Beam localization in HIFU temperature measurements using thermocouples, with application to cooling by large blood vessels

Subhashish Dasgupta\textsuperscript{a}, Rupak K. Banerjee\textsuperscript{a,b,\ast}, Prasanna Hariharan\textsuperscript{c}, Matthew R. Myers\textsuperscript{c}

\textsuperscript{a}Mechanical Engineering Department, University of Cincinnati, Cincinnati, OH 45220, USA
\textsuperscript{b}Biomedical Engineering Department, University of Cincinnati, Cincinnati, OH 45220, USA
\textsuperscript{c}Division of Solid and Fluid Mechanics, Center for Devices and Radiological Health, Food and Drugs Administration, Silver Spring, MD 20993, USA

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\textbf{ABSTRACT}

Experimental studies of thermal effects in high-intensity focused ultrasound (HIFU) procedures are often performed with the aid of fine wire thermocouples positioned within tissue phantoms. Thermocouple measurements are subject to several types of error which must be accounted for before reliable inferences can be made on the basis of the measurements. Thermocouple artifact due to viscous heating is one source of error. A second is the uncertainty regarding the position of the beam relative to the target location or the thermocouple junction, due to the error in positioning the beam at the junction. This paper presents a method for determining the location of the beam relative to a fixed pair of thermocouples. The localization technique reduces the uncertainty introduced by positioning errors associated with very narrow HIFU beams. The technique is presented in the context of an investigation into the effect of blood flow through large vessels on the efficacy of HIFU procedures targeted near the vessel. Application of the beam localization method allowed conclusions regarding the effects of blood flow to be drawn from previously inconclusive (because of localization uncertainties) data. Comparison of the position-adjusted transient temperature profiles for flow rates of 0 and 400 ml/min showed that blood flow can reduce temperature elevations by more than 10\%, when the HIFU focus is within a 2 mm distance from the vessel wall. At acoustic power levels of 17.3 and 24.8 W there is a 20- to 70-fold decrease in thermal dose due to the convective cooling effect of blood flow, implying a shrinkage in lesion size. The beam-localization technique also revealed the level of thermocouple artifact as a function of sonication time, providing investigators with an indication of the quality of thermocouple data for a given exposure time. The maximum artifact was found to be double the measured temperature rise, during initial few seconds of sonication.

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1. Introduction

In the pre-clinical investigations of high-intensity focused ultrasound (HIFU) devices and procedures, tissue phantoms and animal tissues are frequently used to study thermal effects in HIFU procedures. The phantoms or animal tissues can be instrumented with thin-wire thermocouples to provide temperature information at relatively low cost.

Thermocouples embedded in animal tissue or tissue-mimicking materials are subject to two types of errors that must be quantified in order to obtain reliable measures of temperature rise arising from ultrasound absorption. The first type is thermocouple artifact [1–3]. Thermocouple artifacts can arise due to conduction of heat along the thermocouple wire, or from differences in heat capacity or acoustic absorption between the thermocouple and the surrounding medium. These artifacts can be minimized with the use of sufficiently small-diameter thermocouples [2]. However, another type of artifact arising from viscous heating at the surface of the thermocouple occurs even with thin thermocouples. Fry and Fry [4], Parker [5], Dickinson [3], Huang et al. [1] and Morris et al. [2] have developed methods for quantifying and treating viscous-heating artifacts. The second type of error associated with thermocouple measurements is the uncertainty in the position of the ultrasound beam relative to the thermocouple junction. A common method for positioning the beam on the junction is to move the beam until the position of maximum temperature rise during a brief sonication is located. As noted by O’Neill et al. [6], this imprecise beam-positioning technique can lead to significant underestimates of temperature in HIFU applications, due to the small widths of the HIFU beams. O’Neill et al. [6] performed sonications remote from the junction and used the measured transient
temperatures to fit a solution to the bio-heat equation and predict the focal temperature. The projected focal zone temperatures were used to investigate thermal mechanisms of ultrasound-enhanced nanoparticle delivery.

In this paper, another localization technique employing solutions to the heat equation is presented. The method utilizes two thermocouples embedded in the tissue phantom, one near the beam focus. The other is located 2 mm away. Numerical solutions to the wave propagation and heat equations are used to find the location of the focus that produces best agreement with the portions of the thermocouple traces that have low levels of artifact. Distinct from the method of O’Neill et al. [6], the computational procedure is used to determine the position of the focus for a given sonication, but the final temperatures are experimental, not computational. Using positioning errors derived from different sonications, the experimental data sets are extrapolated to form a single data set representative of zero positioning error.

The beam localization method is developed in a context in which the positioning errors have been observed – while experimentally investigating the role of large blood vessels on the efficiency of HIFU ablation procedures. Previous experimental and numerical studies have been performed to study the effect of blood flow through tissues during hyperthermia, along with a limited number of HIFU studies. Theories have been put forward to assess the heat energy convected through arteries during hyperthermia procedures [7–12]. In addition, some experimental studies on hyperthermia have shown that blood flow cooling can cause non-uniform thermal dose distribution [13–17]. Lately, a limited number of investigations have been performed specifically to study large-scale blood-flow effects on HIFU ablation procedures. Huang et al. [1] performed experimental investigations using a tissue phantom and found that convective heat transfer caused by blood flow can significantly lower the temperature at the vessel wall. Several computational studies have also been performed to study the effect of blood flow on HIFU procedures [18,11,19–21]. The present authors previously [22] developed a three-dimensional computational model to study the effect of blood flow through large blood vessels at moderate intensities (\(1000 \text{ W/cm}^2\)). Results showed that when the blood vessel is located within about 2 mm of the ultrasound beam, significant reduction in temperature rise and lesion volume is obtained. In the present study, the positioning uncertainties contained in the experimental data are reduced using a beam localization process, allowing for analyses of blood-flow effects as well as some quantification of thermocouple artifacts.

The following section describes the flow phantom and the localization procedure. Section 3 contains experimental results, before and after application of beam localization. Results regarding the influence of blood flow through a large vessel on HIFU temperature rise are presented. The amount of thermocouple artifact as a function of exposure time is also studied. The merits of beam localization are discussed further in Section 4.

2. Methods

2.1. Phantom construction

A gel-based tissue-mimicking material [22,23] was prepared that simulates the thermal and acoustic properties of human soft tissue (Table 1). A test-section tank was designed with a 6 mm glass rod positioned horizontally, so that when the rod was eventually removed from the solidified tissue-mimicking material, a vessel in the form of a cylindrical void resulted. Prior to pouring the tissue-mimicking material into the test-section frame, chromel-constantan ‘E’ type thermocouples (0.002 in. diameter, Omega Engineering Inc., Stamford, CT) were placed at distances 2 and 4 mm away from the surface of the glass rod. The liquid gel mixture was then poured into a rectangular test section. When the material solidified the glass rod was pulled out to create the 6-mm diameter wall-less vessel. A photograph of the phantom containing the glass rod is shown in Fig. 1A. Fig. 1B shows the placement of the thermocouples relative to the vessel as well as the HIFU transducer described subsequently. Acoustic attenuation and speed of sound for the phantom were measured using an ultrasonic time delayed spectrometry (TDS) system [24]. Thermal conductivity and diffusivity were measured with a thermal property analyzer (KD-2, Decagon Devices Inc., Pullman, WA). The physical properties of the phantom are provided in Table 1.

After the phantom was constructed, a flow loop was developed to circulate fluid through the wall-less vessel at desired rates (Fig. 2). A metering valve was used to control the circulation of degassed water at desired flow rates of 400, 500 and 600 ml/min,
corresponding to velocities 23.5, 29.5 and 35 cm/s, respectively. The flow rates are within the range of physiological blood flow [25]. In all of the experiments, water was used to simulate the flow of blood through the tissue. Water has similar thermal properties to blood but different acoustic properties. However, we were interested only in thermal properties, because the HIFU beam was focused outside the vessel.

2.2. Sonication protocol

Using the vascularized tissue phantom, a variety of simulated HIFU ablation procedures near large vessels were performed. The HIFU source was a 1.5 MHz HIFU transducer (Onda Corp., Sunnyvale CA) of focal length 15 cm and radius 3 cm (Table 2). Tissue temperature rise was recorded during and after sonication, using a OMB-DAQ-3005 (Omega Engg. Inc., Stamford, CT) data acquisition system. Four temperature readings were taken per second.

During each of the blood-flow experiments, the transducer was operated for 30 s and then switched off. In the first experiments, the HIFU beam was focused on the thermocouple located 2 mm away from the vessel (Fig. 1B). Transducer acoustic powers of 5.0, 10.3, 17.3 and 24.8 W were employed. These powers yield spatial-peak temporal-average intensities equal to 240, 495, 832 and 1193 W/cm² respectively. Acoustic powers were measured using a radiation force balance method employing an absorbing brush target, as described by Maruvada et al. [26]. Using these empirical powers as input, intensities were predicted using the KZK propagation model described in Appendix A. The 5 W power produced temperatures that were less clinically relevant than the other powers and is not featured in some of the plots. It was used to determine the trend in thermocouple artifact with power level, though. At each power level, a simulated blood-flow rate of zero was first imposed, followed by flow rates of 400, 500 and 600 ml/min. The experiments were repeated on 3 days (Days 1, 2 and 3) and on each day three trials were performed for each setting of power and flow rate to ensure repeatability of results. The transducer was repositioned each day. Once this battery of experiments was performed at the 2 mm distance, it was repeated with the positioning system by incremental distances and recording the temperature rise after the 10 s sonication. Position increments were made in all three dimensions. The position with maximum temperature rise was taken to be the location of the thermocouple junction.

2.3. Temperature-rise positioning scheme

Prior to performing experiments involving a given thermocouple, a manual procedure was performed to position the ultrasound beam as closely as possible to the junction of the target thermocouple. The HIFU transducer, mounted on a tri-axis positioning system, was switched on for 10 s with the beam located approximately at the thermocouple junction. The temperature rise at this location was then observed. This procedure was repeated at other locations by moving the transducer with the positioning system by incremental distances and recording the temperature rise after the 10 s sonication. Position increments were made in all three dimensions. The position with maximum temperature rise was taken to be the location of the thermocouple junction.

2.4. Localization algorithm

As is demonstrated in the next section, variation in the measurements from day to day made it difficult to discern effects due to blood flow on HIFU-induced temperature rise. It was discovered that the variation in the temperature values was due largely to slight differences in the beam location relative to the target thermocouple. In order to determine the location of the beam on each of the 3 days, the following procedure was developed.

When the beam was targeted at the thermocouple located 2 mm from the vessel (Fig. 1), it was assumed that the viscous-heating artifact at the thermocouple 4 mm from the vessel could be ignored. Our conclusion was based upon the fact that, from hydrophone scans, it was known that the intensity 2 mm off axis in the radial direction is approximately 5% of the on-axis value [27]. Additionally, the low-artifact assumption was verified if the shape of the empirical and numerical curves closely matched, since the numerical curve does not contain artifacts. Similarly, the trace at the 2 mm thermocouple in the cooling phase was assumed to be sufficiently free of viscous-heating artifact beyond a time of 10 s in the cooling period. (The 10 s value is discussed further in Section 4.)

A numerical model was next constructed to predict the temperature as a function of time at a prescribed distance from the target (2 mm) thermocouple. The numerical approach is similar to Hariharan et al. [22], and is described in greater detail in Appendix A. Briefly, the acoustic propagation is simulated using the linearized KZK parabolic wave equation. The absorbed intensity derived from the propagation simulation is used as a source term in the energy equation. Blood-flow modeling is confined to a single large blood vessel. This approximates the clinical situation in which the sonication time is small enough relative to the tissue perfusion time that perfusion through smaller vessels can be ignored. Within the energy equation, convective heat transfer due to flow through the large vessel is simulated, as is conduction through the tissue-mimicking material. Continuity of temperature and heat flux is imposed across the vessel wall. Simulation of convective heat transfer requires solution of the Navier–Stokes equations to obtain the velocity field within the blood vessel. The energy equation is solved using the finite-element method.

In the localization algorithm, an initial prediction or guess is made for the (x,y) coordinates of the HIFU beam focus relative to the 2 mm thermocouple junction. In principle, the z-coordinate can also be included. However, variation of the thermal field is much weaker in the axial direction, and the z-dependence is not considered in this study. Using the coordinates of the thermocouples relative to the focus, the temperature at the thermocouple locations is obtained from the temperature field computed by the model. An optimization error metric quantifying the average difference between the experimental (T_exp) and numerical (T_num) temperature traces was defined by

![Fig. 2. Schematic of experimental flow loop to simulate blood flow through the tissue phantom.](Image Link)
Here the temperature samples $T_i$, $i = 1, 2, \ldots N$ are taken at 1-s increments throughout the heating and cooling phases for the 4-mm thermocouple (i.e. 1–70 s), and for the last 30 s of cooling at the 2 mm location (40–70 s). During the heating phase and initial 10 s of the cooling phase of the 2 mm thermocouple, artifacts exist in the measured temperature rise, hence temperature data during these periods were not considered in calculating the optimization error metric. The prediction for the $(x,y)$ coordinates of the focus is then adjusted in order to locate a position having a lower value of $\delta$. The algorithm uses the Nelder–Mead [28] scheme to adjust the prediction. The Nelder–Mead scheme is a method for minimization of function (in this case $\delta$) that requires no derivative [29]. The process is repeated until no further reduction in $\delta$ can be achieved. The output of the localization algorithm is a set of $(x, y)$ coordinates for the beam focus, relative to the target thermocouple, that provides the best agreement between the computed temperatures and the experimental data minimally affected by artifact.

3. Results

The temperature rise as a function of time at both thermocouple locations is plotted in Fig. 3, for a power of 17.3 W and flow rates of 0 and 400 ml/min. Data from the 3 days and the three trials on each day are averaged together, for a total of nine trials. The curved line represents the mean of the nine trials, and the envelope surrounding each curve represents $+/−$ one standard deviation from the mean. From the overlap of the envelopes of the profiles at flow-rates 0 and 400 ml/min, it cannot be concluded that flow through the large vessel affects the temperature rise, at either the 2 mm or 4 mm locations.

When the 3 days are considered separately (Fig. 4), the envelopes for the flow and no-flow cases at the 2 mm location are clearly distinct, indicating a cooling effect of flow. In Fig. 4, the envelope consists of $+/−$ one standard deviation for the three trials of that day, though the broader 95% confidence intervals (not shown) also display no overlap except at the beginning of heating (where time sufficient for heat to diffuse to the vessel has not yet occurred.) On day 1 (Fig. 4A) blood flow causes an approximately 10% $[100 \times (39–35 \degree C)/39 \degree C]$ drop in temperature rise after 30 s sonication. At the 4 mm location, there is still no evidence of cooling due to the large vessel. (The 4 mm trace was not available for Day 2, due to a thermocouple malfunction.) The difference between the 3 days is attributed to differences in beam positioning. One reason for this conclusion is the difference in the initial slope of the temperature trace, which is proportional to the intensity. The transducer is driven with the same voltage each day, which was measured before each sonication and found to be within 0.3% each day; hence any differences in intensity at the thermocouple junction are likely not due to transducer output variations but instead due to positioning errors. That is, the positioning scheme described in Section 2 results in placement of the beam slightly off from the junction, by amounts that differ on the 3 days.

\[
\delta = \frac{1}{N} \sqrt{\sum_{i=1}^{N} \left[ (T_{\exp,i} - T_{\text{num},i})/T_{\text{num},i} \right]^2}.
\]

Fig. 3. Experimental transient temperature profiles at 2 mm and 4 mm thermocouples. Blood-flow rates are 0 and 400 ml/min. Power level is 17.3 W. Data averaged over days 1, 2 and 3 (three trials per day). Standard deviation about average shown by error bars.

Fig. 4. Experimental transient temperature profiles at 2 mm and 4 mm thermocouples, with each day shown separately. Blood-flow rates are 0 and 400 ml/min. Power level is 17.3 W. Standard deviation of three trials per day is shown by error bars.

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The sensitivity of thermocouple junction temperature to positioning error is manifested in Fig. 5, where the numerical algorithm used in the localization technique has been used to compute junction temperature rise for various focus/junction separations. It can be seen that for a 30-s sonication at a power of 10.3 W, a beam targeted 0.5 mm in the radial direction from the thermocouple junction yields a temperature rise approximately 3° (out of 24) lower. For a positioning error of 1 mm, the temperature error increases to about 8°, or one-third of the total temperature rise.

3.1. Adjustment of data to remove positioning errors

The beam localization procedure described in Section 2 can be used to generate a temperature prediction that is not affected by positioning errors. We illustrate the procedure on a protocol to measure the transient temperature at a thermocouple location \( N \) times, for a fixed set of operational parameters. The procedure is as follows.

(i) Position the beam on the thermocouple using the temperature-rise positioning scheme of Section 2.
(ii) Initiate ultrasound and record the thermocouple reading for the entire sonication duration, as well as a 30-s cooling period.
(iii) Reposition beam (each day in our case) and repeat step (ii) until \( N \) sonications have been performed.
(iv) For each of the \( N \) data sets, implement the beam localization algorithm of Section 2, which generates the coordinates \( (x_B, y_B) \), where \( x_B \) and \( y_B \) are the beam-location coordinates relative to the thermocouple.
(v) Compute the radial positioning error \( r_B = (x_B^2 + y_B^2)^{1/2} \) for each data set.
(vi) Plot the temperature rise vs. \( r_B \) for each of the \( N \) data sets.
(vii) Perform a curve fit through the data.
(viii) Extract the value of the fitting curve at \( r_B = 0 \) to determine an estimate for the temperature not affected by misalignment.

On the basis of symmetry considerations, we require that the extrapolation curve through the \( (r_B, \Delta T) \) pairs have zero derivative at \( r_B = 0 \). Since the \( r_B \) values are small (relative to the distance over which the temperature field changes), we chose a parabolic fitting curve. (The parabola being the lowest-order approximation to the \( \Delta T \) vs. \( r_B \) curve near the axis.) The plotting (of \( \Delta T \) vs. \( r_B \)), curve fitting, and extraction can be performed at each time point for which a corrected temperature value is desired. We chose to correct the entire transient temperature trace.

Applying this generic procedure to our specific set of experiments, in our protocol \( N \) had the value of 3. That is, the beam was repositioned three times, at the beginning of each of the 3 days of experiments. On each day, we also did three repetitions of the given experiment and averaged the data. The radial positioning errors for the 3 days are shown along the accompanying temperatures in Fig. 6, for power levels of 10.3, 17.3, and 24.8 W. The \( (r_B, \Delta T) \) pairs are plotted for both flow (400 ml/min) and no-flow conditions. It was found that the position of the beam with respect to the thermocouple junction was the same for the flow and no-flow conditions on a given day, since the beam was not repositioned between flow and no-flow experiments. As shown in Fig. 6, a parabola was fit through each set of three data pairs. The parabola was used to evaluate at \( r_B = 0 \), to generate a best estimate for the transient temperature trace at the focal location. Fig. 6 pertains to the time of 30 s; this parabolic fitting followed by evaluation at \( r_B = 0 \) was repeated at each instant of time.

The uncertainty in the position-corrected \( (r_B = 0) \) temperature can be obtained using the uncertainties in the off-axis temperatures used to construct the fitting curve. The uncertainties in the off-axis values are represented graphically by the error bars in Fig. 4. We employed the method of Press et al. [32] to determine the uncertainties in regression parameters given the measurement errors in the data. Specifically, given a fitting curve of the form \( y = a + br^2 \), we determined the uncertainties in \( a \) and \( b \) knowing the uncertainties in the temperatures at \( r = 0.55 \) mm and \( r = 0.7 \) mm. The method of Press et al. is based upon a minimization of the least-squares merit function with respect to the regression parameters in Table 3, the uncertainties in the on-axis temperature-rise values are shown for three different times during the procedure, for three different power levels. The uncertainties are normalized by the temperature rise at the given time. For the maximum temperature rise (end of the heating period), the uncertainty is on the order of 1%. Uncertainties are higher during the cooling phase, between 4% and 5%.

The adjusted transient temperature rise obtained from the parabolic fitting procedure in Fig. 6 is shown in Fig. 7, for both the flow and no-flow cases. Hence, Fig. 7 shows the experimental data corrected for positioning error at power level 17.3 W. Also shown in Fig. 7 is the temperature predicted by the mathematical model at the junction of the 2 mm thermocouple. It is seen that the experimental temperature rise is higher than the corresponding computational rise, because of thermocouple artifacts. However, during the cooling phase there is a close agreement (within 3%) between the experimental and computational profiles, especially at later times, since the dissipation time for the localized viscous heating is small. Similar experimental and numerical transient temperature profiles were obtained by extrapolation at the other power levels.

One measure of the cooling effect of blood flow as a function of sonication time is the percent cooling trace, equal to the difference between the experimental temperature rise in the absence of flow minus the experimental temperature rise in the presence of flow, normalized by the temperature rise in the absence of flow. The temperatures used are those adjusted for positioning error, as in Fig. 7. The percent cooling trace is shown in Fig. 8, for a vessel/beam distance of 2 mm, a flow of 400 ml/min, and four different power levels. Cooling due to blood flow has no effect until a threshold of approximately 4 s of heating is achieved. At that point the percent cooling rises rapidly with sonication time for a few seconds, then the rise is gradual. In the cooling period (>30 s), the percent cooling increases very slowly. Near the end of the ablation procedure (30 s), the cooling effect is about 9% at power levels 10.3 and 17.3 W whereas it is 10% at the power level of 24.8 W.

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Another measure of the cooling effect of blood flow is the change in thermal dose. The thermal dose has an inherently exponential dependence upon temperature, and thus it is expected that a small change in temperature will have a significant influence on the thermal dose and lesion size. For thermal dose calculation, we use the method developed by Saperto and Dewey [30]. The thermal-dose parameter is expressed using the relation

$$t_{43}(x, y, z) = \int_{t=0}^{t_{final}} R(t_{final}) \cdot 43 \, dt,$$

where $t_{43}$ is the equivalent thermal dose at the reference temperature of 43°C, and $t_{final}$ is the treatment time. $T(t)$ is the temperature as a function of time obtained experimentally (expressed in degrees), and,

$$R = \begin{cases} 2 & \text{if } T(t) \geq 43 \degree C \\ 4 & \text{otherwise} \end{cases}$$

A trapezoidal scheme was used to perform the integration shown in Eq. (1) with $dt = 0.25$ s. The thermal-dose ratio, equal to the thermal dose in the presence of blood flow divided by the thermal dose in the absence of blood flow, is contained in Fig. 9.

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We note that for these calculations, the temperature rises measured in our experiments were assumed to originate at body temperature (37°C) rather than room temperature. The thermal-dose ratio for the highest power (24.8 W) shows an order of magnitude more effect of blood flow than the lowest power (10.3 W).

To the extent that the numerical prediction represents the true temperature trace in the absence of thermocouple artifact (this assumption is examined in the next section), an estimate of the artifact can be obtained by subtracting the numerical temperature from the experimental temperature trace corrected for positioning errors. Subtracting the numerical curve in Fig. 7 from the experimental, and dividing by the numerical temperature rise, gives the percent artifact as a function of time plotted in Fig. 10. The percent artifact is provided for power levels of 5, 10.3, 17.3 and 24.8 W. The maximum percent artifact is quite similar for the two lower powers (56–61%) and the two higher powers (194–223%), but there is a considerable difference in the amount of artifact between the high-power group and the low-power group. The maximum percent artifact for all power levels occurs at around 1 s following initiation of sonication.

4. Discussion

The beam-localization technique presented in this paper makes use of a computational method, and is thus subject to the limitations introduced by the modeling – the absence of back scattering from the KZK equation, lack of temperature-dependent properties, plane-wave assumption in heat-source modeling, etc. These limitations can be reduced by using more sophisticated propagation models; the localization algorithm is not restricted to any particular model. For example, the linearized KZK model we used should be replaced by a nonlinear version when higher powers are considered, in order to account for additional heat generated by higher harmonics. However, it should be recognized that the modeling is used primarily to predict the beam location; derivation of a position-corrected temperature is performed using extrapolation of experimental temperatures. It is not required that the model predict temperature with high level of accuracy, only that it be able to resolve the temperature difference between one source location and another with reasonable accuracy. The coordinates of the focus are selected on the basis of a minimized error metric (Eq. (1)) between experiment and computation. This error need not be small, though it typically was on the order of 1% for the cases considered. The error metric between the experimental and numerical temperature rise is based on temperature profiles not corrupted by artifact – in this case the cooling profiles of the 2 mm thermocouple after 40 s and the entire heating and cooling profiles of the 4 mm thermocouple.

The present beam-localization technique is related to that of O’Neill et al. [6], in that both methods employ fitting algorithms in conjunction with propagation and heat-transfer models. A difference between the two methods is that the apparatus of O’Neill et al. [6], containing only one thermocouple, is simpler to construct. The tradeoff is that multiple sonications are required to obtain measurements at enough locations to characterize the source. A second difference is that the final prediction for the temperature at the sensor location from the procedure of O’Neill et al. [6] is a numerical one (with the model parameters based on measurements), while the temperature at the thermocouple location from the present technique is more empirical (Fig. 6).

It is important to address how the algorithm handles sources of error that are not due to misalignment. Whenever there is a discrepancy between the computed and measured temperature traces, the algorithm will attempt to minimize the error by repositioning the beam, regardless of the source of the error. However, for errors that are not related to positioning, the algorithm would not be very successful, and this will be apparent to the user from an examination of the convergence curve computed by the optimization algorithm. The convergence curve is a plot of the relative error δ (Eq. (1)) between the computations and experiments as a function of iteration number. When there is a significant positioning error, the algorithm will reduce the error to a low (around 1%, for the data in this study) value quickly (less than 10 iterations). If the error is not related to positioning, the algorithm will usually be able to reduce the difference between experiments and computations by a few percent, but further iterations will not be fruitful. The algorithm will perform a few more iterations without reducing the error much further, and then it will terminate.

To illustrate the process just described, we considered the situation where the difference in focal temperature between experiments and computations is due to a sudden 10% drop in transducer intensity during the experiments, resulting in a 10% (assuming linear acoustics) drop in focal temperature. We developed a simulated experimental data set by performing numerical solutions of the acoustic-propagation and heat-conduction equations, using a transducer power level 10% lower than the value...
assumed by the iterative algorithm. For comparison purposes, we also developed another simulated experimental data set having a positioning error resulting in a 10% lower temperature rise than desired at the target location. Neither simulated data set was corrupted by artifact. In both cases, the algorithm was initialized with a guess for focal position that resulted in a 12% value for \( \delta \). As evidenced by the convergence in Fig. 11, the value of \( \delta \) for the intensity-reduction case drops about 1% with each iteration for the first five iterations, but little progress is made after that. The algorithm terminates at an error value of about 6% after 14 iterations. Hence, by modeling the 10% reduction in intensity as a positioning error, the algorithm is able to reduce the 10% error to 6%. By contrast, for the misalignment case, the error is reduced to zero in eight iterations (Fig. 11). For the actual experiments featured in this paper, where the experimental data is subject to positioning error but also other sources of error such as thermocouple artifact, the algorithm is still able to reduce the error to below 1%, in nine iterations (Fig. 12).

To summarize how the algorithm responds to a general source of error, the beam localization method does not discriminate between sources of error — it treats them all as misalignment. However, the algorithm does not automatically adjust experimental data based upon refined estimates of the focal position. The user decides whether to do data adjustment (using the extrapolation technique of Section 3) based upon the performance of the algorithm as measured by the convergence curve. When misalignment dominates, the error is reduced quickly (within 10 iterations in our experience) to a value much smaller than the initial error at the start of the algorithm (sometimes below 1%). If the convergence curve shows that the algorithm has difficulty reducing the error, other sources besides misalignment are probably dominating, and the user should not adjust the data using the extrapolation approach.

The localization algorithm yields experimental temperature values that are corrected for positioning errors, but not for thermocouple artifact. The data containing thermocouple artifact is still useful for studying the cooling effect of blood flow, if it can be assumed that the artifact is comparable for both the flow and no-flow situations. Given that artifacts are generated on the scale of the thermocouple junction [2], which is a small fraction of a millimeter in size, while the large blood vessel is located multiple millimeters away, this assumption seems reasonable. Hence, thermocouple artifact can be assumed to be small in the temperature difference contained in the percent cooling curves of Fig. 8. Similarly, a constant artifact would affect the numerator and denominator of the thermal-dose ratio in Fig. 9 equally (by roughly a factor of 2\(^n\), where \( n \) is the number of degrees; see Eq. (2)) resulting in little change in the thermal-dose ratio. As a check on the accuracy of the percent cooling values in Fig. 8, percent cooling was also computed using just the numerical model (percent cooling vs. sonication time curves obtained from the model are not shown here), for all power levels and a blood-flow rate of 400 ml/min. The shape of the percent cooling trace as a function of time closely matched that in Fig. 8, with the percent cooling at the end of 30 s residing between 9% and 9.2%, compared with 9.2–10.0% in Fig. 8.

From the cooling curves of Fig. 8, it can be roughly said that for procedures greater than about 5 s, the effect of blood flow through a large vessel on HIFU heating is on the order of 10% reduction in temperature elevation, when the vessel is located 2 mm from the focus. When translated in terms of thermal dose, reductions of up to 70 times were observed (Fig. 9). Unlike the percent cooling, the exact level of thermal-dose decrease depends strongly upon the power level. The amount of cooling also changes very little with increase in blood-flow rate beyond 400 ml/min. Curves nearly identical to those in Fig. 8 were observed at flow rates of 500 ml/min and 600 ml/min.

It can be surmised from Fig. 3 that the effect of cooling via blood flow through the large vessel is likely to be small at the 4 mm location, even though the data in Fig. 3 contains positioning errors. The beam localization procedure was performed with the 4 mm thermocouple as the target, and the 2 mm the remote sensor. After performing the same analysis applied at the 2 mm location, it was found that even in the absence of positioning errors there is essentially no blood-flow effect 4 mm from the vessel, for a 30-s sonication.

The results in this paper concerning the role of blood flow confirm the claim in Hariharan et al. [22] and Zhang et al. [21] that the effect of blood flow on HIFU heating is confined to a distance of around 2 mm for duration of typical HIFU procedures. The insensitivity of temperature rise to blood-flow rate, for flow rates beyond 400 ml/min, is also consistent with computations. As noted in Hariharan et al. [22], the critical factor for blood-flow effects is the distance required for heat to diffuse to the large vessel. The increase in flow rate has a limited influence on cooling effect.

In addition to removing positioning errors from data, as just described for the study of blood-flow effects, the localization algorithm can be used to position the beam focus prior to a battery of experiments. By performing measurements at locations deliberately shifted from the thermocouple junction (or other target location), the localization algorithm can be used to more accurately locate the beam upon the target. Such a procedure requires that the acoustic propagation and heat transfer equations be re-solving.
if critical parameters have been changed from previous experiments. For example, if the transducer power is changed in a regime where nonlinear propagation effects occur, the numerical temperatures could not simply be scaled and would need to be recomputed. Often, however, all that is required to obtain the numerical temperature values required in Eq. (1) is a search through the database of temperature vs. time sets as a function of distance from the beam axis. This initial localization procedure would result in subsequent measurements that are free from beam-localization error. The measurements would still, however, be affected by thermocouple artifacts.

The removal of positioning errors in the temperature measurements allows for study of the thermocouple artifact. Using the computational temperature trace as an estimate of the artifact-free temperature introduces multiple possible sources of modeling error, as noted at the beginning of this section. However, the agreement between the experiments and computations in situations where viscous-heating artifact is likely to be small, namely at the 4 mm thermocouple as well as at the 2 mm thermocouple in the late stages of cooling, gives us some confidence that the computational results are representative of the artifact-free temperature. Using the nomenclature of Morris et al. [Fig. 8 of [2]], we interpret the artifact as the viscous-heating temperature \( T_{\text{exp}} - T_{\text{num}} \), and the numerical temperatures as the absorptive-heating temperature \( T_{\text{num}} \). Fig. 10 then provides the ratio of the viscous-heating temperature to the absorptive-heating temperature. For the two higher powers (24.8 W and 17.3 W), this ratio as a function of time is similar to the corresponding curve of Morris et al. [2] [Fig. 8], in the sense that the ratio reaches a maximum immediately after heating (within about a second in our case, though resolution is limited by the 0.25 s sampling rate), and decays by a factor of about 4 (223–55%) by the end of 5 s of heating. A difference between the results of the present study and those of Morris et al. [2] is the level of artifact; Morris et al. [2] show the ratio of viscous-heating temperature to absorptive-heating temperature to have a maximum value of about 6; in the present study the maximum is about 2.2. One of the important differences between the experimental conditions described in this paper and the conditions of Morris et al. [2] is the medium; we use a tissue-mimicking material and Morris et al. [2] performed experiments in excised porcine liver.

The nearly bimodal character of the percent artifact curves exhibited in Fig. 10 is surprising. The higher powers (17.3 and 24.8 W) show much higher percent artifact and a more rapid decay of artifact with heating time. Morris et al. [2] observed a nearly constant artifact with intensity, though their intensities were all comparable to those associated with the lower two curves (5 and 10.3 W) in Fig. 10. It is tempting to propose cavitation at the higher powers, but the temperature traces (e.g. Fig. 7) do not show evidence of cavitation. Further studies involving a fuller spectrum of transducer powers would be helpful in resolving this issue.

5. Conclusion

A beam-localization technique has been presented for reducing errors in thermocouple measurements due to imprecise positioning of a HIFU beam relative to the target thermocouple junction. The method employs numerical simulations of beam propagation and heat transfer within the HIFU phantom, but the simulations are used to locate the beam position relative to the thermocouple and not to provide a corrected temperature. The corrected temperature derives from an extrapolation of measurements at off-axis positions. The final temperature trace, corrected for positioning errors but not corrected for artifacts, is useful for analyzing subtle effects such as the influence of blood flow through large vessels on HIFU ablation procedures. Such effects can be easily overwhelmed by positioning errors. Using the beam-localization technique, it is found that for representative HIFU conditions, blood flow through a large vessel can significantly influence the procedure when the target location is about 2 mm from the vessel. At a range of 4 mm, however, little effect is seen.

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Appendix A

The following numerical calculations were performed to calculate the temperature rise of the tissue phantom under the influence of blood flow when the HIFU beam is perpendicular to the vessel [22]

A.1. Calculation of HIFU heat source

Sound propagation was modeled using the linear form of the KZK parabolic wave equation to calculate acoustic pressure, \( p(r,z) \).

\[
\frac{\partial}{\partial t} \left( \frac{\partial p}{\partial t} \right) - \frac{D}{2c_l^2} \left( \frac{\partial^2 p}{\partial r^2} + \frac{1}{r} \frac{\partial p}{\partial r} \right) = c_o \frac{\partial^2 p}{\partial z^2} + \frac{1}{c_o} \left( \frac{\partial p}{\partial z} \right)
\]

(A1)

Here \( t = t' + z/c_0 \) is the retarded time, with \( t' \) being time and \( c_0 \) the speed of sound in tissue. The coordinate \( r \) is the radial distance from the center of the beam, and \( D \) is the sound diffusivity of tissue. The time-averaged acoustic intensity \( I(r,z) \) was calculated from the pressure field using the relation \( I(r,z) = \frac{p^2}{c_0^2} \), where \( p \) is the average acoustic pressure, \( c_0 \) is the mean density, \( c_0 \) is the speed of sound, in tissue and the brackets denote time averaging. The HIFU induced power deposition rate, \( Q \), was then calculated from the relation

\[
Q = 2 \pi I
\]

(A2)

where \( x \) is absorption coefficient of tissue.

A.2. Calculation of fluid velocity through vessel

The mass conservation is given by

\[
\rho_b \frac{\partial u_i}{\partial x_i} = 0
\]

(A3)

and momentum conservation equation is given by

\[
\rho_b u_j \frac{\partial u_i}{\partial x_j} = \frac{\partial p_i}{\partial x_j} + \frac{\partial}{\partial x_j} \left[ \frac{\mu}{\partial x_k} \left( \frac{\partial u_i}{\partial x_k} \right) \right]
\]

(A4)

Here \( u_i \) is the fluid velocity \( (i,j = 1, 2, 3) \), \( \rho_b \) is fluid density. The fluid flow in the vessel was assumed to be steady.

A.3. Calculation of tissue temperature rise

To determine the tissue temperature rise \( T(x,y,z,t) \), the tissue was modeled as a solid region. The heat equation (Eq. (A5)) described below was solved. The perfusion term which occurs in Pennes bio-heat transfer equation was neglected because of the absence of microvascularity in the tissue-mimicking material.

\[
(\rho_b c_p) \frac{\partial T}{\partial t} + \rho_b c_p u_i \frac{\partial T}{\partial x_i} = \frac{\partial}{\partial x_k} \left( k_b \frac{\partial T}{\partial x_k} \right) + Q
\]

(A5)

Temperature rise inside the blood vessel was calculated by solving the energy equation:

\[
(\rho_b c_p) \frac{\partial T}{\partial t} + \rho_b c_p u_i \frac{\partial T}{\partial x_i} = \frac{\partial}{\partial x_k} \left( k_b \frac{\partial T}{\partial x_k} \right) + Q
\]

(A6)
where \( u \) is the velocity field estimated earlier from the momentum equation (Eq. [A4]), and \( Q \) is the heat energy absorbed by the fluid. Eqs. (A5) and (A6) were solved using the Galerkin finite-element (FE) method (Fluent Inc. [31]).

References