Optical Coherence Tomography Angiography in the Optovue Device

David Huang, Yali Jia, Simon S. Gao, Bruno Lumbroso, Marco Rispoli

Optovue Angiovue system technology description: The instrument used for optical coherence tomography (OCT) angiography is based on the AngioVue Imaging System (Optovue, Inc., Freemont, CA). This instrument has an A-scan rate of 70,000 scans per second, using a light source centered on 840 nm and a bandwidth of 50 nm. Each OCT angiography (OCTA) volume contains 304×304 A-scans with two consecutive B-scans captured at each fixed position before proceeding to the next sampling location. Split-spectrum amplitude-decorrelation angiography is used to extract the OCT angiography information. Each OCTA volume is acquired in 3 seconds, and two orthogonal OCTA volumes are acquired for orthogonal registration using "Motion Correction Technology" (MCT)[1, 2] to minimize motion artifacts arising from microsaccades and fixation changes. Angiography information is displayed as the maximum of the decorrelation values when viewed perpendicularly through the thickness being evaluated.

Avanti Widefield OCT is a spectral domain OCT system that is the platform for Optovue's OCT angiography technology. When the OCTA software is installed, it becomes an AngioVue system.

OCT Angiography

Initially, Doppler OCT angiography methods were investigated for the visualization and measurement of blood flow.[3-8] Because Doppler OCT is sensitive only to motion parallel to the OCT probe beam, it is limited in its ability to image retinal and choroidal circulation, which are predominantly perpendicular to the OCT beam. An alternative approach has been speckle based OCT angiography. It has advantages over Doppler-based techniques because it uses the variation of the speckle pattern in time to detect both transverse and axial flow with similar sensitivities. Amplitude-based,[9-11] phase-based,[12] or combined amplitude+phase[13] variance methods have been described.

Split-Spectrum Amplitude-Decorrelation Angiography

The split-spectrum amplitude-decorrelation angiography (SSADA) algorithm was developed to minimize scanning time. It detects motion in blood vessel lumen by measuring the variation in reflected OCT signal amplitude between consecutive cross-sectional scans. Decorrelation is a mathematical function that quantifies variation without being affected by the average signal strength, as long as the signal is strong enough to predominate over optical and electronic noise. The novelty of SSADA lies in how the OCT signal is processed to enhance flow detection and reject axial bulk motion noise. Specifically, the algorithm splits the OCT image into different spectral bands, thus increasing the number of usable image frames. Each new frame has a lower axial resolution that is less susceptible to axial eye motion caused by retrobulbar pulsation. This lower resolution also translates to a wider coherence gate over which reflected signal from a moving particle such as a blood cell can interfere with adjacent structures, thereby increasing speckle contrast. In addition, each spectral band contains a different speckle pattern and independent information on flow. When amplitude decorrelation images from multiple spectral bands are combined, the flow signal is increased. Compared to the full-spectrum amplitude method, SSADA using four-fold spectral splits improved the signal-to-noise ratio (SNR) by a factor of two, which is equivalent to reducing the scan time by a factor of four.[14] More recent SSADA implementations use an eleven-fold split to further enhance the SNR of flow detection.[15] As shown by an example from *en face* angiograms of the macular retinal circulation collected using a commercial 70 kHz 840-nm spectral OCT (Figure 1), SSADA provides a clean and continuous microvascular network and less noise just inside the foveal avascular zone (FAZ).

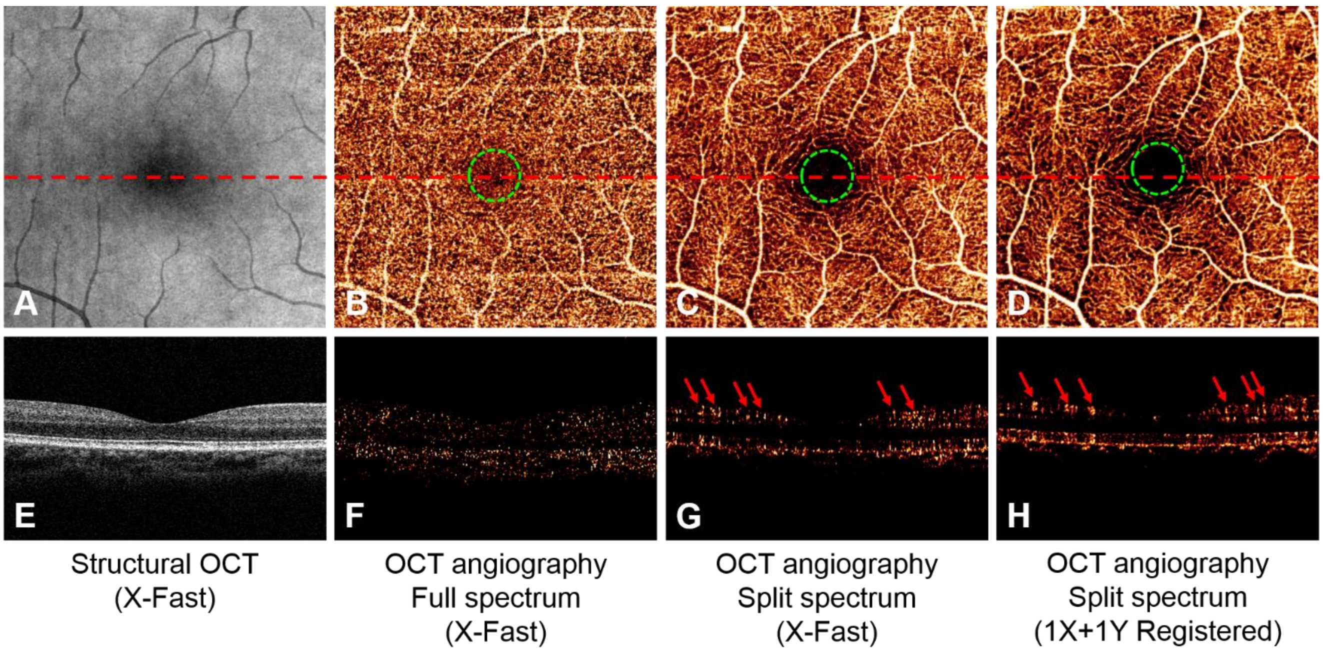

Figure 1. Comparison of structural OCT (A, E) and amplitude-decorrelation angiograms of the macula (3×3 mm area) using full spectrum (B, F), split-spectrum (C, G), and split-spectrum averaged angiograms from one X-fast and one F-fast scans after 3D registration (D, H). *En face* maximum decorrelation projections of retinal circulation showed less noise inside the foveal avascular zone (FAZ, within green dotted circles) and more continuous perifoveal vascular networks using the SSADA algorithm (C) compared to standard full-spectrum algorithm (B). The cross-sectional angiograms (scanned across the red dashed line in B and C) showed more clearly delineated retinal vessels (red arrows in G) and less noise using the SSADA algorithm (G) compared to the standard (F). There are saccadic motion artifacts that appear as artifactual horizontal lines in (B, C). This and other motion artifacts are removed using the 3D registration algorithm that registers a horizontal-priority (X-fast) and a vertical-priority (Y-fast) raster scans to remove motion error. The algorithm then merges the X-fast and Y-fast scans to produce a merged 3D OCT angiogram[2] that shows a continuous artifact-free microvascular network in (D). The registration and averaging of two orthogonal scans also removed motion blur and further improved SNR, allowing the visualization of a greater number of distinct small retinal vessels (microvascular network in D, red arrows in H).

Since OCT angiography generates 3D data, segmentation and *en face* presentation of the flow information can aid in reducing data complexity and serve to reproduce the more traditional view of dye-based angiography. As seen in Figure 1, the retinal angiogram (Figures 1B to 1D) represents the decorrelation or flow information between the internal limiting membrane and the outer plexiform layer. Segmentation performed on the cross-sectional, structural OCT images (Figure 1E) can directly be applied to the OCT angiography images (Figures 1F to 1G). The *en face* angiograms were generated by projecting the maximum decorrelation or flow value for each transverse position within the segmented depth range, representing the fastest flowing vessel lumen in the segmented tissue layers. In healthy eyes, the retinal angiogram shows a vascular network around the FAZ. The layers of the retina and choroid can be more finely separated (Figure 2) to provide additional information to define diagnostic parameters of vascular defects.

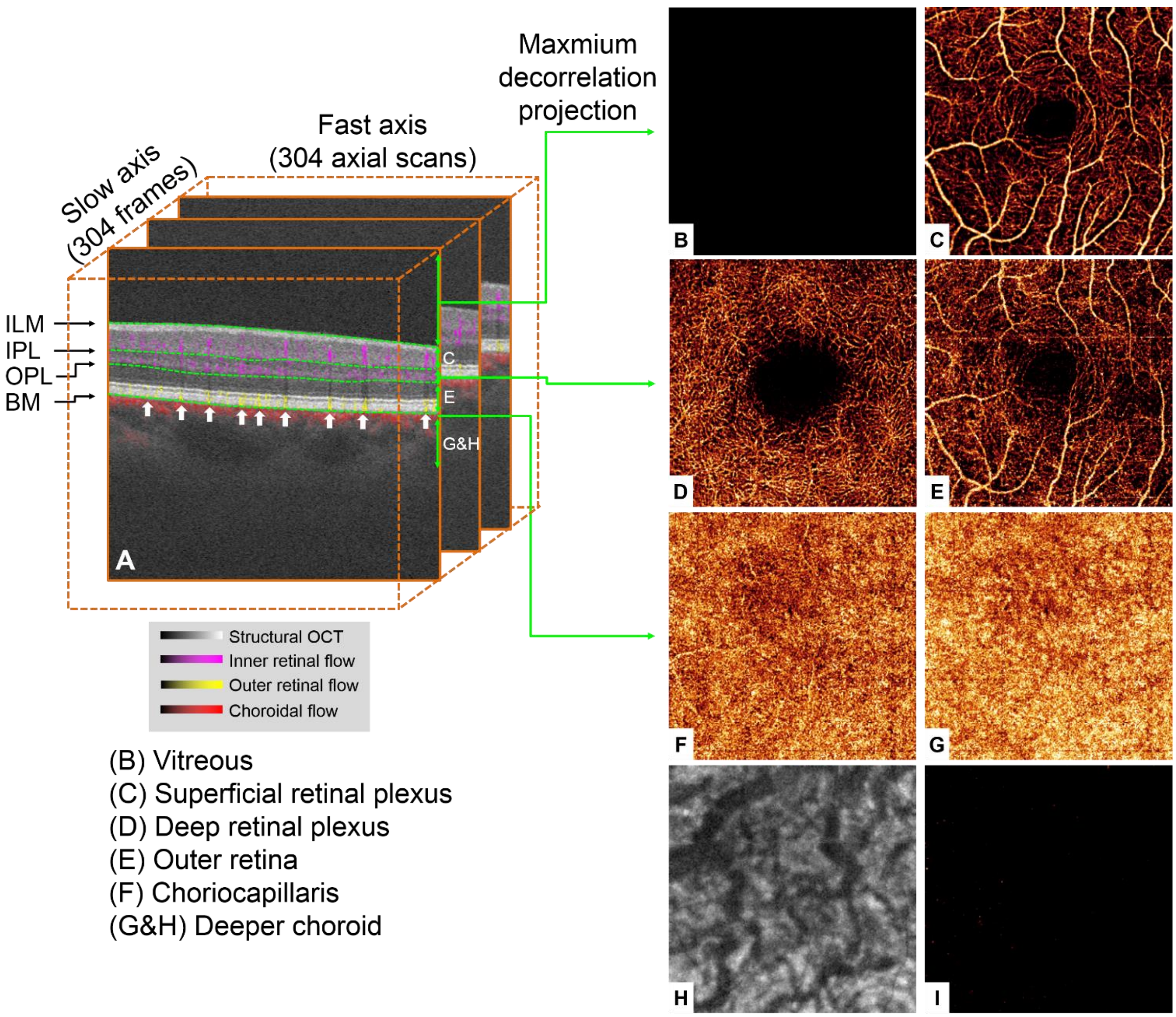

Figure 2. Segmentation and processing of an OCT angiogram of a normal macula. (A) The 3D OCT angiogram comprises 304 frames of averaged decorrelation cross-sections stretched along the slow scan axis. (A) The cross-sectional angiogram shows that flow in the inner retinal vessels (purple) are projected onto bright photoreceptor and retinal pigment epithelium (RPE) layers (indicated by white arrows). Image processing software separates the vitreous, inner retinal layers, outer retinal layer, and choroidal layers along the inner limiting membrane (ILM), outer boundary of the inner plexiform layer (IPL), outer boundary of the outer plexiform layer (OPL), and Bruch's membrane (BM) (dotted green lines). Six segmented flow

volumes are separately projected. The projection algorithm finds the maximum decorrelation value for each transverse position within the segmented depth range, representing the fastest flowing vessel lumen in the segmented tissue layers. (B) The vitreous angiogram shows the absence of vascular flow. (C) The superficial inner retinal angiogram shows normal retinal circulation with a small foveal avascular zone of approximately 0.6 mm in diameter. (D) The deep inner retina angiogram shows the deep retinal plexus which is a network of fine vessels. (E) The outer retina slab shows flow projection artifacts cast by flowing blood in the inner retinal vessels onto the RPE. (F) The choriocapillaris angiogram. (G) The deeper choroid angiogram. (H) The deeper choroid *en face* structural OCT. (I) The outer retinal angiogram after removal of the projection artifact using a post-processing algorithm.

Relationship Between Decorrelation and Velocity

To determine how the decorrelation or flow signal produced by the SSADA algorithm relates to flow velocity, phantom experiments were performed.[16] The study showed that SSADA is sensitive to both axial and transverse flow, with a slightly higher sensitivity for the axial component. For clinical retinal imaging where the OCT beam is approximately perpendicular to the vasculature, the SSADA signal can be considered to be independent of the small variation in beam incidence angle for all practical purposes. In addition, it was found that decorrelation was linearly related to velocity over a limited range. A higher decorrelation value thus implies higher velocity flow. This range is dependent on the time scale of the SSADA measurement. With a 70 kHz spectral OCT system and 200+ A-scans per cross-sectional B-scan, SSADA should be sensitive to even the slowest flow at the capillary level, where flow speeds have been estimated at between 0.4 to 3 mm/s.[17, 18] In larger vessels with higher velocities, the SSADA signal reaches a maximum value (saturates).

Limitations of Optical Coherence Tomography Angiography

OCT angiography has several limitations. First, shadowgraphic flow projection artifact makes the interpretation of *en face* angiograms of deeper vascular beds more difficult. These artifacts are a result of fluctuating shadows cast by flowing blood in a superficial vascular layer that cause variation of the OCT signal in deeper, highly reflective layers. The flow projection artifact from the retinal circulation can be seen clearly on the bright retinal pigment epithelium (RPE). This artifact can be removed by software processing. The projection from the retinal circulation is relatively sparse and can be removed from deeper layers fairly effectively. However, the choriocapillaris is nearly confluent, and its projection and shadow effects are difficult to remove from deeper choroidal layers. A second limitation is the fading of OCT and flow signal in large vessels due to the interferometric fringe washout effect associated with very fast blood flow, especially the axial flow component.[19] This means that central retinal vessels in the disc and large vessels in the deep choroid cannot be visualized using SSADA. Third, the scan area of OCT angiography is relatively small (3×3 to 6×6 mm). Larger-area angiograms of high quality can be achieved, but require higher speed OCT systems that are not yet commercially available.[20] Lastly, because OCT angiography best resolves pathology when viewed as *en face* angiograms of anatomic layers, practical clinical applications require accurate segmentation software. Post-processing software is also needed to reduce motion and projection artifacts. The need for these sophisticated algorithms means OCT angiography still has much room to improve in the foreseeable future.

Comparing Swept-Source and Spectral Optical Coherence Tomography

The SSADA algorithm was initially implemented on a custom-built 100 kHz 1050 nm wavelength swept-source OCT system. To generate high quality angiograms (Figure 3A), 8 consecutive cross-sectional scan at each position were necessary. A scan pattern of 200 cross-sectional scan positions each with 200 axial scans was used. The overall angiographic scan pattern had 200×200 transverse points. A total of 200×200×8 axial scans were acquired in 3.5 seconds.

The commercial implementation of SSADA uses a 70 kHz 840 nm wavelength spectral OCT system. Although the systems acquires fewer axial scans per second, high quality angiograms with more transverse points (304×304, Figure 3B) are produced in less time (3 seconds). The higher performance is due to the lower decorrelation noise on the spectral OCT system, which requires only 2 consecutive cross-sectional scans at one position to compute a reliable decorrelation image. The higher transverse scan density, along with a higher transverse resolution associated with the shorter wavelength, means that the Avanti produces retinal angiograms with higher definition and higher resolution than the swept-source OCT prototype that was originally used (Figures 3C and 3D).

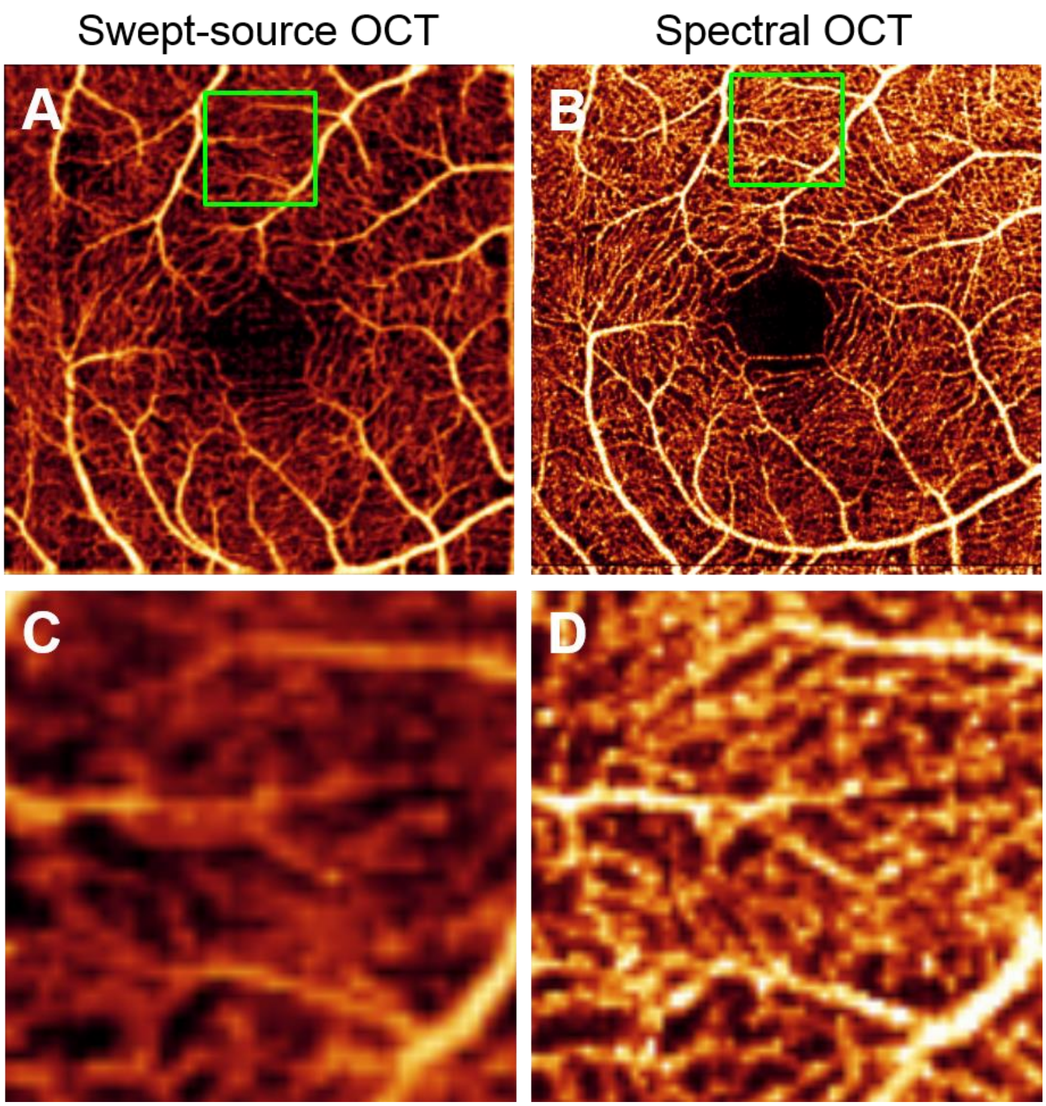

Figure 3: Comparison of 3×3 mm macular angiograms from a 100 kHz swept-source OCT system (A) and 70 kHz spectral OCT system (B). Zoomed-in views

shows improve capillary detail from the spectral OCT system (D) as compared to the swept-source OCT system (C).

Quantitative analysis

The latest developments for OCT angiography relate to methods for quantitative analysis of OCT angiograms.[21-25] Optovue's new quantification tool is called AngioAnalytics, and it provides numerical data about flow area and non-flow area. AngioAnalytics can also generate a flow density map. These metrics may serve as biomarkers in diagnosis and for tracking disease progression or treatment response.

Flow area

Flow area is useful in CNV and preretinal neovascularization during diabetic retinopathy or vascular vein occlusion. In these pathologies, traditional angiography shows new vessels masked by leakage and staining, while OCT angiography allows for direct and clear visualization of the vascular network. In AngioAnalytics, the operator draws the CNV boundary, and the software will calculate the drawn area and vessel area in mm^2. Furthermore, it allows for comparison of all measurements for a given participant.

Non-flow area

The non-flow area is the vascular dropout area. These are regions where there is no detectable flow by SSADA. This tool seems to be useful in all ischemic retinopathies by various etiologies. With OCT angiography, it is possible to separate the inner and deep vascular plexus. After proper *en face* projection, the software will show the non-perfused areas by mouse click selection. Ischemic areas will be shown in yellow. These areas may be saved and matched with others in the study.

Flow density map

This tool is able to measure the percentage of vascular areas on *en face* angiograms. This analysis is based on an ETDRS grid centered on the macula as with the thickness map. This tool works both on inner and outer vascular plexus.

References

1. Kraus MF, Liu JJ, Schottenhamml J, et al. Quantitative 3D-OCT motion correction with tilt and illumination correction, robust similarity measure and regularization. *Biomed Opt Express* 2014;5:2591-2613.
2. Kraus MF, Potsaid B, Mayer MA, et al. Motion correction in optical coherence tomography volumes on a per A-scan basis using orthogonal scan patterns. *Biomed Opt Express* 2012;3:1182-1199.
3. Wang RK, Jacques SL, Ma Z, Hurst S, Hanson S, Gruber A. Three dimensional optical angiography. *Opt Express* 2007;15:4083-4097.
4. Grulkowski I, Gorczynska I, Szkulmowski M, et al. Scanning protocols dedicated to smart velocity ranging in Spectral OCT. *Opt Express* 2009;17:23736-23754.
5. Yu L, Chen Z. Doppler variance imaging for three-dimensional retina and choroid angiography. *J Biomed Opt* 2010;15:016029.
6. Makita S, Jaillon F, Yamanari M, Miura M, Yasuno Y. Comprehensive in vivo micro-vascular imaging of the human eye by dual-beam-scan Doppler optical coherence angiography. *Optics express* 2011;19:1271-1283.
7. Zotter S, Pircher M, Torzicky T, et al. Visualization of microvasculature by dual-beam phase-resolved Doppler optical coherence tomography. *Optics express* 2011;19:1217-1227.
8. Braaf B, Vermeer KA, Vienola KV, de Boer JF. Angiography of the retina and the choroid with phase-resolved OCT using interval-optimized backstitched B-scans. *Optics express* 2012;20:20516-20534.

9. Mariampillai A, Standish BA, Moriyama EH, et al. Speckle variance detection of microvasculature using swept-source optical coherence tomography. *Opt Lett* 2008;33:1530-1532.
10. Motaghiannezam R, Fraser S. Logarithmic intensity and speckle-based motion contrast methods for human retinal vasculature visualization using swept source optical coherence tomography. *Biomed Opt Express* 2012;3:503-521.
11. Enfield J, Jonathan E, Leahy M. In vivo imaging of the microcirculation of the volar forearm using correlation mapping optical coherence tomography (cmOCT). *Biomed Opt Express* 2011;2:1184-1193.
12. Fingler J, Zawadzki RJ, Werner JS, Schwartz D, Fraser SE. Volumetric microvascular imaging of human retina using optical coherence tomography with a novel motion contrast technique. *Opt Express* 2009;17:22190-22200.
13. Liu G, Lin AJ, Tromberg BJ, Chen Z. A comparison of Doppler optical coherence tomography methods. *Biomed Opt Express* 2012;3:2669-2680.
14. Jia Y, Tan O, Tokayer J, et al. Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. *Opt Express* 2012;20:4710-4725.
15. Gao SS, Liu G, Huang D, Jia Y. Optimization of the split-spectrum amplitude-decorrelation angiography algorithm on a spectral optical coherence tomography system. *Opt Lett* 2015;40:2305-2308.
16. Tokayer J, Jia Y, Dhalla AH, Huang D. Blood flow velocity quantification using split-spectrum amplitude-decorrelation angiography with optical coherence tomography. *Biomed Opt Express* 2013;4:1909-1924.
17. Riva CE, Petrig B. Blue field entoptic phenomenon and blood velocity in the retinal capillaries. *J Opt Soc Am* 1980;70:1234-1238.
18. Tam J, Tiruveedhula P, Roorda A. Characterization of single-file flow through human retinal parafoveal capillaries using an adaptive optics scanning laser ophthalmoscope. *Biomed Opt Express* 2011;2:781-793.
19. Hendargo HC, McNabb RP, Dhalla A-H, Shepherd N, Izatt JA. Doppler velocity detection limitations in spectrometer-based versus swept-source optical coherence tomography. *Biomedical optics express* 2011;2:2175-2188.
20. Blatter C, Klein T, Grajciar B, et al. Ultrahigh-speed non-invasive widefield angiography. *Journal of Biomedical Optics* 2012;17:0705051-0705053.
21. Jia Y, Bailey ST, Hwang TS, et al. Quantitative optical coherence tomography angiography of vascular abnormalities in the living human eye. *Proc Natl Acad Sci U S A* 2015;112:E2395-2402.
22. Jia Y, Bailey ST, Wilson DJ, et al. Quantitative optical coherence tomography angiography of choroidal neovascularization in age-related macular degeneration. *Ophthalmology* 2014;121:1435-1444.
23. Jia Y, Wei E, Wang X, et al. Optical coherence tomography angiography of optic disc perfusion in glaucoma. *Ophthalmology* 2014;121:1322-1332.
24. Liu L, Gao SS, Bailey ST, Huang D, Li D, Jia Y. Automated choroidal neovascularization detection algorithm for optical coherence tomography angiography. *Biomed Opt Express* 2015;6:3564-3576.
25. Agemy SA, Scripsema NK, Shah CM, et al. Retinal Vascular Perfusion Density Mapping Using Optical Coherence Tomography Angiography in Normals and Diabetic Retinopathy Patients. *Retina* 2015.