FRACTALS: A NEW LOOK AT BIOLOGICAL SHAPE AND PATTERNING

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It is accepted beyond any doubt that biological shape is related to function. Numerous examples could be mentioned. Folding of a protein is important for its function [1]. The shape of a cell accounts for differential DNA synthesis [2]. Left-handed DNA relates to specific function of genes [3]. The patterning of biological form has intrigued developmental biologists over the last decades. However, there are no satisfactory qualitative and quantitative models from which to infer statistical properties and theories that directly relate biological shape to function.

Part of the problem lies in the fact that biological structures often cannot be described within a straightforward Euclidean framework. Similar problems are encountered in many other fields of science. For example, clouds are not cubes or spheres, coastlines are not circles, lightning is not straight lines, and so forth. Euclidean geometry leaves these structures without a framework that can be used to quantitatively describe them. Nature is full of such structures. As a matter of fact, it is the Euclidean structures that are rarely found in nature. In the absence of a mathematical framework for the "amorphous" patterns, theories or models that are devised in order to explain and/or describe those patterns are inadequate.

Lately, a new geometry has been developed in order to describe the irregular and fragmented non-Euclidean patterns of nature. It is called *fractal geometry*. In order to introduce the reader to the concept of fractals, some familiarity with the notion of dimension is needed. We therefore suggest at this point that the reader consult figure 1.

The authors thank Daniel Fishman for excellent photography and Dr. P. Meakin for sending and permitting the publication of figure 3.

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0031-5982/87/3003-0531$01.00

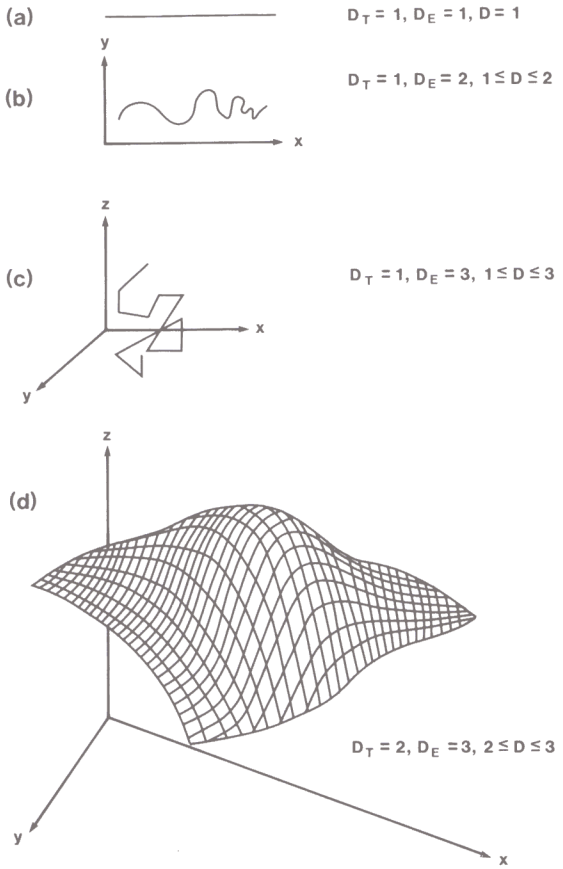

FIG. 1.—There are two basic definitions of dimension: the Euclidean (D_ϵ) and the topological (D_T). They both can assume only the integer values 0, 1, 2, 3, but, for a specific object, they may not be the same. In order to divide space, cuts that are called surfaces are necessary. Similarly, to divide surfaces, curves are necessary. A point cannot be divided since it is not a continuum. Topology tells us that, since curves can be divided by points which are not continua, they are continua of dimension one. Similarly, surfaces are continua of dimension two, and space is a continuum of dimension three. Apparently, the topological dimension of a point is zero. According to the Euclidean definition, a configuration is called E-dimensional if the least number of real parameters needed to describe its points is E. For example, to describe the points of a straight line, one needs only the x, say, coordinates of those points. Therefore, D_ϵ of a straight line is one. On the other hand, to describe the points of the curve (b) above, one needs the coordinates of the points in x and y. Therefore, D_ϵ of that curve is two. Similarly, in order to describe the points of the surface (d), one needs the coordinate of the points in x, y, and z. Therefore, D_ϵ of that surface is three. The quantity D is the fractal dimension (see text for explanation).

The concept of fractals can be introduced by a classic example given by the founder of fractals, Mandelbrot [4]. Let us assume that we measure the length of a given segment of a straight line by employing a measuring unit (yardstick) of length ϵ. With this yardstick we walk along the line, each new step starting where the previous step leaves off. If the number of steps is $N(\epsilon)$, then $\epsilon \times N(\epsilon)$ is a measure of the length, $L(\epsilon)$, of that segment. As we repeat the same procedure but with smaller and smaller ϵ, the number of steps, $N(\epsilon)$, becomes greater and greater. The measured length, however, remains the same. If one plots the logarithm of $N(\epsilon)$ against the logarithm of ϵ, one finds that all the points fall on a straight line of a negative slope, S. One may, therefore, write that $N(\epsilon) \propto \epsilon^S$ and $L(\epsilon) \propto \epsilon^{1+S}$. By setting $S = -D$, one may write that $N(\epsilon) \propto \epsilon^{-D}$ and $L(\epsilon) \propto \epsilon^{1-D}$. The quantity D is called the similarity dimension or the Hausdorff-Besicovitch dimension (see [4] for more details), and by design it preserves the ordinary dimension's role as exponent in defining a measure. In the case of straight lines or other geometrical curves, $D = 1$, which coincides with the topological dimension of any curve. When, however, we repeat the above procedure considering some irregular curve that cannot be described by Euclidean geometry, such as a coastline, we find that, as ϵ becomes smaller and smaller, $L(\epsilon)$ tends to increase without bound. The reason is that for smaller and smaller ϵ, more and more details of the coastline appear that add to the measured length. In such cases, it is again found that $N(\epsilon) \propto \epsilon^{-D}$ and $L(\epsilon) \propto \epsilon^{1-D}$, but now $D > 1$ and need not be an integer! Based on the above, Mandelbrot [4] gives the following definition of a fractal: A fractal is a set for which the Hausdorff-Besicovitch dimension (or fractal dimension), D, strictly exceeds the topological dimension, D_T. The above arguments can be extended for structures of higher topological dimensions. It should also be mentioned that for fractals, $D \leq D_\epsilon$, where D_ϵ is the Euclidean dimension of the space in which the set is embedded. The great success of fractals lies in the fact that shapes of common origin (clouds, for example) exhibit a reproducible fractal dimension (i.e., they exhibit the same D) no matter how different they appear. The fractal geometry thus provided a geometric mathematical framework for the description of irregular and fragmented patterns that appear random and led to the development of models that generate fractal structures, thus throwing light on some of the underlying processes that govern the formation of these patterns.

Recently, fractal geometry has gained popularity, has been applied to several biological systems, and has succeeded in unifying and/or explaining several biological and physiological phenomena. The fractal geometry of vegetation, for example, led to important considerations about the insects inhabiting the leaves and their body-size-related metabolism [5]. It was found that, when the fractal nature of vegetation is considered, there is more usable space for smaller animals living on

vegetation than for larger animals, and it was demonstrated that in this case there are more individuals with a small body length than a large body length. Irregularly shaped cells in vitro have an identical fractal dimension, and so do their tracks as they move [6]. The examination of the degree of irregularity of protein surfaces led to the conclusion that individual regions of protein show considerable variation in their fractal dimension [7]. These variations may be related to structural features, such as active sites, suggesting that protein surface texture may be a factor influencing molecular interactions. At the same time, nonequilibrium models that simulate fractal structures which resemble structures in nature were developed, and fractal geometry provided an invaluable tool in verifying these models. These models involve both determinism and chance, and they are called nonequilibrium growth models because randomness dominates the structures that they produce. The first such model was the so-called Diffusion Limited Aggregation (DLA) model, according to which well-defined fractal structures are generated by adding "particles" to a growing cluster or aggregate via random-walk trajectories [8]. (A point is said to perform random walk if, at successive instants of time separated by the interval Δt, it moves by steps of fixed length $|\Delta l|$ in randomly selected directions. Random walks simulate Brownian motion, which is the motion of a particle suspended in a liquid.) Such a model simulates successfully phenomena like the viscous fingers that are generated if one attempts to use a low-viscosity fluid (like water) to push a high-viscosity fluid (like oil). This process gives rise to a fluid instability phenomenon in which the low-viscosity fluid forms characteristic fingers extending well into the high-viscosity fluid [9, 10]. A number of closely related models followed according to which fractal structures are generated by adding points of a two-dimensional lattice to a growing cluster via a growth probability. According to this technique, at each step there are specific candidates (lattice sites) that can be added to the growing cluster. Each one of those points is associated with a probability (which is termed growth probability). From the probabilities of all candidates, a probability distribution is defined from which a point is selected randomly and added to the evolving structure. For example, in physics, dielectric breakdown was accurately simulated by assuming that the growth probability is, at each time step, a function of the local potential field [11]. Similarly, the development of morphology in biological systems was explored by assuming that the growth probability depends on the local concentration of some substance that diffuses from a surrounding exterior source and is consumed by the growing system [12]. Even though direct comparison with biological patterning was not attempted, models like the above can indeed account for developments of biological systems like the development of blood vessels. Figure 2 shows the observed pattern of developing blood vessels around a 4-day-

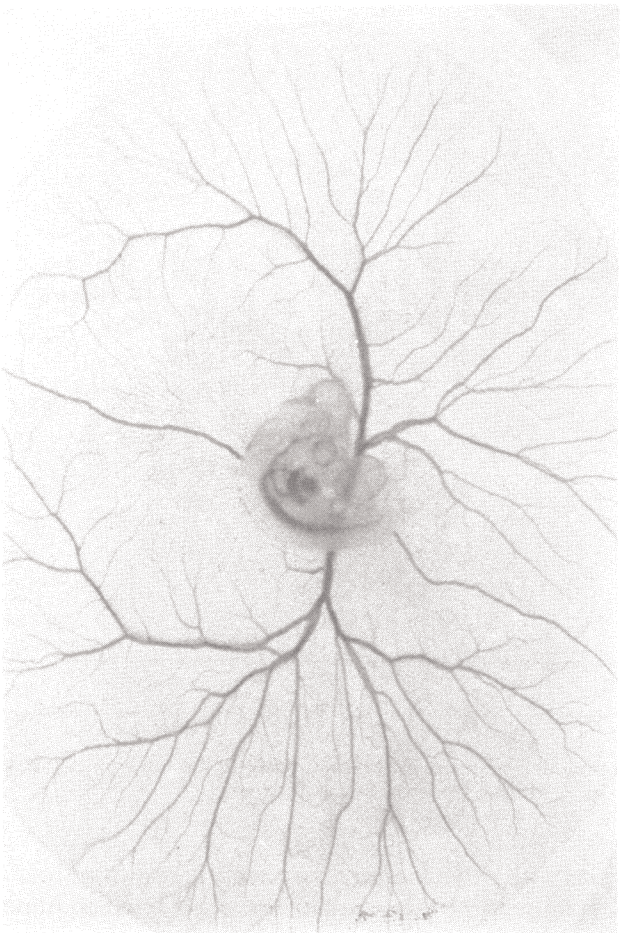

FIG. 2.—Patterns of developing blood vessels around a 4-day chick embryo

old chick embryo. The similarity of this pattern to the pattern in figure 3 which has been generated by Meakin [12] is striking and supports his proposed model for biological pattern formation. The fractal dimension of the pattern in figure 2 is close to 5/3, which is very similar to the fractal dimension of the simulated pattern in figure 3. The approach used to infer the fractal dimension of figure 2 can be found in [11]. In addition, the fractal dimension of the pattern in figure 2 is similar to the fractal dimension of structures that mimic dielectric breakdown [11] and viscous fingering [10].

What is the driving force of generation of such structures in the circulation system (or nervous system)? And, How do these structures account for the physiology? The fractal dimension of the blood vessels and

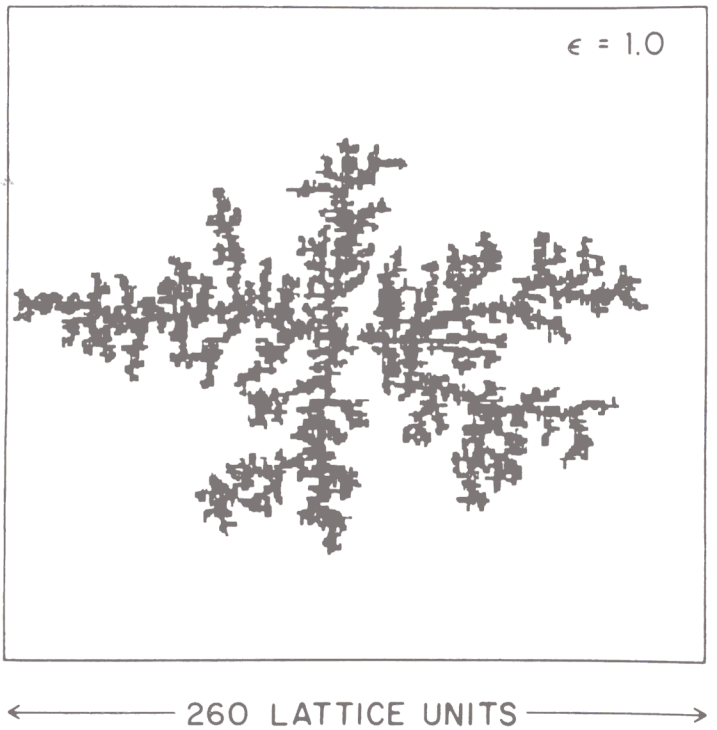

FIG. 3.—Computer-generated pattern according to the nonequilibrium growth model proposed by Dr. P. Meakin (courtesy of Dr. P. Meakin).

the similarities with other defined systems suggest that their generation should be explained by a nonequilibrium growth which depends on the concentration of one or some substance(s) that diffuses from the cells that build up the circulation system, and on chance. The fractal geometry thus allows us (1) to speculate that reactions occurring in physical phenomena can be applied to biological phenomena, (2) to verify models that describe various phenomena, (3) to understand some of the physical and chemical processes behind biological patterning that appear to be random, and (4) to quantitatively establish via a reproducible fractal dimension the relation between shape and function.

The elucidation of the fractal patterns in biological systems and their significance in the physiological events will support the notion of the uniqueness of the fractal geometry of nature. The very question is, Why should physical or biological phenomena develop by fractal geometry? Work by one of us (A. A. Tsonis, unpublished) has related fractal patterning to minimum energy consumption. Such an idea would indeed

make perfect sense. The fractal way of nature should simply be the most economical.

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