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Long-time Interest in Biorhythms Settles Into Fascination with Oscillations in Cognition

By Michelle Sipics

Nancy Kopell of Boston University, guest editor (with Bard Ermentrout and Chris Johnson) of this issue of SIAM News, *will give SIAM's John von Neumann Lecture this summer at ICIAM 2007.*

It's safe to say that Nancy Kopell, a professor of mathematics at Boston University, often has math on her mind. But as a pioneer of computational neuroscience, the co-director of BU's Center for Biodynamics is especially interested in the math *of* the mind, studying networks of neurons and brain rhythms—bands of electrical activity in the brain that are associated with a variety of cognitive states.

"The major scientific question I'm after is how the dynamics of the nervous system contributes to all aspects of cognition—sensory processing through motor planning," Kopell says. "My corner of this concerns the role of brain rhythms in cognition. The electrical activity that can be measured . . . in the nervous system can be parsed into frequency bands; different combinations of frequency bands are associated with different cognitive states."

Kopell explains that experimental work in this area has been done in behaving animals (in vivo), as well as in vitro, using brain slices from many parts of the nervous system.

"The central role of mathematics, modeling, and simulation is to tie together these experimental results, using clues from the physiology to help illuminate the way [brain] rhythms are so prominently correlated with neural function," she says. "Methods of dynamical systems can be used to help understand the dynamical mechanisms underlying the behavior of networks of neurons."

Kopell, who will deliver SIAM's 2007 John von Neumann lecture at ICIAM 2007, came to applied mathematics by an indirect route—she is fond of describing her career as a "biased random walk." As a doctoral student at Berkeley, she originally studied dynamical systems, focusing her thesis on the actions of non-compact abelian groups on manifolds.

"My study of dynamical systems was sufficiently abstract that I didn't learn to actually solve differential equations until I taught the subject," she recalls with a laugh.

Near the end of her graduate career, Kopell began to move in a different direction. "I realized that the kinds of questions that were being asked in my area felt too narrow to me," she says. "I couldn't imagine myself basing an entire intellectual career on those questions."

Kopell says she was drawn to developmental biology, but did a lot of "thrashing around" before she stumbled upon an oscillating and pattern-forming chemical reaction.

"[It] provided a wonderful situation in which to study the same issues as in developmental biology, but with the underlying chemistry and physics much better understood," she says. From there, she became interested in a series of questions involving different aspects of rhythms in biology. One of the first was swimming in the eel-like lamprey; in this work, the focus was mainly on the anatomical structure of the organism's spinal cord. She then moved on to crustacean nervous systems, studying how the dynamics of individual neurons affect the dynamics of the network. More recently, she has been studying oscillations associated with cognition, which she says has been her obsession for the last decade.

One topic that has particularly caught Kopell's attention involves brain rhythm abnormalities associated with mental illness. She is currently working with experimentalists and clinicians to study how rhythms differ in patients with schizophrenia.

"The relevant brain rhythms, in the so-called 'gamma frequency band,' at about 30–90 Hz, are thought by many to be involved in the creation of 'neuronal ensembles'—sets of cells that briefly fire synchronously," Kopell explains. "Schizophrenics have pathologies in the formation of gamma rhythms, and it has been argued that this could account for the disorganized symptoms associated with [the] disease."

The electrical activity within the gamma band is associated with early sensory processing, attention, and awareness. Behavioral symptoms of schizophrenia include hallucinations, problems with attention, and disordered reasoning.

Kopell is working with colleagues Steve Stufflebeam and Peter Siekmeier, and Dorea Vierling-Claassen, a student, to study pathological changes in the responses of gamma rhythms to sensory input—tying abnormalities on the cellular level to clinical symptoms of schizophrenia. Earlier research suggests that most frequency bands display major changes in patients with mental illnesses. Part of Kopell's work is based on a previous study related to the response of schizophrenic patients to certain audio stimuli.

"If a normal human is given 40-Hz click sounds, the auditory cortex records an output of 40 Hz—no surprise," she explains. "But if a schizophrenic is given a 40-Hz input, the output is likely to have a very large component of 20 Hz. We are trying to tie those results, and various related observations, to known pathologies of cells and cell communication in schizophrenia."

Postmortem studies of the brains of schizophrenics have revealed damage to some cells that function mainly as inhibitors of other cells—damage that seems to make inhibitory pulses last longer. Analysis of the group's model, Kopell says, shows that the extended inhibition might explain the different reactions of schizophrenics to auditory phenomena like the click trains.

She is quick to point out, however, that the gamma band is not the only source of abnormal rhythms in schizophrenic pa-tients; many different frequency bands are involved with the coordination of different parts of the nervous system. Another band in which abnormalities are seen is the “theta” frequency band, around 4–12 Hz, which is thought to be involved in many aspects of learning and memory.

“How neural rhythms help coordinate interactions among parts of the nervous system is still the Wild West,” she says. “There are hypotheses floating around about which bands might be involved in which kinds of coordination, [and they’re] still very preliminary.” She also stresses that some of the same pathological rhythms are seen in multiple mental illnesses, including bipolar disorder and schizophrenia.

Despite the many difficulties, Kopell is hopeful.

“I have the sense that the field is on the cusp of a breakthrough, and that mathematics can both make sense of existing data and inspire more experimental work in this area,” she says, adding that the greatest challenge is formulating the specific questions that mathematics and simulations need to address.

“What produces the various frequencies in the nervous system?” she muses. “Why are these frequencies associated with specific cognitive activities and states? . . . How does the brain make use of these dynamics? How can changes at the level of gene expression translate into pathologies of behavior, via changes in neural dynamics?”

The underlying issue in all of those unknowns, she admits, is very close to “How does the brain work, and how does it fail?”—a problem that is obviously daunting. But Kopell thinks that modeling of neural dynamics—combined with mathematical techniques including geometric analysis, reduction of dimension, probability theory, and other areas—could play a key role in unraveling the answers.

“Every result on the nature of the different rhythms, as understood from in vitro, mathematical, and computational work, gives rise to new questions about in vivo use of those rhythms, constrained by behavioral experiments,” Kopell says. “The relation of neural rhythms to disease is a natural follow up to the question of how the nervous system uses its rhythms; what we had to say from modeling has led to a pair of experimental collaborations on different aspects of schizophrenia.”

She doesn’t see the contributions stopping there.

“The more I read, the more I see places where an understanding of the biophysical bases of neural rhythms can provide a new way of looking at diseases as diverse as Parkinson’s disease, schizophrenia, bipolar disorder, and epilepsy,” Kopell says. “I don’t expect to run out of new questions!”

Michelle Sipics is a contributing editor at SIAM News.