Giles F. Filley Lecture

Complex Systems

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Physiologic systems in health and disease display an extraordinary range of temporal behaviors and structural patterns that defy understanding based on linear constructs, reductionist strategies, and classical homeostasis. Application of concepts and computational tools derived from the contemporary study of complex systems, including nonlinear dynamics, fractals and "chaos theory," is having an increasing impact on biology and medicine. This presentation provides a brief overview of an emerging area of biomedical research, including recent applications to cardiopulmonary medicine and chronic obstructive lung disease.

Keywords: chaos theory; chronic obstructive pulmonary disease; fractal; nonlinear dynamics; sleep apnea

Investigators and clinicians attempting to evaluate the potential applications of complex systems analysis are faced with unfamiliar terms and concepts, including "nonlinear dynamics," "fractals," "periodic oscillations," "bifurcations," as well as "chaos" (1–4). This presentation attempts to provide a brief overview of some key aspects of complex systems, with an emphasis on cardiopulmonary applications.

BASIC CONCEPTS OF COMPLEX SYSTEMS

The relevance of nonlinear dynamics to bedside cardiopulmonary medicine is illustrated in Figure 1, which presents 15-min heart rate time series from two subjects, both in sinus rhythm. One is from a healthy individual; the other from a patient during episodes of severe obstructive sleep apnea. The two datasets have nearly identical mean values and variances and, therefore, escape statistical distinction based on conventional comparisons. However, visual inspection of the raw time series (Figure 2) reveals dramatic differences in the temporal structure of the original data. The time series from the healthy subject reveals a complex pattern of nonstationary fluctuations. In contrast, the heart rate dataset from the subjects with sleep apnea shows a much more predictable pattern with a characteristic time scale defined by prominent, low-frequency oscillations at about 0.03 Hz. Both the complex behavior in the healthy case and the sustained oscillations in the pathologic one suggest the presence of nonlinear mechanisms.

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LINEAR VERSUS NONLINEAR MECHANISMS

Two key features of linear systems are proportionality and superposition. Proportionality indicates that the output bears a straight-line relationship to the input. Superposition describes the fact that the output of linear systems composed of multiple components can be fully understood and predicted by the reductionist strategy of parsing out these components and defining their individual input–output relationships. The overall system behavior will be a summation of its constituent parts. The components of a linear system literally "add up."

In contrast, even the simplest nonlinear systems contravene the principles of proportionality and superposition. A well-studied 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 x^2 term. Changes in the output as a function of sequential time increments can be tracked 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 apparently simple logistic equation reveals dynamics that are extraordinarily complex. Depending only on the value of the parameter, a, the same equation can generate a single steady state, sustained periodic oscillations, or highly erratic fluctuations (5, 6). Thus, for nonlinear systems, proportionality does not hold. Small changes can have dramatic and unanticipated consequences, sometimes referred to as the "butterfly effect."

A related complication is that nonlinear systems composed of multiple subunits cannot be understood by analyzing these components individually and treating the global system in a modularized way (1, 4). The superposition paradigm fails because the components of a nonlinear system interact. Examples include the "cross-talk" of pacemaker cells in the heart and of neurons in the respiratory control center of the brain (7). Their nonlinear coupling generates behaviors that cannot be explained using traditional models. Instead, these systems exhibit behaviors that are markers of nonlinear mechanisms, such as self-sustained oscillations (e.g., periodic cardiopulmonary waves in central and obstructive sleep apnea syndromes; Figure 2, *bottom*), abrupt changes (e.g., sudden onset of an apneic episode or cardiac arrhythmia), and irregular dynamics referred to as "deterministic chaos" (1, 5, 6). In the parlance of complex systems, the term "emergence" is used to refer to the often abrupt appearance of qualitatively unanticipated global patterns and behaviors resulting from local interactions. Table 1 gives a more complete, but by no means exhaustive, inventory of nonlinear mechanisms and phenomena with potential relevance to biology and medicine.

A fundamental underpinning of nonlinear dynamics is referred to as universality (1, 3, 4). Surprisingly, nonlinear systems that differ in their specific details may exhibit certain common patterns of response. For instance, nonlinear systems may change in a sudden, discontinuous fashion. One universal class of abrupt, nonlinear transitions is called a bifurcation (1, 3, 4, 6). This term describes situations where a minuscule change in the value of

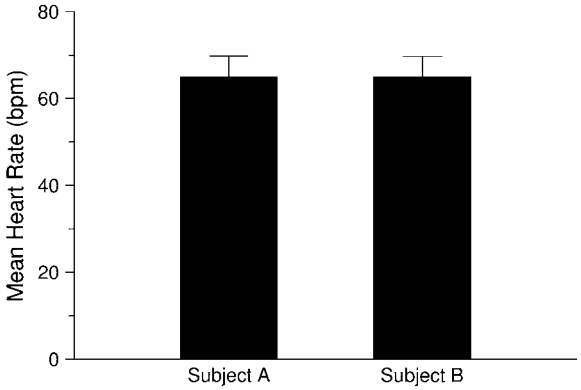

Figure 1. Conventional statistical summary of heart rate dynamics in two subjects over 15 min showing nearly identical mean values and SDs (*error bars*). One subject is healthy; the other was having episodes of severe obstructive sleep apnea. bpm = beats per minute.

some parameter causes the system to change abruptly from one type of behavior to another. A universal class of bifurcations occurring in a wide variety of nonlinear systems is the sudden appearance of regular oscillations that consist of alternation between two values. This type of ABABAB dynamic may underlie the variety of alternans patterns observed in pathologic cardiovascular electrical and mechanical syndromes, including those seen before sudden cardiac arrest from ventricular tachyarrhythmia (T or U wave alternans), with congestive heart failure (pulsus alternans), and with pericardial tamponade (electrical alternans associated with the swinging heart phenomenon) (4, 8). Another example of universality in complex systems is related to fractals (2, 4, 9, 10).

FRACTAL GEOMETRIES AND DYNAMICS

The concept of a fractal is most often associated with irregular objects that display a property called self-similarity or scale-invariance (2, 4, 10). Fractal forms are composed of subunits (and sub-subunits, etc.) that resemble the structure of the macroscopic object (Figure 3, *left*). In an idealized model, this internal "look-alike" property holds on all scales. The real world imposes upper and lower bounds over which such scale-free behavior applies. Many irregular structures in nature, such as branching trees, crenellated coastlines, and craggy mountain surfaces, are fractal (2). A number of complex anatomic structures also display fractal-like geometry (4, 9, 10), including branching networks such as the His-Purkinje conduction system (11), and the tracheobronchial tree (10–18). These self-similar cardiopulmonary structures subserve at least one fundamental physiologic function: rapid and efficient transport over multiscale, spatially distributed networks. Related to this function, the fractal tracheobronchial tree may also support chaotic-like mixing of gases in the distal airways (19) and avalanche-like cascades in pulmonary inflation (20). With aging and pathology, fractal anatomic structures may show degradation in their structural complexity. Examples include loss of dendritic arbor in aging neurons, vascular "pruning" in primary pulmonary hypertension (21), and, possibly, alterations in distal airway architecture with chronic obstructive lung disease (22).

The fractal concept can be applied quantitatively not only to irregular geometric forms that lack a characteristic (single) length scale but also to complex processes that lack a single time scale (2, 4, 9, 10). Instead, fractal processes generate irregular fluctuations across multiple time scales, analogous to scale-invariant objects that have a branching or wrinkly structure across multiple scales of length. A qualitative approximation for the self-similar nature of fractal processes, such as the healthy heartbeat, can be obtained by plotting their fluctuations at different temporal resolutions (Figure 3, *right*). An important methodologic challenge is how to detect and quantify the fractal scaling and related correlation properties of physiologic time series, which are typically not only irregular but also nonstationary since their statistical properties change with time. To help deal with the ubiquitous "complication" of nonstationarity in biological signals, Peng and colleagues (23) have introduced a fractal analysis method termed "detrended fluctuation analysis"

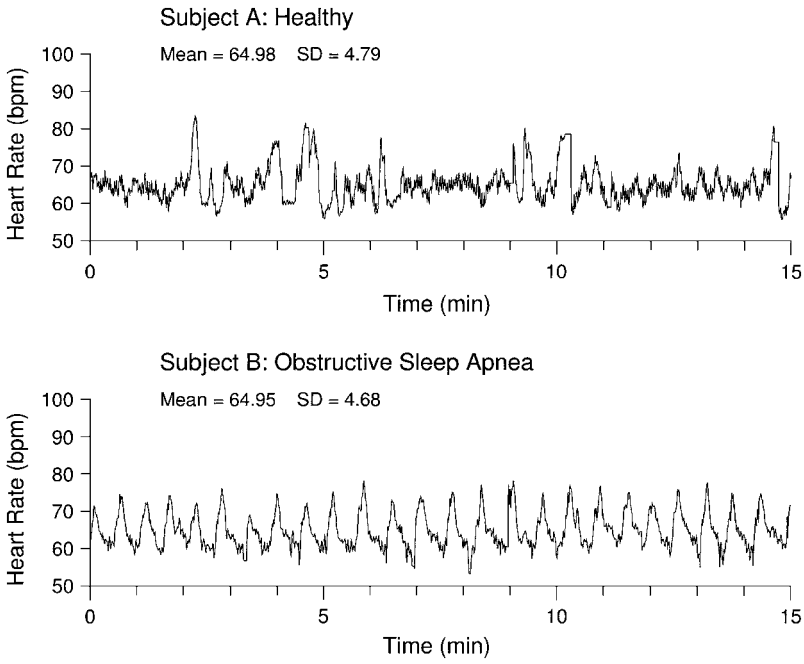

Figure 2. Original ("raw") heart rate time series from the two subjects (one healthy, one during obstructive sleep apnea) whose data are summarized in Figure 1. Note the marked differences in the underlying dynamics despite the essentially identical mean values and SDs. The healthy dynamics (*top*) show the more complex pattern of variability, in contrast to the relatively periodic temporal structure of the sleep apnea dataset (*bottom*).

TABLE 1. NONLINEAR/COMPLEXITY-RELATED MECHANISMS AND PHENOMENA IN PHYSIOLOGY: A SHORT LIST

- Abrupt changes
  - Bifurcations
  - Intermittency and other bursting behaviors
  - Bistability/multistability
  - Phase transitions
- Alternans and period-doubling–type phenomena
- Complex periodic cycles and quasiperiodicities
- Hysteresis
- Nonlinear oscillations
  - Limit cycles
  - Phase-resetting
  - Entrainment phenomena
  - Pacemaker annihilation
- Nonlinear waves: spirals, scrolls, solitons
- Scale-invariance
  - Diffusion limited aggregation
  - Fractal and multifractal scaling
  - Long-range correlations
  - Self-organized criticality
- Stochastic resonance and related noise-modulated mechanisms
- Time irreversibility (asymmetry)

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(DFA), which has been widely applied to cardiopulmonary and other physiologic time series.

Systematic analyses using the DFA technique and a variety of complementary methods have confirmed that the healthy human heartbeat, even at rest, displays fractal (long-range) correlation properties and that this organization breaks down with aging and disease (10, 24). More recent studies (25, 26) have also disclosed a fractal, multiscale organization of breathing dynamics under healthy conditions. The presence of fractal dynamics in spontaneous cardiopulmonary fluctuations has implications for understanding and modeling physiologic regulation. Traditional (homeostatic) models of control that predict a constant, "steady state" output under physiologic conditions do not account for the observed fractal dynamics (27). Analysis of scaling behavior in a number of life-threatening cardiovascular pathologies, including heart failure and after extensive myocardial infarction, indicates significant alterations in short- and long-range fractal heartbeat correlation properties (10, 28). The effects of chronic obstructive lung disease and other pulmonary pathologies on nonlinear and fractal-related breathing dynamics remain to be investigated.

FRACTAL PHYSIOLOGY: IMPLICATIONS FOR THE DYNAMICS OF HEALTH AND DISEASE

A defining feature of healthy function is adaptability, the capacity to respond to often unpredictable stimuli. Physiologic plasticity requires a broad range of integrated multiscale outputs. Fractal physiology, exemplified by long-range correlations in heartbeat and breathing dynamics, may be adaptive for at least two reasons (10): (*1*) long-range correlations serve as an organizing mechanism for highly complex processes that generate fluctuations across a wide range of time scales and (*2*) the absence of a characteristic scale may inhibit the emergence of very periodic behaviors that greatly narrow system responsiveness. This hypothesis is supported by findings from life-threatening conditions, such as chronic heart failure, where the breakdown of fractal correlations is often accompanied by the emergence of a dominant mode (e.g., the Cheyne-Stokes frequency). Abrupt transitions to strongly periodic dynamics are observed in many other pathologies, including at high altitudes and with obstructive

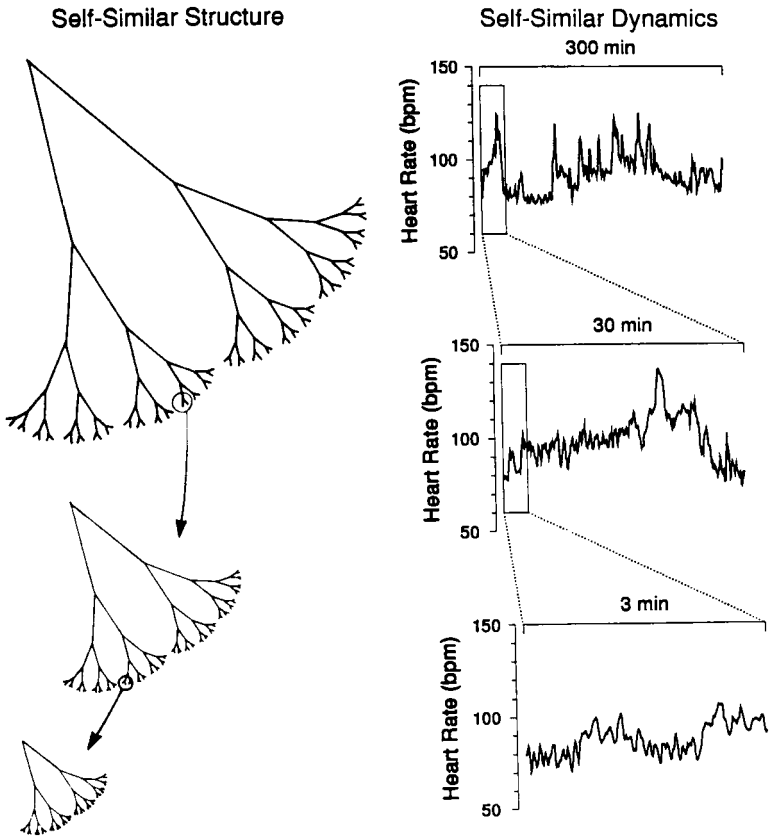

Figure 3. Schematic representations of self-similar structures and self-similar fluctuations. The treelike, spatial fractal (*left*) has self-similar branchings, such that the small-scale structure resembles the large-scale form. A fractal temporal process, such as healthy heart rate regulation (*right*), generates fluctuations on different time scales that are statistically self-similar. Adapted by permission from Reference 4.

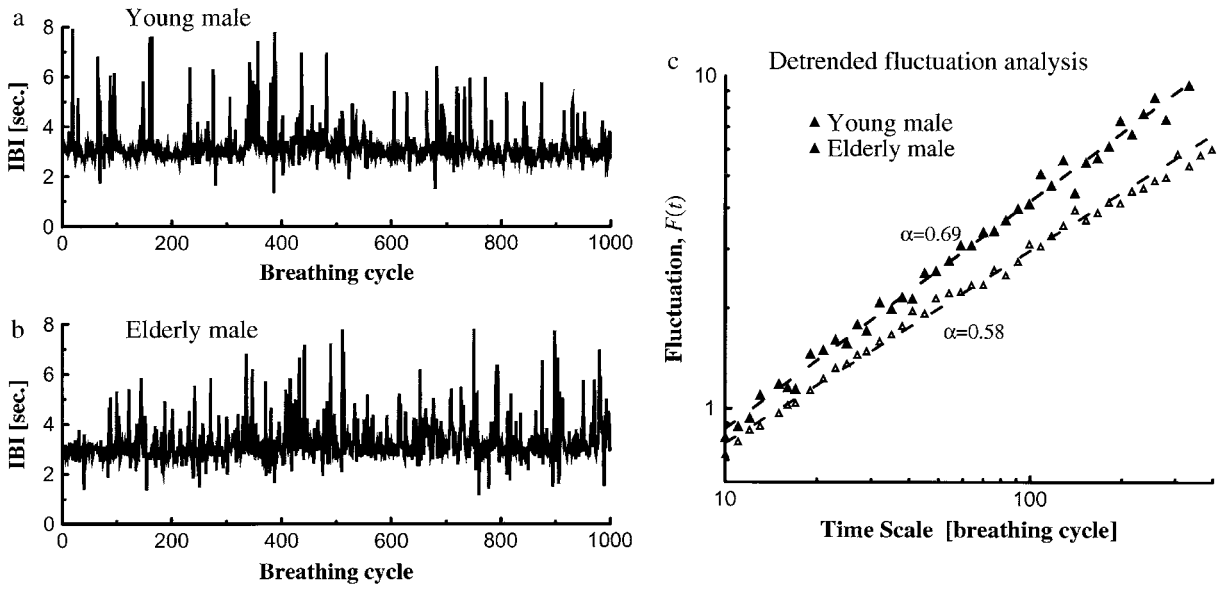

Figure 4. Illustrative interbreath interval (IBI) time series (obtained at rest by inductance plethysmography) for (*a*) a healthy young male adult and (*b*) a healthy elderly male subject. Both time series show an irregular pattern of spontaneous breathing with considerable variability (ordinate) in IBIs over 1,000 consecutive breathing cycles (abscissa). A fractal analysis of the correlation properties of the two datasets is presented in (*c*) on a log-log plot using the detrended fluctuation analysis (DFA) technique. *Dashed lines* give the least-square fits for the data from both subjects. The slope of these fitted lines in the DFA exponent, α. The power-law fits are consistent with fractal dynamics. Of note, the slope for the elderly subject (closer to a value of 0.5 indicative of an uncorrelated process) is consistent with an age-related degradation of the long-range fractal organization of respiratory control (*see* Reference 25). Adapted by permission from Reference 25.

sleep apnea (29, 30) (Figure 2), sudden cardiac death, epilepsy, and fetal distress syndromes, to name but a few (4).

The paradoxical appearance of highly ordered dynamics with pathologic states ("disorders") exemplifies the concept of complexity loss (decomplexification) in aging and disease (4, 10, 31). Physiologic stability appears to relate in part to complex patterns of variability that incorporate long-range correlations, together with distinct classes of nonlinear interactions (10, 24). The opposite of a fractal (scale-free) system (Figure 2, *top*) is one dominated by a characteristic frequency (Figure 2, *bottom*). Physiologic systems evincing only one (or a few) dominant scale(s) become especially easy to recognize clinically because they stereotypically repeat their behavior in a highly predictable fashion (31, 32).

SPECIAL NEEDS FOR OPEN DATABASES AND SOFTWARE TOOLS

A major obstacle to the dynamic analysis of cardiopulmonary signals has been the unavailability of large, well-characterized, open-access databases and open-source computational tools necessary to promote multidisciplinary and collaborative efforts to find "hidden information" in such complex recordings. In September 1999, under the auspices of the National Center for Research Resources of the National Institutes of Health, our colleagues and we inaugurated the "Research Resource for Complex Physiologic Signals" (33, 34). The "PhysioNet" resource has three interdependent components: (*1*) "PhysioBank" is a large and expanding collection of well-characterized digital recordings of physiologic signals. Currently available databases include multiparameter cardiopulmonary, neural, and other biomedical signals from subjects with a variety of conditions with major public health implications, such as life-threatening cardiac arrhythmias, congestive heart failure, sleep apnea, neurologic disorders such as Parkinson's disease, and aging, as well as recordings from healthy subjects. (*2*) "PhysioToolkit" is a library of open-source software for physiologic signal processing and analysis, using both classical techniques and novel methods based on statistical physics and nonlinear dynamics (including fractal and information/entropy-based analyses). (*3*) "PhysioNet" (from which the resource derives its name) is the online forum for dissemination and exchange of recorded biomedical signals and open-source software for analyzing these complex signals.

FUTURE DIRECTIONS

One promising application of dynamic analysis involves strategies to restore complex biological variability (Figures 2–4), including fractal fluctuations, to cardiopulmonary systems (35, 36). Initial results using artificial ventilation in experimental animals and clinical settings suggest the possibility of improving physiologic function with "noisy" versus "metronomic" parameter settings (35–42). The use of dynamic assays to uncover basic and clinical information encoded in time series, such as those in Figures 2 and 4, also promises to provide new, readily implemented diagnostic tests for prevalent conditions such as sleep-disordered breathing (30, 41). The extent to which dynamic measures and complexity-informed models and interventions will enhance diagnostic capabilities and therapeutic options in chronic obstructive lung disease is an intriguing area for future study (19, 22, 42, 43).

Conflict of Interest Statement: A.L.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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Diverse Expression of Antioxidants and Inflammatory Chemokines in Terminal Bronchiolar Epithelium in Chronic Obstructive Pulmonary Disease

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Cigarette smoke has been implicated in the pathogenesis of COPD. Terminal bronchioles are critical zones, but little is known about the cellular and molecular changes in terminal bronchiolar epithelium in smokers, and their relationships with the development of COPD. In this study, laser capture microdissection (LCM) combined with cDNA array and RT-PCR technologies were applied on terminal bronchiolar epithelium, lobar bronchial epithelium, pulmonary macrophages, and alveolar septum in order to obtain site-specific and comprehensive determinations indicative for oxidative stress and inflammatory