

An Automatic Algorithm for Segmentation of the Boundaries of Corneal Layers in Optical Coherence Tomography Images using Gaussian Mixture Model

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ABSTRACT

Diagnosis of corneal diseases is possible by measuring and evaluation of corneal thickness in different layers. Thus, the need for precise segmentation of corneal layer boundaries is inevitable. Obviously, manual segmentation is time-consuming and imprecise. In this paper, the Gaussian mixture model (GMM) is used for automatic segmentation of three clinically important corneal boundaries on optical coherence tomography (OCT) images. For this purpose, we apply the GMM method in two consequent steps. In the first step, the GMM is applied on the original image to localize the first and the last boundaries. In the next step, gradient response of a contrast enhanced version of the image is fed into another GMM algorithm to obtain a more clear result around the second boundary. Finally, the first boundary is traced toward down to localize the exact location of the second boundary. We tested the performance of the algorithm on images taken from a Heidelberg OCT imaging system. To evaluate our approach, the automatic boundary results are compared with the boundaries that have been segmented manually by two corneal specialists. The quantitative results show that the proposed method segments the desired boundaries with a great accuracy. Unsigned mean errors between the results of the proposed method and the manual segmentation are 0.332, 0.421, and 0.795 for detection of epithelium, Bowman, and endothelium boundaries, respectively. Unsigned mean errors of the inter-observer between two corneal specialists have also a comparable unsigned value of 0.330, 0.398, and 0.534, respectively.

Key words: Corneal layers, Gaussian mixture model, optical coherence tomography, segmentation

INTRODUCTION

Optical coherence tomography (OCT) is a non-invasive imaging technique which uses infrared light. Since possible imaging depth using OCT is 2-3 mm, this method has a high compatibility with retinal^[1-8] and corneal^[9-21] tissues. The OCT images have various information such as curvature and thickness of the layers. The method can also provide a high resolution and three-dimensional (3D) view of the living tissues for us.^[22-30] The light wavelength of OCT device used in imaging of the anterior eye segments is 1.3 μm and provides the possibility of imaging of this section because of the relatively good penetration through the sclera.^[31]

The adult cornea is approximately 0.5 mm thick at the center and it gradually increases in thickness toward the periphery.

The shape of the cornea is prolate-flatter in the periphery and steeper centrally which creates an aspheric optical system. The human cornea comprised of five layers: Epithelium, Bowman's membrane, stroma, Descemet's membrane and the endothelium. There are problems such as corneal swelling, acidosis and altered corneal oxygen consumption which change the normal thickness of the corneal layers. Therefore, evaluation of corneal thickness in such cases can improve the diagnosis and treatment. Also, the assessment of the thickness of corneal layers before and after refractive surgery plays an important role in the evaluation of the treatment process. So accurate segmentation of corneal boundaries is necessary. Otherwise, an error of several micrometers can lead to wrong diagnosis. The large volume of these data in clinical evaluation makes manual segmentation time-consuming and impractical.^[29,32,33]

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Graglia *et al.*^[23] proposed an approach for contour detection in the frame of OCT images of the cornea by finding epithelium and endothelium points and tracing the contour of the cornea pixel by pixel from these two points with a weight criterion. The algorithm strongly depends on proper selection of initial points on the epithelium and endothelium boundaries and the smallest error in this section, gives wrong results. Furthermore, the algorithm is not able to detect inner layers and only detects the epithelium and endothelium boundaries. Li *et al.*^[34-36] proposed an automatic method for corneal segmentation using a combination of fast active contour (FAC) and second-order polynomial fitting algorithm. This approach depends heavily on the correct choice of the initial contour which should be close to the desired image feature, typically edges. This algorithm segments epithelium, Bowman and endothelium boundaries. Eichel *et al.*^[33,37] proposed a semi-automatic method for corneal segmentation by utilizing enhanced intelligent scissors and user interaction. This method is semi-automatic and requires the high accuracy of user interaction for accurate segmentation and it is time-consuming because of the presence of user. This method segments all of the corneal layers. Despite the successful demonstrated accuracy in segmenting high-quality corneal images, none of these techniques have demonstrated sufficient accuracy for fully automatically segmenting low-signal-to-noise ratio (SNR) images. Larocca *et al.*^[29] proposed an automatic algorithm to segment boundaries of three corneal layers using graph theory and dynamic programming. This method segments three clinically important corneal layer boundaries (epithelium, Bowman and endothelium). But their method was only tested on 20 corneal images.

In this paper, we segment the boundaries of corneal layers by utilizing Gaussian mixture model (GMM) method. Our method segments three important corneal boundaries in OCT images. These layers are as follows: Epithelium, Bowman and endothelium. The OCT images captured from high-tech devices may have high SNR [Figure 1a], but in many cases, they have a low-SNR [Figure 1b]. Furthermore, some of OCT images may be affected by different types of artifact like central artifact. The central artifact is the vertical saturation artifact that occurs around the center of the cornea due to the back-reflections from the corneal apex, which saturates the spectrometer line camera.^[29] The data used in this work is taken from Heidelberg OCT-spectralis HRA imaging system in Noor Ophthalmology Center in Tehran, Iran. The high-quality of images taken from this system guarantees that we have no central artifact. The paper is organized as follows: section 2 describes the theory of GMM. Section 3 discusses the segmentation method of the mentioned corneal layers by utilizing GMM algorithm. Section 4 compares the results of this method against the corneal specialist manual segmentation and the conclusion is discussed in section 5.

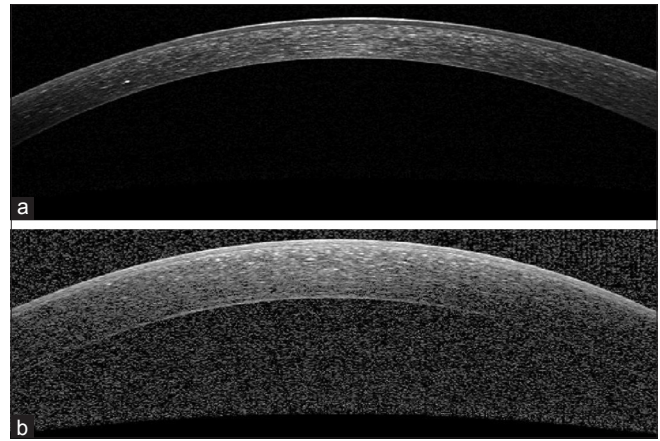


Figure 1: Examples of corneal images of varying signal-to-noise ratio (SNR) used in this study. (a) A high SNR corneal image. (b) A low-SNR corneal image

GMM

Kim and Kang^[38] explained that GMM is a method to estimate the probability density function (PDF) using a combination of Gaussian functions. The elements of mixtures are defined as D-dimensional Gaussians and the equation of a D-dimensional Gaussian distribution is given below:

$$b_i(\vec{x}) = \frac{1}{(2\pi)^{D/2} |\Sigma_i|^{1/2}} \exp \left\{ -\frac{1}{2} (\vec{x} - \vec{\mu}_i)' \Sigma_i^{-1} (\vec{x} - \vec{\mu}_i) \right\} \quad (1)$$

where $\vec{x}$ is a D-dimensional vector of features of the input image, $\vec{\mu}_i$ is the mean vector and Σ_i is the covariance matrix. A weighted mixture of M Gaussian distribution is given in the equation below:

$$p(\vec{x}|\lambda) = \sum_{i=1}^M p_i b_i(\vec{x}) \quad (2)$$

where p_i s are the weights of mixture elements and:

$$\sum_{i=1}^M p_i = 1 \quad (3)$$

μ_i , p_i and Σ_i are parameters of GMM and we show this model with λ . We formulate GMM as a maximum likelihood problem and estimate its parameters by utilizing expectation-maximization (EM) algorithm. EM algorithm starts from an initial λ and estimates the new one $\hat{\lambda}$ as:

$$p(x|\hat{\lambda}) \geq p(x|\lambda) \quad (4)$$

This procedure is repeated until converging to a good model. The number of EM iterations can be control by selecting a threshold. One way to select a threshold is that, GMM going on until the difference between $p(x|\hat{\lambda})$ and $p(x|\lambda)$ be smaller than a value or we can directly choose the number of EM iterations as an input for GMM.

We use the following equations in each iteration of EM algorithm to estimate the parameters (for T training vectors):

$$\bar{p}_i = \frac{1}{T} \sum_{t=1}^T p(i | \bar{x}_t, \lambda) \quad (5)$$

$$\bar{\mu}_i = \frac{\sum_{t=1}^T p(i | \bar{x}_t, \lambda) \bar{x}_t}{\sum_{t=1}^T p(i | \bar{x}_t, \lambda)} \quad (6)$$

$$\bar{\sigma}_i^2 = \frac{\sum_{t=1}^T p(i | \bar{x}_t, \lambda) \bar{x}_t^2}{\sum_{t=1}^T p(i | \bar{x}_t, \lambda)} - \bar{\mu}_i^2 \quad (7)$$

In fact, EM algorithm reaches its goal during two steps: Expectation step (E) and maximization step (M). Step E corrects the PDF and step M maximize it in each iteration. $p(i | \bar{x}_t, \lambda)$ is the posterior probability for class i in step E and is defined as below:

$$p(i | \bar{x}_t, \lambda) = \frac{p_i b_i(\bar{x}_t)}{\sum_{k=1}^M p_k b_k(\bar{x}_t)} \quad (8)$$

As mentioned, $\bar{x}$ is a D-dimensional vector of features of the input image. Various features can be considered for the image like pixel location for 3D plots, RGB space of the image, Luv space of the image and Lab space of the image.

GMM is an automatic method to segment an image based on its statistical properties. This method fits a number of Gaussian functions to the distribution of the image. Since our images often have the same distribution, it can show a good performance in our work. In this way that we can localize the object in the next image by tracking its distribution. GMM has also been used in OCT image processing by.^[39,40] Furthermore, this method has also been utilized in segmentation of fluorescein angiograms in.^[41] So we can say that GMM is capable for segmentation in our work.

THE PROPOSED METHOD

Epithelium, Bowman and endothelium are three important corneal layers [Figure 2].

In this section, the proposed method for segmenting the boundaries of epithelium, Bowman and endothelium layers are explained. At first, the method for segmentation of the boundaries of epithelium and endothelium layers is explained. Then we elaborate how to extrapolate the curves to low-SNR regions. Then, segmenting the boundary of Bowman layer and contrast enhancement of the Bowman boundary is described in the last part of this section.

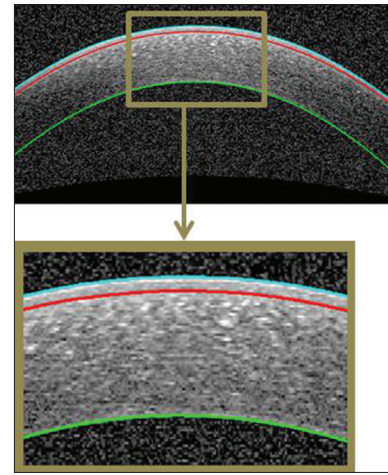


Figure 2: An example of segmented corneal image. The epithelium boundary (cyan), the Bowman boundary (red), and the endothelium boundary (green)

Segmenting the Boundaries of Epithelium and Endothelium Layers

To obtain these two boundaries, we first apply a low-pass filter through a (1×30) Gaussian kernel (sigma of 10) to minimize the effect of noise [Figure 3a]. The selected kernel size leads to uniformity of the image noise and prevents from segmentation of whatever has been affected by noise (as a distinct element). Then we give the denoised image to the GMM algorithm and determine the number of classes to be two. The final result of GMM [Figure 3b] shows the approximate location of these two boundaries. As it can be seen in Figure 3c, the detected boundary is not exactly on the border of epithelium. To overcome this problem, we can use the horizontal gradient of the original image and with the help of the current boundary, we look for the lowest gradient in a small neighborhood [Figure 4].

Extrapolation to Low SNR Regions

Some images have low-SNR areas in two peripheral regions and the obtained boundaries in these regions are not accurate enough. Therefore, we localize the low-SNR regions and extrapolate the central curve in such areas. For this purpose, we use the second derivative of endothelium boundary [Figure 5a] and search around the middle of this vector to find values below zero. It indicates that there is a positive inflection in the second derivative, which should not occur for normal cornea. The location of this positive inflection reveals the low-SNR areas of the image. In this step, a parabolic curve can be fitted to the estimated boundary with finding the coefficients of polynomial of degree 4 for the correct estimated border, in a least squares sense. Suppose that we have m pairs of data:

$$(x_i, y_i), \quad i = 1, \dots, m$$

Consider the fit function with three basic functions:

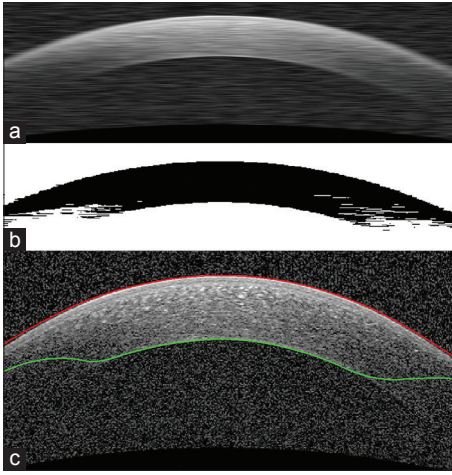


Figure 3: Segmentation of epithelium and endothelium boundaries. (a) Reducing the speckle noise with a Gaussian low-pass filter. This image is used as an input for Gaussian mixture model (GMM). (b) GMM output. This is the image which is used for segmentation of desirable boundaries. (c) Segmentation result (before correction)

$$F(x) = c_1 f_1(x) + c_2 f_2(x) + c_3 f_3(x) \quad (9)$$

The objective is to find the c_j such that $F(x_i) \approx y_i$. Since $F(x_i) \neq y_i$, the residual for each data point is:

$$r_i = F(x_i) - y_i = \sum_{j=1}^m c_j f_j(x_i) - y_i \quad (10)$$

The least square solution gives the c_j that minimize $\|r\|_2$. The over determined system is as below:

$$Ac = y \quad (11)$$

where

$$A = \begin{bmatrix} f_1(x_1) & f_2(x_1) & f_3(x_1) \\ f_1(x_2) & f_2(x_2) & f_3(x_2) \\ \vdots & \vdots & \vdots \\ f_1(x_m) & f_2(x_m) & f_3(x_m) \end{bmatrix}$$

$$c = \begin{bmatrix} c_1 \\ c_2 \\ c_3 \end{bmatrix}, \quad y = \begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_m \end{bmatrix}$$

The least squares method provides the compromise solution that minimizes $\|r\|_2 = \|Ac - y\|_2 = \left(\sum_{i=1}^m \left(\sum_{j=1}^3 c_j f_j(x_i) - y_i \right)^2 \right)^{1/2}$. The c that minimizes $\|r\|_2$ satisfies the normal equations:

$$(A^T A)c = A^T y \quad (12)$$

As mentioned above, we can recognize the starting points of the low-SNR regions using second derivative and

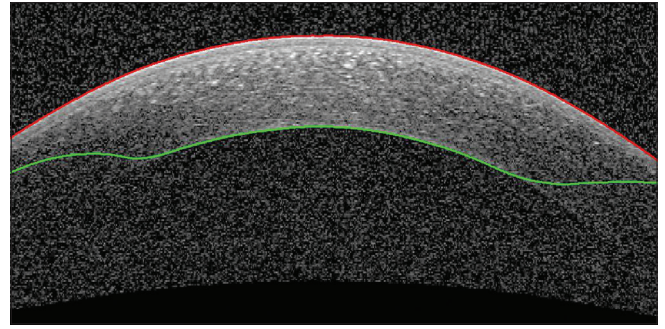


Figure 4: Epithelium boundary after correction

extrapolation will be done using a degree 4 polynomial [Figure 5b]. To create smooth junctions in the final boundary, smoothing operators can then be used. For this purpose, a local regression using weighted linear least squares that assigns lower weight to outliers can be used. To find low-SNR regions for epithelium, we use the unsigned second derivative of epithelium boundary and search for values greater than a threshold. This threshold is 0.0045 and the value is determined based on trial and error.

Segmenting the Boundary of Bowman Layer

For this purpose, we first enhance this boundary because in most cases it is very weak.

Contrast Enhancement to have Detectable Bowman Boundary

For this purpose, we modified a method proposed by Esmaeili *et al.*^[42] This algorithm corrects non-uniform background and increases the contrast of Bowman boundary in Figure 6a. During this process each pixel $f(i, j)$ of the image is adjusted as follows:

$$g(i, j) = 2 \times f(i, j) - 2 \times f_{\text{mean}}(w) + \left(\frac{100 \times f_{\text{min}}(i, j)}{f_{\text{max}}(i, j) + 1} \right) \quad (13)$$

where f_{mean} , $f_{\text{min}}(i, j)$ and $f_{\text{max}}(i, j)$ are, respectively, the mean, minimum and maximum intensity values of the image within a window W of size 10×10 [Figure 6b].

After enhancement, we obtain the horizontal edge response to Sobel gradient of the enhanced image. We use this image as an input of GMM because in this case, the layer distinguishes itself from other parts of the image [Figure 7a]. Figure 7b is the output of GMM and using this image we can localize the Bowman boundary. Since we have obtained the epithelium boundary (as described in Epithelium and Endothelium segmentation part), the Bowman boundary is achievable by tracing epithelium toward down to get a white to black change in brightness. The middle of the Bowman boundary will be detected exactly, but the periphery may be affected by the noise and would create outliers. To overcome this problem, we find the outliers like previously

mentioned method for low-SNR areas in epithelium, and then extrapolate the curve to the outside of these points. The result is shown in Figure 7c.

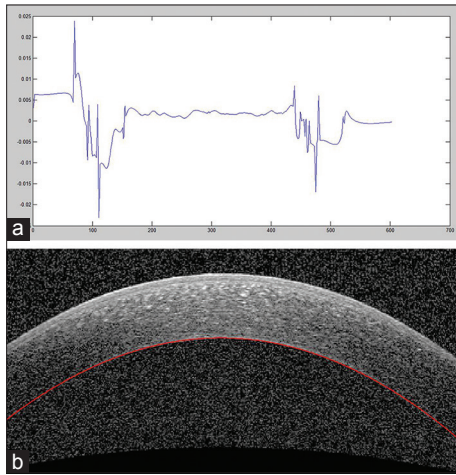


Figure 5: Extrapolation to low-signal-to-noise ratio (SNR) regions. (a) The second derivative plot of endothelium layer boundary to detect low-SNR regions of this boundary. (b) Extrapolation result

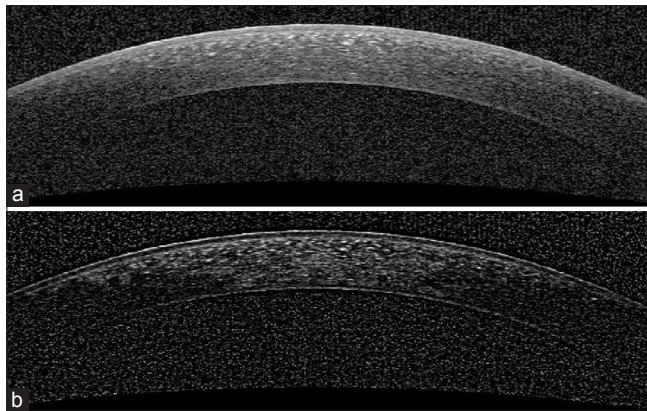


Figure 6: Contrast enhancement of original image for segmentation of Bowman boundary. (a) Original image. (b) The enhanced image

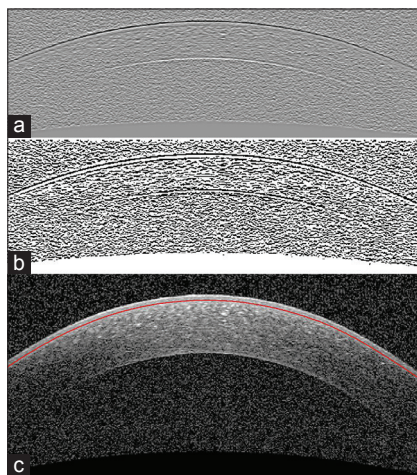


Figure 7: Segmentation of Bowman layer boundary. (a) Horizontal gradient of the enhanced image. (b) Gaussian mixture model output to the input of (a). (c) Segmentation result

EXPERIMENTAL RESULTS

In this study, we used corneal OCT images taken from 10 normal subjects. Each subject includes 40 slices of the whole cornea. The algorithm is tested on images taken from Heidelberg OCT-spectralis HRA imaging system in Noor Ophthalmology Center in Tehran, Iran. This system has a pre-processing stage. To evaluate the robustness and accuracy of the proposed algorithm, we use manual segmentation by two corneal specialists. For this purpose, 20 images selected randomly from all subjects. We calculated the unsigned and signed error of this algorithm against manual results.

The boundaries were segmented automatically using a MATLAB (R2011a) implementation of our algorithm. A computer with Microsoft Windows 7 x32 edition, Intel Core i5 central processing unit at 2.5 GHz, 6 GB random access memory was used for the processing. The average computation time was 7.99 s/image. The mean and standard deviation of unsigned and signed error were calculated and are shown in Tables 1 and 2, respectively. The mean and standard deviation of unsigned error is defined as follows:

Table 1: Mean and SD of unsigned error in corneal layer boundary segmentation between automatic and manual results and among two corneal specialists

Corneal layer boundary	Comparison of automatic and manual expert segmentation Column I (pixels)		Comparison of two manual graders Column II (pixels)	
	Mean difference	SD	Mean difference	SD
Epithelium boundary (before correction)	1.531	0.703		
Epithelium boundary (after correction)	0.332	0.230	0.330	0.303
Bowman boundary	0.421	0.321	0.398	0.301
Endothelium boundary	0.795	0.748	0.534	0.542

Each pixel is approximately 13.3 μm in the cornea. SD – Standard deviation

Table 2: Mean and SD of signed error in corneal layer boundary segmentation between automatic and manual segmentation and among two corneal specialists

Corneal layer boundary	Comparison of automatic and manual expert segmentation Column I (pixels)		Comparison graders of two manual Column II (pixels)	
	Mean difference	SD	Mean difference	SD
Epithelium boundary (before correction)	1.530	0.703		
Epithelium boundary (after correction)	0.011	0.373	-0.104	0.412
Bowman boundary	0.177	0.423	0.015	0.432
Endothelium boundary	0.044	0.893	0.103	0.704

Each pixel is approximately 13.3 μm in the cornea. SD – Standard deviation

$$m_{\text{error}} = \text{mean} \left(\sum_{i=1}^n |b_{\text{manual}}(i) - b_{\text{auto}}(i)| \right) \quad (14)$$

$$\sigma_{\text{error}} = \text{standard deviation} \left(\sum_{i=1}^n |b_{\text{manual}}(i) - b_{\text{auto}}(i)| \right) \quad (15)$$

where m_{error} and σ_{error} are the mean and standard deviation of unsigned error between manual and automatic method, n is the number of points to calculate the layer error (width of the image), b_{manual} and b_{auto} are the boundary layers which are obtained manually and automatically, respectively. The mean value of manual segmentation by two independent corneal specialists is considered as b_{manual} in above equations and the inter-observer errors are also provided in Tables 1 and 2. The direct comparison of these values with the reported errors shows that the performance of the algorithm is acceptable in comparison with manual segmentation. Furthermore, the visual results of automatic segmentation of the corneal layers using proposed algorithm in this study for sample images are shown in Figure 8.

According to the possibility of comparing our results with other methods, it should be mentioned that the only available dataset for corneal OCT is provided by^[29] Unfortunately, the images in^[29] have single Gaussian distribution [Figure 9] and the proposed method is based on classification by GMM method (which needs multiple Gaussians). Therefore, the proposed method is not able to classify these images correctly.

To demonstrate the robustness of our algorithm against noise, we chose a raw image and add a Gaussian white noise with zero mean and variance as below:

$$v = \frac{\text{variance}(I)}{10^{\left(\frac{\text{SNR}}{10}\right)}} \quad (16)$$

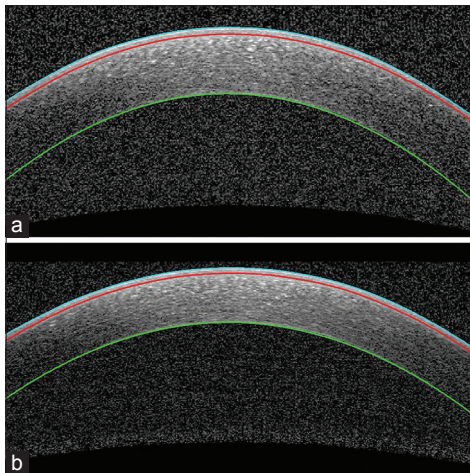


Figure 8: Examples of segmented corneal images, in which the cyan curve is the epithelium boundary, the red curve is Bowman boundary, and the green curve is the endothelium boundary

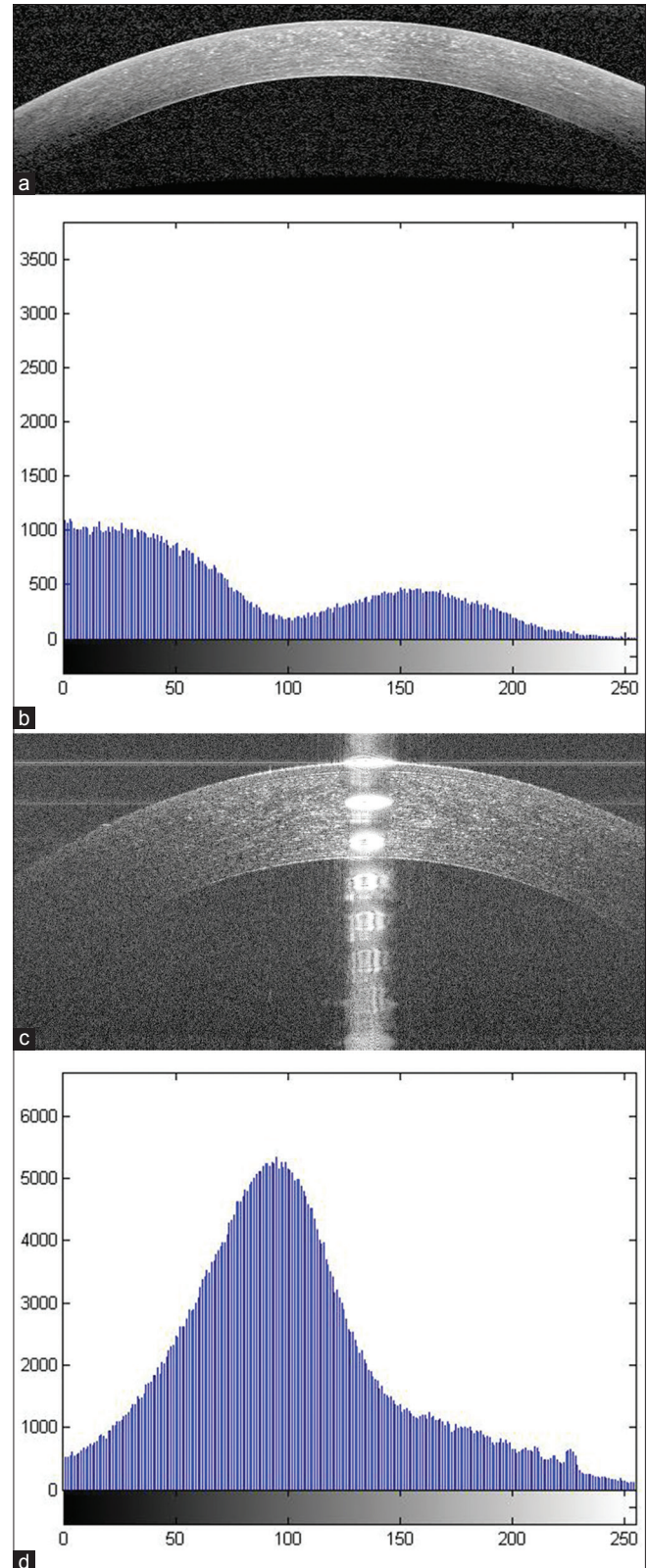


Figure 9: (a) An example of corneal optical coherence tomography (OCT) image used in our work. (b) The histogram of (a) which includes multiple Gaussians. (c) An example of corneal OCT image used by Larocca et al (d) The histogram of (c) which includes a single Gaussian distribution

where v is the Gaussian white noise variance and I is the normalized image. We use MATLAB toolbox and `imnoise` command to add noise with three different SNRs to the image. It should be considered that we don't have any ideal or noise less image and we can only compare our results in the presence of more added noise. Figure 10a and b shows the original image and its noisy image with SNR 4, respectively. Figure 10c shows the layers which obtained for the noisy image with SNR 4. The mean and standard deviation of unsigned and signed error for three different SNRs were calculated and are shown in Tables 3 and 4. As can be observed there are minimum differences from the obtained error between the noisy images and the original image that demonstrate the robustness of our algorithm against noise.

CONCLUSION AND FUTURE WORK

In this paper, we proposed an automatic method for segmentation of three important corneal layers of normal eyes using OCT devices. Our approach has a good performance in noisy images and is accurate in low-SNR regions. The obtained results are very close to the results of the specialists.

The large volume of corneal images in the clinics makes manual segmentation time-consuming impractical and subjective. However, the proposed method does not require

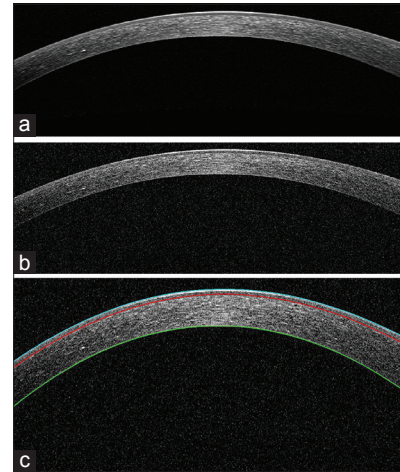


Figure 10: Evaluation of the noise effect on the segmentation of the boundaries of corneal layers. (a) The original image of cornea which is high signal-to-noise ratio (SNR) (raw image). (b) The noisy image of (a) with SNR 4. (c) The boundaries of cornea which is shown in (b)

Table 3: Mean and SD of unsigned error for the original and its noisy images with different SNRs

Corneal image type	Epithelium Mean error (Standard deviation error)	Bowman Mean error (Standard deviation error)	Endothelium Mean error (Standard deviation error)
Original (free noise)	Mean=0.3471 Std=0.2396	Mean=0.5231 Std=0.2582	Mean=0.4359 Std=0.2561
Noisy (SNR 6)	Mean=0.3414 Std=0.2398	Mean=0.5264 Std=0.3749	Mean=0.5860 Std=0.3238
Noisy (SNR 5)	Mean=0.3456 Std=0.2488	Mean=0.5995 Std=0.3047	Mean=0.6143 Std=0.2959
Noisy (SNR 4)	Mean=0.3409 Std=0.2190	Mean=0.6448 Std=0.3250	Mean=0.8438 Std=0.5824

SD – Standard deviation; SNR – Signal-to-noise ratio

Table 4: Mean and standard deviation of signed error for the original and its noisy images with different SNRs

Corneal image type	Epithelium Mean error (Standard deviation error)	Bowman Mean error (Standard deviation error)	Endothelium Mean error (Standard deviation error)
Original (free noise)	Mean=0.1827 Std=0.3804	Mean=0.5007 Std=0.2994	Mean=0.4001 Std=0.3091
Noisy (SNR 6)	Mean=0.1840 Std=0.3746	Mean=0.5137 Std=0.3785	Mean=0.5833 Std=0.3286
Noisy (SNR 5)	Mean=0.2055 Std=0.3732	Mean=0.5900 Std=0.3229	Mean=0.6454 Std=0.3740
Noisy (SNR 4)	Mean=0.2615 Std=0.3718	Mean=0.6229 Std=0.3652	Mean=0.8422 Std=0.5847

SD – Standard deviation; SNR – Signal-to-noise ratio

any user interaction, saves time and produces accurate boundary tracing.

In this paper the standard form of GMM was used for segmentation. More accurate GMMs which are able to better capture the statistical properties of data (such as proposed mixture model in^[43] which employs a local bivariate circular symmetric Laplacian mixture model) can improve the results, also may result in removing the noise reduction step in our algorithm by proposing the noise in the initial mixture model of OCT data.

The 3D analysis can be a valuable step to evaluate changes in corneal volume, as future work.

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