Displacement analysis of diagnostic ultrasound backscatter: A methodology for characterizing, modeling, and monitoring high intensity focused ultrasound therapy

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Accurate monitoring of high intensity focused ultrasound (HIFU) therapy is critical for widespread clinical use. Pulse-echo diagnostic ultrasound (DU) is known to exhibit temperature sensitivity through relative changes in time-of-flight between two sets of radio frequency (RF) backscatter measurements, one acquired before and one after therapy. These relative displacements, combined with knowledge of the exposure protocol, material properties, heat transfer, and measurement noise statistics, provide a natural framework for estimating the administered heating, and thereby therapy. The proposed method, termed displacement analysis, identifies the relative displacements using linearly independent displacement patterns, or modes, each induced by a particular time-varying heating applied during the exposure interval. These heating modes are themselves linearly independent. This relationship implies that a linear combination of displacement modes aligning the DU measurements is the response to an identical linear combination of heating modes, providing the heating estimate. Furthermore, the accuracy of coefficient estimates in this approximation is determined *a priori*, characterizing heating, thermal dose, and temperature estimates for any given protocol. Predicted performance is validated using simulations and experiments in alginate gel phantoms. Evidence for a spatially distributed interaction between temperature and time-of-flight changes is presented. © 2010 Acoustical Society of America. [DOI: 10.1121/1.3436554]

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I. INTRODUCTION

Noninvasive therapies offer the ability to increase outpatient care and avoid complicated surgeries. High intensity focused ultrasound (HIFU) therapy¹ is a noninvasive modality that confines treatment to a well defined focal volume. Unfortunately, left unmonitored, considerable prefocal and postfocal damage may be the inadvertent result of a particular therapy. At the other extreme, HIFU may not deliver the intended therapy to the target region. Hence, there is a practical imperative to identify monitoring techniques which ensure that the desired therapy is the one administered.

Thermal dose² is recognized as a reliable clinical endpoint for cell necrosis, and in particular for HIFU therapy.¹ To quantify the thermal dose at any position, the time-temperature history is needed, motivating noninvasive estimates of temperature. Currently, magnetic resonance imaging (MRI) is the *de facto* standard for providing temperature estimates of noninvasive therapies like HIFU. There are several drawbacks, however, to using MRI, most notably the high expense and inconvenience. Diagnostic ultrasound (DU) monitoring of HIFU therapy offers a convenient and inexpensive alternative to MRI temperature monitoring. The sensitivity of DU to temperature is observed from the backscatter recorded by the DU, which are the measurements from which DU images of tissue properties are formed, ex-

hibiting time-of-flight changes in response to temperature changes in the material.^{3,4} These time-of-flight changes are expressed as either compressions or expansions of the DU image, to which the radio-frequency (RF) backscatter exhibits the greatest sensitivity. The technique of comparing two RF DU frames, one a reference frame taken before therapy and the other a treatment frame captured after therapy, and identifying the relative displacements between them, is a proven method for forming estimates of temperature, as shown in both Refs. 3 and 4. In these studies, cross correlation techniques were used to track the motion of small regions between the reference and treatment frames. The resulting displacement map, which catalogs these shifts nearly continuously, is used to provide the temperature estimates. This displacement estimator is non-parametric since it makes no modeling assumptions in formulating the displacement estimates. If temperature estimates are formed frequently, by interrupting therapy, the thermal dose may be approximately calculated.

There exists, however, considerable structure to DU observations of HIFU therapy. The focusing of ultrasound confines the treated area, heat transfer constrains the rate at which this region changes, and measurement by diagnostic ultrasound interacts with the material in a deterministic way. This knowledge about treatment and monitoring allows the DU measurements to be combined efficiently to produce a more concise description of therapy. In fact, by reducing the degrees of freedom in DU observations of treatment through physical modeling, fundamental limits in the accuracy of DU

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monitoring can be determined quite generally, as well as estimators which attain these bounds. To this approach, estimates of the time-varying heating rate applied during therapy are formed, in which HIFU treatment is assumed to factor into the product of a known spatial distribution with an unknown time variation. Such a factorization is appropriate when the local attenuation properties of the material give rise to heating from a known, spatially distributed intensity profile radiated by the HIFU transducer. This separability into spatial and temporal factors allows the time-varying heating rate to be related to the DU observations in a convenient and tractable manner. In particular, by further representing the heating rate as a combination of linearly independent waveforms, termed heating modes, these can be identified and ordered through the strength of their influence on DU observations. This influence is quantified using techniques from maximum likelihood estimation, from which these waveforms and the variance of their coefficient estimates are determined. By further imposing some reasonable assumptions on the scattering properties of the material, the accuracy of these coefficient estimates can be determined *a priori* from known quantities. This characterizes DU monitoring for a given protocol, since it provides the best possible performance, in terms of monitoring accuracy.⁵ Moreover, the waveform having minimum variance coefficient estimates provides the optimal modulation for monitoring therapy, if there is no uncertainty in administering the heating.

A key result from this development is that any heating mode, if applied as the heating rate during therapy, induces a particular pattern of displacement between ultrasound frames which is linearly independent of the pattern induced by any other heating mode. These linearly independent patterns are termed displacement modes, and the greater the power in the displacement mode, the more accurately the heating mode can be monitored. By aligning the reference and treatment frames using a linear combination of displacement modes, the identical linear combination of heating modes provides the estimate of therapy. The unique relationship between a heating mode and its associated displacement mode means that the process of alignment uniquely identifies the administered therapy if the physical modeling assumptions are correct.

The alignment of backscattered RF frames using displacement modes is termed displacement analysis, since the decomposition into displacement modes allows a regression analysis to be performed. The utility of displacement analysis is twofold. First, it identifies the very displacement estimates central to non-parametric temperature estimation in an efficient manner. Second, displacement analysis is a model verification tool. The use of displacement modes to draw inferences about administered therapy rests critically on the accuracy of the physical modeling. As an example, the procedure is applied to analyze the relative displacements between a reference and treatment frame when the source is known, indicating that the commonly assumed DU ray model oversimplifies the interaction between the DU beam and temperature by failing to identify treatment. By broad-

ening the region of interaction with the temperature distribution using a diffuse DU beam, a correct estimate of therapy is obtained, with the displacement estimates left essentially unchanged.

II. THEORY

The components central to the development of displacement analysis are (i) the time-of-flight model for DU measurement, (ii) the treatment protocol, (iii) the relevant mechanics of heat transfer, and (iv) the statistical measurement model affecting DU observations. The time-of-flight model relates the prevailing spatial distribution of temperature to changes in displacement observed by the DU at a given capture time. The treatment protocol specifies the duration of the exposure, as well as the relative positions of the HIFU and DU array during that interval. Heat transfer relates the prevailing temperature to the heating administered by the HIFU. Finally, by introducing a statistical measurement model, the sensitivity of the DU to the manner of heating can be assessed, identifying observable modes of heating and the accuracy with which they can be resolved. These heating modes, when applied as sources of therapy, induce linearly independent patterns of displacement, which are the displacement modes. It is these patterns which are used to align the reference and treatment frames, in the process providing estimates of the administered heating rate. In turn, estimates of heating provide estimates of the clinical endpoints for HIFU therapy, such as thermal dose, with the accuracy of these quantities determined from that of the heating estimates.

A. Relating time-of-flight and heating

Diagnostic ultrasound monitoring of HIFU therapy is characterized for the configuration shown in Fig. 1. At the left of Fig. 1, HIFU is applied over the interval (t_i, t_f) , inscribing a lesion centered at $y=R_0$, with motion perpendicular to the HIFU transducer axis, i.e., the y axis. Associated with the HIFU transducer is the intensity profile $Q(\mathbf{r})$, a function of the three dimensional coordinate vector $\mathbf{r}$. This radiation pattern is assumed spatially invariant and moving with the transducer, so that at time t , the spatial distribution of radiated intensity is $Q(\mathbf{r}-\boldsymbol{\eta}_t)$, with $\boldsymbol{\eta}_t=(x_t, y_t, z_t)$ the position of the center of the transducer, assumed known. The DU array is positioned to observe the HIFU focal plane, and is oriented parallel to the z -axis, with elements at depth $x=0$ and centered at $y=R_0$. The DU provides a frame of two dimensional beamformed backscattered RF measurements at time t , denoted $\rho_t(j, k)$, composed of K scanlines uniformly spaced along the length of the array, at $z_k, k=1, \dots, K$, where each scanline is a series of J beamformed ultrasonic backscatter measurements formed at uniformly spaced delays $\tau_j, j=1, \dots, J$. The DU captures two RF frames for the analysis procedure, one before treatment at time $t_a < t_i$, termed the reference frame, and one after treatment at time $t_b > t_f$, termed the treatment frame.

As described in Refs. 3 and 4, the DU is sensitive to temperature induced changes in time-of-flight between the reference and treatment frames, with DU beam propagation

FIG. 1. DU monitoring of HIFU in the focal plane. A HIFU transducer is positioned on the left side of the figure, with radiation directed along the y axis and having focus at $y=R_0$. The HIFU transducer is characterized by its radiated intensity $Q(\mathbf{r}-\mathbf{r}_t)$, with $\mathbf{r}_t$ the position of the HIFU center at time t . HIFU motion is constrained to lie in the plane perpendicular to its axis, with the transducer having known trajectory $\mathbf{r}_t=(x_t, y=0, z_t)$. The DU array is positioned to capture frames in the HIFU focal plane, with the DU array mounted so the elements are at depth $x=0$ and centered at $y=R_0$, with the array oriented with the z axis. The individual DU scanlines, illustrated as broken lines emanating from the DU array elements, are directed downward, corresponding to increasing depth x . These scanlines compose a DU frame by recording backscatter at J uniformly spaced delays, with the DU array elements uniformly spaced at positions $z_k, k=1, \dots, K$. Associated with each scanline is a beam pattern $b(\mathbf{r}|\mathbf{r}_k)$ providing the contribution of temperature at $\mathbf{r}$ to the time-of-flight from $\mathbf{r}_k$.

modeled using geometrical acoustics.^{6,7} The effect of temperature on propagation time is illustrated in Fig. 2, where time-of-flight changes between a reference frame (left) and treatment frame (right) are indicated by the apparent motion of scatterers below the treated region, which appear to shift upwards toward the DU array between frames. According to this model, a DU ray is emitted perpendicular to the DU array from one of the k elements, directed along the x -axis, as indicated by arrows in Fig. 1. The time-of-flight for a ray emanating from an array element centered at $\mathbf{r}_k=(x_0, y=R_0, z_k)$ and traveling to depth coordinate $\mathbf{r}=(x, y=R_0, z_k)$ at time t is denoted $\tau_t(\mathbf{r}|\mathbf{r}_k)$, where the notation $(\mathbf{r}|\mathbf{r}_0)$ is a field notation⁷ indicating the dependence of measurement at field point $\mathbf{r}$ on the source coordinate $\mathbf{r}_0$. Since the coordinate system illustrated in Fig. 2 has the DU scanlines oriented with increasing depth x from the array, the time-of-flight to a scatterer is more succinctly expressed as $\tau_t(x|\mathbf{r}_k)=\tau_t(\mathbf{r}|\mathbf{r}_k)$, with the y and z coordinates the same between the source and

FIG. 2. (Color online) Two frames of RF backscattered ultrasound, $\rho_r(j, k)$, captured before (left) and after (right) treatment at times t_a and t_b , respectively. The scanlines are indicated as arrows emanating from the DU array, positioned at the top of each frame. The scanlines are indexed by k , and depth from the DU array by τ . The figure on the right shows the position of scatterers both before and after treatment, indicating an observed compression toward the DU array as a result of increased sound speed in the treated area.

field coordinates. With this notation, the time-of-flight $\tau_{t_b}(x|\mathbf{r}_k)$ from a source at $\mathbf{r}_k$ to a given scatterer at depth x and at time t_b after treatment is the time-of-flight before treatment, $\tau_{t_a}=|x-x_0|/c_0$, at time t_a , linearly adjusted for temperature along the path by a coefficient α to account for changes in sound speed and thermal expansion.⁴ This is written:

$$\tau_{t_b}(x|\mathbf{r}_k) = \tau_{t_a}(x|\mathbf{r}_k) - \alpha \int_{x_0}^x T_{t_b}(x', R_0, z_k) dx'. \quad (1)$$

The DU ray model is an idealization to a beamformed measurement, in which a more realistic spatially diffuse DU beam is differentially backscattered while propagating through the medium. The influence of temperature on the backscatter measurements is described through a DU beam density $b(\mathbf{r}|\mathbf{r}_s)$, measuring the contribution of temperature at field point $\mathbf{r}$ to the time-of-flight measured at array element $\mathbf{r}_s$. The DU beam density $b(\mathbf{r}|\mathbf{r}_s)$ is assumed normalized over cross-sections perpendicular to the DU beam axis such that

$$\int_{-\infty}^{\infty} \int_{-\infty}^{\infty} b(\mathbf{r}|\mathbf{r}_s) dy dz = 1, \quad (2)$$

a simplifying assumption. The time-of-flight experienced by the DU beam is written in terms of the DU beam density as:

$$\tau_{t_b}(x|\mathbf{r}_k) = \tau_{t_a}(x|\mathbf{r}_k) - \alpha \int_{x_0}^x \int_S b(\mathbf{r}'|\mathbf{r}_k) T_{t_b}(\mathbf{r}') dV'. \quad (3)$$

The time-of-flight is measured in units of distance by scaling the propagation time by the equilibrium speed of sound c_0 . Equation (3) can be rewritten to impute the uniform increments $j\Delta_\tau, j=0, \dots, J-1$ in time-of-flight in the treatment frame with scatterer positions in the reference frame, which are denoted τ_{ajk}^b . In this way, each coordinate pair $(j\Delta_\tau, z_k)$ in the treatment frame corresponds to a position (τ_{ajk}^b, z_k) in the reference frame, accounting for the apparent motion of the scatterer. Equation (3) becomes:

$$j\Delta_\tau = \tau_{ajk}^b - \alpha \int_{x_0}^{\tau_{ajk}^b} \int_S b(\mathbf{r}'|x_0, R_0, z_k) T_{t_b}(\mathbf{r}') dV'. \quad (4)$$

The temperature is derived from the treatment, a source of heat, by an influence function⁶ $\Gamma(\mathbf{r}, t|\mathbf{r}', t')$, providing the temperature at field coordinate $\mathbf{r}$ and time t in response to a source applied at time t' and position $\mathbf{r}'$. The temperature in response to HIFU therapy is then given by

$$T_t(\mathbf{r}) = \int_{t_i}^{\min(t, t_f)} \int_V Q(\mathbf{r}', t') \Gamma(\mathbf{r}, t|\mathbf{r}', t') dV' dt'. \quad (5)$$

The heat source $Q(\mathbf{r}, t)$ is assumed to factor into the product of a known spatial distribution $Q(\mathbf{r})$ with an unknown time varying modulation $q(t)$ to describe variability in local attenuation properties at the focus. This representation extends the HIFU heating model¹

$$Q(\mathbf{r}) = 2\gamma I_\omega(\mathbf{r}), \quad (6)$$

with γ the local attenuation and $I_\omega(\mathbf{r})$ the spatial distribution of intensity radiated by the HIFU in a homogenous medium, operating at simple harmonic frequency ω . Incorporating

transducer motion η_t into the spatial component $Q(\mathbf{r}-\eta_t)$, the heat source is assumed to factor as

$$Q(\mathbf{r},t) = q(t)Q(\mathbf{r}-\eta_t), \quad (7)$$

with $Q(\mathbf{r}-\eta_t) \propto I_\omega(\mathbf{r}-\eta_t)$ and $q(t)$ describing varying local attenuation γ at the HIFU focus, accounting for both spatial and temporal variability. Defining

$$\begin{aligned} g_{t|t'}(x|\mathbf{r}_k, \eta_{t'}) \\ \equiv \int_S b(\mathbf{r}|\mathbf{r}_k) \int_V Q(\mathbf{r}'-\eta_{t'}) \Gamma(\mathbf{r},t|\mathbf{r}',t') dV' dydz, \end{aligned} \quad (8)$$

as the proportional effect of temperature on time-of-flight measurements at depth x and time t due to a unit of applied power at time t' , in $^\circ\text{C/s}$, to the HIFU centered at $\eta_{t'}$, then Eq. (4) is written:

$$\begin{aligned} j\Delta_\tau &= \tau_{ajk}^b - \alpha \int_{x_0}^{\tau_{ajk}^b} \int_{t_i}^{t_f} q(t') g_{t_b|t'}(x|\mathbf{r}_k, \eta_{t'}) dt' dx \\ &= \tau_{ajk}^b - \alpha \int_{t_i}^{t_f} q(t') G_{t_b|t'}(\tau_{ajk}^b|\mathbf{r}_k, \eta_{t'}) dt', \end{aligned} \quad (9)$$

with

$$G_{t_b|t'}(x|\mathbf{r}_k, \eta_{t'}) = \int_{x_0}^x g_{t_b|t'}(x'|\mathbf{r}_k, \eta_{t'}) dx', \quad (10)$$

proportional to the time-of-flight change to a scatterer at $\mathbf{r} = (x, R_0, z_k)$ from its equilibrium value in response to unit HIFU heating, in $^\circ\text{C/s}$, at $\eta_{t'}$ and at time t' . Equation (9) relates the position of a scatterer in the treatment frame, at depth $j\Delta_\tau$ within the k^{th} scanline, to its position in the reference frame, at depth τ_{ajk}^b within the same scanline, and adjusted linearly for the applied heating through a physical model and coefficient α . Observe that $G_{t_b|t'}(x|\mathbf{r}_k, \eta_{t'})$ subsumes all known quantities.

B. Heating modes and displacement modes

The key to the present approach to therapy monitoring is to identify how variation in the heating rate $q(t)$ influences the time-of-flight changes between DU measurements. To this end, the unknown heating rate $q(t)$, defined over the exposure interval (t_i, t_f) , is expressed as

$$q(t) = \begin{cases} q_0(t) + \delta q(t), & t_i \leq t \leq t_f, \\ 0 & \text{else,} \end{cases} \quad (11)$$

where

$$\delta q(t) = \sum_{n=1}^N q_n \phi_n(t), \quad (12)$$

and $q_0(t)$ is the *operating point* for the administered heating rate at time t . The functions $\phi_n(t)$ constitute a basis for $q(t)$, are orthogonal, and are normalized to unity over the interval (t_i, t_f) . It is shown in Appendix A that for DU measurements corrupted by additive, independent and identically Normally distributed measurement noise, the functions $\phi_n(t)$ associated with the operating point $q_0(t)=0$ are the modes of an observation kernel $K_t^0(s, s')$, such that

$$\int_{t_i}^{t_f} \int_{t_i}^{t_f} \phi_m(s) \phi_n(s') K_{t_b}^0(s, s') ds' ds = \lambda_n \delta_{mn}. \quad (13)$$

The modes $\phi_n(t)$ are ordered by eigenvalue λ_n from largest to smallest, with $K_t^0(s, s')$ given by:

$$K_t^0(s, s') = \sum_{k=1}^K \sum_{j=1}^J G_{t|s}(j\Delta_\tau|\mathbf{r}_k, \eta_s) G_{t|s'}(j\Delta_\tau|\mathbf{r}_k, \eta_{s'}). \quad (14)$$

The choice of operating point $q_0(t)=0$ provides both computational ease and analytic simplicity for identifying the heating rate $q(t)$; from Eq. (10), $G_{t|s}(j\Delta_\tau|\mathbf{r}_k, \eta_s)$ is proportional to the change in time-of-flight at $(x=j\Delta_\tau, z=z_k)$ from unit applied heating at η_s and time $t_i \leq s \leq t_f$. Thus, the kernel $K_t^0(s, s')$ is composed by spatially correlating the apparent displacements observed by the DU from temporally impulsive and spatially distributed sources of heating at times $t_i \leq s \leq t_f$ and $t_i \leq s' \leq t_f$, respectively.

From Appendix A, the choice of operating point $q_0(t)=0$ means that Eq. (A7) is a strict equality, and hence defining the displacement modes $\Phi_n^{t_b}(x, z)$ as

$$\Phi_n^{t_b}(x, z_k) \equiv \int_{t_i}^{t_f} \phi_n(t') G_{t_b|t'}(x|\mathbf{r}_k, \eta_{t'}) dt', \quad (15)$$

then from Eqs. (13) and (14), exchanging the order of integration and summation,

$$\sum_{k=1}^K \sum_{j=1}^J \Phi_n^{t_b}(j\Delta_\tau, z_k) \Phi_m^{t_b}(j\Delta_\tau, z_k) = \lambda_n \delta_{mn}. \quad (16)$$

This provides the interpretation of the eigenvalue λ_n in terms of the power in observed displacement in response to the corresponding heating mode ϕ_n . Moreover, the displacement modes have the orthogonality property imbued in the heating modes. The significance of this result can be appreciated from a slight reformulation of Eq. (3), which relates time-of-flight at depth x to an applied heating:

$$\begin{aligned} \tau_{t_b}(x|\mathbf{r}_k, \mathbf{q}) \\ &= \tau_{t_a}(x|\mathbf{r}_k) - \alpha \sum_{n=1}^N q_n \int_{t_i}^{t_f} \phi_n(t') G_{t_b|t'}(x|\mathbf{r}_k, \eta_{t'}) dt' \\ &= \tau_{t_a}(x|\mathbf{r}_k) - \alpha \sum_{n=1}^N q_n \Phi_n^{t_b}(x, z_k). \end{aligned} \quad (17)$$

Thus, heating can be identified by fitting the observed time-of-flight using a linear combination of displacement modes $\Phi_n^{t_b}(j\Delta_\tau, z_k)$, each of which is uniquely related to a mode of heating $\phi_n(t)$. The implementation details are discussed further in Section III D.

The impact of the operating point $q_0(t)=0$ in formulating estimates for $0 \leq q(t) \leq q_{\max}$, with $q_{\max}$ the maximum possible administered heating, is assessed in Appendix B. Equation (B8) shows that the minimum variance $\sigma_{\min}^2(\hat{q}_n)$ of coefficient estimates $\hat{q}_n$ is upper bounded by

$$\sigma_{\min}^2(\hat{q}_m) \leq \frac{1}{I_{m,m}^0} (1 + \Lambda_m(q_w^{(m)})) \\ = \left(\alpha^2 \frac{\sigma_{\rho'}^2}{\sigma_{\epsilon}^2} \lambda_m \right)^{-1} (1 + \Lambda_m(q_w^{(m)})) \equiv \sigma_B^2(q_m), \quad (18)$$

with $\Lambda_m(q_w^{(m)})$ given by Eq. (B9), and I_{mm}^0 by Eq. (A10), with the superscript 0 referring to evaluation at the operating point $q_0(t)=0$. These least upper bounds $\sigma_B^2(q_m)$ can be used to determine the error in heating, temperature and thermal dose estimates. The worst expected performance for estimates of clinical endpoints can be found by letting $\text{var}(q_n) = \sigma_B^2(q_n)$. Since the coefficient estimates are decorrelated, and hence independent if Normally distributed,⁸ the variance for heat estimates using the series in Eq. (12) is:

$$\text{var}(q(t)) = \sum_{n=1}^N \text{var}(\hat{q}_n) \phi_n^2(t) = \sum_{n=1}^N \sigma_B^2(q_n) \phi_n^2(t). \quad (19)$$

The variance for temperature estimates is determined using Eq. (5) and the statistical independence of coefficient estimates $\hat{q}_n$. At position r and time t ,

$$\sigma_T^2(r, t) = \sum_{n=1}^N \sigma_B^2(q_n) (\chi_t^{(n)}(r))^2, \quad (20)$$

where

$$\sigma_{TD}^2(r) = c_{TD}^2 \int_0^\infty \int_0^\infty e^{\sum_{n=0}^{N-1} \gamma q_n (\chi_t^{(n)}(r) + \chi_{t'}^{(n)}(r)) + \sigma_B^2(q_n) ((\chi_t^{(n)}(r))^2 + (\chi_{t'}^{(n)}(r))^2 / 2 \gamma^{-2})} \left(e^{\sum_{n=0}^{N-1} (2\sigma_B^2(q_n) \chi_t^{(n)}(r) \chi_{t'}^{(n)}(r) / 2 \gamma^{-2})} - 1 \right) dt dt'. \quad (24)$$

C. Extensions

In practice, there will be uncertainty in both the depth δ_x and lateral offset δ_z of the inscribed lesion within the DU frame, requiring estimates be made of these as well. Moreover, there are shifts ψ_k^b which the DU introduces as jitter into the scanlines between the reference and treatment frames, and these must be removed to estimate correctly those displacements induced by therapy. Estimates of these additional parameters are easily introduced into the Fisher information matrix by assuming that δ_x and δ_z are sufficiently small that $K_b^0(s, s')$ does not change appreciably, leaving the eigenfunctions ϕ_m unaltered, but changing the eigenvalues. The use of these parameters is accounted for in Eq. (9) as:

$$\tau_j = \tau_{ajk}^b + \psi_k^b - \alpha \int_{t_i}^{t_f} q(t') G_{t_b|t'}(\tau_{ajk}^b | r_k, \eta_{t'} + \delta_\eta) dt'. \quad (25)$$

with

$$\delta_\eta = [\delta_x \quad 0 \quad \delta_z]^T. \quad (26)$$

A new parameter vector θ can be defined which concatenates $\mathbf{q}$, δ_x , δ_z , and $\psi_1, \dots, \psi_k$ as:

$$\chi_t^{(n)}(r) = \int_{t_i}^{\min(t, t_f)} \phi_n(t') \int_V Q(r' - \eta_{t'}) \\ \times \Gamma(r, t | r', t') dV' dt'. \quad (21)$$

The thermal dose can be expressed as²

$$TD(r) = \int_0^\infty e^{\gamma(T_t(r) + T_0 - T_{ref})} dt = c_{TD} \int_0^\infty e^{\gamma T_t(r)} dt, \quad (22)$$

where T_0 is the equilibrium temperature, T_{ref} is the reference temperature, and γ is a constant. For $T_{ref} = 43^\circ\text{C}$, $\gamma = \ln 2$. The expected thermal dose is found from the Normally distributed and independent coefficient estimates $\hat{q}_n \sim N(q_n, \sigma_B^2(q_n))$ using the moment generating function for Normally distributed random variables⁸

$$E\{TD(r)\} = c_{TD} \int_0^\infty e^{\sum_{n=0}^{N-1} \gamma q_n \chi_t^{(n)}(r) + (\sigma_B^2(q_n) (\chi_t^{(n)}(r))^2 / 2 \gamma^{-2})} dt, \quad (23)$$

indicating that thermal dose estimates become increasingly biased, and inflated, as the variance of heating estimates increases. By a similar calculation, the variance of thermal dose estimates is

$$\theta^T = [\mathbf{q}^T \quad \delta_x \quad \delta_z \quad \psi_1 \quad \dots \quad \psi_k]. \quad (27)$$

The Fisher information matrix for this parameterization is a straightforward modification of Eq. (A4):

$$I(\mathbf{q}=0) = \frac{\sigma_{\rho'}^2}{\sigma_{\epsilon}^2} \sum_{j=1}^J \sum_{k=1}^K \left. \frac{\partial \tau_{ajk}^b(\theta)}{\partial \theta} \right|_{\mathbf{q}=0} \left. \frac{\partial \tau_{ajk}^b(\theta)}{\partial \theta^T} \right|_{\mathbf{q}=0}. \quad (28)$$

A suboptimal but effective means for determining the shifts ψ_k introduced by the DU is to estimate them in regions unaffected by therapy.

Finally, the case of heat estimation from multiple frames is a straightforward generalization of the analysis for two frames.

III. MATERIALS AND METHODS

A. Gaussian beam in a perfusive medium

A useful approximation to the acoustic intensity radiated by a spherical HIFU transducer⁹ is provided by the Gaussian radiator.¹⁰ Using this distribution for the heating profile, the transducer is allowed to move perpendicular to the HIFU beam axis in the (x, z) plane, corresponding to $y_i = 0$, with spatially distributed heating $Q(r - \eta_t)$:

$$Q(\mathbf{r} - \boldsymbol{\eta}_t) = c_Q \frac{\exp\left\{-\frac{(x-x_t)^2 + (z-z_t)^2}{2\sigma_I^2(y)}\right\}}{2\pi\sigma_I^2(y)} U(y), \quad (29)$$

with $U(\cdot)$ the unit step function.¹¹ The heating density is characterized by a depth-dependent spreading with distance from the transducer,

$$\sigma_I^2(y) = \frac{a_G^2}{4} \left[\left(1 - \frac{y}{R_0}\right)^2 + \left(\frac{y}{\ell_d}\right)^2 \right], \quad (30)$$

and diffraction length

$$\ell_d = ka_G^2/2. \quad (31)$$

The HIFU is operated at frequency ω , with a_G specifying the geometry of the Gaussian radiator, a planar source with Gaussian apodization.¹⁰ Note that $Q(\mathbf{r})$ is dimensionless, and c_Q is introduced to cancel the units of squared distance in $\sigma_I^2(y)$. The influence function or Green's function for heat transfer in a perfusive medium is given by⁶

$$\Gamma(\mathbf{r}, t | \mathbf{r}', t') = \frac{1}{(2\pi\sigma_H^2(t-t'))^{3/2}} \times \exp\left\{-\frac{(\mathbf{r}-\mathbf{r}')^2}{2\sigma_H^2(t-t')}\right\} e^{-(t-t')/\nu} U(t-t'), \quad (32)$$

with time dependent spatial spreading

$$\sigma_H^2(t-t') = 2\chi(t-t'), \quad (33)$$

where χ is the thermal diffusivity and ν is the perfusion rate. These parameters are uniform throughout the material. Equation (29) is a Normal distribution in x and z with respective means x_t and z_t and common variance $\sigma_I^2(y)$. Similarly, Eq. (32) is a Normal distribution for x , y and z , with respective means x' , y' and z' and common variance $\sigma_H^2(t-t')$. The DU beam density $b(\mathbf{r} | \mathbf{r}_k)$ is modeled with a Normal distribution as well,

$$b(\mathbf{r} | \mathbf{r}_k) = \frac{1}{2\pi\sigma_{bz}\sigma_{by}} \exp\left\{-\frac{(y-R_0)^2}{2\sigma_{by}^2} - \frac{(z-z_k)^2}{2\sigma_{bz}^2}\right\}, \quad (34)$$

where σ_{by} and σ_{bz} model the transverse dimensions of the DU beam, assumed independent of focal depth x . Using Eqs. (29), (32), and (34), Eq. (8) can be evaluated approximately with respect to y'' , z'' , x' and z' , as shown in Appendix C:

$$g_{t|t'}(x | \mathbf{r}_k, \boldsymbol{\eta}_{t'}) \simeq c_Q U(t-t') e^{-(t-t')/\nu} \times \frac{e^{-(z_k-z_t')^2/2\sigma_{Htz}^2(t-t')}}{\sqrt{2\pi\sigma_{Htz}^2(t-t')}} \frac{e^{-(x-x_t')^2/2\sigma_{Htx}^2(t-t')}}{\sqrt{2\pi\sigma_{Htx}^2(t-t')}}}, \quad (35)$$

with

$$\sigma_{Htx}^2(t-t') = \left(1 + \frac{a_G^2}{4R_0^2} + \frac{a_G^2}{4\ell_d^2}\right) \sigma_H^2(t-t') + \sigma_I^2(R_0) + \frac{a_G^2}{4} \left(\frac{1}{R_0^2} + \frac{1}{\ell_d^2}\right) \sigma_{by}^2, \quad (36)$$

and

$$\sigma_{Htz}^2(t-t') = \sigma_{Htx}^2(t-t') + \sigma_{bz}^2. \quad (37)$$

Substituting Eq. (35) into Eq. (10) then yields:

$$G_{t|t'}(x | \mathbf{r}_k, \boldsymbol{\eta}_{t'}) \simeq c_Q U(t-t') e^{-(t-t')/\nu} \frac{e^{-(z_k-z_t')^2/2\sigma_{Htz}^2(t-t')}}{\sqrt{2\pi\sigma_{Htz}^2(t-t')}} \times \Phi(\xi) \Big|_{\xi=-x_t'/\sqrt{\sigma_{Htx}^2(t-t')}}^{\xi=x-x_t'/\sqrt{\sigma_{Htx}^2(t-t')}}}, \quad (38)$$

where $\Phi(\cdot)$ is the cumulative distribution function for a Normal distribution.⁸ For the examples considered in this paper, a non-perfusive media is considered, for which $\nu = \infty$ s.

B. Identifying DU beam spreading

The results from Ref. 12 can be generalized to identify the DU beam spreading. Consider the case of a stationary HIFU source applied uniformly over the interval (t_i, t_f) , such that the applied heating is a constant $q(t) = q_e$. The proportional change in time-of-flight, from Eq. (3) with Eq. (10), is denoted $\mathcal{D}(x, z)$, and with Eq. (C12)

$$\mathcal{D}(x, z) = q_e \int_{t_i}^{t_f} G_{t|t'}(x, z | \boldsymbol{\eta}_{t'}) dt' = q_e \int_{t_i}^{t_f} \int_0^x \times \frac{e^{-(z-z_t')^2/2\sigma_{Htz}^2(t-t')}}{\sqrt{2\pi\sigma_{Htz}^2(t-t')}} \frac{e^{-(x'-x_t')^2/2\sigma_{Htx}^2(t-t')}}{\sqrt{2\pi\sigma_{Htx}^2(t-t')}} dt' dx'. \quad (39)$$

Note that for $z_t = z_e$ and $x_t = x_e$ (the point exposure),

$$\int_{-\infty}^{\infty} \mathcal{D}(x, z) dz = q_e \int_{t_i}^{t_f} \left[\Phi\left(\xi = \frac{x-x_e}{\sqrt{\sigma_{Htx}^2(t-t')}}\right) - \Phi\left(\xi = \frac{-x_e}{\sqrt{\sigma_{Htx}^2(t-t')}}\right) \right] dt'. \quad (40)$$

For $x \gg x_e$, $x_e \gg 0$, this is nearly $q_e(t_f - t_i)$. The spread $\sigma_{z|x}^2(t)$ in z at depth x and time t is

$$\sigma_{z|x}^2(t) = \frac{1}{q_e(t_f - t_i)} \int_{-\infty}^{\infty} (z - z_e)^2 \mathcal{D}(x, z) dz \simeq \frac{1}{(t_f - t_i)} \int_{t_i}^{t_f} \sigma_{Htz}^2(t-t') dt', \quad (41)$$

$$= \sigma_{Htz}^2\left(t - \frac{t_f + t_i}{2}\right). \quad (42)$$

The slope and offset for $\sigma_{z|x}^2(t)$ are estimated as a function of the modified acquisition time $t - 0.5(t_f + t_i)$, with these parameters given by Eq. (37). The data-driven estimates are found from displacement analysis, with displacement estimate $\hat{\mathcal{D}}(x, z)$ as

FIG. 3. (Color online) Comparison of (a) axial and (b) trans-axial intensities between spherical and Gaussian radiators, where the spherical radiator has the characteristics in Eq. (48), and the Gaussian radiator has $a_G = 10.5$ mm. The intensities have been normalized by their maximum values.

$$\hat{D}(x, z) = \sum_{n=1}^N \hat{q}_n \Phi_n^{t_b}(x, z). \quad (43)$$

The time and depth dependent spreading $\hat{\sigma}_{z|x}^2(t)$ is estimated as:

$$\hat{\sigma}_{z|x}^2(t) = \frac{\sum_k (z_k - z_e)^2 \hat{D}(x, z_k)}{\sum_k \hat{D}(x, z_k)}. \quad (44)$$

Fitting Eq. (42) to Eq. (44) provides the model parameters.

C. Approximating a spherical radiator with a Gaussian radiator

As heating occurs primarily at the focus for both spherical and Gaussian radiators, the Gaussian radiator used for physical modeling is given focal dimensions similar to those of the spherical radiator, here a model SU-107 transducer, as described in Section III F. To this end, both the transaxial and axial dimensions of the radiation patterns are matched, employing O'Neil's characterization⁹ for the spherical radiator. The transaxial beamwidth at the focus is measured perpendicular to the HIFU beam axis. For the Gaussian radiator, the width of the beam at the focus is found from Eq. (30),

$$\sigma_G = a_G R_0 / 2 \ell_d = R_0 / k a_G. \quad (45)$$

In the case of the spherical radiator, this width is found from Ref. 9 [Eq. (5.3) and Fig. 6]. These indicate that in the focal plane, the beam pattern falls by approximately one standard deviation, or a factor of $\exp(-1/2) \approx 0.6$, when $k a \sin \theta \approx 2$. Here, θ is the angle formed between the beam axis and the line segment connecting the center of the HIFU transducer to the observation point in the focal plane. Letting σ_p denote the width of the pressure distribution, then $\sin \theta \approx \sigma_p / R_0$, and the width of the resulting intensity is approximately

$$\sigma_{sp} \approx \frac{\sqrt{2} R_0}{k a}. \quad (46)$$

Equating the beamwidths between Eqs. (45) and (46), the approximate dimension a_G of the Gaussian radiator is nearly

$$a_G \approx a / \sqrt{2}. \quad (47)$$

The axial dimension of the beam pattern at the focus must also be preserved between Gaussian and spherical radiators, although this is more difficult to characterize. The model SU-107 HIFU transducer has the following dimensions

$$2a = 33 \text{ mm}, \quad R_0 = 35 \text{ mm}, \quad (48)$$

and is operated at frequency $f = 3.5$ MHz in a medium having equilibrium sound speed $c_0 = 1,489$ m/s. These values are substituted into O'Neil's on-axis intensity formula⁹ [Eq. (3.7)]. A good match for the on-axis and transaxial beamwidths is obtained for $a_G = 10.5$ mm, as illustrated in Figs. 3(a) and 3(b).

The Gaussian radiator is particularly useful for power calculations, since it is easy to integrate Eq. (29) over the cross section (x, z) . In fact, the scaling has been chosen so that this integral is unity. This construction then provides the heating after converting from temperature to heat using the specific heat at constant volume,¹³ C_v , and with $q(t)$ estimated in the focal plane,

$$\begin{aligned} C_v q(t) \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} Q(\mathbf{r} - \boldsymbol{\eta}_t) dx dz &= C_v q(t) c_Q \\ &= 2 \gamma_t e^{-2 \gamma_0 d_p} \eta \zeta_M W_0, \end{aligned} \quad (49)$$

where W_0 is the input power, $\eta \approx 0.85$ is the efficiency of the spherical radiator, $\zeta_M \approx 0.85$ is the fraction of intensity in the main lobe of the spherical radiator,⁹ $d_p \leq R_0$ is the propagation distance in the attenuating medium, γ_t is the local acoustic attenuation at time t , and γ_0 is the average attenuation in the medium. Note that $q(t)$ and the product $q(t)Q(\mathbf{r})$ have dimensions of $^\circ\text{C}/\text{s}$, and are converted to units of power per centimeter through the specific heat at constant volume, C_v , in units of $\text{J}/^\circ\text{C}/\text{cm}^3$, and integrating over the cross section (x, z) perpendicular to the axis of HIFU beam propagation, y . Using average properties, the expected administered heating rate for a constant applied power W_0 is

$$\bar{q} = \frac{2 \gamma_0 e^{-2 \gamma_0 d_p}}{C_v c_Q} \eta \zeta_M W_0. \quad (50)$$

For the purposes of modeling alginate in this study, the specific heat C_v is taken from Ref. 12 as $C_v = 4.2 \text{ J}/^\circ\text{C}/\text{cm}^3$. The acoustic attenuation is measured as

$$2 \gamma_0 = 0.2821/\text{cm}. \quad (51)$$

D. Implementation

The parameters $\mathbf{q}$ are estimated from the log-likelihood function found from Eq. (A1). This defines the cost for estimation as:

$$\begin{aligned} \ell(\mathbf{P}_{t_b}|\mathbf{P}_{t_a}, \mathbf{q}) &\propto \sum_{k=1}^K \sum_{j=1}^J (\rho_{t_b}(j\Delta_\tau z_k) - \rho_{t_a}(\tau_{ajk}^b(\mathbf{q}), z_k))^2 \\ &\equiv C(\mathbf{q}). \end{aligned} \quad (52)$$

The cost $C(\mathbf{q})$ is optimized with respect to $\mathbf{q}$ by adjusting $\tau_{ajk}^b(\mathbf{q})$. Equation (3) relates time-of-flight at depth x to an applied heating, herein generalized to account for jitter between frames using the scanline offsets ψ_k^b estimated at time t_b :

$$\tau_b(x|\mathbf{r}_k, \mathbf{q}) = \tau_a(x|\mathbf{r}_k) + \psi_k^b - \alpha \sum_{n=1}^N q_n \Phi_n^{t_b}(x, z_k), \quad (53)$$

with $\Phi_n^{t_b}(x, z_k)$ the displacement modes from Eq. (15). The functions $\Phi_n^{t_b}(x, z)$ are precomputed, so that the optimization is performed quickly. The algorithm proceeds as follows: A given estimate $\hat{\mathbf{q}}$ allows computation of $\tau_b(x|\mathbf{r}_k, \hat{\mathbf{q}})$ from Eq. (53). The offsets ψ_k^b are nuisance parameters estimated in the regions unaffected by therapy, using time delay estimation techniques.¹⁴ The scattering profile $\rho_a(j, k)$, the reference frame of RF backscatter measurements, is assumed to have its measurements shifted to $(\tau_{t_b}(x|\mathbf{r}_k, \hat{\mathbf{q}}), z_k)$ at time t_b , owing to treatment. These measurements are then interpolated to find their values at uniformly spaced points $(j\Delta_\tau, z_k)$, which are substituted into the cost $C(\hat{\mathbf{q}})$. Iterations continue until a minimum for $C(\hat{\mathbf{q}})$ is found. This process of interpolation identifies the position of scatterers at uniform increments $j\Delta_\tau$ at time t_b as having the initial depths $\tau_{ajk}^b(\mathbf{q})$ at time t_a .

E. Tissue modeling for simulation

Simulations of DU backscattered frames $\rho(j\Delta_\tau, z_k)$, $j = 1, \dots, J$, $k = 1, \dots, K$ are performed under the assumption that measurements in the frame are jointly Gaussian random variables, and adhere to the constraint (A5). The correlation between measurements in the frame is estimated from RF data acquired from alginate, from which a Gaussian shaped filter is derived to induce the requisite correlation. The parameters of this filter are its center frequency and bandwidth, which are estimated from the scanline power spectrum $|S(k_x)|^2$. The moments are given by

$$\bar{k}_x^i = \frac{\int_0^\infty k_x^i |S(k_x)|^2 dk_x}{\int_0^\infty |S(k_x)|^2 dk_x}, \quad (54)$$

with the Gabor bandwidth¹⁵

$$B_G = \sqrt{\bar{k}_x^2 - k_x^2}.$$

Using samples of alginate, the Gabor bandwidth (normalized to sampling frequency) is found as $B_G \approx 0.04$, with center frequency $k_x \approx 0.22$, determining the Gaussian filter. The Gabor bandwidth is related to the desired spreading as

$$\sigma_x = \frac{1}{2\pi B_G \sqrt{2}}. \quad (55)$$

The desired spatial filter has the form

FIG. 4. (Color online) Test tank and instrument setup for HIFU dose response experiments. (a) On the left are the HIFU transducer and mounting hardware; in the center are the tissue cassette on the delrin base; on the right are the ‘acoustic calipers’ and the support structure. (b) Right hand coordinate system used in the experiments, corresponding to the view in (a). The (+) sign indicates the direction of increasing coordinates in each axis.

$$h(x) \propto \exp\left(-\frac{1}{2} \frac{x^2}{\sigma_x^2}\right) \sin(\bar{k}_x x), \quad (56)$$

which is scaled to ensure that the spatial derivative of the filtered result has the desired power $\sigma_{\rho'}^2$. Samples of independent, zero mean, Normally distributed noise with variance σ_ϵ^2 are added to the simulated backscattered data to provide the desired SNR.

F. Experimental setup

The HIFU exposure tank is depicted in Fig. 4(a) with coordinate system in Fig. 4(b). An acrylic test tank is filled with distilled water at room temperature. The HIFU transducer (Model SU-107, Sonic Concepts, Woodinville, WA) is attached to a 3-axis positioning system and its position and movement are controlled by a PC using custom software written in LabVIEW (National Instruments, Austin, TX). A function generator (Agilent 33120A) and RF power amplifier (ENI A150, Rochester, NY) provide the drive signal; a digital oscilloscope (Lecroy 9304AM, Chestnut Ridge, NY) is used to establish mechanical registration, monitor signals, and acquire bulk property data. Tissue cassettes are registered mechanically to the motion stage coordinate system for precise and repeatable exposure conditions. The cassettes have four windows to allow for HIFU treatment (‘front’), bulk property measurement using a transmission method (‘sides’), and ultrasound imaging (‘top’). Backscattered ultrasound is captured using the ATL HDI 1000 diagnostic ultrasound scanner with an ATL CL10-5 (Philips Medical Systems, Bothell, WA) imaging probe. This probe has a length of one inch, over which there are 128 elements. In addition, the sampling rate of the HDI is approximately 24.6 MHz.¹⁶

Registration between the acoustic field and the cassette must be precise, and the method described here achieves sub-millimeter precision and repeatability in cassette placement. The tank is aligned with the x -axis of the motion stage using parallel spacers prior to filling it with distilled water, and alignment confirmed afterwards by moving the positioner along the x -axis to measure runout. The bottom of the tank is fitted with pins which mate with holes in a machined delrin block. The top of the block has two pins which mate with matching holes in a cassette base [see Fig. 5(a)]. The acoustic axis of the HIFU field is aligned with the y -axis by

FIG. 5. (Color online) Alignment of acoustic field with cassette. (a) The first step aligns the transducer face with the delrin base. Note the two cassette registration pins are visible on top of the base. (b) Cassette in place with registration needles inserted in the base.

first placing the face of the transducer flush against the x - z plane of the delrin base, as shown in Fig. 5(a), and then securing the transducer mounting fixture. In separate procedures, acoustic field mapping is performed periodically to confirm that the acoustic axis is perpendicular to the front face of the delrin block. The origin of the coordinate system is defined by locating the HIFU focus with respect to the cassette using a pulse-echo technique and a set of stainless steel needles that mount within the cassette base.¹⁶ Figure 5(b) shows an empty tissue cassette equipped with the needles. The pulse-echo procedure uses a 10 V_{pp} pulse where the signal generator is directly connected to the transducer. The 3-axis positioner is adjusted until the reflected signal from the proximal needle tip is located in the vertical, horizontal, and axial directions. Having registered the transducer to the cassette, the transducer is displaced vertically and horizontally to avoid interference from the registration pin. The HIFU exposure control program is then initialized at that location. The alignment procedure is undertaken each time a transducer is mounted to the positioning arm.

The CL10-5 imaging probe, or DU array, is mounted on top of the cassette using a special fixture which orients the scanhead to capture a cross-section of the tissue block perpendicular to the axis of the HIFU transducer. The same registration pin used for aligning the HIFU transducer is again used to position the DU array to capture the HIFU focal plane. Once the registration pin is firmly in view of the DU, the setup is complete.

The material used for the experiment is alginate based hydrogel, a tissue mimicking phantom. The phantom is prepared by dissolving 9.5 g of Jeltrate Dental Impression Ma-

terial (Dentsply Caulk Inc., Milford, DE) in 200 ml of distilled water. The solution is degassed under vacuum for five minutes and left to consolidate for at least half an hour. The sound speed and acoustic attenuation of the phantom were found using acoustic calipers¹⁶ to be 1489 m/s and 0.37 dB/cm/MHz, respectively, at 21 °C.

IV. RESULTS

Experiments are performed for a constant point exposure, in which the position of the HIFU transducer is fixed during the exposure interval. This situation is useful since first, it is the one largely encountered in practice. Moreover, the point exposure, being highly localized, also provides an ideal case for evaluating physical modeling using displacement analysis, and in particular the contribution of the DU beam in formulating therapy estimates. Initially, the commonly assumed DU ray model is used. It is shown that the heating rate $q(t)$ identified under the DU ray model is inconsistent with the administered therapy, a constant exposure. The displacement estimates themselves, however, are comparable to those provided by the non-parametric displacement estimator of Simon *et al.*⁴ The inability of the assumed physical model to infer the administered heating rate $q(t)$ indicates that the DU ray model oversimplifies the interaction between the DU beam and the heated material. Further evidence for a diffuse DU beam is established using the method from Section III B, where the DU beam spreading is identified as the intercept in a linear regression. Using the identified spread, a second analysis is performed in which the applied heating is identified correctly. From the heating estimate, the temperature is determined and compared between the DU ray and diffuse beam models. In addition, performance curves for temperature and thermal dose estimates are presented as functions of acquisition time, indicating the range of applicability for the method. For comparison, the heating estimates are presented as a function of the acquisition time.

A. Point exposure analysis using a ray model

A one second point exposure, using a constant source of 4.2 W of electrical power, is performed in alginate, with the treatment frame captured half a second after therapy. The

FIG. 6. (Color online) Modes and performance for point exposure estimates with DU ray model. (a) Heating modes $\phi_n(t)$, for $t_f - t_i = 1$ s exposure, $t_b = 1.5$ s acquisition. (b) Standard errors for coefficient estimates from: Prediction, simulation, and experiment. The circles are color coded to indicate the associated mode in panel (a), also provided by the mode index. (c) Non-parametric displacement estimate using method from Simon *et al.* (Ref. 4).

FIG. 7. (Color online) (a) First displacement mode $\Phi_1^b(x, z)$. (b) Second displacement mode $\Phi_2^b(x, z)$. (c) Third displacement mode $\Phi_3^b(x, z)$.

thermal diffusivity is taken as that of water,⁷ $0.172 \text{ mm}^2/\text{s}$. The conversion factor α between temperature and displacement is taken from Anand *et al.*¹⁷ as $\alpha = 0.0013/^\circ\text{C}$. The exposure is performed at a depth (x) in the DU frame of approximately 17.5 mm, and with a lateral displacement (z) of 7.8 mm. The HDI-1000 transmit beamforming is focused at the lesion depth to maximize resolution there, with the SNR in the backscatter estimated as $\sigma_p^2/\sigma_\epsilon^2 = 1.52 \times 10^5/\text{mm}^2$. Figure 6(a) shows the heating modes under the ray model using Eq. (13), obtained by substituting Eq. (38) into Eq. (14), with DU beam dimensions $\sigma_y = \sigma_z = 0 \text{ mm}$. Figure 6(b) shows the predicted standard errors associated with these modes, computed from Eq. (18), along with the standard errors obtained from simulation and experiment, as provided by the Matlab function “nlinfit;” the agreement is excellent. The color coding of circles in Fig. 6(b) associates the enclosed standard error with the correspondingly colored heating mode in Fig. 6(a). One thousand Monte Carlo simulations of both noise and alginate backscatter were performed to obtain the simulated variances, providing enough iterations that convergence is strongly indicated.

Figure 6(c) shows the nonparametric displacement estimate in the vicinity of the treated area using the technique from Simon *et al.*,⁴ with the DU jitter ψ_k^b , $k = 1, \dots, K$, described in Section III D, removed in a preprocessing step. The first three displacement modes, associated with the heating modes in Fig. 6(a), are shown in Figs. 7(a)–7(c), again in the vicinity of the treatment. Figure 8(a) shows the statistical significance of the first five coefficients in the heating estimate, confining the analysis to a depth of 30 mm. The pres-

ence of the first four modes is significant at the 0.05 level. Figure 8(b) shows the displacement estimate produced from the first five displacement modes. Comparing the dimensions of the primary displacement mode in Fig. 7(a) with the reconstructed displacement in Fig. 8(b), it is apparent that the higher order modes are required to broaden the interaction region; the spatial variability observed in the higher order modes of Figs. 7(b) and 7(c) is not evident, while the shape of the fundamental displacement mode is apparent. Note the agreement in both the physical extent and magnitude of the displacements between Figs. 8(b) and 6(c). The contradiction in this analysis arises when reconstructing the heating rate $q(t)$ from the higher order modes of heating, associated with the higher order displacement modes required for alignment. The estimated heating rate $C_V C_Q q(t)$ is presented in Fig. 8(c), in units of W/cm, using only the first two modes. The 95% confidence interval is also included in the plot, indicating that the error in estimating a constant exposure cannot be explained by measurement noise. These observations provide strong evidence against the DU ray model for describing the influence of temperature on DU measurement.

B. Point exposure analysis using a diffuse DU beam

The displacement estimate shown in Fig. 9(a) is obtained by using a lateral window of 0.2 mm in the nonparametric displacement algorithm, as opposed to the nominal value⁴ of 0.89 mm used to produce Fig. 6(c). These displacement estimates indicate that the DU beam spreading changes with depth, and exhibits some lateral asymmetry. To

FIG. 8. (Color online) Decomposition from ray model. (a) Coefficient testing indicates that first four heating modes participate in heating estimate. (b) Displacement estimate from five displacement modes. (c) Estimated heating rate $q(t)$ from first two heating modes.

FIG. 9. (Color online) Displacement estimates from distributed DU beam model. (a) Nonparametric displacement estimates using lateral window of 0.2 mm, indicating increasing spread with depth. (b) When identified beam spreading $\sigma_{by}=2$ mm, $\sigma_{bx}=0.2$ mm is used in the model. (c) Displacement estimate from identified beam model.

minimize the impact of these effects in estimating the DU beamwidth in the vicinity of the exposure, the displacements are analyzed to a depth of 20 mm. Table I presents the estimated variances from Eq. (44) versus acquisition time, when evaluating the spread $\sigma_{z|x}^2(t)$ at $x=20$ mm. The intercept η is found from Eq. (42) as 0.27 mm^2 with 95% confidence interval $(0.2, 0.34) \text{ mm}^2$. Similarly, the thermal diffusivity χ is estimated as $0.167 \text{ mm}^2/\text{s}$, with 95% confidence interval $(0.13, 0.2)$, and the nominal thermal diffusivity of $\chi = 0.172 \text{ mm}^2/\text{s}$ cannot be rejected. Estimating the intercept using $\chi = 0.172 \text{ mm}^2/\text{s}$ yields $\hat{\eta} = 0.24 \text{ mm}^2$ with 95% confidence interval $(0.167, 0.32) \text{ mm}^2$. The intercept for the model in Eq. (42) is identified from Eq. (37) as the sum of three terms, the first, $\sigma_I^2(R_0) = 0.05 \text{ mm}^2$, is known from the dimensions of the Gaussian radiator. The other two parts are σ_{by}^2 and σ_{bz}^2 , determined from the geometry of the DU array. The DU ray model assumes that the DU beam spreading in both z and x is the same, and the identified offset is nearly $0.25a_G^2(1/R_0^2 + 1/\ell_q^2)\sigma_{by}^2$. The beamwidth σ_{bz} is determined by the combined transmit and receive beamforming, with array elements spaced by 0.2 mm for the CL10-5, creating an aperture with very small spreading, and $\sigma_{bz}^2 = 0.03 \text{ mm}^2$ is used. The spreading σ_{by}^2 is taken from the interval $(3.39, 10.7) \text{ mm}^2$ as $\hat{\sigma}_{by}^2 = 4 \text{ mm}^2$, and the heating modes and displacement modes are computed for a treatment frame captured 0.5 s after the exposure interval. The significance of coefficient estimates for the heating rate $q(t)$ is presented in Fig. 9(b), providing strong evidence that only the primary heating mode contributes to the observed displacements. Figure 9(c) shows the displacement estimates from this analysis, for comparison with Fig. 9(a); the beam spreading and the magnitude of the displacements agree well through the analysis depth of 20 mm. These differ from the results shown in Fig. 8(b), which used an analysis depth of 30 mm.

The reconstructed heating for the diffuse DU beam is presented in Fig. 10(a), using the first two heating modes. The estimate is consistent with what might be deposited from the 4.2 W source, given propagation losses and the efficiency

of the spherical radiator. Note that the confidence interval includes a constant source, making the estimate consistent with the administered therapy. The expected delivered power is determined from Eq. (50). Using the parameters in that section, and having a 4.2 W exposure, the expected heating rate is $C_v c_Q q_{\max} = 0.56 \text{ W/cm}$, where $c_Q = 1 \text{ mm}^2$ and attenuation losses are incurred over 1.5 cm in the gel. This same quantity is estimated using displacement analysis using the average value $\bar{q}$ of $q(t)$, and $C_v c_Q \bar{q} = 0.94 \text{ W/cm}$, with 95% confidence interval $(0.93, 0.96) \text{ W/cm}$. Thus, the observed heating is 1.67 times larger than that determined from the material properties. It was observed, however, that attenuation properties within the alginate block varied with depth, becoming larger with distance from the HIFU transducer, providing the most likely explanation for observing a larger than expected heating rate, although error in the material parameters cannot be excluded. The attenuation at the HIFU focus is then estimated as $2\gamma = 0.4711/\text{cm}$, or 0.58 dB/MHz/cm. Figures 10(b) and 10(c) show the temperature estimates obtained from the DU ray and diffuse beam models, respectively. Note that the temperature distribution from the DU diffuse beam model, shown in Fig. 10(c), has lateral dimensions consistent with the primary mode from the DU ray model in Fig. 7(a). The larger temperature estimates from the diffuse beam model, with maximum of 9.6°C , as compared to the ray model with maximum of 6.97°C , result from removing the spreading introduced by DU beam interaction. The practical implication is that by accounting for beam spread, the temperature estimates are improved. For example, for the small spreading encountered here, the ray model underestimates the temperature by 27%. When the lesion is not at the focus of DU transmit beamforming, the spreading may be considerably larger, increasing the bias for nonparametric temperature estimates.

The impact of the Gaussian radiator dimension a_G on estimates of heating, temperature, and thermal dose is investigated in Fig. 11. Figure 11(a) shows the change in estimated heating rate with Gaussian aperture dimension a_G over the interval (10, 11) mm, indicating that over this range, estimates are nearly independent of aperture size. From Eq. (50), this suggests that the temperature and thermal dose may be computed as accurately as desired from the true spherical radiation pattern. The estimated temperature history at the

TABLE I. Estimated beam spread at $x=20$ mm versus acquisition time.

$t_a, \text{ s}$	1.51	2.01	2.51	3.01	3.51	4.01	4.51	5.01
$\sigma_{z x}^2(t_a), \text{ mm}^2$	0.614	0.74	1.0	1.17	1.28	1.43	1.61	1.84

FIG. 10. (Color online) Heating and temperature estimates from ray and diffuse beam models. (a) Reconstructed heating from diffuse beam model. (b) Estimated temperature distribution in focal plane from ray model. (c) Estimated temperature distribution in focal plane from diffuse beam model.

lesion center for apertures of size 10 mm and 11 mm is presented in Fig. 11(b), indicating a low sensitivity of temperature estimates to aperture size. The maximum difference in temperature between the two curves is 1.87 °C. The influence of aperture size on thermal dose estimates is presented in Fig. 11(c), with calculations formed at the center of the lesion. The thermal dose calculation shows sensitivity to aperture size, with smaller aperture sizes a_G providing more conservative estimates of the administered thermal dose.

Finally, heating estimates are formed for the series of captured frames up until 132 s, and the estimates are shown in Fig. 12(a) through 100 s, along with the 95% confidence interval. Beyond this acquisition limit, estimates of heating increase nearly exponentially, despite that no evidence of displacement between reference and treatment frames is observed, either by differencing the RF frames, or by using the nonparametric displacement estimator. Moreover, an increasing trend in the heating estimates is observed over all acquisition times in Fig. 12(a), beyond what the confidence intervals predict, and this remains a matter for investigation. The maximum temperature standard error is computed from Eq. (20) and presented in Fig. 12(b). The temperature standard deviation exceeds 1 °C at 1000 s, or 17 min. Additionally, the ratio between the thermal dose, calculated from Eq. (22) using $C_v c_Q \bar{q} = 0.94$ W/cm, and the root mean squared error (MSE), with the MSE defined as the sum of the bias squared and variance

$$MSE = (E\{TD\} - TD)^2 + \text{var}(TD) \quad (57)$$

is shown in Fig. 12(c). From the Figure, this ratio is nearly one at 1000 s, at which point noninvasive thermal dose estimates are unreliable. For this example, the administered thermal dose is approximately 130 min, if the reference temperature is assumed 37 °C, although the choice of reference temperature is removed from the ratio between the thermal dose and root MSE, appearing in a scale factor common to both.

V. CONCLUSIONS

A method for analyzing the relative displacements between frames of backscattered RF data has been presented for HIFU therapy monitoring. It was shown that the accuracy of estimates formed using this technique is determined *a priori* using physical modeling. Moreover, it was shown how observable modes of heating can be identified, each uniquely associated with a displacement pattern, or mode, between the RF frames. By aligning the frames using these displacement modes, the administered heating is identified, providing the mechanism for therapy monitoring. The accuracy of these estimators was seen to attain the prescribed limits, using both simulations of heating in alginate, and results from experiment. The prescribed bounds on coefficient estimates for these modes are expressed using Eq. (A10) in terms of a signal to noise ratio, the power in the mode induced displacements, and the coefficient scaling between time-of-flight and temperature. These variances are in turn used to determine

FIG. 11. (Color online) Impact of Gaussian aperture size a_G on estimates. (a) Heating estimate $C_v c_Q \bar{q}$ versus aperture size a_G . (b) Temperature estimates at lesion center for $a_G = 10$ mm and $a_G = 11$ mm. (c) Thermal Dose estimates at lesion center versus Gaussian aperture size a_G .

FIG. 12. (Color online) Estimator performance versus acquisition time. (a) Heating estimate versus acquisition time, with 95% confidence interval. (b) Maximum error in temperature estimates, with acquisition time. (c) Ratio between calculated thermal dose and root MSE, as defined in Eq. (57), versus acquisition time.

the accuracy of heating, temperature, and thermal dose estimates.

Although estimators are formed using a Gaussian radiator to model the HIFU transducer, a spherical radiator, the sensitivity of estimates to radiator dimension a_G was small. The estimate of administered power through the focal plane was nearly independent of radiator dimension, indicating that from Eq. (50), the temperature history and thermal dose may be determined using the exact spherical radiation pattern, having estimated the heating rate as the power through the focal plane. It remains to determine whether a Gaussian aperture size can be identified which provides the thermal dose delivered by the spherical radiator.

By studying the point exposure, it was seen that the ray model for DU beam propagation does not provide accurate estimates of the administered therapy, a constant heating rate. Using displacement analysis, a beam spreading was identified, and when this spreading was used in the physical model, the administered therapy was identified correctly. As was seen in Fig. 9(a), DU beam spreading appears to increase with depth, and the modeling used here will need to be generalized to exploit the displacements in the frame. Nevertheless, once the correct DU beam interaction with temperature is identified, a similar analysis can be performed to determine the requisite displacement modes, and thereby formulate therapy estimators.

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NOMENCLATURE

- a_G = Dimension of Gaussian radiator, in mm
- $b(\mathbf{r}|\mathbf{r}_s)$ = DU beam, measuring influence of temperature at $\mathbf{r}$ on time-of-flight at $\mathbf{r}_s$, in units of $1/\text{mm}^2$
- c_Q = Spatial heating constant, $1/\text{mm}^2$
- C_v = Specific heat at constant volume, $\text{J}/^\circ\text{C}/\text{cm}^3$
- $g_{t|t'}(x|\mathbf{r}_k, \eta_{t'})$ = Proportional effect of temperature on time-of-flight measurements at depth x

and time t due to a unit of applied power at time t' , in $^\circ\text{C}/\text{s}$, to the HIFU centered at $\eta_{t'}$, dimensionless

$G_{t|t'}(x|\mathbf{r}_k, \eta_{t'})$ = Proportional effect of temperature on time-of-flight change from $\mathbf{r}_k = (x_0, R_0, z_k)$ to $\mathbf{r} = (x, R_0, z_k)$ at time t due to HIFU source applied at time t' and position $\eta_{t'}$, in units of mm

$K_t(s, s')$ = Spatial correlation between time-of-flight changes due to impulses at η_s and $\eta_{s'}$ at times s and s' , respectively, in units of mm^2

ℓ_d = Diffraction length of Gaussian radiator, in mm

$Q(\mathbf{r}, t)$ = Heat source, in $^\circ\text{C}/\text{s}$

$q(t)$ = Temporal dependence of heating, in $^\circ\text{C}/\text{s}$

$Q(\mathbf{r})$ = Spatial distribution of heating, dimensionless

R_0 = Focus and radius of spherical transducer, in mm

t_a, t_b = Acquisition times of reference and treatment frames, respectively, in s

t_i, t_f = Start and stop times, respectively, of HIFU exposure interval, in s

$T_t(\mathbf{r})$ = Temperature distribution in material at time t , in $^\circ\text{C}$

$U(\cdot)$ = Unit step function in argument; $U(z)=0, z<0, U(z)=1, z\geq 0$

α = Conversion factor between temperature and displacement, in units of $1/^\circ\text{C}$

γ_0, γ_t = Local attenuation coefficient in material, in units of $1/\text{mm}$

Δ_τ = DU sampling interval along a scanline, scaled by speed of sound, measured in mm

ζ_M = For a spherical radiator, the fraction of focal plane intensity within the main lobe

η_t = Position of transducer center at time t , parametrizing transducer motion

λ_n = Eigenvalue associated with n^{th} heating mode $\phi_n(t)$, in units of s^2/mm^2

ν = Perfusion constant, in s

- $\rho_t(j, k)$ = Two dimensional array of backscatter measurements, captured at time t , with J uniformly spaced samples along K uniformly spaced scanlines
- σ_ϵ^2 = Noise power in DU measurements of RF backscatter, in the dimensionless units of backscatter $\rho_t(j, k)$
- $\sigma_{\rho'}^2$ = Power in derivative of scattering profile $\rho_t(j, k)$ in scanline direction (τ), in units of $1/\text{mm}^2$
- τ_{ajk}^b = Depth of scatterer in reference frame whose position within k^{th} scanline in treatment frame is $j\Delta_\tau$ in mm
- $\tau_i(\mathbf{r}|\mathbf{r}_s)$ = Time-of-flight from source at $\mathbf{r}_s$ to field point $\mathbf{r}$ at time t , in mm
- $\phi_n(t)$ = n^{th} heating mode given the exposure interval (t_i, t_f) , the transducer motion η_t , material properties, and acquisition time t_b , dimensionless
- q_n = Coefficient of n^{th} heating mode for identifying heating rate, in $^\circ\text{C}/\text{s}$
- $\Phi_n^{t_b}(x, z_k)$ = n^{th} Displacement mode given the exposure interval (t_i, t_f) , the transducer motion η_t , material properties, and acquisition time t_b , in units of mm s
- χ = Thermal diffusivity of material, in mm^2/s
- $\psi_k^{t_b}$ = Jitter introduced by DU into k^{th} scanline of treatment frame relative to reference, in mm
- SNR = Defined as $\sigma_{\rho'}^2/\sigma_\epsilon^2$ for therapy monitoring, in units of $1/\text{mm}^2$

APPENDIX A: DERIVATION OF MODAL EQUATION

The basis $\phi_n(t)$ in Eq. (12) are waveforms ordered by the accuracy of their coefficient estimates. Estimator error is quantified using a statistical measurement model, from which the methods of maximum likelihood estimation are applied. The model is parameterized by the vector $\mathbf{q} = [q_1 \cdots q_N]^T$, with the heat induced displacements denoted by $\tau_{ajk}^b = \tau_{ajk}^b(\mathbf{q})$.

The set of measurements in the treatment frame $\mathbf{P}_{t_b} = \{\rho_{t_b}(j\Delta_\tau, z_k) : j=1, \dots, J, k=1, \dots, K\}$ captured at time t_b are assumed Normally distributed and conditionally independent given $\mathbf{q}$ and the reference frame $\mathbf{P}_{t_a}$. The individual measurements $\rho_{t_b}(j\Delta_\tau, z_k)$ in the treatment frame have expected value $\rho_{t_a}(\tau_{ajk}^b(\mathbf{q}), z_k)$ and variance σ_ϵ^2 , and the joint distribution $p_{\mathbf{q}}(\mathbf{P}_{t_b}|\mathbf{P}_{t_a})$ for measurements in the frame at t_b factors as the product:

$$p_{\mathbf{q}}(\mathbf{P}_{t_b}|\mathbf{P}_{t_a}) = \prod_{j=1}^J \prod_{k=1}^K N(\rho_{t_a}(\tau_{ajk}^b(\mathbf{q}), z_k), \sigma_\epsilon^2), \quad (\text{A1})$$

where the values $\rho_{t_a}(\tau_{ajk}^b(\mathbf{q}), z_k)$ in the initial frame are found using interpolation. The dependence on $\mathbf{q}$ is emphasized by a subscript since it is unknown, as opposed to the observations $\mathbf{P}_{t_a}$. The Cramer–Rao lower bound^{18,19} (CRLB) on parameter estimates $\hat{\mathbf{q}}$ is given by $\text{var}(\hat{\mathbf{q}}) \geq \mathbf{I}^{-1}(\mathbf{q})$, with $\mathbf{I}(\mathbf{q})$ the Fisher information matrix (FIM)

$$\mathbf{I}(\mathbf{q}) = -E \left\{ \frac{\partial^2 \ln p_{\mathbf{q}}(\mathbf{P}_{t_b}|\mathbf{P}_{t_a})}{\partial \mathbf{q} \partial \mathbf{q}^T} \right\}. \quad (\text{A2})$$

For the model in Eq. (A1), direct substitution shows that $\mathbf{I}(\mathbf{q})$ is:

$$\mathbf{I}(\mathbf{q}) = \frac{1}{\sigma_\epsilon^2} \sum_{j=1}^J \sum_{k=1}^K \left(\frac{\partial \rho_{t_a}(\tau, z_k)}{\partial \tau} \bigg|_{\tau=\tau_{ajk}^b(\mathbf{q})} \right)^2 \frac{\partial \tau_{ajk}^b(\mathbf{q})}{\partial \mathbf{q}} \frac{\partial \tau_{ajk}^b(\mathbf{q})}{\partial \mathbf{q}^T}. \quad (\text{A3})$$

From the FIM, the heating modes and displacement modes are identified as the functions which diagonalize it. This is facilitated when the variation of $\partial \tau / \partial q_n \ll \partial \rho_{t_a}(\tau, z_k) / \partial \tau$, in which case, using the modulation theorem⁸ and assuming a stationary and ergodic process, the sum-product in Eq. (A3) can be reduced to the simpler equation

$$\mathbf{I}(\mathbf{q}) \simeq \frac{\sigma_{\rho'}^2}{\sigma_\epsilon^2} \sum_{j=1}^J \sum_{k=1}^K \frac{\partial \tau_{ajk}^b(\mathbf{q})}{\partial \mathbf{q}} \frac{\partial \tau_{ajk}^b(\mathbf{q})}{\partial \mathbf{q}^T}. \quad (\text{A4})$$

where

$$\sigma_{\rho'}^2 \equiv E_{\rho} \left\{ \left(\frac{\partial \rho_t(\tau, z)}{\partial \tau} \right)^2 \right\}, \quad (\text{A5})$$

as the expected power in the backscatter variation with depth. The quantity $\sigma_{\rho'}^2$ is the effective signal power, since variability with depth provides the mechanism for alignment. From Eq. (9), the sensitivity of time-of-flight to heating is

$$\frac{\partial j\Delta_\tau}{\partial q_m} = 0 = \frac{\partial \tau_{ajk}^b}{\partial q_m} - \alpha \int_{t_i}^{t_f} \left[\phi_m(t') G_{t_b|t'}(\tau_{ajk}^b|\mathbf{r}_k, \eta_{t'}) + q_0(t') \frac{\partial \tau_{ajk}^b}{\partial q_m} g_{t_b|t'}(\tau_{ajk}^b|\mathbf{r}_k, \eta_{t'}) \right] dt'.$$

Rearranging,

$$\frac{\partial \tau_{ajk}^b}{\partial q_m} = \frac{\alpha \int_{t_i}^{t_f} \phi_m(t') G_{t_b|t'}(\tau_{ajk}^b|\mathbf{r}_k, \eta_{t'}) dt'}{1 - \alpha \int_{t_i}^{t_f} q_0(t') g_{t_b|t'}(\tau_{ajk}^b|\mathbf{r}_k, \eta_{t'}) dt'}, \quad (\text{A6})$$

$$\simeq \alpha \int_{t_i}^{t_f} \phi_m(t') G_{t_b|t'}(\tau_{ajk}^b|\mathbf{r}_k, \eta_{t'}) dt', \quad (\text{A7})$$

where the last approximation results from the fact that the denominator in Eq. (A6) is quite nearly one, the coefficient α being exceedingly small, and the temperature resulting from $q_0(t)$ being tens of $^\circ\text{C}$ for a few seconds. The result is exact for the operating point $q_0(t)=0$, for which $\tau_{ajk}^b = j\Delta_\tau$. Substituting Eq. (A7) into Eq. (A4) yields

$$\mathbf{I}_{m,n}(\mathbf{q}) \simeq \alpha^2 \frac{\sigma_{\rho'}^2}{\sigma_\epsilon^2} \int_{t_i}^{t_f} \int_{t_i}^{t_f} \phi_m(s) \phi_n(s') K_{t_b}(s, s') ds' ds. \quad (\text{A8})$$

The heating observation kernel $K_i(s, s')$ is given by:

$$K_t(s, s') = \sum_{j,k} G_{t|s}(\tau_{ajk}^b | \mathbf{r}_k, \eta_s) G_{t|s'}(\tau_{ajk}^b | \mathbf{r}_k, \eta_{s'}). \quad (\text{A9})$$

Choosing the functions $\phi_n(t)$ as the eigenfunctions of $K_t(s, s')$ for the operating point $q_0(t)=0$ yields Eq. (13). Moreover, from the Cramer–Rao bound,

$$\text{var}(\hat{q}_n) \geq \frac{1}{I_{nn}} = \left(\alpha^2 \frac{\sigma_{\rho'}^2}{\sigma_\epsilon^2} \lambda_n \right)^{-1}. \quad (\text{A10})$$

For $q_0(t)=0$, the diagonal FIM elements are denoted I_{nn}^0 . Equation (A10) expresses the CRB in terms of physical and statistical parameters: The scaling between temperature and time-of-flight α , the SNR $\sigma_{\rho'}^2 / \sigma_\epsilon^2$, and the power in the observed displacements λ_n , as described by Eq. (16).

APPENDIX B: CHARACTERIZING BOUND DEPENDENCE ON OPERATING POINT

The impact of the operating point $q_0(t)$ on the variance of coefficient estimates is herein assessed. Observe that when the heat induced displacements $\delta\tau = \tau_{ajk}^b - j\Delta_\tau$ are small, a first order Taylor series may be used to approximate $G_{t|s}$. With the aid of Eq. (9), the cumulative effect of temperature from a source η_s at time s is approximately

$$\begin{aligned} G_{t|s}(\tau_{ajk}^b | \mathbf{r}_k, \eta_s) &\approx G_{t|s}(j\Delta_\tau | \mathbf{r}_k, \eta_s) + g_{t|s}(j\Delta_\tau | \mathbf{r}_k, \eta_s)(\tau_{ajk}^b - j\Delta_\tau) \\ &\approx G_{t|s}(j\Delta_\tau | \mathbf{r}_k, \eta_s) + \alpha g_{t|s}(j\Delta_\tau | \mathbf{r}_k, \eta_s) \\ &\quad \times \int_{t_i}^{t_f} q(s'') G_{t|s''}(j\Delta_\tau | \mathbf{r}_k, \eta_{s''}) ds'' \\ &= G_{t|s}^0(j|k, \eta_s) + \alpha \int_{t_i}^{t_f} q(s'') G_{t|s''}^0(j|k, \eta_{s''}) g_{t|s}^0(j|k, \eta_s) ds'', \end{aligned} \quad (\text{B1})$$

where the 0 superscript denotes evaluation at $q_0(t)=0$. Substituting Eq. (B1) into Eq. (A9) and keeping only first order terms yields

$$\begin{aligned} K_t(s, s') &= \sum_{j,k} G_{t|s}(\tau_{ajk}^b | \mathbf{r}_k, \eta_s) G_{t|s'}(\tau_{ajk}^b | \mathbf{r}_k, \eta_{s'}) \\ &\approx \sum_{j,k} G_{t|s}^0 G_{t|s'}^0 + \alpha \int_{t_i}^{t_f} q(s'') \left[\sum_{j,k} G_{t|s}^0 G_{t|s''}^0 g_{t|s'}^0 \right. \\ &\quad \left. + \sum_{j,k} G_{t|s'}^0 G_{t|s''}^0 g_{t|s}^0 \right] ds'' \\ &= K_t^0(s, s') + \alpha \int_{t_i}^{t_f} q(s'') k_t(s, s' | s'') ds'', \end{aligned} \quad (\text{B2})$$

where indices in j, k have been suppressed for simplicity. The Fisher information for coefficient estimates using the basis $\phi_m^0(s)$ is written

$$\bar{I}_{m,n} = \bar{I}_{m,n}^0 + \alpha \int_{t_i}^{t_f} q(s'') \bar{I}_{m,n}(s'') ds'', \quad (\text{B3})$$

where

$$\bar{I}_{m,n}^0 = \alpha^2 \frac{\sigma_{\rho'}^2}{\sigma_\epsilon^2} \int_{t_i}^{t_f} \int_{t_i}^{t_f} \phi_m^0(s) \phi_n^0(s') K_{t_b}^0(s, s') ds ds', \quad (\text{B4})$$

$$\bar{I}_{m,n}(s'') = \alpha^2 \frac{\sigma_{\rho'}^2}{\sigma_\epsilon^2} \int_{t_i}^{t_f} \int_{t_i}^{t_f} \phi_m(s) \phi_n(s') k_{t_b}(s, s' | s'') ds ds'. \quad (\text{B5})$$

For $|(\bar{\mathbf{I}}^0)^{-1} \alpha \int_{t_i}^{t_f} q(s'') \bar{I}(s'') ds''|_p \ll 1$ [see Eq. (B9)], the matrix inverse is found approximately as²⁰

$$\bar{\mathbf{I}}'^{-1} \approx (\bar{\mathbf{I}}^0)^{-1} - (\bar{\mathbf{I}}^0)^{-1} \alpha \int_{t_i}^{t_f} q(s'') \bar{I}(s'') ds'' (\bar{\mathbf{I}}^0)^{-1}. \quad (\text{B6})$$

An upper bound on each diagonal element is found by choosing

$$q_w^{(m)}(t) = \begin{cases} q_{\max}, & \bar{I}_{m,m}(t) < 0, \\ 0 & \text{else,} \end{cases} \quad (\text{B7})$$

with $q_{\max}$ the largest heating that could be applied, providing the least upper bound

$$\sigma_{\min}^2(\hat{q}_m) \leq \frac{1}{\bar{I}_{m,m}^0} (1 + \Lambda_m(q_w^{(m)})) \quad (\text{B8})$$

where

$$\Lambda_m(q_w^{(m)}) = \frac{\alpha \int_{t_i}^{t_f} q_w^{(m)}(s'') |\bar{I}_{m,m}(s'')| ds''}{\bar{I}_{m,m}^0}, \quad (\text{B9})$$

providing a small correction.

APPENDIX C: INTEGRATIONS FROM PROBABILITY THEORY

Substituting Eqs. (29), (32), and (34) into Eq. (8), integration is performed with respect to y'', z'', x' and z' using the formula:

$$\begin{aligned} \int_{-\infty}^{\infty} p_1(x) p_2(x) dx &= \frac{1}{\sqrt{2\pi\sigma_1^2}} \frac{1}{\sqrt{2\pi\sigma_2^2}} \\ &\quad \times \int_{-\infty}^{\infty} e^{-(x-\mu_1)^2/2\sigma_1^2 - (x-\mu_2)^2/2\sigma_2^2} dx \\ &= \frac{1}{\sqrt{2\pi(\sigma_1^2 + \sigma_2^2)}} e^{-(\mu_1 - \mu_2)^2/2(\sigma_1^2 + \sigma_2^2)}, \end{aligned} \quad (\text{C1})$$

such that

$$g_{t|t'}(\mathbf{r}|\eta_{t'}) = \frac{U(t-t')e^{-(t-t')/\nu}}{(2\pi)^{3/2}} \int_{-\infty}^{\infty} \frac{e^{-(x-x_{t'})^2/2\sigma_x^2(t,t',y')}}{\sigma_x(t,t',y')} \frac{e^{-(z-z_{t'})^2/2\sigma_z^2(t,t',y')}}{\sigma_z(t,t',y')} \frac{e^{-(y-y')^2/2\sigma_y^2(t,t')}}{\sigma_y(t,t')} dy'$$

$$= U(t-t')e^{-(t-t')/\nu} E_{y'} \left\{ \frac{e^{-(x-x_{t'})^2/2\sigma_x^2(t,t',y')-(z-z_{t'})^2/2\sigma_z^2(t,t',y')}}{2\pi\sigma_x(t,t',y')\sigma_z(t,t',y')} \right\}. \quad (\text{C2})$$

where

$$\sigma_x^2(t,t',y') = \sigma_H^2(t-t') + \sigma_I^2(y'), \quad (\text{C3})$$

$$\sigma_z^2(t,t',y') = \sigma_H^2(t-t') + \sigma_I^2(y') + \sigma_{bz}^2, \quad (\text{C4})$$

$$\sigma_y^2(t,t') = \sigma_H^2(t-t') + \sigma_{by}^2. \quad (\text{C5})$$

The expectation in Eq. (C2) is taken with respect to y' , a Normally distributed random variable with mean y and variance $\sigma_y^2(t,t')$. Observe that the expectation is itself a probability distribution with respect to x and z , since

$$E_{y'} \left\{ \frac{e^{-(x-x_{t'})^2/2\sigma_x^2(t,t',y')-(z-z_{t'})^2/2\sigma_z^2(t,t',y')}}{2\pi\sigma_x(t,t',y')\sigma_z(t,t',y')} \right\}$$

$$= \int_{-\infty}^{\infty} p(x,z|y',x_{t'},z_{t'},t,t') p(y'|y=R_0,t,t') dy'$$

$$= p(x,z|x_{t'},z_{t'},y=R_0,t,t'), \quad (\text{C6})$$

so that the expectation provides the marginal joint distribution of x and z . A Normal approximation to this joint density can be found by using the first two moments of the exact joint density. The variance is found using iterated expectation. For the x coordinate, the variance is:

$$\text{var}(x|x_{t'},z_{t'},y=R_0,t,t')$$

$$= E_{y'} \{ \text{var}(x|x_{t'},z_{t'},y',t,t') \}$$

$$+ \text{var}_{y'} (E\{x|x_{t'},z_{t'},y',t,t'\})$$

$$= \sigma_H^2(t-t') + E_{y'} \{ \sigma_I^2(y') \}$$

$$= \left(1 + \frac{a_G^2}{4R_0^2} + \frac{a_G^2}{4\ell_d^2} \right) \sigma_H^2(t-t') + \sigma_I^2(R_0)$$

$$+ \frac{a_G^2}{4} \left(\frac{1}{R_0^2} + \frac{1}{\ell_d^2} \right) \sigma_{by}^2 \equiv \sigma_{HLx}^2(t-t'). \quad (\text{C7})$$

For z , a similar calculation shows

$$\text{var}(z|x_{t'},z_{t'},y=R_0,t,t') = \sigma_{HLx}^2(t-t') + \sigma_{bz}^2 \equiv \sigma_{HLz}^2(t-t'). \quad (\text{C8})$$

In the same way, it is found that x and z are independent. Combining results, Eq. (C2) is rewritten as:

$$g_{t|t'}(\mathbf{r}|\eta_{t'}) = U(t-t')e^{-(t-t')/\nu} p(x,z|x_{t'},z_{t'},y=R_0,t,t'), \quad (\text{C9})$$

$$= U(t-t')e^{-(t-t')/\nu} \frac{e^{-(z-z_{t'})^2/2\sigma_{HLz}^2(t-t')}}{\sqrt{2\pi\sigma_{HLz}^2(t-t')}} \frac{e^{-(x-x_{t'})^2/2\sigma_{HLx}^2(t-t')}}{\sqrt{2\pi\sigma_{HLx}^2(t-t')}}. \quad (\text{C10})$$

Substituting Eq. (C10) into Eq. (10) then yields:

$$G_{t|t'}(x,z_k|\eta_{t'}) = U(t-t')e^{-(t-t')/\nu} \int_{x_0}^x p(x',z|x_{t'},z_{t'},y)$$

$$= R_0,t,t') dx', \quad (\text{C11})$$

$$= U(t-t')e^{-(t-t')/\nu} \frac{e^{-(z-z_{t'})^2/2\sigma_{HLz}^2(t-t')}}{\sqrt{2\pi\sigma_{HLz}^2(t-t')}} \Phi(\xi) \Big|_{\xi=-x_{t'}/\sqrt{\sigma_{HLx}^2(t-t')}}^{\xi=x-x_{t'}/\sqrt{\sigma_{HLx}^2(t-t')}}. \quad (\text{C12})$$

- ¹G. ter Haar, "Acoustic surgery," *Phys. Today* **54**(12), 29–34 (2001).
- ²S. A. Sapareto and W. C. Dewey, "Thermal dose determination in cancer therapy," *Int. J. Radiat. Oncol., Biol., Phys.* **10**, 787–800 (1984).
- ³R. Maass-Moreno, C. Damianou, and N. Sanghvi, "Noninvasive temperature estimation in tissue via ultrasound echo-shifts. Part I: Analytical model," *J. Acoust. Soc. Am.* **100**, 2514–2521 (1996).
- ⁴C. Simon, P. VanBaren, and E. S. Ebbini, "Two dimensional temperature estimation using diagnostic ultrasound," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control* **45**, 1088–1099 (1998).
- ⁵G. Speyer, P. Kaczowski, A. Brayman, M. Andrew, and L. Crum, "Bounds on thermal dose estimates using ultrasonic backscatter monitoring of heating," in *Proceedings of the ISTU 2008*, Minneapolis, Minnesota (American Institute of Physics, Melville, NY, 2009).
- ⁶L. Landau and E. M. Lifshitz, *Fluid Mechanics* (Butterworth-Heinemann, Burlington, MA, 1977).
- ⁷P. M. Morse and K. Uno Ingard, *Theoretical Acoustics* (Princeton University Press, Princeton, NJ, 1968).
- ⁸A. Papoulis, *Probability and Random Variables* (McGraw-Hill, New York).
- ⁹H. T. O'Neil, "Theory of focusing radiators," *J. Acoust. Soc. Am.* **21**, 516–526 (1949).
- ¹⁰B. K. Novikov, O. V. Rudenko, and V. I. Timoshenko, *Nonlinear Underwater Acoustics* (Acoustical Society of America, Melville, NY, 1987).
- ¹¹J. P. Keener, *Principles of Applied Mathematics* (Addison-Wesley, Reading, MA, 1988).
- ¹²A. Anand and P. J. Kaczowski, "Noninvasive measurement of local thermal diffusivity using backscattered ultrasound and focused ultrasound heating," *Ultrasound Med. Biol.* **34**, 1449–1464 (2008).
- ¹³W. L. Nyborg, "Solutions of the bio-heat transfer equation," *Phys. Med. Biol.* **33**, 785–792 (1988).
- ¹⁴G. C. Carter, "Coherence and time delay estimation," *Proc. IEEE* **75**, 236–255 (1987).
- ¹⁵R. E. Blahut, "Theory of remote surveillance algorithms," in *Radar and Sonar Part I*, edited by R. E. Blahut (Springer-Verlag, New York, 1992), pp. 1–65.
- ¹⁶A. Anand, "Noninvasive temperature estimation technique for HIFU therapy monitoring using backscattered ultrasound," Ph.D. thesis, University of Washington, Seattle, WA, 2005.

- ¹⁷A. Anand, D. Savary, and C. Hall, "Three-dimensional spatial and temporal temperature imaging in gel phantoms using backscattered ultrasound," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control* **54**, 23–31 (2007).
- ¹⁸S. M. Kay, *Fundamentals of Statistical Signal Processing, Volume I: Estimation Theory* (Prentice–Hall, Upper Saddle River, NJ, 1993).
- ¹⁹E. L. Lehmann, *George Cassella Theory of Point Estimation* (Springer-Verlag, New York, 1998).
- ²⁰G. H. Golub and C. F. Van Loan, *Matrix Computations*, 3rd ed. (Johns Hopkins University Press, Baltimore, MD, 1996).