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ORIGINAL PAPER

Effects of Microbubble Size on the Dynamical Behaviour of Encapsulated Sonovue® Contrast Agents in Ultrasonic Fields

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ABSTRACT

Bubble sizes have been shown to have profound effects on the nonlinear response of microbubbles. This paper endeavours to apply a theoretical model to predict and understand the effects of bubble size to the overall bubble dynamics such that bubble-mediated applications may be optimized, controlled and the desirable effects are achieved. The Hoff model for SonoVue® was solved numerically and the effects of varying bubble radii are examined. It has been found that the effects of bubble sizes are significant and may alter a bubble's bifurcation characteristics and route to chaos. The finding also suggests the possibility of suppressing the chaotic oscillations of microbubbles by reducing the bubble size. Furthermore, by increasing the bubble size, the transition from order to chaos occurs at lower driving pressure amplitudes.

INTRODUCTION

Microbubbles and ultrasound are rapidly emerging as a promising tool for noninvasive therapy and drug delivery (Lee, 2016; Nejad, 2016; Orde, 2016). In the context of non-invasive therapy, for example, the operational transition of using microbubbles and ultrasound from an imaging modality to a therapeutic modality is an increase of average acoustic intensity (Moyer, 2015) for which the end result is a beam of high-intensity focused ultrasound (HIFU). The operation is dependent on inertial cavitation and aimed at producing bioeffects such as tissue destruction and vascular occlusion (Moyer, 2015).

Despite the substantial amount of theoretical and experimental research that has been conducted, the dynamics of microbubbles subjected to ultrasound is yet to be fully understood. It is important to appreciate that, unlike other medical imaging contrast agents, microbubbles have a complex nonlinear interaction with ultrasound.

For example, a physical behaviour in acoustic cavitation is inertial cavitation for which microbubbles experience violent collapse. When the microbubbles are close to a wall, micro jets which are associated with puncturing the cell membrane (Nejad, 2016) may occur. While this is desirable for drug/gene delivery, it may also cause tissue damage if not properly controlled.

Drug/gene delivery also undergo stable cavitation upon entering the blood stream until the targeted site is reached. It is therefore important to identify the parameters that will result in such response and to avoid premature drug release due to inertial cavitation. Thus, the ability to understand and predict bubble dynamics is of paramount importance such that the desirable effects are achieved and bubble-mediated applications are optimized and controlled.

Studies have shown that acoustical response of microbubbles are highly dependent on microbubble size (Van der Meer, 2007).

Microbubbles have a size distribution resulting in a mean size and a size range. For SonoVue® microbubbles, the mean radius is $R"$ = 1.5μm and 95% of the bubbles smaller than 10μm (Gorce, 2000). Since microbubble size may vary quite significantly in the bubble cluster, it is thus important to understand and clarify how the size may affect the response and how we may control the oscillations.

Here, we compare the theoretical model with experimental data from (Van der Meer, 2007) to validate the model and the code implemented throughout this paper. We then analyse the bifurcation characteristics and study the various aspects of the microbubble dynamics with changing the radius. We will also investigate the chaotic behaviour of an ultrasound contrast agent based on the shell modelling of a SonoVue® microbubble in an ultrasonic field and explore ways to suppress chaotic oscillations.

NUMERICAL MODELING

Consider the following equation of Hoff form with shell encapsulation terms for a SonoVue® microbubbles as used by (Hoff, 2001):

$$\rho R\ddot{R} + \frac{3}{2}\rho\dot{R}^2 = P_0\left(\frac{R_0}{R}\right)^{3\gamma} - 4\eta_L\frac{\dot{R}}{R} - 12\eta_s\frac{d_sR_0^2}{R^3}\frac{\dot{R}}{R}$$
$$-12G_s\frac{d_sR_0^2}{R^3}\left(1-\frac{R_0}{R}\right) - P_0 - P_{drv}(t) \qquad (1)$$

where R t, $R"$, ρ, γ, η5, $P"$ and P9?@ represent the instantaneous bubble radius, equilibrium bubble radius, density of liquid, polytropic exponent for bubble gas, effective liquid viscosity which accounts for thermal damping, atmospheric pressure, and acoustic driving force. The parameter values of ρ = 1000 kg mI0, γ = 1.07, η5 = 2×10I0$Pa.$ s and $P"$ = 101.3 kPa for bubbles in water at 20NC, would be used for the simulations in this paper following (Tu J., 2009).

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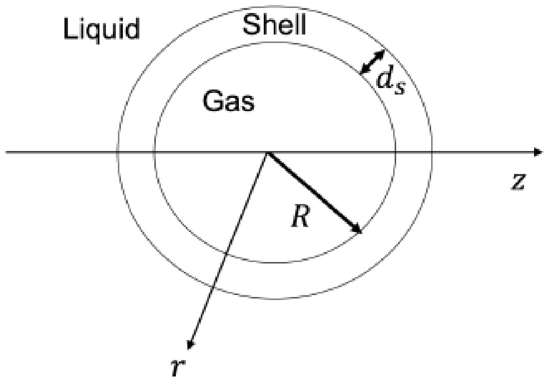

Fig. 1 Schematic sketch of an encapsulated bubble

The microbubble in Eq. (1) describes the oscillation of a bubble shown in Fig. 1 which consists of a continuous layer of elastic and incompressible shell encapsulation with thickness denoted by $d6$. The shell separates the gas microbubble from the bulk Newtonian liquid and stabilizes the microbubbles against dissolution. The parameters for shell encapsulation is given by shell shear viscosity, $\eta6$ and shell shear modulus, $G6$. In this paper, the values for the shell encapsulation parameters which will be used are $d6$ = $4nm$, $\eta6$ = 0.5 $Pa\ s$ and $G6$ = 23 MPa (Hoff, 2001)

COMPARISON WITH EXPERIMENTAL DATA

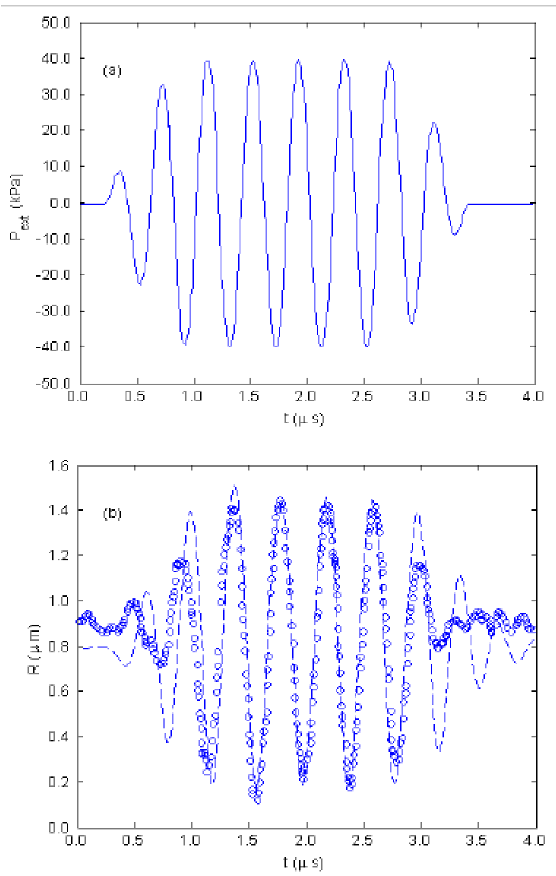

Fig. 2 (a) An ultrasound forcing function of 8-cycle, 2.5-MHz, 40-kPa, whose two first and two last cycles are modulated by a Gaussian envelope as used in experiment (b) The simulated responses for the Hoff Model (--) are compared to the experimental data (o) for $R"$=1.7μm

To check the validity of the code written to solve the mathematical model, Eq. (1) was solved using the parameter values defined in the previous section and compared to with the results of the experiment performed by (Van der Meer, 2007), where they studied the effect of shell encapsulation on the dynamical behaviour of microbubbles by measuring the bubble radius using optical imaging.

The forcing function in Fig. 2(a) shows an external driving ultrasound burst of 8-cycles with the two first and two last cycles being modulated by a Gaussian envelope as done in the experimental setup from Fig. 4 in (Van der Meer, 2007) for $R"$ = 1.7μm. The amplitude and frequency of the signal are PRST = 40kPa and fRST = 2.5MHz respectively as shown in row 4, Fig. 4 in (Van der Meer, 2007).

The results are shown in Fig. 2(b) suggest that code written to solve the Hoff model performs well as it is in good agreement with experimental data in the central region. The simulation data show deviations from the experimental data at the beginning and end stages.

This is due to the fact that numerical data will undergo a transient phase before reaching a steady-state. This will not be an issue for the numerical simulations in the remainder of this study because only oscillations in the post-transient state will be considered.

RESULTS AND DISCUSSION

Our goal is to perform bifurcation analysis that can help us understand the effects of initial radius to the dynamical behaviour of an encapsulated microbubble, SonoVue® in an ultrasonic field. The range of initial radius values considered here is from 1.5μm to 2μmwhich are within the range used in clinical trials (May, 2002). The pressure-bifurcation diagram plotted in Fig. 3 is produced by solving Eq. (1) as a function of the following forcing function:

$$P_{drv}(t) = P_{ext}\sin(2\pi f_{ext} t) \qquad (2)$$

where the driving frequency, fRST, is 1.3 MHz. The bifurcation diagrams have been obtained in the following way. Starting from PRST = 10kPa, the time-radius curve was solved until steady-state is reached. Using the bubble expansion ratio at every forcing period (T = 1/fRST) from the stroboscopic maps as the state variable (Parlitz, 1990). After the projection has been plotted, the control parameter is increased by a small step ΔPRST = 1kPa and the new bifurcation points are calculated for PRST + ΔPRST. This procedure is repeated until PRST = 2 MPa.

For $R"$ = 1.5μm, the bifurcation diagram of Fig. 3(a) clearly reveals a sequence of period-doubling at PRST ≈ 0.7 MPa, 1.1 MPa and 1.3 MPa which indicates the existence of several frequencies of oscillation for the bubble. This state, however, does not persist indefinitely as it undergoes period undoubling for higher PRST. The smallest bubble does not undergo chaos even at higher driving pressure amplitudes.

The slight increase of initial bubble radius to $R"$ = 1.7μm significantly changes the route to chaos. An inspection of Fig. 3(b) reveals that, unlike the smaller bubble $R"$ = 1.5μm, there exists a region of chaos between 0.9 MPa ≤ PRST ≤ 1.4 MPa before settling down to periodic oscillations at higher PRST.

By further increasing the initial radius to $R"$ = 2.0μm in Fig. 3(c), the bifurcation analysis shows a classical period-doubling route to chaos with windows of order for 0.95 MPa ≤ PRST ≤ 1.05 MPa. The bubble undergoes a saddle-node bifurcation at PRST ≈ 1.8 MPa. This is characterised by a jump in the bubble expansion ratio which indicates the destruction of a stable limit cycle and the birth of a new one.

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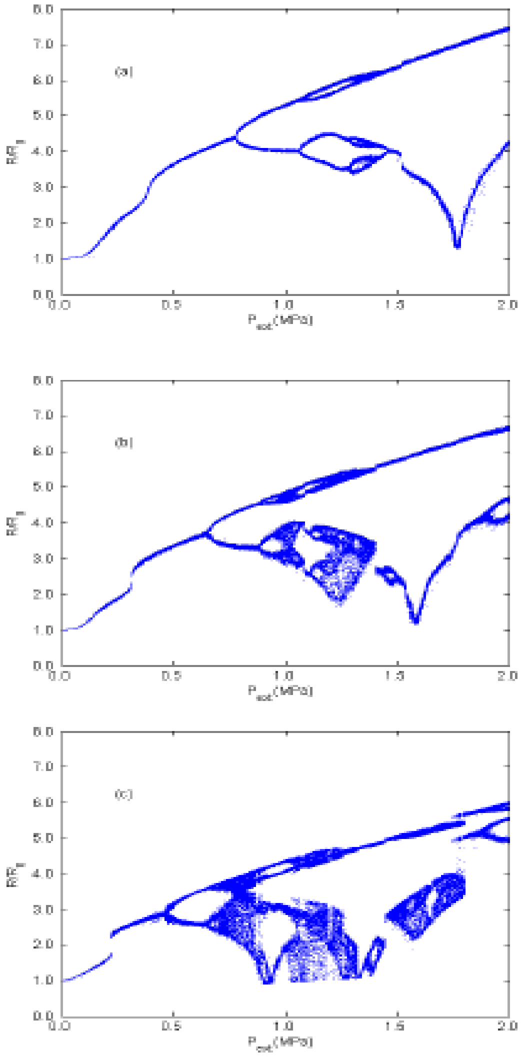

Fig. 3 Bifurcation diagrams of microbubbles for fRST = 1.4 MHz with initial bubble radius (a) R" = 1.5μm (b) R" = 1.7μm and (c) R" = 2.0μm.

The effects of the initial radius are complicated as it adds another degree of nonlinearity to the readily highly-nonlinear equation modelled by the Hoff equation. However, it is apparent from the results of this section that the smaller initial radius plays an important role in reducing the bubble's degree of chaos. This is a very useful finding as it demonstrates the ability to suppress chaotic oscillations according to the bubble size. This may well serve as an alternative to the dual forcing frequency approach (Zhang, 2017). By studying the bifurcation characteristics ins Fig. 3, it is also found that the route to chaos for a larger bubble transitions from order to chaos at lower driving pressure amplitudes.

CONCLUSION

A Hoff theoretical model with shell encapsulation parameters for SonoVue® microbubbles was implemented for predicting dynamics of bubbles in various sizes. Numerical simulations were performed and it was found that the bubble size may alter a bubble's bifurcation characteristics and route to chaos. The finding also suggests the possibility of suppressing the chaotic oscillations of microbubbles by reducing the bubble size. Furthermore, by increasing the bubble size, the transition from order to chaos occurs at lower driving pressure amplitudes.

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