MATHEMATICS

# Smart Neurons Offer Neuroscience a Math Lesson

SAN DIEGO—The modern metaphor of the brain as computer might suggest it is nothing more than billions of simple on-off switches, elaborately wired together. Far from it, neuroscientists are learning: Real neurons are exceedingly complex devices that can, for example, change their threshold or time lag for responding to incoming signals as the properties of their membranes change. But which properties are important for which processes? Some of the answers, says Nancy Kopell of Boston University, may emerge from a synapse between two disciplines: mathematical analysis of patterns of neurological activity.

In a presentation at the joint meetings of the American Mathematical Society and the Mathematical Association of America, held here last month, Kopell described how she and her mathematically minded colleagues are probing phenomena such as the synchronized oscillation of neurons during sleep and the choreographed firing of neurons controlling the lobster gut. By analyzing sets of differential equations describing a neuron's properties and behaviors, the theorists are learning how biophysical changes in individual cells can, in effect, "rewire" a neural circuit, altering how it processes signals. In short, Kopell says, "smart neurons can do smart things, and analysis helps us see how."

Much like its crude silicon counterpart, a neuron responds to electrical input arriving from its neighbors through junctions called synapses, which can be either excitatory or inhibitory. It can then respond in a variety of ways, including firing a pulse, bursting (that is, firing rapid salvos of pulses), or switching between firing continually and being silent. Shaping the neuron's response is a range of neuromodulators: chemicals that affect the electrical properties of its membrane.

Differential equations are the mathematical tool of choice for describing this behavior, just as they are for other time-varying flows of material or energy. Computational neuroscientists have assembled these equations into computer simulations of networks of neurons that can be run much like laboratory experiments. The modeler sets the properties and connections of individual neurons and compares the output of the network with that of real neural systems. The models are becoming sophisticated enough that "you can actually predict certain things," says Christof Koch of the California Institute of Technology's Computational and Neural Systems Program.

But they have limitations. It's hard to identify cause and effect in the simulations—which properties of the neurons being simulated are at the root of the observed behavior. And that gets in the way of extrapolating results from networks of computationally tractable size to actual networks several orders of magnitude larger in the brain, says Roger Traub of IBM's T. J. Watson Research Center in New York, who is himself a pioneer in neuron-network modeling. As Koch puts it, "Analytical approaches are crucial if we are ever to make sense of the data."

That's where Kopell and other theoretically minded researchers come in, he says. In addition to running computational experiments on models of neurons, they analyze the underlying mathematics to gain a sense of which neuronal properties are crucial for particular behaviors. For example, working with David Somers at the Massachusetts Institute of Technology, Kopell found from studying the differential equations for certain models how biophysical changes that affect only the shape of the electrical wave form of a bursting neuron can alter the behavior of an entire network of neurons. The wave form, their analysis showed, determined whether the array of cells would synchronize their firing or fire as a traveling wave, in which each cell fires just after the adjacent one—modes of behavior, says Kopell, that "are ubiquitous in the nervous system."

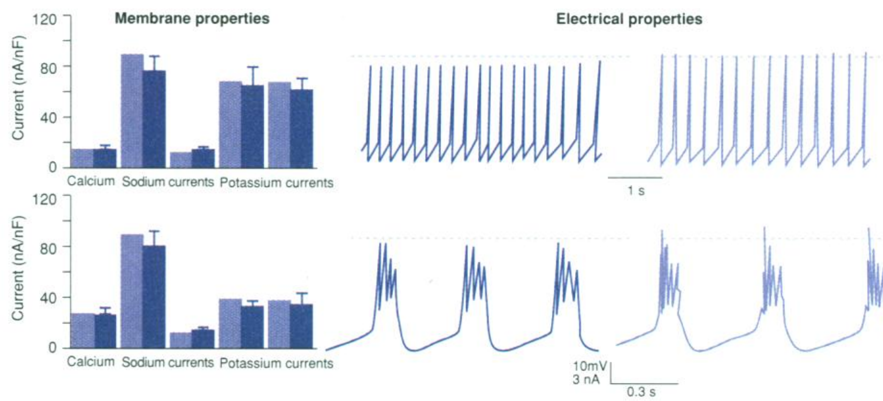
Similar analysis helped explain a long-standing puzzle about synchronized neural activity. Neuroscientists have known that inhibitory signals play a role in the synchronized oscillations seen in the thalamus and cortex during different stages of sleep—but just how these signals could get neurons to fire in concert was a mystery. Kopell worked with David Terman at Ohio State University and Amit Bose at the New Jersey Institute of Technology to show how slowly decaying inhibition can synchronize networks of neurons that have particular membrane properties.

Kopell is also testing her theoretical tool kit against an actual system of neurons studied by Eve Marder of Brandeis University and her colleagues Larry Abbott and Scott Hooper, now at Ohio University: a simple, two-cell component of the stomatogastric ganglion, which controls digestion in crustaceans such as lobsters and crabs. "There is an enormous amount of detail known about the biophysics of each of the cells that are in the network," Kopell explains, "but what is still reasonably mysterious is how those cells work with one another to create the functionally important output of the network."

In the two-cell subnetwork, one cell is bistable, meaning it can remain at either a high or low potential, while the other is a bursting oscillator. The puzzle, Marder explains, is that on its own, the bursting neuron responds to changes in input only by changing the silent interval between bursts. In the two-cell network, however, it changes the duration of both the bursts and the silent phases. In 1991, Marder, Abbott, and Hooper traced the bursting neuron's complex responses to changes in the membrane properties of its companion. Now, Kopell, Abbott, and Cristina Soto, Kopell's student, are extending the analysis to other two-cell networks in which the cells have very different dynamical "personalities."

Such analyses are an important adjunct to computer simulations, Kopell says, because they help theorists get to the root of neurons' enormous versatility. If nature can produce surprises with a pair of smart neurons in a lobster's gut, just think what it can do with billions of skillful cells inside a human skull.

**–Barry Cipra**




**Model behavior.** A mathematical model of a neuron (light color) mimics a real cell's ability to change its electrical properties depending on the strength of ion currents across its membrane.

SOURCE: TURRIGIANO, LEMASSON, AND MARDER, J. NEUROSCI.