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Noninvasive determination of *in situ* heating rate using KHz acoustic emissions and focused ultrasound

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Abstract

For High Intensity Focused Ultrasound (HIFU) to be widely applicable in the clinic, robust methods of treatment planning, guidance and delivery need to be developed. These technologies would greatly benefit if patient specific tissue parameters could be provided as inputs so that the treatment planning and monitoring schemes are customized and tailored on a case by case basis. A noninvasive method of estimating the local *in situ* acoustic heating rate using the Heat Transfer Equation (HTE) and applying novel signal processing techniques is presented in this paper. The heating rate is obtained by experimentally measuring the time required to raise the temperature of the therapeutic focus from a baseline temperature to boiling (here assumed to be 100°C for aqueous media) and then solving the heat transfer equation iteratively to find the heating rate that results in the onset of boiling. The onset of boiling is noninvasively detected by measuring the time instant of onset of acoustic emissions in the audible frequency range due to violent collapse of bubbles. *In vitro* experiments performed in a tissue mimicking alginate phantom and excised turkey breast muscle tissue demonstrate that the noninvasive estimates of heating rate are in good agreement with those obtained independently using established methods. The results show potential for the applicability of these techniques in therapy planning and monitoring for therapeutic dose optimization using real-time acoustic feedback.

Keywords

Thermal ablation; HIFU; FUS; Ultrasound treatment monitoring; Tissue characterization; Therapy planning

INTRODUCTION

The clinical success of ablative thermal therapies such as High Intensity Focused Ultrasound (HIFU) (Sanghvi et. al. 1999, ter Haar 2001, Vaezy et. al. 1999, Vaezy et. al. 1997, Wu et. al. 2002) depends on the delivery of an accurate thermal dose at the treatment site. Local changes in tissue acoustic and thermal properties such as *in situ* tissue absorption, perfusion and thermal diffusivity, and also intervening tissue attenuation and sound speed, could result in variability

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in the treatment with respect to the treatment plan. These tissue properties play important roles in the final therapeutic outcome as they influence the temperature distributions achieved in the tissue. The characterization of the acoustic and thermal properties of specific tissues, or at a minimum, the characterization of their effect on the *in situ* field, is therefore an important prerequisite to determining the optimal exposure parameters for individual treatments. Moreover, for HIFU to be widely applicable in the clinic, robust methods of treatment planning and delivery need to be developed. These technologies would greatly benefit if patient-specific tissue parameters, or more specifically, their impact on therapeutic exposure, can be provided as inputs to the treatment planning and monitoring schemes for each case.

A number of previous studies (Curra 2001, Kolios et. al. 1999, Meaney et. al. 1998) have reported on the development of numerical simulation tools, based on the Pennes BHTE (Pennes 1948) and the thermal dose formalism proposed by Sapareto and Dewey (Sapareto and Dewey 1984) to predict the temperature distribution and thermal dose for therapy dosimetry planning applications. These simulation tools typically use *a priori* knowledge or assume standard values for tissue acoustic parameters such as ultrasound absorption, intervening tissue attenuation and path inhomogeneities, and thermal parameters such as diffusivity and perfusion. However, these tissue specific properties vary between tissue types and also across individuals. Errors in the values of these parameters can result in significant errors in the temperature distribution, and consequently the thermal dose. If *in situ* estimates of these tissue properties could be provided as inputs to the simulation tools, it could reduce errors in the predicted temperature distributions, and enable them to effectively adapt to varying local conditions.

Methods to estimate tissue acoustic and thermal properties using ultrasonic techniques have been previously reported in the literature. A technique to calculate the local ultrasonic absorption by locally measuring the heating rate was proposed earlier (Fry and Fry 1954, Parker 1983). In this approach, a short ultrasound pulse is used to heat the tissue locally and the resulting temperature rise is measured using embedded thermocouples. The local heating rate is then computed from the measured temperature profiles. The method is invasive since it requires physical placement of thermocouples at the focus and hence has limited applicability in clinical situations. We presented (Anand et. al. 2004) an early form of the idea that both unknown terms in the HTE, the thermal diffusivity K and the magnitude of the heat source Q , could be determined in the HIFU focal region by conducting two calibration exposures and monitoring the resulting changes in backscattered RF ultrasound waveforms. Independently around the same time, Yao and Ebbini (Yao et. al. 2004) demonstrated the feasibility of reliably estimating the initial heating rate noninvasively at a localized heating spot by inducing a temperature change on the order of 1°C and proposed that the ultrasonically estimated initial heating rate can be used to compute the local tissue absorption. They also demonstrated that the ultrasonically determined initial temperature decay rate after turning off the heating demonstrates excellent agreement with the decay rate obtained from invasive thermocouple readings and conclude that the local perfusion can be estimated from these decay rate measurements. However, no quantitative estimates of the local tissue properties were reported in that study. Civale et. al. (Civale et. al. 2007) have reported on the use of noninvasive estimation of backscatter attenuation and backscatter temperature imaging (BTI) to estimate case specific tissue parameters, namely, attenuation and absorption, and adjust the applied power to achieve the pre-determined clinical thermal dose. In the BTI approach, backscattered ultrasound echo signals are analyzed to derive an estimate of a small temperature rise produced by a short HIFU exposure, which will be influenced by the total attenuation experienced by the HIFU beam, the absorption coefficient at the HIFU focus, and the thermal dissipation properties of the tissue in the vicinity of the focus. The BTI approach is inherently a low signal-to-noise measurement, and requires *a priori* knowledge of the temperature dependence of sound speed for the given tissue type which also demonstrates tissue variability. The challenges

in estimation of backscatter attenuation in reflection mode include the fact that the technique will be limited to providing useful information only for large tissue regions with homogeneous ultrasonic attenuation and backscatter. We have also recently proposed a noninvasive ultrasound based quantitative method of estimating the local tissue thermal diffusivity by measuring spatiotemporal variations in the RF echo shifts induced by the temperature related sound speed changes (Anand and Kaczkowski 2008). In addition, studies have reported on the noninvasive measurement of tissue temperature by tracking sound speed changes and tissue thermal expansion for the guidance of ultrasound therapy (Seip and Ebbini 1995, Simon et. al. 1998). While these studies do not explicitly report the measured heating rate, it could be inferred that the heating rate could be estimated from knowledge of the temperature profiles. However, the temperature measurements in these studies require knowledge of the relationship between temperature and ultrasound echo shifts through a calibration step. Ribault et. al. (Ribault et. al. 1998) has reported on the use of differential attenuation imaging to monitor the progress of HIFU treatment. Seip et. al. (Seip et. al. 2002) reported on a comparison of various real-time lesion imaging algorithms to monitor the treatment progress. However, these algorithms were designed to track the relative changes in tissue parameters (e.g. signal energy, tissue displacement, entropy, and tissue attenuation) during the treatment. No quantitative estimates of the tissue parameters are however presented. In this paper, a noninvasive technique for estimating the local heating rate *in situ* using a novel acoustic technique is presented. The technique is based on determining unknown acoustic parameters from the Bioheat Transfer Equation (BHTE). Our current work is limited to *in vitro* experimental scenarios and hence the contribution of perfusion as a heat transport mechanism is not considered in this paper. In this case, the BHTE simplifies to the Heat Transfer Equation (HTE). The techniques are designed such that the estimation can be performed as part of a calibration procedure conducted prior to the therapy delivery session in the treatment region. The *in situ* heating rate estimation methodology assumes that an *in situ* estimate of thermal diffusivity is already available. Furthermore, it is assumed that the medium is locally homogenous and isotropic in the local region where the thermal and acoustic parameters are estimated. The methodology used in our previous paper (Anand and Kaczkowski 2008) can be used to perform the thermal diffusivity measurement and the result can then be provided to the local heating rate estimation step described in this paper. The heating rate is obtained by experimentally measuring the time required to raise the temperature of the therapeutic focus from the baseline temperature (typically body temperature $\sim 37^{\circ}\text{C}$ or ambient temperature $\sim 25^{\circ}\text{C}$) to boiling (here assumed to be 100°C for aqueous media) and then solving the bioheat transfer equation iteratively to find the heating rate that results in the onset of boiling at that time. The onset of boiling is noninvasively detected by measuring acoustic emissions in the audible frequency range due to the violent creation of vapor bubbles. Kilohertz-frequency emissions, consistent with tissue boiling have been previously detected during HIFU exposures (McLaughlan J et. al. 2006, Sanghvi et. al. 1999), and are colloquially named “popcorn” sounds. The techniques proposed in this paper were validated on tissue-mimicking phantoms and excised turkey breast tissue.

THEORY

The technique adopted in this work for the estimation of the acoustic heating rate is based on determining unknown thermal parameters from the BHTE. For the *in vitro* case, in the absence of perfusion, the BHTE reduces to the Heat Transfer Equation (HTE). In this analysis, it is assumed that the medium is locally homogenous and isotropic in the region where the thermal parameters are estimated, that is, in the region encompassing the HIFU focal zone.

Bio Heat Transfer Equation

The differential equation describing the transient BHTE and using a linear acoustic propagation model can be written in axisymmetric cylindrical coordinates as,

$$\frac{\partial T}{\partial t} = K \nabla^2 T - bT + \frac{2\alpha_{abs} I_{eff}(r, z)}{\rho C}, \quad (1)$$

where $T(r, z, t)$ is the temperature change from the initial body temperature in $^{\circ}\text{C}$, K is the thermal diffusivity (m^2/sec) and $I_{eff}(r, z)$ is the local *in situ* acoustic intensity in W/cm^2 as a function of the spatial distance perpendicular to and along the beam propagation axis (r and z respectively). The value b is given by $w_b \rho_b C_b / \rho C$, where w_b is the blood perfusion rate ($\text{ml}/\text{s}/\text{ml}$), ρ_b and ρ represent the density of blood and tissue respectively in kg/m^3 , C_b and C represent the heat capacity of blood and tissue respectively in $\text{J}/\text{kg}/^{\circ}\text{C}$. The value α_{abs} represents the local tissue absorption coefficient (Np/m). It may be noted that $I_{eff}(r, z)$ includes the effect of the intervening tissue attenuation from the transducer to the treatment location and can be mathematically expressed as,

$$I_{eff}(r, z) = I_0(r, z) e^{-2\alpha_{attn} x} \quad (2)$$

where α_{attn} represents the combined tissue attenuation (Np/m) due to one or more intervening tissue layers, x represents the cumulative acoustic propagation distance (m), and $I_0(r, z)$ represents the free-field acoustic intensity excluding the attenuation losses. Defining $I_{norm}(r, z)$ as the normalized spatial acoustic intensity distribution profile with values between 0 and 1, Eq. (2) can be expressed further as,

$$I_{eff}(r, z) = I_0 e^{-2\alpha_{attn} x} I_{norm}(r, z) \quad (3)$$

where I_0 represents a scalar equal to the maximum of $I_0(r, z)$. $I_{norm}(r, z)$ is a unitless two dimensional matrix with the rows representing r and the columns representing z . Substituting Eq. (3) in Eq. (1) and rearranging the terms,

$$\frac{\partial T}{\partial t} = K \nabla^2 T - bT + Q \cdot I_{norm}(r, z). \quad (4)$$

where $Q = \frac{2\alpha_{abs} I_0 e^{-2\alpha_{attn} x}}{\rho C}$, defined as the local effective *in situ* heating rate due to ultrasound energy absorption, is a scalar quantity with units of $^{\circ}\text{C}/\text{s}$. It can be noted that Q is a lumped quantity that includes the intervening tissue attenuation, local tissue absorption and represents the local tissue heating rate.

For the *in vitro* case the BHTE reduces to the HTE with $b=0$, and hence, Eq. (4) reduces to,

$$\frac{\partial T}{\partial t} = K \nabla^2 T + Q \cdot I_{norm}(r, z) \quad (5)$$

We distinguish between the heating rate Q ($^{\circ}\text{C}/\text{s}$) and the heat energy deposition rate, Q' (W/cm^3) = $Q \cdot \rho C$, also known as the Specific Absorption Rate (SAR)..

Estimation of local heating rate Q

In this section, a novel noninvasive approach of estimating the local *in situ* heating rate at the HIFU focus is described. The methodology is motivated by the fact that typically in HIFU

treatments, focal heating rates on the order of 10 °C or more per second are observed (Vaezy et. al. 2001a, Vaezy et. al. 2001b) and temperatures nearing boiling (100°C at atmospheric pressure) (Malcolm and ter Haar 1996, P. P. Lele 1986) have been reported. From Eq.(5), it can be observed that by measuring the rate of temperature rise at the therapeutic focus from ambient temperature to boiling (term on left side in Eq. (5) and accounting for the temperature decay due to thermal conduction loss (first term on right side), the heating rate Q due to ultrasonic absorption can be estimated for a known spatial HIFU beam profile $I_{norm}(r,z)$. In this work, $I_{norm}(r,z)$ is *a priori* computed for the experimental HIFU transducer configuration using a linear acoustic wave propagation model and is a constant during the iterative estimation procedure to estimate Q . As mentioned above, our approach effectively combines all variation in local tissue absorption, acoustic path attenuation, and field distortion into an effective magnitude Q . In particular, we assume that the undistorted form of beam profile I_{norm} can still be used when the field is distorted by path refraction, by simply adjusting the value of Q , because refractive distortions are expected to introduce negligible error once an appropriate value for Q is chosen. The case of highly nonlinear focused fields with enhanced heating on axis, which result in much shorter boiling inception times than would be anticipated by use of the linear acoustic beam profile (Khokhlova et. al. 2006), would require use of the correct beam heating profile to interpret the time to boiling measurement; such cases are beyond the scope of this paper, though the approach is analogous to that described here.

For a given transducer geometry and spatial intensity beam profile, the time t_{boil} required to raise the temperature of the tissue sample from ambient temperature to its boiling point is noninvasively detected using a passive acoustic sensor sensitive to characteristic acoustic emissions (crackling and popping sounds related to the violent expansion of vapor bubbles) in the audible frequency range (<20 KHz) that accompanies boiling (Mast et. al. 2008). Starting with an initial guess value for Q and an *a priori* estimate of K , $T(r,z,t)$ is computed iteratively using a finite element implementation of Eq. (5) in FEMLAB™ (now COMSOL Multiphysics, by COMSOL AB, Stockholm, Sweden) to find the best estimate Q_{est} such that $T(r=0, z=0, t=t_{boil}) = 100^{\circ}\text{C}$ where $(r, z)=(0,0)$ represents the location of the HIFU focal spot.

The initial guess value Q_{cal} for this iterative estimation procedure is provided by Eq. (6) which provides the acoustic heating rate assuming linear acoustic propagation in an attenuating medium,

$$Q_{cal}=2\alpha f I_{sp}e^{-(2\alpha f x)} \text{ W/cm}^3 \quad (6)$$

where α is the acoustic attenuation coefficient (Np/cm/MHz), I_{sp} is the normalized spatial peak temporal average intensity (W/cm^2), f is the HIFU frequency (MHz), and x represents the beam propagation distance (cm). It is assumed that the absorption coefficient was approximately 80% of the attenuation, and losses due to scattering are negligible (Goss et. al. 1980, Hill 1986, Pauly and Schwan 1971). After the first iteration, the time when $T(r=0, z=0)$ reached 100 degrees Celsius is noted. By comparing this value with the experimentally measured boiling time t_{boil} , the value Q is either increased or decreased in the second iteration and a new set of temperature maps $T(r,z)$ are generated. The process of updating Q and estimating $T(r,z)$ continues until $T(r=0, z=0)$ is 100 °C at time $t=t_{boil}$, within an acceptably small error (typically $\pm 1^{\circ}\text{C}$) that the user chooses depending on the heating rate. The updated value of Q in the final iteration is recorded as Q_{est} , and compared with the calculated value Q_{cal} obtained from Eq. (6). The estimation procedure was performed manually in this work and could be automated using an optimization algorithm.

I_{SP} in Eq. (6) was obtained using the following equation (Damianou 2003, Hill et. al. 1994),

$$I_{SP} = 1.8 I_{SAL}$$

where,

$$I_{SAL} = \frac{0.87 \cdot W \cdot \eta}{d^2} \quad (7)$$

where I_{SAL} represents the spatial average intensity (linear) (W/cm^2), W represents the electrical power input to the transducer (W), d represents the full width half maximum (FWHM) of the transducer measured from the acoustic pressure profile (cm) and η represents the electro-acoustic efficiency of the HIFU transducer. The parameters W , d and η were measured during independent calibration experiments performed before the HIFU therapy experiments and are reported in the next section.

For comparison between Q_{cal} and noninvasively estimated heating rate (Q') in the same units (W/cm^3), Q_{est} was multiplied by the product of density (ρ) and specific heat (C). In practice, it is not necessary to have independent knowledge of Q' , ρ and C . Only the lumped parameter Q appears in the HTE of Eq. (5). The estimation procedure is noninvasive (though clearly damaging to tissue in the focal region) and only requires measuring t_{boil} experimentally.

MATERIALS AND METHODS

Phantom Experiments

A set of experiments were performed in alginate-based (Anand and Kaczkowski 2008, Anand et. al. 2007) phantoms placed in specially designed sample holders ($5 \times 5 \times 6.5 \text{ cm}^3$). The phantom preparation procedure has been described in detail in Anand *et al.* (Anand and Kaczkowski 2008, Anand et. al. 2007). A 5 MHz HIFU therapy transducer (SU-104, Sonic Concepts, Woodinville, WA, USA) with an aperture diameter of 16 mm and a focal depth of 35 mm was used to deliver the HIFU heating pulse. A schematic diagram of the experimental setup is presented in Fig. 1. The HIFU transducer was rigidly attached to a 3-D translation stage and moved to the desired location so that the therapy focus is placed inside the sample. The driving electronics for the HIFU transducer consisted of a signal generator (HP 33120, Hewlett Packard, Palo Alto, CA, USA) driving a power amplifier (A300, ENI, Rochester, NY, USA). A commercially available stethoscope (Littmann, 3M Corp, Minneapolis, MN) was used as a passive sensor to detect the acoustic emissions in the audible frequency range (up to a few KHz) that are characteristic of the onset of boiling. The diaphragm of the stethoscope was attached to a microphone and placed against the alginate sample on the far side from the HIFU transducer as shown in Fig. 1. The microphone output was sampled using the sound card on the PC at 44.1 KHz and stored for offline processing. The total HIFU ON time was approximately 45 seconds with brief interruption of the HIFU delivery (for 100 ms) every 2 s to enable acquisition of interference free B-mode images. The experiments were performed at *in situ* intensities (I_{SAL}) of $406 \pm 80 \text{ W/cm}^2$ and $523 \pm 104 \text{ W/cm}^2$. For each HIFU intensity, exposures were performed in five different locations within the sample. Bulk sound speed and attenuation of the sample were measured using the sample replacement technique (Bloch et. al. 1998, Madsen et. al. 1999) with a pair of 7 mm diameter PVDF transducers (Sonic Concepts, Woodinville, WA, USA); measured bulk values for the sample used in this example were $c = 1483 \pm 12 \text{ m/s}$ and $\alpha = 0.3 \pm 0.03 \text{ dB/cm/MHz}$ respectively.

In vitro turkey breast muscle experiments

In vitro experiments on turkey breast muscle were performed using the same physical setup described above for the phantom study. Prior to the experiments, store bought tissue samples were cut into convenient sizes so that pieces could be placed in the sample holders. The cut samples were then immersed in de-ionized water and degassed under vacuum. The degassing process was continued until no visible outgassing from the sample was evident. This process typically lasted 30–40 minutes. Chunks of tissue where the muscle fiber orientation could be visually recognized to be straight were carefully selected for use in the experiment. This orientation is important because of the anisotropy of muscle fibers. In muscle, the attenuation along the fibers exceeds that across the fibers by a factor of 2 or 3 (Duck 1990). The sample was then carefully suspended in the holder ensuring that the direction of propagation of the ultrasound therapy beam were perpendicular to the fiber orientation. With the sample held in this position, alginate gel was poured into the holder to encase the tissue sample. This arrangement ensured that the tissue sample was positioned in the center of the holder allowing easy insertion of thermocouples into the tissue. It also ensured that the ultrasound therapy beam enters through a relatively flat front surface. The propagation distance through the gel was approximately 1 cm. The attenuation and sound speed were measured using the sample replacement technique for each of the samples in the experiment. The average sound speed and attenuation measured over 4 samples was 1567 ± 12 m/s and 1.2 ± 0.1 dB/cm/MHz respectively. These attenuation measurements were performed with the muscle fibers oriented perpendicular to the beam propagation direction. HIFU exposures at an *in situ* intensity of 173 ± 50 W/cm² (calculated) were performed to raise the focal temperature of tissue to boiling to noninvasively estimate the heating rate $\dot{Q}$. The exposures were repeated at different locations in each sample to evaluate the uniformity of results.

RESULTS

Figure 2(a) shows a typical time domain output of the stethoscope recorded during the HIFU exposure in the alginate phantom. At approximately $t = 30$ s after the HIFU is turned on, a marked increase in the amplitude of the stethoscope output signal due to acoustic emissions is seen. The periodic spikes every 2 seconds throughout the HIFU exposure are correlated with the HIFU beam turned OFF and then ON after 100 ms. In our experimental setup, the stethoscope was placed facing the HIFU transducer on the opposite end of the sample holder. The acoustic radiation force is constant for a given acoustic power, and results in a transient displacement of the stethoscope diaphragm at each transition between ON and OFF states, and provides a convenient time stamp in the audio record. The frequency domain representation (spectrogram) of the 700 Hz high-pass filtered time domain signal computed using the short time Fourier transform (STFT) is shown in Fig. 2(b). The occurrence of strong broad band signatures starting at $t = 30$ s extending in frequency up to 1.5 KHz clearly indicates a change of acoustic regime, and correlates with onset of boiling. The power computed from the spectrum of Fig. 2(b) by summing along the vertical axis at each time instant is illustrated in Fig. 2(c). In the current implementation of the method, the time of boiling is determined manually from the cumulative energy plot by determining the first time instant where the cumulative energy exceeded the mean baseline value by 5%. The time interval from 0 to 10 s was used to calculate the mean baseline value. Following this methodology, $t = 30$ s was estimated to be the time instant of start of boiling in the example presented in Fig. 2. This methodology could also be employed in an automated boiling detector to determine the time instant t_{boil} when boiling started. The energy before boiling commenced is attributed to the ambient noise picked up by the stethoscope. The estimated time to reach boiling was 27 ± 1.9 s and 38 ± 1.8 s at 523 W/cm² and 406 W/cm² respectively. Table 1 presents the non-invasive estimate of the heat source along with the calculated value obtained using Eq. (6). A maximum difference of 12 percent is seen between $\dot{Q}_{est}$ and $\dot{Q}_{cal}$, which is well within the uncertainty range in the value of $\dot{Q}_{cal}$.

The experimentally measured bulk acoustic attenuation of the sample, measured transducer characteristics (such as input electric power, electro-acoustic conversion efficiency), and the transducer beam profile, have uncertainties of about 10%, 15%, and 3%, respectively.

A sample time series output of the stethoscope during a HIFU exposure in turkey breast muscle tissue is presented in Fig. 3(a) along with the spectrogram in Fig. 3(b). It can be observed from the spectrogram plot that the onset of boiling can be clearly detected, and this spectral information can also be used for automated boiling detection. The mean boiling times recorded during 4 exposures in 4 different tissue samples were 21 ± 2 seconds. Table 2 presents a comparison between the non-invasive local heat source estimate obtained from the boiling times with the calculated value. A maximum difference of approximately 6 percent is seen between Q_{est} and Q_{cal} .

DISCUSSION

This paper reports on a *noninvasive acoustic* method for determining the *in situ* local heating rate (Q), which is the magnitude of the heating field source term in the HTE. The motivation is twofold: first, knowledge of the two parameters K and Q in the HTE (Eq. (5)) permit simulation of the evolution of temperature in the focal region, and second, accurate *in situ* calibration of the exposure can be done noninvasively without detailed knowledge of the acoustic path or of the local tissue properties. This “calibration” experiment is ultimately used as part of an ultrasonic temperature estimation process, in which the mapping between sound speed and temperature is required. This mapping is obtained from diagnostic ultrasound data acquired during the heating of the medium to the boiling point, and is described elsewhere (Kaczkowski and Anand 2004). The estimation method is designed so that the same transducer used for delivering the therapy dose is used to determine the tissue-dependent HTE parameters noninvasively. One can foresee a clinical scenario in which the HIFU therapy system used for ablating a region is first used to determine both K (Anand and Kaczkowski 2008), and Q using the method developed in this paper during a test sonication inside the target region. The measured heating rate step, is then used to tailor the original therapy plan, which is based on literature values for tissue properties, to the specific conditions characterizing the patient. The techniques developed in this manuscript have been applied to homogenous tissue mimicking phantoms and excised animal tissue to demonstrate a proof of principle.

The challenge of obtaining a noninvasive calibration for internal heating is addressed by using the fact that the boiling phase transition of water occurs within a very small range of temperature. Estimation of the heating rate Q is based on experimentally measuring the time required to raise the temperature at the focal point from ambient to boiling, and then applying the HTE to simulate the experiment and thus iteratively obtain the best fit to the observed time. Boiling in tissue produces a wide frequency range of sound emissions, including audible popping or crackling sounds produced by the sudden expansion and collapse of tissue by production and condensation of water vapor, at very close to 100°C . The time series output of the stethoscope hydrophone and the corresponding power spectrum in Fig. 2 illustrate that t_{boil} can be clearly detected. The boiling times measured for different locations within a given sample exhibited low variance for both of the field intensities used. This is consistent with the fact that the phantom samples are prepared to be spatially homogeneous, and that the tissues selected for initial experiments also proved to be relatively uniform. Q_{est} obtained using the noninvasive technique and Q_{cal} shows a maximum difference of 12 percent. This difference is on the order of the uncertainty in the measured values of attenuation (α) and free-field spatial peak intensity (I_{sp}) in Eq. (6). Uncertainties in I_{sp} result from measurements of the input electrical power and corresponding acoustic output power using a radiation force balance technique, and simulated and hydrophone-scanned focal field maps.

Errors in estimating the exact time of onset of boiling can affect the determined heating rate (Q_{est}). A detailed error analysis to relate the boiling time with the heating rate was not performed in this paper, and would be the next step in this research. The magnitude of error would also depend on the relative significance of thermal diffusivity, heat conduction and the magnitude of the incident acoustic energy. Specifically, if the boiling occurred very shortly after HIFU exposure started, the temperature evolution profile at the focus would be approximately linear. On the other hand, if boiling occurred well after thermal conduction contributed to the heat transfer, the temperature evolution profile would start to flatten and the instantaneous slope of the temperature versus time plot would be smaller compared to the former situation. Consequently, the effect of error in measuring the exact time instant of boiling would be less severe in the latter compared to the former scenario.

Since this work is limited to *in vitro* experimental conditions, the contribution of perfusion as a heat transport mechanism was not considered in this paper. The method can be expanded to account for presence of perfusion *in vivo* if flow is not in large vessels (resulting in a directional and advective heat loss) but rather through perfusion modeled as a non-directional heat sink term in the BHTE. The non-directional (isotropic) heat sink term, typically represented by $w_b T$ (where w_b is the blood perfusion rate (ml/s/ml) and T is the temperature change), would lower the heating rate as $(Q - w_b T)$. Since our proposed method is focused on determining the net local heating rate and not the individual tissue properties, it could potentially be used to estimate the effective heating rate in the presence of perfusion as well.

In this paper, a linear acoustic propagation model has been adopted to compute the *in situ* beam profile $I(r, z)$ used in Eq. (1) and Q_{cal} in Eq. (6). This resulted in relatively lengthy and easily measured boiling inception times. However, clinical HIFU exposures extend from linear to highly nonlinear acoustic regimes, and thus this paper only treats a subset of the clinical range. Indeed, the work of Khokhlova et al. (Khokhlova et al. 2006) addresses the role of acoustic nonlinearity in producing heating rates that are many times greater than that expected from linear considerations. Nonlinear acoustic heating enhancement can be so strong as to decrease the time-to-boil to a few milliseconds, albeit in an extremely small volume that lies within the linear focal zone on the beam axis. Under such conditions, the spatial heating profile is more difficult to compute, and is a strong function of field parameters (including intervening path attenuation), thus significantly complicating the inversion for Q ; this problem is the subject of follow-on study. Under weakly nonlinear conditions, that is, for field intensities that produce some enhanced heating without strong spatial deviations from the linear field profile, the estimated best-fit heating rate might still produce a useful result for therapy planning, but this assumption must be evaluated in studies at higher field intensities than were used here. In this analysis, the medium was considered to be spatially homogenous and isotropic. In heterogeneous media, spatial variations in the thermal properties (thermal conductivity, heat capacity) can be expected. To account for these spatial variations, measurements of K and Q at a number of spatial locations within the region of interest can be repeated and a spatial map of the thermal properties could be constructed.

The shape of the acoustic beam profile is assumed to be constant and known *a priori* in this paper. Even under linear conditions, errors are introduced if the *in situ* beam shape deviates significantly from this assumption. If the target region lies beneath many tissue layers, presence of these multiple intervening tissue layers with varying acoustic properties could defocus the beam pattern (due to phase aberration) and result in deviations from the assumed profile, $I(r, z)$. It is unclear whether the inclusion of all such variations in beam shape by empirically fitting the magnitude Q to the measured boiling time as done here is sufficiently accurate to be useful in practice. The next step in this research would be to analyze the effect of these deviations on the estimates of the heating rate and then on the use of those estimates in planning and delivering therapy. In a practical system, it may be possible to estimate the *in situ* beam

profile using noninvasive temperature estimation techniques (Simon et. al. 1998). If a low intensity HIFU exposure is applied to the tissue during a test sonication at subablative intensities, the estimated temperature maps could provide an estimate of the actual beam profile compared to the *a priori* assumed beam profile. This independently obtained spatial information could be incorporated in the heating rate estimation process described in this paper to obtain the effective heating rate.

The methods developed in this paper can be used in therapy planning applications to measure the applied heating at the treatment site and accordingly to tailor the treatment protocol to the patient. Currently, these therapy planning and simulation tools must use standard values for thermal and acoustic parameters derived from the literature. Using noninvasive *in situ* estimates can reduce the uncertainty due to these parameters and thus improve the accuracy of the treatment. This approach has applications in noninvasive estimation of temperature rise and we use this *in situ* heating rate estimation technique as part of a calibration procedure for HIFU therapy monitoring using ultrasound backscatter (Kaczkowski and Anand 2004).

CONCLUSIONS

A noninvasive technique of determining the local *in situ* heating rate during thermal therapy treatments has been developed and presented in this paper. The results from *in vitro* experiments performed in tissue mimicking phantoms and excised turkey breast tissue show good agreement between the noninvasive estimation approach and independent estimates using current established methods for linear acoustic fields. The applicability of these techniques can be extended to assess the heterogeneity of biological tissue and construct spatial maps of the variation of these tissue specific parameters. The techniques developed in this paper have applications in therapeutic dosimetry planning, quantitative temperature imaging and potentially as a tissue characterization tool.

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Fig. 1.
Schematic of experimental setup for noninvasive heat source estimation.

Fig. 2.

(a) Time domain output of stethoscope recorded during a HIFU exposure lasting 42 seconds
 (b) Spectrogram of the time domain signal shown in (a) computed using the Short Time Fourier Transform. White arrow indicates the onset of broad band signatures corresponding to boiling
 (c) Power as function of time. The marked increase at $t=30$ s represents the onset of boiling.

Fig. 3.

(a) Time domain output of stethoscope recorded during a HIFU exposure in excised turkey breast muscle (b) Spectrogram of the time domain signal shown in (a) computed using the Short Time Fourier Transform. White arrow indicates the broad band signatures corresponding to the onset of boiling at 21 s (c) Power as function of time.

Table 1

Comparison between noninvasively estimated (Q_{est}) and calculated (Q_{cal}) *in situ* heat source for two HIFU intensities in the alginate phantom

Intensity [I_{SAL}] (W/cm ²)	Estimated <i>In-situ</i> Q (W/cm ³)	Calculated <i>In-situ</i> Q (W/cm ³)	% Difference
406±80	292±3	261±48	11.8
523±104	308±4	312±56	1.3

Table 2

Comparison between mean noninvasively estimated (Q_{est}) and calculated (Q_{cal}) *in situ* heat source in the four independent samples of excised turkey breast tissue.

Intensity [I_{SAL}] (W/cm ²)	Estimated <i>In-situ</i> Q (W/cm ³)	Calculated <i>In-situ</i> Q (W/cm ³)	% Difference
173±50	204±7	192±58	6.3