Semi-Automated 2D Bruch’s Membrane Shape Analysis in Papilledema Using Spectral-Domain Optical Coherence Tomography

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ABSTRACT

Recent studies have shown that the Bruch’s membrane (BM) and retinal pigment epithelium (RPE), visualized on spectral-domain optical coherence tomography (SD-OCT), is deformed anteriorly towards the vitreous in patients with intracranial hypertension and papilledema. The BM/RPE shape has been quantified using a statistical-shape-model approach; however, to date, the approach has involved the tedious and time-consuming manual placement of landmarks and correspondingly, only the shape (and shape changes) of a limited number of patients has been studied. In this work, we first present a semi-automated approach for the extraction of 20 landmarks along the BM from an optic-nerve-head (ONH) centered OCT slice from each patient. In the approach, after the manual placement of the two Bruch’s membrane opening (BMO) points, the remaining 18 landmarks are automatically determined using a graph-based segmentation approach. We apply the approach to the OCT scans of 116 patients (at baseline) enrolled in the Idiopathic Intracranial Hypertension Treatment Trial and generate a statistical shape model using principal components analysis. Using the resulting shape model, the coefficient (shape measure) corresponding to the second principal component (eigenvector) for each set of landmarks indicates the degree of the BM/RPE is oriented away from the vitreous. Using a subset of 20 patients, we compare the shape measure computed using this semi-automated approach with the resulting shape measure when (1) all landmarks are specified manually (Experiment I); and (2) a different expert specifies the two BMO points (Experiment II). In each case, a correlation coefficient \(\geq 0.99\) is obtained.

Keywords: shape analysis, optical coherence tomography, Bruch’s membrane, papilledema

1. INTRODUCTION

Papilledema is a type of optic-nerve-head swelling due to elevated intracranial pressure and can be difficult to differentiate from other causes of optic-nerve-head swelling. Having non-invasive tests for raised intracranial pressure (thus potentially avoiding invasive and uncomfortable tests such as lumbar punctures) would be of tremendous benefit. Recent work has demonstrated that an inverted-U shape (towards the vitreous) of Bruch’s membrane (BM) and retinal pigment epithelium (RPE) as visible from spectral-domain optical coherence tomography (SD-OCT) scans of the optic disc may suggest raised intracranial pressure.\(^{1-3}\) For example, Sibony et al.\(^2\) used a statistical-shape-analysis approach to demonstrate the presence of an overall inverted-U shape of the BM/RPE in papilledema patients, whereas a V-shape was present in normals and patients with anterior ischemic optic neuropathy (another cause of optic-nerve-head swelling). However, manually marking 20 landmarks to compute shape parameters as in\(^2\) is too tedious and time-consuming to enable the analysis of large datasets.

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Figure 1. Increased visibility of BMO using high-definition 5-line raster protocol when compared to volumetric SD-OCT protocol. (a) Central slice from volumetric SD-OCT image of non-swollen optic nerve head (ONH). (b) The same non-swollen ONH from central slice of high-definition 5-line raster image. (c) Central slice from volumetric SD-OCT image of a swollen ONH. (d) The same swollen ONH from central slice of high-definition 5-line raster image. Yellow arrows represent the BMO region. The physical dimensions of the B-scans in the volumetric slice and high-definition slice are $6 \times 2$ and $9 \times 2 \text{mm}^2$, respectively.

The purpose of this work is to present a semi-automated approach for the placement of 20 BM/RPE landmarks (only two landmarks are placed manually; the remaining 18 are placed automatically using a graph-based approach), to compute a statistical shape model using the baseline OCT data from 116 patients in the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), to compare the shape parameters computed using the proposed semi-automated approach with those from a fully manual approach, and to compute the sensitivity of the shape parameters obtained with the semi-automated approach with respect to placement of the two manual landmarks.

2. METHODS

2.1 Manual Placement of Bruch’s Membrane Opening Points

In the IIHTT OCT substudy,4,5 two SD-OCT imaging protocols (Carl Zeiss Meditec, Dublin, CA) were used that captured images of the BM/RPE complex passing through the optic nerve head (ONH): the high-definition 5-line raster SD-OCT protocol and the volumetric SD-OCT protocol. In this work, central B-scans from images acquired using the high-definition 5-line raster protocol were used rather than images from the volumetric SD-OCT protocol because of the increased visibility of the BMO in cases of optic-nerve-head swelling. Figure 1 (a, b) and (c, d) show the differences in BMO visibility from a non-swollen and swollen optic-nerve-head, respectively. While the BMO is visible using both protocols in the non-swollen case [Figure 1(a), Figure 1(b)]; in the swollen case [Figure 1(c), Figure 1(d)] the BMO is more readily visible with the 5-line raster protocol [Figure 1(d)] than with the volumetric protocol [Figure 1(c)].

The first step of our approach was to resize the central high-definition OCT images to reflect the physical aspect ratio and to manually mark the two BMO points on each image. In particular, the central B-scan (from images acquired using the 5-line raster Cirrus high-definition SD-OCT protocol at baseline) from each subject in the IIHTT OCT substudy4,5 was first resized to reflect the 9:2 width-to-height ratio of the physical dimensions ($1024 \times 1024$ to $4608 \times 1024$ in this work). Then, the GNU Image Manipulation Program (GIMP, version 2.8.10) was used to manually place two Bruch’s membrane opening (BMO) landmarks in each input B-scan [i.e. the red dots in Figure 2(a) and 2(b)]. The BMO placement was the only manual step in this work.

2.2 Automated Retinal Layer Segmentation & Semi-Automated Landmark Placement

After obtaining the BMO landmarks, automated retinal layer segmentation was performed using our previously reported graph-based approach specifically designed to be robust in cases of optic-nerve-head swelling6,7 to obtain
the internal limiting membrane (ILM) and the BM/RPE boundaries. Figure 2(c) provides example segmentation results, where the red boundary is the ILM, the green boundary is the BM/RPE, and the two red dots are the manually placed BMO points from the previous step.

Then, on the each half of the image (nasal and temporal sides), starting with the manually placed BMO point (i.e., one of the red dots), 9 extra equal-distant points [the yellow dots in Figure 2(d) on each side] were automatically placed along the segmented BM/RPE (the green boundary) to provide a total of 10 landmarks covering 2.5 mm in physical length. Thus, when including both sides, there were a total of 20 landmarks (two manually placed BMO points and 18 automatically placed landmarks), each with an x- and y-coordinate, to describe each BM/RPE shape:

\[ s_i = (x_{i,1}, y_{i,1}, \ldots, x_{i,10}, y_{i,10}, x_{i,11}, y_{i,11}, \ldots, x_{i,20}, y_{i,20})^T, \]  

where \( 1 \leq i \leq N \), and \( N \) represents the total number of the available input B-scans (\( N = 116 \)).

### 2.3 Statistical BM/RPE Shape Models

Procrustes analysis and principal component analysis (PCA) are the two main steps for generating statistical shape models.\(^8\) In general, Procrustes analysis includes scaling, rotation and translation to align shapes. However, in this work, in order to preserve meaningful distances between landmarks (as our landmarks are defined based on physical distances along the BM/RPE from the BMO), we only aligned shapes using rotation and translation (i.e., excluding the scaling step). Figure 2(e) illustrates the realigned BM/RPE shapes after Procrustes analysis without scaling, where the red dots indicate manually placed BM points and the blue dots indicate semi-automated landmarks. [Different colors of dots were used in Figure 2(e) for better visualization.]

After all the available input BM/RPE shapes were aligned, PCA was used to compute the statistical shape model. To achieve that, first, the mean BM/RPE shape was computed using

\[ \overline{s} = \frac{1}{N} \sum_{i=1}^{N} s_i, \]
where $s_i$ indicates each individual shape, and the covariance matrix was computed using

$$cov(s) = \frac{1}{N} \sum_{i=1}^{N} (s_i - \bar{s})(s_i - \bar{s})^T.$$  \hspace{1cm} (3)

Next, the eigenvectors ($\mathbf{e}_i$) of $cov(s)$ were calculated by solving

$$cov(s)\mathbf{e}_i = \lambda_i \mathbf{e}_i, \text{ where } \mathbf{e}_i^T\mathbf{e}_i = 1.$$  \hspace{1cm} (4)

The principal eigenvectors ($\mathbf{e}_{L1}, \mathbf{e}_{L2}, \mathbf{e}_{L3}$) with the corresponding largest three eigenvalues ($\lambda_{L1}, \lambda_{L2}, \lambda_{L3}$), enables the description of each reconstructed individual shape as

$$\hat{s}_i = \bar{s} + \sum_{j=1}^{3} c_{sLj} \sqrt{\lambda_{Lj}} \mathbf{e}_{Lj},$$  \hspace{1cm} (5)

where $c_{sLj}$ is the shape coefficient corresponding to principal component $\mathbf{e}_{Lj}$.

3. EXPERIMENTAL METHODS AND RESULTS

In the IIHTT OCT substudy, of the 126 patients originally included, 116 had right-eye 5-line-raster scans available in the baseline dataset. (In the IIHTT, the baseline data was prospectively collected from subjects at study entry prior to initiating treatment.) Figure 3 illustrates the statistical shape models resulting from right-eye baseline central B-scans from these 116 patients. In particular, the shape resulting from varying the coefficient of the first three principal components is shown. We can observe that the first principal component ($\mathbf{e}_{L1}$) roughly models the size of the BMO (with more positive values of the coefficient reflecting a larger BMO), the second principal component ($\mathbf{e}_{L2}$) models the BM/RPE anterior/posterior directionality (with more negative values of the coefficient reflecting an inverted U-shaped BM/RPE, meaning that the BM/RPE tends to point towards the vitreous, and more positive values reflecting a V-shaped BM/RPE, meaning that the BM/RPE tends to point away from the vitreous), and the third principal component models the degree of tilt. Of particular clinical interest for a given set of BM/RPE landmarks is the coefficient ("shape measure") associated with the

\begin{table}[h]
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\begin{tabular}{|c|c|c|c|}
\hline
& $s_{L1} = \hat{s} + c_{sL1} \cdot \sqrt{\lambda_{L1}} \mathbf{e}_{L1}$ & $s_{L2} = \hat{s} + c_{sL2} \cdot \sqrt{\lambda_{L2}} \mathbf{e}_{L2}$ & $s_{L3} = \hat{s} + c_{sL3} \cdot \sqrt{\lambda_{L3}} \mathbf{e}_{L3}$ \\
\hline
$c_{sL1}$ & -3 & & \\
$c_{sL2}$ & -2 & & \\
$c_{sL3}$ & -1 & & \\
$c_{sL4}$ & 0 & & \\
$c_{sL5}$ & 1 & & \\
$c_{sL6}$ & 2 & & \\
$c_{sL7}$ & 3 & & \\
\hline
\end{tabular}
\end{table}
second principal coefficient. Figure 4 and 5 demonstrate how the individual shape was reconstructed by the three principal components using Eq. (5) and how the BM/RPE anterior/posterior measure \( c_{S_{L2}} \) changes with different degrees of optic-nerve-head swelling due to raised intracranial hypertension. Figure 6 provides more examples of the BM/RPE shape with different values of \( c_{S_{L2}} \).

Shape measure \( c_{S_{L2}} \) was evaluated further in two experiments as follows. First, a subset of 20 central high-definition B-scans were selected from the original 116 eyes to cover the range of shape variations of the data. In Experiment I, all 20 landmarks were manually placed on each of these slices using the methodology described in and then the resulting \( c_{S_{L2}} \) values using this fully manual approach were compared with those resulting from the proposed semi-automated approach using the same manually placed BMO points. In other words, the purpose of Experiment I was to compare the differences of the BM/RPE shape measure between all the 20 landmarks.
Figure 6. Examples of the BM/RPE shape changing with various $c_{SL2}$; the order is ranked by the values of $c_{SL2}$ from top-left to bottom-right.

being fully manually traced (a very time consuming process) and using two manually placed BMO points along with the 18 automatically placed landmarks (only requiring one to two minutes per B-scan).

In Experiment II, the sensitivity of the semi-automated approach in computing $c_{SL2}$ to the placement of the BMO landmarks was evaluated by having a second expert mark the two BMO points on the same 20 high-definition B-scans and comparing the resulting shape measures from the semi-automated method using expert 1’s BMO points to those using expert 2’s BMO points.

Table 1 shows the mean signed/unsigned differences of $c_{SL2}$ in Experiment I and II. In Experiment I, the mean signed difference ($\pm$ standard deviation) in the shape measure between the approach using all manual points and the proposed semi-automated approach was -0.182 ($\pm$ 0.179), and the mean unsigned difference was 0.208 ($\pm$ 0.147). The negative signed difference in Experiment I implies that the fully manual method tends to provide slightly smaller values of $s_{1,2}$ than the semi-automated method. In Experiment II, the mean signed difference ($\pm$ standard deviation) between the proposed approach using BMO points provided by expert 1 with those provided by expert 2 was 0.039 ($\pm$ 0.172), and the mean unsigned difference was 0.128 ($\pm$ 0.118). The scatter plots and correlation coefficients in Experiment I and II are shown in Figure 7 and also Table 1. The
Table 1. BM/RPE Shape Measure ($c_{sL^2}$) Results of Experiment I and II

<table>
<thead>
<tr>
<th></th>
<th>Mean Signed Difference (± Standard Deviation)</th>
<th>Mean Unsigned Difference (± Standard Deviation)</th>
<th>Correlation Coefficient ($p$-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment I*</td>
<td>-0.182 (± 0.179)</td>
<td>0.208 (± 0.147)</td>
<td>0.991 ($p &lt; 0.001$)</td>
</tr>
<tr>
<td>Experiment II**</td>
<td>0.039 (± 0.172)</td>
<td>0.128 (± 0.118)</td>
<td>0.990 ($p &lt; 0.001$)</td>
</tr>
</tbody>
</table>

* Comparison between fully manual and proposed methods (using the same manually placed BMO points).
** Comparison between two experts’ BMO landmark points using the same semi-automated method.

Figure 7. Scatter plots with linear regression equations and correlation coefficients ($r$-values) of Experiment I and II.

correlation coefficients in both experiments were ≥ 0.99.

4. DISCUSSION AND CONCLUSIONS

The proposed semi-automated method dramatically accelerates the current fully manual method by only requiring two manual BMO landmarks rather than 20 manual landmarks. This makes it feasible for the first time to analyze the shape of the BM/RPE in large datasets (such as the longitudinal data for patients enrolled in the IIHTT).

The low mean signed/unsigned differences as well as the high correlations ($r \geq 0.99$) in both experiments demonstrate that the proposed method is robust and nonsensitive. In addition, applying the shape models in a large dataset ($N = 116$) gives strong evidence that the BM/RPE shape measure ($c_{sL^2}$) indeed reflects different degrees of papilledema. When the value of the BM/RPE shape measure ($c_{sL^2}$) was negative, the inverted-U shape of the BM/RPE shape (toward the vitreous) indicated optic-nerve-head swelling due to the raised intracranial pressure. This observation is consistent with the previous results from Sibony’s et al.2, 3

Overall, this work has presented a practical method for the semi-automated analysis of shape of the BM/RPE in SD-OCT image slices passing through the optic nerve head. Using the shape model, only two manual landmarks (along with the semi-automated approach for obtaining the remaining 18 landmarks) are needed to obtain the BM/RPE anterior/posterior shape measure. In future work, combining and comparing the BM/RPE shape measure with other quantitative measurements (such as the Friisen scale grade, cerebrospinal fluid pressure, intraocular pressure, total retinal volume, retinal nerve fiber layer thickness, total retinal thickness, and treatment outcome) and performing a longitudinal analysis is expected to enable a more comprehensive analysis of BM/RPE shape in cases of optic-nerve-head swelling. Use of such shape models may also prove to be useful in other diseases...
affecting the optic nerve head, such as glaucoma. In addition, the role of 3D shape models rather than 2D shape models may also prove to hold additional benefits.

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