Published in final edited form as:

Ultrasound Med Biol. 2011 December ; 37(12): 2013–2027. doi:10.1016/j.ultrasmedbio.2011.09.005.

Performance assessment of HIFU lesion detection by Harmonic Motion Imaging for Focused Ultrasound (HMIFU): A 3D finite-element-based framework with experimental validation

Gary Y. Hou^{*}, Jianwen Luo^{*}, Fabrice Marquet^{*}, Caroline Maleke^{*}, Jonathan Vappou^{*}, and Elisa E. Konofagou^{*,†}

^{*}Department of Biomedical Engineering, Columbia University, New York, NY, USA

[†]Department of Radiology, Columbia University, New York, NY, USA

Abstract

Harmonic Motion Imaging for Focused Ultrasound (HMIFU) is a novel high-intensity focused ultrasound (HIFU) therapy monitoring method with feasibilities demonstrated *in vitro*, *ex vivo* and *in vivo*. Its principle is based on Amplitude-modulated (AM) - Harmonic Motion Imaging (HMI), an oscillatory radiation force used for imaging the tissue mechanical response during thermal ablation. In this study, a theoretical framework of HMIFU is presented, comprising a customized nonlinear wave propagation model, a finite-element (FE) analysis module, and an image-formation model. The objective of this study is to develop such a framework in order to 1) assess the fundamental performance of HMIFU in detecting HIFU lesions based on the change in tissue apparent elasticity, i.e., the increasing Young's modulus, and the HIFU lesion size with respect to the HIFU exposure time and 2) validate the simulation findings *ex vivo*. The same HMI and HMIFU parameters as in the experimental studies were used, i.e., 4.5-MHz HIFU frequency and 25 Hz AM frequency. For a lesion-to-background Young's modulus ratio of 3, 6, and 9, the FE and estimated HMI displacement ratios were equal to 1.83, 3.69, 5.39 and 1.65, 3.19, 4.59, respectively. In experiments, the HMI displacement followed a similar increasing trend of 1.19, 1.28, and 1.78 at 10-s, 20-s, and 30-s HIFU exposure, respectively. In addition, moderate agreement in lesion size growth was also found in both simulations (16.2, 73.1 and 334.7 mm²) and experiments (26.2, 94.2 and 206.2 mm²). Therefore, the feasibility of HMIFU for HIFU lesion detection based on the underlying tissue elasticity changes was verified through the developed theoretical framework, i.e., validation of the fundamental performance of the HMIFU system for lesion detection, localization and quantification, was demonstrated both theoretically and *ex vivo*.

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Address Correspondence to: Dr. Elisa E. Konofagou, Department of Biomedical Engineering, Columbia University, 351 Engineering Terrace, mail code 8904, 1210 Amsterdam Avenue, New York, NY 10027 USA, ek2191@columbia.edu, Tel: 212-854-9661/212-342-0863, Fax: 212-342-5773.

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Keywords

Finite element analysis; Therapeutic ultrasound; High intensity focused ultrasound monitoring; Elasticity Imaging; Harmonic Motion Imaging for Focused Ultrasound

INTRODUCTION

High Intensity Focused Ultrasound (HIFU) aims at thermally coagulating the tissue at the focus of the transducer through application of a continuous high energy acoustic beam. Irreversible cell damage, also known as a thermal lesion, is formed through absorption of focal acoustic energy in soft tissues. Moreover, it can be confined only in the focal region without inducing irreversible thermal damage to the surrounding medium. In the past, the ability of HIFU to induce noninvasive, localized and irreversible tissue necrosis has led to numerous investigations of its application for solid tumor ablation (Bamber and Hill 1979, Burov and Andreevskaya 1956, Corry et al. 1984, Frizzell 1988, Fry and Johnson 1978, Goss and Fry 1984, Kennedy 2005, Linke et al. 1973, Taylor and Connolly 1969). Nevertheless, a few major hurdles still exist in the path of widespread clinical translation of HIFU surgery. This includes both the capability of efficient monitoring of lesion formation as well as online characterization of the effective region of treatment (thermal lesion), i.e., the optimization of detecting the onset of lesion formation.

Until now, numerous imaging approaches have been established and implemented for HIFU lesion monitoring and treatment assessment in both MRI (Cline et al. 1995, Gianfelice et al. 2003, Huber et al. 2001, Hynynen et al. 2001) and ultrasound (Lele 1966, Takeuchi 1963, Ter Haar et al. 1989, Yang et al. 1993). Magnetic Resonance Imaging (MRI) is currently held as the standard noninvasive guidance and monitoring of HIFU because it can provide quantitative spatial maps of the induced temperature rise at high spatial resolution. Widely known as MR-guided focused ultrasound surgery (MRgFUS) (Cline et al. 1995, Furusawa et al. 2006, Gianfelice et al. 2003, Huber et al. 2001, Hynynen et al. 2001), the system includes a MR-compatible focused ultrasound transducer whose focus lies inside the target tumor region while T1-weighted images are acquired to detect the tumor and monitor the treatment based on the mapped temperature change. In addition, MR-based tissue elasticity imaging, namely magnetic resonance elastography (MRE) (Kruse SA 2000, Lewa 1991, Multhupillai R. 2001, Sinkus et al. 2000) has shown feasibility in HIFU monitoring (Wu et al. 2001). In MRE, shear waves within the tissue are first induced by an external mechanical exciter. Displacements resulting from the propagation of such shear waves are recorded through a motion-sensitizing gradient sequence. As a result, the underlying mechanical properties can be directly estimated based on the shear wave velocity. Among the ultrasound based techniques, detection criteria can be categorized under three different physical measurements: B-mode, temperature elevation, and elasticity change. Conventional B-mode imaging (Lele 1966, Ter Haar et al. 1989, Yang et al. 1993) detects thermal lesion formation based on its associated hyperechoic change. However, the nature of the backscattered signal change is highly dependent on the onset of boiling and its uncertainty often limits the reliability of B-mode imaging as an optimal onset lesion detection technique (Chavrier et al. 2000, Kennedy 2005, Vaezy et al. 1997). Non-invasive temperature-induced echo-shift

imaging relies on the changes of tissue sound speed in the backscattered ultrasound signal. Although limited by an upper limit in detectable temperature rise (Simon et al. 1998), this technique has been validated theoretically and experimentally in thermal lesion assessment (Pernot et al. 2004) and real-time monitoring of HIFU lesion formation *in vitro* (Liu and Ebbini 2010). Ultrasound-based tissue elasticity imaging techniques are developed based on the fact that HIFU lesions correspond to significant tissue stiffening. The Acoustic Radiation Force Impulse (ARFI) imaging technique utilizes a modified linear array transducer to transmit a high-intensity continuous wave pulse, i.e., a localized radiation force and subsequently perform a standard-pulse-echo sequence in order to obtain the tissue relaxation response following force application using a one dimensional (1D) cross-correlation technique (Nightingale et al. 2001). In previous studies, ARFI was shown capable of detecting thermal lesions in both *in vitro* and *in vivo* tissues (Fahey et al. 2006, Fahey et al. 2004) where the tracked displacement was much smaller in the coagulated tissue than in the untreated tissue.

Amongst the aforementioned techniques, several studies have dealt with imaging-based characterization of the mechanical properties of HIFU-induced thermal lesion with comparison to mechanical testing measurement. Wu et al. (2001) showed that the MRE was capable of quantitatively estimating the differences in shear modulus between the HIFU lesion and the untreated tissue, indicating that the ablated regions were stiffer than the untreated ones. In addition to MRE, other ultrasound-based elasticity imaging studies also investigated the Young's Modulus of HIFU lesions for comparative analyses with mechanical testing. In Sonoelasticity Imaging (Parker et al. 1990), Zhang et al. (2010) applied dynamic mechanical analysis (DMA) to measure the Young's Modulus of *ex vivo* bovine liver lesions following *in vivo* HIFU and found the HIFU lesion-to-background Young's Modulus ratio to be as high as 12 to 1. Other such comparative studies between outcomes of elasticity imaging and mechanical testing on HIFU lesions have been performed on *in vitro* canine liver (Righetti et al. 1999), *in vitro* porcine liver (Shi et al. 1999) and *ex vivo* bovine muscle (Wu et al. 2001). Based on these studies, the Young's Modulus of the HIFU lesions was found to be 2 to 12 times higher than the untreated tissue.

Given the clear contrast in mechanical properties between the HIFU-induced thermal lesions compared to those of normal tissues, imaging the HIFU lesions based on their distinct mechanical properties has been investigated by numerous techniques. Ultrasound elastography (Ophir et al. 1991) has been shown capable of assessing the extent of thermal lesions based on this strain difference (Bharat et al. 2005, Curiel et al. 2005, Kallel et al. 1999, Righetti et al. 1999, Stafford et al. 1998). Following HIFU *in vivo*, strain imaging showed a significant decrease in the average strain within the treated region with respect to the peripheral normal tissue in both *ex vivo* prostate (Souchon et al. 2003) and *ex vivo* liver (Chenot et al. 2010). Vibroacoustography (Fatemi and Greenleaf 1998) utilized two confocal therapeutic ultrasound beams to generate a localized oscillatory radiation force in tissues. Acting as a localized acoustic source, the transmitted acoustic reflection is recorded by a hydrophone. Several studies have shown that such oscillatory acoustic radiation force can be generated in biological soft tissues internally at variable depths (Bercoff et al. 2003, Bercoff et al. 2004, Chen et al. 2009, Fatemi and Greenleaf 2000, Konofagou et al. 2001, Konofagou

and Hynynen 2002, Konofagou and Hynynen 2003, Lizzi et al. 2003, Michishita et al. 2003, Mitri et al. 2008, Sarvazyan et al. 1998). On the other hand, the potential of using an acoustic radiation force for monitoring thermal lesion formation during HIFU surgery was first reported by (Konofagou et al. 2001), who showed the feasibility of using Vibroacoustography for monitoring of the temperature during thermal therapy and thermal lesion formation.

Localized harmonic motion (LHM) imaging (Konofagou and Hynynen 2003) is a dynamic radiation force technique, which utilizes two sets of therapeutic beams from a pair of confocally aligned HIFU transducers excited under burst mode for noninvasive tissue probing. Simultaneously acquired RF signals are used for estimation of the induced focal tissue oscillatory motion. Applying the same excitation principle as Vibroacoustography, this technique is a localized, noninvasive, non-ionizing, cost-effective alternative for HIFU ablation guidance, real-time monitoring, and lesion detection. Harmonic Motion Imaging (HMI) was proposed utilizing a simpler configuration consisting of a single transducer for both interrogating and/or ablating tissue (Maleke et al. 2006) with improvement in the stability of the focal zone and real-time displacement tracking during application of the acoustic radiation force by an Amplitude modulated (AM)-HIFU beam. Maleke and Konofagou (2001) further extended this technique as a real-time monitoring application for HIFU, namely Harmonic Motion Imaging for Focused Ultrasound (HMIFU). The current HMIFU setup consists of a 4.5-MHz HIFU transducer using an AM-HIFU beam for tissue probing, and a confocal 7.5-MHz single-element, pulse-echo transducer used for simultaneous acquisition of the RF signals. The system is also coupled with a 3D positioning system for raster scanning (Fig 1).

HIFU using HMIFU is typically composed of three stages: 1) Surgical planning, e.g., tumor localization, 2) HIFU application with real-time monitoring, and 3) HIFU lesion assessment. The excitation waveform of the transducer is controlled at a relatively lower intensity of HMI for stages 1 and 3 whereas stage 2 involves a higher intensity. Further details are provided elsewhere (Maleke and Konofagou 2008). Previously, experimental studies have shown the feasibility of HMIFU *in vitro* (Maleke et al. 2006), *ex vivo* (Maleke and Konofagou 2008) and *in vivo* (Curiel et al. 2009, Maleke and Konofagou 2009). In addition, past simulation studies showed initial feasibility in monitoring the onset of thermal lesion formation based on the change in the tissue mechanical response (Konofagou et al. 2003). Through the development of an interdisciplinary framework comprising an acoustic, FE-based mechanical response, and image formation module, Maleke et al. (2010) and Heikkila et al. (2010) investigated feasibilities in the tumor localization and coagulation detection using 1-D imaging and direct measurements, respectively. However, a theoretical framework study on the feasibility of HIFU lesion detection has yet to be developed, i.e., in order to assess the capability of HMI for HIFU lesion localization and quantification based on a geometry independent, complete 3D analysis with consideration of nonlinear acoustic wave propagation during lesion formation under ablative AM-HIFU beam (i.e., Stage 2 of HMIFU). Our hypothesis is that HMIFU is fundamentally capable of detecting HIFU lesions based on the aforementioned change in stiffness and correctly depict the increase in HIFU lesion size with treatment duration. In order to validate this hypothesis, we have developed a

comprehensive, easily implementable 3-D model (Fig. 2), which links 1) a nonlinear-acoustics based model coupled with the Bioheat Transfer (BHT) equation solver for simulating both the pressure field and lesion map, 2) a finite-element (FE) based mechanics module for simulating the acoustical-mechanical response in the focal region within a simulated tissue-mimicking phantom, and 3) an image-formation model, which validates the feasibility of our RF based motion-estimation technique. Under the same input parameters, *ex vivo* experiments using canine liver specimens were performed to validate the results from each module of the simulation framework.

Materials and Methods

The developed simulation framework was comprised of three modules: a nonlinear-acoustics based model coupled with a Bioheat Transfer (BHT) equation solver, a finite-element (FE) based mechanics module, and an image-formation model. All three modules have been linked in the following order: (1) the nonlinear-acoustic module simulates the acoustic intensity and radiation force maps; (2) the BHT module simulates the size and distribution of the thermal lesion using the acoustic intensity map simulated in step (1); (3) following assignment of the lesion-to-background Young's modulus based on existing literature, the FE mechanics module calculates the acoustic-mechanical motion response map using both the simulated acoustic intensity and lesion map (from (1) and (2)); (4) the image-formation module simulates the RF signals before and after the motion response calculated from step (3); (5) a cross correlation technique was applied on simulated RF signals from step (4) for the estimation of the displacements. In the subsequent sections, details of each module are described separately.

Simulations: Customized HIFU-simulator for acoustic module

An existing HIFU-Simulator (Soneson 2009) was customized to the HMI configuration. The HIFU simulation framework assumes a 2D axisymmetric propagation geometry and is composed of two parts: 1) a Khokhlov-Zabolotskaya-Kuznetsov (KZK) (Zabolotskaya and Khokhlov 1969) based nonlinear acoustic module for simulation of the pressure and intensity field, and 2) a conventional BHT based thermal module for simulation of the temperature change and a binary lesion map based on the calculated thermal dose surrounding the focal region.

In this manuscript, our objective was solely to validate that the HMIFU is capable of detecting HIFU lesions based on the relative change in stiffness (lesion-to-background contrast) and of accurately depicting the increase in HIFU lesion size at distinct exposure durations. Therefore, in order to overcome the limitation of the acoustic simulation module, we defined the geometry of the transducer as plane circular, i.e., with an equivalent surface area to the experimental transducer. In other words, both the distribution and magnitude of the experimental force field was approximated in simulations. Two modifications were applied to the HIFU-simulator. First, the HIFU transducer used in HMI is a spherical transducer with a void center, i.e., outer radius of 70 mm and inner radius of 45 mm. The reduction in the active surface area corresponded to the experimental annular void that accommodated the pulse-echo transducer. In order to approximate the actual pressure field,

we converted the original spherical geometry with a void center into a plane-circular with radius of 57 mm but equivalent surface area and *apparent F-number*, $\frac{f}{d}$, which can be derived using Fraunhofer diffraction of Gaussian beams in the case of a generic spherical transducer (Goodman 1985, Marquet 2009) such that:

$$\frac{f}{d} = \sqrt{\frac{\ell}{7\lambda}}, \quad (1)$$

where f is the focal length, d is diameter of the transducer, ℓ and λ represents the axial focal spot diameter and wavelength, respectively. In this study, the apparent F-numbers were 0.86 and 0.88 under the adapted (customized plane circular simulated transducer) and experimental geometries. The simulated *in situ* acoustic intensities were 196 W/cm² and 942 W/cm² under imaging and ablation settings, respectively. Secondly, the input signal to the HIFU transducer is amplitude modulated, i.e., it is composed of both the carrier and modulation frequency, we thus modified the excitation sequence in the BHT module of the model from a binary signal to one oscillating at twice the AM frequency used in experiments. A complete set of simulation parameters can be found in Tables 1 and 2 (Duck 1990, Lu et al. 1997). In HIFU-simulator, the focusing is calculated by assuming a uniform pressure distribution on the transducer surface with the phase shift corresponding to a quadratic approximation of a spherical converging wave. It is noteworthy that the theory of KZK has a paraxial assumption limiting its accuracy within 20° of the axis of propagation (Lee 1986). This implies that transducers with a F-number smaller than 1.74 will suffer a loss of accuracy. However, previous studies (Canney et al. 2008) have been performed under this limitation and considered such inaccuracies to be minor in practice (Lee 1986).

Simulations: Finite-element (FE) mechanics module

In order to calculate the oscillatory tissue response induced by the acoustic HMI radiation force, both the simulated acoustic intensity fields and lesion maps were translated into a COMSOL™ (Comsol Inc., Burlington, MA, U.S.A.) based 3D FE geometry through MATLAB (Mathworks, Natick, MA, U.S.A.). The acoustic intensity field was first approximated into the HMI force field through the conventional plane-wave body force equation (Nyborg 1958, Palmeri et al. 2005)

$$F = \frac{2\alpha I}{c}, \quad (2)$$

where I is the simulated intensity field, α is the absorption coefficient, and c is the speed of sound. Similarly, the generated lesion maps were also translated onto a 3D simulated phantom. As mentioned in the introduction, previous studies have found a lesion-to-background Young's modulus ratio of 2–12 (Maleke and Konofagou 2008, Righetti et al. 1999, Shi et al. 1999, Wu et al. 2001, Zhang et al. 2010). Since the stiffness of the HIFU lesion increases with the exposure duration, the modulus of simulated HIFU lesion map after a 0-, 10-, 20- and 30-s HIFU exposure was assigned to be 1, 3, 6, and 9 times that of the background (10 kPa), respectively. At a first order of approximation, the temperature rise within the formed HIFU lesion was assumed uniform, i.e., the assigned modulus was

assumed to be homogeneous across the lesion in each case. In order to retain the accuracy of the tracked focal displacement at low computational cost, a finer mesh was applied surrounding the focus of the HMI force field, i.e., the distance between neighboring nodes inside and outside the force field was set to be 0.085 mm and 0.57 mm, respectively (Fig. 3a, Table 3). The HMI force field was moved in a raster-scan format in order to compute the displacements within a region of interest (ROI) within an axial view surrounding the thermal lesion.

Simulations: 3D static versus 3D dynamic simulation

In previously reported studies (Heikkilä et al. 2010, Maleke et al. 2010), transient analysis was used to evaluate the simulated mechanical response profile in 1D imaging and direct measurements, respectively. In this paper, we investigated the full two dimensional (2D) displacement profile based on the true three dimensional (3D) HMI problem, i.e., without axisymmetric assumption while maintaining a feasible computational cost. Here, a static computation approach was performed instead of the conventional dynamic approach such that in a linear, purely elastic medium while ignoring any initial transient forces, the peak-to-peak steady-state displacement under the dynamic sinusoidal HMI force was assumed equivalent to the displacement induced by a single quasi-static deformation using the maximum HMI force (Fig. 3d). As a result, this method allowed us to obtain displacement profiles at a 96% reduction in computational time compared to the dynamic method. In order to demonstrate equivalency of the 3D static alternative to that of the 3D dynamic method, 1D comparison of the dynamic and static analysis was performed along the central plane through the HIFU lesion. For a lesion-to-background modulus contrast of 3, 6 and 9 (which corresponds to lesions formed at 10-, 20-, and 30-s HIFU exposure, respectively), the lesion-to-background displacement contrast values under static and dynamic analyses were found to be comparable, i.e., 2.50, 4.11 and 5.41, and 2.42, 3.93 and 5.33, respectively; hence validating the assumed equivalence (Fig. 4).

Simulations: 2D image formation model

The FE displacement solution was applied in a series of simulated ultrasound radio-frequency (RF) signals in MATLAB 2008b (Mathworks, Natic, MA, U.S.A.) generated using a 2D linear convolutional scattering model (Bamber and Dickinson 1980, Seggie et al. 1983). The simulated linear array had 128 elements, center frequency of 7.5 MHz, beamwidth of 1 mm, 60% bandwidth with a sampling frequency of 80 MHz. Additive Gaussian random noise at 40 dB was implemented to all simulated RF signals.

Simulations: Displacement estimation

As mentioned, in the FE mechanics module section, the FE-computed outputs are the displacement maps obtained by moving the HMI force field within a region of interest (ROI) surrounding the thermal lesion. Therefore, estimating the displacement using our RF-based motion estimation algorithm must be repeated for every coordinate investigated during raster scan simulation, i.e., every pixel of the FE-generated mechanical response map. This procedure is as follows: 1) tissue motion was induced using the FE-generated mechanical response map on all of the simulated RF frames generated by the 2D linear convolutional scattering model; 2) only the center line of every RF frame was selected to simulate the

acquisition from a single-element, pulse-echo transducer used in the experiments; 3) a 1-D cross-correlation technique was applied on the RF signals using a window size of 1 mm and 85% overlap. As a result, displacements are estimated from step 1) to step 3), representing the peak-to-peak displacement. In order to estimate the 2D displacement map, this sequence was repeated for every coordinate investigated in the FE module. Lastly, upon completion of the 2D displacement map, a 3×3 median filter was used in conjunction with bilinear interpolation to enhance the visualization.

Ex vivo experiments

Fresh canine liver specimens were excised immediately after animal sacrifice and immersed into a Phosphate buffered saline (PBS) solution at room temperature. All procedures were approved by the Institutional Animal Care and Use Committee of Columbia University. Each specimen was fixed using a metallic needle on an acoustic absorber submerged in a de-ionized and degassed water bath. The HMIFU system was comprised of a 4.5MHz focused (outer diameter 70 mm, inner diameter 45 mm, focal depth 5 cm) transducer (Imasonic S.A., Voray/l'Ognon, France) used to probe the tissue using an AM frequency of 25 Hz. The active element was fabricated utilizing a 1–3 piezocomposite technique and materials such as a large number of lead zirconate titanate ceramic (PZT) rods embedded into a matrix of epoxy or polyurethane (Fleury et al. 2002, Smith et al. 1989). A confocally-aligned, 7.5 MHz single element pulse-echo transducer (Panametrics, Waltham, MA, U.S.A.) (diameter 15 mm, focal length 6 cm) was used for simultaneous acquisition of the RF signals (Fig 1). The extrapolated *in situ* acoustic intensities were 363 W/cm^2 and 1452 W/cm^2 under imaging and ablation settings, respectively. The focal acoustic beam profile was characterized through a hydrophone based calibration experiment. The HIFU transducer assembly was framed onto a metallic clamp in a degassed water tank. A hydrophone (HGN-0200, Onda Corp, Sunnyvale, CA, USA) is attached to a PC-controlled 3D axis positioning system (Velmex Inc., Bloomfield, NY, USA), which enabled the mechanical translation during raster scanning. The acquired RF signals were filtered through an analog band-pass filter (Reactel, Inc., Gaithersburg, Maryland, USA) with cutoff frequencies of $f_{c1} = 5.84 \text{ MHz}$ and $f_{c2} = 8.66 \text{ MHz}$ (at -60dB) and recorded using a data acquisition unit (Gage applied, Lockport, IL) at a sampling frequency of 80 MHz. 2D-HMI displacement maps were obtained through raster scans before and after lesion formation across a 1-cm^2 region of interest (ROI) surrounding the HIFU lesion (Fig. 5). 2D-HMI displacement maps were formed as follows: at every acquisition point during the raster scan, a M-mode consisting of 600 RF lines was acquired using the single-element, pulse-echo transducer at a frame rate of 5.4 kHz. Displacements were then estimated using a 1-D normalized cross-correlation (window size of 1 mm and 85% overlap) technique on the received RF signals. Subsequently, a third-order median filter was applied in conjunction with bilinear interpolation on the displacement map to enhance the image resolution. Based on findings from previous studies, the stiffness increased with HIFU exposure; thus a decrease of displacement was expected within the thermal lesion (Maleke and Konofagou 2008). The same method was repeated in the 10-, 20-, and 30-s HIFU treatment cases on three separate liver samples. All liver specimens were sectioned along the raster scan plane immediately following the ablation protocol and gross pathology images were acquired upon completion

of the study and thresholded in contrast and brightness to enhance the visualization of the formed lesions.

Results

Simulations

Based on the customization of the HIFU simulator mentioned in the methods section, the simulated pressure distribution is based on an approximated intensity field from a plane-circular transducer with equivalent active surface area. Figure 6 compares the maps of the simulated intensity fields obtained from the original (Fig. 6a) and adapted (customized plane circular simulated transducer) (Fig. 6b) geometries to the experimental case (Fig. 6c), indicating a closer agreement in both magnitude and pressure distribution after customization. Regarding the consequences of assuming a plane circular transducer with equivalent surface area in simulations, a similar emitted power is obtained but with a notable difference in the shape of the beam profile (simulation: axial $1.75 \times$ lateral 0.29 mm vs. experimental: axial $2.0 \times$ lateral 0.25 mm).

Subsequently, this simulated intensity map was truncated to its -6 dB Full-Width-at-Half-Maximum (FWHM) before incorporating into the finite element module. The AM implementation of HIFU excitation was confirmed through calculation of the low-amplitude oscillatory component in the temperature rise computed by the BHT module (Fig. 7). Assuming a 3D ellipsoidal shape, the transverse area of the simulated HIFU lesion followed an increasing trend under 10-, 20-, and 30-second HIFU exposure, respectively (Table 4), and the lesion sizes were validated with previously available experimental gross pathology (Hou et al. 2010). As previously mentioned, the HIFU lesion maps were assigned to have a lesion-to-background Young's modulus ratio of 1,3,6, and 9 for treatment durations of 0, 10, 20, and 30 seconds with the background remaining constant at 10 kPa (Fig. 8). Accordingly, the generated displacement profile showed a similar increasing lesion-to-background ratio trend for the 10-, 20-, and 30-s HIFU exposure case, respectively (Fig. 9, Table 5). Consequently, the estimated HMI displacement maps (Fig. 10) also depicted similar incremental trends in both the lesion size and lesion-to-background contrast at the same HIFU exposure durations with a mean average error (over three HIFU exposure cases) of 8.48% and 12.7%, respectively in reference to the true displacement calculated by the finite-element mechanics module (Table 4, Table 5).

Experiments

The 2D estimated HMI contrast maps were shown to be in moderate agreement with gross pathology images obtained after completion of the HMI experiments (Table 4) in depicting the lesion boundaries as well as the growth in lesion size with an average error of 7.57 %. As previously mentioned, the HMI contrast maps were generated by computing the difference between the two HMI displacement map obtained before and after HIFU exposure. It was also shown that the HMI lesion-to-background displacement contrast linearly increased with the treatment time, i.e., indicating a positive correlation between stiffness and HIFU exposure duration (Fig. 11).

DISCUSSION

HIFU remains the only non-contact, non-ionizing, noninvasive technique for tumor treatment based on thermally inducing cell necrosis with high energy acoustic beams. However, improvements are needed for HIFU in its real-time monitoring and onset lesion detection. To date, numerous techniques for HIFU imaging in both the field of MRI and ultrasound have been developed based on the associated changes in temperature (e.g., MRgFUS, echo shift-based imaging), B-mode, or tissue elasticity (e.g., MRE, Elastography). HMI is a dynamic ultrasound elasticity imaging technique using a simple configuration, i.e., a pair of confocally-aligned HIFU and diagnostic transducers, for respectively inducing stable focal oscillatory motion while estimating the displacement in real time. HMIFU applies HMI for tumor localization, simultaneous monitoring of HIFU surgery as well as assessment of treatment outcomes. Previous experimental studies have demonstrated the feasibility of HMI and HMIFU *in vitro*, *ex vivo*, and *in vivo*. Previous theoretical studies have investigated the planning and monitoring stages using 1D imaging and direct measurements. In this paper, a theoretical framework was developed to assess the fundamental capability of the third stage in the HMIFU process, i.e., thermal lesion mapping. The hypothesis was that HMIFU is capable of detecting HIFU lesions based on the change in stiffness and can accurately depict the increase in HIFU lesion size at distinct exposure durations. The objective of this study was to test this hypothesis through the development of a comprehensive 3D theoretical framework that could include the nonlinear wave propagation within a geometry-independent medium. The developed framework included a customized nonlinear acoustic and BHT module for simulation of both the acoustic field and lesion maps, a FE-based mechanical response module, and an image formation module. The simulated findings from the complete sets of the 2D analysis were validated with experiments using canine liver specimens *ex vivo* and the same experimental parameters as in the simulations. Both the simulation and experimental findings demonstrate the feasibility of HMI in both inducing the lesion and detecting the onset of coagulation at different treatment duration based on change in elasticity (Chenot et al. 2010, Maleke and Konofagou 2008, Righetti et al. 1999, Shi et al. 1999, Wu et al. 2001, Zhang et al. 2010) as well as quantifying the increase in lesion size with respect to treatment duration (Chenot et al. 2010, Dasgupta et al. 2010, Kun and Wan 2005, Maleke and Konofagou 2008).

Simulations

In the FE mechanics module, the displacement maps clearly depicted the increase in the lesion size i.e., 13.6, 72.0, 319.3 mm² with treatment duration (10-, 20-, and 30-s HIFU treatment, respectively). Similarly, an increase in the lesion-to-background ratio (1.83, 3.69, 5.39) was obtained for the modulus contrast of 3, 6, and 9, respectively. Note that the computed displacement profiles had lower values compared to the experimental case (Fig. 11a, 11b, 11c). In our framework, we assumed a purely elastic medium with a constant absorption and no scattering, which may not fully represent the actual tissue properties. In addition, a significant contribution to the total body force was found to be induced by the increased sidelobes specific to the transducer geometry used (Vappou et al. 2011), which were not taken into account in this study. Nevertheless, the FE-based framework provided

an easily implementable, geometry independent, full 3D model that can be adapted to a variety of configurations.

In the estimated HMI displacement profile in simulations, both the mapped lesion sizes as well as the lesion-to-background displacement contrasts, respectively, followed an increasing trend with the assigned modulus contrast and treatment time (Tables 4 and 5). Therefore, the hypothesis that HMIFU is capable of detecting lesions under different HIFU exposure times based on the associated lesion-to-background stiffness increase was validated through the presented framework. Average errors of 8.5% and 12.7% were respectively found in the HMI estimation of the lesion-to-background displacement contrast and lesion size (Table 4). Nevertheless, the aforementioned findings demonstrated the value of the developed framework in predicting the performance of HMI under a specific set of parameters and design of the experimental HMIFU system.

Experiments

In the experimental HMI displacement maps, both the detected lesion-to-background displacement contrast and lesion size showed an increasing trend with treatment time, which is in agreement with findings from the theoretical framework (Tables 4 and 5). Therefore, the experimental findings could validate the theoretical framework and prove the hypothesis regarding the capability of HMIFU to map the increase in both lesion size and stiffness with the HIFU exposure time. As shown, there was a difference in the lesion-to-background displacement ratio between the simulations and experiments, which could be due to the lower rate of increase of lesion modulus compared to what was modeled in simulations. This will be further investigated in future studies. Some discrepancies were found in both the lesion size and displacement contrast between the simulations and experiments. This is in part due to the use of a convolutional model in simulations, the ignored change of absorption in simulations, the depth-dependent attenuation in experiments (Figure 5a, 5b), the difference in SNR and the boundary effects due to hepatic pores and vessels. Framework improvements are ongoing taking these effects into account.

CONCLUSION

A 3D, FE-based simulation framework comprised of a nonlinear wave propagation model coupled with a Bioheat Transfer (BHT) module, a finite-element (FE) based mechanics module and an image-formation model, was developed for assessing the feasibility of HMIFU lesion mapping. In both simulations and experiments, HMI was capable of depicting the lesion size increase as well as the lesion-to-background displacement contrast. Therefore, given the experimental validation of this theoretical framework, it can be used to design and predict experimental HMIFU systems.

Acknowledgments

This study was supported by National Institute of Health (R21EB008512). The authors would like to thank Joshua Sonesson, Ph.D., from U.S. Food and Drug Administration (FDA) for providing the source code of the HIFU Simulator, Yukiko Oe, M.D. at Columbia University for experimental assistance, and Professor Francisco Camarena, Ph.D. from Polytechnic University of Valencia for valuable discussions on nonlinear acoustic simulations.

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Figure 1.

HMIFU experimental set up. The focal depth of the HIFU is 5 cm, i.e., the propagational medium consists of 3 cm water and 2 cm soft tissue, which is same as simulation. Note the 3D positioning system is responsible for HMI raster scan.

Figure 2.

Theoretical framework flow diagram. The three modules within the frame are: Customized HIFU Simulator (green), FE mechanical response (yellow), and 2D convolutional model (blue) followed by 1D cross-correlation (brown)

Figure 3.

Finite-element implementation. (a) 3D mesh, 2D raster scan analysis was performed in the cross-plane in red. (b) Mesh of raster-scan plane. Note the finer mesh contained rectangular box is where the (c) simulated force field was being implemented. (d) Typical normalized displacement profile generated inside focus. Under pure elastic medium with neglecting initial force, red dots denote the peak-to-peak transient force can be approximated as a static force.

Figure 4.

1D analysis showing feasibility of static replacing dynamic analysis approach. (a), (c), (e), static, and (b), (d), (f), dynamic raster-scan were performed in a single line with length of 3, 7, and 11 mm along the axial direction enclosing the expected lesion depth on simulated lesion maps with modulus contrast of 3, 6, and 9, respectively.

Figure 5.

HMI experimental displacement map: (a) Before HIFU exposure, (b) after HIFU exposure, and (c) after minus before, i.e., HMI displacement contrast map.

Figure 6.

(a) -6dB simulated force field without the customization ($1.15 \text{ mm} \times 0.26 \text{ mm}$), (b) simulated force field with customization ($1.75 \times 0.29 \text{ mm}$), (c) experimental beam profile ($2.0 \times 0.25 \text{ mm}$). At the electric power of 0.20 W , the simulated original, simulated adapted, and experimental acoustic intensities were 21.3 W/cm^2 , 17.5 W/cm^2 , and 18.5 W/cm^2 , respectively. Therefore, a closer agreement between simulations and experiments in the absolute magnitude of the acoustic intensities was achieved by implementing the adapted geometry. However, by ignoring the center aperture in the simulated transducer geometry, a notable difference remains between the experimental and customized simulated force fields.

Figure 7.

(a) Four representative temperature monitoring curves. From top to bottom: in the focus (navy), 0.2 (green), 0.4 (red) and 0.6 mm (cyan) laterally away from the focus, respectively (10 sec HIFU exposure followed by 10 seconds cooling), (b) finer view of a window indicated by the red box in (a), showing the temperature elevation with an oscillatory pattern due to implementation of AM-HIFU beam.

Figure 8.

Input lesion map assigned at different Young's modulus. Simulated lesion formed under (a) 0 sec, (b) 10 sec, (c) 20 sec and (d) 30 sec HIFU exposure.

Figure 9.

Output displacement map generated by FE raster-scan: Displacement map for lesion formed under (a) 0 sec, (b) 10 sec, (c) 20 sec and (d) 30 sec HIFU exposure.

Figure 10.

Estimated HMI displacement map: Displacement map for lesion formed under (a) 0 sec, (b) 10 sec, (c) 20 sec and (d) 30 sec HIFU exposure.

Figure 11.

HMI displacement contrast map of lesion formed under (a) 10 sec, (c) 20 sec and (e) 30 sec HIFU exposure. Gross pathology for lesion formed under (b) 10 sec, (d) 20 sec and (f) 30 sec HIFU exposure. White contour lines have been manually added to facilitate depiction of the induced lesion (bright red).

Table 1

Simulation parameters for KZK module in HIFU Simulator

Medium 1: Water	
<i>Parameter</i>	<i>Value</i>
Speed of sound (m/s)	1482
Mass density (kg/m ³)	1000
Attenuation at 1 MHz (dB/m)	0.217
Power of attenuation vs. frequency curve	2
Nonlinear parameter	3.5
Medium 2: Liver	
<i>Parameter</i>	<i>Value</i>
Speed of sound (m/s)	1597
Mass density (kg/m ³)	1050
Attenuation at 1 MHz (dB/m)	75
Power of attenuation vs. frequency curve	1.5
Nonlinear parameter	7.9

Table 2

Simulation parameters for BHT module in HIFU Simulator

Medium 1: Water	
<i>Parameter</i>	<i>Value</i>
Heat capacity (J/Kg/K)	4180
Thermal conductivity (W/m/K)	0.6
Perfusion rate (Kg/m ³ /s)	0
Medium 2: Liver	
<i>Parameter</i>	<i>Value</i>
Heat capacity (J/Kg/K)	3510
Thermal conductivity (W/m/K)	0.51
Perfusion rate (Kg/m ³ /s)	0

Table 3

FE mesh parameters using COMSOL™. The computational time per point in the simulation were 10 minutes and 4.5 hours under static and dynamic, respectively.

FE analysis parameters		
<i>Parameter</i>	3D transient	3D static
	<i>Value</i>	<i>Value</i>
No. of vertex elements	16	16
No. of edge elements	140	204
No. of boundary elements	>2100	>2600
No. of elements	>17000	>26000
Computation time	>300 min per point	<10 min per point

Table 4

Comparison of simulated, experimentally mapped HMI lesion sizes. Note the consistent increments in sizes with HIFU exposure duration for all cases.

HIFU exposure time (sec)	10	20	30
Lesion Size (mm²)			
Simulation (FE)	13.6	72.0	319.3
Simulation (HMI)	16.2	73.1	334.7
Experimental HMI	26.2	94.2	206.2
Gross pathology	28.2	83.3	201.1

Table 5

Comparison of simulated and experimentally mapped HMI lesion-to-background contrast. Note the consistent increments in contrast with HIFU exposure duration for all cases.

HIFU exposure time (sec)	10	20	30
Lesion-to- background contrast			
Simulation (FE)	1.83	3.69	5.39
Simulation (HMI)	1.65	3.19	4.59
Experimental HMI	1.19	1.28	1.78