The Evolution of Spectral-domain Optical Coherence Tomography

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Optical coherence tomography (OCT) is a diagnostic imaging technology that provides cross-sectional images of biological tissues. In ophthalmology, OCT can perform "optical biopsy" noninvasively, imaging the retina with a resolution higher than any other imaging modality other than histology. Now, nearly two decades since its introduction, OCT has become indispensable for research, screening, diagnosing, and monitoring diseases of the macula and optic nerve head.

Optical coherence tomography was developed by researchers at the Massachusetts Institute of Technology and collaborators and was first reported in *Science* in 1991.[1] Because ocular media are transparent, the retina provided an ideal tissue for OCT imaging. The first in vivo studies of the human retina were published in 1993,[2,3] and these were soon followed by clinical studies performed at New England Eye Center[4] and other medical centers. Although OCT was originally commercialized through a startup company, Advanced Ophthalmic Devices, in 1994 the technology was transferred to Humphrey Instruments, a subsidiary of Carl Zeiss (Jena, Germany).[5] In 1996, the first commercial OCT instrument, the Zeiss OCT, was introduced. As imaging speed increased, ergonomics improved, and standardized clinical data and clinical experience became more available, the first-generation device was succeeded by OCT2 and Stratus OCT. Stratus OCT is now accepted as a standard-of-care instrument in ophthalmology, with more than 6,000 units sold by 2006.[6] A summary of major milestones in the development of ophthalmic OCT is depicted in Figure 1.

Commercial Development of Ophthalmic OCT

1991	Demonstration of OCT in vitro
1993	First in vivo images of the retina
1994	Technology transfer to Humphrey Instruments
1995	Clinical studies (glaucoma, AMD, diabetic retinopathy)
1996	Commercial ophthalmic OCT instrument introduced
2000	2nd-generation ophthalmic OCT2 instrument introduced
2002	3rd-generation Stratus OCT introduced
2004	OCT becoming a standard of care
2006	6,000 Stratus OCT systems sold
2006	Multiple companies introduce OCT instruments

Figure 1. Summary of major milestones in the commercial development of ophthalmic OCT.

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PRINCIPLES OF OCT

OCT imaging is analogous to B-scan ultrasonography, except that OCT measures light rather than acoustic

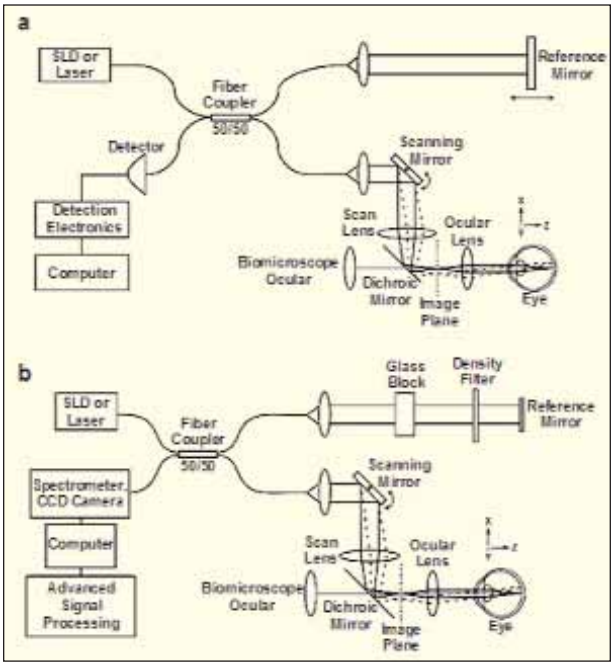

Figure 2. Comparison of schematics for OCT with (A) time-domain detection and (B) SD/FD detection.

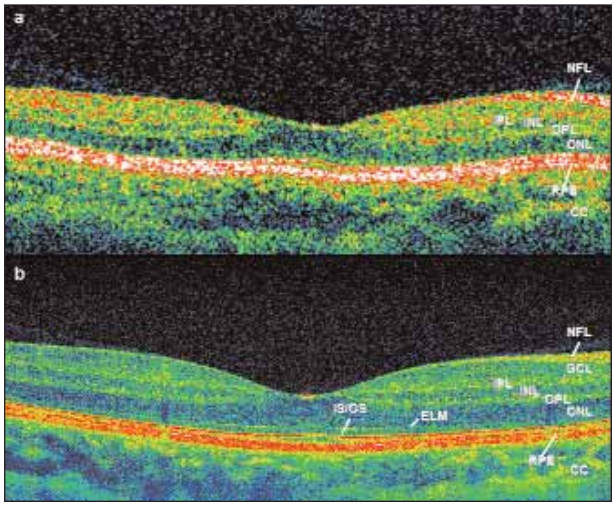

Figure 3. Comparison of normal retina scanned by (A) Stratus OCT (512 A-scans taken in 1.3 sec) and (B) prototype SD/FD ultrahigh-resolution OCT (8,192 A-scans taken in 0.36 sec). SD/FD OCT shows sharper delineation of intraretinal layers, less motion artifact, and finer speckle. NFL = nerve fiber layer, GCL = ganglion cell layer, IPL = inner plexiform layer, INL = inner nuclear layer, OPL = outer plexiform layer, ONL = outer nuclear layer, ELM = external limiting membrane, IS/OS = inner-outer segment junction, RPE = retinal pigment epithelium, CC = choriocapillaris/choroids.

waves. OCT is performed by measuring the echo delay and intensity of backscattered light from the internal tissue microstructure. Because the echo time delays of light are too fast to measure directly, an optical correlation technique, known as Michelson low coherence interferometry, is used. Low-coherence light from a superluminescent diode (SLD) is directed through a beam splitter and divided into a sample beam that is focused onto the patient's retina and a reference beam that travels a calibrated delay path (Figure 2A). Light backscattered by retinal structures interferes with light from the reference beam, and the interference of the echoes is detected to measure the backscattering signal versus delay or depth.

Conventional OCT systems use time-domain (TD) detection, in which the reference mirror is mechanically scanned to produce axial scans (A-scans) of the light echoes vs depth. The optical beam is scanned in the transverse direction to obtain 2-D cross-sectional images (B-scans) of microstructure. Stratus OCT, the third-generation instrument, uses TD detection and acquires 400 A-scans per second.

The axial image resolution depends on the bandwidth of the light source. Stratus OCT utilizes a near-infrared superluminescent diode light source centered at ~820 nm with a ~25 nm bandwidth to attain an axial resolution of ~8 to 10 µm in the eye. Conversely, transverse resolution is determined by size of the focused optical beam. Due to the tradeoff between spot size and depth of focus, commercial OCT systems typically use 20 to 25 µm transverse resolution to achieve adequate depth of focus for retinal imaging.

Application of OCT in the ophthalmology clinic has enabled imaging of the retina with previously unprecedented detail. The restricted speed of OCT with TD detection, however, limits image quality and retinal coverage. Eye movements introduce motion artifacts that require digital processing, which may obscure important pathologic features. The number of A-scans that can be acquired is limited, restricting retinal coverage and increasing sampling errors for detecting focal pathologies.

ULTRAHIGH-RESOLUTION OCT

In 1999, ultrahigh-resolution OCT, with an axial resolution of 2 to 3 µm was first demonstrated.[8] This resulted from improvements in light-source technology, replacing the SLD with a broad-bandwidth femtosecond titanium:sapphire laser and later with multiplexed SLDs.[9] This advance enabled improved delineation of intraretinal layers[10] (Figure 3), enabling "optical biopsy" of the retina. In vitro studies correlating ultrahigh-resolution OCT images with histology from animal retinas[11]

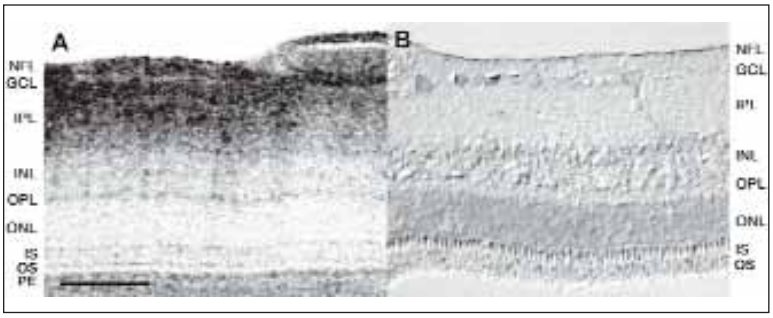

Figure 4. Correlation of pig retinal layers from (A) ultrahigh-resolution OCT with (B) histology.

(Figure 4) confirmed these findings, and qualitative studies demonstrated new information regarding specific layer involvement and photoreceptor integrity in pathologies such as age-related macular degeneration (AMD), central serous chorioretinopathy, macular hole, and choroidal neovascularization (CNV).[12]

Despite these advances in resolution, however, several limitations remained. Although high-performance SLD light sources became available, which could achieve ultrahigh-resolution OCT without the need for expensive femtosecond lasers, the limited detection sensitivity of OCT with TD detection limited the image acquisition speeds.

HIGH-SPEED OCT

Advances in detection techniques, known as Fourier-domain (FD) or spectral-domain (SD) detection, helped overcome many of the speed limitations of TD detection. SD/FD detection uses an interferometer with a high-speed spectrometer (Figure 2B) and measures light echoes from all time delays simultaneously, rather than sequentially as in TD detection. This enables increases of more than 50 times in axial scanning speeds. A similar technique, swept source/FD detection, also known as optical frequency-domain imaging, uses a frequency-swept light source and a photodetector instead of spectrometer.[13-15] Although the principle of SD/FD detection was introduced in 1995,[16] it was not applied for retinal imaging until 2002,[17] and its speed and sensitivity advantages were not realized until 2003,[18-20] after charged-coupled device (CCD) camera technology matured.

The faster acquisition speeds of OCT with SD/FD detection improve image quality by reducing eye motion artifacts, resulting in a more accurate portrayal of the true retinal contour. Furthermore, the improved transverse sampling and increased axial resolution enable more detailed images to be produced without having to increase power-exposure levels. Faster acquisition speeds also enable greater retinal coverage and more precise registration of OCT images with fundus features. While Stratus OCT mapped the macula based on interpolated data from six radial line scans,[21] SD/FD OCT enables dense raster scans composed of closely spaced B-scans acquired as 3-D–OCT data sets. Clinically, this enables physicians to identify focal lesions near the fovea in poorly fixating patients, eccentric macular holes, drusen, or pockets of fluid in AMD.

After acquisition of the 3-D–OCT data set, an OCT fundus image showing landmark features, such as blood vessels and optic disc, may be constructed by summing the data in the axial direction, with each OCT image or B-scan registered to the fundus image.[22] This feature allows physicians to pinpoint pathology on the fundus image and simultaneously examine the lesion in greater detail in the corresponding cross-section. In addition, by importing and aligning images from subsequent visits or from other modalities such as fundus photography, indocyanine green angiography (ICGA), or fluorescein angiography (FA), it will be possible to longitudinally track changes in retinal pathology and enable a more complete understanding of disease mechanisms. Figure 5 depicts longitudinal tracking of neovascular AMD after treatment by ranibizumab (Lucentis, Genentech) injection.

Three-dimensional OCT also improves the quantification of thickness and volume. By interpolating less than TD OCT, greater accuracy in thickness measurements may be attained with SD/FD OCT. 3-D–OCT data may also be used to quantify intraretinal lesions, such as drusen, fluid, retinal detachment, or tumors, to objectively assess disease progression. Figure 6 demonstrates volumetric segmentation in CNV.

Three-dimensional OCT is ideal for application in animal models. Ultrahigh resolution is required for imaging rodent retinas in order to visualize the major intraretinal layers. Although OCT was used in mouse models in 2001,[23] limitations in resolution and difficulties in registration limited its potential. 3-D OCT with SD/FD detection allows quantitative measurements at higher resolutions to be performed with precise registration to fundus features,[24] enabling longitudinal tracking in rodent models.[25] The technology avoids histological processing artifacts and minimizes the number of sacrificed animals. To date, 3-D–OCT images have been correlated with histology in several rodent knockout models of retinal degeneration,[26] and OCT promises to be a powerful tool for drug discovery and development.

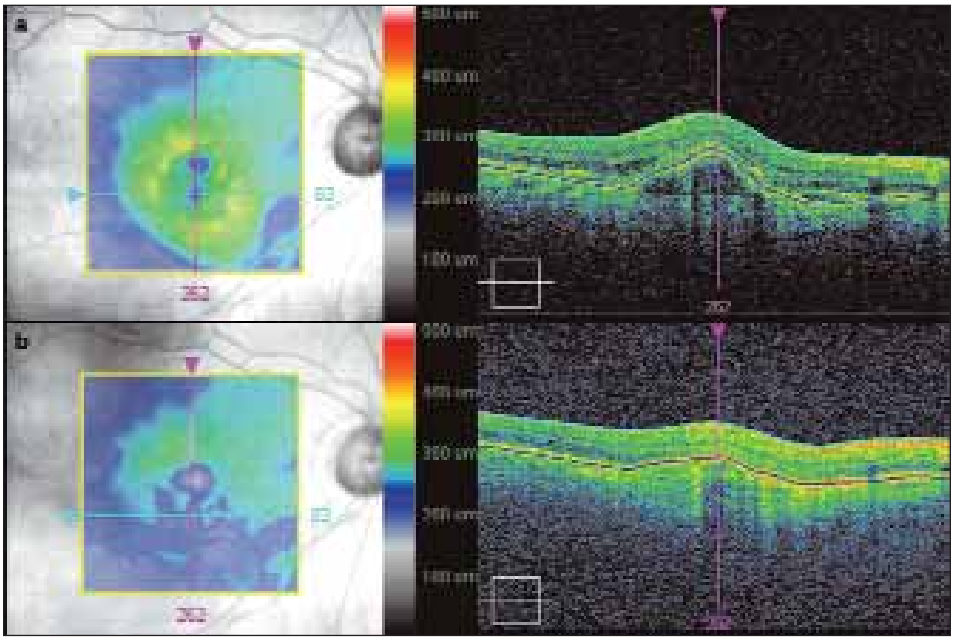

Figure 5. Longitudinal tracking of neovascular AMD. Patient was imaged on Cirrus HD-OCT (A) before intravitreal ranibizumab injection and (B) 1-month post-injection. Reduction of perifoveal pigmented epithelial detachment and subretinal fluid accumulation can be seen. By registering scans, cross-sections of the same regions across visits can be compared for changes in focal pathologies.

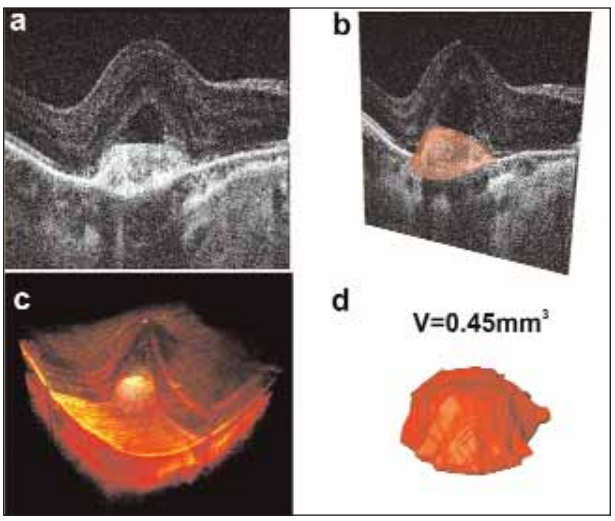

Figure 6. Volumetric analysis of 3-D–OCT data measured in an eye with choroidal neovascularization. (A) Central horizontal cross-sectional OCT image of a patient with a choroidal neovascular membrane secondary to high myopia. (B) Segmentation of the neovascular lesion across the full image set and displayed in 3-D (orange) in relation to the central cross-sectional OCT image. (C) Volumetric rendering of the retina with segmented neovascular lesion. (D) Volume calculation of the lesion.

COMMERCIAL SD/FD OCT

With the advent of broad-bandwidth, SLD light sources and recognition of performance gains offered by SD/FD detection, at least seven manufacturers have introduced OCT instruments since 2006. These instruments offer similar specifications, with axial image resolution in the ~4 to 7 µm range and acquisition speed in the 20,000 to 40,000 A-scans per second range. All models offer the benefits of improved coverage and precise registration over OCT with TD detection. Some units are designed as standalone OCT (Bioptigen SD OCT [Research Triangle Park, NC], Optopol/ Reichert Copernicus, [Zawierce, Poland], Optovue RTVue-100 [Fremont, CA], Carl Zeiss Meditec Cirrus HD-OCT [Dublin, CA]), while others combine OCT with microperimetry (Opko/OTI Spectral OCT/SLO [Toronto, Canada]), color fundus photography (Topcon 3D OCT-1000 [Paramus, NJ]), FA, ICGA, autofluorescence, or red-free imaging (Heidelberg Spectralis HRA+OCT [Heidelberg, Germany]). Most models offer importation of images from other instruments for direct comparison with OCT images.

Different products have different ergonomic features as well as differences in software. Scan protocols can differ in type and density, depending on the clinician's preference for sampling resolution vs the patient's ability to fixate reliably for a long time. Motion artifacts and registration are dealt with through software, although one model (Spectralis HRA+OCT) employs eye tracking. Two models (Copernicus, RTVue-100) currently offer normative databases for macular thickness to aid in analysis. Segmentation algorithms used to define layer boundaries for macular thickness measurements vary as well. Retinal thickness measurements on the Stratus OCT were previously defined from the internal limiting membrane to the inner segment/outer segment junction. In cases of photoreceptor loss,

however, this approach is likely inadequate. 3-D OCT systems are able to resolve photoreceptor outer segment structure, so the standard for thickness calculations may change as companies adopt either the inner or outer border of retinal pigment epithelium as the convention for the posterior retinal boundary. Currently, however, there is no consensus of which boundaries to use, adding to the disparity in thickness measurements between instruments.[27]

Despite the performance gains in speed and sensitivity, SD/FD OCT still has notable limitations. First, SD/FD OCT cannot distinguish between positive and negative echo delays, which results in mirror artifacts (Figure 7A). Second, the detection sensitivity, dynamic range, and axial image resolution vary as a function of depth. This occurs because of resolution limitations in the spectrometers used in SD/FD instruments and means that the retina will have different intensities if the distance from the eye to the instrument is changed (Figure 7C). Finally, because OCT relies on an estimate of boundaries of the retina to measure thickness, media opacities, such as cataracts, may degrade image quality and make detection of boundaries less reproducible. Different estimates for the refractive index of tissue, different segmentation algorithms, and different scan protocols among manufacturers may also contribute to the systematic variability in thickness measurements. These limitations may be minimized through skilled operation and continued refinement in image data processing.

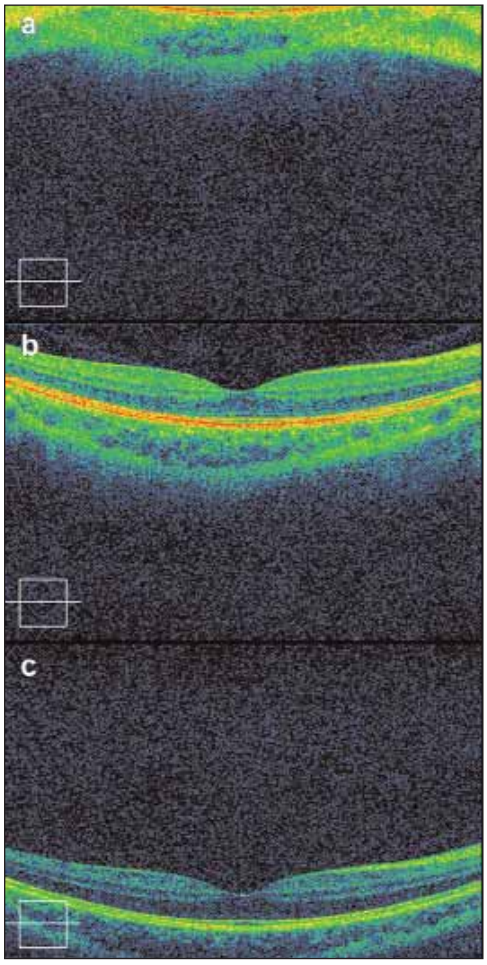

Figure 7. Demonstration of limitations of SD/FD detection. Dense raster scans were acquired on Cirrus HD-OCT in succession in a normal subject. (A) "Mirror" artifact caused by inability to distinguish between positive and negative echo delays. (B) Normal B-scan. (C) Loss of sensitivity as a function of depth.

FUTURE DEVELOPMENTS

Current commercial OCT instruments offer clear performance gains compared with previous OCT technology, although clinical gains are still being assessed. Manufacturers continue to update their software features, such as the addition of normative database and postprocessing options. Improved ability to quantitatively analyze data, with refinement of segmentation algorithms, is anticipated as clinicians learn to deal with the massive increase in data sets. As cost decreases for CCD cameras and broad-bandwidth multiplexed superluminescent light sources, ultrahigh-resolution OCT may become commercially available.

Developments in several fields of OCT research promise exciting advances in performance and clinical applications. First, imaging at a 1050-nm wavelength enables deeper choroidal penetration and improvements in signal levels over imaging at 850 nm in cataract patients.[28] Second, improvements in light source technology, such as Fourier-domain mode-locking (FDML) lasers, enable swept source/FD OCT acquisition at greater than 200,000 A-scans per second, 10 times faster than SD/FD OCT and 500 times faster than TD detection,[29] although increases in line scan camera detection rates may eventually yield similar results. Higher sampling densities enabled by these acquisition speeds should allow new scan protocols and even better visualization of intraretinal layers. Third, adaptive optics, in which a deformable element corrects ocular aberrations, improves transverse resolution by decreasing spot size of the sample beam on the retina.[30,31] Coupled with OCT, isotropic cellular-resolution imaging may be achieved,[32] which may be useful for studying photoreceptor morphology in greater detail.

CONCLUSION

In the past decade, OCT has established itself as a clinically useful diagnostic modality and a standard for the evaluation of macular and optic nerve diseases. With fourth-generation SD/FD OCT, clinicians now have unprecedented advantages in retinal coverage, precise

registration of OCT images to fundus features, and 3-D imaging. More accurate diagnosis, longitudinal monitoring of disease progression and response to treatment, as well as enhanced understanding of disease pathogenesis and drug development, can be achieved using the newest OCT technology. These advances promise to further solidify the role of OCT as an integral part of both the clinical and research settings. ■

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