And I became convinced this was going to be a promising direction."

Figure 2. In molecular diagnostics, RNA from a biological sample is isolated and labeled with a fluorescent dye, and then it binds to complementary genetic material on a microarray for identification.



Agilent Technologies

The three men began working on simple lattice models of proteins soon afterward. Wingreen credits the flexibility and a sabbatical program afforded researchers at NEC for the ease of his transition. He spent a year at the University of California, Berkeley, where he took classes to better acquaint himself with his new field and "learn the language," and collaborated with a senior biologist.

The bioinformatics group primarily focuses on designing new protein folds (Figure 1). "Proteins are the workhorses of the cell, but to do their job they have to be properly folded," Wingreen explains. Although millions of protein sequences are available, the number of qualitatively different folded structures found in nature is relatively small—a few hundred to a thousand. "Part of our work has been to gain insight into the question of why we see such a small number of protein folds," says Wingreen. "We have learned that some structures intrinsically make better proteins than others. We think that is what limits the number found in nature. But it is also our view that there are still many possible folds out there not currently being used." The group's goal is to demonstrate that precept and to develop new folded-protein structures. "The new folds, in principle, could produce new catalysts and new pharmaceutical drugs," Wingreen says.

He and his colleagues are also exploring biological networks, such as intracellular and protein signaling systems, and looking beyond abstract properties to learn how specific networks may elucidate the broad classes of activities that take place in a cell. In signal transduction networks, for example, proteins on a cell's surface detect information from outside the cell. That signal is transduced to other proteins inside the cell and ultimately goes on to modify gene expression. Much of his group's signal transduction work is currently aimed at microorganisms such as bacteria and yeast because they are the most tractable experimental systems.

In some respects, Wingreen says, his work in biology is similar to what he did in physics—attempting to find simple models that capture the essential features of a system. "No one would argue with the notion that all of biology at root is physics, so it seems to me to be a kind of artificial distinction," he says. And because there has been so little theoretical work in molecular biology, there is a rich diversity of problems from which to choose. "In physics, I had to invest years just to get to the point where I could identify the interesting problems. The theory has been worked on by so many people for so long that the remaining problems are very subtle and deeply embedded," says Wingreen. "But in biology there are plenty of theoretical problems just under the surface."

Molecular diagnostics

Stephen Laderman's current position as manager of the molecular diagnostics department in Agilent's Life Science Technologies Laboratory (Palo Alto, CA) might seem a world apart from his early educational background in chemistry, physics, and materials science. But for him, the transition has been a natural continuum. Each stage of his career bears some logical link to the next—although he admits that in college, "I would never have predicted that I would be doing what I am today."

Laderman found himself attracted to science and math as a child. Although he earned a bachelor's degree in physics from Wesleyan University in 1976, he also took an equivalent amount of course work in chemistry. "I have always been interested in thinking about the relationship between atomic- and molecular-scale phenomena and structure, and their macroscopic- or human-scale manifestations, because it is related to what is of practical interest," says Laderman. With that in mind, he opted to pursue graduate studies in materials science and engineering at Stanford University, earning a Ph.D. in 1983. He remained at Stanford for a two-year postdoctoral fellowship and continued his thesis work of characterizing atomic-scale structures with X-rays, using the then relatively new technology of synchrotron radiation sources.

In 1984, Laderman joined Hewlett-Packard—from which Agilent later emerged—as a member of the technical staff in the materials research laboratory. Over the years, he served as a project manager in the company's integrated-circuit and solid-state-technology R&D centers, and in 1996 he became manager in chemical and biological systems. "Even before moving into the life sciences, I had been heavily involved in managing interdisciplinary projects," says Laderman. "So I saw the change as an additional opportunity to extend my management work to encompass some new disciplines."

Agilent spun off from Hewlett-Packard in 1999, but it maintains the philosophy of simultaneously advancing the fundamental underlying science along with practical implications. "Bill Hewlett liked to say that creativity works best when it is not too structured, but in the long run it must be tamed, harnessed, and hitched to the wagon of man's needs," says Laderman. "I think there's a lot of truth to that. It's been a continuous theme throughout my career, and it certainly applies to my department these days."

Agilent's molecular diagnostics department uses computational biology, molecular biology, and biochemistry to develop analytical systems for work in genetics, genomics, and proteomics, the effort to identify and determine the roles and interactions of all proteins encoded in the genome. Its staff includes scientists trained in biochemistry, molecular biology, and computational biology. Much of the research aims at elucidating behavior at the molecular scale and using that knowledge to develop new and better measurement systems. Indeed, a physicist in the department created data analysis software for Agilent's DNA microarray devices, one of its extremely successful products (Figure 2).

The work of Laderman's department is inherently interdisciplinary and lends itself to collaborative research. For example, it has an active collaboration in cardiology with researchers from institutions such as Stanford University and with a Harvard University group to develop single-molecule detection systems based on nanopore technology.

Laderman credits Agilent's firm commitment to its employees' continued development with easing his path into his new field. But he cautions those seeking to do likewise that they must be patient about the inevitable learning process. "It takes time and energy to learn the new material, and it is important to set realistic personal milestones," says Laderman, who learned primarily from his interactions and collaborations with other scientists. From them, he gained valuable expertise in molecular biology and its tools, and a smattering of cancer biology and cardiology. But more importantly, he says, "I have developed a great respect for how biologists accomplish their work and further their understanding of the field, which is impressive given the complexity and ambiguities they face."

Transition tips

Physicists who switch from pure physics to the biology–physics interface may work in academia, industry, or government labs, as well as in a wide range of specialized areas. Yet all have useful insights about preparing for such a change, gleaned from their own varied experiences.

Andrea Liu, a professor of chemistry and biochemistry at the University of California, Los Angeles, recognizes the benefits of making the transition early in one's career. She made the switch as an untenured professor and found that the most difficult aspect lay in finding a problem of equal interest and relevance to both physicists and biologists. In contrast, graduate students and postdocs can simply join a different research group without having to select their own problem. However, she says, "the advantage of switching later is that you have a very solid grounding in physics before moving into biology."

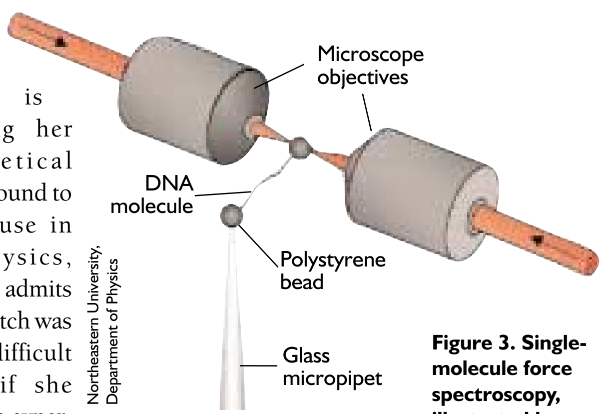


Figure 3. Single-molecule force spectroscopy, illustrated by this optical-tweezer technique, is a field of biophysics that has been developed with a lot of help from physicists.

Liu is putting her theoretical background to good use in biophysics, yet she admits her switch was more difficult than if she were an experimentalist. "There has been no biological theory in the past," she says. "For many biologists, theory is related to data analysis or devising equations to describe something, whereas to a physicist, theory is developing a new way to look at the entire problem."

Mark Goulian, assistant professor of physics at the University of Pennsylvania, also struggled with finding his niche in biophysics, and he credits a fellowship at Rockefeller University's new Center for Studies in Physics and Biology with helping him identify his research interests. He advises following one's interests rather than currently fashionable topics. "If I had really listened to my inner voice and followed what truly excited me, I would have immersed myself immediately in a biology lab," he says. Instead, he followed a circuitous path, from high-energy physics to soft condensed matter to biology. "My CV looks a little odd, but in the end it worked out well for me," Goulian says.

One way to make the transition is to focus on an area in biology that is instrument-intensive, such as single-molecule manipulation or imaging. **Mark Williams**, now an assistant professor of physics at Northeastern University, has found his experience building optical tweezers especially useful for biological problems (Figure 3). "That's definitely one significant strength of physicists: the ability to build instruments to perform research on whatever experiment is put in front of us," he says.

Wingreen says he found it helpful to be a student again when making his transition into biology. Although it is not necessary to take extra classes, it is vital to gain a thorough understanding of what is known in your area of interest and to learn how to communicate with biologists. "Physicists have to make a little bit of an investment to learn to talk to biologists," says Wingreen. "The good news is, it is pretty much a one-time effort. There is a lot of unity in biology."

It is also useful to choose good mentors or collaborators. "It's easy to discount or not realize the difficulties of actually doing some of these experiments, and a good mentor can bring you down to Earth." Interdisciplinary interactions can lead to intriguing new research areas: Williams' current studies of DNA–protein interactions were a direct result of an interdisciplinary group interested in nucleic acids. And collaborating with experimental biologists is absolutely essential if you are working in biophysics theory, Liu says. "As a theorist, you can only progress so far before you need to check your ideas experimentally." Ω