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PROFILE

Physics Meets the Brain

How Terry Sejnowski went from a grad student in theoretical physics to computational neuroscience's White Knight.

It was the grueling

Courtesy of the Salk Institute

qualifying exam for his doctorate in theoretical physics in the 1970's that sparked Terry Sejnowski's interest in neuroscience. The exam "takes a week in which every morning or afternoon is a different topic in physics," he says. "Cramming all of physics into your head for that week is so concentrated that you need to be able to take a break and do something else. That summer I started to read books about the brain."

His light summer reading revealed, among other things, that neuroscientists had a lot to learn. "They didn't know the answers to basic questions, fundamental questions, like how memory is stored," says Sejnowski. His full transformation from a theoretical physicist to an experimental neuroscientist didn't take place until 1978, when Sejnowski, then a postdoc at Princeton, signed up for a summer course in neurobiology at Woods Hole. There he encountered his first set of frog legs. "It was an epiphany for me to be able to learn how to dissect under the microscope and to be able to identify what a synapse looks like on the muscle," he says. "Unlike the frontiers of physics, which are either at the infinitely small or infinitely large, fundamental problems in biology are at your fingertips. Something you can see under the microscope. Not something that requires a superconducting supercollider to get to the next step. It's something that can be done on a desktop with your own hands. This is why I was so attracted to the field."

Although his eye was on the brain, in the early part of his career Sejnowski focused more on machine learning and artificial neural networks. While a junior faculty member in the department of biophysics at Johns Hopkins University in the mid-1980s, Sejnowski and Geoff Hinton invented the Boltzmann machine, a logical network that can train itself to solve problems. In some ways the network works like the brain, handling data by tweaking the strength of the connections among its many nodes. The approach was "a tremendous breakthrough, quite unlike anything that had been developed before," says John Allman of the California Institute of Technology.

The Birth of NetTalk

Sejnowski's most striking work on learning algorithms, however, made its debut at a workshop on computational neuroscience held in Woods Hole in 1984.

There, Sejnowski unveiled NetTalk, an algorithm that allowed a computer to teach itself to translate written text into speech. "I remember vividly that in the early iterations of this program it sounded like a jumbled mess, then it sounded like an infant babbling, and at the end it wound up with what sounded like recognizable speech," says Allman. "We could actually hear it learn how to effectively pronounce words over a period of about a day. Everyone was awfully impressed."

"NetTalk was a spectacular result," says Patricia Churchland, University of California, San Diego. "It showed that, just using a relatively simple neural net with feedback correction, a machine could actually learn." Hooking the device up to a set of speakers, she says, "was a bit of theater. But it was a bit of theater that really helped you see that this was an important result."

"Terry was the first major person to come along who had both training in experimental science and in computation." -Eric Kandel

Launching Computational Neuroscience

Sejnowski, today a Howard Hughes Medical Institute investigator who joined the Salk Institute and UCSD in 1988, never abandoned his training in physics. Instead, he combines his flair for modeling and computation with his interest in experimentation to explore a variety of neural processes, including how suites of neurons can act together to encode memories and handle information. What makes his approach even more unusual is his willingness to tackle the brain on many levels: from neurotransmitters and receptors to synapses, cells, neural populations, and even complex behaviors such as sleep and social interaction.

"He seems to be one of very few people in the world who knows enough to work at every one of these levels," says Jack Cowan of the University of Chicago. "Terry goes from molecules to sleep. You don't get many people who have that range. I think he's one of the really remarkable scientists around at the moment."

By weaving together theory and experimentation, Sejnowski effectively launched the field of computational neuroscience. "Prior to his arrival on the scene, every generation of neurobiologists felt that computation had done nothing in the previous 10 years, but that it would be extremely important in the next 10 years. And after that 10 years was over, one was exactly where one started," notes Columbia University's Eric Kandel. "The problem was that computation was independent of experimentation. Terry was the first major person to come along who had both training in experimental science and in computation."

"He developed models based upon experiments that either he or his colleagues or collaborators carried out, then used those models to make predictions that demanded further physiological experiments to either falsify or strengthen the model," he adds. "That approach has been key to his success and is now the standard in the field."

The combined approach has several practical benefits. "Being an experimentalist, Terry recognizes the limitations of data and produces more realistic work as a consequence," says Allman. By leading a team that includes individuals who work at the computer and at the bench, "you have people having tea together every afternoon who are driven by examining different sides of the same question," says Steve Zucker of Yale University, who plotted the idea of a Woods Hole computational neuroscience workshop with Sejnowski when the two were stranded by bad weather at the Denver airport in the early ‘80s. Indeed, Sejnowski's lab takes tea every afternoon at 4:00, an event that was frequented by Francis Crick when he was alive.

Talking About Sleep

As an example of Sejnowski's ability to master both theory and technique, Zucker cites his formulation and use of independent component analysis (ICA) for extracting patterns from electroencephalograms (EEGs) to more accurately describe the rhythms of sleep. Sejnowski's access to computational tools such as ICA and to data gathered by his lab, in this case the EEG traces, "puts him in a unique position to gain real insight into what's going on "in a working brain," says Zucker.

"There are other people who are more focused and deeper in one little area. But none have this long chain of interactions that goes through theory and problem and experiment and technique all in the same head," Zucker says. "So he's able to put these things together in ways that are unmatched." Sejnowski is currently collaborating with Scott Makeig at the Swarz Center for Computational Neuroscience at UCSD to apply the same approach (using ICA to analyze EEG patterns) to problems in social neurobiology - studying, for example, what happens in the brains of people as they engage in conversation.

Courtesy of the Salk Institute

Another product of the marriage of computation and experimentation is MCell, a cell simulation that models the activity of neurons in the chick ciliary ganglion. The program models everything that goes on in an active synapse, including neurotransmitter release, receptor binding, channel opening, and cell firing. Running the program until he could best fit the experimental data, Sejnowski discovered that upward of 90% of the neurotransmitters released spontaneously in the chick ciliary ganglion are released outside the synapse.

What role could such extrasynaptic transmitter release serve? "That's the next question," says Sejnowski. "Clearly synapses evolved in order to have reliable transmission. You have a store of vesicles sitting there ready to be released. Ectopic transmission may serve a completely different function that we don't understand or know." Sejnowski and his collaborators are also developing a similar simulation for cells from the hippocampus, so they can study the biophysical mechanisms underlying the changes in synaptic strength that underlie learning and memory. Such a model, he notes, could be used to help develop drugs that enhance or interfere with memory.

Guiding the Community

Perhaps even more important than his science has been his service to the scientific community. "He has kept the field of computational neuroscience going," says Zucker. "Communities have ups and downs and periods when they're more in focus or out of focus. Terry has been like a beacon riding through that, which has played a role well beyond his own research. He's helped to guide the community in ways I think are really productive."

"I like to call him the White Knight of computational neuroscience," adds Rodney Douglas of the University of Zurich. Among his broad accomplishments, Sejnowski has been the power behind countless meetings and workshops, including the computational neuroscience workshop that he launched in Woods Hole, the Helmholtz Club at UC, Irvine, and NIPS, the neural information processing systems conference. "If you look at NSF or NIH or many of the other private funding agencies in the United States and you look to see what kinds of workshops they're offering in computational neuroscience, you see how often Terry is involved," says Douglas. "He's sought after as a participant and very frequently as an organizer for these kinds of things, because he has this broad knowledge, broad contacts, and he knows how to promote discussion in a very democratic and easy kind of way. He is a real force for good in neuroscience."

"Terry is a master at bringing people together and organizing very productive meetings," agrees Allman, a skill made possible by his "energy and his ability to spot interesting new work going on, often at very early stages in its development. Science would probably not be quite the same had these meetings not occurred."

Sejnowski also founded and runs the journal *Neural Computation*, which serves as a one-stop shopping place for those interesting in the details of computational neuroscience. "It is a huge undertaking, which in his hands boils down to yet another one of those things that he knocks off between 3 and 4 a.m.," laughs Zucker.

Indeed, Sejnowski is legendary for requiring little sleep. "If you write him an email, five minutes later you get a reply, no matter what time of day or night it is," says Douglas. "I've never met anyone with his level of energy," adds Cowan. "He's one of the few people I know who has a permanent gold card from American Airlines, which means he's flown over a million miles on American Airlines alone. And he flies with other airlines, too. He's everywhere!"

And that's not just geographically. "He has that spirit of intellectual and scientific adventure and is willing to break out into territory that's somewhat new," says UCSD's Churchland, who, along with Sejnowski, coauthored the textbook *The Computational Brain.*

Together, the experimental rigor and the ability to recognize interesting new ideas is a powerful combination. "Francis Crick once explained to me that if anybody was going to figure out how the brain worked, it was going to be done Terry's way and that Terry had adopted exactly the right approach," Hinton says. "Of course, Francis was not necessarily right. But it's a good bet."

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