The Fractal Organization of the Nervous System

Gabriele A. Losa

Introduction

The original conception of Galeno (Pergamo) (129–216 D.C.), confining the superior functions of human brain within three cerebral cells (spheres), has spanned several centuries up to the Renaissance period culminating with Leonardo da Vinci (1452–1519). A first outstanding breakthrough was accomplished by Andreas Vesalius who, in his famous work *De humani corporis fabrica* (1543), described the surface cerebral convolutions even tough failed to provide a reliable identification of peculiar morphological pattern. Relevant investigations were successively performed by Marcello Malpighi (1628–1694) who suggested the existence of a nervous fluid filling within cerebral glands, by Thomas Willis (1621–1675) who evidenced an arterial circuit by anastomosis of internal carotids and vertebral artery, and by Vicq d'Azyr (1746–1796) who revealed convolutions in unidentified areas of the brain external surface. Albrecht von Haller (1708–1777) underlined the secretive function of human brain by means of a nervous fluid. Franz Joseph Gall (1758–1828) and Johann Spurzheim (1776–1828) by examining the brain shape identified phrenologic maps with specific functions. Paul Broca (1824–1880) localized cerebral functions such as the langage arguing that "Nous parlons avec l'hemisphère gauche". Carl Wernicke (1848–1905) identified an area of the temporal lobe, whose damage may provoke the selective loss of the capacity of listening words. Back in the early twentieth century appeared the outstanding contributions of two coeval scientists: Camillo Golgi (1843–1926) [1] who postulated that ramified nerve fibers could support the "reticular theory", considering that the nervous system is a syncytial system which consists of nervous fibers forming an intricate diffuse network along which the nervous impulse may propagate. On the other side Santiago Ramón y Cajal: (1852–1934) [2] for which the relationship between nerve cellsdeveloped the "neuron theory" for which the relationship between nerve cells was not one

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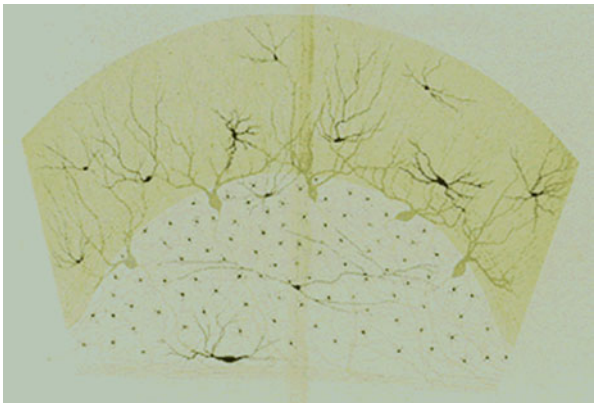

Fig. 1 The human cerebellar cortex as stained and drawn by Golgi (from the Opera Omnia, 1903). The staining procedure consisted on the reaction of silver nitrate with potassium dichromate that formed a black deposit within the soma, axon and dendrites of nerve cells of cerebellum

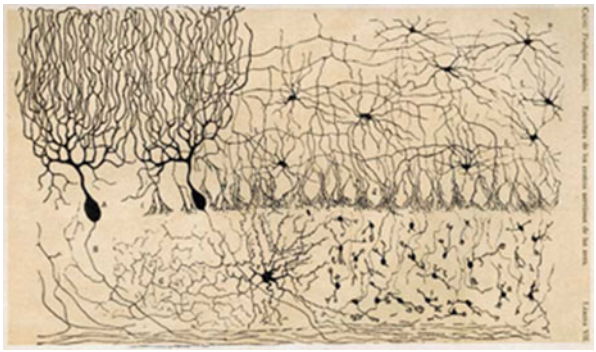

Fig. 2 The cerebellum cortex (Golgi staining) as drawn by Santiago Ramon y Cajal. (1888) Rev. Trim. Histol. Normal. Patol

of continuity, but rather of contiguity, accomplished through small membranous spines protruding from a neuron's dendrite that typically receives input from a single synapse of an axon (output) Piccolino [3] (Figs. 1 and 2).

In the last decades relevant new imaging techniques, such as Positron Emission Tomography (PET), Functional Magnetic Nuclear Resonance (fMNR), Computed Axial Tomography (CAT), etc., have been implemented that, in concomitance with the increase of the theoretical knowledge provided by the modern Mathematics and the innovative Fractal Geometry (power law scaling, self-similarity), have enabled to deepen into the morphological/ structural complexity leading to the analytical representation of the biological elements and to the objective description of living processes.

Main Properties of Fractal Elements

According to Mandelbrot [4] "A fractal set is a set in metric space for which the Hausdorff-Besicovitch dimension D is greater than the topological dimension DT." In nature, a fractal object is defined by its structural properties, namely by surface rugosity, irregularity and absence of smoothness, form invariance, geometrical or statistical self-similarity, morpho-functional complexity, represented by a fractional/non-integer dimension. The Richardson-Mandelbrot equation provides the mathematical basis for understanding geometric and spatial fractal structures, and for measuring and interpreting them, namely:

$$L(\varepsilon) = N(\varepsilon).(\varepsilon) \tag{1}$$

where $L(\varepsilon)$ represents the contour length (e.g. the perimeter) of the biological component under investigation, (ε) the unit length of measure, and $N(\varepsilon)$ the number of unit lengths (ε) needed to cover the contour $L(\varepsilon)$. By substituting $N(\varepsilon)$ with [lo D ε-D] into (1), the above equation can be transformed by logarithmic procedure and rewritten as:

$$\log [L(\varepsilon)/lo] = (1 - D) \log [\varepsilon/lo] \tag{2}$$

which is the equation of a straight line with slope 1-D, and from which the dimensional exponent D can be calculated to yield the numerical value of the fractal dimension FD. FD is a statistical non-integer quantity that gives a measure of geometric complexity of form. lo is a reference scale without influence on the determination of D. In contrast to mathematically generated fractals, biological structures and objects observed in Nature are self-similar within a limited range of scales. Only within this scale interval or scaling window can the scale-invariant (fractal) properties of an irregular object of finite size be observed [5]. A real "fractality" exists only when the experimental scaling range covers at least two orders of magnitude, although fractality over many orders of magnitude has been observed in various natural fields. The fractal window characterizing biological and natural fractals also called "biasymptotic fractals" is graphically represented by the region II in the middle of three typical regions, limited by a lower (ε_{min}) and an upper bound (ε_{max}) of the bi-asymptotic curve, where a straight line can be drawn and the fractal dimension [FD] calculated from its slope (Fig. 3). Losa and Nonnenmacher [6]. Defining a "scaling range" appears an inescapable requisite for assessing the fractality of every biological element. While the practical evaluation of the fractal dimension could be obtained by various quantitative approaches, the most reliable method is by far the box counting easily based on counting of the nonempty boxes N at a variable grid length (ε). Döllinger et al. [7]. It is obvious that the fractal theory is in opposition to the ancient, conventional vision based on Euclidean geometry and to its widely adopted concepts, such as homeostasis, linearity, smoothness, and thermodynamic reversibility, which stem from a more intuitive but artificially

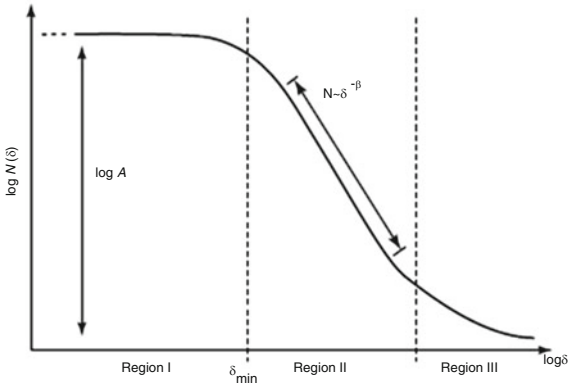

Fig. 3 The three typical regions of a biasymptotic fractal: the fractality is confined to the region II (From Döllinger et al 1998)

ideal view of reality. In the chapter of his work entitled < Epilog: The Path to Fractals >, Benoit Mandelbrot wrote "The reader knows well that the probability distribution of fractals is hyperbolic, and that the study of fractals is rife with other power law relationships." Although Mandelbrot's famous seminal paper on statistical self-similarity and fractal dimension dates back to [8] and the first coherent essay on fractal geometry was published earlier, Mandelbrot [9], it is worth here recalling that the "heuristic introduction" of this innovative discipline or, more vividly expressed "the irruption of fractal geometry" into the life sciences such as biology and medicine, Belaubre [10], actually took place in the early 80 years of the last century. Paumgartner et al. [11]. A critical review of fractal concepts was recently addressed encompassing the definition of dimensional imbalance, the modified capacity dimension and the analytical calculation of its value, the relationship with the scaling exponent, and showing that such a definition satisfies basic demands of physics, before all the dimensional balance in mathematical equations used in applied sciences. Since some concepts in fractal geometry are determined descriptively and/or qualitatively, the paper provides their exact mathematical definitions and explanations, including the Richardson's coastline method Ristanovic and Losa [12].

The Complexity of human Brain

The evolutionary concourse of two major events, "the tremendous expansion and the differentiation of the neocortex," as reported by De Felipe [13] has contributed to the development of the human brain. Today, modern neurosciences recognize the presence of fractal properties in brain at various levels, i.e., anatomical, functional,

pathological, molecular, and epigenetic, but not so long ago there was no analytical method able to objectively describe the complexity of biological systems such as the brain. The intricacy of mammalian brain folds led Mandelbrot to argue that "A quantitative study of such folding is beyond standard geometry, but fits beautifully in fractal geometry." At that time however, there was no certainty about the brain's geometry or about neuron branching. Anatomical-histological evidence that the complexity of the plane-filling maze formed from dendrites of neural Purkinje cells of cerebellum was more reduced in non-mammalian species than in mammals led Mandelbrot 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" affirmed Mandelbrot. Since then, a wealth of investigations have documented the fractal organization of the brain and nervous tissue system, and the implication of fractals for neurosciences has been unambiguously affirmed. Among the first applications of fractal analysis to nervous and brain tissue were the pioneering studies of Smith et al. [14, 15]. These authors showed that the fractal dimension is an unbiased measure of the complexity of neuronal borders and branching pattern and of the time course of morphological development and differentiation of spinal cord neurons in culture, increasing from 1.1 for the less differentiated neuron up to 1.5 for the most differentiated cell . Moreover, power-law scaling and other manifestations of fractal and self-similar patterns in space and/or time can be identified at all levels of neural organization. Werner [16]. Further studies have confirmed that the fractal dimension correlates with the increase in morphological complexity and neuronal maturity, Bernard et al. [17]); Milosevic et al [18]. The brain consists of distinct anatomical areas formed by nervous tissue mainly composed of neurons and glial cells of distinct types. Neurons contain the axon (a long cytoplasmic process associated with the cell body, which communicates with target organs), and the dendrites (shorter cytoplasmic processes off the cell body which allow communication between neurons), while glial cells of various types have a structural physio-immunologic role as a net via their branched and unbranched protoplasmic processes. These anatomical, morphological, and physiological properties combine to create the brain's complexity, which can only be modeled by a supercomputer, as proposed recently, Markram [19]; De Felipe [13] (Fig. 4). While three-dimensional digital reconstructions of axonal and dendritic branching are indispensable for exploring neural function, the computational approaches enabled to quantify the intricate relationship between neuronal morphology (structure) and physiology (activity) [20]. The importance of neuronal morphology has been recognized from the early days of neuroscience. Nowadays, increasing efforts are directed to elucidate the functional roles of axonal and dendritic arbors in synaptic integration, signal transmission, network connectivity, and circuit dynamics which in turn require quantitative analyses of digital three-dimensional reconstructions. Reconstructing complex neuronal branching in digital 3D format may help map brain circuitry with its billions of connections Halavi et al. [21].

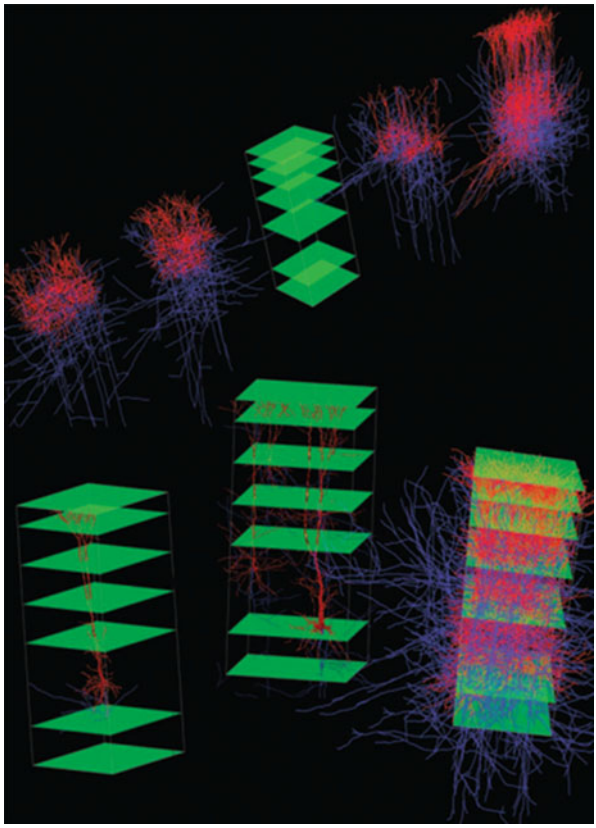

Fig. 4 Reconstructing the neocortical column. The images show the neocortical column (NCC) microcircuit in various stages of reconstruction. *Red* indicates the dendritic and *blue* the axonal arborizations. The columnar structure (*green*) illustrates the layer definition of the NCC. *Upper row*: The microcircuits (from *left* to *right*) for layers 2, 3, 4 and 5. *Lower row*, *left image*: A single thick tufted layer 5 pyramidal neuron located within the column. *Lower row*, *middle image*: One pyramidal neuron in layer 2, a small pyramidal neuron in layer 5 and the large thick tufted pyramidal neuron in layer 5. *Lower row*, *right* : an image of the NCC, with neurons located in layers 2–5. From H. Markram, 2006

Healthy and Diseased Brain Tissues

Fractal analysis was applied to anatomical/ histological images and high-resolution magnetic resonance images in order to quantify the developmental complexity of the human cerebral cortex, the alterations in diseased brain with epilepsy, schizophrenia, stroke, multiple sclerosis, cerebellar degeneration, and the morphological differentiation of the peripheral nervous system. The cortical ribbon showed a highly significant reduction of the fractal dimension in Alzheimer's Disease patients with respect to control subjects King et al. [22]. The fractal analysis has enabled to quantitatively describe the complex morphological forms in which astrocytes occur in brain of ischemic/hemorrhagic stroke and Alzheimer's disease (AD) patients Pirici et al. [23]. Fractal dimension (mean FD: 2.68) values were found higher in the Gray Matter (GM) of Multiple Sclerosis patients (MS) compared to controls (mean FD: 2.67), indicated that GM tissue in MS has higher morphological complexity, perhaps due to the presence of the inflammatory component (i.e. microglia activation) and cellular changes (synapse pruning, demyelination, brain-blood barrier changes, etc.) in the GM. Esteban [24]. In the normal human retina, blood vessels or vascular

trees exhibited an FD of 1.7, the same fractal dimension found for a diffusion-limited growth process, a finding which may have implications for the understanding of the embryological development of the retinal vascular system Masters [25]. Rat retinal ganglion cells have been classified by means of the fractal dimension Milosevic et al. [26]. Lastly, it has been shown that the quantitative evaluation of the surface fractal dimension may allow not only to measure the complex geometrical architecture [27], but also to model the development and growth of tumor neovascular systems and explore the morphological variability of vasculatures in nature, in particular the microvasculature of normal and adenomatous pituitary tissue. Di Ieva et al. [28]. The fractal analysis was recently applied on patients with cerebral arteriovenous malformations (AVM). Increased FD values related to structural vascular complexity were due to the increased number of feeding arteries in patients suffering from AVM Reishofer et al [29].

Gabriele A. Losa 

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