Crazy Rhythms

Confronting the complexity of chaos in biological systems

By IVARS PETERSON and CAROL EZZELL

Listen to the heartbeat.

Cardiologist Ary L. Goldberger believes that subtle warnings of an impending heart attack lie in the intricate, spiky tracings of an electrocardiogram (ECG). If only physicians could detect and decipher these clues, asserts the Harvard Medical School researcher, they might identify and monitor more closely those patients at high risk of sudden death from heart disease.

The key to unraveling these obscure clues lies in the mathematical techniques of nonlinear dynamics, Goldberger says.

He is one of a growing number of scientists interested in probing the mathematical underpinnings of biology. More than 100 of these researchers met at a June conference entitled "The Head and Heart of Chaos," held at the National Institutes of Health (NIH) in Bethesda, Md.

"Nonlinear dynamics is ubiquitous in clinical cardiology," says Goldberger. "Hopefully, [by using this mathematics] we'll be able one day to predict sudden death during normal [cardiac] rhythm, and not after [a heart attack has begun]."

Goldberger leads a research group that is particularly intrigued by a nonlinear phenomenon called chaos: complex, inherently unpredictable – but not random – fluctuations. In the early 1980s, Goldberger and his colleagues began reporting evidence that healthy hearts behave in a chaotic manner, while the so-called "abnormal" rhythms of diseased hearts reflect a loss of chaotic behavior that could herald sudden cardiac arrest.

In analyzing the ECGs of laboratory animals and those of a handful of people who died of sudden heart failure while their heart activity was being monitored, Goldberger and his colleagues found that a loss of complexity in the heartbeat pattern precedes sudden death.

"As the system breaks down . . . it loses its variability," Goldberger contends. This variability, he suggests, gives a living, dynamic system, such as the heart, the robustness it requires to cope with change.

Sudden cardiac arrest causes roughly 60 percent of the approximately 500,000 fatal heart attacks that occur annually in the United States. These sudden deaths are usually preceded by fibrillation, an incoherent beating pattern that to the untrained eye appears much less regular and periodic than a normal heartbeat.

However, by plotting the electrical frequency of cardiac fibrillations, Goldberger and his colleagues have found that cardiac fibrillation is a much more periodic process than it seems at first glance. They report that while the electric waves of healthy heartbeats encompass a broad range of frequencies, fibrillations occur across fewer and fewer frequencies, until death eventually transpires.

Earlier this year, Goldberger and Harvard researcher Lewis A. Lipsitz proposed that similar losses in complexity occur as an individual ages. In the April 1 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, they report that older individuals tend to have brain nerve cells with fewer branches, a more restricted range of electroencephalographic (EEG) signals, more regular pulses of hormone release, and a less variable heart rate and blood pressure. They suggest that these simplifying changes might partially explain the general physiological breakdown characteristic of aging.

The June NIH meeting marked an important stage in the development of mathematical biology. Intrigued by the irregularities that seem to pervade cardiovascular, neurological, and other physiological systems, a motley assortment of mathematicians and scientists have started over the last decade to develop and apply mathematical tools for deciphering these erratic, perplexing signals and illuminating their significance in biological systems.

These researchers are bucking the overwhelming tendency in biomedical research toward working out the tiniest details of how specific enzymes, genes, or molecules perform their functions. In this reductionist, "lock-and-key" approach, researchers seek evidence of the particular interactions that cause certain effects.

In contrast, many of the researchers interested in chaos and nonlinear dynamics focus on general trends. They look at how one level of organization relates to another, how pieces of a biological system are linked and work together.

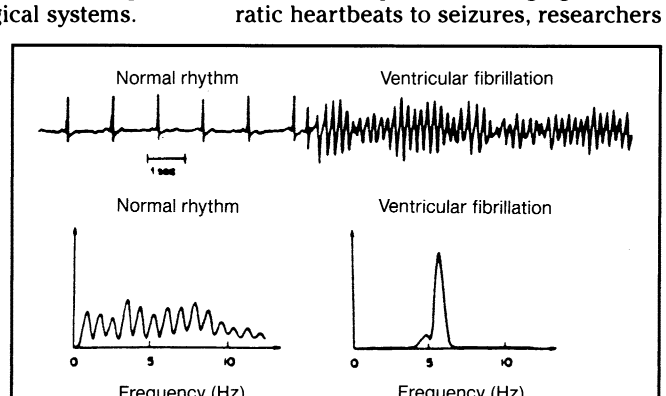
From this viewpoint, the difference between life and death lies not in the structure by itself but in how things change, argues John Guckenheimer, an applied mathematician at Cornell University. That notion immediately introduces dynamics – especially nonlinear dynamics – as a tool for interpreting these changes.

Traditionally, scientists have focused on studying systems that can be described by linear equations. In such situations, a slight change in a system's starting point would mean only a slight difference in its final state.

By way of contrast, a nonlinear system offers the possibility that a small change can cause a considerable difference in the final result. One can even get outputs that look random, yet follow from situations apparently described by simple, nonlinear equations. Such systems are termed chaotic, but they are not the only possible examples of intricate behavior. Nonlinear dynamics encompasses much more.

"The human body is a complex mosaic of nonlinear dynamical systems," says physiologist Leon M. Glass of McGill University in Montreal. "These systems interact with one another and the outside world, all under feedback control. A detailed understanding of the dynamics of such systems must necessarily be carried out in the context of the mathematics of nonlinear systems."

Faced with a menagerie of puzzling, time-dependent behaviors in biomedical processes ranging from erratic heartbeats to seizures, researchers



As normal cardiac rhythm switches to deadly ventricular fibrillation at the onset of sudden cardiac arrest (top), the heart's electrical activity changes from a healthy, broad-frequency range (bottom left) to an abnormal, narrow band of frequencies (bottom right).

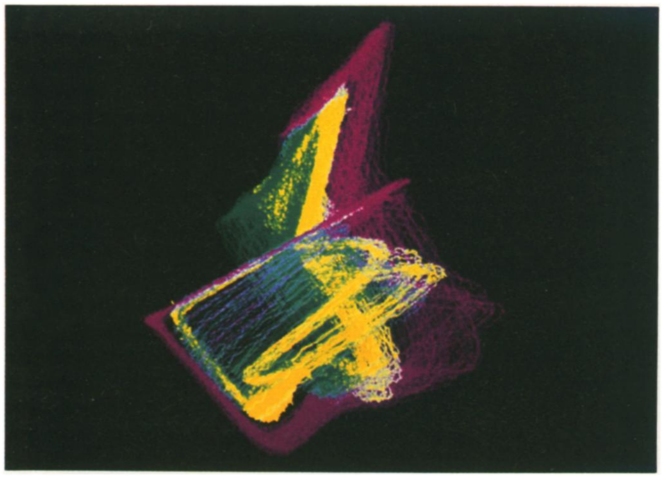
Goldberger/YALE JOURNAL OF BIOLOGY & MEDICINE are looking for a new framework within which to try to understand these diverse patterns. The hope is that "maybe the underlying mechanisms are not as complicated as the observed behaviors," says William F. Raub of the White House Office of Science and Technology Policy.

Nonlinear mathematics provides a possible avenue for illuminating these behaviors, he adds. "But there are no ready-to-wear answers and techniques."

Moreover, working at the interfaces between disciplines has its drawbacks. Proposals for research projects often fall between the cracks at discipline-oriented funding agencies. Individuals seeking university appointments generally find no niche in which to pursue their specific interests. Vocabulary differences stymie communication and prompt misunderstandings. Even the efficacy of applying mathematics to biological problems evinces suspicion and skepticism among many biologists.

"It's hard to bridge the levels," admits William S. Yamamoto, professor of computer medicine at George Washington University in Washington, D.C.

Nonetheless, "there's an inevitable evolution toward [the use of] quantitative methods in the biological sciences," notes Charles DeLisi, a biomedical engineer at Boston University.



Ditto et al.

This computer-generated image represents one way of mathematically and graphically encapsulating the chaotic beating of a rabbit's heart. Researchers can use this information to devise strategies for stabilizing the heartbeat.

For researchers interested in biomedical applications of nonlinear dynamics, the NIH meeting presented an opportunity to plead for increased open-mindedness from funding agencies and from their peers in various disciplines. "We need to define [research] leads and persuade scientists to give them the attention they deserve," Raub says.

Though still small in number, biomedical research projects that involve nonlinear dynamics already cover a wide range of topics. Goldberger's work on cardiac rhythms was one of several glimpses provided at the NIH meeting of both the promise and the

Troubling complexities

Everyday life is full of erratic, intricate behavior, whether in the zigzagging flight of a rapidly deflating balloon across a room, the fluctuations of the stock market, or the spiky tracks of brain waves recorded by an electroencephalograph.

In many cases, this irregularity represents the net effect of many separate events. The resulting behavior is random.

In other instances, this complexity apparently arises out of systems governed by an underlying principle and described by surprisingly simple mathematical equations. Such systems are termed chaotic when they display an extreme sensitivity to initial conditions. In other words, a slight change in a system parameter can produce startling, unexpectedly large changes in the system's behavior. These systems often appear random, but researchers can alter their behavior – even switch between order and chaos – simply by adjusting an appropriate system parameter.

"Not everything that looks random is random," says Larry S. Liebovitch of the Columbia University College of Physicians and Surgeons in New York City. "Simple systems can have complex outputs."

In studies of the dynamics of biological systems, researchers face the dilemma of determining from experimental data whether observed variations represent random fluctuations or the chaotic state of a deterministic system. If they can demonstrate that the system is chaotic rather than random, they have a better chance of developing a strategy to understand and control this erratic behavior.

"Complex aperiodic rhythms that are observed in natural systems might be due to deterministic chaos, random 'noise,' or some combination of the two different mechanisms," says Leon M. Glass of McGill University in Montreal. "Thus, the interpretation of the dynamical basis of complex aperiodic rhythms in natural systems is a difficult and hotly debated topic."

The trouble is that many researchers apply techniques used to characterize chaotic systems without knowing whether the systems in question are really deterministic rather than random. In general, the results of these commonly used techniques do not establish unambiguously that a system is either deterministic or random.

"They fail in a particularly pernicious way," says Paul E. Rapp of the Medical College of Pennsylvania in Philadelphia. "Rather than simply failing to produce a result, they can produce spurious results. Even when applied rigorously, care must be exercised when interpreting results."

Rapp applied a variety of tests – commonly used to identify and characterize chaotic systems – to a set of random numbers, modified slightly to reflect the kind of "filtering" typically imposed on experimental measurements as signals pass from sensor to amplifier to computer. Five widely used tests failed to identify correctly the underlying randomness in this artificial data set.

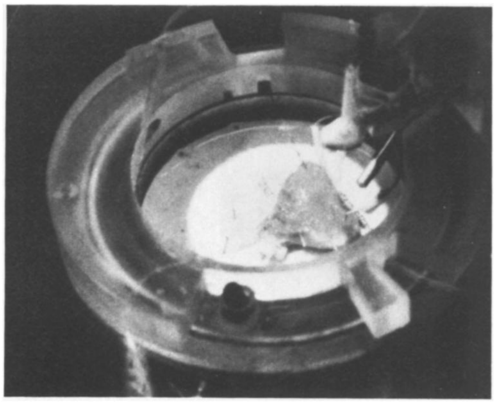
"These calculations produced vivid examples of how the casual application of the methods of dynamical analysis produce fallacious conclusions," Rapp says. "By implication, these results suggest that many of the putative identifications of chaotic behavior, particularly in biological data, are almost certainly spurious."

"Many published claims for 'chaotic' dynamics in biological systems need reexamination," Glass adds. "One has to be very careful reading the chaos literature."

But all is not lost. In the Jan. 27 PHYSICAL REVIEW LETTERS, Glass and colleague Daniel T. Kaplan present details of a direct test for distinguishing between deterministic and random dynamics, given data in the form of a sequence of observations made at certain time intervals.

Similarly, Rapp observes that certain sophisticated tests, heedfully used, can provide useful insights even when applied to "noisy" biological data. Moreover, an increasing number of researchers are starting to recognize "the importance of obtaining data from carefully controlled and well-characterized biological systems," he says.

Rapp concludes, "There is a case for guarded optimism combined with extreme caution." – *I. Peterson*



Ditto et al.

The drug ouabain induces a chaotic heartbeat in this specially prepared portion of a rabbit's heart.

difficulties of research in this field.

Glass and his collaborators have been studying the effects of periodic electrical stimulation on spontaneously beating assemblages of embryonic chicken heart cells (SN: 7/30/83, p.76). The researchers find that stimulation at different frequencies and amplitudes induces various sorts of both regular and irregular dynamical behavior.

An irregular signal, however, doesn't necessarily indicate chaos, Glass says. On occasion, the signal is actually random.

Nonetheless, the mathematics of nonlinear dynamics has offered a useful theoretical framework for understanding complex rhythms in carefully controlled experimental situations. "Unfortunately, the successes in studying comparatively simple systems are not easily extended to the difficult clinical problems that confront the practicing cardiologist," Glass says.

Pharmacologist Jorge M. Davidenko and his colleagues at the State University of New York Health Science Center in Syracuse study heart rhythms by looking for waves of electrical activity when signals pass through heart tissue isolated from sheep. In recent experiments, reported in the Jan. 23 NATURE, the researchers induced and observed spiral waves propagating through an experimentally prepared heart.

Such waves of electrical activity may be the cause of certain life-threatening arrhythmias, Davidenko suggests. But because this behavior was induced under rather special experimental conditions, "this doesn't mean this will occur in a normal heart," he adds.

The investigations of neuroscientist Avis H. Cohen of the University of Maryland in College Park and her co-workers have focused on the way electrical signals traveling along nerve cells activate muscles, especially to produce the coordinated, rhythmic movements characteristic of locomotion, breathing, and chewing. By modeling individual neurons or groups of neurons as oscillators, which generate periodic electrical bursts, the researchers obtain important insights into such behaviors as how a snake-like creature such as the lamprey swims and how a lobster chews its food (SN: 1/18/92, p.39).

"Although we know that the models we have produced are not 'correct,' they do seem to capture a great deal of the qualitative nature of the [biological] system," Cohen remarks.

One recent, intriguing result, of which only a hint was given at the NIH meeting, concerns initial attempts to control an evidently chaotic heartbeat. In contrast to Goldberger's approach, which focuses on the "soft" chaos evident in the tiny variations from a regular heartbeat in a normal heart, this research focuses on a particular, deadly type of arrhythmia.

An overdose of the drug ouabain has a disruptive effect on the heart. It interferes with currents of ions passing into and out of cells, upsetting the delicate electrical balance that helps maintain a rhythmic heartbeat.

The resulting fluctuations in the concentration of calcium ions trigger spontaneous beats, adding extra heartbeats to the heart's normal rhythm. At first, these additional beats appear at fairly regular intervals, but gradually the beating becomes more rapid and the overall pattern more complex. Eventually, the heart shifts into a highly irregular pattern of spontaneous beats.

This drug-induced activity, with its progression from periodic to erratic beating, has many of the characteristics expected of a chaotic system. If it were truly chaotic, even small disturbances would drastically alter the system's behavior. At the same time, a string of tiny adjustments of the right sort could potentially stabilize its activity.

To investigate the possibility of controlling cardiac chaos, cardiologist James N. Weiss and physiologist Alan Garfinkel of the University of California, Los Angeles, began working with physicists Mark L. Spano of the Naval Surface Warfare Center in Silver Spring, Md., and William L. Ditto of The College of Wooster in Wooster, Ohio. In 1990, Ditto and Spano had demonstrated that they could snatch order out of chaos by using judiciously applied magnetic fields to control the irregular oscillations of a magnetoelastic ribbon, which changes its stiffness in accordance with the strength of an applied magnetic field (SN: 1/26/91, p.60; 10/12/91, p.229).

"Thinking that we might actually be able to get our technique to work [in a biological system], we were looking for somebody who had a suitable experimental heart preparation," Ditto says.

The four researchers performed their experiments on portions of rabbit hearts, through which flowed a solution containing ouabain. Initially, a regular train of electrical pulses provided the jolts needed to keep the heart beating at a particular rate.

However, as the drug entered the system, it induced extra beats in addition to the electrically stimulated ones. The researchers then turned off the electrical stimulator to allow the drug-pervaded heart preparation to establish its own, irregular pattern.

Using a computer to monitor the intervals between beats, the researchers could draw an abstract, mathematical "portrait" of the erratically beating heart, and then use this portrait to decide when to apply electrical stimuli that would

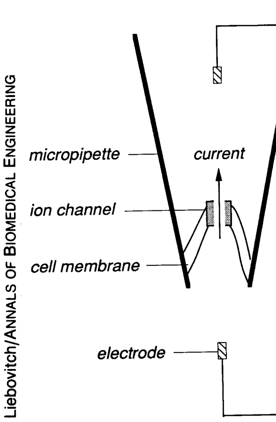
Chaos and the

For many years biochemists have thought that ion channels – the tunnel-like surface proteins that ferry charged atoms into or out of a cell – operate much like light switches: One position turns the light on, the other turns the light off, and the same amount of effort is required to flick the switch in either direction.

Under this hypothesis, the ion channels that cause nerve cells to fire and muscle cells to move were thought to have only a handful of states: open, closed, and a smattering of discrete in-betweens. And nudging those channels between one state and another was thought to require a specific amount of energy that never varied.

Now, researchers armed with the mathematical techniques of nonlinear dynamics are finding that this old model of ion-channel action just doesn't add up. Larry S. Liebovitch and his colleagues at the Columbia University College of Physicians and Surgeons in New York City have evidence that ion channels really behave more like minuscule machines, with tiny movements in various parts of the molecule triggering larger movements of the molecule as a whole.

The Columbia group has found that ion-channel movements have the properties of mathematical constructs called fractals: The closer one looks, the more the pattern of larger movements resembles that of the tiny ones, and the more



Liebovitch/ANNALS OF BIOMEDICAL ENGINEERING nudge the heart into beating at a regular rate. In effect, the computer analyzed the heart's activity, then added electrically stimulated beats at sporadic intervals while the activity was going on.

"Once we decided what we wanted to measure and how we wanted to measure it, getting the system set up and implementing the chaos control was pretty straightforward," Weiss says. "The main problem—as with any biological system—was that there's a lot of variability from heart to heart in terms of whether chaos develops, how long it lasts, and whether the pattern is stable enough for the computer to recognize [the right features] and learn them quickly enough to implement control."

Nevertheless, this strategy worked, and the researchers found they could stabilize the heartbeat in most cases. In contrast, strictly periodic and purely random pacing failed abysmally in smoothing out heartbeat irregularities.

Only by adhering to the sporadic pattern of stimuli mandated by the strategy to control chaos could the researchers make the heartbeat nearly periodic. In the absence of these stimuli, the heart would revert to its erratic beating.

"In retrospect, given the number of variables, it's sort of amazing to me that it worked as well as it did," Weiss notes. "I think it speaks well of the power of the new technique that you just have to approximate what you need to know in order for it to work – at least at the first level."

The four researchers report their results in the Aug. 28 SCIENCE.

Researchers still don't know how applicable a control strategy based on chaos may be in treating heart patients. For one thing, it isn't clear yet which of the various irregular heartbeat patterns typically observed in patients really correspond to a chaotic system.

It is conceivable, however, that a chaos control strategy – implemented in the form of a "smart" cardiac pacemaker – may ultimately succeed in restoring erratic cardiac rhythms to normal patterns in a variety of life-threatening situations. "We've applied for a patent on what would be a chaos-aware pacemaker," Ditto says.

Weiss and his colleagues are now interested in taking a closer look at the irregular heartbeat patterns produced during atrial fibrillation, when the upper chambers of the heart muscle contract at an irregular rate. They would also like to see whether they can refine their control strategy not only to convert an irregular rhythm to a periodic pattern but also to slow its rate.

"We want to develop a computer model that will simulate many of the features we have observed in the actual [rabbit heart] model," Weiss says. "If we can successfully reproduce the chaotic patterns we see in the real animal, then we may be able to test some of these ideas on how we might refine the chaos control program. If we're successful, we could go back and apply them to the [rabbit heart]."

Although nonlinear dynamics, especially chaos, has captured public attention, it remains in some sense a suspect field in the world of science. To many researchers, especially in biology and medicine, the mathematical tools of nonlinear dynamics look like "magic boxes" that find patterns where none seem to exist according to conventional methods of analysis.

In contrast, to those who have taken the trouble to delve into this mathematical realm, nonlinear theory offers a possible framework for gleaning insights into the behavior of biological systems. "This is a new way of looking at things," says McGill's Daniel T. Kaplan. "It suggests new questions to pursue."

However, "there's no complete theory in hand yet," Glass notes.

Nonetheless, as techniques improve and researchers gain more experience, they may eventually obtain useful results even from systems in which noise, or randomness, also plays a role.

"The mathematics is very, very difficult," Cohen adds. "We need more collaborations, but it's going to take a lot of hard work and a lot of patience."

"Lot's of things are wrong. That's what happens at the frontiers of science," says Paul E. Rapp of the Medical College of Pennsylvania in Philadelphia. "But we've learned a lot in the last 10 years." □

single ion channel

ments resemble even tinier ones – just as a coastline appears similarly jagged whether you look at it from an airplane or while standing on the shore. This suggests that ion channels have a multitude of very similar states with only tiny energy differences between them.

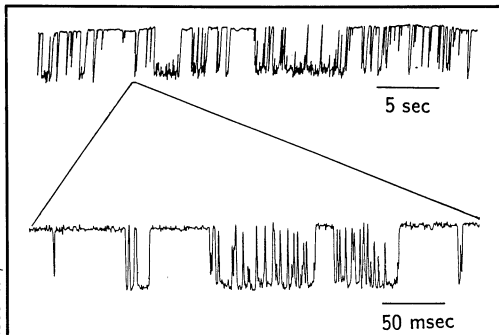
Liebovitch's team uses a technique called patch clamping to isolate and study the action of a single ion channel. In this technique – for which its developers won the 1991 Nobel Prize in Physiology or Medicine (SN: 10/12/91, p.231) – researchers use suction to clamp a microscopic pipette against a patch of cell membrane. Ions passing through an open ion channel produce a tiny, measurable electrical current. When the channel closes, ions can no longer traverse the membrane and the current flow stops. Researchers can record on paper the alternating valleys and peaks that correspond to the channel's opening and closing.

Ion channels are particularly important to the Columbia team's research topic: the cornea. In order to keep this thin outer layer of the eyeball transparent enough for clear vision, corneal cells must continually expel water. They do this by exporting ions to create a difference in ion concentration between their insides and outsides. This difference draws fluid out of the cells, keeping them from becoming waterlogged and murky.

While recording electrical signals from patch clamps of corneal tissue, Liebovitch noticed an interesting phenomenon: The resulting tracing was equally rough and jagged no matter what time scale he used to plot the recording. For example, he found that an enlarged tracing of an extremely brief, 50-millisecond recording contained just as many deep valleys and sharp peaks as one taken over a time period 100 times longer and at a lower resolution. In other words, the tracing was fractal.

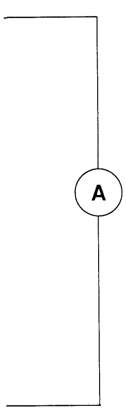
Liebovitch hypothesizes that enlarging the tracing would reveal the ever smaller wobblings of atoms that make up the ion channel. A given channel opens or closes, he suggests, only when a multitude of these tiny wobbles occur in concert – a phenomenon called chaos.

"There are many processes happening at many scales" within ion channels, Liebovitch concludes. As a result, he says, "there are no such things as discrete states [between a channel's opening and closing].... There's a continuum of many states." – *C. Ezzell*



Liebovitch/ANNALS OF THE N.Y. ACAD. OF SCI.

An amplified region of a patch-clamp recording (bottom) appears just as jagged as a recording taken over a longer time scale (top), revealing the fractal nature of ion-channel opening and closing.



Schematic illustration of patch-clamp technique. An ammeter (A) records changes in electrical current as the ion channel opens and closes.