Silicon dreams in the biology lab

For many biologists, the idea of creating a computer model of a living cell is anathema. But for mathematicians and physicists, the pursuit of such a goal is proving irresistible, says Diane Gershon.

Computational cell biology, although not a new field, has not been given much weight until relatively recently. But as genomic and proteomic data grow more prevalent and computers become more powerful, scientists are making greater efforts to build computational models for cellular activity — from whole cells to entire systems, complete with gene expression, and regulatory and metabolic pathways. Several fledgling institutions and initiatives mean more opportunities for biologists willing to marry their skills with maths and computer science. But, ironically, biologists seem to be the most resistant to this new area of activity.

ENTRENCHED RESISTANCE

John Carson, a professor in the biochemistry department at the University of Connecticut Health Center in Farmington, says that he has found it easy to recruit mathematicians, physicists and engineers to work on computational cell biology because it is a grand and novel challenge for them. "We've found it a little bit more difficult to recruit biologists, or to convince biologists that computational approaches are going to be valuable," he says, "because many biologists feel that biology is just too complicated to deal with computationally."

At least some of biologists' resistance lies in their training. For the new work, they need to understand differential equations and rate constants, for example, and historically biology has not been taught that way. In the experience of John Tyson, a professor in the department of biology at Virginia Tech in Blacksburg, most of the people who move into computational biology do not come from traditional biology backgrounds but rather from physical chemistry, chemical engineering, applied mathematics, numerical analysis and biophysics.

More resistance lies in taking a leap of faith away from their tried-and-tested methods. Many mainstream cell and molecular biologists still need convincing that it can be done, says Leslie Loew, director of the Center for Biomedical Imaging Technology at the University of Connecticut Health Center. "There are a lot of biologists who are very content to chip away at their own very highly restricted problem and not really try to build a full picture of cell-biological systems," he says.

One criticism levelled at computational cell biology in the past was that it was often pretty irrelevant to what was going on in the lab. Loew agrees that this has not helped its image. "But if computational modelling is closely linked to experiment," he says, "then it becomes a very valuable adjunct to experimentation."


John Tyson sees computational cell biology as the logical extension of bioinformatics.

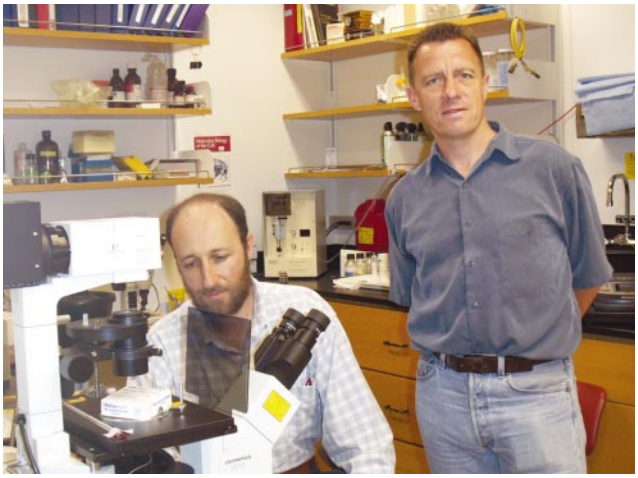
BEYOND BIOINFORMATICS

Modelling is a logical next step from existing bioinformatics, argues Tyson. "People with a little further vision are seeing that computational cell biology is just around the corner," he says.

Identifying genes, determining the structure of proteins and investigating protein–protein interactions is all very well but "we think that gives you a kind of static picture of the cell", Tyson says. To understand how the components of a cell interact in a dynamically changing environment, "you need to convert the interactions into mathematical equations and animate them on a computer", he explains.

Some proponents of computational biology think that an increase in the number of initiatives that combine experimentation with modelling might bridge the gap and quash the scepticism. Such efforts would require experimental biologists to rub shoulders with theoretical physicists, mathematicians, engineers and computer scientists.

Several recent initiatives — although broader in scope than just computational cell biology — are already set up this way, such as the Institute for



Alex Mogilner (left) and Jonathan Scholey are aiming to marry experimental biology and mathematics at the University of California, Davis.

Systems Biology in Seattle, Washington, which is headed by Leroy Hood. Another example is the Institute for Quantitative Biomedical Research, a multi-campus effort, based at the University of California, San Francisco, and directed by Marvin Cassman, former director of the National Institute of General Medical Sciences.

On a more modest scale, the University of California, Davis, will this autumn open a new Laboratory of Cell and Computational Biology within the Center for Genetics and Development, which will house both experimental and theoretical scientists under one roof. The lab will focus on a combination of experimental cell biology, under the direction of Jonathan Scholey of the university's molecular and cell-biology section, and mathematical modelling of cell-biological phenomena, under the direction of Alex Mogilner of the institute's department of mathematics. A particular emphasis for the new lab will be on cytoskeleton dynamics, cell motility, mitosis and cell division.

IMPROVING ACCESSIBILITY

These types of initiative are providing a few examples of high-profile, but relatively isolated, activity. If computational cell biology is to be accepted by more mainstream molecular and cell biologists, "we have to have some user-friendly interfaces that lower the activation barrier for experimental biologists to start thinking about mathematical models", says Tyson.

Efforts such as the Virtual Cell project, developed as part of the University of Connecticut's National Resource for Cell Analysis and Modeling (NRCAM) and funded by the National Institutes of Health (NIH), have helped. Virtual Cell, which is available free on the Internet for non-commercial use, provides a generalized modelling and simulation framework that biologists without a mathematical background — and with a little training — can use.

Other examples include the E-CELL simulation software, developed at Keio University in Japan (see "Computerized role models", page 7), and the Gepasi biochemical kinetics simulator, developed at the University of Wales, Aberystwyth, UK.

The US defence department's Defense Advanced Research Projects Agency also began a major biocomputing initiative last year. The agency plans to spend US$50 million over five years to fund projects to create an open-source framework and tool kit for modelling dynamic cellular-network functions.

GETTING THE MESSAGE OUT

The field is gaining visibility. "Whereas before we mostly talked among ourselves, now we're trying as hard as we can to branch out and take the message to practising experimental cell biologists," says Tyson.

The second International Symposium on Computational Cell Biology, organized by the NRCAM, will be held on 22–25 March 2003 in Lenox, Massachusetts. Last year's meeting attracted a healthy mix of theoreticians and experimentalists, although many of the latter were already converts. Al Gilman, Nobel laureate and professor of pharmacology at the University of Texas Southwestern Medical Center in Dallas, will be the keynote speaker at next year's meeting.

Gilman heads the Alliance for Cellular Signaling — a consortium funded in part by one of the NIH's 'glue' grants — which is studying the G-protein-mediated, and related, signalling systems in two different cell types (see *Naturejobs* 4–5; 19 April 2001). The initiative has had a computational modelling component from the outset, albeit a smaller part of the overall project. Another glue grant is focused on the area of cell migration.

But how well and how fast computational cell biology meshes with the mainstream remains an open question. The development of interdisciplinary research and training initiatives and user-friendly computational modelling tools that bring quantitative modelling methods to the general biologist will undoubtedly help. When asked: "What will it take?" Tyson quips: "Some very striking and counterintuitive prediction that's confirmed by experiment." And perhaps more biologists willing to take a leap out of their experimentally driven boxes. ■

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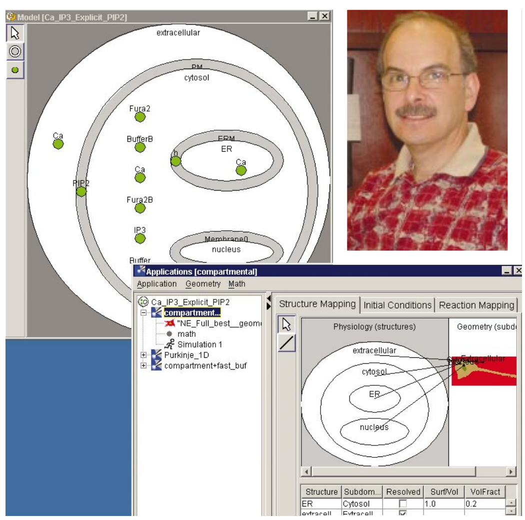
Virtual Cell modelling and simulation framework
- **www.nrcam.uchc.edu**

Gepasi biochemical kinetics simulation package
- **www.gepasi.org**

Alliance for Cellular Signaling
- **www.cellularsignaling.org**

Cell Migration Consortium
- **www.cellmigration.org**



Leslie Loew believes computational efforts such as the Virtual Cell project have a lot to offer experimental biologists.