Recent progress in high resolution imaging of anterior eye: From Time-domain Full-field OCT to Transmission Interferometric Microscopy

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1. Main Text

In this presentation, we will discuss the key physical ides that have supported progress in in vivo anterior eye imaging.

For the past three decades, in vivo confocal microscopy (IVCM) has been the standard technique for histology-like imaging of the human cornea [5]. The high resolution and optical sectioning capabilities of confocal microscopy were achieved through spatial filtering in both illumination and detection. In recent years, a new class of corneal and crystalline lens imaging methods has emerged, based on the interference properties of light [1, 2, 3, 4]. In this presentation, we will focus in particular on two interferometric techniques for ophthalmology that were developed in our laboratory: time-domain full-field optical coherence tomography (TD-FF-OCT) and, more recently, transmission interferometric microscopy.

2. Methods and results

First published in 2018, corneal TD-FF-OCT employed an incoherent light-emitting diode (LED) and a Linnik interferometer to produce en face images of corneal cells and nerves in vivo [6]. Compared to confocal microscopy, TD-FF-OCT offered a larger field of view and did not require contact with the eye. Over time, TD-FF-OCT evolved to provide two major advancements: 1) single-shot tomographic imaging, enabled by neural networks that extract tomographic image from a single camera frame [7], 2) an even broader field of view through Curved-Field OCT, a variation of TD-FF-OCT in which the flat mirror in the reference arm is replaced with a curved mirror matching the corneal curvature [8]. However, all the designs above required manual readjustment of the reference arm for imaging different corneal layers. This limitation was later overcome by integrating spectral-domain OCT (SD-OCT) into the TD-FF-OCT setup, allowing automatic realignment of the reference arm to compensate for depth shifts and eye movements [9]. This advancement enabled imaging of clinical cases such as keratoconus and Fuchs' endothelial dystrophy [10]. However, the increased complexity and cost of the system limited its widespread clinical adoption. To address this challenge, we began exploring alternative optical architectures.

In parallel, our lab had been developing transmission imaging technology for virus detection [11]. Transmission imaging has the inherent advantage of resembling a common-path interferometer, where the interference occurs between the wave that is transmitted (0-order diffraction) through the sample and the wave that is scattered by the sample. The relative phase between these two waves can be controlled via the Gouy phase effect (a π phase shift across focus) by slightly defocusing the sample layer. This interference can be used to either enhance the contrast of otherwise transparent ocular structures or enable tomographic sectioning via 2-phase demodulation. This configuration is particularly easy to realize for imaging of ex vivo tissues [12, 13].

To implement a transmission configuration in vivo in the eye, we drew inspiration from early work on retroillumination imaging [14] and phase-gradient retroillumination microscopy [15]. These methods exploited the back-scattering properties of the sclera to illuminate anterior eye structures from behind, creating a pseudo-transmission geometry. Our specific contribution was to approach retroillumination from an interference perspective. We recognized that greater interference contrast between transmitted and scattered waves could be achieved when their phase relationship was well defined—this occurs when the secondary light source at the back of the eye has higher spatial coherence. To enhance coherence, we projected a relatively small (2 mm) illumination spot onto the posterior eye, effectively increasing the spatial coherence of the secondary source.

As a result, all corneal layers were visualized with 3× higher contrast compared to conventional broad-illumination retroillumination methods. Notably, for the first time, the crystalline lens epithelial cells and fibers became clearly resolved. An extended 2

mm field of view was achieved without contact with the eye. These results are summarized in our recent preprint [16]. Thanks to its common-path interferometric design, the new device is both robust and significantly less expensive to build than TD-FF-OCT. This opens the door to wider clinical adoption, including in resource-limited settings and developing countries. We will further discuss the technical perspectives for evolution of this new method.

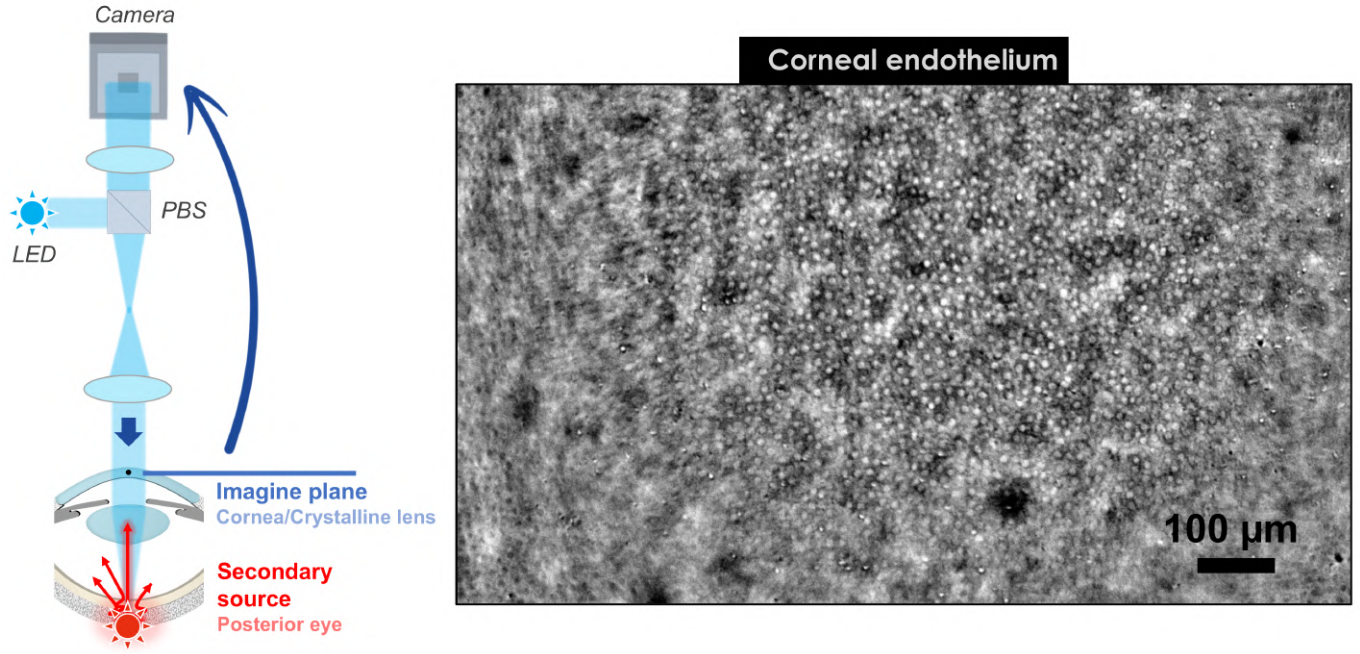

Fig. 1. Transmission interference microscope and view on in vivo human corneal endothelium.

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