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Nonlinear response to ultrasound of encapsulated microbubbles

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ABSTRACT

The acoustic backscatter of encapsulated gas-filled microbubbles immersed in a weak compressible liquid and irradiated by ultrasound fields of moderate to high pressure amplitudes is investigated theoretically. The problem is formulated by considering, for the viscoelastic shell of finite thickness, an isotropic hyperelastic neo-Hookean model for the elastic contribution in addition to a Newtonian viscous component. First and second harmonic scattering cross-sections have been evaluated and the quantitative influence of the driving pressure amplitude on the harmonic resonance frequencies for different initial equilibrium bubble sizes and for different encapsulating physical properties has been determined. Conditions for optimal second harmonic imaging have been also investigated and some regions in the parameters space where the second harmonic intensity is dominant over the fundamental have been identified. Results have been obtained for albumin, lipid and polymer encapsulating shells, respectively.

1. Introduction

Gas-filled microbubbles stabilized against dissolution by lipid, polymeric or albumin shells, irradiated by an ultrasound field, enhance the acoustic backscattering from blood-filled regions and, hence, improve diagnostic ultrasound imaging [1,2]. More recently they also have been used for targeted therapeutic gene and drug delivery [3]. In the above applications, a precise knowledge of the acoustic properties of the backscatter signal is essential, mainly for ultrasound fields of moderate to high pressure amplitudes for which microbubbles are driven into nonlinear radial oscillations. As a consequence of this nonlinear behavior, the scattered signal is composed by integer multiples (harmonics) of the transmitted frequency. This harmonic content is the basis of diagnostic techniques known under the generic term of harmonic imaging which rely on transmitting an incident signal at a fundamental frequency and filtering the returned echoes at higher harmonic frequencies, specially the corresponding to the second harmonic that besides the fundamental is the harmonic of highest intensity. Therefore, a quantitative analysis of the harmonic intensities as well as the harmonic resonance frequencies is required.

To fulfil the above purposes, the dynamic and sound emission of a single bubble must be investigated. Usually, the dynamics of encapsulated gas bubbles irradiated by sound fields has been studied following a generalized Rayleigh–Plesset approach, by including in the analysis elastic and viscous properties of the encapsulating layer. In pioneering works [4,5], these mechanical properties of the layer were introduced by adding to the usual surface tension coefficient, shell elasticity and shell friction terms in the normal stress condition at the gas liquid interface. A general analysis considering a viscoelastic layer of finite thickness was performed by Church [6]. In this basic work, where the shell was modeled by means of the Kelvin–Voigt rheological equation, it was established that the resonance frequency of individual microbubbles increases approximately as the square of the modulus of elasticity of the shell. The Church model was subsequently applied by Hoff et al. [7] to bubbles encapsulated by polymeric shells. It was found that the resonance frequency is about four times higher than the one corresponding to a free bubble of the same radius. The dynamics of encapsulated gas bubbles surrounded by a compressible viscoelastic fluid was investigated by Khismatullin and Nadim [8]. Their results show the strong influence of viscous damping on resonance frequency which produces significant divergences from the undamped natural frequency. Additional results concerning the influence of viscous damping and harmonic resonance frequencies were obtained later by Khismatullin [9].

The assumption of a homogeneous and isotropic layer has been discussed by Chatterjee and Sarkar [10], and Sarkar et al. [11]. They have proposed a different approach based on interfacial models with intrinsic surface rheology. Similar predictions about resonances are found, i.e., the encapsulation increases the resonant frequency. A nonlinear extension of these interfacial elasticity models has been recently developed [12]. In the model of Stride [13], it is assumed that the bubble is encapsulated by a homogeneous molecular monolayer with surface tension and interfacial viscosity depending on the surface molecular concentration. Numerical results obtained from this model show a clear influence of coating properties on the resonance frequency.

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For small acoustic amplitudes some theoretical predictions concerning the quantitative influence of the viscoelastic properties of the shell on the resonance frequency have been experimentally confirmed. In particular, optical experiments carried out by Van der Meer et al. [14] show that, in comparison with a free uncoated bubble, shell elasticity increases the resonance frequency by about 50%, shell viscosity being the first damping factor. Recently, experiments on phospholipid-coated contrast agents performed by Overvelde et al. [15] have shown a significant decrease of the frequency corresponding to the maximum response with increasing pressure and a pronounced skewness of the resonance curve. It is surprising, however, that these nonlinear responses are observed for acoustic pressures as low as 10 kPa. These experimental results have been appropriately described by the model proposed by Marmottant et al. [16], a heuristic model based on the behavior of phospholipid monolayer coating, with surface tension depending on bubble area, which takes into account shell buckling and rupture. This model predicts other characteristic nonlinear responses of lipid coated bubbles observed for small acoustic pressures like the one termed "compression-only" behavior [17].

The problem for high acoustic amplitudes has been less explored. A numerical study of the dependence of the resonance frequency, defined as the driving frequency which maximizes the scattering cross-section of the backscatter signal, on the pressure amplitude in the range 0.1–1 MPa, was performed by MacDonald et al. [18]. Their calculations show a shift of the resonant frequency values to lower frequencies as the pressure amplitude increases. For large bubbles the discrepancies between linear and nonlinear values may reach even 40%. In this analysis the problem was formulated by means of the general Keller–Herring equation modified to incorporate viscoelastic properties of the shell. A model previously developed by Morgan et al. [19], was also used by Wu et al. [20] in a theoretical study on the nonlinear properties of encapsulated bubbles. In this work it was also confirmed that the frequency at which a peak of the radial oscillation occurs is a decreasing function of the driving acoustic amplitude pulse. In the regime of nonlinear oscillations, results obtained by Doinikov et al. [21] for lipid-shelled microbubbles, confirm a decrease in resonance frequencies with increasing acoustic pressure.

A basic aspect in the theoretical analysis of bubble dynamics in the nonlinear regime is the formulation of the governing equations with an appropriate constitutive equation for the encapsulating shell. In this sense, it must be remarked that the Kelvin–Voigt model is restricted to infinitesimal displacements and velocity gradients, consequently, such a model should be limited to small amplitudes of the external pressure fields. For bubbles coated by shells of finite thickness, some approaches including nonlinear constitutive equations to describe the rheological behavior of the shell have also been considered. The constitutive equation of a neo-Hookean material has been discussed by Allen and Rashid [22] and Jiménez-Fernández [23]. The more general Mooney–Rivlin constitutive law along with the Skalak and Kelvin–Voigt models were investigated by Tsiglifis and Pelekasis [24] in order to describe strain-softening as well as strain-hardening behaviors of membranes following the approach used in the study of biological cells. It was concluded that if the membrane is strain-softening, as it is predicted by the Mooney–Rivlin equation, the resonance frequency decreases with increasing sound amplitude. The Mooney–Rivlin model has been also used to predict the behavior observed in acoustic experiments on lipid-shelled Definity microbubbles [25]. For lipid coating, the equation of a viscoelastic Maxwell fluid has been considered by Doinikov and Dayton [26].

In this work, the scattering of gas bubbles encapsulated by a viscoelastic shell of finite thickness immersed in a liquid and subject to driving acoustic fields of high amplitudes, is studied

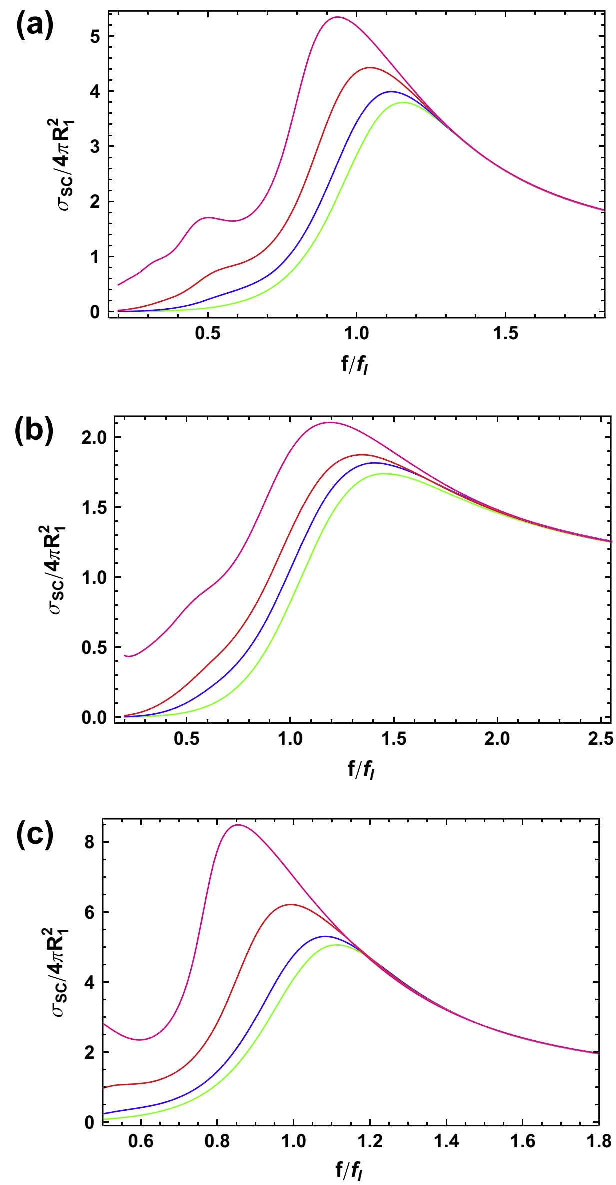

Fig. 1. Scattering cross-section normalized with $4\pi R_1^2$ versus driving frequency normalized with the linear resonance frequency f_l for: (a) albumin-shelled bubbles in water: initial bubble radius $R_1 = 3\ \mu m$, pressure amplitudes: $p_A = 300$ kPa (blue), $p_A = 500$ kPa (red), $p_A = 700$ kPa (pink). (b) Polymer-shelled bubbles in blood: initial bubble radius $R_1 = 4\ \mu m$, pressure amplitudes: $p_A = 500$ kPa (blue), $p_A = 700$ kPa (red), $P_A = 1000$ kPa (pink), (c) lipid-shelled bubbles in water: initial bubble radius $R_1 = 1.5\ \mu m$, pressure amplitudes: $p_A = 100$ kPa (blue), $p_A = 200$ kPa (red), $P_A = 300$ kPa (pink). In each graphic the green line corresponds to the linear first harmonic scattering-cross section σ_{s1}. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

theoretically. Emphasis has been focused to analyze the different harmonic components of the backscatter signal.

The paper is organized as follows. In Section 2, the equations for radial bubble oscillations are derived. The problem is formulated by considering for the viscoelastic shell, an isotropic hyperelastic neo-Hookean model for the elastic contribution, in addition to a viscous component. Because ultrasound fields of high pressure amplitude will be considered, high values of the bubble wall velocity are expected, consequently, compressibility effects in the liquid phase have been also included in the formulation. In Section 3, a linear analysis of the governing equations is carried out, based on which, analytical expressions for the resonance frequency as well