

DYNAMICS OF CARDIAC ARRHYTHMIAS

An elderly gentleman with heart disease was admitted to hospital for treatment of an abnormal heart rhythm called ventricular tachycardia. This potentially fatal rhythm can occur days, or even years, after a heart attack. It is associated with an abnormally rapid heartbeat that arises from tissue in the heart attack-damaged portions of the ventricles—the two main pumping chambers of the heart. (See the box on page 41.)

Treatment of ventricular tachycardia is difficult. Drugs are often ineffective, and they can produce adverse side effects; surgery is possible only in a small minority of patients; and implantable devices that terminate this arrhythmia by direct electrical stimulation of the heart do not prevent its recurrence. In the case of the elderly gentleman, the physicians decided to use a new approach called catheter ablation.¹ With the patient under local anesthetic, they first inserted three catheters into blood vessels and advanced them into specified sites in the patient's heart. (See figure 1.) The function of the three catheters was to record electrical activity at these sites and deliver short electrical stimuli. (See figure 2.)

With the three catheters in place, the physicians reinitiated the ventricular tachycardia. They could then localize the abnormal region in the left ventricular wall by delivering short stimuli during the induced tachycardia and carrying out an on-line analysis of the subsequent changes in timing of the arrhythmia from different sites within the ventricle. Then they guided a fourth, "ablation" catheter to the pathological region thus identified. This catheter is designed to ablate the abnormal tissue by delivering 40 to 50 watts of radio-frequency heating directly to the offending spot. The local temperature was thus raised above 50 °C, destroying the abnormal tissue.

The RF ablation put an end to the patient's induced tachycardia. After that it could not be reinitiated, and the patient went home the next day.

This episode happened at Beth Israel Hospital in Boston, where I was spending a sabbatical year. That year strengthened my conviction that complex cardiac arrhythmia is as much a problem in physics and mathematics as it is a medical problem.

I will describe some basic properties of excitable media and pacemaker oscillations, and show how they can lead

Physicists, considering the heart as an excitable medium driven by limit-cycle oscillators, can help cardiologists gain important insights into the prevention and control of deadly arrhythmias.

Leon Glass

to novel theoretical insights into the dynamics of cardiac arrhythmias. I make two main theoretical assumptions:

▷ **The heart is an excitable medium.** That is to say, a small but finite perturbation from equilibrium can lead to a large excursion away from equilibrium—an excitation—before equilibrium is restored.² In the

case of the heart, the excitation is associated with an electromechanical wave that induces the cardiac-muscle contractions that pump deoxygenated blood to the lungs and oxygenated blood to the rest of the body.

In a spatially extended system the excitation waves propagate through the medium following three rules:

(1) Some time after a wave has passed through the medium, a so-called refractory period sets in, during which a second wave cannot be initiated.

(2) The longer the elapsed time between one excitation wave and the next, the greater will be the duration of the refractory period following the second excitation wave. This correlation is called the restitution property.

(3) The propagation velocity of an excitation wave increases with the time elapsed since the passage of the last excitation wave. This correlation is called the recovery property, or the dispersion property.

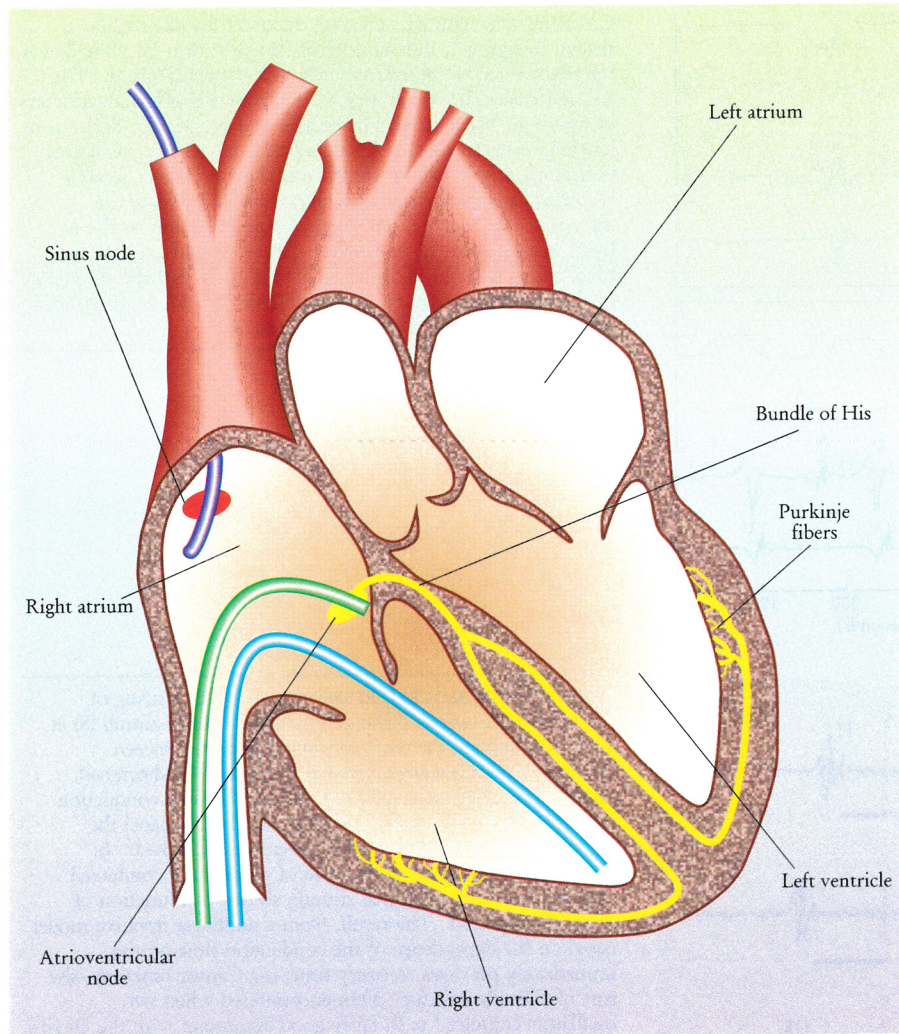
▷ **The heart's natural pacemakers can be thought of as limit-cycle oscillators.** The heart walls normally have a single specialized pacemaker region. In general, perturbations delivered to this pacemaker tissue will lead to a resetting of its rhythm. This resetting can be partially understood in terms of the topology of nonlinear oscillators, without recourse to details of the heart's physiological mechanisms. The oscillation is rapidly reestablished by a single stimulus. Therefore the effects of multiple stimuli delivered to the heart can be predicted in terms of the resetting of pacemakers by a single stimulus.³ (See the article by Arthur Winfree in *PHYSICS TODAY*, March 1975, page 34.)

Though these basic properties are straightforward, their playing out in concrete experimental and clinical settings leads to unexpected subtleties. To illustrate, I will briefly survey theoretical analyses of two different cardiac problems: atrioventricular heart block and re-entrant tachycardia.

Atrioventricular heart block

In the normal heart rhythm, there is a synchronization between the activity in the atria and the ventricles. This synchronization is accomplished by a conductive pathway

LEON GLASS is a professor of physiology at McGill University, in Montreal.



HUMAN HEART'S electrical system, with three catheters (shown in colors) inserted for clinical investigation of an abnormally fast rhythm called ventricular tachycardia. The catheter termination points are: near the sinus node in the high right atrium (purple catheter), in the right atrium near the bundle of His (green), and in the right ventricular apex (blue). (Adapted from E. Horowitz, *Electrophysiology Study*, Health Trend Publ., Menlo Park, Calif., 1996.)
FIGURE 1

that propagates the electrical activation from its origin in the sinus node to the ventricles by way of the atrioventricular node. But abnormalities in the region of the atrioventricular node can upset the synchronization between the atria and the ventricles. In one type of abnormality, called atrioventricular heart block, there are regular repetitive sequences in which there are more atrial contractions than ventricular contractions. In a so-called 2:1 atrioventricular block, for example, there is a repeating pattern of two atrial contractions for each ventricular contraction. Physicians readily diagnose atrioventricular heart block by means of electrocardiograms, and serious cases are treated by implanting a prosthetic pacemaker that drives the ventricles at a sufficiently rapid rate.

An early theoretical model of atrioventricular heart block was put forward in 1924 by the German physician Woldemar Mobitz.⁴ He showed that if the conduction time through the atrioventricular node depends only on the recovery time since the previous excitation, then sufficiently rapid activation of the atria should induce the rhythms of atrioventricular heart block. The block would appear, he argued, when the stimuli became so premature that they began to infringe upon the refractory period.

A direct test of Mobitz's theory was not carried out until 1987, when Michael Rosengarten, a clinical colleague of mine at McGill University, carried out specialized stimulation protocols during clinical electrophysiological test-

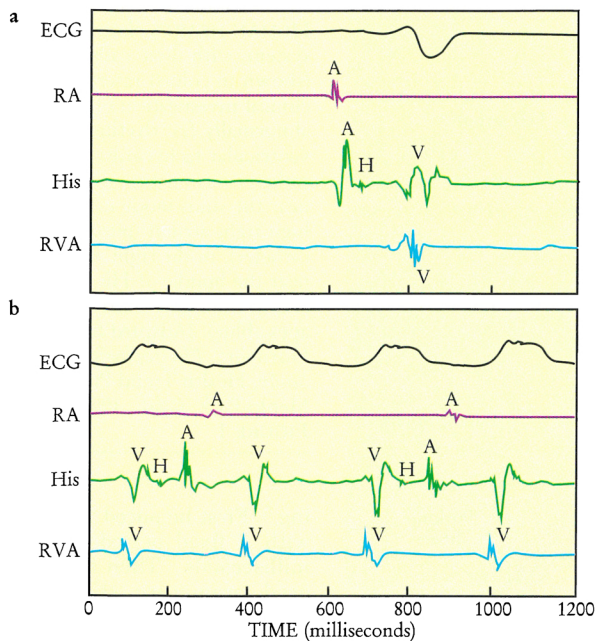
ing.⁵ First he paced the atria with a fixed period of 1000 milliseconds. Then he delivered premature stimuli at various intervals following every eighth regular stimulus. Figure 3a shows the results from a human subject. As the recovery time between an activation of the His bundle (labeled H) and the application of the next stimulus (labeled S) is made successively shorter, the following conduction time (to the next activation) becomes progressively longer. Finally, when the recovery time becomes too short, the conduction is blocked.

These results let us construct a nonlinear iterative model based solely on clinical

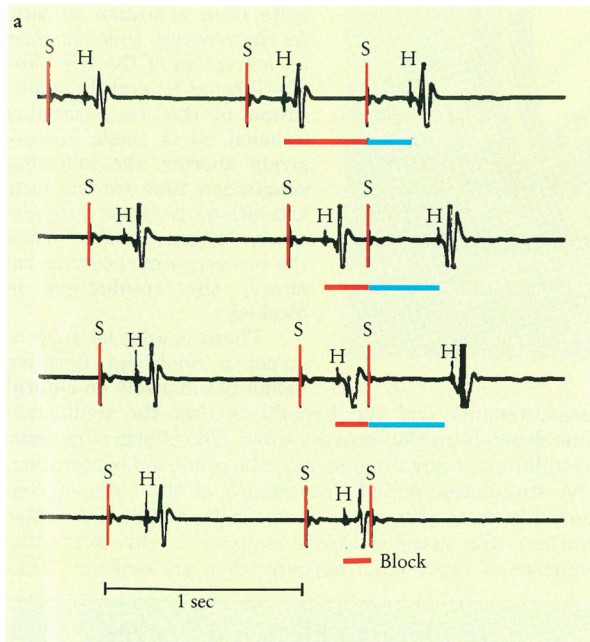
measurements and the hypothesis that the conduction time depends on the recovery time. The effects of periodic stimulation at any frequency can be predicted by iteration. The stimulation-period dependence of the ratio of conducted beats to stimuli, as shown in figure 3b, is a Cantor function—the so-called Devil's staircase.⁶ This interesting sequence of ratios often appears when an oscillator “locks

The Heart's Electrical System

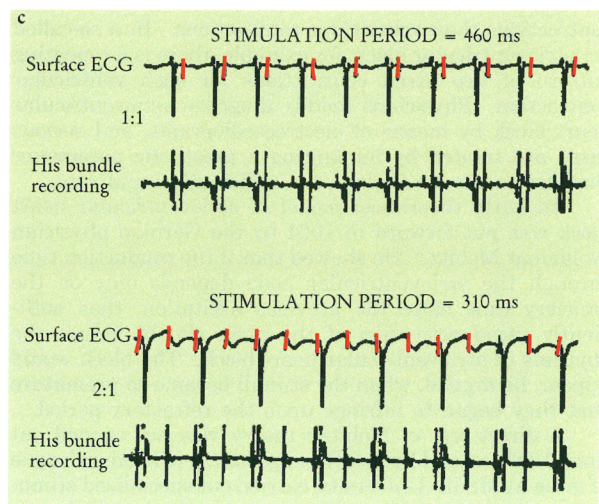
The mammalian heart is separated into four chambers: the right and left atria and the right and left ventricles. (see figure 1.) The atria collect blood returning from the body, and pass it down to the ventricles, which pump it back out into the arterial system. The normal cardiac rhythm is generated in a specialized region in the right atrium called the sinus node, an autonomous natural pacemaker, whose frequency can be modulated by environmental needs. For humans at rest, the normal heart beats between 60 and 100 times per minute. Faster rhythms are called tachycardias. In the normal heart, the atria are electrically insulated from the ventricles except in the region of the atrioventricular node. The excitation originating in the sinus node travels through the atria, through the atrioventricular node and then into the ventricles through a specialized conduction system consisting of the bundle of His and the Purkinje fibers.



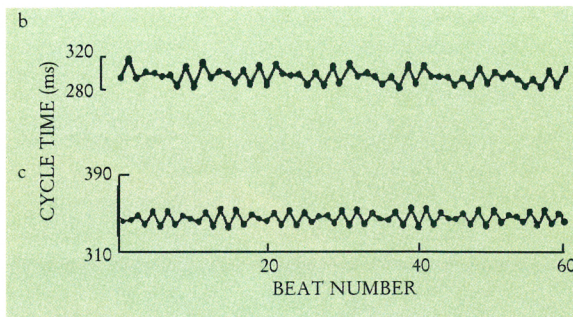
CARDIAC ELECTRICAL ACTIVITY recorded by the catheters shown in figure 1, during normal sinus rhythm (a). The black reference trace is a standard surface electrocardiogram. The colored traces shows activity recorded by the internal catheters of figure 1. With atrial, His-bundle and ventricular deflections labeled, respectively, by A, H and V, one sees the passage of excitation activity from the atria to the ventricles. Traces recorded during ventricular tachycardia (b) indicate the retrograde travel of the pathological rapid rhythm to the atria from its origin in the ventricles. Every second excitation is blocked, so that the atria are excited at only half the frequency of the ventricles. (Courtesy of T. Hadjis and M. E. Josephson, Beth Israel Hospital, Boston.) **FIGURE 2**



STIMULUS AND BLOCKED RESPONSE. a: After a string of His-bundle activations (H) paced by regular atrial stimuli (S) at 1-second intervals, the recovery time (red bars) between activation and subsequent stimulus was gradually shortened, causing a progressive lengthening of the following conduction time (blue bars) to the next response. In the last panel the recovery time is so short that the response is blocked.⁵ b: Theoretical calculation of the ratio of successfully conducted heart beats to imposed atrial stimuli, shown as a function of stimulation period. The result, from a nonlinear iterative model based on the dependence of the conduction time on the immediately previous recovery time, is a Cantor function—the sort of “Devil’s staircase” often encountered when two oscillators compete.⁶ c: In fairly good agreement with the Devil’s staircase prediction, atrial stimulation with a period of 460 ms (top pair of traces) produces one His-bundle response every atrial stimulus pulse (marked in red). At the faster 310-ms stimulation rate, by contrast, the bottom pair of traces shows a His-bundle response only for every second stimulus pulse. The failed excitations have been blocked in the atrioventricular node. (Adapted from ref. 5.) **FIGURE 3**



a



REURRENT ARRHYTHMIA IN A RING of heart muscle. **a:** A ring of tissue cut from a dog's right ventricle in 1913 by George Mines.⁷ He demonstrated that the ring could support periodic circulating excitation and suggested that such a mechanism might underlie some tachycardias in people. **b:** Experimental measurement, in 1988, of the timing of impulses traveling around a ring of canine heart tissue shows fluctuations in cycle time from one beat to the next. (Adapted from ref. 9.) **c:** Theoretical computation of cycle time fluctuation, which is associated with degenerate Hopf bifurcation. (Adapted from Ito and Glass, ref. 11.) **FIGURE 4**

on" to a periodic driver with a competing period. (See the article by Per Bak in *PHYSICS TODAY*, December 1986, page 38.)

For any stimulation period, there is a predicted percentage of conducted beats. Any rational ratio is permitted, but the relevant issue is the parameter range for a particular rational ratio. The range of stimulation periods for most ratios is small. The most common patterns of atrioventricular heart block, such as 4:3, 3:2 and 2:1, have the greatest ranges in parameter space. In the situation under discussion, stimulation of the atria with a period of 460 milliseconds yields a 1:1 rhythm; a stimulation period of 310 ms yields 2:1; and various intermediate periods generate other rhythms. (See figure 3c.) The observed boundaries for different atrioventricular heart block rhythms correspond to the predictions within about 10%.

Reentrant tachycardia

From the perspective of a cardiologist, these theoretical results are largely of academic rather than clinical interest. Atrioventricular heart block is easily diagnosed without mathematics, it is often benign and it can readily be treated. By contrast, reentrant tachycardias, in which an excitation travels a circuitous path, are often dangerous or even fatal. Ventricular tachycardias following a heart attack are believed to occur generally as a consequence of reentrant arrhythmias.

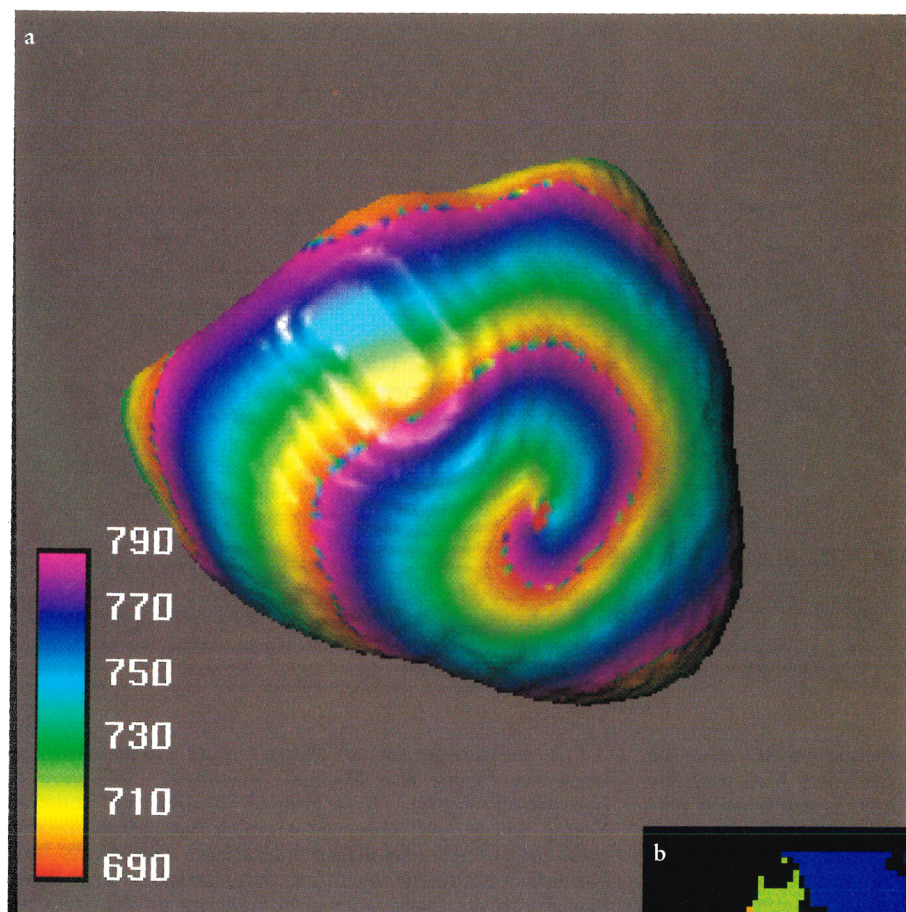
The beginning of the theory of reentrant tachycardias also goes back to the turn of the century. In 1913 the Canadian physiologist George Mines generated a reentrant excitation in a ring of cardiac muscle derived from a dog's heart.⁷ (See figure 4a.) Rapid stimulation of one point on the ring led to the development of a circulating pulse, and cutting the ring stopped the activity. The first theoretical analysis of the circulation of an excitation on a one-dimensional ring was carried out in 1946, by the mathematician Norbert Wiener and the physiologist Arturo Rosenblueth.⁸ If v is the propagation velocity and L is the ring's circumference, there should be a stable excitation wave of period L/v if that period exceeds the refractory time.

A reexamination of Mines's ring experiment by Lawrence Frame and Michael Simson in 1988 showed unexpected results. In a ring of canine heart muscle, Frame and Simson observed complex fluctuations in the cycle times during reentrant excitation.⁹ (See figure 4b.) Numerical studies of excitation propagation in rings have also shown the appearance of fluctuations as the ring size becomes smaller.¹⁰

These observations led my colleagues and me to extend the Wiener-Rosenblueth analysis by taking into account the recovery and restitution properties during reentrant excitation. If, in our models, there is a steep decline in the duration of the contraction phase with decreasing recovery time, we find that shrinking the ring size calls forth a kind of instability called a degenerate Hopf bifurcation. This instability in our numerical and analytical studies leads to the development of local alternating fluctuations of cycle time and contraction-phase duration that are quite similar to experimental observations with heart muscle rings.¹¹ (See figure 4c.)

Excitation waves traveling around a one-dimensional ring spring additional surprises. Cardiologists recognize that a single stimulus delivered during reentrant tachycardia can either reset or annihilate the tachycardia, depending on the phase and location of the stimulus.¹ Theoretical models of reentrant excitation in a one-dimensional ring provide a mathematical underpinning for these clinical observations. These models demonstrate that the outcome of a single, low amplitude stimulus depends on its amplitude, phase and spatial location. Moreover, one can predict the effects of periodic stimulation from the resetting induced by a single stimulus pulse.¹²

Wiener and Rosenblueth also proposed that waves on two-dimensional sheets of tissue might underlie serious arrhythmias. But they did not recognize that two-dimensional reentrant waves could be found in a homogeneous two-dimensional medium. The demonstration of spiral waves in spatially homogeneous chemical media in the 1960s and 1970s led to increased interest in theoretical and experimental studies of reentrant waves.¹³ Nowadays the work is focused on analysis of reentrant waves in the



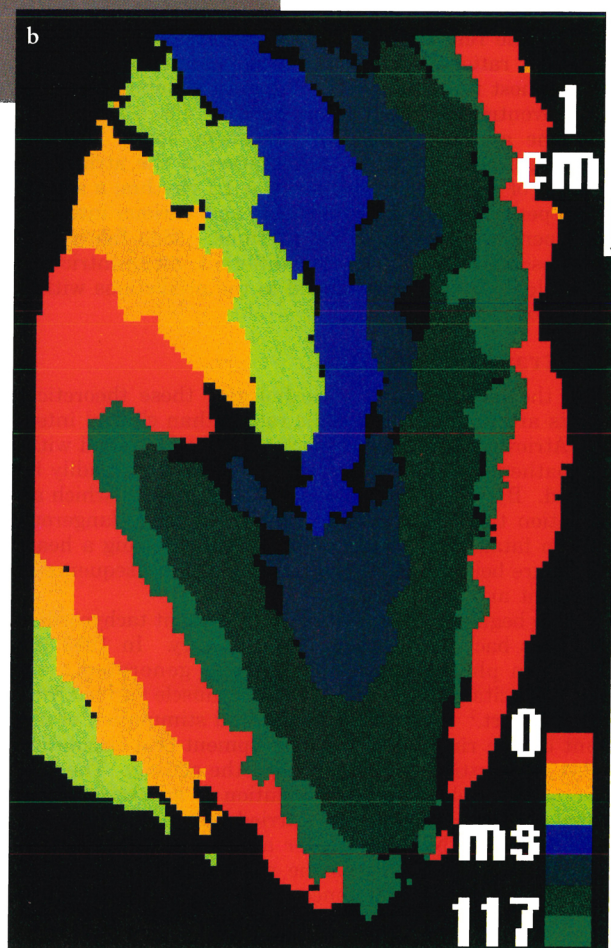
REENTRANT SPIRAL WAVE excitation. a: In this anatomically correct model of a dog heart the excitable medium was modeled by the FitzHugh-Nagumo equation, a partial differential equation that provides a simplified model. The color code indicates calculated activation times (in milliseconds) of various regions of the heart muscle. (Adapted from ref. 14.) **b:** Reentrant spiral-wave excitation observed in a rabbit heart with voltage-sensitive dyes demonstrates the theoretically predicted spiral waves of excitation on the heart's surface. The color code indicates measured activation times in milliseconds. (Adapted from ref. 15.) **FIGURE 5.**

heart itself. Theoretical computations of the propagation of excitable waves in anatomically correct models of the heart demonstrate the possibility of spiral waves,¹⁴ as shown in figure 5a.

Another outstanding recent success is the optical observation of spiral reentrant waves in intact rabbit hearts. Voltage-sensitive dyes injected into tissue can exhibit differential fluorescence that depends on the local membrane voltage. One can thus record wave propagation in heart tissue by measuring fluorescence during the course of induced ventricular tachycardias in laboratory animals.¹⁵ (See figure 5b.)

Despite such successes, it is often difficult to determine the anatomical and physiological basis of serious cardiac arrhythmias in an individual patient. If, for example, an arrhythmia is associated with a reentry path of which a portion is essentially one-dimensional, then catheter ablation might be the most effective therapy. But if the reentrant wave is essentially two- or three-dimensional, always activating broad fronts, the small lesion inflicted by an ablation catheter would be unlikely to succeed.

The recent lively debate in the pages of *Science*¹⁶ over the stability of single and multiple reentrant waves in cardiac tissue has highlighted the difficulties of understanding the geometry of ventricular tachycardia or its lethal cousin, ventricular fibrillation. These are areas in which a blending of theoretical, experimental and clinical insights is essential for progress. The ongoing research is focusing on the many challenges of measuring and analyzing reentrant wave propagation in the clinic, the laboratory and the nonlinear partial differential equations.



Prospects

If the work of physicists in this area is to have an impact in the practice of medicine, it is essential to translate our mathematical and physical insights into useful guidelines for clinical procedures. Here I discuss two different approaches:

Extensive clinical data have indicated that the transition from the normal sinus rhythm to reentrant tachycardia is often preceded by alternation in the timing of complexes recorded on the electrocardiogram. Although such alternations may be theoretically attributed to instabilities or blocked conduction, their origin in particular clinical settings is often obscure. Nevertheless, Richard Cohen (MIT) and colleagues have demonstrated that the appearance of such alternation in electrocardiograms during normal sinus rhythm places patients at high risk for reentrant tachycardia and sudden death.¹⁷ Cohen and his colleagues are developing specialized software and hardware to guide therapy and facilitate risk stratification for seriously ill patients.

An alternative strategy for the clinical application of nonlinear dynamics is based on the hypothesis that cardiac arrhythmias may be associated with complex dynamics in comparatively simple mathematical models. For example, laboratory experiments have demonstrated deterministic chaos in laboratory experiments with parts of animal hearts.¹⁸ Because it is likely that some cardiac arrhythmias can be modeled by deterministic equations for wave generation and propagation in the heart, understanding the dynamics may well yield fruitful new proposals for forestalling or controlling dangerous arrhythmias through the application imposed stimuli.

In the study of chaotic phenomena in recent years, attention has been given to the notion of controlling chaos. (See the article by Edward Ott and Mark Spano in *PHYSICS TODAY*, May 1995, page 34.) Experimental cardiac studies motivated by progress in this area have been initiated, but they are still at the very early stages.¹⁹ The widely used cardiological devices, such as pacemakers, defibrillators and antitachycardia devices, have been developed largely by engineers and cardiologists using empirical methods. Though these devices have proven themselves highly reliable, I expect that development of the theory will lead to new breakthroughs.

Many of the heart's rhythms can be classified and analyzed through methods of nonlinear dynamics. Direct electrical stimulation of the heart leads to predictable changes that can often be interpreted with simple theoretical models. The analysis and classification of complex arrhythmia parallels similar advances in our qualitative understanding and mathematical modeling of dynamics and bifurcations in inanimate physical systems.

Mathematics can predict what will happen in human hearts in a wide variety of settings. But the development of this area has been hampered by the physician's lack of formal training in mathematics and physics, and by the physical scientist's lack of appreciation of the beautiful and deep problems of clinical cardiology. In each patient, the playing out of the basic principles sketched out in this article, perhaps in concert with important phenomena we don't yet understand, leads to rhythms of unexpected complexity. This is an area in which interdisciplinary studies are absolutely essential. I encourage physicists to seek out their local cardiologists and get started.

I thank the Canadian Heart and Stroke Foundation and the John Simon Guggenheim Memorial Foundation for supporting my sabbatical leave at Beth Israel Hospital in Boston. I benefited from many interactions with staff, fellows and physicians there, but my greatest thanks go to Ary Goldberger and Mark Josephson, for their gracious sharing of resources, knowledge and time. Thanks to A. Panfilov for figure 5a, and to R. Gray for figure 5b. Thanks also to T. Hadjis and A. Winfree for helpful suggestions on the preparation of this article.

References

1. For a description of these procedures, see M. E. Josephson, *Clinical Cardiac Electrophysiology: Techniques and Interpretations*, 2nd ed., Lea and Febiger, Philadelphia (1993); and E. N. Prystowsky, G. J. Klein, *Cardiac Arrhythmias: An Integrated Approach for the Clinician*, McGraw-Hill, New York (1994).
2. J. Rinzel, in *Research Notes in Mathematics. Nonlinear Diffusion*, W. E. Fitzgibbon, H. R. Walker, eds., Pitman, London (1977), p. 186. A. T. Winfree, *When Time Breaks Down: The Three-Dimensional Dynamics of Electrochemical Waves and Cardiac Arrhythmias*, Princeton U. P., Princeton, N.J. (1987). C. F. Starmer et al., *Biophys. J.* **65**, 1775 (1993). J. Starobin, Y. I. Zilberter, C. F. Starmer, *Physica D* **70**, 321 (1994). A. Karma, *Chaos* **4**, 461 (1994).
3. A. T. Winfree, *The Geometry of Biological Time*, Springer-Verlag, New York (1980). L. Glass, M. C. Mackey, *From Clocks to Chaos: The Rhythms of Life*, Princeton U. P., Princeton, N.J. (1988).
4. W. Mobitz, *Z. f. d. ges. Exp. Med.* **41**, 189 (1924).
5. A. Shrier, H. Dubarsky, M. Rosengarten, M. R. Guevara, S. Nattel, L. Glass, *Circulation* **76**, 1196 (1987).
6. J. P. Keener, *J. Math. Biol.* **12**, 215 (1981). M. R. Guevara in *Theory of the Heart: Biomechanics, Biophysics, and Nonlinear Dynamics of Cardiac Function*, L. Glass, P. J. Hunter, A. McCulloch, eds., Springer-Verlag, New York (1991), p. 313.
7. G. R. Mines, *Trans. R. Soc. Can.* **3**, sect. 4, **8**, 43 (1914).
8. N. Wiener, A. Rosenblueth, *Archos. Inst. Cardiol. Méx.* **16**, 205 (1946).
9. L. H. Frame, M. B. Simson, *Circulation* **78**, 1277 (1988).
10. W. Quan, Y. Rudy, *Circ. Res.* **66**, 367 (1990). W. Quan, Y. Rudy, *PACE* **14**, 1700 (1991). A. Vinet, J. L. Leon, *IEEE Eng. Med. Biol. Soc. Int. Conf.* **13**, 508 (1991).
11. H. Ito, L. Glass, *Physica D* **56**, 84 (1992). M. Courtemanche, L. Glass, J. P. Keener, *Phys. Rev. Lett.* **70**, 2182 (1993). M. Courtemanche, J. P. Keener, L. Glass, *SIAM J. Appl. Math.* **56**, 119 (1996).
12. L. Glass, M. E. Josephson, *Phys. Rev. Lett.* **75**, 2059 (1995). T. Nomura, L. Glass, *Phys. Rev.* **53**, 6353 (1996).
13. V. I. Krinskii, *Systems Theory Research* (translation of *Prob. Kib.*) **20**, 46 (1968). A. T. Winfree, *Science* **175**, 634 (1972). For a recent review, see J. M. Davidenko, in *Cardiac Electrophysiology: From Cell to Bedside*, D. P. Zipes, J. Jalife, eds., 2nd ed., W. B. Saunders, Philadelphia (1995), p. 478. See also several articles in *Computational Biology of the Heart*, A. Panfilov, A. V. Holden, eds., Wiley, Chichester, UK (1995).
14. A. Panfilov, J. P. Keener, *Chaos, Solitons and Fractals* **5**, 681 (1995).
15. R. A. Gray, J. Jalife, A. Panfilov, W. T. Baxter, C. Cabo, J. M. Davidenko, A. M. Pertsov, *Circulation* **91**, 2454 (1995).
16. A. T. Winfree, *Science* **266**, 1003 (1994). R. Gray, J. Jalife, A. Panfilov, W. T. Baxter, C. Cabo, J. M. Davidenko, A. M. Pertsov, *Science* **270**, 1222 (1995). A. V. Panfilov, P. Hogue, *Science* **270**, 1223 (1995). A. T. Winfree, *Science* **270**, 1224 (1995).
17. D. S. Rosenbaum, L. E. Jackson, J. M. Smith, H. Garan, J. N. Ruskin, R. J. Cohen, *New Engl. J. Med.* **330**, 235 (1994).
18. M. R. Guevara, L. Glass, A. Shrier, *Science* **214**, 1350 (1981). D. Chialvo, R. F. Gilmour, J. Jalife, *Nature* **343**, 653 (1990).
19. A. Garfinkel, M. L. Spano, W. L. Ditto, J. N. Weiss, *Science* **257**, 1230 (1992). L. Glass, W. Zeng, *Int. J. Bif. Chaos* **4**, 1061 (1994). ■