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Research Article

Chaos and Chaos Control in Biology

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Introduction

Chaos, in its mathematical sense, refers to irregular behavior that appears to be random, but is not. The recognition that an irregular behavior is chaotic, rather than random, signifies that a set of precise rules, rather than chance, governs the irregular behavior of the system. Therefore, if the system is sufficiently well understood, the irregular behavior can be predicted, eliminated, or controlled. Chaos theory has been applied very successfully to a wide variety of phenomena exhibiting irregular behavior, ranging from astrophysics to quantum mechanics, chemistry, biology and medicine, social sciences, and even the stock market (1). In the biomedical field, chaos theory has been used successfully to explain observed phenomena such as the response of cardiac and neural tissue to pacing stimuli (2–8), fluctuations in leukocyte counts in patients with chronic myelogenous leukemia (4), variations in renal blood flow in hypertensive versus normal rats (9), and the epidemiology of measles in an urban environment (10). A particularly exciting new area has been the development of a method for controlling chaotic behavior that does not depend on a detailed understanding of the mechanisms producing chaos in the system (11). In this Perspective, we illustrate how this new technique has been applied to a biological problem by describing our results applying chaos control to a chaotic form of ventricular tachycardia induced by the drug ouabain in isolated rabbit ventricular muscle (12). We begin with a general description of chaos, without assuming that the reader has any mathematical background in chaos theory.

Some general background in chaos theory

As noted above, chaotic behavior, although irregular, is actually generated by an underlying deterministic, i.e., nonprobabilistic, process. As an illustration, consider the data set in Fig. 1, which appears to be completely irregular and has no repeating pattern. Statistical autocorrelation tests applied to these data are negative. One possibility is that the fluctuations are random; but it is also possible that an underlying deterministic process is governing the irregular fluctuations. By deterministic, we mean that the value of the system at the previous point (x_{n-1}) has determined the value of the current point (x_n) according to some set of rules (i.e., mathematical equations). An obvious way, then, to look for a deterministic relationship between one point and the next is simply to plot x_n vs. x_{n-1} for all the data points, i.e., point 2 against point 1, point 3 against point 2, etc. When the data in Fig. 1 are plotted in this manner, known as a Poincaré plot, a very simple relationship between x_n and x_{n-1} becomes apparent (Fig. 2). In this example, the relationship is simply the curve described by the equation for a parabola:

$$x_n = \alpha x_{n-1}(1-x_{n-1}).$$

As the successive data points appear in Fig. 1, they do not fill out the parabola in a particular sequence, but instead bounce back and forth between different regions, producing the complex irregular behavior. But despite the irregularity in the values of successive points, the relationship between one point and the next is always very simple, though nonlinear.

The ability of this simple nonlinear equation to produce such complex behavior, however, is critically dependent on the value of the parameter α in eq. 1. This is illustrated in Fig. 3. If α has a low value, such as 2, no matter what initial value x_0 you begin with, the system comes to an equilibrium after several iterations of eq. 1 and remains there (Fig. 3 *A*). If α has a somewhat higher value of 3.2, then regardless of the initial value (x_0), successive values eventually oscillate between two values in an ABABAB . . . pattern (Fig. 3 *B*). A mathematician calls this period-2 behavior; a cardiologist calls it bigeminy. If α has a higher value still, 3.5, then more complex but still periodic behavior occurs, such as the ABCDABCD . . . period-4 (or quadrigeminal) pattern shown in Fig. 3 *C*. At a critical value of α, slightly greater than 3.8, however, the system becomes completely irregular and aperiodic, and has no repeating patterns whatsoever (Fig. 3 *D*). The value of α, therefore, determines whether the system behaves in a stable periodic fashion, or in an irregular chaotic fashion.

The chaotic behavior produced by eq. 1 can be attributed to a defining feature of all chaotic systems, their extreme sensitivity to initial conditions. A famous example is the "butterfly effect," described by meteorologist Edward Lorenz (13). Using a relatively simple set of nonlinear differential equations to simulate atmospheric weather changes, he assigned a set of initial conditions and computed the subsequent behavior of the system. The system evolved over time in an irregular chaotic pattern. If he used a slightly different value for the initial conditions of the same equations, by changing one part in a million, the system initially behaved in a similar manner; however, after time, it started to diverge and evolved a completely different pattern. Fig. 4 illustrates this phenomenon using the data in Fig. 1, obtained from eq. 1 with $\alpha = 4.0$. When the initial value

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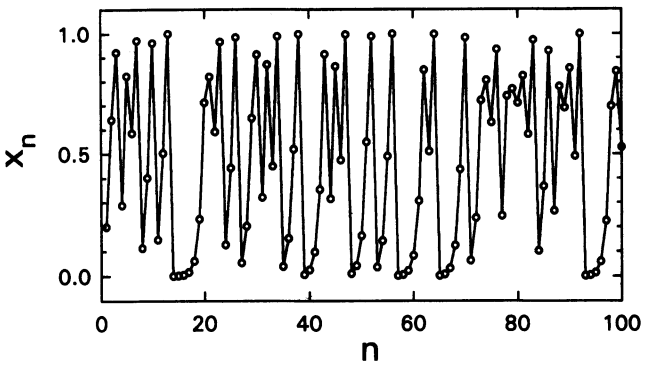

Figure 1. A sequential data set (x_n) showing a very irregular (nonperiodic) pattern.

of x_0 was changed from 0.2000000 (solid line) to 0.2000001 (dashed line), the curves remained virtually superimposed for the first 20 iterations of eq. 1, but then rapidly diverged and evolved completely different behavior. This extreme sensitivity to initial conditions, in which small differences diverge exponentially, is a feature that characterizes all chaotic systems. (A system in which initial differences diverge exponentially rather than linearly is a nonlinear system, and for this reason, chaos theory is also called nonlinear dynamics.) The "butterfly effect" is so-named because one can imagine that even a butterfly flapping its wings could create enough of a disturbance in the initial conditions of a chaotic weather system to cause a completely different weather pattern to evolve over time, perhaps generating a hurricane that would not have occurred otherwise. A key corollary to this property is that the accuracy to which the initial conditions are defined determines how accurately the future behavior of a chaotic system can be predicted, even when the exact equations governing the system are known. Since computers can perform calculations only to a finite number of decimal places, the ability to predict future behavior of a chaotic system is always limited from a practical standpoint. This is an important reason why the accuracy of weather forecasts falls off dramatically as the forecast period increases, and it applies equally well to any physical or biological system that exhibits chaotic behavior.

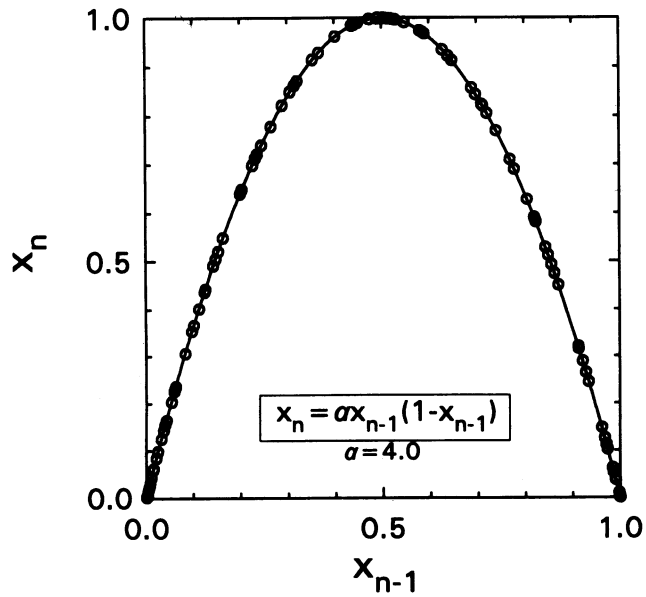

Figure 2. A Poincaré plot of the data from Fig. 1, in which the current value of x (x_n) is plotted against the previous value (x_{n-1}), revealing a simple underlying relationship.

The appreciation that a simple equation, such as eq. 1, can produce extremely irregular behavior has profound implications: it suggests that despite the very complex behavior that is typical of most physical and biological phenomena, they may yet be governed by a simple set of rules. Whereas previously many of these phenomena seemed too hopelessly complex to solve by traditional analytic methods, chaos theory offers a fresh approach. First, identify the underlying equations describing a system; next, locate a critical parameter equivalent to α in eq. 1; then, modulate the value of the critical parameter by some intervention to eliminate chaos and restore periodic behavior to the system. Of course, this approach assumes that the system is simple enough to develop an accurate mathematical model, and that the model contains a critical parameter that can be manipulated in a practical fashion. In reality, a physical or biological system may be too complex to develop a sufficiently accurate model, or the critical parameters determining its behavior may not be accessible or easily manipulated. Recently, however, a new technique has been developed that focuses on controlling, rather than eliminating, chaos (11). This method does not require a detailed knowledge of the system, but only the ability to observe the chaotic behavior in real time and to apply brief small perturbations to the system. The method has now been applied successfully to several physical and chemical systems (14–17). It also has been speculated that chaos control may be a physiologic mechanism of information processing by the brain (18). We adapted chaos control theory for its first biological application, the chaotic cardiac arrhythmia described below.

Applying chaos theory to a cardiac arrhythmia

When two or more oscillators are coupled together so that their feedback influences each other, chaotic behavior often occurs. In heart, intracellular Ca is closely regulated by a number of coupled processes that cyclically augment and decrease intracellular Ca, analogous to a system of coupled oscillators. Furthermore, cyclical fluctuations in intracellular Ca are a cause of afterdepolarizations and triggered activity in heart, a well-known arrhythmogenic mechanism. We therefore reasoned that intracellular Ca overload in heart might produce irregular beating patterns due to chaos. To test this idea, we exposed an intact cardiac muscle preparation, consisting of the interventricular septum of a rabbit heart, isolated and arterially perfused through the left coronary artery (Fig. 5), to a toxic concentration of the cardiac glycoside ouabain (± epinephrine) to induce intracellular Ca overload. A monophasic action potential was recorded continuously, digitized by a computer, and analyzed on-line to calculate the interbeat intervals (I_n) between successive beats. As the ouabain took effect, the heart first started beating on its own at a fast but regular rate (Fig. 6 *A*). When we plotted the current interbeat interval (I_n) against the previous interbeat interval (I_{n-1}), we obtained a single point on the line of identity (where $I_n = I_{n-1}$), since all the intervals were the same (Fig. 6 *B*). Subsequently, the heart began beating in a bigeminal or period-2 pattern, with a long interval followed by a short interval in a repeating ABABAB . . . pattern. The Poincaré plot now showed two groups of points on either side of the line of identity, corresponding to the long interval followed by a short interval, and the short interval followed by a long interval, respectively. Typically, the arrhyth-

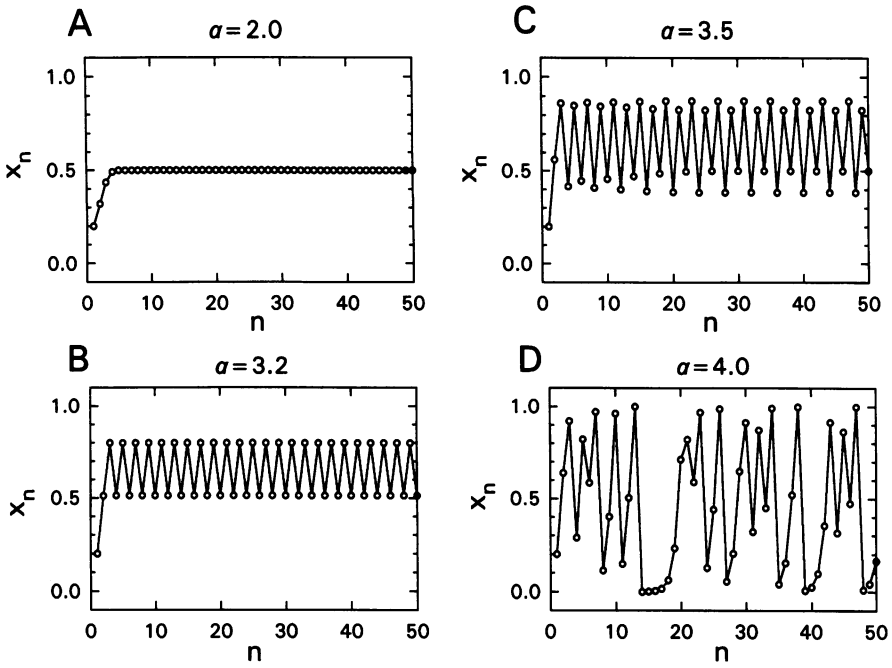

Figure 3. The behavior of eq. 1 with different values of α. (*A*) α = 2.0; (*B*) 3.2; (*C*) 3.5; and (*D*) 4.0 (the same as in Fig. 1). See text for details.

mia spontaneously developed higher order periods, such as quadrigeminy (period-4), the ABCDABCD . . . pattern shown in Fig. 6 *E*, with the corresponding Poincaré plot illustrated in Fig. 6 *F*. In ~ 85% of hearts, the arrhythmia eventually became completely irregular, with no repeating pattern whatsoever (Fig. 6 *G*). The Poincaré plot no longer showed a discrete set of points, but instead a cloud of points (Fig. 6 *H*). However, the cloud of points was not a diffuse cloud, as would expected if the interbeat intervals during the irregular arrhythmia were occurring in a random pattern. Instead, there were areas that were much more highly populated than other areas. This is the classic hallmark of chaos. The rough structure outlined by the densely populated regions is known as a strange attractor, since the points are preferentially attracted to these regions.

The observation that the ouabain-induced ventricular tachycardia was chaotic is generally consistent with the idea that intracellular Ca level is a critical parameter, analogous to the parameter α in eq. 1, that can push the heart from periodic into chaotic beating. However, our understanding of the detailed mechanisms by which chaos developed in this setting is limited by the lack of an exact mathematical model that can account for all of the complexities of intracellular Ca regulation in the biological preparation. Aside from avoiding ouabain toxicity, we have no real insight into how to prevent or eliminate the chaotic arrhythmia by manipulating a critical parameter of

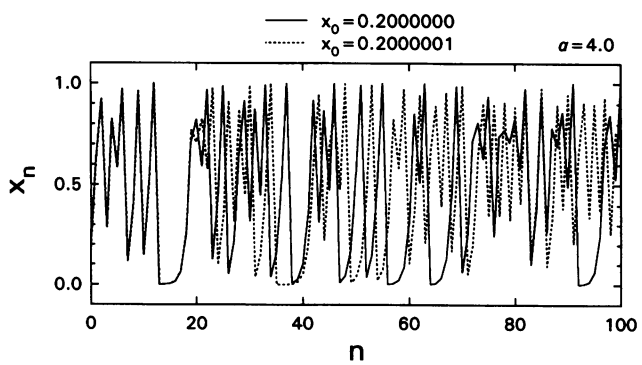

Figure 4. Illustration of extreme sensitivity to initial conditions. Eq. 1, with α = 4.0, was iterated 100 times, starting with an initial value (x_0) of 0.2000000 (*solid line*) or 0.2000001 (*dashed line*). The curves begin to diverge markedly after 20 iterations.

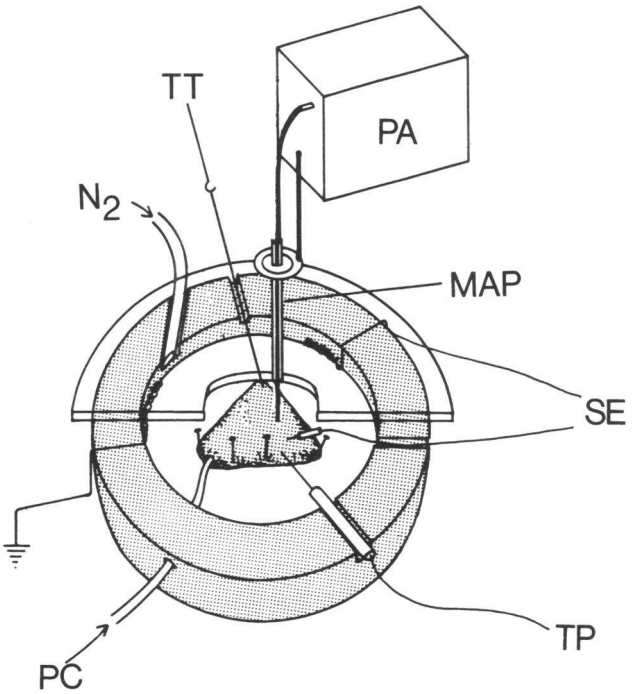

Figure 5. Schematic diagram of the isolated arterially perfused rabbit interventricular septal preparation. The triangular-shaped septum is mounted in a chamber and arterially perfused through a perfusion cannula (*PC*) at 37°C in a nitrogen-filled (N_2) atmosphere. Temperature is continuously monitored with a probe (*TP*), and the preparation is stimulated via stimulating electrodes (*SE*) connected to an electronic pacemaker. A monophasic action potential catheter (*MAP*) connected to a preamplifier is used to monitor electrical activity, and contraction is recorded with a tension transducer (*TT*) tied to the apex.

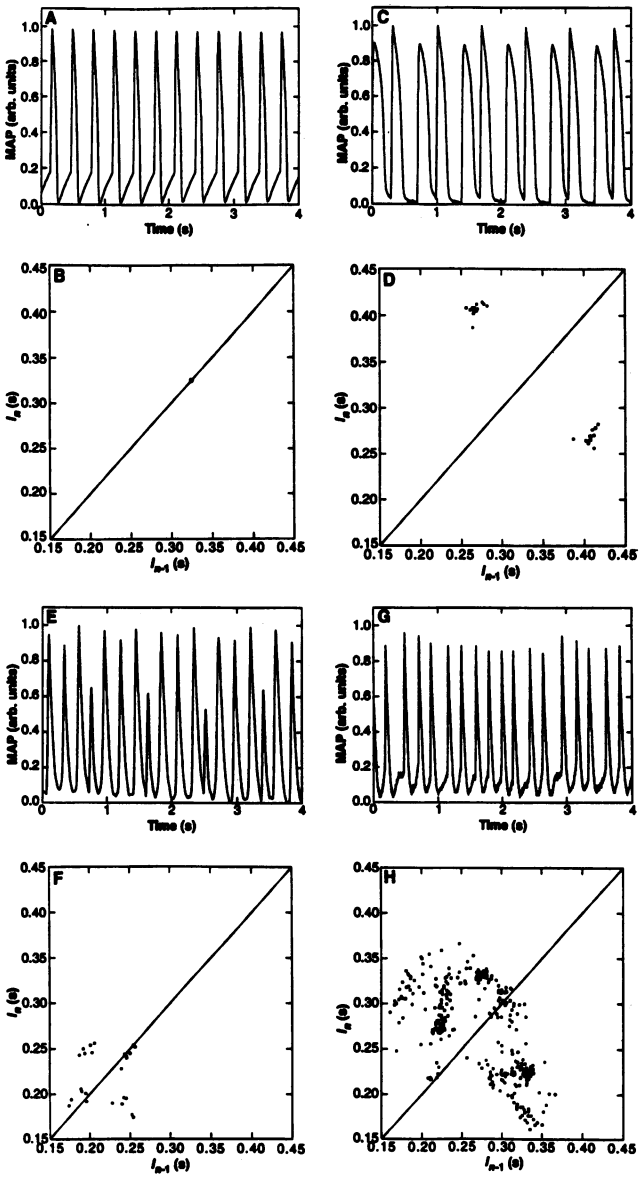

Figure 6. Recordings of monophasic action potentials (MAPs) (*A, C, E,* and *G*) and the respective Poincaré plots of interbeat intervals (*B, D, F,* and *H*) at various stages of ventricular tachycardia induced by ouabain (± epinephrine) in typical rabbit septal preparations. See text for details. Note that in the Poincaré map of the final stage (*H*), the points form an extended structure that is not space filling (i.e., not random), consistent with chaos. (Reprinted from reference 12, with permission.)

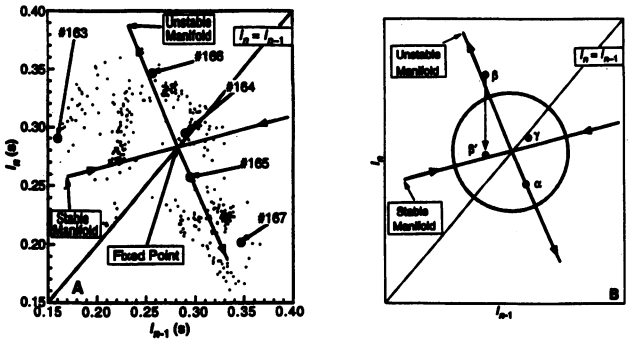

Figure 7. (*A*) The position of the unstable equilibrium point, stable, and unstable (linearized) manifolds for the Poincaré plot in Fig. 6 *H*. The numbers refer to successive pairs of interbeat intervals, illustrating the characteristic approach and departure from the unstable equilibrium point, as described in the text. The heavy arrows are linear approximations of the directions of the stable and unstable manifolds in the vicinity of the unstable equilibrium point. (*B*) Schematic of our method of chaos control, using the features of the unstable equilibrium point (intersection of diagonal lines) and its associated stable and unstable manifolds. See text for details. (Reprinted from reference 12, with permission.)

the system. This is where the concept of controlling, as opposed to eliminating, chaos is useful.

To understand how to control chaos, it is important to examine the Poincaré plot more closely (Fig. 7 *A*). Note the region where the attractor crosses the line of identity (near coordinates 0.30, 0.30). A point on this line means that the current interbeat interval is the same as the previous interbeat interval, which defines an equilibrium point. The equilibrium point is unstable, because when a point falls very close to this equilibrium point, it quickly wanders away. However, if one closely observes the sequence by which points approach and depart from this unstable equilibrium point, one finds that the approach consistently occurs along a characteristic direction (called the stable manifold, illustrated approximately by points 163 and 164). Similarly, departure from the unstable equilibrium point also consistently occurs along a different direction (called the unstable manifold, illustrated by points 164, 165, 166, and 167, which alternately flip across the line of identity, each time landing further away from the unstable equilibrium point). This structure of an unstable equilibrium point with associated stable and unstable manifolds is known mathematically as a saddle point, and the analogy is intuitive. Imagine balancing a ball on a saddle. If placed exactly at the center of the saddle, the ball will remain there (in unstable equilibrium) until any small perturbation, such as a whiff of air, displaces the ball to one side or the other. The ball will then accelerate away from the center, but always in the transverse direction (towards one of the stirrups) and never towards the front or the back along the centerline of the saddle. The transverse direction is therefore equivalent to an unstable manifold. Conversely, if the ball is placed on the centerline towards the front or back of the saddle, it will roll towards the center of the saddle. The centerline of the saddle is therefore equivalent to a stable manifold. Mathematically, all chaotic systems exhibit saddle points or, more generally, periodic saddle cycles.

To control chaos, one takes advantage of this saddle point structure. Continuing with the ball and saddle analogy, if one wishes to keep the ball in the center of the saddle (i.e., near the unstable equilibrium point), one could either move the saddle to compensate every time the ball shifted off-center, or give the ball a nudge to move it back towards the centerline of the saddle. With either perturbation, it is not necessary to keep the ball near the center of saddle, but only near the centerline of the saddle, since the ball will always roll closer to the center of the saddle from any position on the centerline (i.e., the stable manifold).

Fig. 7 *B* illustrates schematically how we used this method to control the chaotic ouabain-induced arrhythmia in the rabbit heart. The computer program computed on-line each interbeat interval from the monophasic action potential recordings. By keeping track of the sequence of points as they were plotted on a Poincaré plot, the program estimated the location of an unstable equilibrium point. By watching how successive points

moved towards and away from this point, the program then estimated positions of the stable and unstable manifolds by a linear regression method. After this learning phase was completed, the computer waited for a pair of interbeat intervals to fall near the unstable equilibrium point, such as the point α in Fig. 7 *B*. The point α represents a long interbeat interval (the coordinate on the I_{n-1} axis) followed by a shorter interbeat interval (the coordinate on the I_n axis). By construction of the Poincaré plot, the short interbeat interval becomes the I_{n-1} axis coordinate for the next point (β), so β must fall somewhere on the line defined by the vertical arrow in Fig. 7 *B*. Since α was located very close to the unstable manifold, β will tend to be propelled further away from the unstable equilibrium point near the intersection of the vertical arrow and the unstable manifold. That is, the saddle property of the unstable equilibrium point predicts that the point β will consist of a short interbeat interval followed by a long interbeat interval. We designed the computer program to introduce an electrically stimulated premature beat (delivered by an electronic pacemaker) to shorten the predicted long interbeat interval, so that the position of the next point after α was deflected to the position β' instead of β. The point β' was chosen since it falls near the stable manifold instead of the unstable manifold. Thus, the natural dynamics of the system will cause the next point γ to fall even closer to the unstable equilibrium point. As long as the subsequent points remain near the stable manifold, they continue to approach closer to the unstable equilibrium point. Every time a point falls near the unstable manifold, another paced beat is introduced to reposition the subsequent point back close to the stable manifold. In principle, all of the points on the Poincaré plot could be confined within a small region of the unstable equilibrium point using this pacing algorithm. That is, all of the interbeat intervals would be nearly identical and the heart rhythm would be regularized.

The results of applying this pacing algorithm based on chaos control theory to the rabbit ventricular preparation are shown in Fig. 8. As illustrated by the three examples, when the chaos control pacing algorithm was activated during the aperiodic phase of the ouabain-induced ventricular tachycardia, the irregular chaotic beating pattern was controlled and replaced by periodic beating, typically with a period-3 or -4 pattern. When chaos control pacing was terminated, the arrhythmia reverted to its irregular pattern. During chaos control, only every third or fourth beat was an electrically paced beat, indicating that we were not simply overdrive-pacing the heart. Furthermore, periodic or random pacing of the preparation at a similar average rate, as during chaos control pacing, did not eliminate the irregularity of the arrhythmia, and generally seemed to make the irregularity more marked (Fig. 8 *C*). Overall, we were successful in converting aperiodic beating to periodic beating in 8 of 11 preparations using this chaos control pacing algorithm.

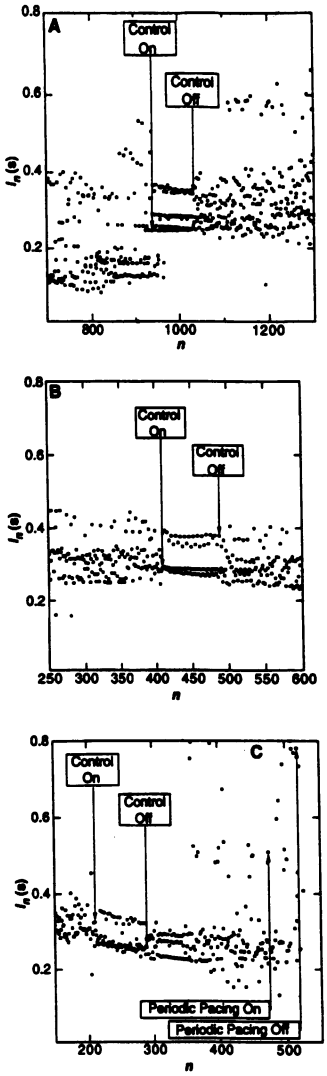

Figure 8. Chaos control of the ouabain-induced ventricular tachycardia in the isolated rabbit heart. Interbeat interval I_n is plotted vs. the beat number n during the chaotic phase of the arrhythmia. The chaos control pacing algorithm was applied during the period indicated, and successfully converted the aperiodic arrhythmia to a period-3 pattern (ABCABC. . .) in *A*, to a period-4 pattern (ABCDABCD. . .) in *B*, and to a period-2 pattern (ABAB. . .) in *C*. *A–C* are from different hearts. In *C*, periodic pacing delivered at the same average rate failed to stabilize the arrhythmia. See text for details. (Reprinted from reference 12, with permission.)

Implications for cardiac arrhythmias.

These observations support previous studies demonstrating that the heart is capable of chaotic behavior (2–6). More generally, they demonstrate that chaos control techniques are adaptable to the biological setting. It is still controversial whether chaos plays a role in clinically important cardiac arrhythmias. It is likely that the irregular conduction patterns sometimes seen during second degree atrioventricular block and modulated parasystole are examples of chaos (6). Of the tachyarrhythmias, the most likely candidates for chaos are the irregular arrhythmias such as multifocal atrial tachycardia, polymorphic ventricular tachycardia, Torsade de pointes, and atrial and ventricular fibrillation. From a clinical standpoint, atrial and ventricular fibrillation remain the most common and vexing of these arrhythmias. Evidence both for and against the presence of low-dimensional chaos during fibrillation has been reported (19–24). We are currently investigating whether human atrial fibrillation shows hallmarks of chaos in patients undergoing cardiac electrophysiology studies. Our analysis is still preliminary, but results such as those illustrated in Fig. 9 are encouraging. Not only does the Poincaré plot of human atrial fibrillation show evidence of nonrandom structure, but features such as saddle points (unstable equilibrium points with associated unstable and stable manifolds) are detectable. If further studies indicate that fibrillation is chaos, and that structures such as saddle points needed to implement chaos control are consistently present, then this raises an interesting issue. Can a pacing algorithm based on chaos control theory, perhaps implemented by a "smart pacemaker," be developed as a new therapeutic strategy? Although intriguing, whether this possibility can be realized will depend on surmounting a number of critical obstacles, such as dealing with the spatiotemporal complexity of fibrillation and determining how to terminate the arrhythmia once chaos is controlled.

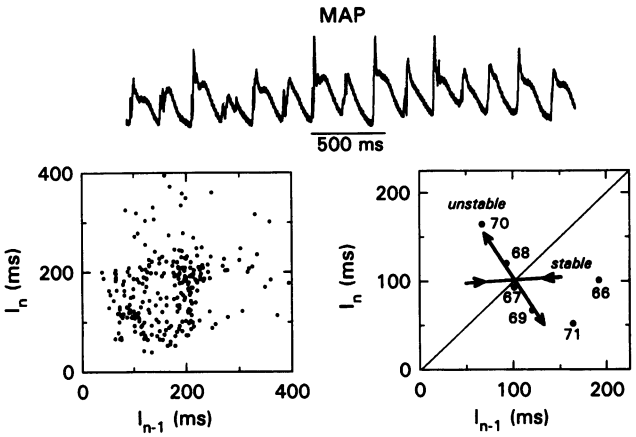

Figure 9. A Poincaré plot of interbeat intervals (I) recorded during human atrial fibrillation in a patient undergoing a clinical cardiac electrophysiology study. An intracardiac catheter was used to record monophasic action potentials (*MAP*) from the high right atrium during spontaneous atrial fibrillation (*top tracing*). (*Left*) The Poincaré plot of interbeat intervals (I_{n-1} vs. I_n) illustrates an extended structure that is not space filling (i.e., not random), consistent with chaos. (*Right*) The presence of a saddle point (unstable equilibrium point with associated stable and unstable manifolds) similar to that in Fig. 7. The numbers refer to successive pairs of interbeat intervals (*67–71*), demonstrating the approach towards and departure from the unstable equilibrium point (at the intersection of the arrows) along characteristic and consistently observed directions. The heavy arrows are the linear approximations of the directions of the stable and unstable manifolds in the vicinity of the unstable equilibrium point.

Implications for biology.

Biomedical research has traditionally focused on analyzing the behavior of an organ system by breaking it down into individual components and studying these in increasing detail. The remarkable success of this reductionist approach, however, has limitations when one tries to reassemble the whole from the individual components to predict behavior in a system as complex as a biological organ. This is especially true when the interactions between the components are nonlinear and the potential for chaos exists. Whether chaotic behavior defines the difference between health and disease states is still a matter of debate in most instances. However, the development of practical chaos control strategies strengthens the significance of detecting chaos in biological systems, since it offers a novel strategy for therapeutic intervention. Any disease state in which a key physiological parameter, e.g., blood pressure, hormone levels, immunological responses, etc., is shown to be chaotic is potentially amenable to control by introducing small, critically timed perturbations based on this technique.

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