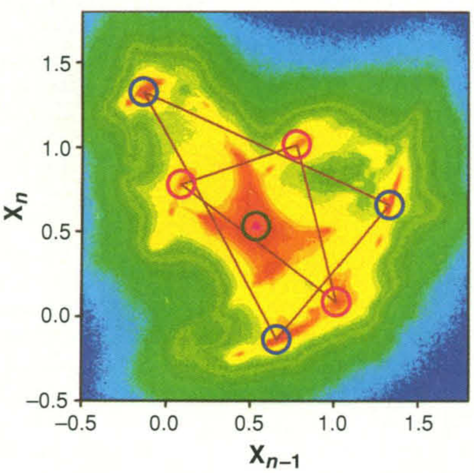
Mastering the Nonlinear Brain

By applying concepts from mathematical physics, researchers hope to understand the collective dynamics of billions of neurons—and perhaps control them in epilepsy

CHICAGO—Wearing shorts and a blue T-shirt with the word "adidas" printed over his heart, George K. sits cross-legged on a hospital bed as his mother looks on, waiting for him to have an epileptic seizure. A bundle of multicolored wires emerges from a huge bandage on the boy's skull and runs to a computer, where rows of jagged traces on a screen record the electrical activity of his brain. The stamp of a seizure on those traces could reveal whether cutting out a piece of George's brain might safely cure his intractable epilepsy.

Traces like those scrolling from George's brain are also feeding a new interdisciplinary field of research, which might one day make such surgery unnecessary. Recordings of epileptic seizures, along with other studies of electrical activity in human and animal brains, are linking neuroscience with a rarefied branch of mathematics called nonlinear dynamics. This discipline was born as theorists tried to make sense of the complicated rhythms of everything from wildly swinging pendulums connected by springs, to the patterns formed by chemical reactions on a metal surface, to wave trains steepening and crashing on a beach. Now a coterie of neuroscientists, biophysicists, and mathematicians is finding that the same concepts can also help them understand the collective dynamics of billions of interconnected neurons in the brain.



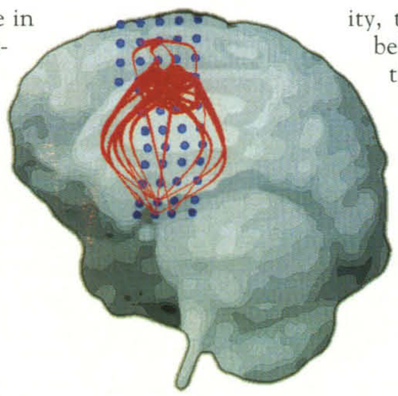
PAUL SO

Abstract topography. The high points on this landscape are "unstable periodic orbits"—repetitive patterns where a nonlinear system like the brain briefly lingers.

Unlike traditional neuroscience, which often focuses on the details of the brain—neurotransmitters, receptors, and neurons, alone or in small groups—nonlinear dynamics aims to identify the large-scale patterns that emerge when neurons interact en masse. Studies of epilepsy dominate the work, in part because the widespread, convulsive firing of neurons in epileptic seizures offers such a clear case of collective dynamics. But some neuroscientists think these studies ultimately could shed light on the workings of the normal brain as well. "We're at an extremely interesting time in terms of looking at potential interfaces between the biological sciences, clinical medicine, and mathematics," says Michael Mackey, a mathematical physiologist at McGill University in Montreal.

In the meantime, there's a practical goal: finding a way to control seizures without major surgery or drugs. "All of this is very clinically motivated," says John Milton, a neurologist, mathematician, and director of the Epilepsy Center at the University of Chicago, who is also George's physician. "If you could avoid both the side effects of drugs and cutting out pieces of brain, that would have a tremendous impact." As he and others picture it, a computer chip would receive traces like those coming from George's brain, detect the approach of a seizure, and apply spurts of current or electric fields to specific regions of the brain, using electrodes inside the skull to nudge the dynamical system away from catastrophic firing. Indeed, one protocol for testing these ideas in human epileptic patients, led by Steven Schiff of the Children's National Medical Center in Washington, D.C., has already been approved.

Before the approach comes into its own, though, two camps of researchers will need to agree on the fundamental dynamical structure of the brain. One analysis of brain recordings, by physicists Radu Manuca, Robert Savit, and collaborators at the University of Michigan, Ann Arbor, suggests that for all its complexity, the epileptic brain might behave as a "bistable" entity—like a ball that can be knocked into one of two cups. Controlling this system could involve preventing it from jumping wildly between the two states. A second effort, by Schiff and a number of collaborators, portrays the brain's electrical state as wandering over a subtler dynamical "landscape" of peaks and valleys. Controlling this system might involve nudging the state up some of the peaks and balancing it there, like a beach ball on a walrus's nose.



ERIC BERKSON AND JOHN MILTON

Nervous harmony. An electrode grid detects correlations (lines) in the firing of distant pairs of neurons.

Mathematical playground

The techniques now being applied to the brain were first developed to identify statistical or "global" properties in systems of interacting particles, whose details were far too complicated to understand. For mathematicians schooled in these systems, epilepsy, with its millions or even billions of misfiring neurons, offers "just the ideal playground," says Peter Jung, a mathematical physicist at Ohio University in Athens.

The clinical motivation is also plain. Out of about 3 million epileptics in the United States, half a million suffer from forms of the disease that are not well controlled by drugs. Many of those, including young George, have what is called focal epilepsy, in which seizures originate from a "focus" of damaged tissue in the temporal lobe. If electrical measurements like his show the focus is not too close to regions of the brain governing speech or locomotion, these patients are candidates for surgery to remove it—a procedure requiring a year of preparation and costing up to $200,000. Electrical control, if it worked, would be vastly cheaper, quicker, and more widely accessible.

But which model of the dynamical brain should it be based on? Laboratory evidence for the simplest possibility—bistability—dates back to the early 1980s, when John Rinzel, now at the Center for Neural Science of New York University, and the late Rita Guttman showed that the firing of a single neuron can jump between two different states. These re-

Sharpening the Senses With Neural 'Noise'

The science of nonlinear dynamics (see main text) would seem to be far from the practical concerns of Casey Kerrigan, a physical rehabilitation specialist at Harvard Medical School in Boston. Kerrigan helps stroke patients, along with diabetics and elderly people with "peripheral neuropathy"—a deadening of sensation in the extremities—cope with their condition and relearn simple tasks.

But that effort has led her straight into a collaboration for exploring the nonlinear effect called stochastic resonance (SR). This counterintuitive effect relies on "noise"—any random, or stochastic, background fluctuation—to make a system sensitive to an otherwise undetectable signal. In the last year, a series of experiments has shown that sensory stimulation consisting of mechanical or electrical noise can sharpen everything from the sense of touch to proprioception—the ability to perceive where a limb is in space. Not only do these results offer insights into the normal workings of the nervous system, but they also open new strategies for rehabilitating patients like Kerrigan's, she says. "The sensory loop is so essential [in rehab]," says Kerrigan. "They use the feeling to relearn a motor task. This could really help."

> **"[Neural noise] doesn't have clinical applications yet, but it's getting close."**
> **—Faye Chiou Tan**

The theory of SR, developed 15 years ago by mathematicians and physicists, describes how an optimum level of noise can boost a signal over a threshold of detection. To see this effect, says Boston University bioengineer James J. Collins, "you need a dynamical system with a threshold; you need a weak signal; and you need noise. And that's it." Consider a coin resting in one of two indentations on the dashboard of a car winding through a mountain road. Forces on the coin might not be enough, by themselves, to push it from one receptacle to another. But if the road is bumpy enough, the lateral component of this "noise" could sometimes allow the regular forces to nudge the coin across. If the road is too rough, though, the coin can move whether the car is turning or not, and the "signal" of the curves gets drowned out.

Similar effects have turned up in physical systems like noisy lasers, superconductors, and electronic circuits. Now add sensory neurons, whose cloud of dendrites "integrate" or add up stimuli until they reach a threshold and the neurons fire. Several years ago, Frank Moss of the University of Missouri, St. Louis, and co-workers monitored how sensory cells on a crayfish's tail fan respond to a weak pressure signal, such as that generated by the approach of a distant predator, in the presence of noise produced by, for example, random water currents. Moss found the classic SR rise and fall as he cranked up the noise, suggesting that the turbulent surroundings of these animals might sharpen their perceptions. More recent experiments have revealed the same sensitivity hump in cricket neurons responding to wind currents and in slices of rat brain subjected to electric fields.

Now Collins and co-workers have demonstrated SR in humans. Subjects rest a finger on a computer-controlled indentation that pulses up and down. Without noise, its action is imperceptible. Then the experimenters add either mechanical or electrical noise to the indentation, and the subjects are asked when they can feel the regular movements. The percentage of correct responses rises, then falls, as the noise gets stronger.

A separate set of experiments, led by Paul Cordo of the Robert S. Dow Neurological Sciences Institute in Portland, Oregon, shows that mechanically jiggling the muscle with a sort of vibrator can enhance a normal subject's ability to sense whether his or her wrist has been flexed by a small amount—the essence of proprioception. "It just makes your jaw drop," says Cordo of the dramatic influence of the tiny, 10-micrometer jiggle.

These experiments have taken "two big leaps," says Jacob Levin of the Massachusetts Institute of Technology, who did the cricket experiments: "One, this work was done in humans; two, it went all the way to the level of perception." Now, researchers are taking it another step: to the level of the neurons themselves. Separate sets of recent experiments led by Cordo and Faye Chiou Tan of the Baylor College of Medicine in Houston suggest that the nervous system may pump up its own sensitivity in this way.

Both groups found that as a muscle is exercised, its sensory neurons can become more sensitive, although they think different mechanisms are at work. Chiou Tan's group detected increasing electrical noise levels in the exercising muscle; the Cordo group traced a humped curve of sensitivity that may have resulted from noise generated in the brain itself during precision movements. Together, the findings suggest that the brain and its peripheral neurons are generating noise and making use of SR. "Everyone is very intrigued and perplexed at this point," says Chiou Tan.

Rehabilitation specialists are already hoping to exploit these effects by developing gloves and socks outfitted with perhaps thousands of piezoelectric noise inducers. If they worked, such devices could help patients maintain an accurate posture and keep them aware of their numb limbs, reducing injuries and infections. Kerrigan, Collins, and Harvard's Lewis Lipsitz plan to take a first step toward testing this promise in a couple of months, when they will repeat Collins's earlier SR experiments in patients. Says Chiou Tan, who also does rehabilitation: "[SR] doesn't have clinical applications yet, but it's getting close." –J.G.

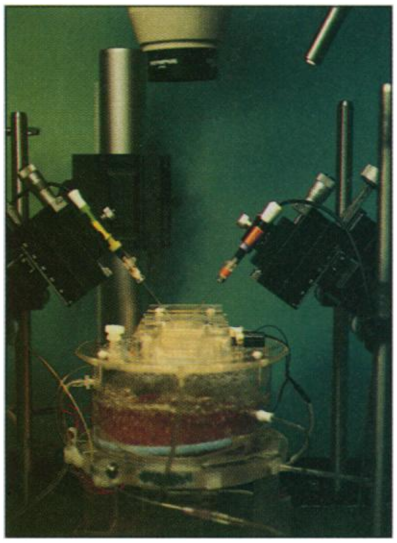
searchers stimulated a squid giant axon—a long process extending from a neuron—with an electrical current, and noticed that the axon fired repetitively at high values of the current and shut off at low values. At some values in between, though, slight perturbations in the current could make the axon jump between the firing and quiet states—in other words, push it between two bistable states.

The drastic jump meant the system's response was not "linear," or simply proportional to some parameter like the strength of the push. Recent modeling suggests that when such neurons are linked in a network, says Rinzel, they can behave like dogs in the backyards of a neighborhood: If one dog barks, all the rest may start up, but once they fall silent, most of them may sleep through the afternoon. "The network itself would be bistable," says Rinzel.

The University of Chicago's Jack Cowan, Jennifer Foss, Milton, and several others have suggested that "waves" of excitation could spread through such a bistable network, just as the dogs on one block may already have grown tired while those two blocks away have only started barking. Such waves haven't been seen directly in human brains during seizures, but measurements made by Milton's group through grids of electrodes reveal correlations in the firing of distant neurons, which could result from these excitation waves.

The most dramatic hints of bistability, however, emerge from studies that apply complex mathematical tools to search for subtle coherence in data recorded by electrodes implanted deep in epileptic brains. Ordinary linear measures of synchrony might show whether two sine waves, say, are locked in phase, like synchronized swimmers. Nonlinear measures can pick up much more general relationships of arbitrary wave trains—like noticing that all the scattered swimmers plying different strokes in the late stages of a medley are in the same race. Such work, by Manuca, Savit, and others, including University of Michigan epileptologist Ivo Drury, identified a particular kind of nonlinear synchrony in epileptic brains.

What changed in concert across these brains was the probability that each site would switch between one of two different states, which could be spiky firing patterns, noisy fluctuations, or smooth wave forms, depending on the location of each probe in the brain. But the discovery that the switching probability changed in synchrony means "there could be bistability [across] many regions of the brain," says Savit. As the group reports in a paper submitted to *Mathematical Biosciences*, both states always seem to be present in epileptic brains, although not in normal brains, and a clinical seizure only occurs at certain switching probabilities. A seizure might then be thought of as a wavelike disturbance that kicks regions of the brain from one state to another. The finding could ultimately help neurologists determine when to apply a pulse to change the switching rate and head off a full-blown seizure, says Milton.


SCHIFF

Therapy in dish? Electric fields control seizurelike activity in a slice of rat brain.

Landscape of the brain

If Schiff, Paul So, and Bruce Gluckman of the Children's National Medical Center and George Washington University in Washington, D.C., and Timothy Sauer of George Mason University in Fairfax, Virginia, are on the right track, controlling seizures with electrodes could be a trickier proposition. As this group sees it, the brain's state can roll like a ball over an entire dynamical terrain, corresponding to various firing patterns, and occasional, irregularly timed jolts would be required to keep the system trapped in regions corresponding to nonseizing behavior, where the healthy brain ordinarily resides.

This approach got its start several years ago in a striking experiment by Schiff, Bill Ditto of the Georgia Institute of Technology in Atlanta, and Mark Spano of the Naval Surface Warfare Center in Silver Spring, Maryland, on slices of rat brain that had been chemically induced to display seizurelike firing (*Science*, 26 August 1994, p. 1174). The team plotted the time interval between any two voltage bursts from the neurons (call it X_n) against the immediately preceding interval (X_{n-1}) and found what appeared to be "unstable periodic orbits," or UPOs: At places where X_n was, say, some particular multiple of X_{n-1}, the system would linger, then roll away to other firing patterns like a marble falling off a saddle. The shortest orbits are those in which $X_n = X_{n-1}$, while others take longer to repeat a pattern of bursts.

By delivering precisely timed electrical jolts through implanted electrodes, the team was able to control the system, balancing it on one of the saddles or knocking it off prematurely. Still, says Schiff, "I came away from that experiment terribly ill at ease with the simple, seat-of-the-pants method we used to identify the mathematical saddles." Some outside critics also took the group to task for what was essentially an eyeball approach, and James J. Collins of Boston University later published a paper in *Physical Review Letters* showing that random noise and linear dynamics, not UPOs, could be enough to explain the results.

Such criticism, along with work by Frank Moss of the University of Missouri, St. Louis, on detecting UPOs in noisy biological data, motivated the team to develop a more rigorous method. The team based its method on mathematical ideas put forth by Predrag Cvitanović, of Northwestern University and the Niels Bohr Institute in Copenhagen, who has shown that the locations of the shortest UPOs, and the system's trajectory as it "rolls" near them, give a disproportionate amount of information about the underlying dynamics and perhaps the anatomical connections of the neurons themselves. It's as if you wanted to reconstruct a three-bumper pinball machine just by listening to a typical game, says Cvitanović. The rapid, briefly periodic bounces within the triangle of bumpers—a short UPO—would yield better information about how they are arranged than would longer bounces from bumpers to wall. So and colleagues accordingly devised a mathematical transformation to zoom in on the behavior of the system around the shortest UPOs. "They have come up with very strong methods for identifying the UPOs," says Collins.

Although Schiff declines to comment on human data because a new paper on the topic will soon be under review, a team member confirms that the technique has now enabled the group to identify UPOs in human epileptic tissue. Schiff thinks that the UPOs might even be recognizable in normal brains.

Still, investigators are far from pinning down the precise nature of the brain dynamics that lead to seizures. An experiment led by Gluckman, for example, has shown that seizurelike firing in rat brains can be shut down entirely just by applying a dc electric field of sufficient strength—a simple switching action that could support bistability. And last July, the U.S. Food and Drug Administration approved an electrical device marketed by Cyberonics Inc. of Webster, Texas, that reduces the frequency of seizures in some intractable epileptics. In standard operation, that device simply applies a pulsed stimulus to the vagus nerve in the neck every 5 minutes, says J. Walter Woodbury of the University of Utah, who performed early testing of the device with his late brother Dixon. But no one knows just why the device works.

In spite of the uncertainties, Schiff and his colleagues plan to test the new approach in several patients a year for the next 5 years. Taking advantage of the electrode grids routinely used to monitor the brains of epileptics who are candidates for surgery, the researchers plan to apply slight electrical jolts to see if they can avert seizures. The protocol, says Schiff, is designed to test the whole range of approaches to analyzing the brain's nonlinear dynamics—from bistability to the chaotic, wandering UPOs—to see which of them is best at anticipating and stopping seizures. He may find that the two approaches don't exclude each other, says Mackey of McGill: "I suspect what the two [groups] are talking about may just be different sides of the die, so to speak." Depending on how brain data are analyzed, he says, seizing and nonseizing regions of the UPO landscape could look like separate bistable states.

That conclusion would be fine with Milton, who applauds Schiff's work and hopes to do similar human studies. "I'm much more interested in seeing the patient get better than worrying about some esoteric scientific principle," he explains. "The final analysis is you want people to get better."

–James Glanz