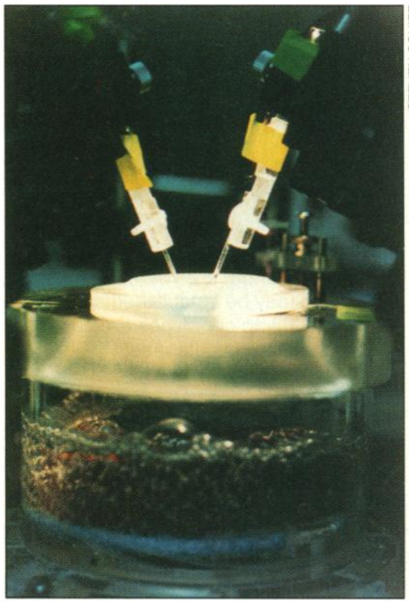
MATHEMATICAL BIOLOGY

Do Chaos-Control Techniques Offer Hope for Epilepsy?

Some epileptics who suffer from intractable seizures face a choice no one would like to make: a future of recurring seizures or the surgical removal of the parts of their brain where the problems originate. That drastic step can quiet the seizures, but it carries with it the risk of losing some degree of motor function, memory, or language skills. Now a glimmer of hope has appeared that might ultimately make such terrible choices unnecessary. And it comes from an unlikely source: the mathematical theory that allows researchers to control chaos in lasers, circuits, and oscillating ribbons of metal.

In this week's issue of *Nature*, researchers describe how they applied mathematical chaos control to the erratic firing of neurons in a section of rat brain—a model for the electrical behavior that can lead to seizures in human brains. By tracking the firing of the excitable neurons and delivering tiny, precisely timed electrical jolts, the group, led by neurosurgeon Steven Schiff of the Children's National Medical Center and George Washington University, was able to control the erratic firing—making it more erratic or more regular. The researchers believe that step might be enough to avert a seizure in humans, and therefore they argue that their observation could one day lead to radically new treatments for focal epilepsy.



STEVEN SCHIFF

Calming influence. Electrodes deliver precisely timed jolts to a slice of rat brain, bringing regularity to its chaotic rhythms.

The work is a "tour de force experimentally," says Lou Pecora, a chaos researcher at the Naval Research Laboratory in Washington. Schiff and his colleagues think it's important theoretically, as well, by implicating chaos in the genesis of epileptic seizures. But Pecora and others aren't convinced that the neurons' behavior is chaotic, strictly speaking. In a chaotic system, minute differences in starting conditions can lead to wildly different outcomes. Although the team sees indications of that kind of hair-trigger sensitivity in the rat neurons, "we can't prove [it] beyond the shadow of a doubt," admits Bill Ditto of the Georgia Institute of Technology, one of the paper's authors. "But whether it's chaos or not, we're controlling it."

Their strategy builds on the fact that chaos, unlike random behavior, contains the seeds of regularity. The by-now-classical way to understand chaos is to imagine a system with some sort of punctuated behavior—say, a dripping faucet or a black box that delivers a series of voltage spikes—and measure the intervals between successive drips or spikes. Call a given interval X_n and the one just before it X_{n-1}, and make a plot of X_n over X_{n-1} for each successive spike. A truly random system will yield points spread evenly all over the plot; a periodic system might have just one point (if X_n and X_{n-1} are always the same) or several (if the intervals vary in a regular way). But if the system is chaotic, the points will hop around inside a structure called the chaotic attractor. The attractor is actually filled with many different periodic points, and the system sometimes lingers near one or another of them before flying off again.

Such a plot, called a Poincaré section, is key to schemes for controlling the behavior of a chaotic system. In 1990, Edward Ott, Celso Grebogi, and James Yorke at the University of Maryland at College Park predicted that slight nudges applied at just the right moments could keep such a system near one of the periodic points, effectively converting its chaotic behavior into regularity. These ideas were first tested with circuits and oscillating magnetic ribbons. Later, a variant of them enabled a group including Ditto and another author of this week's *Nature* paper, Mark Spano of the Naval Surface Warfare Center in Silver Spring, Maryland, to build a "chaotic pacemaker" that regularized the erratic beating of a piece of rabbit heart. Unlike a normal pacemaker, which simply forces a heart to beat at a predetermined pace, the chaotic version fires irregularly and just often enough to keep the system near one of its natural periodic rhythms.

Schiff, who says he was intrigued by a paper in *Science* describing that result (28 August 1992, p. 1230), wondered whether the same techniques could tame the wild neuronal discharges of epileptic seizures. When he ran into Ditto and collaborators at a conference on experimental chaos, they decided to join forces to find out. The first step was to search for evidence of chaotic behavior in slices of rat hippocampus, a brain structure that in human epileptics is often what Schiff calls "the bad actor"—the focus of seizures. When the rat tissue is bathed in a concentrated potassium solution, its neurons begin firing in a way reminiscent of the "interictal spikes" that may lead to the rapid, uncoordinated firing of a seizure. Normal neuronal behavior is like the unsynchronized noise of a crowd of people; the spikes appear when ensembles of neurons begin firing together, at irregular intervals, like a crowd being led in cheers.

By using a computer to graph the interval from one spike to the next on a Poincaré plot, the team found that the timing is reminiscent of chaos, sometimes lingering near a periodic point, then abruptly flying away from it. But an electrical stimulus applied to the hippocampal tissue at just the right time, the researchers found, could keep it near the periodic point. In the human brain, says Schiff, it is still unclear whether increasing or decreasing the periodicity might better avert seizures, so the researchers also performed an exercise they dubbed "anti-control": knocking the system away from periodicity whenever it got close.

The success of both control and anti-control has the team thinking about human trials of a system that would monitor the spikes at an epileptic focus and intervene whenever Poincaré-type diagnostics indicated that a seizure may be approaching. Schiff notes that small arrays of electrodes are already implanted in some patients to pinpoint their epileptic foci. Because stimulating these electrodes according to control theory presumably would not expose a patient to additional risks, Schiff believes feasibility trials within a year or two are possible.

Others share his optimism about the general strategy, among them physiologist Leon Glass of McGill University, who calls it "a very promising point of view for potential therapies." But like Pecora, Glass, who studies mathematical approaches to biological systems, doubts that an airtight case for chaos has been made in such systems.

Schiff's response to such criticisms is a practical one: "If we achieve control, it becomes immaterial why it's working." Epileptics facing their current dismal choice would certainly agree.

–James Glanz

James Glanz is a science writer in Chicago.