LOCALIZED HARMONIC MOTION IMAGING: THEORY, SIMULATIONS AND EXPERIMENTS

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Abstract—Several techniques have been developed in an effort to estimate mechanical properties of tissues. These techniques typically estimate static or harmonic motion resulting from an externally or internally applied mechanical stimulus. In this paper, we discuss the advantages of utilizing a new technique that performs radiofrequency (RF) signal tracking to estimate the localized oscillatory motion resulting from the harmonic radiation force produced by two focused ultrasound (US) transducer elements with overlapping beams oscillating at distinct frequencies. Finite-element and Monte-Carlo simulations were performed to characterize the range of oscillatory displacements produced by a harmonic radiation force. In the experimental verification, three transducers were used: two single-element focused transducers and one lead zirconate-titanate (PZT) composite 16-element probe. Four agar gels were utilized to determine the effect of stiffness on the motion amplitude. Estimates of the displacement relative to the initial position (i.e., at the onset of the application of the radiation force) were obtained during the application of the radiation force that oscillated at frequencies ranging between 200 Hz and 800 Hz. In the simulations, the estimated oscillatory displacement spanned from ~800 to 600 µm and the frequencies of excitation could easily be estimated from the temporal variation of the displacement. In addition, a frequency upshift (on the order of tens of Hz) was estimated with stiffness increase. Furthermore, an exponential decrease of the displacement amplitude with stiffness was observed at all frequencies investigated. An M-mode version to depict both the spatial and temporal variations of the locally induced displacement was used. In experiments with gels of different stiffness, the resulting amplitude of the harmonic displacement estimated oscillated at the same frequencies and ranged from ~300 to 250 µm. An exponential decrease of the displacement amplitude with the gel stiffness was also observed. In tissue experiments, the results showed that the method is feasible in tissues and that focused US surgery (FUS) ablation can be detected. These preliminary results demonstrate the feasibility of imaging localized harmonic motion as induced by an oscillatory US radiation force. Due to the highly localized and harmonic nature of the estimated response, this technique may be proven to be highly suitable for simple and accurate estimation of the elastic modulus variation in tissues due to disease. (E-mail: elisak@bwh.harvard.edu) © 2003 World Federation for Ultrasound in Medicine & Biology.

Key Words: Displacement, Harmonic, Localized, Modulus, Motion, Radiation force, Stiffness.

INTRODUCTION

Mechanical properties of tumor tissues are known to differ from the surrounding tissues, as indicated by the use of palpation as a diagnostic tool. Infiltrating ductal carcinomas have average moduli of 558 ± 180 kPa compared with 48 ± 15 and 20 ± 8 kPa for normal glandular and fat tissue, respectively, in the breast (Krouskop et al. 1998). As a result, several methods have been developed to estimate tissue stiffness.

In the field of ultrasound (US), Krous cope et al. (1998) estimated vibration motion amplitudes and related them to estimates of elastic modulus by measuring the Doppler shifts of ultrasonic tone bursts. Parker et al. (1990) measured the tissue response to mechanical vibrations for “sonoelasticity imaging” and have reported results on the applications on in vitro muscle (Levinson et al. 1995) and in vitro prostate (Taylor et al. 2000). Ophir et al. (1991) developed the method of elastography that applies a small external static compression (on the order of 1%) and uses cross-correlation techniques on radiofrequency (RF) ultrasonic signals to estimate the displacement and strain in the tissue resulting from the compression. This method has been proven to produce...
Fig. 1. Localized harmonic motion imaging diagram.

good quality strain images (or, elastograms) in several tissues, such as in vivo breast cancer (Cespedes et al. 1993; Garra et al. 1997; Ophir et al. 2001), in vitro normal prostate (Konofagou and Ophir 1998) and in vitro kidney (Ophir et al. 2001). Finally, to overcome the shortcomings of an external excitation, the remote application of the mechanical stimulus using an ultrasonic beam has been of particular interest in the last few years (Fatemi and Greenleaf 1998; Nightingale et al. 2001; 2002) with applications on artery calcifications (Fatemi and Greenleaf 1998) and in vivo normal breast (Nightingale et al. 2001). In the field of MRI, magnetic resonance elastography (Muthupullai et al. 1995) is the only technique that provides a direct estimate of the shear modulus due to its direct link to the speed of the propagating shear wave induced by the shear-wave motion of an externally applied piston. In ultrasound, a more recent technique, transient elastography, also utilizes the propagation of low frequency pulsed shear waves in order to measure the underlying shear modulus (Sandrin et al. 2002). The physics of the external shear-wave application and shear-wave propagation may, however, limit these methods in their accurate speed and, thus, modulus estimation.

Another method that induces vibration remotely and attempts to detect mechanical properties is “US-stimulated acoustic emission (USAE) imaging” by Fatemi and Greenleaf (1998). This method uses US-induced radiation force to probe tissue properties. As an US beam propagates through tissue, part of its energy is absorbed and part of it scattered away. The momentum change of the beam results in a force that acts on the tissue. In this new technique, two US beams are operating at slightly different frequencies \(f_1\) and \(f_2\), \(f_1 = f_2\), the beams overlap at the focal region where the waves interfere and generate a wave that is amplitude-modulated by their difference frequency \(f_d = f_2 - f_1\). An object at the

erasing zone experiences an average energy density \(\langle E \rangle\) that fluctuates at the frequency of \(f_d\) (Fatemi and Greenleaf 1998). This varying force causes the tissue to move at the frequency \(f_d\) and, thus, generates an acoustic source.

The magnitude of the acoustic wave emitted by the source depends on the radiation force and the mechanical frequency response of the tissue at the frequency of \(f_d\). The stimulated acoustic signal propagates through the tissue and can be detected by an external hydrophone (Fatemi and Greenleaf 1998; Konofagou et al. 2002). The resulting acoustic signal, however, is a combination of the mechanical and acoustical properties of the tissue, the resonance characteristics of the transducer housing and its surroundings, and its interaction at the hydrophone. Therefore, stiffness estimation using this method is extremely challenging. To avoid the artifacts and drawbacks of the overall USAE application, we propose to utilize the radiation force of the overlapping US beams, but use a separate US beam to probe the induced tissue motion (Fig. 1). The amplitude, as well as frequency content, of this motion should provide us with information about the mechanical properties of the tissue. In addition, the use of US to detect the motion using cross-correlation techniques may constitute a technique for the successful decoupling of US attenuation effects from the mechanical effects in different tissues.

The development of localized harmonic motion imaging is, thus, hereby proposed (Fig. 1). The main concept behind the proposed work is that local harmonic motion can be precisely estimated in tissues as induced by an oscillatory, internally applied radiation force \(F_0\). The local elastic modulus \(E\) can be directly estimated from the characteristics of the underlying tissues and its harmonic motion; more precisely, the tissue area \(A\), the tissue Poisson’s ratio \(\nu\) (assumed to be equal to 0.495 for most soft tissues) (Krouskop et al. 1998) and tissue radius \(r\) undergoing motion, and the magnitude \(X_0\) of the resulting harmonic displacement under a uniform load applied on the boundary of a semi-infinite elastic solid (Timoshenko and Goodier 1970; Lambe and Whitman 1969), \(x (x = X_0 \cos(2\pi f_0 t)\) with \(f_0\) the frequency of oscillation and \(t\) time) that is:

\[
E = \frac{2(1 - \nu^2) F_0 r}{X_0 A},
\]

(1)

where

\[
F_0 = \frac{2 \alpha I}{c},
\]

(2)

where \(\alpha\) is the absorption of the tissue, \(I\) is the intensity
of the radiation force generating transducer(s) and \( c \) is the speed of sound (Nightingale et al. 1999, 2001, 2002). From eqn (1), it can be inferred that the stiffness is inversely proportional to the magnitude of the vibration induced within the tissue, for the same radiation force amplitude and tissue area under motion. This theoretical result based on a model of uniform load on a homogeneous elastic solid also correlates well with the simulation results presented in this paper, as will be described in the next section.

In harmonic motion imaging, the oscillatory motion is estimated at different snapshots of the motion \( (t_1, t_2, \text{ etc.}) \) using cross-correlation of RF ultrasonic signals acquired at the same location undergoing vibration by a separate US beam (Fig. 2). This method is distinctly different from alternative techniques, such as remote palpation (Nightingale et al. 2001; 2002) and shear wave elasticity imaging (SWEI) (Barrannik et al. 2002), which estimate motion during relaxation of the tissue after application of the force instead of during its application, such as is the case of USAE and the proposed method.

**METHODS**

**Finite-element simulations**

To assess the optimal parameters to be used with this technique, finite-element simulations and a previously developed signal-generation model for the RF signal simulation were utilized (Konofagou 1999). To model tissues containing tumors, finite-element simulations of mechanical targets, of size 40 mm by 40 mm, that contain inclusions of distinct stiffness from the surrounding medium, were considered (Konofagou et al. 2001). The center of the inclusions (of diameter 6.6 mm) was always located at a 20-mm depth. The healthy tissue (or, background) had a stiffness equal to 30 kPa and tumorous tissue (or, inclusion) varied from 20 kPa to up to 50 kPa in stiffness (Konofagou et al. 2001).

Loading at different nodes of the mesh (as described for different examples) occurred at frequencies ranging from 200 Hz to 800 Hz, sampled at 3 kHz (same as in the experiments, see below). Because the radiation force depends on the intensity (a nonnegative parameter), eqn (2), the input force in the finite-element simulation oscillated around a nonzero mean (Fig. 3a) (Konofagou and Hynynen 2003). An example of the finite-element solution for the resulting displacement at 800 Hz excitation is given in Fig. 3b. Note the existence of two distinct frequencies: the frequency equal to that of the applied radiation force and a lower frequency. The lower frequency is most likely due to the nonzero mean of the radiation force and this issue, despite it being investigated, goes beyond the scope of this paper. Because, in experiments, motion was estimated within a window of 4 to 5 ms, only the higher frequency component was tracked (Fig. 3b). To preserve the consistency between simulations and experiments, in all examples shown in this paper, only the oscillation at the excitation frequency was considered, and the lower frequency component was removed through high-pass filtering, unless indicated otherwise. The filtering performance can be later assessed in Fig. 7a. Because the displacement amplitude sought to be estimated (at the higher frequency) is relatively smaller, the force applied in the simulation examples shown are 10-fold of that shown in Fig. 3a so as to establish the highest range of displacements that can be estimated using this technique.

Four different cases were studied to assess the effect of
loading frequency on the displacement estimate. For each one of those cases, simulated RF lines were generated through convolution of a Gaussian-modulated pulse with the random scatterer distribution based on the node distribution of the finite-element mesh. Tracking of RF lines was performed using cross-correlation techniques (Konofagou and Ophir 1998; Konofagou 1999) and the displacement was estimated at a frequency of 3 kHz to adequately sample the harmonic motion (Fig. 2). Parameters, such as loading frequency and tissue modulus, were studied regarding their influence on the resulting estimate.

Phantom experiments

The method was tested on agar gel phantoms made using Sigma agar powder in 460 mL of distilled water. Table 1 shows the concentration of agar in the gels and the subsequent modulus change (Hall et al. 1997). The agar gel phantoms were prepared as follows. The distilled water was mixed with the agar powder by slowly pouring the latter into the former while stirring constantly at approximately 0.5 revolution/s. During the mixing of the agar powder in the distilled water, the solution was slowly brought to a near boiling temperature (about 90°C) so as to accelerate the dilution of the agar powder and, thus, for the mixture to become clear. At that time, glass beads (Spheriglass®; 71 μm in diameter) were added for scattering purposes. Then, the mixture was placed inside a water bath at 50°C and the remaining bubbles inside the phantom rose to the surface. The mixture was then poured into a square mold of 5 × 5 cm² and hermetically sealed with a Mylar sheet. The thickness of the mold was at 3 cm. The sample was then constantly manually rotated to allow for the uniform distribution of the beads and then, after the mixture was homogenized (i.e., the beads no longer moved inside the gel matrix), the sample was left to congeal (for approximately 5 to 6 h) at room temperature. The absorption of the agar gel phantoms varies very little, if at all, with agar gel concentration (Hall et al. 1997) and the radiation force applied was, hence, assumed to be of the same amplitude in each case studied, eqn (2).

Two focused single-element transducers were utilized (Fig. 1), operating around a frequency of 2.27 MHz and at slightly different frequencies; by the difference frequency indicated. The transducers’ efficiencies were equal to approximately 65% and were used to convert the electrical power measured using the amplifiers (one for each transducer; models 3100L and A150; Electronic Navigation Industry, Rochester, NY) to acoustical power. A PZT composite, 16-element diagnostic transducer (Imasonics, Inc.) was also operated at pulse/receive mode (Panametrics, Inc.) at a frequency of 1.1 MHz and the two beams were always focused at a depth of 100 mm inside the gel or tissue. The reader should not confuse the depth of focus in the experiments with the “apparent” depth of focus on some of the images in the figures. The focused transducers and the diagnostic probe were all focused on the same region of the tissue-mimicking gel phantoms to ensure highest signal-to-noise ratio (SNR) of the signal to be tracked (Fig. 2). No steering or translation was performed; the same part of the gel/tissue is always interrogated at different frequencies. RF signals were acquired simultaneously (i.e., during the application of the radiation force). Several pulses were fired during the radiation force application to track the oscillatory displacement at different time instants (Fig. 2). The area of the overlapping beams was estimated to be on the order of 2 mm. The pulse duration was equal to 0.28 ms and a pulse-repetition frequency (PRF) of 3 kHz was used. RF data were of total duration equal to 10 ms (same as the FUS exposure time) and acquired at a sampling frequency equal to 50 MHz. The data were acquired and digitized on a digital oscilloscope (Yokogawa DL 7100, Tokyo, Japan) and stored on disk.

RF signal tracking was performed using cross-correlation techniques with a window on the order of 1 to 2 mm. Estimates of the displacement relative to the initial position (i.e., at the onset of the application of the radiation force) were obtained during the application of the radiation force that oscillated at frequencies ranging between 200 Hz and 800 Hz. The focused US intensity used was approximately equal to 1015 W/cm² because a preliminary study showed that displacement could be accurately estimated beyond 900 W/cm²; mainly due to the fact that the higher-frequency displacement component, which typically has a smaller amplitude than the lower-frequency one (Fig. 3b), can be estimated more precisely at higher force amplitudes. Before displacement estimation, the signals received were filtered using a notch filter that filtered the fundamental frequency of the radiation force generating transducers (in this case 2.27 MHz) and all its harmonics. The displacements were also imaged in an M-mode-like fashion to study both their spatial and temporal variation.

Porcine muscle experiments

Fresh porcine thigh muscle tissue samples were excised from euthanized animals and immediately im-

<table>
<thead>
<tr>
<th>Gels</th>
<th>Agar concentration (g/L)</th>
<th>Modulus (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gel 1</td>
<td>5</td>
<td>7.1</td>
</tr>
<tr>
<td>Gel 2</td>
<td>10</td>
<td>25.9</td>
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<td>Gel 3</td>
<td>15</td>
<td>55.2</td>
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<tr>
<td>Gel 4</td>
<td>20</td>
<td>94.6</td>
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mersed in a 0.9% saline. They were then kept in room temperature until the measurements were made (usually 1 to 4 h later). The approximate dimensions of the muscle samples were 50 mm by 100 mm by 40 mm. The methods used in this case were identical to those used in the case of the gels. To cause FUS thermal coagulation in the tissue, continuous-wave (CW) excitation was used at an electrical power equal to 1500 W/cm² for 10 s.

RESULTS

Finite-element simulations

In the simulations, the estimated oscillatory displacement spanned from $-800$ to $600 \mu$m (Figs. 4 and 5) and the frequencies of excitation could easily be estimated from the temporal variation of the displacement. Furthermore, an exponential decrease of the displacement amplitude with stiffness was observed at all frequencies investigated. An M-mode (Fig. 4) version to depict both the spatial and temporal variation (Fig. 5) of the locally induced displacement was used. Figure 6 shows in more detail the cases of all different frequencies and the displacement plot at each (stiffness, frequency) pair. The reader should note the consistent decrease of the amplitude with stiffness increase at all frequencies. A small upshift in the frequency (on the order of tens of Hz) estimated can also be observed as the stiffness increases (Fatemi and Greenleaf 1999; Konofagou et al. 2003)

Fig. 4. Harmonic displacement applied at 20 mm depth and frequency of 400 Hz. (a) M-mode version of true (calculated from the finite-element simulation) displacement (mm) with time, (b) M-mode version of estimated displacement (mm) with time (0 to 4 ms) using cross-correlation.

Fig. 5. Details of Fig. 4. (a) Lateral plot at 20 mm depth, (b) mean true (----) and estimated (—) displacement with time.

Fig. 6. Displacement tracings at the inclusion with stiffness equal to 20 kPa (---), 40 kPa (•••), 60 kPa (----) and 80 kPa (—) at frequencies of (a) 200 Hz, (b) 400 Hz, (c) 600 Hz, and (d) 800 Hz.
(i.e., the number of cycles in the displacement plot consistently increases as the stiffness increases). A summary of all the findings in the simulations is shown in Fig. 7b. An exponential decrease of the displacement amplitude is observed with stiffness increase at all frequencies and a higher displacement amplitude is observed at smaller frequencies; possibly due to the natural frequencies lying in the lower-frequency range for this model. Figure 8 shows an image of the modulus distribution (Fig. 8a) and the displacement image (Fig. 8b). The inclusion is clearly depicted in the displacement image.

**Phantom experiments**

The M-mode images of the displacement at 800 Hz are shown with time in Fig. 9. At the absence of excitation frequency, no harmonic motion is observed (Fig. 9b). At the onset of harmonic motion excitation as induced by the overlap of the two beams, harmonic motion is observed at 20 mm depth (Fig. 9d), confirming what was observed in the simulations. Figure 10 illustrates the
spatial distribution of the displacement profiles in the two cases. The focal spot at which motion is induced can clearly be observed between 15 and 23 mm. The reader should note that Figs. 9 and 10 are shown before filtering out a lower-frequency component (Fig. 3b); hence, the negative mean of the displacement denoting motion away from the transducer due to the application of the radiation force (Fig. 3a). A summary of the results in the gels after filtering out the lower-frequency component is shown in Fig. 11. At the absence of radiation force, the displacement stays virtually at zero (Fig. 11a). At frequencies of 200 Hz, 400 Hz, 600 Hz and 800 Hz, the displacement undergoes a periodic variation at the same frequency as the excitation frequency. Figure 11b shows the temporal variation of the mean displacement in gels 1 to 4 at the frequency of 800 Hz, and Fig. 12 summarizes the results in all gels at the frequency with the highest number of cycles (i.e., that of 800 Hz). A steady decrease in amplitude was noted with increasing stiffness, similar to that observed in the case of the simulations (Fig. 7b).

**Porcine muscle experiments**

Figure 13 shows the M-mode RF images and displacements before and after thermal coagulation of the tissue. Before coagulation, the tissue is shown to vibrate at the depth of 21 mm. After ablation, the tissue is no longer undergoing the same amplitude of harmonic displacement at 21 mm; in fact, the displacement estimates appear to be lower. The origin of these bright bands in Fig. 13d is not known, but definitely corresponds to errors in the estimation, most likely through phase aberration following coagulation and/or cavitation. Figure 14 summarizes these results by...
showing the displacement plots with depth at 1.5 ms (Fig. 14a) and time at 21 mm (Fig. 14b; after low-frequency component filtering).

**DISCUSSION**

In recent years, there have been a multitude of techniques for the estimation of mechanical properties to develop new imaging modalities for the detection of disease. In this paper, we propose a new technique that combines the precision of static techniques with the simplicity of the harmonic excitation methods. It has been long established that remotely applied vibratory methods are the preferred techniques for the estimation of moduli of materials, due to their simplicity and higher safety (ASTM 2002). However, frequency-dependence, reverberation and poor estimation quality have hindered the development and application of these techniques, rendering static techniques as the more reliable alternative.

Harmonic motion imaging applies a remote, harmonically variable radiation force deep inside the tissue and estimates the resulting harmonic displacement using cross-correlation techniques. The high precision of the cross-correlation techniques permits the estimation of even μm-level displacements without the interference of standing waves, tank resonance or ambient noise, which may contaminate the signal in US-stimulated acoustic emission methods (Fatemi and Greenleaf 1998; Konofagou et al. 2002; 2003). In addition, although not demonstrated here, the proposed method localizes the induced motion with high precision along the beam, and may potentially provide information on the acoustic attenuation of the tissue based on the variation of the acquired signal amplitude. This becomes very important in situations where acoustical and mechanical effects may need to be separated to monitor distinct mechanisms (e.g., temperature effects). More importantly, information on both the radiation force and the displacement can yield a direct measurement of the local modulus, eqn (1). In
simulations and phantom experiments, we showed that the frequency of the estimated displacement corresponds to the excitation frequency, but that this frequency content varies with stiffness variation. In fact, a small frequency shift occurs with varying stiffness (Fig. 6), but was deemed too small to be observed in experiments where the accuracy of the method is further challenged. This element could be used in the future to estimate stiffness directly.

Most importantly, the amplitude of the displacement estimated decreases with stiffness in an exponential fashion (Figs. 7b and 12) and can yield an accurate image for lesion localization (Fig. 8), rendering this method highly sensitive for differentiation of tissues based on their stiffness. In tissue experiments, the stiffening of the muscle following FUS ablation could be detected by the substantial decrease of the displacement amplitude. A direct estimation of modulus is the ultimate and very difficult goal, as encountered by many others in this field. However, the information on a small tissue region undergoing vibration at different frequencies could easily be modeled by a point load, and mechanical harmonic responses can, thereby, be more closely linked to the underlying stiffness. Future investigations should further clarify the potential of this technique for mechanical property assessment.

CONCLUSION

These preliminary results demonstrate the feasibility of imaging localized harmonic motion as induced by an oscillatory US radiation force. Due to the highly localized and harmonic nature of the estimated response, this technique may be proven highly suitable for accurate estimation of the elastic modulus variation in tissues due to disease, or local treatment. Ongoing research will determine the required parameters for the optimal performance of the harmonic motion imaging technique and, thereby, the type of potential impact it could have in clinical applications.

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