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Drusen Quantification for Early Identification of Age Related Macular Degeneration (AMD) Using Color Fundus Imaging

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***Abstract*— Age-related macular degeneration (AMD) is a major cause of visual impairment in the elderly and identifying people with the early stages of AMD is important when considering the design and implementation of preventative strategies for late AMD. Quantification of drusen size and total area covered by drusen is an important risk factor for progression. In this paper, we propose a method to detect drusen and quantify drusen size along with the area covered with drusen in macular region from standard color retinal images. We used combined local intensity distribution, adaptive intensity thresholding and edge information to detect potential drusen areas. The proposed method detected the presence of any drusen with 100% accuracy (50/50 images). For drusen detection accuracy (DDA), the segmentations produced by the automated method on individual images achieved mean sensitivity and specificity values of 74.94% and 81.17%, respectively.**

I. Introduction

Age-related macular degeneration (AMD) is the leading cause of vision loss in people over the age of 50 years in developed countries [1], [2]. The number is expected to increase by 12 to 20 fold over ten years due to aging population [2], [3]. While the treatment of AMD with anti-vascular endothelial growth factor (VEGF) is effective in maintaining or improving vision in the neovascular form of advanced disease, it does not provide a cure. Currently there are no specific interventions available to stop the development of AMD, whilst the use of supplements has been reported to slow progression in some groups with early stage of AMD. Therefore, identifying people with early signs of the disease and then determining their risk based upon their fundus characteristics is important considering both the social and economic impact of AMD.

Existing AMD grading systems require human grader's subjective manual interaction, which is time consuming and difficult to maintain intra or inter-rater agreement [4], [5], [6], [7]. Due to the high degree of graders' involvement, the methods can be prone to inaccuracy and poor repeatability if experienced graders are not used [8]. Although a number of automated methods have been proposed for drusen detection, they mainly focus on detecting the presence of drusen without quantifying its area [12], [8], [9], [10], [11]. In addition, to identification and quantification of drusen, their classification (e.g., hard and soft drusen, soft distinct or soft indistinct drusen) is also important. Aiming to achieve these, in this paper we proposed a method which can automatically detect and quantify drusen for early AMD detection.

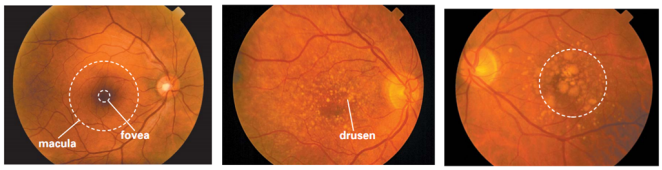

Fig. 1. Retinal image showing macula in the center (left), hard drusen (middle) and soft drusen (right).

II. Retinal Imaging for AMD Grading

Retinal color fundus imaging has been widely used for AMD grading. A number of grading protocols has been established for grading drusen and identify AMD stage using color fundus imaging. Among them Wisconsin Age-related Maculopathy Grading System, the International Classification and Grading System for Age-related Maculopathy and Age-related Macular Degeneration and its modified version are widely used [1], [4], [13]. The methods mainly use computer software tools that a grader uses to manually count the drusen by drawing different sizes of circles in the software interface. This is very time consuming, tedious and prone to human error. Although a number of automated methods have been proposed to detect drusen, they mainly identify the absence or presence of drusen. The techniques rely on image analysis algorithms such as global intensity thresholding [14], stochastic classification of pixels into object classes [15], histogram thresholding [1] and textures [9]. The challenging issues associated with drusen detection include the range in size, shape and intensity distribution for the same type of drusen. A huge improvement is required to achieve high accuracy with an automated system to identify drusen area [8]. An automatic, accurate and efficient detection and quantification of drusen can provide a useful tool to define the severity of AMD. Use of such a tool would help determine the severity of risk for progressing to vision threatening advanced AMD. This will become more important as new interventions need to be trialed on high risk individuals and the ability to monitor the outcome through accurate measurement of macular changes becomes important.

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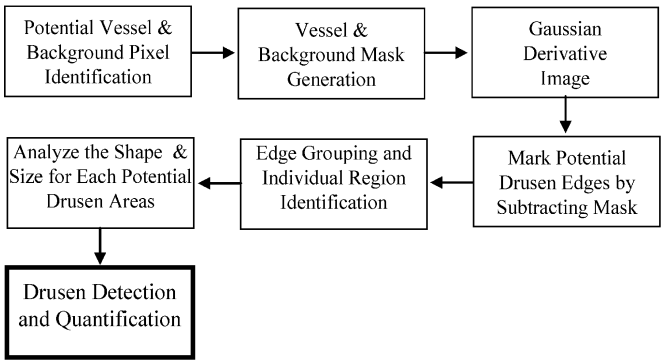

Fig. 2. Block diagram of the proposed drusen detection and quantification method.

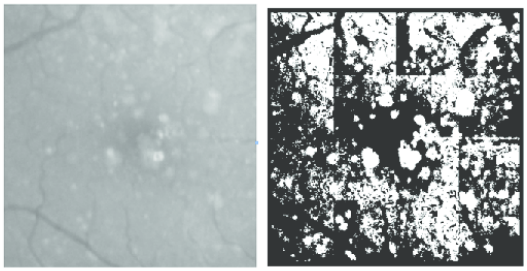

Fig. 3. Retinal cropped image showing drusen, vessel and background (left) and mask showing region of interest with removing vessel and partial background (right).

III. Materials and Methods

Our focus is on an automated technique for drusen identification and quantification. The overall method is shown in Fig. 2. The proposed method can be subdivided into two major modules: 1) drusen segmentation and 2) detection and quantification of individual drusen area.

A. Drusen Segmentation

1) Vessel and Background Mask Generation: A healthy retinal image depicts the optic disc, blood vessels and macula. Drusen show up in the retina as bright objects. Thus, in order to detect drusen, the pixels of any retinal image are divided into three pixel groups based on the intensity levels for any retinal image; these are dark pixel, medium range of intensity pixel and bright pixel. The vessel and macula pixels mostly belong to dark pixel group, the background pixels belong to medium range intensity pixel and the bright pixel group represents the drusen, optic disc and other bright objects. The image is analyzed by using local histograms by splitting the image into a number of blocks of pixel window. For each block of the image, the pixels are ranked based on intensity levels and appropriate cluster number is added. For this, we analyze the intensity histogram and compute a cutoff intensity level based on the histogram signal. In general, it is less than 10% of the pixels which are vessel pixels in the retinal image. We use this percentile value in the macular area to find the cutoff intensity value for vessel pixels using an intensity histogram. We use 50x50 pixels window of image region to compute the histogram and intensity distribution. This allows us to adjust the local intensity level in the image. Once we compute the pixel cluster we construct a mask. Figure 3 shows the mask for potential drusen areas in white color to be considered for final drusen detection. Most of the vessel areas are removed after applying this mask. We aim to remove only the noise and background from this mask generation. Our final drusen detection is based on using the drusen pattern which is described in the next subsections.

B. Preprocessing with Gaussian Derivative

We apply Gaussian derivative in the image to produce edges of the potential drusen regions. The Gaussian derivative is applied on the Green channel image, which returns the highest contrast between vessel and background from all three color channels in the original retinal RGB image. The Gaussian distribution in 2-D form is as follows [18]:

$$G(x,y) = \frac{1}{2\pi\sigma^2} e^{-\frac{x^2+y^2}{2\sigma^2}} \tag{1}$$

where σ is the standard deviation of the distribution and x and y define the kernel position. We used 5x5 window sized Gaussian kernel with standard deviation of 3. First Derivative operation is implemented for using the magnitude of the gradient. The gradient of $M(x,y)$ at location (x,y) is defined as the two dimensional vector $G(x,y) = [G'_x, G'_y] =$

$$M(x,y) = mag(G[f(x,y)]) \approx |G_x| + |G_y| \tag{2}$$

$M(x,y)$ is created as an image of the same size as the original one, when x and y are allowed to vary over all pixel locations. It is common practice to refer to this image as the gradient image and for edge detection, we are focusing in the magnitude $M(x,y)$.

1) Filtering Vessel and Background for Potential Drusen Area Detection: Once we apply Gaussian derivative and produce the gradient image, we then map and remove the small vessel regions based on vessel and background mask which we produced earlier. Simple AND logical operation between the gradient image and vessel mask will produce the desired output. Then we filter out the vessel pixels from the gradient magnitude image and consider the rest of the pixels for drusen detection.

2) Edge Pixel Grouping: Edge pixel grouping is applied after filtering the background and vessel from the gradient image. The seeded region growing operation [21] is applied to the filtered gradient image to find the potential drusen edges. This is accomplished by scanning the image from the beginning and start of the region growing process once an edge pixel is found. The initial seed pixel is selected by searching a particular intensity pattern from a window w of 1x5 pixels (Fig. 4). Within a window w, the center pixel i is considered as an edge pixel if it satisfies the criteria: $w[i-2] <= w[i-1] <= w[i] >= w[i+1] >= w[i+2]$. Once the initial seed pixel is selected, the region is mapped by the

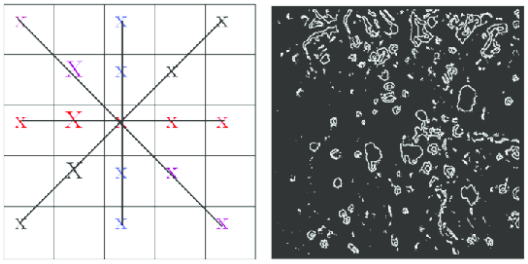

Fig. 4. Mask showing edge pixel detection in horizontal , vertical and both diagonal directions (left) and edge image after removing most vessel and background (right).

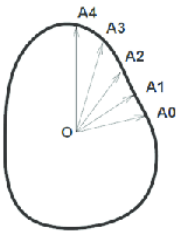

Fig. 5. The Centroid to boundary distance approach.

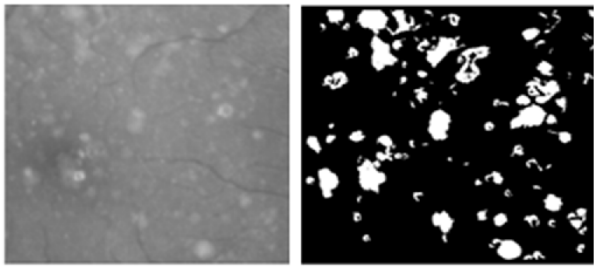

Fig. 6. Original retinal cropped gray scale image of the macula (left) and processed image for drusen detection output (right).

seeded region growing technique. We apply this technique as it is robust in fuzziness of the edge and able to detect real edges other than noisy edges (Fig. 4). Due to the fuzziness of the edge in soft drusen, the edge pixels are detected considering the specific pattern in the gradient distribution rather than thresholding the gradient magnitude.

3) Filter Discrete Noise Points: Discrete noises due to impulse noise and background irregularities are removed by measuring the area or number of pixels. After detecting the edges, individual regions are traced based on the detected edges. Finally, regions having area or number of pixels less than a certain threshold are discarded and otherwise, assigned a unique identification number for each region.

After noise removal, the size and shape of each region is analyzed to detect the region as a druse as follows.

C. Drusen Shape Analysis

A druse is circular or oval shaped region. These shapes are 2-D and can be represented using a real or complex 1-D function. Our focus is to determine the shape of the identified regions, to verify whether it is circular or oval, using the boundary and centroid. The region, its centroid and boundary points are shown in Fig. 5. In the first variation of the idea, the values of the 1-D function for circular or oval shapes are equal to distances between centroid and boundary points [16]. Boundary points are selected so that the central angles are equal. In this study, we use the distance between subsequent boundary points for the 1-D function values and compute the ratio of the minimum and maximum radius to determine the shape as circular or oval. Drusen with shapes different from circular or oval are discarded at this stage.

D. Drusen Size Analysis

After shape filtering, drusen are filtered based on the size. Since, all drusen are now either circular or oval shaped, the diameter of the region provides the size of the region. In this study, we calculate diameter of each shape filtered drusen and then discard regions with diameter more than 600 microns (1 pixel=7 microns). These size filtered regions are finally detected as the drusen of the retinal image.

E. Define and Quantify True Drusen Areas

Each druse detected in the gradient image is inversely mapped in the druse image using the center of the druse. The true area is calculated based on the druse boundary and region information from the image which includes drusen (Fig. 6). Calculation of individual druse area allows us to map individual size and the total drusen area in the macula, which allow us to define the severity of early AMD. For each druse we count the number of pixels, and compute the area in microns. The calibration factor between the pixels per distance is utilized for finding the area in microns. We used seeded region growing technique [18] to map the pixels belonging to each regions which are identified as drusen earlier. Finally, we provide a summary of drusen based on the size in diameter and area.

IV. Evaluation Method

In this study, we compared our automated drusen detection method with manually graded retinal images. We test 50 images for measuring the accuracy for drusen absent or present. For drusen area quantification, we considered twelve images randomly selected by an experience retinal image grader which included variety of drusen types. The reason for selecting the smaller subset is that manual grading is very time consuming (approximately an hour and half for each image) and expensive with respect to grader's time. The performance is measured in two steps:

1) Drusen detection accuracy (DDA): DDA represents the percentage of retinal images with the presence or absence of drusen detected correctly.

TABLE I

SENSITIVITY AND SPECIFICITY FOR DRUSEN AREA ACCURACY INDIVIDUAL IMAGES.

Image	Sensitivity(%)	Specificity(%)
image 1	53.40	98.32
image 2	68.56	87.38
image 3	76.37	67.51
image 4	71.21	76.91
image 5	81.32	69.75
image 6	72.48	92.94
image 7	100	51.92
image 8	79.20	88.94
image 9	73.78	89.30
image 10	77.72	74.08
image 11	55.29	92.59
image 12	90.13	84.84

2) Drusen area accuracy (DAA): For DAA the same grader marked the drusen regions (we call them hand-labeled ground truth images) from the images using a software tool i.e., Photoshop. We then quantified the areas as the sensitivity and specificity by comparing the drusen detected output images with the hand-labeled ground truth (GT) images.

Considering drusen pixel positive and background pixel negative, we used the following formula and computed the sensitivity and specificity:

Sensitivity= TP/(TP+FN)

Specificity= TN/(TN+FP)

where, TP is the number of overlapped positive pixels in drusen and GT image FP is the number of positive pixels in drusen image does not match with GT image, TN is the number of overlapped negative pixels in drusen and GT image, FN is the number of negative pixels in drusen image does not match with GT image.

V. RESULTS AND DISCUSSIONS

We achieved 100% (50/50 images) for drusen detection accuracy as absent or present drusen in the image. For drusen segmentation accuracy in pixel-by-pixel, we achieved an overall mean sensitivity of 74.94% (53.40% to 100%, median 75.10%) and specificity of 81.17% (51.92% to 98.32%, median 86.15%). Table I shows the sensitivity and specificity for the individual images in drusen area accuracy.

In this paper, we present a novel method of drusen detection which will enable fast, accurate automated method to determine the characteristics of drusen. We achieved high accuracy in the quantification of individual druse area with 74.94% sensitivity and 81.17% specificity. We consider this as high accuracy where some soft drusen area is very difficult to identify due to the fuzziness of the boundary, even for human eye. While the existing drusen detection algorithms achieve similar results (maximum sensitivity on drusen detection reported as 74% [17]) our method outperforms them in the area of efficiency (takes less than 0.5 seconds for an image) which is important to grade large datasets and drusen grading with human grader intervention for poor quality images. We aim to achieve higher accuracy in the soft drusen area detection with combining texture based pixel segmentation method. We also aim to identify soft drusen based on the druse area and shape.

We emphasize that there is no existing method to grade drusen with 100% accuracy, thus a human grader intervention is a necessity to select all drusen types. As our method is very efficient, involving a human grader should provide an accurate and efficient system. However, this system needs to be validated in terms of repeatability of producing the results by grading the same image with two individual graders. We plan to conduct this study in future.

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