Versatile optical coherence tomography for imaging the human eye

Aizhu Tao,1,2 Yilei Shao,1,2 Jianguang Zhong,1,3 Hong Jiang,1 Meixiao Shen,2 and Jianhua Wang1,4,*

1Bascom Palmer Eye Institute, University of Miami, Miami, FL 33136, USA
2School of Ophthalmology and Optometry, Wenzhou Medical College, Wenzhou, Zhejiang 325027, China
3Hangzhou First People’s Hospital, Hangzhou, Zhejiang 310006, China
4Electrical and Computer Engineering, University of Miami, Miami, FL 33136, USA
*JWang3@med.miami.edu

Abstract: We demonstrated the feasibility of a CMOS-based spectral domain OCT (SD-OCT) for versatile ophthalmic applications of imaging the corneal epithelium, limbus, ocular surface, contact lens, crystalline lens, retina, and full eye in vivo. The system was based on a single spectrometer and an alternating reference arm with four mirrors. A galvanometer scanner was used to switch the reference beam among the four mirrors, depending on the imaging application. An axial resolution of 7.7 μm in air, a scan depth of up to 37.7 mm in air, and a scan speed of up to 70,000 A-lines per second were achieved. The approach has the capability to provide high-resolution imaging of the corneal epithelium, contact lens, ocular surface, and tear meniscus. Using two reference mirrors, the zero delay lines were alternatively placed on the front cornea or on the back lens. The entire ocular anterior segment was imaged by registering and overlapping the two images. The full eye through the pupil was measured when the reference arm was switched among the four reference mirrors. After mounting a 60 D lens in the sample arm, this SD-OCT was used to image the retina, including the macula and optical nerve head. This system demonstrates versatility and simplicity for multi-purpose ophthalmic applications.

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1. Introduction

Precise measurements of each component element of the eye, including the cornea, crystalline lens, and retina, are critical for the ophthalmic clinic and research. OCT is a powerful imaging modality for high-resolution cross-sectional imaging [1]. It has been widely applied for imaging both the anterior and posterior segments of the eye using different system designs, such as anterior segment OCT and posterior segment OCT [2–5]. Compared with time domain OCT, Fourier domain OCT enhanced the imaging speed. Generally, there are two types of Fourier domain OCT: swept light source OCT (SS-OCT) and spectral domain OCT (SD-OCT). SS-OCT offers a significant advantage by extending the depth range with only a small loss of sensitivity [6–8]. High-speed multiple ophthalmic applications in one instrument utilizing vertical-cavity surface emitting laser (VCSEL) SS-OCT have been reported [9]. SD-OCT has become a standard technology applied in the ophthalmic clinic. Compared with SS-OCT, the signal-to-noise ratio (SNR) of SD-OCT dropped with the scan depth, which limits it for whole anterior segment or full eye imaging. Some techniques have been proposed to extend the scan depth of SD-OCT. A phase shift doubled the image depth with a single focus and successfully imaged the whole anterior segment [2,10,11]. A dual-channel, dual-focus OCT system was used to simultaneously image the anterior segment and retina [12,13]. With a switchable reference arm using a galvanometer, the zero delay line was alternatively placed on the anterior cornea or posterior lens with the acquisition of two images, and the whole anterior segment was visualized by registering and overlapping the two images by our group [14,15]. Furthermore, Ruggeri et al. imaged the anterior segment and the retina using a CMOS-based OCT with an optical switch in the reference arm and stitching of the two images [16]. Improved from our previous SD-OCT system, a CMOS camera was used to replace the charge-coupled device (CCD) camera to increase the scan speed, and a reference arm with four mirrors was applied to increase the scan depth to image the entire eye including the vitreous chamber. We imaged the corneal epithelium, limbus, ocular surface, contact lens, crystalline lens, retina and full eye and demonstrated the versatility of the multi-purpose use of OCT in ophthalmic imaging.

2. Methods

2.1 Experimental SD-OCT system

The schematic of this SD-OCT system is illustrated in Fig. 1. The superluminescent diode light source (InPhenix, IPSDD0808, Livermore, CA) has a 50-nm bandwidth and is centered at a wavelength of 840 nm. The light is split into the reference arm and the sample arm by a 50:50 fiber coupler. The light was focused on the anterior segment of the eye by an objective lens (f = 100 mm). The power of the incident light was 1.25 mW when imaging the ocular anterior segment. When imaging the retina, an ocular lens (60 D, Volk Optical, Mentor, OH) was added to the sample arm, the focus of the objective lens was changed to 75 mm, and the power delivered to the sample was decreased to 748 μW, which is within the safe ANSI Z136.1 value [17].

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A spectrometer consisting of a collimating lens (f = 50 mm, OZ Optics, Ottawa, Canada), a 1,800 line/mm transmission grating (Wasatch Photonics, Logan, UT) and an achromatic imaging lens (f = 240 mm, Schneider, NY) with a CMOS camera (Basler sprint spL4096-140k; Basler AG, Germany) were used to detect the reference and sample lights. Dispersion compensation was added in the reference arm to ensure the imaging system worked correctly (Fig. 1). Additional dispersion compensation was done during image processing to ensure each camera pixel corresponded to one wavelength. Different dispersion compensation factors were used in imaging anterior and posterior segments of the eye.

2.2 Switchable reference arm

Similar to our previous study and others [14,16,18], a switchable reference arm with a telecentric design was incorporated into this system to extend the scan depth (Fig. 1). A galvanometer optical scanner was employed to sequentially switch the light among the four refractive mirrors (M1, M2, M3, and M4 in Fig. 1). M1 is used for corneal imaging, and the zero delay line is near the front surface of the cornea. M2 is used for the crystalline lens, and the zero delay line is near the back surface of the lens. The axial offset between M1 and M2 is approximately 11 mm. M2 is slightly adjustable during imaging to enable the back surface of the lens to be moved near the zero delay line. M1 and M4 are used for vitreous and retina imaging, respectively. The axial offset between M1 and M4 is 25.14 mm, which has been precisely calibrated. The optical path difference between M1 and M4 is always 37.71 mm.

2.3 Sample arm and Badal system for visual targeting

A telecentric design X-Y optical scanning probe is co-axially aligned and mounted on a modified slit-lamp [19]. X-Y cross aiming was applied to control the position of the subject’s eye. Two Badal systems were combined on the sample arm to provide the far and near vision targets during imaging (Fig. 2). Each Badal system is composed of lens 1 (focus = 50 mm, Achromatic Doublet, ARC: 400-700 nm, Thorlabs, Newton, NJ), lens 2 (focus = 75 mm, Achromatic Doublet, ARC: 400-700 nm) and a liquid-crystal display (LCD) visual target. The distance between lens 2 and the eye is 75 mm. The distance between lens 1 and the LCD visual target is fixed at 100 mm. Lens 1 and the LCD can be moved together towards the eye to induce a step accommodative stimulus from 0 to 10.0 diopters (D). The LCD visual target is controlled by a PowerPoint with the letter “E”. As illustrated in Fig. 2, two LCD monitors were used and both screens displayed a slide controlled by the PowerPoint. These LCD
monitors were placed in the two arms of the Badal system. The accommodation stimulus depends on the position of each of the LCD through the two channels of the two arms. Two LCD monitors were placed on different positions for a far vision target (no accommodation) or a near vision target as the accommodation stimulus. The right side of one screen was viewed from one channel and the left side of the other screen was viewed through the other channel. When the letter “E” was displaced on the right side of both monitors, only one monitor was viewed as a target. When the PowerPoint turned to the next slide which displayed the “E” on the left side, the target was viewed through the other channel. A translating stage is used in this system to adjust the vertical and horizontal target positions.

![Fig. 2. Badal system alternatively switching between the far and near visual targets. f = focus; LCD = liquid-crystal display.](image)

2.4 The performance of this SD-OCT system

Figure 3(A) shows the spectrum of the light source used in this OCT system. The calculated spectral sampling interval was 0.015 nm [20], corresponding to a scan depth of 12.57 mm in air. The point spread function (PSF) and sensitivity was characterized by imaging a mirror in the sample arm at different depth positions. A neutral density filter (ND = 2.0, NE20A, Thorlabs, Newton, NJ) was used to reduce the signal intensity. The power in the reference arm was 1.40 mW. Figure 3(B) shows the point spread function at a path length difference of 0.5 mm. The calculated axial resolution was 7.7 μm in air, and the corresponding axial resolution was 5.6 μm in the cornea, assuming the refractive index of the cornea is 1.387. The theoretical resolution determined by the light source in this system was 6.3 μm in air [21]. The transverse resolution was ~20 μm for this system. Figure 4 shows the signal-to-noise (SNR) of the OCT system detected at different depth positions. The sensitivity decreased from 97 dB at the zero-delay plane to 47 dB at the imaging depth of 11 mm. The combination of images obtained with a pair of mirror positions (M1 + M2 or M3 + M4) compensated the SNR drops. The combination of the M3 and M4 may facilitate imaging the eyes with short axial lengths (See Section 3.3: Axial length measurements). The scan width was up to 18 mm in air.
Fig. 3. (A): Spectrum of the light source used in this OCT system. (B): Point spread function at an imaging depth of 0.5 mm. The measured axial resolution is 7.7 μm in air.

Fig. 4. Measured sensitivity at different imaging depths. One full eye image (A, B and C) is from an emmetrope, and another full eye image (D, E, F and G) is from a subject with a short axial length. (A) and (D): Combined images of the first and second reference mirror positions; (B) and (E): Image of the third reference mirror position; (C) and (F): Image of the fourth reference mirror position. Note the flipped retina was visible in the image of the Mirror 3 position (E). A normally oriented retina existed which was almost invisible (due to the SNR drop) in the image of the Mirror 4 position (F). (G): Combined images of the third and fourth mirror positions from the subject with the short axial length, showing the normally oriented retina. M1-4: refractive mirror position; OPD: optical path difference. The transverse line artifacts were observed in the image, and the sources of these artifacts may be due to the parasitic reflection in the system. Bars = 1 mm in air.
3. Results: imaging of the human eye

Five eyes of five subjects were recruited for this study, which was approved by the University of Miami review board. Each subject signed the consent form and was treated in accordance with the tenets of the Declaration of Helsinki. The subjects were free of ocular diseases or systemic diseases.

3.1 Corneal imaging

High-speed and high-resolution corneal images can be performed when one reference mirror was used. Figure 5 shows the OCT images of the cornea at the center (A) and limbus (B). The epithelium and Bowman’s layer were clearly visualized. The exposure time of the camera was set to 33 μs, corresponding to a scan speed of 24,000 A-scans/second. The image size was 4,096 × 4,096 pixels. After inserting a soft contact lens (PureVision, Bausch & Lomb, Rochester, NY), the subject was imaged again. The center and edge of the contact lens images in vivo are shown in Figs. 5(C) and 5(D). The conjunctiva buildup (the percentage of the edge covered by the conjunctiva) was categorized as 50% after optical correction for the distortion [22]. Figure 6 shows the corneal thickness map, with the scan width set to 14 mm. The volume consisted of 2,048 × 4,096 × 32 pixels acquired in 2.7 seconds. The scan speed was set to 24,000 A-scans/second. Custom-built software was used to correct the optical distortion before determining the corneal thickness [23]. The zero delay line was placed at the top of the cornea.

![Corneal images](image)

Fig. 5. Images of the cornea at the center (A) and limbus (B); (C) and (D) were imaged after inserting one contact lens. The lens edge was clearly visualized. EP = epithelium; BW = Bowman’s layer. CL = contact lens. Bars = 0.25 mm in air.
Fig. 6. OCT image of the entire cornea and its thickness map. (A): Cross-sectional image of the entire cornea in a normal eye. (B): Thickness map of total cornea with a diameter of 14 mm. Bars = 0.5 mm in air.

Figure 7(A) shows the ocular surface image with a 17.6 mm scan width. A single B-scan image consisting of $4,096 \times 4,096$ pixels required approximately 58 ms. Similar to our previous study [24], the entire ocular surface including the limbus, which connects the cornea and sclera, was visualized. Custom-built Matlab software was used to automatically analyze the surface shape information (Fig. 7(B)).

Fig. 7. Analysis of the entire ocular surface for one subject. (A). Cross-sectional image of the ocular surface at the horizontal meridian; (B). Sagittal height of the ocular surface. Bars = 0.5 mm in air.

Upper and lower tear menisci were present simultaneously in Fig. 8, which can be used for analyzing the tear system in normal and dry-eye subjects.

Fig. 8. Cross-sectional image of the upper and lower tear menisci. LTM = lower tear meniscus; UTM = upper tear meniscus. LL = lower lid; UL = upper lid. Bars = 0.5 mm in air.
3.2 Entire ocular anterior segment imaging

To image the anterior segment from the front surface of the cornea to the back surface of the lens, a scan depth of at least 10 mm in air is needed, but the sensitivity will decrease when the scan depth increases using standard SD-OCT. In this study, we used a switchable reference arm to image the anterior segment. The galvanometer employed the reference arm, sequentially changing from one mirror to another; therefore, the zero delay line was alternatively placed on the top of the cornea and the bottom of the lens, and custom software was used to register and overlay the two images [25]. The optical correction was performed before yielding the biometric measurements, with the results shown in Fig. 9. The entire cornea, anterior chamber, anterior and posterior surfaces of the crystalline lens, capsule, nucleus, and cortex are visible. The scan speed was set to 17,500 A-lines/second and the scan width was set to 15 mm. An X-Y aiming system was applied to adjust the position of the human eye [24]. Figure 10 shows images with relaxed and 6.00 D accommodative stimulation. The imaging was conducted on a 27-year-old subject with −3.00 D myopia.

Fig. 9. An image of the full anterior segment from a 27-year-old subject. (A). The combined anterior segment image by overlapping two images. (B). The longitudinal reflectivity profiles of the entire anterior segment. The transverse line artifacts were observed in the image, and the sources of these artifacts may be due to the parasitic reflection in the system. Bars = 1 mm in air.
3.3 Axial length measurements

The reference arm sequentially switches among four mirrors when measuring the axial length. Figure 11 shows the result. Figure 11(A) shows an emmetrope whose retina image is in the fourth reference mirror position. Figure 11(B) is a hyperope whose axial length is short and the retinal image is flipped for mirror position three. Figure 11(C) is a subject with a middle cataract and a short axial length. The retina image is also clearly visualized in the third mirror position. We realized that in Figs. 11(B) and 11(C), the oriented retina in the normal way position may also exist for the fourth mirror because of the consequence of mirror images in SD-OCT and two adjacent imaging ranges. However, the image obtained with the fourth mirror position appeared very faint due to the drop of SNR. Using the combination of the mirror positions 3 and 4, the normally oriented retina was visible at the right position. Figure 11(D) is a high myope whose axial length is long and the retina image is reversed in the fourth reference mirror. Figure 11(E) is a subject with an intraocular lens (IOL). The scan speed was set to 17,500 A-lines/second, and the scan width was set to 15 mm. The measurement time for the full eye imaging was 0.46 seconds. Each subject was asked to look at the target in the scan center during imaging.
Fig. 11. Full eye imaging in different refractive error subjects. (A) Emmetrope; (B) and (C): Hyperope; (D): Myope; (E): Subject with an intraocular lens (IOL). The transverse line artifacts were observed in these images, and the sources of these artifacts may be due to the parasitic reflection in the system. Note the normally oriented retina in (B) and (C) was visible in the combined images obtained with the Mirror 3 and 4 positions. The flipped retina was also visible in the image of the Mirror 3 position due to placement of the zero-delay line inside the eye (bottom of the image). M1-4: refractive mirror position; AL: Axial length. Bars = 1 mm in air.

3.4 Retina imaging

A 60 D lens was inserted into the sample arm, and the focal distance of the objective lens was changed to 75 mm when imaging the retina. Figure 12 shows an OCT image in the macular region, with the scan speed set to 70,000 A-lines/second and the scan width to 10 mm. Different structural layers can be identified. At the bottom of the outer nuclear layer (ONL), the external limiting membrane was noted in the center. Figure 13 shows an optic nerve head image (B) and the en face view (A) obtained with OCT, with the scan speed set to 70,000 A-lines/second and the en face view image obtained in 0.9 seconds. The cup and disk ratio was calculated to be 0.4 in the horizontal meridian.

Fig. 12. Different structural layers, including the retina nerve fiber layer (RNFL), ganglion cell layer (GCL) + inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), and retinal pigment epithelium (RPE) + choriocapillaries, were identified in the macular image. Bars = 0.5 mm.
4. Discussion

OCT has been rapidly developed for ophthalmic imaging since it was invented 20 years ago, and some challenges have been overcome, especially with respect to the axial resolution, scan speed, and scan depth. The depth range is determined by the spectrometer design and the bandwidth of the OCT light source and commercially available SD-OCT devices have limited scan depth up to 7 mm. The axial resolution of OCT is determined by the light source and is affected by the appropriate design of the spectrometer [21]. Ultra-high resolution with a shallow scan depth has been achieved using a broadband superluminescent diode as the light source, which was employed to image the contact lens, central cornea, and retina [26–28]. Our previous approach using a CCD camera has shown the capability for both ocular anterior and posterior segment imaging [26,29,30], but the spectrum projection was truncated to 2,048 camera pixels. Although it can be used for studying the ocular surface [24], the scan depth of 7.2 mm may not be enough to image the entire anterior segment. To provide topographic and keratometric information for the cornea and study accommodation, the scan depth may need to be extended. However, the resolution was compromised with a long scan depth due to the limit of the pixel line width of the camera. The sensitivity roll-off is defined by the pixel size and the spectral resolution of the spectrometer. The SNR decrease is an inevitable defect in SD-OCT. Another disadvantage of long-scan-depth SD-OCT is the limited focus of the objective lens. Therefore, to achieve an extended scan depth and sufficient resolution for the whole ocular anterior segment, some special techniques, including complex conjugate image removal [2,10,11], dual-channel dual-focus [12,13], and optical switching, have been proposed [14,16]. To overcome the SNR drop-off, we used the two-mirror reference arm approach [15], and others used three mirrors in the reference arm to acquire multiple images [16]. The entire anterior segment with a sufficient resolution can be obtained by overlaying [14] or stitching two images [16]. These approaches enable only portions of the eye, but not the entire eye, to be imaged, possibly resulting in the inconvenience of using multiple OCT devices for each application. The currently commercially available OCT systems have provided high resolution posterior segment images, but the development of the anterior
segment imaging has lagged. Some commercial OCT systems, such as the Cirrus (Carl Zeiss Meditec, Inc.), RTVue (Optovue, Meridianville, AL), Spectralis (Heidelberg Engineering, Dossenheim, Germany), 3D OCT (Topcon Medical Systems, Oakland, NJ), and Bioptigen SD-OCT (Bioptigen Inc., Research Triangle Park, NC), separately image the retina and anterior segment after removing or adding optics in the sample arm. The scan width and scan depth are often limited.

Imaging the full human eye is challenging because the full range of the whole eye structure is approximately 24 mm. Our current SD-OCT system was primarily used to image the anterior segment, but it can be used to evaluate the details of the retina after simple modifications. With four reference mirrors, the full-length ocular biometry was sequentially obtained, which may be used for the precise measurement of the axial length and intraocular lens calculation. Compared with IOLMaster (Carl Zeiss Meditec, Dublin, CA) or LENSTAR (Haag-Streit USA, Mason, OH) [31,32], the two-dimensional image of each component element of the anterior segment and the retinal image were obtained during the biometric measurement, although the repeatability and accuracy of each part was not validated. For some hyperopes with a short axial length, the retinal image was also present in the image obtained with the fourth mirror position. However, the images presented from the fourth mirror position in Figs. 11(B) and 11(C) were almost invisible due to the SNR drop (not poor alignment and/or image processing errors) as demonstrated in Fig. 4. It may be the only way to image the eyes with short axial lengths by adding the third mirror if the position of the fourth mirror is static. Continuous alternation of the reference mirror may add inconvenience of imaging operation and may also introduce measurement errors due to the move of the reference mirror. Using the static design of the reference arm may be also suitable for further development of the system for clinic studies, in which clinicians and researchers with limited training may operate the system. Imaging the retina with high SNR using the third mirror in the eyes with short axial lengths may also facilitate automated axial biometry as we demonstrated previously [33]. To view the normally oriented retina in the eyes with short axial lengths, we realized that we could alternatively use the combined images of the third and fourth mirrors to enhance the SNR for imaging the retina. In this case, the normally oriented retina was displayed (Fig. 11). The same concept was used to improve the anterior segment imaging using the first and second mirrors. This may further justify the use of the additional mirror. With the 4-mirror switchable reference arm, the scan depth was sufficient enough for imaging the full eye without a gap. The full range of the whole eye structure is approximately 24 mm. Although all key elements of the eye were imaged successfully using the 3-mirror approach [16], an un-scanned gap remained in the vitreous chamber. Li et al. have characterized the anterior chamber cell grading using time-domain OCT [34], and swept-source OCT has been used to observe the vitreous structure by Liu et al. [35]. The information of the vitreous in the present study could be used for quantifying the vitreous muddy in future studies. Adding an extra mirror will extend the measurement time for full eye imaging, in trade off for the gained benefit of enhanced SNR for imaging the retina in some eyes with short axial lengths and the ability of imaging the vitreous. The benefit gain may overweight the drawback. With the 4-mirror setup, if we have to consider the speed, we can use three mirrors without changing any hardware. We could also flexibly choose one, two, three, or four reference mirrors, depending on the imaging application as we demonstrated in the present work. SS-OCT has shown the capability of imaging the entire eye from the cornea to the retina in one image [9]. Dai et al. proposed an SD-OCT system with two interferometers and two spectrometers to image the anterior segment and retina simultaneously [13]. The cornea is not clear due to the 50% attenuation of the reflected light. A single spectrometer with two illumination sources and interlaced detection has been set up to acquire the anterior segment and retinal tomograms simultaneously [3]. The entire lens was not imaged in that system due to the scan depth being nearly 6.0 mm after the complex artifact removal algorithm was employed. The lens information is important for the eye clinic, such as in studies of accommodation. Because we used a 4096 pixel camera instead of one with 2048 pixels, the imaging depth was increased to more than 12.0 mm, which is long enough to image
the entire anterior segment. When imaging the cornea and retina simultaneously with dual-channel SD-OCT systems [3,13], the relative motion between the two regions can be estimated. The disadvantage of our system is the retina obtained from the current study was a small plane line due to the telecentric scanning when measuring the axial length. The details of the retina only can be obtained after mounting a Volk lens.

The scan speed may be an issue when acquiring the images. Time domain OCT has a long scan depth, but the scan speed is slow compared with SD-OCT [36,37]. A fast scan speed will minimize artifacts due to eye motion [38] and is critical for good repeatability and 3 dimensional (3D) reconstruction. Currently, no commercial OCT system has used a CMOS camera in the clinic. Based on the CMOS camera in this system, 3D volumetric data could be obtained in 0.9 seconds at a scan speed of 70,000 A-lines/second. As demonstrated by previous work, a CMOS-based SD-OCT system enables us to perform real-time imaging and calculate the lens refractive index [16,25,39]. Enhancement of the image quality may be accomplished by decreasing the scan speed or averaging the images [9,40].

The last factor for examining the entire eye scanning system may be the image quality of each individual component of the eye that can be separately imaged. Based on a single spectrometer and an alternating reference arm, multiple scan modalities were introduced in one instrument. Compared with the ultra-high OCT images with resolutions below 5 μm [30,41], although the tear film was not clear with this SD-OCT system due to the limited axial resolution, we still clearly visualized the Bowman’s layer and contact lens edge using one reference mirror. A telecentric system was incorporated into the probe for 3D scanning. A Badal system was introduced into this system to induce different accommodative stimulations. Except for the ciliary muscle, high-quality images of the center cornea, limbus, ocular surface, contact lens, tear meniscus, crystalline lens, retina, and full eye were achieved, which can meet different needs in future clinical care. SS-OCT has been proposed to provide multiple ophthalmic applications in one instrument [9], but the cost is more expensive and the design is more complex. The current system may be used for studying accommodation, axial length measurement, and cornea imaging. It might suitable for developing countries or entry labs to study OCT. It may also help the field to widen OCT usage for both research and clinical care.

We have developed some software for corneal mapping and overlapping two images for the entire anterior segment. Further development of automatic software for biometric measurements is truly needed for multi-purpose OCT. Notably, the multi-purpose system has its limitations with respect to the axial resolution and scan speed compared with specially designed commercial systems. Therefore, this system may not replace these devices specifically designed for anterior or posterior segment imaging.

5. Conclusions

In conclusion, we have developed a versatile ultra-long scan depth SD-OCT to image the entire eye, including the corneal epithelium, limbus, ocular surface, contact lens, entire anterior segment, and retina, as well as the entire axial biometry. This system’s versatility for the multi-purpose use of OCT in ophthalmic imaging may help widen the use of OCT in the future. However, the all-in-one system has compromised the axial resolution and scan speed, which may not replace currently available, specially designed systems.

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