A Note on the Nonlinear Attenuation of an Ultrasound Contrast Agent Calculated by Rayleigh-Plesset Equation

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Abstract
The dynamics of microbubble-based Ultrasound contrast agents (UCAs) is governed by the Rayleigh-Plesset equation, of which the linearization is used to formulate the attenuation of an UCA under the excitation of ultrasound. Recent experimental observations of encapsulated microbubbles showed nonlinear behaviors of energy attenuation at very low excitation pressures inconsistent with the linear attenuation theory. In this note, we formulate the attenuation computation employing a nonlinear Rayleigh-Plesset equation. Comparisons between linear attenuation are presented.

Keywords: UCA, ODE, nonlinear attenuation

Introduction
Microbubbles with encapsulated shells have been successfully applied in the medical field as Ultrasound Contrast Agents (UCAs) for imaging purposes. Their dynamics is governed by the Rayleigh-Plesset equation. The physical properties of shells, playing an essential role in the characterization of the dynamical behaviors of an UCA, are determined by attenuation measurements of the UCA suspension with low acoustic pressures. The estimation of shell properties usually done by fitting experimental attenuation data to a model equation (Xia, Porter et al. 2015).

Recent experimental observations (Gong, Cabodi et al. 2014, Xia, Paul et al. 2014, Xia, Porter et al. 2015) and numerical simulations (Overvelde, Garbin et al. 2010) on UCAs with lipid shells have shown nonlinear behaviors even the excitation pressure kept sufficient low (then the oscillations of the bubbles are linear), which is inconsistent with the linear attenuation theory. We have interpreted the nonlinear attenuation in details when the dynamics of lipid-coated UCAs is linear (Xia, Porter et al. 2015). Later on, we also observed the nonlinear phenomena relevant to the attenuation in the characterization of polymer-coated UCAs(Xia, Paul et al. 2014, Xia 2018). Since the interpretation of the lipid-coated UCAs may not readily apply to the polymer-coated UCAs, we try to resolve the discrepancy by checking the attenuation theory.
Attenuation of UCAs suspension can be calculated using two different theories. One is using the analogy of a simple harmonic oscillator (Medwin 1977), and the other is using the method of an effective medium (Commander and Prosperetti 1989). We have shown that these two calculations are identical at low bubble volume fractions (Xia 2018).

In this note, we adopt the first method for calculating of the attenuation of an UCA. Using an equation for balancing the mechanical energy of the UCA, a formula that is capable of computing attenuation coefficient of the UCA oscillating nonlinearly is obtained. The linear approximation of the new formula is also compared with the classical formula.

**Mathematical Derivation**

**Linear attenuation theory**

Recall the equation for a linear oscillator

\[ \ddot{X} + \omega_0^2 \delta \dot{X} + \omega_0^2 X = F \sin(\omega t) \]  

(1)

where \( \omega_0 \) is the resonance frequency and \( \delta \) is a dimensionless frequency-dependent damping constant. The above equation admits the following steady-state solution

\[ X(t) = \frac{F}{\omega_0 \sqrt{\left( \delta \omega_0 \right)^2 + \frac{1}{\omega_0^2} \left( \omega_0^2 - \omega^2 \right)^2}} \sin(\omega t + \phi) \]  

(2)

and

\[ \phi = \arctan \left( \frac{\omega \omega_0 \delta}{\omega^2 - \omega_0^2} \right) \]  

(3)

The dynamical equation for a spherical microbubble of equilibrium radius \( R_0 \), undergoing forced linear pulsations (\( R(t) = R_0 + X(t) \) and \( \sup \{ X(t) \} \ll R_0 \)) at external force can be written in the form (Chatterjee and Sarkar 2003)

\[ \ddot{X} + \frac{4 \mu + 4 \kappa'}{\rho R_0^2} \dot{X} + \frac{3k \mu_0 + 2 \gamma \frac{3k - 1}{R_0}}{\rho R_0^2} X = \frac{P_A}{\rho R_0^3} \sin(\omega t) \]  

(4)

with

\[ \delta_1 = \frac{4 \mu}{\omega_0 R_0^2 \rho}, \quad \delta_2 = \frac{4 \kappa'}{\omega_0 R_0^3 \rho} \]  

(5)
\[ \omega_0^2 = \frac{1}{\rho R_0^2} \left( 3kP_0 + \frac{2\gamma(3k-1)}{R_0} \right) \quad \text{and} \quad F = \frac{P_a}{\rho R_0} \quad (6) \]

where \( \omega_0 \) is the bubble’s pulsation resonance frequency, \( \rho \) is the density of the surrounding liquid, \( k \) is the polytropic constant, \( \gamma \) is the surface tension, \( c \) is the acoustic wave speed, \( P_a \) is the amplitude of the excitation pressure. Also \( \delta = \delta_v + \delta_i \), which the left-hand side stand for liquid viscous and interfacial damping, respectively.

Medwin gave the extinction cross-section \( \sigma_e \) as (Medwin 1977)

\[ \sigma_e = 4\pi R_0^2 \frac{\delta c}{\omega_0 R_0^2} \frac{\Omega^2}{\left(1 - \Omega^2\right)^2 + \delta^2 \Omega^2} \quad (7) \]

\( \Omega = \omega / \omega_0 \). The attenuation coefficient \( \alpha \) for a single bubble then can be computed readily by multiplying a constant parameter, which is widely used to estimate shell parameters of encapsulated microbubbles. Therefore, without losing generality in the article, the extinction cross section is treated as the final result for attenuation calculations.

**Nonlinear attenuation theory**

To develop a nonlinear attenuation formula, we assume an UCA oscillates spherically without thermal dissipation in the incompressible liquid, the kinetic energy of the UCA can be written as

\[ K = \frac{1}{2}mv^2 = 2\pi\rho R^3 \dot{R} \quad (8) \]

and the work of force

\[ W = \int_{R_0}^R \left( p(R,t) - p_\infty(t) \right) 4\pi R^2 dR \quad (9) \]

The balance of mechanical energy gives

\[ K = W \quad (10) \]

\[ 2\pi\rho R^3 \dot{R}^2 = \int_{R_0}^R \left( p(R,t) - p_\infty(t) \right) 4\pi R^2 dR \quad (11) \]

Take derivative for Eq.(11) with respect to \( t \)
\[ 4\pi \rho R^2 \dot{R} \left( R\ddot{R} + \frac{3}{2} \dot{R}^2 \right) = \left( p(R,t) - p_\infty(t) \right) 4\pi R^2 \dot{R} \]  

(12)

The above Eq.(12) is the equation of power, and it can be simplified to the so-called Rayleigh-Plesset equation after dividing both sides by \( 4\pi \rho R^2 \dot{R} \). Recall the Newtonian model again (Chatterjee and Sarkar 2003), the pressure on the outside shell is

\[ p(R,t) = P_{g0} \left( \frac{R_0}{R} \right)^{3k} - 4\mu \frac{\dot{R}}{R} - 2\gamma \frac{1}{R} - 4\kappa^2 \frac{\dot{R}}{R^2} \]  

(13)

And the far field pressure is

\[ p_\infty(t) = P_0 - P_A \sin(\omega t) \]  

(14)

Substituting Eq.(13) and Eq.(14) into Eq.(12) and dividing it by \( 4\pi \rho R^2 \), we obtain an equation for intensity with the following form

\[ \rho \dot{R} \left( R\ddot{R} + \frac{3}{2} \dot{R}^2 \right) = 16 \left( p(R,t) - p_\infty(t) \right) \dot{R} \]  

(15)

\[ \rho_k \ddot{R} \left( R\ddot{R} + \frac{3}{2} \dot{R}^2 \right) + 2\gamma \frac{\dot{R}}{R} + \left( 4\mu \frac{\dot{R}}{R} + 4\kappa^2 \frac{\dot{R}}{R^2} \right) \dot{R} + \left( P_0 - P_{g0} \left( \frac{R_0}{R} \right)^{3k} \right) \dot{R} = \dot{R} P_A \sin(\omega t) \]  

(16)

Let denote the following quantities briefly

\[ I_k = \rho_k \dot{R} \left( R\ddot{R} + \frac{3}{2} \dot{R}^2 \right), \quad I_p = 2\gamma \frac{\dot{R}}{R} \]  

(17)

\[ I_q = \left( 4\mu \frac{\dot{R}}{R} + 4\kappa^2 \frac{\dot{R}}{R^2} \right) \dot{R}, \quad I_u = \left( P_0 - P_{g0} \left( \frac{R_0}{R} \right)^{3k} \right) \dot{R} \]  

(18)

\[ I_A := \frac{P_A^2}{2\rho c} \]  

(19)

of which the meanings are explained in Eq.(16). The instantaneous extinction cross section thus can be defined as

\[ \sigma_e(t) := \frac{\Pi_d}{I_A} \]  

(20)
where $\Pi_d = 4\pi R^2 I_d$ is the power supplied to the bubble (Xia 2018), and $I_d = p_A \dot{R} = I_k + I_p + I_q + I_u$. Therefore

$$\sigma_e(t) = 8\pi \rho c R^2 \frac{p_A \dot{R}}{P_A^2}$$

(21)

is the formula for calculating the energy extinctions. For numerical calculation, we can simplify the formula using the conservation of energy and assuming the bubble at the status of maximum kinetic energy, such that $R(t) = R_0$ and $I_p + I_u = 0$, then the average value of $I_d$ is

$$\langle I_d \rangle = \frac{1}{2} (I_{k,max} + I_{q,max})$$

(22)

Finally, the general formula for numerical calculating extinction cross section is written as

$$\sigma_e = 4\pi R_0^2 \rho c \frac{I_{k,max} + I_{q,max}}{P_A^2}$$

(23)

Note that the above equation can be easily approximated to that of linear attenuations by comparing that the extinction cross section is the sum of absorption and scattering cross-section, which is $\sigma_e = \sigma_a + \sigma_s$.

**Results**

In order to compare the difference between the nonlinear formula Eq.(23) and the linear Eq.(7), we take an encapsulated microbubble of a radius $R_0 = 2.5 \times 10^{-6}$ m, the dilatational viscosity $\kappa' = 2.0 \times 10^{-8}$ N.s/m, and the surface tension (compares to elasticity) $\gamma = 0.5$ N/m. The above values are typical properties of a lipid encapsulated microbubbles (Paul, Russakow et al. 2013). The simulation results are presented in Figure 1. It is easy to see that at the lowest excitation pressure of 5 kPa, the linear and nonlinear curves are almost the same. With increasing the excitation pressures from 5 kPa to 100 kPa, the maximum $\sigma_e$ at each peak also increases proportionally. However, since the linear attenuation formula does not contain the term of the excitation pressure, all the linear curves keep the same. This indicates that taking attenuation measurements at higher excitation pressures may be subjected to potential bias. For the purpose of illustration, the nonlinear curves at 500 kPa are also plotted in Figure 1. At this high excitation pressure, the curve loses its smoothness, which means the bubble is oscillating most nonlinearly.
From the same figure, a conspicuous fact is that the resonance frequency does not change in response to the excitation pressures. Thus, although bubble may oscillate nonlinearly, solely increasing the excitation pressure does not shift its resonance frequency. Therefore, the experimental observation of frequency shifting (Gong, Cabodi et al. 2014) may relate to the change of the shell structure.

![Figure 1: The extinction cross section vs. excitation frequency at four different excitation pressures.](image)

We should also admit that, in this article, only a single bubble is studied. A bubbly liquid in which the attenuation is the group effects of the bubble suspension may exhibit totally distinct characteristics. To check this, we can compare the energy absorbed by oscillating bubbles. For instance, at 50 kPa, we can calculate that the energy stored in a single UCA is $4\pi R^2 \rho c l_d = 20 (N/m^3)^2$, whereas the energy of the incoming wave is $P_A^2 = 2.5 \times 10^9 (N/m^3)^2$. It is evident to see that the bubble won’t affect the external force since the difference is too much. As for a bubble suspension, suppose the bubbly liquid is dilute, and the total number of bubbles $N \leq 10^9$, the total energy related to the bubbles is about 1/100 of the incoming wave. Then the impacts of the bubbles in the liquid might be negligible either. Therefore, for accurate measurements of the attenuation coefficient, it
suggests that the bubble number should be \( N \leq 10^5 \), which is close to the bubble volume fraction less than \( 10^{-4} \) (Xia 2018).

**Conclusion**

A nonlinear attenuation formula has been presented by using mechanical energy equation of a single bubble. Some nonlinear phenomena, such as attenuation depending on excitation pressures and jagged attenuation curve, have been recovered using the new nonlinear formula. The accuracy of linear attenuation theory was also examined, of which the results guarantee the validity experiments for attenuation measurements as long as the excitation pressures are low, and the bubbly liquid is dilute.

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