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Can physics deliver another biological revolution?

Cultural, institutional, conceptual and linguistic barriers are being overcome as physicists and biologists recognize the scientific stimulus they can gain from each other. The United States is showing the way.

What can physics do for molecular biology? This may seem an odd question in an era when biomedical science is lavishly funded, attracts widespread public interest and shows no sign of slackening its pace of discovery. Surely molecular biology, of all the sciences, should be able to take care of itself.

Yet the question is being asked — and answered — by increasing numbers of biologists and physicists, and by those who employ and fund them. And the conspicuous success of molecular biology is one of the main drivers of the trend. The genetic engineer's tool kit has been enormously powerful, but only recently have techniques become available that can provide high volumes of quantitative biological information. For example, it is now becoming routine to monitor the expression of up to 10,000 genes at a time, using DNA microarray technology. From genome sequencing to protein structure determination, biologists are increasingly thinking about how to manage 'floods of data' — and realizing that physical scientists have been coping with this problem for decades.

Beyond simply 'managing' the data — for which the tools of computer science and informatics are proving essential — biologists are finding that they also need new ways of thinking about the data. It is only a small exaggeration to say that the main method of analysis in molecular biology has been the cartoon representation of networks, pathways and complexes; indeed, superb papers have been written for the purpose of adding a single arrow to an existing cartoon. But to really understand the biochemical network thus represented, one needs to have numbers attached to the arrows, and equations relating the numbers. The paper by Alon *et al.* on pages 168–171 of this issue shows how such a model — combined with the powerful methods of genetic engineering — has led to a deeper understanding of bacterial chemotaxis.

So what's new?

If this were just a story of biologists co-opting tools from the physical sciences, nothing much would be new. Nor is the story one of physicists simply 'doing physics' in biological systems — for example, studying the properties of DNA as a model for other polymers. What's new is that many physicists — not just a few isolated pioneers — are getting excited by the challenge of tackling important questions in biology, using the tools, both physical and mental, of physics.

One should not underestimate the extent of this challenge. History records many sad cases of physicists enthusiastically attacking biological problems that they could solve, only to find that biologists considered these problems uninteresting. Physicists are also addicted to simplification — a habit viewed with suspicion by biologists, who know from hard-won experience how much small details can matter. Thus, the experimental physicist will find that it is no trivial matter to control all but one of the variables in a biological system. Meanwhile, the theorist, used to the productive interplay of theory and experiment that seems essential for progress in physics, will find that most molecular biologists have little time for mathematical theory, which has played no significant role in their field's great advances.

Then there is the language barrier, and the sheer number of facts and labels to be assimilated before a physicist can have a productive conversation with a biologist collaborator. The biologist, in turn, will probably have had very little quantitative training — increasing the difficulties of finding common ground. The determined interdisciplinarians who surmount all of these hurdles may then find institutional obstacles in their way. Physics departments may be loath to hire physicists who work on biological problems, for fear that they will spend all their time in the biology department. Cries of 'That's not really physics!' and 'But can he teach quantum mechanics?' have been known to resound in department meeting rooms when biophysicists have been considered for faculty positions.

The physics–biology agenda

The good news is that there seems to be a considerable will to overcome these and other institutional obstacles. Several universities in the United States have announced plans to put physical scientists and biologists together in interdisciplinary institutes, while they retain their appointments in existing departments (*Nature* **397,** 3; 1999). Physics and biology departments are learning to make joint appointments, sometimes with one department providing the post and the other providing laboratory space. And one physicist has spoken of the thrill of installing the first real biology laboratory in a physics building — "although there are no mice or monkeys running around yet".

In the United States, government and private funding agencies are also promoting the physics–biology agenda. The National Institutes of Health (NIH) has several initiatives designed to bring physical scientists into biology, and a National Science Foundation programme funds mathematical and physical scientists and engineers who want to collaborate with scientists at NIH. The Sloan Foundation (with the US Department of Energy) funds fellowships for physical scientists in computational molecular biology, and the Burroughs Wellcome Fund gives five-year grants to institutions that provide graduate and postdoctoral training at the physics–biology interface.

It should be stressed that, appropriately, all of this activity amounts to a small part of physics and biology. No one is suggesting that a large fraction of condensed-matter physicists should abandon their inanimate pursuits to get their hands wet in biology labs; and in biology there is still plenty of mileage left in developing cartoons. But it may be well to recall that today's molecular biology had its origins half a century ago in the work of a small band of (mostly) physicists. And although Max Delbrück's model for the molecular origin of mutations, popularized in Erwin Schrödinger's classic book *What is Life?*, proved to be wrong, these physicists introduced ways of approaching biological problems that stimulated a revolution in biology. Today, with physicists who can manipulate single molecules in the laboratory, and simulate and quantitatively analyse complex systems, who can say what might not be possible? □