From scepticism to acceptance

Computational neuroscientists, with skills developed in the physical sciences, are becoming integrated into the effort to solve the mysteries of the brain, says Hemai Parthasarathy.

HEBREW UNIV. JERUSALEM

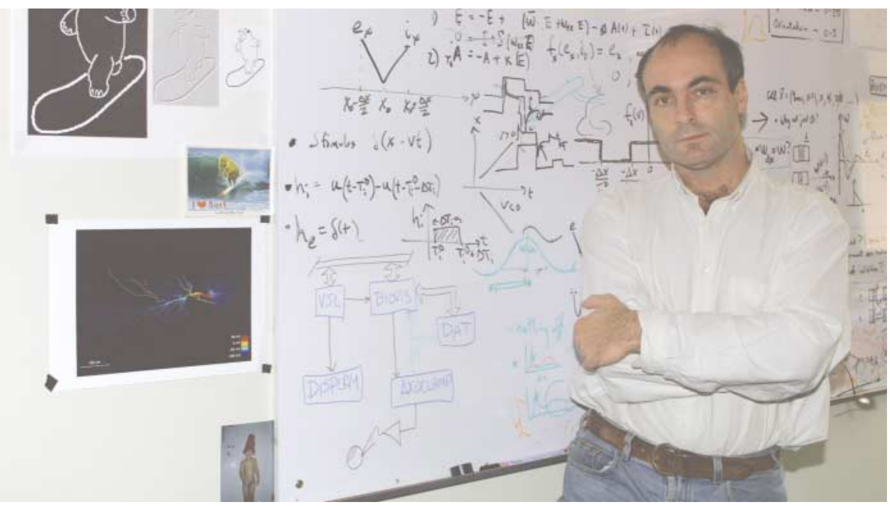
Open arms: how the octopus's brain controls movement is the focus of studies at the Center for Neural Computation in Jerusalem.

Modelling neuronal systems was once considered to be a marginal activity. But with more data and better computational techniques now available, opportunities for research and education are opening up. Terry Sejnowski, one of the discipline's current leaders, began to model neural processes as a secret side-project while he pursued his postgraduate course in astrophysics at Princeton University in New Jersey. Back then, in the mid-1970s, doing neural modelling in a physics department was "radical and unthinkable", says Robert Desimone, scientific director of the US National Institute of Mental Health in Bethesda, Maryland. Over 20 years later, Sejnowski now runs the computational neuroscience laboratory at the Salk Institute for Biological Studies in La Jolla, California. And around the world physicists are playing an important part in transforming neurobiology.

But this shift in opinion took time. Neuroscientist Lyle Graham, who is now at the Laboratory for Computational Neuroscience in Gif-sur-Yvette, France, had similar experiences to Sejnowski. In the 1980s, while doing graduate work at the Massachusetts Institute of Technology, Graham began to do some neural modelling. The members of the electrical engineering faculty on his thesis committee gave him a hard time, he says. "Modelling had a huge reputation for being incredibly vague," says Graham. "I'm not sure I ever did convince them."

Even about 10 years ago, some biologists remained unconvinced about how useful or feasible modelling could be, and they viewed the approach with "hostility", says Charles Stevens, a neuroscience professor at the Salk Institute. But in the past few years more and more neurobiologists have begun to integrate computational and experimental approaches. They may be making this move because they now find themselves facing huge data sets and they need computationally sophisticated analysis — not only to handle the data but to design the questions.

With 60 billion neurons and 60 trillion synapses, the brain is arguably the most sophisticated computing device on the planet. And, of course, the brain is also a biological organ. As a result, physicists and engineers have had to join forces with biologists



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On course: Lyle Graham believes the training given in recent years has laid a strong foundation for the future of computational neuroscience.

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What is neuroinformatics?

Although it requires strong computing skills, neuroinformatics is primarily about developing the tools and databases to aid neuroscientists manipulate, store and share their data. It is more closely related to engineering than to basic science. The newly launched journal *Neuroinformatics* advertises itself as the "first journal devoted to the information-science infrastructure of neuroscience". And next year, the Marine Biological Laboratory in Woods Hole, Massachusetts, is launching a two-week neuroinformatics summer course. With its own journal, workshops and funding initiatives, neuroinformatics is a field of its own. H.P.

to form a multipronged attack on the brain's secrets. A new breed of computational neuroscientist seems to be emerging that is trained specifically to study the brain with an interdisciplinary tool kit.

And, based on anecdotal evidence, the job market for computational neuroscientists seems to be quite healthy. Faculty and postdoc adverts in neuroscience often explicitly mention computational neuroscience, and many physics departments are also moving into biological physics, including some aspects of neuroscience.

Broadly speaking, computational neuroscientists come in three flavours. First and most obvious are those who make analytical or computational models of the nervous system, either at the level of single neurons or as neural networks. Another set devises tools to find the best ways to analyse experimental data. The third group informs experimental design by developing more sophisticated questions — creating stimulus sets to test neuronal response, for instance.

Physicists and mathematicians already have some basic skills in all three categories. But for those with strong quantitative skills and computer knowledge who want to get into neuroscience there is one major challenge — learning the biology, says Laurence Abbott, a physicist-turned-computational neuroscientist at Brandeis University in Waltham, Massachusetts. "It's like moving to a foreign country and learning a new language," he says. "One day you wake up and find yourself part of the culture."

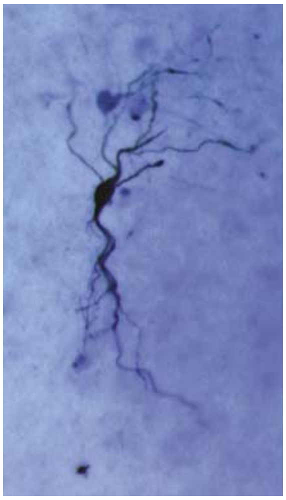
For Abbott, the secret was finding someone to help him learn that language and culture. Eve Marder, a neurophysiologist at Brandeis University acted as his guide and colleague in the foreign world of experimental biology.

One of the biggest obstacles in learning the language is the different way in which physicists and biologists approach scientific inquiry, notes Stevens. In physics, people know what the big questions are — the problem is finding a way to answer them. But biologists often don't know what the question is.

A DIFFERENT APPROACH

Without a history of thinking about the biological problems involved, physical scientists may be tempted to use their analytical tools to address questions that they are not suited to. This is so common a mistake that the computational vision course held in the summer at Cold Spring Harbor Laboratory in New York doesn't accept people straight out of a physics PhD, says Paul Glimcher, a primate neurophysiologist at New York University and one of the course's organizers. He and his colleagues focus instead on educating experimental neurobiologists to think more quantitatively.

There is another way to make the switch — involve a collaborator with complementary expertise. Yuan Liu, a programme director at the US National Institute of Neurological Disorders and Stroke in Bethesda, Maryland, emphasizes



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Model behaviour: understanding how neurons work lies at the heart of computational neuroscience.

Learning the trade

Aspiring computational neuroscientists have some excellent options for learning or honing their skills outside their home institutions. The Marine Biological Laboratory in Woods Hole, Massachusetts, offers a four-week summer course on methods in computational neuroscience. Its counterpart in Europe, the European Union advanced course in computational neuroscience, is currently based in Portugal. Both courses offer hands-on training in computational methods.

There are several shorter, more specialized courses and workshops, often based on specific software. Cold Spring Harbor Laboratory in New York also offers a course in computational neuroscience, but it concentrates on the visual system.

Robert Gütig, a doctoral student at the University of Freiburg, Germany, took the Woods Hole course in 2000. His background is in theoretical physics, although he was working in a computational neuroscience laboratory. Meeting Haim Sompolinsky, a professor at the Hebrew University of Jerusalem who was lecturing on the course, shifted the focus of his studies and their collaboration has continued for two years. "The environment that this course allows is very good, says Gütig. "You get the chance to really become friends and if there is a scientific match, you have everything you need to start a collaboration."

Lyle Graham, a neuroscientist at the Laboratory for Computational Neuroscience in Gif-sur-Yvette, France, who taught on the Woods Hole course at its inception, echoes the view of many. "These courses have done a great job in building a generation," he says. H.P.

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Neuroscience and beyond

The route from the physical sciences into neurobiology doesn't necessarily stop there. Zoubin Ghahramani, who trained in computational neuroscience at the Massachusetts Institute of Technology, has recently moved into bioinformatics while working at the Gatsby Computational Neuroscience Unit at University College London.

He notes that the switch has helped him to deal with many of the frustrations he encountered working in neuroscience, notably the gulf between the ability to develop a sophisticated theory and the availability of experimental tools to test its relevance to biological systems.

He finds it satisfying that computational models in bioinformatics are clearly of practical importance. "A model of the genes interacting to produce the immune responses underlying rheumatoid arthritis is obviously useful," he says. And he feels that the field is extremely receptive to computational methods.

"Who knows. Maybe the bubble will burst soon. But I really feel that there are still a huge number of open problems waiting for good technical solutions." H.P.

that experimental neuroscientists who want help in designing sophisticated analytical tools should start collaborations before they start collecting the data. Once you have trained the rat, implanted electrodes in specific parts of its brain, and saved your data as averages, it is too late to realize that you could best test a theory by comparing activity in one brain region with another simultaneously, or by looking at responses over single trials.

To help bridge the divide between physical and biological sciences in neuroscience, a number of dedicated institutes have been created over the years. The five Sloan-Swartz Centers for Theoretical Neurobiology, set up in 1994, have set the standard for excellence in computational neuroscience. They are based at Brandeis University, the California Institute of Technology, New York University, the Salk Institute, and the University of California, San Francisco.

Outside the United States, institutes with the goal of integrating theory and experiment have also emerged. In Zurich, the Institute of Neuroinformatics has fostered an interdisciplinary approach since it was founded in 1995, and in Germany, computational neuroscience centres are being discussed at several universities to concentrate and enhance existing research activities. In France, the organizational structure of research does not easily accommodate such centres — instead, there are several research groups whose mission statement explicitly refers to computational neuroscience. And the Hebrew University of Jerusalem has established a strong centre for computational neuroscience at the graduate student level.

T. DELBRUCK/INI

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Causing a reaction: Rodney Douglas, director of the Institute of Neuroinformatics in Zurich, stimulates a processor designed to emulate visual processing in the brain (bottom). The institute's work made an appearance at the Swiss Expo. 02 in the form of 'Ada' an artificial creature that interacted with visitors using tools such as the intelligent floor (below).

A NEW BREED

The doctoral programme at the Interdisciplinary Center for Neural Computation at the Hebrew University is 10 years old, and has students from biology, computer science, physics, mathematics and psychology. There are five compulsory courses given over three semesters that cover the basics — anatomy/physiology of the nervous system, neural networks, information theory, psychology and neuroscience methods.

The programme encourages theoreticians to consider problems of the nervous system. Training students in both theoretical and experimental approaches helps the graduates of the programme collaborate with others better — independently of which side of the fence they favour, says Eilon Vaadia, director of the centre's graduate programme.

Mayank Mehta, a physicist-turned-neuroscientist at the Massachusetts Institute of Technology, is encouraged by the new generation of computational neuroscientists who are comfortable in both worlds. At a recent visit to the University of California, San Diego, he was impressed that the students in the computational neuroscience programme had to rotate between experimental and theoretical labs. He asked every single student whether they had written a code in any language beyond Fortran, and whether they had dealt with live animals. "Every one of them had done both," he says.

But Abbott cautions that fluency in both languages is difficult to achieve. "It's pretty hard for students to learn both," he says. Computational neuroscientists are likely to continue to specialize in one side or the other. But another skill — communication — will be the key to making that specialism work. ■

Hemai Parthasarathy is a biological sciences editor at *Nature*.

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