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MODELING MICROBUBBLE DYNAMICS IN BIOMEDICAL APPLICATIONS*

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Abstract

Controlling microbubble dynamics to produce desirable biomedical outcomes when and where necessary and avoid deleterious effects requires advanced knowledge, which can be achieved only through a combination of experimental and numerical/analytical techniques. The present communication presents a multi-physics approach to study the dynamics combining viscous- in-viscid effects, liquid and structure dynamics, and multi bubble interaction. While complex numerical tools are developed and used, the study aims at identifying the key parameters influencing the dynamics, which need to be included in simpler models.

Keywords

microbubble; biological; contrast agents; thick shell; ultrasound

Introduction

Microscopic bubbles are ubiquitous in nature and could interact significantly with their environment once excited. Extensive studies have elucidated these effects in diverse fields of application, e.g., ocean acoustics^[1], hydrodynamics^[2], sound and erosion structure protection^[3,4], environmental technologies^[5], and medical and biological applications^[6,7].

In biological media, either naturally suspended microbubbles or man-made introduced contrast agents, can be activated through ultrasound application or as a result of significant changes in the ambient pressure due to high accelerations (astronauts, jetfighter pilots) or to rapid changes in the depth of submergence (divers, submariners). Application of ultrasound is now a common practice in medicine for both diagnostic and therapeutic use. Main applications include: sonography, Shock Wave Lithotripsy (SWL), tissue ablation, ultrasound mediated drug delivery, wound healing and tissue regeneration. High Intensity Focused Ultrasound (HIFU) is very successful in the treatment of tumors. However, numerous studies have also established that the cavitation activity could result in deleterious bio-effects such as hemolysis and hemorrhage^[8–14] resulting from ultrasound-based medical treatments such as SWL or HIFU. SWL can produce acute renal injury, such as hematuria, kidney enlargement, and renal and perirenal hemorrhage and hematomas. SWL-induced injury in the kidney involves primarily vascular lesions, which extend throughout the thickness of the kidney^[15]. This vascular injury is characterized by extensive damage of the endothelial cells and rupture of blood vessels, with capillary and small blood vessels being much more susceptible to SWL injury than large vessels^[16]. Although experimental studies^[17–19] were able to show that cavitation bubbles are primarily responsible for the

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damage, the actual mechanism is still not well understood due to the difficulty in conducting experimental observations. Therefore, there is a need to complement difficult experimental observations with advanced computational tools.

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^[20,21]. Using a high intensity source and a large number of cycles may be applicable to all types and sizes of contrast agent, but cannot be applied safely in a clinical environment. Understanding of the forces involved in the breakup 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 breakup are not well understood. These mechanisms become even more complicated when the contrast agent “bubble” has a thick shell and interacts with other agents and/or nearby tissues.

Experimental observations^[18,19,22–25] have shown that the SWL-induced cavitation bubbles behave very differently *in vivo* than *in vitro*. Because of confinement, cavitation bubbles produced *in vivo* have their expansion significantly constrained and asymmetric and subsequent bubble collapse can be substantially weakened. These observations suggest that to accurately predict numerically cellular and tissue dynamics and potential damage due to cavitation bubbles, a full 3-D Fluid/Structure Interaction (FSI) approach is necessary. In addition, tissue surfaces are soft and deformable under stress, and the instantaneous variations in the tissue surface actually impose time dependent boundary conditions which modify the flow field and the bubble dynamics strongly influencing the resulting pressure loading from the bubble dynamics. Importance of including FSI simulation on bubble jetting has been reported by Gracewski et al.^[26], which used our axisymmetric bubble dynamics code, 2DYNAFS^{©[27,28]} and coupled it with a simple tube deformation model by Miao et al.^[29]. In addition to fluid structure interactions, interaction among many bubbles is known to play an important role^[30–32]. By studying interaction of laser-generated tandem microbubbles with rat mammary carcinoma cells, Sankin et al.^[33] showed that a single bubble did not form a reentrant jet toward the nearby cell and thus no membrane poration was observed. However, by introducing a second bubble with appropriate delay time and location, the first bubble was driven to form a reentrant jet toward the cell, which resulted in a localized and directional membrane poration. This parallels our studies of bubble dynamics where flexible boundaries delay or even reverse reentrant jet formation, while presence of other nearby bubbles could provide an even stronger attractive/repulsive effect to direct the jet toward the boundary^[30–32].

In this contribution we present first models to describe the dynamic behavior of 3-D encapsulated bubbles with a highly viscous thick shell. We then consider microbubble interaction with nearby responding and deforming bio-materials boundaries.

1. Thick shell encapsulated microbubbles

The capability of delivering drug to a targeted area makes therapeutic ultrasound contrast agents attractive to chemotherapy drug development since many chemotherapy drugs are toxic to normal tissues. One such application is to suspend the drug within a highly viscous thick liquid shell encapsulating the bubble^[34]. The high viscosity stabilizes the microbubble and keeps it inert until it reaches its specific target. It is then excited with an appropriate acoustic amplitude and frequency to get it to break up and release the drugs. The correct selection of the shell properties and thickness and the appropriate ultrasound characteristics renders the contrast agents powerful targeted drug delivery vehicles. Understanding breakup mechanisms is essential to control delivery.

It is known that a collapsing bubble near a boundary forms a re-entrant jet with a direction dependant on the nature of the boundary and an intensity dependant on the standoff distance^[35,36]. A similar non-spherical behavior is expected with encapsulated bubbles and is the subject of the present study.

Many studies have been dedicated to developing numerical models for ultrasound contrast agents. They are most often limited to spherical models and follow Church's approach^[37]. Using a thin-shell assumption, the constitutive equation of the shell is simplified and incorporated into a generalized Rayleigh-Plesset. The resulting model has been adapted to study encapsulated microbubble dynamics with known shell properties^[38-41]. 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. To study the dynamics and shell breakup of a thick liquid shelled contrast agent Allen et al.^[42,43] extended the spherical model to include a thick liquid shell.

1.1 3-D model domain decomposition

To investigate the dynamic mechanisms which cause encapsulated bubble shell nonspherical breakup, we have developed a 3-D finite-thickness shell model which couples a Navier-Stokes solver, 3DYNAFS-VIS[®], which uses a finite volume scheme and a potential flow solver, 3DYNAFS-BEM[®], which uses a Boundary Element Method (BEM)^[44]. The code enables modeling of inter bubble and boundary interactions. The computational domain is subdivided into inner domains constituted of each microbubble thick viscous shell layer and an outer domain composed of the liquid hosting the shelled microbubbles (see Fig. 1). In the inner domains we solve the Navier-Stokes equations to best describe the dynamics of the highly viscous liquid shells. 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 need to discretize the whole computational domain. This reduces the dimensions of the problem by one, allows the model to work on complicated boundary geometries, and addresses non-spherical deformations.

The outer domain includes any nearby walls or free surfaces. The two solvers communicate with each other by exchanging the values of the flow variables at the shell-liquid interfaces.

1.2 Outer domain liquid problem

The outer domain liquid flow due to the contrast agent's motion is assumed to be irrotational and incompressible. These are conventional assumptions for bubble dynamics and allow the definition of a potential, φ , for the velocity $\mathbf{u}$,

$$\mathbf{u} = \nabla \varphi, \quad \nabla^2 \varphi = 0 \quad (1)$$

A boundary integral method is used to solve Eq.(1) using Green's formula, where $\mathbf{x}$ is a fixed point in the "outer" liquid domain and $\mathbf{y}$ is a point on the boundary surface S comprising all inner domains and any other boundaries,

$$\Omega \varphi(\mathbf{x}) = \int_S n_y \left[\nabla \varphi(\mathbf{y}) \frac{1}{|\mathbf{x} - \mathbf{y}|} - \varphi(\mathbf{y}) \nabla \left(\frac{1}{|\mathbf{x} - \mathbf{y}|} \right) \right] dS \quad (2)$$

Ω is the solid angle under which point $\mathbf{x}$ sees the liquid domain.

This equation states that if the velocity potential φ and its normal derivatives are known on the boundary surface S of the liquid domain, where φ satisfies the Laplace equation, then φ

can be determined anywhere by integration over the boundary surface. This reduces by one the dimension of the problem of solving the Laplace equation.

1.3 Inner domain shell model

To solve the viscous flow in the inner domains, the unsteady Navier-Stokes equations are used. The continuity and momentum equations in non-dimensional form can be written

$$\frac{\partial u_i}{\partial x_i} = 0, \quad \frac{\partial u_i}{\partial t} + u_j \frac{\partial u_i}{\partial x_j} = -\frac{\partial p}{\partial x_i} + \frac{1}{Re} \frac{\partial \tau_{ij}}{\partial x_i} \quad (3)$$

where u_i are the Cartesian components of the velocity, x_i are the Cartesian coordinates, and p is the pressure. $Re = \rho_s^* u^* L^* / \mu_s^*$ is the Reynolds number of the viscous shell, u^* and L^* are the characteristic velocity and length, ρ_s^* is the shell density, and μ_s^* is its dynamic viscosity.

The effective stress tensor τ_{ij} is given by

$$\tau_{ij} = \left[\left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) - \frac{2}{3} \delta_{ij} \frac{\partial u_k}{\partial x_k} \right] \quad (4)$$

where δ_{ij} is the Kronecker delta. The flow field in the inner domain is directly simulated using Eq.(3) without any turbulence model because the Reynolds number is very small and the flow is laminar for all cases studied.

In order to simplify the treatment of the boundary conditions for complex geometries, Eq.(3) is expressed into a general time-dependent body-fitted curvilinear coordinate system (ξ, η, ζ) . 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. This provides a computational domain that is better for applying spatial differencing and the boundary conditions.

1.4 Boundary conditions

1.4.1 Shell-gas interface—Kinematic and dynamic boundary conditions are applied at the gas-liquid interfaces. The kinematic conditions ensure that a particle on any surface remains on that surface. This can be written $D\mathcal{F}/Dt = 0$, with $\mathcal{F}(x_i, t) = 0$ being the equation of the considered surface. The dynamic conditions at $\zeta = 0$ (gas-shell interfaces) impose zero shear stresses and balance of normal stresses at the interfaces

$$\left. \frac{\partial U}{\partial \zeta} \right|_{\zeta=0} = 0, \quad \left. \frac{\partial V}{\partial \zeta} \right|_{\zeta=0} = 0, \quad p = p_{gv} + \frac{2}{Re} \left. \frac{\partial W}{\partial \zeta} \right|_{\zeta=0} - \frac{C_{gs}}{We_{gs}} \quad (5)$$

where (U, V, W) are contravariant velocity components in the curvilinear coordinates and C_{gs} is the local curvature at the interface. For each microbubble the Weber number and the normalized gas content pressure are given by

$$We_{gs} = \frac{\rho_s^* u^{*2} L^*}{\gamma_{gs}}, \quad p_{gv} = \frac{p_g^* + p_v^* - p_\infty^*}{\rho_s^* u^{*2}} \quad (6)$$

where γ_{gs}^* is the surface tension at the gas-shell interface and p_g^* , p_v^* and p_∞^* are the dimensional gas and vapor partial pressures inside the bubble and the amplitude of the imposed driving pressure far from the bubble. 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

$$p_g^* V^{*k} = \text{constant} \quad (7)$$

where V^* is the gas volume and k is a gas compression constant.

1.4.2 Shell-liquid interface—The shell-liquid interface^[45,46] 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 velocities. These can be written in non-dimensional format as

$$\begin{aligned} \frac{\partial U}{\partial \zeta} \Big|_{\zeta=1} &= \frac{\mu_l}{\mu_s} \tau_{l,\xi}, \quad \frac{\partial V}{\partial \zeta} \Big|_{\zeta=1} = \frac{\mu_l}{\mu_s} \tau_{l,\eta}, \\ p - \frac{2}{Re_s} \frac{\partial W}{\partial \zeta} \Big|_{\zeta=1} &= P_l - \frac{1}{Re_s} \frac{\mu_l}{\mu_s} \tau_{l,\zeta} + \frac{C_{sl}}{We_{sl}}, \\ W \Big|_{\zeta=1} &= \mathbf{u}_s \cdot \mathbf{n} \end{aligned} \quad (8)$$

In the above expressions, μ_l and μ_s are the dynamic viscosities of the host liquid and the shell liquid and C_{sl} is the normalized curvature of the shell-liquid interface, and γ_{sl}^* is the surface tension at the shell-liquid interface,

$$We_{sl} = \frac{\rho_s^* u^{*2} L^*}{\gamma_{sl}^*} \quad (9)$$

$\mathbf{n}$ and $\mathbf{u}_s$ are respectively the local unit normal and the shell liquid velocity at the boundary. $\mathbf{u}_s$ is provided by the solution of the outer domain. $\tau_{l,\xi}$, $\tau_{l,\eta}$ are the normal derivatives of the host liquid tangential velocity components in the ξ and η directions. $\tau_{l,\zeta}$ is the derivative along the normal of the normal velocity component, and P_l is the pressure in the host liquid.

1.4.3 Other boundaries—At rigid boundaries no flow across the boundary is enforced. For a rigid and stationary body surface this can be written as

$$\frac{\partial \varphi}{\partial n} = 0 \quad (10)$$

and for a moving/deforming boundary

$$\frac{\partial \varphi}{\partial n} = u_n \quad (11)$$

At any given time step, if the velocity potential φ on the boundary surface S is known, the normal velocity φ / n can be obtained from Eq.(2). For a point $\mathbf{x}$ on the boundary, the pressure, $P(\mathbf{x})$, is provided by the Bernoulli equation

$$P_l(\mathbf{x}) + \rho_l \left(\frac{\partial \varphi}{\partial t} + \frac{1}{2} \nabla \varphi \cdot \nabla \varphi \right) = P(t) \quad (12)$$

where $P(t, \mathbf{x})$ is the imposed ultrasound pressure at the particular bubble location, $\mathbf{x}$. Once P_l is determined, Eq.(12) can provides φ / t . Then, the rate of change of φ at a given point $\mathbf{x}$ followed in its motion can be obtained by

$$\frac{D\varphi}{Dt} = \frac{\partial \varphi}{\partial t} + \mathbf{u}_s \cdot \nabla \varphi \quad (13)$$

where $\mathbf{u}_s$ is the velocity at $\mathbf{x}$, at the shell-liquid interface.

2. Zero-thickness shell model

2.1 Spherical model

In Eq.(12) P_l can be determined by considering the normal stress balance across the liquid/shell interface computed in the inner domain. Great CPU advantages can be gained if the inner problems could be replaced by an equivalent zero-thickness thin shell with properties reproducing the real finite thickness shell behavior. To do this the stresses exerted by the liquid on the encapsulated bubble have to be properly captured. For the study of microbubble rupture by acoustic excitation the normal stresses are predominant and can be expressed through the normal stress boundary condition across the liquid/shell/gas interface. To do this, let's consider the dynamics of a spherical thick shell microbubble with inner and outer shell radii, R_1 and R_2 , respectively. The continuity equation and incompressibility of the shell material and host liquid fluid leads to

$$u_r = \frac{\dot{R}_1 R_1^2}{r^2} = \frac{\dot{R}_2 R_2^2}{r^2}, \quad \dot{R}_1 = \dot{R}_2 \frac{R_2^2}{R_1^2} \quad (14)$$

where u_r is the radial velocity. This provides a direct relationship between R_1 and R_2 , the inner and outer radius of the shell.

Applying the momentum equations to both the inner and outer domain problem with the boundary equations described above leads to a non-dimensional Rayleigh-Plesset-like differential equation for R_2 , which describes the time variation of R_2 and thus R_1 too because of Eq.(14), which has the following non-dimensional expression^[42,47]

$$R_2 \ddot{R}_2 \left[(1 - \rho_s) + \rho_s \frac{R_2}{R_1} \right] + (1 - \rho_s) \frac{3}{2} \dot{R}_2^2 + \rho_s \dot{R}_2^2 \left[\frac{2R_2}{R_1} - \frac{1}{2} \left(\frac{R_2}{R_1} \right)^4 \right] = p_v + p_g - P_\infty - \left(\frac{2}{We_{gs} R_1} + \frac{2}{We_{sl} R_2} \right) - 4 \frac{\dot{R}_2^2}{R_2} \cdot \left[\frac{1}{Re_l} + \frac{1}{Re_s} \left(\frac{R_2}{R_1} \right)^3 - 1 \right] \quad (15)$$

where $\rho_s = \rho_s^* / \rho_l^*$ and $Re_l = \rho_l^* u^* L^* / \mu_l^*$. The characteristic length L^* is chosen to be the initial outer radius R_{20}^* and the characteristic velocity is $u^* = R_{20}^* / T^*$. T^* is the selected characteristic time and is the smallest of the period of the imposed acoustic waves or the bubble Rayleigh period based on ΔP the amplitude of the imposed acoustic waves

$$T^* = \min \left[f^{-1}, R_{20}^* \left(\frac{\rho_l^*}{\Delta P} \right)^{1/2} \right] \quad (16)$$

In the case of a highly viscous liquid shell of thickness, d , which tends towards zero, we have

$$R \approx R_2 \approx R_1, \frac{d}{R_2} = \frac{R_2 - R_1}{R_2} \ll 1, \quad \frac{R_2}{R_1} = \frac{R_2}{R_2 - d} \approx 1, \quad \frac{1}{Re_s} \gg \frac{1}{Re_l} \quad (17)$$

and Eq.(15) becomes

$$R\ddot{R} + \frac{3}{2}\dot{R}^2 = p_v + p_g - p_\infty - \frac{2}{R} \left(\frac{1}{We_{gs}} + \frac{1}{We_{sl}} \right) - 4 \frac{\dot{R}}{R} \frac{1}{Re_l} - 12 \frac{d}{Re_s} \frac{\dot{R}}{R^2} \quad (18)$$

If we ignore in the thin-shell model the layer thickness variations, d can be replaced by its initial value d_0 , and we can define an equivalent Weber number, We a dilatational parameter, κ^s , and a simplified thin-shell differential equation

$$R\ddot{R} + \frac{3}{2}\dot{R}^2 = p_v + p_g - p_\infty - \frac{2}{R} \frac{1}{We} - 4 \frac{\dot{R}}{R} \left(\frac{1}{Re_l} - \frac{\kappa^s}{R} \right) \quad (19)$$

$$\frac{1}{We} = \frac{1}{We_{gs}} + \frac{1}{We_{sl}}, \quad \kappa^s = \frac{3d_0}{Re_s}$$

In dimensional form the dilatational coefficient is given by

$$\kappa^{s*} = 3d_0\mu_s \quad (20)$$

2.2 3-D nonspherical model

This same concept can be applied to develop a 3-D zero-thickness shell model. In this model, the dynamics boundary condition at the contrast agent/liquid interface is obtained by analogy with the spherical zero-thickness model, through balancing the pressure in the liquid at the interface with the partial gas and vapor pressures, an equivalent surface tension, and equivalent viscous and dilatational normal stresses

$$P_l = p_g + p_v - \frac{2}{We} \frac{1}{R} - 4 \frac{\dot{R}}{R} \left(\frac{1}{Re_l} - \frac{\kappa^s}{R} \right) \quad (21)$$

To adapt Eq.(21) to a 3-D equivalent zero-thickness model, the boundary condition at the microbubble liquid interface Eq.(5) is modified such that, as in the spherical bubble case, the Weber number and the curvature between the gas and the shell liquid are replaced by an equivalent Weber number and an equivalent curvature respectively, i.e.,

$$\begin{aligned} We_2 &\rightarrow \text{is replaced by} \rightarrow We, \\ C_{gs} &\rightarrow \text{is replaced by} \rightarrow C \end{aligned} \quad (22)$$

Similarly the simple viscous normal stress term is replaced, by analogy to the spherical case, by an equivalent term that accounts for both the viscosity of the bulk liquid the viscosity of the shell material and the thickness of the material

$$\frac{2}{Re} \frac{\partial W}{\partial \zeta} \Big|_{\zeta=0} \rightarrow 2 \dot{R} C \left(\frac{1}{Re_l} - \frac{C\kappa^s}{2} \right) \quad (23)$$

As a result, the normal stress boundary condition is written as

$$P_l = p_v + p_g - \frac{C}{We} - C \left(\frac{2}{Re_l} - \frac{\kappa^s C}{2} \right) \frac{\partial \varphi}{\partial n} \quad (24)$$

In the equivalent zero-thickness model, as expressed in Eq.(17), the inner and outer bubble shell radii become the same, and we chose here the outer radius, R_{20}^* , as the equivalent microbubble radius to track and use for the computations.

3. Finite element structure model

To simulate the interaction between the encapsulated bubbles and deformable tissues, we couple the fluid solvers with a structure dynamics solver. With σ being the Cauchy stress tensor, the structure motion equations are

$$\rho \frac{d\mathbf{u}}{dt} = \rho \mathbf{g} + \nabla \cdot \sigma \quad (25)$$

If we denote $\mathbf{F}$ the deformation gradient tensor, then the Cauchy stress tensor is

$$\sigma = \det(\mathbf{F}) \mathbf{F} \mathbf{S} \mathbf{F}^T \quad (26)$$

where $\mathbf{S}$ is the second Piola-Kirchoff stress tensor

$$S_{ij} = 2 \frac{\partial W}{\partial C_{ij}} \quad (27)$$

The Cauchy deformation tensor is $C_{ij} = F_{ki} F_{kj}$ and W is the strain energy function which can be modeled differently according to the types of tissues^[48,49].

The boundary condition at the surface of the tissue with the pressure provided by the BEM solution is

$$\mathbf{n} \cdot \sigma \cdot \mathbf{n} = P \quad (28)$$

The motion of the tissue in response to the fluid pressures is simulated using finite elements. This provides the new position of the structure and the normal velocities at the surface (or φ/n) needed for the BEM procedure, and allows the solution to proceed in time.

4. Numerical methods

4.1 Potential flow solver

To solve Eq.(2) numerically with the boundary element method, we discretize the surfaces of all objects into triangular panels. The surface integrals become a summation over all panels of the influence of singularity distributions over each individual panel. It is necessary to assume a relation between φ and φ/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 with the values determined by the values at the surrounding nodes. Equation (2) can then be expressed in a matrix form as

$$\overline{\mathbf{B}} \frac{\partial \varphi}{\partial n} = (a\pi \mathbf{I} + \overline{\mathbf{A}}) \varphi \quad (29)$$

where $\mathbf{I}$ is an $N \times N$ identity matrix, and $\overline{\mathbf{A}}$ and $\overline{\mathbf{B}}$ are $N \times N$ influence coefficient matrices. With φ known on all boundary nodes, Eq.(29) is a linear system of N equations and can be readily solved for N unknowns of φ/n , using classical methods such as LU decomposition and Gauss elimination.

4.2 Viscous Navier-Stokes flow solver

To solve Eq.(3), 3DYNAFS-VIS[®] uses a finite volume formulation and the artificial-compressibility method^[50], in which a time derivative of the pressure is added to the continuity equation with β an artificial compressibility factor

$$\frac{1}{\beta} \frac{\partial p}{\partial t} + \frac{\partial u_i}{\partial x_i} = 0 \quad (30)$$

The solution procedure is then to march in pseudo-time until continuity is satisfied. To obtain a time-dependent solution, a Newton iterative procedure is performed at each physical time step. First-order Euler implicit difference formula are applied to the time derivatives. The spatial differencing uses a flux-difference splitting scheme based on Roe's method^[51] and Van Leer's MUSCL method^[52] 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^[53] in which symmetric block Gauss-Seidel sub-iterations are performed before the solution is updated at each Newton iteration.

4.3 Coupling the two liquids and a deformable structure

The boundary conditions given in Section 1.4.2 are key for coupling the Navier-Stokes solver and the potential flow solver. The procedure, illustrated in Fig. 2, is summarized as follows:

1. Volume grids are generated for the inner domains, and surface grids are generated for the outer host liquid domain.
2. The Navier-Stokes equations are solved for the viscous liquid in the shells with the shell-liquid interfaces normal velocities provided by the host liquid potential solver.
3. Shell interfaces are updated with the kinematic boundary conditions and the boundary pressures are calculated.

4. Green's equation is solved to provide the velocity potential at the shell/liquid interface.
5. Structure dynamics equations are solved using computed liquid pressures. This provides new normal velocities and positions, then the procedure is repeated as time evolves.

5. Example applications

5.1 Encapsulated bubble dynamics near rigid wall

The results and computations in this study focus on oil-shelled microbubbles developed for drug delivery, e.g., triacetin shell (ImaRx Therapeutics). We consider triacetin-shelled bubble in water. Triacetin has a density: $1,100 \text{ kg/m}^3$, viscosity: 0.028 kg/ms , surface tension at gas-triacetin interface: 0.008 kg/s^2 , surface tension at triacetin-water interface: 0.006 kg/s^2 . Unless specified otherwise, we consider the initial bubble radii $R_{10} = 1.2 \text{ }\mu\text{m}$, $R_{20} = 1.7 \text{ }\mu\text{m}$ for all the results shown below.

5.1.1 Finite-thickness shell model—The non-spherical deformations due to the presence of the wall become much more significant as the driving pressure amplitude becomes higher. To study the effect of a rigid wall on contrast agent dynamics, we present below 3-D numerical simulations for an acoustically driven contrast agent near a rigid wall at two initial standoffs, $X = 2.6$ and $4.6 \text{ }\mu\text{m}$.

Figure 3 and Fig. 4 show the encapsulated bubble 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 going through the bubble center. The shelled bubble is initially in a uniform pressure field with of 0.1 MPa , and is subjected to a sinusoidal acoustic wave with $P_a = 1 \text{ MPa}$ and $f = 2.5 \text{ MHz}$. As expected, the smaller standoff case results in more significant non-spherical deformations. The presence of the wall imparts a non-spherical pressure distribution on the shell which deforms. More importantly the dynamics lead to a non-uniform shell liquid thickness distribution during the oscillations. During the bubble growth phase, the shell retains a more or less uniform thickness, then becomes thicker and thicker on the side opposite to the wall, where a jet usually takes place. Concurrently, the shell becomes thinner and thinner at the side nearest to the wall potentially leading to starvation of the shell liquid and breakup.

Using a linear stability analysis^[47], we have also confirmed that the most unstable mode due to a 3-D perturbation is when the bubble starts a jet at one end and breaks up through thinning at the other end.

Figure 5 and Fig. 6 show the encapsulated microbubble shape variations and normal velocity contours at three time steps as seen in the outer domain. (Two bubbles are shown because a plane of symmetry was used to represent the rigid wall.)

In the figures, the second set is at the time the microbubble attains its maximum size, while the third set is the last time step before the simulations were terminated for the $X = 2.6 \text{ }\mu\text{m}$ case and the last time step before the rebound for the $X = 4.6 \text{ }\mu\text{m}$ case

Figure 7 shows a comparison of the time history of the microbubble equivalent radius for three standoff cases. It is seen that the presence of the wall only has a slight influence on the maximum growth size of the bubble. The simulations for the $2.6 \text{ }\mu\text{m}$ and $3.6 \text{ }\mu\text{m}$ cases were terminated due to numerical instability as the shell became extremely thin and the 3-D grid became overly squeezed, while the simulation for the $X = 4.6 \text{ }\mu\text{m}$ case was able to continue and the rebound was observed.

Figure 8 shows more solution details 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 $X = 3.6$ μm cases. Figure 9 shows the solutions at the time steps before and after the rebound for the $X = 4.6$ μm case. A re-entrant jet with a high normal velocity is seen for the 2.6 μm and 3.6 μm cases just starting to form at the thick-shell side away from the wall. At the thin-shell side, close to the wall, the shell is seen stretching with high tangential velocities pulling the shell apart. Continuous shell thinning and stretching at the near-wall side indicate the tendency of the shell to break up there. For the $X = 4.6$ μm case, the shell remained thick everywhere and was not stretched near the wall side. As a result the microbubble was able to rebound after reaching its minimum volume.

5.1.2 Shell thickness and standoff effects on shell break-up—Figure 10 shows the comparison of the bubble shape variations between the 3-D finite-thickness model and the zero-thickness shell model at several time steps during the first bubble oscillation cycle. It has been shown that an explosion bubble may become pinched off into an hourglass shape and cut into two instead of forming a re-entrant jet during its collapse, depending on its initial distance above a cylindrical or flat boundary^[54]. For the current problem, other parameters such as shell thickness, shell material, initial bubble radius, acoustic pressure amplitude, and frequency may also influence the type of bubble breakup. To focus only on the effect of standoff and shell thickness on the shell breakup a series of simulations for a triacetin-shelled bubble with an initial mid-thickness radius of 1.45 μm under ultrasound acoustic excitation with $P_a = 1$ MPa, and $f = 2.5$ MHz were conducted. The simulations for each case were continued for more than one oscillation cycle unless breakup occurs earlier.

Figure 11 shows a diagram of the bubble shapes at the end of the first bubble oscillation cycle. We can subdivide the diagram into four zones. In Zone A, a classical re-entering jet is formed. In Zone B, a ring type jet is formed. In Zone C, the bubble is found to pinch off into two. In Zone D, the bubble survives and the surface does not become multi-connected during the first cycle. Based on this diagram, the bubble break-up in Zones A and B could be the best conditions for drug or gene delivery. This is because the break-up of the bubble in the first cycle allows lower ultrasound doses and the re-entrant jet can help drug or gene particles penetrate the cell membrane. Although the bubble also breaks up due to pinch-off in Zone C within the first cycle, there is no vectoring jet to enhance sonoporation.

5.2 Tandem bubbles between two parallel plates

The models presented above were applied for the simulation of the studies conducted by Zhong's group^[24,25,33]. In the model the 3-D interaction between two bubbles confined between two parallel disks 50 μm apart is considered. The liquid density is $\rho = 1\,000$ kg/m³, the kinematic viscosity is $\gamma = 10^{-6}$ m²/s, the ambient pressure is $p_{\text{amb}} = 1\,01\,235$ Pa, the vapor pressure is $p_v = 2\,300$ Pa, and the max bubble radius $R_{\text{max}} = 25$ μm . The radius of the considered disk is 1 mm. Actually, the radius of the disk, even though much larger than the maximum bubble size, is quite important as we will show later.

In Fig. 12 a top view of the dynamics of in-phase tandem bubbles is shown. The bubbles are generated simultaneously. During collapse, re-entrant jets develop in opposite directions. It is seen that 3DynaFS[®] reproduces quite well the observations.

Figure 13 shows an out-of-phase tandem bubbles case. The second bubble is generated with a 2 μs delay after the initiation of the first bubble. It expands, causing the jet forming in the first bubble to speed up to a much faster speed. This is used to produce poration of nearby single cells^[24,25,33]. Here again, it is seen that 3DynaFS[®] reproduces well the observations.

In both the experimental and numerical configurations, because of the confinement, it is very important to know where the “ambient” or “reference” pressure is imposed. Assuming the bubble dynamics occurs in channels or in between disk plates and that the pressure is imposed at the edges of these channels of disks, the sizes of the confined space have a strong influence on the bubble dynamics. For example, Fig. 14 shows the dynamics (equivalent radius vs. time) of a confined bubble between two disk plates, when everything is kept the same but the diameter of the disks. The figure shows both 3DYNAFS results as well as the Navy compressible code, Gemini, results^[55]. This is to remove arguments made that this is a compressibility effects. The reason for the behavior is purely dynamics and is directly connected to the inertia of the liquid in the confined region, which changes with the size. Thus, one has to be very careful in identifying where the reference pressure is imposed for fine experiments or simulations involving such conditions.

5.3 Bubble dynamics near deformable bio-materials

The interaction of a collapsing bubble with a nearby tissue is complex and has received a lot of attention by the research community because of the potential for tissue or vessel damage^[19,24,25,33,56,57]. The tissue significantly deforms during the bubble dynamics and observations indicate potential occurrence of both poration^[53] and invagination^[19] depending on the experimental configuration. In this section, we investigate modeling the tissue as an elastic material and we compute its dynamics using a structure code. The process is simulated with the BEM/FEM coupling method described above. We illustrate this with the interaction between a flat thick tissue block and a bubble initially at equilibrium before a sinusoidal acoustic pressure is applied. The acoustic pressure starts with a negative half cycle so that the bubble initially grows and then collapses near the tissue. Figure 15 shows the geometric set-up where the tissue is modeled as a large and thick rectangular plate. In the simulations, the bottom of the plate is held rigid. To better resolve the dynamics near the bubble, the grid size is locally refined. The dynamics are related to the initial bubble size R_0 , initial standoff distance X to the tissue, the material properties such as the density ρ_{tissue} , elasticity modulus E , and the frequency f and amplitude P_a of the acoustic pressure. The elastic modulus of bio-materials varies in a very wide range (see Ref.[57]). Since the elasticity is a crucial parameter for this problem, we show the results for three elastic moduli: $E = 10$ kPa, 100 kPa and 1 000 kPa.

Figure 16 shows sequential snapshots of the tissue deformation and bubble shapes for an initial standoff $X = 1.5R_0$ ($3 \mu\text{m}$) and $E = 10$ kPa. Figure 17 shows the corresponding bubble equivalent radius and the 3-D view of the tissue surface shape at collapse. Initially, while growing, the bubble pushes in and dimples the tissue locally, while the surrounding low pressure sucks the tissue surface towards the bubble. When the positive half cycle of the pressure starts, the growth rate is reduced and at approximately $3/4$ cycle the bubble reaches its maximal size and then collapses forming a reentrant jet towards the much raised surface of the material. For this case, a reentrant jet is formed toward the tissue at the end of the collapse as shown in the 3-D view in Fig. 17.

Figure 18 shows snapshots of the tissue deformation and bubble shapes for similar conditions but with an initial standoff $X = 3.0R_0$ ($6 \mu\text{m}$) and an elastic modulus $E = 1,000$ kPa. Figure 19 shows the corresponding equivalent bubble radius and the 3-D view of the tissue surface shape at the bubble collapse for this case. Compared with the case shown above, since the bubble is farther away from the tissue, the suction effect is much weaker and it takes a longer time for the bubble to touch the tissue. At the same time, the bubble size varies with time due to the pressure change. The bubble collapses on the tissue surface after two pressure cycles. The overall tissue deformation is less than that for $E = 10$ kPa case and there is no crater in this case.

The bubble shapes and tissue deformation at bubble collapses for different elastic modules and initial standoff distances are shown in Fig. 20. For all the cases shown, the tissue ends up with a bulge and the overall bulge size decreases as the rigidity increases.

5.4 Bubble dynamics in a tube

Simulations of a bubble dynamics in a flexible tube were carried out for studying the dynamics of a cavitation bubble inside a blood vessel simulated as a circular tubular linear elastic material with density $0.96 \times 10^3 \text{ kg/cm}^3$. The Young's modulus is set at 1.08 MPa and the Poisson ratio at 0.499. The dynamics of a bubble initially spherical and initially placed at an off center location inside the circular tube is shown in Fig. 21 (side and top views). As the bubble size expands, it pushes the liquid and the tube outward. As it collapses, two jets aligned with the tube center axis form on the bubble. This creates large pressures at the vessel wall, causing it to deform significantly.

To illustrate the effect of the wall flexibility on the bubble dynamics, Fig. 22 compares for the same geometry and initial conditions a rigid and a flexible tube ($\rho = 10^3 \text{ kg/m}^3$, $E = 2.017 \text{ MPa}$ and $\nu = 0.48$). The inner radius of the tube is $1.5 \times 10^{-4} \text{ m}$, the outer radius is 0.32 mm, and the length is $1.25 \times 10^{-3} \text{ m}$. A $20 \text{ }\mu\text{m}$ bubble is placed at the center of the tube. As shown in the figure, in the flexible tube the bubble expands slightly faster, reaches a slightly larger maximum volume, while the motion of the wall causes oscillation. Then the bubble collapses slower and the jet takes longer time to develop.

As for the case of the confined bubbles between two plates, for a finite tube the length affects the bubble dynamics significantly for the same reasons. Figure 23 shows for a rigid tube the effect of the tube length. The bubble period continues to increase as the tube length is increased and it is essential to know the correct dimensions to conduct an accurate experiment or a correct modeling. This again is due to the changes in the inertia of the liquid entrained by the motion of the bubble in the tube.

6. Conclusions

We have presented in this communication our on-going efforts to develop computational tools to enable the study of the complex interaction between acoustic forcing, natural or encapsulated microbubbles, confinement areas, tissues, and vessels. To be able to do so, 3-D descriptions of the dynamics are required and involve viscous flow modelling, large free surface deformations, large free surface oscillations, as well as fully coupled fluid-structure interaction capabilities. We have mainly described the methods applied and illustrated this with some examples. We used these examples to discuss some physical aspects of the problems studied.

Concerning the dynamics of microbubbles encapsulated with a highly viscous liquid shell, it appears that the shell exerts a strong effect on the stability of the microbubble making the formation of a re-entrant jet more difficult. Indications are that the breakup mechanism for a thick-shelled microbubble near a wall may be dominated by drainage of the film around the bubble in the bubble region closer to the wall as opposed to re-entrant jet breakup for a regular microbubble. We have also presented here a diagram, which illustrate that the breakup mechanism depends highly on the combination shell thickness and standoff of the bubble from the boundary.

Numerical modelling of bubble dynamics near tissues is dominated by the use of the appropriate constitutive properties of the modelled tissue. The examples we have shown here indicate that an elastically deforming material experiences strong extensions and compressions indicating potential for both invagination and poration. Accurate modelling

requires better understanding of the tissue properties and the proper mechanical models to be used.

The numerical tools presented here are very useful in helping design advanced concepts and conduct experiments such as those involving tandem microbubbles. Effects such as confinement, interaction between the bubbles, and deformation of the boundaries can be accurately studied and desirable outcome for a new design can be predicted quite accurately. Finally, such studies illustrate the need for accurate experimental definition of the conditions to enable correct simulation setups.

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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, potential flow, and structure dynamics solvers

Fig. 3.

Encapsulated microbubble shape variations and pressure contours near a rigid wall when subjected to a sinusoidal acoustic wave with $P_a = 1 \text{ MPa}$, $P_{\text{atm}} = 0.1 \text{ MPa}$ and $f = 2.5 \text{ MHz}$. Initial standoff of $2.6 \mu\text{m}$

Fig. 4.

Encapsulated microbubble shape variations and pressure contours near a rigid wall when subjected to a sinusoidal acoustic wave with $P_a = 1 \text{ MPa}$, $P_{\text{atm}} = 0.1 \text{ MPa}$ and $f = 2.5 \text{ MHz}$. Initial standoff of $4.6 \mu\text{m}$.

Fig. 5. Encapsulated microbubble shape variations and normal velocity 3-D contours at three times as seen in the outer domain. Conditions of Fig. 3

Fig. 6. Encapsulated microbubble shape variations and normal velocity contours at three time steps as seen in the outer domain. Conditions of Fig. 5

Fig. 7.
Encapsulated microbubble equivalent radius versus time for three different standoff cases

Fig. 8. Encapsulated microbubble shape near a wall at the last time step before the simulations were terminated. The velocity vectors are shown plotted on both the shell/liquid and the shell/gas interfaces

Fig. 9. Encapsulated microbubble shape near a wall right before and after rebound for the $X = 4.6 \mu\text{m}$ case. The velocity vectors are shown plotted on both the shell/liquid and the shell/gas interfaces

Fig. 10.

Comparison of the bubble shape variations between the 3-D finite-thickness model and the zero-thickness shell model at several time steps during the first bubble oscillation cycle

Fig. 11.
Diagram of bubble shapes for different shell thicknesses and standoffs

Fig. 12.
In-phase tandem bubbles dynamics, top view, and comparison with experiment

Fig. 13.
Out-of-phase tandem bubble dynamics, top view, and comparison with experiment of Zhong et al.^[24,25,33]

Fig. 14. Effect of the disk size on dynamics bubble between two rigid plates at a gap of $50\text{ }\mu\text{m}$ for $R_0 = 2\text{ }\mu\text{m}$, $R_{\text{max}} = 50\text{ }\mu\text{m}$, $P_{\text{amb}} = 1\text{ atm}$. Incompressible and compressible solutions. Notice that in all cases the diameter of the disk is very large compared to the bubble size and to the size of the gap between disks

Fig. 15.
Geometry of the problem and the grid

Fig. 16. Snapshots for the deformation and bubble shape for the initial standoff $X = 1.5R_0$ and the elastic modulus $E = 10$ kPa, $R_0 = 2$ μm , $f = 2$ MHz, $P_a = 1$ MPa

Fig. 17.

Equivalent bubble radius Re_q (a) and the 3-D view of the tissue surface shape at the bubble collapse (b) for the initial standoff $X = 2R_0$ and the elastic modulus $E = 10$ kPa, $R_0 = 2$ μm , $f = 2$ MHz, $P_a = 1$ MPa

Fig. 18.

Snapshots for the deformation and bubble shape for the initial standoff $X = 3R_0$ and the elastic modulus $E = 1\,000\text{ kPa}$, $R_0 = 2\text{ }\mu\text{m}$, $f = 2\text{ MHz}$, $P_a = 1\text{ MPa}$

Fig. 19. Equivalent bubble radius Re_q (a) and the 3-D view of the tissue surface shape at the bubble collapse (b) for the initial standoff, $X = 3R_0$ and the elastic modulus $E = 1000$ kPa

Fig. 20.
Side view of the tissue deformation at different elastic modulus and initial standoff distance conditions

Fig. 21.
Pressure field for a bubble collapse in blood vessel

Fig. 22.
Bubble equivalent radius versus time inside flexible and rigid tubes with a diameter of 50 μm for $R_0 = 20 \mu\text{m}$, $R_{\text{max}} = 200 \mu\text{m}$ and $P_{\text{amb}} = 1 \text{ atm}$

Fig. 23.
 Tube length effect on bubble dynamics inside a rigid tube with a diameter of $50\text{ }\mu\text{m}$ for $R_0 = 20\text{ }\mu\text{m}$, $R_{\text{max}} = 200\text{ }\mu\text{m}$ and $P_{\text{amb}} = 1\text{ atm}$