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The physics of nanoshelled microbubbles

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Abstract

Nanoshelled microbubbles are suitable markers for perfused areas in ultrasonic imaging, and have potential applications in therapy. With radii up to 5 microns, their resonance frequencies are in the lower megahertz range. We explored the physics of nanoshelled microbubbles, with special attention to the influence of the nanoshell on the oscillation offset with respect to the driving phase. Microbubbles above resonance size oscillate π rad out of phase with respect to microbubbles under resonance size. As the damping becomes less, this transition in offset becomes more abrupt. Therefore, the damping due to the friction of the nanoshell can be derived from this abruptness. We support our results with some high-speed optical observations of oscillating microbubbles in an ultrasonic field.

1 Introduction

Ultrasound contrast agents consist of gas bubbles with equilibrium radii R_0 up to $5 \mu\text{m}$. These microbubbles are small enough to be transported intravascularly and to pass through capillary vessels. Because their resonance frequencies coincide with those applied in ultrasonic imaging, they are suitable markers for the detection of perfused areas. The only ultrasound contrast agent currently allowed for clinical use in Europe is SonoVueTM. It is a second generation ultrasound contrast agent, consisting of SF₆ gas microbubbles encapsulated by an elastic lipid nanoshell. To enhance detection techniques, predicting the dynamic behavior of ultrasound insonified nanoshelled microbubbles has been of much clinical interest.

In this paper, we present a brief overview of the physics of ultrasound-insonified oscillating microbubbles that are encapsulated by a nanoshell. More specifically, we investigate the influence of the nanoshell on the oscillation offset with respect to the driving phase. We support our results with some high-speed optical observations of oscillating microbubbles in an ultrasonic field.

2 Theory

Let us consider a microbubble with an equilibrium radius R_0 and a shell thickness $a \ll R_0$. In equilibrium, the gas pressure inside the bubble p_{g0} can be expressed as:

$$p_{g0} = p_0^\infty - p_v + \frac{2\sigma}{R_0}. \quad (1)$$

Here, p_0^∞ is the static pressure of the liquid, p_v is the vapor pressure, and σ is the surface tension.

For an encapsulated gas bubble, the oscillating behavior has been described by a modified RPNNP equation, named after its developers Rayleigh, Plesset, Noltingk, Neppiras, and Poritsky [1]:

$$\rho R \ddot{R} + \frac{3}{2} \rho \dot{R}^2 = p_{g0} \left(\frac{R_0}{R} \right)^{3\gamma} + p_v - p_0^\infty - \frac{2\sigma}{R} - 2S_p \left(\frac{1}{R_0} - \frac{1}{R} \right) - \delta \omega \rho R \dot{R} - p_a(t), \quad (2)$$

where $p_a(t)$ is the acoustic pressure in time, R is the instantaneous microbubble radius, S_p is a shell elasticity parameter, δ is the total damping coefficient, γ is the polytropic exponent, ρ is the liquid density, and ω is the angular driving frequency.

The total damping coefficient is a summation of the damping coefficient due to radiation δ_r , the damping coefficient due to the friction of the shell δ_s , the damping coefficient due to heat conduction δ_t , and the damping coefficient due to the viscosity of the surrounding liquid δ_v [1]:

$$\delta = \delta_r + \delta_s + \delta_t + \delta_v, \quad (3)$$

$$\delta_r = \frac{\omega R}{c}, \quad \delta_s = \frac{S_f}{m\omega}, \quad \delta_v = \frac{4\eta}{\rho \omega R^2},$$

$$\delta_t = \frac{\frac{\sinh z + \sin z}{\cosh z - \cos z} - \frac{2}{z}}{\frac{z}{3(\gamma-1)} + \frac{\sinh z - \sin z}{\cosh z - \cos z}},$$

where c is the speed of sound in the liquid, m is the replace mass of the microbubble [2], S_f is the shell friction, η is the viscosity of the liquid, and $z = R_0/l_D$, in which l_D is the thermal boundary layer thickness:

$$l_D = \sqrt{\frac{K_g}{2 \omega \rho_g C_p}}. \quad (4)$$

Here, C_p is specific heat of the gas, K_g is the thermal conductivity of the gas, and ρ_g is the density of the gas.

For $a \ll R_0$, δ may be assumed constant over an oscillation.

3 Materials and methods

We simulated the oscillating behavior of free microbubbles with various sizes in a harmonic acoustic field $p_a(t) = p^+ \sin \omega t$, where p^+ is the pressure amplitude. Equation (2) was computed with a MATLAB[®] (The MathWorks, Inc., Natick, MA) program. The following fixed parameters were used: $c=1480 \text{ m s}^{-1}$, $C_p=1000 \text{ J kg}^{-1} \text{ K}^{-1}$, $K_g=0.0234 \text{ J m}^{-1} \text{ s}^{-1} \text{ K}^{-1}$, $p_0^\infty=1 \text{ atm}$, $p_v=2.33 \text{ Pa}$, $S_p=0 \text{ kg s}^{-2}$, $\gamma=1.4$, $\eta=0.001 \text{ Pa s}$, $\rho=998 \text{ kg m}^{-3}$, $\rho=1 \text{ kg m}^{-3}$, $\sigma=0.072 \text{ kg s}^{-2}$, and $\omega/2\pi=0.5 \text{ MHz}$. For microbubble radii $R_0 < 10 \mu\text{m}$, the offsets ϕ between p_a and R were computed by comparing the maximal microbubble radii $R(\omega t - \phi) = R_{\text{max}}$ with $p_a(\omega t) = p^+$.

4 Results and Discussion

An example of simulated oscillating behavior of a microbubble is shown in the figure below.

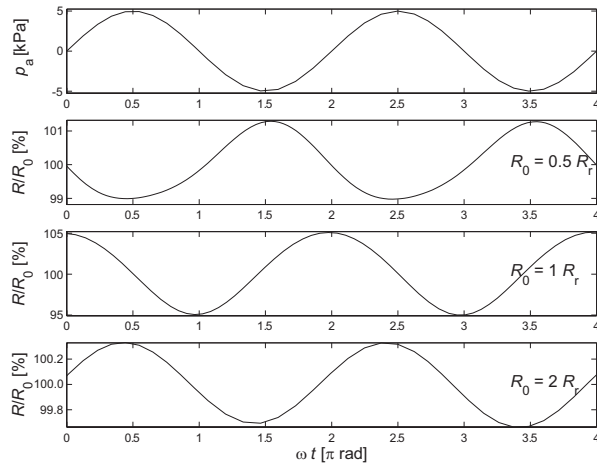


Figure 1: Simulations of the relative bubble surface excursion as a function of the driving phase for underdamped ($\delta = 0.2$) microbubbles with equilibrium radii $R_0 = \frac{1}{2}R_r, 1R_r, 2R_r$, where R_r is the resonant radius, during insonification at $\omega/2\pi=0.5 \text{ MHz}$ and $p^+=5 \text{ kPa}$.

The microbubble with half resonance size oscillates exactly $\phi = \pi$ rad out of phase with the driving pressure. At resonance, $\phi = \frac{3}{2}\pi$ rad, and at double resonance $\phi = 2\pi$ rad. As the damping becomes less, the transition in offset becomes more abrupt, as Figure 2 demonstrates.

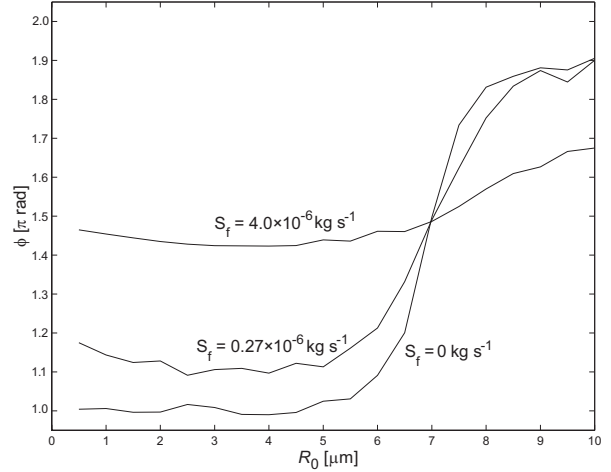


Figure 2: ϕ as a function of R_0 , for typical values of the shell friction: $S_f=0 \text{ kg s}^{-1}$ (unencapsulated), $S_f=0.27 \times 10^{-6} \text{ kg s}^{-1}$ (SonoVueTM), and $S_f=4 \times 10^{-6} \text{ kg s}^{-1}$ (Albunex[®]).

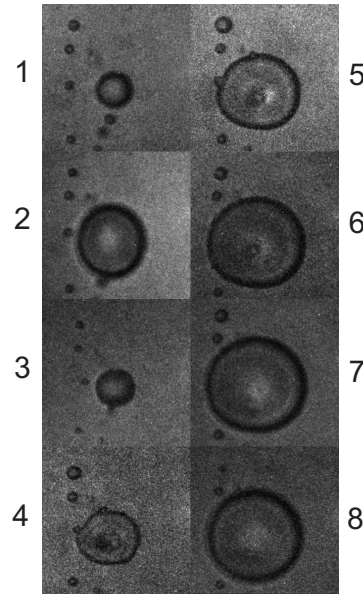


Figure 3: High-speed movie of experimental nanoshelled microbubbles (Bracco Research SA, Genève, Switzerland). Frame 1 has been captured prior to ultrasound arrival. The other seven frames cover one full ultrasonic cycle. Each frame corresponds to a $40 \times 40 \mu\text{m}^2$ area. The central bubble oscillates $\frac{1}{3}\pi$ out of phase with the upper left microbubble. Clearly, the damping due to the shell friction is minimal in this example.

References

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