35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

In-Vitro Quantification of Rat Liver Viscoelasticity with Shear Wave Dispersion Ultrasound Vibrometry

Yan-rong Guo, Xin Chen*, Haoming Lin, Xinyu Zhang
National-Regional Key Technology Engineering Laboratory for Medical Ultrasound
Guangdong Key Laboratory for Biomedical Measurements and Ultrasound Imaging
Department of Biomedical Engineering, School of Medicine, Shenzhen University,
Shenzhen, 518060, China.

Abstract—**As a new imaging method for tissue mechanical properties, ultrasound elastography has always been the research focus in the field of medical ultrasound imaging ever since it has been proposed. This paper developed an ultrasound viscoelasticity measurement system based on shear wave dispersion ultrasound vibrometry (SDUV). This system applied acoustic radiation force to excite harmonic vibration in soft tissue. The propagation of the shear wave induced by the vibration was detected and the tissue viscoelasticity properties were calculated. Based on this system, rat livers were measured *in vitro*. The results shows that the system can measure the viscoelasticity reliably, offering a potential alternative to diagnosis of liver fibrosis.**

Key word: Ultrasound elastography; Shear wave dispersion ultrasound vibration; Viscoelasticity; Acoustic radiation force; Liver fibrosis

I. INTRODUCTION

Studies have found that shear elastic modulus, having the dynamic range of several orders of magnitude for various biological tissues [1], is highly correlated with the pathological statues of human tissue such as livers. Therefore, the information of tissue elasticity has important significance for tissue lesions diagnosis. The traditional medical imaging techniques (ultrasound, X-ray, CT, MRI) are mainly focused on tissue and organ anatomy imaging, but cannot provide the information of tissue elasticity [2]. Therefore, reliable, simple, and noninvasive methods for assessing liver fibrosis are needed.

Many techniques have been proposed to measure tissue elasticity. These methods are mostly based on ultrasound elastography [3] and magnetic resonance elastography (MRE) [4]. Compared with the high cost of MRE, ultrasound elastography is more convenient in clinical practice. According to the different excitation and detection ways of tissue, many methods have been developed about image tissue elasticity, including shear wave elasticity imaging (SWEI) [5], acoustic radiation force impulse imaging (ARFI) [6], supersonic shear imaging (SSI) [7], and Vibro-acoustography (VA) [8] etc..

Shear wave dispersion ultrasound vibrometry (SDUV) [9], using amplitude modulation ultrasound wave focused in a tiny region inducing acoustic radiation force to excite tissue, can promote the spatial resolution of the image. Meanwhile, the detection sensitivity of vibration signal will be advanced by estimating the shear wave phase velocities at several frequencies over a short distance. This paper developed an ultrasound viscoelasticity measurement system based on SDUV and finished the experiment of rat liver *in vitro* by system.

II. Methods

A. System Development

The diagram of the experiment system is shown in Figure 1. This system mainly consists of a transducer to produce the ultrasound radiation force and a receiver unit using a Sonix-RP system. Two arbitrary signal generators are utilized to generate the system timing and excitation waveform. The waveform is amplified by a power amplifier

Supported by the National Natural Science Foundation of China (61031003 81000637, 81271651, 61101025), Shenzhen Basic Research Programs (JC201005280518A, JC201005280501A).

*Correspondence to: Xin Chen, with the Shenzhen University; E-mail: chenxin@szu.edu.cn

having a gain of 50dB to drive an excitation transducer for inducing vibrations in a tissue region. The SonixRP system is applied to detect the vibration using pulse-echo mode with a linear array probe. The SonixRP is a diagnostic ultrasound system packaged with an Ultrasound Research Interface (URI). It has some special research tools which allow users to perform flexible tasks such as low-level ultrasound beam sequencing and control. The center frequency of the excitation transducer is 1.04MHz. The center frequency of the linear array probe is 5MHz and sampling frequency of SonixRP is 40 MHz. The excitation transducer and the detection transducer are fixed on multi-degree adjustable brackets and are controlled by three-axis motion stage.

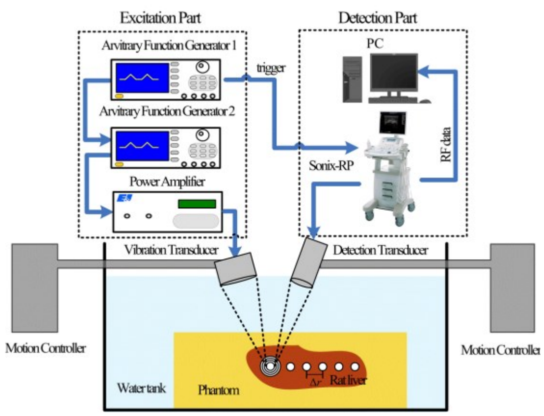

Figure 1. Diagram of the experiment system

B. Data Processing Algorithm

The purpose of data processing is to estimate vibration phase of shear wave from echo wave signal, and calculate the tissue viscoelasticity [9].

A harmonic motion at a location can be represented:

$$d(t) = D\sin(\omega_s+\varphi_s) \tag{1}$$

where ω_s is the vibration angular frequency, the vibration displacement amplitude D and phase φ_s are constants at a location. Applying detection pulses to the motion, the received echo wave becomes:

$$r(t, k) = |g(t, k)|\cos(\omega_0 t+\varphi_0+\beta\sin(\omega_s(t+kT)+\varphi_s)) \tag{2}$$

where T is the period of the detection pulses and the modulation index is $\beta=2D\omega_0\cos(\theta)/c$, c is the sound propagation speed in the tissue, ω_0 is the angular modulation frequency of detection tone bursts, $g(t, k)$ is the complex envelope of $r(t, k)$, φ_0 is a transmitting phase constant and θ is an angle between the ultrasound beam and the tissue vibration direction. The tissue motion information is carried by modulation index β and phase φ_s. A quadrature demodulator is used to extract the motion information from $r(t, k)$. The complex envelop consists of the in-phase and quadrature term:

$$g(t, k) = I(t, k)+jQ(t, k) \tag{3}$$

Operating on the in-phase and quadrature components I and Q with input $r(t, k)$, we obtain the tissue motion feature:

$$\begin{aligned} s(t, k) &= \tan^{-1}(Q/I) - \text{mean of } \tan^{-1}(Q/A) \\ &= \beta\sin(\omega_s(t+kT)+\varphi_s) \end{aligned} \tag{4}$$

The signal $s(t, k)$ represents the tissue motion at a particular location, and its amplitudes and phases change over distances. The phase difference can be obtained by comparing phase φ_s of the signals $s(t, k)$ at two locations z and $z+\Delta z$:

$$\Delta\varphi = \varphi_s(z)-\varphi_s(z+\Delta z) \tag{5}$$

This paper uses Fourier transform method to estimate the phase φ_s.

For a homogeneous medium, the shear wave propagation speed c_s is related to its angular frequency ω_s by:

$$c_s = \sqrt{\frac{2(\mu_1^2+\omega_s^2\mu_2^2)}{\rho(\mu_1+\sqrt{\mu_1^2+\omega_s^2\mu_2^2})}} \tag{6}$$

Where ρ, μ_1, and μ_2 are the density, shear elasticity, and shear viscosity of the medium, respectively. The speed of shear waves can be estimated from phase shifts of the harmonic motion over the distance propagated:

$$c_s = \omega_s\Delta r/\Delta\varphi_s \tag{7}$$

Where $\Delta\varphi_s$ is the phase difference over the distance Δr. The elasticity and the viscosity can be estimated at different frequency by equation (6) and equation (7).

III. IN VITRO EXPERMENTS AND RUSULTS

The experiment was conducted to quantitatively measure the elasticity and viscosity of the rat liver *in vitro* based on the experiment system. As the rat liver is uniform relatively inside and blood vessels are small, so the rat is fit for tumor experimental research.

A. Experiment

Six healthy male Sprague-Dawley (SD) rats (Guangdong Medical Laboratory Animal Center, Foshan, Guangdong) weighing 200−220 g were used in this study. The rats were anaesthetized in lethal dose using pentobarbital sodium and sacrificed. Then the left lateral lobes of livers were harvested for ultrasound measurements. All the procedures of studies were approved by Animal Care Committee guidelines of Shenzhen University and Guangdong Medical Laboratory Animal Center. The freshly excised rat liver was embedded in a transparent gelatin block (15 by 15 by 5cm) in this experiment. This paper conducted on six rat livers with different position in the experiment.

B. Data Processing

A rat liver was embedded in gen phantom and placed in water tank. Before experiment, the Sonix-RP URI was run first to preview the internal structure of the liver. Computer programs based on software development kit (SDK) of Sonix-RP were developed for detecting the vibration and shear wave propagation. The programs defined a specific detection sequencing and timing that repeatedly transmit pulses to a single scan line, and repeatedly receive the echoes with a PRF of 2 kHz. The timing of the excitation and detection pulses was shown in Figure 2. The pulse repetition frequency of the excitation pulses was 100Hz.

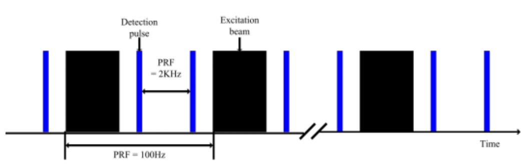

Figure 2. Timing sequence of the experiment system

The vibration of shear wave at a location was extracted from I and Q channels. Figure 3 shows the vibration displacement and Figure 4 showed the spectral amplitude of the vibration.

The extracted displacement signal s(t, k) was processed by the Fourier transform method that estimated phases of the fundamental frequency and all harmonics. Figure 5 shows estimated vibration phase shifts of the first four harmonics over distance up to 2.28 mm. Linear regression was conducted to calculate the shear wave propagation speed for each frequency.

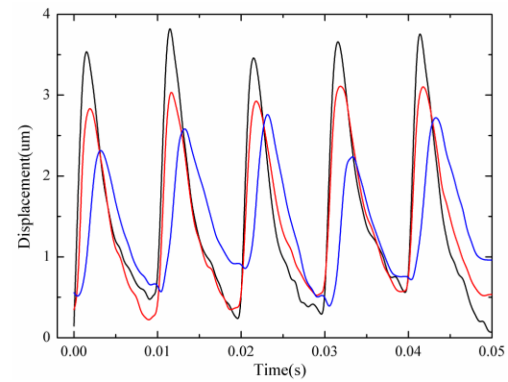

Figure 3. Displacements of the vibration

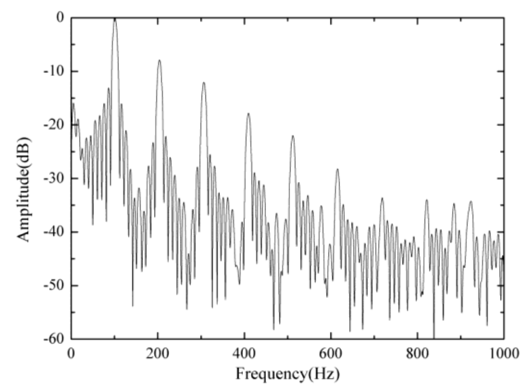

Figure 4. Frequency spectrum of the vibration

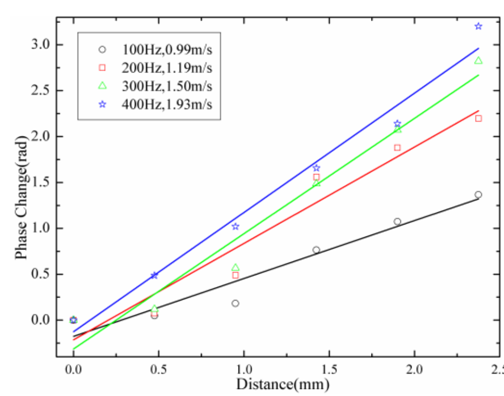

Figure 5. Estimates of phase shifts over distance

The measuring average results were elasticity value u_1 = (0.806±0.370) kPa, and viscosity value u_2 = (1.116±0.414) Pa·s.

IV. Discussion

Accurate estimates of elasticity and viscosity moduli require an extended frequency range over an extended distance. The current technology is only effective for few hundred Hz in the frequency. Shear wave having a high frequency attenuates very quickly as distance increases. Orthogonal frequency ultrasound vibrometry (OFUV) vibration method [10] can compensate higher loss at higher frequency in the tissue with limited peak intensity, and it is worth to explore.

Boundary conditions play a very important role in shear wave propagation and its phase velocity. The solution of the wave equation with boundary conditions should be considered for a tissue region that has a limited physical size. The viscoelasticity estimated from a superficial tissue region and from a deep tissue region may be different. The depth of detection in our experiment is setting at 5 millimetre, and it is meaningful to try to detect the different depth in the tissue.

As the shear wave generated by tissue vibration is very weak and decays fast, it becomes a very critical problem to accurately calculate the vibration phase over the distance. At present, the method of calculating the phase is Fourier transform, which is suitable to the motion model that is simply sinusoidal. The Kalman filter has great potential to include more complicated tissue models and motion models that are not fully explored yet. We expect to realize the Kalman filter to make more accurate phase estimation.

The experiment was conducted to quantitatively measure the viscoelasticity of rat liver phantom. Currently there is no gold standard for tissue viscoelasticity measurements. Salameh [11] got the viscoelasticity value of rat liver by MRI : $u_1 = (1.59 \pm 0.45)$ kPa, $u_2 = (0.51 \pm 0.22)$ Pa·s. Comparing with the results of our method above, their viscoelasticity value are in the same order of magnitude. Considering the differences of measurement method, the results have certain reference significance.

V. Conclusion

This paper develops a research platform based on SDUV. The entire platform is highly flexible and can automatically measure the elasticity and viscosity at one location very quickly. This fast acquisition makes multiple locations measurement in a relatively short time, leading to high efficiency and resolution. Experiment results demonstrate the effectiveness of the platform for characterizing liver stiffness.

VI. References

[1] Y. Fung, and S. Cowin, “Biomechanics: Mechanical properties of living tissues”, Journal of Applied Mechanics, 1994. 61: p. 1007.

[2] B.S. Garra, E.I. Cespedes, J. Ophir, S.R. Spratt, R.A. Zuurbier, et al, “Elastography of breast lesions: initial clinical results” , Radiology, 1997. 202(1): p. 79-86.

[3] J.Ophir, I. Cespedes, H. Ponnekanti, Y. Yazdi and X. Li, “Elastography: a quantitative method for imaging the elasticity of biological tissues”, Ultrasonic Imaging, 1991. 13(2): p. 111-134.

[4] R. Muthupillai, D. Lomas, P. Rossman, J. Greenleaf, A. Manduca, et al, “Magnetic resonance elastography by direct visualization of propagating acoustic strain waves”, Science, 1995. 269(5232): p. 1854.

[5] A.P. Sarvazyan, O.V. Rudenko, S.D. Swanson, J.B. Fowlkes and S.Y. Emelianov, “Shear wave elasticity imaging: a new ultrasonic technology of medical diagnostics”, Ultrasound in Medicine & Biology, 1998. 24(9): p. 1419-1435.

[6] K. Nightingale, “Acoustic radiation force impulse (ARFI) imaging: a review”, Current Medical Imaging Reviews, 2011. 7(4): p. 328-339.

[7] M. Tanter, J. Bercoff, A. Athanasiou, T. Deffieux, J.L. Gennisson, et al, “Quantitative assessment of breast lesion viscoelasticity: initial clinical results using supersonic shear imaging”, Ultrasound in Medicine and Biology, 2008. 34(9): p. 1373-1386.

[8] M. Fatemi, and J.F. Greenleaf, “Ultrasound-stimulated vibro-acoustic spectrography”, Science, 1998. 280(5360): p. 82-85.

[9] Y. Zheng, S. Chen, W. Tan, R. Kinnick and J.F. Greenleaf, “Detection of tissue harmonic motion induced by ultrasonic radiation force using pulse-echo ultrasound and Kalman filter”, Ultrasonics, Ferroelectrics and Frequency Control, IEEE Transactions on, 2007. 54(2): p. 290-300.

[10] Y. Zheng, A. Yao, Y. Liu, K. Chen, S. Chen, et al. “Composed vibration pulses for ultrasound vibrometry”, in Ultrasonics Symposium (IUS), 2010 IEEE, 2010. p. 17-20.

[11] M.H. Wang, M.L. Palmeri, C.D. Guy, L. Yang, L.W. Hedlund, et al, “In-vivo quantification of liver stiffness in a rat model of hepatic fibrosis with acoustic radiation force”, Ultrasound in Medicine & Biology, 2009. 35(10): p. 1709.