

Fractals in Physiology and Medicine

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Nonlinear dynamics, a branch of the basic sciences that studies complex physical systems, offers novel approaches to long-standing problems of physiological form and function. The nonlinear concept of fractals, introduced and developed over the last decade, provides insights into the organization of complex structures such as the tracheobronchial tree and heart, as well as into the dynamics of healthy physiological variability. Alterations in fractal scaling may underlie a number of pathophysiological disturbances, including sudden cardiac death syndromes.

Problems of scale, size, and shape are commonly encountered in anatomy and physiology. For example, is there a characteristic scale factor that governs the decrease in mean bronchial dimensions from the trachea to the terminal bronchioles? Does the type of architecture seen in the pulmonary tree share any basic morphogenetic link with branching networks in the heart, vascular tree, kidney, and liver? What is the "true" surface area of irregular, wrinkly structures such as the brain, the small bowel lumen, or the endocardium of the heart? How will the answer vary depending on the degree of magnification used for measurement? Is "regular" sinus rhythm really regular—does it have a characteristic scale of time?

Questions like these, which have been of traditional interest in biology [1-3], can now be reexamined using concepts developed in an active branch of the basic sciences called *nonlinear dynamics* [4-8]. In particular, a number of these concepts derive from the study of *fractals*. Nonlinear dynamics, as implied by the name, is concerned with systems whose output is not a linear function of their input. Nonlinearities are, indeed, the rule rather than the exception in biology. In physiology, nonlinear relationships are also commonplace, as a plot of pressure vs. volume in the ventricles illustrates.

A major advance in the study of nonlinear form and function has been the introduction and development of the concept of *fractals* by the mathematician B. Mandelbrot [9,10]. In the decade since its introduction, the fractal concept has already permeated the physical sciences, with applications in the study of turbulence, meteorology, astronomy, magnetization, and polymer chemistry, to name but a few [9,11]. The first papers discussing fractals in physiology have only recently begun to appear [2,7,12-17]. Since this concept remains unknown to the vast majority of medical practitioners and investigators, the present brief overview is intended to provide background on this relatively new field, focusing on incipient efforts to apply nonlinear analysis and fractal constructs to physiology and medicine.

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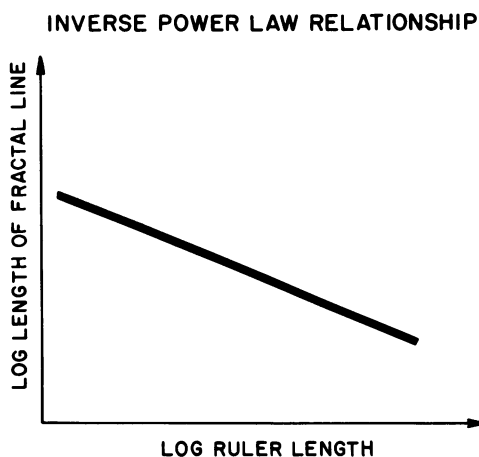
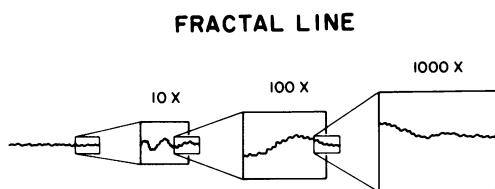


FIG. 1. A fractal “wrinkly” line will have wrinkles upon wrinkles upon wrinkles. As a consequence, the measured length will increase as the size of the measuring stick decreases. Therefore, such a line has no characteristic scale of length. A plot of the log of the ruler length vs. the log of the measured length will yield a straight line with negative slope. This type of scaling is referred to as an inverse power law. Compare with Figs. 2 through 6.

WHAT IS A FRACTAL?

The term “fractal” refers to objects having a *fractional dimension* [9]. Classical geometry deals with regular forms having an integer dimension. A line has dimension 1, a rectangle dimension 2, a cube dimension 3; however, structures in nature are usually irregular (e.g., the outline of a tree or a coastline on a map). Compared with a smooth, classical geometric form, a fractal curve appears wrinkly. Furthermore, if the wrinkles on a fractal are examined at higher magnification, more wrinkles become apparent. If these smaller wrinkles are now examined at even higher magnification, still smaller wrinkles (wrinkles on the wrinkles on the wrinkles) appear, with seemingly endless levels of irregular structure emerging (Fig. 1).

What then is the length of a fractal line? Clearly, there can be no simply defined length for such an irregular curve, since the smaller the ruler used to measure it, the longer the line appears to be. If the logarithm of the ruler size is plotted against the logarithm of the measured length of the line, a linear plot with negative slope will be seen (Fig. 1). Such a straight-line plot on log-log graph paper is a *power-law* relationship. When the slope is negative, the plot is known as an *inverse power-law* relationship. The fractal (fractional) dimension of the wrinkly line is determined by the slope, and it turns out that, for a fractal line such as the coastline on maps of increasing resolution, this value lies between 1 and 2. Thus, a fractal curve of this kind will have a dimension greater than that of a classical line (dimension = 1) but less than that of the rectangular surface (dimension = 2) which could be drawn to enclose the wrinkly curve.

This simple example illustrates three related features of fractal forms: *heterogeneity*, *self-similarity*, and the *absence of a well-defined (characteristic) scale of length*.

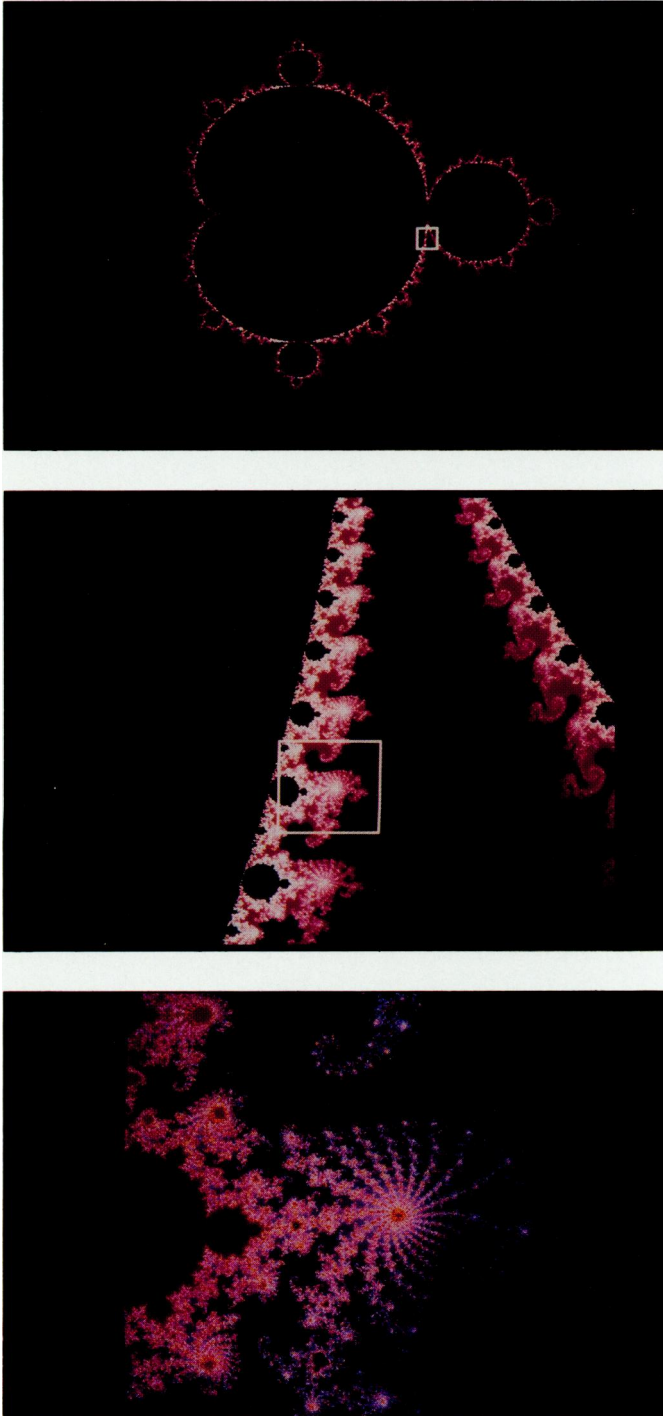


FIG. 2. Computer-generated fractal [10] illustrates features of heterogeneity, self-similarity, and absence of a characteristic scale of length. Panel B shows a blow-up of the region outlined in panel A, and panel C shows a blow-up of the outlined section in panel B. The more closely you inspect these fractal forms, the more layers of detail you will see. Furthermore, the small-scale structure is similar to the large-scale structure. Many forms in nature have these properties (trees, turbulent waves, clouds, coral, mountain ranges, and so forth). Compare with anatomic forms in Figs. 4 through 6.

Fractals are not homogeneous. The more closely they are inspected, the more details are revealed. Classical geometrical forms, in contrast, do not yield greater detail when inspected at higher magnification. Furthermore, the smaller-scale structure of fractals resembles the larger-scale structure: the small-scale and large-scale wrinkles in the fractal curves are said to be *self-similar*. (Fractals, however, do not necessarily have infinite layers of detail.) The multiplicity of these self-similar scales makes it impossible to assign fractals a length independent of the scale of measurement. Figure 2 shows a computer-generated fractal that illustrates these three properties.

The power of fractal mathematics derives in part from its capacity to describe the types of irregular but complex shapes that predominate in nature where straight lines, circles, and spheres are exceptional. The “case history” of the wrinkly line just presented is a model for describing a natural coastline [9] whose length will become longer as it is planimetered from a satellite photograph, measured by the strides of a human hiker, or estimated from the track of a perambulating ant.

Coastlines and abstract computer-synthesized fractals [9,10] have much in common with physiological objects. The geographic features of heterogeneity, multiple scales, and self-similarity are characteristic of a variety of seemingly unrelated biological forms, such as trees, hearts, lungs, and vascular networks, to which we shall return shortly.

FRACTAL TIME [3,9,18,19]

The concept of fractals may be used not only to analyze complex physiological *structures*, but also for modeling certain aspects of physiological *dynamics*. Consider a complex process that cannot be characterized by a single rate or frequency. One discovers that the process in question shows structure (fluctuations) over multiple orders of temporal magnitude (e.g., minutes to milliseconds) in the same way that fractal forms exhibit detail over several orders of spatial magnitude. These temporal variations, consequently, will have a frequency spectrum with a broad profile of responses (*broad-band frequency spectrum*). The term “broad-band spectrum” applies in cases where there is a relatively wide range of low through higher frequencies. If the process is characterized by a single frequency or only a few, closely spaced frequency components, the term “narrow-band spectrum” applies. For example, if a subject’s heart rate fluctuates in an apparently erratic fashion, a broad-band spectrum will be observed. In contrast, if the rate is very regular or if it oscillates in a highly periodic (sinusoidal) manner, a narrow-band spectrum will be seen.

What will be the shape (i.e., the distribution) of the frequency spectrum associated with a fractal process (Fig. 3)? A fractal process, which has self-similar variations on different time scales, will produce a frequency spectrum having a form already mentioned: namely, that of an inverse power-law distribution. With an inverse power-law spectrum, the higher the frequency component the lower its power. A plot of log frequency vs. log power will reveal a straight-line graph of negative slope. This type of broad-band frequency spectrum is sometimes also referred to as *1/f-like*, because of the inverse relationship between frequency (f) and power [18,19].

The concept of fractals, therefore, applies not only to complex geometric forms with self-similar structures and multiple scales of length, but also to certain dynamic processes which have fluctuations over multiple scales of time. These fractal time processes will be represented by power spectra having a broad band of frequencies, with a long, low-amplitude, high-frequency tail (Fig. 3). With this background, we can

INVERSE POWER-LAW ($1/f$ -LIKE) SPECTRUM

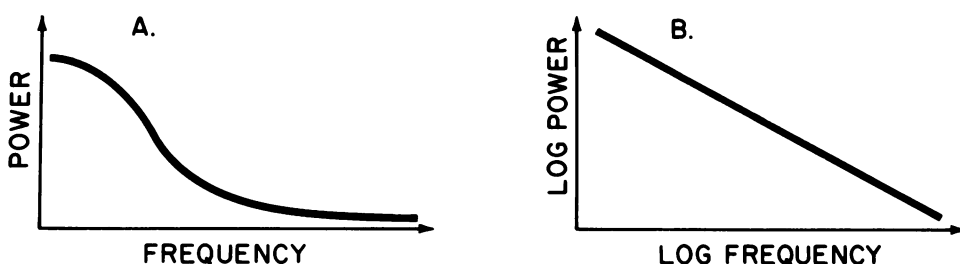


FIG. 3. Fractal dynamics are seen in certain complex processes that show fluctuations (temporal “wrinkles”) over multiple scales of time. Evidently, this kind of process has no characteristic time scale (frequency response), analogous to the lack of a characteristic scale of length in wrinkly fractal structures (Fig. 1). The frequency spectrum of such a fractal time process will show a broad-band pattern with a long, low-amplitude tail of higher frequency components (A). Replotting these data on a log-log plot (B) yields a straight line with negative slope. The term *inverse power law* or *1/f-like* applies to these broad-band spectra in which the higher the frequency, the lower its power.

consider the relevance of fractals to physiological structures and functions that are fractal, using the cardiopulmonary system as a paradigm.

FRACTAL LUNGS AND HEARTS

How can one identify anatomical fractals? The criteria of heterogeneity, multiple scales, and self-similarity are met by a number of structures (Figs. 4 through 6), including the vascular network and the tracheobronchial tree, as well as neural networks and the multiply enfolded mammalian brain [9]. In each case, microscopic examination reveals greater and greater detail and the small-scale structure is reminiscent of the larger-scale form. The biliary network, the pancreatic ducts, and the urinary collecting system are also self-similar branching structures. Additional examples of this nonlinear geometry are provided by cardiac anatomy where fractals appear at multiple levels, from the bifurcating coronary vascular tree beginning on the epicardium to the trabeculated, endocardial “coastline” of the ventricles and the irregular branching pectinate muscle in the right atrium (Fig. 4) [7,17]. The chordae tendineae appear as fractal canopies (Fig. 4), tethering the atrioventricular valve leaflets to the papillary muscles. Embedded within the myocardium is the His-Purkinje system (Fig. 6), an irregular, but self-similar, bifurcating network of conduction tissue that gives rise to multiple generations of daughter branches on progressively smaller scales.

What is the significance of fractal structure and what are the links between fractal structure and physiological function? From a developmental viewpoint, fractals provide a new morphogenetic principle underlying the construction of many apparently unrelated, highly complex, irregular structures by means of a simple code. The basis of this code is self-similarity, so that a complex, branching structure like the bronchial tree or His-Purkinje system can be generated by adding the same structure on progressively smaller scales. Such a fractal algorithm will also serve to minimize constructional error, since it relies primarily on a self-similar, iterative mechanism [2,13,17].

The fractal hypothesis of morphogenesis can be tested in the pulmonary tree (Fig. 5)

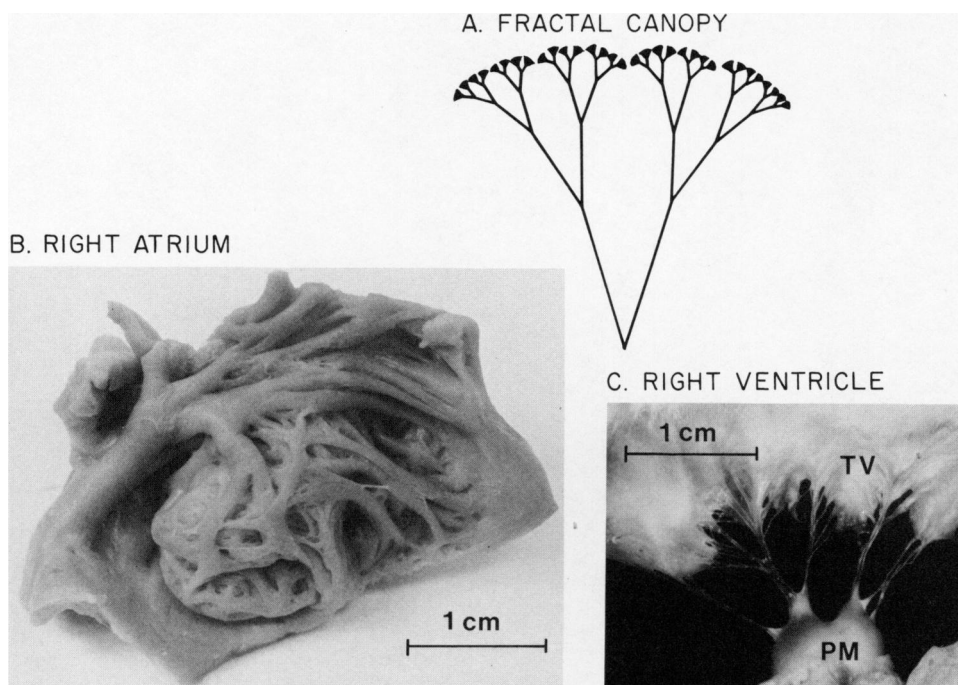


FIG. 4. Computer-generated fractal canopy [9] in panel A shows self-similar branching pattern reminiscent of the right atrial pectinate musculature (panel B), chordae tendineae (panel C), and tracheobronchial tree (Fig. 5). Note the greater variability and irregularity of natural fractals compared with stylized, computer representations. Anatomic specimens are from canine heart. TV, tricuspid valve; PM, papillary muscle.

where detailed measurements of bronchial dimensions have already been made [20]. Traditionally, bronchial scaling from one level of branchings to the next has been fitted to a simple exponential curve: $d(z) = d_0 e^{az}$, where $d(z)$ is the average diameter of tubes in the z^{th} generation, d_0 is the tracheal diameter, and a is the characteristic scale factor [20]. (In this schema, the first generation is composed of the left and right main-stem bronchi, the second generation of the four daughter branches, and so on.) This representation only satisfactorily accounts for data from the first ten bronchial generations, however. The data points for higher generations systematically deviate from the simple exponential regression (Fig. 5A). Weibel and Gomez [20] attributed this discrepancy to a change toward diffusive gas transport in the smaller tubes of the higher generations.

By comparison, if the pulmonary tree is a fractal structure, then there should be no single characteristic scale factor such as that given in the exponential model. For a fractal tree, a *multiplicity of scales* will contribute, each with a different weighting or probability of occurrence. The multiple scales in the fractal model lead to the prediction [16] that the average bronchial diameter per generation (z) should decrease, not as an exponential, but as a type of inverse power law. Therefore $d(z)$ should be proportional to $1/z^\mu$ where μ is the power-law index. Weibel and Gomez's replotted data, as well as data from other mammalian lung casts (Figs. 5B and 5C) do in fact show a good fit to the anticipated power-law scaling, not just for the first ten, but for the twenty-plus generations of branchings that were measured [16].

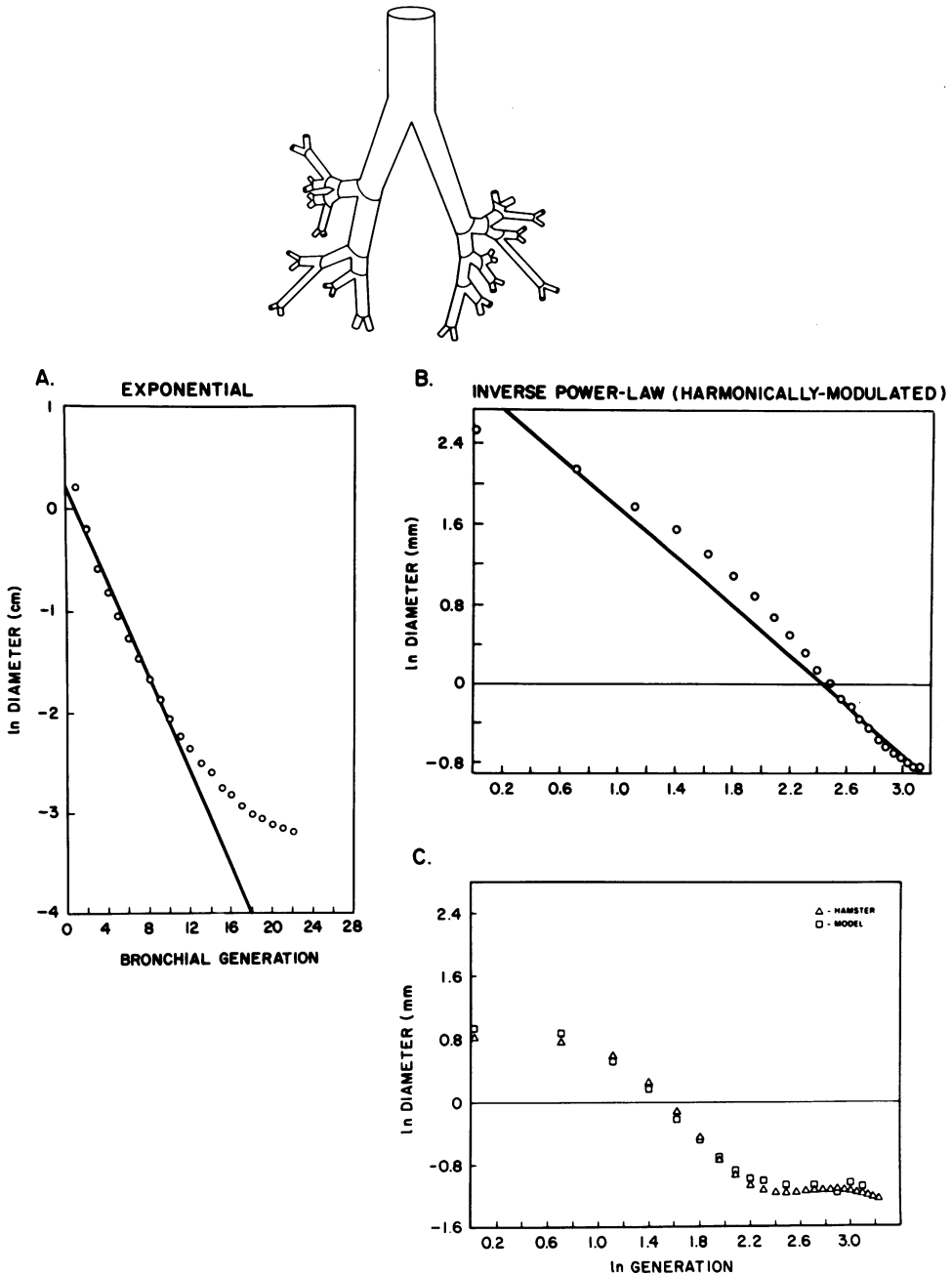


FIG. 5. The tracheobronchial tree, an irregular structure with multiple generations of self-similar branchings, exemplifies fractal architecture. The first four generations are shown here for a human lung cast. (Modified from Weibel ER; *Morphometry of the Human Lung*. New York, Academic Press, 1963.) Simple exponential model (panel A) of mean bronchial diameter scaling only accounts for the first ten generations of human lung; higher generations deviate from the regression line. Replotting the same data (panel B) in a log-log format shows a good fit to an inverse power-law regression. Note "waviness" of data points around the pure power-law regression line. This harmonic modulation is an anticipated consequence of the fractal scaling [16]. A similar type of inverse power-law scaling pattern is observed in a hamster lung cast (panel C) with a strong fit between measurements and fractal model. (Adapted from [16].)

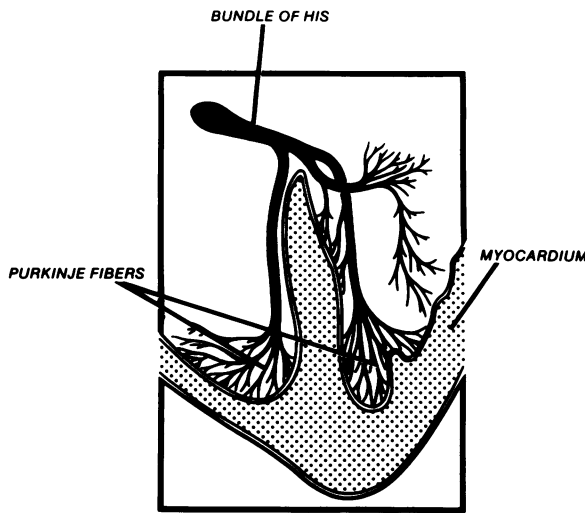
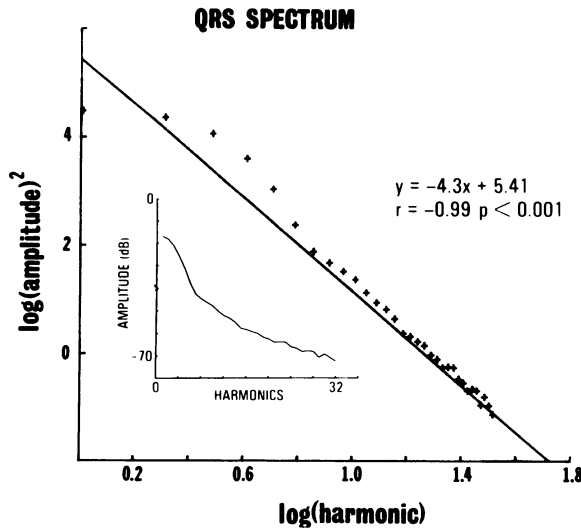


FIG. 6. A, conduction down the fractal-like His-Purkinje system generates the QRS complex. B, the power spectrum of the QRS waveform (*inset*) reveals a broad-band frequency profile, with a long, low-amplitude tail of higher frequencies (>100 Hz). Replotting these data (obtained with a bipolar chest lead in a group of 21 healthy men) in a log-log format reveals an inverse power-law distribution. Fundamental frequency = 7.8 Hz (e.g., 12th harmonic corresponds to about 93.6 Hz). (Adapted from [13].)



From an anatomic viewpoint, this fractal model with multiple contributing scales affords a novel mechanism for structural variability [16]. The marked variations in tube sizes *within* any given bronchial generation noted by Weibel and Gomez are a natural consequence of having many scales with different probabilities of occurrence. This variability, however, is not accounted for by the simple exponential model, which only predicts differences in mean tube size *between* generations.

From a functional viewpoint, the fractal geometry of the lungs may provide an optimal solution to the problem of maximizing surface area for diffusion of oxygen and carbon dioxide [9]. Gas exchange in the lungs over this broad surface area is mediated by the interleaving of three fractal networks: pulmonary arterial, pulmonary venous, and bronchial alveolar [12,17]. Fractal structure, in essence, provides a mechanism for converting a *volume* of dimension three (blood in large vascular tubes and air in the upper respiratory tract) into something approaching an alveolar-capillary surface *area* of dimension two, thereby facilitating gas exchange. Therefore, the fractal dimension

of this system lies between two and three [2]. Similarly, the multiple, self-similar folds and wrinkles of structures such as the small bowel and placenta also provide a fractal surface (of dimension between two and three) to facilitate nutrient exchange.

In terms of cardiac electrophysiology, a related question arises: what is the functional consequence of depolarizing the ventricles via the fractal His-Purkinje conduction network [13]? The effect of the self-similar, irregular network (Fig. 6A) will be to "shatter" a cardiac impulse starting at the His bundle into myriad stimuli, cascading down the His-Purkinje system toward the myocardium. This shattering phenomenon therefore acts to *decorrelate* the impulses, staggering their arrival times at the Purkinje-myocardial interface. Because the process is fractal, however, it cannot be characterized by a single average decorrelation rate. Instead, there will be an infinite series of terms needed to describe this decorrelation process. Each term in this series gives the probability of a higher decorrelation rate contributing to the overall process, analogous to the probabilities associated with the multiple scales in the lung. Mathematically, it can be shown that for a fractal process the distribution of decorrelation rates based on this infinite series will take the form of an inverse power law [13]. Furthermore, since the frequency spectrum of the resultant QRS complex will depend in part on the statistics of the arrival times of impulses at the myocardium, the frequency spectrum of the QRS complex should also take the form of an inverse power law.

Using standard techniques of spectral (Fourier) analysis, we demonstrated that the power spectrum of the normal QRS waveform is consistent with the fractal depolarization hypothesis [13]. Fourier analysis decomposes a waveform into its constituent frequencies and reveals how much each frequency component contributes (i.e., its power) to that waveform. For example, if the QRS were a perfect sine wave, its spectrum would contain only a single frequency component (the fundamental or first harmonic). If, on the other hand, the QRS were a sharp spike (like a pacemaker spike) the spectrum would reveal a white noise pattern; that is, a broad-band frequency pattern with approximately equal contributions from low and higher frequencies. The normal QRS is, in fact, neither a spike nor a sine wave, and its power spectrum shows a distinctive broad-band pattern with a predominance of low-frequency components, as well as a long, low-amplitude tail of higher frequencies (>100 Hz) (Fig. 6B). Furthermore, if one replots these data in a log-log format on which an inverse power-law distribution will appear as a straight line having negative slope, a good fit is obtained [13] (Fig. 6B).

FRACTAL PATHOLOGIES

These findings are consistent with the proposed link between the fractal structure of the His-Purkinje branchings and a fractal time process which is associated with the inverse power-law spectrum of the QRS. What should happen when the His-Purkinje fractal structure is partially disturbed, and what happens when depolarization occurs in a fashion that completely precludes the normal fractal depolarization mechanism? The fractal model of His-Purkinje conduction leads to a specific prediction; namely, that pathologies which disrupt fractal depolarization should be associated with narrowing of the spectrum and a suppression of the high-frequency components of the QRS spectrum [13]. Preliminary support for this prediction comes from data showing a loss of very high-frequency potentials in certain cases of chronic myocardial infarction [21]. The selective decrease of high-frequency potentials in the terminal

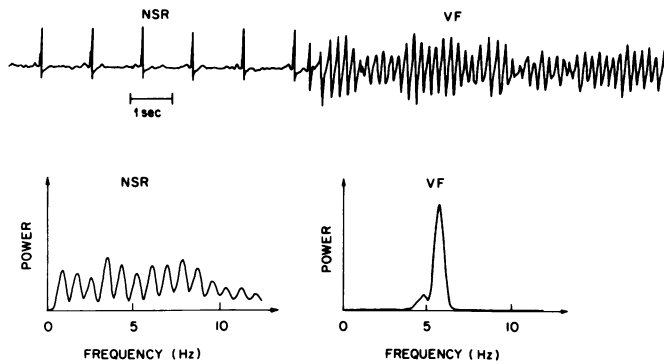
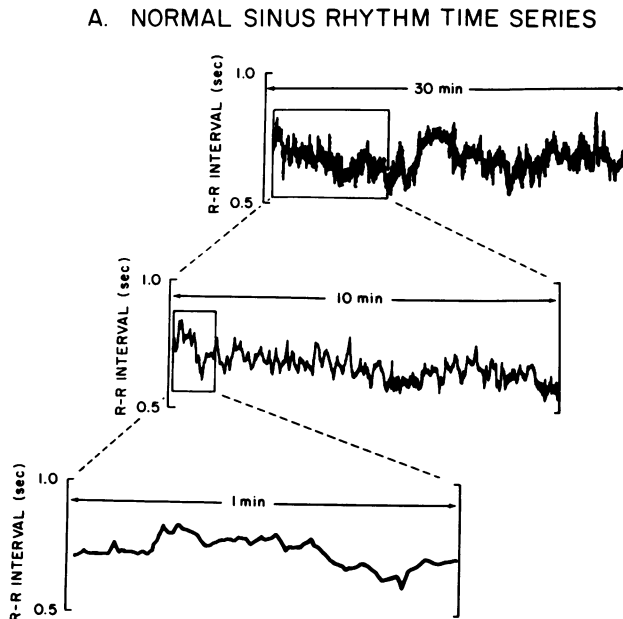


FIG. 7. Transition from normal sinus rhythm (NSR) to ventricular fibrillation (VF) is marked by a change from a broad-band to a narrow-band type of spectrum. The nature of fibrillation is controversial [25,28–30]; however, the narrow-band type of spectrum supports the view that fibrillation is not completely chaotic, as often supposed. (Adapted from [23].)

part of the QRS complex (excluding the ST segment) in patients at high risk for ventricular tachyarrhythmias is also of interest in this regard [22]. Bundle branch blocks would also be predicted [13] to be associated with a relative decrease in the contribution of higher-frequency components.

Finally, the narrowest spectra are associated with arrhythmias where ventricular conduction does not occur to any extent down the fractal system. Frequency analysis of arrhythmias such as ventricular fibrillation [23–25] and torsades de pointes [26] does in fact reveal a very narrow-band spectrum (Fig. 7). These spectral observations are of interest because of the prevailing viewpoint that fibrillation represents a chaotic or turbulent process [27,28], which should have a broad-band spectrum. The data suggest, on the contrary, that the broad-band spectrum corresponds to physiological ventricular activation mediated via the fractal depolarization mechanism (Fig. 7). The narrow-band spectrum of ventricular fibrillation indicates a much more periodic process than generally believed [25]. The counterintuitive observation of a narrow-band spectrum in sudden cardiac death syndromes is actually consistent with recent epicardial [29] and endocardial [30] recordings revealing unexpected spatial and temporal periodicities in canine ventricular fibrillation.

Not surprisingly, inverse power-law ($1/f$ -like) spectra represent a variety of other, apparently unrelated physiological processes with fluctuations over multiple scales of time [31–33]. Under normal conditions, heart rate is commonly assumed to follow an orderly, periodic pattern, implicit in the clinical description of “regular sinus rhythm.” Time series analysis (Fig. 8A) of beat-to-beat heart rate fluctuations in healthy subjects reveals, however, a surprisingly erratic pattern with considerable R-R interval variability. Furthermore, these irregular fluctuations appear over multiple time intervals (Fig. 8A). As shown in Fig. 8B, spectral analysis of this healthy variability demonstrates a broad-band distribution with a relatively wide range of low to higher frequencies. Furthermore, the higher the frequency component the lower its power [33]. This observation of inverse power-law scaling suggests that fractal mechanisms may be involved in the regulation of heart rate variability, giving rise to self-similar fluctuations over multiple time scales [3,13,17]. The details of such a fractal



B. NORMAL SINUS RHYTHM:
INVERSE POWER-LAW SPECTRUM

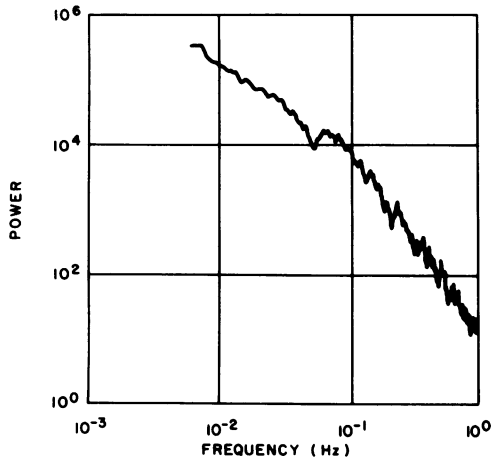


FIG. 8. **A**, normal sinus rhythm (data from a healthy, active, 61-year-old woman) is not strictly regular but shows apparently erratic fluctuations across multiple time scales. **B**, power spectrum of this typical heart rate time series shows broad band of frequencies with inverse power-law scaling, consistent with a fractal process. (Note that normal subjects at rest will show a superimposed frequency peak at about 0.2 Hz, corresponding to the respiratory rate; however, a broad-band $1/f$ -like spectrum as shown here is seen even at bed-rest in normal subjects [33]).

regulatory system are as yet unknown but must involve a complex neuro-humoral feedback network. The higher-frequency heart rate fluctuations are predominantly related to parasympathetic regulation, while lower-frequency fluctuations probably reflect parasympathetic-sympathetic interactions [34].

From a pathophysiological viewpoint, perturbation of a fractal control system may narrow the frequency response of the system, just as disruption of the fractal His-Purkinje system may lead to narrowing of the QRS spectrum [7,13]. This spectral shift, reflecting alterations in fractal scaling, may be of diagnostic and prognostic value. Loss of heart rate variability has already been described in numerous settings, including multiple sclerosis [35], diabetes mellitus with neuropathy [35], fetal distress

[36], bed-rest deconditioning [37], aging [38], and in certain patients at risk for sudden cardiac death [5,39]. Spectral analysis may be useful in quantitating this loss of physiological variability [5,37]. Presumably, the more severe pathologies will be associated with the greatest loss of spectral power, analogous to that seen with the most serious arrhythmias, which begin to resemble a “sine-wave” pattern. We have referred to such narrowing of the frequency spectrum as a *loss of spectral reserve* [7,17]. Another prototypical example of spectral reserve loss is *presbycusis*. With aging, the frequency response of the auditory system typically narrows, with a selective impairment in high-frequency hearing.

The application of spectral analysis to cardiovascular monitoring is attractive because it suggests that Holter records may be the repositories of vast stores of untapped prognostic and diagnostic information contained in the sequencing of normal sinus beats [5,7,17]. Furthermore, this kind of frequency information will not be apparent through conventional data analysis. As an extreme illustration, consider two data sets (e.g., R-R interval time series from two subjects or from one subject under different conditions) with nearly identical means and variances. *T*-test analysis would indicate no significant difference. Yet the power spectra (and the underlying dynamics) could be markedly different, depending on the order of the data points.

CONCLUSIONS AND FUTURE DIRECTIONS

The related concepts of *fractals*, *self-similar scaling*, *broad-band frequency spectra*, and *inverse power-law distributions* offer novel ways of describing certain basic aspects of anatomic form and physiological function. In addition, the disruption of fractal scaling, with its attendant effects on the frequency spectrum (loss of spectral reserve), suggests new approaches to monitoring pathophysiological changes in a variety of settings. At the same time, the application of nonlinear concepts to physiology and medicine raises many questions that serve as a focus for future investigations [7,17]. How, for example, is the fractal scaling information that governs the morphogenesis of a number of complex anatomic forms actually encoded and processed? What are the consequences of fractal architecture for air flow down the branching tracheobronchial tree? What are the consequences of blood flow through the fractal vasculature? What are the mechanisms that underlie the $1/f$ -like scaling observed in heart rate regulation and other complex processes with fluctuations across multiple scales of time? Answers to such questions may uncover basic links between investigations in apparently unrelated fields. One of the most appealing aspects of nonlinear science is that it promises to provide a universal, quantitative language for subspecialists who, unknowingly, have been grappling with complex structures and processes that do not have any characteristic scale of length or time [3].

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