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Curved-field optical coherence tomography: large-field imaging of human corneal cells and nerves

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Cell-resolution optical imaging methods, such as confocal microscopy and full-field optical coherence tomography, capture flat optical sections of the sample. If the sample is curved, the optical field sections through several sample layers, and the view of each layer is reduced. Here we present curved-field optical coherence tomography, capable of capturing optical sections of arbitrary curvature. We test the device on a challenging task of imaging the human cornea *in vivo* and achieve a $10 \times$ larger viewing area comparing to the clinical state-of-the-art. This enables more precise cell and nerve counts, opening a path to improved monitoring of corneal and general health conditions (e.g., diabetes). The method is non-contact, compact, and works in a single fast shot (3.5 ms), making it readily available for use in optical research and clinical practice. © 2020 Optical Society of America under the terms of the OSA Open Access Publishing Agreement

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1. INTRODUCTION

The cornea is the curved outermost part of the eye. Corneal transparency provides a unique opportunity to optically observe live microstructures of the eye and use them as indicators of ocular and general health. Clinical protocols (e.g., for refractive surgeries [1-3]) rely on counts of cells and nerves, located in en face corneal planes and therefore require en face corneal images with a large field-of-view (FOV). Unfortunately, the FOV of existing high-resolution clinical modalities, such as in vivo confocal microscopy (IVCM) and specular microscopy (SM), is optically limited to about 0.5 mm [4]. Emerging in vivo research devices originating from the conventional Fourier-domain optical coherence tomography (OCT), such as UHR-OCT [5,6], GDOCM [7], and μOCT [8] can increase the FOV up to about 1 mm, however, the cellular mosaics on that scale are free of motion artifacts only in anaesthetized animals, immobilized during the prolonged laser beam scanning in the en face plane. The faster corneal Fourier-domain full-field optical coherence tomography (FD-FF-OCT) modality by Auksorius et al. [9] can capture images free of scanning-related artifacts with 0.615 mm FOV, but requires costly hardware, such as a high-speed camera and swept-source laser. Alternative to the above backscattering detection methods, the retroillumination microscopy by Weber and Mertz [10] demonstrates a 0.820 mm \times 0.580 mm FOV. Beer *et al.* [11,12] acquired flattened images of the entire corneal layers by using

conical illumination OCT, however, resolution was insufficient to resolve cells and nerves.

Recently, we developed an *en face* optical sectioning method, namely in vivo time-domain full-field optical coherence tomography (TD-FF-OCT) [13,14], which can obtain celldetail in vivo corneal images with a 10× larger viewing area at $1.2 \text{ mm} \times 1.2 \text{ mm}$. Nevertheless, as the cornea exhibits natural curvature, the flat field optically sections through several corneal layers at once, keeping the FOV of each fine curved corneal layer limited. Here we demonstrate a method, termed curved-field optical coherence tomography (CF-OCT), which can capture optical sections of arbitrary curvature. Applied to the in vivo human cornea, this method enables full-field views of the curved sub-basal nerve plexus (SNP) and endothelial corneal layers at 1.13 mm × 1.13 mm and beyond. Moreover, a high en face imaging speed of CF-OCT (0.6 billion pixels/s) ensures that images are free of eye or head movement artifacts. Large-field views of the SNP, obtained in a non-contact way, open a path for simple and precise monitoring of the progression of diabetes, known to alter the corneal nerve density and tortuosity [15]. In addition, larger views of the endothelial cell mosaic are expected to improve the outcome of corneal transplantation and cataract surgeries, which are today performed upon confirming endothelial health and a minimal cell count [16].

2. METHODS

To achieve the curved optical sectioning, we implemented a simple optical lens in the conventional interferometric TD-FF-OCT design (Fig. 1).

The light from the light-emitting diode (LED) (M850LP1, Thorlabs, USA) with near-infrared (NIR) 850 nm central wavelength and 30 nm bandwidth is first separated by the 50:50 beam splitter (BS) (BS014, Thorlabs, USA) into the sample and reference arms of the interferometer and then focused by the $10 \times air$ microscope objectives with moderate numerical aperture (0.3 NA) (LMPLN10XIR, Olympus, Japan) on the sample and on the front surface of the curved optical lens, acting as a curved mirror with 4% reflectivity (given the glass material of the lens). The reference interference arm with the curved-mirror is pre-aligned to account for defocus (mismatch between the focus and coherence plane) [13,14,17], when imaging the selected corneal layer of interest. The reflected light from this curved mirror and the backscattered light from the different layers of the sample recombine on the BS, producing interference. However, due to the low-temporal coherence of the LED, interference happens only for the backscattered light originating from the curved section of the sample, which matches with the curved mirror in terms of the path length to the BS. All the light (interfering and non-interfering) is detected by the 2D CMOS camera (Q-2A750-CXP, Adimec, Netherlands),

composed of 1440 × 1440 pixels with high (2Mē) full-well capacity. Following the conventional TD-FF-OCT tomographic image retrieval scheme [18,19], the camera rapidly (at 550 frames/s, 1.75 ms per image) captures two consecutive images with different optical phases (typically two to four), modulated by a piezo mirrorshifter (STr-25/150/6, Piezomechanik GmbH, Germany), and the simple algebraic post-processing on the images reveals the curved optical section of the sample. The above general approach can be used to obtain optical sections of any shape. We experimentally confirmed the 1.7 µm lateral and 7.7 µm axial resolutions, similar to the former TD-FF-OCT configurations [13,14].

To achieve a correct curved optical sectioning, the apex of the curved mirror should match to the corneal apex, however the latter is constantly shifting due to *in vivo* ocular and head movements. In order to match the apexes, we mounted the interferometer on a 3-axis motorized stage [composed of two horizontal (NRT150/M, Thorlabs, USA) and a vertical (MLJ150/M, Thorlabs, USA) translation stages], controlled with a joystick (MJC001, Thorlabs, USA), while using the images as feedback (Fig. 2 and Visualization 1). More precisely, when imaging the SNP and endothelium, we looked at the mirror-like fringe patterns at the outermost and innermost corneal surfaces, respectively. The high fringe density along the X or Y axes indicated misalignment, which could be compensated for by shifting the interferometer along the corresponding direction, until the fringe density decreased.



Fig. 1. Comparison of curved-field OCT and conventional time-domain full-field OCT designs. The optical interferometer is equipped with the incoherent LED light source, 2D camera, and microscope objectives (MO). The location of a coherence plane, corresponding to the position of the reference arm is depicted in yellow. Use of a simple optical lens instead of a flat mirror allows to curve the coherence gate and obtain the optical sections of arbitrary curvature. Green inset–CF-OCT configuration with a lens having 7.7 mm radius of curvature, optimal for optical flattening the 7.79 \pm 0.27 (SD) mm curved anterior cornea. Blue inset–CF-OCT configuration with a lens having 6.2 mm radius of curvature, sufficient for optical flattening the 6.53 \pm 0.25 (SD) mm curved posterior cornea.



Fig. 2. Curved-field OCT device. The custom-made optical interferometer is mounted on three motorized stages. The stages, controlled with a joystick, are used to center the interferometer optics at the corneal apex, achieving a correct, curved optical sectioning. A small motorized stage beneath the reference arm is used to select the corneal layer to be imaged (e.g., SNP or endothelium). The 3D model of the prototype is shown in Visualization 1.

3. RESULTS

A. Test of Curved Sectioning: Flat Target, Model Eye, In Vivo Eye

In application to human corneal imaging, we use two different lenses with radii of curvature of 7.7 mm (LA1540, Thorlabs, USA) and 6.2 mm (LA1576, Thorlabs, USA) to optically flatten the anterior and posterior cornea, which exhibit the normal curvatures of 7.79 \pm 0.27 (SD) mm and 6.53 \pm 0.25 (SD) mm, respectively [20]. We experimentally confirmed the close matching of mirror and corneal curvatures by looking at the density of the fringes, analogous to optical metrology, using for example a Twyman Green interferometer (Fig. 3).

More precisely, the light beams, reflected from the surfaces of similar shape in the two interferometric arms, will have similar phase delay over the entire field. The resulting interference pattern on the camera will show only a few fringes, indicating an optical path delay of a few half-wavelengths. This is the case with the conventional TD-FF-OCT with identical flat reflectors in both interferometer arms (Fig. 3A) and CF-OCT with the curved reflector matching to the shape of the eye up to several μ m, which is confirmed by counting about 10 fringes across the field from the center of the curvature (Figs. 3D and 3F). On the contrary, when the surface curvatures in both arms do not match, the fringe frequency that is low at the curvature apex is gradually increasing to the edges of the field, reflecting an increase in optical path length difference between the arms (Figs. 3B, 3C, and 3E).

B. Proof of Concept Imaging of In Vivo Human Cornea

The proof of concept test was carried out on a healthy subject (female, aged 37 years), which was confirmed by routine eye examination in the hospital preceding the experiment. Approval for the study was obtained (study number 2019-A00942-55), in conformity with French regulations, from the CPP (Comité de Protection de Personnes) Sud-Est III de Bron and ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé). Prior to experimental procedures, which adhered to the tenets of the Declaration of Helsinki, informed consent was obtained from the subject after the nature of the study was explained. Examination was non-contact and without prior introduction of any cycloplegic or mydriatric agents, or topical anesthetics. The pulsed light irradiance was below the maximum permissible exposure (MPE) levels of up-to-date ISO 15004-2:2007 (below the 18% of MPE for cornea and 1% of MPE for retina) and ANSI Z80.36-2016 (below the 1.3% of MPE for cornea and 1% of MPE for retina). The detailed safety evaluation is provided in [14]. These values reflect that the light beam is focused onto the cornea and widely spread on the retina. Note that up-to-date ISO and ANSI standards specify different MPE levels for corneal imaging at an 850 nm wavelength, which leads to the different safety margins. The subject's head was comfortably positioned with temple supports and a chin rest. While one eye was imaged, the second eye was fixating on a target. Illumination was comfortable for viewing, due to the low sensitivity of the retina to NIR light.



Fig. 3. Correlation between interference fringe density and degree of curvature matching between the surfaces in the sample and reference arms of the interferometer. The fringe density is small, when the curvatures of the reflecting surfaces in the sample and reference arms are similar, as in the case of the conventional TD-FF-OCT with identical flat reflectors (A) and CF-OCT with the curved reflector of 7.7 mm radius, matching to the shape of the artificial (D) or *in vivo* (F) anterior eye surfaces. Alternatively, the fringe density is high (see zoomed view), when the curvatures of the reflecting surfaces in the sample and reference arms do not match, like in (B), (C), and (E) cases. Model eye was OEMI-7 (Ocular instruments, USA) with anterior curvature of 7.8 mm. All scale bars are 0.1 mm.

Figure 4 illustrates the comparison between IVCM (clinical state-of-the-art) (HRT II with Rostock cornea module and $0.3 \text{ mm} \times 0.3 \text{ mm}$ FOV; Heidelberg Engineering, GmbH, Germany), TD-FF-OCT and CF-OCT images of the SNP, acquired from the same heathy subject.

CF-OCT revealed the 2–4 μ m thick corneal nerves within 1.13 mm × 1.13 mm FOV, which is about 10× larger (in area) than the clinical IVCM. Although this field is smaller comparing to the recent research version of IVCM that was able to achieve enlarged FOV of more than 2 mm × 2 mm by using a moving fixation target and mosaicking of more than 1000 conventional

IVCM images [21,22], the latter approach required perfect fixation of the subject during a prolonged period (about a minute), which is impossible in many clinical cases. As another limitation, IVCM requires introduction of an ocular anesthetic and physical contact with the patient's eye, resulting in discomfort for the patient, increased risk of corneal trauma, and appearance of corneal folding artifacts in the images. On the contrary, CF-OCT is a non-contact modality, and the increased FOV, which is rapidly captured in 3.5 ms, simplifies locating of the same region of interest over time and increases the accuracy of measured nerve density, which is an important disease indicator, such as for diabetes progression.



Fig. 4. Curved-field OCT versus full-field OCT and confocal microscopy for imaging of the SNP in the human cornea *in vivo*. By matching the curvature of optical sectioning with that of the cornea, CF-OCT substantially increases the FOV of the SNP layer, in comparison to the state-of-the-art TD-FF-OCT [9] and CM. Non-contact CF-OCT is free from corneal applanation artifacts, which typically complicate SNP imaging with a contact CM. All scale bars are 0.1 mm.

Figure 5 shows the comparison of endothelial images acquired with a clinical specular microscope (SM) (SP-3000 P, Topcon, Japan with 0.25×0.5 mm FOV), TD-FF-OCT, and CF-OCT.

While SM and TD-FF-OCT are both non-contact methods and show the increased FOV over CM, CF-OCT demonstrates further improvement, reaching a $1.13 \text{ mm} \times 1.13 \text{ mm}$ view of the endothelium. We performed a quantitative comparison. We counted 1743 cells over the best focus 0.85 mm circular area within the CF-OCT field, equivalent to a cell density of 3072 cells/mm², within the normal range for human corneas [23]. Similarly, with SM, we counted 387 cells and measured the matching cell density of 3096 cells/mm². Note that defocus decreases the sharpness of cells at the edge of CF-OCT FOV, despite the fact that the lateral resolution of TD-FF-OCT with spatially incoherent illumination is less affected by optical aberrations [24]. The reason is that defocus is present in both arms of the CF-OCT interferometer, therefore optical aberrations affect CF-OCT as much as a conventional microscope.

Further note that obtaining endothelial images in Fig. 5 required an additional post-processing step, highlighted in Fig. 6.

More precisely, the endothelium, being the last corneal layer, acts as a mirror, producing strong regular interference fringes in the camera and tomographic images. We remove these fringes by first averaging about 16 tomographic images to reduce the sharpness (and therefore the spatial frequency) of the fringe borders, and then by applying a disk mask filter in the Fourier domain. Manual endothelial cell counting in Fig. 5 was done with the Multi-point Tool in ImageJ.

Next, we explored the following two possibilities for simplified use of the device in a clinical setting: 1) single frame imaging without averaging, 2) using a single curved lens for both anterior and posterior corneal imaging.

C. Simplified Curved-Field OCT: Fast Single Frame Imaging

Figure 7 shows an image of the endothelium, obtained from a single tomographic frame, captured in 3.5 ms. As image averaging was not performed, the Fourier mask filter needed to be extended to filter the higher spatial frequencies, comparing to the filter in Fig. 6, to remove the sharp fringe borders. This filtering affected the image



Fig. 5. Curved-field OCT versus full-field OCT and specular microscopy for imaging of the endothelium in the human cornea *in vivo*. By matching the curvature of optical sectioning with the curvature of the cornea, CF-OCT substantially increases the FOV of the corneal endothelial layer, in comparison to the state-of-the-art TD-FF-OCT and SM. All scale bars are 0.1 mm.

contrast, nevertheless, the cell count could be performed similarly, as in the averaged image.

D. Curved-Field OCT: Single Configuration for Entire Cornea

Figure 8 explores the possibility of using a single 7.7 mm lens for imaging the anterior and posterior cornea instead of the two separate lenses of 7.7 mm and 6.2 mm radii of curvature. Having a matching curvature with the anterior cornea, the 7.7 mm lens produces fringes with densities increasing to the edge of the field in the posterior cornea. The spatial frequency of the fringes at the edge is close to the frequency associated with cell borders, therefore the fringes cannot be filtered in the Fourier domain without affecting the visibility of cells. As discussed above, one can still remove the fringes by reducing the fringe border frequency through averaging of several 2-phase tomographic images before filtering in the Fourier domain. Alternatively, we show that in



Fig. 6. Retrieving endothelial cell mosaic from curved-field OCT camera images, obscured with interference fringes. Interference fringes originating from the mirror-like reflection can be removed by subtracting the consecutive camera images and averaging, followed by filtering in the Fourier domain. All scale bars are 0.1 mm.



Fig. 7. Comparison of curved-field OCT images captured in a single shot (3.5 ms) and averaged (52.5 ms) from *in vivo* human cornea. Single shot image of the endothelium, obtained by subtracting the two camera images and by Fourier filtering with a mask extended to higher spatial frequencies, has a different contrast comparing to SM or averaged CF-OCT images. Nevertheless, the same cells are revealed. Images were obtained from the same subject. All scale bars are 0.1 mm.



Fig. 8. Comparison of endothelial images obtained with lenses of 6.2 mm (matching to the posterior corneal curvature) and 7.7 mm (matching to the anterior corneal curvature) radii of curvature. Tomographic FF-OCT images before and after Fourier filtering are shown on the left and right, respectively. The curvature mismatch is highlighted by the fringes with increased density at the border of the image, which are difficult to filter without affecting the underlying cells. Fringes can still be removed by either performing averaging before Fourier filtering or using a 4-phase tomographic image retrieval scheme. All scale bars are 0.1 mm.

occasional moments, when the eye is static during the acquisition of four images (7 ms), the four-phase modulation scheme can be used to substantially decrease the fringe sharpness comparing to the two-phase scheme and, after filtering in the Fourier domain, reveal the cell mosaic.

4. DISCUSSION AND CONCLUSION

Curved-field OCT is a novel method for optical sectioning with arbitrary selected curvature, enabling optical flattening of curved samples *in vivo*. Applied to *in vivo* human cornea, it demonstrates a large 1.13 mm \times 1.13 mm view of sub-basal nerves and endothelium, at the same time providing benefits of a fast (3.5 ms) and non-contact imaging procedure. Imaging the corneal endothelium on a large scale has the potential to improve the outcome for patients undergoing corneal transplantation or cataract surgeries, which are today performed upon confirming endothelial health. Large FOV reduces the chance of missing the disease-affected area as well as improves the accuracy of cell counts, improving diagnosis in a variety of ocular conditions, including Fuchs' dystrophy, endothelial trauma, iridocorneal endothelial syndrome, keratoconus, and others. Large-field views of the sub-basal nerves open a path for simple and precise monitoring of the progression of diabetes, known to alter the corneal nerve density.

Although the current device implementation has a reduced flexibility, as changing the curvature of optical sectioning would require changing the lens in the reference arm and realigning, the future versions can potentially provide flexible curvature adjustment by using a combination of static and tunable lenses. The future versions of the CF-OCT device can also benefit from incorporating automatic cell-counting techniques [25], reducing the screening time in busy clinical settings. The in-focus FOV, presently limited to 0.85 mm, can be greatly extended by utilizing microscope objectives with smaller NA. For example, reduction in

NA from 0.3 to 0.2 will increase the depth of focus by more than twice, while the reduced lateral resolution from 1.7 μ m to 2.5 μ m will still be sufficient to resolve nerves and cells, as was confirmed in [5,9].

Aside from ophthalmic imaging, CF-OCT may prove useful for non-contact exploration of various *in vivo* as well as *ex vivo* human and animal tissues exhibiting a curved structure.

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