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Fractal and multifractal analysis of human retinal vascular network: a review

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Abstract. The objective of this paper is to present a synthesis concerning the results obtained in fractal and multifractal analysis of vascular network geometry of the human retina. The numerical results are useful in mathematical models based on parametric representations, used in vitreo-retinal biomechanical studies. The fractal and multifractal analysis of retinal vascular network provides noninvasive powerful tools that allow physicians the early detection of patients with different retinal vascular diseases.
Key Words: retina, retinal microcirculation, fractal and multifractal analysis, fractal dimension.

Rezumat. Obiectivul acestei lucrări este de a prezenta o sinteză privind rezultatele obţinute în analiza fractală şi multifractală a geometriei reţelei vasculare din retina umană. Rezultatele numerice sunt utile în modelele matematice bazate pe reprezentări parametrice, utilizate în studiile de biomecanică vitreo-retiniană. Analiza fractală şi multifractală a reţelei vasculare retiniene oferă instrumente puternice neinvazive care permit medicilor depistarea precoce a pacienţilor cu diferite boli vasculare retiniene.
Cuvinte cheie: retina, microcirculaţie retiniană, analiză fractală şi multifractală, dimensiune fractală.

Introduction. Very complex and irregular forms and self-organized spatial structures in multiple hierarchical levels found in biology and medicine that are not fully understood by traditional methods, can be reproduced in much detail if are considered as fractal objects (Losa et al 2005).

The term "fractal" was coined by the mathematician Benoît Mandelbrot (1924-2010) in 1975 and was derived from the Latin "frāctus", derived from "frangere" which signifies to break, to form irregular fragments, in order to describe irregular shapes in mathematics and in nature that exhibit self-similarity (Mandelbrot 1982; Falconer 2003).

In Euclidian geometry, for the topologic objects, the dimension is an integer (0 for the point, 1 for a straight line, 2 for a plain surface, and 3 for a three-dimensional volume). In this way, Euclidean geometry is suited for quantifying objects that are ideal, man-made, or regular (Reljin & Reljin 2002; Grizzi et al 2005).

Fractal objects are mainly characterized by three "properties": a) irregularity of the shape; b) self-similarity of the structure; c) non-integer or fractional dimension (Mandelbrot 1982; Falconer 2003; Grizzi et al 2005).

The fractal dimension contains information about its geometrical structure, strictly exceeds topological dimension and it may be understood as a characterization of the fractal object self-similarity (Mandelbrot 1982).

The self-similarity can be geometrical or statistical. Unlike geometrical self-similarity, which only concerns mathematical fractal objects in which every smaller piece is an exact duplicate of the whole, statistical self-similarity concerns all anatomical systems (Grizzi et al 2005).

The fractal dimension describes how irregular a fractal object is and how much of the space it occupies. Alternatively, the fractal dimension can be used as an index of growth or development (Masters 2004).

Multifractals can be considered as an extension of fractals.

A multifractal object is more complex in the sense that it is always invariant by translation, although the dilatation factor needed to be able to distinguish the detail from the whole object depends on the detail being observed (Lopes & Betrouni 2009). Also, multifractals are characterized by fractional dimensions that vary in scale, and so require an infinite number (distributional spectrum) of scaling exponents for their description.

The main idea behind the multifractal analysis is to make a description of a measure over a region both locally and globally (Nilsson 2007; Falconer 2003).

There are two different ways to approach multifractal analysis: fine theory, where we examine the structure and dimensions of the fractals that arise themselves, and coarse theory, where we consider the irregularities of distribution of the measure of balls of small but positive radius r and then take a limit as $r \to 0$ (Falconer 2003).

The fine theory is more useful for mathematical analysis and the coarse theory is more convenient for physical examples or computer experiments.

The fractal and multifractal analysis is applied to the fractal objects that can't be measured properly using regular Euclidean geometry (Mandelbrot 1982; Falconer 2003).

The fractal geometry has different computerized methods to estimate the fractal dimension or multifractal spectral of a fractal object.

As no biological entity corresponds to a regular Euclidean shape, their dimension is always expressed by a non-integer (fractal dimension) falling between two integer topological dimensions (Grizzi et al 2005).

During the last decades an important research effort has been directed to understand different aspects of the human retina using different computational methods, ranging from the physical to the biological process involved (Ţălu 2005; Ţălu et al 2009; Holz & Spaide 2010; Ţălu et al 2011).

The ophthalmology has benefited from fractal and multifractal analysis in the evaluation of patient data, which makes it to be a useful tool in the human retina studies (Masters 2004; Patton et al 2006; Abramoff et al 2010; Gould et al 2011).

The development of modern digital imaging systems over the past two decades offered very high resolution images in optic fundus imaging and allowed to apply extensively fractal and multifractal geometries in optic fundus assessment in order to detect and diagnose vascular and non-vascular pathology (Family et al 1989; Stosic & Stosic 2006; Jelinek et al 2010; Azemin et al 2011).

The mechanisms and factors implied in the developing of retinal vasculature are not fully understood and no fully comprehensive theory has been yet emerged (Kyriacos et al 1997; Masters 2004).

Various studies have shown that the alterations in the retinal architecture, as reflected by variations in retinal vascular caliber, obtained with new retinal photographic imaging techniques, can reveal signs of hypertension (Hughes et al 2006), arteriosclerosis (Hubbard et al 1999), cardiovascular disease (Liew et al 2008), stroke (Cheung et al 2010) and diabetes (Avakian et al 2002; Walter & Klein 2005; Kunicki et al 2009; Lim et al 2009; Grauslund et al 2010).

The retinal vascular tree is subject to glucose and insulin levels, nutrient availability, changing pressures and pressure gradients, the constitution of its external environment, interactions with cellular components, growth factors, genetic and developmental factors, the confines of the physical space within the eye etc. (Antonetti et al 2006).

The human retinal vascular network, including the pattern of branching, it has been demonstrated to be statistically self-similar and fractal. It can be observed in its natural living state using a retinal camera (Kyriacos et al 1997; Masters 2004).

The first study concerning the fractal analysis and fractal growth processes to the network of blood vessels of the normal human retinal circulation was made by Masters who worked in collaboration with Platt and Family (Family et al 1989; Masters 2004).

Experimental results have shown that the estimated fractal dimension depends on the experimental and methodological parameters involved as: diversity of subjects, image acquisition, type of image, its processing, fractal analysis methods, including the algorithm and specific calculation used (Kyriacos et al 1997; Masters 2004).

In order to describe the complexity of normal vascular network geometry in the human retina, fractal and multifractal analysis can be used as part of a screening tool for early detection of retinal vascular diseases.

Hausdorff measure and dimension. Felix Hausdorff (1869-1942) introduced in 1919 Hausdorff dimension as the principal definition of fractal dimension. It has the advantage of being defined for any mathematical set, but usually it is difficult to be estimated by computational means (Falconer 2003).

Let's consider *U* as any non-empty subset of *n*-dimensional Euclidean space R^n. The diameter of *U* is defined as $|U| = sup\{|x - y| : x, y \in U\}$, i.e. the greatest distance apart of any pair of points in *U*. If $\{U_i\}$ is a finite collection of sets of diameter at most δ that cover *F*, i.e. $F \subset \bigcup_{i=1}^{\infty} U_i$ with $0 \le \lfloor U_i \rfloor \le \delta$ for each *i*, we say that $\{U_i\}$ is a δ-cover of *F*. Let's consider *F* as a subset of R^n and *s* as a non-negative number. For any $\delta > 0$ it is defined (Falconer 2003):

$$H_{\delta}^{s}(F) = \inf\left\{\sum_{i=1}^{\infty}|U_i|^s : \{U_i\} \text{ is a } \delta\text{ - cover of F}\right\} \qquad (1)$$

Thus we look at all covers of *F* by sets of diameter at most δ and seek to minimize the sum of the s^{th} powers of the diameters. As δ decreases, the class of permissible covers of *F* in (1) is reduced. Therefore, the infimum $H_{\delta}^{s}(F)$ increases, and so approaches a limit as $\delta \to 0$. It can be expressed as (Falconer 2003):

$$H^{s}(F) = \lim_{\delta \to 0} H_{\delta}^{s}(F) \qquad (2)$$

$H^{s}(F)$ is called the *s*-dimensional Hausdorff measure of *F*. The Hausdorff dimension of *F* (Hausdorff dimension or Hausdorff–Besicovitch dimension) is defined for any set $F \subset R^n$ and is written as $dim_H F$ (Falconer 2003):

$$\dim_{\mathrm{H}} \mathrm{F} = \inf\left\{s \ge 0 : H^{s}(F) = 0\right\} = \sup\left\{s : H^{s}(F) = \infty\right\} \quad (3)$$

Box-counting dimension. In mathematical calculation box-counting or box dimension is intuitive and easy to apply. The lower and upper box-counting dimensions of a subset $F \subset R^n$ are respectively defined by (Falconer 2003):

$$\underline{\dim}_B(F) = \underline{\lim}_{\delta \to 0} \frac{\log N_{\delta}(F)}{-\log \delta}; \qquad \overline{\dim}_B(F) = \overline{\lim}_{\delta \to 0} \frac{\log N_{\delta}(F)}{-\log \delta} \quad (4)$$

If these are equal then the common value is referred to as the box-counting dimension of *F* and is denoted by (Falconer 2003):

$$\dim_B(F) = \lim_{\delta \to 0} \frac{\log N_{\delta}(F)}{-\log \delta} \qquad (5)$$

(if this limit exists), where $N_{\delta}(F)$ is any of the following:
(i) the smallest number of closed balls of radius δ that cover *F*;
(ii) the smallest number of cubes of side δ that cover *F*;
(iii) the number of δ-mesh cubes that intersect *F*;
(iv) the smallest number of sets of diameter at most δ that cover *F*;
(v) the largest number of disjoint balls of radius δ with centers in *F*.

Two different fractal objects with the same fractal dimension can have a different fractal lacunarity. In this way, the term called lacunarity is a measure of the structural heterogeneity within an object. The usage of lacunarity provides the determination of gaps or lacuna in the pattern. Greater lacunarity reflects a greater size distribution of the lacunae.

Multifractal analysis. Let's consider a structure with mass (i.e. number of pixels) M_0 and linear size L, covered with a grid of boxes of linear size L. The generalized dimension D_q for the mass distribution is defined as (Stosic & Stosic 2006):

$$\sum_i \left[M_i / M_0\right]^q \propto \left[l / L\right]^{(q-1)D_q} \qquad (6)$$

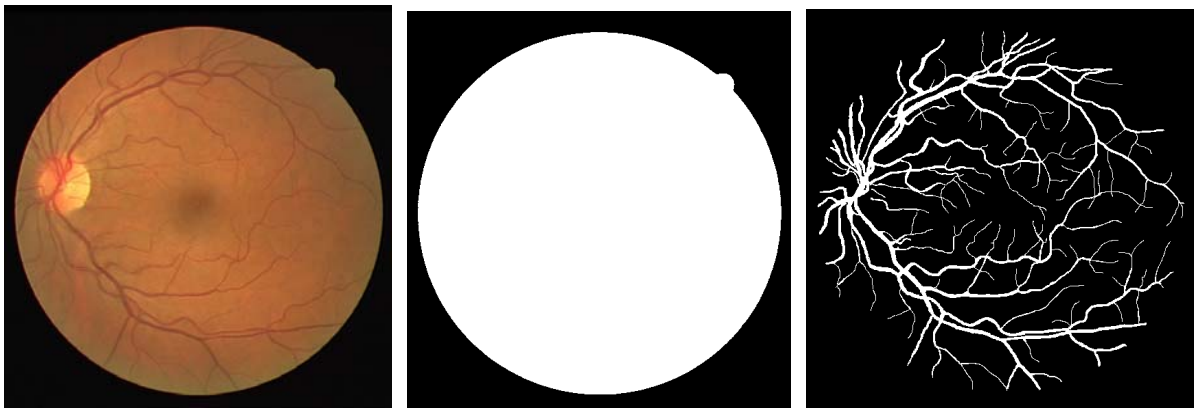
where M_i is the mass (number of pixels) within the ith box, and q is a continuous and adjustable variable that makes it possible to examine fractal properties of the object at different scales. The generalized dimensions D_0, D_1, and D_2 correspond to the capacity (or box-counting) dimension, information dimension, and correlation dimension, respectively. All dimensions are different, satisfying $D_0 > D_1 > D_2$. Finally, $D_{-\infty}$ and D_{∞} represent the limits of the generalized dimension spectrum. All the generalized dimensions for monofractals coincide, being equal to the unique fractal dimension. The multifractal spectrum is represented by the functional dependence $D(q)$, where for (mono)fractals of dimension D it is constant for all q, and for multifractals it is a monotone decreasing function of q (Stosic & Stosic 2006).

Let's consider the generalized sand box method which involves randomly selecting N of the M_0 points belonging to the structure, and counting for each point i the number of pixels $M_i(R)$ that belong to the structure, inside boxes of growing linear dimension R, centered at the selected pixels. When the box centers are chosen randomly, the equivalent of relation (6) becomes (Stosic & Stosic 2006):

$$\left\langle \left(M(R)/M_0\right)^{q-1} \right\rangle \propto \left(R/L\right)^{(q-1)D_q} \qquad (7)$$

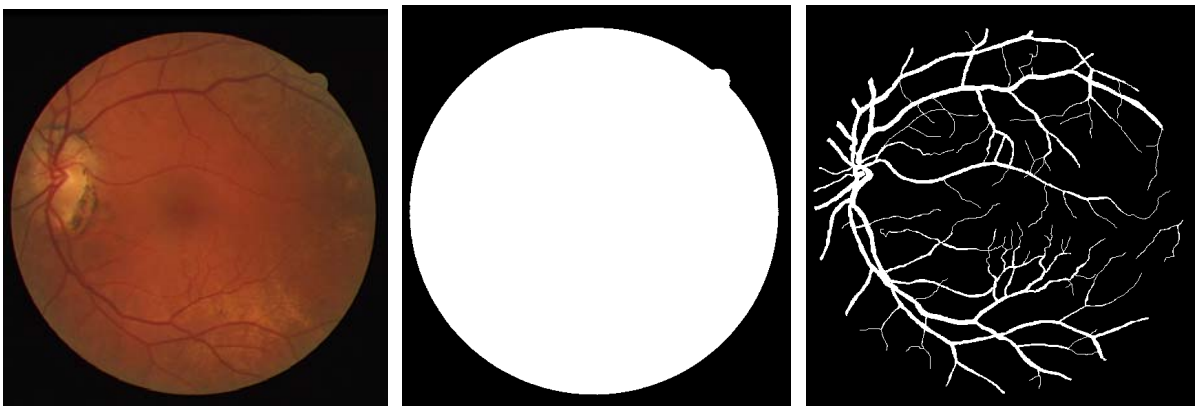
The multifractals spectrum computing methods are: box-counting methods and wavelet methods (Lopes & Betrouni 2009).

Fractal analysis of vascular network of the human retina. Let's consider some retinal images from the Digital Retinal Images for Vessel Extraction: DRIVE database (http://www.isi.uu.nl/Research/Databases/DRIVE/; Staal et al 2004; Niemeijer et al 2004) corresponding to both normal and pathological states of the retina. Each image has been jpeg compressed. The images were acquired using a Canon CR5 non-mydriatic 3CCD camera with a 45 degree field of view (FOV). Each image was captured using 8 bits per color plane at 768 by 584 pixels. The FOV of each image is circular with a diameter of approximately 540 pixels. For this database, the images have been cropped around the FOV. For each image, a mask image is provided that delineates the FOV.



a) b) c)

Figure 1. Image of a typical normal retinal vessel structure (a), with a mask (b) and the skeletonized version (c) (http://www.isi.uu.nl/Research/Databases/DRIVE/).



a) b) c)

Figure 2. Image of a pathological state retinal vessel structure (a), with a mask (b) and the skeletonized version (c) (http://www.isi.uu.nl/Research/Databases/DRIVE/).

In the digital images, the arteriovenous retinal vascular network has many observable characteristics, including diameter, color, tortuosity (relative curvature) and opacity (reflectivity). After adjustments of digital images (filtering all unwanted material and correcting optical errors), arteries and veins of the retinal circulation are seen as white vessels in the black background.

Four main techniques are used to segment the vasculature form retinal images: matched filters, vessel tracking, neural networks and morphological processing (Patton et al 2006; Niemeijer et al 2004) and many different approaches for automated vessel segmentation have been reported (Al-Rawi & Karajeh 2007; Salem et al 2007).

This diversity of subjects, image acquisition, type of image, its processing, and fractal analysis computerized methods results in a range of the value of the fractal dimension. These studies suggested that the fractal dimension of the vascular network in the normal human retina is approximately 1.7. This is the same fractal dimension that was found for a diffusion-limited aggregation process (DLA) (Kyriacos et al 1997; Masters 2004).

Table 1

Summary of estimated mean fractal dimension on retinovasculature (Kyriacos et al 1997)

No.	*Method of calculation*	*Value of fractal dimension*	*Concluded mechanism*
1	Mass-radius, density- density computerized	1.7	Diffusion limited aggregation
2	Density-density validated	Initial state ≈ 1.67 New vessels ≈ 1.8 After regression ≈ 1.71	
3	Box-counting validated	1.63 - 1.76	Laplacian processes
4	Box-counting	1.68 - 1.72	Laplacian processes

Table 2

Summary of estimated mean fractal dimension of the different networks of retinovasculature: (mean ± standard deviation) (Kyriacos et al 1997)

No.	*Arterial network*	*Venous network*	*Arteriovenous network*
1	1.537 ± 0.036	1.532 ± 0.030	1.664 ± 0.025

The range of results obtained in other studies are due to the utilization of digital retinal images with different resolution of retinal fundus, different location of optic disk

on the retinal image, different methods for image acquisition, different segmentation methods and a different method to calculate fractal dimensions (Kyriacos et al 1997).

For the same digital retinal images, the fractal dimension value obtained by the density-density correlation method does not always agree with the fractal dimension obtained using the box-counting or mass radius method. It was demonstrated that different variations in the experimental determination of the fractal dimension can be attributed to the comparison of red-free retinal photographs with fluorescein angiograms in which the time of the image capture affects the visibility of the arteries and the veins in the retinal circulation, and comparison of computerized box-counting techniques with the more variable and subjective density-density correlation methods (Masters 2004).

The above mentioned factors partly explain the variations in results encountered in the literature. Different investigators have also found different trends in the fractal dimension associated with an increase in pathological status (Avakian et al 2002).

Multifractal analysis of vascular network of the human retina. Different investigators have found that vascular network of the human retina represents geometrical multifractals, characterized by a hierarchy of exponents rather than a single fractal dimension (Stosic & Stosic 2006; Gould et al 2011).

A vascular network is only considered a multifractal structure if there is a statistically significant difference between D_0, D_1 and D_2.

In the multifractal analysis of digital retinal images, the capacity dimension D_0 (which corresponds to box counting method), was always found to be larger than the information dimension D_1, which was in turn always larger than the correlation dimension D_2 (corresponding to methods such as radius of gyration or the density–density correlation function); all the three being significantly lower than the diffusion limited aggregation (DLA) fractal dimension ($D \approx 1.7$) (Stosic & Stosic 2006).

The multifractal spectrum can be plotted to visualize the distribution of the space occupied by vascular structures (Gould et al 2011).

Table 3

Summary of estimated generalized fractal dimensions and lacunarity parameter for retinal vessels: (average ± standard deviation) (Gould et al 2011)

No.	*Generalized fractal dimensions*			*Lacunarity parameter b*
	D_0	D_1	D_2	
1	1.75 ± 0.06	1.72 ± 0.04	1.69 ± 0.03	0.49 ± 0.01

Conclusions. Fractal and multifractal analysis provides powerful tools for the characterization of the human retina vascular network geometry and can be used as part of a screening tool for early detection of retinal diseases.

The advantage of this geometry compared to traditional processing methods, lie in the way of how the non-regularities are assumed.

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