31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

# Liver Elasticity and Viscosity Quantification Using Shearwave Dispersion Ultrasound Vibrometry (SDUV)

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***Abstract*—Noninvasive quantification of liver elasticity is a promising alternative to liver biopsy to stage liver fibrosis, a condition afflicting hundreds of millions of patients worldwide. Quantitative measurement of elasticity (in unit of Pascal) is required in this application because liver fibrosis is a diffuse disease where abnormality is not confined to a local region and there is no normal background tissue to provide contrast. SDUV uses an ultrasound "push" beam to stimulate formation of propagating harmonic shear waves in the studied tissue. The propagation speed of induced shear waves is frequency dependent (dispersive) and relates to the tissue's mechanical properties. Shear wave speeds at multiple frequencies (typically hundreds of Hertz) are measured by a separate ultrasound "detect" beam in pulse echo mode and fit with a theoretical dispersion model to inversely solve for tissue elasticity and viscosity. A special pulse sequence has been developed to facilitate a single ultrasound array transducer for both push and detect function, which makes SDUV compatible with current ultrasound scanners. Feasibility of this pulse sequence is demonstrated by *in vivo* SDUV measurements in porcine liver using a dual transducer prototype.**

## I. Introduction

Liver fibrosis and cirrhosis are a response to chronic liver injury from a variety of causes including viral, autoimmune, drug induced, cholestatic and metabolic diseases [1]. Liver cirrhosis may ultimately lead to hepatic failure and is associated with primary liver cancer, which increases the relative mortality rate. Cirrhosis affects hundreds of millions of patients worldwide and its prevalence in the United States is estimated at 900,000, which accounts for 30,000 deaths per year [1]. Liver biopsy is currently the gold standard for diagnosis and staging of liver fibrosis. However, this method has important limitations. A) Liver biopsy is an invasive technique, which can be painful and some patients decline to have it performed. B) Significant complications occur in 1-5% of patients with a reported mortality rate of between 1:1000 and 1:10,000 [2]. C) Needle liver biopsy samples only about 1/50,000 of the liver and so is limited by sampling variability. Therefore, there is a need for noninvasive assessment of hepatic fibrosis for screening of at-risk population, treatment response monitoring, and follow-up.

Recently it has been demonstrated that liver elasticity (i.e., stiffness) can be used for fibrosis staging [3, 4]. MRI based elastography technologies are expensive and not widely available. Therefore, ultrasound based technologies [5-8] may be more attractive. Ideally, the ultrasound method should *quantitatively* resolve tissue *viscosity* in addition to tissue elasticity for the following reasons. A) Elastography techniques providing a 2D *relative* mapping of tissue elasticity are inadequate here because liver fibrosis is a diffuse disease and there is no normal background liver tissue to provide a contrast. Therefore, quantitative measurement is required. B) Tissue viscosity may provide useful diagnostic information and neglection of tissue viscosity usually will introduce bias to estimation of stiffness. Therefore, it is important to revolve both elasticity and viscosity. In addition, the technique should be compatible with commercial ultrasound scanners.

Toward these aims, here we propose a new method, Shearwave Dispersion Ultrasound Vibrometry (SDUV), for fast and economical quantification of both liver elasticity and viscosity for in vivo fibrosis staging.

## II. Methods

### A. Principle of SDUV

The principle of SDUV has been described in our previous paper [9] and is briefly summarized here. For a homogeneous Voigt medium, the shear wave propagation speed $c_s$ depends on the frequency of shear wave $\omega_s$ (i.e. "dispersive"):

$$c_s(\omega_s) = \sqrt{2(\mu_1^2 + \omega_s^2\mu_2^2)/\rho(\mu_1 + \sqrt{\mu_1^2 + \omega_s^2\mu_2^2})}, \qquad (1)$$

where $\rho$, $\mu_1$, and $\mu_2$ are the density, shear elasticity, and shear viscosity of the medium, respectively. The density of various soft tissues shows very little variance and can be assumed to be 1000 kg/m$^3$. Therefore, the variation of $c_s$ versus frequency (typically in the range of hundreds of Hertz) can be measured in the studied medium and fit by Eq. (1) to solve inversely for elasticity and viscosity.

As shown in Fig. 1, SDUV uses a "push" transducer operating in amplitude modulated (AM) mode to generate harmonic vibration within the studied medium at the transducer focus. A harmonic shear wave of frequency $\omega_s$

This work was supported in part by the National Institute of Health under grant EB02167. **Disclosure:** Dr. Chen, Dr. Greenleaf, and Mayo have a potential financial interest in SDUV. Patent applications have been filed for the technology, which has been licensed.

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propagating outwards from the vibration center can be monitored by the "detect" transducer operating in pulse-echo mode at two locations along the propagation path. The propagation speed of a shear wave at $\omega_s$ is estimated by tracking the phase change of the wave over the distance it has propagated:

$$c_s(\omega_s) = \omega_s \Delta r / \Delta\phi_s, \quad (2)$$

where $\Delta\phi_s = \phi_1 - \phi_2$ is the phase change over the traveled distance $\Delta r$. The frequency of the shear wave is then varied by changing the modulation frequency of the push ultrasound to obtain shear speed measurements at other frequencies. The dispersion characteristic of the studied tissue is fit with Eq. (1) to solve for its elasticity and viscosity. It is important to note that SDUV is not a 2D imaging method, but provides a local average of tissue viscoelasticity within the shear wave propagation path $\Delta r$ (typically a few millimeters).

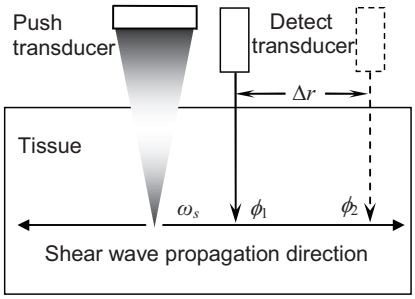


Fig. 1. Principle of SDUV. Phase of shear wave generated by the push transducer is detected at two locations and used to calculate shear wave speed.

### B. Detection of shear wave by pulse echo ultrasound

The challenge for shear wave detection is that vibration caused by the push ultrasound beam is usually small and can be affected by various environmental noises such as body, breathing, and cardiovascular motions. Because the vibration is a pure tone and its frequency is known, one can apply Kalman filtering to extract the vibration phase only at the shear wave frequency and reject all out of band noises. More specifically, ultrasound pulses are repeatedly transmitted to the same detection location with a PRF (pulse repetition frequency) of several kilohertz. A fixed time point in the echo corresponding to a selected tissue region along the ultrasound beam is demodulated across all echoes to obtain the vibration versus time record as the shear wave passes that tissue region. A Kalman filter is then applied to the vibration-time record to lock-in and extract only the signal at the shear wave frequency. Although estimates of both amplitude and phase of tissue vibration are provided by the Kalman filter, only phase is used by SDUV. Then the detect ultrasound beam is focused at another location along the shear wave propagation path to obtain a second shear wave phase at the same shear wave frequency. Shear wave speed at this frequency is calculated from the phase shift and distance between these two locations using Eq. (2). The whole process is repeated for several shear wave frequencies to characterize dispersion. Details about shear wave detection with ultrasound can be found in the paper by Zheng *et al*. [10].

### C. SDUV with a single transducer

The SDUV setup in Fig. 1 requires two separate transducers: one push transducer to generate shear waves and one detect transducer to monitor shear wave propagation. This can be rather cumbersome and limit the clinical applications of SDUV. An intermittent pulse sequence that may allow SDUV measurements using one commercial array transducer is proposed to avoid this limitation. The intermittent pulse sequence for SDUV has both spatial and temporal features.

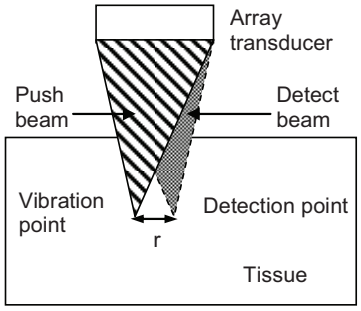


Fig. 2. Spatial relationship between the push and detect beam, which are steered electronically to focus at different locations.

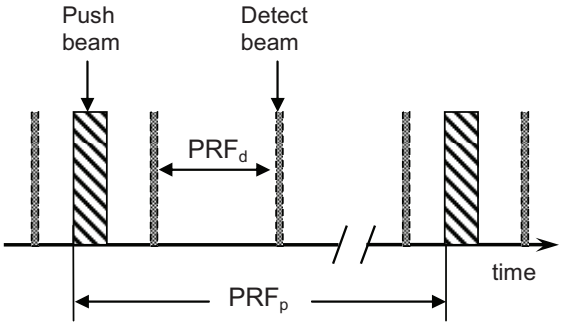


Fig. 3. Timing of the push and detect beam shown in Fig. 2.

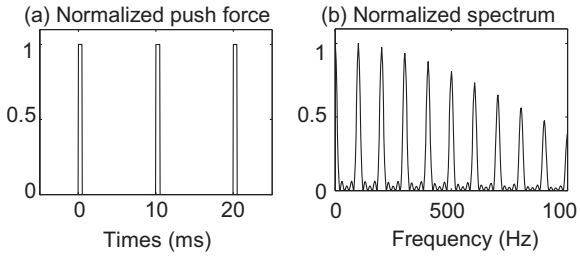


Fig. 4. Force exerted on tissue by the ON/OFF push sequence in time (a) and frequency (b) domain.

As illustrated in Fig. 2, the push beam and the detect beam are focused at different locations. Current commercial array transducers can electronically steer the ultrasound beam to different locations without mechanically moving the transducer. The push beam is used to generate a shear wave within the studied tissue. The detect beam is in pulse echo mode to monitor and record shear wave propagation. Furthermore, the detect beam needs to be steered to at least two different locations in order to obtain a phase difference for shear wave speed estimation using Eq. (2) (only one

detect location is shown in Fig. 2 to avoid making the figure too busy).

The timing of the pulse sequence is shown in Fig. 3. The push and detect beams are shade coded the same way as in Fig. 2. The push sequence and detect sequence in Fig. 3 are focused at different locations, as shown in Fig. 2. The push beam has a pulse repetition frequency of $PRF_p$ = 100 Hz and exerts a pushing force of constant amplitude, every 10 ms, to the same tissue region at the transducer focus (see Fig. 4(a)). The Fourier transform of Fig. 4(a) shown in Fig. 4(b) indicates that the spectrum of such repeated ON/OFF push force contains not only the fundamental ON/OFF frequency at 100 Hz, but also its harmonics at 200, 300, and 400 Hz, etc. Therefore, shear wave dispersion information at multiple frequencies is intrinsically available with this push sequence and repeating the push pulses at different frequencies is not required. As a result, SDUV measurement time is reduced and heating by ultrasound to tissue is also minimized.

## III. Experiments and Results

A pilot *in vivo* experiment was performed in liver of normal swine to test the feasibility of the intermittent pulse sequence in the presence of breathing and cardiac motions. Two separate transducers were used in this experiment to simulate the operation of the single array transducer shown in Fig. 2. The pulse sequence in Fig. 3 was decomposed into two groups: the push pulses and the detect pulses. The push pulses drove a push transducer to generate push beams in the studied tissue, while the detect pulses drove a separate detect transducer (positioned beside the push transducer) to generate detect beams. The push pulse operating the push transducer and the detect pulses operating the detect transducer followed the exact timing in Fig. 3. Therefore, results obtained with this arrangement should be a reliable prediction of the pulse sequence's performance on a single array transducer.

The experiment conformed to the policy of the Institutional Animal Care and Use Committee (IACUC) at Mayo Clinic. A farm pig was anesthetized and mechanically ventilated. B-mode imaging of the liver was performed to find suitable locations for SDUV measurements. SDUV measurements were then performed in liver through the intact abdominal wall with one push transducer and one detect transducer as shown in Fig. 1. The operation of these two transducers followed the timing shown in Fig. 3, with $PRF_p$ equal to 100 Hz and $PRF_d$ equal to 1.6 kHz. The push transducer (45 mm diameter, spherically focused at 7 cm) was driven by a 40 dB power amplifier. Each push beam had an ultrasound frequency of 3 MHz and duration of 0.3 ms. The detect transducer (19 mm diameter, spherically focused at 9 cm, center frequency of 5 MHz) was operated by a home made pulser and echoes were recorded at 100 MHz. Mechanical ventilation was temporarily suspended during SDUV measurements and ECG signal was used to trigger SDUV measurements when cardiac motion was minimal during a heart cycle. Shear wave phase at two locations 4 mm apart was used to calculate shear wave speed using Eq. (2).

Fig. 5 shows the intermediate steps of a typical SDUV measurement in the liver of a normal swine. Fig. 5 (a) and (b) are examples of shear waves measured at two locations 2 mm apart along the shear wave propagation path. One can see shear waves of the fundamental frequency (100 Hz) as well as its higher harmonics (200, 300, 400 Hz, etc.). Phase shift and amplitude decay due to propagation of the shear waves are also visible. The phase of shear waves at frequencies 100-400 Hz was estimated from these vibration-time records by the Kalman filter and shown in Fig. 5(c), which demonstrates that the shear wave phase changes linearly with propagation distance for all frequencies studied. Shear wave speed, shown as circles in Fig. 5 (d), is calculated using phase information at location 0 mm and 4 mm in Fig. 5 (c). The solid line is the LMS fit by Eq. (1) to measured shear wave speeds, which gives $\mu_1$ = 2.4 kPa and $\mu_2$ = 2.1 Pa·s [11].

The means and standard deviations of liver elasticity and viscosity obtained from nine separate SDUV measurements are $\mu_1 = 2.2 \pm 0.63$ kPa and $\mu_2 = 1.96 \pm 0.34$ Pa·s. We are not aware of previous literature reports on elasticity and viscosity measured in vivo in porcine liver. However, these

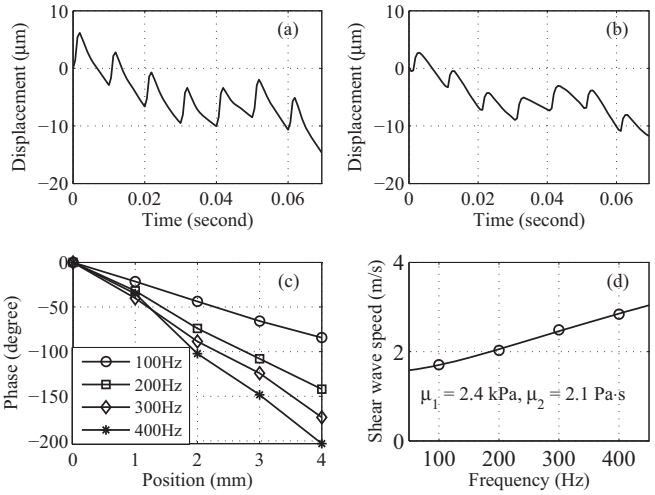


Fig. 5. A typical SDUV measurement. (a) & (b): vibration-time records at two locations 2 mm apart. (c): shear wave phase vs. location calculated from vibration time records. (d): Shear wave speeds calculated from locations 0 mm and 4 mm in (c).

results are close to those reported for *in vivo* MRE study in healthy human livers [12] ($\mu_1 = 2.06 \pm 0.26$ kPa and $\mu_2 = 1.72 \pm 0.15$ Pa·s).

## IV. Discussion and Conclusion

SDUV is capable of providing quantitative measurements of tissue viscosity, in addition to elasticity, and has several beneficial features. First, shear wave propagation is governed by material properties but is independent of the ultrasound intensity and beam shape at the focus. Therefore, SDUV is not affected by these unknown factors and measurements are device independent. Second, shear waves generated by the push ultrasound beam in SDUV have small amplitudes and decay quickly when propagating through soft tissue. Therefore, the risk of interference caused by shear wave reverberation is minimized. Finally, each SDUV acquisition

takes about 0.1 second and therefore measurements can be selectively placed at a time window during the heart cycle when tissue motion due to cardiac activity is minimum at the measurement sites, if found necessary. Short acquisition time also allows fast acquisition of multiple measurements at different locations within the liver to get a comprehensive assessment of tissue state to avoid sampling variability. SDUV also has some limitations. For example, it is a point measurement technique and can not provide a 2D image. In addition, tissue motion generated by ultrasound radiation force in SDUV is usually small. Therefore, SDUV measurements in obese patients may be challenging. However, compared to other radiation force methods that produce transient shear waves, SDUV produces and detect harmonic shear waves which is advantageous in terms of SNR (Signal to Noise Ratio).

The ON/OFF push sequence shown in Fig. 4 will produce excitation force at higher harmonics, which may cause aliasing if the frequency of pulse echo detection is not high enough. Experiments in tissues indicate that shear waves above 500 Hz generated by such ON/OFF push sequence are very weak. There are several reasons: A) The force at higher frequencies has lower magnitude, as shown in Fig. 4(b). B) Tissue vibration in response to a push force of fixed amplitude decreases when frequency increases. C) Higher frequency shear waves attenuate more quickly when propagating in tissue. The combined result is that shear waves above 500 Hz are negligible with this push sequence. Therefore, as far as the multi-frequency shear waves are sampled by the ultrasound detect beam at a pulse repetition frequency ($PRF_d$) higher than 1 kHz, there should be no aliasing. In current practice, we typically use a $PRF_d$ greater than 1.6 kHz and limit the dispersion analysis up to about 400 Hz.

The shear wave dispersion equation (Eq. (1)) used in SDUV is based on a Voigt model. There are other choices of rheological models. It is not yet clear which one is the best model to describe the response of soft tissues. The Voigt model is widely used in MRE for soft tissues. A recent paper compares the Voigt and Maxwell models and concludes that the Voigt model is better for the agar-gelatin phantom and bovine muscle studied [13]. The excellent fits between Eq. (1) and shear wave speed dispersion measured in liver (Fig. 5) also suggest that the Voigt dispersion model is sufficient at least for the frequency range used in SDUV.

Potential risks (thermal and mechanical effects) associated with the push beam in SDUV need to be assessed. The *in vivo* animal experiment reported here used an ultrasound push beam with an *in situ* MI and spatial peak temporal peak intensity of 1.68 and 520 W/cm$^2$, respectively. A worst case estimate of the tissue heating can be calculated by solving the bioheat equation and neglecting heat conduction and blood perfusion [7]:

$$\Delta T = 2\alpha It / c_v , \qquad (3)$$

where $\Delta T$ is temperature increase, $\alpha$ is the ultrasound absorption coefficient of tissue, $I$ is the temporal average intensity of the ultrasound beam, $t$ is ultrasound application time, and $c_v$ is the volume specific heat for tissue. Using this approach, the upper limit of tissue heating for each SDUV measurement in this *in vivo* animal study is estimated to be 0.13 ºC ($\alpha$ = 0.5 dB/cm/MHz, $I$ = 520 W/cm$^2$, $t$ = 10 × 0.3 ms, $c_v$ = 4.2 W·s/cm$^3$/ ºC).

In summary, this study demonstrates that the frequency dispersion characteristic of shear wave speed in tissue as measured by SDUV can be used to quantify both tissue elasticity and viscosity. Feasibility of an intermittent pulse sequence that makes SDUV compatible with current ultrasound scanners is demonstrated with *in vivo* experiments using a dual transducer prototype.

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