Bifurcation structure of the ultrasonically excited microbubbles undergoing buckling and rupture

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Bubbles exposed to ultrasound are long known to exhibit highly nonlinear and chaotic dynamics. Bubbles stabilized by a shell material (MBs), are widely used as contrast agents in diagnostic ultrasound. However, the nonlinear behaviour of the shell significantly increases the complexity of the dynamics. In order to realize the full potential of the MBs, better understanding of the MB behaviour is necessary. In this study the bifurcation structure of the MB with nonlinear shell behaviour is investigated for the first time. The Marmottant model was numerically solved and the bifurcation diagrams of the radial oscillations of the MB were plotted versus the control parameters (e.g. buckling radius). In agreement with recent experimental observations, results predict the generation of subharmonics at very low acoustic pressures. In addition, the numerical simulations predict the generation of higher order subharmonics (e.g. period 3) at very low acoustic pressures (<300 kPa and 25 MHz), which contradicts the predictions by free bubble and viscoelastic shell MB models. Results revealed the strong influence of the buckling radius on the order of the subharmonics. The numerical results were verified by experimental observation of higher order subharmonics in the oscillations of Definity at 25 and 55 MHz.
INTRODUCTION

Nonlinear oscillations of ultrasound contrast agents (UCAs) (e.g., subharmonic (SH) oscillations) can be exploited in ultrasound imaging to increase the contrast to tissue ratio CTR [1]. Due to the fact that tissue cannot generate SHs, the SH emissions of oscillating UCAs can significantly increase the CTR [2]. Capturing suharmonic emissions is particularly relevant to high frequency ultrasound imaging applications where methods based on harmonic imaging fail, due to the increased nonlinear propagation of ultrasound [3] (i.e. propagation of ultrasound through the tissue can generate harmonics reducing the UCA CTR).

Despite the advantages related to utilizing UCA SH oscillations to increase the CTR, there is not yet a comprehensive understanding of the oscillatory behavior of UCAs at frequencies above 10 MHz [4]. In this regard, nonlinear properties of the UCA shell recently reported and experimentally validated (e.g. buckling and rupture) significantly increase the complexity of the UCA oscillatory patterns [4-6]. For example, it has been shown that the initial surface tension \(\sigma_0\) before the ultrasound wave interacts with the microbubble is critical to the oscillatory dynamics of a lipid shell UCAs. UCAs with \(\sigma_0\) close to 0 tend to exhibit compression only behavior while UCAs with \(\sigma_0\) close to \(\sigma_{water}\) are near the ruptured state and tend to exhibit mainly expansion dominated behavior [7].

However, the contribution of the shell nonlinear behavior to the generation and enhancement of the UCA SH oscillations is not well understood. In order to realize the full potential of the MBs, a more comprehensive understanding of the effect of the shell nonlinearities on the UCA behavior is necessary.

METHODS

In this study the dynamics of the UCAs are studied both experimentally and numerically.

Experimental procedure

Dilute solutions of Definity microbubbles were sonicated at 25 and 55 MHz with 30 cycle train pulses with pressures which were varied over a range of \(~0.1-3.8\) MPa using a Vevo 770 ultrasound imaging system (Visualsonics Inc. Toronto, Ontario). The signals of single UCA oscillations were extracted and their nonlinear behavior were investigated using a similar methodology we have developed to study scattering from a single object in dilute suspensions [8].

Simulations

The dynamics of the UCAs were simulated using the Marmattont model [7]:

\[
\rho_L \left( \frac{\dot{R} R}{2} + \frac{3}{2} \frac{\dot{R}^2}{R} \right) = \left[ P_0 + \frac{2 \sigma(R)}{R_0} \right] \frac{R_0}{R} \left( 1 - \frac{3}{c} \frac{\dot{R}}{R} \right) - P_0 - \frac{2 \sigma(R)}{R} \frac{\dot{R}}{R} - 4 \mu_L \frac{\dot{R}}{R} - 4 \kappa_s \frac{\ddot{R}}{R} - p_A(t)
\]

(1)

where \(R_0\) is the initial radius, \(\rho_L\) is the density of the liquid, \(P_0\) is the equilibrium pressure inside the bubble, \(\Gamma\) is the polytropic exponent, \(\mu_L\) is the viscosity of the surrounding liquid, \(\mu_L\) is the liquid viscosity, \(\kappa_s\) is the surface dilational viscosity of the shell, and \(\sigma(R)\) is the initial surface tension which is given by equation 2:

\[
\sigma(R) = \begin{cases} 
0 & \text{if } R \leq R_b \text{ (buckled)} \\
\chi \left( \frac{R}{R_0} - 1 \right)^2 & \text{if } R_b < R < R_r \text{ (elastic)} \\
\sigma_{water} & \text{if } R \geq R_r \text{ (ruptured)}
\end{cases}
\]

(2)

where \(\chi\) is the shell elasticity, \(R_b = \frac{R_0}{\sqrt{1 + \frac{\sigma(R_0)}{\chi}}}\) and \(R_r = R_b \sqrt{1 + \frac{\sigma_{break-up}}{\chi}}\).

In eq. 1, \(p_A(t)\) is the driving acoustic pressure and is given by equation 3:

\[
p_A(t) = P_A \sin(2\pi ft)
\]

(3)
In order to study the effect of a) frequency and b) the shell properties on the dynamics of the UCA oscillations, the results of the numerical simulations were visualized using the method of bifurcation diagrams as previously employed for the analysis of UCA oscillations [9]. In this method the bifurcation structure of the normalized UCA oscillations (R/R0) are plotted versus a control parameter (e.g. frequency, pressure or buckling radius).

In this study, the bifurcation diagrams of the normalized radial oscillations (R/R0) of the UCAs were plotted over a continuous wide range of frequency (8-30 MHz) and shell properties (σ(R0) and σ_{break-up}). The bifurcation diagrams were generated for different values of the initial surface tension σ0.

Results

Backscattered pressure signals from individual UCAs were recorded for different pressure values as described in the methods. In addition to the conventional SHs at half the driving frequency, higher order SHs can be generated at very low acoustic pressures. Figure 1a shows an example of the experimentally detected period two (conventional SH) oscillations at ~200 kPa and 25 MHz insonation. The signal has two distinct maxima which repeat themselves once every two acoustic cycle for the whole 30 cycle insonation. The frequency spectrum of the signal is presented in Fig. 1b. The signal has a clear SH at 12.5 MHz. Figure 1c shows an example of experimentally measured higher order SHs. The signal is of period 3 and has 3 distinct maxima which repeat themselves once every 3 acoustic cycles. The frequency spectrum of the signal in Fig. 1d has 2 distinct SHs at 8.33 and 16.66 MHz. It should be noted that these signals are presented here as representative signals of scattering from an individual contrast agent. In addition to period 3 signals we were able to detect period 4 and 5 signals.

![Figure 1](image)

**FIGURE 1.** The experimentally detected RF signals (right column) from individual Definity oscillations insonified with pulse trains of 30 cycles with 25 MHz of frequency and ~200kPa of pressure and the corresponding signal spectrum (left column) (a) period 2 (conventional SH) backscattered pressure, (b) frequency spectrum of (a), (c) period 3 backscattered pressure, (d) corresponding frequency spectrum of (c).

In order to study the effect of the frequency on the UCA oscillations, the bifurcation diagram of the normalized radial oscillations of the UCAs (R/R0) were plotted as a function of the driving frequency. Figure 2a shows the bifurcation structure of the R/R0 of a UCA plotted as a function of frequency (8-30 MHz) when the driving pressure is 250 kPa. The representative UCA in figure 2a, has R0 =1.5 μm, χ =2.35 N/m. σ(R0) =0.055 N/m and
\(\sigma_{\text{break-up}}=0.072\) N/m. This model predicts the generation of period 2 and period 4 oscillations at a very low pressure of 250 kPa. The representative UCA exhibits period 2 (P2) oscillations for \(f < 10\) MHz and 13.1 MHz < \(f < 16.2\) MHz, while for the frequency values of 20.9 MHz < \(f < 25.0\) MHz and 27.8 MHz < \(f < 28.1\) MHz the UCA exhibits P4 oscillations. Figure 2b shows the bifurcation structure of the R/R0 of a UCA with \(R_0=1.9\) \(\mu\)m, \(\chi=2.35\) N/m, \(\sigma(R_0)=0.055\) N/m and \(\sigma_{\text{break-up}}=0.072\) N/m. For lower frequencies 9 MHz < \(f < 10\) MHz the UCA exhibits P3 oscillations. As the frequency increases the UCA exhibits P4 oscillations for 12.2 MHz < \(f < 15.4\) MHz and P5 oscillations for 17 MHz < \(f < 21.4\) MHz.

![Figure 2](image1.png)

**FIGURE 2.** Bifurcation structure of R/R0 of two UCAs with \(\chi=2.35\) N/m, \(\sigma(R_0)=0.055\) N/m and \(\sigma_{\text{break-up}}=0.072\) N/m versus frequency when driven with 250 kPa of pressure for (a) \(R_0=1.5\) \(\mu\)m and (b) \(R_0=1.9\) \(\mu\)m.

In order to investigate the effect of the shell nonlinearity on the dynamical behavior of the UCAs the bifurcation structure of the R/R0 is plotted versus \(\sigma(R_0)\). Figure 3 shows the bifurcation structure of R/R0 plotted against \(\sigma(R_0)\) for an UCA with \(R_0=0.87\) \(\mu\)m, \(\chi=2.35\) N/m and \(\sigma_{\text{break-up}}=0.072\) when insonified with \(f=25\) MHz and \(P_0=250\) kPa. The initial surface tension of the shell which determines the likelihood of buckling or rupture, plays a very important role on the subsequent dynamics of the UCA. For 0.0045 < \(\sigma(R_0) < 0.0135\) N/m the UCA exhibits P3 compression only oscillations. For 0.018 < \(\sigma(R_0) < 0.023\) N/m and 0.023 < \(\sigma(R_0) < 0.029\) N/m the UCA exhibits compression only P4 and P2 oscillations respectively. For 0.044 < \(\sigma(R_0) < 0.0535\) N/m and 0.0535 < \(\sigma(R_0) < 0.0575\) N/m the UCA exhibits P2 and P4(2) oscillations, respectively. And finally for 0.0605 < \(\sigma(R_0) < 0.072\) the UCA exhibits expansion dominated P3 oscillations. One of the interesting properties of the bifurcation structure is the symmetry of the nonlinear behavior for the representative UCA. The UCA exhibits enhanced nonlinear oscillations at lower pressures both when it is close to buckling and when it is close to the ruptured state.

![Figure 3](image2.png)

**FIGURE 3.** Bifurcation structure of the R/R0 versus \(\sigma(R_0)\) for a UCA with \(R_0=0.85\) \(\mu\)m, \(\chi=2.35\) N/m and \(\sigma_{\text{break-up}}=0.072\) N/m driven with 25 MHz of frequency and 250 kPa of pressure.
Discussion

The dynamics of UCAs was investigated both experimentally and numerically. Bifurcation diagram analysis was employed to study the effect of different control parameters on the dynamics of the system. In this method the bifurcation structure of the normalized UCA oscillations (\(R/R_0\)) are plotted against the control parameter of interest \[6\]. This method reduces the complexity of the analysis of the discrete time-series data by providing a comprehensive analysis of the effect of a control parameter over a continuous wide range of values. Experimental results at 25 and 55 MHz showed that in addition to the generation of conventional \(1/2\) order SHs at very low acoustic pressures, higher order SHs (e.g. 1/3, ¼…) can also be generated in the oscillations of the Definity UCAs. The bifurcation structure of the Marmottant model was studied as a function of the driving frequency and the initial surface tension of the shell. In agreement with experimental results, the numerical simulations showed that, the nonlinear behaviour of the shell (buckling and rupture) has an enhancing effect on the generation of higher order SHs at low acoustic pressures (<300 kPa) over a range of low to high frequencies (8-30MHz here). It should be emphasized that the models which assume that the shell is as a pure viscoelastic material (e.g . Hoff model \[10\]) cannot predict the generation of higher order SHs at such low pressures. The previous study \[9\] on the generation of higher order SHs in the oscillations of the viscoelastic shell UCAs, predicted pressures thresholds in the MPa range. However, as it is shown both experimentally and numerically that the higher order SHs can be generated at lower pressures ~200 kPa when the UCA shell undergoes buckling or rupture.

Another interesting finding of this study was the effect of buckling and rupture on the generation of enhanced nonlinear oscillations. Previously, it was known that SH oscillations can be generated at very low acoustic pressures due to the compression only behavior of the UCAs close to or in the buckling state \[5\]. However, experimental and numerical results showed that UCAs close to rupture state can also exhibit enhanced nonlinear oscillations at low acoustic pressures. In this regard, UCAs with \(\sigma(R_0)\) close to rupture state exhibit expansion dominated oscillations which can enhance the generation of the \(1/2\) order SHs and higher order SHs. Recently Helfield et al. \[4\] have also reported the generation of \(1/2\) order SHs due to expansion dominated behavior at 25 MHz.

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