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# *In vivo* estimation of elastic wave parameters using phase-stabilized swept source optical coherence elastography

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**Abstract.** We report a highly sensitive method based on phase-stabilized swept source optical coherence elastography (PhS-SSOCE) to measure elastic wave propagation in soft tissues *in vivo*. The waves were introduced using a mechanical stimulus and were assessed using the phase response of the swept source optical coherence tomography signal. The technique was utilized to measure age-related changes in elastic flexural wave velocity and attenuation in mice cornea *in vivo*. Results demonstrate that the wave velocity increases with animal age, supporting previous observations that stiffness of mice cornea gradually increases with age. Our studies suggest that the PhS-SSOCE technique could potentially be used to obtain biomechanical properties of ocular tissues *in vivo*. © 2012 Society of Photo-Optical Instrumentation Engineers (SPIE). [DOI: 10.1117/1.JBO.17.10.100501]

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The cornea is a transparent connective tissue that provides approximately two-thirds of the optical refracting power of the eye. Its shape and structure are critical for normal vision. Alterations in the biomechanical characteristics of the cornea can have a profound influence on its health, structural integrity, and normal function, and can lead to significant visual losses and even to permanent blindness.<sup>1</sup> Therefore, it is critically important to understand the interplay between the mechanical properties of the cornea and its physiological function. Quantitative characterization of the biomechanical properties of the cornea could provide useful diagnostic information for early

detection of corneal pathologies and for planning refractive surgery.<sup>2,3</sup>

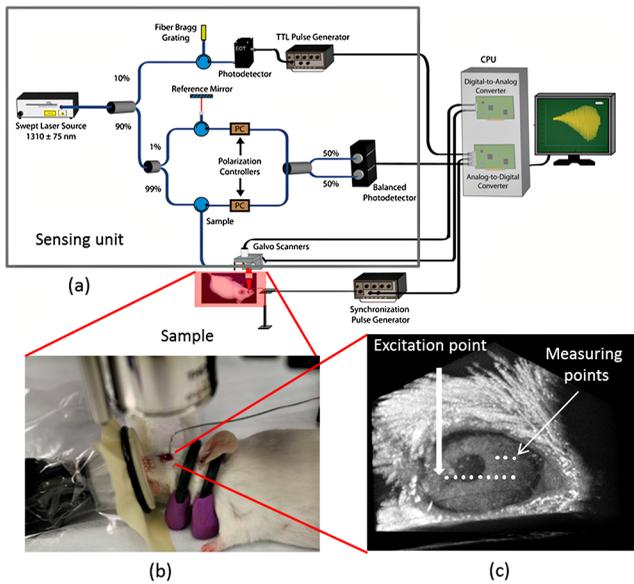
Several studies have demonstrated that significant changes in the corneal microstructure take place with age, including increasing fibril diameter<sup>4</sup> and stiffness.<sup>5</sup> Most approaches to measure the biomechanical properties of the biological tissue have relied on inducing a stimulus and measuring the tissue's response to that stimulus. The stimulus can be induced in many ways, e.g., exciting with mechanical force,<sup>6,7</sup> acoustic radiation force,<sup>8</sup> or by using a laser pulse.<sup>9</sup> Combining different stimuli and methods to measure the mechanical response to these stimuli, several elasticity imaging modalities have been proposed such as magnetic resonance elastography,<sup>7,10–12</sup> ultrasound elastography,<sup>13,14</sup> acoustic radiation force imaging,<sup>15,16</sup> and supersonic shear imaging.<sup>8,17,18</sup> However, all of these methods require significant amplitude of tissue stimulation in order to produce a measurable signal.

The only clinically accepted instrument for measurement of corneal biomechanics is ocular response analyzer (ORA), which uses a controlled air pulse to induce mechanical deformation of the eye.<sup>19</sup> The ORA utilizes an electro-optical system to record applanation (flattening) of the corneal surface during both inward and outward deflection in response to an air pulse. Biomechanical properties are then estimated from the time taken for the corneal applanations to occur.<sup>19,20</sup> Therefore, ORA also requires a large displacement of the corneal surface for evaluating biomechanical properties. However, the predictability of this system is still under investigation.<sup>21</sup>

Our method utilizes optical coherence tomography (OCT), a noninvasive in-depth imaging technology, to detect the vibrations on anterior and posterior corneal surfaces. OCT was first applied in 1998 by Schmitt to measure microscopic deformations due to compressive stress.<sup>22</sup> Since then, several groups have been utilizing OCT to obtain the biomechanical properties of tissues.<sup>9,23–26</sup> De la Torre et al. have measured displacement fields with a sensitivity of 10 nm in porcine cornea *ex vivo*.<sup>27</sup> Corneal biomechanics using OCT have been demonstrated by Li et al. and Ford et al. in *ex vivo*<sup>28</sup> and *in situ*<sup>29</sup> conditions, respectively. Recently, Alonso-Caneiro et al. measured corneal dynamics *in vivo* by observing the corneal response to an air pulse from a series of depth-wise images generated from swept source OCT.<sup>23</sup> However, they had to displace the cornea to the order of 1 mm in order to perform measurements. No work related to estimation of corneal biomechanics *in vivo* with minute corneal displacement has been reported yet, mainly due to the difficulty of inducing vibrations and detecting small amplitudes simultaneously in life conditions. In this work we utilize a previously developed method to detect vibrations on corneal surface *in vivo* with high sensitivity.<sup>30,31</sup> The method measures the parameters required for estimating biomechanical properties of the cornea from a very low amplitude (~ a few microns) excitation. To the best of our knowledge, this is the first time the wave parameters have been quantified in *in vivo* mice cornea using very low amplitude vibrations.

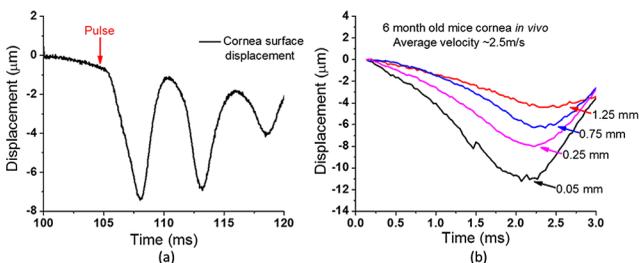
In proof-of-principle studies, we utilized mechanical stimulus for inducing waves in the sample and phase-stabilized OCT for sensing the tissue response (Fig. 1). The details of the phase-stabilized swept source optical coherence elastography (PhS-SSOCE) and the method of obtaining phase response of the sample can be found in our previous publications.<sup>32–34</sup>

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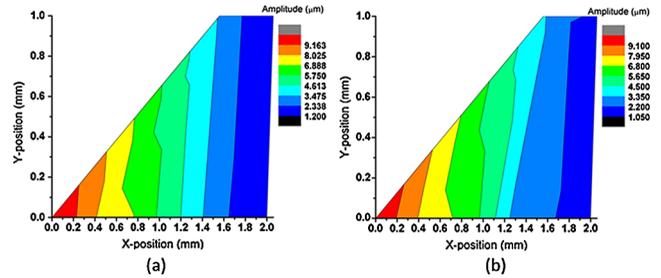


**Fig. 1** PhS-SSOCE system: (a) overall schematic diagram; (b) insert showing a photograph of *in vivo* imaging of mouse cornea; and (c) insert showing acquired 3-D OCT image of the eye and indicating the location of the mechanical excitation and a set of points where the measurements were performed.

Briefly, the PhS-SSOCE consists of an electrically driven excitation unit and PhS-swept source optical coherence tomography (SSOCT) for sensing the vibrations. The excitation unit consists of a thin wire attached to a speaker diaphragm that responds to a rectangular pulse generated by a pulse generator (duration of 0.1 ms). The tip of the wire was rounded to remove sharp edges (contact area of  $\sim 0.6 \text{ mm}^2$ ) to insure no damage was introduced to the tissues. With the onset of the adjustable input pulse, the tip of the wire comes in contact with the sample and introduces elastic flexural waves in the cornea. The PhS-SSOCT consists of a Mach-Zehnder interferometer for imaging and a fiber Bragg grating (FBG) for triggering. The phase-stability of the system is measured as 0.09 rad that corresponds to 1.9 nm of displacement sensitivity. We chose PhS-SSOCT for these studies due to its ability to extract phase information from extended tissue depths. PhS-SSOCE readings were performed at different spatial locations as shown in Fig. 1(c). From these measurements of the phase responses, the wave attenuation and wave velocity were quantified. Wave attenuation was directly obtained from the amplitude of the phase response, whereas the wave velocity was measured from the delay observed in the phase response



**Fig. 2** (a) Typical displacement produced by mechanical pulse (indicated by the red arrow) on the corneal surface; (b) typical phase responses of 6-month-old mouse cornea recorded at increasing distances from the point of the stimulation.

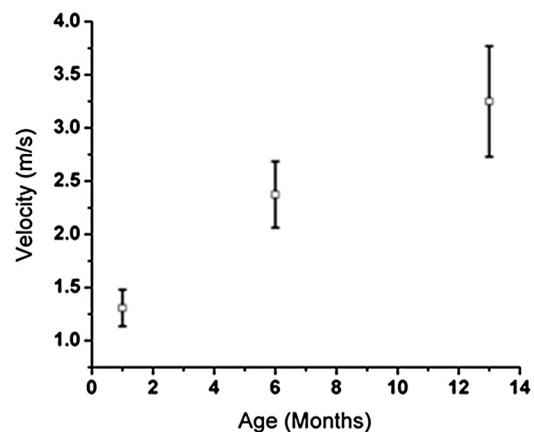


**Fig. 3** Amplitude of shear wave on (a) anterior and (b) posterior surface of mouse cornea.

between two points of known distances. Therefore, as shown in the insert c of Fig. 1, phase responses were measured at increasing 0.5 mm incremental distances away from the location where mechanical stimulus was applied.

A typical temporal response of the corneal surface to the mechanical excitation measured at an arbitrary spatial location is shown in Fig. 2(a). The corneal surface displacements measured at increasing distances relative to the excitation pulse are shown in Fig. 2(b). These data clearly depict that the amplitude of the wave decreases with an increase in the distance from the point of stimulus induction. These amplitudes were used to plot a wave propagation tomogram from both anterior and posterior surfaces of mice cornea as shown in Fig. 3(a) and 3(b), respectively, where the attenuation of the wave amplitude with the increasing distances is clearly seen. In these experiments, amplitudes of the mechanical waves recorded at different spatial locations were from approximately  $10 \mu\text{m}$  to  $2 \mu\text{m}$ , highest near the excitation point and gradually decreasing as they propagate in the cornea.

Data shown in Fig. 2(b) also demonstrate that the measured amplitude is delayed for the points located farther away from the excitation point. This phase delay can be used to estimate the time taken by the wave to travel over that distance. Therefore, by taking the ratio between the distance and the time delay, velocity of the elastic wave can be calculated. As a proof-of-concept, these velocities were calculated from the anterior surface of the mouse cornea for 1, 6, and 13-month-old animals. In these pilot studies, only one mouse has been used for each age group; however, the measurements were made three times at different spatial locations of the excitation/recording. The velocity as a



**Fig. 4** Shear wave velocity as a function of age. Velocities were averaged over 1 mm distance with three measurements at each point.

function of age is shown in Fig. 4 and demonstrates clear increase of the velocities with the animal age. Our previous phantom studies showed that higher velocities correspond to stiffer phantoms.<sup>30</sup> Additionally, recent studies demonstrate clear dependence of ocular tissue elasticity as a function of age.<sup>35</sup> Therefore, higher velocities measured in corneas of older mice suggest that the elasticity of the cornea is increasing with the age.

The results shown in this letter demonstrate the capability of the PhS-SSOCE technique to measure tissue response to very minute stimulus. This method can be directly applied to any kind of stimulus to measure the wave parameters. Furthermore, using the theory of elasticity and reconstructive approaches, the wave parameters can be used to evaluate the biomechanical properties of tissue *in vivo* and completely noninvasively.

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