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***En face* projection imaging of the human choroidal layers with tracking SLO and swept source OCT angiography methods**

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ABSTRACT

We tested and compared the capability of multiple optical coherence tomography (OCT) angiography methods: phase variance, amplitude decorrelation and speckle variance, with application of the split spectrum technique, to image the choroiretinal complex of the human eye. To test the possibility of OCT imaging stability improvement we utilized a real-time tracking scanning laser ophthalmoscopy (TSLO) system combined with a swept source OCT setup. In addition, we implemented a post- processing volume averaging method for improved angiographic image quality and reduction of motion artifacts. The OCT system operated at the central wavelength of 1040nm to enable sufficient depth penetration into the choroid. Imaging was performed in the eyes of healthy volunteers and patients diagnosed with age-related macular degeneration.

Keywords: Fourier domain OCT, swept source OCT, scanning laser ophthalmoscopy, eye tracking, optical coherence angiography, phase variance OCT, amplitude decorrelation OCT, speckle variance OCT, choroid, choriocapillaris

1. INTRODUCTION

Optical coherence tomography (OCT) is a widely utilized imaging technique in ophthalmology, primarily for structural imaging of the retina, choroid and optic disc. Numerous studies have demonstrated its applicability in diagnosing disease, and monitoring the progression and effects of therapy. Clinically useful methods of functional OCT continue to be developed which aim to detect and visualize activity in various retinal layers and structures of the optic disc, as well as in the vascular systems supplying the retina.

Two distinct vascular systems are visible in the fundus of the eye: the retinal and the choroidal vasculature. The retinal vasculature is responsible for maintaining the constant inflow of nutrients and outflow of metabolic waste materials necessary for proper functioning of the inner retina. The choroidal vasculature plays a critical role in supporting the proper function of the photoreceptor cells and the retinal pigment epithelium (RPE). Disruptions in vascular structure and function may be a cause or result of developing ocular pathology. Specifically, degenerative disorders affecting the photoreceptor layer and the RPE (e.g., age-related macular degeneration - AMD) are closely related to pathological changes occurring in the choroidal layers (most notably: loss of choriocapillaris or neovascular changes). Imaging methods are required to enable detection and monitoring of the development of abnormalities in the choroidal vascular system, preferably in connection with changes occurring in outer retinal structures.

Imaging the choroidal vasculature in clinical settings is achieved with indocyanine green (ICG) angiography. It requires intravenous administration of this fluorescent dye and subsequent imaging with fundus photography or scanning laser ophthalmoscopy, with appropriate excitation illumination. OCT¹⁻¹¹ may offer an alternative technique for imaging the choroidal layers noninvasively.

A variety of OCT methods have been developed to enable imaging of the ocular vasculature. Doppler OCT methods, were introduced by different research groups to quantify the retinal blood flow. OCT angiography methods were developed to enable visualization of the vascular structure using speckle variance^{12, 13, 23}, amplitude decorrelation^{14 15}, or phase variance¹⁶⁻¹⁹. Some of the OCT angiography methods have been shown to enable quantification of blood flow velocity. All OCT angiography methods have the capability to produce images of the structure of the retinal vasculature down to the level of retinal capillaries. However, imaging of the choroidal vasculature is challenging due to its location underneath highly scattering RPE (scattering in relatively static structures). Also, the choriocapillaris layer further “scrambles” the OCT signal due to light scattering by blood cells (i.e., scattering in a highly dynamic medium).

Imaging of the choroidal complex with swept-source OCT (SSOCT) systems combined with tracking SLO (TSLO) was demonstrated previously with a phase-resolved OCT technique, and proved capable of generating images of the choroidal vessels down to the level of the choriocapillaris²⁰⁻²². Here, we implement this approach to compare several OCT angiographic techniques.

2. MATERIALS AND METHODS

Figure 1. Schematic of the combined swept source OCT and tracking SLO imaging system

Swept source OCT setup

Imaging was performed with a combined SSOCT and TSLO system (Fig. 1). The SSOCT setup uses a rapidly tunable light source (Axsun Technologies) with 1040nm center wavelength and 100nm spectral width yielding $\sim 6\mu\text{m}$ axial imaging resolution in ocular tissue. The sweep rate was 100,000 spectra/s. For the stabilization of spectral sweeps we used a fiber Bragg grating⁹. The optical system used a Mach-Zehnder interferometer layout; the light was split between the reference and sample arms by a 80:20 fiber coupler and combined to produce the interference signal in a 50:50 fiber coupler. The OCT signal was registered with a dual balanced detector. Details of the OCT system performance are presented in Table 1.

Tracking SLO

For the correction of the transverse eye motion we utilized a TSLO system²¹. The tracking was performed with cross-correlation methods applied to SLO images acquired with a custom-programmed field programmable gate array (FPGA) board²¹. The correction voltages generated by the TSLO were applied as real-time offsets to the galvanometer scanners of the SSOCT system. The optical layout of the SLO setup used a combination of refractive and reflective optics. The light source was a superluminescent diode with 840nm central wavelength. The two imaging systems were combined with a dichroic mirror and shared the scan and objective lenses. The TSLO system had transverse imaging resolution of $\sim 10\mu\text{m}$. The details of the TSLO system performance are given in Table 2.

Table 1. Performance of the swept source OCT system

Sweep rate	100 000 spectra/s
Central wavelength	1040 nm
Optical bandwidth	100 nm
Power at the cornea	1.3 mW
Axial imaging resolution (tissue)	~6 μ m
Transverse imaging resolution	~14 μ m
Imaging range (air)	3.7 mm

Table 2. Performance of the tracking SLO system

Line rate	15 000 lines/s
Frame rate	~30 frames/s (512x512)
Field of view	5deg x 5deg (1.5 x 1.5 mm)
Central wavelength	840 nm (bandwidth 40nm)
Power at the cornea	400 μ W
Tracking method ²¹	Strip –wise correlation with reference frame (32 strips per frame, reporting rate ~960 updates/s)
Implementation	FPGA programmed

To enable evaluation of the performance of the eye tracking system we simultaneously acquired real time stabilized SLO images, images with no stabilization and the eye tracking traces generated by the real-time cross-correlation algorithm performed in a local GPU graphics card²¹. We used the unstabilized images to perform post-processing image stabilization which calculated cross-correlations between 150 x 150 pixels regions of interest in the set of SLO images. We used the post-processed tracking results (stabilized images and tracking traces) as a reference for comparison with the real-time tracking results.

As a measure of the eye tracking performance, we calculated the root mean square (RMS) of the intensity distribution in the average TSLO images, known in the literature as the RMS image contrast. The better the eye tracking performance, the higher the contrast of features visible in the images, and the higher the RMS value. To compare the results of the post-processing tracking and real-time tracking we calculated the relative change of the RMS contrast in the averaged SLO images normalized in the range [0, 1]:

$$\text{Relative } \Delta RMS = \frac{RMS_{\text{PostProc}} - RMS_{\text{RealTime}}}{RMS_{\text{RealTime}}} \quad (1)$$

OCT angiography imaging methods

OCT angiography methods were applied to OCT data acquired in MB scan mode (multiple B-scans at subsequent vertical locations). This enabled calculations between B-scans required by the selected OCT angiography methods. The phase variance method calculates the variance of phase resolved OCT data¹⁶. The amplitude decorrelation method computes the magnitude of decorrelation between structural images¹⁵. The speckle variance technique analyses the variance of the intensity in the OCT structural images²³. The details of the scan protocol are given in Table 3. In our implementation of the split spectrum method the spectra were divided into 4 equally spaced, overlapping parts, each having half of the original full width at half maximum, i.e., the axial imaging resolution was decreased by about a factor of 2.

Data processing and visualization methods

After application of the OCT angiography algorithms the 3-D data were processed to enable *en face* visualization of the choroidal layers. The retinal pigment epithelium (RPE) was automatically segmented to provide data points for the surface-fitting algorithm which utilized Zernike polynomials to generate the best approximation of the RPE surface. The fit surfaces were used to flatten the images of the retina. *En face* projections were generated by depth filtering of the flattened 3-D OCT data with a Gaussian window and depth averaging. In the final visualization step we used ImageJ²⁵ software to reduce noise by removal of the bright outliers (Process/Noise/Remove outliers, radius 0.1, threshold 0), smoothen the images by Gaussian blur (Process/Filters/Gaussian blur, sigma radius 0.5), and adjust brightness and contrast (Image/Adjust/Brightness-Contrast).

Table 3. OCT angiography scan protocol

Number of BM scans	3
Number of B-scans	300
Vertical step size	$\sim 7.2 \mu\text{m}$ (spot size: $\sim 10 \mu\text{m}$)
Number of A-scans	300
Horizontal step size	$\sim 6.6 \mu\text{m}$ (spot size: $\sim 10 \mu\text{m}$)
Number of scanner flyback points	100
Time between BM-scans acquisitions	4 ms

Volume averaging method

The OCT volume averaging method requires acquisition of a few 3-D data sets. Each of the volumes undergoes the same processing procedures as single OCT angiography volumes. After the flattening to the RPE layer is completed, motion-affected OCT angiography B-scans are automatically detected as outliers having mean intensity higher than the average in the analyzed 3-D data set. The OCT volumes are broken into smaller "volume chunks" at the locations of motion-affected B-scans. In this way a set of volume chunks is generated out of the initial set of OCT volumes. A user-aided correlation is then performed to overlap the chunks and generate the final average volume.

Subject preparation

Imaging of normal volunteers and patients was performed under a protocol approved by the UC Davis Institutional Review Board. Written informed consent was obtained prior to imaging. The pupil of the imaged eye was dilated with 1% Tropicamide. A bite-bar and forehead rest were used to improve the stability of head. Fixation points were presented on an LCD screen coupled with the TSLO/SSOCT optics.

Figure 2. OCT angiography imaging of the normal retina. Bottom right: intensity B-scan. Arrows indicate a boundary between the retina and the choroid.

3. RESULTS

Comparison of the OCT angiography methods

A side-by-side comparison of the three OCT angiography methods and the split-spectrum technique in imaging of the human choroid is shown in Figures 2 - 4. Cross-sectional OCT angiography images (Fig.2) reveal a clear boundary between the retina and the choroid at a depth position corresponding to the location of Bruch's membrane. A sharp increase of the OCT angiography signal strength is visible at this location especially in the phase variance method. The boundary is less clear in the speckle variance and amplitude decorrelation methods in which the capillaries in the inner retina have poorer visualization. Images obtained with the split spectrum technique show improved visualization of the choroidal boundary, comparable to the phase variance method.

In *en face* projections of the choriocapillaris (Fig. 3), a granular structure is visible which vaguely resembles the loop like appearance of this layer,²⁴ with the dark "gaps" inside the loops more convincingly visualized in the phase variance method and with application of the split spectrum technique. The retinal vessels are visible as dark shadows in the speckle variance and amplitude decorrelation OCT projections while in the phase variance method they are visible as bright "Doppler traces".

Figure 3. Normal retina, OCT projections of the choriocapillaris. Arrows indicate motion artifacts. Lines in OCT B-scan indicate depth location of the *en face* projections. Images location: 8deg nasal, 8 deg inferior. Image sizes: 2 x 2mm. *En face* projection slice thickness: 14 μ m.

The choroidal vessels in Sattler's layer can be visualized with all tested OCT angiography methods, as demonstrated in Figure 4. The phase-variance method provides a better vessel visualization contrast than the two other methods, which is especially visible in the top right corner of the *en face* projections in the top row of Figure 4. Application of the split-spectrum technique improves the contrast of Sattler's layer vessels.

Figure 4. Normal retina, OCT projections of Sattler's layer. Arrows indicate motion artifacts. Lines in OCT B-scan indicate depth location of the *en face* projections. Images location: 8deg nasal, 8 deg inferior from the fovea. Image sizes: 2 x 2mm. *En face* projection slice thickness: 28 μ m.

Figure 5. Normal retina, OCT projections of the retinal vessels. Arrows indicate motion artifacts. Images location: 8deg nasal, 8 deg inferior from the fovea. Image sizes: 2 x 2mm. *En face* projection slice thickness: 28 μ m.

Motion artifacts in the OCT angiography images

Although the OCT angiography methods can provide images of the human choroid, the main difficulty of these techniques is the data acquisition time required to collect volumetric data. It usually takes 3 - 4 s to acquire data sets enabling visualization of the vessels in the choroid and the retina. During this time involuntary eye motion introduces artifacts to the OCT images. In OCT angiography, motion artifacts are visible in B-scans with erroneous angiography signal detected in all imaged retinal and choroidal structures (i.e., static tissue as well as blood vessels). These artifacts

are visible in OCT angiography *en face* projections as white horizontal lines, as visualized in Figure 5, left. Motion-affected B-scans can be detected automatically and removed from the data set prior to visualization (as demonstrated in Figure 5, middle and right). However, discontinuities in the vessel images introduced by saccadic motion of the eye remain and thus cause difficulties in the interpretation of the OCT angiography data. In an attempt to reduce motion artifacts in OCT angiography data we have combined the OCT setup with the TSLO.

Figure 6. Normal retina, average SLO images. Boxes indicate locations of the subsets displayed under SLO images. The bright circular features are cone photoreceptors. RMS - root mean square of the intensity distribution. Imaged area: 1.5mm x 1.5mm. Acquisition time of 150 frames: 5s.

Real-time SLO tracking of the human retina

The performance of the TSLO system is demonstrated in Figures 6 and 7.

The top and middle rows in Figure 6 show the averages of 150 SLO images of the retina acquired over 5s. The left panels show the average of the unstabilized images. The images in the middle panels were generated by averaging of the real-time motion stabilized data. The images on the right were created by averaging of the unstabilized data after application of post-processing image stabilization.

Not surprisingly, averaging of the unstabilized SLO data resulted in a blurred image while the real-time and post-processing stabilization provided sharp images of the retina. The squares in the top row of images indicate locations of the insets presented in the middle row of Figure 6. The bright circles in the SLO images are cone photoreceptors. The RMS of the unstabilized image is as low as half of the RMS in the stabilized images. The post-processed stabilized image has RMS slightly higher than the real-time tracked data set:

$$\text{Relative } \Delta\text{RMS}=0.012.$$

The bottom row of Figure 6 shows XY eye motion traces. The left plot was generated from the saved real-time tracking traces. The right plot is a result of post-processed tracking. The two XY traces look similar but not identical. The plot in the middle panel shows the results of post-processing image stabilization applied to the real-time tracked images. Thus, it shows residual eye motion not corrected by the real-time stabilization algorithm. The middle plot shows a cloud of less than $5\mu\text{m}$ oscillations around 0 and occasionally large ($40 - 70\mu\text{m}$) corrections introduced to the real-time tracking trace by the post-processing method. Since there are only 3 large departures from the well-tracked 147 SLO frames, the real-time stabilization can be considered successful.

Figure 7. Normal retina, average of 120 SLO images. Boxes indicate locations of the subsets displayed under SLO images. RMS - root mean square of the intensity distribution. Imaged area: $1.5\text{mm} \times 1.5\text{mm}$. Acquisition time of 120 frames: 4s.

We have also observed a number of instances when the real-time image stabilization was less successful. Figure 7 shows results of one such case. Although the visual inspection of the average SLO images may not indicate substantial errors (the mosaic of cone photoreceptors is still well visualized), the plot of the residual XY eye motion reveals a number of large (over $40\mu\text{m}$) departures from the well-tracked SLO frames. The relative ΔRMS of the intensity distribution is:

$$\text{Relative } \Delta\text{RMS}=0.035.$$

Influence of the real-time tracking errors on OCT angiography imaging

Figure 8 demonstrates the influence of the eye tracking errors introduced by the TSLO to the simultaneously acquired and real-time corrected OCT angiography data. The images were obtained in the eye of a patient diagnosed with geographic atrophy. The upper part of the phase-variance OCT projection image (top row in Figure 8) is free from motion artifacts. The lower part is highly affected by the real-time eye tracking errors. The image of the vascular structure in Sattler's layer is highly obscured by OCT angiography noise visible as horizontal white lines. In the intensity projection (top left) the real-time tracking errors are visible as a horizontal "jitter" of image lines. The phase variance OCT cross-section (top right image) shows high OCT angiography signal in the static tissue image, i.e., high OCT angiography noise. For comparison, the bottom row of Figure 8 shows the OCT images of the same area of the eye not affected by the eye motion. A very detailed image of the choroidal vessels in Sattler's layer can be appreciated in the phase variance OCT projection.

Figure 8. Geographic atrophy, OCT projections of Sattler's layer in the choroid. Top row: illustration of the tracking errors influence on the OCT images. Bottom row: OCT images unaffected by motion artifacts. Projection locations are indicated by lines in cross-sectional phase-variance (PV) OCT images. Images location: 3deg nasal, 3deg inferior from the fovea. Image sizes: 1.5 x 1.5mm. *En face* projection slice thickness: 24 μ m.

Reduction of motion artifacts in OCT angiography methods by a volume averaging method

Since the current implementation of the SLO real-time eye motion stabilization often introduces tracking errors to the OCT data, we have developed an alternative method to reduce motion artifacts. The effects of application of this method to three OCT volumes is shown in Figures 9 and 10. The imaged area of the eye is the same as presented in Figures 2-4.

Comparison of OCT angiography cross sections in Figure 9 with Figure 2 shows substantial improvement of the imaging contrast of the retinal capillaries as well as higher contrast of the visualization of the choroidal boundary.

Figure 9. Normal retina, OCT angiography cross sections, averages of 3 OCT volumes.

Comparison of the OCT angiography projections in the top row of image 10 with image 5 shows substantial reduction of motion artifacts. Discontinuities in the images of vessels were removed. An intricate pattern of the capillaries located in the outer plexiform layer was visualized in all three OCT angiography methods without substantial motion artifacts. The *en face* projection of the choriocapillaris (third row) shows a pattern similar to the expected loop-like structure with dark "gaps" between the loops. The choroidal vessels in Sattler's layer (bottom row) have improved visualization contrast with the volume averaging of the phase variance data providing the most clear image of the vascular network.

Figure 10. Normal retina, averages of 3 OCT volumes. Images location: 8deg nasal, 8 deg inferior from the fovea. Image sizes 2 x 2mm.

4. DISCUSSION AND CONCLUSIONS

In our imaging experiments we have tested the capability of three OCT angiography methods: speckle variance, amplitude decorrelation, and phase variance to visualize the human choroidal vasculature. In all methods the OCT angiography cross sections revealed a boundary between the retina and the choroid in a form of a sharp increase of the OCT angiography signal. This signal increase is caused by the blood flow in the choriocapillaris located directly under the retinal pigment epithelium (RPE) and Bruch's membrane. Although present in all tested methods, the visualization contrast of this boundary is highest in the phase variance OCT method. Also, PV OCT shows better imaging contrast of the retinal vessels. In the *en face* projections PV OCT angiography revealed the most convincing visualization of the choriocapillaris and had the visually highest contrast of the vessels in Sattler's layer.

Application of the split spectrum technique improved the performance of the speckle variance and amplitude decorrelation methods, resulting in images that are comparable to the basic phase variance OCT method. This improvement can be attributed to the averaging of OCT data split into different spectral channels, each having high correlation with the signal and low correlation with the noise (different spectral noise bandwidths). Further improvement of the imaging quality can be achieved by volume averaging techniques. In our method, motion artifacts were substantially reduced allowing for uninterrupted visualization of the retinal vessels and capillaries. We also achieved improved visualization of the structure of the choriocapillaris and visualization contrast of the vessels in Sattler's layer.

The TSLO provided visualization of the human retina down to the level of the cone photoreceptors at 4deg eccentricity from the fovea. Their presence in the averaged SLO images not only indicates that our system has sufficient lateral resolution to image the photoreceptors but also that the eye tracking accuracy is at the level of the size of cones. As a first approximation, the performance of the image stabilization may be evaluated by analysis of the XY residual motion traces. In our tests they revealed small oscillations around the residual motion value equal to zero. These oscillations may be considered as cumulative errors introduced by the real-time tracking and post-processing stabilization methods. The larger "residual" motions indicate instances of real-time tracking failures, i.e., incorrectly tracked SLO frames. They

decrease the RMS contrast however no severe decrease of image quality can be perceived by visual inspection. Although the occasional errors in the tracking system have little influence on the quality of the average SLO images, they introduce noise to B-scans in the OCT angiography data. In extreme situations when real-time tracking fails, the OCT angiography methods cannot be implemented due to high intensity and phase decorrelation noise of the OCT data. Nevertheless, real-time tracking can potentially reduce motion artifacts, notwithstanding frequently introduced artifacts due to torsional motion and reference frame errors.

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