Computer-aided Diagnosis of Proliferative Diabetic Retinopathy via Modeling of the Major Temporal Arcade in Retinal Fundus Images

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Published online: 16 April 2013
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Abstract Monitoring the openness of the major temporal arcade (MTA) and how it changes over time could facilitate diagnosis and treatment of proliferative diabetic retinopathy (PDR). We present methods for user-guided semiautomated modeling and measurement of the openness of the MTA based on Gabor filters for the detection of retinal vessels, morphological image processing, and a form of the generalized Hough transform for the detection of parabolas. The methods, implemented via a graphical user interface, were tested with retinal fundus images of 11 normal individuals and 11 patients with PDR in the present pilot study on potential clinical application. A method of arcade angle measurement was used for comparative analysis. The results using the openness parameters of single- and dual-parabolic models as well as the arcade angle measurements indicate areas under the receiver operating characteristics of $A_z = 0.87, 0.82$, and 0.80 , respectively. The proposed methods are expected to facilitate quantitative analysis of the architecture of the MTA, as well as assist in detection and diagnosis of PDR.

Keywords Gabor filters · Hough transform · Parabolic modeling · Proliferative diabetic retinopathy · Retinal fundus imaging · Retinal vessels · Temporal arcade · Temporal arcade angle

Introduction

Changes in the Architecture of the Major Temporal Vessels

Diabetic retinopathy (DR) is the leading cause of preventable blindness among the people of working age in developed countries [1–6]. DR is generally categorized into the classes of nonproliferative DR (NPDR) and proliferative DR (PDR). Signs of NPDR include microaneurysms, cotton wool spots, hemorrhages, venous beading, and occasional changes in the tortuosity and width of retinal vessels [1, 4, 7–9]. The presence of such features has been shown to correlate with the progression and severity of NPDR [10, 11], which is broken down into four stages of mild, moderate, severe, and very severe [12]. Severe and very severe stages of NPDR are also referred to as preproliferative diabetic retinopathy (PPDR), as their presence is an indicator of subsequent neovascularization and escalation of the disease from NPDR to PDR [13]. However, the characteristic intraretinal lesions that primarily define the preproliferation stage are not always present when new vessels are first observed, because of the temporary nature of such lesions [13].

Even though there are many screening programs in effect for the detection and diagnosis of NPDR, only early signs of PDR warrant preventive measures to stop the progression of PDR into later stages which can ultimately lead to blindness. It has been shown that the number of patients who

This work was supported by the Natural Sciences and Engineering Research Council of Canada. We thank Dr. A. Hoover for help with the STARE images.

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can develop PDR is significant even in a developed country such as the United States [6]. As shown by the results of a screening program for DR, performed by California Health-Care Foundation as part of the state's health care safety net, out of the 53,188 people who were screened for DR over a period of three years, approximately 2 % (1000 people) were diagnosed with PDR [6]. An additional 2 % were diagnosed with PPDR [6]. Hence, there is a need for improved detection, diagnosis, and analysis of changes in the retina due to NPDR as well as PDR in screening programs.

PDR, as well as myopia and retinopathy of prematurity (ROP), are known to affect the structure of the retinal vasculature [13–16]. The narrowing (or straightening) of the major temporal arcade (MTA) has been used as an indicator of compromised structural integrity of the macular region, which is responsible for visual acuity; such changes may result in loss of vision [9, 13–16].

There has been an extensive amount of research conducted on computer-aided detection or diagnosis (CAD) of NPDR [1, 8, 17–22]. However, it is only in the presence of PDR (when considering the consequences of diabetes) that the architecture of the MTA is known to be affected, due to proliferation of fibrovascular tissue over the surface of the retina [13, 14]. Contraction of the retinal surface as well as the fibrovascular proliferation of the pathological tissue near the optic nerve head (ONH) cause traction of the arcades, tractional retinal detachment, macular dragging, and subsequently loss of vision [13, 14]. Even though such changes in the architecture of the MTA have been observed qualitatively, no quantitative analysis of the abnormal architecture of the MTA in the presence of PDR has been reported.

Quantitative Analysis of the Architecture of the MTA

Despite the clinical importance of abnormal changes in the architecture of the MTA, it has been quantified, in various manners, in only three studies: a study dealing with myopia [15] and two studies dealing with ROP [16, 23]. In order to quantify the openness of the MTA, an angle of insertion of the MTA has been loosely defined as the angle between the superior and inferior temporal arcades (STA and ITA) as they diverge from the ONH towards the periphery of the retina [15, 16, 23]. Even though the three studies cited above have shown statistical significance of the changes in the MTA angles with respect to the stages of the diseases studied, they have used different definitions. Only the location of the vertex of the MTA angle has been consistently defined as the center of the ONH. The locations of the other two points used have been defined in different manners. Our implementation and exploratory study of the method of Wong et al. [16] has shown the differences between arcade angle measurements of normal cases

as compared to cases with PDR to be statistically highly significant [24].

As shown in our previous studies [25–27], the parabolic shape of the MTA, or the dual-parabolic nature of the STA and ITA, allow for effective single- and dual-parabolic modeling in an automated environment using a form of the generalized Hough transform (GHT). In such models, changes in the architecture of the MTA, STA, and ITA are expected to be reflected as changes in the openness parameters of the parabolic models.

The aim of the present pilot study is CAD of PDR [27] by quantitative measurement of the changes in the openness of the MTA due to PDR via single- and dual-parabolic modeling of the MTA, STA, and ITA, as well as comparative analysis with arcade angles in a semiautomated procedure via a graphical user interface (GUI) [24, 26, 27].

Materials and Methods

Database of Fundus Images of the Retina

The proposed methods were tested with images from the STARE (STRUCTURED Analysis of the RETina) database [28]. The images of the STARE database have a size of 700×605 pixels and a field of view (FOV) of 35° . The spatial resolution of the images is approximately $15 \mu\text{m}/\text{pixel}$; however, the spatial resolution and FOV appear to vary from one image to another. Eleven normal cases and 11 cases of PDR were obtained. The STARE database has 22 cases that are diagnosed with PDR; however, eleven cases were not used because either the MTA was not in the FOV or the major vessels were not distinguishable. The eleven images of normal cases were selected starting from the lowest image number in the subset of images of the STARE database that are used for the detection of the ONH; cases that either did not clearly show the entire MTA or possessed very low contrast within the FOV were not selected. The PDR cases are not part of the publicly available subset of images of the STARE database and were provided by Dr. A. Hoover (Clemson University) upon request.

In recent years, there has been an increase in the number of publicly available databases of retinal images of diabetic cases. These databases include, but are not limited to, DiaRetDB1 [29], HEI-MED [30], and MESSIDOR [31]. However, all of the mentioned databases only include cases of NPDR and do not contain any images of cases of PDR. The STARE database is the only available database that includes cases of PDR; however, as previously mentioned, the PDR cases are not part of the publicly available subset of images in the STARE database. For these reasons, the number of fundus images used in the present pilot study to explore clinical application of our methods is limited.

Procedure for Measurement of Arcade Angle

Using the module for the measurement of the arcade angle via the GUI prompts the user to mark the center of the ONH, after which a circle of radius $r = 120$ pixels is automatically drawn on the image [16]. This requirement for user input could be replaced with the location of the automatically detected center of the ONH by one of the available methods [32–35]. The user is then prompted to mark the point of intersection of the circle with the superior venule; the same is repeated for the inferior venule. The arcade angle is measured as the angle between the three points, as defined above, with the center of the ONH being the vertex, using $\arctan[(m_1 - m_2)/(1 + m_1 m_2)]$, where m_1 and m_2 are the slopes of the two lines joining the intersection points marked with the center of the ONH, and $m_2 > m_1$. Please see Oloumi et al. [24] for more details on the procedure for the measurement of the arcade angles.

Overview of the Image Processing Methods to Detect and Model the MTA

There are three main steps involved in the detection and modeling of the MTA, STA, and ITA, as performed using the GUI; these steps are only presented in point form, as they have been described in detail in our previous publications [25, 36].

1. Detection of blood vessels using Gabor filters [36]:

- (a) Normalizing each color component in the original image.
- (b) Computing the luminance component.
- (c) Thresholding the luminance component to obtain the effective area.
- (d) Extending the luminance component beyond the effective area to avoid the detection of its edges.
- (e) Obtaining the Gabor magnitude response using 45 Gabor filters over the range of $[-90^\circ, 90^\circ]$.

2. Binarization of the detected vessels [25, 26]:

- (a) Separating the Gabor magnitude response image into its superior and inferior parts to represent the STA and the ITA, respectively.
- (b) Binarizing the Gabor magnitude response images of the MTA, the ITA, and the STA.
- (c) Applying the morphological process of area open to filter the binary images.

3. Detection of parabolas and semiparabolas using the GHT [25, 26]:

- (a) Skeletonizing the binary images.

- (b) Reflecting each skeleton image from left to right if the MTA opens to the left (i.e., the image is of the right eye).
- (c) Cropping each skeleton image horizontally.
- (d) Applying the GHT to the preprocessed skeleton images of the MTA, the STA, and the ITA.
- (e) Obtaining the parameters of the best-fitting parabolas from the resulting Hough space.

The accuracy of the procedure to detect blood vessels was measured using the area under the receiver operating characteristic (ROC) curve [37] in one of our previous studies [36]. Using an automated detection method with multiscale Gabor filters, an area under the ROC curve of $A_z = 0.96$ was achieved [36]. In order to measure the accuracy of the parabolic modeling procedures, in a related study [25], the mean distance to the closest point (MDCP) was measured from the parabolic model for each image to the corresponding hand-drawn trace of the MTA. For automated single-parabolic modeling (MTA) and dual-parabolic modeling (STA and ITA) procedures, MDCP measures of 16.06, 15.01, and 12.07 pixels were obtained, respectively [25]. Using the semiautomated GUI-guided method, the results of single-parabolic modeling (MTA) and dual-parabolic modeling (STA and ITA) procedures, in terms of the MDCP measure, were improved to 12.98, 9.28, and 9.86 pixels, respectively [26].

Detection of Blood Vessels and Modeling of the MTA via the GUI

In order to detect the blood vessels, the user has the option of manually specifying the Gabor filter parameters [thickness (τ), elongation (l), and number of filters (K)]. As mentioned in section “Database of Fundus Images of the Retina”, the spatial resolution of the images of the STARE database may vary; hence, a large value for the thickness ($16 \leq \tau \leq 26$ pixels) is used, with $l = 2$, to emphasize the presence of the MTA. The number of filters is kept constant at $K = 45$ (see references [25] and [36] for more details on Gabor filters and related information).

The Gabor magnitude response image can be thresholded using a sliding threshold via the GUI. In order to remove unwanted small vessel segments that may remain even after the thresholding step, the user can specify the maximum number of connected pixels to be removed (via the morphological operation of area open [38]) in the editable text field provided via the GUI.

The modeling procedure requires a binary image in order to perform the GHT procedure. The user is required to indicate if the current image is an image of the right eye or the left eye and is then prompted to mark the approximate

location of the ONH in a separate window by clicking on the image. By default, the GUI leads to single-parabolic modeling; however, the user has the option of performing dual-parabolic modeling. The Gabor magnitude-updated version of the GHT with vertex restriction is used in the present work (see reference [25] for more information). The range of the openness parameter a , used in the parabolic modeling procedure, was set to $20 \geq a \geq 420$ for the images of the STARE database.

To assess the diagnostic performance of the results of single- and dual-parabolic modeling, as well as the arcade angle measurements, ROC [37] analysis was performed using the ROCKIT [39] software. The ROCKIT provides the area under the ROC curve, A_z , as well as the standard error (SE) in the estimation of A_z . The p -values, indicating the statistical significance of the differences between values of the parameter a as well as the arcade angles for the normal cases as compared to the values of the same for the cases of PDR were also obtained via the t -test.

Results

Figure 1 shows the main window of the GUI and the “Open File” dialog box that allows the user to open commonly used types of image files. The three steps involved in detection and modeling of the MTA, as explained in

section “Overview of the Image Processing Methods to Detect and Model the MTA”, are implemented as separate modules in the GUI. The angle measurement procedure is also designed as a module.

For all of the images used in the present work, $l = 2$ and $K = 45$ were used to detect the MTA. The range of values of τ used is [16, 26], which was needed due to the large variability of vessel thickness in the STARE images. For each image, a suitable threshold was selected using the sliding threshold, provided by the GUI, to obtain a binary image containing only the MTA. Varying numbers of connected pixels were removed for each image to ensure that no vessel other than the MTA would influence the modeling procedure. On the average, it took about one minute to obtain the parabolic models (single and dual) for an image via the GUI using a Lenovo Thinkpad T510, equipped with an Intel Core i7 (Hyper-threaded-dual-core) 2.67-GHz processor, 4 MB of level 2 cache, and 8 GB of DDR3 RAM, running 64-bit Windows 7 Professional, and using 64-bit Matlab software.

For the arcade angle measurements, the method of Wong et al. [16], using a circle of radius 120 pixels, was used on all images [24]. On the average, it took about 30 seconds to obtain the arcade angle measure for a single image using the same system as explained above.

Figure 2 illustrates the results of dual-parabolic modeling and arcade angle measurement for a normal case as well as a

Fig. 1 The main GUI window showing a selected retinal image (im0164) from the STARE database and the “Open File” dialog box

Fig. 2 **a** Single-parabolic model ($a_{MTA} = -153$) and **b** dual-parabolic model ($a_{STA} = -138$, $a_{ITA} = -420$) and **c** arcade angle measure = 157.8° for image im0164 of the STARE database, which is a normal case. It can be observed that the single-parabolic modeling procedure

is matching only the STA and not the entire MTA. **d** Single-parabolic model ($a_{MTA} = 55$) and **e** dual-parabolic model ($a_{STA} = 36$, $a_{ITA} = 48$) and **f** arcade angle measure = 110.4° obtained for image im0347 of the STARE database, which is a PDR case

PDR case. There are large differences between the values of the openness parameters of the ITA models obtained for the normal case as compared to the PDR case; the same is also true for the difference between the arcade angle measure (values given in the caption of Fig. 2).

Table 1 provides the mean, standard deviation (STD), and area under the ROC curve (A_z) for the results of single- and dual-parabolic modeling, as well as the arcade angle measurements of the normal and PDR cases. The differences between the absolute values of the openness parameters of the MTA ($|a_{MTA}|$) and the ITA ($|a_{ITA}|$) models for the normal cases as compared to the PDR cases were found to be statistically significant (p -value < 0.05). The same is true for the differences between the arcade angle measures for the normal cases as compared to the PDR cases. The low mean obtained for the absolute values of the openness parameters of the STA models ($|a_{STA}|$) for the normal cases

can be due to the asymmetric nature of the STA and ITA in several of the STARE images used, where the STA has a narrower opening as compared to the ITA. The A_z values indicate high diagnostic accuracy for the detection of PDR cases using $|a_{MTA}|$, $|a_{ITA}|$, and the arcade angle measures, in decreasing order.

Discussion and Conclusion

Even though it is possible to prevent loss of vision by early diagnosis and proper management of PDR, lack of urgency and proper health care with regard to regular eye examination, as well as poor access to DR screening programs can leave many diabetic patients, who have developed DR, to continue being undiagnosed and untreated. As shown by the results of the Expanding Access to Diabetic Retinopathy

Table 1 Values of the mean $\pm$ STD, area under the ROC curve (A_z), standard error (SE) of A_z , and p -value for the $|a|$ parameters of the single- and dual-parabolic models as well as the arcade angle measurements obtained for normal and PDR cases

Parameter	Normal ($n = 11$) Mean $\pm$ STD	PDR ($n = 11$) Mean $\pm$ STD	A_z (SE)	p -value
Arcade angle (degrees)	151.00 $\pm$ 11.23	139.01 $\pm$ 11.96	0.80 (0.093)	0.0156
$ a_{MTA} $	140.40 $\pm$ 61.35	86.27 $\pm$ 26.76	0.87 (0.096)	0.0026
$ a_{STA} $	84.93 $\pm$ 27.66	88.36 $\pm$ 46.28	0.49 (0.122)	0.7839
$ a_{ITA} $	166.80 $\pm$ 98.72	89.18 $\pm$ 51.43	0.82 (0.088)	0.0164

Screening Initiative [6], the number of patients who develop PDR can be substantial, even in one of the wealthiest countries among the industrialized nations. This emphasizes the need for diagnostic screening methods for DR, including various stages of PDR.

By combining time series of fundus images into short video clips, Ells and MacKeen [40] illustrated that the changes that occur in the MTA in the presence of progressive ROP are dynamic as they alter the posterior architecture of the MTA. Based on these observations, we believe that arcade angle measures may not accurately reflect such changes that occur over the entire structure of the MTA, as they only define the openness of the MTA based on three points and are similar to fitting a triangle to the MTA. Furthermore, the value of the arcade angle is sensitive to the exact position of the ONH provided by the user; a difference of 10 pixels in the location of the manually marked center of the ONH can result in a difference of 10° in the measured arcade angle. The parabolic modeling procedure is dependent only on an approximate location of the ONH instead of the specific location of the center of the ONH, as the GHT algorithm constrains the vertex of the resulting parabolic models to be within a radius of $0.25 \times$ the average ONH diameter from the user-marked location of the center of the ONH. Please see references [24] and [25] for details of the arcade angle measurement and parabolic modeling procedures, respectively.

The GHT for the detection of semiellipses has been previously applied to fundus images of the retina for the detection of the MTA [41]. However, in the work of Fleming et al. [41], the MTA was only detected for the purpose of localization of other anatomical features, such as the ONH and the fovea, and not for quantification of its openness.

Even though the $|a_{\text{MTA}}|$ parameters for the normal and PDR cases used in the present study have provided a larger A_z value than the $|a_{\text{ITA}}|$ parameters of the same cases, the results of single-parabolic modeling may be biased, because, in cases of asymmetric arcades, the single-parabolic modeling procedure captures the more dominant parabola and may not incorporate both the STA and ITA. The dual-parabolic modeling procedure may be more suitable for parameterization of the openness of the architecture of the MTA in fundus images of the retina, because it provides two independent estimates of the parabolic model parameters for the STA and ITA.

The procedures for the detection and binarization of the blood vessels could be automated by setting fixed values for the required parameters, which can be determined empirically. The parabolic modeling procedure requires an approximate location of the center of the ONH, which can be detected automatically using various methods as indicated in section “[Procedure for Measurement of Arcade Angle](#)”.

Although the results of the present pilot study are encouraging, more cases of PDR are needed for further analysis; however, the number of publicly available databases of retinal images that provide detailed diagnostic information is limited. This is the first study on quantification of changes in the overall architecture of the MTA to perform diagnostic discrimination between normal cases and PDR. Further work is in progress to evaluate the proposed methods with larger databases of cases of PDR as well as ROP, and to assess the statistical significance of the differences between the A_z values related to the various parameters. The proposed methods could assist in quantitative analysis of the architecture of the MTA in terms of its openness or narrowing, and lead to improved diagnosis and clinical management of not only PDR, but also ROP and myopia.

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