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Publication Date

2008

DOI

10.1117/12.819169

Peer reviewed

Challenges and possibilities for developing adaptive optics - ultra-high resolution optical coherence tomography for clinical *in vivo* retinal imaging

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ABSTRACT

Recent developments in adaptive optics - optical coherence tomography (AO-OCT) allow for ultra-high isotropic resolution imaging of the *in-vivo* retina, offering unprecedented insight into its volumetric microscopic and cellular structures. In addition to this promising achievement, the clinical impact and application of this technology still needs to be explored. This includes assessment of limitations and challenges for existing as well as future AO-OCT systems, especially in the context of potential transfer of this technology from an optical bench to a portable imaging system. To address these issues we will describe our current AO-UHR-OCT focusing on its sub-components, as well as application for clinical imaging. Additionally, we describe some directions for future development of our AO-OCT instrument that would improve its clinical utility including: new compact AO-OCT design, new improved AO sub-system (extreme AO), and new generations of Fourier-domain-OCT.

Keywords: (110.4500) Optical coherence tomography; (010.1080) Adaptive optics; (170.0110) Imaging system; (120.3890) Medical optics instrumentation; (170.4470) Ophthalmology; (220.1000) Aberration compensation

1. INTRODUCTION

Adaptive optics - optical coherence tomography (AO-OCT) [1-12] developed over the last 4 years at UC Davis [5,11,12] has realized an improvement in lateral resolution for ultra-high resolution (UHR) OCT, resulting in real-time imaging with high volumetric resolution ($\sim 3.5 \mu\text{m}$ in all three dimensions). Its components include a Fourier-domain OCT (Fd-OCT) engine with chromatic aberration correction and AO correction using two deformable mirrors (DMs). The AO-OCT system presented in this paper has already been described in detail elsewhere [5,11,12]. A brief overview of the system is provided, followed by examples of system performance and application for clinical imaging. Finally, we describe possible future directions for the UC Davis AO-OCT system, with a list of challenges to be overcome, and some examples of future upgrades to AO and OCT sub-systems.

2. MATERIALS AND METHODS

Figure 1 is a simplified schematic of a generic AO-OCT system that consists of a Michelson interferometer with AO system (with wavefront corrector and wavefront sensor) in the OCT interferometer sample arm [11]. The light from the source (usually a superluminescent diode (SLD) or Ti:Saph laser) is split by a beam splitter (or fiber directional coupler for fiber-based OCT systems) into sample and reference arms. The light in the reference arm is back-reflected by the mirror that is placed at the optical distance that matches the distance to the sample structure placed in the sample arm. The back-scattered light from the sample is collected by the detector where it interferes with the reference arm light allowing OCT detection. Different OCT detection schemes (Time domain (Td) or Fd) implement different detectors and signal modulation [13]. However an interferometer similar to the one presented in Fig 1, allowing interference between the reference light and that back scattered from the sample, is common for all OCT systems. Note that in Fig. 1 OCT light is also used by the wavefront sensor to detect aberrations of the optics of the subject's eye. It is also possible to use a separate beacon for wavefront sensing and controlling the adaptive optics sub-system.

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Fig. 1: Simplified schematic of a Michelson Interferometer based AO-OCT instrument. The AO subsystem is inserted into the OCT sample arm. The same light is used for OCT detection and wavefront sensing. The achromatizing element is designed to compensate the eye's longitudinal chromatic aberrations over spectral bandwidth of the light source [10].

The achromatizing element that is placed at the entrance of the sample arm is important for UHR-OCT systems to compensate for the eye's longitudinal chromatic aberrations (LCA). This is achieved by introducing negative LCA by this element.

2.1. UC Davis AO-OCT experimental system

In the UC Davis AO-OCT instrument we use a fiber-based Fd-OCT to acquire retinal images. The entire AO-OCT system occupies a 5 ft x 6 ft laboratory optical table. In the optical design, we used a cascade of focal telescopes (created by pairs of spherical mirrors) to produce conjugate planes of the eye pupil with all key optical components, including horizontal (X) and vertical (Y) scanning mirrors, two wavefront correctors (DM1 and DM2) as well as a Hartmann-Shack (H-S) wavefront sensor (which uses a portion of the OCT imaging light for wavefront reconstruction). The schematic of the UC Davis AO-OCT instrument is shown below.

Fig. 2: UC Davis AO-UHR-OCT system layout [11].

The AO-OCT control system is implemented with two PCs, one for AO and one for OCT. The light source for both OCT and AO subsystems is an SLD operating at ~ 840 nm with ~ 110 nm spectral bandwidth (Superlum LTD), allowing $3.5\text{ }\mu\text{m}$ axial resolution in the retina. To reduce head motion, a bite-bar and a forehead-rest assembly have been mounted on an X-Y-Z translation stage. This also allows precise positioning of the subject's eye. Eye fixation is directed to an external target to minimize head and eye motion and to allow precise imaging of different retinal locations.

2.1.1. AO sub-system

To extend the dynamic range of our AO subsystem we implemented two wavefront correctors. The use of two DMs permits the focus to be optimized for layers of interest without reducing the second DMs usable stroke (MEMS DM) to correct the eye's higher-order aberrations. The pupil diameter of 6.7 mm used in our imaging system allows for up to $3\text{ }\mu\text{m}$ lateral resolution with good AO correction. An AO-PC operates the AO closed loop by reading lenslet-spot data from the H-S wavefront sensor CCD and driving the two deformable mirrors (consecutively). The $35 + 2$ actuator bimorph Deformable Mirror (DM1) from AOptix is used for low-order ocular aberration correction (defocus and astigmatism) eliminating the need for trial lenses to correct individual subject's refractive errors up to ± 3 diopters defocus and ± 1 diopters astigmatism. A 140-actuator MEMS Deformable Mirror (DM2) from Boston Micromachines corrects residual aberrations, primarily higher-order aberrations. As a H-S Wavefront sensor we use a lenslet array from Adaptive Optics Associates (0500-30-S-A): 20×20 lenslet array (284 active); $500\text{ }\mu\text{m}$ pitch; 30 mm focal length placed in front of the CCD Dalsa 1M60 camera: 1024×1024 pixels; Pixel size $12\text{ }\mu\text{m} \times 12\text{ }\mu\text{m}$; 12 bit; 60 fps acquisition; 100% fill factor. Figure 3 shows pictures and scaled geometry of the wavefront sensor and deformable mirrors used in our system.

Fig. 3. An image (top row) and scaled geometry (bottom row) of the H-S Wavefront sensor (left); Bimorph DM (center) and 140-element MEMS DM (right). The gray area represents the image of the subject's eye pupil (diameter 6.75 mm) and has a diameter of $\sim 10\text{ mm}$ for both wavefront sensor and the bimorph and $\sim 3.1\text{ mm}$ for the MEMS.

After preliminary wavefront correction performed by the bimorph DM, our AO system is switched to the MEMS DM correction mode, which continues in closed loop during AO-OCT data acquisition, lowering residual aberrations (not corrected by first DM). An example of performance of our 2DM's wavefront correction [11] is shown on Figure 4.

Fig. 4: Example traces of the wavefront RMS (μm) - left and PSF Strehl Ratio - right reconstructed from H-S centroid displacements (measured on a healthy volunteer's eye) plotted as a function of time for 2 DM-AO system operation [11].

During the experiment, the subject's eye is dilated and cyclopleged by 1% Tropicamide and 2.5% Phenylephrine to ensure a pupil size > 7 mm and to paralyze accommodation. No trial lenses are used during testing when subject's refractive error is within the dynamic range of the AO system correction. For subjects with larger refractive error we have been able to successfully use contact lenses that correct for defocus and astigmatism and then use AO to reduce remaining aberrations.

2.1.2. OCT sub-system

The detection channel of the OCT system consists of a custom-design spectrometer allowing 2 mm axial imaging depth in the eye. Fd-OCT data acquisition software developed by Biophtigen Inc. has been used to acquire and display B-scans in real time with an acquisition speed of $\sim 18,000$ lines/s (for $50 \mu\text{s}$ line exposure). Figure 5 shows a picture of the Fd-OCT detector (spectrometer).

Fig. 5: Fd-OCT detector (spectrometer) used in our system.

As a detector we used a CCD camera - ATMEL ET71M2C14: pixel size $14 \times 14 \mu\text{m}$; 12bit, 2048 pixels; Camera Link interface. It is connected to the OCT-PC via PCI frame grabber: National Instruments PCI-1428. In our spectrometer design we used a diffraction grating – 1200 l/mm; Wasatch Photonics; Fiber collimator $f = 100\text{mm}$ from OZoptics and Objective lens - air spaced doublet $f = 150\text{mm}$ from Thorlabs. Our OCT sub-system usually operates at an exposure time of $50 \mu\text{s}$ (line acquisition speed 18k A-scans/s). This results in acquisition rates of 18 frames/s (1000 lines/frame) and 72 frames/s (250 lines/frame). In one of our standard volume acquisition modes of 100 B-scans (1000 A-scans) it takes about $T \sim 5.5$ s to acquire a full volume. In a second commonly used volume acquisition mode of 300 B-scans (250 A-scans) it takes about $T \sim 4.2$ s to acquire a volume.

As already mentioned, in AO-UHR-OCT imaging it is critical to compensate for the eye's LCA. In our system it is achieved by placing an achromatizing element at the beginning of the sample arm. Its special design allows cancellation of longitudinal chromatic aberrations of the human eye and therefore permits high lateral resolution imaging using polychromatic light with large pupil diameters. The figure below shows schematically how the achromatizing element cancels the eye's LCA. Note the reduction in the axial displacement between focal points for different wavelength (colors) from the incoming collimated beam.

Fig. 6: Effect of the eye's LCA. Left - axial separation between focal points for different wavelength (colors). Right - canceling LCA by introduction of negative chromatic aberrations by the achromatizing element.

3. RESULTS

Our AO-UHR-OCT system has been implemented successfully in clinical studies of healthy as well as diseased retinal structures. Over the last three years we have presented several of these results [14-16]. In this manuscript we will show just a few examples of clinical applications of AO -OCT systems.

2.1. Volumetric imaging of cellular retinal structures.

Here the AO-OCT system is implemented to acquire UHR volumes over small retinal areas ($\sim 300\mu\text{m} \times 250\mu\text{m} \times 600\mu\text{m}$) that have the potential to reveal cellular structures within the retina. The bimorph DM can be adjusted to shift the focus of the AO-OCT image to different layers. In the figure below we present two ultra high resolution volumes acquired at the same retinal eccentricity with AO-focus set at the photoreceptor layer in one case and at inner retina layers in other.

Fig. 7: Example of the UHR volume acquisition with AO-OCT. Left - volume with the AO focus set at the photoreceptor layers. Center- fundus photo denoting the retinal eccentricity where AO-OCT volumes were acquired. Right – volume with the focus set at the inner retina layers.

2.2. Clinical imaging with AO-OCT.

In this application the AO-OCT system is implemented to acquire data at different retinal eccentricities to allow high-resolution sampling of retinal features. This is especially important in clinical settings where at the moment it is not practical to acquire UHR images of the whole retina (it is too time consuming). Instead, images are obtained only in specific areas of interest. Figure 8 shows results of an AO-OCT imaging session during which several retinal eccentricities were imaged with 1 mm x 1 mm sampling volumes.

Fig. 8: Example of the AO-OCT application for clinical imaging. Several retinal eccentricities that were imaged with AO-OCT are denoted on the fundus photo and examples of the AO-OCT B-scans from these locations are shown [16].

2.3. ONH imaging with AO-OCT.

AO performance is degraded and chromatic aberration effects (especially transverse chromatic aberrations) increase with retinal eccentricity. Nevertheless, imaging of eccentric locations such as the optic nerve head (ONH) may become an important application area for AO-OCT. Even with somewhat reduced resolution of AO-OCT at higher retinal eccentricities, structures may be revealed that are not visible with OCT having no AO correction. Information about microscopic ONH structures may be critical for diagnosis and monitoring the progression of ONH diseases. The figure below shows results of ONH imaging with AO-OCT.

Fig. 9: Example of AO-OCT imaging of the ONH. Left - fundus photo with superimposed OCT-fundus reconstructed from the AO-OCT volumes. Right - representative B-scans and C-scans (at the location of the horizontal lines in the B-scans) from three volumes shown on the left.

4. FUTURE DEVELOPMENTS FOR UC DAVIS AO-OCT

Here we consider some limitations of the current UC Davis AO-OCT instrument. Additionally, we discuss some directions for future improvements of AO and OCT sub-system as well as new designs for AO-OCT.

4.1. Challenges for existing AO-OCT system

One of the biggest challenges for every new retinal imaging modality, including AO-OCT, is how to make it clinically friendly (i.e., easy to use in everyday clinical practice without significant technical background). The expectations for a clinically friendly high-resolution retinal imaging instrument would include, but are not limited to:

- ability of easily targeting different retinal locations (with a view finder)
- robustness of system components (especially the AO sub-system)
- robustness and/or automation of calibration procedures
- automated and normalized screening procedures and tests

Beside these practical requirements there are some challenges specific for AO-OCT instruments that have to be addressed to enhance results achieved with AO-OCT. These include but are not limited to:

- correction of eye motion artifacts (this is critical due to high magnification of AO-OCT instruments)
- reduction of speckle for single B-scan viewing (this can be achieved by averaging multiple frames acquired over the same retinal location, but requires more acquisition time).

AO-OCT would be potentially more valuable by combining it with independent functional imaging modalities. This would allow direct correlation between structure and function on the cellular level and would have a huge impact in all current applications of retinal imaging.

4.2. Challenges and future directions for AO-sub-system development

The biggest limitation of our current AO-sub-system is the dynamic range of AO correction. In the future this will be an important area of development for manufacturers of wavefront correctors. There is also room to improve wavefront measurement and correction by quantifying error of centroiding algorithms as well as reconstructor error. We plan to test a Fourier reconstructor [17] that may improve AO sub-system performance. To better quantify and calibrate the AO sub-system we plan to build into our AO-OCT a far-field camera to measure the double-pass PSF. Regarding isoplanatic error in our AO sub-system, its current maximum field of view (FOV), or lateral size of the B-scan, stays within 1mm ($\sim 3^\circ$). Thus the degrading effect over larger scans is greatly suppressed. However for future AO-OCT system design this should be taken into account.

Another potential area for AO sub-system improvement lies in the application of novel deformable mirrors that could offer a higher number of actuators with higher stroke resulting in increased AO dynamic range both in amplitude and spatial sampling (higher Zernike modes). These developments may bring us closer to the area of so-called Extreme AO that is currently being tested and developed for astronomical applications (extra-solar planet detection).

4.3. Challenges and future directions for OCT-sub-system developments

In contrast to the AO sub-system, the OCT sub-system is fairly robust. However, one of its main limiting factors that should be overcome in the future is its acquisition speed. It is possible to expect 10 x increase in acquisition speed due to constant improvements in linescan camera and frame grabber technology. One of the questions that has to be resolved is if the system sensitivity for these short exposure times ($<10\mu\text{s}$) will be sufficient to see all retinal structures of interest.

Further improvement in OCT axial resolution may help to increase contrast on OCT B-scans as well as to reduce the degrading effect of speckle (by reducing its size). This, however, may require new designs for correction of the eye's longitudinal and transverse chromatic aberrations.

4.4. New AO-OCT system designs.

There are a few directions that should be considered for future AO-OCT system designs. For example one could focus on designing a compact AO-OCT instrument that could be easily used in the clinic. Or, one may add other imaging modalities (e.g., AO-SLO). The direct correlation between retinal structure and function provided by a hybrid instrument might provide information that is potentially missing from either modality by itself.

CONCLUSIONS

We described the current status of the UC Davis AO-OCT instrument that allows *in-vivo* imaging of retinal structures with 3 μ m volumetric resolution. Example images of the retina and ONH are presented. Challenges of the existing system and future developments of the AO and OCT sub-systems were described.

ACKNOWLEDGEMENTS

We gratefully acknowledge help with the AO system from Steven Jones, Diana Chen and Scot Olivier from the Lawrence Livermore National Laboratory. Contributions of Joseph A. Izatt, from the Dept of Biomedical Engineering, Duke University, Durham, NC and from Bioptigen Inc. facilitated the development of our OCT subsystem. Support and fruitful discussions with Barry Cense, Yang Zang and Donald Miller from Indiana University through several years of AO-OCT system development is appreciated. We also thank Alfred Fuller and Bernd Hamann from IDAV, UC Davis for their help with volumetric rendering of OCT data. Julia W. Evans has been partially supported by funding from the National Science Foundation. The Center for Biophotonics, an NSF Science and Technology Center, is managed by the University of California, Davis, under Cooperative Agreement No. PHY 0120999. This research was supported by the National Eye Institute (EY 014743).

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