Nonlinear Dynamics, Fractals, and Chaos Theory:

Implications for Neuroautonomic Heart Rate Control in Health and Disease
by Ary L. Goldberger

I. Basic Concepts

Clinicians and basic investigators are increasingly aware of the remarkable upsurge of interest in nonlinear dynamics, the branch of the sciences widely referred to as "chaos theory." Those attempting to evaluate the biomedical relevance of this field confront a daunting array of terms and concepts, such as *nonlinearity, fractals, periodic oscillations, bifurcations* and *complexity*, as well as *chaos* (1-4). Therefore, the present discussion provides an introduction to some key aspects of nonlinear dynamics, with a particular emphasis on heart rate control. A major challenge is in making these concepts accessible, not only to basic and clinical investigators, but to medical and graduate students at a formative stage of their training.

A. Introduction: The Concept of a Time Series

To appreciate the general clinical relevance of dynamics to the heartbeat, consider the following common problem. What is the best way to compare a sequence of measurements obtained from two subjects, or from one individual or experimental procedure under different conditions? Conventionally, clinicians and investigators rely primarily on a comparison of means using appropriate statistical tests. However, the limitations of such traditional analyses become apparent when evaluating the data in Fig. 1, showing sinus rhythm heart rate plots collected from a healthy subject and one with congestive heart failure. Recording the instantaneous signal from any system over a continuous observation period generates a *time series*. What is noteworthy in this example is that these two time series have nearly identical means and variances, suggesting no clinically relevant differences. Yet, visual inspection indicates that the two sequences of data display a markedly different organization. The healthy heartbeat trace shows a complex, "noisy" type of variability, whereas the data set from the patient with heart failure reveals periodic oscillations in heart rate repeating about 1 cycle/minute (~.02 Hz). Time series analysis is concerned with quantifying the *order* of data points; nonlinear dynamics provides a deeper understanding of the mechanisms of patterns and differences such as those in Fig. 1.

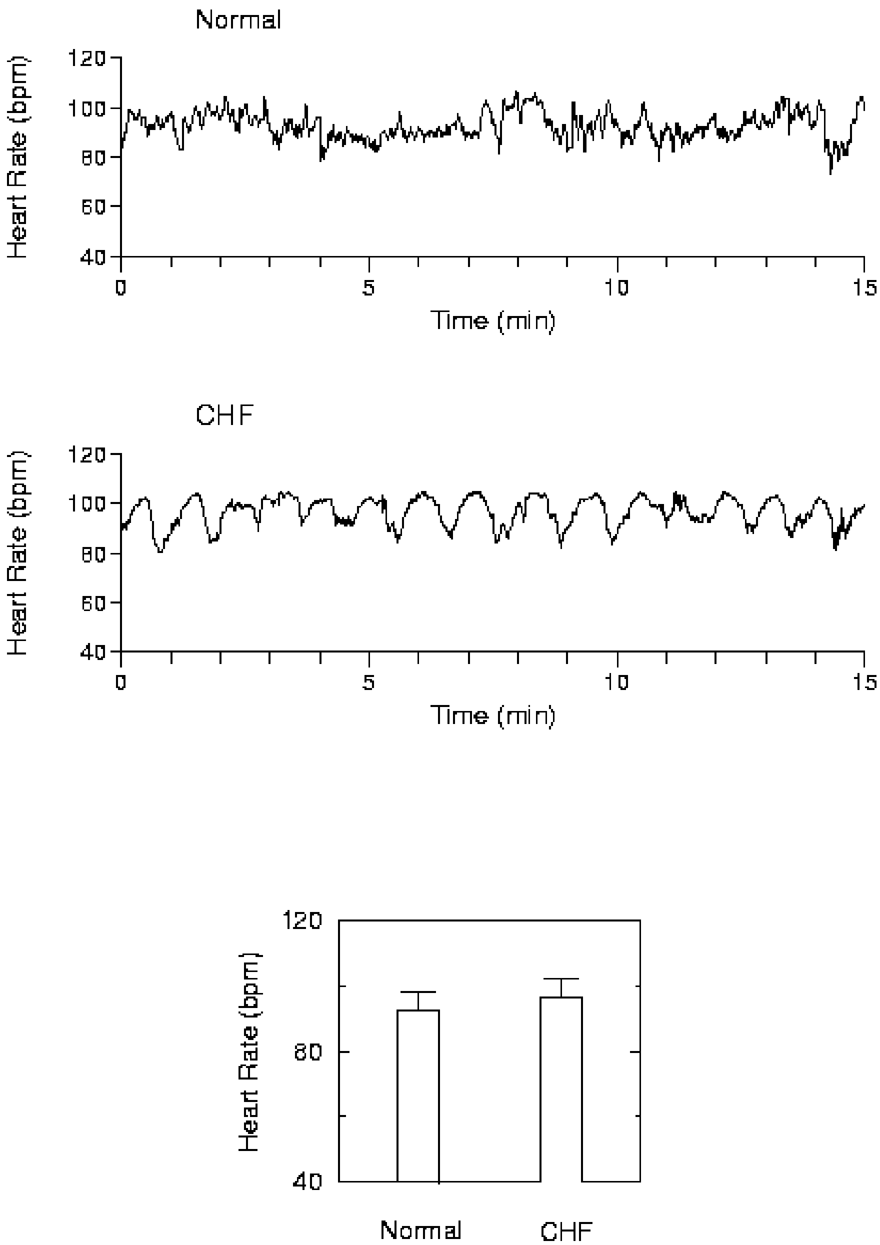

Figure 1. Two heart rate time series, one from a healthy subject (*top*) and the other from a patient with severe congestive heart failure (CHF) (*middle*) have nearly identical means and variances (*bottom*), yet very different dynamics. Note that according to classical physiological paradigms based on homeostasis, neuroautonomic control systems should be designed to damp out noise and settle down to a constant equilibrium-like state. However, the healthy heartbeat displays highly complex, apparently unpredictable fluctuations even under steady-state conditions. In contrast, the heart rate pattern from the subject with heart failure shows slow, periodic oscillations that correlate with Cheyne-Stokes breathing.

B. Linear versus Nonlinear Systems

In linear systems, the magnitude of the output (*y*) is controlled by that of the input (*x*) according to simple equations in the familiar form $y=mx+b$. A well-known example of such a relationship is Ohm's law: V=IR where the voltage (V) in a circuit will vary linearly with current (I), provided the resistance (R) is held constant. Two central features of linear systems are *proportionality* and *superposition*. Proportionality means that the output bears a straightline relationship to the input. Superposition refers to the fact that the behavior of linear systems composed of multiple components can be fully understood and predicted by dissecting out these components and figuring out their individual input-output relationships. The overall output will simply be a summation of these constituent parts. The components of a linear system literally "add up" - there are no surprises or anomalous behaviors.

In contrast, even simple nonlinear systems violate the principles of proportionality and superposition. An example of a deceptively complex nonlinear equation is $y = ax\,(1-x)$, referred to as the *logistic equation* in population biology (5). The nonlinearity of this equation, which describes a parabola, arises from the quadratic (*x*) term. Changes in the output as a function of sequential time steps can be readily plotted by a feedback procedure in which the current value of the output becomes the next value of the input, and so on. Iteration of the simple-in-form logistic equation reveals dynamics that are extraordinarily complex; depending on the value of the single parameter, *a*, the same equation can generate steady states, regular oscillations, or highly erratic behavior (4, 5). Thus, for nonlinear systems, proportionality does not hold: small changes can have dramatic and unanticipated effects. An added complication is that nonlinear systems composed of multiple subunits cannot be understood by analyzing these components individually. This reductionist strategy fails because the components of a nonlinear network interact, i.e., they are coupled. Examples include the "cross-talk" of pacemaker cells in the heart or neurons in the brain. Their nonlinear coupling generates behaviors that defy explanation using traditional (linear) models (Fig. 2). As a result, they may exhibit behavior that is characteristic of nonlinear systems, such as self-sustained, periodic waves (e.g., ventricular tachycardia) (6, 7); abrupt changes (e.g., sudden onset of a seizure) (8) and, possibly, chaos (see below). Table 1 gives a more complete, but not exhaustive list of nonlinear mechanisms with potential relevance to biology and medicine (1-4, 6-14).

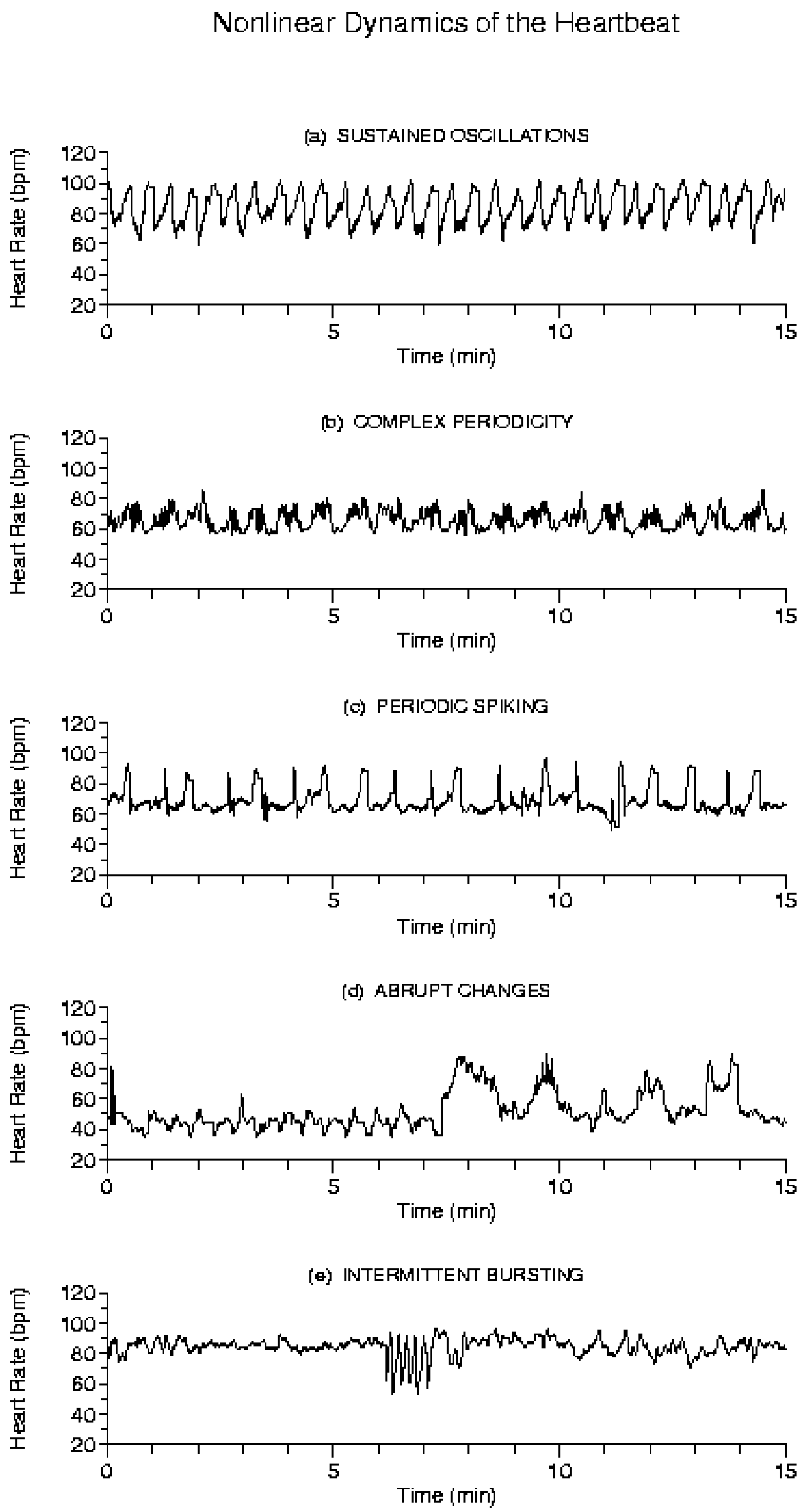

Figure 2. Examples of nonlinear dynamics of the heartbeat. Panels (a-c) are from subjects with obstructive sleep apnea syndrome. Panels (d and e) are from healthy subjects at high altitude (~15,000 ft).

A related and noteworthy property of nonlinear dynamics is referred to as *universality* (1, 4). Surprisingly, nonlinear systems that appear to be very different in their specific details may exhibit certain common patterns of response. For instance, nonlinear systems may change in a sudden, discontinuous fashion. One important and universal class of abrupt, nonlinear transitions is called a *bifurcation* (1, 9). This term describes situations where a very small increase or decrease in the value of some parameter controlling the system causes it to change abruptly from one type of behavior to another. For example, the output of the same system may suddenly go from being wildly irregular to a highly periodic, or vice versa. A universal class of bifurcations occurring in a wide variety of nonlinear systems is the sudden appearance of regular oscillations that alternate between two values (15). This type of dynamic may underlie a variety of *alternans* patterns in cardiovascular dysfunction. A familiar example is the beat-to-beat alternation in QRS axis and amplitude seen in some cases of cardiac tamponade (16). This kind of electrical alternans is related to the back and forth swinging motion of the heart within the pericardial effusion. Multiple other examples of alternans in perturbed cardiac physiology have been described, including ST-T alternans which may precede ventricular fibrillation (17), and pulsus alternans during heart failure.

C. Chaos

Although the focus of much recent attention, chaos *per se* actually comprises only one specific subtype of nonlinear dynamics. Prior to the work of the renowned French mathematician, Henri Poincaré, in the early 1900s, science was dominated by the seemingly inviolable tenet that the behavior of systems for which one could write out explicit equations (e.g., the solar system) should be, in principle, fully predictable for all future times (18). What Poincaré discovered (and what was more recently rediscovered) is that a complex type of variability can arise from the operation of even the simplest nonlinear system, such as that governed by the logistic equation mentioned earlier. Because the equations of motion which generate such erratic, and apparently unpredictable behavior do not contain any random terms, this mechanism is now referred to as *deterministic chaos* (1, 4). The colloquial use of the term chaos - to describe unfettered randomness, usually with catastrophic implications - is quite different from this specialized usage.

The extent to which chaos relates to physiological dynamics is a subject of active investigation and some controversy. At first it was widely assumed that chaotic fluctuations were produced by pathological systems such as cardiac electrical activity during atrial or ventricular fibrillation (19). However, this initial presumption has been challenged (20) and the weight of current evidence does not support the view that the irregular ventricular response in atrial fibrillation or that ventricular fibrillation itself represents deterministic cardiac chaos (21). Further, there is no convincing evidence that other arrhythmias sometimes labeled "chaotic," such as multifocal atrial tachycardia, meet the technical criteria for nonlinear chaos. An alternative hypothesis (22) is that the subtle but complex heart rate fluctuations observed during normal sinus rhythm in healthy subjects, even at rest, are due in part to deterministic chaos, and that a variety of pathologies, such as congestive heart failure syndromes, may involve a paradoxical decrease in this type of nonlinear variability (Fig. 1). Because the mathematical algorithms designed for detecting chaos are not reliably applied to nonstationary, relatively short and often noisy data sets obtained from most clinical and physiological studies, the intriguing question of the role, if any, of chaos in physiology or pathology remains unresolved (22-28).

D. Fractal Anatomy

The term *fractal* is a geometric concept related to, but not synonymous with chaos (29, 30). Classical geometric forms are smooth and regular and have integer dimensions (1,2, and 3, for line, surface, and volume respectively). In contrast, fractals are highly irregular and have non-integer, or fractional, dimensions. Consider a fractal line. Unlike a smooth Euclidean line, a fractal line, which has a dimension between 1 and 2, is wrinkly and irregular. Examination of these wrinkles with the low-power lens of a microscope, reveals smaller wrinkles on the larger ones. Further magnification shows yet smaller wrinkles, and so on. A fractal, then, is an object composed of subunits (and sub-subunits) that resemble the larger scale structure, a property known as self-similarity (Fig. 3). A wide variety of natural shapes share this internal look-alike property, including branching trees and coral formations, wrinkly coastlines, and ragged mountain ranges. A number of cardiopulmonary structures also have a fractal-like appearance (2, 3, 30, 31). Examples of self-similar anatomies include the arterial and venous trees, the branching of certain cardiac muscle bundles, as well as the ramifying tracheobronchial tree and His-Purkinje network.

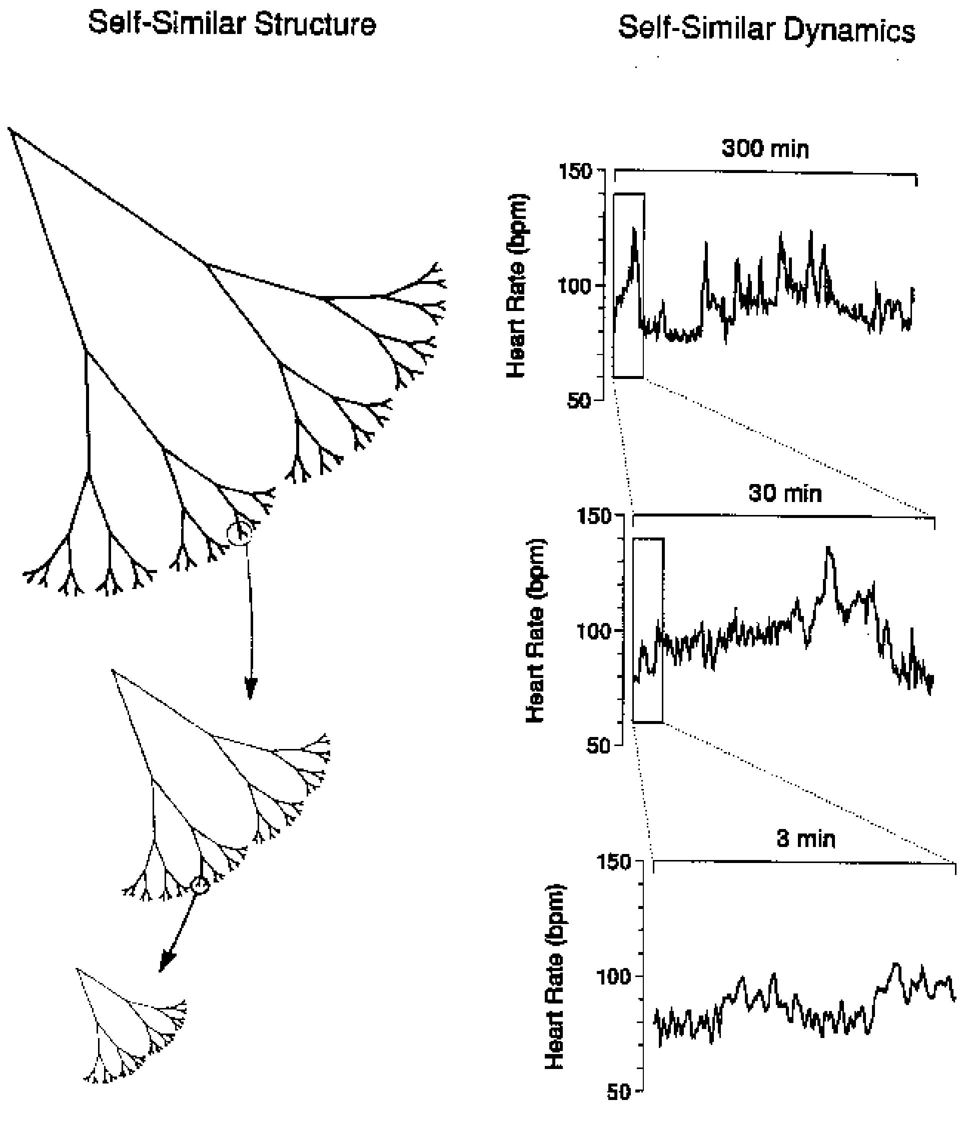

Figure 3. Left, schematic of a tree-like fractal has self-similar branchings such that the small scale (magnified) structure resembles the large scale form. Right, a fractal process such as heart rate regulation generates fluctuations on different time scales (temporal "magnifications") that are statistically self-similar. (Adapted from Goldberger AL. Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. *Lancet* 1996;**347**:1312-1314.)

From a mechanistic viewpoint, these self-similar cardiopulmonary structures all serve a common physiologic function: rapid and efficient transport over a complex, spatially distributed system. In the case of the ventricular electrical conduction system, the quantity transported is the electrical stimulus regulating the timing of cardiac contraction (31). For the vasculature, fractal branchings provide a rich, redundant network for distribution of O_2 and nutrients and for the collection of CO_2 and other metabolic waste products. The fractal tracheo-bronchial tree provides an enormous surface area for exchange of gases at the vascular-alveolar interface, coupling pulmonary and cardiac function (30). Fractal geometry also underlies other important aspects of cardiac function. Peskin and McQueen (32) have elegantly shown how fractal organization of connective tissue in the aortic valve leaflets relates to the efficient distribution of mechanical forces. A variety of other organ systems contain fractal structures that serve functions related to information distribution (nervous system), nutrient absorption (bowel), as well collection and transport (biliary duct system, renal calyces) (2, 3, 30).

E. Scaling in Health and its Breakdown with Disease

An important extension of the fractal concept was the recognition that it applies not just to irregular geometric or anatomic forms that lack a characteristic (single) scale of length, but also to complex processes that lack a single scale of time (29, 33). Fractal processes generate irregular fluctuations on multiple time scales, analogous to fractal objects that have wrinkly structure on different length scales. Furthermore, such temporal variability is statistically self-similar. A crude, qualitative appreciation for the self-similar nature of fractal processes can be obtained by plotting the time series in question at different "magnifications," i.e., different temporal resolutions. For example, Fig. 3 plots the time series of heart rate from a healthy subject on three different scales. All three graphs have an irregular ("wrinkly") appearance, reminiscent of a coastline or mountain range. The irregularity seen on different scales is not visually distinguishable, an observation confirmed by statistical analysis (34, 35). The roughness of these time series, therefore, possesses a self-similar (scale-invariant) property.
Since scale-invariance appears to be is a general mechanism underlying many physiological structures and functions, one can adapt new quantitative tools derived from fractal mathematics for measuring healthy variability. Complex fluctuations with the statistical properties of fractals have not only been described for heart rate variability, but also for fluctuations in respiration (36), systemic blood pressure (37), human gait (38) and white blood cell counts (39), as well as certain ion channel kinetics (3).

Furthermore, if scale-invariance is a central organizing principle of physiological structure and function, we can make a general, but potentially useful prediction about what might happen when these systems are severely perturbed. If a functional system is self-organized in such a way that it does *not* have a characteristic scale of length or time, a reasonable anticipation would be a *breakdown* of scale-free structure or dynamics with pathology (35). How does a system behave after such a pathologic transformation? The antithesis of a scale-free (fractal) system (i.e., one with multiple scales) is one that is dominated by a single frequency or scale. A system that has only one dominant scale becomes especially easy to recognize and characterize because such a system is by definition *periodic* - it repeats its behavior in a highly predictable (regular) pattern (Fig. 4). The theory underlying this prediction may account for a clinical paradox: namely, that a wide range of illnesses are associated with markedly periodic (regular) behavior even though the disease states themselves are commonly termed "dis-orders" (39).

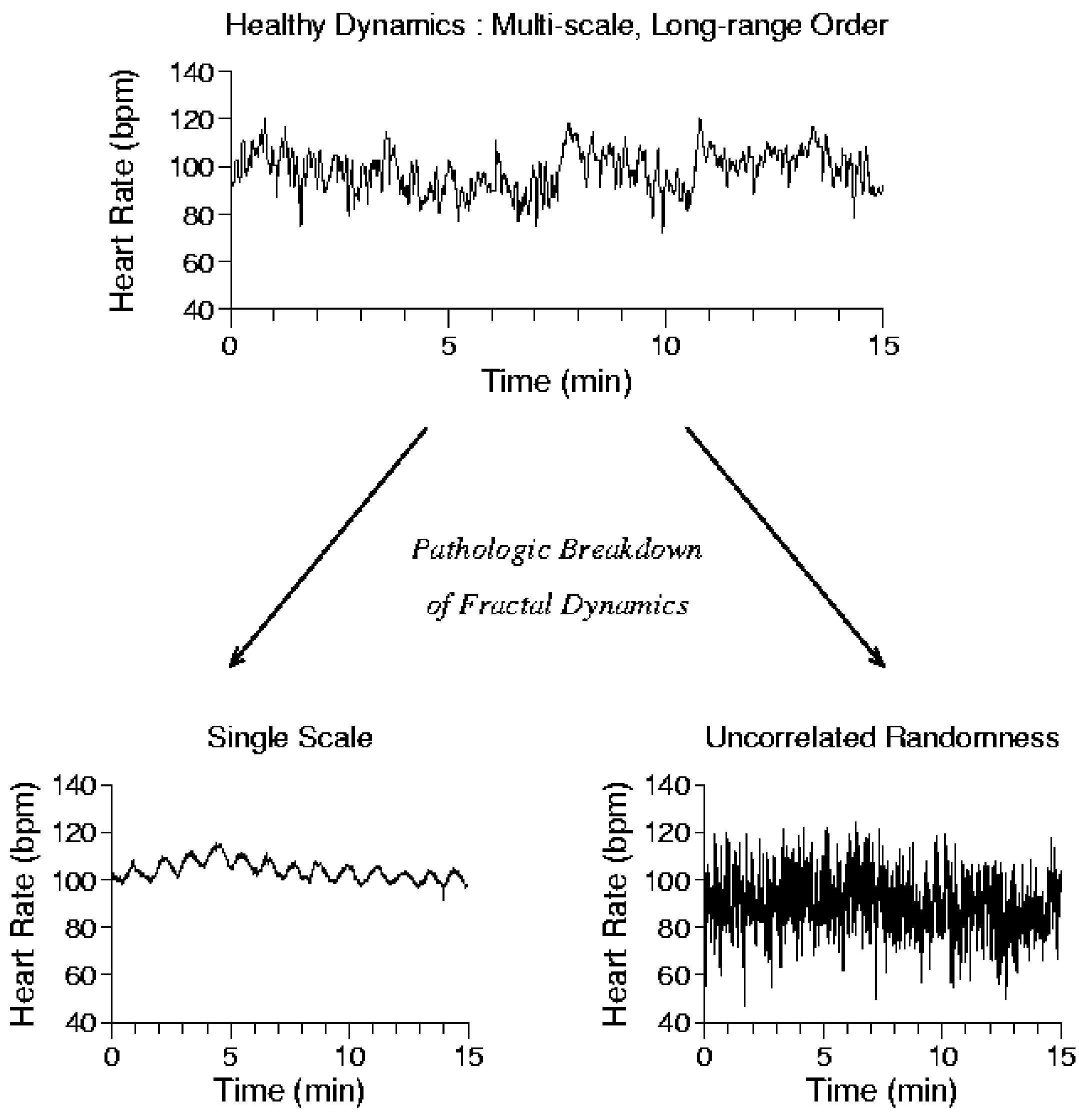

Figure 4. Breakdown of a fractal physiological control mechanism can lead ultimately either to a highly periodic output dominated by a single scale or to uncorrelated randomness. The top heart rate time series is from a healthy subject; bottom left is from a subject with heart failure; and bottom right from a subject with atrial fibrillation. (Adapted from Goldberger AL. Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. *Lancet* 1996;347:1312-1314.)

II. Fractal Scaling of the Heartbeat in Health and its Breakdown with Disease

A. Periodic Disease and the Loss of Fractal Complexity

The appearance of highly periodic dynamics in many disease states is one of the most compelling examples of the notion of *complexity loss in disease* (40). Complexity here refers specifically to a multiscale, fractal-type of variability in structure or function. Many disease states are marked by less complex dynamics than those observed under healthy conditions. This *de-complexification* of systems with disease appears to be a common feature of many pathologies, as well as of aging (40). When physiologic systems become less complex, their *information content* is degraded (41). As a result, they are less adaptable and less able to cope with the exigencies of a constantly changing environment. To generate information, a system must be capable of behaving in an unpredictable fashion (2, 42). In contrast, a highly predictable, regular output (i.e., a sine wave) is information-poor since it monotonously repeats its activity. (The most extreme example of complexity loss would be the total absence of variability - a straightline output.)

Quantitative assessment of periodic oscillations can be obtained by analyzing the time series of interest with a variety of standard mathematical tools. For systems producing a highly periodic output, the most widely used methods are based on spectral analysis. Remarkably, the time series of many severely pathologic systems have a nearly sinusoidal appearance; the spectrum shows a dominant peak at this characteristic frequency. An example is the heart rate variability sometimes observed in patients with severe congestive heart failure (Fig. 1) (43, 44) or with fetal distress syndromes (45). In contrast, systems with a fractal output (such as normal heart rate variability) show a type of broadband spectrum which includes many different frequencies (scales).

Probably the first explicit description of the concept of *periodic diseases* was provided over 30 years ago by Dr. Hobart Reimann (46). He called attention to a number of conditions in which the disease process itself could be shown to *flare* or *recur* on a regular basis of days to months; ranging from certain forms of arthritis to some mental illnesses and hereditary diseases, such as familial Mediterranean fever. In the late 1970s, Michael Mackey and Leon Glass (47, 48) helped to rekindle interest in this dormant field when they introduced the term *dynamical disease* to encompass the types of periodic syndrome Reimann had catalogued, as well as irregular dynamics thought possibly to represent deterministic chaos.

Reimann's original list was premised on the assumption that periodic conditions were somewhat unique, and even idiosyncratic, in clinical medicine. However, to the extent that healthy function is often characterized by a multi-scale fractal complexity, we would anticipate that the emergence of single-scale (i.e., non-fractal) states might be considerably more common, if not ubiquitous, in pathophysiology. Indeed, a recent survey of the literature (49) indicates that Reimann, rather than compiling a list of the exceptional, was more likely sampling a widespread, even generic manifestation of the dynamics of disease. From the most general perspective, the practice of bedside diagnosis itself would be impossible without the loss of complexity and the emergence of pathologic periodicities. To a large extent, it is these periodicities and highly-structured patterns - the breakdown of multi-scale fractal complexity under pathologic conditions - that allow clinicians to identify and classify many pathologic features of their patients. Familiar examples include periodic tremors in neurologic conditions, AV Wenckebach patterns, the "sine-wave" ECG pattern in hyperkalemia, manic-depressive alterations, and cyclic breathing patterns in heart failure.

B. Irregular Dynamics and the Breakdown of Fractal Mechanisms

While fractals are irregular, not all irregular structures or erratic time series are fractal. A key feature of the class of fractals seen in biology is a distinctive type of long-range order. This property generates *correlations* that extend over many scales of space or time. For complex processes, fractal long-range correlations are the mechanism underlying a "memory" effect; the value of some variable, e.g., heart rate at a particular time, is related not just to immediately preceding values, but to fluctuations in the remote past. Certain pathologies are marked by a breakdown of this long-range organization property, producing an uncorrelated randomness similar to "white noise." An example is the erratic ventricular response in atrial fibrillation over relatively short time scales. Peng et al. (50) have recently described a simple algorithm for quantifying the breakdown of long-range (fractal) correlations in physiological time series.

C. Future Applications

Practical applications of nonlinear dynamics are likely within the next few years. Probably the first bedside implementations will be in physiological monitoring. A number of indices derived from chaos theory have shown promise in forecasting subjects at high risk of electrophysiologic or hemodynamic instability, including

- automated detection of the onset and end of pathologic low frequency (<.10 Hz) heart rate oscillations (Figs 1, 2 and 4) (43, 52-59);
- detection of subtle ST-T alternans (17, 51);
- detection of a breakdown in fractal scaling with disease and aging (43); and
- quantification of differences or changes in the nonlinear complexity or dimension of a physiological time series (59, 60).

In addition to these diagnostic applications, perhaps the most exciting prospects are related to novel therapeutic interventions. An important recent finding is that certain mathematical or physical systems with complex dynamics can be controlled by properly timed external stimuli: chaotic dynamics can be made more regular (*chaos control*) and periodic ones can be made chaotic (*chaos anti-control*) (61-63). One proposal, based on the earlier notion that certain arrhythmias, particularly ventricular fibrillation, represent cardiac chaos, is to develop chaos control algorithms to electrically pace the heart beat back to sinus rhythm (63). A more recent proposal is to use chaos anti-control protocols to treat or to prevent cardiac arrhythmias or epilepsy based on the hypothesis that restoration of a kind chaotic-like variability may actually be advantageous (62). Chaos theory also holds promise for illuminating a number of major problems in contemporary physiology and molecular biology. Nonlinear wave mechanisms may underlie certain types of reentrant ventricular tachyarrhythmias (6, 7). Appreciation for the rich nonlinearity of physiological systems may have relevance for modeling enormously complicated signal-transduction cascades involved, for example, in neuroautonomic dynamics in which interactions and "cross-talk" occur over a wide range of temporal and spatial scales, as well as for understanding complex pharmacologic effects. Fractal analysis of long DNA sequences has recently revealed that non-coding, but *not* coding sequences possess long-range correlations among nucleotides (64). This finding has implications for possible functions of introns as well as for understanding molecular evolution (65) and developing new methods for distinguishing coding from non-coding sections of long DNA sequences (66). Findings from nonlinear dynamics have also challenged conventional mechanisms of physiological control based on classical homeostasis, which presumes that healthy systems seek to attain a constant steady state. *In contrast, nonlinear systems with fractal dynamics, such as the neuroautonomic mechanisms regulating heart rate variability, behave as if they were driven far from equilibrium under basal conditions. This kind of complex variability, rather than a regular homeostatic steady state, appears to define the free-running function of many biological systems* (Fig. 1) (2, 39). Finally, a fundamental methodologic principle underlying these new applications and interpretations is the importance of analyzing continuously sampled variations in physiological output, such as heart rate, and not simply relying on averaged values or measures of variance. Dynamical analysis demonstrates that there is often hidden information in physiological time series and that certain fluctuations previously considered "noise" actually represent important signals (67-70).

Table 1
Nonlinear Mechanisms and Manifestations

1. Abrupt Changes (10)

    Bifurcations (1, 9)
    Intermittency / Bursting (9, 10)
    Bistability; Multistability (11)
    Phase transitions

2. Hysteresis (12)
3. Nonlinear Oscillations (1, 2)

    Limit cycles
    Phase resetting
    Entrainment
    Pacemaker annihilation

4. Fractals (2, 3)

    Scale-invariance
    Long-range correlations
    Self-organized criticality
    Diffusion limited aggregation

5. Alternans (9)
6. Nonlinear waves: spiral; scroll (6, 7)
7. Complex periodic cycles; quasiperiodicities (13)
8. Stochastic resonance (14)
9. Time irreversibility
10. Chaos

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