Ultrahigh speed spectral / Fourier domain ophthalmic OCT imaging

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Ultrahigh Speed Spectral / Fourier Domain Ophthalmic OCT Imaging

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ABSTRACT

Ultrahigh speed spectral / Fourier domain optical coherence tomography (OCT) using a CMOS line scan camera with image acquisition rates of 70,000 - 312,500 axial scans per second is investigated. Several design configurations are presented to illustrate design trade-offs between acquisition speed, sensitivity, resolution and sensitivity roll-off performance. We demonstrate: extended imaging range and improved sensitivity roll-off at 70,000 axial scans per second with 4096 camera pixels, high speed and ultrahigh resolution imaging at 106,382 axial scans per second, and ultrahigh speed imaging at 250,000-312,500 axial scans per second. Each configuration is characterized through optical testing and the trade-offs demonstrated with in vivo imaging of the fovea and optic disk in the human retina. We show dense homogeneous 3D-OCT volumetric data sets that were acquired by raster scanning at 250,000 axial scans per second, which is an order of magnitude faster than most current generation spectral / Fourier OCT instruments. OCT fundus images constructed from the 3D-OCT data have no noticeable discontinuity of retinal features and show that there are minimal motion artifacts. Using an improved sensitivity roll-off configuration at 70,000 axial scans per second, long cross sectional scans are acquired at high resolution for imaging large areas of the retina, including the fovea and optic disk. Using an ultrahigh speed configuration at 250,000 axial scans per second, the fine porous structures of the lamina cribrosa can be seen from slices extracted from a dense 3D data set. Rapid repeated imaging of a small volume (4D-OCT) enables time resolved visualization of the capillary network surrounding the INL and may show individual red blood cells. This capability could create the possibility for alternative techniques for quantifying capillary blood flow, which cannot be measured with Doppler OCT methods because of the capillary’s perpendicular orientation to the optical beam. The results of this study suggest that high speed CMOS cameras can achieve a significant improvement in performance for ophthalmic imaging. This promises to have a powerful impact in clinical applications by improving early diagnosis, reproducibility of quantitative measurements and enabling more sensitive assessment of disease progression or response to therapy.

Keywords: Ultrahigh Speed Optical Coherence Tomography; Spectral / Fourier Domain OCT; Ophthalmology; Fovea and Optic Nerve Head; CMOS Camera; Medical and biological imaging.

1. INTRODUCTION

Optical Coherence Tomography (OCT)1 is becoming an increasingly important tool for the early diagnosis of ocular disease and for performing fundamental ophthalmic research. High sensitivity, large dynamic range, and micron level resolution imaging are achieved with OCT by interferometric detection of backscattered light from the sample. Capable of two and three dimensional non-invasive structural and quantitative imaging of the retinal tissue and anterior segment, OCT enables the identification of pathologies for disease diagnosis or monitoring responses to therapy.2

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The earliest implementations of OCT used low coherence interferometry with time domain detection in which the echo delay of backscattered light was measured by mechanically sweeping a mirror in a reference arm.3–5 Commercial ophthalmic OCT instruments using this time domain approach operated with imaging speeds of 400 axial scans per second. Being very susceptible to motion of the eye, the conventional approach for clinical ophthalmic OCT imaging was to collect individual cross sectional images of the retina.1, 4, 6 With the development of high speed spectral / Fourier domain OCT7,8 and swept source OCT,9, 10 it became possible to acquire three dimensional volumetric data sets using raster scanning. However, the 25,000-29,000 axial scans per second imaging speed of the majority of spectral / Fourier domain systems demonstrated to date11, 12 is still too low to enable dense, volumetric OCT data acquisition in ophthalmic applications because the images are often compromised by ocular motion. Recent advances in wideband light source and sensor technologies are enabling a next generation of ultrahigh speed OCT imaging systems with adequate sensitivity for ophthalmic imaging.

Ultrahigh speed swept source retinal imaging was recently performed using a Fourier domain model locked (FDML) laser operating at 1050 nm with an axial scan rate of 236 kHz13 and at 1060 nm with an axial scan rate of 249 kHz.14 Swept source OCT systems have reduced sensitivity roll-off with imaging depth when compared to spectrometer based systems13, 15 and can readily operate in the 1050 nm wavelength range, which may have advantages for deeper tissue penetration.16, 17 Swept source systems require rapidly tunable, narrow linewidth lasers, but have the advantage that they use high speed A/D converters and single point detectors, rather than bulky spectrometers.

Most of the current generation ophthalmic OCT systems use spectral / Fourier domain detection based on a spectrometer design and there are currently no FDA approved swept source systems commercially available. Spectrometer based systems can make use of superluminescent diode (SLD) light sources with broad bandwidths for high axial resolutions, as well as leverage the existing infrastructure of economically priced high speed line scan cameras and frame grabbers used in machine vision. The sensitivity and dynamic range requirements for ophthalmic OCT imaging are quite demanding because the incident power is limited by safety considerations. This governs the selection of suitable linear sensor arrays for spectral / Fourier domain OCT. The standard sensor for spectrometer based systems has been a low noise, high sensitivity, and high dynamic range CCD line scan camera. Commercial systems typically operate with 2048 pixels at scan rates of ~25kHz. However, ophthalmic spectral / Fourier domain OCT has been demonstrated in research systems at an axial scan rate of 29 kHz with 2048 camera pixels,11, 18, 19 75 kHz with 512 camera pixels,20 and 12 kHz with 4096 camera pixels.21 It has been recognized for some time that CMOS technology has the potential to achieve faster sustained imaging speeds than CCD technology because it is possible to directly integrate digital communication circuitry, gain stages, A/D converters, and photosensitive pixels on the same chip. However, CMOS has traditionally suffered from lower sensitivity and higher noise than CCD,22 reducing its suitability for OCT. Recent advances in CMOS imaging technology and sensor architecture are beginning to address these issues with a next generation of high speed line scan cameras. Indeed, ultrahigh speed Ophthalmic OCT imaging has been recently shown in a related paper at up to 312,500 axial scans per second using a high speed CMOS camera.23

This paper presents and compares several ultrafast swept source OCT system designs based on a recently developed CMOS line scan camera (Sprint spL4096-140k from Basler Vision Technologies) that exhibits exceptional sensitivity and noise characteristics while running at high speeds. The OCT system designs were chosen to investigate trade-offs in acquisition speed, sensitivity, sensitivity roll-off, resolution and imaging depth. The designs investigated differ in number of pixels used on the camera, light source/spectrum, spectrometer design, ophthalmic imaging module optics, and line rate/exposure time. Acquisition speeds for the four configurations tested range from 70,000 axial scans per second to 312,500 axial scans per second. A first configuration demonstrates improved sensitivity roll-off with imaging depth by using a high resolution spectrometer configuration while imaging at a speed of 70,000 axial scans per second. A second configuration demonstrates that it is possible to simultaneously achieve a higher axial resolution and larger spectrometer pixel count than any currently available commercial ophthalmic OCT system, while imaging at over 100,000 axial scans per second. A third configuration images at 250,000 axial scans per second, which is an order of magnitude faster than commercial systems, while maintaining good sensitivity performance. A fourth configuration images at 312,500 axial scans per second. Each configuration is characterized through optical testing and the trade-offs between acquisition speed, sensitivity, sensitivity roll-off, and resolution demonstrated with in vivo imaging of the fovea and optic disk in the human retina.
2. OCT SYSTEM DESCRIPTIONS AND PERFORMANCE CHARACTERIZATION

2.1 Experimental apparatus

The overall layout of the experimental apparatus is shown in Fig. 1. In order to illustrate design trade-offs between speed, resolution, imaging range and sensitivity roll-off, four system configurations were studied. The systems demonstrate: (A) low sensitivity roll-off and long imaging range at 70,000 axial scans per second, (B) high speed and high resolution imaging at 106,382 axial scans per second, (C) ultrahigh speed imaging with good image quality at 250,000 axial scans per second, and (D) ultrahigh speed imaging, approaching acceptable sensitivity performance limits, at 312,500 axial scans per second. Detailed descriptions of each configuration are listed in Table 1.

A light source consisting of either a multiplexed super luminescent diode (SLD) source (Superlum Broadlighter T870) or a custom built, femtosecond Titanium Sapphire laser was used to generate a broadband spectrum. A circulator was used with the Broadlighter as an isolator to protect the SLDs from back reflections. Only the two long wavelength SLDs were used for design configuration A in order to achieve high spectral resolution as well as match the spectrometer bandwidth, resulting in 3.7 mW of power exiting the fiber after the circulator with a 144 nm full width at half maximum (FWHM) bandwidth centered at 892 nm. All three SLDs were used for design configuration B to achieve a wide bandwidth for ultrahigh resolution, resulting in 4.6 mW of power exiting the fiber after the circulator with a 181 nm FWHM bandwidth centered at 873 nm. For configurations C and D, a custom built femtosecond Titanium Sapphire laser was tuned and filtered to create an adjustable bandwidth light source. When the femtosecond laser was used, light was coupled into a long length of fiber to dispersively broaden the femtosecond pulses, reducing their peak intensity. Average power out of the fiber was 16 mW with a 33 nm FWHM bandwidth centered at 846 nm for configuration C and 16 mW with a 27 nm FWHM bandwidth centered at 845 nm for configuration D. The source power was attenuated in all design configurations by adjusting the length of the air gap at the fiber connector to reach safe levels when imaging the eye in vivo. The attenuated source was split by a fiber optic coupler with either a 50/50 or 90/10 coupling ratio depending on the configuration. Given the short exposure times required for the high speed operation of configurations C and D, a 90/10 fiber optic coupler was used in order to increase the amount of light returning from the sample to the spectrometer. This approach increases the instrument sensitivity, but requires high power light sources to achieve the desired incident power level on the sample because the fiber optic coupler passes only 10% of the light from the source to the sample arm. A 50/50 fiber optic coupler was used for the high resolution and longer
Table 1: System Design Configurations and Performance Measures

<table>
<thead>
<tr>
<th>Design Configuration</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camera pixels</td>
<td>4096</td>
<td>2528</td>
<td>800</td>
<td>576</td>
</tr>
<tr>
<td>Camera line rate (lines per second)</td>
<td>70,000</td>
<td>106,382</td>
<td>250,000</td>
<td>312,500</td>
</tr>
<tr>
<td>Camera line period</td>
<td>14.2 μs</td>
<td>9.4 μs</td>
<td>4.0 μs</td>
<td>3.2 μs</td>
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<td>Camera exposure time</td>
<td>13.0 μs</td>
<td>8.2 μs</td>
<td>2.8 μs</td>
<td>2.0 μs</td>
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<td>Camera starting pixel</td>
<td>1</td>
<td>801</td>
<td>1633</td>
<td>1761</td>
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<tr>
<td>Light source</td>
<td>2 × SLD</td>
<td>3 × SLD</td>
<td>Ti-Sapph</td>
<td>Ti-Sapph</td>
</tr>
<tr>
<td>Light source FWHM</td>
<td>144 nm</td>
<td>181 nm</td>
<td>33 nm</td>
<td>27 nm</td>
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<tr>
<td>Fiber optic coupler ratio</td>
<td>50/50</td>
<td>50/50</td>
<td>90/10</td>
<td>90/10</td>
</tr>
<tr>
<td>Spect. collimating lens focal length</td>
<td>70 mm</td>
<td>50 mm</td>
<td>50 mm</td>
<td>50 mm</td>
</tr>
<tr>
<td>Spect. focusing lens focal length</td>
<td>160 mm</td>
<td>80 mm</td>
<td>80 mm</td>
<td>80 mm</td>
</tr>
<tr>
<td>Calculated depth range in air</td>
<td>4.4 mm</td>
<td>2.1 mm</td>
<td>2.0 mm</td>
<td>2.0 mm</td>
</tr>
<tr>
<td>Calculated depth range in tissue</td>
<td>3.3 mm</td>
<td>1.6 mm</td>
<td>1.5 mm</td>
<td>1.5 mm</td>
</tr>
<tr>
<td>Measured beam diameter on cornea</td>
<td>1.6 mm</td>
<td>1.6 mm</td>
<td>1.6/2.3 mm</td>
<td>2.3 mm</td>
</tr>
<tr>
<td>Performance Measure</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Measured sensitivity</td>
<td>94 (93) dB</td>
<td>92 (91) dB</td>
<td>91 dB</td>
<td>89 dB</td>
</tr>
<tr>
<td>Measured 10 dB roll-off depth</td>
<td>2.36 mm</td>
<td>1.13 mm</td>
<td>1.43 mm</td>
<td>1.26 mm</td>
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<tr>
<td>Measured axial resolution in air</td>
<td>3.6 (4.0)μm</td>
<td>2.8 (3.3)μm</td>
<td>11.4 μm</td>
<td>11.6μm</td>
</tr>
<tr>
<td>Estimated axial resolution in tissue</td>
<td>2.7 (3.0)μm</td>
<td>2.1 (2.5)μm</td>
<td>8.6μm</td>
<td>8.7μm</td>
</tr>
</tbody>
</table>

* ( ) indicates sensitivity or axial resolution after spectral shaping.

exposure time configurations A and B to accommodate the lower output power of the multiplexed SLD light source.

The subject’s eye was positioned such that the eye’s pupil was coincident with the pivot point of the collimated beam exiting the ophthalmic patient interface module. By selecting an appropriate focal length of the ocular lens, the projected spot size on the cornea could be changed from a 1/e² diameter of either 1.6 mm or 2.3 mm, as measured by a beam profiler (DataRay WinCamD). Imaging of the fovea and optic disk was performed with a 1.6 mm beam diameter for configurations A-C because beams of this size are relatively easy to align during ophthalmic imaging (important for clinical usage) and because the lateral resolution is not significantly degraded by aberrations of the eye at this beam size. A beam diameter of 2.3 mm was used for design configuration D in order to increase the light collection efficiency of the instrument to compensate for the extremely short integration time of 2 μs. This higher numerical aperture configuration had a shorter depth of field, but also provided improved transverse resolution on the retina, up to limits imposed by ocular aberrations. For the small volume, rapid repeated imaging presented in Section 3.3, a 2.3 mm beam size was used with design configuration C to achieve higher transverse resolution for resolving individual cone cells and capillary flow. A more detailed description of the imaging system can be found in a previously published paper.

2.2 System configuration performance comparison

The performance specifications for each of the four design configurations are summarized in the bottom four rows of Table 1. Using all 4096 camera pixels, Configuration A has a measured sensitivity of 94 dB at a camera exposure time of 13.0 μs, corresponding to an imaging speed of 70,000 axial scans per second (a fixed 1.2 μs readout overhead increases the line period to 14.2 μs and applies to all configurations). By reducing the number of pixels read, configurations B, C and D achieve progressively faster imaging speeds with an associated decrease in the exposure time and sensitivity. Configuration D achieves imaging with a measured sensitivity of 89 dB at an exposure time of 2.0 μs, corresponding to 312,500 axial scans per second. The system sensitivities were measured at an incident power level of 750 μW for all configurations.

Because of the significant modulation present in configurations A and B using the multiplexed SLD light source, spectral shaping was performed to reduce the height of the sidelobes in the axial PSFs, which reduced the sensitivity by approximately 1 dB. Spectral / Fourier domain OCT systems exhibit a roll-off in sensitivity
with imaging depth due to optical resolution limits, finite pixel width,\textsuperscript{25} aliasing at high spatial frequencies, and interpixel cross-talk\textsuperscript{26} in the spectrometer. Sensitivity roll-off characterization of each configuration was performed by setting equal power in the reference and sample arms, placing a silver mirror after the ophthalmic patient interface module, then translating a retro-reflecting mirror in the reference arm by 0.1 mm increments. The sensitivity roll-off in designs B through D is approximately 20 dB at 2 mm (in air) and is comparable to that previously reported for ultrahigh resolution spectral / Fourier domain systems.\textsuperscript{11}

Although differing in axial resolution due to the difference in light source bandwidth, designs B through D exhibit the same spectral resolution at the spectrometer, and hence demonstrate similar sensitivity roll-off performance. An improvement in the sensitivity roll-off can be achieved with a high resolution spectrometer design. However, spectral bandwidth is reduced as the spectral resolution is increased for a given number of camera pixels in a spectrometer. Thus, in order to preserve the axial resolution while increasing the imaging depth range and reducing sensitivity roll-off, it is necessary to improve the spectrometer resolution while maintaining a broad spectral bandwidth. Design configuration A accomplishes this by using a longer focal length spectrometer focusing lens that increases the linear dispersion in order to illuminate and use a larger number of camera pixels. The high spectral resolution spectrometer design of configuration A reduces the sensitivity roll-off and almost doubles the available imaging depth range compared with designs B through D, while maintaining high axial resolution and imaging at 70,000 axial scans per second. In ophthalmic imaging, the improved sensitivity roll-off performance is important for imaging deep structures, such as the optic nerve head, as well as for obtaining usable data, without excessive sensitivity loss, in patients who have axial eye motion during imaging.

3. OPHTHALMIC IMAGING RESULTS

The four OCT system configurations as described were used to acquire \textit{in vivo} images of the fovea and optic disk in the human retina. Study protocols were approved by the investigational review board of the Massachusetts Institute of Technology. Written informed consent was obtained prior to the study. Retinal imaging was performed with an incident average power of 750 μW, consistent with safe retinal exposure as determined by the American National Standards Institute (ANSI)\textsuperscript{27} and with exposure levels used in commercial ophthalmic OCT imaging instruments. Imaging was performed using several different scanning and acquisition protocols.

3.1 Configuration comparison with cross sectional images

Figures 2 shows 500 axial scan (transverse pixels) and 2000 axial scan images of the optic disk. Design configurations A through C used a 1.8 mm beam diameter on the cornea, while design configuration D used a 2.3 mm beam diameter to increase the light collection efficiency of the instrument, as explained in Section 2.1. All images in Fig. 2 are shown with a log\textsubscript{10} intensity grey scale with thresholding to reduce noise. For comparative purposes, the lower threshold value was chosen such that the mean value of the background noise was the same for all images. In all cases, the 2000 axial scan images show improved contrast when compared to the 500 axial scan images for any given design configuration. This improvement in contrast is due to an effective increase in signal to noise ratio from averaging of adjacent lines.

As expected from the sensitivity roll-off characterization measurements, images obtained with configuration A at 70,000 axial scans per second demonstrate superior imaging at a given depth when compared to configurations B through D, as indicated by better visualization of the choroidal structure and deeper penetration into the optic nerve head. With significantly higher axial resolutions than design configurations C and D, images obtained with design configurations A and B show clear axial separation between the photoreceptor layers near the optic nerve head. Design configuration B exhibits the highest resolution, however, the increased sensitivity roll-off restricts the imaging depth, making structures in the choroid less visible than in configuration A. Configuration C trades off resolution to achieve higher imaging speed by reading a smaller number of pixels in the spectrometer. The ultrahigh speed images obtained with configuration C at 250,000 axial scans per second have lower axial image resolution and more noise than configurations A or B, but maintain clear visibility of the photoreceptor and inner retinal layers. The fastest acquisition images obtained with configuration D at 312,500 axial scans per second and a 2 μs exposure time exhibit noticeably more noise and less detail compared to the other configurations, but still show clear retinal structure in the optic disk.
500 axial scans acquired in 7.1 ms  
2000 axial scans acquired in 28.6 ms  
Zoom from 2000 axial scan image

500 axial scans acquired in 4.7 ms  
2000 axial scans acquired in 18.8 ms  
Zoom from 2000 axial scan image

500 axial scans acquired in 2.0 ms  
2000 axial scans acquired in 8.0 ms  
Zoom from 2000 axial scan image

500 axial scans acquired in 1.6 ms  
2000 axial scans acquired in 6.4 ms  
Zoom from 2000 axial scan image

Figure 2: OCT cross sectional images of the optic disk with 500 axial scans per B-scan (left) and 2000 axial scans per B-scan (middle) for each configuration. Zoomed in images (right) of the photoreceptors near their termination at the optic nerve head are extracted from the corresponding 2000 axial scan image. All scale bars represent 100 μm.

3.2 Ultrahigh speed 3D volumetric acquisitions and dense 2D cross sectional scans

Prior to the development of high speed Fourier domain OCT detection techniques, the conventional approach for clinical ophthalmic imaging was to collect individual cross sectional OCT images of the retina. This approach undersamples the retina, raising the probability of missing focal disease pathology, as well as making it difficult to longitudinally correlate imaging results from visit to visit. With the development of high speed spectral / Fourier domain OCT, it became possible to acquire three dimensional volumetric data sets using raster scanning. To date, the majority of spectral / Fourier domain systems have had acquisition speeds of ~25,000 axial scans per second. These imaging speeds are still too low to enable dense, volumetric OCT data acquisition in ophthalmic applications because the imaging time is limited by ocular motion.

Using the high speed design configuration C, which acquires 250,000 axial scans per second, it is possible to acquire dense homogeneous volumetric data sets an order of magnitude faster than most current generation spectral / Fourier OCT instruments. Figures 3(a) and 3(d) show select cross sectional images from a 512 × 512 × 400 voxel volumetric 3D-OCT data set of the fovea and disk, respectively. The data sets were obtained by raster scanning to collect 512 sequential B-scans, consisting of 512 axial scans each, with 400 pixels in depth, in a total time of 1.3 seconds. Figures 3(b) and 3(e) show the corresponding OCT fundus images constructed
Figure 3: Dense 3D volumetric data sets acquired at 250,000 axial scans per second. (a) Select cross sectional scans of the volumetric fovea acquisition. (b) OCT fundus image of the fovea. (c) Axial motion corrected 3D rendering of the fovea data. (d) Select cross sectional scans of the volumetric optic disk acquisition. (e) OCT fundus image of the optic disk. (f) Axial motion corrected 3D rendering of the optic disk. All scale bars represent 500 μm.

from the 3D-OCT data by summing the linear intensities along the axial direction for each transverse point in the image. The OCT fundus images have no noticeable discontinuity of retinal features and show that there are minimal motion artifacts in the x-y plane at this very fast acquisition speed. By correcting for slight axial ocular motion occurring during the acquisition by using alignment frames acquired perpendicular to the slow axis scan direction,23 a rendering of the 3D data can be generated, as shown in Figs. 3(c) and 3(f). OCT cross-sectional images with arbitrary orientation can be extracted from the volumetric 3D-OCT data set and the OCT fundus images enable the precise and reproducible registration of these images to fundus features.

Long retinal scans spanning the fovea and optic disk can be obtained with minimal motion artifacts as shown in Figs. 4(a) and 4(b), which contain 5000 and 10000 axial scans per image respectively. As is typical when displaying OCT cross sectional images, Fig. 4(e) has been vertically cropped to show only the relevant depths containing retinal tissue data. Figure 4(f), however, is uncropped to show the entire imaging range. The improved imaging range of the 70,000 axial scan per second configuration allows imaging at depths approximately twice as deep as a standard design (e.g. configurations B, C, and D) because of the sensitivity roll-off characteristics. The improved roll-off performance enables long scans of the retina where features of interest span several mm in depth due to tissue topologies. The extended imaging depth range and wide scan range are also helpful in obtaining usable data when the patient has difficulty with head stability and fixation, as good sensitivity performance can be obtained far from the zero delay.

OCT enface imaging has been used to reveal the porous structure of the lamina cribrosa14,28 imaged in vivo. Figure 5(a) shows a cross sectional image of a 3D volumetric data set of the optic nerve head acquired at 106,382 axial scans per second using Configuration B. The image was formed by median filtering 5 cross sectional scans. The zero delay is located at the bottom of the image to exploit the reduced roll-off at this location in order to increase the sensitivity at the elevation of the lamina cribrosa structure. Figure 5(b) shows an OCT fundus image of the 3D data formed by summing the linearly scaled intensities in the axial direction for every transverse point in the image. An enface image of the lamina cribrosa can be created from the 3D data set by
extracting a cross sectional slice at a depth within the lamina cribrosa. Figure 5(c) shows an enface image of the 3D data that was formed by summing the linearly scaled intensity values over a narrow ($\sigma = 13 \mu m$) gaussian windowed depth profile in the axial direction for every transverse point in the image. The high imaging speed allows both the gross morphology and the small structures in the lamina cribrosa to be revealed because motion artifacts and motion induced discontinuities are reduced. Changes in the mechanical properties and shape of the lamina$^{29,30}$ are thought to lead to retinal ganglion cell death and the associated onset of glaucoma. The ability to investigate the structure of the lamina cribrosa, as well as track changes to the morphology over time, could prove to be important in understanding how the eye changes with age and ultimately lead to improved diagnostics and treatments for glaucoma.

Figure 5: (a) Cross sectional image of a 3D volumetric acquisition of the optic nerve head acquired at 106,382 axial scans per second. This image was formed by median filtering of 5 adjacent cross sectional scans. (b) OCT fundus image of the 3D volume acquisition of the optic nerve head. (c) OCT enface view of the optic nerve head showing the porous structure of the lamina cribrosa. Scale bars represent 200 $\mu m$.

### 3.3 4D-OCT: Repeated volumetric imaging of photoreceptors and retinal capillaries

Rapid repeated imaging of small volumes with high lateral resolution is enabled by the high speed acquisition of design configuration C using the 2.3 mm beam diameter. Data from 25 sequentially acquired volumes repeated over the same region of the retina is shown in Fig. 6(a). Each $128 \times 100 \times 400$ voxel volume is acquired in 0.08 sec,
Figure 6: Rapid repeated volumetric imaging. (a) 4D-OCT is generated from 25 3D volumetric acquisitions of the same region. (b) The 25th volume shown with two axial plane images at the depths of the capillaries above and below the INL layer. (c) Zoom in on the capillary layers with red arrows pointing to bright spheres along the capillary network that could be individual red blood cells. (d) 3D representation of the photoreceptor layers, showing individual cone cells. (e) OCT maximum projection view shows the cone structure from volume 12. (f) OCT enface maximum projection views from layers surrounding the INL. Frames 1-25 of the 4D-OCT acquisition are shown in sequence to demonstrate the enhanced capillary visualization offered by including temporal information (motion contrast).

with the entire sequence acquired in 2.0 seconds (12.5 volumes per second). Figure 6(b) shows the last volume in the sequence. Capillaries surrounding the inner nuclear layer (INL) are clearly visible and are highlighted by the
two axial plane images inserted into the volume. Zooming in on the capillary layers, as shown in Fig. 6(c), the 3D structure of the capillaries becomes evident. There appears to be a periodicity to the bead-like bright spheres that define the capillary network. With each sphere being on the order of approximately 8 \( \mu m \) in diameter (4 transverse pixels at 2 \( \mu m \) per pixel), each bright spot may be an individual red blood cell being observed just within the resolving limits of the instrument.

It has previously been shown that cones in certain regions of the eye can be seen using OCT without the use of adaptive optics.\textsuperscript{23,31} Isolating the photoreceptor layer from the 25\textsuperscript{th} volume, a 3D visualization of the cone structure can be seen in Fig. 6(d). A maximum projection enface image of the photoreceptor layers (±100 \( \mu m \) centered at the IS/OS junction) from the 12\textsuperscript{th} volume is shown in Fig. 6(e). Individual cones are visible at the lower discernable resolution limits for this region of the eye, located at approximately 5 degrees peripheral to the fovea. Photoreceptors in other regions of the retina can be smaller and more closely spaced, which would require higher transverse image resolutions and adaptive optics for visualization. However, high speed imaging would still be important for visualizing photoreceptors because their small size makes them highly susceptible to motion induced and possibly noncontinuous image distortion from eye motion.

In addition to enabling visualization of very small features without motion artifacts, ultrahigh speed imaging also allows the visualization of volumetric features as a function of time. Visualization of the capillary network surrounding the inner nuclear layer (INL) can be improved using 4D-OCT. Figures 6(f) volumes 1-25, show the resulting enface image created by taking the maximum value (maximum projection) of the linearly scaled and truncated Gaussian windowed axial intensity data (sigma = 150 \( \mu m \), truncated at ± 100 \( \mu m \), and centered at the INL). The additional temporal information offered by the high frame rate movies aids in identifying the topology of the capillary network and may show blood flow. The advantages of “motion contrast” for revealing small vessels, as well as differential imaging from subtraction of sequential images for quantifying blood flow, has previously been shown with high frame rate fundus photography.\textsuperscript{32} Direct observation and measurement of leukocytes in the parafoveal capillaries has been shown with an adaptive optics scanning laser ophthalmoscope.\textsuperscript{33} When imaging with OCT, the visualization techniques presented in this paper could lead to new contrast-agent-free methods of quantifying blood flow in these capillaries, which cannot be measured with Doppler OCT because of their perpendicular orientation to the optical beam.

4. CONCLUSIONS

We have developed, characterized, and demonstrated several configurations of a spectral / Fourier domain OCT imaging system that use a high speed CMOS line scan camera to facilitate ultrahigh speed image acquisition. Configuration (A) uses a high spectral resolution spectrometer with 4096 pixels to achieve reduced sensitivity roll-off for improved imaging over long depths, while still imaging faster than any commercially available ophthalmic OCT system. Design configuration (B) simultaneously demonstrates higher speed, higher resolution, and a larger number of camera pixels in the spectrometer than any commercially available ophthalmic OCT system currently available. Configuration (C) images at 250,000 axial scans per second, which is an order of magnitude faster than commercial systems, while producing good quality images. The highest speed configuration (D) runs at 312,500 axial scans per second. We use the high speed configuration (C) to perform densely sampled volumetric data acquisition. OCT fundus images of the fovea and disk show minimal motion artifacts in the transverse plane at these high speeds. The ability to visualize topography without motion artifacts will be especially important for clinical applications such as imaging the optic disc in glaucoma. Data sets from repeated measurements can be more precisely registered to each other and could be used to detect and quantify small morphological changes occurring from visit to visit, aiding in longitudinal studies.

We also demonstrate rapid imaging of small volumes which enables visualization of small retinal features without motion induced image distortion and stabilized imaging without eye tracking. Cone photoreceptors in some areas of the retina can be seen in 3D renderings and en face images without the use of adaptive optics or head stabilizing with a bite bar. 4-D OCT was used to demonstrate imaging the capillary network surrounding the INL. Volumetric movies acquired at extremely high speed enable better visualization and identification of the capillary structure due to the additional temporal information and suggest the potential for visualizing blood flow. Individual 3D frames of the sequence show distinct bright spheres, which may be individual red blood cells, while 2D enface images show capillary motion from frame to frame. Because Doppler OCT does not
allow for quantifying flow in the capillaries due to their predominately perpendicular orientation to the optical interrogation beam, high speed repeated volume imaging may facilitate new direct visualization techniques for capillary activity quantification.

The results of this study suggest that high speed CMOS cameras can achieve a significant improvement in performance for ophthalmic imaging. This promises to have a powerful impact in clinical applications, improving early diagnosis, reproducibility of quantitative measurements and enabling more sensitive assessment of disease progression or response to therapy. The ability to acquire volumetric data without motion artifacts, as well as to perform repeated volumetric imaging to measure dynamic functional processes promises to be a powerful tool for ophthalmic research as well as many other fields.

ACKNOWLEDGMENTS

This research is sponsored in part by the National Institutes of Health R01-EY11289-21, R01-EY13178-07, R01-CA75289-11, National Science Foundation BES-0522845; Air Force Office of Scientific Research contract FA9550-07-1-0014 and Medical Free Electron Laser Program contract FA9550-07-1-0101.

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