Automated Segmentation of Neural Canal Opening and Optic Cup in 3-D Spectral Optical Coherence Tomography Volumes of the Optic Nerve Head

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ABSTRACT

Purpose:

To develop an automated approach for segmenting the neural canal opening (NCO) and cup at the level of retinal pigment epithelium (RPE)/Bruch’s membrane (BM) complex in spectral-domain optical coherence tomography (SD-OCT) volumes. To investigate the correspondence and discrepancy of the NCO-based metrics and clinical disc margin on fundus photographs in glaucoma subjects.

Methods:

SD-OCT scans (Cirrus™ HD-OCT) and corresponding stereo fundus photographs (Nidek 3Dx) of the optic nerve head (ONH) are obtained from 68 eyes of 34 patients with glaucoma or glaucoma suspicion. Manual planimetry is performed by three glaucoma experts to delineate a reference standard (RS) for cup and disc margins from 3Dx images. An automated graph-theoretic approach is used to identify the NCO and cup. The NCO-based metrics are compared with the RS.

Results:

Compared with the RS disc margin, we find mean unsigned and signed border differences of 2.81 ± 1.48 pixels (0.084 ± 0.044 mm) and -0.99 ± 2.02 pixels (-0.030 ± 0.061 mm) respectively for NCO segmentation. The correlations of the linear cup-to-disc (NCO) area ratio, disc (NCO) area, rim area, and cup area of the algorithm with the RS are 0.85, 0.77, 0.69, and 0.83, respectively.

Conclusions:

In most eyes, the NCO-based 2-D metrics, as estimated by the novel automated graph-theoretic approach to segment the NCO and cup at the level of RPE/BM complex in SD-OCT volumes, correlate well with RS. However, a small discrepancy exists in NCO-based anatomic structures and the clinical disc margin of the RS in some eyes.
1. INTRODUCTION

Glaucoma is a chronic neurodegenerative disease of the optic nerve that, if left untreated, may result in increasing visual field (VF) loss and blindness. It is characterized by the degeneration of the retinal ganglion cell axons [1-2]. It has been suggested that the initial axonal insult occurs in the optic nerve head (ONH), which leads to optic disc cupping and visual field loss through retinal ganglion cell apoptosis [1]. The risk of VF loss due to glaucoma can be minimized by early diagnosis and careful monitoring of disease progression. However, the latter requires a reproducible measurement of the disease state. Currently available methods include VF, planimetry based on stereo disc photographs, optic nerve head tomography (HRT), and peripapillary nerve fiber layer thickness analysis (using polarimetry or OCT) [3-7]. Many of these modalities involve a subjective component either by the patient or examiner, which can decrease reproducibility.

Spectral domain optical coherence tomography, or SD-OCT, is a relatively new modality which provides a cross-sectional, micro-scale depiction of the optical reflectance properties of the biological tissues [8]. The high-resolution SD-OCT scans of the ONH provide a potential to identify glaucomatous changes using 3-D information. However, it is currently unclear which ONH parameters derived from SD-OCT can be best used to quantify glaucomatous changes.

We have recently described a voxel classification approach for automatically segmenting the clinical familiar glaucomatous parameters - the ONH rim and cup - directly from the SD-OCT volumes [9] by extending our prior approach for automated planimetry on stereo fundus photographs [10-11]. However, this approach has the ultimate limitation that the algorithm essentially mimics the subjective assessment of 2-D parameters by human experts. It is not based on objective, anatomical landmarks within the 3-D volumes, and we and others have found that the optic disc margin does not overlap with a single constant anatomic structure in volumetric OCT, consistent with the recent comparisons of clinical and SD-OCT optic disc margin anatomy by Strouthidis et al. [12-13]. They found that the varying combinations of the termination of Bruch’s membrane, border tissue, or the anterior scleral canal opening may manifest as the 2-D disc margin seen on photographs, depending upon the border tissue architecture and anatomy.
With the wealth of volumetric information available with SD-OCT, it is likely that better parameters can be obtained for measuring glaucomatous change that move beyond what is possible using stereo fundus photography alone. A central requirement for the detection of the ONH structural change is a longitudinally stable zero reference plane. As described by Burgoyne et al. [12-13], the ‘neural canal opening’ or NCO - the termination of Bruch’s membrane/retinal pigment epithelium (BM/RPE) complex can serve as a basis for a stable reference plane from which various optic nerve morphometric parameters can be derived, based on the assumption that the NCO is not likely to change substantially with glaucomatous progression [12-13].

Thus, the core hypothesis motivating our present study is that the segmentation of a stable three-dimensional structure – the NCO – from SD-OCT will enable more reproducible and objective glaucomatous parameters than that which is currently possible from manual planimetry alone (even using a consensus of glaucoma experts). This is fundamentally different from our prior segmentation method [9] which, by construction (using training data), attempts to obtain parameters as close as possible to that which would be obtained using manual planimetry of stereo fundus photographs. While the present study does not directly test this hypothesis, it sets the necessary underlying framework for being able to automatically detect the NCO and better understand its relationship with the widely accepted optic disc margin from manual planimetry.

More specifically, the purpose of the present study is to describe an algorithm for automatic delineation of the NCO from SD-OCT volumes, as well as optic disc metrics derived from the NCO (NCO and cup boundaries), and compare these with the reference standard (disc and cup margins) obtained from human expert planimetry of stereo photographs of the same eye.

2. MATERIALS AND METHODS

2.1. Patients

34 consecutive patients with the diagnosis of glaucoma suspect, open-angle glaucoma, angle closure glaucoma, or combined mechanism glaucoma from the Glaucoma Clinic at the University of Iowa were included in this study [9]. Non-glaucomatous optic neuropathy was excluded. The patient cohort has been described in detail in a previous report [9]. The diagnoses were made by the
treating glaucoma specialist. The study was approved by the Institutional Review Board of the University of Iowa, and adhered to the tenets of the Declaration of Helsinki, and all subjects gave written informed consent.

2.2. Image acquisition

68 ONH-centered SD-OCT scans of the 34 consecutive study subjects were acquired using a Cirrus™ HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA) device. The OCT scans were exported in an uncompressed raw format (40Mb per scan), preserving the voxel intensities. Each SD-OCT scan consisted of $200 \times 200 \times 1024$ voxels and the physical dimensions were $6 \times 6 \times 2 \text{ mm}^3$. Thus the voxel resolution was $30 \times 30 \times 2 \mu\text{m}$ [9]. The voxel depth was 8 bits in grayscale. 68 corresponding stereo color fundus photographs of the optic disc were also acquired on the same day using a Nidek 3Dx stereo retinal camera with a fixed stereo base with a digital camera back (Nidek, Newark, NJ). The size of the stereo color fundus disc photographs was $4096 \times 4096$ pixels and the pixel depth was $3 \times 8$-bit in red, green, and blue channels.

2.3. OCT volume flattening

Because of the shape of the globe, the scanner position relative to the patients’ pupil, and the eye movement, the original raw OCT image is deformed elastically. Thus four intraretinal surfaces were segmented in 3-D [14-15] and the raw OCT volume was flattened based on the second segmented surface as described previously [16]. From the top to bottom (Figure 1.b and 1.e), surface 1 corresponds to the internal limiting membrane (ILM). Surface 2 is located between the inner and outer segments of the photoreceptors. Surface 3 is the inner boundary of the RPE/BM complex and surface 4 is the outer boundary of the RPE/BM complex. Surface 2 was chosen as the flattening surface (in this stage) for consistency with our prior work; however, surface 3 would have worked equally well in this flattening stage as one of its major purposes was only to remove the motion artifacts across B-scans to make the NCO and cup segmentation easier. As shown in Figure 1.c and 1.f, the geometrical distortion across B-scans was improved after the flattening, though not perfect. The flattening also provides a possibility to create a projection image from a thin layer at the RPE/BM complex for correspondingly comparing the NCO-based parameters to those of fundus photographs.
Due to the large variations in the surface of the ONH, intraretinal layer segmentation differences can occur and cause a non-optimal flattening problem, i.e., the NCO points do not lie on a plane after flattening. Therefore we first established an estimated NCO region, a circular region centered on the geometric center of the OCT volume with a radius certain to be larger than the estimated NCO boundary. A projection image (Hu Z. et al. IOVS 2009; 50: ARVO E-3334) was formed by taking the thin layer between surface 2 (orange) and surface 4 (yellow) (Figure 2.a), by extrapolating the average position outside the estimated NCO region for surface 2, 3, and 4 to the inside region radially. The outer boundary in the projection image (Figure 2.b) corresponds to the NCO and the inner boundary corresponds to the cup at the level of the RPE/BM plane.

**2.4. NCO and optic cup segmentation at the RPE/BM plane**

An example illustration of the SD-OCT volume flattening. (a) Central slice from the original raw SD-OCT. (b) Four surface segmentation of the original raw volume. (c) 3-D rendering of the surface segmentation by mapping the projection image texture onto the top surface. (d) Central slice from the flattened SD-OCT. (e) Four surface segmentation of the flattened volume. (f) 3-D rendering of the surface segmentation of the flattened volume by mapping the projection image texture onto the top surface.

**Figure 1.** An example illustration of the SD-OCT volume flattening. (a) Central slice from the original raw SD-OCT. (b) Four surface segmentation of the original raw volume. (c) 3-D rendering of the surface segmentation by mapping the projection image texture onto the top surface. (d) Central slice from the flattened SD-OCT. (e) Four surface segmentation of the flattened volume. (f) 3-D rendering of the surface segmentation of the flattened volume by mapping the projection image texture onto the top surface.
We then transformed the projection image to polar coordinates by unwrapping from the center of the projection image. A signed edge-based term, favoring a dark-to-bright transition in the vertical direction (Figure 2.c) from the transformed projection image, was used as the cost function, and we modeled the resulting cost image as a weighted, directed graph similar to the one described by K. Li et al. [17]. We used graph search to simultaneously segment the (optimal) NCO and cup boundaries [18]. In shallow cups, or if the cup is absent, the deepest point of the top surface did not extend down to the level of the RPE/BM plane, i.e., the extrapolated surface 3 (green) (Figure 2.a), the algorithm automatically switched from using two-boundary graph search to one-boundary graph search and we then determined the NCO using a single boundary graph search method. The NCO and cup boundaries were finally smoothed using a B-spline.

Figure 2. An example illustration of the NCO and optic cup segmentation at RPE/BM plane. (a) Planar surfaces near RPE/BM complex. (b) Projection image. (c) Segmented two boundaries overlapping with the unwrapped cost image. (d)-(e) Segmented NCO and cup overlapping with (d) projection image and (e) a cross-sectional slice of OCT volume. (f) 3-D rendering of the NCO and cup segmentation overlapping with the mapping of the projection image texture onto the top surface.
2.5. Comparison of the algorithm to expert planimetry stereo color photographs

Computer-aided planimetry was performed by three fellowship-trained glaucoma experts on stereo color photographs of the optic disc, as described previously [9]. A reference standard (RS) was obtained from the three expert segmentations on the color fundus image in a “majority-win” manner, i.e., each pixel was assigned a class that received the majority of votes. For example, if two votes were for a pixel to be rim and one vote for a pixel to be cup, the pixel was assigned to rim [9][15]. The linear cup-to-disc area ratio, or LCDR, was defined as the square root of the cup area over disc area.

In order to determine the transformation necessary to convert the expert segmentations on the stereo color fundus images to the SD-OCT space, manual registration was performed as described previously [9]. More specifically, a projection image was created by averaging the voxels between the second and fourth intraretinal surfaces (i.e. the surfaces indicated by the orange and yellow lines in Figure 1.e). Note that this projection image was different from the projection images created for finding the NCO. The goal of creating this projection image was to obtain the RS for OCT scans and referred to as “RS-aimed projection image”. The manual registration was performed by matching blood vessels between the stereo retinal fundus images and the corresponding RS-aimed projection images. The RS and the three expert segmentations from the stereo fundus images were also converted to the SD-OCT space by applying the same transformation [9][15].

The algorithm NCO boundary was compared to the RS disc margin, using mean unsigned and signed border differences, i.e., the closest Euclidean distances between the segmented NCO points from our algorithm and those from the RS and vice versa. The signed difference was measured in terms of the disc center of the RS. If the distance of the NCO points to the disc center of the RS was greater than that of the optic disc margin of the RS to its center, the signed difference was positive, and vice versa.

The algorithm was also compared to the RS in terms of the correlations of linear cup-to-NCO/cup-to-disc area ratio, cup area, rim area and also NCO/disc area. The inter-observer correlations of the same parameters were investigated.
3. RESULTS

Table 1 shows the mean border positioning differences of the NCO with the optic disc from the reference standard for the 68 eyes of the 34 patients. The mean unsigned and signed difference of the algorithm with the RS for 68 eyes are 2.81 ± 1.48 pixels (0.084 ± 0.044 mm) and -0.99 ± 2.02 pixels (-0.030 ± 0.061 mm) respectively.

Table 2 compares the algorithm segmentation results of the 68 eyes with the RS in terms of the correlations with the confidence intervals (CIs) for the linear cup-to-NCO/cup-to-disc area ratio, NCO/disc area, rim area, and cup area. The correlations of the linear cup-to-NCO/cup-to-disc area ratio, NCO/disc area, rim area, and cup area of the algorithm with the RS for the 68 eyes are 0.85, 0.77, 0.69, and 0.83 respectively.

The scatter-plots of the NCO/disc area, rim area, and cup area are illustrated in Figure 3. The scatter-plots of the LCDR and the inter-observer variability are illustrated in Figure 4, with the perfect correlation line indicated as a reference. From Figure 3, the algorithm NCO area is similar to the disc area of the RS, the rim tends to run slightly greater than that of the RS, and the cup tends to run slightly smaller than the RS cup. Correspondingly the algorithm LCDR is slightly smaller than that of the RS (Figure 4).

While the 68-eye analyses were performed to obtain additional statistical power, we have also computed the border positioning differences and the correlations of the measured metrics by randomly choosing one eye from each of the 34 patients. The mean border positioning differences are 2.68 ± 1.14 pixels (0.080 ± 0.034 mm) and -0.74 ± 1.76 pixels (-0.022 ± 0.053 mm) respectively, which are similar to the 68-eye results. The correlations of the measured metrics for the 34 eyes are also similar to those of the 68 eyes.

Figure 5 shows the algorithm segmentation from 7 right eyes of 7 randomly chosen patients. The right eye was chosen simply for ease of display (the left eye showed similar results). Each row corresponds to an eye.

From the quantitative results and qualitative visual inspection, there is a reasonable match in most eyes between the algorithm’s objectively determined NCO and cup and the glaucoma expert’s subjectively determined disc margin and cup of the RS.
Figure 6, 7, and 8 visually demonstrate three example segmentation comparisons of our present algorithm, previous algorithm [9], and the RS overlapping with the transformed fundus image and the SD-OCT volume. More specifically, Figure 6 is an example demonstrating a good match between the three approaches. Figure 7 and 8 are two examples demonstrating a discrepancy between the present algorithm and the RS, as well as the previous algorithm. The previous algorithm and the RS segment the clinically appreciable defined optic disc margin. The present algorithm instead segments the “true” SD-OCT-based anatomic structures – NCO and optic cup at the RPE/BM complex. From these examples, one can clearly see the sources of the small discrepancies of the NCO and the clinical optic disc, although in most scans, the NCO demonstrates a good match with the clinically appreciable defined optic disc margin obtained by planimetry.

Table 1. The NCO border positioning differences from the 68 eyes

<table>
<thead>
<tr>
<th></th>
<th>Algorithm vs. RS</th>
<th>Expert 1 vs. 2</th>
<th>Expert 1 vs. 3</th>
<th>Expert 2 vs. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean unsigned difference (pixel)</td>
<td>2.81 ± 1.48</td>
<td>3.82 ± 1.48</td>
<td>3.39 ± 1.65</td>
<td>2.06 ± 0.95</td>
</tr>
<tr>
<td>Mean unsigned difference (mm)</td>
<td>0.084 ± 0.044</td>
<td>0.115 ± 0.045</td>
<td>0.102 ± 0.049</td>
<td>0.062 ± 0.028</td>
</tr>
<tr>
<td>Mean signed difference (pixel)</td>
<td>-0.99 ± 2.02</td>
<td>-2.52 ± 1.40</td>
<td>-1.18 ± 1.14</td>
<td>1.36 ± 1.42</td>
</tr>
<tr>
<td>Mean signed difference (mm)</td>
<td>-0.030 ± 0.061</td>
<td>-0.075 ± 0.042</td>
<td>-0.035 ± 0.034</td>
<td>0.041 ± 0.043</td>
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</tbody>
</table>

* Col 1: the mean unsigned and signed border positioning differences between the automated NCO segmentation and the optic disc segmentation of the RS. Col 2-4: the inter-observer variability.
Table 2. The correlations (CIs) of the algorithm with the expert segmentation from the 68 scans

<table>
<thead>
<tr>
<th></th>
<th>Algorithm with RS</th>
<th>Expert 1 with 2</th>
<th>Expert 1 with 3</th>
<th>Expert 2 with 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCDR correlation (95% CI)</td>
<td>0.85 (0.76–0.90)</td>
<td>0.88 (0.82–0.93)</td>
<td>0.92 (0.87–0.95)</td>
<td>0.88 (0.81–0.93)</td>
</tr>
<tr>
<td>Disc area correlation (95% CI)</td>
<td>0.77 (0.64–0.85)</td>
<td>0.86 (0.79–0.92)</td>
<td>0.91 (0.87–0.95)</td>
<td>0.88 (0.81–0.92)</td>
</tr>
<tr>
<td>Rim area correlation (95% CI)</td>
<td>0.69 (0.55–0.80)</td>
<td>0.78 (0.66–0.86)</td>
<td>0.84 (0.75–0.90)</td>
<td>0.80 (0.69–0.87)</td>
</tr>
<tr>
<td>Cup area correlation (95% CI)</td>
<td>0.83 (0.73–0.89)</td>
<td>0.93 (0.88–0.95)</td>
<td>0.95 (0.91–0.97)</td>
<td>0.90 (0.85–0.94)</td>
</tr>
</tbody>
</table>

* Col 1: the correlations of NCO, rim, and cup at RPE/BM plane from the algorithm with disc, rim, and cup from RS respectively. Col 2-4: the correlations between different expert segmentations.

Figure 3. The scatter-plots of the NCO, rim, and cup area at RPE/BM plane from the algorithm to disc, rim, and cup area from RS for the 68 eyes. The diagonal line indicates a perfect correlation of 1.0.
Figure 4. The scatter-plots of linear cup-to-NCO of algorithm to LCDR of RS for 68 eyes. The diagonal line indicates a perfect correlation of 1.0.
Figure 5. Random selection of example NCO segmentations. From left to right: Col. A: Projection image. Col. B: Corresponding fundus image. Col. C-D: NCO and cup at RPE/BM plane from present algorithm and disc and cup from RS transposed to projection image respectively. Col. E-F: NCO and cup at RPE/BM plane from present algorithm and disc and cup from RS transposed to fundus image respectively.
Figure 6. Example comparison of present algorithm, expert, and previous algorithm segmentations with a good match. From top to bottom: raw SD-OCT and corresponding fundus image (top), present algorithm (row 2), RS (row 3), and previous algorithm (bottom) segmentations overlapping with raw SD-OCT and corresponding fundus image. From left to right: SD-OCT central B-scan (left) and fundus image (right).

The yellow arrows indicate the position of the NCO from the algorithm (with the dashed yellow line indicating the projected NCO position). The blue arrows indicate the clinical disc from the RS. The green and red colors indicate each method’s projected rim and cup regions, respectively.
Figure 7. Example comparison of present algorithm, expert, and previous algorithm segmentations with discrepancy. From top to bottom: raw SD-OCT and corresponding fundus image (top), present algorithm (row 2), RS (row 3), and previous algorithm (bottom) segmentations overlapping with raw SD-OCT and corresponding fundus image. From left to right: SD-OCT central B-scan (left) and fundus image (right). The yellow arrows indicate the position of the NCO from the algorithm (with the dashed yellow line indicating the projected NCO position). The blue arrows indicate the clinical disc from the RS. The green and red colors indicate each method’s projected rim and cup regions, respectively.
Figure 8. Example comparison of present algorithm, expert, and previous algorithm segmentations with discrepancy. From top to bottom: raw SD-OCT and corresponding fundus image (top), present algorithm (row 2), RS (row 3), and previous algorithm (bottom) segmentations overlapping with raw SD-OCT and corresponding fundus image. From left to right: SD-OCT central B-scan (left) and fundus image (right). The yellow arrows indicate the position of the NCO from the algorithm (with the dashed yellow line indicating the projected NCO position). The blue arrows indicate the clinical disc from the RS. The green and red colors indicate each method’s projected rim and cup regions, respectively.
4. DISCUSSION AND CONCLUSIONS

In this study, 1) we present an algorithm to automatically segment the NCO and optic cup at the RPE/BM plane in SD-OCT volumes. 2) Using human expert planimetry on the stereo photographs as reference standard, we show that the NCO border positioning differences (Table 1) between the algorithm and RS for the 68 eyes are as good as inter-observer differences. The linear cup-to-NCO area ratio (Table 2) for the 68 eyes correlates reasonably well with the LCDR of the RS ($r = 0.85$). Other objectively derived 2-D SD-OCT metrics (Table 2) correlate reasonably well with those of the RS ($r = 0.69$-$0.83$). In addition, we qualitatively (Figure 5 and 6) demonstrate the good match of the present algorithm and RS. We conclude that in most eyes the NCO in SD-OCT is consistent with the clinically appreciable defined optic disc margin obtained by planimetry.

However, even though the NCO boundary and clinical disc margin correspond reasonably well in most eyes, it is interesting to note the example discrepancies as well (Figure 7 and 8). These example discrepancies are consistent with the findings reported by Strouthidis et al. [12-13]. In particular, we also found that the clinical disc margin may sometimes correspond to the varying combinations of different structures other than the NCO, such as the border tissue of Elschnig. For instance, in the example SD-OCT B-scan shown in Figure 7, the RS defines the innermost termination of the border tissue as the temporal optic disc margin (blue arrow) and in Figure 8, the RS defines the border tissue as the temporal optic disc margin (blue arrow), which are obviously different from the NCO (yellow arrow) of the algorithm.

Because of such underlying differences, compared with the parameter correlations by planimetry between different experts, the relatively smaller correlations of the NCO-based metrics with those of the RS (Table 2) are not surprising. However, the fact that the algorithm demonstrated smaller unsigned border positioning differences than that between the experts (Table 1), yet had lower correlations (Table 2) is perhaps surprising. This may in part be due to the fact that correlation (measuring the direction and noisiness of linear relationships) does not take into account any bias (e.g., a consistent over- or under-estimation of a parameter), while the unsigned border positioning errors are influenced by any bias between the measurements. Because the experts tended to have a larger bias than that between the algorithm and RS (as indicated by the signed errors in Table 1),
this may have contributed to the larger unsigned errors as well. In addition, it is important to note that the definition of the algorithm’s ‘cup boundary’ is different from the traditional clinical definition of cup margin. The algorithm simply defined cup as the crossing point of the reference plane with the retinal surface, while the human experts tend to delineate the cup margin at the inflection point of the surface slope of the cup as seen in stereo photographs [19]. This may also explain our observation the cup area at the level of the RPE/BM plane are often smaller than the clinically visible cup area on stereo fundus photographs as seen by human experts (Figure 3).

There are several advantages of the current automated segmentation approach over manual planimetry. 1) Although planimetry is the current gold standard for quantifying glaucoma progression, it introduces a great inter-observer variability [5]. Its subjective nature is one of the potential sources of the inter-observer variability. However, the present automatic algorithm based on SD-OCT is completely objective and therefore, should be more reproducible (assuming the NCO is relatively stable landmark), compared to subjective, manual segmentation by human experts, though this has yet to be rigorously demonstrated. 2) As reported [5], manual segmentation by planimetry is cumbersome and time-consuming and remains as a research tool. However, the algorithm when properly implemented should take just a few minutes to produce the analysis and would be compatible with routine clinical use. 3) As found by our automated and others’ manual [12-13, 20] studies, the clinical optic disc margin seems to be the projection of a number of different recognizable anatomic landmarks, introducing a greater variability between experts depending on the landmarks they appreciate to define ‘their’ rim, and thus a great variability for the quantification of glaucoma progression. The landmarks of the NCO will remain the same and therefore are expected to be relatively stable throughout the course of the glaucoma. An ideal reference plane based on a stable structure is critical in longitudinal imaging, glaucomatous and neuropathy analysis of the optic nerve head. The NCO-based reference plane has the potential to more sensitively detect specific glaucomatous ONH changes – such as the alterations in the anterior laminar surface and prelaminar neural tissue internal limiting membrane [12-13]. Although NCO-based metrics cannot replace the clinically appreciated optic disc margin, because the NCO is expected to be
stable, it has the potential to provide a basis for other 2-D and/or 3-D ONH parameter quantification and this would aid clinicians to more easily and better interpret the progression of glaucoma.

Thus, one of the major advantages of our present approach over our previous voxel classification approach [9] is that the present approach is able to segment natural ONH anatomic structures of NCO and optic cup at the RPE/BM complex to enable all of the advantages such structures may provide (such as the ability to compute 3-D parameters based on a reference plane). In the previous approach, the RS from fundus photographs was used as truth in the training phase for the voxel classification and this resulted in mimicking the subjective assessment of the clinical defined optic disc margin and optic cup seen on photographs. As shown in the examples of Figure 7 and 8, although the segmentation of the previous approach closely corresponds to that of the RS, it does not overlap with a single constant structure in SD-OCT volumes. However, our core hypothesis, i.e., that segmentation of NCO will allow a better estimation of glaucoma progression, than the voxel-classification based approach needs to be tested and this is only possible in a prospective study of sufficient duration.

There are several limitations in this preliminary study. 1) Close-to-isotropic SD-OCT volumes are used in this study. Potentially, a fully isotropic SD-OCT can lead to more accurate segmentation and corresponding parameter measurements. The 2-D measurements of this work are not substantially influenced because they are computed on an isotropic XY plane. However, for future volumetric measurements, if applicable, it may be desirable to compute the volumetric parameters in the isotropic OCT space. 2) The flattening of the raw SD-OCT greatly improves the motion artifacts and also provides an ability to correspondingly compare the NCO-based 2-D metrics to those 2-D metrics of the clinical optic disc margin. However it is not perfect as shown is Figure 2. For the 2-D measurements on the projection image, we correct the non-optimal flattening problem by extrapolating the average radial positions outside the estimated NCO to those of inside NCO (Section 2.4). But for the volumetric measurements, it might be necessary to transform the NCO-based reference plane back to the original raw SD-OCT space and compute the volumetric parameters in the non-flattened isotropic space. 3) As reported [21], with the glaucomatous damage of the lamina cribrosa and peripheral scleral connective tissue, the cup enlarges and the NCO
position may change relative to the peripheral sclera. Strouthidis et al. has suggested an alternative reference plane that is further away from the “center” of the NCO boundary [12]. This alternative reference plane can be obtained in a fixed distance from the segmented NCO and is less likely to deform posteriorly. Such change in reference plane position can be readily implemented in our algorithm, if desired.

In summary, we developed a novel automated graph-search-based machine algorithm to segment the NCO and optic cup at the level of RPE/BM complex in 3-D OCT volumes of the ONH. In most eyes, the algorithm parameters correlated well with the RS parameters. However, a small discrepancy exists between the NCO and the clinical disc margin in some eyes. In addition, because of the relative stability of the NCO reference plane and objective nature of the algorithm, we predict that the measurements of the NCO-based 2-D and/or 3-D glaucomatous parameters in volumetric OCT would be more reproducible than those of the RS parameters based on fundus photographs or even the OCT parameters of the previous generation time-domain OCT. Additional work will be necessary to test our core hypothesis and explore novel, objective, reproducible NCO-based parameters that correlate well with disease stage and progression.

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