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Abstract: Timely intervention for diabetic retinopathy lessens the possibility of blindness and can provide considerable cost savings to the health system. To aid automated detection of proliferative retinopathy we introduced here a method that relies on automated segmentation of retinal blood vessels using the continuous wavelet transform and determination of feature parameters using fractal analysis. Our method is the first to show that automated segmentation combined with fractal dimension as a feature parameter can distinguish between images with nonproliferative characteristics and proliferative changes in the retinal vasculature associated with diabetes, where images showing greater pathology had a significantly greater local connected fractal dimension ($p=0.05$). Overall, our results suggest that the local connected fractal dimension is a good index of proliferative retinopathy, and that, when coupled with automated segmentation, may prove to be an important part of developing accessible diabetic retinopathy assessment and screening.

Author Address: hjelinek@csu.edu.au

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Automated detection of proliferative retinopathy in clinical practice

Audrey Karperien¹, Herbert F. Jelinek^{1,2}, Jorge J.G. Leandro³, João V.B. Soares³,
Roberto M. Cesar, Jr.³ and Alan Luckie⁴

¹School of Community Health, Charles Sturt University, Albury, Australia

²Centre for Research in Complex Systems, Charles Sturt University, Albury, Australia

³ Creative Vision Research Group, Department of Computer Science, IME – University
of São Paulo, Brazil.

⁴ Albury Eye Clinic, Albury, Australia

Corresponding author

Herbert F. Jelinek

School of Community Health

Charles Sturt University

Albury, 2640

Ph: + 61 2 60516946

Fax: +61 2 60516772

Email: hjelinek@csu.edu.au

Keywords Diabetes, proliferative retinopathy, automated clinical assessment, fractal
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Running header: Automated assessment of proliferative diabetic retinopathy

Abstract

Timely intervention for diabetic retinopathy lessens the possibility of blindness and can provide considerable cost savings to the health system. We introduce here a method that objectively identifies vascular patterns and quantitatively distinguishes between images with nonproliferative and proliferative changes in the retinal vasculature associated with diabetic retinopathy (images showing greater pathology had a significantly greater index, $p=0.05$). Overall, our results suggest that this method can complement existing methods by including an automated and objective measure obtainable at a lower level of expertise that the expert can use in assessing and monitoring diabetic retinopathy.

Introduction

Diabetes is a significant and growing global public health problem, significant not just in itself but also for its associated complications.(Taylor and Keeffe 2001) One common major complication of the disease is diabetic retinopathy (DR). Currently, between 22 and 36% of people with diabetes have some form of DR, and in one-third of them, the disease has progressed to a severe, vision-threatening stage.(NHMRC 1997)

From a clinical perspective, the disease is generally considered to progress through two broad stages that correspond to respectively lesser and greater levels of visual impairment. From a pathological perspective, DR can be considered in terms of changes in retinal vascularization, where the two stages are classified with respect to the absence or presence of abnormal neovascularization as either 1) nonproliferative (NPDR) or 2) proliferative (PDR). These categories are usually further graded by severity and the characteristics of lesions present within each.(ETDRS 1991; NHMRC 1997) During the earlier NPDR stages, microaneurysms and hemorrhages typically occur, the macula may swell as small retinal vessels leak fluid, and cotton wool spots may also appear. Over time, retinal vessels may eventually close, leading to further vascular abnormalities, more hemorrhaging, and the formation of exudate. During the PDR stages, the pathology progresses to include abnormal neovascularization. In essence, as the disease continues, the number of non-perfused capillaries and resultant ischemia increase and this eventually leads to new vessel growth, where the new vessels are abundant but dysfunctional and, rather than resupplying a starving retina, introduce further problems largely because they are fragile and often misplaced, with severe consequences. Neovascularization may extend into the vitreous, for example, where it can cause hemorrhaging and contribute to retinal traction and detachment, leading to

irreversible blindness.(Osborne, Casson et al. 2004) Retinal holes may also develop near the proliferation.(Kanski 1989; Yam and Kwok 2007)

The research reported here examined ways to characterize changes in retinal vasculature in DR, which is why this paper naturally focuses on that aspect of the pathology. It is important to emphasize, however, that DR is more than simply disordered retinal vascularization, and that the precise mechanisms at every stage have not yet been identified. Indeed, the knowledge base about underlying pathophysiologic changes in DR is currently changing dramatically and researchers are being challenged to approach the disease with new paradigms and perspectives. (Antonetti, Barber et al. 2006)

As the knowledge base continues to grow, investigators are identifying potential leads that may eventually yield treatments (eg, changes in growth factors affecting neovascularization), but currently there is no cure for DR. Despite that it is incurable, it is not currently unalterable. There are excellent opportunities for intervention at the incipient stages (such as improving glycemic control) that have the potential to reverse or prevent further progress of the disease.(De La Cruz, Gonzalez-Correa et al. 2004) Moreover, there are limited opportunities for intervention even at advanced stages. If disease is detected early enough, for instance, laser treatments can diminish visual loss (albeit in a trade off which may introduce other visual problems).(Lövestam-Adrian and Agardh; Doft and Blankenship 1984; Ferris 1993; Icks, Trautner et al. 1997; Lee, McCarty et al. 2001a; Bek and Erlandsen 2006)

Diabetic retinopathy assessment

Although early detection and monitoring of DR are important to save vision, paradoxically, a great deal of evidence has amassed indicating that patients often do not get the necessary screening and monitoring to optimally apply even the interventions that are available. The problem exists globally, and many barriers to screening affecting different populations to different degrees have been identified, including factors like inadequate access to care, patient misconceptions about the value of regular eye examinations, costs of visits to specialists, distance required to travel, and cultural reasons (eg, indigenous people may remain in their communities rather than seeking health advice in larger urban centers).

To address this serious problem, goals have been set nationally and internationally to increase the proportion of people being screened for DR (the Australian national target, for example, is 80%).(NHMRC 2001) Many programs with the goal of increasing awareness in the community have been implemented accordingly, but to solve the underlying problem—that is, to globally reduce the numbers of individuals seriously affected by PDR—another important goal is to develop and implement new or complementary models for effective assessment and monitoring of DR.(Lee, Sicari et al. 2001)

One particular step towards ensuring that early and regular eye examinations become routine for people with diabetes regardless of geographic, economic, cultural, etc., considerations, is to simplify current procedures in order to hand over responsibility to a more accessible level of technical training.(Taylor and Keeffe 2001) The rising use of telemedicine has started to shift the burden of DR screening and has stimulated opportunities to develop the technology around digital retinal imaging (e.g.,

incorporating digital images in an electronic patient record can help in ensuring diagnostic accuracy and monitoring and measuring outcomes) and new methods of acquiring and assessing information about retinal pathology are being developed at a rapid pace. (Hutchinson et al 2000, Neubauer et al 2003, P Conlin et al 2006).

Whereas some studies so far having non-specialist health professionals identify PDR have found detection rates to be no better than 50%, with the success rate decreasing with features such as eye obstruction and early stages of proliferation, several other recent studies have indicated that problems with the identification of PDR can be overcome using digital retinal photography and automated computer-based processes.(Frame, Undrill et al. 1998; Olson, Sharp et al. 2006; Soares, Leandro et al. 2006)

Computer-based diabetic retinopathy detection

Identifying and quantitating patterns of the retinal vasculature associated with the proliferative stage of disease involves two main steps, the first of which is to identify blood vessels within the images. Several segmentation methods that identify retinal vessels in either fluorescein or color digital images of the fundus have been reported in the literature, including the use of mathematical morphology, matched filters, threshold probing, supervised classification, deformable models and tracking.(Englmeier 1997; Gao, Bharath et al. 2000; Hoover, Kouznetsova et al. 2000; Zana and Klein 2000; Jiang and Mojon 2003; Kirbas and Quek 2004; Nain, Yezzi et al. 2004; Staal, Abramoff et al. 2004). The work we report here assessed digital images of fluorescein angiograms using two-dimensional continuous wavelets. Recent advances using wavelet-based techniques have shown particular promise as these methods remove noise from images,

are accurate, and can provide additional parameters that can be used to classify PDR and follow disease progression.(Leandro, Soares et al. 2003; Cornforth, Jelinek et al. 2005; Cree, Jelinek et al. 2005; Cree, Leandro et al. 2005; Soares, Leandro et al. 2006)

The second step is measuring the vessel pattern obtained. Many features that can be extracted from digital images of blood vessels (eg, density, total length, and curvature) have been used to quantitate patterns in the retinal vasculature. In the present study, we assessed complex branching features of the retinal vascular tree that defy description with traditional Euclidean geometry but reflect principles of fractal geometry. (Daxer 1993; Landini 1996; Cornforth, Jelinek et al. 2002)

Fractal Geometry in Proliferative Retinopathy

Fractal geometry was first introduced in 1960 by Richardson to describe coastlines. He pointed out that depending on the scale used to measure a coastline, the total length arrived at would vary.(Richardson 1960) Specifically, with a decrease in scale would come a nonlinear increase in length. What Richardson described was a general phenomenon applicable to many types of objects whereby as the scale or magnification at which something is observed changes, the detail measured, be that length, area, or volume, changes nonlinearly. This basic principle of fractal geometry is illustrated in Figure 1. (Bittner, Sernetz et al.; Liebovitch and Sullivan 1987; Amthor 1988; McGinley, Smith et al. 1994; Gitter and Czerniecki 1995; Iannaccone and Khokha 1995; Bernard, Bossu et al. 2001; Feltrin, Macchi et al. 2001; Goldberger, Amaral et al. 2002; Masters 2004; Naschitz, Rosner et al. 2004)

PUT FIGURE 1 HERE

Richardson's general idea of fractal geometry was popularized by Mandelbrot and developed into fractal analysis, which is in use today in many parts of pure and clinical science. (Losa and Nonnenmacher 1996) Fractal analysis rests on the general point that the relationship between the resolution or scale at which an object is measured and the measured outcome can be quantitatively expressed as the fractal dimension of the object. (Mandelbrot 1993)

To elaborate, the similarity dimension (D_s), is one example of a fractal dimension. Its derivation is perhaps easiest understood starting with simple ideal shapes. A straight line segment, for example, when measured using pieces 3^{-1} times its size, is found to be made of 3 such scaled pieces, in a relationship that holds through an infinite number of such scalings. Formally, a power law defines this trivial (ie, simple) but infinite self-similar scale-invariance, the D_s being the exponent in that power law as in the equation below:

$$N_r = r^{-D_s}$$

In this equation, N_r is the number of equal pieces that resemble the original form when r is the ratio or scale applied to the object to make the equal pieces. Manipulating this equation gives a solution for the D_s :

$$D_s = \frac{\log N_r}{\log r^{-1}}$$

The D_s , thus, quantitates *complexity* defined as how the detail or number of self-similar parts changes as scale changes (eg, the D_s for the line described above is $\log 3 / \log 3 = 1.0$ and for Figure 1 it is $\log 32 / \log 8 = 1.67$).

Various measures related to the D_S are readily calculated by different types of morphological image analysis software. The box counting dimension (D_B), which is used in this paper, is calculated using a method that approximates the D_S by measuring patterns in digital images using a square of decreasing size, r instead of actually counting new parts at decreasing scales. In this case, N_r is the number of squares required to cover the image for each size, r , and the D_B is the slope of the log-log regression line for these two values. More details on obtaining fractal dimensions are provided elsewhere. (Feder 1988; Smith, Marks et al. 1989; Peitgen, Jürgens et al. 1992; Iannaccone and Khokha 1995)

Correlation dimension

Another numerically simple approximation for the fractal dimension that can be applied in clinical science and ophthalmology is the correlation dimension. (Grassberger 1983; Family, Masters et al. 1989; Daxer 1992; Masters 2004) It is a probabilistic dimension that allows the differentiation of true stochastic processes from deterministic chaos. The correlation dimension is based on the integral function $C(\varepsilon)$ that defines the probability that two arbitrary points on an orbit are closer together than ε and is expressed as:

$$CD = \lim_{\varepsilon \rightarrow 0} \frac{\log C(\varepsilon)}{\log \varepsilon}$$

Local connected fractal dimension

Yet another fractal dimension relevant to retinal vessels is the connected dimension.

True fractals are scale invariant, meaning one scaling factor holds for all magnifications

at which the fractal is measured. Biological objects, in contrast, are generally only statistically invariant, meaning they scale consistently over only a defined range limited by the physical size of the biological object (eg, in the case of the retinal vasculature tree, vessel size is a limiting factor).(Voss and Wyatt 1991; Dollinger, R et al. 1998; Fernandez and Jelinek 2001) In addition, biological structures are generally influenced by many processes, both microscopic and macroscopic, that can create local variation in scaling.(Vicsek and Vicsek 1997) The retinal vascular tree, for instance, 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, Barber et al. 2006) As such, whereas the vascular tree may unto itself bear a certain scaling dimension, it may also carry areas of unique subscaling within it.

One way to measure the complexity of any number of subsections within an object is to calculate local fractal dimensions (D_{local}) or local connected fractal dimensions (D_{conn}).(Voss and Wyatt 1991) In contrast to global fractal analyses, these types of analysis generate arrays of local dimensions that can be summarized using the mean and standard deviation or visualized over an area using color coding. The D_{local} considers scaling over all parts of an image within particular areas, but the D_{conn} takes into consideration the degree of contiguous branching within a particular area (see Figure 2). (Landini, Murray et al. 1995) The D_{conn} has so far only been used to differentiate between normal and occlusion angiograms in manually traced retinal vascular patterns.(Landini, Murray et al. 1995) Our work expanded on this to use the D_{conn} to differentiate PDR from images with no proliferative changes based on variation in the

complexity of patterns extracted from the retinal vasculature tree using automated segmentation procedures.

PUT FIGURE 2 HERE

Methods

Twenty seven fluorescein labeled images from patients with varying degrees of retinopathy and eye disease ranging from no eye disease to PDR, both with and without neovascularization, were collected from patients attending the Albury Eye Clinic for eye assessment. All patients had fluorescein injected under supervision of an ophthalmologist and images were acquired using a Topcon digital camera (1024*1024 pixels) combined with the Image 2000 software package, and then analyzed using global and local fractal dimensions. Two sets of images for analysis were prepared from these initial images. For one, the pattern of the retinal vasculature was traced manually and the resulting pattern was skeletonised using a computer, and for the other, an automated segmentation was applied and then the result skeletonised.

Automated blood vessel segmentation

Blood vessels were segmented as described in detail elsewhere.(Soares, Leandro et al. 2006) The continuous wavelet transform (CWT) is a powerful tool to analyze non-stationary signals.(Costa and Cesar Jr 2001) Vessel-pixels responded strongly to the two-dimensional Gabor wavelet, because the wavelet is directional and could be specially tuned for vessel detection.(Antoine, Carette et al. 1993) The wavelet was superimposed onto each pixel of the image at various angles and scales. In order to

detect the blood vessels, for each scale value chosen, the transform was calculated over the range of 0 to 170 degrees, at steps of 10 degrees, and the feature space was updated with the maximum value at each pixel position. The magnitude of the parameters associated with the Gabor wavelet transform were empirically determined in order to reach the best matching between wavelet and vessels. Once determined, the parameter configuration did not have to be changed from image to image. The modulus of the wavelet transform using four different wavelet scales—chosen as to span all possible vessel widths—at each pixel was taken as a pixel feature, as well as the original gray scale intensity, yielding five wavelet coefficients per pixel to compound the final feature space.

A normal transformation was applied to all features to obtain dimensionless values, which allows a comparison between features and avoids mistakes in classification. With the normal transformation, all features present zero mean and unitary standard deviation with respect to the training set.

The final segmentation was obtained by classifying the original input image pixels into two classes, namely vessel-pixels and non-vessel pixels, according to the supervised classification approach.(Costa and Cesar Jr 2001) A Bayesian classifier was adopted in which class likelihoods were described using Gaussian mixture models, providing a fast classification while still allowing complex decision surfaces. The class priors were estimated by the fraction of each class's pixels present in the training set composed of labeled samples, while the distribution parameters for each class's Gaussian mixture model were estimated from the training set through the Expectation-Maximization algorithm.(Theodoridis 1999) The training set was obtained from manually segmented

fundus images, providing us with the 2 classes (ie, vessels and non-vessels). Once the normalized training set from the hand-drawn vascular trees was obtained and the classifiers parameters were estimated, the classification itself took place.

The classifier output is a binary image with pixels labeled as vessel or non-vessel. Some misclassified pixels appeared as undesirable noise in the output and as only boundaries were classified for some vessels, post-processing was necessary. The post-processing operations applied were ‘area open’ to eliminate small noisy components, ‘dilation’ and ‘area close’ to fill the vessels, followed by ‘skeletonization’ to extract the vessel pattern and resulting in a 1-pixel-wide connected structure. The multiscale skeletonization algorithm based on exact dilations was applied in this last step.(Costa and Cesar Jr 2001)

Determination of fractal dimensions

The CD was calculated as previously discussed in the literature.(Family, Masters et al. 1989) This procedure leads to a graph $C(\epsilon)$ versus ϵ from which a log-log plot-based line fitting is able to estimate the correlation dimension. The extremities of the linear portion of the log-log slope are determined by taking the wavelet transform of the log-log plot using the 3rd derivative of the Gaussian as mother wavelet and finding its zero-crossing points.(Cesar and Jelinek 2003)

The D_B and D_{conn} were calculated using the morphological image analysis software FracLac (v2.5a) and ImageJ. The D_B was calculated using a relative maximum box size of 50% of image size and a minimum box size of 2 pixels. D_{conn} values for each image were determined by selecting each point that fell on the skeletonised vascular tree as a

centre at (x, y) , and finding the connected set within a square 31 pixels wide centered at that point. Squares of size $r = 2$ to 31 were then overlaid onto the image at each (x, y) , and for each square the number of pixels that were part of the connected set at (x, y) was determined (see Figure 2 shown earlier). For each point on the image, D_{conn} was calculated as the slope of the regression line for the double logarithmic plot between r and the number of connected pixels at r . To obtain an equivalent global dimension value, the average of the individual D_{conn} values was determined. [FracLac 2007] (Fernandez and Jelinek 2001; Karperien 2007)

Results

Receiver operating characteristics provided an indication of precision when using automated segmentation of the 27 images compared to the manual drawings used as the gold standards (Figure 3).

PUT FIGURE 3 HERE

Validity of the Images: Global fractal dimensions

We assessed the overall validity of the two sets of patterns extracted from the images using the D_B (Figure 4 shows the global D_B for both methods). For the entire sample of manually segmented images, the mean global D_B was 1.61 ± 0.05 and for the entire sample of automatically segmented images, it was 1.52 ± 0.06 .

PUT FIGURE 4 HERE

The lower value for the automatically segmented images appears to be an effect of noise that obscures essential features of the vasculature tree and leaves gaps in the final image when using the automated method. The ultimate effect is that some areas that are traced by the manual method tend to be “erased” by the automated method. Further evidence for this interpretation is found in the point that the average number of foreground pixels was lower in the automatically segmented images compared to the manually segmented ones. Inspection of the images revealed that common areas of differences were fine vessels at the ends of branches (these were sometimes omitted in the automated method), images where fluorescein was unevenly distributed (see Figure 5), and images with noteworthy hemorrhages or laser scars.

PUT FIGURE 5 HERE

Despite these difficulties, on the whole the automated segmentation method identified the retinal vascular tree very well. An automated segmented blood vessel pattern is indicated in Figure 6 as a dark vessel pattern over the fluorescein-labelled (white) vessels. The fluorescein image clearly shows a homogenous distribution of the dye throughout the vessel pattern and was correctly segmented using the wavelet approach.

PUT FIGURE 6 HERE

Comparison of pathological status using means

Tables 1a and 1b show the results for the four feature parameters we analysed for the automated and manually segmented images respectively: the D_B , global correlation dimension (CD_g), median correlation dimension (CD_m), and the average local connected fractal dimension (D_{conn}).

PUT TABLE 1 HERE

The distribution of the D_{conn} comparing control versus proliferative retinopathy for all of the automatically segmented images is shown in Figure 7. As shown in the tables above and in the figure, overall the D_{conn} for non proliferative images is significantly lower compared to the proliferative retinopathy images.

PUT FIGURE 7 HERE

Comparison of pathological status using the distribution of the D_{conn}

To further investigate the significant results reported above, we looked in more depth at the distribution of the mean D_{conn} over individual images. As Figures 7 below indicates, this analysis further suggests that the D_{conn} is a suitable index that is able to differentiate PDR from other patterns in retinal vasculature in automatically segmented images.

PUT FIGURE 7 HERE

The two images were significantly different from each other (mean $D_{conn} = 1.13 \pm 0.17$ for PDR versus 1.10 ± 0.16 for NPDR; $\alpha = 0.05$).

Discussion

Global increases in the age of the population and the prevalence of diabetes are bringing a concomitant increase in diabetic retinopathy. On the heels of that increase is a mounting need for accessible, early, and effective identification of proliferative changes

and monitoring of disease progress and treatment outcomes. Practical and effective quantitative indices of DR are therefore essential, and may be found in fractal analysis.

The global fractal dimension of the retinal vasculature has been studied for some time.(Family, Masters et al. 1989; Masters 1989) Several research groups have demonstrated that the normal retinal vasculature has fractal-like properties with a global fractal dimension generally falling between 1.60 and 1.88.(Masters 1989; Daxer 1992; Landini, Misson et al. 1993; Cesar and Jelinek 2003; Jelinek, Leandro et al. 2005) This range in values reported in the literature reflects a host of methodological issues known to influence the absolute results of fractal analyses (e.g., the type of fractal dimension, image size and resolution, feature extraction methods such as variation in the use of skeletonization, and whether red free or fluorescein images are used).(Masters 2004) Our results suggest that the images we used were valid inasmuch as the global D_B for manually segmented images was within the usually reported range (Table 1). The mean D_B for automatically segmented images, in contrast, fell below the range reported in the literature. The entire sample was pushed to a consistently lower D_B probably by an overall relative insensitivity to the finest level of branching, and certain images were further affected by factors such as uneven signaling and scarring.

The results for the D_{conn} were also generally lower than the reported range for the global D_B , where in this case the means for both the manually and automatically segmented sets of images were low, but this is expected as the D_{conn} is not based on a global characterisation of the image. Moreover, despite the potentially troubling issues identified for the automated method, overall relative differences between images with

PDR and without were evident, and the D_{comm} was significantly different between PDR and NPDR for both type of pattern extraction.

The first study that reported automated segmentation of blood vessels combined with fractal analysis used 30mm SLR photographs of the retinal posterior pole that were scanned into a computer and segmented by the continuous wavelet transform (CWT).(Cesar and Jelinek 2003) Automated segmentation of fluorescein-labelled retinal vessels and analysis using the correlation dimension has also been reported. This study of fluorescein-labelled digital images of the posterior pole and automated vessel segmentation followed by using 8 feature patterns including the correlation dimension was able to differentiate proliferative changes.(Jelinek, Leandro et al. 2005) However the correlation dimensions did not contribute significantly to our outcome. This is reflected again in Table 1.

The CWT is a powerful and versatile tool that has been applied in many different image processing problems, including shape analysis.(Costa and Cesar Jr 2001) We found in pilot work for our study (results not shown) that selecting only images that convey what are considered the essential patterns associated with neovascularization and comparing these with control images that have no visible retinopathy improves the discerning ability of the D_{comm} and indeed of any feature parameter. To be practical, however, DR screening methods will have to be able to address all the possibilities that will arise in retinal imaging scenarios. Thus, our test sample was deliberately not idealized; rather, we included images with various commonly encountered complicating factors. These factors, such as laser scars and vessel drop out, as well as microaneurysms and haemorrhage, probably did affect the results for each image. Nonetheless, segmentation

using the CWT overcame these differences for D_{conn} calculations, which is a very promising result in support of automated DR screening.

Although we found no significant differences in the global fractal dimensions for the patterns of retinal vasculature (refer to Table 1), we did find a significant difference when applying D_{conn} for skeletonised automated as well as manually drawn images and non-skeletonized manually drawn images, which, unlike skeletonised images, preserve differences in vessel diameter in the final pattern. In general, our results showed that the D_{conn} distinguishes between images of pathological and non-pathological retina, where the mean D_{conn} is higher for pathological as compared to nonpathological retinal branching patterns (Figure 7).

Previous studies using fractal dimensions have found various types of local differences within the retinal vascular tree. Differences have been reported between the dimensions for arteries and veins, for example.(Mainster 1990; Landini, Misson et al. 1993)

However, different investigators have found different trends in the fractal dimension associated with an increase in pathological status. Avakian and collaborators, for example, reported the use of fractal analysis of region-based vascular changes in non-proliferative retinopathy.(Avakian, Kalina et al. 2002) They found that the fractal dimension was significantly higher in the normal macular region compared to the NPDR macular region, although not elsewhere in the retina. Daxer also used fractal analysis of region-based vascular changes, but applied to proliferative retinopathy, using a method which requires that neovascularization be identified in the first instance. More in keeping with the results we found, Daxer reported that the fractal dimension was significantly higher for vessel patterns with NVD than without.(Daxer 1993)

Such seemingly contradictory results can be reconciled using the D_{conn} . To elaborate, if vessels disappear from an extracted pattern for any reason, such as from being occluded or by being obscured to the camera by haemorrhage, for instance, the local fractal dimensions calculated in that area of the pattern would be expected to decrease. Conversely, if vessels increase over some area, as seen in proliferative retinopathy, the local fractal dimensions in that area would be expected to increase. The D_{conn} is likely to capture and quantitate this interplay without conflict because it quantifies complexity over the entire branching pattern but also locally within it, thus, does not lose important details inherent in that local variation. This was illustrated in Figure 7 shown earlier, which compared the distribution of the D_{conn} over two automatically segmented skeletonised patterns. The patterns shown in the figures were extracted from one image of PDR with extensive capillary closure and one of normal retinal vasculature. The two images differ significantly in the frequency distribution of the D_{conn} , which provides an objective index of the relative differences in pathology between them. Further work is required, however, to fully investigate the utility of the D_{conn} in this regard.

Automated procedures should aim to be comparable to the results obtained by ophthalmologists in identifying neovascularization. Using an automated method that can detect changes in the eye associated with diabetes with a minimum sensitivity of 60% is therefore a useful advancement as it would lessen the burden on ophthalmologists during initial population screening.(Daxer 1993) However for clinical use the methods should exceed 80% accuracy.(BDA 1994; NHMRC 2001) Our work reported here suggests that CWT-based segmentation and local connected fractal dimension analysis can provide the required levels of sensitivity and accuracy.

Conclusion

Timely screening of people with diabetes for the development of diabetic retinopathy has the potential to reduce blindness and provide considerable cost savings to the health system. Any person with diabetes should expect to undergo ophthalmic examination at least annually. To have real benefits, 80% of people with diabetes would have to be screened, which is not possible with current methods especially in rural areas where a shortage of ophthalmologists places this beyond the scope of available resources. Segmentation using the CWT and analysis with the D_{conn} shows promise in automated DR assessment. With advances in digital imaging and the development of computerised grading systems as suggested by the work reported here, automated reading and assessment of diabetic eye disease especially in rural and remote areas is coming closer to being a reality.

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