THREE-DIMENSIONAL MODELING OF THE DYNAMICS OF THERAPEUTIC ULTRASOUND CONTRAST AGENTS

Chao-Tsung Hsiao, Xiaozhen Lu, and Georges Chahine
Dynaflow Inc., Jessup, MD

Abstract

A 3-D thick-shell contrast agent dynamics model was developed by coupling a finite volume Navier-Stokes solver and a potential boundary element method flow solver to simulate the dynamics of thick-shelled contrast agents subjected to pressure waves. The 3-D model was validated using a spherical thick-shell model validated by experimental observations. We then used this model to study shell break-up during nonspherical deformations resulting from multiple contrast agent interaction or the presence of a nearby solid wall. Our simulations indicate that the thick viscous shell resists the contrast agent from forming a re-entrant jet, as normally observed for an air bubble oscillating near a solid wall. Instead, the shell thickness varies significantly from location to location during the dynamics, and this could lead to shell break-up caused by local shell thinning and stretching.

Keywords

Ultrasound contrast agent; Encapsulated microbubble; Bubble dynamics; Numerical modeling; Drug delivery

INTRODUCTION

Ultrasound contrast agents (UCAs) are encapsulated microbubbles usually formed of a high-molecular-weight gas core and a viscous shell (Raisinghangi and Demaria 2002). A wide variety of materials have been used for the shell material such as oils, lipids, rigid polymers and albumins. UCAs, originally developed to enhance diagnostic imaging, have recently been incorporated into therapeutic applications. The capability of delivering drug to the targeted area makes therapeutic UCAs attractive to chemotherapy drug development because many chemotherapy drugs are toxic to normal tissues. For therapeutic UCAs, the drug is suspended within a highly viscous thick liquid shell (Unger et al. 1998). The highly viscous shell stabilizes the encapsulated bubble and remains inert until the contrast agent reaches a specific target. The encapsulated microbubble is then excited with an appropriate acoustic amplitude and frequency to force the shell to break and release the drugs or gene (Ferrara et al. 2007; Mayer and Bekeredjian 2008). A correct selection of shell material and thickness and an appropriate use of ultrasound renders the contrast agents powerful targeted drug delivery vehicles.

Characterization and understanding of the fragmentation mechanism of a contrast agent is pivotal to its use for drug delivery. The ultrasonic fragmentation threshold depends on the initial size, shell thickness and shell and gas properties (Ferrara et al. 2007; Chen et al. 2003;
May et al. 2002; Chang et al. 2001). Using a high-intensity source, a large number of cycles may be applicable to all types and sizes of contrast agents but cannot be applied safely in a clinical environment. Understanding the forces involved in the break-up of a particular type of agent is therefore paramount to avoiding expensive and lengthy trial-and-error experiments, and to minimizing risk to patients. Presently, however, the dynamic mechanisms involved in shell break-up are not well understood. Studies based on instability analysis of a spherical model (Prosperetti 1984; Plesset and Mitchell 1956) have shown that break-up of a bubble may commence as deviations from spherical shape growing to the size of the bubble radius. A stability analysis was conducted by Hsiao et al. (2007) for a thick-shelled bubble and showed similar trends.

However, shell break-up mechanisms may become even more complicated when the contrast agent “bubble” interacts with other agents and/or nearby tissues. From previous studies on bubble dynamics (Chahine 1974; Crum 1979; Chahine 1982, 1993; Zhang et al. 1993), it is known that an oscillating bubble near a boundary may form a re-entrant jet during its nonspherical collapse depending on its distance to nearby bubbles and boundaries. A similar behavior is expected with the UCAs. Indeed, microjetting and microstreaming associated with the agent violent nonspherical break-up have been hypothesized as mechanisms to enhance drug delivery (Miller 2000).

Many studies have been dedicated to developing numerical models for ultrasound contrast agents. Many models stem from Church’s pioneering work (Church 1995). By modeling albumin as a linear elastic solid with an additional viscous dissipative component, the constitutive equation of the shell was simplified and incorporated into a generalized Rayleigh-Plesset formulation, with a balance of the radial stress at the solid-liquid interface. The resulting model has been adapted to study the effect of the encapsulating shell properties on the microbubble dynamics (Hoff et al. 2000; Allen et al. 2003) and to estimate the acoustic nonlinearities of the liquid containing encapsulated microbubbles (Ma et al. 2004). Marmottant et al. (2005) modeled the shell break-up for a monolayer lipid contrast agent by introducing a critical shell tension, above which gas is assumed to be directly exposed to water. More recently, Sarkar et al. (2005) proposed a further refined model. The assumption of a thin, solid shell is reasonable for contrast agents designed for imaging purpose, with a very thin lipid or protein shell on the order of a few nanometers. However, prototype therapeutic contrast agents are designed with a thick liquid shell to enable drug transport (Unger 1998). Allen et al. (2003) extended Church’s model to take into account the thick liquid shell and compared their results with experimental measurements (May et al. 2002). All of the aforementioned studies are however limited to spherical agents, and no deformations were included such as what results from the interaction between the agent and its surroundings, or what happens at bursting under a strong acoustic field.

To investigate the detailed dynamic mechanisms that cause shell break-up, we have developed in the work presented here a 3-D nonspherical finite-thickness shell model that couples a Navier-Stokes solver, 3DynaFS-Vis (Dynaflow, Inc., Jessup, MD, USA) using a finite volume scheme and our potential flow solver, 3DynaFS-Bem, using a boundary element method (BEM). The computational domain was subdivided into an inner domain constituted of the thick viscous shell layer and an outer domain, that of the liquid containing the shelled bubble. In the inner domain, we solve the Navier-Stokes equations to best describe the dynamical behavior of the highly viscous liquid shell. In the outer domain, we use the BEM. The main advantage of using the BEM is its unique ability to provide a complete solution in terms of boundary values without the need to discretize the whole computational domain. This reduces the dimensions of the problem by one and allows the model to work on complicated boundary geometries and address nonspherical deformations.
Numerical models

Domain decomposition—Consider a problem in which multiple thick-shelled bubbles interact with each other and with nearby boundaries. The computational domain for this problem, as illustrated in Fig. 1, is composed of as many inner domains as there are bubbles, each made of a thick liquid shell around each gas bubble, and an outer domain covering the host liquid medium. The outer domain includes any nearby walls or free surfaces. In the model developed here, the inner domains bounded by the gas-shell interfaces and the shell-liquid interface are volume-discretized. The flow field within the shell layers is solved using the unsteady Navier-Stokes equations, whereas the flow field in the outer domain, which is much less viscous, is solved assuming a potential flow. The two solvers communicate with each other by exchanging the values of the flow variables at the shell-liquid interfaces.

Model for the Shell Liquid: Inner Domain

Governing equations—To solve the highly viscous flow in the inner domain composed of the viscous shells, the unsteady incompressible Navier-Stokes equations are used. The continuity and momentum equations in nondimensional form and Cartesian tensor notations are given as:

\begin{align}
\frac{\partial u_i}{\partial x_i} &= 0, \\
\frac{1}{Re} \frac{\partial u_i}{\partial t} + u_j \frac{\partial u_i}{\partial x_j} &= - \frac{\partial p}{\partial x_i} + \frac{1}{Re} \frac{\partial^2 u_i}{\partial x_j},
\end{align}

where \( u_i = (u, v, w) \) are the Cartesian components of the velocity, \( x_i = (x, y, z) \) are the Cartesian coordinates and \( p \) is the pressure. \( Re = \frac{\rho_s u^* L^*}{\mu_s} \) is the Reynolds number in the viscous shell, \( u^* \) and \( L^* \) are the characteristic velocity and length, \( \rho_s \) is the shell density and \( \mu_s \) is its dynamic viscosity.

We select as characteristic length the contrast agent initial inner radius. The characteristic velocity, \( u^* = \frac{L^*}{T^*} \), can be selected by two ways depending on the characteristic time, \( T^* \), which could be the inverse of the frequency of the imposed acoustic waves or could be based on \( \Delta p \) the amplitude of the imposed acoustic waves,

\[ T^* = \frac{L^*}{\sqrt{\frac{\mu_s}{\Delta p}}}. \]

In our computations, \( T^* \) was selected to be the smaller of the two choices.

The effective stress tensor \( \tau_{ij} \) is selected to be the smaller of the two.

The effective stress tensor \( \tau_{ij} \) is given by:

\[ \tau_{ij} = \left( \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) - \frac{2}{3} \delta_{ij} \frac{\partial u_k}{\partial x_k}, \]

where \( \delta_{ij} \) is the Kronecker delta. The flow field in the inner domain is directly simulated with eqns (1) and (2) without any turbulence model.
To simplify the treatment of the boundary conditions for complex geometries, eqns (1) and (2) are transformed to a general time-dependent body-fitted curvilinear coordinate system. The time-dependent nature of this transformation allows all computations to be carried out in a fixed uniform computational domain even though components of the physical domain may be in motion. The curvilinear coordinates are defined as:

\[ \tau = t, \quad \xi = \xi(x, y, z, t), \quad \eta = \eta(x, y, z, t), \quad \zeta = \zeta(x, y, z, t). \]  

(5)

The transformation provides a computational domain that is better for applying spatial differencing and the boundary conditions.

**Boundary conditions at the gas-shell interface**—The gas-shell interface is treated as a standard gas-liquid interface, which can be best described by a free-surface boundary condition, satisfying both kinematic and dynamic boundary conditions. The kinematic condition is that a particle on the surface remains on the surface. For a surface of equation \( F(x_i, t) = 0 \), this can be written \( \frac{DF}{Dt} = 0 \).

The dynamic condition imposes zero shear stress (we ignore here stress generated by the air in the bubble) and balance of normal stresses at the interface. With the same simplifications used by Batchelor (1967) for deriving the dynamic boundary condition in the Cartesian coordinate system, Hodges et al. (1996) derived a dynamic boundary condition in a curvilinear coordinate system by requiring the grid to be normal to the boundary. Following their work with a further assumption that \( \partial W / \partial \xi \) and \( \partial W / \partial \eta \) are small, we write the dynamic boundary condition at \( \zeta = 0 \) (gas-shell interface) in nondimensional form as:

\[ \left. \frac{\partial U}{\partial \xi} \right|_{\zeta=0} = 0, \]  

(6)

\[ \left. \frac{\partial V}{\partial \eta} \right|_{\zeta=0} = 0, \]  

(7)

\[ p = p_g + \frac{2}{e_{gs}} \frac{\partial W}{\partial \xi} \left|_{\zeta=0} \right. \frac{C_{gs}}{W_{e_{gs}}}, \]  

(8)

where \( (U, V, W) \) are contravariant velocity components in the curvilinear coordinates and \( C_{gs} \) is the curvature of gas-shell interface.

\[ W_{e_{gs}} = p_g u^2 L^* / \gamma_{gs}, \]  

(9)

is the Weber number, with \( \gamma_{gs} \) being the surface tension at the gas-shell interface. The term \( p_g v \) in eqn (8) is the nondimensional pressure difference between ht pressure inside the bubble and the reference pressure, \( P_\infty \)

\[ p_g = (p_g - p_\infty) / \rho_g u^2, \]  

(10)
where $p_g$ is the gas pressure, $p_v$ is the vapor pressure.

To determine the gas pressure, we assume that the amount of gas inside the bubble remains constant and that the gas satisfies the polytropic relation:

$$p_g^{1/v} \text{constant,}$$

where $v$ is the gas volume.

**Boundary condition at the shell-liquid interface**—The shell-liquid interface is a liquid-liquid interface at which the boundary conditions are continuity of the shear stresses, balance of the normal stresses and continuity of the velocity:

$$\frac{\partial U}{\partial \xi} \bigg|_{\xi=1} = \frac{\mu_l}{\mu_s} \tau_{l\xi},$$

(12)

$$\frac{\partial V}{\partial \xi} \bigg|_{\xi=1} = \frac{\mu_l}{\mu_s} \tau_{l\eta},$$

(13)

$$p - \frac{2}{R_s} \frac{\partial W}{\partial \xi} \bigg|_{\xi=1} = P_l - \frac{1}{\mu_s} \tau_{l\xi} + \frac{C_{sl}}{W_{e,sl}},$$

(14)

$$W_{|\xi=1} = u_s \cdot n,$$

(15)

where $\mu_l$ is the dynamic viscosity of the surrounding liquid, $\rho_l$ is its density, $C_{sl}$ is the curvature of the shell-liquid interface,

$$W_{e,sl} = \rho_l a^2 L^* / \gamma_{sl},$$

(16)

is the Weber number, where $\gamma_{sl}$ is the surface tension at the shell-liquid interface.

$\tau_{l\xi}, \tau_{l\eta}$ are the normal derivatives of the tangential velocity components in the $\xi$ and $\eta$ directions, respectively, at the liquid side of the interface. $\tau_{l\xi}$ is the normal derivative of the normal velocity component and $P_l$ is the pressure on the liquid side of the shell-liquid. $n$ is the local unit normal vector to the boundary and $u_s$ is the viscous liquid velocity at the boundary, which is provided by the solution of the outer domain.

In this study, we further simplify the boundary conditions and consider cases where viscosity of the shell material used for therapeutic ultrasound contrast agents is much higher than the viscosity of the surrounding liquid. This is usually the case to stabilize the contrast agent during transit. For example, ImaRx Therapeutics (Tucson, AZ, USA) has produced two types of prototype agents with a triacetin shell and a soybean oil shell. The viscosities of triacetin and soybean oil are 28 centipoise and 110 centipoise, respectively, which are much larger (at least one order larger) than the viscosity of blood (2.7 centipoise at 37°C). If the viscosity ratio $\mu_l/\mu_s$ are very small, eqns (12)–(14) can be reduced to:
Numerical approach—The 3DynaFS-Vis© code is based on the artificial-compressibility method (Chorin 1967), in which a time derivative of the pressure is added to the continuity equation as

\[
\frac{\partial U}{\partial t} = 0,
\]  

(17)

\[
\frac{\partial V}{\partial t} = 0,
\]  

(18)

\[
p + \frac{2}{\beta} \frac{\partial W}{\partial t} = P_{r,1} \frac{C_d}{W_{r,1}},
\]  

(19)

where \( \beta \) is an artificial compressibility factor. As a consequence, the hyperbolic system of equations formed can be solved using a time-marching scheme.

The solution procedure is to march in pseudo-time until reaching a steady-state solution. To obtain a time-dependent solution, a Newton iterative procedure is performed at each physical time step to satisfy the continuity equation. The numerical scheme in 3DynaFS-Vis© uses a finite volume formulation. The first-order Euler implicit difference formula is applied to the time derivatives. The spatial differencing of the convective terms uses the flux-difference splitting scheme based on Roe’s method (Roe 1981) and van Leer’s MUSCL method (van Leer 1979) for obtaining the first-order and the third-order fluxes, respectively. A second-order central differencing is used for the viscous terms. The flux Jacobians required in an implicit scheme are obtained numerically. The resulting system of algebraic equations is solved using the discretized Newton relaxation method (Vanden and Whitfield 1993) in which symmetric block Gauss-Seidel subiterations are performed before the solution is updated at each Newton interaction.

Model for surrounding liquid medium: Outer domain

Governing equations—The outer domain liquid flow as a result of the contrast agent’s motion is assumed to be irrotational and incompressible. These are conventional assumptions for bubble dynamics (Chahine et al. 1993, 1997). The assumption of irrotational flow for the outer domain allows the definition of a velocity potential, \( \phi \), such that

\[
u = \nabla \phi,
\]  

(21)

where \( \mathbf{u} \) is the velocity vector. The assumption that the liquid is incompressible leads to Laplace’s equation for the potential:
A boundary integral method is used to solve eqn (16). This method is based on an integral solution of the Laplace equation using Green’s theorem, which can be written in the following form:

$$\nabla^2 \phi = 0. \quad (22)$$

In this expression, $\Omega$ is the domain of integration having elementary volume $d\Omega$. The boundary surface of $\Omega$ is $S$, which includes the surface of the contrast agent and the nearby boundaries with elementary surface element $dS$ and local normal unit vector $n$. $\phi$ is harmonic in the fluid domain $\Omega$, and $G$ is Green’s function. If $G$ is selected to be harmonic everywhere but at some discrete points, eqn (23) simplifies considerably. For instance, if

$$\int_{\Omega} (\phi \nabla^2 G - G \nabla^2 \phi) d\Omega = \int_{S} n \cdot (\phi \nabla G - G \nabla \phi) dS. \quad (23)$$

where $x$ is a fixed point in $\Omega$ and $y$ is a point on the boundary surface $S$, eqn (21) reduces to Green’s formula, with $\alpha \pi$ being the solid angle at $x$ enclosing the domain $\Omega$:

$$\alpha \pi \phi(x) = \int_{S} n \cdot [\phi(y) \nabla G(x, y) - G(x, y) \nabla \phi(y)] dS. \quad (25)$$

$x = 4$, if $x$ is a point in the fluid,

$\alpha = 2$, if $x$ is a point on a smooth surface and

$\alpha < 4$, if $x$ is a point at a sharp corner of the discretized surface.

This equation states that if the velocity potential $\phi$ and its normal derivatives are known on the boundary surface $S$ of a domain $\Omega$, where $\phi$ satisfies the Laplace equation, then $\phi$ can be determined anywhere in $\Omega$ by integration over the boundary surface. Using this expression, the boundary integral method reduces by one the dimension of the problem of solving the Laplace equation.

**Boundary conditions**—At any given time step, if the velocity potential, $\phi$, on the boundary surface, $S$, is known, then the interface normal velocity, $\partial \phi / \partial n$, can be obtained by eqn (25). For a point $x$ on the boundary, $S$, the Bernoulli equation gives

$$P + \rho \frac{\partial \phi}{\partial t} + \frac{1}{2} \nabla \phi \cdot \nabla \phi = P(t). \quad (26)$$

where $P(t)$ is the acoustic pressure imposed and the pressure on the interface $P_l$ is obtained by eqn (19). Equation (26) provide $\partial \phi / \partial t$, and the rate of change in potential at a given point followed in its motion can be obtained by

$$\frac{D \phi}{Dt} = \frac{\partial \phi}{\partial t} + \mathbf{u} \cdot \nabla \phi. \quad (27)$$
where \( \mathbf{u}_s \) is the shell velocity at the shell-liquid interface as defined in eqn (15). Because no liquid is allowed to cross the shell-liquid interface, the normal velocity component of the shell velocity at the interface must be equal to the normal velocity component of the liquid, i.e.,

\[
\mathbf{u}_s \cdot \mathbf{n} = \frac{\partial \mathbf{g}}{\partial n}.
\]  

(28)

**Numerical approach**—To solve eqn (25) numerically with the boundary element method, it is necessary to discretize the surfaces of all objects. As a result of this discretization, every surface integral evaluated at any field point \( x \) becomes a summation over all panels of the influence of singularity distributions over each individual panel. This enables us to write Green’s identity in the form

\[
a \pi \phi(x) = \sum_{s=1}^{M} \int_{S_i} \left( \phi(y) \frac{\partial G}{\partial n}(x,y) - G(x,y) \frac{\partial \phi}{\partial n}(y) \right) dS_s.
\]  

(29)

where \( M \) is the number of surface elements on the boundary. To evaluate the integrals given in eqn (29), it is necessary to assume a relation between the values of \( \phi \) and \( \frac{\partial \phi}{\partial n} \) at a surface node with the values of these quantities at the discretized nodes. Here, we assume that these quantities vary linearly over a panel and can be described by the surrounding nodes. By applying a linear interpolation for each panel \( S_k \), each elementary integral can be written as a linear combination of the values of \( \phi \) or \( \frac{\partial \phi}{\partial n} \) at the surrounding nodes. The integration expressions are complex, and details can be found in our previous studies (Chahine et al. 1989). With the integration over each panel performed, the discretized eqn (29) can be expressed as:

\[
a \pi \phi = \sum_{s=1}^{M} \sum_{j=1}^{N} \left[ B^i_k \phi_i - A^i_k \left( \frac{\partial \phi}{\partial n} \right)_i \right], \quad j=1, N,
\]  

where \( \phi_i \) and \( \frac{\partial \phi}{\partial n}_i \) are the potential and its normal derivative at node \( i \) of panel \( k \), and \( A^i_k \) and \( B^i_k \) are influence coefficients obtained from elementary integration and \( N \) is the total number of nodes.

Following a “collection” approach in which the contributions caused by the same node are collected from the various contiguous elementary surfaces and summed up, eqn (30) can be rewritten as

\[
a \pi \phi = \sum_{i=1}^{N} \left[ B_i \phi_i - A_i \left( \frac{\partial \phi}{\partial n} \right)_i \right], \quad j=1, N.
\]  

(31)

where \( A_i \) and \( B_i \) are the altered influence coefficients as a result of summation of the same node. It is noted that the “collection” approach transfers panel contributions in eqn (30) to node contributions in eqn (31). Equation (31) can be expressed in a matrix form as:
where I is an $N \times N$ identity matrix, and $\bar{A}$ and $\bar{B}$ are $N \times N$ influence coefficient matrices. With $\phi$ known on all boundary nodes, eqn (32) is a linear system of $N$ equations and can be readily solved for $N$ unknowns of $\partial \phi / \partial n$, using classical methods such as LU decomposition (a matrix decomposition which writes a matrix as the product of a lower triangular matrix and an upper triangular matrix) and Gauss elimination.

**Coupling between inner and outer domain**

The boundary conditions given by eqns (15), (19) and (26) are key for coupling the Navier-Stokes solver and the potential flow solver. The procedure is illustrated in Fig. 2 and is summarized as follows:

i. A volume grid is generated within each inner domain to discretize the shells according to the shape of the gas-shell interfaces and of the shell-liquid interfaces.

ii. The Navier-Stokes equations are solved for the velocity and pressure fields in the inner domains using the boundary conditions specified at the gas-shell interfaces with the gas pressure, $p_g$, and the shell-liquid interfaces with the normal velocity $u_s \cdot n = \partial \phi / \partial n$ provided by the potential solver. The gas-shell interface and the shell-liquid interface are updated according to the kinematic boundary condition and the boundary pressure $P_l$ is calculated.

iii. The discretized Green’s equation is solved for the normal velocity, $\partial \phi / \partial n$, on the boundary surfaces knowing the velocity potential, $\phi$. Using the boundary conditions specified at the shell-liquid interface with the boundary pressure, $P_l$, provided by the Navier-Stokes solver, the rate of change of the potential, $D \phi / Dt$, is obtained and the velocity potential, $\phi$, at the next time step is updated.

**Volume and surface grids**

To solve the Navier-Stokes equations using the finite volume scheme, we discretize each inner domain describing the viscous thick shell using an O-type grid as shown in Fig. 3. For most computations, we select a grid number of 41 in the azimuthal direction, 21 in the latitude direction, and 25 in the radial direction. The grid is evenly distributed in both azimuth and latitude directions while it is clustered near the air/shell and shell/liquid interface in the radial direction. Concerning the outer domain, we use two types of grids shown in Fig. 4: an O-type structured grid and a triangular panel unstructured grid to represent the bubble outer surface. In the O-type structured grid, the grid points are the same as those in the outer surface of the grid used in 3DynaFS-Vis© so that the exchange of variables between 3DynaFS-Vis© and 3DynaFS-Bem© is straightforward. However, because the singular points on the two poles result in low numerical precision in 3DynaFS-Bem©, we used the unstructured grid to solve the BEM problem. For the results shown next, we used a total number of 402 nodes and of 800 panels for the unstructured surface grids. Because the grid points are not the same as those used in the viscous code, the communication of the variables between 3DynaFS-Vis© and 3DynaFS-Bem© requires interpolation between the two grid systems and additional CPU time. However, using this unstructured grid is stable and avoids having singular unstable points as with the O-type grid.
RESULTS AND DISCUSSION

Spherical model and validation with experimental measurements

We have derived and implemented a spherical thick-shell model similar to that derived by Allen et al. (2002). The derivation and resulting equations can be found in (Hsiao et al. 2007). We validated this model against experimental results (May et al. 2002) and then used it to validate the 3-D shell model at different insonation conditions. We consider a driving acoustic pressure, \( P(t) \), with the following format:

\[
P(t) = P_{atm} - P_a \sin(2\pi ft),
\]

where \( P_{atm} \) is the ambient pressure, \( P_a \) is the amplitude and \( f \) is the frequency. The bubble is initially at equilibrium when the initial gas pressure, \( p_{g0} \), is written as

\[
p_{g0} = \frac{2\gamma_1}{R_{10}} + \frac{2\gamma_2}{R_{20}} + p_v,
\]

where \( p_v \) is the vapor pressure of shell liquid, \( \gamma_1 \) and \( \gamma_2 \) are the surface tension at gas-shell and shell-liquid interfaces, respectively, and \( R_{10} \) and \( R_{20} \) are the initial shell inner and outer radius, respectively.

In the present study, we consider a triacetin-shelled bubble in water and have the following liquid properties: triacetin density \( \rho_1 = 1100 \, \text{kg/m}^3 \), viscosity \( \mu_1 = 0.028 \, \text{kg/ms} \), surface tension at gas-triacetin interface \( \gamma_1 = 0.008 \, \text{kg/s}^2 \), water density \( \rho_2 = 1100 \, \text{kg/m}^3 \), viscosity \( \mu_2 = 0.001 \, \text{kg/ms} \), surface tension at triacetin-water interface \( \gamma_2 = 0.06 \, \text{kg/s}^2 \). Unless specified explicitly, we set the initial bubble radii \( R_{10} = 1.2 \, \mu\text{m}, R_{20} = 1.7 \, \mu\text{m} \) for all the results shown next.

Figure 5 shows a 2-D optical streak image from Allen et al. (2002) of a triacetin-shelled bubble insonified by an acoustic pulse with a transmitted center frequency of 2.5 MHz and peak negative pressure of 1.6 MPa shown in the top of the figure from a hydrophone recording of the transmitted signal. The initial bubble radius was 1.7 \( \mu \text{m} \). In Fig. 5a, our numerical solution is laid over the optical image. A quantitative comparison of the time history of the radius of the contrast agent is shown in Fig. 5b. It can be seen that the spherical model reasonably captures the contrast agent oscillation amplitude and period except, as expected, when the breakup occurs.

Validation of the 3-D model using spherical contrast agent dynamics

Small amplitude driving pressure—To validate our 3-D numerical model, we first simulate the motion of a triacetin-shelled contrast agent driven by an acoustic pressure in an infinite medium. In this case, in absence of radial perturbations, the bubble remains spherical during the oscillations and the results should be the same as those predicted using a spherical model. Figure 6 shows a comparison between the 3-D and spherical models. This is illustrated using the inner and outer radial motions of the shell driven by a sinusoidal acoustic wave with \( P_a = 0.1 \, \text{Mpa} \) and \( f = 3 \, \text{MHz} \) at an ambient pressure of 0.1 Mpa. The initial inner radius of the shell is \( R_{10} = 1.2 \, \mu\text{m} \) and the outer radius is \( R_{20} = 1.7 \, \mu\text{m} \). The comparison shows that the 3-D numerical results agree very well with the spherical solution with very small differences resulting from the nonperfect discretization of the sphere.

Large amplitude driving pressure—Figures 7 and 8 show the radial motion of the contrast agent bubble driven at \( f = 2.5 \, \text{MHz} \), with \( P_a = 0.5 \, \text{MPa} \) and 1 MPa, respectively. Here
the pressure amplitudes are much larger than in the previous case and bubble oscillations are more intense. During the first period, there are large differences between the 3-D results and the spherical model results. The 3-D code exhibits more damping than the spherical model during the transient period and may require further of the time-stepping scheme at the start of the dynamics. However, the results become very close after the first bubble oscillation period.

Figure 9 show the comparison of the minimum shell thickness between the 3-D and results at three different frequencies for the first and second bubble periods. The lines show the spherical model predictions, whereas the symbols show the 3-D numerical simulations. The differences of the numerical results in the first period are about 10%, whereas they drop to 1% for the second maxima. With small amplitudes, the 3-D numerical solution agrees very well with the spherical solution, whereas for large amplitudes, the numerical solution agrees with the spherical solution much better after the second bubble period.

Simulation of contrast agent dynamics near a rigid wall

When a contrast agent bubble oscillates near a wall, its dynamics deviate from spherical oscillations. To simulate contrast agent dynamics near a wall, a rigid boundary condition is added in the outer computational domain. There are two ways of doing this: one way is to actually discretize the solid wall with a boundary element mesh in addition to the contrast agent. The other is to indirectly account for the wall by adding an image of the contrast agent relative to the wall, as show in Fig. 10. For the simulations next, we have used the image method.

Small-amplitude driving pressure—With a small-amplitude driving pressure, the nonspherical deformations are small; however, the motion of the volume center of the contrast agent (based on the shell/liquid interface) is not negligible. Figure 11 shows the x-coordinates of the shelled bubble center, \(X_{CV}\), when the bubble is driven at \(P_{atm}=0.1\) Mpa, \(P_{a}=0.1\) Mpa and \(f=3\) MHz in the presence or absence of a rigid wall. The contrast agent initial inner and outer radii are \(R_{10}=1.2\) \(\mu\)m and \(R_{20}=1.7\) \(\mu\)m, respectively. The contrast agent is initially located at \(X=0\) and the wall is located at \(X=1.715\) \(\mu\)m. The figure shows that the shelled-bubble center location moves away from the wall during its expansion and gets closer to the wall during its compression. However, the cumulative effect is for the bubble to move closer to the wall at each cycle.

Large-amplitude driving pressure—The nonspherical deformations caused by wall effects become much more significant and interesting as the driving pressure amplitude becomes higher. It is known from previous studies (Chahine 1993, 1982; Zhang et al. 1993) that nonspherical dynamics can result in the formation of reentrant jets directed toward rigid walls or moving away from free surfaces (Chahine 1977). To study the effect of a rigid wall on contrast agent dynamics, we present next 3-D numerical simulations for an acoustically excited contrast agent oscillating near a rigid wall at three different initial standoffs, \(X=5.6, 3.6\) and \(2.6\) \(\mu\)m. The contrast agent initial inner radius is \(R_{10}=1.2\) \(\mu\)m and its outer radius is \(R_{20}=1.7\) \(\mu\)m.

Figures 12 through 14 show for the three standoffs the contrast agent shape time variations during the first oscillation period. Also shown are the pressure contours in the viscous liquid of the shell. All shapes are shown in a cut plane perpendicular to the wall and going though the bubble center. The shelled bubble was initially in a uniform pressure field with \(P_{atm}=0.1\) Mpa, and was subjected to a sinusoidal acoustic wave with \(P_{atm}= 1\) Mpa and \(f= 2.5\) MHz. As expected, the smallest standoff case has the most significant nonspherical deformations. The presence of the wall imparts a nonspherical pressure distribution on the shell, which
deforms it nonspherically. More importantly, the dynamics lead to a nonuniform shell liquid thickness distribution during the collapse. During the bubble growth phase, the shell retains a more or less uniform thickness, then becomes thicker and thicker on the side opposed to the wall, where a jet usually takes place. Concurrently, the shell becomes thinner and thinner at the side nearest the wall, potentially leading to starvation of the shell liquid and potential break-up. Using a linear stability analysis (Hsiao et al. 2007), we have also confirmed that the most unstable mode caused by a 3-D perturbation of the spherical shape is when the bubble forms a jet at one end and breaks up on the other end.

The simulations for the $X = 2.6$ and $3.6 \mu m$ cases, however, were terminated because of numerical instability as the shell became extremely thin and the 3-D grid became overly squeezed, whereas the simulation for the $X = 5.6 \mu m$ case was able to continue and the rebound was observed. Figure 15 shows the grid near the end of the simulation at the time before the simulation was terminated for the case of $0.26-\mu m$ standoff. It can be seen that the grid is forced to be normal to the boundaries locally.

Figure 16 illustrates the contrast agent shape variations and normal velocity contours at three time steps as seen in the outer domain in which two contrast agents are present as a result of the plane of symmetry used for $X = 2.6 \mu m$ cases. In the figures, the second set is at the time the contrast agent grew to its maximum size, and the third set is the last time step before the simulations were terminated.

Figure 17 shows a comparison of the time history of the contrast agent two equivalent radii (inner and outer) for the three standoff cases. It is seen that the presence of the wall only has a slight influence on the maximum size of the contrast agent, but a strong influence on the variation of the shell thickness. The time history of the shell thickness at polar location close to the wall side for the three cases is shown in Fig. 18.

Figure 19 shows the solutions with the velocity vectors plotted on both shell/liquid and shell/gas interfaces at the last time step before the simulations were terminated for the $X = 2.6$ and $X = 3.6 \mu m$ cases. Figure 20 shows the solutions at the time steps before and after the rebound for the $X = 5.6 \mu m$ cases. It is seen that, at the time the computations stopped for the $X = 2.6$ and $X = 3.6 \mu m$ cases, a re-entrant jet with a high normal velocity was just starting to form at the thick-shell side while the shell was stretching with a high tangential component of velocity at the thin-shell side. Continuous shell thinning and stretching at the near-wall side may indicate the tendency of the shell to break up here. For the $X = 5.6 \mu m$ case, the shell remained thick everywhere and was not stretched near the wall side. As a result, the contrast agent was able to rebound after reaching its minimum volume.

**Simulations of contrast agent dynamics between two rigid walls**—To demonstrate the capabilities of the developed 3-D model, we have simulated the dynamics of two contrast agent bubbles located between two discretized walls separated by a distance of $12 \mu m$ (Fig. 21). The shelled bubbles were subjected to a sinusoidal acoustic wave with $P_{atm}=0.1$ Mpa, $P_a=1$ Mpa and $f=2.5$ MHz. Figure 22 shows the contrast agent shape variations and pressure contours during the first oscillation period. It is seen that the presence of the two walls leads the contrast agent to oscillate in ellipsoid shapes from oblate to oblong with the axes switching between horizontal and vertical directions during growth and collapse. Figure 23 shows the contrast agent shape variations and normal velocity contours at two time steps.
CONCLUSIONS

In this study, we have considered the dynamics of thick viscous shell contrast agents. We have developed a 3-D thick viscous shell model where the dynamics of the shell material was followed using a Navier-Stokes solver, and the dynamics of the overall bubble was described with a boundary element method. This shell model allowed us to simulate multiple contrast agent dynamics and their interactions with nearby solid walls. We have validated this model with experimental results available in the literature for spherical deformations. Further validation is needed for nonspherical deformations.

We also exercised this model under different conditions and have derived the following conclusions:

- The thick viscous shell resists the contrast agent forming a re-entrant jet toward a nearby boundary.
- The shell thickness varies significantly from location to location during the thick shell dynamics.
- The thick shell of the contrast agent may break because of local shell thinning and stretching.

Our simulations seem to indicate that in the presence of a wall or another interacting contrast agent, shell thinning and potential for breakup may occur on the shell side nearest to the wall or to the other agent.

Acknowledgments

This work was supported by the National Institute of Biomedical Imaging and Bioengineering under SBIR Phase I and Phase II program.

References

Allen, JS.; Kaneko, Y.; Yoshizawa, S.; Matsumoto, Y. Development and application of contrast agent model. Osaka, Japan. Fifth International Symposium on Cavitation; November 1–4 2003;


Hsiao, CT.; Lu, XZ.; Chahine, GL. Dynaflow, Inc. Report 2M6018-NIH-1. 2007. 3D Modelling of the dynamics of therapeutic ultrasound contrast agents.


Vanden K, Whitfield DL. Direct and iterative algorithms for the three-dimensional Euler equations. AIAA-93–3378. 1993

Fig. 1.
Sketch for illustration of the thick shell bubble problem with domain decomposition.
Fig. 2.
Flow chart of the numerical procedure for coupling the Navier-Stokes solver, 3DynaFS®-Vis and the potential flow solver, 3DynaFS-Bem®.
Fig. 3.
O-type grid used in 3DynaFS-Vis© for the liquid shell (inner domain).
Fig. 4.
The two types of grids used in the outer domain for the 3DynaFS-Bem computations: (a) O-type structured grid, (b) unstructured triangular-panels grid.
Fig. 5.
Comparison of the spherical thick shell model results with a steak image of a triacetin-shell bubble with initial radius of 1.7 μm under insonation at 2.5 MHz and 1.6 MPa, (a) overlaid numerical solution and image of bubble outer shape and hydrophone recording of transmitted pulse, (b) comparison of time history of contrast agent outer radius.
Fig. 6.
A triacetin-shelled bubble driven by a sinusoidal acoustic wave with $P_a = 0.1$ Mpa, $P_{atm} = 0.1$ Mpa and $f = 3$ MHz. Comparison between 3-D and spherical solutions for inner and outer radius.
Fig. 7. A triacetin-shelled bubble driven by a sinusoidal pressure with $P_a = 0.5$ Mpa, $P_{atm} = 0.1$ Mpa and $f = 2.5$ MHz. Comparison between 3-D and spherical solutions for inner and outer radius.
Fig. 8.
A triacetin-shelled bubble driven by $P_a = 1$ Mpa, $P_{atm} = 0.1$ Mpa and $f = 2.5$ MHz. Comparison between 3-D and spherical solutions for inner and outer radius.
Fig. 9.
Comparison of the minimum shell thickness during (a) the first bubble period and (b) the second bubble period.
Fig. 10.
Geometrical setup of the contrast agent dynamics near a wall using an image bubble.
Fig. 11.
The location of the center of gravity of the contrast agent driven near a wall located at $X = 1.715 \mu m$ by a sinusoidal acoustic wave with $P_a = P_{atm} = 0.1$ Mpa and $f = 3$ MHz.
Fig. 12.
Contrast agent shape variations and pressure contours near a rigid wall as seen in the inner domain when subjected to a sinusoidal acoustic wave with $P_a = 1$ Mpa, $P_{atm} = 0.1$ Mpa and $f = 2.5$ MHz at an initial standoff of 5.6 $\mu$m during (a) growth and (b) collapse with $R_{10} = 1.2$ $\mu$m, $R_{20} = 1.7$ $\mu$m.
Fig. 13.
Contrast agent shape variations and pressure contours near a rigid wall when subjected to a sinusoidal acoustic wave with $P_a = 1$ Mpa, $P_{atm} = 0.1$ Mpa and $f = 2.5$ MHz at an initial standoff of $3.6 \mu m$ using (a) growth and (b) collapse with $R_{10} = 1.2 \mu m$, $R_{20} = 1.7 \mu m$. 
Fig. 14.
Contrast agent shape variations and pressure contours near a rigid wall when subjected to a sinusoidal acoustic wave with $P_a = 1$ Mpa, $P_{atm} = 0.1$ Mpa and $f = 2.5$ MHz at an initial standoff of $2.6 \mu m$ during (a) growth and (b) collapse with $R_{10} = 1.2 \mu m$, $R_{20} = 1.7 \mu m$. 
Fig. 15.
Grid construction inside a deformed shell. (a) Overall view; (b) zoom in the left upper corner.
Fig. 16.
Contrast agent shape variations and normal velocity 3-D contours at three times as seen in the outer domain. Excitation sinusoidal acoustic wave with $P_a = 1$ Mpa, $P_{atm} = 0.1$ Mpa and $f = 2.5$ MHz at an initial standoff of 2.6 $\mu$m during with $R_{10} = 1.2 \mu$m, $R_{20} = 1.7 \mu$m.
Fig. 17.
Contrast agent inner and outer equivalent radius *versus* time for three different standoff cases.
Fig. 18.
The time history of the shell thickness at a polar location close to the wall for three different standoff cases.
Fig. 19.
Contrast agent shape near a wall at the last time step before the simulations were terminated for (a) \( X = 2.6 \) and (b) 3.6 \( \mu m \) cases. The velocity vectors are shown plotted on both the shell/liquid and the shell/gas interface.
Fig. 20.
Contrast agent shape near a wall at the time steps before and after rebound for the $X = 5.6 \mu m$ case. The velocity vectors are shown plotted on both the shell/liquid and the shell/gas interfaces.
Fig. 21.
Numerical setup of the outer computational domain.
Fig. 22. Contrast agent shape variations and pressure contours for two contrast agents in between two walls and subjected to a sinusoidal acoustic wave with $P_a = 1$ Mpa, $P_{atm} = 0.1$ Mpa and $f = 2.5$ MHz during (a) growth and (b) collapse during the first oscillation period.
Fig. 23.
Contrast agent shape variations and normal velocity contours for two contrast agents in between two walls at two time steps. Excitation by a sinusoidal acoustic wave with $P_a = 1$ Mpa, $P_{atm} = 0.1$ Mpa and $f = 2.5$ MHz.