AUTOMATIC MACULA DETECTION IN HUMAN EYE FUNDUS AUTOFLUORESCENCE IMAGES: APPLICATION TO EYE DISEASE LOCALIZATION

ADNAN RASHID CHAUDHRY1, CAREN BELLMANN2, VALERIE LE TIEN3, JEAN-CLAUDE KLEIN1 AND ESTELLE PARRA-DENIS1

1 Mines Paris Tech, Centre de Morphologie Mathématique, 35 rue Saint Honoré 77305 Fontainebleau, France,
2 Institut Curie, 26 rue Ulm 75005 Paris, France,
3 Centre Hospitalier Intercommunal de Créteil, 40 avenue de Verdun 94010 Créteil, France

E-mail: adnan.rashid@mines-paristech.fr, caren.bellmann@curie.net, Valerie.LeTien@chicreteil.fr,
jean-claude.klein@mines-paristech.fr, estelle.parra@mines-paristech.fr

ABSTRACT

Fundus AutoFluorescence (FAF) images are widely used in the diagnosis and follow-up of Age-related Macular Degeneration, which is the leading cause of blindness in people over 55. There are two kinds of AMD: wet and dry. The most common is the dry form. It is characterized by atrophies of the retinal pigment epithelium (RPE) with subsequent photoreceptor degeneration. The atrophy severity depends on its size and its location with regard to fovea. The fovea is the macula center, which is the retina central zone (about 2mm of diameter). The macula has a high density of cone photoreceptors and is not supplied by the retinal capillaries; it receives its blood supply from the choroid. For the determination of the lesions location, we developed an automatic positioning and orientation of a retinal grading grid. Centered on the fovea, it provides information on the spatial distribution of pathologies and thus helps to determine the severity and the danger associated to the detected retinal lesions. This automatic positioning is based on a top down approach, which starts with the vascular tree segmentation and skeletonization. The detected vessels help in localization and detection of the Optic Disc (OD). An approximate OD centre is found by ellipse fitting to the boundary of OD. The vascular tree and the ellipse fitting help in detection of the macula and its center the fovea in relation to the OD center.

Keywords: Retinal images, Grading grid, Fundus autofluorescence image.

INTRODUCTION

Fundus AutoFluorescence (FAF) imaging is a fast and non-invasive technique developed over the last ten years for studying the retina. It uses the fluorescent properties of a pigment, called Lipofuscin (LF), located in the Retinal Pigment Epithelum (RPE) cells. It allows us to study the health and viability of the RPE (Schmitz-Valckenberg et al., 2008; Bellmann et al., 2003). The images obtained with FAF techniques correspond to LF distribution in the RPE. The normal FAF pattern (Fig. 1a) shows a higher level of LF in the parafoveal area and a decrease of LF toward the periphery. It decreases in the macular zone with a lowest value corresponding to the fovea (i.e., the macula center which is the retina central zone measuring about 2mm of diameter). This decrease corresponds to the absorption of the short wavelength light by melanin and luteal pigment and also partly to decreased LF content in that area. There is also a reduced autofluorescence at the Optic Disc (OD) due to the absence of the RPE and at the blood vessels due to the masking of the RPE by the blood circulation.

Retinal pathologies in FAF images correspond to a FAF abnormal increase resulting from LF accumulation, or a FAF decrease or a FAF lack (for example RPE atrophies Fig. 1b). Thus FAF imaging may provide ideas about the RPE metabolic state. It represents a useful diagnostic and prognostic tool for ophthalmologists to identify specific FAF changes having been associated with retinal disease.

In this paper, the studied FAF images are acquired with an angiograph equipped with a Scanning Laser of 488 nm wavelength and an appropriate barrier filter (Scanning Laser Ophthalmoscope). The images, centered onto the fovea, correspond to a 30°field of view, which encompasses almost the posterior pole of the retina (Fig.1). Their size is 768 × 768 pixels.

This paper is organized as follows. The first part is dedicated to the automatic detection of the macular zone by a top-down approach. This approach starts with the vascular tree segmentation and the skeletonization, the detected vessels help with the OD localization and detection. The vascular tree and the OD help with the detection of the macular zone. The second part deals with the automatic grading grid setting in two steps. The first step is the detection of the macular zone center to place the grid center. The second step is the estimation of the OD center by using an ellipse fitting algorithm to orientate the grading.
grid. The third part concludes the paper and looks at the prospective works.

Fig. 1. Example of typical FAF image obtained for a normal eye (a), and for a pathologic one (b).

AUTOMATIC DETECTION OF THE MACULAR ZONE

Fig. 2. The top-down approach used to determine the macular zone.

This section presents the automatic detection of the macular zone. First a state of the art is provided. Second we present an original method to automatically detect the macular zone by a top down approach (Fig. 2).

MACULA DETECTION: STATE OF THE ART

In the literature there are few papers dealing with the macular localization in FAF modality. In (Sinthanayothin et al., 1999), on color images, a typical template of the macular region is formed and correlated with the image to localize the fovea in the OD neighborhood. On the fluorescein angiography, mathematical morphology and region growing algorithms are applied for the macular zone localization in (Zana et al., 1998); in (Gutierrez et al., 2000), an active contour is performed based on B-snakes with greedy minimizing algorithm to characterize the foveal zone boundary. In (Li and Opas, 2004) an automated extraction of the macula on color images is performed by detecting the main vessels by a modified active shape model. The latter is fitted with a parabola to specify the candidate region. The fovea is then located by a clustering of the darkest pixels as the macular candidate region. In (Tobin et al., 2007), the parabolic model of a vascular tree is used to estimate the fovea position. Our approach is derived from these two last presented methods.

MACULA DETECTION APPROACH

We propose an original method developed in two stages: the macular zone detection and localization. This method is based on the hypofluorescence of the macular region in FAF images. The use of its position with regard to the vessel endpoints and the OD defines a mask region which contains the macula. This two-step method gives a robust technique in normal subjects as well as in patients with retinal disease.

Extraction of the vessel endpoints In FAF images, the blood vessels are the most distinctive feature, they appear as a tree like structure originating from the OD. Their characteristics are: a diameter of less than 15 pixels, an elongated piecewise linear shape and a gray level darker than the background. In the literature, the retinal blood vessel segmentation algorithms are categorized into a wide variety of techniques reviewed in (Kirbas and Quek, 2004). We have designed a fast and robust algorithm to extract the vessels on FAF imaging based on mathematic morphology (Serra, 1982). It is divided into 5 steps (illustrated on Fig. 3): preprocessing, vessel segmentation, skeletonization, post filtering and refined vessel skeleton.

The preprocessing step consists of filtering the FAF image with a gaussian filter (of size 5 and standard deviation 1.2) followed by a morphological closing (with a square structuring element of size 3 × 3 pixels). The vessel segmentation step is composed of 3 stages: highlighting of the vessels by application of a Black Top-Hat operator (BTH) (with a square structuring element of size 31 × 31 pixels) (Serra, 1982), thresholding of the obtained image (the threshold value is the mean gray value of the BTH image) and an area filtering to remove small components which are not connected to the vascular tree. The skeletonization is then applied to extract the medial axis of the vessels by using the pattern thinning proposed by Zhang and Suen (1984). The obtained skeleton is then filtered to extract undesirable branches and loops. The result is a refined vessel skeleton which is finally used to determine vessel endpoints.
Fig. 3. Steps of vessel endpoints extraction: (a) FAF image, (b) gaussian filtering of (a), (c) application of a BTH operator on (b), (d) thresholding of (c), (e) area opening of (d), (f) skeletonization of (e), (g) refined skeleton, (h) endpoints superposed on the refined skeleton.

Optic Disc detection  In the studied FAF images, the OD appears as a dark oval region with a diameter of about 180 pixels. In the literature algorithms are often divided into two main steps: the localization and the OD boundary detection. As for the macula, the OD detection algorithms are image modality specific (more often performed on angiography and color images). In the color images, the high gray level value and the elliptical shape features of the OD are exploited for its localization (Sinthanayothin et al., 1999; Narasimha-lyer et al., 2006). In (Siddalingaswamy and Prabhu, 2007), an optimal iterative threshold with connected component analysis is applied to identify the bright OD. In (Foracchia et al., 2004; Tobin et al., 2007; Abdel-Razik Youssif et al., 2008), the geometrical relationship between the OD and the vessels is used to localize the OD. In (Walter et al., 2002), a watershed based segmentation technique using morphological filtering and shade correction is applied for the OD segmentation.

The proposed algorithm for an automatic OD localization and detection is based on mathematical morphology operators (Serra, 1982), it is divided into 5 steps (illustrated on Fig. 4): preprocessing, extraction of the large dark Connected Components (CCs) of size comparable to the one of the OD, selection of a candidate (from the set of the detected CCs by analysis based on the endpoints of the blood vessels), extraction of the OD boundary by a marker-controlled watershed and boundary smoothing, OD modeling by ellipse fitting in order to fix its center.

The preprocessing step is the same as the one applied for the preprocessing step of vessel endpoints extraction. The OD localization consists in detecting OD marker by application of a closing operator (with a square structuring element of size 41 × 41 pixels), which removes all thin dark details including vessels. The large components like the OD are preserved (Fig. 4b).

For the extraction of large CCs, we propose an iterative threshold segmentation method controlled by a square shape constraint. In this method, the threshold value is progressively lowered from the mean gray level. At each new thresholding step, the segmented CCs smaller than the maximum OD size are added to the resulting image. The OD extraction steps are illustrated on the Fig. 4c.

The next task is to select a candidate component from the set of the CCs obtained at the end of the iterative process. As blood vessels originate from the OD, at each endpoint falling in the search window around the CCs (1.5 times bigger than its bounding box) is assigned a weight regarding the angle between the vessel endpoint tangent and the CC center. The CC presenting the maximum of vessel endpoints cumulative weight is selected as a likely OD candidate (see Fig. 4d). The selected component is either a part of the OD or is slightly bigger than the OD in the presence of pathologies around it.

The OD boundary is extracted by a marker-imposed watershed (Fig. 4e). The inner and outer markers are generated respectively by erosion and dilation of the selected CC. The extracted OD has an irregular shape, caused by the similarity of the gray values between the vessels and the OD. No significant edges exist between the OD and the adjoining blood vessels.
In order to approximate the OD center, and to reduce the distortion in the extracted OD boundary, an ellipse fitting is applied on the watershed image (Fig. 4f). The method used is based on a least square minimization proposed by Halir and Flusser (1998). It guarantees an ellipse-specific solution even for scattered or noisy data. Therefore, this algorithm overcomes the distorted boundary of OD and gives a smooth ellipse shape. It gives also the opportunity to determine the center of the ellipse which could be associated as the one of the OD.

Macula detection algorithm
It consists of 3 steps: a macular mask generation, a BTH by diameter closing to exploit the hypofluorescence of the macula and a post processing step which uses together the two previous step results.

Anatomically, the fovea is located in the temporal direction with regard to the OD center, the distance between them is twice the OD diameter and there is an angle of about -15° (resp 195°) in the left eye (resp right) between the horizontal line passing through the OD center and the line joining the OD center to the fovea (Li and Opas, 2004; Siddalingaswamy and Prabhu, 2007). Furthermore, the macular zone is located in the smallest convex hull of the central avascular zone of the vessels. This convex hull can be automatically determined from the blood vessel endpoints. From this convex hull, a mask could be designed to locate the likely region for the macular zone.

The macular mask generation is performed as follows (see Fig. 5a): extraction of the vessel endpoints, positioning of a radial histogram (in relation to the OD center), application of the peeling onion algorithm. The onion peeling algorithm consists in removing the outer endpoints iteratively considering that radial bin contains at least one point.

The BTH by diameter closing is a morphological operator defined by equation 1 where $\phi^\lambda(f)$ is the closing by diameter introduced by Walter (2003). For the studied FAF images, parameter $\lambda$ of the diameter
closing is 200 pixels. A thresholding with a threshold value automatically selected by the mean gray value of the BTH image is applied to the BTH image. It extracts all dark regions of diameter lower than $\lambda$ size (Fig. 5). 

$$BTH = \phi^o_{\lambda}(f) - f$$  \hspace{1cm} (1)$$

Then an area filter combined with a hole filling is used to retain only significant CCs from the thresholded BTH image (Fig. 5b). Finally, all the unwanted structures, including pathological components outside of macular zone, are removed by taking the intersection between the segmented component image and the macular mask previously defined (Fig. 5c).

Fig. 6. Automatic positioning and orientation of a grading grid centered onto the fovea (Two images corresponding to the follow-up of a patient).

**GRADING GRID AUTOMATIC SETTING**

The objective is to automatically center the grading grid onto the fovea and to determine its orientation so that the dotted line joins the fovea with the OD center, even if anatomically the fovea and the OD are not located on the same horizontal plane (Fig.6). This automatic positioning of the grading grid always allows an efficient positioning not influenced by rotations due to the acquisition process. Therefore, it gives an efficient tool for automatically setting the grading grid on a large ophthalmological database, and thus for having a precise description of the pathological location of diseases. The follow-up of pathologies (number, surface, location) during a large period of time will be eased by using this kind of automatic setting of a grading grid.

Fig. 7. (a)Manual annotation of macular zone by the ophthalmologist on fluorescein angiography modality (a). (b) Registration of the fluorescein angiography with the FAF image to compare the automatic and manual grading grid setting.

**Validation**

The validation consists in comparing the automatic and manual determinations of the fovea location (Fig.7). The macular zone and the fovea cannot easily be determined by hand on FAF images under pathological conditions or with poor image quality. Consequently, when a manual annotation is not possible with an FAF image, another modality acquired during the same examination can be used. In the presented paper, the ophthalmologist has selected the image with the most visible capillaries: a Fluorescein Angiography (FA). In this modality a polygon passing by the vascular endpoints is drawn manually in the avascular region. Then, a geodesic circle is automatically drawn inside the polygonal region marking out the zone likely to contain the fovea. The manually annotated FA image is registered with the studied FAF image. The registration algorithm is an extension of the one presented by Chaudhry et al. (2008). If the fovea determined automatically falls within the geodesic circle, the result is classified as true. In manual annotation, the size and the shape of the polygon are operator dependent. Even then this method provides a good guideline for the validation of the grading grid positioning in FAF images. The test database contained 55 FAF images, which included 33 normal subjects and 22 subjects presenting retinal pathologies. The results are summarized in Table 1.

<table>
<thead>
<tr>
<th>Image type</th>
<th>Number of subjects</th>
<th>True setting of grading grid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>Pathological</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 1. Results of automatic grading grid setting
CONCLUSION

This paper has demonstrated a fully automatic macula detection and an automatic grading grid setting system for FAF images. A prototype software system has been designed based on the proposed algorithms. Its use may be valuable in the retinal image analysis. A novel validation scheme has been proposed to measure the reliability of the results obtained from the presented algorithms and a manual annotation. The latter can be performed on any retinal image modality (FAF, color, angiographies, infra-red and red free) taken during the same examination and showing the best visible macular zone. The system has shown promising results on a small database of 55 patients. We obtained a grading grid positioning success rate of 94% and 86% in normal and in pathological images respectively. The robustness and efficiency of the proposed system has to be validated over a larger image database to make it suitable for clinical purposes.

REFERENCES