Temperature Rise Measured Noninvasively During Thermal Therapy Using Backscattered Ultrasound

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Abstract— **Quantitative knowledge of the spatial distribution of tissue temperature is an essential indicator of thermal therapy progress, and is needed to assure treatment safety and efficacy. Measured changes in ultrasonic travel time from an imaging transducer to backscattering sites in and around the heated region can provide clinically useful temperature estimates from which thermal dose throughout the imaged region can be obtained. Previous studies have noted the difficulty in inverting travel time to obtain temperature, due to lack of sensitivity over a temperature interval often encompassing the therapeutic range. In this work, it is shown through in vitro experiments that temperature rise can be accurately obtained from ultrasonic measurements during therapy delivery and post-treatment cool down phases, using RF backscatter data collected with a commercial scanner and a heat transfer model. The temperature estimation problem is divided into two parts: first, non-invasive HIFU calibration experiments are conducted prior to therapy to estimate local model-relevant tissue properties, and second, temperature rise is estimated during therapy. Variability in observed dose response is modeled as a directly related change in the magnitude of the HIFU heat source, while assuming that the acoustic beam pattern is constant.**

I. Introduction

The advent of non-invasive surgical modalities for the treatment of cancer such as High Intensity Focused Ultrasound (HIFU) and other thermal therapies has spurred the development of new monitoring approaches for guidance and feedback. Monitoring is essential because of the effects of tissue heterogeneity, both at the site of treatment and in the intervening path. For the foreseeable future, treatment planning cannot determine all of the variations in local dose (and bioeffect) resulting from such heterogeneities; thus, effective and efficient treatment will only be possible if non-invasive methods of measuring tissue response to therapeutic exposure are available.

Magnetic Resonance Imaging (MRI) is under development for thermal therapy guidance, by groups developing HIFU surgery [1, 2]. While MRI provides high quality diagnostic and guidance information, it is still slow (a few seconds per frame) at producing accurate temperature data, is expensive, and places significant design constraints on robotic and energy delivery devices which must be made compatible with the RF magnetic fields. To provide a less expensive and higher frame rate alternative to the current 'gold standard' of MRI guidance we are developing ultrasound methods for real-time and non-invasive monitoring of HIFU therapy. However, challenges arise from the lack of sensitivity of acoustic propagation speed to changes in temperature in the range at which tissue is coagulated. Our goal is to address this problem by constraining the inversion of RF strain using a heat transfer model. It is also possible to detect the onset of cavitation using backscattered ultrasound. Cavitation is important in HIFU therapy because the presence of microbubbles is likely to change the local heating rate [3], and larger bubbles can provide an indication of boiling (see the companion paper, [4]).

II. Background

A. Monitoring HIFU therapy in real-time

Our prior studies of scanned transducer protocols [5] indicate that moving the HIFU transducer while ensonifying makes better use of treatment time, in part by exploiting non-linear phenomena at high acoustic intensities. These experiments illustrate the significant variation in bioeffect given constant exposure conditions (Fig. 1). Monitoring temperature in real-time may be the only way to conduct practical therapy and optimize both safety and efficacy.

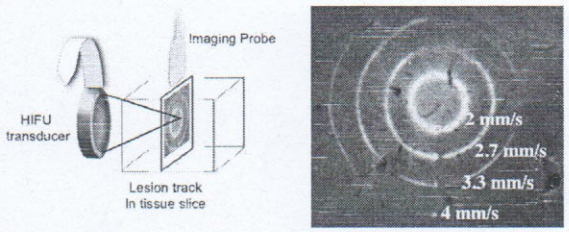

Figure 1. Scanned lesion formation experiment. Prior HIFU experiments perfomed in fresh *ex vivo* bovine liver to examine the lesions created with constant velocity motion of a HIFU transducer indicate that uniform exposure *does not* lead to a uniform bioeffect, even for a single tissue type [5]. HIFU transducer displacement along transverse circular tracks is diagrammed on the left, and an example of resulting lesion tracks is presented on the right. The exposure was varied between tracks by changing the circumferential velocity (while keeping HIFU power constant). One can clearly see the variation of lesion width along any given track. Such variation, even for a relatively uniform tissue type, indicates that safe and efficient HIFU treatment for cancer will require real-time monitoring and feedback for dose control.

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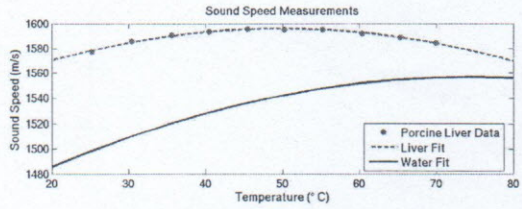

Figure 2. Temperature dependence of sound speed in water and freshly excised porcine liver. The measurements are taken in a temperature regulated water bath using a transmission ultrasound method. The curves indicate the challenges in using ultrasound: lack of sensitivity, and non-monotonicity.

B. *Temperature induced travel time change*

Many mechanical properties of soft tissues closely resemble those of water. Indeed, due to the thermal dependence of density and compressibility in water, the acoustic sound speed c(T) is non-monotonic; see Fig. 2 for an illustration of the empirical function c(T) in water and freshly excised degassed porcine liver [6]. While the idea of using changes in sound speed to measure temperature non-invasively is appealing, the peak sound speed in tissue (where sound speed is insensitive to changes in temperature) occurs near the coagulation threshold and prevents direct inversion of sound speed measurements for temperature estimation. The relative concentration of fatty tissue can further modify the relationship [7], and variability of tissues between different organs and between individuals makes the use of non-invasive measurements of acoustic travel time very difficult to relate to absolute temperature changes without independent knowledge of the c(T) curve.

C. *Temperature estimation by cross-correlation*

Ultrasonic temperature estimation requires collection and processing of the RF signal waveforms because the temperature related changes in backscatter travel time are very small. The changes in travel time appear as slight deformations of the backscattered waveform as the tissue heats. When scaled by the medium sound speed, we call this travel time distortion "apparent displacement" and refer to the time derivative (derivative in image depth) as "local strain". Generally, we have used correlation processing methods such as those used in elastography [8] to track echo shifts from particular locations. Past investigations into the use of ultrasound specifically for temperature estimation have used similar methods [7, 9] but have generally restricted their investigations to small temperature changes below the coagulation threshold where the inversion for temperature is straightforward.

We have estimated apparent displacements by tracking the travel time changes between corresponding A-lines on temporally adjacent RF data. Specifically, RF voltage time series are reconstructed from the I/Q samples in each scan line in each RF frame, and are subdivided into a series of segments of length 1 mm with 20% overlap. For each segment on a given scan line in a frame, a 1-D cross-correlation is used to find the best match for this segment within a search region defined around the same spatial location on a temporally adjacent frame acquired later in time. Sub-sample time shifts are estimated using a polynomial spline matched to several points in the cross-correlation. The time shift within the search region for which the best match was obtained is the local travel time

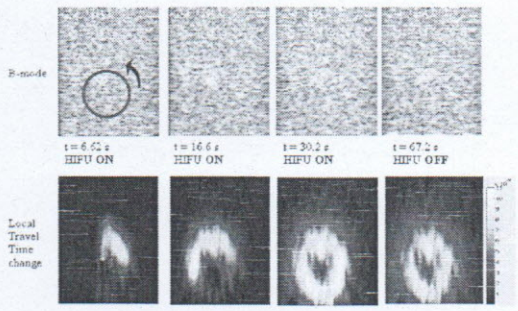

Figure 3. Movie frames from a circular scan experiment. Several frames from a circular HIFU scan imaged using an HDI 1000. The top row illustrates the lack of a signature in B-mode, and the bottom row the local acoustic travel-time change due to temperature rise, estimated using frame-to-frame RF cross-correlation. The measured apparent strain corresponds to a temperature rise of less than 10 degrees and is readily detected.

change, and leads to the apparent displacement for the segment. This procedure is repeated for all segments in a frame to obtain a 2-D travel time change map corresponding to two temporally adjacent RF frames. Consecutive pairs of frames in the acquired data set are processed in this way, and integrated in time to provide 2-D maps of the *total* accumulated travel time changes up to any given frame. Finally, (local) strain estimation is performed by differentiation in depth, using a least squares algorithm to reduce effects of noise. An example of the result of this procedure is presented as an image in Fig. 3 for a circular HIFU scan. This imaging modality is compelling because it provides a high contrast image of the heated region which is not discernible in the B-mode. However, the method is not easily adapted to temperature measurement because of the lack of knowledge of the mapping between sound speed (hence travel time) and temperature, c(T), nor of a robust method for dealing with the low sensitivity in the coagulation temperature range.

III. HTE-BASED TEMPERATURE ESTIMATION ALGORITHM

A. *The heat transfer model*

The transfer of heat deposited acoustically is here assumed to be governed by the Heat Transfer Equation (HTE) in which there is no net loss of thermal energy, and conduction is the only transport mechanism:

$$\frac{\partial T(X,t)}{\partial t} = K\,\nabla^2 T(X,t) + Q \cdot B(X). \qquad (1)$$

The temperature T is a function of both space (denoted by the 3-D vector X) and time, K is the thermal diffusivity, Q is the magnitude of the heat source due to the conversion of acoustic power to heat within the HIFU beam, characterized by the spatial function B. We assume that both K and Q are locally (near the heated region) uniform and isotropic tissue properties, and do not change with temperature. Further, we assume that the heat source is due to conversion of acoustic power to heat by absorption under linear acoustic conditions. We recognize that these assumptions must be evaluated in tissues of interest, both in excised tissues where there is no perfusion and *in vivo* where many factors may affect their validity. Nonlinear behavior of the acoustic field is likely to occur to some degree,

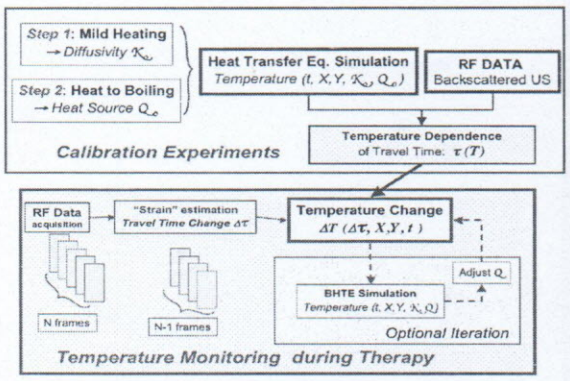

Figure 4. Block diagram for temperature monitoring of thermal therapy. To calibrate dose for local conditions, two initial calibration exposures are conducted using HIFU. The first uses a moderate exposure and observes heating and cooling rates in a linear regime. A second exposure raises local temperature to boiling, detected by B-mode "brightening" and audio frequency detection of "popping" emissions. Monitoring during therapy proceeds by acquiring a sequence of RF US frames, estimating apparent strain and inverting for temperature rise. Further use of the HTE permits modeling of spatial variability of heat source magnitude Q.

but we do not believe that this will significantly change the method because both Q and B (representing the HIFU heat deposition rate) can be adjusted to account for nonlinearity.

B. *The temperature dependence of sound speed*

The sound speed variation with temperature can be well modeled by a simple quadratic polynomial, where the coefficients of the equation are assumed constant in space and time

$$c(T) = \alpha T^2 + \beta T + \gamma. \qquad (2)$$

Furthermore, we assume that $\alpha < 0$, and that the peak of the function occurs at a temperature that is different than the initial temperature (room or body temperature).

C. *Algorithm outline*

The temperature estimation procedure is outlined in Fig. 4. Essential to the process are the two pre-therapy "calibration" steps that determine *in situ* values for HTE parameters K and Q. These two parameters can be measured at single points throughout the treatment region of interest, and provide tissue and acoustic path characterization necessary for accurate therapy planning and execution. The calibration also estimates the local c(T) curve parameters (related to τ(T) in Fig. 4) used to monitor temperature during therapy. We have developed noninvasive methods for this purpose, described in the companion paper [4].

D. *Estimation of sound speed dependence on temperature*

The process of determining the coefficients in (2) using ultrasound backscatter is outlined as follows:

1. For any given scanline location through tissue, gather the RF signal from two different frames taken at times t1 (RF1) and t2 (RF2). Often, t1 is taken to be the frame collected before or immediately after HIFU exposure begins.

2. Given values for K, Q, (as determined from the calibration experiments), and beam geometry B, compute the temperature profiles for the scanline at the two frame times using the HTE. This temperature field simulation is assumed to represent the true temperature evolution in the tissue, and will be compared to the observed strain to determine the function c(T).

3. Iteratively determine the values of coefficients α, β, and γ that result in the best match between RF signal waveforms for the temperature field given by step 2, where the objective function for the optimization uses the correlation coefficient. The procedure involves iteratively deforming line RF1 until the applied deformation results in the best match with RF2.

E. *Estimating temperature*

This optimal c(T) "transfer function" mapping the acoustic sound speed to temperature can then be used to interpret observed strains and estimate temperature in and near a treated zone. It is important to recognize that a straightforward estimate of temperature can be done simply by numerically simulating the heating using the values for K and Q determined by the calibration experiments, *without* going through the process of estimating c(T). However, to permit changes in the thermal dose as the HIFU focus is moved from point to point in tissue, the value of Q is allowed to change over distances larger than the focal heating zone. We believe that the randomness of lesion size observed in tissue experiments can be modeled by spatial fluctuation of the heat source magnitude applied to a *uniform* medium. Therefore, we will solve for the local value of Q using our temperature estimation approach, with the requirement that c(T) be known from calibration experiments. In so doing, the HTE model that simulates the true dose can be updated as HIFU treatment progresses, to reflect the observed spatial variation of heat sources determined from backscatter measurements. This information will ultimately be used to adapt HIFU exposure settings to compensate for observed fluctuation in Q and thus achieve desired therapeutic endpoints.

The method described above permits estimation of temperature throughout the therapeutic range, including the portion in which ultrasound is not sensitive to changes in temperature. This property is a consequence of constraining the solution using the HTE which provides a smooth spatial and temporal "filter" for the temperature field, using the physical constraints imposed by heat diffusion. The underlying assumption that the heat source is due to a known HIFU beampattern is important, and the degree to which variability in the beampattern (due to distortion by tissue heterogeneity, and by acoustic nonlinearity) can be represented by a simple scaling in magnitude Q remains to be explored.

IV. GEL PHANTOM EXPERIMENTS

RF ultrasound (US) data was acquired (ATL HDI 1000) during and after thermal exposures at 2 to 10 frames/second, in a tissue mimicking phantom made of alginate. The experiments were conducted using a 3.5 MHz HIFU heat source (model SU-107, Sonic Concepts, Woodinville, WA) over a range of intensities and exposure times. Processing of the RF frames was performed offline using Matlab. Calibration experiments were performed as described above and in [4], and two types of

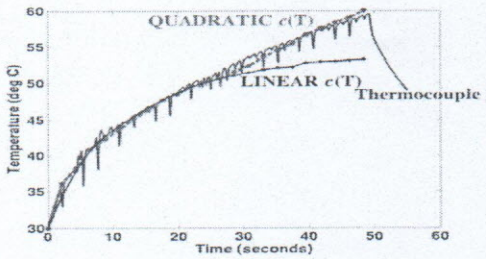

Figure 5. Comparison between thermocouple data and ultrasound based temperature estimation using strain estimation followed by mapping strainto temperature. The importance of the quadratic term increases with temperature.

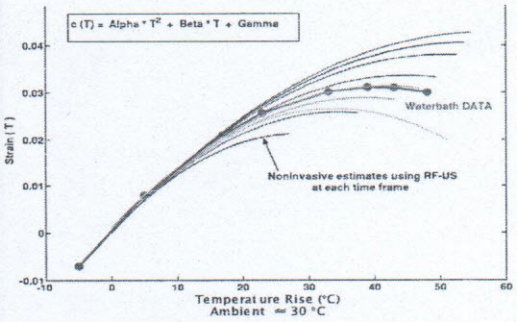

Figure 6. Estimation of c(T) parameters from backscattered ultrasound.

estimation experiments followed. One study sought to estimate temperature given independently measured c(T), and the other study explored the estimation of c(T) as parameterized in (2). Thermocouples were used to measure temperature directly at locations near the HIFU focus, in the imaging plane.

Figure 5 illustrates the role of the quadratic term in (2) for temperature estimation. Here, strain was explicitly estimated using cross-correlation methods (Section II-C), and then mapped to temperature using measured c(T) parameters for the alginate gel which behaves very much like water [4]. We observe that temperatures are very accurately estimated for moderate temperature rise using a linear approximation, but the quadratic term is required for sub-degree accuracy above 50 C.

The procedure used to estimate the parameters of c(T) is in early stages of development. Using one A-line from each of one pair of frames at a time, a best fit set of coefficients α, β, and γ, was obtained, and the estimated c(T) curves was compared to the independently measured data (plotted as strain in Fig. 6). In early frames, before the temperature rises 25 degrees (to 50 °C) in the focal region, the strain contains little information with which to constrain the quadratic term. As the temperature rises well into the nonlinear region (e.g. more than 35 degrees rise to about 65 °C) the estimated c(T) curves approach the true dependence, but do not appear to converge except in the linear region. The estimation procedure is expected to improve in accuracy with use of surrounding scanlines, and proper weighting of information from different frames.

V. Conclusions

Temperature estimation during HIFU therapy using RF backscattered ultrasound is very promising, even though the problem is inherently challenging due to a lack of sensitivity of the temperature dependence of sound speed c(T) in the critical therapeutic range. Temperature induced changes in travel time have been measured using a commercial scanner in a water based phantom and in freshly excised animal liver tissue. Imaging those changes provides greatly improved visualization of treated regions when compared to echographic B-mode. We have estimated temperature rise by combining RF strain information with a heat transfer model. In the algorithm described here, heat transfer equation (HTE) parameters and c(T) parameters are estimated in pre-therapy calibration steps that involve monitoring and analyzing RF backscatter from two test HIFU exposures. This information is used with real-time RF data to estimate temperature during therapy under the assumption that the parameters are constant in time and uniform in space. Currently, only variability in the magnitude Q of the HIFU-induced heat source due to heterogeneity is considered, and can be obtained using a similar procedure, to monitor therapy. Accuracy of temperature estimates is within a degree for phantom experiments in which c(T) is known, but further research is needed to provide robust estimates of c(T) with HIFU heating.

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