MATHEMATICAL BIOLOGY

Chaos Breaks Out at NIH, But Order May Come of It

Roughly 300,000 Americans drop dead each year when their hearts start beating wildly, often without provocation, in a fatal arrhythmia. Many of those fatal episodes are virtually unpredictable now. But some researchers would just about bet their lives that long before the fatal episodes, the hearts of some of the victims exhibit telltale precursors. These researchers suspect that an arrhythmic heart, rather than behaving randomly and unpredictably, might be acting—in the arcane jargon of nonlinear dynamics theory—as a "deterministically chaotic" system. To the clinician that could mean more cardiac arrhythmias might be predictable from electrocardiogram traces of patients at risk—if only doctors knew what to look for.

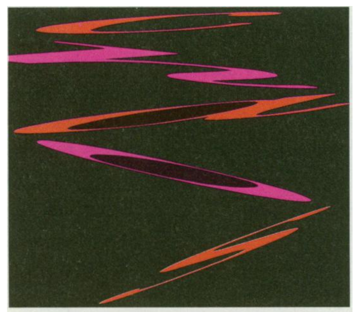
That's just one example of the kind of potential that brought cardiologists, neurophysiologists, applied mathematicians, statisticians, engineers, computer modelers, sundry other researchers and clinicians, and curious onlookers together last week at the National Institutes of Health for a workshop titled "The Head and Heart of Chaos: Nonlinear Dynamics in Biological Systems." The common hope was that by applying nonlinear dynamics—the conceptual framework that encompasses chaos theory and a bin of mathematical tools for understanding complex phenomena—to biological systems, biologists and physicians could gain insight into the complex dynamics of living systems, and ways to cure them when they go awry.

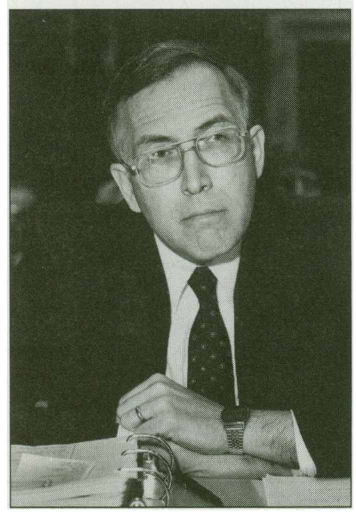
Finding rhyme and reason. The workshop presented dazzling evidence for the potential of nonlinear dynamics for understanding everything from beating hearts to firing neurons to protein-based ion channels opening and closing in cell membranes. But it also pointed to hurdles to be overcome: chiefly the cultural chasm between most biologists and the small group of mathematically inclined initiates who have been touting these tools. "There is a problem with getting the different cultures working together," remarks meeting speaker Leon Glass, a McGill University professor of physiology with a strong background in physics, chemistry, and math.

Few biologists would dispute that at the simplest level, many biological systems exhibit nonlinear dynamics. Consider a neuron: If it behaved with linear dynamics, like a gas expanding when it is heated, the neuron's response would increase proportionally with the stimulus. Instead, a neuron gives a nonlinear, all-or-nothing response. So long as a stimulus is at or above a threshold, the neuron fires completely. Below the threshold, it doesn't fire at all.

In that case, the nonlinear response is relatively clear, but participants presented evidence that nonlinear dynamics governs other biological systems, including some that at first glance appear random—fibrillating hearts, for example. Such systems might instead be displaying deterministically chaotic behavior—behavior that can change dramatically with slight changes in its initial condition and therefore can easily appear random. Jorge M. Davidenko, a pharmacologist at the State University of New York at Syracuse, presented a dramatic case in point: a video of animal heart tissue prepared with dyes that reveal the pattern of electrical activity in the tissue's cells.

In a healthy heart that activity produces a quasiregular heartbeat, though careful analysis reveals subtle, complex variations in the heart's beat-to-beat interval. By applying pairs of precisely timed electrical stimulations to heart tissue preparations, Davidenko and his colleagues were able to elicit predetermined nonlinear behaviors: They deliberately induced self-sustaining spiral waves of cellular excitations in their tissue samples. The spiral waves closely mimic those seen in the Belousov-Zhabotinsky reaction, a chemical system that has become a classic example of nonlinear dynamics.





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New dynamics for biology. The chaos meeting's logo *(top)* and its opening speaker, William Raub.

Slightly different initial excitations yielded dramatically different spiral waves (for example, ones traveling in opposite clock senses), which led Davidenko to speculate that life-threatening cardiac arrhythmias arise when the normal nonlinear dynamics of the electrical activity evolves into chaos. That might mean that the dynamics of arrhythmias are amenable to the same sort of mathematical descriptions used for analyzing the Belousov-Zhabotinsky reaction and computer models designed to mimic that reaction's behavior.

With striking possibilities like that and others described at the workshop, some initiates in the heady nonlinear dynamics club sometimes wonder why biologists and clinicians aren't beating down the doors. One reason, other participants noted, is that it's not obviously an experimental biologist's kind of club. Applying nonlinear dynamics to biological and medical questions often pushes the frontiers in mathematics, says McGill University's Glass. Yet "few biologists have decent mathematical training," he adds. The culture clash works both ways, of course; mathematicians and theorists confront a myriad of unfamiliar concepts when they try applying their models to real, complex biological phenomena.

What's more, such endeavors can fall between disciplinary cracks. Publishing, departmental, and funding infrastructures in the biological and medical communities have been sluggish in recognizing and supporting nonlinear dynamics approaches, remarks workshop organizer Kathleen Madden, a neuroscientist at the Children's National Medical Center in Washington, D.C. "The math and physics [of nonlinear dynamics] are advancing at a fast rate, but clinicians [probing its applicability] can't get their results communicated," she says.

Barriers of suspicion can also slow this kind of cross-disciplinary work. Molecular biologists and physiologists, in their reductionist approach, tend to focus on mechanisms, and some biologists at the workshop voiced concern that models derived from nonlinear dynamics analysis wouldn't help them in that quest. The models might succeed in describing the dynamics of biological processes, the researchers worried, but would fail to uncover actual biological mechanisms responsible for the processes. "It may be difficult to get back into the physiology from the modeling," suggested Niels-Henrik Holstein-Rathlou, a physician and physiologist at the University of Southern California School of Medicine, during a panel discussion.

There's also the danger, even some researchers in nonlinear dynamics admitted, that some of the mathematical patterns they are chasing may turn out to be phantoms. Paul Rapp, a physicist and physiologist at the Medical College of Pennsylvania, described how the mathematical and statistical techniques of nonlinear dynamics can have an insidious way of finding patterns in data where none, in fact, may exist. To counter this pitfall, he and others are developing sophisticated methods for determining whether a data set is truly random or may actually contain hidden patterns that nonlinear dynamics analyses might discern.

Should the biological and medical community embrace nonlinear dynamics despite the new methodology's pitfalls and uncertainties? William Raub, special assistant for health affairs in the White House Office of Science and Technology Policy and former acting director of NIH, thinks they ought to at least give it a try. Raub, who presented opening and closing remarks at the workshop's Monday session, notes that right now, "in an intensive care unit, with the best [diagnostic] equipment and most capable doctors around, someone can drop dead and no one will have seen it coming. It may be that the info [of the impending heart failure] is not in the [electrocardiographic] trace," admits Raub. "But most of us think it has got to be there." Finding it—and other possible signatures of chaos in complex biological systems—will, however, require some changes in the dynamics of the biological research community.

–Ivan Amato

CHEMISTRY

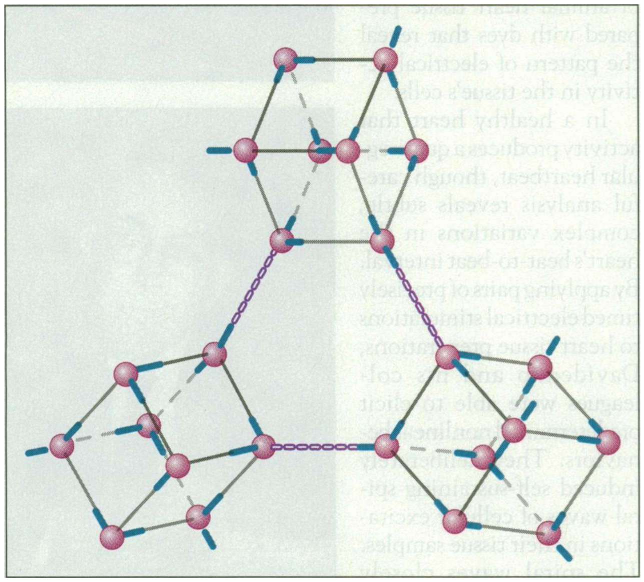
A New Blueprint for Water's Architecture

Liquid water—the stuff of oceans, the medium of life, and the most highly researched fluid of all time—continues to baffle scientists seeking its molecular structure. As water theorist H. Eugene Stanley of Boston University admits, most ideas about how the V-shaped H_2O molecules interact in liquid water "are just wild conjectures, including my own." But in the 20 May *Journal of the American Chemical Society (JACS)*, a pair of California chemists propose an idea that, to other water researchers, appears a little wilder than most.

At the heart of liquid water, suggest chemists Sydney Benson, distinguished professor emeritus at the University of Southern California, and Eleanor Siebert of Mount Saint Mary's College in Los Angeles, are tiny cubes and rings of water—octamers and tetramers made of eight and four water molecules, respectively. These and similar clusters in turn link into small chains or networks that continuously form and break up. The glue holding these clusters together and linking them to one another consists mostly of hydrogen bonds—weak and transient links that can form between electrically polarized molecules like water.

To Benson and Siebert, this surprisingly ordered microstructure can account not only for water's fluidity but for some of its other tricks as well, such as its high heat capacity—its ability to absorb anomalously large amounts of heat as its temperature rises. To some other theorists, though, this new octamer-tetramer picture represents too radical a departure from the prevalent, more random pictures of water's liquid structure. "I don't like the idea much," says Alfons Geiger, a water theorist at the University of Dortmund in Germany and Stanley's intermittent collaborator. But he admits he can't exclude the possibility.

Water researchers agree that the H_2O molecules in liquid water, with their strong tendency to hydrogen-bond, must form transient networks of some kind. But tracing those networks lies out of experimenters' reach. The stable hydrogen-bonded structure of ice can be laid bare via x-ray crystallography, but there's no instrument capable of taking a detailed snapshot of liquid water's structure. The resulting experimental vacuum has become the domain of computer models, speculations, and polemics—a veritable Rorschach test for theorists.



SOURCE: JACS ILLUSTRATION: SUSAN NOWOSLAWSKI

Hidden order. Small networks of hydrogen-bonded water clusters could acount for water's physical quirks.

Based on computer simulations of interacting water molecules, most researchers envision a completely random network of bonds. Rather than locking the molecules into gel-like stasis, the bonds shift continuously—in a second the hydrogen bonds between a single water molecule and its neighbors can break and reform 500 billion times—in a dance that allows water to flow. But Benson argues that water's high heat capacity presents another puzzle that these kinds of random-network models can't readily solve.

What soaks up the large input of heat needed to raise water's temperature a given amount, Benson argues, must be a large increase in entropy, or disorder. To explain how the entropy could be increasing so much, he and Siebert surmise that the structure of liquid water must offer more places for disorder to creep in than existing structural proposals would allow. In other words, it has to include an extra measure of order in the first place.

Computer modelers have tended to overlook that thermodynamic puzzle, says Benson. "I don't have faith in computer models," he says. Despite the ability of well-programmed computers to simulate many of water's properties, he argues, a combination of assumptions, approximations, and ad hoc adjustments in the calculations put the simulations on thin ice. In their *JACS* paper, he and Siebert rely instead on thermodynamic arguments, together with their own healthy dose of assumptions and corrections, to support their octamer-tetramer structural theory, which Benson has been developing since the late-1970s. They argue that when a hydrogen bond breaks between the orderly clusters of their model, the entropy of the structure increases far more than it does for similar bond breakage in a random network—enough to explain liquid water's high heat capacity.

Charles A. Angell, a physical chemist at Arizona State University who studies water both in vitro and in computer models, Stanley, and others insist that other properties of water reproduced in computer simulations can explain its high heat capacity. There's no need, Angell says, to posit a structure as elaborate as Benson and Siebert's. So confident is Angell in the numerical methods that he says, "If there were any truth to Benson's model, the structures should show up in computer models."

Benson is stalwart. "What is remarkable to me is that the mainstream has never explained the properties of water," he says. Still, he concedes that the less traveled tributary that he and Siebert paddle in their *JACS* paper may end up just as dry. "Is there any direct evidence for the structures we have discussed here?" the two ask rhetorically in their paper. Like all other theorists pushing a particular model of water's microstructure, they have to concede: "Unfortunately, no."

–Ivan Amato

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