Microbubble surface modes

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Abstract—**We have investigated surface vibrations generated by ultrasound excitation of individual unencapsulated micron-sized bubbles. In addition, we present surface modes (n = 2 and 3) observed for phospholipid-coated ultrasound contrast agents excited through excitation of radial modes at frequencies between 1 and 4 MHz. Even higher modes of vibration (up to mode 5) are observed for coated microbubbles at insonation frequencies of 10 and 19 MHz. The potential relevance of surface modes for medical ultrasound is discussed, including the possible implications for current theoretical models of ultrasound contrast agents.**

microbubbles, surface modes, high-speed imaging, spherical harmonics, contrast agents, subharmonics

I. INTRODUCTION

Bubbles insonified by ultrasound will generally exhibit a radial oscillation mode. In addition, surface waves can be generated through instabilities at the interface of the liquid medium and the gaseous content of the bubble. These so-called surface modes have been studied extensively for droplets and millimeter-sized bubbles generated through needle injection [1]. The complex radius excursions can be described in terms of a small regular perturbation which is composed of a linear superposition of a set of spherical harmonics:

$$R(t) = R_0 + \varepsilon(\theta,\phi,t) = R_0 + A_n Y_n^{\,0} \cos(\omega_n t + \vartheta) \qquad (1)$$

where n represents the mode number of the spherical harmonic. $n = 0$ corresponds to the radial oscillation, $n = 2$ to an ellipsoid oscillating between a stretched horizontal or stretched vertical direction. Surface modes were first analyzed theoretically by Plesset and later by Neppiras, Eller and Crum and Prosperetti. The overwhelming interest in sonoluminescing microbubbles in the late nineties also lead to investigations into surface mode oscillations by several groups [Apfel, Holt and Crum, Leighton, Lohse and Matsumoto]. In the course of an experiment on ultrasound radiation forces on microbubbles we came across shape-unstable bubbles; at moderate ultrasound pressure the bubbles were deformed while for higher pressures the bubbles momentarily split. To understand the shape instability mechanisms for these types of bubbles to a better extent we conducted a set of controlled measurements for a variety of bubble diameters and ultrasound pressures. The results of these findings are the subject of the first part of this proceeding. In the second part we report on the observations of surface modes of encapsulated microbubbles.

II. FREE MICROBUBBLE EXPERIMENT

Single air bubbles with diameters ranging from 30 µm to 120 µm were generated in a regulated co-flow micropipette injector [2]. The injector allowed for a controlled production of microbubbles, both in diameter and in separation distance. The bubbles were left to rise to the test section at a downstream distance of 4 cm from the injector. The bubbles were insonified with a pulse of ultrasound from a flat transducer consisting of a burst of 8 cycles at a frequency of 130 kHz. The dynamics of the free air bubbles was recorded with an ultra high-speed camera [3] at a frame rate of 1.25 million frames per second. Fig. 1 shows a selection of the observed vibration modes for these bubbles. It was found that at low pressures of approximately 20 kPa the bubble accurately follows the radial oscillations as predicted by the Keller model [4]. For higher pressures we observe the generation of surface modes after six radial oscillations. We have observed modes up to n = 7. It was found that bubbles of a given size have a preferred surface mode. It was also found that a change in pressure did not alter the preference of surface mode oscillations. A plot of the preferred surface mode as a function of the microbubble diameter is given in Fig. 2. It appears that a linear relationship exists between the bubble size and the observed surface mode vibration. Following Lamb's expression for surface mode vibrations:

$$\omega_n^{\,2} = (n-1)(n+1)(n+2)\frac{\sigma}{\rho R_0^{\,3}} \qquad (1)$$

Figure 1. A selection of surface modes observed for free air bubbles with a diameter ranging from 30 to 120 µm. The preferred mode of vibration is linearly dependent on the initial radius R₀ and is independent of the applied pressure.

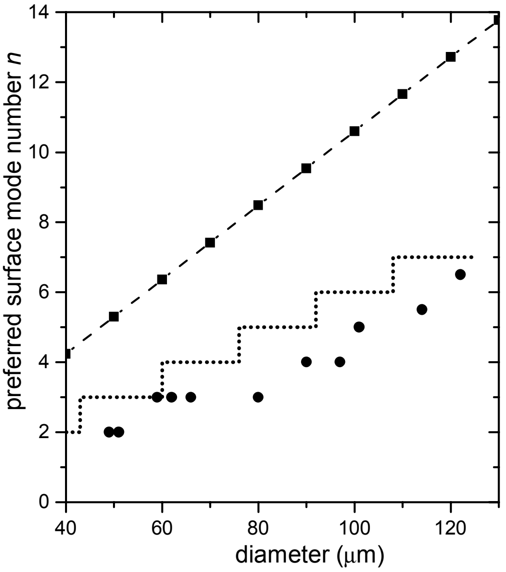

Figure 2. Preferred mode of surface vibration as a function of the bubble diameter. Dots represent measured values for free microbubbles. Dashed line with squares represent preferred mode vibration following Lamb's expression. Dotted line represents the threshold value fro driven microbubbles.

containing cubic terms for both the mode number *n* and the bubble radius *R*, one would indeed expect a linear relationship. This line is drawn in Fig. 2 and lies somewhat higher than the observed data points. Eq. 1 holds for freely oscillating bubbles, however, while in our case the bubbles are driven by ultrasound. The mode preference of driven bubbles can be calculated in a more sophisticated theory following the work of Fransecutto [5]. Here, one calculates the thresholds at which a microbubble of given size will start to exhibit a preferential surface mode. These thresholds are depicted in Fig. 3. From the thresholds the mode preference can be derived and these are plotted in Fig. 2. It is seen that there is a good comparison to the observed data points.

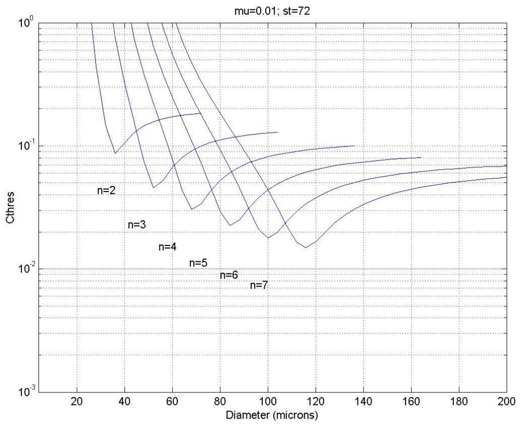

Figure 3 Threshold for mode vibrations as a function of the mode number and the bubble diameter.

III. THEORY OF SURFACE MODE OSCILLATIONS

Looking at the growth over time of the surface mode vibrations they may well be induced by a parametric instability. The parametric instability manifests itself in the growth of initially small perturbations. Following the same spirit of the classical derivation of the Rayleigh-Plesset equation results in a dynamical equation for the distortion amplitude $a_n(t)$:

$$\ddot{a}_n + \dot{a}_n\left\{\frac{3\dot{R}}{R}+\frac{2(n+2)(2n+1)\eta}{\rho R^2}\right\} + a_n(n-1)\left\{\frac{(n+1)(n+2)\sigma}{\rho R^3}+\frac{2(n+2)\eta\dot{R}}{\rho R^3}-\frac{\ddot{R}}{R}\right\}=0 \qquad (2)$$

where $R, \dot{R},$ and $\ddot{R}$ represent the radius, velocity and acceleration of the bubble wall, σ the surface tension, η the viscosity. This expression can be solved in Matlab to give the distortion amplitude as a function of time for a give mode *n*. A typical result for an 80 μm diameter bubble driven with a burst of 10 cycles of 130 kHz at a pressure of 97 kPa is given in Fig. 4. It is seen that in this case the mode 5 develops strongly while other modes are hardly excited. We also see that the instability grows beyond the resting radius of the bubble. At this instant we stop our calculations as in the physical case such a bubble would split up. It is interesting to see that the number of initial fragments is related to the mode number. Fig. 5, for example, shows a bubble that exhibits a mode *n* = 3 surface mode vibration and splits up into three fragments. The fragmentation continues, as also explained in a recent paper by Brennen [6] who concluded that there is a cubic dependence of the number of fragments and the surface mode *n*. In our setup the total number of bubbles is difficult to track quantitatively as there is a fair amount of optical shielding.

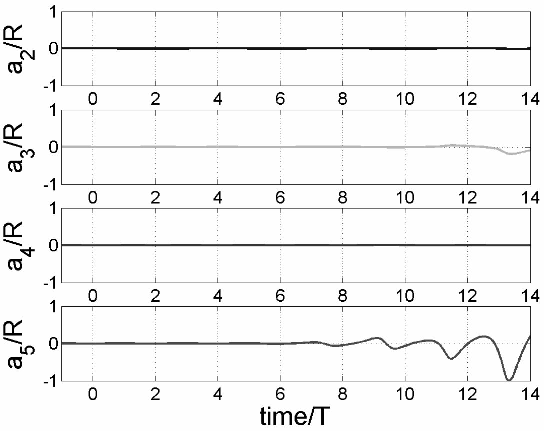

Fig. 4 Calculated distortion amplitudes $a_n(t)$ of free microbubbles showing a strongly developing surface mode $n = 5$. The bubble diameter was 80 μm and the bubble was driven with an ultrasound burst of 10 cycles of 130 kHz at pressure of 97 kPa.

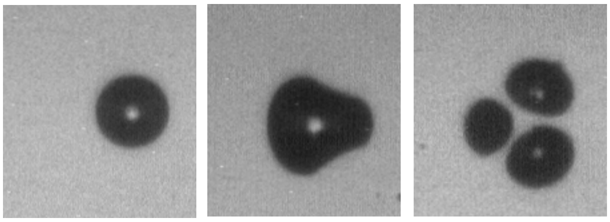

Figure 5. A free microbubble exhibiting *n* = 3 surface mode vibrations splits up into 3 fragments.

IV. CONTRAST AGENT SURFACE MODES

Sonovue microbubbles contained in a 150 µm diameter fiber were subjected to ultrasound from a focused transducer at low (1-4 MHz) and high frequencies (10 and 19 MHz). The experiments were conducted with mechanical indices in the range of 0.1-0.6. The dynamics of the contrast agents were recorded with the Brandaris camera [3] at a frame rate of 16 million frames per second for the low frequency experiments. A strobe technique was used to record the vibration modes of the microbubbles in the high-frequency experiments, with sampling at an offset of 0.8 MHz with respect to the transmit frequency. Fig. 6 shows a 4 µm diameter Sonovue™ bubble before the transmit pulse (burst of 10 cycles; f = 3.5 MHz) was applied. The figures 6^b-6^d show that the microbubble had developed a mode *n* = 3 vibration along the interface. Fig. 7 shows a small microbubble (diameter 1.4 µm) of the experimental agent BR14 (Bracco Research, Geneva) which was insonified with a transmit pulse (burst of 40 cycles) at a frequency of 19 MHz. The recorded images show a mode *n* = 4 vibration, while a second experiment (bottom of Fig. 7) clearly shows a mode of order 5. For both free and encapsulated microbubbles, we observed surface wave oscillations with a periodicity at the half subharmonic of the transmit frequency. This is consistent with previous theoretical and experimental investigations of free millimeter sized bubbles.

V. DISCUSSION

The relevance of the observation of surface modes of ultrasound contrast agents may extend in several directions. First, the ability to initiate active surface modes may have implications for imaging, particularly of subharmonics, though at present this remains unexplored. Further investigations will examine the conditions under which the surface modes are generated, the potential for coupling between these modes and monopolar radiated energy, and whether surface waves may play a role in the generation of acoustically observable subharmonic energy. Second, for modeling purposes, surface modes may provide more insights into the shell properties of contrast agents, leading to a better description of shell elasticity and friction. In addition, none of the current theoretical models for encapsulated microbubbles incorporate surface modes. Third, as known from the literature, surface modes can give rise to intense microstreaming very close to the bubble which may conceivably be exploited for local drug delivery in cell permeability studies [7]. Finally, as the surface vibrations are directly coupled to the fragmentation of the bubble (in fact the mode number is directly related to the number of fragments formed) these interesting observations of surface mode vibrations may lead to a better understanding of contrast agent break up and destruction.

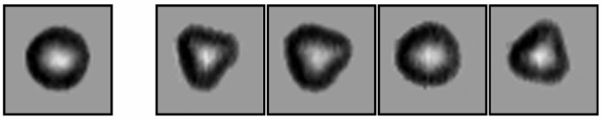

Figure 6 Mode vibrations for a Sonovue™ bubble with a diameter of 4 µm. Here a mode *n* = 3 is observed, however a range of modes is observed for a transmit frequency of 3.5 MHz.

Figure 7. Mode *n* = 4 (top) and mode *n* = 5 (bottom) vibrations for small microbubbles of 1.4 µm diameter. The transmit frequency is 19 MHz. The images were recorded using a strobe technique on the Brandaris camera.

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