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Visualizing ultrasonically-induced shear wave propagation using phase-sensitive optical coherence tomography for dynamic elastography

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Abstract

We report on the use of phase-sensitive optical coherence tomography (PhS-OCT) to detect and track temporally and spatially shear wave propagation within tissue induced by ultrasound radiation force. Kilohertz-range shear waves are remotely generated in sample using focused ultrasound emission and their propagation is tracked using PhS-OCT. Cross-sectional maps of the local shear modulus are reconstructed from local estimates of shear wave speed in tissue-mimicking phantoms. We demonstrate the feasibility of combining ultrasound radiation force and PhS-OCT to perform high-resolution mapping of the shear modulus.

Soft tissue stiffness can provide clinically valuable information in addition to conventional structural images. Different elastography techniques have been developed based on magnetic resonance imaging (MRI) [1][2] or ultrasound (US) [3][4] modalities. The latest developments include dynamic elastography methods that provide quantitative and repeatable measurement of tissue stiffness derived from the speed of propagating waves launched within tissue [5][6][7][8]. Dynamic elastography has recently emerged in the optical coherence tomography (OCT) field [9][10]. High spatial resolution and high sensitivity make OCT an ideal modality to assess the biomechanical properties of tissues for ophthalmic, dermatologic, or vascular applications.

We recently reported a shear wave elastography method based on phase-sensitive OCT (PhS-OCT) combined with a mechanical vibrator as a shear source [11][12]. However, a non-contact or remote shear source is preferable for clinical translation. US radiation force is commonly used in US-based elastography to remotely generate shear waves deep within

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tissue [5][13][14], and is now gaining increasing interest for optical coherence elastography [15][16][17]. The latter works showed interesting measurements of elastic parameters from US-induced displacements detected by PhS-OCT. However, they do not, to our knowledge, provide maps of the local shear modulus. Such maps are extremely important for functional imaging and clinical decision making because elastic properties are registered with tissue structures and elastic heterogeneities are highlighted. Here, we combine US radiation force with PhS-OCT to reconstruct quantitative cross-sectional maps of the shear modulus of tissue-mimicking phantoms.

Figure 1 illustrates the experimental setup. We used a spherically-focused, single element US transducer (central frequency 7.5 MHz, focal distance 35 mm, diameter 23 mm, Sonic Concept, Bothell, WA, USA) as a remote shear wave source. The transducer was first calibrated with a hydrophone (Onda, Sunnyvale, CA, USA). The dimensions of the US focal spot were estimated to be $\sim 0.4 \text{ mm} \times 3 \text{ mm}$ (lateral $\times$ axial), thus spanning the entire OCT imaging depth with a reasonable lateral extension. The transducer was driven using bursts of 750 cycles at 60V peak-to-peak voltage, corresponding to a 100 μs emission with a pressure of $\sim 3 \text{ MPa}$. Subsequent medium relaxation induces a transient shear wave that propagates perpendicular to the US beam.

The PhS-OCT system we used to detect dynamic shear wave propagation was based on a spectral-domain OCT setup illuminated by a super-luminescent diode (SLD, 1310 nm central wavelength, $\sim 56 \text{ nm}$ bandwidth, DenseLight Semiconductors Ltd., Singapore). A detailed description can be found in our previous publications [12]. Briefly, M-B scans were performed to image shear wave propagation. Each M-scan consists of 256 A-lines repeated at the same location at a 47 kHz line rate. Each B-scan consists of 128 M-scans swept transversally across the sample while the US emission is repeated. A full M-B scan is completed within $\sim 1\text{s}$.

The sample is illuminated from the top while the US transducer is placed at the bottom. The US transducer was mounted on two linear translation stages so that the shear wave source could be swept across the sample. Echographic coupling gel was placed at the bottom of the sample to enable US propagation as well as at the top of the sample to avoid strong US reflection at the sample surface. The US transducer was accurately positioned by emitting low-energy US bursts and by visualizing in real-time OCT the resulting phase changes to detect and localize the US waves.

The layer of echographic gel placed at the top of the phantom also helps to reduce surface artifacts in the OCT imaging. Surface ripple artifacts can indeed occur due to the refractive index difference at the air-sample interface when the interface moves axially, as described in [18]. In addition, we covered the echographic gel layer with a thin cover glass to ensure complete removal of this artifact (see Figure 1).

In PhS-OCT, phase differences ϕ between successive A-scan signals within M-scan provide local axial displacements z :

$$\Delta z(x, z, t) = \Delta \phi(x, z, t) \cdot \lambda / (4\pi n) \quad (1)$$

where (x, z) are the spatial coordinates of a given pixel, t is time, $\lambda = 1310$ nm is the SLD central wavelength, and n is the sample refractive index.

Upon obtaining the displacement field within the sample by PhS-OCT, the local shear wave speed was then retrieved using a time-of-flight algorithm, based on autocorrelations of the displacement field along time. More details about the time-of-flight algorithm can be found in [19] and [20]. For each pixel of the imaging region, the position of the maximum of the autocorrelation gives the travel time at a given lateral position x , yielding the local propagation speed $c_s(x, z)$. Speed maps were then converted to shear modulus maps using [21]:

$$\mu(x, z) = \rho c_s^2(x, z) \quad (2)$$

where (x, z) are, respectively, the lateral and axial coordinates of a given pixel, $\mu(x, z)$ is the local shear modulus, and ρ is the density of a homogenous and incompressible medium.

To verify the ability of PhS-OCT to temporally and spatially track induced shear waves, we performed experiments on agar phantoms. Different agar concentrations yield different stiffnesses. Latex nanospheres (0.3 μ m diameter, 10% weight/weight solution, Duke Scientific Corporation, Palo Alto, CA, USA) were added to the phantoms as optical scatterers, providing sufficient backscattered signal to reach a 2-mm imaging depth.

Axial displacements induced by US radiation force and detected by PhS-OCT in a homogeneous agar phantom are displayed in Figure 2a for different time steps, showing the propagation of the shear wave front. Since the shear source has a larger extension in the axial direction than in the lateral direction, it generates a cylindrical wave [5]. Measured displacements have amplitudes of ~ 0.6 μ m close to the shear source (see Figure 2b) and a wide spectrum ranging from 200 Hz to a few kHz (see Figure 2c). The shear wave has a spatial resolution of ~ 1 mm (one shear wavelength, calculated as the quotient of the shear wave speed to the central frequency at the source). Axial displacements were detected with a signal-to-noise ratio of ~ 21 dB. For this acquisition, the lateral and axial pixel sizes of the OCT image were respectively 58.5 μ m and 4.15 μ m.

Figure 3 illustrates the shear modulus map reconstructed for a 0.5% agar phantom. Correlations are performed in the spatio-temporal plane (Figure 3a), leading to the shear wave propagation speed that is then converted to the shear modulus using Eq. (2). The lateral window size used for correlation is $dx = 8$ pixels. It should be noted that the annotations dx and dt reported on Figure 3a are not to scale, but were exaggerated for illustration purposes only. The dash line in Figure 3a and Figure 3b delineates the near field of the shear source (distance smaller than a shear wavelength) where shear modulus estimation is biased by the coexistence of longitudinal, transverse and coupling modes [22] [23]. A threshold is applied to the shear modulus display: only correlations with a coefficient above 0.9 are considered, resulting in presentation of the modulus in part of the phantom, as illustrated in Figure 3b.

We performed repeated measurements ($N = 5$) on a 0.5% agar phantom. The shear modulus estimated from these multiple measurements was 5.5 ± 0.3 kPa (median value $\pm$ inter-

experiments deviation). For each single measurement, the spatial heterogeneity of the shear modulus map was found to be smaller than 10% of the shear modulus.

We then investigated the case of a heterogeneous, bi-layered, phantom. Top and bottom layers were respectively made from a 1% and 2%-agar solution. For this experiment, the lateral and axial pixel sizes of the OCT image were respectively 23.4 μm and 4.15 μm . The thickness of the top layer is about 0.5 mm. Figure 4d shows a B-mode image of the phantom. The dash line delineates the boundary between both layers. The US beam was placed at three different lateral locations and each of the corresponding acquisitions yield a partial shear modulus map (Figure 4a, 4b, 4c). The partial maps were then recombined to reconstruct a shear modulus map across the whole imaging plane (Figure 4e). A weight based on the correlation coefficient was applied for the recombination, where low correlation results were eliminated from the final image but high correlation results were equally weighted. The shear modulus was estimated to be 12.9 ± 0.1 kPa for the top layer and 16.4 ± 0.3 kPa for the bottom layer (median value $\pm$ spatial variance). The shear modulus of the upper layer appears to be much smaller than that reported in the literature for an equivalent agar concentration [24]. This could be due to the way that the phantom was made because we noticed the shear modulus of agar phantom is highly dependent on the fabrication process, e.g. temperature, heating rate and cooling rate. One should note that the soft region (red) of the elastic map extends below the top layer boundary, due to limited axial resolution of the shear wave: the shear wavefront must be continuous at the interface between both layers. Thus, there is a shear wave speed gradient at that interface rather than a sharp transition. However, the shear modulus map clearly identifies the elastic heterogeneity whereas the B-mode image does not exhibit any significant contrast.

In addition, B-mode images acquired simultaneously with the US emission exhibit a low-intensity region corresponding to the US beam location (Figure 4a, 4b, 4c). This could be due to slight thermal effects within the sample induced by US emissions or acousto-optic interactions. However, this effect was transient and reversible as it was not observed on B-mode images acquired immediately after the US emissions.

The use of a US radiation force is a significant improvement to previous systems using a mechanical actuator primarily because shear waves can be generated efficiently at depth. This could be particularly valuable to characterize the elasticity of the peripheral vasculature or the intraocular lens where mechanical shear sources cannot be applied. In addition, it provides good reproducibility compared to mechanical actuation because the latter can be biased by contact issues. In our experimental configuration, we obtained a shear wave with a ~ 1 kHz central frequency, leading to a millimeter lateral resolution of the shear modulus map in soft tissues that have a typical shear wave speed of a few m/s. The shear wave central frequency (and thus the spatial resolution) can be increased by increasing the US emission central frequency in order to reduce the US focal spot width or by adjusting the emission duration [5]. The shear wave spatial resolution is also affected by the signal-to-noise ratio of the detected displacements.

The *in vivo* applicability of our PhS-OCT system has been demonstrated on skin in previous studies [11]. US radiation force has been used clinically on different organs (breast [25],

liver [26][27]). Although our technique requires repeated US emissions (typical duty cycle of 1%), it requires relatively low acoustic pressures (< 3 MPa, mechanical index $MI < 1.09$) to generate detectable displacements given the high sensitivity of PhS-OCT. The Food and Drug Administration limitations on acoustic emission for ophthalmic applications are more restrictive ($MI < 0.23$), but higher US frequencies (20 MHz) can be used for ocular tissues and would tend to decrease the MI. Besides, the efficiency of the shear wave generation can be improved by increasing the application surface, i.e. the focal spot cross-section. This could be achieved by using cylindrically-focused transducers instead of spherically-focused transducers. Future work will focus on the optimization of the US shear source for *in vivo* implementation of PhS-OCT combined with US radiation force for skin and ocular tissues.

In conclusion, we demonstrated the feasibility of combining US radiation force and PhS-OCT to perform remote shear wave elastography measurements and obtain cross-sectional maps of the shear modulus of tissue-mimicking phantoms. To our knowledge, this is the first report on spatially localized measurements of the shear modulus combining US radiation force and PhS-OCT.

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Figure 1. Experimental setup for shear wave elastography combining a PhS-OCT system with US radiation force. The bottom-left inset shows details of the sample arrangement.

Figure 2.

(a) Snapshots of shear wave propagation at different time steps (the US emission starts at $t = 0$ ms and lasts 0.1 ms) in a homogeneous agar phantom. The black arrow indicates the lateral position of the US beam ($x = 1.3$ mm). The color scale represents axial displacement magnitude and is superimposed on the B-mode image of the medium (gray scale). (b) and (c) Temporal profile and spectral content of the displacement field averaged over the sample depth at different lateral positions.

Figure 3.

(a) Spatio-temporal representation of axial displacements at a given depth. The correlation of two rows distant from dx gives the travel time dt yielding the local shear wave speed $c_s = dx/dt$. (b) Reconstructed shear modulus map (color scale) of a homogeneous 0.5% agar phantom superimposed on the B-mode image (gray scale). In both figures, the black arrow indicates the lateral position of the US beam and the dash line delineates the near field of the shear wave.

Figure 4.

Results obtained on a bi-layered phantom. (a– c) Partial shear modulus maps reconstructed from shear waves generated at different locations. Shear modulus maps (color scale) are superimposed on the B-mode image (gray scale). The black arrows indicate the lateral position of the US beam ($x=2.3$, 1.3 and 0.3 mm respectively). (d) B-mode image of the phantom, made of a 1%-agar top-layer and a 2%-agar bottom-layer. The dash line delineates the boundary between both layers. (e) Shear modulus map obtained from the combination of the partial maps shown in (a–c).