

# Real-Time Monitoring Of Regional Tissue Elasticity During FUS Focused Ultrasound Therapy Using Harmonic Motion Imaging

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**Abstract.** The feasibility of the Harmonic Motion Imaging (HMI) technique for simultaneous monitoring and generation of focused ultrasound therapy using two separate focused ultrasound transducer elements has previously been shown. In this study, a new HMI technique is described that images tissue displacement induced by a harmonic radiation force induced using a single focused ultrasound element. First, wave propagation simulation models were used to compare the use of a single Amplitude-Modulated (AM) focused beam versus two overlapping focused beams as previously implemented for HMI. Simulation results indicated that, unlike in the two-beam configuration, the AM beam produced a consistent, stable focus for the applied harmonic radiation force. The AM beam thus offered the unique advantage of sustaining the application of the spatially-invariant radiation force. Experiments were then performed on gelatin gel phantoms and *tissue in vitro* bovine liver. The radiation force was generated by a 4.68 MHz focused transducer using a low-frequency Amplitude-Modulated (AM) RF-signal. RF data were acquired at 7.5 MHz with a PRF of 6.5 kHz and displacements were estimated using a 1D cross-correlation algorithm on successive RF signals. Furthermore, taking advantage of the real-time capability of our method, the change in the elastic properties was monitored during focused ultrasound (FUS) ablation of *tissue in vitro* bovine liver. Based on the harmonic displacements, their temperature-dependence, and the calculated acoustic radiation force, the change in the relative, regional stiffness could be monitored during heating and ablation, both using the displacement amplitude and the resulting phase shift change of the displacement relative to the radiation force temporal profile. In conclusion, the feasibility of using an AM radiation force for HMI for simultaneous monitoring and treatment during ultrasound therapy was demonstrated in phantoms and *tissues in vitro*. Further study of this method will include, *ex vivo* and *in vivo*, stiffness and temperature.

**Keywords:** Acoustic radiation force, Harmonic Motion Imaging, Noninvasive measurement, Elastography, HIFU.

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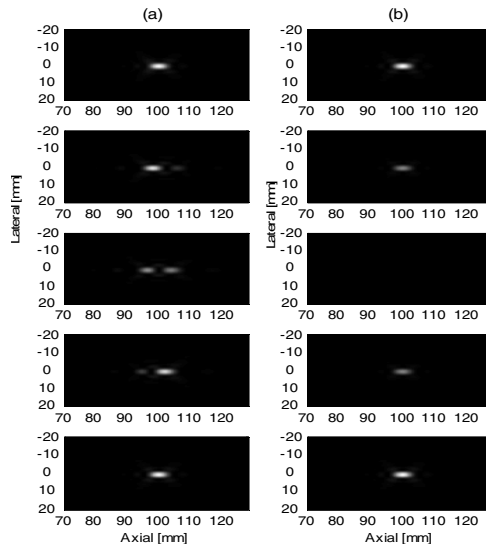
## INTRODUCTION

Several studies have shown that the acoustic radiation force can be generated, and thus capable of perturbing, at variable depths within the tissue [1-7]. The acoustic radiation force produces localized displacements of the soft tissue in the region of the focal zone. The displacements of the tissue can be monitored in real-time using consecutively acquired RF signals [2-4].

Harmonic motion imaging (HMI) technique estimates unidirectional tissue displacements remotely induced by the acoustic radiation force [1]. In this paper, a

new HMI method is discussed, in which the harmonic radiation force is produced by a single focused element and applied locally within gel phantoms and *tissue in vitro* bovine liver. The displacements are estimated inside the same region as that of the applied radiation force using 1D cross-correlation techniques. One major advantage of the HMI technique is that the displacements are measured during application of the acoustic radiation force and thus, this method can be used for real-time monitoring of the mechanical properties of tissues during focused ultrasound (FUS) therapy.

In a previous study, we proposed a similar technique for monitoring of FUS focused ultrasound therapy using two separate focused ultrasound transducer elements working at different frequencies ( $f$  and  $f+\Delta f$ ) [1,6]. The two overlapping focused beams produced an acoustic radiation force field moving at the difference frequency ( $\Delta f$ ) (Fig 1(a)).



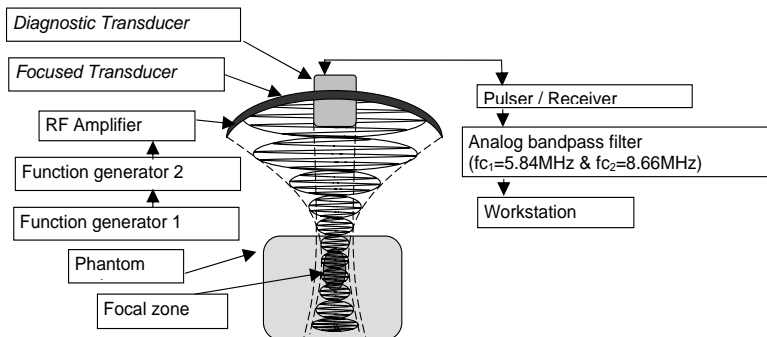
**FIGURE 1.** The acoustic radiation force field at 4 ms intervals (from top to bottom) produced by (a) two overlapping focused ultrasound beams at two different frequencies ( $f + \Delta f$ ) with  $\Delta f = 50$  Hz and (b) one-beam modulated at  $f = 50$  Hz. Note, the spatial invariance of the radiation force field using the one-beam configuration versus the alternative.

In this paper we propose to use one AM focused ultrasound beam to generate the harmonic acoustic radiation force (Fig 1(b)). The AM beam thus offered the advantage of sustaining the application of the radiation force at one steady location within tissue region *and* a simpler transducer design without incurring complex aligning and calibration of multiple focused elements or transducers.

The feasibility of the technique is shown in homogeneous tissue-mimicking phantoms with different stiffnesses, and an inhomogeneous cylindrical inclusion phantom. The results show that HMI is able to map the mechanical properties of the material with high resolution. Finally, FUS therapy combined with HMI is performed in *tissue in vitro* bovine liver. The displacements of the tissue are monitored during sonication and the results indicate that HMI may be able to detect the formation of lesions in real-time.

## METHOD

The experimental setup used in this study is shown in Fig 2. Gelatin gel material (Gelatin 50 bloom – MP Biomedicals) was used in order to construct the tissue mimicking phantoms. Five homogeneous phantoms with different elastic moduli (20 kPa, 30 kPa, 40 kPa, 50 kPa, and 60 kPa) and one 20 kPa tissue mimicking phantom with 40 kPa cylindrical inclusion were generated. Phantom preparation was completed according to [7]. Acoustic radiation force was generated by a 4.68 MHz focused transducer using a low-frequency AM RF-signal. A function generator (Agilent (HP) 33120A) was used to produce the RF signal driving the FUS transducer at 4.68 MHz. The amplitude of the RF signal was then modulated using a second function generator that generates the low frequency modulation.



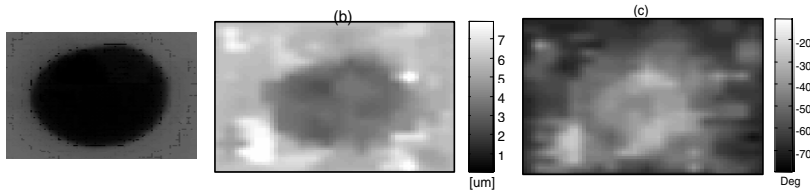
**FIGURE 2.** Experimental setup to generate harmonic acoustic radiation force and measure displacement.

The AM frequencies used were varied from 10-100 Hz. The output of the function generator is varied from 100-600 mVpp and then amplified by a 50dB RF-amplifier (EIN 3100L). The sonication time was adjusted to induce 100 oscillations at the frequency of the modulation. A 7.5 MHz single-element pulse echo transducer was placed through the center of the focused transducer and thus the two beams were properly aligned. A bandpass analog filter (Reactel, Inc.) with  $f_{c1} = 5.84 \text{ MHz}$  and  $f_{c2} = 8.66 \text{ MHz}$ , was used to filter out the spectrum of the focused beam. Consecutive filtered RF signals were acquired with PRF of 6.5 kHz (Panametrics 5051PR). An acquisition board (Gage Applied Technologies) was used to capture filtered RF data at a sampling frequency of 80 MHz. 1D cross-correlation techniques were employed in order to calculate axial displacements between two successive RF images [1]. As a result, this method is simple to implement, computationally efficient, and provides an accurate estimation of minute displacements (on the order of 10  $\mu\text{m}$ ). Two attributes of the resulting displacement were measured with time, i.e., a) the amplitude of the oscillatory displacement and b) the phase shift between the induced radiation force and the estimated displacement.

## EXPERIMENTAL RESULTS

### A. Tissue-Mimicking Phantom Experiments

In this experiment we showed the displacement variation in the five homogeneous phantoms of different stiffness. The intensity of the focused beam used was  $658.5 \text{ W/cm}^2$  at AM frequency of 50 Hz. The displacement amplitude decreases non-linearly from 10.3 microns to 4.15 microns with gel stiffness increases from 20 kPa to 60 kPa. The HMI displacements clearly reflect the underlying stiffness differences. The phase shift displacement decreases from  $-66.4^\circ$  to  $-30.4^\circ$  consistent with the increasing gel stiffness [10].



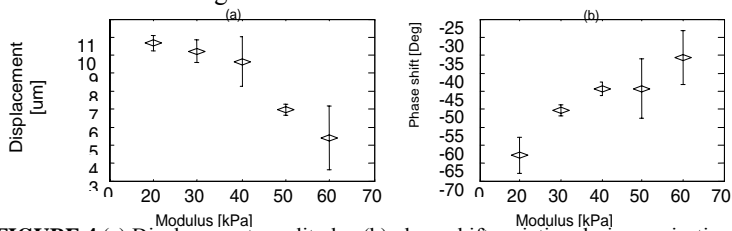
**FIGURE 3** (a) Optical image of a phantom with inclusion ( $30 \times 30 \text{ mm}^2$ ), (b) Displacement measurement, and (c) phase shift in a gelatin gel phantom with inclusion.

The inhomogeneous, 20 kPa gelatin phantom containing a 40 kPa cylindrical inclusion (Fig 3(a)) was imaged using HMI. The diameter of the cylindrical inclusion was 20 mm. A  $30 \times 30 \text{ mm}^2$  area was thus raster-scanned at a step size of 1 mm. The 2D maps of displacement amplitude and phase shift are shown in Fig 3(b) and (c), respectively. The average displacement within the inclusion is 3.3 microns and the phase shift is  $-34^\circ$  (Fig 3(b)). The average displacement in the surrounding gel is 6.1 microns and the phase shift is  $-65.9^\circ$  (Fig 3(c)). These results are consistent with the inverse relationship between displacement and elastic modulus [8]. The phase shift between the applied oscillatory radiation force and the resulting harmonic displacement may thus also be used to estimate the change in both the elastic and viscoelastic properties in tissues.

### B. Monitoring FUS Ablation

A sample of *tissue in vitro* bovine liver was submerged in degassed water with an approximate volume of  $50 \times 50 \times 20 \text{ mm}^3$ . In this experiment, the intensity of the focused ultrasound beam was  $948.23 \text{ W/cm}^2$  at the focus, to simultaneously generate the harmonic radiation force and the required tissue ablation using the same focused element. The AM frequency was 50 Hz and the total sonication time was approximately 288 sec to ensure tissue coagulation. The displacements were monitored in real-time. The variation of the displacements and the phase shift are shown in Fig 4(a) and (b). The oscillatory displacement amplitude and displacement-force phase shift start to rapidly decrease beyond 120 sec of continuous sonication, possibly indicating tissue coagulation beyond that sonication period in the same fashion as was observed using the tissue-mimicking phantoms. A raster-scan could not

be obtained in this case as it could not be performed fast enough for sampling temperature increase during ablation.



**FIGURE 4** (a) Displacement amplitude, (b) phase shift variation during sonication.

Furthermore, it should be noted that another advantage of the HMI technique is successful decoupling of the temperature-induced speed of sound effect on the resulting displacement from the higher frequency displacements induced by the harmonic radiation force and imaged here. This is because the speed of sound change induces a clear DC offset that can be distinguished from the oscillatory nature of the displacements. This technique is therefore capable of accurately monitoring the heating process and possibly detecting the onset of coagulation.

## CONCLUSION

The feasibility of using an amplitude-modulated radiation force for harmonic motion imaging and simultaneous monitoring of tissue elasticity variation during ultrasound therapy was shown. Further study of this method will include localized stiffness and viscoelastic properties measurements, as well as temperature and coagulation mapping, both in *ex vivo* and *in vivo* tissues.

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