Contrast agent shell properties effects on heat deposition in bubble enhanced high intensity focused ultrasound

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ABSTRACT:
The effects of the viscoelastic shell properties of ultrasound contrast agents on heat deposition in bubble enhanced high intensity focused ultrasound (HIFU) are studied numerically using a model that solves the ultrasound acoustic field and the multi-bubble dynamics. The propagation of the nonlinear acoustic waves in the test medium is modeled using the compressible Navier-Stokes equations in a fixed Eulerian grid, while the microbubbles are modeled as discrete flow singularities, which are tracked in a Lagrangian fashion. These two models are intimately coupled such that both the acoustic field and the bubbles influence each other at each time step. The resulting temperature rise in the field is then calculated by solving a heat transfer equation applied over a much longer time scale than the computed high frequency dynamics. Three shell models for the contrast agent are considered, and the effect of each of these models on the heat deposition at the focus is studied. The differences obtained in the bubble dynamics results between the shell models are discussed. The importance of modeling the elasticity of the shell is addressed by comparing the results between Newtonian and non-Newtonian shell models. Next, a parametric study varying the shell properties is carried out, and the relative roles of the shell viscosity and elasticity in affecting the heat deposition are discussed. These observations are then used to give recommendations for the design of innovative contrast agents, specifically for the purpose of obtaining higher heat deposition in bubble enhanced HIFU.

I. INTRODUCTION

Applying high intensity focused ultrasound (HIFU) clinically is a therapeutic technique that uses the focused energy of high frequency ultrasound to elevate the target tissue temperature locally, causing thermal ablation. HIFU’s noninvasive nature and its potential to treat cancers, such as those in the liver and brain (Kennedy, 2005; Kennedy et al., 2004), has garnered a lot of attention in the scientific community in recent years. However, a major impediment to its use to efficiently treat deep-seated cancer is the need for long treatment times. Because this is required for deep penetration, high intensity sound waves may also cause unwanted tissue damage along the waves’ path before reaching the targeted region. In order to reduce undesirable damage of surrounding tissues, medical practitioners resort to long resting times between successive insonations to allow the pre-focal region to cool down, which lengthens even further the overall treatment time. It is, therefore, desirable to find means to enhance the heat deposition in the target region only and use unharmful moderate intensity levels elsewhere (100–1000 W/cm²; Harirahan et al., 2007). One such means is to introduce microbubbles in the form of ultrasound contrast agents (UCAs) in the target region subjected to HIFU. This has been shown to increase HIFU local heat deposition in the targeted area in both in vitro (Kajiyama et al., 2010; Razansky et al., 2006) and in vivo experiments (Chung et al., 2012; Kaneko et al., 2005).

Concerning the development and application of such a technique, numerical modeling can reduce lengthy and expensive experimental tests. Accurate modeling of bubble enhanced HIFU needs sophisticated modeling approaches that handle the proper simulation of the acoustic field, the UCA dynamics, and their strong interaction and coupling. Recently, the authors of this work developed an Euler-Lagrangian based spatio-temporal multiscale model (Gnanaskandan et al., 2019a,b) to simulate bubble enhanced HIFU and demonstrate enhanced heating effects in the presence of microbubbles. Previous studies (Holt and Roy, 2001) suggested two mechanisms for heat enhancement: heating through acoustic emission and heating through viscous dissipation. Our two-way coupled model (Gnanaskandan et al., 2019a) was used to demonstrate that for gaseous bubbles (i.e., bubbles with no shells), viscous damping was the primary mechanism for bubble enhanced heat deposition in addition to ultrasound absorption and acoustic emission. However, in practical HIFU treatment, UCAs, which have acoustic and dynamics properties that are different than those of air bubbles, are used and their interaction with the HIFU acoustic field needs to be addressed.

UCAs are stabilized microbubbles, encapsulated by a shell of surface active materials, such as lipids or albumin, to provide stability against premature dissolution in the...
blood stream (Goldberg et al., 1994). The viscoelastic shell significantly affects the dynamic response of the contrast agent to the acoustic field, and neglecting shell properties like those in gas bubbles is not appropriate. In some previous studies (Church, 1995; Hoff et al., 2000; Ma et al., 2004; Sarkar et al., 2005), the UCA shell was modeled as a linear elastic solid with viscous dissipation, and under a spherical shape assumption, this model was incorporated into a generalized Rayleigh-Plesset (Lord Rayleigh, 1917; Plesset and Prosperetti, 1977) formulation with a balance of the normal stresses at the shell–liquid interface. To resolve the aspherical dynamics of thick shell enclosed UCAs, a three-dimensional (3D) model coupling a finite-difference Navier-Stokes solver and a boundary element method (BEM) potential flow solver were also developed (Hsiao and Chahine, 2010, 2013). This 3D shell model was further simplified to use the BEM solver alone by applying a zero-thickness approximation (Hsiao et al., 2010). This approximation has been found adequate for shells of nanometer thickness (Chatterjee and Sarkar, 2003) and is preferred due to the simplicity of the resulting model. In the current study, we consider three different zero-thickness UCA models (Marmottant et al., 2005; Sarkar et al., 2005) and assess the effects of these models and of different shell parameters on the UCA behavior in the acoustic field and the resulting heat deposition enhancements. We use three models, viz., Sarkar’s Newtonian model (Sarkar et al., 2005), Sarkar’s non-Newtonian model (Sarkar et al., 2005), and Marmottant’s non-Newtonian model (Marmottant et al., 2005).

The paper is organized as follows. We first present the governing equations and the numerical methodology combining the Eulerian and Lagrangian approaches. We then recall the results from our earlier work using gas microbubbles in HIFU and heat enhancement predicted in that setup. Next, we present the effect of different rheological models for one type of contrast agent and discuss the effects of these models on the HIFU pressure field, temperature field, and microbubble dynamics. We consider, for illustration, two commercially available contrast agents, Sonazoid and Optison, which have different properties, and discuss the effect of one rheological model for various UCA properties. Finally, we discuss the importance of shell viscosity and elasticity and offer suggestions for designing new UCAs specifically for the purpose of heat enhancement in HIFU.

II. ACOUSTIC FIELD AND BUBBLE DYNAMICS MODELING

The modeling of the acoustic field and UCAs and their interaction is based on an Eulerian-Lagrangian method, which was developed earlier by Gnanaskandan et al. (2019a). The ultrasound propagation in the viscous medium, hosting the microbubbles, is solved using the compressible Navier-Stokes equations in an Eulerian framework, whereas the microbubble oscillations in the viscous medium, resulting in heat deposition, are solved in a Lagrangian framework using a discrete singularity method (Chahine, 2009; Ma et al., 2015). This coupled approach provides the heat source terms required to solve a heat equation, which addresses the longer time scale heat deposition in the target area.

A. Compressible flow solver

The compressible flow solver, describing acoustic wave propagation through a two-phase medium, solves the following governing equations for conservation of mass, momentum, and energy in a fixed reference frame:

\[
\begin{align*}
\frac{\partial \rho_m}{\partial t} + \nabla \cdot (\rho_m \mathbf{u}_m) &= 0, \\
\frac{\partial \rho_m \mathbf{u}_m}{\partial t} + \nabla \cdot (\rho_m \mathbf{u}_m \mathbf{u}_m + p_m \mathbf{I} + \mathbf{\sigma}) &= 0, \\
\frac{\partial \rho_m E_m}{\partial t} + \nabla \cdot ((\rho_m E_m + p_m) \mathbf{u}_m) + \mathbf{\sigma} \cdot \mathbf{u}_m &= 0,
\end{align*}
\]

where \( \rho_m, E_m, \) and \( \mathbf{u}_m \) are the mixture density, total energy per unit mass, and velocity vector, respectively, and the stress tensor \( \mathbf{\sigma} \) is

\[
\begin{align*}
\mathbf{\sigma} &= \left( \lambda_m + \frac{2}{3} \mu_m \right) \mathbf{I} \\
&+ \mu_m \left( \nabla \mathbf{u}_m + (\nabla \mathbf{u}_m)^T - \frac{2}{3} (\nabla \cdot \mathbf{u}_m) \mathbf{I} \right),
\end{align*}
\]

where \( \mu_m \) and \( \lambda_m \) are the mixture shear and second viscosity, respectively. The first term in Eq. (2) is the bulk viscosity, which is assumed to be three times the shear viscosity. The mixture density is defined using the mixture components’ densities, \( \rho_i \), and volume fractions, \( x_i \) (the \( i \) components are the tissue or phantom medium and the gas inside the bubbles), and is given by

\[
\rho_m = \sum_i \rho_i x_i, \quad \text{with} \quad \sum_i x_i = 1.
\]

Similarly the mixture viscosity (Gnanaskandan and Mahesh, 2015; Perigaud and Saurel, 2005) is defined as

\[
\mu_m = \sum_i \mu_i x_i, \quad \text{with} \quad \sum_i x_i = 1.
\]

in this study. Although tissue phantoms may exhibit non-Newtonian behavior, modeling such behavior is out of scope of the present study and the medium is modeled here as a Newtonian fluid. This assumption will be revisited in the future. The total energy per unit mass \( E_m \) is also given by

\[
E_m = \varepsilon_m + 0.5 \mathbf{u}^2, \quad \text{where} \quad \rho_m \varepsilon_m = \sum_i \rho_i \varepsilon_i x_i.
\]

In Eq. (1), \( p_m \) denotes the mixture pressure and is obtained from a mixture equation of state (EOS) given by (Gnanaskandan and Mahesh, 2016; Pelanti and Shyue, 2014)
\[ p_m = (\Gamma - 1) \rho_m e_m - \Gamma \Pi, \]
\[ \Gamma = 1 + \left( \sum_i \frac{\phi_i}{\Psi_i - 1} \right)^{-1} \]
\[ \Pi = \Gamma - 1 \sum_i \phi_i \frac{\Psi_i \pi_i}{\Psi_i - 1}, \]

where \( \Psi \) and \( \pi \) are material specific constants. These equations are solved using a fully conservative higher order Monotonic Upwind Scheme for Conservation Laws (MUSCL) (van Leer and Woodward, 1979) and an approximate Riemann solver (Colella, 1985; Kapahi et al., 2015). The only unknown required to close this system of equations is the gas volume fraction, \( \phi_b \), which is obtained from the knowledge of the local spatial distribution of the microbubbles and their individual volumes. We compute this by tracking the bubbles using the discrete singularity model (DSM) described below (Choi et al., 2007; Hsiao and Chahine, 2012).

### B. DSM—Bubbles’ motion and dynamics

The dynamics of a gas bubble, assumed in the first approximation to be spherical, moving at the speed \( \mathbf{u}_b(t) \) in a viscous and elastic medium can be described by a modified Keller-Herring equation (Prosperetti and Lezzi, 1986) for the bubble equivalent spherical radius, \( R(t) \),

\[
\left( 1 - \frac{\dot{R}}{c_m} \right) R \ddot{R} + \frac{3}{2} \left( 1 - \frac{\dot{R}}{3c_m} \right) \dot{R}^2 = \frac{1}{\rho_m} \left( 1 + \frac{\dot{R}}{c_m} + \frac{R \rho_m \dot{R}}{d} \frac{d}{dt} \right) \left[ p_g - p_m - \frac{2\eta}{R} - 4 \mu \frac{\dot{R}}{R} \right]
- \frac{4}{3} G_m \left[ 1 - \frac{R_0}{R} \right] \gamma + \frac{(\mathbf{u}_m - \mathbf{u}_b)^2}{4}. \tag{7}
\]

In this equation, \( \dot{R} \) and \( \ddot{R} \) are the bubble interface radial velocity and acceleration, respectively, and \( c_m \) is the sound speed in the host medium. \( p_g \) is the gas pressure inside the bubble, \( \gamma \) is the surface tension, and \( G_m \) is the shear elasticity of the medium surrounding the bubble. \( p_m(t) \) and \( \mathbf{u}_m(t) \) are the pressure and local velocity encountered by the bubble along its path, respectively, and they are obtained by averaging over the bubble surface the surrounding medium pressure and velocity, respectively. The speed of sound for the mixture is given by

\[
c_m = \sqrt{\frac{1}{\rho_m \sum_i \frac{\phi_i}{\Psi_i(p + \pi_i)}}}. \tag{8}
\]

It should be noted that the speed of sound in the mixture depends on the local void fraction, mixture density, and material specific constants but does not contain any spectral content from the bubbles (Kargl, 2002). Thus, any dispersion effect due to the presence of bubbles in not modeled. Such an assumption is valid only for dilute flows (void fractions \(<10^{-4}\) as used in this study). Any attempts to model higher void fractions using this model should include necessary modifications to the speed of sound to model the dispersion effects. The last two terms in Eq. (8) are additional terms to the classical Rayleigh-Plesset-Keller-Herring equation. The first term, \( \frac{2}{3} G_m \left[ 1 - \left( R_0/R \right)^3 \right] \), accounts for the normal stresses due to the elasticity of the host medium (Okita et al., 2013), while the second term, \( (\mathbf{u}_m - \mathbf{u}_b)^2/4 \), accounts for the additional pressure due to the potential presence of a slip velocity between the bubble and the medium (Chahine, 2009). Numerically, the surface averaged quantities are obtained through an arithmetic averaging of the mixture pressures and velocities at six polar points on the bubble equivalent sphere surface. The gas is assumed to follow a polytropic gas compression law,

\[
p_g = p_0 \left( R_0 \right)^{3k}, \tag{9}
\]

where \( k \) is the polytropic constant and the subscript “0” indicates the initial condition. Note that the viscous term in the bubble dynamics equation includes the mixture viscosity. This is to include the effects of the presence of surrounding bubbles on an individual bubble in the viscous term. In a dense bubble population, this leads to an accurate encountered field for the bubbles. For a dilute bubble population, this expression automatically tends toward the values of the viscosity of the liquid alone. Further, Eq. (7) only captures bubble volume change effects by considering the first order spherical term. However, depending on the strength of the interaction with the surrounding medium and the other bubbles, the bubbles could undergo nonspherical deformations, which require additional study. Unless, using small perturbation studies, which we have performed in other studies (Chahine and Duraiswami, 1992), capturing nonspherical deformations requires the bubble to be resolved, which will lead to an exponential increase in the computational cost. This study aims to develop a reduced order model to capture effects of bubble oscillations on heat deposition and, hence, does not yet consider nonspherical deformations.

The bubble location can be tracked in a Lagrangian fashion using the following bubble motion equation (Johnson and Hsieh, 1966), which accounts for viscous drag lift, and slip velocity between the bubble and the mixture,

\[
\frac{d \mathbf{u}_b}{dt} = - \frac{3}{\rho_m} \nabla p_m + \frac{3 C_D}{4} \left( \mathbf{u}_m - \mathbf{u}_b \right) |\mathbf{u}_m - \mathbf{u}_b| + \frac{3 C_L}{2\pi R} \frac{\rho_m (\mathbf{u}_m - \mathbf{u}_b) \times \omega}{\sqrt{|\omega|}} + \frac{3 \dot{R}}{R} (\mathbf{u}_m - \mathbf{u}_b). \tag{10}
\]
forces on the bubble. The first term on the right-hand side accounts for the flow field pressure gradient while the second term accounts for the drag force (Haberman and Morton, 1953) experienced by the bubble. The third term is a lift force acting on a bubble (Saffman, 1965). The last term on the right-hand side of Eq. (10) is the Bjerknes force (Akhatov et al., 1997), expressing the coupling between the bubble volume variations and bubble motion. The bubble motion and volume evolution are obtained by integrating over time Eqs. (8) and (10) with an explicit fourth order Runge-Kutta scheme.

C. UCA bubble modeling

An UCA exhibits a similar nonlinear response as a gas bubble, but the presence of an encapsulating shell generates additional stress due to the shell properties. The zero-thickness shell model allows us to account for this by introducing a shell viscosity term and shell elasticity term as discussed below. In the current work, we examine the zero-thickness shell encapsulation models of Sarkar et al. (2005) and Marmottant et al. (2005) and compare them with each other and with the simple gas bubble model.

1. Sarkar’s Newtonian model

The Sarkar et al. (2005) UCA zero-thickness shell model was derived as follows. The dynamic force balance at the interface between a shelled bubble and the host medium is given by the Boussinesq-Scriven constitutive expression (Edwards et al., 1991; Scriven, 1960),

\[ \mathbf{\tau} = \gamma \mathbf{I} + (\kappa^s - \mu^s)(\nabla \cdot \mathbf{D}) \mathbf{I} + 2 \mu^s \mathbf{D}^s, \]

(11)

where \( \kappa^s \) and \( \mu^s \) are the interfacial dilatational and shear viscosities, respectively, \( \mathbf{I} \) is the identity tensor, and \( \mathbf{D}^s \) is the surface strain rate tensor. The jump in the surface stress at the interface is then given by

\[ [\mathbf{\tau} \cdot \mathbf{n}]_{\text{surface}} = \nabla_s \cdot \mathbf{\tau}_s, \]

(12)

where \( \mathbf{n} \) is the normal to the surface and \( \nabla_s \) is the surface gradient operator. Using the radial part of the jump conditions (Edwards et al., 1991), one can write the interface condition as

\[ p_{r=R} = p_S - \frac{2\gamma}{R} - \frac{4\mu^s \dot{R}}{R} - \frac{4\kappa^s \dot{R}}{R^2}, \]

(13)

where we can see the additional term \( -4\kappa^s \dot{R}/R^2 \) when comparing with a gas bubble balance equation. The dilatational viscous term can be explained by noting that the bubble undergoes an area dilatation at the rate

\[ \frac{1}{\pi R^2} \frac{d}{dt} (\pi R^2) = 2 \frac{\dot{R}}{R}. \]

(14)

This results in a uniform tension of magnitude \( 2\kappa^s \dot{R}/R \). The bubble dynamics equation [Eq. (7)] with this model for an UCA can then be written as

\[ \frac{1}{\rho_m} \left( \frac{1 + \frac{\dot{R}}{3c_m}}{\frac{\dot{R}}{3c_m}} \right) \dot{R}^2 = \frac{1}{\rho_m} \left( 1 + \frac{\dot{R}}{c_m} + \frac{R}{c_m} \frac{d}{dt} \left[ p_s - p_m - 4\mu^s \frac{\dot{R}}{R} \right] - \frac{4}{3} Gm \left[ 1 - \left( \frac{R_0}{R} \right)^3 \right] \right) - \frac{4}{3} \kappa^s \frac{\dot{R}}{R^2} \]

\[ + \frac{(u_m - u_0)^2}{4}, \]

(15)

where \( 4\kappa^s \dot{R}/R^2 \) is the additional Newtonian rheological term.

2. Sarkar’s non-Newtonian model

In the Newtonian model shown above, the encapsulation properties are purely viscous and characterized only by dilatational viscosity \( \kappa^s \). When the original authors applied it to predict acoustic attenuation by Optison UCA, they found that in order to fit with the experimental results (Sarkar et al., 2005), all of the elastic effects combined into the surface tension term results in unphysically large surface tension values. To alleviate this issue, they augmented the model by including surface tension gradient effects. Edwards et al. (1991) showed that the dilatational elasticity, \( E^s \), can be accounted for by accounting for the effects arising from the surface tension gradients due to the effective area change of the UCA. This can be expressed as

\[ \gamma = \gamma_0 + E^s \frac{dA}{A}, \]

where \( E^s \equiv \left( \frac{d\gamma}{d(\log A)} \right)_{dA/A=0} \)

\[ \text{and} \quad dA/A = \left( \frac{R}{R_E} \right)^2 - 1. \]

(16)

\( dA/A \) is the fractional change in area from the equilibrium that represents an unstrained equilibrium condition, corresponding to an equilibrium radius \( R_E \). \( \gamma_0 \) is the reference surface tension at zero area change of the bubble.

With this modification to the surface tension, the dynamic boundary condition at \( r = R \) becomes

\[ p_{r=R} = p_S - \frac{2\gamma_0}{R} - \frac{4\mu^s \dot{R}}{R} - \frac{4\kappa^s \dot{R}}{R^2} \]

\[ - 2E^s \left( \frac{R}{R_E} \right)^2 - 1, \]

with \( R_E = R_0 \left( 1 - \frac{\gamma_0}{E^s} \right)^{-0.5} \).

(17)

The bubble dynamics equation (8) then becomes
where $4\kappa R^2$ and $(-2E^*/R)(R/R_b)^3 - 1$ are the two additional rheological terms.

### 3. Marmottant’s non-Newtonian model

The model by Marmottant et al. (2005) takes into account the physical properties of a lipid monolayer coating on a gas microbubble through a more complex surface tension term. It uses three regimes to characterize the properties of the shell, dependent on the deviation of the UCA from its equilibrium radius. The UCA is assumed to buckle if its radius decreases below a buckling radius, $R_{\text{buckling}}$. In this case, the surface tension force disappears. The UCA is also assumed to rupture if its radius exceeds a shell rupture radius, $R_{\text{rupture}}$. In this case, the only remaining surface tension force is that of the air/medium. Therefore, during the oscillation, the tension force due to the shell elasticity, $E^s$, will vary with the bubble surface area and the shell elasticity as in the Sarkar model, $E^s(R_b^2/R_{\text{buckling}}^2 - 1)$.

With the above description of the area dependent surface tension, $\gamma(R)$, the normal stress balance can be expressed as

$$p_r - p_s = \frac{2\gamma(R)}{R} - \frac{4\mu R}{R} - \frac{4\kappa R^2}{R^2},$$  \quad (19)

with

$$\gamma(R) = \begin{cases} 0 & \text{if } R \leq R_{\text{buckling}}, \\ \gamma_0 + E^s \left( \frac{R^2}{R_0^2} - 1 \right) & \text{if } R_{\text{buckling}} \leq R \leq R_{\text{rupture}}, \\ \gamma_{\text{water}} & \text{if } R \geq R_{\text{rupture}}. \end{cases}$$  \quad (20)

$E^s$ is the same “shell elasticity” term that was seen in the Sarkar model, also dubbed “compression modulus” in the Marmottant model. $R_{\text{buckling}}$ was assumed to be the initial equilibrium radius in this model (Marmottant et al., 2005).

The variation of this effective surface tension with the bubble radius is represented in Fig. 1, which shows the three different regimes of the UCA behavior, namely, buckling, elastic, and rupture. The final UCA dynamics equation can now be written as

$$\frac{1}{\rho_m} \left( 1 + \frac{R}{c_m} \frac{d}{dt} \frac{R}{d} \right) \left[ p_r - p_s - p_m - 4\mu_m \frac{R}{R} - \frac{4\kappa}{R} \right]$$

\[ \times \left[ 1 - \left( \frac{R_0}{R} \right)^3 \right] - 2\gamma_0 \frac{R}{R} - 2E^s \left( \frac{R}{R_b} \right)^2 - 1 \right] + \frac{(u - u_c)^2}{4} = \left( 1 - \frac{R}{c_m} \right) \frac{R}{R} + \left( 1 - \frac{R}{3c_m} \right) \frac{R}{R}^2, \quad (18)$$

with $\gamma(R)$ expressed using Eq. (20).

### D. Coupling bubble dynamics with continuum flow field

Once all of the bubbles’ instantaneous sizes are computed, it is necessary to collect and communicate this information back to the compressible flow solver in terms of the local void fraction computed in each computational Eulerian cell. This is achieved by computing an effective void fraction derived from the contribution of each bubble to its surrounding Eulerian computational cells using a Gaussian distribution (Gnanaskandan et al., 2019a; Ma et al., 2015). The Gaussian distribution scheme computes $v_{i,j}$, the $j$th bubble volume contribution to the void fraction computation in grid cell $i$, using

$$v_{i,j} = V_j \delta e^{-|x_i - x_0|^2/\lambda^2}, \quad (22)$$

Here $V_j$ is the volume of bubble $j$, $x_{0,j}$ is the bubble center’s coordinate, $x_i$ is the coordinate center of grid cell $i$, and $\lambda$ is the simulation selected characteristic radius of influence of the bubble. In order to guarantee that the total volume of the bubbles is conserved in this procedure, a cell volume-
weighted normalization scheme is adopted to normalize the volume contribution, i.e.,

$$\bar{v}_{i,j} = \frac{v_{i,j}V_{cell}}{\sum_k v_{k,j}V_{cell}},$$

(23)

where $V_{cell}^i$ is the $i$th cell volume. Because each bubble only contributes its volume to a limited number of nearby cells as a result of the Gaussian decay, the normalization is computed only for a total number $N_{cell}$, which is influenced by the bubble $j$. To finally obtain the void fraction for the cell $i$, we then sum up the contributions of all bubbles within the “influence range” and divide by the cell volume to obtain

$$\alpha_i = \sum_{j=1}^{N_i} \bar{v}_{i,j} = \frac{\sum_{j=1}^{N_i} v_{i,j}V_{cell}^j}{\sum_k v_{k,j}V_{cell}^k},$$

(24)

where $N_i$ is the number of bubbles that are in the influence range.

E. Modeling heat deposition in the target volume

Once the acoustic and bubble fields are obtained as described above, the heat deposited in the tissue is computed by a Penne’s bio heat transfer equation (Shih et al., 2007), given by

$$\rho_C p \frac{\partial T}{\partial t} = K \nabla^2 T + q_{US, AC} + q_{VIS},$$

(25)

Here, $C_p$ is the specific heat of the medium, $K$ is its thermal conductivity, and $T$ is its temperature. The heat source, $q_{US, AC}$, in this equation, is due to heating from the primary ultrasound source and the corresponding acoustic emission from bubble oscillations. The heat source, $q_{VIS}$, is a result of heating from the medium viscous damping of the bubble oscillations. Both $q_{US, AC}$ and $q_{VIS}$ are obtained as time-averaged values computed during the solution of the Eulerian-Lagrangian two-phase problem. These time-averaged source values are then used to derive the heat equation. The time averages are computed over at least ten cycles after the initial transients are removed and the primary ultrasound wave reaches the geometric focus. It has been shown in previous studies (Farny et al., 2009) for bubbles of sizes on the order of a micron or smaller (which is the case in this study), the bubble oscillations are essentially isothermal, leading to minimal heating from the thermal dissipation. The heat source $q_{US, AC}$, due to the primary ultrasound absorption and acoustic emissions of the bubble, is given by

FIG. 2. (Color online) Schematic of the numerical simulation setup.

FIG. 3. Temperature history at two different locations (39 mm $\leq Z \leq 40$ mm) near the focus for gas microbubble. NS, no shell model.

FIG. 4. (Color online) Effect of dilatational viscosity, $\kappa'$, and dilatational elasticity, $E'$, on the radius evolution of a bubble with initial radius $R_0 = 10$ $\mu$m and initial pressure 10 atm, oscillating in a medium with ambient pressure 1 atm.
where $\varepsilon_{ij}$ is the strain rate tensor and the double indices are standard Einstein notation, indicating summation over each direction, with $\delta_{ij}$ representing the Kronecker delta function. The heat addition due to the viscous damping of a single bubble is given by (Okita et al., 2013)

$$q_{vis}^b = \left(4\pi R^2\right)\left(4\mu_m R^2 / R\right). \quad (27)$$

In all of the shell models, the effects of shell viscosity and elasticity are communicated to the heat deposition term primarily through the bubble dynamics. Because the heat deposition terms are strong functions of the bubble radius and bubble wall velocity, any change in the properties of the shell parameters will affect the heat deposition in the target volume.

### III. RESULTS AND DISCUSSION

The acoustic flow fields for the cases presented in this paper are obtained through axisymmetric simulations. Bubbles are distributed in a 3D cylindrical sector $[0, \theta_{sector}]$. The contribution of each bubble to the void fraction inside this 3D volume is obtained using the 3D Gaussian distribution described in Eq. (24). This 3D void fraction distribution, $\alpha(r, z)$, is then used to obtain an average axisymmetric void fraction distribution through

$$\alpha_{axi}(r, z) = \frac{1}{\theta_{sector}} \int_0^{\theta_{sector}} \alpha(r, \theta, z) d\theta. \quad (28)$$

In the Eulerian background flow computations, a CFL number of 0.1 is used for all of the simulations. The grids used in the simulations are determined primarily by the wavelength of the imposed ultrasound. It was ascertained through
numerical experiments in a previous study (Gnanaskandan et al., 2019a) that at least 20 points per wavelength are needed to capture the wave propagation with negligible dissipation. This resolution also ensures that higher harmonics are captured partially, although there is no guarantee that numerical dissipation will not affect the higher harmonics.

Results from the four different bubble interface models discussed above are presented in this paper, i.e., air bubble with the no shell (NS) model, Sarkar’s Newtonian shell (SNS), Sarkar’s non-Newtonian shell (SNNS), and Marmottant’s non-Newtonian shell (MNNS) model.

A. HIFU simulations in a polyacrylamide (PA) phantom with microbubbles

The models described above are applied to study HIFU/microbubble interactions, starting with the case of gaseous microbubbles (no shell as in contrast agents) to serve as a baseline. The simulations correspond to the in vitro experiments with the UCA microbubbles of Kajiyama et al. (2010). The schematic of the experimental setup is shown in Fig. 2. In the experiments, a spherical transducer with diameter 40 mm and focal length 40 mm was used to insonate a phantom tissue made of a PA gel at a frequency of 2.2 MHz. Levovist microbubbles with a void fraction of $1 \times 10^{-5}$ were distributed inside the gel in a cylindrical space of radius 5 mm and height 10 mm around the transducer geometric focus. The maximum diameter of the inserted microbubbles was 10 μm and the average diameter is 1.3 μm. Although the code can handle distributions of bubble sizes, in the present numerical simulations, for simplicity, we use the average diameter size of 1.3 μm for all of the microbubbles considered. This results in a concentration of $1 \times 10^7$ microbubbles/ml. The density of the phantom medium is

![FIG. 6. (Color online) Temperature contours at $t = 60$ s for the four different models considered. (a) NS model, (b) SNS model, (c) SNNS model, and (d) MNNS model with $R_{\text{buckling}} = 0.65 \mu m$ and $R_{\text{rupture}} > 1.0 \mu m$, and (e) the MNNS model with $R_{\text{buckling}} = 0.65 \mu m$ and $R_{\text{rupture}} = 0.85 \mu m$. All of the shell models use the Sonazoid UCA with shell viscosity, $\eta^s = 10^{-8}$ kg/s, and shell elasticity, $E^s = 0.51$ N/m.](https://doi.org/10.1121/10.0002948)
1060 Kg/m³, the viscosity is 0.01 Pa s, and the shear elasticity is 0.1 MPa. In the experiments, the insonation time was 60 s and the peak intensity at the focus was 1000 W/cm². Because we follow an approach that decouples the acoustic field from the thermal field, the acoustic calculations that run over a few insonation cycles with the same peak intensity as in the experiments are used to drive the thermal field, which is solved for the entire insonation time. In the simulations, acoustic calculations are carried out for 0.1 ms with time-averaging of the source terms for the heat equation over 0.01 ms. The heat equation is then solved for 60 s with the derived source terms.

The temperature rise obtained from the simulations in the focal region is compared with the experimental data in Fig. 3. In the reported experimental results, it is not exactly clear where the measurement was done in the focal region. Numerically, two locations near the geometric focus (z = 40 mm and z = 39 mm) are chosen and compared with the experiment. It can be observed that the temperature rise obtained using air bubbles with no shell is much higher than the experimental values. We have shown previously (Gnanaskandan et al., 2019a) that the primary contribution to heat deposition in bubble enhanced HIFU comes from the viscous damping of the bubble oscillations compared to the ultrasound absorption and acoustic emission. Hence, it is reasonable to conclude that the larger amplitude oscillations obtained with air bubbles as compared to shelled bubbles will lead to a larger heat deposition. This is illustrated in Fig. 4 where adding the shell dilatational viscosity and elasticity is seen to significantly affect the bubble radius variations versus time. Hence, the primary motivation of the study is to first see if the addition of the shell properties can capture the heat rise evolution better and then to understand the effects of the UCA shell properties as captured by the various models.

B. Effects of including the presence of a shell

The effects of including a shell with the bubble dynamics are studied here for Sonazoid contrast agents with the following properties (Sarkar et al., 2005): shell dilatational viscosity, \( \kappa^s = 10^{-8} \) kg/s, and shell dilatational elasticity, \( E^s = 0.51 \) N/m. Figure 5 shows the time history of the temperature at two field points close to the transducer focus using each of the three zero-thickness models introduced.

![Graph](https://doi.org/10.1121/10.0002948)
above. The results obtained with air bubbles are also plotted for comparison. In the case of the Marmottant model, two different rupture radii are considered, viz., \( R_{\text{rupture}} = 0.85 \mu m \) and any \( R_{\text{rupture}} > 1.0 \mu m \) where no rupture occurs. These values are arrived at after observing that the maximum radius of the bubble in the focal region lies in the range \( 0.8 \mu m < R_{\text{max}} < 0.95 \mu m \). Besides the microbubble properties (or model used), the grid, boundary conditions, microbubble distribution, initial conditions, and the numerical procedures are all the same for all of these cases.

Figure 5 shows that the presence of a properly acting shell immediately brings the results closer to the experimental data, thus, illustrating the importance of a shell model. Both the non-Newtonian models (SNNS and MNNS) in the absence of shell rupture result in a measurably larger reduction in temperature (when the shell does not rupture) compared to the Newtonian model. However, when the shell ruptures, it acts in the MNNS model as gas bubbles and this leads again to higher heat deposition and deviation from the experimental results. The heat rise in this case is still less than the heat rise for air bubbles as the rupture occurs only during a portion of the dynamics and not all of the UCA bubbles undergo the rupture, depending on their position in the acoustic field.

Figure 6 shows the temperature distribution in the focal regions shown as color contours obtained at the end of 60 s of insonation for all five cases. The gas bubble model (NS) shows a more extended high temperature region and the maximum heat region is ahead of the geometric focus, resulting in pre-focal heating. A similar observation can be made with the Marmottant model with rupture that predicts heat rise in the pre-focal regions. However, the maximum amount of heat is still deposited in the focal region. With the SNS, SNNS, or MNNS models without rupture, we can observe that the maximum temperature is obtained in the vicinity of the geometric focus. The magnitude of the maximum temperature, however, is different for each model. This fact is further corroborated in Fig. 7, which shows the variation of temperature along the axis of the transducer at \( t = 60 \) s. One can clearly observe the temperature peak for the gas microbubbles at \( z = 36 \) mm, whereas for all of the other models, it is in the vicinity of \( z = 40 \) mm, the geometric focus.

The change in the temperature field for shelled microbubbles can be explained by examining the microbubbles’ behavior. We examine two representative bubbles: one at the front edge of the cloud along the path of the ultrasound and the other near the geometric focus. In Fig. 8, the behavior of the bubble at the cloud front edge (\( z = 36 \) mm) is compared for different models by showing both the bubble radius evolution and the bubble interface velocity evolution. Several cycles are plotted for both quantities. It is evident that the gas microbubbles oscillate with much higher amplitudes while the shelled microbubbles show considerably smaller amplitude oscillations. Even with rupture considered, since the bubble at the cloud edge does not undergo rupture (due to their radius not exceeding rupture threshold), the oscillations of the MNNS model with rupture is similar to that of the MNNS model without rupture. Large amplitude oscillations of the bubbles at the front edge of the cloud can lead to acoustic shadowing, resulting in the focal region experiencing much smaller pressures than in absence of bubbles. Large amplitude oscillations at the cloud front edge also result in heat deposition at the cloud edge, which corroborates the heating peak observed at \( z = 36 \) mm for gas microbubbles. The evolution of the bubble interface velocity also shows a similar behavior with the gaseous bubble experiencing large bubble interface velocities. Bubble wall velocities for shelled microbubbles are reduced in the pre-focal region as compared to the gaseous bubble wall.
velocities. The differences in bubble behavior at the cloud front edge between the various shell models investigated is not significant.

Figure 9 shows the bubble behavior for a bubble located close to the focus at \( z = 39 \text{ mm} \). The radius evolution in Fig. 9(a) shows that both the gaseous bubble (NS) and the shelled Newtonian bubble (SNS) models exhibit higher oscillations as compared to the two viscoelastic models (SNNS and MNNS). The higher oscillations of the shelled Newtonian bubble model (SNS) explain the higher temperature obtained at the focus compared to the other two non-Newtonian models. This result indicates the importance of using a shell elasticity with a non-Newtonian rheology to predict better heat deposition with Sonazoid UCAs. When rupture occurs, the bubble oscillations become comparable to those of an air bubble or a Newtonian shell. This is evident in the sudden increase in the amplitude of oscillations once the rupture threshold is reached due to the reduced surface tension post rupture. No significant difference is observed between the two viscoelastic models SNNS and MNNS, indicating the insensitivity of the results to the elastic model used as long as the microbubbles are not assumed to be ruptured. The increased amplitude of oscillations with the SNS model, however, is not due to a much different pressure environment encountered by the bubble when compared to the SNNS and MNNS models as evidenced by Fig. 9(b). This is not the case for the gaseous bubbles and ruptured bubbles in MNNS, which are subjected to lower pressures than the other models due to acoustic shielding.

C. Comparison between Sonazoid and Optison UCAs

Since the shell properties of the Levovist contrast agent used in the experiment conducted by Kajiyama et al. (2010) is not available, two different contrast agents, viz., Sonazoid and Optison are considered here and the MNNS model is used to ascertain the effect of the actual contrast agent used. The properties of Optison are as follows (Sarkar et al., 2005): shell viscosity, \( \kappa^\prime = 7 \times 10^{-8} \text{ kg/s} \), and shell elasticity, \( E^\prime = 0.7 \text{ N/m} \). The shell of the Optison contrast agent is more viscous and elastic than that of Sonazoid and, hence, the radial oscillations of Optison are expected to be more damped and to result in lower heat deposition in the focal region. Due to the increased shell viscosity and elasticity of Optison, the maximum radius of the bubbles even in the focal region does not exceed the rupture threshold of 0.8 \( \mu \text{m} \). For this reason, the MNNS model with and without rupture considers exactly the same results for the Optison UCA as illustrated in Fig. 10.

However, for Sonazoid, the MNNS model with and without rupture gives different results as per the reasons explained above.

The reduced oscillations of Optison are clearly seen in Fig. 11(a). Sonazoid with rupture exhibits maximum oscillations while Optison exhibits the most damped oscillations. The pressures encountered by a bubble very close to the focus for each UCA is shown in Fig. 11(b). This illustrates that the pressure environment experienced by the bubbles is not much different and leads to the conclusion that the reduced bubble oscillations are primarily due to the shell properties as long as the shell is not ruptured. Figure 12 shows the temperature history at the focus compared to the experimental results. The results obtained with the Optison contrast agent agree well with the experimental data, indicating that the properties of the contrast agent used in the experiment (Kajiyama et al., 2010) are probably closer to Optison.

D. Effect of shell properties

UCAs play an important role in enhancing heat deposition at the focus, and the shell properties determine the
magnitude of the heat enhancement. In this section, we ascertain the influence of shell viscosity, \( \kappa_s \), and elasticity, \( E^s \), on the temperature to understand which property affects heat deposition more using the Sarkar non-Newtonian model.

Figure 13 shows the temperature evolution at the focus for three different values of shell viscosity, \( \kappa_s \), viz., \( 7 \times 10^{-8} \), \( 3 \times 10^{-8} \), and \( 1 \times 10^{-8} \) kg/s. For all three cases, the shell elasticity, \( E^s \), is maintained at 0.7 N/m. Reducing the shell viscosity, \( \kappa_s \), from \( 7 \times 10^{-8} \) to \( 3 \times 10^{-8} \) (by 57%) enhances the temperature rise by about 50%, whereas reducing it further to \( 1 \times 10^{-8} \) enhances the temperature rise by 160%.

Figure 14 shows the temperature evolution when the shell elasticity, \( E^s \), is modified while keeping the shell viscosity, \( \kappa_s \), constant at \( 7 \times 10^{-8} \) kg/s. It is seen that even decreasing the elasticity by 85% does not lead to a significant rise in temperature as compared to changing the same percentage of the shell viscosity. This implies that a contrast agent’s shell viscosity plays a more important role than the shell elasticity in determining the bubble enhanced heat deposition. Thus, while designing contrast agents for bubble enhanced heating, shell viscosity should be used as a design parameter to maximize heat deposition.
FIG. 14. (Color online) Temperature history for the Optison contrast agent using different values of shell elasticity and the SNNS model. The shell viscosity $\eta$ is fixed at $7 \times 10^{-8}$ kg/s.

IV. CONCLUSIONS

The effect of the presence of a shell on contrast agents in microbubble enhanced HIFU is studied numerically using an Eulerian-Lagrangian model. The nonlinear acoustic field, modeled in an Eulerian framework, is coupled to a bubble dynamics solver in which the individual bubbles are tracked in a Lagrangian framework.

The heat deposition obtained at the focus using different zero-thickness shell models are compared to the heat deposition obtained when no shell model is used. In the absence of a shell, the bubbles at the front edge of the cloud (away from the focus and closer to the transducer) are seen to exhibit high amplitude oscillations, resulting in acoustic shielding of the incoming ultrasound and pre-focal heating. However, with the inclusion of the shell, only bubbles in the focal region are seen to exhibit high amplitude oscillations, resulting in focal heating. It is also observed that Newtonian models that lump the shell elasticity effects into the surface tension term predict notably higher temperatures at the focus compared to non-Newtonian models as a result of enhanced bubble oscillations. This illustrates the importance of an accurate non-Newtonian shell model. Inclusion of the UCA rupture in the Marmottant model drastically alters the behavior of the ruptured bubbles as compared to the unruptured bubbles and results in an increased heat deposition. However, since all bubbles do not rupture, the heat rise is still less than that obtained when no shell model is used.

Two different contrast agents (Sonazoid and Optison) are then used and their behaviors are studied using a non-Newtonian model. It is observed that the oscillations of Optison are much more damped as compared to Sonazoid, leading to a smaller heat deposition at the focus. Finally, the influence of the shell parameters, specifically the shell viscosity and shell elasticity in heat deposition, is studied. It is observed that modifying shell viscosity has a larger effect in modifying the heat deposition, whereas changing the shell elasticity has relatively minor effects. Thus, while designing contrast agents for the purpose of the bubble enhanced HIFU, the shell viscosity should be minimized to obtain the maximum heat deposition.

While the presence of a shell model improves the agreement between experiments and simulations considerably, there is still some discrepancy, and further studies are needed to elucidate the uncertainties both in the simulations and experiments to explain this inconsistency.

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