

# It's Got A Beat, and You Can Think to It

By Barry A. Cipra

*Man is obviously made for thinking.*  
—Blaise Pascal

When two people think alike, they're said to be on the same wavelength. Substitute a pair of neurons for the people, says Nancy Kopell, and the saying is no longer strictly metaphoric. It may well be that the brain does its job in large part by synchronizing the rhythmic firing patterns of spatially distant cells—and mathematics will certainly play a key role in figuring out how it all works.

In an invited presentation last summer at the SIAM annual meeting in Puerto Rico, Kopell, who is co-director of the Center for BioDynamics at Boston University, described recent research on rhythms in the nervous system. Mathematical analysis, she says, has already shed light on the synchronizing strategies of nature's most ambitious dynamical system.

The occurrence of rhythmic electrical activity in the brain has been known since 1924, when the Austrian psychiatrist Hans Berger put electrodes to his son's head. (Mathematics has played a role from the very beginning: Berger reportedly had young Klaus doing arithmetic problems during the experimental sessions.) Researchers classify rhythms by frequency, with alpha waves in the 8–12 Hz range, beta waves ranging from 12 to 30, gamma from 30 to 80, delta from 4 to 6, and (skipping over most of the Greek alphabet) theta waves from 6 to 8 Hz. These boundaries are rough and controversial, Kopell points out. One goal that she and her colleagues have set is to understand the differences between the rhythms from a more fundamental, biophysical point of view.

Different activities have been associated with different rhythms. A moving bar of light, for example, evokes gamma waves in the visual cortex, whereas sensorimotor tasks can produce beta waves in the part of the cortex that deals with sensorimotor coordination. Alpha's what you get when you close your eyes and relax. And delta and theta have been associated with sleep and learning, respectively. Whether the observed rhythms are truly meaningful, however, is controversial, Kopell notes. Some scientists still think they're an incidental feature; a few, who measure electrical activity in a different way, don't see the gamma and beta rhythms at all. But evidence is mounting that rhythms are real, that they're a natural product of the brain's "wiring diagram" and the cells' internal dynamics, and that rhythms play a central role in brain function.

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*The Brain, within its Groove*  
*Runs evenly—and true—*  
—Emily Dickinson

"There's been an explosion of data in the last decade," Kopell points out. In particular, neurophysiologists have managed to elicit network activity among the neurons in brain slices, the razor-thin samples of tissue long used in anatomical studies. In the mid-1990s, Miles Whittington at the University of Leeds and colleagues in the United Kingdom perfected a technique for studying slices of hippocampus (from rats), a tiny region of the brain associated with learning and memory. "They saw details that were really unexpected," Kopell says.

Like the rest of the brain, the hippocampus is a mesh of excitatory (E) and inhibitory (I) neurons, which communicate across gaps called synapses. Roughly speaking, when an excitatory neuron "fires" (that is, when the voltage across its membrane spikes), the neurotransmitters it spews at its synapses lift the neighboring neurons toward their own firing thresholds. Conversely, an inhibitory neuron tends to depress the cells around it. What's crucial is that multiple time scales are involved, those intrinsic to the cell membrane and those associated with the synaptic signals. The interaction of these time scales is responsible for some counterintuitive results: For example, a network of purely inhibitory neurons can wind up firing in synchrony, even though the cells are ostensibly telling each other not to fire at all!

In the rat hippocampus experiments, the researchers found that mild stimulation of a slice produced synchronized gamma waves. But at higher levels of stimulation, the gamma rhythm gave way to beta (Figure 1). Most impressively, mild stimulation hours later produced the transition to beta again, instead of just gamma—as if the slice had learned something. A similar gamma-to-beta transition has been seen in humans presented with a sequence of tones; transitions occurred when subjects heard novel tones.

Detailed computer simulations, done mainly by Roger Traub of the University of Birmingham, reproduced key features of the slice experiments, including the gamma-to-beta transition and synchronization of oscillations over significant distances. But one thing was missing from all this laboratory and computer phenomenology: insight. Even when you know what the neurons are doing, it's not necessarily clear what's driving their dynamics.

That's where Kopell and colleagues come in.

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*My own brain is to me the most unaccountable of machinery—always buzzing, humming, soaring roaring diving, and then buried in mud. And why? What's this passion for?*

—Virginia Woolf

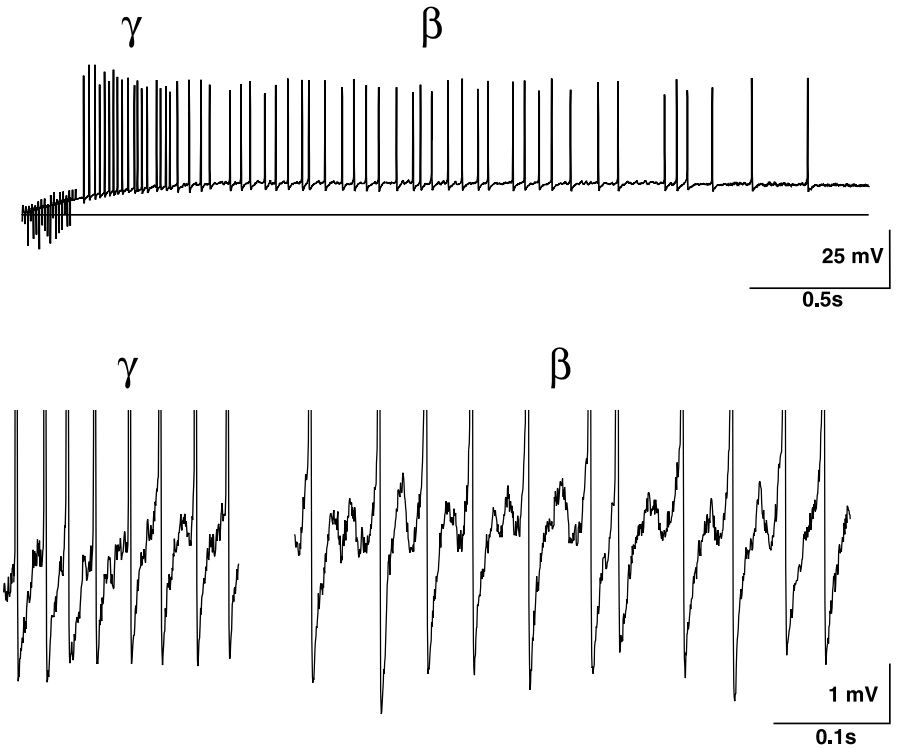
The starting point for any mathematical analysis (or computer simulation) of neural activity is a set of nonlinear partial differential equations known as the Hodgkin–Huxley equations. Introduced in the 1950s by British physiologists Alan Hodgkin and Andrew Huxley, the Hodgkin–Huxley equations describe the electrical properties of neurons. They are to neurophysiology what the Navier–Stokes equations are to fluid mechanics, Kopell notes.

Kopell and Bard Ermentrout of the University of Pittsburgh tackled the issue of long-distance synchronization for gamma waves by analyzing the simplest possible network, consisting of two excitatory and two inhibitory cells (Figure 2). Each I-cell pairs up with one E-cell in a “local” circuit, and receives signals from the other, “external” E-cell. The network is tuned so that each pair oscillates at a gamma frequency, controlled by the decay time of the inhibition; the network is thus a pair of coupled oscillators.

Even in this minimal setting, direct analysis of the relevant Hodgkin–Huxley equations is impossibly complicated. Ermentrout and Kopell snuck up on the solution, constructing a low-dimensional approximation to the Poincaré map, valid only near the observed periodic trajectory. The Poincaré map in this case takes the time lag between the spikes of the two E-cells in one cycle to the time lag in the next. The key is to see whether the synchronous solution (i.e., zero time lag) is stable—and, if so, why.

The major hint was the surprising earlier finding, both in experiments and in Traub’s large-scale simulations, that when distant circuits synchronize, the I-cells produce a characteristic “doublet,” or two spikes in rapid succession. What the doublet does, Kopell and Ermentrout found, is to encode information about the relative phases of the two E-cells. In each local circuit, the I-cell fires first in response to the local E-cell, because the local signal arrives first. The second spike in the doublet is a response to the firing of the external E-cell, whose signal arrives after a conduction delay. The timing of the excitatory cells’ next round of firings is determined by the timing of the second spike in the I-cells’ doublets. The details of the time delays determine a region of parameter space (the main parameters being the conduction delay and the strength of the local and nonlocal inhibitory synapses) within which the synchronized state is stable.

More recently, Kopell and Jan Karbowski, who is now at the University of Pittsburgh, have looked at what happens when there are many local circuits instead of just two. They have found that a lattice of these coupled oscillators permits triplets and higher-order spikes in addition to doublets; the configurations displaying doublets, however, are seen to be stable over a much greater range of parameters.



**Figure 1.** Gamma to beta. The top illustration shows the transition that occurs at sufficiently high levels of stimulation. Details of gamma and beta waves are shown at the bottom. Data and figures courtesy of Miles Whittington. Bottom figure reprinted with permission from N. Kopell et al., PNAS 97 (2000), pages 1867–1872.

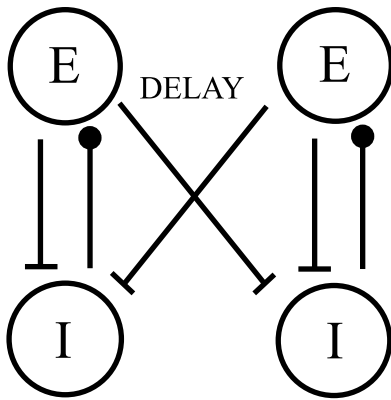
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*The notes I handle no better than many pianists. But the pauses between the notes—ah, that is where the art resides.* —Artur Schnabel

Is beta just a slower version of gamma? No—the rat hippocampus experiments showed that when the transition occurs, the I-cells continue to fire at the gamma rate; the E-cells, however, begin to skip some cycles, hence firing at the subharmonic beta frequency. What makes the beta rhythm observable is the fact that the E-cells mostly skip the same cycles.

Experiments and simulations of Whittington and Traub and their collaborators showed that the gamma-to-beta transition seems to result not only from changes in the ionic currents involved, but also—amazingly—from the appearance of new functional connections among the E-cells. With Whittington and Traub, Kopell and Ermentrout showed that the transition can be reproduced in small (“minimal”) networks, making it possible to analyze the properties of long-distance synchronization for the beta as well as the gamma rhythm.

The analysis showed that beta rhythms behave differently than gamma when confronted with significant conduction delays. In particular, separated networks displaying beta are capable of synchronizing over greater distances (measured in terms of conduction delays) than networks displaying gamma waves. According to the model, synchronization between separated networks displaying the gamma rhythm is stable for delays of up to about 12 ms, while separated networks displaying beta can produce stable



**Figure 2.** Pair of coupled oscillators: Each inhibitory cell in the simple network pairs up with one excitatory cell, forming a “local” circuit, and receives signals from the other, “external” E-cell. Each pair oscillates at a gamma frequency, controlled by the decay time of the inhibition. Direct analysis of the Hodgkin–Huxley equations is impossibly complicated even in this simple setting.

synchronization more than twice as long. As Kopell puts it, “gamma is good, but beta is better.” The better performance of the beta rhythm at long-distance synchronization, she explains, is due to the new ionic currents involved in producing beta and the new E–E connections formed during the gamma rhythm. (The even slower alpha rhythm, by the way, is “awful” at long-distance synchronization.)

The ability of networks displaying beta to synchronize over longer distances helps explain data suggesting that beta rhythms are used for higher-order processing involving the integration of disparate information—for example, memories of your grandmother’s name, her face, voice, and the peculiar way her house smelled—into a coherent whole. The prediction that networks displaying beta can synchronize in the presence of longer delays was supported by later simulations of Traub with large detailed networks.

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*They said, “You have a blue guitar,  
You do not play things as they are.”  
The man replied, “Things as they are  
Are changed upon a blue guitar.”*  
—Wallace Stevens

If beta is better than gamma, why is gamma so prevalent in the nervous system? An answer, it turns out, depends on the question “better for what?” Long-distance communication is one criterion; the formation of so-called cell assemblies is another.

A cell assembly is a collection of neurons whose synchronous firing during some window of time is believed to encode information to be processed as a “population code”: Which cells participate at a given time is critical information to the downstream neurons. Along with Ermentrout, Whittington, and BU postdoc Mette Olufsen, Kopell has investigated the role of rhythms in the formation of cell assemblies. They have found that networks producing the gamma and beta rhythms have different reactions to incoming signals—and a network in which a gamma rhythm is followed by a beta rhythm has still other properties.

A network displaying gamma, it turns out, is masterly at creating cell assemblies. That is, if some cells are excited more than others, and if the network has the parameters associated with gamma, then the cells that are the most excited participate in the rhythm, while the others are almost completely suppressed. On the other hand, if ionic currents associated with the beta rhythm are added in, the network becomes incapable of producing a sharp threshold between cells “inside” and “outside” the cell assembly.

The network in which the gamma rhythm is followed by a transition to beta gives the biggest surprise of all. Olufsen et al. hypothesized (based on related experimental data) that the synchronization of some cells during gamma modifies the connections of the network, increasing the strength of connections of E-cells participating in the gamma cell assembly, and decreasing the effect of the other E-cells on the I-cell population. Under that hypothesis, they predicted that when the network switched to the beta rhythm, there would be a temporal separation in the firing of the E-cells: Those that were suppressed in the gamma rhythm could reassert themselves during the beta rhythm, but they would fire only on the gamma cycles that the other E-cells missed.

This was a direct and surprising theoretical prediction. But does it actually happen in the brain? Whittington showed that it does. He was able to construct an experimental analogue of the cell assembly network, and found that the predicted temporal separation did indeed happen. “It is really cool that Whittington’s experiment worked!” Kopell says.

This finding, along with those on long-distance synchronization, helps explain why gamma and beta seem to appear in the nervous system as a kind of “tag-team,” Kopell says. “A network displaying the gamma rhythm is excellent at creating cell assemblies, and is able to pass along a cell assembly to the beta rhythm via changes in network interactions. In beta mode, the network can coordinate with others in distant geographical regions.”

In sum, the mathematical models are getting better and better at understanding and explaining how a hundred billion or so neurons do the things they do. Of course, the brain is an amazingly complicated organ. That’s what makes it attractive mathematically, Kopell says: “The number of open questions is essentially unlimited.”

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## BU Inaugurates Computational Neuroscience Program

Nancy Kopell of Boston University, whose work on rhythms in the nervous system is described in the accompanying article, is co-director (with Howard Eichenbaum) of the university’s new Program in Mathematical and Computational Neurosciences, which began January 1, 2001.

The program has been created, under the auspices of the Burroughs Wellcome Fund, to facilitate the transition of a small and outstanding set of predoctoral and postdoctoral fellows from the mathematical and physical sciences to a range of areas in neuroscience. Financial support for both PhD candidates and postdoctoral fellows is available. The program features special seminars, mentoring by faculty and advanced trainees, and a dynamic and well-networked intellectual life provided by multiple supporting institutional modules. Among them are a new degree-granting Program in Neuroscience: Experimental and Computational Neuroscience (<http://www.bu.edu/Neuro/ecn.html>), the graduate program in the Department of Biomedical Engineering (<http://www.bme.bu.edu>), and the Center for BioDynamics, of which Kopell is also co-director

(<http://www.cbd.edu>).

Predoctoral fellows enroll in one of two PhD programs (in the Program in Neuroscience or in the Department of Biomedical Engineering) that focus on the combination of experimental and computational neuroscience. Burroughs Wellcome Postdoctoral Fellows design individualized programs that include neuroscience courses and one or more research projects that emphasize combined computational and experimental approaches to neuroscience. In addition, all fellows participate in the Center for BioDynamics, which helps physical scientists and engineers to address research problems at the interfaces among mathematics, physics, biology, and engineering.

The senior faculty of the PMCN and their research interests are: Laurel Carney (biomedical engineering), computational modeling, neurophysiology and behavioral studies of the auditory system with an emphasis on issues of temporal coding; Jim Collins (biomedical engineering), application of nonlinear dynamics to experimental work in human postural control, genetic engineering, and neurophysiology; Steve Colburn (biomedical engineering), computational modeling and psychophysical studies on sound localization; Paul Cook (biology); cellular electrophysiological properties of the retina, focusing on its ability to identify important spatial and temporal cues using multiple intra- and intercellular mechanisms; Howard Eichenbaum (psychology), physiology of cortical and hippocampal networks involved in memory processing, with a focus on building models of the fundamental cognitive mechanisms and coding properties of neural networks in these areas and their interactions; Kristen Harris (biology), cellular physiology and synaptic ultrastructure of the hippocampus, with computational issues arising from the impact of different types of synapses interacting on a particular cell or within a network; Michael Hasselmo (psychology), neuromodulatory regulation of dynamical states in cortical networks; Tasso Kaper (mathematics), application of singular perturbation to problems arising in pattern formation, fluid mechanics, systems of mechanical oscillators, and neurophysiology; Nancy Kopell (mathematics), dynamics of the nervous system, especially rhythmic networks of neurons and their functions in cognition and motor control; David Somers (psychology), functional MRI, psychophysical, and computational modeling studies of visual perception and attention; Chantal Stern (psychology), functional magnetic resonance imaging (fMRI) studies of cognition, with a focus on computational problems related to MR signal processing, image analysis, cortical modeling, and surface reconstruction; Gene Wayne (mathematics), qualitative solutions of partial differential equations arising in neurobiology; and John White (biomedical engineering), computational modeling and electrophysiology of cortical cells and networks.

For further information, see the program's Web site at <http://pmcn.bu.edu> or e-mail [pmcn@bu.edu](mailto:pmcn@bu.edu). Information can also be obtained from: Program in Mathematical and Computational Neuroscience, c/o N. Kopell, Department of Mathematics, Boston University, 111 Cummington Street, Boston, MA 02215.