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# Computer-aided diagnosis of plus disease via measurement of vessel thickness in retinal fundus images of preterm infants

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ABSTRACT

Changes in the characteristics of retinal vessels such as width and tortuosity can be signs of the presence of several diseases such retinopathy of prematurity (ROP) and diabetic retinopathy. Plus disease is an indicator of ROP which requires treatment and is signified by an increase in posterior venular width. In this work, we present image processing techniques for the detection, segmentation, tracking, and measurement of the width of the major temporal arcade (MTA), which is the thickest venular branch in the retina. Several image processing techniques have been employed, including the use of Gabor filters to detect the MTA, morphological image processing to obtain its skeleton, Canny's method to detect and select MTA vessel-edge candidates, least-squares fitting to interpolate the MTA edges, and geometrical procedures to measure the width of the MTA. The results, obtained using 110 retinal fundus images of preterm infants, indicate a statistically highly significant difference in MTA width of normal cases as compared to cases with plus disease ($p < 0.01$). The results provide good accuracy in computer-aided diagnosis (CAD) of plus disease with an area under the receiver operating characteristic curve of 0.76. The proposed methods may be used in CAD of plus disease and timely treatment of ROP in a clinical or teleophthalmological setting.





## 1. Introduction

### 1.1. Pathological changes in retinal vasculature

Digital imaging of the retinal fundus has become a valuable tool in noninvasive detection, diagnosis, and prognosis of diseases such as diabetic retinopathy (DR) [1–5], retinopathy of prematurity (ROP) [6–8], glaucoma [9,10], and cardiovascular complications [11,12] via computer-aided image-analysis methods. It has been shown that changes that occur in retinal vasculature can be indicative of the presence of DR [13–15], ROP [7,16–18], and hypertension [19], to name a few diseases. Physical attributes of arteriolar and venular vessels, such as their tortuosity and width, are changed in the presence of such diseases. In particular, the width of both the arterioles and venules increases in the presence of ROP, DR, and hypertension. Given the average vessel widths of 86 μm and 96 μm in premature infants with no ROP and those with threshold ROP, respectively [7], changes that occur in vessels in the presence of diseases such as ROP are not easily detected by the human eye, even when analyzed using a funduscope or fundus imaging devices. This limitation indicates the need for computer-aided methods to detect and quantify such small changes.

Plus disease is an indicator of the severity of ROP; it represents a stage that is progressing and requires immediate treatment [20]. It has been established that the presence of plus disease is strongly associated with the early detection and treatment of ROP [18,20–24]. Plus disease is defined as the presence of certain levels of abnormal venular thickness and arteriolar tortuosity [25]. There are several theories that attempt to explain the cause of the observed vascular changes in the presence of plus disease [26]. One theory relates the changes to increased levels of certain vascular growth factors [27,28]. In the case of changes in venular thickness, it has been theorized that increased levels of blood pressure, and the fact that venules are more distensible than arterioles, could lead to dilation of venules [29,30].

Plus disease is clinically diagnosed by qualitative comparison to a standard retinal fundus image [25] that exhibits abnormal levels of thickness and tortuosity. However, the standard image is considered to be atypical since it shows more vascular dilation and less tortuosity as compared to most retinas with plus disease [21]. Furthermore, the range of vascular changes is smaller and more challenging to distinguish in premature infants in the presence of

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plus disease even for experts, since the retinal vasculature is not fully developed as compared to the situation in adults. Indeed, it has been shown in a study that 22 recognized ROP experts agreed on diagnosis of plus disease only in 21% of the images analyzed [22]. Considering such facts, it can be concluded that there is a great need of methods for computer-aided diagnosis (CAD) of plus disease, which can lead to timely treatment of ROP.

The major temporal and nasal arcades (MTA and MNA) are the two thickest branches of blood vessels (venules) on the temporal and nasal sides of the retina with reference to the optic nerve head (ONH), respectively. It has been observed that the changes that occur in the width of venules in the presence of ROP and plus disease are predominantly or specifically seen in the MTA [23,18,17], but are also observed in the MNA [31,18,32].

### 1.2. Measurement of vessel width

Computer-aided methods used for measurement of vessel thickness typically fall into two categories. The first category of methods initially attempt to detect and segment vessels, then obtain the vessel center-line and edge pixels, and finally compute a thickness measure based on the distance between the associated edge and center-line pixels [13,7,33]. The second category of methods employ vessel detection techniques via a modeling approach. The models are mainly Gaussian-based since the intensity profile of a vessel at a given vessel center-line pixel resembles an inverted Gaussian curve [34,6,11]. As a result, the spread or standard deviation (STD) of the Gaussian model used to detect the vessel could be employed to estimate the width of the vessel. A brief review of a few such methods proposed for analysis of retinal fundus images of preterm infants is presented below.

Using semiautomated methods, Heneghan et al. [7] obtained a binary image of retinal vessels via multiscale analysis of the second-order derivative of the original intensity images combined with preprocessing and postprocessing morphological methods, as well as a two-level thresholding strategy. Heneghan et al. measured the vessel width by extending a line from the two opposite sides of a given vessel pixel until it reached the boundary of the vessel and noting the length of the line. This procedure was repeated for lines of various orientations originating from the same pixel. The vessel width at the given pixel was taken as the minimum distance obtained for all orientations.

Martínez-Pérez et al. [35,36] developed a semiautomated image analysis software called RISA for detection, segmentation, and measurement of vessel width in retinal images. RISA uses a region-growing algorithm in order to segment (binarize) blood vessels based on two features of edge-strength and ridge-strength. The edge-strength feature is derived as the gradient of the intensity image. The ridge-strength feature is based on the eigenvalue of the Hessian matrix of the intensity image. The resulting binary image is skeletonized and broken into several segments based on the detected branching points. RISA estimates the width of each vessel segment as the total area (in pixels) of the segment, divided by its length. RISA requires manual user correction at the stage of detection of branching points, as well as manual input regarding the vessel segment to analyze and to distinguish between venular and arteriolar branches.

Based on tracking and extraction of skeletons of manually selected vessels via multiscale ridge detectors, Wallace et al. [6] determined a vessel width estimate at each detected ridge point using the spread of a Laplacian-of-Gaussian model.

Fiorin and Ruggeri [33] used a web-based software package to draft manually the center-line of a retinal vessel segment. Canny's edge detection method was then used to obtain a set of vessel-edge pixels around the selected center-line. Two edge curves were then estimated on either side of the selected center-line by fitting a cubic spline to the previously detected edge pixels. The width of the selected vessel segment at each pixel was defined as the distance along the normal at a center-line pixel between the two estimated edge curves.

Using RISA, a few studies [31,23,18,32] have attempted to measure vessel width in retinal fundus images of premature infants and have correlated their findings to the presence of plus disease in the images. The results of these and two other studies [7,6] on CAD of plus disease are presented and compared with the results obtained using the proposed methods in Section 4.

### 1.3. Limitations of previously published methods

Locating vessel edges based on binarization of the intensity image obtained using a vessel detection algorithm is prone to error due to sampling, the scale of the model used, as well as the threshold value used to binarize and segment vessels [7]. Furthermore, estimation of vessel width using the STD of Gaussian-based models is also prone to error since a Gaussian model is a continuous curve that does not contain a clear-cut point to indicate the exact location of the vessel edges. Such a method for estimation of width requires an assumption regarding suitable, yet arbitrary, weighting of the STD of the Gaussian model to estimate vessel width [37]. Methods that use a vessel's center-line for measurement of width are prone to error in case the center-line is not precisely in the middle of the vessel; it is especially challenging to guarantee such a requirement. Furthermore, such methods require accurate detection and subpixel representation of vessel edges. In addition, the methods available in the literature for measurement of vessel width in case of plus disease either manually distinguish between venular and arteriolar branches [31,23,18,32], or do not distinguish between them at all [7]; these methods also obtain the width measurement for only manually selected vessel segments.

### 1.4. The proposed approach

In this paper, we present methods for detection, segmentation, and extraction of the MTA skeleton as well as detection and interpolation of the edges of the MTA, and ultimately, computation of the width of the MTA at several pixels along its skeleton in retinal fundus images of preterm infants. Gabor filters, which have been shown to be effective in detection of oriented patterns in biomedical applications [38–41], are used for the detection of vessels in the present work. Gabor filters have been applied for the detection of retinal blood vessels in previous works by Soares et al. [42] and Rangayyan et al. [43]. Furthermore, the methods include morphological image processing techniques to extract the MTA skeleton, Canny's method for selection of vessel-edge candidates, least-squares fitting to interpolate the vessel edges, and geometrical procedures to measure vessel width. The diagnostic performance of the average MTA width measure in distinguishing between cases with and without plus disease is analyzed in terms of sensitivity, specificity, area ($A_z$) under the receiver operating characteristic (ROC) curve, and $p$-value. The obtained results are compared with results of similar studies in the literature. The present paper is an expanded and revised version of a related conference presentation [44].

## 2. Materials and methods

### 2.1. Database of retinal images

The proposed methods were tested with retinal fundus images from the Telemedicine for ROP In Calgary (TROPIC) database [45]. The TROPIC images were captured using the RetCam II equipped



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