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Automatic fovea location in retinal images using anatomical priors and vessel density

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ABSTRACT

The aim of this paper is to devise an automatic algorithm locating the fovea centre in retinal fundus images. We locate the fovea center as the region of minimum vessel density within a search region defined from anatomical priors, i.e., knowledge on the structure of the retina. Vessel density is computed from a binary vessel map, providing good invariance against image quality. Priors include the approximate distance from the optic disc, expressed in multiple of the disc diameter for generality. The disc is located automatically. We learn the distribution of disc-macula distances from clinical annotations on a sample of images independent of the test sample. We use the same sample of images to optimize the standard deviation of the Gaussian mask, which is used to weigh vessel density for cost estimation. We tested performance on a sample of 116 fundus images from the Tayside diabetic screening programme (TENOVUS) and 303 fundus images from MESSIDOR public data set. To test resilience to quality variations, TENOVUS images were divided into three quality groups and MESSIDOR images were divided into images with no risk of macula edema and with risk of macula edema. Algorithm result on TENOVUS images show good localization performance with all groups compared to manual ground truth annotations (92% estimates within 0.5 disc diameters of ground truth location with
good quality, 70% with poor quality images). For MESSIDOR images, our algorithm recorded an accuracy of 80% for images with no risk of macula edema and 59% for images with risk of macula edema.

Keywords:
Fovea, automatic fovea detection, computer-assisted image analysis, retina, computer-assisted image interpretation

The manuscript includes 5 figures and 3 tables.

1. INTRODUCTION

The fovea is the depression of the inner retinal surface at the centre of the macular region, responsible for central photopic and high-resolution vision [1]. The fovea size is similar to that of the optic disc (approximately, 1.5mm) [3]. The fovea contains an avascular zone, the exact diameter and limits of which can be determined with accuracy only by fluorescein angiography. Abnormal changes may lead to serious or extreme vision loss (poorer than 3/60 vision). Together with the optic disc, the fovea is a defining element of fundus coordinate systems, as the horizontal axis of which goes through both. Such coordinate systems, in turn, are essential to characterize the spatial distribution retinal features, e.g., lesions. Automatic and semi-automatic systems for retinal image analysis [2] establish retinal co-ordinates as the first step; hence reliable detection of the eye anatomical landmark (disc and macula) is essential.

A common approach in macula and fovea detection algorithms is feature-based location of the fovea centre within a pre-defined search region. Liang et al [4] constrained the search to a 300x300 pixels region centered on the fundus image, locating the fovea therein as the centroid of the largest group of pixels with minimum intensity value. Tan et al [5] defined the search region as a rectangle of size 1.5DDx3DD (DD = disc diameter) centered on the optic disc, and again located the darkest region therein. Sinthanayothin et al [6] performed template matching using inverted Gaussians to model the low-intensity fovea region, constraining the fovea location roughly at 2.5DD from optic disc, and again locating the darkest region.
Chutatape et al [10] and Li et al [11] searched for dark regions within a pre-defined search region, a circle of radius 1DD with center 2DD away from the optic disc. In summary, [4-6,10-11] use an intensity model (dark region) as the main feature for location. This assumption alone may not work in general; e.g., some diseases make the macular region appear lighter than usual or severely pigmented.

Ying et al. [9] defined the search region as a circle within the main vessel arcades and constrained the fovea centre location using the distance from the circle centre, vessel density and pixel intensity. The authors complemented intensity feature with structural information. Tobin et al [8], however, used only structural information by defining the fovea center to be at 2.5DD along the line passing through fovea and optic disc.

The optic disc to macula distance (DM:DD) should not be taken as a constant as it varies quite significantly between individuals due to different age and pathology in the eye. Patients with physiological macrodiscs usually have a smaller DM:DD ratio; values as low as 1.84DD have been reported [12]. For patients with optic nerve hypoplasia (underdeveloped optic disc appearing abnormally small), for example, the DM:DD ratio has been reported to be more than 3DD and to have a largest value of 4.2DD in adults [13].

In this paper, we detect the fovea by locating an avascular zone [2] of the same size as the optic disc and lying within a search region defined by anatomical priors. The avascular zone is located as the zone with minimum estimated vessel density weighted by a Gaussian.

2. MATERIAL

To test our system we used 146 anonymized images (right and left eye from 58 patients) from the Tayside diabetic screening programme (TENOVS) at Ninewells Hospital, Dundee, obtained in accordance to current regulations. Images are type-2 and were acquired by Topcon cameras at a resolution of 2336x3504 pixels. To test the algorithm performance with varying quality, the images were divided into three difficulty (quality) levels by one of the clinical authors (Wilson), a practicing ophthalmologist: good (66 images), medium (30), and difficult (20). Quality was determined by the visibility and integrity of the macula region (e.g., significant lesions, abnormal texture) and by imaging quality (e.g., poor focus). No images considered unusable for clinical purposes were considered.

We also tested our algorithm on 303 images from the MESSIDOR[22] public data set for comparison with other algorithms, including 203 images with no risk of macular edema and 100 images with risk of macular edema.
MESSIDOR images were acquired by 3 ophthalmologic departments using a color video 3CCD camera on a Topcon TRC NW6 non-mydriatic retinograph with a 45 degree field of view. The images were acquired at resolution of 1440x960, 2240x1488 or 2304x1536 pixels. All MESSIDOR images we used for our experiments are of resolution 2240x1488. The grading for risk of macular edema was provided by medical experts involved in the MESSIDOR project. The vessel detection algorithm we used requires training, in the sense of machine learning; we refer the reader to [14] for details. For generality, we trained vessel detection with 20 fundus images from the Lothian Birth Cohort [21]. These are images of a Scottish healthy population with a resolution of 2336x3504, similar to that of the MESSIDOR images, and acquired with a standard protocol for studies on retinal biomarkers for cognitive performance. Further details on this set can be found in [21].

3. METHODS

3.1 Algorithm overview

Figure 1 shows the overall fovea detection algorithm. At stage I, the algorithm first establishes a retinal co-ordinate frame centered on the optic disc. The optic disc contour is approximated by an ellipse and located using our algorithm, reported elsewhere [15]. The disc radius is estimated as the average of the ellipse axes. A vasculature map giving the location of blood vessels is then computed using the method due to Soares et al. [14] and implemented within the VAMPIRE software tool developed by the authors [16]. The output of stage I is optic disc location and vasculature map. Next, at stage II, we determine the search region. Our search region is formed based on anatomical priors, i.e., knowledge on the anatomical structure of the retina (mutual position of optic disc, macula, vessels). A parabola with vertex in the centre of the optic disc is fitted to the vessel map to locate the approximate path of the main arcade visible. Search region for the fovea is then formed from anatomical priors and their spatial distribution as estimated from sample images. The output of this stage is a region of interest where the fovea center is searched. Finally at stage III, to locate fovea center, a likelihood is defined for each candidate location within the search region; the location with the highest likelihood is taken as the best estimate of the fovea center. Details of each stage are given in the following sections. Henceforth, \( r \) will denote the radius of the optic disc.
3.2 Establishing a co-ordinate frame

We establish automatically a retinal co-ordinate frame centred on the optic disc. To account for variations in vertical alignment of the patient’s head, the $x$ axis is defined as the symmetry axis of a parabola approximating path of the temporal arcade (Figure 2). To obtain arcade points for the parabola fit, a binary map of the vasculature is computed and skeletonized to find the vessel centerlines. Vessel density and average vessel width are estimated in a $r \times r$ square neighbourhood centered in each skeleton point. A vessel density map and an average width map are then calculated and combined by linear summation. Vessel points are then clustered into four clusters using the combined map and a K-means [19] algorithm. Points in the highest-valued cluster are chosen for parabola fitting. The parabola is $ay^2 = x$ with rotation to new axes $X$, $Y$ and parameterized as

$$a[(X - h)^2 \sin^2 \theta + (Y - k)^2 \cos^2 \theta] = [(X - h) \cos \theta - (Y - k) \sin \theta]^2.$$  \hspace{1cm} (1)

Here, $\theta$ is the orientation angle of the parabola axis with respect to the $x$ axis of the image, $a$ controls the parabola’s curvature, and $(h, k)$ are the vertex co-ordinates. The vertex is chosen as the point inside the optic disc with the highest vessel density, estimated by the number of vessel pixels in the vessel map within a $r \times (r/2)$ search window. The fit estimates the two parameters, $a$ and $\theta$. The parabola is fitted by minimizing the algebraic distance, i.e., the residual of Equation (1), with the MATLAB Nelder-Mead optimizer [17].
3.3 Determining a Search Region

We consider three anatomical constraints to identify a search region for the fovea. First, we establish a distance interval from the disc, detailed below. Second, we constrain the search area to be located slightly below the optic disc (relative to the image x axis). Third, we further confine the search region to be within the parabola approximating the main arcade. We obtain the final search region by intersecting the three constraints. Within it, candidate pixels are sampled for cost evaluation with a spatial step of 1/6 of the estimated optic disc radius.

To establish a search interval, we express the disc-macula distance in disc diameters, denoted DM:DD. We estimated the probability distribution for DM:DD from another sample set of 126 TENOVSUS images not used in our tests. We approximate this distribution with a Gaussian (Lilliefors normality test at 5% significance level, p = 0.4303), and define the search region for the fovea center within 3 standard deviations from the mean (1.82DD to 3.56DD).

3.4 Fovea Center Localization

To locate the fovea, we evaluate each sampled location in the search region. As the fovea is taken to be about the size of the optic disc (Section 1), the size of the local support square window is $r \times r$. Within the window, vessel pixels (as indicated by the vessel map) are summed but weighted by a centered 2-D Gaussian mask. The weights are normalized to sum to 1. The final score for a candidate location is the sum over the square window of the mask weights located at vessel pixels. The window with the lowest score within the search region is taken as the best estimate of the fovea center.
4. RESULTS AND DISCUSSION

4.1 Ground truth for accuracy estimation

Detection accuracy was quantified by comparing the fovea locations estimated by the algorithm and ground truth provided by annotators. Ground truth for fovea center on MESSIDOR images were provided by Dr. Thomas P. Karnowski[8]. The annotators for TENOVUS images, a practicing ophthalmologist (Ling) and a trained image processing expert (Chin), were asked to mark the fovea center using a software tool from the VAMPIRE suite [16]. To estimate intra-observer variability the images were annotated twice by each observer in independent sessions. The two observers acted independently. The paired Euclidean differences for intra-observer and inter-observer are shown in Table 1. The absolute entity of the differences is modest given that $r \approx 191$ pixels in the training set. As expected, inter-observer differences have a larger mean than intra-observer ones and increase with difficulty.

Table 1: Mean and standard deviation of intra- and inter-observer variations, as percentages of disc diameter for TENOVUS images

<table>
<thead>
<tr>
<th>Intra-observer</th>
<th>Good</th>
<th>Medium</th>
<th>Difficult</th>
<th>All Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observer 1</td>
<td>4.42% ± 2.98%</td>
<td>8.09% ± 10.05%</td>
<td>10.63% ± 8.01%</td>
<td>6.44% ± 6.85%</td>
</tr>
<tr>
<td>Observer 2</td>
<td>5.99% ± 3.85%</td>
<td>6.96% ± 5.03%</td>
<td>10.37% ± 7.72%</td>
<td>6.99% ± 5.21%</td>
</tr>
<tr>
<td>Inter-observer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observer 1 vs Observer 2</td>
<td>5.52% ± 3.09%</td>
<td>8.66% ± 4.48%</td>
<td>16% ± 6.36%</td>
<td>8.14% ± 6.36%</td>
</tr>
</tbody>
</table>

Bland-Altman plots [20] were used to assess the agreement between intra-observer and inter-observer. The analysis was performed separately for X and Y values of the fovea center coordinate.
Figure 3. (a) Bland Altman plots of X and Y values for intra-observer difference in Observer 1. (b) Bland Altman plots of X and Y values for intra-observer difference in Observer 2. (c) Bland Altman plot of X and Y value for inter-observer difference

Figure 3 show Bland-Altman plots, respectively, for intra- and inter-observer differences for X and Y values, where X and Y are the co-ordinates of the points selected as fovea center. The two clusters for the X plots reflect the different location of the fovea in left and right eyes. The inter-observer differences have a larger mean than intra-observer differences, as expected, but the limits of agreement (mean±2SD in unit of pixel) are comparable. For example, the limit of agreement of X value for Observer 1 is between -62.4 and 66.7 pixels. In disc diameter units, the limit of agreement is expressed as -0.16DD and 0.17DD, which is small enough for us to be confident that there is strong agreement between
the two annotations taken by Observer 1. The limits of agreement are also comparatively small for Observer 2 (-0.13DD to 0.15DD) as well as for inter-observer difference between the two observers (-0.12DD to 0.18DD).

4.2 Determining the optimal mask size

The size of the weighting Gaussian mask, fixed by its standard deviation, \( \sigma \), is the only free parameter of the algorithm. We fixed its value as the one which led to optimal performance (minimal average distance between estimated and ground truth fovea location) on the training set. We computed the fraction of training images for which the distance between program estimate and observer annotation is within 25\% and 50\% of the optic disc diameter (DD = 382 pixels) for 5 different \( \sigma \) values of the Gaussian mask (\( r/8, r/4, r/2, r, 2r \)) as well as with uniform weights, for each of the 3 image quality classes. The best average performance was achieved for \( \sigma = r/2 \) at 25\% and with \( \sigma = r/2 \) and \( \sigma = r/8 \) (equal score) at 50\%. Hence, we fixed \( \sigma = r/2 \) for all tests of fovea location performance.

4.3 Algorithm Result

We analyzed the performance of our algorithm on 116 TENOVUS images which were divided into 3 quality levels; good, medium and difficult. For comparison with other algorithms, we run tests on both TENOVUS and MESSIDOR images. Figure 4 shows the difference histograms and associated cumulative histogram for the optimal Gaussian size, \( \sigma = r/2 \). The cumulative histograms show that 90\% of the error histogram lies within 0.35DD (about 130 pixels) for good-quality images, 0.73DD (observer1) and 0.8DD (observer2) for medium quality, 0.8DD (observer1) and 0.73DD (observer2) for difficult quality. Finally, Figure 5 gives examples of visual results of the automatic fovea detector on 3 images from each of the 3 quality classes.
Figure 4. Result on TENOVUS images. First, third rows: Histograms of distance differences per quality class for $\sigma = r/2$

(P = program, O = observer). Second, fourth rows: corresponding cumulative histograms. Bin axis values in OD

diameters (DD $\approx$ 382 pixels).
Figure 5. Result on TENOVOUS images: Illustrations of fovea location with images in the 3 quality classes, showing automatically located disc boundary, fitted parabola and axis, and estimated fovea center (blue cross).

We had also run tests to compare algorithms reported in related work [4,6,8]. The algorithms reported by Sinthanayothin et al [6] and Liang et al [4] used for this comparison study are programmed by us, based on our understanding on the method reported in their respective paper. The algorithm result reported by Tobin et al [8] on MESSIDOR images was provided by the authors themselves. Table 2 shows the algorithm performance of our algorithm and algorithms reported
in [4,6,8]. Sinhanayothin et al [6] and Liang et al [4] reported the highest accuracy in MESSIDOR images. Our algorithm performed well on images with no risk of macular edema (80%) but less accurate on images with risk of macular edema (59%). As our algorithm is dependent on the quality of vessel segmentation, its relatively poor performance in diseased images could be caused by poor performance of vessel segmentation on diseased images, particularly around the macula region.

Table 2: Algorithm performance comparison on MESSIDOR images

<table>
<thead>
<tr>
<th>Author</th>
<th>No risk of Macular edema</th>
<th>Risk of Macular Edema</th>
<th>No risk of Macular edema</th>
<th>Risk of Macular Edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinhanayothin et al [6]</td>
<td>173/203</td>
<td>67/100</td>
<td>179/203</td>
<td>69/100</td>
</tr>
<tr>
<td>Liang et al [4]</td>
<td>166/203</td>
<td>73/100</td>
<td>196/203</td>
<td>91/100</td>
</tr>
<tr>
<td>Tobin et al [8]</td>
<td>40/203</td>
<td>18/100</td>
<td>154/203</td>
<td>76/100</td>
</tr>
<tr>
<td>Our algorithm</td>
<td>114/203</td>
<td>28/100</td>
<td>162/203</td>
<td>59/100</td>
</tr>
</tbody>
</table>

Table 3: Algorithm performance comparison on TENOVUS images

<table>
<thead>
<tr>
<th>Author</th>
<th>Good</th>
<th>Medium</th>
<th>Difficult</th>
<th>Good</th>
<th>Medium</th>
<th>Difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liang et al [4]</td>
<td>0/66</td>
<td>0/30</td>
<td>0/20</td>
<td>0/66</td>
<td>1/30</td>
<td>0/20</td>
</tr>
<tr>
<td>Our algorithm</td>
<td>51/66</td>
<td>19/30</td>
<td>13/20</td>
<td>61/66</td>
<td>24/30</td>
<td>14/20</td>
</tr>
</tbody>
</table>

However, when tested on TENOVUS data set (Table 3), algorithm by Liang et al [4] does not perform as well as it does on the MESSIDOR data set. This is because the algorithm by Liang et al. [4] tends to constrain the search region to be at the center of the image, limiting location accuracy when tested on images where the macula is not central in the image.

Sinhanayothin et al [6] tested their algorithm on images of resolution 570x550 pixels. For the experiment reported in their paper, they used an inverted Gaussian template of size 40x40 pixels with the standard deviation of the Gaussian distribution fixed at 22. These parameters are dependent on the size of images and optic disc. Hence, when testing on MESSIDOR images (2240x1488), we changed these parameters to 130x130 for Gaussian template size and 73 for standard deviation, which were calculated using the ratio of the template area to the image area. For TENOVUS images (2336x3504), these parameters have to be changed because due to difference in resolution and optic disc size. However,
the performance of the algorithm on TENOVS set are not as good as its’ performance on MESSIDOR dataset. This could be caused by the difference in the characteristic of fovea region in TENOVS images which could not be approximated by inverted Gaussian.

Our algorithm does not require parameter adjustments when running on images of different resolution or sizes. It is however, dependent on the quality of vessel segmentation. All experiments were implemented with Matlab running on a 64 bit Operating system, Quad core A8-3520M processor at 1.6GHz with 6GB of RAM. The processing time for different stages is as follows; stage I (optic disc detection = 400s, vessel segmentation= 3.616s), stage II (search region) = 43.57s and stage III (fovea center localization) = 13.95s.

5. CONCLUSIONS

The reported experimental results suggest that the proposed algorithm is an effective method to locate the fovea in retinal images of varying qualities in the TENOVS dataset. The appearance of the avascular region may be severely altered in retinas of patients with advanced-stage macular diseases; our algorithm is capable to generate reasonable location estimates with difficult images (as defined above). The quality of fovea centre location seems adequate to establish retinal co-ordinate systems for automatic analysis [2]. At least with good and medium-quality images in our test set, fovea centre location seems accurate enough to locate the avascular region for automatic lesion analysis. Results depend of course on the quality of vessel masks, but achieving accurate vessel density is a less demanding target than accurate vessel contours [2]. In the MESSIDOR dataset however, our algorithm perform poorly on images with risk of macular edema. This is due to the presence of hard exudates around the macular area which are sometimes wrongly detected as blots of vessel pixels. Moreover, the vessel segmentation classifier was trained on Lothian Birth cohort images which have similar resolution with TENOVS images. Therefore performance of vessel segmentation will be better in TENOVS images than in MESSIDOR images, which affect the fovea localization result as it is dependent on quality of vessel map. However, it is still able to perform reasonably well in MESSIDOR images with no risk of macular edema.

Compared to algorithm reported in [4] and [6], which performed very well in MESSIDOR images but poorly in TENOVS images, our algorithm performs reasonably well in TENOVS images of variable quality and healthy eye images from the MESSIDOR dataset.
ACKNOWLEDGEMENTS

We thank Dr Alex Doney for procuring the Ninewells screening images under a TENOVS grant. This work is part of the VAMPIRE (Vasculature Assessment and Measurement Platform for Images of the REtina) project [16]. We would also like to thank Thomas P. Karnowski, Ph.D., of the Imaging, Signals and Machine Learning Group at Oak Ridge National Laboratory, USA and Edward Chaum, M.D., Ph.D. of the Hamilton Eye Institute, University of Tennessee Health Sciences Center, USA for providing us their algorithm [8] result on MESSIDOR images for the purpose of comparison.

COMPETING INTERESTS

None.

FUNDING STATEMENT

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REFERENCES

Highlights

- Modelled the fovea as an avascular region instead of as a dark region
- Used structural information of macula as anatomical priors to detect macula region
- Used distribution of DM:DD ratio from annotated images rather than a constant ratio
- No parameters re-adjustment required for images of different resolution or optic disc size