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Lightning and the Heart: Fractal Behavior in Cardiac Function

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Abstract

Physical systems, from galactic clusters to diffusing molecules, often show fractal behavior. Likewise, living systems might often be well described by fractal algorithms. Such fractal descriptions in space and time imply that there is order in chaos, or put the other way around, chaotic dynamical systems in biology are more constrained and orderly than seen at first glance. The vascular network, the syncytium of cells, the processes of diffusion and transmembrane transport might be fractal features of the heart. These fractal features provide a basis which enables one to understand certain aspects of more global behavior such as atrial or ventricular fibrillation and perfusion heterogeneity. The heart might be regarded as a prototypical organ from these points of view. A particular example of the use of fractal geometry is in explaining myocardial flow heterogeneity via delivery of blood through an asymmetrical fractal branching network.

Introduction

The general ideas of fractal systems have been described with vigor and enthusiasm by Mandelbrot [15], [16]. Fractal algorithms are descriptive of many processes in nature. At the extremes are the descriptions of the spread of galaxies by Vicsek and Szalay [26a] and of molecular diffusion [5]. The idea of recursive phenomena leading to interesting mathematical features is not new (e.g., [9]) but the application to wide ranges of phenomena in physical and biological systems is recent and has really been inspired by Mandelbrot's extensive writings.

An introduction to the mathematics of fractals, and extensive and beautiful illustrations of the Mandelbrot set are given by Peitgen and Richter [18]. The basic fractal expression is a summarizing statement describing a recursion. Such expressions are found to define figures which show "infinite" amounts of detail and have "infinitely" complicated boundaries with "infinite" lengths. Many fractals display a form of structure or dynamics that appears the same over a wide range of scale, and have characteristics which are the same at each level of scale relative to the scale of the observation. For a one-dimensional variable the recursion is

$$x_{n+1} = f(x_n, c). \quad (1)$$

The $(n + 1)$ th value of the recursive feature is a function of the n th value plus a constant. The recursion may be deterministic, stochastic, or some combination of both, e.g., deterministic with scatter of a specified form. An example of a purely deterministic recursion is simply $Z_{n+1} = Z_n^2 + C$, where Z and C are complex numbers; this recursion serves as a basis for the definition of both the Mandelbrot set and the Julia sets. These fractal sets portrayed in the complex plane shows an irregular shape, with a boundary of "infinite" complexity. See Peitgen and Richter [18] not only for pictures, but for a lucid explanation. Other examples

are the recursive algorithms used to generate fractal trees for animated pictures. If the parameters remain constant through various generations of branching, a regular tree looking like a fern emerges. If the parameters for each branching are random, irregular, gnarled trees can be generated [17].

Fractal Lengths

Simple examples of fractal measures are found in the lengths of coastlines for example, or the length of the path taken by a lightning bolt. Mandelbrot [16] shows that the apparent length of a coastline (L) depends upon the length of the measuring stick (ϵ), the apparent coast length being longer when a shorter measuring stick is used. A descriptor for the apparent length is given by

$$L(\epsilon) = L(\epsilon_0) \cdot \left(\frac{\epsilon}{\epsilon_0} \right)^{1-D} \quad (2)$$

The reference point at ϵ_0 is arbitrary. The rationale is that when one uses a long measuring stick one misses the bays, inlets and promontories that can be included by using shorter and shorter measuring sticks, thereby adding to the length.

An illustration of a lightning bolt in Seattle is shown in Fig. 1. The length of the lightning bolt can be measured from the photograph using rulers of decreasing length which give increased measures of the total length. For this lightning bolt, we do not have an actual scale for the illustration, but this is of no consequence in determining the fractal dimension D_L . Fig. 1 (right panel) shows the nearly straight line relationship between estimated length of the lightning bolt and measuring stick length.

Another purely mathematical example of a fractal is the Koch snowflake which is derived from an equilateral triangle. The recursion is to take the middle third of each straight line segment and double the length of that third by forming an equilateral triangle with the removed segment (see Fig. 2), and pointing the triangle away from the center of the original equilateral triangle. This is repeated *ad infinitum* on each straight line segment (see Fig. 2). The length of the circumference becomes the original length times $4/3$ to the infinite power and the fractal D (see (2)) is 1.2619 , which is $\log 4 / \log 3$. However, the area encompassed by the snowflake only goes to 1.6 times the original area of the initial equilateral triangle.

Coherence or correlation is implied in fractal systems. In a fractal mountain there is spatial correlation between the heights of peaks which are not too far from each other, and the occurrence of a peak of similar height gets less and less likely as distance away from the starting point increases. Similar coherence is seen in population densities; in the neighborhood of a high population density the population is likely to be dense whereas in the neighborhood of a low population density region the population is likely to be sparse. We will see that in the heart this also applies to regional myocardial blood flows.

Fractal Time

Gaussian noise on a signal is common enough. As one uses shorter and shorter time intervals over which to average a noisy signal, the variance increases as the size of the interval decreases. It turns out that the fractal D in (2), with $L(\epsilon)$ replaced by the variance and ϵ by the time interval length, is 2.0, just as it is for path length due to Brownian motion. Dynamical events which show fractal time scaling seem also to occur with respect to reactions with large molecules such as enzymes [3].

Limits to Fractal Nature

Mathematically, the recursive rule for a fractal system goes on to infinity. In the physical world, there are limits. Galactic clustering follows fractal rules for over two orders of magnitude, but fails to do so at larger distances [14]. Likewise, the lengths of coastlines might seem to increase until one gets down to the level of sand grains or atoms, beyond which a definition of coastal length makes no sense. The fractal rules fail at both ends of the scale.

Temporal fluctuations also have their finite limits. In general, fluctuations in physical systems or chemical systems consume energy, and the more rapid the fluctuations the more energy is required. In an oscillating flow in a tube, large amplitudes at high frequency imply a high amount of kinetic energy, so amplitudes must become vanishingly small at very high frequencies. We think that one can generalize to say that no systems in nature are fractal to zero or infinity.

The Heart

Botanical and Vascular Trees

The form of trees, ferns, corals, and other growing systems are well described by fractals. Lucas Films (now Pixar), the animators for Star Wars, uses fractal algorithms to create trees of many varieties for scenery[4]. Fractal growth has been investigated [20]. The production rules or grammar [12a] and some very nice illustrations of fractal or graftal plants are given by Smith [22]. The vascular tree in the heart, illustrated in Fig. 3, does not look so different from some of these artificial trees. This is not so surprising when one appreciates that vascular growth comes by the budding of capillaries into regions of cell division and differentiation. It would, however, hardly be surprising if there were deviations in the vascular patterns for high generations of branching as the space for growth approaches a limit.

Most physiologists would expect flows to be uniform in the heart, since it contracts regularly throughout, and it requires much energy to perform the work. However, when the blood flow is measured in small pieces of the heart using microspheres or a completely extracted “molecular microsphere,” a broad distribution of flows is found to exist [1]. The probability density functions of regional flows in the heart are quite broad in dogs, baboons, sheep and rabbits, and follow the kind of pattern shown for baboons in Fig. 4. When the heart is cut into large pieces the density functions are narrow. The greater the number of pieces into which the heart is cut, the broader the apparent distribution of flows.

A measure of the dispersion of regional flows is the standard deviation divided by the mean, which we call relative dispersion (and is also known as the coefficient of variation). The relationship between relative dispersion and the mass of the individual pieces of a baboon heart in which observations are made is shown in Fig. 4, right panel. Apart from the very largest pieces, the data fall on a straight line fitted by the power law

$$RD(m) = RD(m=1) \cdot m^{1-D_m} \quad (3)$$

where $RD(m=1)$ is the relative dispersion at an arbitrary mass of 1 g, and D_m is the fractal dimension describing the slope of the relationship. This is similar in form to (2). In various animals the values of D are around 1.2 for data without correction for measurement noise.

Does a Log-Log Relation Expression Prove That the Phenomenon is Fractal?

At this point, taking the data of Fig. 4 at face value, one can say that the log-log description of (3) is not only adequate but pretty good. But log-log relationships are all too common in a variety of situations, and the users of log-log plots are often accused of using such plots to hide noise. So the question is, “Can one go beyond description to explanation?” The log-log relationship between RD and piece size is suggestive of a fractal principle of self-similarity upon scaling. What might the underlying recursion be?

Space-Filling Networks

Trees branching into open space and fractal snowflakes have room to expand. But hearts and lungs and other organs occupy a limited space and the networks of nerves or vessels that penetrate them are servants to the principal occupants of the space, the functioning parenchymal cells of the organ. In fact, the form of the structure of the microvascular network is virtually completely defined by the cells of the organ. In skeletal and cardiac muscle the capillaries are arrayed parallel to the muscle cells, with some cross-branches. The same kind of master-slave relationship can be seen for nerves, secretory ducts, lymphatics, the bronchial tree, and so on. In general, these servant structures penetrate the interstitial space and are molded by that space. This is quite understandable if one looks at the system as being guided in its growth by the need for the nerve or the vascular system to invade the interstitium and follow the lines of least resistance, as do electrical currents whether they be in the myocardium, or between the clouds and the earth. This leads to the question of whether the fractal growth and form of the vascular network can give rise to observed heterogeneities of flow in the heart.

Dispersion of Flows in an Asymmetrical Branching Network

We want to find out what the distribution of flow is in a branching network of vessels. The first network we consider is an asymmetrical branching network. We start out with a main stem vessel of length L_0 and radius r_0 . This is the parent vessel of two daughter vessels which have their lengths decreased by a factor f_L and f_S with respect to L_0 . Their respective lengths are then $f_L L_0$ (subscript L indicates longer vessel) and $f_S L_0$ (subscript S indicates shorter vessel). The radius of the longer daughter vessel is ar_0 and that of the shorter vessel becomes br_0 . The two daughter vessels form the first generation of branches (see Fig. 5). Each of the first generation of branches again forms branches and their daughter branches (the second generation of branches) have the same ratios of length and radius to their parent (the first generation of branches), as described above. The resistance of each branch segment R is taken to be proportional to length divided by r^4 (Poiseuille's law), so that $R = K \cdot L/r^4$, where $K = 8\eta/\pi$, with η = viscosity. We then find the resistances R in generation 0 to 2 as indicated in Fig. 6.

The branching goes on for N generations, with f_L , f_S , a and b constant for all branch points. This branching tree represents the arterial part of the network. It connects to a venous tree of the same form. Each branch in the arterial network has a corresponding branch in the venous network of the same length. The radius of the corresponding vein is increased by a factor f_v from the arterial branch. Corresponding end branches in the arterial and venous tree are connected via capillary units with resistance proportional to that of the arterial end branch. Consider now any branch point in the arterial network and the corresponding branch point in the venous network. There is a pressure difference between the two branching points which is the same for the pathway via the long branch (and the tree that it generates) as for the pathway via the short branch (and the tree that it generates). The resistance for the tree depending on the long branch is proportional to f_L/a^4 while that of the short branch path is proportional to f_S/b^4 . We want to determine the fraction γ of flow which goes down the long branch. Of course a fraction $1 - \gamma$ then goes down the short branch. Since the pressure

difference from an arteriole to its paired venule is the same for both pathways, and flow is inversely proportional to resistance we get

$$\frac{\gamma}{1-\gamma} = \frac{f_s a^4}{f_t b^4}. \quad (4)$$

The relative distribution of flow between the two branches does not depend on the branch level or the absolute value of the resistance. But the total resistance and the flow F_0 for a given pressure head depends on the number of generations of branching. The flows F emerging from the network after n branchings have the value

$$F = \gamma^k (1 - \gamma)^{n-k} F_0 \quad (5)$$

where k assumes integer values from 0 to n . The result is a discrete distribution of flows. The frequency of occurrence of the k th flow of n discrete levels of flow is $n!/(k!(n-k)!)$; the fraction of the n th generation of branches having the k th flow is $n!/[k!(n-k)!2^n]$. The average flow F_{av} after n branchings is $2^{-n}F_0$. The discrete density distributions of flows for three values of γ are shown in Fig. 7 (upper), and their pseudocontinuous representations in the lower panel. The distributions broaden and skewness increases as γ deviates further from 1/2. The relative dispersion RD is

$$RD = \sqrt{2^n (\gamma^2 + (1 - \gamma)^2)^n - 1}. \quad (6)$$

The number of arterial endings N is 2^n and $n = \log(N)/\log(2)$. Therefore we find for RD

$$RD = \sqrt{N (\gamma^2 + (1 - \gamma)^2)^{\log(N)/\log(2)} - 1}. \quad (7)$$

This fractally-based expression cannot be reduced to the form of (2).

We fitted this expression to the data on the relative dispersion of regional flows measured in the heart of a baboon (see Fig. 8). To begin with we assumed that the total number of branchings was $\log N / \log 2$ with N the number of pieces. However, the fit was much improved when we assumed that the first generation of branching was symmetric and did not contribute to the dispersion of flows. This gave values of γ around 0.45. The slope of the relation was about right. However, we should be aware that the RD in the model is for flows in the arterial tree after branching n times. In order to interpret these flows as regional perfusion the additional assumption must be made that each vessel after n branchings supplies an equal volume of tissue and that the tissue is at sampling precisely divided into the supply regions of the vessels. The model fails to account for cutting the tissue in pieces that includes part of regions supplied from more than one artery of the appropriate generation. Letting the first generation be symmetric partially compensates for this source of error.

This simple algorithm for a branching network gives rise to an appropriate probability density function of regional flow, and a roughly appropriate slope. The slope tends to flatten too much at finer spatial resolution. The model offers a naive explanation for the distribution of flows, but does not prove that this particular fractal network describes the vascular system

of the heart. It is likely that quite a few different fractal models can give rise to the correct relative dispersions.

The distributions of regional flows in the hearts of awake baboons over a series of observations made at different times did not appear to be Gaussian, but rather were somewhat leptokurtic (higher peaked) than the Gaussian distribution. In certain animals the distributions were consistently slightly left-skewed and in others slightly right-skewed. Certainly the fractal network described above could not be left-skewed since for all values of γ different from 0.5 we would get right-skewed distributions. So looking at the higher moments of the distributions may yield further insight into the form of the vascular network required to give the observed results.

A next approach is to make the measurements of branching lengths, radii, branching angles, and so on. Engelson *et al.* [6] have made measurements of lengths and diameters in the spinotrapezius muscle in rats, as did Suwa *et al.* [26] and Suwa and Takahashi [25], on the mesentery and the kidney. Suwa *et al.* measured not only lengths and diameters, but also wall thicknesses and in some cases, intravascular pressures, and in the kidney, the number of glomeruli attached to arterioles of the given dimension. Such work needs to be done on other organs, in order to be able to model the microvascular network.

Fractals in Other Biological Systems

Mandelbrot's [16] illustration of a fractal bronchial network, space-filling in two dimensions, is inspiration to apply these approaches to the lung. A rather successful initial approach is provided by Lefevre [10]. Another example is in the fractal nature of the alveolar surface as measured by Rigaut [19]. Rigaut's work is stimulating in that the apparent length of the cut alveolar surface on the log-log plot against the measuring stick length is curved, tending toward a plateau for small measuring stick length. One can think of this as being an approach to a physical limit. In this case, since the minimum radius of curvature of a cell membrane is about 300 Å, roughness at higher spatial frequencies could occur only with rupture of the membranes. The other possibility is that it is not truly fractal in itself, but like the curve of Fig. 8, has an innate curvature which derives from a basically fractal source. The curvature of our plot of Fig. 8, as in Rigaut's data, serves to remind us that a system which is fractal in one feature need not yield power laws for every aspect of its overall behavior.

Fractal Kinetics

In the heart, as in other organs, one can expect transport phenomena to show fractal characteristics. The first example is Brownian motion. Hindered diffusion, as for hydrophilic solutes penetrating the fibrous meshwork of the interstitium, can also be expected to be fractal. Of greater interest and curiosity is the fractal behavior of ionic channels. Liebovitch *et al.* [12] have shown that corneal endothelium cells have ion channels whose opening and closing times appear to behave fractally. What's more, the precise fitting of the fractal relationship to the observed fluctuations was better than fits with models using one, two or three state Markovian kinetics. Large proteins are likely to have fractal kinetics; Careri *et al.* [3] pointed out that the ranges of observed rate constants are wide; it would not be surprising if all integral proteins and ionic carriers followed fractal kinetics over some limited range. Such is the case for calcium reactions with the calcium photoprotein, aequorin [2], and the same kind of phenomena may be showing up in the variety of rate constants for the association and dissociation of fatty acids from albumin [23], [28]. This fractal behavior may be important for fatty acid transport in the heart since blood fatty acids are bound to albumin. We have found in our laboratory that fatty acid extraction during transcapillary

passage is slowed at high albumin concentrations, the hallmark of a saturable binding or transport process [27].

Chaos

Fractals have some links with another recently burgeoning branch of mathematics, that of nonlinear and chaotic dynamics. A system is said to display chaotic behavior when it is governed by deterministic equations (which can be relatively simple), yet seems to behave in an erratic way, and never reaches a stable periodic behavior. Many such systems have been described and have suggested explanations for phenomena in physics, chemistry, population dynamics, etc. The paths taken by the system through its state space are irregular but bounded. These paths can be continuous or discontinuous and seem to have a fractal geometry [16]. As for fractals, recursive algorithms play an important part in the field of chaos.

It has therefore been discovered that seemingly chaotic processes can be remarkably organized and that simple deterministic mathematical expressions have solutions which appear to be chaotic. The apparent irregularity of the mathematical solution is tempered with the observation that under specified conditions one can define probability distributions for the expected solutions.

Growth Cycles; Predators and Prey, etc

Peitgen and Richter [18] give a nice illustration of the chaotic population growth model which is called Verhulst dynamics or logistic growth. The period of the iteration is a year and the general expression for the population x_N at year N is determined by the difference equation

$$x_{N+1} = f(x_N) = (1+r)x_N - rx_N^2$$

where r is a growth parameter and x_N is population size as a fraction of its stable maximum value. When its growth in one iteration (e.g., one year) makes x_N exceed $x_{\max}$, then the next iteration produces a decrement. High values of r (>2) produce oscillatory phenomena, and values of $r > 2.57$ result in an apparent chaotic nonperiodic change of population sizes over time. The Verhulst process illustrates that even under chaotic circumstances there are periods of nearly periodic behavior followed by periods of apparent chaos.

Turbulence

Turbulence in fluids has been notably difficult to characterize. Both fractals [16] and chaotic dynamics [24] have been applied for the description and explanation of turbulence in fluids. McDonald [13] characterized disturbed flow. This flow was not strictly Newtonian, neither was it what we thought of as turbulence at that time (where there was total mixing throughout a region) but something in between. This something in between is seen at the confluence of rivers, with Reynolds numbers in the hundreds of thousands. Whirls of algae in the converging streams give evidence of turbulence, but the algae from the two converging streams scarcely mix at the interface which remains only a foot or two wide over many hundreds of yards. This can be called stable instability, and illustrates that turbulence does not necessarily mean mixing over broad regions.

Turbulence can be the basis of limit cycling as can be shown with water flowing through a cylindrical pipe. By raising the pressure head, flow can be increased and the Reynolds number increases until, at a critical Reynolds number which is dependent upon the exact nature of the system, the flow becomes turbulent at the entrance to the pipe. The onset of

turbulence increases the resistance and slows the flow, and under the right conditions will bring the turbulence at the entrance back into a stable laminar flow regime, and so it will remain as the bolus of turbulence moves along the pipe. However, when the turbulent bolus exits from the other end of the pipe, the resistance is decreased, the flow goes up with the same pressure head, and the same cycle of events repeats itself. In this situation the turbulent bolus and the stable flow regions were in close proximity but nevertheless maintained their distinctive behavior. In this way chaos gives rise to events structured in time and space.

Control Systems

A variety of control systems produce oscillations. All one has to do is turn the gain too high in a proportional or derivative controller to create oscillations. It might be expected that some oscillating control systems show chaotic behavior. Similar things can be seen with numerical techniques where the integration step size is too large or with various kinds of optimizers. All of these can be set into oscillations which have some structure, and do not resemble white noise.

Chaotic Behavior in Excitable Organs

Atrial and ventricular fibrillation are the classic myocardial phenomena that appear chaotic. The clinical statement on the heart rate in atrial fibrillation is that it is irregularly irregular, and the observations are that the surface of the atrium is pulsing in an apparently chaotic fashion. However, the studies of reentry phenomena and of ventricular fibrillation show that there are patterns of excitation [21] again illustrating that this is organized chaos. A fractal or chaotic algorithm for this has been described by Glass *et al.* [7]. Many other interesting applications of chaos are exposed in the book *Chaos* edited by Holden [8]. Gleick's [7a] book by the same title gives a most readable overview of the development and nature of the field.

Conclusion

Often we see patterns in biology that suggest an underlying fractal geometry. One can regard the phenomena of fractal geometry of systems and of fractal or chaotic behavior as new tools for the modeling of biological phenomena.

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Biography

James B. Bassingthwaight, photograph and biography not available at the time of publication.

J. H. C. M. van Beek, photograph and biography not available at the time of publication.

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Fig. 1.

Left: Lightning over Seattle. (Photograph by Greg Gilbert, *Seattle Times*. Published with permission.) Right: The apparent length of the lightning bolt is a fractal function of the measuring stick length.

Recursive Extension of a Line ... a Simple Fractal System

Fig. 2.

Recursive lengthening of line. Left: Replacing the middle 1/3 by two straight lines increases length by 4/3 each iteration. Right: Starting with an equilateral triangle gives the Koch snowflake.

Fig. 3. Vasculature of the chinchilla myocardium. The tissue is intact, with the vascular space filled with a silicon elastomer, Microfil, and the extravascular tissue made transparent by clearing with alcohol and methyl salicylate. Short intervals on scale are 1 mm.

Fig. 4.

Left: Probability density functions of regional flows in a baboon heart at three sample sizes. The larger samples are obtained by forming aggregates of adjacent pieces. RD = standard deviation/mean, m = average mass of samples. Right: Fractal relationship between the relative dispersion RD of regional flows in this heart (measured by the deposition density of a microsphere) and the mass m of the pieces into which the heart has been divided. The rightmost point was not used for the regression. The regression equation is $RD(m) = 16.9m^{-0.249}$ and $r = 0.996$.

Fig. 5.
An asymmetrical branching network with fractal recursions for branch lengths and radii.

Fig. 6. Distributions of resistances (left panel) and flows (right panel) in an asymmetrically branching network. Two levels of branching are shown.

Fig. 7.

Upper panels: Discrete density of the frequency of occurrence of a certain flow value. The sum of the heights of the bars is one. Lower panels: “Pseudo-continuous” representation of the density given in the upper panels. This was obtained by dividing the frequency at each flow by the range of the flow axis in which the points were closer to that particular flow than to its neighbors. For the highest and lowest flow the distance to the nearest flow was used to divide the frequency.

Fig. 8.

Fit of the fractal vascular geometry model to observed relative dispersions of flows in the baboon heart of Fig. 4. N is the number of pieces into which the heart was cut. The theoretical (continuous line) curve fits the data (points and dashed line) moderately well. A fractal straight line relationship (equivalent to that in Fig. 4 but using N pieces instead of m , mass of pieces) fits well except that the point for $N = 4$ is far off the line.