Human & Veterinary Medicine
International Journal of the Bioflux Society HVM

OPEN ACCESS
Review

Characterization of retinal vessel networks in human retinal imagery using quantitative descriptors

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Abstract. Objective: The objective of this paper is to present an overview of researches concerning the morphology of human retinal vessel network using quantitative descriptors. To describe the morphology of human retinal vessel network in fundus eye images, different automated methods are used in modern ophthalmology. The quantification methods include vessels morphology analysis based on the measurement of tortuosity, width, branching angle, branching coefficient, fractal dimension and of multifractal spectra. The vessel morphology analysis is useful, as a noninvasive research tool, to describe, measure and quantify subtle variations and abnormalities in the retinal vasculature. The obtained results may also be used in mathematical models of the human retina.

Key Words: human retinal vessels, quantitative descriptors, retinal image analysis.

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Introduction

Over the last few decades with the advances of computer technology, important studies have been made in computer-aided diagnosis of medical images to improve a clinician's confidence in the analysis of retinal medical images (Kyriacos et al 1997; Ţălu 2005; Ryan et al 2006; Ţălu et al 2009; Ţălu et al 2011; Ţălu 2011a). Investigating retinal medical images using computer analysis methods is of both scientific and clinical importance, as understanding the retinal vascular network may be helpful for improving specific treatments of retinal disorders (Holz & Spaide 2010; Ţălu & Ţălu 2012).

Mathematical morphology exploits features of the vascular pattern (Joshi 2012).

The retinal vascular network may be imaged non-invasively, photographed, and subjected to image analysis, as a part of an in-vivo analysis. Retinal vessels and arteries have many observable features, including diameter, color, tortuosity, and opacity (Ryan et al 2006; Holz & Spaide 2010).

The vessel network arrangement is based on Murray's law (Murray, 1926), which states that the cube of the radius of a parent vessel equals the sum of the cube of the radii of the daughters (Liu & Kassab 2007; Joshi 2012). Also, the retinal vascular network is determined by a complex set of physiological demands (Joshi 2012).

Abnormalities in the vascular pattern of the retina, highlighted in morphologic changes in vessel shape, width, tortuosity, length, branching pattern or the appearance of retinal lesions, may be associated with retinopathies or cardiovascular diseases (Ryan et al 2006; Joshi 2012).

For detection and differentiation of retinal lesions are often used the morphologic changes in retinal vessels based on their luminance, local contrast and intensity properties. Several intensity and morphological properties of vascular structures, such as linearity, and connectivity, and width, can provide important information in diagnosis/prognosis in clinical practice (Joshi 2012). Quantitative analysis and measurements of these features of retinal vessel changes may be an important indicator for early detection of clinical signs of retinopathies (Ţălu 2005; Joshi 2012).

The aim of this work is to characterize the vascular pattern of human retina using the following properties of retinal vessels: 1) vessel tortuosity; 2) vessel width; 3) branching angle; 4) branching coefficient; 5) fractal dimension; 6) multifractal spectra.

Material and method

Vessel tortuosity

Tortuosity is a type of geometrical irregularity that can be defined as a measure of curvature and twists or kinks produced in the vessel course (Joshi 2012). Vascular tortuosity is the result of accumulation of curvature along blood vessel length. The tortuosity of a vessel influences its flow haemodynamics (Johnson & Dougherty 2007).

There are different mathematical methods of tortuosity estimation in 2D and in 3D.

By modelling the retinal blood vessels as curves in 2D or 3D, a measure of tortuosity will enable automatic diagnosis. Normal retinal blood vessels are straight or gently curved, but they become dilated and tortuous in a number of retinal diseases (Hart et al 1999).
The simplest mathematic method to estimate tortuosity (τ) is arc-chord ratio: ratio of the length of the curve (L) to the distance between the ends of it (C) (Azegrouz et al 2006):

$$\tau = L/C \qquad (1)$$

In equation (1) tortuosity (τ) equals 1 for a straight line and is infinite for a circle.
Lotmar et al (1979) first described a quantitative tortuosity measurement and this was extended by Bracher (Bracher 1982). According this method, the vessel is decomposed into a series of circular arcs, for which the chord lengths l_i and arrow heights h_i are measured. The tortuosity (τ) is measured as the relative length variation (based on an approximation of a blood vessel with a sinusoidal model):

$$\tau = \frac{L}{l} - 1 \approx \frac{8}{3}\sum_{i=1}^{n}\left(h_i / l_i\right)^2 \qquad (2)$$

where L is the length of the blood vessel and l is the chord length.
A numeric index based on spatial frequencies to determine the tortuosity (τ) was proposed by Capowski et al (1995).
Another method for distinguishing tortuous and non-tortuous blood vessels in angiograms was proposed by Zhou et al (1994).
A method to determine the tortuosity (τ) based on the integral curvature along a blood vessel was proposed by Katz et al (1990).
Grisan et al (2008) proposed a new method to determine the tortuosity (τ) as:

$$\tau = \frac{n-1}{L} \cdot \sum_{i=1}^{n}\left(\frac{L_i}{S_i} - 1\right) \qquad (3)$$

where: L is the total length of the curve; S_i is the chord length of a curve i; L_i is the length of a curve i. For n=1, the tortuosity τ=0 and thus vessels with a constant convexity have zero tortuosity.
Joshi (2012) proposed a computational method for tortuosity index (TI) as:

$$\boldsymbol{T} = \frac{(n+1)\cdot\left(\sum_{i=1}^{m}\theta_i\right)\cdot\left(\sum_{i=1}^{m}\left(L_{\dot{c}} / L_{\dot{x}}\right)\right)}{L_c \cdot m \cdot m} \qquad (4)$$

where: n is the number of changes in curvature sign; m is the number of segments in the vessel; θ_i is the magnitude of angle of curvature; L_{ci} is the length of the respective arc; L_{xi} is the length of the respective chord, and L_c is the total length of the vessel. The parameters with subscript i describe the values for ith segment.
To determine the tortuosity (τ) in 3D, several ways to adapt methods estimating tortuosity in 2D have been proposed (Johnson & Dougherty 2007).

In clinical practice, ophthalmologists integrate information about how many times a vessel twists (changes in convexity, or curvature sign), and how large is the amplitude of each of the recognized twist (Grisan et al 2008).
Ophthalmologists visually estimate blood vessel tortuosity considering the total curvature and/or local curvature and changes in the vessel course or direction. Also, the grade tortuosity is estimated using a gross qualitative scale (mild, moderate, severe, and extreme) (Johnson & Dougherty 2007).
Automatic measurement of blood vessel tortuosity is an important diagnostic indicator, in order to assess its severity and progression and to investigate the link between tortuosity and the evolution of retinal disease processes (Joshi 2012; Dougherty et al 2010).

Vessel width

Different clinical studies highlighted that the vessel width increases with wall shear stress and the vessel wall thickness increases with the circumferential wall stress (Joshi 2012).
A method to determine the retinal vessel width may be obtained by measuring the standard deviation of Gaussian model fit at the vessel cross section or by using the measure of isotropic contrast at the vessel centerline and at the edges (Wilson et al 2008; Joshi 2012). A new proposed method determines the blood vessel width by means of a two-slice 3D surface segmentation problem (Xu et al 2011; Joshi 2012).

Branching angle

Bifurcation is an important geometric factor, having a significant influence on the circulation in the retinal vasculature network (Joshi 2012).
A retinal vascular network can be characterized in terms of bifurcation angles and junction exponents (a measure of the relative diameters of parent and daughter branch vessels) at branching points. These parameters have implications for efficiency of space-filling by vascular networks (Chapman et al 1997).
The basic variables at an arterial bifurcation are the lengths and diameters of the three vessel segments involved, and the angles that the two branches make with the direction of the parent vessel (Zamir 2001). Retinal branching/bifurcation angle is defined as ($\theta_1 + \theta_2$), as an angle between two daughter vessels at the bifurcation (Fig. 1).

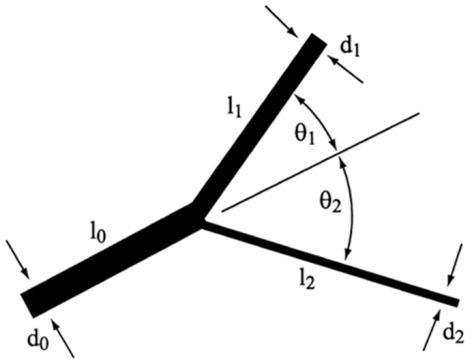

Figure 1. The retinal branching angle.

The deviation in absolute angles from the theoretical optimum branching angle may suggest the abnormalities in the branching architecture caused by a disease altering the ability of the vascular network to distribute blood (Doubal 2010).

Branching angles are related to energy spent in blood transport, the efficiency of flow, the diffusion distance, and the degree of asymmetry between the two daughter vessels. The optimum value of this angle is approximately in range 72°-75° (Joshi 2012).

Branching coefficient

Conventionally, the relationship between parent and daughter vessels at vascular bifurcations has been expressed by the junction exponent (x), defined by the relationship (Joshi 2012; Witt et al 2010):

$$d_0^x = d_1^x + d_2^x \qquad (5)$$

where: d_1 is the width of branch vessel 1 (larger width of one of the daughter vessels), d_2 is width of branch vessel 2 (smaller width of the other daughter vessel), and d_0 is the width of the trunk vessel (Fig. 1).

Murray's law predicts that under conditions of optimum power loss in the bifurcation, the junction exponent (x) is equal to 3 (Joshi 2012; Witt et al 2010). The deviations of this parameter from the optimal conditions predicted by Murray's law (x=3, at the branching point to optimize the circulatory efficiency in case of healthy subjects) have been shown to be associated with retinal vascular disease (Joshi 2012).

The branching coefficient (ω) is defined as (Patton et al 2006; Yogesan et al 2006):

$$\omega = (d_1^2 + d_2^2) / d_0^2 \qquad (6)$$

The theoretical optimum value for the branching coefficient of a dichotomous, symmetrical junction is 1.26 (Patton et al 2006; Yogesan et al 2006). This value was demonstrated by Murray in 1926, in his paper on the relationship between parent and daughter vessel widths at vascular junctions (Yogesan et al 2006).

The asymmetry ratio (λ) is defined as (Joshi 2012):

$$\lambda = d_2^2 / d_1^2 \qquad (7)$$

The optimality ratio (γ), equivalent to the junction exponent, is defined as (Joshi 2012; Witt et al 2010):

$$\gamma = [(d_1^3 + d_2^3) / 2d_0^3]^{1/3} \qquad (8)$$

Fractal dimension

The application of fractal analysis allows us to obtain a measure of complexity of the retinal vessel branching. The human retinal vascular network, including the pattern of branching, it has been demonstrated to be a fractal structure in a "scaling window", which normally ranges in two to three orders of magnitude (Losa et al 2005; Lopes & Betrouni 2009).

Computerized medical image visualization and advances in analysis methods and computer-aided diagnosis of the human retinal photographs using the fractal geometry and its multifractal extension is a part of the early detection and diagnosis of retinal diseases (Kyriacos et al 1997; Masters 2004; Stosic & Stosic 2006; Mendonça et al 2007; Ţălu 2011b; Ţălu & Giovanzana 2011; Ţălu & Giovanzana 2012; Ţălu 2012a; Ţălu 2012b; Ţălu 2012c; Ţălu 2012d; Ţălu et al 2012; Ţălu et al 2013a).

TThe fractal and multifractal analysis of human retinal microvascular network depends on the experimental and methodological parameters involved as: diversity of subjects, image acquisition, type of image, image processing, fractal analysis methods (box-counting, mass-radius, density-density correlation function method etc.), and multifractal methods (box-counting, fixedmass, fixed-radius method etc.), including the algorithm and specific calculation used etc. (Kyriacos et al 1997; Ţălu 2012c, Ţălu & Ţălu 2013)In fractal analysis, box-counting or box dimension is one of the most widely used dimension, which seems to be easy to calculate (Falconer 2003).

The lower and upper box-counting dimensions of a subset $F \subset R^n$ are respectively defined by (Falconer 2003):

$$\underline{\dim}_B(F) = \underline{\lim}_{\delta \to 0} \frac{\log N_\delta(F)}{-\log \delta}; \qquad \overline{\dim}_B(F) = \overline{\lim}_{\delta \to 0} \frac{\log N_\delta(F)}{-\log \delta} \qquad (9)$$

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

$$\dim_B(F) = \lim_{\delta \to 0} \frac{\log N_\delta(F)}{-\log \delta} \qquad (10)$$

(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 centres in F.

The fractal dimension contains information about object geometrical structure, strictly exceeds topological dimension and it may be understood as a characterization of the fractal object self-similarity (Falconer 2003). The fractal dimension D of retinal vascular network is a key characteristic that quantifies the global measure of complexity of the vascular branching pattern (Masters 2004).

Several fractal studies have established that the average values of the estimated fractal dimensions of normal human retinal vascular network were approximately 1.7 (Kyriacos et al 1997; Masters 2004; Ţălu 2011b; Ţălu & Giovanzana 2012).

It was demonstrated that an increased fractal dimension represents increased branching complexity and a decreased fractal dimension represents decreased branching complexity (Ţălu et al 2012). Different investigators have also found contradictory trends in the fractal dimension associated with the retinal pathological status (Avakian et al 2002; Lakshminanarayanan et al 2003; Kunicki et al 2009; Olujić et al 2011; Ţălu et al 2012; Ţălu et al 2013a; Ţălu et al 2013b).

Multifractal spectra

Some investigators (Azemin et al 2012) observed a significant decrease in the fractal dimensions of human retinal vascular network with aging, consistent with observations from other human organ systems.

Multifractals are intrinsically more complex and inhomogeneous than fractals (Falconer 2003). Multifractal analysis reveals more information about geometrical features and spatial distribution and is far more sensitive in detecting small changes of the retinal microvasculature than the fractal analysis (Stosic & Stosic 2006; Ţălu 2012d; Ţălu 2013). Multifractal spectra

can be calculated in different ways (Falconer 2003; Lopes & Betrouni 2009).
The generalized dimension D_q (for all $D_q \neq 1$) can be expressed as (Ţălu 2012d):

$$D_q = \frac{1}{q-1} \lim_{\varepsilon \to 0} \frac{\ln Z(q,\varepsilon)}{\ln \varepsilon} \qquad (11)$$

where: $Z(q, \varepsilon)$ is the partition function; q is a real parameter that indicates the order of the moment of the measure and ε is the size of the boxes used to cover the sample.
Theoretically, q should range from $-\infty$ to $+\infty$ to get a complete multifractal spectrum (since $\varepsilon \to 0$). For the particular case where q=1 equation (11) becomes indeterminate, so D_q is estimated by l´Hôpital's rule. The generalized dimension D_q is defined for all real q and q ranges from $-\infty$ and $+\infty$.
The generalized dimensions D_q for q=0, q=1 and q=2, are known as the capacity (or box-counting), the information (Shannon entropy) and correlation dimensions, respectively. The capacity dimension D_0 is independent of q and provides global (or average) information about the structure, D_1 quantifies the degree of disorder present in the distribution, and D_2 measures the mean distribution density of the statistical measure (Ţălu 2013). All dimensions are different, satisfying $D_0 > D_1 > D_2$. The limits of the generalized dimension spectrum are $D_{-\infty}$ and D_{∞}.
In practical applications, by applying the multifractal analysis methods are determined the functional dependences D_q versus q or $f(\alpha)$ versus α.
The relationship between the D_q spectrum and the $f(\alpha)$ spectrum is established via the Legendre transformation (Stosic & Stosic 2006; Ţălu 2012d):

$$f(\alpha(q)) = q\alpha(q) - \tau(q) \qquad (12)$$

where $\alpha(q)$ represents Hölder exponents of the qth order moment expressed as:

$$\alpha(q) = d\tau(q)/dq \qquad (13)$$

and $\tau(q)$ is the mass correlation exponent of the qth order related to D_q by the following equation:

$$\tau(q) = (q-1)D_q \qquad (14)$$

$\tau(q)$ could be considered as a characteristic function of the fractal behavior. If $\tau(q)$ versus q is a convex function, the data set is multifractal. If, however, $\tau(q)$ versus q is a straight line, then the data set is fractal. For q=0, $\tau(0) = -D_0$ (Shi et al 2009).
The curve $f(\alpha)$ is single-humped for a multifractal, it reduces to a point for a fractal (Ţălu 2012b). The $f(\alpha)$ spectrum at the left and right of the maximum corresponds to $q > 0$ and $q < 0$, respectively (Hu et al 2009). $f(\alpha) \geq 0$ and α is defined in $[\alpha_{min}, \alpha_{max}]$.

$$\alpha_{\min} = \frac{d\tau(q)}{dq}\Big|_{q\to\infty}; \quad \alpha_{\max} = \frac{d\tau(q)}{dq}\Big|_{q\to-\infty} \qquad (15)$$

The maximum fractal dimension $f_{max} = D_0$, and then the magnitude decreases around when $q > 0$ and $q < 0$. The $f(\alpha)$ curve is tangent to the curve $f=\alpha$, and the point of tangency occurs at q=1. $\Delta\alpha = \alpha_{max} - \alpha_{min}$, when $f(\alpha) > 0$, represents a quantitative measurement of the degree of multifractality. The degree of fluctuation in different fractal exponents is correlated with the asymmetry of the $f(\alpha)$-α spectrum shape (Hu et al 2009). The degree of asymmetry can be calculated with the formula (Hu et al 2009):

$$A = (\alpha_0 - \alpha_{\min})/(\alpha_{\max} - \alpha_0) \qquad (16)$$

If the $f(\alpha)$ spectrum is symmetric, then A=1.
The retinal microvascular network is considered a multifractal structure if there is a statistically significant difference between D_0, D_1 and D_2 (Ţălu & Giovanzana 2011).
Ţălu (Ţălu 2012d) determined that the averaged generalized fractal dimensions (average ± standard deviation), computed applying the standard box-counting algorithm to the digitized data, for normal retinal blood vessels were: D_0=1.6968 ± 0.0014; D_1=1.6246 ± 0.0011 and D_2=1.5921 ± 0.0008. However, researchers have not reached a general consensus concerning the correlations between generalized fractal dimensions and pathological retinal diseases (Stosic & Stosic 2006; Ţălu et al 2012; Ţălu et al 2013a).
The microvascular geometry of the human retina network represents geometrical multifractals, characterised through subsets of regions having different scaling properties (a description over the retinal regions both locally and globally), that are not evident in the fractal analysis (a globally description over the retinal regions).
Fractal and multifractal analysis of retinal vascular network pattern and geometry is a useful screening tool for quantifying and detecting retinal vascular diseases.

Conclusions

The retinal diseases and the cardiovascular dysfunctions modify the morphology of human retinal vessel network. Therefore, the automated assessment of morpholoy of retinal vascular network may allow us to detect or diagnose the retinal diseases.
The retinal eye images obtained by color fundus imaging may be utilized for the computer-aided diagnosis using the automated analysis methods. The tools needed to analyze the morphology of human retinal vessel network require an interdisciplinary approach.

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Citation	Ţălu, Ş., 2013. Characterization of retinal vessel networks in human retinal imagery using quantitative descriptors. HVM Bioflux 5(2):52-57.
Editor	Ştefan C. Vesa
Received	15 April 2013
Accepted	9 June 2013
Published Online	12 June 2013
Funding	None reported
Conflicts/ Competing Interests	None reported