Nonspherical Dynamics and Shape Stability of Ultrasound Contrast Agent Microbubbles near a Rigid Boundary

Michael L. Calvisi, Department of Mechanical and Aerospace Engineering, University of Colorado, Colorado Springs, USA

Sean S. Neu, Department of Mechanical and Aerospace Engineering, University of Colorado, Colorado Springs, USA

Long Abstract

Introduction

Ultrasound contrast agents (UCAs) are encapsulated gas-filled bubbles that are a few micrometers in diameter [1] with a shell typically comprised of lipid, protein, or polymer. When injected into the bloodstream, the high compressibility of these microbubbles, relative to the surrounding blood and tissue, and their highly nonlinear response to ultrasound, leads to strong enhancement of the blood-tissue contrast in the resulting ultrasound image. While UCAs have been commercially available since 1991 [2], they have more recently generated interest for use in therapeutic applications, for example, as vehicles for drug delivery and gene therapy, and thermal and mechanical tissue ablation [3].

In order to effectively utilize UCAs in biomedical applications, it is necessary to understand the interplay between the incident ultrasound and the dynamics of the encapsulated microbubbles. While several theoretical models have been proposed to model UCAs, they have been mainly restricted to the case of spherical oscillations [4-6]. Here, we use the boundary element method (BEM) to investigate the dynamics and shape stability of *nonspherical* oscillations of an ultrasonically-forced, encapsulated microbubble near a rigid boundary. Stability diagrams are developed to delineate regions of stability from instability in parameter ranges of ultrasound frequency and acoustic pressure relevant to medical applications.

1. Methods

We assume the flow of the exterior liquid is irrotational, which permits the use of a fluid potential, ϕ. We further assume the liquid is incompressible, which reduces the equations governing the flow of the exterior liquid to Laplace's equation for ϕ. We apply an axisymmetric BEM model for nonspherical, uncoated bubbles based on prior work by Blake *et al.* and Pearson *et al*. [7-8]. The presence of a nearby rigid boundary is simulated through addition of a term for an image bubble in the Green's function used in the integral solution of Laplace's equation for ϕ. The influence of a shell is incorporated into the model by adapting a model by Hoff [6] for spherical contrast agents to the case of nonspherical oscillations [9]. The Hoff model assumes an infinitesimally thin shell described as an incompressible, viscoelastic solid that imparts a radial pressure difference, ΔP_S, across the bubble surface according to,

$$\Delta P_S = 12\frac{d_s}{R_0^2}\left(\frac{R_0}{R}\right)^4 \left(G_s(R-R_0) + \mu_s\dot{R}\right),$$

where d_s is the shell thickness, R and R_0 are the instantaneous and initial bubble radii, respectively, and G_s and μ_s are the shear modulus and shear viscosity of the shell, respectively. The overdot represents a derivative with respect to time. To adapt the Hoff model [6] to nonspherical bubbles, we treat ΔP_S as a local quantity that varies along the bubble surface and replace the first radius *R* on the right hand side of the above equation with $R_c = 1/K$, where R_c is the radius of curvature and *K* is the local mean curvature [9]. The second radius term is determined from the equivalent radius of a sphere that has the same volume, V, as the nonspherical bubble. The radial velocity, $\dot{R}$, is substituted with the absolute value of the local normal velocity at the bubble surface. To incorporate the influence of ΔP_S on the bubble dynamics, we include it in the dimensionless dynamic boundary condition at node i of the bubble surface, which is determined from Bernoulli's equation,

$$\frac{D\phi_i}{Dt} = 1 + \frac{|\boldsymbol{v}_i^*|^2}{2} + \frac{K_i^*}{We} - P_b^* + P_\infty^*(t) + \Delta P_{Si}^* ,$$

where $\boldsymbol{v}_i$ is the liquid velocity at node i, K is the mean curvature, We is the Weber number, P_b is the pressure inside the bubble (determined by the polytropic equation), P_∞ is the far-field pressure, and the asterisk (*) denotes a dimensionless quantity. The ultrasonic forcing is simulated by adding a sinusoidal term to the far-field pressure in addition to the hydrostatic pressure.

2. Results

Simulations are run for a maximum of ten acoustic cycles if no unstable conditions are met, such as contact with the rigid boundary or jet penetration through the entire bubble volume. The duration of the acoustic forcing reflects the maximum pulse length typically used in medical ultrasound. The range of pressure amplitude and acoustic frequency studied here reflects typical clinical ranges used for medical ultrasound (0.5-3 atm and 0.5-18 MHz). The dimensionless standoff distance, h^* (the ratio of the initial distance between the bubble center and the rigid boundary to the initial radius, R_0), is varied to determine the effect of standoff distance on stability. The dimensionless acoustic frequency, f^*, is the ratio of the acoustic driving frequency to the natural frequency of the initial bubble. In Figure 1 is shown a representative stability diagram for the case h^* = 1.5.

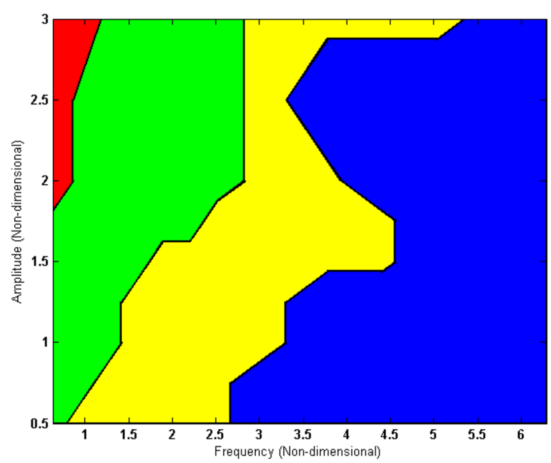

Figure 1. Stability diagram of an encapsulated, argon-filled bubble in water with R_0 = 4.5 µm, dimensionless standoff distance h^* = 1.5, G_S = 10 MPa, μ_S = 0.4 Pa-s, and d_S = 15 nm. Various stability conditions are color-coded: blue = bubble does not contact rigid boundary and jet does not penetrate the bubble, yellow = bubble contacts rigid boundary but jet does not penetrate the bubble, green = jet penetrates through the entire bubble prior to contact with the rigid boundary, and red = jet penetrates through the entire bubble after contact with the rigid boundary. Acoustic frequency and amplitude are normalized with respect to the natural frequency of the initial bubble and the hydrostatic pressure, respectively.

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