Characterizing the Impact of Off-Axis Scan Acquisition on the Reproducibility of Total Retinal Thickness Measurements in SDOCT Volumes

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Purpose: Off-axis acquisition of spectral domain optical coherence tomography (SDOCT) images has been shown to increase total retinal thickness (TRT) measurements. We analyzed the reproducibility of TRT measurements obtained using either the retinal pigment epithelium (RPE) or Bruch’s membrane as reference surfaces in off-axis scans intentionally acquired through multiple pupil positions.

Methods: Five volumetric SDOCT scans of the macula were obtained from one eye of 25 normal subjects. One scan was acquired through a central pupil position, while subsequent scans were acquired through four peripheral pupil positions. The internal limiting membrane, the RPE, and Bruch’s membrane were segmented using automated approaches. These volumes were registered to each other and the TRT was evaluated in 9 Early Treatment of Diabetic Retinopathy Study (ETDRS) regions. The reproducibility of the TRT obtained using the RPE was computed using the mean difference, coefficient of variation (CV), and the intraclass correlation coefficient (ICC), and compared to those obtained using Bruch’s membrane as the reference surface. A secondary set of 1545 SDOCT scans was also analyzed in order to gauge the incidence of off-axis scans in a typical acquisition environment.

Results: The photoreceptor tips were dimmer in off-axis images, which affected the RPE segmentation. The overall mean TRT difference and CV obtained using the RPE were 7.04 ± 4.31 μm and 1.46%, respectively, whereas Bruch’s membrane was 1.16 ± 1.00 μm and 0.32%, respectively. The ICCs at the subfoveal TRT were 0.982 and 0.999, respectively. Forty-one percent of the scans in the secondary set showed large tilts (> 6%).

Conclusions: RPE segmentation is confounded by its proximity to the interdigitation zone, a structure strongly affected by the optical Stiles-Crawford effect. Bruch’s membrane, however, is unaffected leading to a more robust segmentation that is less dependent upon pupil position.

Translational Relevance: The way in which OCT images are acquired can independently affect the accuracy of automated retinal thickness measurements. Assessment of scan angle in a clinical dataset demonstrates that off-axis scans are common, which emphasizes the need for caution when relying on automated thickness parameters when this component of scan acquisition is not controlled for.
Introduction

Optical coherence tomography (OCT) is used frequently for the diagnosis and management of a variety of retinal diseases.\(^1\)-\(^4\) The introduction of spectral domain OCT systems (SDOCT) provided an improvement in image quality compared to time domain systems,\(^5\),\(^6\) and also dramatically improved speed, allowing for volumetric imaging.\(^4\),\(^7\) The development of numerous retinal layer segmentation approaches further allowed for the automated assessment of retinal parameters, such as the total retinal thickness (TRT), and for the tracking of disease progression over time.

Off-axis acquisition of SDOCT scans has been shown to affect TRT estimates (Antony et al. \textit{IOVS} 2014;55:ARVO E-Abstract 4791), where increases up to 33 \(\mu\)m have been reported.\(^8\) In these scans, measuring retinal layers axially along A-scans\(^9\) will induce an artifactual thickness increase due to the geometry of the structure. However, the observed increases in TRT are larger than what will arise from this simple geometrical effect, which we show later in this report to be only 1.91\% for an angle of 11.13\%. Thus, the angle-dependent thickness increase cannot be attributed to the geometry alone.

Segmentation accuracy in SDOCT volumes could be affected by a variety of factors, such as the presence of retinal pathology,\(^10\) density of B-scans obtained in a volume,\(^11\) and axial length of the eye.\(^12\) While these have been recognized as sources of error, none of these factors can completely explain the systematic thickness changes due to alteration in the pupil entry position.

The optical correlate of the Stiles-Crawford effect\(^13\) has been described as the change in photoreceptor light acceptance and reflectivity as a function of angle relative to its axis, or pointing direction.\(^14\),\(^15\)

Data

The Western Institutional Review Board approved the protocol, each subject gave written informed consent to participate in the study, and the Declaration of Helsinki guidelines were followed throughout the study. Patients were dilated using 2.5\% phenylephrine and 1\% tropicamide. Subjects were screened for a normal macula without retinal pathology.

Volumetric SDOCT images were acquired from 25 normal subjects on Cirrus HDOCT (Carl Zeiss Meditec, Inc., Dublin, CA). The images were obtained from a 6 \(\times\) 6 \(\times\) 2 mm region centered on the fovea containing 512 \(\times\) 128 \(\times\) 1024 voxels. For the first scan, the pupil entry location was chosen carefully so that the B-scans in the horizontal and vertical directions appeared “flat” (see Fig. 1A). Subsequently, four more scans were obtained so that the scan appeared “tilted” in the horizontal and vertical directions as depicted in Figure 1B.\(^25\)

Retinal Thickness

The TRT was defined in two ways, using the ILM as the upper reference surface and either the RPE or Bruch’s membrane as the lower reference surface. Total retinal thickness based on the distance between the ILM and RPE was segmented using a Carl Zeiss (Carl Zeiss Meditec, Inc.) prototype version of the Cirrus algorithm. Total retinal thickness based on the distance between the ILM and Bruch’s membrane (visualized as the bottom of the RPE/Bruch’s membrane complex in SDOCT images) was segmented using the Iowa Reference Algorithm.\(^19\),\(^26\),\(^27\)

Before assessing the thickness, the volume scans acquired from different pupil positions the off-axis scans were registered to the on-axis scan.\(^28\) The retinal vasculature was visualized in projection images, which were created by averaging the A-scans between the IS/
OS junction and Bruch’s membrane. A MATLAB (MathWorks, Natick, MA) user interface was used to manually select the correspondence points in the projection images (usually vessel branching points), which then were used to estimate the transformation (rotation and translation) parameters. The TRT maps created using the on- and off-axis scans from a single subject then were transformed using the estimated transformation matrix, bringing all the TRT maps of the subject into the same reference frame. The average total retinal thickness in micrometers was computed in nine regions (Fig. 2), where the three concentric circles centered on the fovea have diameters of 1, 3, and 5 mm, respectively, and the sectors are 90° wide.

Angular Deviation

In addition to assessing the TRT, the angle of “tilt” in the images also was estimated. First, a plane was fit to the subfoveal region of the segmented Bruch’s membrane. The normal to this then was used to estimate the angular deviation with respect to the z-axis (vertical depth axis) as depicted in Figure 3. The anisotropy of the voxel scale was corrected before the angle was computed.

The geometrical errors due to oblique scan angles were corrected as $T = T' \cos \theta$, where $T'$ is the measured thickness and $T$ is the correct thickness. This simple correction assumes that no refraction takes place at any of the retinal interfaces between the ILM and posterior retina. If, for example, the retina

Figure 1. Illustration depicting on-axis and off-axis scans. The on-axis scan (top row) is acquired by selecting a pupil location so that the B-scans in the horizontal (marked in green) and the vertical (marked in red) directions appear flat. The off-axis scan is acquired by selecting a pupil location eccentric to the previous location. Here, a location to the right of the on-axis scan pupil position induces a tilt in the B-scan (marked in green) corresponding to the horizontal direction. Similarly, a pupil location above or below the on-axis scan pupil location would induce a tilt in the B-scan corresponding to the vertical axis.

Figure 2. (A) The total retinal thickness is computed using the segmented ILM and Bruch’s membrane. The average thickness is then computed within (B) the nine sectors defined by 3 concentric circles 1, 3, and 5 mm in diameter, respectively. (C) The average thickness in the nine sectors.
had an overall higher refractive index than the vitreous, an obliquely incident OCT beam would be refracted toward the normal to the retina surface, thereby diminishing the angle-dependent thickness artifacts. However, these secondary effects are expected to be negligible. This expected trigonometric change was computed for the scans and compared to the changes in thickness observed when using the RPE or Bruch’s membrane.

Assessing Reproducibility of Thickness Measures

The TRT measurements in the nine Early Treatment of Diabetic Retinopathy Study (ETDRS) regions in the on-axis scans were compared to those obtained in the off-axis scans by computing the mean unsigned difference (mean ± SD μm). As multiple off-axis scans were available, the mean unsigned difference was averaged across these scans. The mean difference obtained when using the RPE as the reference surface was statistically compared to the mean difference obtained with Bruch’s membrane using a paired t-test.

In addition, the coefficient of variation (CV%), expressed as the ratio of the standard deviation of the difference of the thickness measurements to the mean thickness measurement observed in the flat scans, as well as the intraclass correlation coefficient (ICC) and its corresponding 95% confidence interval were computed. These statistical tests were performed using the statistical package R.\(^{30,31}\)

Incidence Rates of Off-Axis Scans

To gauge the prevalence of off-axis scan acquisition in a typical data acquisition environment, a second set of scans also were analyzed retrospectively. This dataset consisted of 2172 macular SD-OCT scans obtained from one eye of 2172 subjects participating in the Rotterdam Study, a prospective population-based cohort study investigating age-related disorders.\(^{32-34}\) This study population consisted of 14,925 individuals aged 45 years or older living in the Ommoord district of Rotterdam, The Netherlands. These scans were acquired on a SD-OCT 1000 spectral-domain scanner (Topcon Corp., Tokyo, Japan) and imaged an area 6 × 6 × 2 mm and had dimensions of 512 × 128 × 665 voxels or 512 × 128 × 896 voxels.

Scans that showed acquisition-associated errors, such as clipped corners, were excluded. Scans acquired from myopic subjects also were excluded, as the retinal curvature in these scans is typically larger than in emmetropes. The angular deviation was computed for the final set of 1545 good quality scans using the steps described above.

### Results

The results of the reproducibility analysis have been summarized in Table 1, which indicates that the reproducibility of TRT when using Bruch’s membrane as the reference surface is better than when using the RPE. Figure 4 shows the mean difference, CVs, and ICCs within the nine regions. The overall
Figure 4. An illustration of the reproducibility of the TRT when using the RPE and Bruch's membrane as the reference surfaces. The top row shows the mean ± SD (μm), the middle row shows the CV%, and the bottom row shows the ICC.
The mean difference in TRT when using the RPE was 7.04 ± 4.31 μm (2.39%) and when using Bruch’s membrane as the reference surface was 1.16 ± 1.00 μm (0.32%). The mean difference in each of the nine regions also was statistically compared using a paired t-test, where the estimates using Bruch’s membrane were significantly smaller (*P*, 0.001) than the mean difference obtained when using the RPE. The overall CVs (%) in the TRT measurements when using the RPE and Bruch’s membrane as the reference surface were 1.46% and 0.30%, respectively. The ICC and its corresponding 95% confidence interval for the central TRT were 0.982 (0.958, 0.992) and 0.999 (0.997, 0.999), respectively.

Figure 5A shows a scatterplot depicting the change in TRT (%) when using the RPE (red circle) and Bruch’s membrane (blue diamond) as the reference surface with respect to the angle of tilt in the images. The geometry-induced error that was modeled (green) is presented for comparison. (B) The thickness change (%) noted when using the RPE and Bruch’s membrane after accounting for the geometry-induced errors.

Figure 7 provides a closer look at a section of the photoreceptors in an on-axis and two off-axis SDOCT images, where the variability in the brightness of the PTOS can be observed. Bruch’s membrane (visualized as the bottom of the RPE/Bruch’s membrane complex in SDOCT images) on the other hand, is not affected by the optical Stiles-Crawford effect.

Figure 8 shows a histogram of the incidence rates of angular deviations in the secondary set of 1545 SDOCT scans. Of the scans, 3% showed small tilts (0°–3°), 56% showed moderate tilts (4°–6°), and 41% of the scans showed larger tilts (≥6°).

**Discussion**

The off-axis acquisition of SDOCT images has been observed to result in an increase in TRT estimates (Antony et al. IOVS 2014;55:ARVO E-Abstract 4791). While the axial measurement of TRT
in off-axis scans can induce an error due to the geometry of the structure, the thickness increase observed is larger than expected, indicating that this is not the only contributing cause for the anomaly. Addressing this artifact will ensure that the most precise OCT measurements are obtained. The careful acquisition of on-axis scans would eliminate the geometry-induced errors and improve the reproducibility of TRT estimates. However, this may not always be possible. For instance, media opacities may compel the use of an offset pupil position to obtain a scan with acceptable signal strength. Offsets in the
pupil position along the vertical axis also are particularly difficult to detect, as the tilts will not be visible in the B-scans. However, the IS/OS junction and the PTOS will still exhibit diminished signals, which could impact the segmentation accuracy. Moreover, in highly myopic eyes, the signal strength is likely to vary even in on-axis scans due to the increased retinal curvature, with diminished signals

![Figure 7](image-url). Central B-scans from an on-axis SDOCT volume and two off-axis SDOCT volumes with a closer look at the IS/OS and PTOS. The zoomed in images come from the sections marked in red.

![Figure 8](image-url). Summary of the incidence rates of angular deviation in 1545 scans (1545 patients) obtained from the Rotterdam study. A plane was fit to the sub-foveal region of the segmented RPE and the angular deviation of the plane with respect to the z-axis was computed.
that Bruch’s membrane is the more stable reference surface, in practice, there are situations when the RPE could be the better choice. For instance, in the presence of pathology, such as pigment epithelial detachments (PED), the TRT obtained using Bruch’s membrane would include the contents of the PED. This may not always be desirable, as it would impede the assessment of changes in the retinal tissue.

In conclusion, the TRT obtained using Bruch’s
membrane is more robust than the measurements obtained using the RPE to off-axis perturbations. While the careful acquisition of on-axis SD-OCT volumes would be preferable when assessing retinal structures, extenuating circumstances could make this impossible. In such situations, it is important to recognize the impact that the off-axis acquisition may impose on the visibility of retinal structures, such as the IS/OS and PTOS, as well as the challenges it subsequently may present to automated analysis methods.

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References


