Natural frequencies of two bubbles in a compliant tube: Analytical, simulation, and experimental results

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Motivated by various clinical applications of ultrasound contrast agents within blood vessels, the natural frequencies of two bubbles in a compliant tube are studied analytically, numerically, and experimentally. A lumped parameter model for a five degree of freedom system was developed, accounting for the compliance of the tube and coupled response of the two bubbles. The results were compared to those produced by two different simulation methods: (1) an axisymmetric coupled boundary element and finite element code previously used to investigate the response of a single bubble in a compliant tube and (2) finite element models developed in COMSOL Multiphysics. For the simplified case of two bubbles in a rigid tube, the lumped parameter model predicts two frequencies for in- and out-of-phase oscillations, in good agreement with both numerical simulation and experimental results. For two bubbles in a compliant tube, the lumped parameter model predicts four nonzero frequencies, each asymptotically converging to expected values in the rigid and compliant limits of the tube material.

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I. INTRODUCTION

Accurate prediction of the dynamic response of oscillating gas bodies, suspended in a liquid medium, surrounded by a compliant vessel has become a topic of importance in diagnostic and therapeutic ultrasound due to increased interest in medical applications of ultrasonically excited bubbles in vessels. Techniques are being developed and used to enhance diagnostic ultrasonic imaging by injecting ultrasound contrast agents (UCAs), which are stabilized gas bubbles of a few microns in diameter, into the vasculature. Over the past few decades, harmonic and subharmonic imaging techniques have been developed based on the interaction of ultrasound with contrast agents (de Jong *et al.*, 2000). The response of a bubble in the presence of a neighboring structure (Oguz and Prosperetti, 1998) and other bubbles (Strasberg, 1953; Zabolotskaya, 1984) can be significantly different from that of a bubble in an infinite medium. In addition to diagnostic applications, potential therapeutic applications for microbubbles have been proposed, such as vehicles for drug or gene delivery or for ultrasound molecular imaging (Klibanov, 1999; Ferrara *et al.*, 2007; Dayton and Rychak, 2007; Yoshida *et al.*, 2008). Energy transfer to a microbubble is increased as the ultrasonic central frequency approaches the bubble's resonance frequency. Therefore, it is important to understand the effects of a surrounding capillary or nearby

bubbles on the bubbles' natural frequencies, in order to optimize therapeutic applications of ultrasonically excited echo contrast agents.

While the behavior of an oscillating bubble in an open volume has been thoroughly studied during the past several decades (Leighton, 1994; Young, 1989), interactions between microbubbles and a surrounding vessel or tube are less well established. If the bubble radius is sufficiently small compared to the wavelength of an ambient acoustic field, and the acoustic amplitude is low, then the resulting response of a bubble in an essentially open volume can be simplified to that of a spherically symmetric, one-degree-of-freedom linear oscillator (Leighton, 1994; Young, 1989). Neglecting surface tension, the natural frequency of a bubble in a liquid is inversely proportional to the bubble radius (Minnaert, 1933). This spherically symmetric model can be used to approximate the behavior of a bubble in a vessel only if the bubble radius is much smaller than the vessel radius. For the opposite extreme, if the bubble radius is comparable to the vessel radius, a one-dimensional linear model of a cylindrical bubble can be used to approximate the behavior of the bubble in a rigid tube (Oguz and Prosperetti, 1998; Sassaroli and Hynynen, 2004; Sassaroli and Hynynen, 2005). Oguz and Prosperetti (1998) present simulation results using a boundary integral method for a bubble in a rigid tube that indicates that the large bubble approximation accurately predicts the bubble's natural frequency when the ratio of bubble radius to tube radius is greater than 0.2. In a more recent work, a theoretical model for a bubble

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oscillation in an elastic tube was considered, where two frequencies are found with the lower one converging toward the rigid tube value for increasing stiffness of tube (Martyanov *et al.*, 2009). In addition, experimental measurements of the oscillations of elastic balloons in plastic tubes (Jang *et al.*, 2009) and cylindrical bubbles in glass tubes (Geng *et al.*, 1999) were in good agreement with the Oguz and Prosperetti (1998) model. Other experiments to investigate the behavior of ultrasonically excited bubbles in tubes (Caskey *et al.*, 2007; Zheng *et al.*, 2007), gel tunnels (Sassaroli and Hynnen, 2007), and *ex vivo* microvessels (Caskey *et al.*, 2007) focused on the bubble's oscillation amplitude, translational velocity, fragmentation, and/or inertial cavitation threshold. As the tube diameter decreases, the bubble oscillation amplitude and translational velocity decreased.

Finite volume and finite element models of a bubble in a compliant tube have recently been developed to investigate the interaction of an ultrasonically excited bubble and a microvessel (Gao *et al.*, 2007; Qin and Ferrara, 2006; Qin *et al.*, 2006; Miao *et al.*, 2008). These models were used to predict the amplitude and asymmetry of bubble response and the stresses on the tube wall. Typically, the bubble expansion decreased and the bubble asymmetry and tube wall stresses increased as the tube radius decreased or as the tube stiffness increased. Qin and Ferrara (2007) used a model of a bubble in a liquid surrounded by a compliant vessel and tissue layer developed using COMSOL Multiphysics 3.2 to investigate the natural frequency of ultrasound contrast agents in microvessels of various thickness and materials. They used a nonlinear lumped parameter model of the surrounding vessel and tissue as a boundary condition on the outer surface of the viscous, incompressible liquid, modeled with finite elements. Their predicted bubble natural frequency agrees with the one-dimensional cylindrical bubble model (Sassaroli and Hynnen, 2005) when the tube is rigid, however, the frequency increases as the vessel rigidity index, accounting for vessel thickness as well as stiffness, decreases.

The goal of the present study is to investigate the effect of a surrounding compliant vessel on the natural frequencies of two gas bodies, analytically, computationally, and experimentally. A 5-degree-of-freedom lumped parameter model is developed and its results are compared to results from three simulations. The first model uses a coupled boundary element method (BEM) and finite element method (FEM) code developed and used previously to investigate the dynamic response of a single bubble in a tube. (Miao and Gracewski, 2008, Jang *et al.*, 2009) The other models were developed using either the acoustics module or the coupled fluid-structure module in COMSOL Multiphysics 3.5a. Comparisons are also made with experimental measurements of the resonance frequencies of two bubbles in a rigid tube and one bubble in a compliant tube.

II. FIVE-DEGREE-OF-FREEDOM MODEL

A 5-degree-of-freedom lumped parameter model is developed for the system of two bubbles with equilibrium radii R_1 and R_2 , respectively, in a compliant tube of

unstretched radius r_{tube} illustrated in Fig. 1(a). The initial axial location of the i th bubble center measured from the tube center is denoted by z_i . The equations of motion for the system are derived using the Euler-Lagrange equation

$$\frac{d}{dt} \frac{\partial L}{\partial \dot{x}_i} - \frac{\partial L}{\partial x_i} = 0, \quad (1)$$

with the Lagrangian L defined as $L = \text{KE} - \text{PE}$, where KE is the kinetic energy and PE is the potential energy of the system and x_i is the i th generalized coordinate. For air bubbles oscillating in liquid, the liquid surrounding the gas bodies contributes the majority of the kinetic energy due to the liquid density ρ_l being significantly greater than the gas density, whereas gas bodies and surrounding tube contribute the majority of the potential energy due to their compliances. Therefore, the liquid is assumed to be incompressible. The resulting system of equations is used to investigate the effect of bubble separation distance and tube compliance on the natural frequencies of the bubbles.

In the model as shown in Fig. 1(b), each spherical bubble is approximated by a cylindrical bubble of the same volume and with radius equal to the tube radius r_{tube} , so that the initial width of the i th bubble is

$$h_i = \frac{4R_i^3}{3r_{\text{tube}}^2} \quad \text{for } i = 1, 2. \quad (2)$$

This approximation was previously shown to be an accurate representation for a single bubble in a rigid tube, if the equilibrium bubble radius $R_0 > 0.2 r_{\text{tube}}$. (Oguz and Prosperetti, 1998; Jang *et al.*, 2009).

The 5-degree-of-freedom lumped parameter model is illustrated in Fig. 2(a). The expansion of a cylindrical bubble is approximated by a change in width and a change in radius. A change in width of the left and right bubbles can be written as $x_2 - x_1$ and $x_3 - x_2$, respectively, where x_i is the axial

FIG. 1. (a) Schematic diagram for two bubbles in a tube, showing bubble radii, R_1 , R_2 , bubble positions with respect to center of the tube, z_1 , z_2 , tube inner radius, r_{tube} , tube thickness, t_{tube} , and tube length, L . (b) Each spherical bubble is replaced with a cylindrical body of equal volume and radius equal to tube inner radius, so that the width of the i th cylindrical bubble is $h_i = 4R_i^3/3r_{\text{tube}}^2$.

FIG. 2. (a) Schematic diagram showing five degrees of freedom for the two bubbles in a compliant tube. (b) Schematic diagram of a tapered tube of angle θ with a single bubble positioned in the middle of the tube, as simulated with COMSOL Multiphysics.

displacement of the i th lateral air-liquid interface from its initial equilibrium position. (Because the liquid is assumed incompressible, the two inner interfaces have the same displacement, x_2 .) Therefore, x_1 , x_2 , and x_3 are the axial displacements of masses m_1 , m_2 , and m_3 corresponding to the left, center, and right columns of liquid, respectively. The radial expansions of the left and right bubble are denoted by dr_1 and dr_2 , respectively.

It is assumed that the gas pressure in each bubble is homogeneous and obeys the polytropic gas law $p_g V^k = p_{g0} V_0^k$, where p_g is the gas pressure, V the volume, k the polytropic gas constant, and the subscripts 0 indicate equilibrium conditions. If surface tension of the bubble is neglected, $p_{g0} = p_0$, where p_0 is the ambient pressure. Thus, the potential energy for a single bubble is

$$PE = - \int_{V_0}^V (p_g - p_0) dV = -p_0 \int_{V_0}^V \left(\left(\frac{V_0}{V} \right)^k - 1 \right) dV \approx \frac{1}{2} \frac{p_0 k}{V_0} dV^2. \quad (3)$$

For constant values of p_0 , k , and V_0 , the potential energy is a function of the differential volume due to oscillation. For small displacements, the volume change for left and right bubbles can be approximated as

$$dV_1 = \pi r_{\text{tube}}^2 (x_2 - x_1) + 2\pi r_{\text{tube}} h_1 dr_1 = \pi r_{\text{tube}}^2 (x_2 - x_1 - x_4), \quad (4a)$$

$$dV_2 = \pi r_{\text{tube}}^2 (x_3 - x_2) + 2\pi r_{\text{tube}} h_2 dr_2 = \pi r_{\text{tube}}^2 (x_3 - x_2 - x_5), \quad (4b)$$

respectively, where $x_4 = -(2h_1/r_{\text{tube}})dr_1$ and $x_5 = -(2h_2/r_{\text{tube}})dr_2$ have been defined for convenience. Additionally, the strain energy of the deformed tube can be approximated as

$$PE = \frac{1}{2} \frac{2\pi E_{\text{tube}} h_i t_{\text{tube}}}{r_{\text{tube}}} dr_i^2, \quad (5)$$

where E_{tube} is the modulus of elasticity for the tube and t_{tube} is the thickness of the tube as shown in Fig. 1(a). Equation

(5) assumes that only the section of the tube in contact with the cylindrical gas bodies expands radially outward. Associated spring constants k_i , can be written for each bubble as

$$k_i = \frac{\pi p_0 k r_{\text{tube}}^2}{h_i}, \quad \text{for } i = 1, 2 \quad (6a)$$

and for each tube section as

$$k_i = \frac{\pi E_{\text{tube}} r_{\text{tube}} t_{\text{tube}}}{2h_{i-3}}, \quad \text{for } i = 4, 5. \quad (6b)$$

As in the Rayleigh–Plesset model (Leighton, 1994; Young, 1989) for spherical oscillation of a single bubble in an infinite liquid domain, the liquid is assumed to be incompressible. The kinetic energy of the i th column of liquid is $m_i \dot{x}_i^2$ for $i = 1, 2, 3$. For cylindrical liquid columns of constant cross sections, the mass terms are given by

$$m_i = \rho_l \pi r_{\text{tube}}^2 L_{i,e}, \quad \text{for } i = 1, 2, 3, \quad (7a)$$

where the effective length terms $L_{i,e}$ are

$$L_{1,e} = \frac{L}{2} - \frac{h_1}{2} - z_1 + \Delta L, \quad (7b)$$

$$L_{2,e} = z_1 + z_2 - \frac{h_1}{2} - \frac{h_2}{2}, \quad (7c)$$

and

$$L_{3,e} = \frac{L}{2} - \frac{h_2}{2} - z_2 + \Delta L. \quad (7d)$$

In Eqs. (7b)–(7d), z_i is the axial distance from the center of the i th bubble to the center of the tube [Fig. 1(a)]. As in the Oguz and Prosperetti (1998) model, a length correction factor, $\Delta L = 0.62 r_{\text{tube}}$ (Levine and Schwinger, 1948), is added to account for the additional inertia if the tube is immersed in an unbounded liquid. Additionally, assuming that the oscillating portion of the tube is the annulus enveloping the cylindrical gas bodies with same ring width h_i , the kinetic energy of each expanding tube section is approximated as $m_{\text{tube},i} dr_{i-3}^2/2$ for $i = 4, 5$, where $m_{\text{tube},i} = \rho_{\text{tube}} 2\pi r_{\text{tube}} t_{\text{tube}} h_{i-3}$. Therefore, define

$$m_i = (m_{\text{tube},i} + m_{\text{liq},i}) \left(\frac{r_{\text{tube}}}{2h_{i-3}} \right)^2 \quad \text{for } i = 4, 5, \quad (8)$$

where $m_{\text{liq},i}$ accounts for the inertia of the liquid outside the tube

By substituting Eqs. (3)–(8) into Eq. (1), a coupled system of equations results that can be written in the matrix form

$$\mathbf{M} \ddot{\mathbf{x}} + \mathbf{K} \mathbf{x} = 0. \quad (9)$$

The mass and spring matrices $\mathbf{M}$ and $\mathbf{K}$ can be expressed in terms of the previously defined m_i and k_i as

$$\mathbf{M} = \begin{pmatrix} m_1 & 0 & 0 & 0 & 0 \\ 0 & m_2 & 0 & 0 & 0 \\ 0 & 0 & m_3 & 0 & 0 \\ 0 & 0 & 0 & m_4 & 0 \\ 0 & 0 & 0 & 0 & m_5 \end{pmatrix} \quad (10a)$$

and

$$\mathbf{K} = \begin{pmatrix} k_1 & -k_1 & 0 & k_1 & 0 \\ -k_1 & k_1 + k_2 & -k_2 & -k_1 & k_2 \\ 0 & -k_2 & k_2 & 0 & -k_2 \\ k_1 & -k_1 & 0 & k_1 + k_4 & 0 \\ 0 & k_2 & -k_2 & 0 & k_2 + k_5 \end{pmatrix}. \quad (10b)$$

If harmonic motion $\mathbf{x}(t) = \mathbf{X}e^{i\omega t}$ is assumed, Eq. (9) reduces to an eigenvalue problem with eigenvalues and eigenvectors that correspond to the natural frequencies and mode shapes, respectively.

Limiting cases of this 5-degree-of-freedom model will be considered. For two bubbles in a rigid tube, the fourth and fifth degrees of freedom are eliminated, thus simplifying equations (10a), (10b) to

$$\mathbf{M} = \begin{pmatrix} m_1 & 0 & 0 \\ 0 & m_2 & 0 \\ 0 & 0 & m_3 \end{pmatrix} \quad (11a)$$

and

$$\mathbf{K} = \begin{pmatrix} k_1 & -k_1 & 0 \\ -k_1 & k_1 + k_2 & -k_2 \\ 0 & -k_2 & k_2 \end{pmatrix}. \quad (11b)$$

The two non-zero natural frequencies of this 3-degree-of-freedom system are the asymptotes of the 5-degree-of-freedom model in the limit of high tube stiffness.

For one bubble in a compliant tube, the second and fifth degrees of freedom are eliminated, thus simplifying equations (10a), (10b) to

$$\mathbf{M} = \begin{pmatrix} m_1 & 0 & 0 \\ 0 & m_3 & 0 \\ 0 & 0 & m_4 \end{pmatrix} \quad (11c)$$

and

$$\mathbf{K} = \begin{pmatrix} k_1 & -k_1 & k_1 \\ -k_1 & k_1 & -k_1 \\ k_1 & -k_1 & k_1 + k_4 \end{pmatrix}, \quad (11d)$$

where

$$L_{1,e} = \frac{L}{2} - \frac{h_1}{2} + z_1 + \Delta L \text{ and } L_{3,e} = \frac{L}{2} - \frac{h_1}{2} - z_1 + \Delta L.$$

III. SIMULATIONS: COUPLED BEM-FEM

Simulations of the three phase system, consisting of one or two gas bubbles, the surrounding liquid, and a solid elastic

tube, were done using a coupled BEM-FEM model developed in Miao and Gracewski (2008). The model geometry is axisymmetric with initially spherical gas bubbles, each with its center located on the axis of symmetry and a circular cylindrical tube with its generator along the axis of symmetry. Acoustic excitation is modeled as a pressure applied at infinity in the surrounding liquid similar to that used in the Rayleigh–Plesset and Gilmore models for spherically symmetric bubble dynamics (Leighton, 1994; Young, 1989).

The gas inside a bubble is assumed to be spatially uniform and to obey the polytropic gas law stated above Eq. (3) (Prosperetti, 1991). A pressure jump is applied at the gas-liquid boundary equal to the product of the surface tension and the local curvature (Miao and Gracewski, 2008; Harland, 2004). The liquid is assumed to be incompressible, irrotational, and inviscid, and therefore modeled with the potential flow equations using the boundary element method. A linear elastic finite element method was employed to solve the dynamic equations in the solid structure domain. Traction and the normal velocity are assumed continuous across the fluid-solid boundary to couple the finite element and boundary element domains.

To obtain the natural frequencies of two bubbles in a tube using the BEM-FEM model, two excitations are used. In-phase bubble responses were excited by a tensile half pulse of amplitude 1 kPa and frequency 1 kHz, applied at infinity. To excite out-of-phase bubble motion, the initial bubble radius and pressure of the first and second bubble were prescribed to correspond to the maximum expansion or the minimum contraction, respectively, of an oscillation cycle. To determine the free vibration frequencies from resulting equivalent bubble radius versus time responses, either a simple calculation of the inverse peak-to-peak time period was used or a spectral analysis was performed using a discrete Fourier transform (DFT) after a dc filter and Hanning window were applied to the time domain response.

IV. SIMULATIONS: COMSOL

Two different model types were used in COMSOL Multiphysics 3.5a. First, acoustics models were used to investigate multiple bubble interactions within rigid tubes. The effects of tube tapering, tube branching, tube cross-sectional shape, and radial position of a single bubble on a bubble's natural frequency were also explored with acoustic models. Second, coupled fluid-solid interaction models were used to investigate the effects of tube compliance.

The basic acoustics model consists of one or two air-filled bubbles within a cylindrical liquid-filled tube, submerged in a tank of liquid. The tank dimensions are either set to match experimental conditions (radius of 0.1275 m and a height of 0.355 m) or chosen to be large enough to minimize boundary effects (radius of 0.5 m and a height of 1.4 m). Unless otherwise stated, the radius of each bubble is 1 cm, and the tube has a radius $r_{\text{tube}} = 1.27$ cm, a thickness $t_{\text{tube}} = 0.3175$ cm, and a length $L = 20$ cm. Assuming time harmonic motion with angular frequency ω , the resulting eigenvalue problem is solved for the mode shapes and the

free vibration frequencies. The governing equation solved throughout each fluid subdomain is

$$\nabla^2 p + \frac{\omega^2}{c_s^2} p = 0, \quad (12)$$

where p is the pressure, and c_s is the sound speed. The above equation is solved along with specified boundary conditions on an axisymmetric domain. On the tank's boundaries, a sound-soft boundary, $p = 0$, is applied. A sound-hard boundary, $\partial p / \partial n = 0$, is applied to the surfaces of the rigid tube. On the axis of symmetry, $\partial p / \partial r = 0$ at $r = 0$.

A coupled fluid-solid model was used to investigate the effects of a compliant tube, using an identical geometry. The Navier–Stokes equations for an incompressible Newtonian liquid and the equations for a linear elastic, isotropic solid are solved simultaneously. Within the liquid subdomain,

$$\rho_l \frac{\partial \mathbf{u}}{\partial t} - \nabla \cdot [\eta (\nabla \mathbf{u} + (\nabla \mathbf{u})^T)] + \rho_l (\mathbf{u} \cdot \nabla) \mathbf{u} + \nabla p = \mathbf{0}, \quad (13)$$

where η is the dynamic viscosity, ρ_l is the liquid density, $\mathbf{u}$ is the velocity field, and p is the pressure. The continuity equation

$$\nabla \cdot \mathbf{u} = 0 \quad (14)$$

for an incompressible fluid is also satisfied. The values used for the liquid density is 1000 kg/m^3 and the liquid viscosity is 0.1 Pa s . Lower values of viscosity produced unstable results in COMSOL and increasing viscosity should not significantly affect the natural frequencies.

Along the axis of the tube and tank, there are axisymmetric boundary conditions

$$u_r = 0 \quad (15)$$

and

$$\sigma_{rz} = 0, \quad (16)$$

where σ_{rz} is the shear stress in the z direction. Fixed open boundary conditions subjected to atmospheric pressure are used on the walls of the tank. On these walls,

$$(-p\mathbf{I} + \eta (\nabla \mathbf{u} + (\nabla \mathbf{u})^T)) \mathbf{n} = -F_0 \mathbf{n}, \quad (17)$$

where F_0 is the magnitude of the stress vector in the negative normal direction. Equation (17) is also satisfied along the bubble's boundary, where the stress in the tangential direction is assumed to be zero. The pressure on this boundary is defined by using the polytropic gas law previously mentioned in the derivation of the 5-degree-of-freedom model. For investigating the effects of surface tension on micro-sized bubbles, a weak form of this boundary condition was used and the pressure

$$p = \left(p_0 + \frac{2\sigma}{R_0} \right) \left(\frac{V_0}{V} \right)^k - 2\sigma \bar{\kappa}, \quad (18)$$

was applied to the boundary, where σ is the surface tension and $\bar{\kappa}$ is the mean curvature. Continuity of normal stress and velocity across the tube-liquid interface is enforced.

The equation solved throughout the solid subdomain of the tube is

$$-\nabla \cdot \boldsymbol{\sigma} = \mathbf{F}, \quad (19)$$

where $\mathbf{F}$ denotes the traction force and $\boldsymbol{\sigma}$ is the stress tensor. The solid subdomain is linear elastic, where the elasticity modulus is varied, Poisson's ratio is 0.499, and density of the material is 1200 kg/m^3 . On the boundary of the solid,

$$\mathbf{F}_p = -\mathbf{n}_s p, \quad (20)$$

where $\mathbf{F}_p$ is the pressure load, in force per unit area, p is the liquid pressure, and $\mathbf{n}_s$ is the unit normal vector pointing from the solid domain into the fluid domain. The inner and outer boundaries of the tube are unconstrained. To increase stability, the ends of the tube are constrained to move only in the r direction, using a roller boundary condition.

In order to compare directly with the 5-degree-of-freedom model, an additional coupled fluid-solid model was created accounting only for the tube, the bubble(s), and the liquid inside the tube. The boundary conditions were identical to the previous model, with one exception. In the structural mechanics application mode, the ends and outer surface of the tube were subjected to atmospheric pressure and only the inside surface of the tube was subjected to the continuity condition stated in Eq. (20).

Both models use the moving mesh module with Laplace smoothing. A generalized α solver is used with a nonuniform triangular mesh. In order to excite the bubbles, half sine wave pressure pulses are applied to the boundaries of the bubbles. To excite in-phase oscillations, both pulses were given a positive sign, and to excite out-of-phase oscillations, the pulses were given opposite signs. Peaks in the discrete Fourier transform of the bubble radius versus time responses were used to determine the natural frequencies of the bubbles' oscillations.

V. EXPERIMENTS

Experiments were performed to obtain results corresponding to the 3-degree-of-freedom models for two bubbles in a rigid tube and for one bubble in a compliant tube. The experimental model for the rigid tube case consisted of two spherical bubbles with radii $R_0 \approx 1.1 \text{ cm}$ inside a tube with radius $r_{\text{tube}} = 1.75 \text{ cm}$, thickness $t_{\text{tube}} = 0.64 \text{ cm}$, and length $L = 20 \text{ cm}$. The tube material was acrylic with a modulus of elasticity $E = 3200 \text{ MPa}$ and a density of 1200 kg/m . The experimental model for the compliant tube consisted of a single spherical bubble with radius $R_0 \approx 0.78 \text{ cm}$ inside a tube with radius $r_{\text{tube}} = 1.27 \text{ cm}$, thickness $t_{\text{tube}} = 0.32 \text{ cm}$, and length $L = 20 \text{ cm}$. Bubble size varied slightly from experiment to experiment. Even though repeated experiments showed similar trends, it was not possible to average the results and therefore, plots of typical results are shown. The tube

material was latex with a modulus of elasticity $E = 1.7$ MPa (measured using an MTS Alliance RT/50) and a density of 1200 kg/m. Resonance frequencies for a single bubble in a compliant tube were compared with resonance frequencies of the same bubble in a rigid tube (Plexiglas with $E = 2200$ MPa and density of 1200 kg/m) with nominally the same dimensions.

The model of the spherical air filled bubble was created using a spherical air cavity within a cylinder consisting of a 3% weight mixture of agarose and water. The agar was chosen because it is acoustically similar to water and has low attenuation. The agar cylinder had the same diameter as the tube being tested allowing for accurate and secure placement within the tube. The air cavity was created by pouring the liquid agar at a temperature of 40°C into a cylindrical mold, which contained an ice sphere. Due to the low temperature of the ice, the agar solidified rapidly around the outer surface of the ice sphere. A syringe was then injected into the cavity in order to remove the excess water left by the melted ice. Once the syringe was removed, a small amount of gelatin was placed in the hole created by the syringe.

Although the ice spheres had a radius of 1.1 cm for the rigid tube case and 0.95 cm for the compliant tube case, the resulting bubble sizes differed slightly. The radii of the resulting cavities were inferred from measured values of the open volume resonance frequencies using the Minnaert equation (Minnaert, 1933)

$$f_0 = \frac{1}{2\pi R_0} \sqrt{\frac{3kp_0}{\rho_l}}. \quad (21)$$

The inferred radii were close to 1.1 and 0.95 cm, respectively, for the rigid and compliant tubes. When analyzing the final results for two bubbles with nearly equal radii, the radius was taken to be the average of the two bubbles' radii calculated from the Minnaert equation.

As shown in Fig. 3, a stainless steel cylindrical exposure chamber with a shaker (Labworks, Inc., model ET-140) on the bottom was used to measure the resonance frequencies of the system of bubbles. The chamber, 25.5 cm in diameter and 35.5 cm in height, was filled with degassed, deionized water at room temperature. The bubbles were located inside the tube at equal distances from the tube center. The tube was clamped horizontally inside the tank and located using a three-way positioner such that the bubble centers were 10 cm below the water surface and the tube was centered in the exposure chamber. The shaker was excited by a digital signal generator (Hewlett-Packard HP33120A) and power amplifier (Labworks, Inc., PA141). For the rigid tube case, the signal was swept through a range of frequencies, 90–400 Hz, at a rate of 4 Hz per second with a 0.5 s dwell every 2 Hz. For the compliant tube case the signal was swept through a range of frequencies from 80–600 Hz with a 0.5 s dwell every 2 Hz. These excitation frequencies were well below the first tank resonance so that the spatial variation of the pressure field across the bubble was negligible, as would be the case for micron-sized bubbles in an ultrasonic pressure wave field.

FIG. 3. (Color online) A stainless steel cylindrical exposure chamber (25.5 cm in diameter and 35.5 cm in height) is filled with degassed, deionized water at room temperature, with a shaker, mounted on the bottom, controlled by a digital signal generator and a power amplifier. A tube was clamped horizontally inside the tank and located using a three-way positioner, such that the bubble centers were consistently 10 cm below the water surface. A hydrophone was placed in a hole at the center of the tube to measure the pressure in the vicinity of the bubble(s). The resonance frequencies were identified by the peaks in the pressure versus frequency plot.

A hydrophone (B&K 8103) was placed within a small hole that was drilled at the center of the tube. The hole was plugged during testing so no water was able to exit or enter the tube.

The hydrophone was used to measure the pressure near the bubble(s). The resonance frequencies of the bubble system were identified by peaks in a pressure versus frequency plot.

VI. RESULTS AND DISCUSSION

The model for two bubbles in a rigid tube will first be compared to published models for two bubbles in an open volume. The 5-degree-of-freedom model reduces to a 3-degree-of-freedom model for a rigid tube with stiffness and mass matrices given by Eqs. (11a) and (11b) when $x_4 = x_5 = 0$. In the particular case of two equal sized-bubbles ($R_1 = R_2$) equidistant from the center of the tube ($z = z_1 = z_2$), the resulting eigenvalues are 0, k_1/m_1 , and $k_1(1/m_1 + 2/m_2)$. The mode shape for the zero frequency is the translational mode $(x_1, x_2, x_3) = (1, 1, 1)$, where the two bubbles are moving in the same direction without oscillatory motion. The first nonzero frequency corresponds to the in-phase bubble oscillation $(x_1, x_2, x_3) = (-1, 0, 1)$, where the liquid between the two bubbles remain stationary and liquid bodies to the left and the right are moving in the opposite directions with the same amplitude. The second nonzero frequency corresponds to the out-of-phase bubble oscillation $(x_1, x_2, x_3) = (1, -2m_1/m_2, 1)$, where the left bubble expands as right bubble contracts. Oguz and Prosperetti (1998) discussed the natural frequency of a bubble in rigid tube with one closed end, and stated that the liquid on the closed side of the bubble does not partake in the oscillation. It is clear that the in-phase oscillation of identically sized and symmetrically spaced bubbles is analogous to such an arrangement.

Results for equal sized bubbles in a rigid tube are shown in Fig. 4(a), where the abscissa is the separation distance

FIG. 4. Normalized natural frequencies for two equal-sized bubbles ($R_{10}=R_{20}=1$ cm) as a function of normalized separation distance $2z/L$, for bubbles (a) inside a rigid tube of $r_{\text{tube}}=1.27$ cm and $L=20$ cm and (b) in an open volume. Frequencies are normalized by f_0 , the natural frequency of a single bubble of radius $R_0=1$ cm in an open volume, represented by dashed line in (b). In (a), the solid lines are the results of the 3-degree-of-freedom model, and the circle markers are results from both simulations: coupled BEM-FEM and COMSOL acoustics model for two bubbles in a rigid tube. The dashed line represents the normalized frequency of a single bubble of radius $R_0=1$ cm situated at the same axial position as one of the two bubbles. In (b), the solid lines are calculated using Eq. (22).

normalized by the tube length $2z/L$ and the ordinate shows the natural frequency normalized by the open volume frequency of one bubble f/f_0 . The geometric constants used for the plot are $R_1=R_2=1.0$ cm, $r_{\text{tube}}=1.27$ cm, and $L=20$ cm. Results from the lumped parameter 3-degree-of-freedom model (solid lines) agree well with results from coupled BEM-FEM and COMSOL acoustics model for two bubbles in a rigid tube (circle markers), when the bubbles are close together and well within the tube. When the bubbles are near the tube opening, the limit of lumped parameter model is reached and the prediction becomes less accurate. In comparison, the simulation models show correct asymptotic behavior of frequencies tending to that of the open volume frequency. When the bubbles are further apart (near the tube ends), both the in-phase and out-of-phase frequencies approach the frequency of a single bubble in a rigid tube positioned at the same location, given by the dashed line in Fig. 4(a). As the bubbles approach each other and the center of the rigid tube, the two frequencies deviate away from the single bubble frequency. This behavior can be understood by comparing to the behavior of two bubbles in an open volume of liquid shown in Fig. 4(b).

Strasberg (1953) and Zabolotskaya (1984) developed models for two spherical gas bubbles interacting in an infinite liquid. The in-phase and out-of-phase natural frequencies are determined by their relative sizes and separation distance. In the case of equal radii, the normalized frequencies can be approximated by

$$\left(\frac{f}{f_0}\right)^2 = \left(1 \pm \frac{R_0}{2z} - \left(\frac{R_0}{2z}\right)^4\right)^{-1}, \quad (22)$$

where the plus sign is for bubbles oscillating in-phase, and the minus sign is for out-of-phase oscillation (Strasberg, 1953). As shown in Fig. 4(b), both frequencies tend toward f_0 as the separation distance $2z$ increases. As the separation distance between the two bubbles decreases, the in-phase frequency decreases below and the out-of-phase frequency increases above the single-bubble frequency.

Figure 5 shows the comparison plots for three different bubble size arrangements as predicted by lumped parameter model and COMSOL simulation. The tube dimensions are identical to ones used in Fig. 4, $r_{\text{tube}}=1.27$ cm and $L=20$ cm. One bubble size remains constant with $R_{10}=1.0$ cm, and three values for the radius of the second bubble are used: $R_{20}=0.50, 0.75$, and 1.0 cm. All three arrangements show both in- and out-of-phase frequencies and there is a good agreement between the lumped parameter model and the simulation when the bubbles are close together and are placed well within the tube. Whereas the predicted frequencies of the lumped parameter model deviate from the simulation results more when the bubbles are near the ends of tube. Again, the simulations results correctly show the asymptotic convergence toward the normalized single-bubble, open-volume frequencies, 1.0, 1.3, and 2.0 for $R_{20}=0.50, 0.75$, and 1.0 cm, respectively.

The axisymmetric acoustics model in COMSOL was extended to three-dimensions to investigate the effect of the tube's cross sectional shape and the radial position of a single bubble on the natural frequency of the bubble. For both square (2.54 by 2.54 cm) and rectangular (2.54 by 5.08 cm) cross-sections, the natural frequency differs from the lumped parameter model for a single bubble in a rigid tube with circular cross section (Oguz and Prosperetti, 1998) by less than 3% if an equivalent tube radius is obtained by setting the cross-sectional areas equal. As a single bubble is moved radially from the center of the rigid tube's cross section until it touches the inner surface of the tube, the maximum difference in frequency is 0.70%.

Vessel diameter gradually changes and vessels branch as blood travels from the heart to small blood vessels around the body. The axisymmetric acoustics model was used to investigate the effect of a tapering vessel on the natural frequency of a single bubble at the center of a rigid tube, as shown in Fig. 2(b). As the tapering angle of the tube θ increases, the frequency increases by less than 3% for a 20 cm long tube with a 2.54 cm diameter and for θ up to 7.3° . A 3-dimensional acoustics model was used to investigate the effect of tube branching on the natural frequency of a single bubble near the center of a rigid tube, using the same bubble and tube size as was used to obtain the simulation results in Fig. 4. A second tube, with the same diameter, was connected to the center of the first tube either at 45° or 90° . In the presence of the branching tube, the natural frequency at the center of the tube was less than 15% higher than if the branching tube was not present. This increase in natural frequency is expected because the additional tube would

FIG. 5. Comparison of normalized frequencies f/f_0 versus normalized separation distance $2z/L$ for two different sized bubbles equidistant from the center of the tube. Three sets of curves, corresponding to $R_2/R_1 = 0.5$ (triangular markers), 0.75 (square markers), and 1.0 (circular marker), show both in-phase (lower) and out-of-phase (upper) frequencies. Lumped parameter model (solid line) and COMSOL acoustics model results for two bubbles in a rigid tube (markers) agree well when the bubbles are placed deep inside the tube.

decrease the constraint on the bubble. As the angle between the tubes decreases, the frequency approaches that expected without the presence of a branching tube. (Results not shown.)

Figure 6 shows the result from the 5-degree-of-freedom lumped parameter model showing four nonzero natural frequencies plotted as a function of the elasticity modulus E . Two equal sized bubbles with radii are $R_1 = R_2 = 1.0$ cm are positioned with $z_1 = z_2 = 1.5$ cm within a compliant tube with $r_{\text{tube}} = 1.27$ cm, $L = 20$ cm, and $t_{\text{tube}} = 0.25$ cm. In Fig. 6, the solid lines correspond to the frequencies for bubbles oscillating in-phase and the dashed lines correspond to the frequencies for bubbles oscillating out-of-phase. In the limit of increasing stiffness, the lower two frequencies asymptote to the in- and out-of-phase frequencies observed for two bubbles in a rigid tube. For the results in Fig. 6, $m_{\text{liq},4} = m_{\text{liq},5}$ are chosen so that as the stiffness of the tube decreases, the third highest frequency asymptotically approaches the in-phase frequency for two bubbles in an open medium. In this limit of decreasing stiffness, the highest frequency in Fig. 6 approximately converges (within 7%) to the out-of-phase

FIG. 6. Plot of the four natural frequencies f versus elastic modulus E for two bubbles ($R_{10} = R_{20} = 1$ cm) equidistant from the tube center ($z_1, z_2 = \pm 1.5$ cm) in a compliant tube with $r_{\text{tube}} = 1.27$ cm, $t_{\text{tube}} = 0.25$ cm, and $L = 20$ cm. Lines show the analytical results from the 5-degree-of-freedom lumped parameter model and markers show the simulation results from COMSOL coupled fluid-structure interaction model for two bubbles in a flexible tube. The solid lines and filled markers correspond to in-phase frequencies. The dashed lines and open markers correspond to out-of-phase frequencies.

frequency for two bubbles in an open medium, whereas the lower two frequencies approach zero. The effects of the tube elastic modulus on the natural frequencies of the two bubble system were obtained using the coupled fluid-structure COMSOL model. Both the COMSOL results and the lumped parameter results follow the same trends, but the lumped parameter results are shifted to lower elastic modulus. The difference is likely due to the assumption in the lumped parameter model that the tube radial displacement is uniform over the entire contact area between the cylindrical bubble and the tube. Considering the simplifying assumptions, the agreement between the lumped parameter model and the COMSOL simulation is quite good.

Figure 7 shows typical experimental results for equal-sized bubbles in a rigid tube and for a single bubble in a rigid tube. The open squares correspond to the experimental in-phase natural frequency, the closed squares correspond to the out-of-phase experimental natural frequency and the circles correspond to the experimental natural frequency of a single bubble. Measured resonance frequencies are compared to the natural frequencies predicted by the lumped parameter 3-degree-of-freedom model (solid lines) and the normalized frequency of a single bubble situated at the same axial position as one of the two bubbles (dashed line). Although the experimental results are consistently higher than the numerical predictions, the general trend of the experimental results was in good agreement with that of the lumped parameter model. On the experimental pressure versus frequency plots measured by the hydrophone for two bubbles in a rigid tube, the lower (in-phase) resonance frequency had a significantly greater amplitude, indicating that this frequency may be the more easily excited by an acoustic source.

Figure 8 shows typical experimental results for one bubble in a compliant tube and the same bubble in a rigid tube with nominally the same dimensions as the compliant tube. The closed and open squares correspond to the upper frequency and lower frequency, respectively, obtained from the experimental results for one bubble in a compliant tube. The

FIG. 7. Normalized natural frequencies for two equal-sized bubbles ($R_1 \sim R_2 \sim 1.1$ cm) and a single bubble ($R_0 \sim 1.1$ cm) inside a stiff tube ($r_{\text{tube}} = 1.75$ cm, $t_{\text{tube}} = 0.64$ cm, $L = 20$ cm, $E = 3200$ MPa). The frequencies are normalized by the average of the two bubbles experimental free field natural frequencies, f_0 . The solid lines correspond to the 3-degree-of-freedom model for two bubbles in a rigid tube, and the squares are from the experimental results for two bubbles in a tube. The dashed line represents the numerical prediction of the frequency of a single bubble at the same axial positions as one of the two bubbles, and the circles represent the single bubble experimental results.

FIG. 8. Normalized natural frequencies for one bubble in a compliant tube (solid lines and squares) and one bubble in a rigid tube (dashed line and circles) for $R_0 = 0.78$ cm, $r_{\text{tube}} = 1.27$ cm, $t_{\text{tube}} = 0.32$ cm, $L = 20$ cm. The frequencies are normalized by the experimental free field natural frequency, f_0 . The solid lines are from the 3-degree-of-freedom model for one bubble in a compliant tube and the squares are the corresponding experimental results. An elastic modulus of $E = 0.6$ MPa in the 3-degree-of-freedom model minimized the least squared error between the predicted and measured frequencies, so was used for this plot. The dashed line is the numerical prediction from the 1 -degree-of-freedom model for one bubble in a rigid tube and the circles are the corresponding experimental results.

circles correspond to the experimental frequency for one bubble in a rigid tube. The experimental values are compared to the 3-degree-of-freedom lumped parameter model for one bubble in a compliant tube (solid lines) and the 1-degree-of-freedom lumped parameter model for one bubble in a rigid tube (dashed line). An elastic modulus of $E = 0.6$ MPa in the 3-degree-of-freedom model minimized the least squared error between the predicted and measured frequencies, so was used for this plot. The agreement between the lumped parameter models and the experimental data is quite good, differing by less than 20%. On the experimental pressure versus frequency plots measured by the hydrophone for one bubble in a compliant tube, the higher resonance frequency had a significantly greater amplitude, indicating that this frequency may be the more easily excited by an acoustic source.

The effect of surface tension on the natural frequencies of microbubbles within vessels was investigated using the COMSOL coupled fluid-structure interaction model. All geometry was scaled by a factor of 2500 so that the bubbles and tube were approximately the size of ultrasound echo contrast agents within a capillary. Figure 9 is a plot of normalized natural frequency versus bubble position for two bubbles with $R_0 = 4$ μm in a rigid tube with $r_{\text{tube}} = 5.08$ μm . The natural frequencies of bubbles with and without surface tension were normalized by the free-field natural frequencies of the bubbles with and without surface tension, respectively. Although the surface tension increases the natural frequency of the bubble, surface tension has negligible effect on the behavior of the normalized frequency f/f_0 for a bubble within a tube.

VII. SUMMARY

A 5-degree-of-freedom lumped parameter model was developed for analytical solution of the natural frequencies of two bubbles in a compliant tube. The proximity of the bubbles and the compliance of the surrounding vessel can

FIG. 9. Normalized natural frequencies for two equal-sized bubbles ($R_{10} = R_{20} = 4$ μm) as a function of normalized separation distance $2z/L$, for bubbles inside a rigid tube of $r_{\text{tube}} = 5.08$ μm , $L = 80$ μm , and $t_{\text{tube}} = 1$ μm . The open and closed markers correspond to COMSOL model results with and without surface tension ($\sigma = 0.0643$ N/m), respectively. The lines represent the lumped parameter model for two bubbles within a tube (solid) and one bubble within a tube (dotted).

significantly alter the resulting natural frequencies of the system, when compared to either the case of two bubbles in an open medium or one bubble in a rigid tube. Both bubble-tube and bubble-bubble interactions may be important for ultrasound contrast agents administered in capillaries. First, an average contrast agent bubble radius is comparable to the inner radius of the capillaries. Second, the maximum value of the average separation distance is approximately 8–14 times the radius of bubbles, often much lower (Allen *et al.*, 2003). The 5-degree-of-freedom lumped parameter model developed in this paper provides more insight into the system of interest than previously developed models, such as one bubble in a rigid tube, and includes this model as a limiting case.

The 5-degree-of-freedom model can be reduced to a 3-degree-of-freedom model for two bubbles in a rigid tube. This 3-degree-of-freedom system was shown to have 2 non-zero natural frequencies, corresponding to in- and out-of-phase bubble oscillations. In the case of two bubbles equidistant from the tube center, the two non-zero frequencies converge toward their respective single-bubble frequencies as the separation distance increases. Although the 3-degree-of-freedom model result deviates from the expected value for bubbles at the ends of tubes due to limitations of the model, it agrees well with the simulation results for bubbles situated sufficiently inside the tube.

The results from this 3-degree-of-freedom model showed good agreement with less than 5% difference on average for in-phase frequencies and less than 8% difference for out-of-phase frequencies, when compared with the results obtained by two different simulation methods: a coupled boundary element method-finite element method (BEM-FEM) code and a COMSOL Multiphysics acoustics model. Experimental measurements of the resonance frequencies of two bubbles in a rigid tube, obtained using approximately spherical cavities in agarose cylinders, exhibited the same trends as the models, but were approximately 14% higher for the in-phase natural frequency and 20% higher for the out-of-phase and single bubble natural frequencies. Previous experimental results obtained using a balloon model rather than agarose cylinders (Jang *et al.*, 2009,

Young, 2006) were only 5% higher than the numerical predictions for a single bubble in a rigid tube. The increased difference is most likely due to the added effect of the agarose stiffness on the bubble response.

The 5-degree-of-freedom model can be reduced to a 3-degree-of-freedom model for one bubble in a compliant tube. Experimental measurement of the resonance frequencies for one bubble in a compliant tube showed two frequencies that agreed well with the 3-degree-of-freedom model for this case. The measured pressure amplitude was higher for the higher of the two frequencies, indicating that the higher frequency may be more easily excited by an acoustic source.

The results from the 5-degree-of-freedom model show four non-zero frequencies accounting for two in- and two out-of-phase oscillations for two bubbles in a compliant vessel. As stiffness increases, the two lower frequencies converge to frequencies corresponding to in- and out-of-phase oscillations of two bubbles in a rigid tube. In the opposite limit as the stiffness decreases, the two upper frequencies approximately converge to frequencies corresponding to in- and out-of-phase oscillations of two bubbles in an open-medium. All of these results agree well with the COMSOL model simulations.

This lumped parameter model is limited to small amplitude motions and linear vessel response. To investigate damage mechanisms of ultrasonically excited bubbles, a coupled boundary element and nonlinear finite element method is being developed, that accounts for large deformations and the nonlinear elasticity of the vessel.

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