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Neuron Function: The Mystery Persists

by Keri Schreiner, *keri@grooveline.com*

In his speech on biologically inspired computing last year at the University of Virginia, Chris Diorio quoted aviation pioneer Orville Wright, who said that learning the secret of bird flight was akin to unmasking a magician. Once you know how the trick works, you begin to see things that previously escaped your notice. According to Diorio, when it comes to understanding the "trick" of how the brain works, we're far from getting off the ground. In his words, we're still taking "baby steps."

"We still don't really have a fundamental understanding of how the brain stores information, how it processes information, how it learns," said Diorio, who teaches computer science and engineering at the University of Washington. "Biologists have done an incredible amount of good work in understanding structural biology and the molecular basis of what nervous systems do—everything from individual molecules to DNA to proteins, and up to single cells and what they do. But we don't fundamentally understand the underlying basis that lets us put together collections of these cells to make a machine that can process information."

Terrence Sejnowski, professor of computational neurobiology at the Salk Institute for Biological Studies in La Jolla, California, said that while we're long past our view of neurons as digital processors, we've only begun to grasp their complexity.

"What we did not know until recently is how nonlinear the processing is inside of neurons. Even more astonishing is that during sleep the nonlinearities are completely different, so that neurons really are two different types of computers depending on their state. They have the ability to adapt to whatever the world throws at them," said Sejnowski. "The more we study them, the more respect we have for the variety and complexity of neurons in the brain."

Essential elements

The brain has billions of neurons that communicate with each other through electrochemical pulses, which are responsible for our mental and physical function, from thoughts and feelings to movements and dreams. A neuron comprises a cell membrane, which conveys nerve signals as electrochemical pulses; dendrites, which receive and deliver signals; the axon, which conducts the signals; and synapses, which are the contact points for passing information between cells. Figure 1 shows pictures of neurons from Brazil's Brain and Mind Neuroscience Art Gallery (www.epub.org.br/cm/gallery/gall_coimbra/gallery2.htm), taken with an optical fluorescence microscope.

Neurons process information through nerve impulses, sending out spikes of electrical activity through the axon, which transmits the signals to another cell's dendrite by releasing a chemical substance—these then attach themselves to chemical receptors in the target neuron's membrane. The dendrites are tree-like structures that, like axons, have roots in the cell body, or soma. A single axon on a neuron might form synapses with as many as 100,000 other neurons.

Underlying and entwined with this known functionality are many questions about how neurons work, both individually and collectively. For example, what is the role of noise—which is produced by unpredictable behavior in neuron components—in signal detection and estimation? What is the function of oscillation patterns in cortical neurons? What are the implications of spiking behavior?

According to Sejnowski, the most important question at the moment is the role of calcium-binding proteins in how neurons function. Sejnowski noted that calcium is by far the most important ion for a neuron and it is kept at a very low concentration in the neuron, relative to the outside concentration.

"During special conditions, such as those that lead to long-term changes in the strengths of synapses between neurons, calcium enters the neuron and causes a local cascade of enzymes, leading to permanent changes," he said. "Finding out more about internal calcium-binding proteins is the most important uncertainty about how neurons work."

Another question involves the relative importance of glial cells, which are specialized, external cells that nourish and support neurons. For example, Schwann cells are a type of glial cell that insulate axons by spiraling around them, forming a myelin sheath that helps accelerate message trans-

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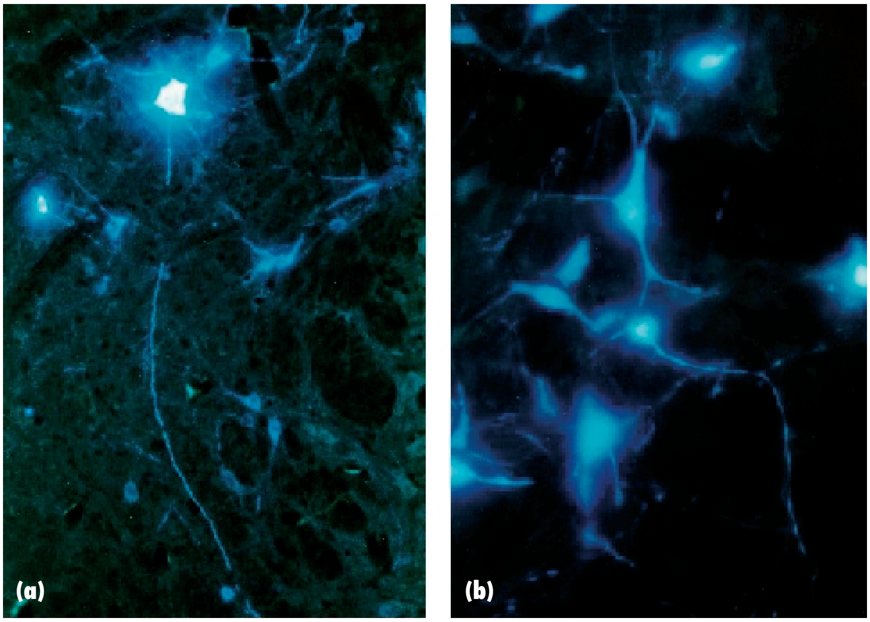

Figure 1. (a) A midbrain neuron. (b) Neurons from the midbrain's substantia nigra, which is involved in motor control through projections to the basal ganglia. Images courtesy of Norberto Coimbra, Laboratory of Neuroanatomy and Neuropsychobiology, University of Sao Paulo, Brazil.

mission. The importance of glial cells, like the actual underlying basis of neuron communication itself, is unclear at this point.

"You can kind of argue that the more we learn about biology, in some sense, the more confused we get. The more we learn about glial cells and their impact on neurons and their function, the more we realize that they might be a bigger player than we thought," says Diorio. "Maybe neurons aren't the whole story."

A related mystery is how dendrites maintain signal strength across longer relative distances. Unlike axons, which are insulated by myelin, dendrites "leak." Scientists thus have assumed that either neuron function was flawed or some method existed for boosting signals to ensure they were strong enough to survive longer journeys. Recent research by Jeff Magee of Louisiana State University and Erik Cook of the Baylor College of Medicine confirms the latter scenario. In the September 2001 issue of *Nature Neuroscience*, Magee and Cook confirmed that many signals arrive at the soma with the same strength, regardless of the dendrite's distance from it. How? According to their work, the signals that must travel farther start out stronger. This, in turn, requires that the synapse know how far the signal must travel and provides further evidence for *backward* information flow—that is, from soma to dendrites.

Such discoveries might one day culminate in a big picture of how the brain works. At the moment, many fundamental questions remain. "Right now, we have a bunch of models and a lot of biologists doing work on single cells and collections of cells, trying to understand what neurons do, what information they're sending around," said Diorio. "But the pieces haven't come together yet in a way that lets us understand how our brains do the things they do."

Of models and multiplication

There are currently three primary models of how neurons function, each with its uses and variations, according to James McClelland, a professor of psychology and computer science at Carnegie Mellon University and codirector of the Center for Neural Basis of Cognition. The first and simplest is the integrate-and-fire model, which is based on the idea that the neuron adds and subtracts excitatory and inhibitory inputs until it reaches a threshold, at which point it fires a single impulse or action potential.

Another model is the sigmoid transfer function, in which the neuron adds up excitatory and inhibitory inputs (as in the integrate-and-fire model) but treats the output as a continuous quantity. Finally, in the sigma-pi unit model, a neuron's output is equal to the sum of many products, each consisting of a multiplication of several inputs. "This makes the neuron a more complex and interesting computing device," said McClelland.

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Beyond the Petrie Dish

One problem with attempting to discover how neurons work is that this often requires removing them from their context. To circumvent this, Chris Diorio and a team of researchers from several disciplines, including biology, zoology, and electrical engineering, are working on implanting microelectronics into a hawk moth (*Manduca sexta*) to track neural activity on the fly.

"Most biology experiments involve taking out a little patch of brain and putting it in a dish, putting some probes into it, and measuring it," said Diorio, adding that in that context, "You can't do anything that represents the normal behavior of an animal. You completely isolate it and basically don't know what the inputs and outputs are. You can put in any stimuli, but you don't know if they're real. In any kind of isolated prep, you don't get at the fundamentals of what the animal brain is doing."

The moth experiments, along with similar ones they are conducting on a sea slug, aim to correlate neuronal signaling and control with environmental stimuli to better understand the neural substrates of behavior. Figure A shows examples from the hawk moth experiment. The implant is a two-channel instrumentation amplifier test circuit that weighs .38 grams. The circuit is powered by two batteries and provides output through fine trailing wires.

Diorio says they are now preparing to test the integrated microchips in the hawk moth, recording from the nerve bundles that mediate wing strokes during free flight. They'll then compare that recorded data with simultaneously recorded videos of the animal's flight and see if they can learn something about controlling flight.

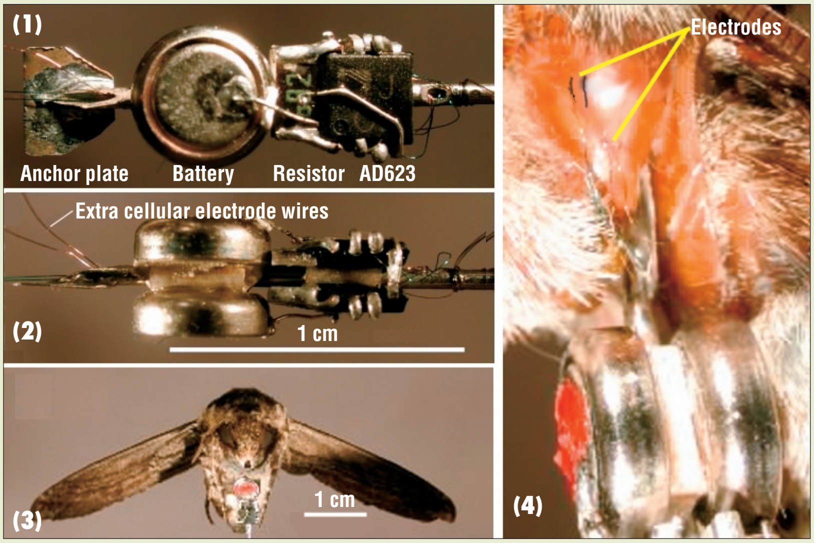

Figure A. An implantable microelectronics experiment. (1) The circuit is assembled on the shaft of a hypodermic needle. (2) Two pairs of 0.001-inch diameter insulated stainless steel electrode wires, threaded through the needle's bore, emerge at the anchor plate. (3) The adult hawk moth carries the circuit. The anchor plate is glued onto the moth between the bases of the hind and midlegs. (4) A close-up lateral view of the circuit shows two pairs of electrode wires inserted directly through the exoskeleton into two units of the subalar muscles for bipolar recording.

Recent work by a team at the California Institute of Technology offers further evidence for the multiplication model. In April, José Luis Peña and Masakazu Konishi identified the neural mechanism that lets barn owls locate sound sources by processing two auditory signal cues to "compute" their prey's position. The owl first hears the sound in the ear closest to the sound, then in the other ear a fraction of a second later. The owl's ears simultaneously detect slight differences in sound intensity.

According to Peña and Konishi, both the sound and intensity cues are transmitted to the same specialized neurons in the midbrain, which respond to a specific combination of time and intensity differences. Thus, the neurons act like switches, responding not to time or intensity alone but to particular combinations of both. The experiment supports the theory that neurons multiply because with addition, a big input along the time pathway might drive the neuron to a firing level, whereas multiplication reduces the effects of a big input on one side.

Building the adaptable machine

Most studies of specific neurons remove them from the host and study them in isolation, simulating inputs. But Diorio, like Peña and Konishi, is running experiments aimed at measuring nervous system behavior in the host creature (see the sidebar, "Beyond the Petrie Dish"). He's also working on a project exploring artificial learning at the chip level, where output depends on not only present input but also on a past history of inputs. The work is based primarily on machine learning.

"In the early years of artificial intelligence, studies of AI were linked to understanding the brain, but people are now pursuing what has grown up to be this big field of machine learning, and that's taken a significant direction away from our either needing an understanding of biology or even desiring an understanding of biology," said Diorio. "But just because we didn't succeed previously in learning a lot from biology about how to build these artificial learning systems, doesn't mean we shouldn't do it in the future. I would expect that as we learn more about brains, it may have significant impact on the field in the future—but I can only say 'may.'"

According to McClelland, the effort to understand how experience shapes neuron function and connectivity is driving research in both neurobiology and machine learning. In McClelland's view, cognitive functions emerge from the parallel, distributed processing activity of neural populations, and learning occurs through the adaptation of connections among participating neurons.

His current research focuses on how children develop their conceptual understanding of the world on the basis of experience. He and his team are using artificial neural networks trained on simplified linguistic propositions. "From this information," he said, "the networks come to mimic—in a small-scale way—some of the emerging conceptual abilities of children."

"We are learning more and more about the processes that allow neurons to change their connections, and are beginning to understand how larger structural changes—such as the extension and pruning of dendrites and axon branches—are produced by alterations of experience," said McClelland. "There have been terrific breakthroughs in our appreciation of the effects of experience on the wiring and organization of brain function, and a growing appreciation within the machine intelligence community that truly intelligent machines will have to be able to adapt on the basis of experience."

Ultimately, it is neurons' malleability that Sejnowski finds most impressive. This same factor makes it seem far less likely that a single machine of our own making will ever measure up to the human brain's complexity.

Understanding the complexity of how neurons compute internally has upped the ante. I once calculated that the human brain had the power of 1,000 teraflops, but it is now clear that that was only a lower bound," said Sejnowski. "But what most impresses me is the extent to which neurons are reconfigurable—between different states of arousal—to perform many different functions. It is as if you had a 'transformer' in your head that could warp into a wide range of computers, depending on the demands of the moment."

VISUAL DIAGNOSTICS

Computer Vision Test Holds Promise

NASA has developed a vision test, using a laptop computer with a touch-sensitive screen, to help diagnose the onset of eye diseases and certain types of brain tumors.

With one eye covered, a person sits in front of a computer screen, which is divided into a grid. Staring at a central spot on the screen and using a finger, the user or test taker outlines missing areas of the grid. The computer records, processes, and displays a 3D image of the subject's visual field. The test takes about eight to 10 minutes for both eyes.

"It is a non invasive, quick-and-easy process that gives astronauts and physicians on the ground an almost instant autodiagnosis," says Wolfgang Fink, physicist and senior member of the technical staff at NASA's Jet Propulsion Laboratory. "This type of technology will be useful for long-term space missions where early detection and advance monitoring will be key to the health of the astronauts."

Fink developed the 3D Computer-Based Threshold Amsler Grid Test with Alfredo Sadun, the Thornton professor of ophthalmology at USC.

"This new test is not only more revealing than standard visual field tests, but it is also much quicker and simpler than existing methods," Sadun said.

Undergoing testing in clinical trials at the Doheny Eye Institute in the USC Keck School of Medicine, the results show that the screening test helps detect a variety of eye conditions, such as glaucoma and macular degeneration—the two leading causes of blindness. Early detection of these conditions and appropriate treatment are crucial in preventing further loss of sight.

Future uses could include monitoring the effects of intracranial pressure elevation in low-gravity environments and evaluation of possible stroke onset and acute and chronic stroke conditions. ■

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