Bridging the culture gap

Molecular biologists are deluged with data, and physicists, used to reducing complex systems to basic principles, might help to make sense of it all. But bringing the two disciplines together isn't easy, says Jonathan Knight.

In late July, several dozen physicists with an interest in biology gathered at the Colorado mountain resort of Snowmass for a birthday celebration. Hans Frauenfelder, a physicist who began studying proteins decades ago, turned 80 this year. But unofficially, the physicists were celebrating something else — a growing feeling that their discipline's mindset will be crucial to reaping the harvest of biology's postgenomic era.

Of course, physics and its techniques have played a significant role in biology for decades. X-ray crystallography and nuclear magnetic resonance are essential tools for structural biologists. Biophysicists study everything from the forces exerted by molecular motors to the energetics of enzyme catalysis. And electrophysiologists need a working knowledge of the Nernst equation, which describes the movement of ions across cell membranes.

Many of the founders of molecular biology were also originally physicists. But in the 50 years since people such as Max Delbrück and Francis Crick created the field, it has abandoned its roots. Physics is theory-driven; molecular biology has become an empirical and descriptive science. Physics uses mathematics to represent the laws of nature; molecular biology relies on words and diagrams to describe the functions of living things. The essence of physics is to simplify, whereas molecular biology strives to tease out the smallest details. To cynics, the latter has become an exercise in molecular stamp-collecting, slotting new components and interactions into ever more complex biochemical pathways.

The two cultures might have continued to drift apart, were it not for the revolution in genomics. But thanks to a proliferation of high-throughput techniques, molecular biologists now find themselves wading through more DNA sequences and profiles of gene expression and protein production than they know what to do with. It may be time to take a step back from the details and try to see the big picture.

"Biology today is where physics was at the beginning of the twentieth century," observes José Onuchic, who is the co-director of the new Center for Theoretical Biological Physics (CTBP) at the University of California, San Diego. "It is faced with a

Deeper understanding: José Onuchic believes that physics can offer biology fundamental explanations.

lot of facts that need an explanation."

Physicists believe that they can help, bringing a strong background in theory and the modelling of complexity to nudge the study of molecules and cells in a fresh direction. "What has been all too rare in biology is the symbiosis between theory and experiment that is routine in physics," says Laura Garwin, director of research affairs at Harvard University's Bauer Center for Genomics Research, who has made her own transition to biology — she was once *Nature's* physical-sciences editor.

Opportunity knocks

Funding agencies agree that there are real opportunities for progress in the area. In late July, for instance, the US Department of Energy awarded a \$36.6-million, five-year grant to a cross-disciplinary team at the Lawrence Berkeley National Laboratory in California. Headed by physical chemist Adam Arkin, the group plans to develop computational models of bacterial responses to stressful environments. New centres are also being established at the interface of physics and biology, and job opportunities abound. Acknowledging the trend, the American Physical Society will later this month hold a meeting in Boston — entitled

'Opportunities in Biology for Physicists' — aimed primarily at biology-curious graduate students and postdocs.

But there are pitfalls. Although some molecular biologists are happy to welcome physicists into their labs, others perceive them as interlopers who don't really understand what they are getting into. Meetings intended to bring the two disciplines together still sometimes end up with the two camps failing to communicate. And even physicists who have made the jump into molecular biology say that framing biologically relevant questions poses a huge challenge for those coming from outside.

Onuchic is in the vanguard of this new breed. Originally trained in theoretical physics in his native Brazil, the centre he now co-directs was last month given \$5.5 million over five years by the US National Science Foundation to seed collaborations between biologists and physicists. Onuchic owes his introduction to biology to physicist John Hopfield, under whom he studied for his PhD at the California Institute of Technology in Pasadena in the late 1980s, working on the theory of biological electron-transfer reactions.

Onuchic's mentor is an inspirational figure for biological physicists in general.

John Hopfield's work on neural networks (inset) showed physics can model biological processes.

Hopfield, who now works in the molecular-biology department at Princeton University in New Jersey, made his own transition to biology in the early 1980s when he developed computer models of neural networks that displayed properties of animal nervous systems. His networks consisted of virtual neurons, equivalent units that could activate their neighbours according to certain mathematical rules. Although others had been designing artificial neural networks since the 1950s, Hopfield's were the first that could recognize familiar patterns, correct errors and remember a sequence of events¹.

Neural networks "were a demystifying concept", says Charles Stevens, a neurobiologist at the Salk Institute for Biological Studies in La Jolla, California. They showed, for example, that complex behaviour could arise from simple repeating units, and that this behaviour could be modulated by altering the strength of the connections between the simulated neurons.

Today, physicists are exploring applications for network theory in molecular

biology. One of the projects at Onuchic's centre is investigating whether networks of gene regulation have parallels in neural networks. Just as neurons activate and repress other neurons, gene products can activate and repress other genes, directly or indirectly. The parallels may even extend to similarities between learning — which alters the firing pattern of individual neurons and hence the network's overall behaviour — and the way in which evolutionary pressures alter patterns of gene expression.

Hopfield, meanwhile, is now championing the idea of 'modular' biology. Together with cell biologist Andrew Murray, director of the Bauer centre, geneticist Leland Hartwell of the Fred Hutchinson Cancer Research Center in Seattle, and physicist Stanislas Leibler of Rockefeller University

All for one: computer models are revealing how slime-mould amoebae join forces to form these multicellular spore-bearing structures.

in New York, Hopfield has proposed that discrete biological functions rarely lie with individual genes or proteins but instead with modules comprising many interacting molecules². Examples include the ribosome, which manufactures proteins, and the signalling network of proteins that controls cell division. The researchers have suggested a number of ways to explore this idea, including efforts to reconstitute or build functional modules in the test tube, the behaviour of which would shed light on how well the underlying principles are understood.

Cracking the mould

Physicists are also helping to explain molecular influences on the behaviour of entire cells. Herbert Levine, a condensed-matter physicist at the University of California, San Diego, and co-director of the CTBP, is collaborating with biologists at Cornell University in Ithaca, New York, to model the way in which cells detect and migrate towards chemical signals. The team is focusing on the slime mould *Dictyostelium discoideum*, which lives as individual soil-living amoebae unless food becomes scarce, when the amoebae aggregate to form a multicellular organism. This produces resilient spores that hatch into new amoebae when conditions improve.

The amoebae aggregate by sending and receiving biochemical signals such as cyclic adenosine monophosphate (cAMP). But because cAMP diffuses rapidly, it isn't clear how individual cells know which direction the signal came from. Levine has devised a model that depends on the time delay from the moment a new wave of cAMP reaches one side of the cell until it completely surrounds it. The cell-surface receptors that bind to cAMP first send a repressive signal to all other receptors in the cell that prevents them from binding for about 30 seconds, Levine's model proposes³.

This basic idea did not require any special insight, Levine admits. But his background in modelling enabled him to generate

a set of quantitative predictions that can now be tested experimentally. "A biologist in principle could do the same thing, but in practice physicists have been trained to model complex systems," says Levine.

Projects such as Levine's are a promising start. But the ultimate goal for the physicists now entering the world of molecular biology is to derive fundamental principles that help to explain the characteristics of many biological systems. It is early days, but biological physicists point to Leibler's ideas about 'robustness'.

Traditionally, biologists have thought of cellular processes as exquisitely sensitive and well-balanced. But Leibler argues that cells can withstand a great deal of noise and perturbation. For example, circadian clocks, which govern organisms' daily cycles of activity, tick at the same speed regardless of temperature or the supply of nutrients. Yet the rate constants of any chemical or enzymatic process should vary with temperature, and gene expression should decline under starvation conditions. These sources of 'noise' in the system put strict theoretical limits on the type of oscillation mechanism that cells may use, Leibler argues. According to his models, a system that relied on a simple negative feedback loop to cause the production of a biochemical signal to oscillate up and down over time would not tick reliably against a noisy background, whereas one based on a fluctuating balance of positive and negative influences would be relatively insensitive to this interference⁴.

Such theoretical work should enable molecular biologists to sharpen the focus of their experiments. But in many cases, collaboration is being held back by a

Study guide: Hans Frauenfelder uses myoglobin in his work on complex matter.

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John Hopfield

communication breakdown. This proved a problem in April at a workshop on DNA held at the Wellcome Trust Genome Campus in Hinxton, near Cambridge, UK. The meeting, co-organized by the Institute of Physics, Britain's main professional body for physicists, aimed to foster collaborations across the disciplinary divide. But the two camps struggled to understand one another. "The talks were too highly specialized," says Chris Phillips, a solid-state physicist at London's Imperial College who chaired a discussion session at the meeting. "A lot of physicists would have come away none the wiser. We needed an overview."

Fresh perspectives

More fundamentally, molecular biologists and physicists tend to ask different questions when presented with the same biological system. For example, when considering a network of interacting proteins, a biologist may first ask about the chain of events that occurs after one protein binds to another, whereas a physicist might want to know the rate constants of all the reactions. In a discussion session at the Snowmass meeting, a similar gulf opened up over the phenomenon of protein phosphorylation. Phosphate groups are often added or removed from proteins to modulate their activity. The biologists in the room were interested in which proteins were switched on or off in this way. But the physicists pondered a deeper question: why phosphate, as opposed to some other chemical group?

By asking different questions, physicists may in some cases bring fresh and useful insights. But one of the greatest concerns for the Snowmass participants was the risk of wasting time on issues that have no biological meaning. As several attendees pointed out, not every feature of a biological system has a functional importance, nor is every system likely to operate with optimal efficiency. Evolution doesn't choose the best option, just the best available option. Physicists stumbling into this minefield risk wasting their time on apparently interesting but ultimately trivial questions.

It's a serious concern, because there are

still lingering doubts about the relevance of earlier forays by physicists into biology. Frauenfelder was feted at Snowmass for his work on the energetics of protein folding—he developed the concept of the 'energy landscape', in which valleys represent the stable forms of the protein and hills are barriers to changing shapes⁵. But many biophysicists question whether Frauenfelder's work on the oxygen-transport protein myoglobin will lead to useful generalities about protein folding, as the principles are based on this single example. And for all their power, it remains unclear whether neural networks are genuinely mimicking the nervous system. "We still don't know to what extent they have anything to do with life," says Stevens.

Frauenfelder is unfazed by such concerns, as he is interested in myoglobin as a system in which to study the behaviour of complex matter. He likes to quote what Stanislaw Ulam, the mathematician who helped to develop the hydrogen bomb, once said to him: "Ask not what physics can do for biology, ask what biology can do for physics."

But Hopfield and others argue that it is critical for the physicists now flirting with molecular biology to sit down with their new colleagues and agree on what are the important questions. "The word 'function' doesn't exist in physics, but physicists are going to have to learn about it," says Hopfield. "Otherwise they will be off playing in a sandbox by themselves."

Onuchic believes that immersing young physicists in the culture of biology is the key. At the CTBP, postdocs train in both disciplines simultaneously, developing projects that involve two labs, one in biology and one in physics. They attend two sets of group meetings, and so learn the language and mentality of both disciplines at the same time. "They get inside the culture of the two fields," Onuchic says. "They get comfortable with the vocabulary and the journals. Life in both labs is more important than any classes you can take."

Time will tell whether the new generation of biological physicists avoid becoming the lonely children of biology. But for now, the prospects look bright. "We have always been the odd kids in the playground," says Onuchic. "But we never gave up, and now we are becoming very popular."

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Opportunities in Biology for Physicists

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