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Retinal Blood Vessel Tortuosity: Quantifying and Grading- A Review

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Abstract:
Blood vessel tortuosity is utilized to detect various vascular and non-vascular diseases like diabetic retinopathy (DR), retinopathy of prematurity (RoP). Early detection and grading of these diseases could prevent further complications. Hence, the accurate detection and grading is paramount for this purpose. A good number researcher has proposed automated tortuosity grading algorithm based upon different methods of classification and grading. In literature, numerous definitions and measurement methods of tortuosity have been reported by different researchers. In this work, an attempt has been made to compare and discuss various automated and manual tortuosity measurement systems in terms of their merits and demerits. Further, a study has been carried out on different publicly available datasets and an attempt has also made to compare these data sets on the basis of size, variety and suitability of the vessels segment algorithm used in these data sets.

Keywords*: Microfinance, Self Help Group, Women Empowerment, Poverty, Financial Inclusion.*

1. INTRODUCTION

Retina, the window of brain, is the only place from where blood vessels can be visualized. Retinal vasculature can be visualized non-invasively. There is a close analogy between cerebral circulation and retinal vasculature. In general, healthy human beings have the blood vessels gently curve and regular. However, with the age and many retinal diseases blood vessels bends irregularly making them more tortuous. Here, tortuous means the twisting of vessels randomly. The degree of tortuosity gives the indication of retinal diseases. Though the proposed definition of tortuosity measure in literatures are not globally accepted but they have the agreement with relative characteristics of blood vessels tortuosity from their experience. The tortuosity is also function of width, location, distance from optical nerve and counts of twists.

Retinal tortuosity of patient may be viewed as repulsive along the blood vessels. Ophthalmologists suggested that this repulsion of blood vessel are due to its natural behavior to accommodate changes in the body, age or diseases [1]–[4]. Though globally not accepted, the tortuosity of retinal blood vessels is characterized with their abnormality, loop-like or kinky shapes along the blood vessel length before it bifurcated into branches. The tortuosity increases when the blood vessel dilates, elongated and become curvier and more twisty to an abnormal condition. Tortuosity occur only the small part of individual vessel thus only small region of whole vasculature of retina are tortuous [5]. Last few years, researchers trying to correlate tortuosity of vessels structure as early medical indication of various retinal diseases like DR, Hypertensive retinopathy, facio-Scapulo Humeral Muscular Dystrophy (FSHD) [6], ROP and Coats diseases [7].

In general, ophthalmologists use ophthalmoscope to view the inner structure of eyes also known as fundus images manually. Manual diagnosis has low accuracy as human error involves. Recently stronger image processing software has been developed which gives more accurate results. Developed image processing algorithms can accommodate more complications and prevent misdiagnosis.

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In literature, a few review articles have been reported [41]. This paper is organized as follows: the tortuosity measures proposed in the literature has been discussed in Section II, Section III described all the datasets available used in these studies and finally in Section IV conclusion has been drawn on this study.

2. MEASUREMENT TECHNIQUES FOR EVALUATING TORTUOSITY

Though most of the definitions of blood vessel tortuosity, stated by researchers, are not unanimously accepted by ophthalmologists, they come on an agreement that tortuosity measure must carry some clinical information. Ophthalmologist also suggested that measurement of tortuosity for a given fundus image should be translation, rotation and scaling invariant. A large number of algorithms to measure tortuosity have been proposed in the last few decades. These measurement algorithms are developed to quantify tortuosity to single vessel segments or total vasculature [5]. Researchers find a strong correlation between vascular tortuosity and retinal diseases [10]–[12]. Hence, it is very much essential that the algorithm for tortuosity measure developed must be accurate and automated which will able to classify different diseases accurately. However, there is a rich literature of different class of tortuosity measure algorithm which has been used to quantify vessels tortuosity. Some improved algorithm incorporates the features associated with blood vessels' structure like thickness vessel wall, width of the vessels and frequency and radius of curvature vessels. In the literature, some integrated automated and semi-automated screening algorithm are reported which are able to segment, classify and quantify in pathological meaning of blood vessel features. Two of these algorithms are 'Retinopathy Of Prematurity Tool (ROPtool)' [13] and 'Computer Assisted Image Analysis of the Retina(CAIAR)' [14]. The following paragraphs will present some of algorithms frequently cited in literature are discussed.

A. Algorithm Based on Distance

In this approach, the measurement of tortuosity is mainly based on the path length of the blood vessel segment or curve, defined as the Arc and denoted by Ac; and the Chord is defined as the length of the straight line between the two end points of the blood vessel under consideration and denoted by Lc. Then tortuosity is calculated as the ratio of arc and cord. Some of techniques based on these are discussed below.

1) Relative Length Variation:

The algorithm based on relative length variation was introduced first by L. Freiburghaus [15], and later it was modified by Bracher [16]. In this method, a vessel segment is divided into sets of single arcs and then the height curve from base line h_i and chord lengths l_i is measured each individual arcs. Finally, tortuosity is calculated as the relative length variation in equation (1), where L is the length of the blood vessel. The blood vessel segments are modelled as the sinusoidal curve. But this technique involves the manual selection of points on the vessel of the fundus image to divide the vessel into a series of single arcs and hence, it is not fully automated. Using this measuring techniques, WE Hart could achieve 91% in the classification of segments and for the classification of a whole vascular tree, it was 95% [17] on a private dataset used by authors.

$$\text{Relative length variation (RLV)} = \frac{A_c}{L_c} \approx \frac{8}{3}\sum_{i=1}^{N}\left(\frac{h_i}{l_i}\right)^2 \quad (1)$$

2) Arc to Chord Ratio:

One of the earliest definitions of tortuosity is arc to chord ratio. It is the simplest and greatly used techniques of tortuosity measure. This was first introduced by WE Hart et. al. [5]. Consider curve(S) be an individual segment of blood vessel, Ac be the total length of the curve, and Lx (known as the chord length) be the straight distance between the two end

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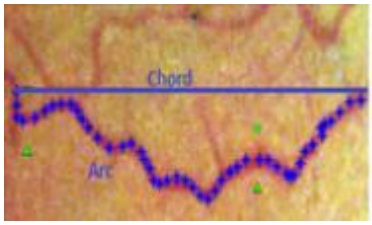
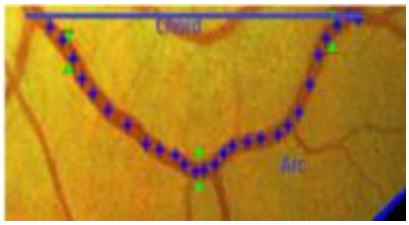
points of the blood vessel segment defined in equation (5). The equation (2) gives the measure of curvature in terms of length Lx and cord Ac. The value of equation (2) returns to zero for a straight line indicating zero tortuosity measure and the value increases in positive direction as its length Lx increases compared to Ac indicating more and more tortuous.

$$\tau_{AOC} = \frac{A_c(S)}{L_x(S)} - 1 \qquad (2)$$



A



B

Fig.1: Both the vessel segment has same tortuosity using arc over chord method [41].

$$A_c = \sum_{i=1}^{n-1} \sqrt{(x_i - x_{i+1})^2 + (y_i - y_{i+1})^2} \qquad (3)$$

$$A_{c2} = \int_{t_0}^{t_1} \sqrt{x'^2(t) + y'^2(t)} \qquad (4)$$

$$L_x = \sqrt{(x_n - x_1)^2 + (y_n - y_1)^2} \qquad (5)$$

Arc over Chord measure is seems to be well suited with short segments; but main disadvantage of this method is that the value of tortuosity for a long smooth curved vessel and a very twisted same length segment results to same, See fig.1. E. Trucco et al. [18] concluded that tortuosity measures based on distance is unable to evaluate retinal vessels and also has concluded that the ratio of the curve to the chord gives how the vessels deviates from a straight line, which seems to be a global measure, whereas tortuosity is directly related to local measures such as curvature. Table I represents the comparative evaluation of tortuosity reported in the state of art based on distance approach measures.

3) **Tortuosity as Function of Distance:**

K.M. Keck et al proposed a new tortuosity measure definition [19]. He has defined tortuosity as the ratio of vessel length to straight line end points of segment. His significant contribution is that tortuosity was calculated as a function of distance in terms of disk diameter (DD) from the disk edge using computer-based methods developed by the authors. Main finding of this paper are (i) as distance increases from optic disk, the tortuosity increases. (ii) Vascular tortuosity is much more in case of plus disease and (iii) tortuosity of arteries are more than veins.

Table I: Implementation Results of Algorithm Based on Arc Over Chord Lengths Ratio:

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Algorithm	*Database*	*Performance measure*
W.E. Hart (1997) [5]	*Private*	*0.91*
C. Heneghan(2002) [12]	*Private*	*Tortuosity increases as severity of disease*
DK Wallace (2003) [13]	*Private*	*0.80 sensitivity and 0.91 specificity*
E. Bullitt et al. (2003) [8]	*Private*	-----
E. Grisan (2003)	*Public*	*For Arteries τ=0.857 for veins τ =0.036*
E. Grisan (2006)	*Public*	*Spearman's coefficient(ρ).* *For Arteries ρ =0.792, for veins ρ =-0.656*
E. Grisan (2008)	*Public*	*For Arteries ρ =0.792, for veins ρ =-0.656*
R. Turior (2012)	*Private*	*Maximum classification achieved 0.73*

B. Algorithm Based on Curvature

Literal meaning of curvature is the amount angular deviation from its straight line. The measurement of the twist or deviation can be quantified in different approach such as rate of change of angles of tangent drawn at each point along the length of vessels. Another approach may be geometric approach, where angles between two tangents drawn on two point along a blood vessel with concavity (equation 15) or inflectivity (as equation 21). Third approach may be algebraic approach. Here, the curvature is measure as the function of derivative vessel path. The most of curvature measures proposed in literature to estimate tortuosity are based on these approaches and some of them are formulated here

1) Point Curvature Along A Blood Vessel:

Consider, a blood vessel S is represented by the coordinates of centre line points along the curvature as S =[(x1 , y1), (x2 , y2), .., (xn-2 , yn-2), (xn , yn), (xn , yn)], and represent in terms of Cartesian coordinates as S(t) = (x(t), y(t)), The curvature at point (x(t) y(t)) is defined as follows:

$$C(t) = \frac{\frac{dx(t)}{dt}\cdot\frac{d^2y(t)}{dt^2} - \frac{d^2x(t)}{dt^2}\cdot\frac{dy(t)}{dt}}{\left[\frac{dx(t)}{dt} + \frac{dy(t)}{dt}\right]^{\frac{3}{2}}} \quad (6)$$

2) **Total Curvature**:

Again consider the previous curve (S), and the (x_n , y_n) points representing the point on skeleton line of

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blood vessel. The total curvature is calculated taking the integration of curvatures obtained in each points on vessel segment as in equation (6) and represented as

$$C_T(S) = \int_{t_1}^{t_n} C(t)dt \qquad (7)$$

As the curvature C(t) may be positive and negative along the vessel segment, the CT(S) may not give correct information of tortuosity. Hence, another term named total square curvature is defined.

3)Total Squared Curvature:

The total squared curvature is expressed by taking integration of square of all point curvatures along the segment as:

$$C_{TS}(S) = \int_{t_1}^{t_n} C^2(t)dt \qquad (8)$$

4) Normalized Total Curvature:

Tortuosity is computed by the ratio of the total curvature calculated in equation (7) to the length of arc of blood vessels as:

$$C_{T,norm}(s) = \frac{C_T(s)}{L_C(s)} \qquad (9)$$

5) Normalized Total Squared Curvature:

Tortuosity is computed by the ratio of the total squared curvature obtained in equation (8) to the blood vessels' arc length as:

$$C_{TS,norm}(s) = \frac{C_{TS}(s)}{L_C(s)} \qquad (10)$$

6) Total Chord Length Normalized Curvature:

This tortuosity is mathematically represented in terms of curvature per unit arc length as:

$$C_{T,norm,arc}(s) = \frac{C_T(s)}{L_x(s)} \qquad (11)$$

7) **Total Squared Chord Length Normalized Curvature:**

Tortuosity is defined as total squared curvature per unit chord length and computed by normalizing total squared curvature by length of vessel cord.

$$C_{TS,norm,arc}(s) = \frac{C_{TS}(s)}{L_x(s)} \qquad (12)$$

8) Tortuosity Coefficient:

Geoffrey Dougherty et. al [3] proposed a quantitative tortuosity index, computed by taking the second order differences (σ_i) along central line coordinates of vessels and then summing all differences followed by normalization with the sampling interval P. Though the tortuosity measure is computed for second dimensional images, can also be generalized for three dimensional images also. Tortuosity is represented mathematically as

$$T_{Coe} = \left\{ \sum_{j=1}^{N} |\sigma_i| \right\} / P \qquad (13)$$

9) **Chain Code Base Tortuosity:**

Tortuosity using Chain code first proposed by E Bribiesca [20]. The tortuosity is the function chain code of slopes of successive small vessel segments assuming straight line. Initially each vessel is broken into a small piece wise linear segments and then slope is calculated between two consecutive segments coded into chain code known as Slope Chain Code (SCC). Calculated SCC of these line segment has the values from −1 to +1. The important properties of the SCC of a curve is that they are translation-invariant, rotation-invariant and even scaling-invariant. The mathematical representation of this measure represented as

$$T_{SCC} = \sum_{i=1}^{x_n} |\alpha_i| \qquad (14)$$

10) Sum of Angles Metric (SOAM):

Semdby et. al. [21] proposed the concept of Sum of angles metric (SOAM) and latter improved by Elizabeth Bullitt et al. [8], [9]. This approach is similar to that of chain code but angle are measure between two cords made by three consecutive points along the vessel skeleton of curve space, and then

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divided by total length of vessel path. These are measures in radians/cm. Vessels with high curvature have elevated SOAM values.

$$SOAM = \frac{\sum_{k=1}^{n-3} CP_k}{\sum_{k=1}^{n-1} |P_k - P_{k-1}|} \quad (15)$$

Where CP_k is curvature of k-th path and P_k is k-th path.

11) Mean Curvature (MC):

The Mean Curvature is a curve fitting technique proposed by S. Chanjira et al. [22], in this technique blood vessels are divided into smaller segment such that these segments exactly fit on circles of some radius or its arc. Radii of all such circles of arcs are used to measure tortuosity of given fundus image and mathematically represented in equation (16). MC with zero value represent low tortuosity image and as MC increases tortuosity also increases to high as it approaches to 1.

$$MC = avg\left[\sum_{i=1}^{n} \frac{1}{r_r}\right] \quad (16)$$

12) Mean Direction Angle Change (MDAC):

Mean direction angle change is defined on the principle of average change in angles along the blood vessels. In this technique, blood vessels are marked with several points P with discrete steps along the vessels' centreline. Then two points P+i and P-i is taken before and after all the points P marked earlier respectively and form vectors $\overrightarrow{P_{-1}P}$ and $\overrightarrow{PP_{+1}}$. Next the angles between these two vectors are calculated by taking inverse cosine of dot product of these two vectors after normalization. Finally, MDAC is then computed by taking averages of all such angles along the entire vessel length. But this definition works satisfactorily with only few points preferably less than 10 points. MDAC measure is proposed by Chandrinos et al. [23] and represented as

$$T_{MDAC} = \frac{1}{t_{length} - 2 \times step} \sum_{n=step}^{length-step} \cos^{-1}(UV(\overrightarrow{P_{n-step}P_n}).UV(\overrightarrow{P_nP_{n+step}})) \quad (17)$$

13) **Absolute Direction Angle Change (ADAC):**

Another definition of tortuosity reported in literature by K.G. Goh, et al. [24] is absolute direction angle change (ADAC). The principle of this technique is the modification of MDAC with following changes. Firstly, it takes absolute values of angles obtained and secondly, angles that more than π/6 are only considered. Finally, tortuosity is measured as the number of time vessel changes its direction.

$$T_{ADAC} = \sum_{i=1}^{N-n} \left(\theta(i) \geq \frac{\pi}{6}\right) \quad (18)$$

14) Methods Based On Fast Fourier Transform:

Another promising evaluating tortuosity measure was introduced by Martin Rodriguez et al. [25]. In this method, curvature has been redefined as the rate of change of direction of the tangent drawn on centre point of blood vessel. Therefore, acute angle between two consecutive tangents is the rate of change of unit tangent vector per unit distance. This angle θ_c can be calculated by inner product of two vector representing two cords.

$$\theta_c = \cos^{-1}\left(\frac{\overrightarrow{T_{c-1}}\overrightarrow{t_{c+1}}}{\left|\overrightarrow{T_{c-1}}\right|\left|\overrightarrow{T_{c+1}}\right|}\right) \quad (19)$$

The overall TC is calculated as the average sum of curvatures obtained at each centroid using equation (19) and represented in rad/mm:

$$T_{SCC} = \sum_{C} \frac{\theta_C}{D_C} \quad (20)$$

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Table II: Implementations of Tortuosity Algorithm Based on Curvature:

Tortuosity measure	*Implementation*
Total curvature	*E. Grisan et al. [27, 28, 29], Chanjira et al. [22], R Turior et al. [32]*
Total squared curvature	*E. Grisan et al. [27, 28, 29]*
Normalized total curvature	
Normalized total squared curvature	
Total chord length Normalized curvature	
Total squared chord length normalized curvature	
Tortuosity Coefficient	*G. Dougherty(2000) [3]*
Tortuosity based chain code (T_SCC)	*E. Bribiesca [20]*
Sum of Angle Metric (SOAM)	*Semdby et. al. [21], Elizabeth Bullitt et al. [8], [9]*
Mean Direction Angle Change (MDAC)	*Chandrinos et al. [23].*
Absolute direction Angle change (ADAC)	*K. G. Goh, et al. (2001) [24].*
FFT based method (T_{SCC})	*M. Rodriguez et al. [25]*

C. Mixed Methods

Recently researchers are trying to improve the tortuosity algorithm by fusing two or more algorithms. All the algorithms discussed above deals with only one parameter which do not fulfil the expectation of ophthalmologists. To overcome this problem researchers, combine two or more features of existing techniques. Some of these algorithms are also incorporate other parameter like thickness, width, and inflection point counts of blood vessels. Some of these methods are discussed below.

1) Inflection Count Metric (ICM):

Inflection count metric was developed by Smedby for 2D curves [19] is extended to 3D image implementation by Elizabeth Bullitt [8], [9]. Infection count metric is defined as the product of 'infection points' counts and the ratio of the curvature length and the cordial distance between two points. This algorithm can also be used for space curve.

$$ICM = (n_{ic} - 1)\frac{L_x}{L_c} \qquad (21)$$

2) Curvature and Improved Chain Code Tortuosity Measure (TCCC):

This algorithm is the fusion of chain code algorithm and the inflection count measure. It was proposed by

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proposed by D. Onkaew et al. [26]. If n_{ic} be the number of inflections count and L be the total arc length, then tortuosity is calculated as the product of sum of curvatures calculated at every pixels and inflection point count at each sub-vessel. The tortuosity calculated in this algorithm is based on individual vessels, hence it is independent of segmentation of the total vessel tree.

$$T_{CCC} = \frac{n_{ic} - 1}{n_{ic}} \frac{1}{L} \sum_{i=1}^{n} K(P_i, K) \qquad (22)$$

3) Tortuosity Based on Sub-Curves and Distance:

E. Grison developed a new tortuosity measurement technique based on sub-curves and distance [27]. In this algorithm, at first each vessel partitioned on the basis of segments of constant-sign curvature and then combined the number of segments and the curvature measure to calculate tortuosity. This algorithm further improved by many researchers [28-29]. The following three equations is defined for measurement.

$$T_1 = \frac{n-1}{L_c} \sum_{i=1}^{n} \left[\frac{L_{csi}}{L_{xsi}} \right]$$

$$T_2 = \frac{n-1}{L_c} \frac{1}{L_c} \sum_{i=1}^{n} \left[\frac{L_{csi}}{L_{xsi}} \right]$$

$$T_3 = \frac{n-1}{n} \frac{1}{L_c} \sum_{i=1}^{n} \left[\frac{L_{csi}}{L_{xsi}} \right] \qquad (25)$$

where n is the total number of inflection in the vessels segment. However, this algorithm involves manual extraction of vessel and finding the position of inflection.

4) Tortuosity Index (TI):

S. Q. Longmuir et. al. proposed tortuosity index (TI) [30]. The tortuosity index is the function of following parameters. (i) angle of ith curvature is denoted by θ_i, (ii) Lci represents the length of ith vessel segment, (iii) Lxi gives the corresponding cord length and (iv) m and n are the number of curvature segment of individual vessels and number of times it changes its sign respectively. Then the tortuosity indexed is defined as

$$TI = \left[\frac{(n+1)\left[\sum_{i-1}^{m} \theta_i\right]\left[\sum_{i-1}^{m} \frac{L_{ci}}{Lxi}\right]}{L_c mm} \right] \qquad (26)$$

6) Tortuosity as Function of Vessel Wall Thickness:

In this technique, tortuosity is defined as function of wall thickness of vessel and curvature. Tortuosity is measured as the weighted Minkowski norm of curvature along the vessel boundary. This algorithm is reported by H. Azegrouz et al. [31] and further improved by HAE. Trucco [18].

$$TW = \left(\sum_{n=3}^{N} \frac{\left|K_{B1(n)}\right| + \left|K_{B2(n)}\right|}{2} \right)^{\frac{1}{p}} \qquad (27)$$

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TABLE III: Implementation of the mixed tortuosity measures

Tortuosity measure	*Implementation*
Inflection count metric (ICM)	*Smedby for 2D curves [19], E. Bullitt [8], [9] also for 3D*
Curvature and improved chain code tortuosity measure (T_{CCC})	*D. Onkaew et al. [26]*
Tortuosity as function of vessel wall thickness (TW)	*H. Azegrouz et al. [31], HAE. Trucco [18]*

D. Angle Variation Tortuosity (Avt):

1) F. Oloumni et. al [33] proposed a new tortuosity measure known as angle variation tortuosity (AVT) [30]. Angle-variation-index is defined based on Gabor angle as

$$AVI(p)=\frac{1}{2}\left\{\left|\sin\left[\phi(p)-\phi(p-1)\right]\right|+\left|\sin\left[\phi(p)-\phi(p+1)\right]\right|\right\}$$

where p, p-1 and p+1 are present, previous and next pixel and ϕ denotes the Gabor angle. Therefore, normalized AVI for a given vessel segment is calculated as

$$AVI=\frac{1}{N}\sum_{p=1}^{N}AVI(p) \qquad (28)$$

where N is number of pixels in the vessel segment.

2) F. Oloumni et. al [34] further improved the algorithm by removing linear portion of vessels and then calculate the tortuosity. Authors shows that normal vessel tortuosity have AVI<0.07 and if AVI is greater than 0.15 vessels are abnormal.

E. Tortuosity Grading Systems

It is very much important to have a strong and globally accepted grading system which may be automatic or semi-automatic system. It also includes segmentation, extraction and classification of retinal blood vessels [35]. In literature, a good number of grading systems are reported such as ROPTool traces retinal blood vessels of ROP patient and measures their tortuosity of retinal blood vessels [13], [36], [37] and CAIAR (Computer Assisted Image Analysis of the Retina) which estimates the width of vessel wall and tortuosity of retinal vessels [14]. ROCKIT Metz ROC Software [38] is another strong software based tortuosity grading system used by F. Oloumni et. al [33] and [34].

F. Tortuosity Grading Using Deep Learning

Recent past, researchers in biomedical field are shifting their focus on deep convolutional network to extract features automatically. Feature maps obtained from deep convolutional neural network (CNN) can be directly used to visualized the pathologies and grade the disease [41]. DE Worrell et al. proposed a deep learning network to grade ROP directly from fundus images of premature babies. This algorithm uses GoogLeNet [42], binary cross entropy (BCE) loss function and adopt target level as RMSProp [43]. Networks consists of Seven convolutional layers with 3×3 1-padded kernel and 3×3 stride 2 max-pooling every even convolutional layer with 31×31 output feature maps.

3. DATASETS FOR FUNDUS IMAGES

The major problem faced by researchers of this community is the non-availability of private datasets to evaluate their algorithms. However, some private and public datasets are available but they differ by size, segment length, resolution etc. Hence, a comparative study of all the algorithms available in literature is quite challenging. In table IV, some of the tortuosity datasets reported in the literature are presented.

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TABLE IV: Databases of tortuosity along-with their classification

Author	*Nature of datasets*	*Pathology/method of measure*	*Availability*
WE. Hart (1997,1999) [5], [17]	*20 retinal image*	*Only segments and whole tree*	*Private*
G. Dougherty, (2000) [3]	*Aortograms of 82 patients*	*Abdominal/Arterial/tortuosity*	*Private*
C. Henghen (2002) [12]	*23 subjects*	*ROP/Width and tortuosity*	*private*
E. Bullitt (2003) [9]	*11 normal and 6 patients*	*Brain tumours/vessels/ Tortuosity*	*private*
E. Bullitt (2005) [10]	*34 images of healthy persons and 30 patients with deases*	*Brain tumours/vessels /Tortuosity*	*private*
E. Bullitt (2005) [10]	*60 images of normal and hypertensive patients.*	*Tortuosity*	*private*
C G. Owen (2008) [12]	*53 patients*	*Diabetes/Tortuosity*	*Private*
S Q. Longmuir, et al. (2010) [8]	*7 patients*	*FSHD /Tortuosity*	*private*
MM, Reinhartshuber (2015]	*30 arteriols and 30 venules*	*Hypertension/Tortuosity (TORT)*	*private*
P. L. Hildebrand et al. [40]	*Total 110 images*	*ROP/Tortuosity (TROPIC)*	*private*

4. CONCLUSION

From the literature review, a strong conclusion can be drawn that the vascular and non-vascular diseases are closely correlated with the abnormal tortuosity of retinal blood vessels. Hence, there is a big challenge to research community to design accurate and robust tortuosity measurement which help in early detection and thereby prevention of diseases. In literature, a good number of tortuosity algorithms are proposed in recent years by prominent researchers, but lacks full-scale acceptance by the clinical experts. In this review, a few problems that may greatly affected the progress of finding such measure are presented.

- The definition of tortuosity itself is ambiguous which makes confusion. This misleads

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researchers, what to measure and for what disease.

- From the literature it is known that unified public datasets with gold standard for retinal blood vessels segmentation for tortuosity are absent. Although some private datasets are available in literature but not available for use.
- As available datasets are smaller in sizes, whether they are private or public, tortuosity validations process reflect negatively on the tortuosity measures.
- The definition of tortuosity itself is ambiguous which makes confusion. This misleads researchers, what to measure and for what disease.
- Most tortuosity grading system depends on only few factors like curvature, number of twists, distance from optic disk, vessel wall thickness etc.

Given those problems, we suggest and appeal to design some publicly available unique databases. These databases should contain all possible pathological component associated with retina like vessels tortuosity, size, orientation, field of view (FOW). Authors shall be focusing on designing a robust algorithm for measuring tortuosity which will be invariant of datasets, pathologies and degree of abnormality and attempt also to be taken to design a database incorporating all the problems discussed above. Authors are also looking to measure the tortuosity using recently developed deep learning algorithm.

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