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Fractals in the Neurosciences, Part I: General Principles and Basic Neurosciences

Antonio Di Ieva[1,2], Fabio Grizzi[3], Herbert Jelinek[4,5], Andras J. Pellionisz[6], and Gabriele Angelo Losa[7]

Abstract

The natural complexity of the brain, its hierarchical structure, and the sophisticated topological architecture of the neurons organized in micronetworks and macronetworks are all factors contributing to the limits of the application of Euclidean geometry and linear dynamics to the neurosciences. The introduction of fractal geometry for the quantitative analysis and description of the geometric complexity of natural systems has been a major paradigm shift in the last decades. Nowadays, modern neurosciences admit the prevalence of fractal properties such as self-similarity in the brain at various levels of observation, from the microscale to the macroscale, in molecular, anatomic, functional, and pathological perspectives. Fractal geometry is a mathematical model that offers a universal language for the quantitative description of neurons and glial cells as well as the brain as a whole, with its complex three-dimensional structure, in all its physiopathological spectrums. For a holistic view of fractal geometry of the brain, we review here the basic concepts of fractal analysis and its main applications to the basic neurosciences.

Keywords

brain, complexity, fractal analysis, fractal geometry, microglia, neuroanatomy, neuron, neurosciences

Early Principles of Structural-Functional Organization of the Nervous System

The decisive pathbreaker in the brain's cognition and its anatomic understanding occurred in the Renaissance and in the following centuries. In less than half a millennium, the field of geometry advanced from Euclidean geometry to the nonlinear dynamics of fractals and chaos (Gleick 1987) in a quest for geometric unification of neuroscience with genomics: "Our understanding of both the genome and the brain will remain partial and disjointed until we reach a unification of the intrinsic mathematics of structuro-functional geometry of both—as the first is without question a foundation of the second" (Pellionisz and others 2013). Progress could not have occurred without accomplishing major paradigm shifts. Empowered by light microscopy, pioneering studies of Camillo Golgi (1843–1926) clashed with a drastically different interpretation by Santiago Ramón y Cajal (1852–1934). Golgi developed the black silver staining method, suitable for detailed visualization of cells of neural tissue (Fig. 1A). He first recognized the intracellular Golgi complex as well as Golgi type I neurons (i.e., pyramidal cells with long axons) and Golgi type II neurons (i.e., stellate neurons with short or no axons) in the human cerebral cortex and cerebellar cortex. However, Golgi (1873) postulated his mistaken "reticular theory" in which nervous fibers form a continuous network. Ramón y Cajal (1899) proposed an opposing concept, the neuron theory, according to which the relationship between nerve cells was not one of continuity but rather of contiguity, mediated by spines

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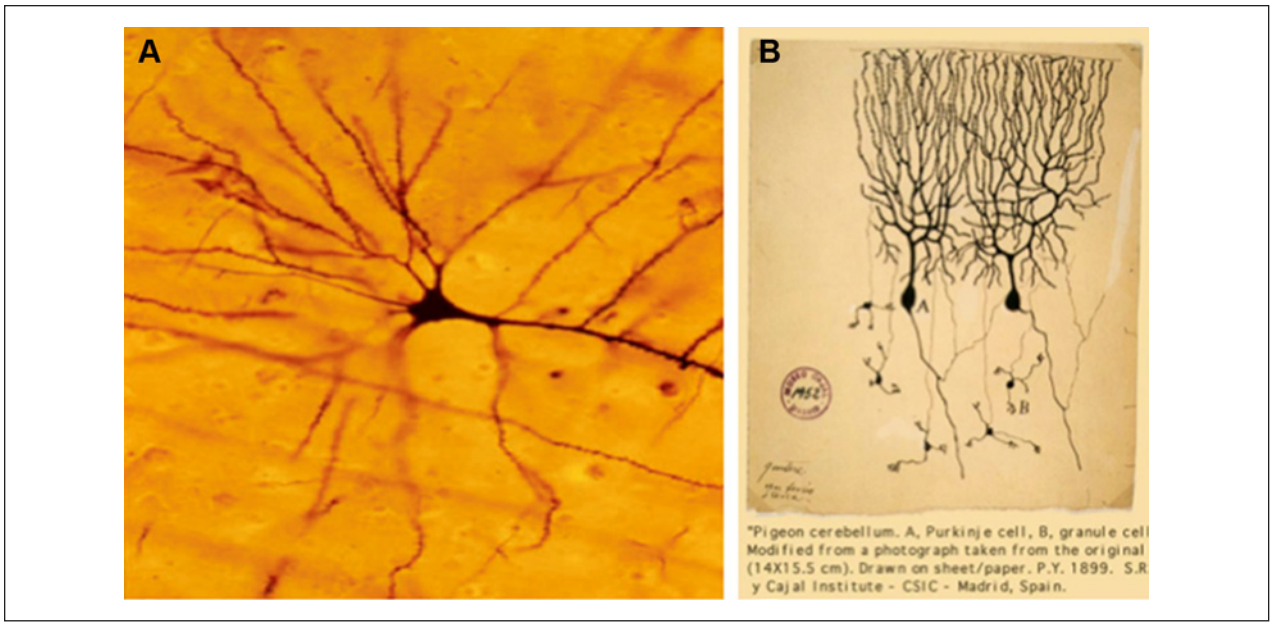

Figure 1. (A) Pyramidal cell of the prefrontal cortex stained by the Golgi method (black reaction): potassium dichromate + silver nitrate → silver chromate (microcrystallization). Image provided by Bob Jacobs (Laboratory of Quantitative Neuromorphology, Department of Psychology, Colorado College, Colorado Springs, CO, USA). (B) Ramón y Cajal drawing of two cerebellar Purkinje cells (pigeon's cerebellum).

protruding from dendrites fitted to receive input from the synapses of other neurons and emitting their output along a single axon. Figure 1B shows that granule cells appear on the diagram-like small blobs. The large Purkinje cell body looks like a giant blob with an elaborate two-dimensional (2D) framework of dendrites that mesmerized generations after the publication of Ramón y Cajal's (1911) epic two-volume book, a veritable bible of neural structures.

Complex System Theory

The umbrella term used to brand the main characteristics of natural objects as "complex," including features of biological entities, was temporary shorthand to sum up poorly understood descriptors, such as "regularity," "irregularity," "shape," and even "behavior." The term "complexity" was introduced by Ludwig von Bertalanffy (1901–1972) (von Bertalanffy 1969), along with Joseph Henry Woodger (1894–1981) and John Burdon Sanderson Haldane (1892–1964). The study of the complex relations underlying the structure and behavior of a system represents the primary goal of complex systems theory. Its proponents described natural systems as consisting of parts differently interrelated to each other but in a largely unexplained manner. Neil Fraser Johnson (1961–) stated, "Even among scientists, there is no unique definition of complexity" (Johnson 2007).

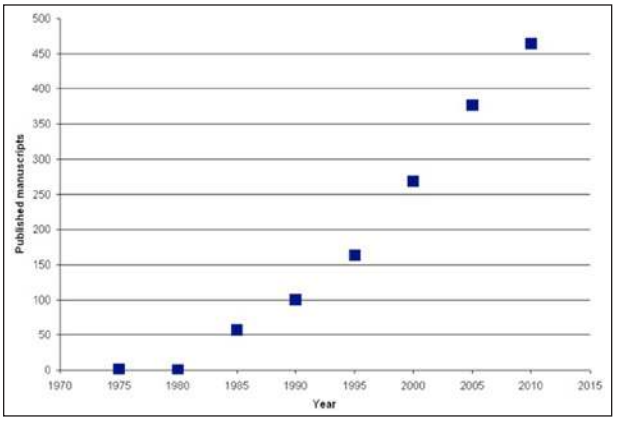

Figure 2. Fractal geometry, originally introduced by Benoit B. Mandelbrot (1924–2010), is currently applied in different fields of investigation. The number of published articles that use fractal geometry in the PubMed database has rapidly increased during the last years.

The need for a better way of classifying natural as well as pathological anatomic forms, and objectively quantifying their dynamic changes, prompted an increasing number of investigators to adopt fractal geometry, a branch of nonlinear mathematics (Fig. 2), over mathematically heterogeneous and nonspecific theories of "complex systems." The physical-mathematical but overly vague concept of "complexity" that reigned by the end of the 19th century (Poincaré 1905) is generally regarded by the

contemporary scientific community as not sufficiently operational. Consequently, it yielded to the theoretical/heuristic breakthrough provided by fractal geometry (Mandelbrot 1983).

From Euclidean to Fractal Geometry

Unlike ancient Euclidean geometry, so simplistic in the representation of most man-made objects and so distant from the power to depict natural forms, fractal geometry is ascertained as a discipline suitable for representing the profiles of a mountain or a coast, the clouds, crystalline or molecular structures, and various biological dynamic processes. As stated by Grizzi and Chiriva-Internati (2005), subcellular components, cells, tissues, and organs exhibit a pivotal property of all anatomic systems, with their description advancing from Euclidean to fractal geometry. At macroscopic as well as at microscopic levels of observation, intrinsic complexity is apparent. One of the pre-eminent characteristics of the entire universe is a tendency to form multilevel structures of "systems within systems," each of which forms a "whole in relation to its parts and is simultaneously part of a larger whole" (Grizzi and Chiriva-Internati 2005).

The concepts of fractal geometry were developed by Benoit B. Mandelbrot (1924–2010) based on prior pioneering work by Jules Henri Poincaré (1854–1912), Georg Ferdinand Ludwig Philipp Cantor (1845–1918), and Lewis Fry Richardson (1881–1953). Mandelbrot first used the term "fractal" in his book entitled *Les Objets Fractals: Forme, Hasard et Dimension* (Mandelbrot 1975) and subsequently in *The Fractal Geometry of Nature* (Mandelbrot 1983). He came forward with a universal mathematical code for interpreting the multifarious world of natural forms. As Michael Fielding Barnsley (1946–), a British mathematician, entitled his books, we find *Fractals Everywhere* (Barnsley 1988), not only as monofractals, but *SuperFractals* (Barnsley 2006).

It is now recognized that the "rough" shape is the most important property of every anatomic system, strongly influencing its behavior and different relationships with surrounding components. The definition of the concepts of "form" and "function" of a particular cellular or subcellular structure and its description in quantitative terms represent two problems. Even today, the concept of "form" and its quantitation are not completely resolved, leading to broad debates among morphologists. According to D'Arcy Wentworth Thompson (1860–1948), "it is in terms of greatness and direction that we have to report every conception of our forms. The form of an object is defined in fact when we know its greatness, absolute or relative in the different directions" (Thompson 1992). Morphometric analyses based on the concepts of area, perimeter, form factor, or Feret diameter, although largely used in the quantitative analysis of morphological forms, only approximately define the object under measurement. Such an approximation derives from the rigidity of the reported linear measures.

As opposed to "regular measures," natural objects are characterized by irregularity and rough shapes that are seemingly very complex. We are used to thinking that natural objects have a certain form and that a characteristic scale determines this form. To correctly measure the properties of the object, such as length, area, or volume, we measure it at a resolution finer than the characteristic scale of the object. This simple idea is the basis of Euclidean geometry and the theory of measurement. However, Mandelbrot (1967) brought to the world's attention the fact that many natural objects simply do not have this preconceived form. The concept was furthered by pointing out that living objects also have structures in space that cannot be characterized by one spatial scale (Bassingthwaighte and others 1984). Based on these assumptions, the fractal dimension (FD) was introduced as an estimator of the space-filling properties of irregularly shaped objects. Since the "golden age" of cell biology that started in about 1960, there has been an eruption of fractal geometry into the life sciences in biology and medicine (Belaubre 2006; Losa and others 1997, 2005; Losa 2009).

In a holistic view of fractal geometry of the brain, part I of this series will introduce the general concepts of fractal geometry and its application to basic neuroscience, while part II will discuss the applications of fractals in the clinical neurosciences.

Basic Principles of Fractal Geometry and Applications in Biology

Mathematical fractal structures arise commonly in systems that involve iteration, that is, procedural repetition, and recursion in which the input of a new iteration is the previous state of the system. As shown by Mandelbrot (1983), the simplest underlying principle of fractals is a recursive iteration. For example, the "complex" Mandelbrot set (Fig. 3A) arises from the utterly simple $Z = Z \wedge 2 + C$ recursive algorithm, where any new Z complex number is generated by its predecessor.

Natural fractal entities are mainly characterized by four properties: 1) irregularity of their shape, 2) self-similarity of their structures, 3) noninteger or fractional (fractal) dimension, and 4) scaling, which means that measured properties depend on the scale at which they are measured. The most important property of fractal objects is that the schemes that characterize them are similarly found again and again at descending orders of magnitude

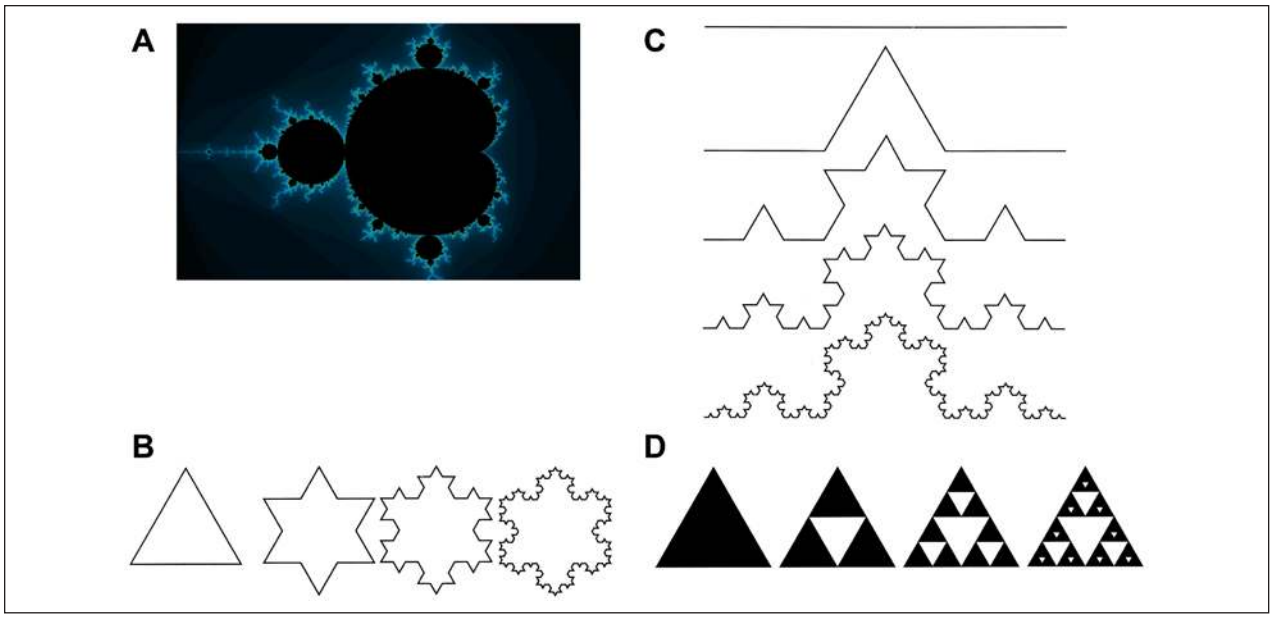

Figure 3. Examples of geometrically self-similar fractals. (A) The Mandelbrot set. The "curve" (B) and the "snowflake" (C), described by Niels Fabian Helge von Koch (1870–1924), and the "Sierpinski triangle" (D), described by the mathematician Waclaw Sierpinski (1882–1969).

so that their component parts, in all dimensions, have a form similar to the whole. Coastline shapes are prototypical examples of complex curves with the property that, in a statistical sense, each portion can be considered a reduced-scale copy of the whole (Mandelbrot 1967). This property is referred to as "self-similarity." Self-similarity can be defined geometrically or statistically. An object is geometrically self-similar when every smaller piece of the object is an exact, or nearly exact, duplicate of the whole object. The classic examples of geometrically self-similar objects are the "snowflake" and the "curve," from Niels Fabian Helge von Koch (1870–1924), a Swedish mathematician who described these peculiar geometric forms for the first time in 1904 (Ristanović and Losa 2013) (Fig. 3B and 3C). Another important geometrically self-similar figure is the "Sierpinski triangle" (Fig. 3D). It was originally described in 1915 by the Polish mathematician Waclaw Sierpinski (1882–1969). Statistical self-similarity, also indicated with the term "self-affinity," concerns biological objects, including all anatomic forms. Small pieces that constitute anatomic systems are rarely identical copies of the whole system. If we consider a portion of tree branches or vascular vessels, they are not a copy of the whole tree but represent the same self-similarity and structural "complexity" (i.e., roughness and spatial pattern). Various statistically self-similar anatomic structures include not only the general circulatory system, the bronchial tree, and the biliary tree of the liver but also the dendritic structure of the neuronal cells, the ductal system of a gland, the cell membrane, and the fibrous portion in chronic liver disease (Cross 1987, 1994; Losa 2009; Pellionisz 1989) (Fig. 4).

Measurement of Fractal Properties

Self-similarity measurement methods are a potent tool in the study of natural objects, which appear too complex to be quantified by Euclidean geometry. A fundamental concept for the evaluation of geometric objects is that of dimension, which is a characteristic value of the system. Two main definitions of dimension have been proposed. The first, named "topological dimension," was introduced by the Austrian mathematician Karl Menger (1902–1985). The topological dimension assigns an integer number to every point in Euclidean space, indicated with the symbol E3, and attributes a dimension of 0 to the "point," dimension 1 to the "straight line," dimension 2 to the "plain surface," and dimension 3 to the "three-dimensional figure" (or volume). The second definition of dimension came from Felix Hausdorff (1868–1942) and Abram Samoilovitch Besicovitch (1891–1970). They attribute a real number to every natural object in E3, lying between the topological dimension and 3. Mandelbrot (1967) indicates the dimension of Menger with the symbol Dγ and that of Hausdorff and Besicovitch with the symbol D. For all Euclidean figures, Dγ and D are

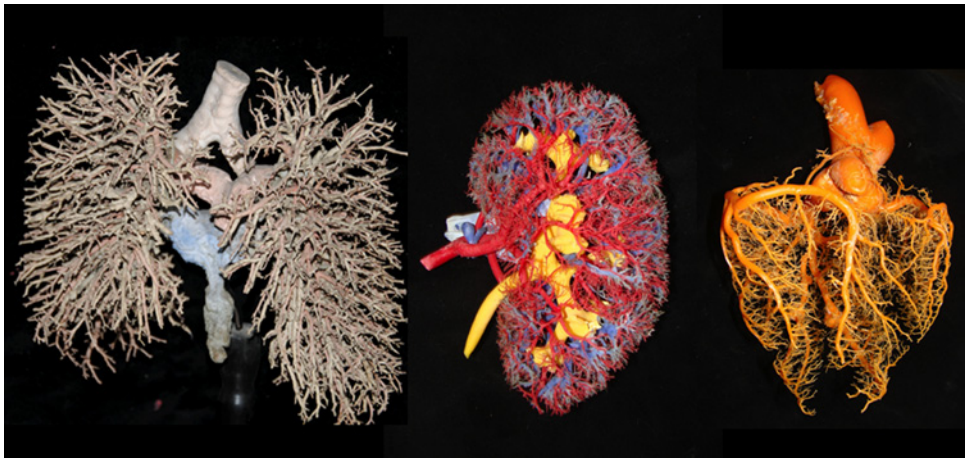

Figure 4. Examples of "tree-like" fractal anatomic systems. From left to right: bronchial tree, renal vascular and urinary systems, and heart coronary system. By kind concession from Prof. Dr. Manfred Tschabitscher (Centre for Anatomy and Cell Biology, Medical University of Vienna, Vienna, Austria).

coincident (Dγ = D). This equality is not valid for all the fractal natural objects, however, because the inequality D > Dγ is verified. Natural objects can be roughly represented by Euclidean shapes (i.e., a tree resembles a cylinder, the sun is similar to a sphere, a mountain can be interpreted as a cone), but in reality, these shapes are not Euclidean figures. As suggested by Mandelbrot (1967), it is possible to determine the Hausdorff-Besicovitch dimension or FD, of irregularly shaped objects through the covering procedure of the topological space of the object being measured.

Several methods have been described to estimate the FD (Falconer 2003; Hastings and Sugihara 1993). The most widely used in the biomedical sciences is called the "box-counting method," offering the "box-counting" dimension as an estimator of the space-filling properties of natural objects in 2D and 3D space (Barnsley 1988; Falconer 1997, 2003). This method applies the following formula:

$$D_B = \lim_{\varepsilon \to 0} \frac{LogN(\varepsilon)}{Log(1/\varepsilon)}, \quad (1)$$

where D_B is the box-counting FD of the object, ε is the side length of the box, and N(ε) is the smallest number of boxes of side ε required to cover the outline of the object completely. Because the zero limit cannot be applied to natural objects, the dimension was estimated by the formula

$$D = d, \quad (2)$$

where d is the slope of the graph of Log {N(ε)} against Log (1/ε). The linear segments of these graphs were identified using the least-squares method of regression, and the gradients of these segments are calculated using an iterative resistant-line method. Simply put, the FD represents an estimate of morphological complexity (Cutting and Garvin 1987); the more irregular an object, the higher its D value, providing a quantitative index of the roughness of natural objects (Mandelbrot 1983). It should be emphasized that, according to the logarithmic calculation, small changes in the FD correspond to large differences in the shape of the object. Several further methodologies have been proposed for the measurement of the FD (Lopes and Betrouni 2009), and other parameters and techniques have been introduced for the analysis of fractal systems (i.e., Hurst coefficient, detrended fluctuation analysis) (Fernández and Jelinek 2001; Stadnitski 2012). Another fractal parameter is "lacunarity." Where the FD measures how much space is filled, lacunarity complements the FD value by measuring how the object fills the space (Mandelbrot 1983; Tolle and others 2003). Being a measure of the "gappiness" of the patterns, and then an index of the heterogeneity of the object, lacunarity is often analyzed in combination with the FD. Fractal systems may also show a gradient of FDs, meaning that their pattern generates multifractal spectra. When a fractal system cannot be described by a single exponent, as occurs in several systems in nature, it is defined as a multifractal system; in such a case, the continous spectrum of exponents can be analyzed by means of multifractal analysis, aimed to describe the variation of the scaling exponent across the dataset (Harte 2001; Lopes and Betrouni 2009; Stanley and Meakin 1988).

In the last 20 years, fractal geometry has vastly expanded (Fig. 2) as a method able to model several

natural phenomena in a simple and efficient manner. In addition, the FD has been applied to many different fields of biological science, among which are histology, normal and pathological anatomy, botany, molecular biology, and zoology.

Investigation into the clinical importance of this nonlinear mathematical tool, and why it is important to the study of the fractal properties of anatomic structures or their irregular pathological changes, has recently accelerated (Fudenberg and others 2011; Grosberg and others 1988, 1993; Lieberman-Aiden and others 2009; Pellionisz 2008, 2012). Continuous technological development has produced sophisticated computer-aided systems that are able to produce images with maximum detail. Furthermore, it has been realized that sometimes overcoming the limits of the human eye in distinguishing among the different shapes of anatomic lesions creates new opportunities of interpretation. The field of imagery has entered a new era made possible primarily by the advent of fast computers, sophisticated imaging software, and a computer-generated higher order of information display, all driven by the need for human comprehension. A number of nonlinear mathematical methods, including fractal geometry, have been proposed to measure the complex morphologies of natural systems (Cross 1994; Dokukin and others 2011). The application of the principle of fractal geometry, unlike conventional Euclidean geometry, enables the measurement of the FD of almost all irregular biological entities.

Functional Irregularity and Morphological Intricacy of the Nervous Tissue

The evolutionary concourse of two major events, the tremendous expansion and the differentiation of the neocortex, as recently reported (DeFelipe 2011), has contributed to the development of the human brain (Fig. 5). Nowadays, modern neurosciences admit the prevalence of fractal properties in the brain at various levels, that is, anatomic, functional, pathological, molecular, and epigenetic, but not so long ago, there was no analytical way to objectively describe complex biological systems such as the brain. Facing the intricacy of mammalian brain folds, Mandelbrot (1983) first argued, "A quantitative study of such folding is beyond standard geometry but fits beautifully in fractal geometry." Mandelbrot (1967) suggested interpreting the results related to cellular morphometrics with the likely effect of the "resolution scale" in analogy with the "coast of Britain effect" (Losa 2009). At that time, however, there was no certainty about the brain's geometry, or neuron branching and interconnections, and connectomics. The anatomic histological evidence that the complexity of the plane-filling maze formed by dendrites of cerebellar neural Purkinje cells was reduced in nonmammalian species compared to mammals led Mandelbrot (1983, 1998) to comment, "It would be very nice if this corresponded to a decrease in D (fractal dimension), but the notion that neurons are fractals remains conjectural." Since then, a wealth of investigations have documented the fractal organization of the brain and nervous tissue systems (Milošević and others 2009; Milošević and others 2010; Losa and others 2011; Smith and others 1989; Smith and Lange 1995; Werner 2010). The brain consists of distinct anatomic areas formed by the nervous tissue, which is mainly composed of neurons and glial cells. The former comprises the axon, which is a long cytoplasmic process associated with the cell body used to communicate with target organs, and the dendrites, which are shorter cytoplasmic processes off the cell body used to communicate between neurons. Glial cells of various types are structured as a net through branched and unbranched protoplasmic processes. The brain forges its complexity by combining these different anatomic, morphological, and physiological properties, which can only be modeled by a supercomputer (Markram 2006). The growth and morphological differentiation of spinal cord neurons in culture and the degree of dendrite branching of thalamic and retinal neurons were among the first applications of fractal analysis in neuroscience (Smith 1994). Further studies have confirmed that the FD correlates with the increase in morphological complexity and neuronal maturity (Bernard and others 2001; Milošević and others 2009; Pirici and others 2009; Jelinek and others 2008) towards the complex structure of the whole highly convoluted brain cortex, which has also been shown to have a fractal structure (Hofman 1991). Hofman (1991) showed that the convolutions of the brain are the result of the fractal folding and compartmentalization of neurons into modular circuits, governed by simple iterative rules aimed to generate the actual brain design.

Fractal analysis has also been applied to anatomic/histological images and neuroimaging for quantifying the developmental complexity of the human cerebral cortex and several neurophysiological states. This topic will be covered in the second part of this series.

Non-Euclidean Geometry of Neurons and Microglia

Neurons and microglia take on many shapes related to function and position within the nervous system. This makes it difficult to objectively quantify any structural attributes, especially as these do not correspond to Euclidean shapes. Using cell area or cell diameter, for instance, will not always differentiate subtypes of cells, as may be the case with cat retinal ganglion cells (Fig. 6A), or will not be sensitive to changes in form associated with changes in function, as found with

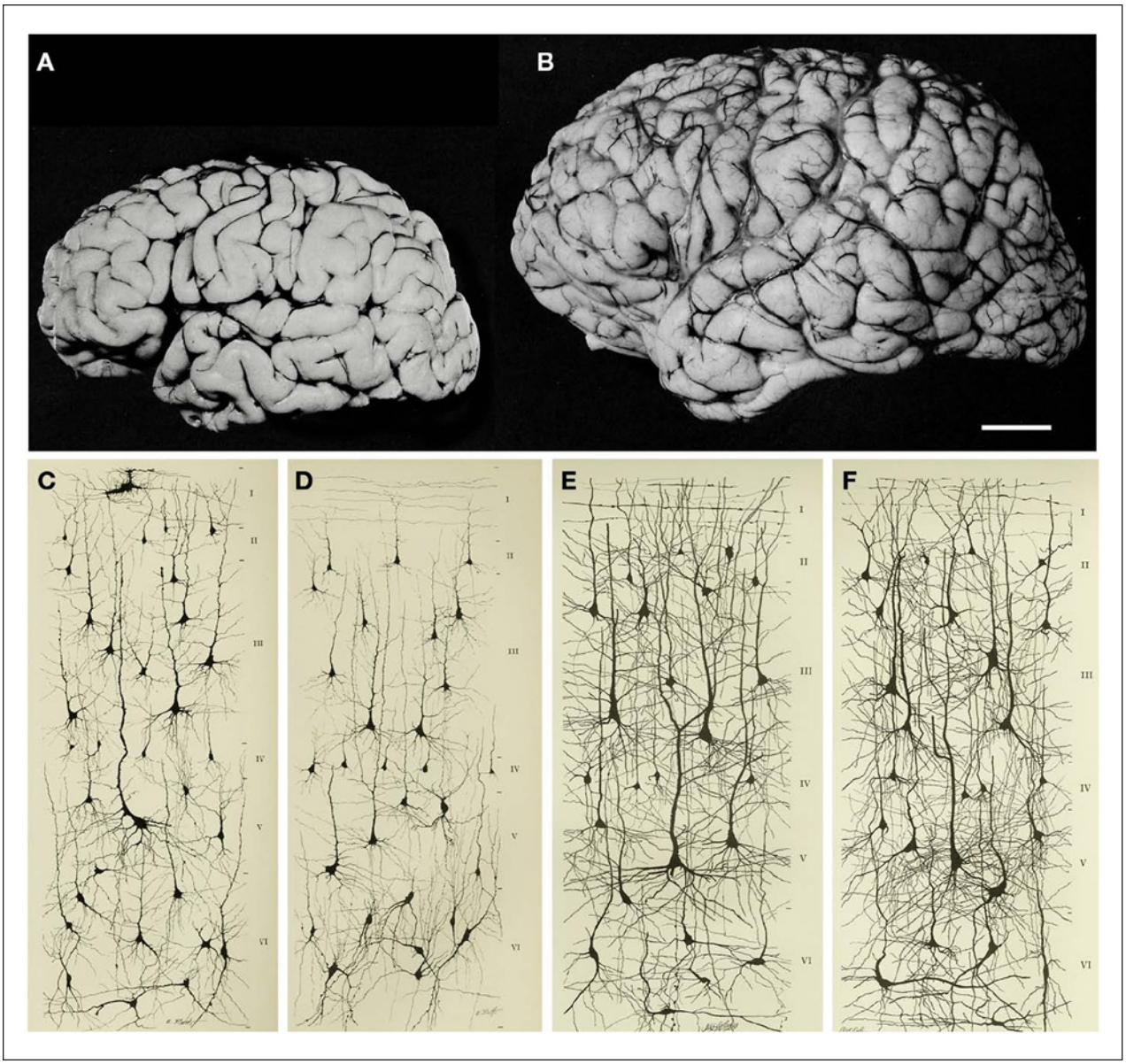

Figure 5. Increase in brain size and the maturation of cortical circuits. The maturation of mental processes and motor skills is associated with an approximate fourfold enlargement in brain size. (A, B) Photographs of the brains of a 1-month-old and 6-year-old child, respectively. An increase in complexity is clearly evident in the drawings of Golgi-stained cortical neurons from the cerebral cortex of a 1-month-old (pars triangularis of gyrus frontalis inferior [C] and orbital gyrus [D]) and 6-year-old (pars triangularis of gyrus frontalis inferior [E] and orbital gyrus [F]) child. Scale bar (A, B): 2 cm. Reproduced from DeFelipe (2011), with permission from the publisher.

activated microglia (Fernández and Jelinek 2001; Karperien and others 2013a, 2013b). Subjective classification combined with Euclidean parameters may lead to varying subgroup classification (Boycott and Wässle 1974; Jelinek and Spence 1997; Kolb and others 1981). Fractal analysis has been applied to differentiate between various visually similar but functionally different neuronal types in different animal species (Bernard and others 2001; Caserta and others 1995; Elston and Jelinek 2001; Henry and others 2001; Jelinek and Elston 2004; Jelinek and others 2011; Kniffki and others 1993; Kolb and others 1994; Losa and others 1997; Milošević and others 2010; Neale and others 1993; Porter and others 1991; Schierwagen 1989; Schierwagen and others 2007; Skrzat and others 1996; Smith and Lange 1995; Wingate and others 1992). Fractal analysis has also been used to

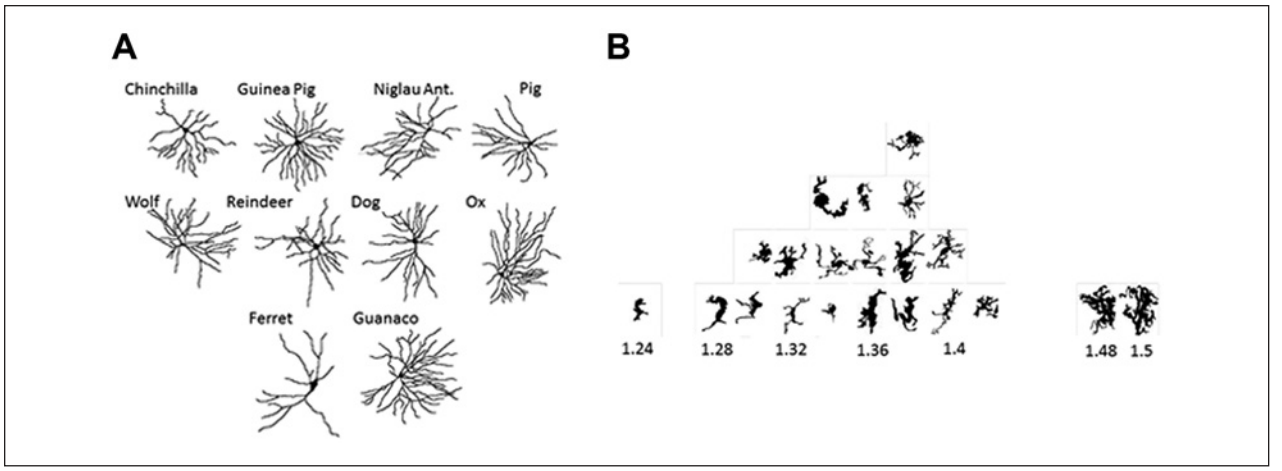

Figure 6. (A) Types of α retinal ganglion cells in different mammals. Camera lucida drawings from cell images provided by Leo Peichl. (B) Box-counting dimension of microglia in the human cortex. Drawing provided by Audrey Karperien.

highlight subtle morphological differences in glia and neurons and to classify these cell types into morphological and functional subgroups (Bernard and others 2001; Borodinsky and Fiszman 2001; Jelinek and Fernández 1998; Jelinek and others 2004; Orlowski and others 2003; Porter and others 1991; Senitz and others 1995; Soltys and others 2001) (Fig. 6B). Furthermore, it can be used to follow the changes in dendritic complexity induced by drugs, such as in hippocampal cells after cortisone treatment (Alfarez and others 2009). Also, the FD has been shown to classify different morphotypes of astrocytes in physiological as well as in pathological states (i.e., stroke, dementia) (Pirici and others 2009) (Fig. 7). Figure 8 shows the application of the box-counting method to a dendritic branching pattern, with the slope of the log/log graph representing the FD of the patterns itself. To summarize, the FD of a neuron increases with the ruggedness of the cellular border, the degree of dendritic branching, and the space-filling capacity of the neuron as a whole (Borodinsky and Fiszman 2001; Smith and others 1989). Lacunarity and FD have been used to show the physiological decline of neuronal and glial structures in the processes of aging, whereby the FD decreases and lacunarity increases in neurons, while the contrary occurs in glial cells, giving rise to a holistic representation of the neuroglial network (Suckling and others 2008).

Fractal analysis in experimental neuroscience was introduced by Smith and others (1989), who published a simple open-access code within Image J (http://rsbweb.nih.gov/ij/) that used box covering of an image at different scales and determined the double logarithmic relationship between the scale and area for a neuron. This development soon led to an increase in the availability of computer-based algorithms to analyze neurons and microglia. These methods, including the box-counting, caliper, and mass-radius methods, provide the FD (Fernández and Jelinek 2001; Landini 1996) as well as multifractal dimensions and local connected FDs or lacunarity (Jelinek and others 2005; Karperien and others 2013b; Voss and Wyatt 1991). However, more work has to be done to obtain a stronger statistical framework for analysis and interpretation of monofractals and multifractals, the place for multiscale and local connected FDs, and the role of lacunarity. Changes in microglial morphology associated with a change in function can be easily overlooked but may be important markers of pathological processes. In some types of biological cells, subtle differences in cellular morphology may not be quantifiable by Euclidean measures such as area or diameter but are, nevertheless, characterized by space-filling attributes that indicate structural complexity and quantified by the FD. Why microglia change form in many pathologies, and what functional and structural consequences accompany these subtle abnormalities, is not known. Methods for characterizing microglia that are more sensitive than those currently reported in the literature may shed light on the matter. Such methods comprise the use of Lindenmayer systems (L-systems) modeling (Pellionisz 1989), combined with morphological parameters based on pattern recognition research (Ascoli 1999; Costa and Cesar 2001), as well as computational operations such as the second moment of a blurred histogram, second moment of a wavelet, entropy, and lacunarity (Behar 2001; Cesar and Jelinek 2003; Cornforth and others 2005; Costa 2001; Jelinek and others 2003; Soares and others 2006).

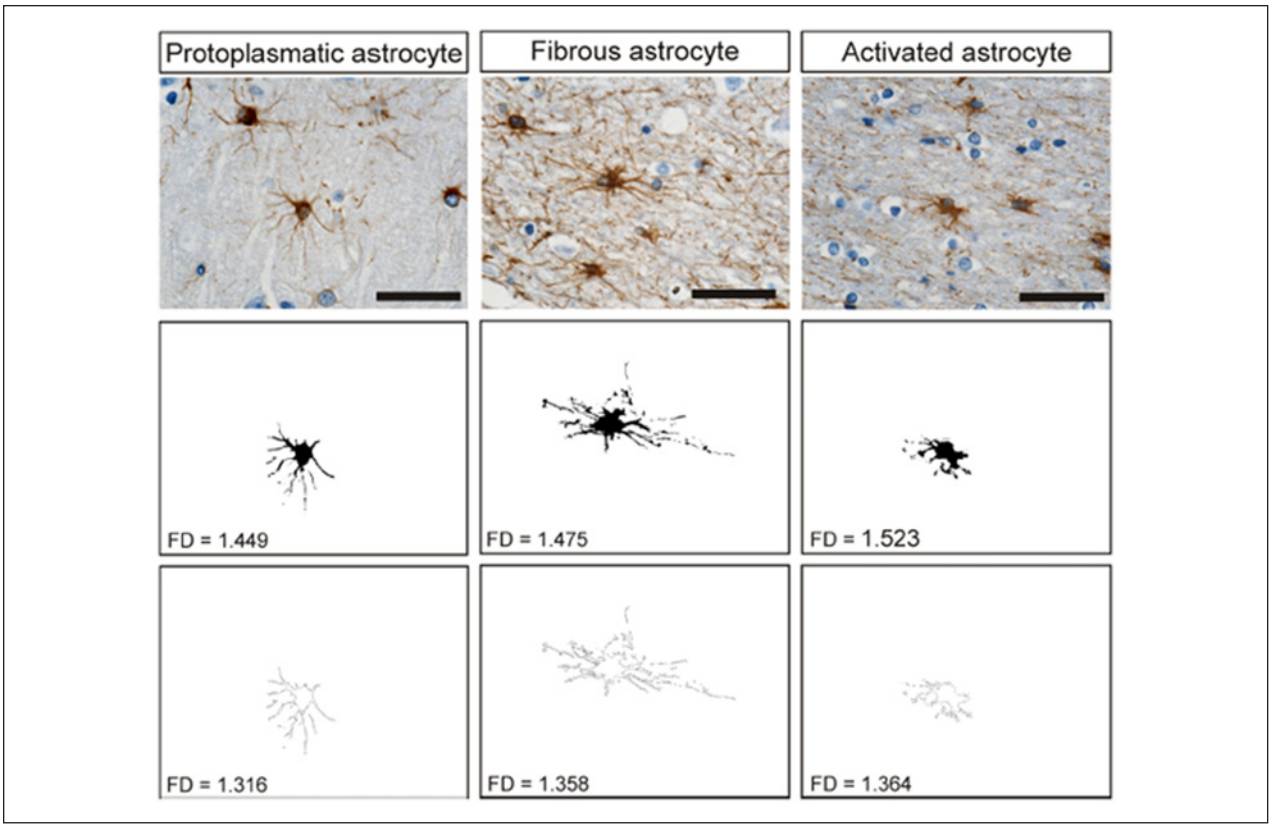

Figure 7. Fractal analysis of three different types of astrocytes. The first row shows the original images, the second row shows the binary silhouette of the cells, and the third row shows the outline mask, with the corresponding fractal dimension values. Reprinted from Pirici and others (2009), with permission from the publisher.

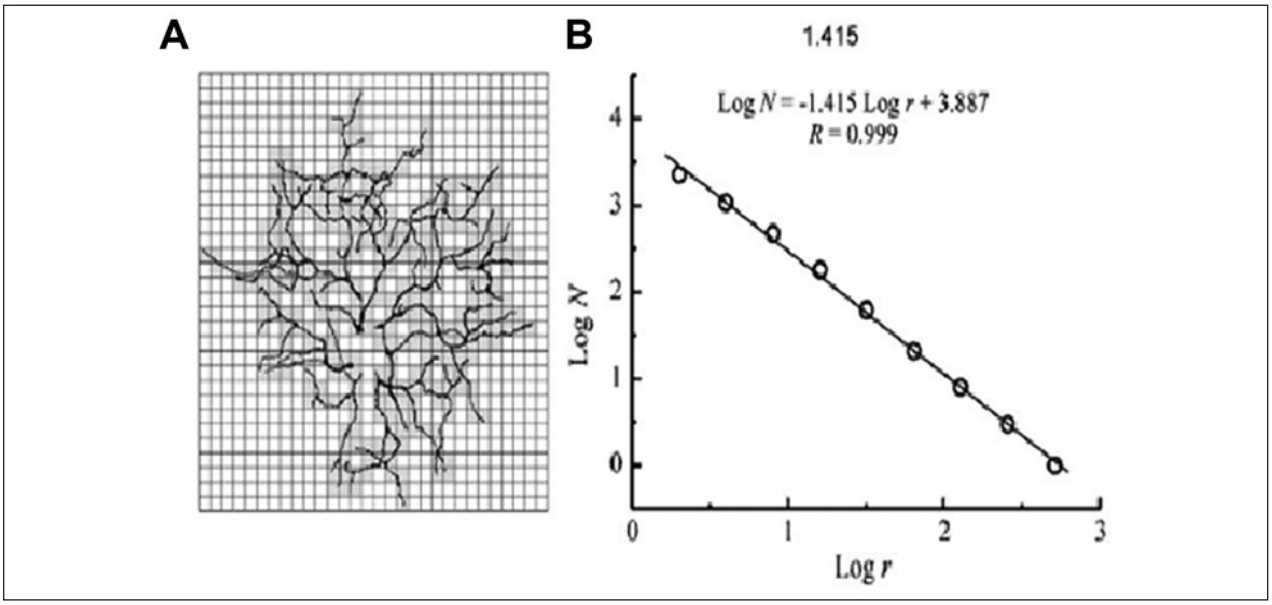

Figure 8. Application of the box-counting method to a dendritic branching pattern: (A) the whole image is covered with a set of squares, and the squares that cover the dendrites are counted. (B) Log-log plot between the numbers of squares (N) and square size (r) is fitted by a straight line. The fractal dimension D is calculated from the slope of the straight line. R is the corresponding correlation coefficient. Reprinted from Milošević and others (2009), with permission from the publisher.

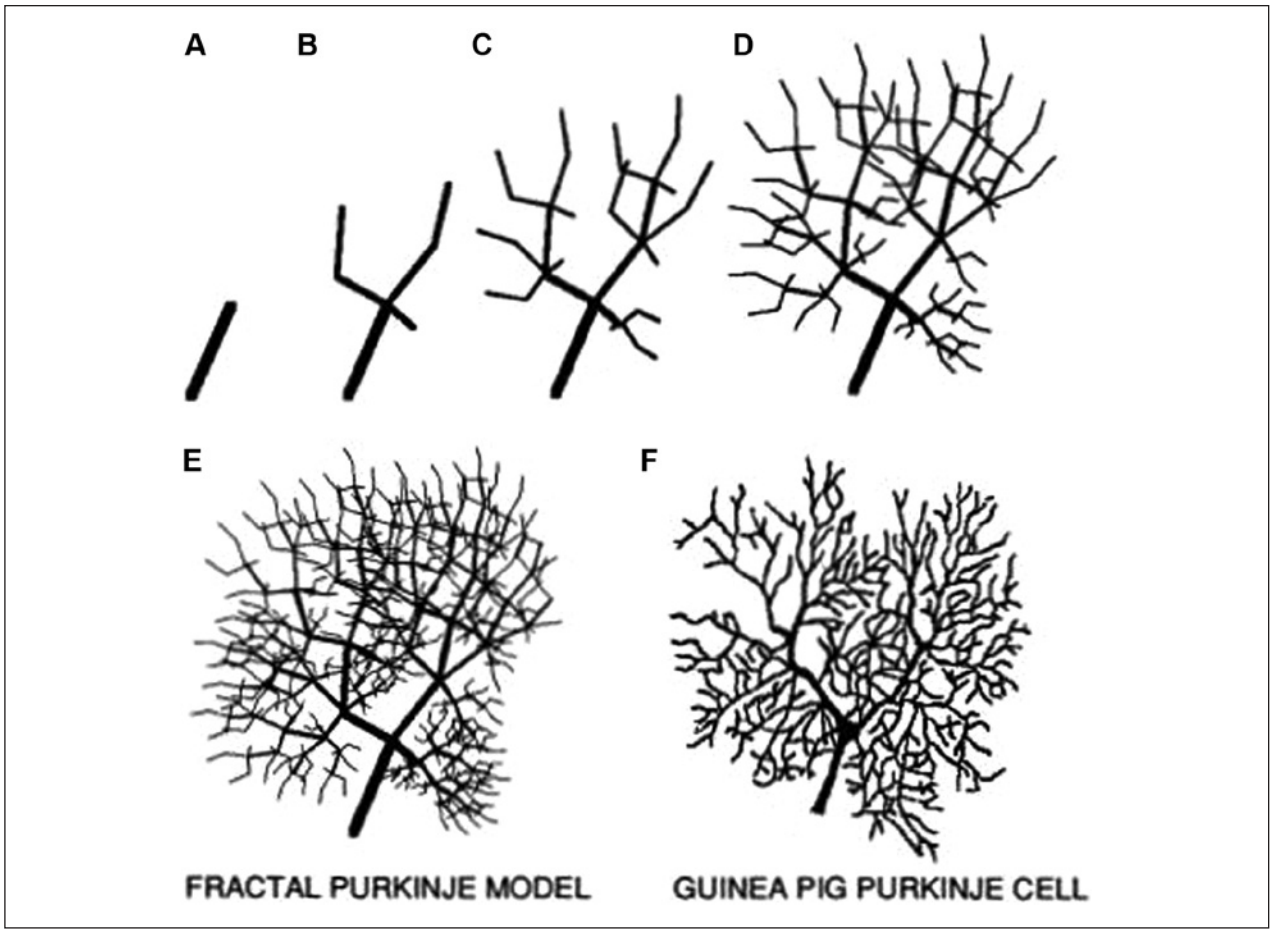

Figure 9. Fractal model (A-E) of the Purkinje neuron (of the guinea pig [F]). The model illustrates how the dendritic tree can be built up by a process of "self-similar repetition." As shown (B-E), the Lindenmayer string replacement algorithm yields the fully developed fractal model in just four recursive steps to be compared to the dendritic tree. At each step (B-E), all branchlet ends of the former are replaced by the fractal template (B). The emerging fractal neural modeling corroborates a spatial "code repetition" of the growth process with repetitive access to the genetic code. This conceptual link between the two metageometries of the double helix and "fractal seed" may ultimately lead to precisely pinpointing those exact differences in the "genetic" code that lead to differentiation to Purkinje, pyramidal, Golgi, or other types of specific neurons. The "fractal recursive model" led to the notion of "FractoGene" for conceptual linkage of the fractal nature of growth of organisms driven by a "repetitive access to genetic code" (Pellionisz 1989; Simons and Pellionisz 2006). Reproduced with permission from Pellionisz (1989).

With the advent of 3D image reconstruction using scanning electron microscopy or confocal microscopy, fractal analysis has also moved into this realm (Lopes and Betrouni 2009; Dokukin and others 2011; de Resende and others 2013). Schierwagen and others (2007) have published an interesting article on 3D multiscale analysis of cortical pyramidal cells, providing additional information on pyramidal neurons and proposing novel features derived from this method, such as peak fractality. The continuous evolving nature of fractal analysis within biology in medicine requires stringent criteria for establishing the attributes that define an object as fractal (Delignières and Marmelat 2012; Jelinek and others 2013; Milošević and others 2009). Preprocessing of images, whether they are analyzed in a binary grayscale format or as outlines, will have an effect on the results. Applying box-counting, mass-radius, or Minkowski-Bouligand dimensions, among others, will also affect the magnitude of the FD and needs to be carefully considered (Jelinek and Fernández 1998). Various mammalian astroglial cell types have also been classified by means of fractal analysis (Reichenbach and others 1992), but the same analysis has not been able to discriminate the different patterns shown by the astroglial cytoskeletal profiles (Reisin and Colombo 2002) for lack of self-similarity and for the simple linear morphology of the cytoprofiles.

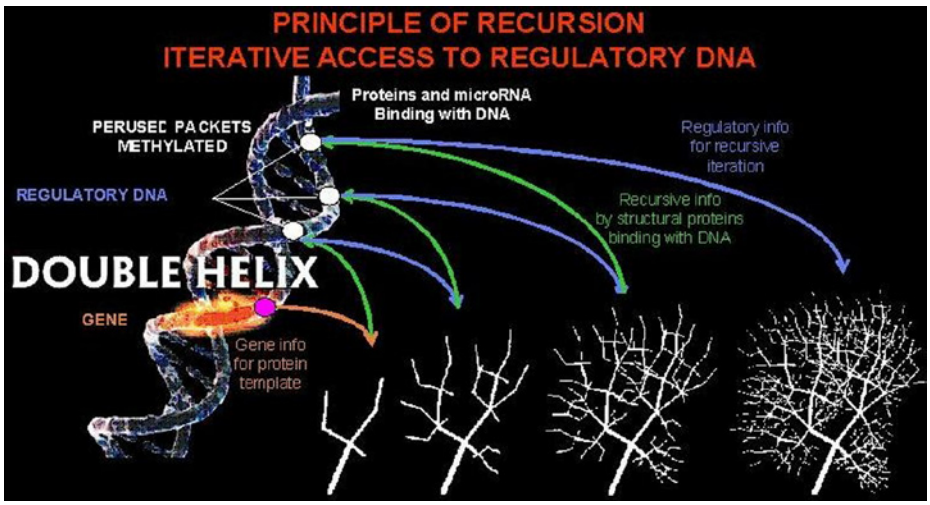

Figure 10. Fractal model of the Purkinje neuron (of the guinea pig), which links for the first time the fractality of the genome with the fractality of neurons. The bottom row shows the Y-shaped fractal template, arising from "protein coding" the DNA > RNA > PROTEIN chain. Such a structure, however, is not an "end product" as postulated by the "central dogma" of Crick. It is known by the vast literature of "protein signaling" and "transcription factors" that proteins do bind with noncoding DNA (that is now widely known as "anything but junk"). The principle of recursive genome function interprets such a function as the buildup of protein structures in every step of the L-string replacement retrieves auxiliary information, relayed by noncoding RNA, to sustain fractal growth. The breakthrough by the new principle replacing old dogmas thus reveals that the genomic-epigenomic system permits the implementation of an entire class of "recursive algorithms." The four-step fractal development of the Purkinje cell is visible, as illustrated also in Figure 9. A quantitative analysis established that not only are the protein structures fractal, but the self-similar repetitive segments of DNA also show the fractal signature: they follow the "Zipf-Mandelbrot fractal parabolic distribution curve" (Pellionisz and others 2013). The theoretical significance is that the fractality found in DNA and organisms, for a long time "apparently unrelated," was put into a "cause and effect" relationship by the principle of recursive genome function (Pellionisz 2008). Reproduced with permission from Pellionisz (1989).

Towards a Unified Fractal Model of the Brain

There is an increasing interest in both the fractal properties of DNA (Cattani and Pierro 2013; Flam 1994; Pellionisz and others 2013; Perez 2010; Petoukhov 2011) as well as fractal organelles (i.e., neurons) and in the fractal character of organs and organisms (Elnitski and others 2011; de Resende and others 2013; Pellionisz 1989; Losa 2009). The spatial organization of DNA into chromatin has also been shown to have a fractal topological architecture (Bancaud and others 2009), as a model of the "fractal globule" (Mirny 2011; Barbieri and others 2012).

Mandelbrot's (1983) musings about neurons were directly addressed by a fractal model of the guinea pig's Purkinje neuron (Fig. 9), linking for the first time the fractality of the genome with the fractality of organelles such as neurons (Pellionisz 1989, 2008) (Fig. 10). Decades of computer modeling of neurons and neuronal networks (Pellionisz and Szentagothai 1973; Pellionisz and others 2013; Simons and Pellionisz 2006) suggested that the amount of information necessary to build just a tiny fraction of the human body, that is, just the cerebellum of the nervous system, was a task for which 1.3% of the information that the genome could contain was totally insufficient: "Fractal genome grows fractal organism; yielding the utility that fractality, e.g. self-similar repetitions of the genome can be used for statistical diagnosis, while the resulting fractality of growth, e.g. cancer, is probabilistically correlated with prognosis, up to cure" (Pellionisz 2008). For recursive iterative development of a brain cell, see Pellionisz (1989), with the generalized principle of recursive genome function enabling fractal iteration (Pellionisz 2008; Landini 2011; Pellionisz and others 2013).

The brain is now accepted as one of nature's complex networks (West 2012). The hierarchical organization of the brain, seen at multiple scales from genes to molecular networks (Agnati and others 2008), to building neurons organized in micronetworks and macronetworks, has a fractal structure as well, with various modules that are interconnected in small-world topology (Gallos and

others 2012a, 2012b). Fractal analysis can help scientists to speak a common language for the quantitative understanding of natural complexity (Grizzi and others 2012) and, in this case, of the brain itself. It is realistically expected, therefore, that the "fractal approach" may be a kind of Rosetta stone in neurosciences for translating different discoveries and fields of research into a holistic view of the brain. The various clinical applications of this field will be described in part II of this series.

Note

All the authors are members of the web community "The Virtual Fractal Lab" at www.fractal-lab.org.

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